Ministério da Educação
Universidade Federal do Rio Grande
Programa de Pós-Graduação em Ciências da Saúde

REVISÃO SISTEMÁTICA DA LITERATURA SOBRE O EFEITO DE ANTI-INFLAMATÓRIOS ESTEROIDAIS E NÃO ESTEROIDAIS EM ENSAIOS PRÉ-CLÍNICOS EM EPILEPSIA

Kathiane Samara Padovani

Rio Grande, 2025

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Kathiane Samara Padovani

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Orientador(a): Profa. Dra. Anna Maria Siebel

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A epilepsia é uma doença neurológica crônica e debilitante que afeta aproximadamente 1% da população mundial. É caracterizada pela ocorrência de crises epilépticas imprevisíveis e recorrentes. O tratamento farmacológico é a primeira linha de escolha com uso isolado ou combinado de fármacos antiepilépticos de primeira, segunda e terceira geração. No entanto, mais de 30% dos pacientes não respondem aos medicamentos disponíveis, o que representa um grande desafio para a saúde pública e impulsiona a busca por novas terapias que atuem por meio de diferentes mecanismos de ação. Considerando a relação entre epilepsia e neuroinflamação, os anti-inflamatórios esteroidais (AIEs) e não esteroidais (AINEs), emergem como promissores para o tratamento da epilepsia. Os principais efeitos terapêuticos desses fármacos se baseiam na supressão da síntese de prostanoides em células inflamatórias. Portanto, com o objetivo de investigar os efeitos de anti-inflamatórios em modelos experimentais *in vivo* de crises tipo-convulsivas induzidas quimicamente, foi redigida esta revisão sistemática de acordo com o protocolo PRISMA. A busca foi realizada nas bases de dados PubMed, WoS e SciELO. Para avaliação do risco de viés e qualidade foram utilizadas as ferramentas SYRCLE e CAMARADES. Com base nos critérios de elegibilidade, 96 estudos foram incluídos e avaliados. A maioria dos artigos (n = 78; 81,25%) incluiu pelo menos um AINE e prevaleceram estudos com indometacina, celecoxibe e dexametasona. Dentre os desfechos, aspirina foi o fármaco com melhor ação no comportamento tipo-convulsivo e a indometacina teve piores efeitos em camundongos. Diversos estudos destacaram a modulação de mediadores inflamatórios como um dos principais mecanismos envolvidos. Também foi evidenciada ação antioxidante, envolvimento da COX-1 e COX-2 na homeostase e plasticidade neuronal, além da modulação dos receptores gabaérgicos e glutamatérgicos. Houve limitações como a grande heterogeneidade dos estudos e falta de informações completes sobre a toxicidade e efeitos adversos. Apesar disso, esta revisão sistemática evidenciou o efeito neuroprotetor dos anti-inflamatórios na maioria dos artigos, provavelmente através de vias anti-inflamatórias, o que pode servir como base para futuros estudos na área.

Palavras-chave: Anti-inflamatórios, epilepsia, não esteroidais, esteroidais, inibidores COX, crise tipo-convulsiva, modelos animais, neuroinflamação.

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LISTA DE ABREVIATURAS E SIGLAS

AIEs – Anti-inflamatórios esteroides

AINEs – Anti-inflamatórios não-esteroides

AMPA – Alfa-amino-3-hidroxi-metil-5-4-isoxazolpropiónico

Anti-LGI1 – Anti-glioma rico em leucina inativado 1

Ca^{2+} – Íon cálcio

Cl^{-} – Ânion cloreto

COX – Ciclo-oxigenase

COX-1 – Ciclo-oxigenase-1

COX-2 – Ciclo-oxigenase-2

EROs – Espécies reativas de oxigênio

FAEs – Fármacos Antiepilépticos

GABA – Ácido Gama-Aminobutírico

$GABA_A$ – Receptor de Ácido Gama-Aminobutírico tipo A

$GABA_B$ – Receptor de Ácido Gama-Aminobutírico tipo B

GABA-T – GABA transaminase

IL-1 – Interleucina-1

IL-1β – Interleucina-1 Beta

ILAE – International League Against Epilepsy

K^{+} – Íon potássio

Na^{+} – Íon sódio

MKP-1 – MAPK fosfatase-1

NMDA – N-metil-D-aspartato

NF-kB – Fator nuclear kappa B

OMS - Organização Mundial da Saúde

PTZ – Pentilenotetrazol

SE – Status epilepticus

SV2A – Glicoproteína 2A da vesícula sináptica

TCE – Traumatismo Cranioencefálico

t – Tempo

TNF-α – Fator de necrose tumoral *alpha*

1. INTRODUÇÃO

A epilepsia é uma condição neurológica crônica não transmissível amplamente prevalente no mundo. Afeta milhões de indivíduos, de todas as faixas etárias, e representa um desafio significativo para o sistema de saúde (OMS, 2024; Feigin *et al.*, 2025; Gaurav *et al*., 2025). É caracterizada por uma predisposição persistente a crises decorrentes de atividade neurofisiológica exacerbada (Fisher *et al.*, 2005, 2014).

Em relação às opções terapêuticas, o tratamento farmacológico, realizado com fármacos antiepilépticos (FAEs), é a primeira abordagem para o distúrbio (Pong *et al.*, 2023). Esses fármacos são classificados pelo estágio de desenvolvimento como de primeira, segunda ou terceira linha (Hakami, 2021) e podem ser utilizados em monoterapia (Nevitt *et al.*, 2022; Ziganshina *et al.,* 2023) ou associação (Margolis *et al.*, 2014; Pipek *et al.*, 2022; Li *et al.*, 2025).

O tratamento farmacológico tem como objetivo propiciar a melhor qualidade de vida possível para o paciente. Isso é alcançado através um adequado controle com um mínimo de efeitos adversos, buscando idealmente, a remissão total das crises (Goldenberg, 2010; Ministério da Saúde, 2019; Mohammed *et al.*, 2023). Estima-se que mais da metade dos indivíduos acometidos poderiam ter uma redução considerável na quantidade de crises se diagnosticados e tratados adequadamente. No entanto, mais de 30% dos pacientes não respondem a nenhum dos tratamentos farmacológicos disponíveis (OMS, 2024; Haneef *et al.*, 2025).

Ainda, há o tratamento não-farmacológico composto por dieta cetogênica (Herrero *et al.*, 2022; Mendonça *et al.*, 2024), neuroestimulação com estimulação do nervo vago, estimulação cerebral profunda e neuroestimulação responsiva, e tratamento cirúrgico (Nordli *et al.*, 2024), indicados especialmente se ocorrer falha no tratamento farmacológico após meticulosa avaliação de risco-benefício. A dieta cetogênica produz efeitos neuroprotetores e melhoram o estado cognitivo dos pacientes epilépticos. No entanto, os efeitos adversos são frequentes e podem e podem afetar o estado nutricional e o crescimento principalmente nos pacientes pediátricos (Herrero *et al.*, 2022). Os benefícios clínicos da neuroestimulação são medidos apenas ao longo de muitos meses (Trevelyan *et al.*, 2025). Já a cirurgia passa pelo conflito de que a área de ressecção pode privar os pacientes do controle total das crises se poupada, enquanto ressecar a mais pode comprometer a cognição muito mais do que deveria ter sido necessário para alcançar o controle das crises (Bauer *et al.*, 2023).

Considerando que (i) a epilepsia acomete em torno de 1% da população mundial, (ii) mais de 30% dos pacientes não respondem aos tratamentos farmacológicos disponíveis e (iii) têm sua qualidade de vida comprometida pela ocorrência de crises epiléticas e pelos efeitos adversos dos fármacos existentes, é evidente a necessidade de encontrar alternativas terapêuticas. Dessa maneira, este estudo buscou identificar a aplicabilidade de anti-inflamatórios no controle de crises e, consequentemente, no tratamento da epilepsia.

Embora vários estudos tenham avaliado o uso de anti-inflamatórios em epilepsia, nenhuma revisão sistemática foi realizada a fim de investigar os efeitos do uso de anti-inflamatórios em modelos experimentais *in vivo* de crises tipo-convulsivas. Uma revisão sistemática que reúna o máximo de evidências disponíveis quanto aos efeitos dos anti-inflamatórios em modelos animais com indução química de crises pode fornecer uma melhor interpretação dos mecanismos de ação, potenciais terapêuticos e limitações de uso desses fármacos servindo como base para futuros ensaios clínicos em busca de opções terapêuticas para pacientes com epilepsia.

2. REVISÃO BIBLIOGRÁFICA

2.1 Epilepsia e crises epilépticas

A epilepsia é uma desordem neuronal caracterizada por uma predisposição duradoura a crises epilépticas e pelas consequências neurobiológicas, cognitivas, psicológicas e sociais dessa condição. As crises epilépticas representam a ocorrência transitória de sinais e/ou sintomas decorrentes de atividade neuronal anormal, excessiva ou síncrona no cérebro (Fisher *et al.*, 2005, 2014). Assim, elas são classificadas em quatro classes principais: focais, generalizadas, desconhecidas (focal ou generalizada) e não-classificadas, as quais se subdividem em vinte e um tipos de crises (Figura 1) (Beniczky *et al.*, 2025).

Crises focais são definidas como originárias redes neurais limitadas a um hemisfério cerebral, podendo ser discretamente localizadas ou mais amplamente distribuídas bem como originadas em estruturas corticais ou subcorticais. Para cada tipo de crise, o início ictal é consistente de uma crise para outra, com padrões de propagação preferenciais que podem envolver o hemisfério contralateral. Em alguns casos, no entanto, há mais de uma rede e mais de um tipo de crise, mas cada tipo individual de crise tem um local consistente de início. Crises focais a tônico-clônicas bilaterais são crises focais nas quais a atividade ictal se propaga para ambos os hemisférios, enquanto a semiologia evolui para comprometimento e, eventualmente, perda completa da consciência e ativação muscular tônica bilateral, seguida por uma fase clônica com diminuição progressiva da frequência, devido a um aumento gradual na duração dos períodos de silêncio que interrompem a atividade muscular tônica (Sinha *et al*., 2021; Beniczky *et al.*, 2025; Modi *et al*., 2025).

As crises generalizadas são originárias de algum ponto dentro de redes distribuídas bilateralmente e que se envolvem rapidamente nelas. O início das crises pode parecer localizado, e podem ser assimétricas. As crises categorizadas como “desconhecidas” podem ser focais ou generalizadas. Essa terminologia é utilizada quando os dados são insuficientes para uma caracterização clara como focais ou generalizadas. De outro modo, quando não há informações disponíveis para caracterizar a crise, apesar de se tratar de uma crise epiléptica, ela é descrita como “Não Classificada”. À medida em que as informações se tornam suficientes para uma classificação, a reclassificação pode ser instituída mesmo que posteriormente (Hirsch *et al.*, 2022; Kodankandath *et al.*, 2023; Beniczky *et al.*, 2025).

Crises focais e crises desconhecidas, se focais ou generalizadas são classificadas de acordo com o estado de consciência do paciente (percepção e responsividade) durante a crise: comprometida ou preservada, sendo um critério de classificação importante. Se o estado de consciência for indeterminado, a crise é classificada sob o termo original. Quando comprometido o estado de consciência implica ter manifestações observáveis (Beniczky *et al.*, 2025).

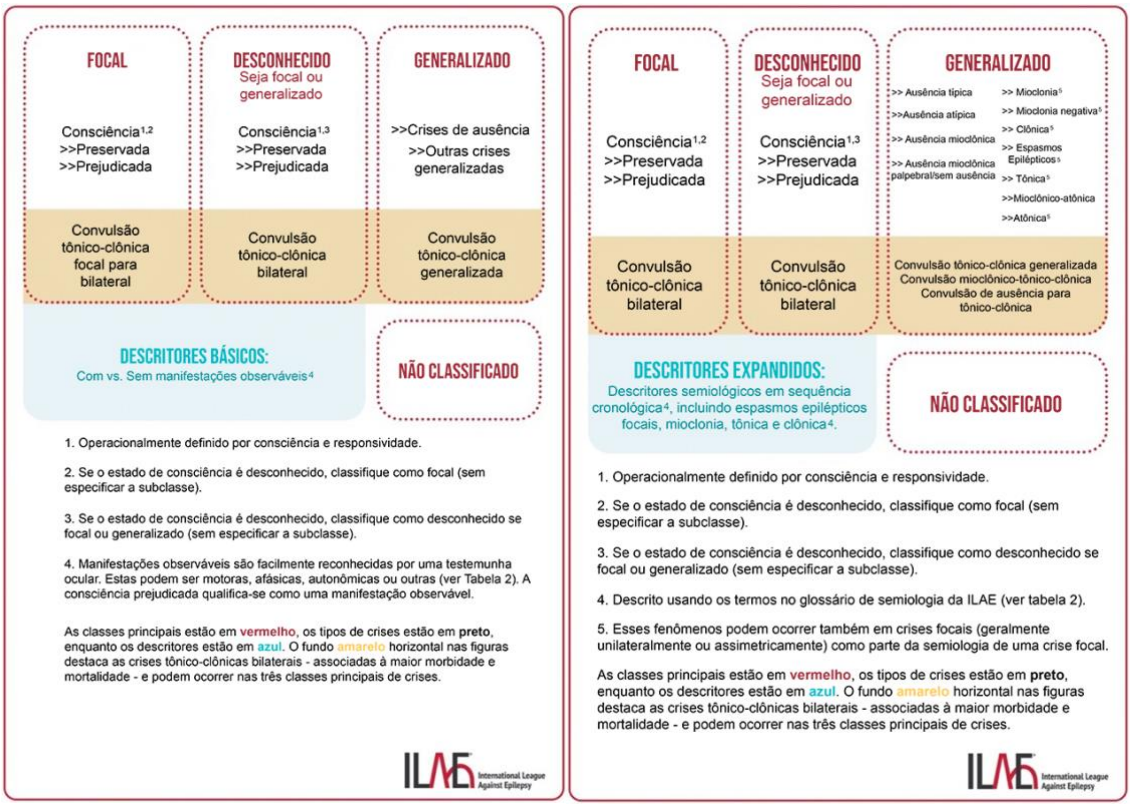

Figura 1: Versão básica e versão expandida da classificação de crises epilépticas propostas pela ILAE em 2025. Na versão básica, as crises são descritas como tendo manifestações observáveis ou não. Na versão expandida, as crises epilépticas são descritas em detalhes, listando em ordem cronológica as características semiológicas que ocorrem durante a crise. Extraído de Beniczky *et al.* (2025).

2.2 Etiologia da epilepsia

A epilepsia é uma patologia multifatorial, podendo ser classificada em mais de uma categoria etiológica na qual a classificação é valorosa para a consideração da terapêutica adicional. Pode ser de causa estrutural, genética, infecciosa, metabólica, imunológica, desconhecida (Scheffer *et al.*, 2017) ou neurodegenerativa. A etiologia estrutural se refere a anormalidades visíveis em neuroimagem estrutural, onde a avaliação eletroclínica, juntamente com os achados de imagem, leva a uma inferência

razoável de que a anormalidade de imagem é a causa provável das crises do paciente. As etiologias estruturais podem ser adquiridas a partir de insultos, como acidente vascular cerebral e trauma (Zelano *et al.*, 2020; Quiles *et al.*, 2025).

Epilepsias de etiologia genética resultam diretamente de mutações genéticas conhecidas ou presumidas, e as crises são um sintoma central dos transtornos (Scheffer *et al.*, 2017) provocados pelas mutações. São conhecidos mais de 700 genes associados à epilepsia (Macnee *et al.*, 2023) com associações fenotípicas ao transtorno (Chi; Kiskinis, 2024). As causas infecciosas de epilepsia são as mais comuns globalmente, resultando diretamente de uma infecção conhecida na qual as crises são um sintoma central do transtorno. Neurocisticercose e tuberculose são exemplos de infecções que provocam epilepsia (Scheffer *et al.*, 2017). Causas metabólicas são provenientes diretamente de um distúrbio metabólico conhecido ou presumido, referindo-se a um defeito metabólico bem delineado com manifestações ou alterações bioquímicas em todo o corpo, como porfiria, uremia, aminoacidopatias ou convulsões dependentes de piridoxina. A etiologia imunológica é conceituada como a presença de evidências de inflamação do sistema nervoso central (SNC) mediada por mecanismos autoimunes diagnosticados com testes de anticorpos. Exemplos são a encefalite anti-receptor N-metil-D-aspartato (NMDA) e encefalite anti-glioma rico em leucina inativado 1 (anti-LGI1). Causas criptogênicas são ainda desconhecidas em que ainda não foi possível fazer um diagnóstico específico além da semiologia eletroclínica básica (Scheffer *et al.*, 2017). Outras causas dispersas nas classificações são causas perinatais e infantis (crises neonatais e pós-neonatais, paralisia cerebral, vacinação e imunização) e distúrbios cerebrovasculares (hemorragia e infarto cerebral, doença vascular degenerativa, malformação arteriovenosa e hemangioma cavernoso) (Shorvon, 2011).

2.3 *Status epilepticus* (*SE*)

O *SE* é uma condição resultante da falha dos mecanismos responsáveis pela interrupção das crises ou do início de mecanismos que levam a crises anormalmente prolongadas (após o ponto de tempo de duração da crise t^1), podendo ter consequências a longo prazo (após o ponto de tempo t^2), incluindo morte neuronal, lesão neuronal e alteração de redes neuronais (dependendo do tipo e duração das crises). É avaliada a duração da crise e o ponto de tempo (t^1) além do qual a crise deve ser considerada como "atividade convulsiva contínua". O segundo ponto de tempo (t^2) é o tempo de atividade

convulsiva contínua após o qual há risco de consequências a longo prazo. No caso de *SE* convulsivo (tônico-clônico), ambos os pontos de tempo (t^1 aos 5 min e t^2 aos 30 min) são baseados em experimentos com animais e pesquisa clínica (Trinka *et al.*, 2015).

2.4 Epidemiologia e impacto social da epilepsia

A epilepsia acomete globalmente mais de 50 milhões de indivíduos, ocorrendo predominantemente em países de baixa e média renda (83,7%), sendo a maior prevalência no Equador e a menor na Coreia do Norte (Feigin *et al.*, 2025). O distúrbio acomete todas as faixas etárias. A distribuição por idades é bimodal, com picos nos mais jovens e nos maiores de 60 anos, sendo responsável por mais de 0,5% da Carga Global de Morbidade (CGD). Também agrega alto risco de incapacidades, comorbidades psiquiátricas, isolamento social e morte prematura, sendo essa três vezes maior do que na relação a população geral. O impacto econômico é representado tanto pela atenção sanitária requerida como pela perda de produtividade laboral, com redução importante da qualidade de vida (OMS, 2019, 2024).

As previsões indicam um aumento na incidência de epilepsia idiopática em todas as faixas etárias até 2035. Estima-se aumento da taxa de mortalidade decorrente, especialmente entre idosos com 80 anos ou mais, o que se explica por distúrbios neurodegenerativos, complicações cerebrovasculares, efeitos adversos de medicamentos antiepilépticos (Zhang *et al.*, 2023) e interações farmacológicas (Seo *et al.*, 2020) nessa faixa etária.

A epilepsia é um dos transtornos neurológicos mais debilitantes, podendo provocar déficits motores, como deterioração da marcha, distúrbios do movimento, escoliose, sono e distúrbios gastrointestinais (Scheffer *et al.*, 2017) além de que com a ocorrência de crises recorrentes e imprevisíveis desencadeia diferentes comorbidades, incluindo disfunção sexual, prejuízo intelectual, depressão, ansiedade (Devinsky *et al.*, 2018), aumento do risco de suicídio (Alejos *et al.*, 2023) e associação com esquizofrenia (Drapier, 2024) e autismo. Isso corrobora a relação da epilepsia com incapacidade, redução da qualidade de vida e morte prematura (Zhang *et al.*, 2023).

2.5 Fármacos antiepilépticos

Os fármacos antiepilépticos (FAEs) tiveram sua descoberta e desenvolvimento iniciados entre o final do século XVIII e início do século XIX, quando bromidas eram usadas no tratamento de epilepsia. Em 1912, o fenobarbital teve seu uso iniciado (Shorvon, 2009). Entre os principais FAEs disponíveis atualmente, encontram-se o ácido valpróico, carbamazepina e levetiracetam. Os de primeira (ditos tradicionais), segunda (ditos recentes) e terceira (ditos novos) geração têm eficácia equivalente, porém o perfil de efeitos adversos e de interações farmacológicas é mais favorável aos mais recentes (Ministério da Saúde, 2019; Hakami, 2021).

Os FAEs reduzem os disparos neuronais exacerbados mediante mecanismos de ação que são a modulação de canais iônicos dependentes de voltagem, a diminuição da neurotransmissão excitatória glutamatérgica e a potencialização da neurotransmissão inibitória gabaérgica (Figura 2) (Bialer; White, 2010). A despolarização e excitação de um neurônio ocorrem com o fluxo interno de íons sódio (Na^+) e cálcio ($Ca2^+$) para dentro da célula e a hiperpolarização e inibição de um neurônio ocorrem com o fluxo interno de cloreto ($Cl^–$) e o fluxo externo de potássio (K^+). Portanto, mudar o equilíbrio entre excitação e inibição em direção a uma maior inibição pode ser alcançado bloqueando os canais Na^+/Ca^{++} ou potenciando os canais $Cl^–/K^+$. A maior parte da atividade excitatória no cérebro é controlada por três tipos de receptores ativados por glutamato: cainato, αlfa-amino-3-hidroxi-metil-5-4-isoxazolpropiónico (AMPA) e NMDA. A neurotransmissão inibitória no cérebro é controlada pelo ácido γ-aminobutírico (GABA), com dois subtipos de receptores, o ácido γ -aminobutírico tipo A ($GABA_A$) e o tipo B ($GABA_B$) atuando através dos canais de $Cl^–$ e K^+ (Haneef *et al.*, 2025).

Assim, os alvos dos FAEs na via de sinalização glutamatérgica incluem canais de Na^+ dependentes de voltagem, glicoproteína 2A da vesícula sináptica (SV2A), subunidade α2δ do canal de $Ca2^+$ dependente de voltagem, receptores NMDA e AMPA (Bialer; White, 2010) e cainato (Chen *et al.*, 2023). Em contraste, em sinapses gabaérgicas, incluindo como alvos o transportador de GABA, GAT1, GABA-transaminase (GABA-T) e $GABA_A$. A inibição do GAT1 leva a uma diminuição na captação de GABA nos terminais pré-sinápticos e na glia circundante e a inibição da GABA-T diminui o metabolismo do GABA nos terminais pré-sinápticos e nas células gliais, elevando os níveis deste neurotransmissor. Já o receptor $GABA_A$ atua mediando

as correntes Cl^- as quais são moduladas alostericamente de forma a aumentar a neurotransmissão inibitória (Bialer; White, 2010).

O ácido valproico é um dos principais antiepilépticos utilizados, com eficácia estabelecida para múltiplos tipos de crises. Picos máximos de concentração são atingidos 2 horas após a ingestão oral. Seu mecanismo de ação pode envolver redução na frequência de disparos dos canais de sódio, ativação da condutância do potássio e, possivelmente, ação direta sobre outros canais iônicos. O ácido valpróico tem um efeito GABAérgico por meio da elevação do GABA cerebral por diversos mecanismos: inibição da GABA-T, aumento das enzimas sintetizadoras do GABA, aumento da liberação e inibição da recaptação do GABA (Romoli *et al*., 2019; Haneef *et al.*, 2025).

A carbamazepina inibe as descargas neuronais corticais repetitivas, sustentadas e de alta frequência pelo bloqueio dos canais de sódio dependente de voltagem. Também possui uma discreta ação anticolinérgica (Verrotti *et al.*, 2007; Hirsch *et al*., 2020). O levetiracetam é um análogo do piracetam, introduzido no mercado em 2000, com suas propriedades antiepilépticas se ligando especificamente à glicoproteína 2A da vesícula sináptica, interferindo com a exocitose e liberação de neurotransmissor na fenda sináptica (Contreras-García *et al.*, 2022; Haneef *et al.*, 2025). A fenitoína tem seu principal mecanismo de ação no bloqueio dos canais de sódio dependentes de voltagem, sendo eficaz no tratamento de crises epilépticas de início focal (Patocka *et al*., 2020). O fenobarbital possui amplo espectro de ação com efetividade similar à de outros FAEs. É seguro e disponível em apresentações orais e parenterais. Seu principal mecanismo de ação é o prolongamento da abertura dos canais de cloro, dos receptores $GABA_A$ e consequente hiperpolarização da membrana pós-sináptica. O fenobarbital também pode bloquear os canais de sódio e potássio, reduzir o influxo de cálcio pré-sináptico e, provavelmente, reduzir as correntes mediadas pelo glutamato. Os benzodiazepínicos, barbitúricos, topiramato e felbamato aumentam a neurotransmissão inibitória ao modular alostericamente as correntes cloreto (Cl^-) mediadas pelo receptor $GABA_A$ (Kanner; Bicchi, 2022; Kishihara *et al*., 2024; Haneef *et al.*, 2025).

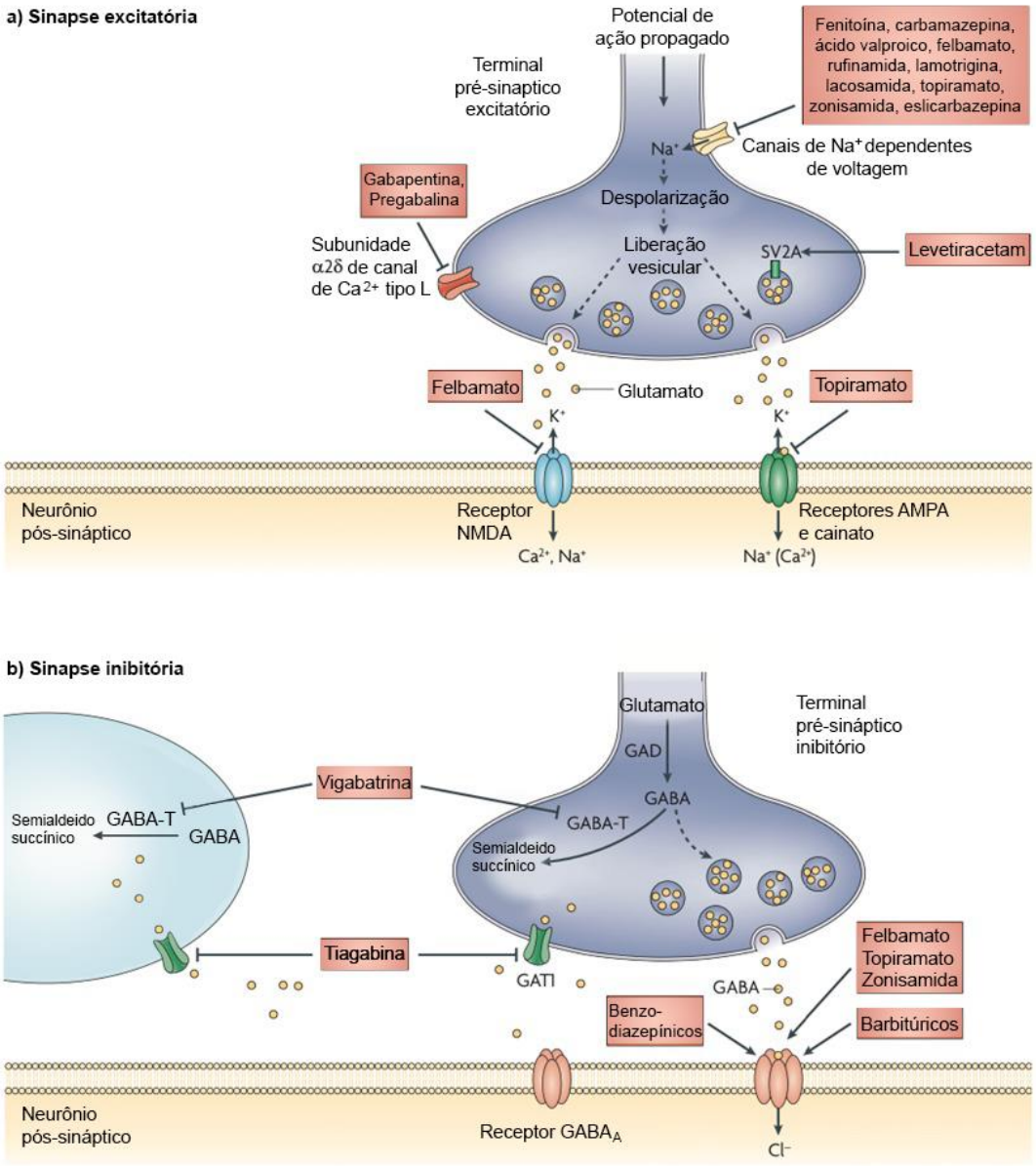

Figura 2: Alvos farmacológicos dos fármacos antiepilépticos. **a**. sinapse excitatória. **b**. sinapse inibitória. Extraído de Bialer; White (2010).

2.6 Tratamento farmacológico da epilepsia

Quando diagnosticadas e devidamente tratadas com os medicamentos antiepiléticos disponíveis, mais de dois terços das pessoas afetadas (70%) podem viver livres de crises (OMS, 2024). A decisão de iniciar um tratamento antiepiléptico se baseia fundamentalmente no risco de recorrência de crises, consequências da continuação das crises para o paciente e eficácia e efeitos adversos do fármaco escolhido para o tratamento. Nesse contexto, o Protocolo Clínico e Diretrizes

Terapêuticas (PCDT) da Epilepsia estabeleceu as orientações sobre o tratamento da doença considerando particularidades, como as comorbidades presentes, juntamente com medicações padrão, doses terapêuticas, tempo de tratamento e critérios para troca ou associação do fármaco e suspensão do tratamento farmacológico (Ministério da Saúde, 2019).

Os critérios para troca de fármaco são intolerância à primeira monoterapia ou falha no controle ou exacerbação de crises. A intolerância pode ser devido a efeitos adversos dos FAEs (Akyüz, 2021; Dang *et al.*, 2021). O período de avaliação da resposta é de 3 meses com o tratamento em doses máximas toleradas. Uma associação de fármacos é proposta quando há controle inadequado de crises com duas monoterapias sequenciais, sendo composta por um fármaco de espectro amplo (como ácido valproico, lamotrigina, topiramato, levetiracetam) com um de espectro restrito (como carbamazepina, fenitoína, fenobarbital), evitando a utilização de dois fármacos com o mesmo mecanismo de ação (Engel, 2014; Ministério da Saúde, 2019; Sing *et al.*, 2020).

São considerados refratários ao tratamento farmacológico os pacientes que, apesar do uso de pelo menos dois antiepilépticos adequadamente escolhidos e utilizados em esquemas adequados de doses, tanto em monoterapia como em combinação, permanecerem apresentando crises, sendo considerado tratamento não farmacológico. O paciente é considerado livre de crises quando elas não ocorrerem após um intervalo três vezes maior que o intervalo de crises vigente anteriormente à introdução do tratamento, ou por pelo menos um ano (Ventola, 2014; Chen *et al*., 2018).

2.7 Desafios no tratamento da epilepsia

Atualmente existem mais de trinta FAEs com uso regular na prática clínica e mais de vinte outros potenciais terapêuticos em distintas fases de investigação clínica (Perucca *et al.*, 2023), sendo a maioria dos utilizados de segunda linha (Perucca *et al.*, 2020). Apesar disso, supracitando, mais de 30% dos pacientes não respondem a nenhum dos tratamentos farmacológicos isolados ou combinados disponíveis (Figura 3) (OMS, 2024; Haneef *et al.*, 2025). Além disso, há a descontinuidade do tratamento por não tolerância a efeitos adversos dos FAEs (Alsfouk *et al.*, 2020; Barnard *et al.*, 2024).

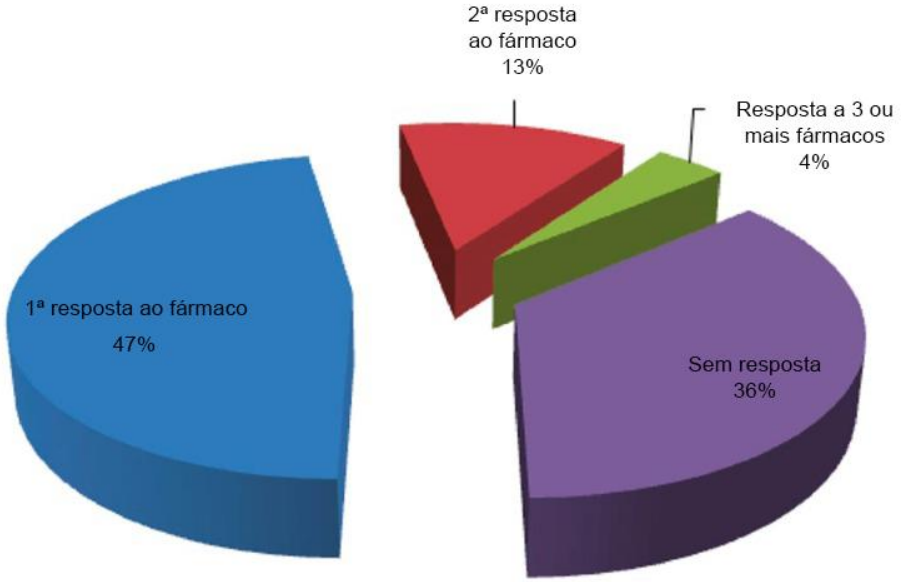

Figura 3: Resposta terapêutica ao tratamento farmacológico na epilepsia: quase metade dos pacientes respondem à monoterapia farmacológica na Epilepsia, sendo 17% com a associação de dois ou três fármacos. Ainda assim, 36% dos pacientes não respondem a nenhum dos tratamentos farmacológicos. Extraída de Haneef *et al.* (2025).

2.8 Epilepsia e neuroinflamação

Considerando que a epilepsia tem alta prevalência e que aproximadamente 1/3 dos pacientes não responde aos fármacos disponíveis, é necessária a identificação de alternativas para seu tratamento considerando fármacos com mecanismos de ação distintos dos antiepilépticos usuais. Assim, têm-se investigado diferentes aspectos patológicos da epilepsia.

É conhecida a associação entre a neuroinflamação e a epilepsia. A ativação da microglia e dos astrócitos por neurônios hiperativos leva à liberação de mediadores pró-inflamatórios (fator de necrose tumoral alpha (TNF-α), interleucina 6 (IL-6), interleucina 1-beta (IL-1β)) e à ativação da via de sinalização do fator nuclear kappa B (NF-kB). Além disso, os astrócitos liberam quimiocinas (CXCL10, CCL2, CCL5) que chegam ao sangue. Lá, atraem diferentes células imunes periféricas (neutrófilos, monócitos e linfócitos T) que se infiltram no parênquima cerebral. Lá, expressam diferentes mediadores pró-inflamatórios que, por um lado, aumentam as propriedades pró-inflamatórias dos astrócitos e da microglia; por outro, pioram o cenário pró-inflamatório. Eventualmente, os neurônios morrem e liberam padrões moleculares associados ao dano (DAMPs), que reiniciam o ciclo (Figura 4) (Sanz *et al.*, 2024).

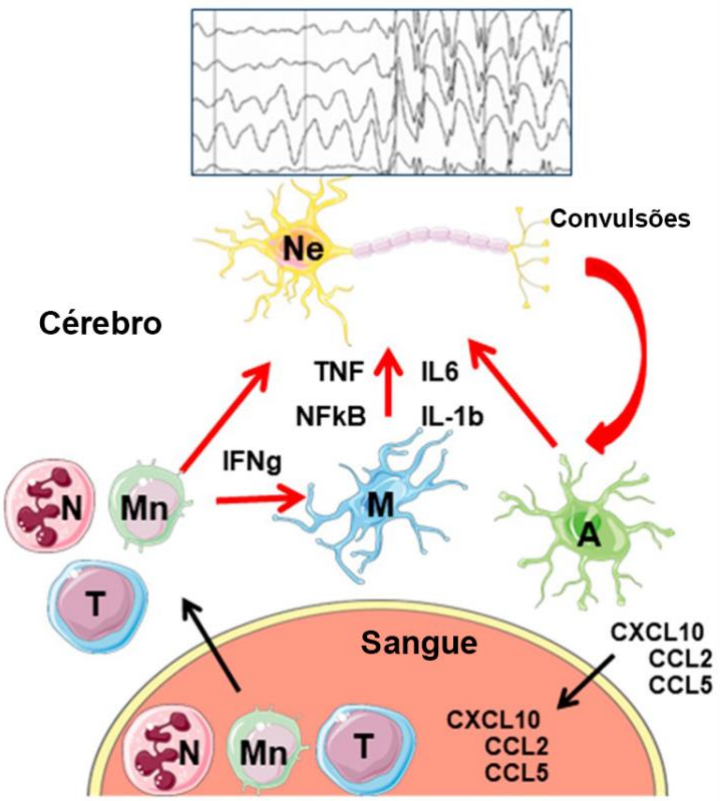

Figura 4: Modelo geral de Neuroinflamação na Epilepsia: mostrando um diagrama simplificado de picos de crise. Ne: neurônios; A: astrócitos; M: microglia; N: neutrófilos; Mn: monócitos; T: linfócitos T.

2.9 Anti-inflamatórios

No tecido cerebral, tanto a COX-1 quanto a COX-2 são expressas constitutivamente (Aïd; Bosetti, 2010). A COX-1 é superexpressa pela micróglia, células endoteliais e perivasculares durante a neuroinflamação em animais e parece ser um evento precoce no processo inflamatório (Ghazanfari *et al*., 2021) enquanto a COX-2 é encontrada nos dendritos pós-sinápticos e terminais excitatórios do neocórtex, hipocampo, amígdala e corno dorsal da medula espinhal (López *et al*., 2020) possuindo papel fundamental na atividade sináptica e na plasticidade sináptica de longo prazo (Choi *et al.*, 2009). Assim, as isoformas da ciclo-oxigenase (COX) foram associadas a propriedades anti-inflamatórias e neuroprotetoras em modelos animais.

Os fármacos inibidores da COX têm três efeitos terapêuticos principais, fundamentados na supressão da síntese de prostanoides em células inflamatórias por inibição da COX-1 e COX-2 do ácido araquidônico. São eles o efeito anti-inflamatório, analgésico e antipirético. O efeito anti-inflamatório é atingido mediante a redução da prostaglandina E2 (PGE2) e da prostaciclina, que reduzem a vasodilatação e,

indiretamente, o edema. Já o efeito analgésico é explicado através da redução da produção de prostaglandinas, diminuindo a sensibilização de terminações nervosas nociceptivas aos mediadores inflamatórios como a bradicinina e a 5-hidroxitriptamina. Por outro lado, o efeito antipirético é explicado no sistema nervoso central, onde na inflamação a interleucina-1 libera prostaglandinas que elevam o ponto de ajuste hipotalâmico para o controle da temperatura, causando febre. Esse mecanismo é impedido pelos AINEs. Os inibidores da COX-2 desempenham um papel significativo no contexto de traumatismo cranioencefálico (TCE) devido à sua atuação na produção de metabólitos de prostaglandina e espécies reativas de oxigênio (EROs), que podem exacerbar a lesão cerebral (Hiskens *et al.*, 2024; Rang; Dale, 2025).

Exemplos de AINEs muito utilizados na prática clínica são a aspirina, ibuprofeno, naproxeno, indometacina e piroxicam. Outros AINEs com inibição mais seletiva da COX-2 também possuem menos efeitos adversos sobre o trato gastrointestinal. São exemplos deles o celecoxibe e o etoricoxibe. O paracetamol, possui ação distinta dos AINEs tradicionais, com fraca ação anti-inflamatória e antiplaquetária, além segurança gastrointestinal superior. Assim, a inclusão dele como AINEs é contraditória apesar de possuir relação com a inibição da COX (Esh *et al*., 2021; Rang; Dale, 2025).

Os AIEs com mecanismos genômicos e não genômicos envolvidos (Adcock, 2020) também apresentam diversas ações, mesmo considerando estarem em menor número. Os glicocorticoides e o receptor de glicocorticoides residem no ápice de uma rede regulatória que bloqueia diversas vias inflamatórias. Podem inibir a produção de prostaglandinas por meio de três mecanismos independentes: a indução e ativação da anexina I, a indução da MAPK fosfatase-1 (MKP-1) e a repressão da transcrição da COX-2. A potência dos glicocorticoides como inibidores de diversas doenças inflamatórias garante seu uso contínuo como agentes terapêuticos (Rhen; Cidlowski, 2005).

Como exemplo, a dexametasona, que como alguns dos fatores positivos, apresentou redução no tempo de duração das crises (Yang, 2019), aumento no tempo de latência (Yang, 2020), redução da COX-2 e PGE2 na sintetase de níveis de mRNA (mostrando sua ação nesses alvos já conhecidos) com aumento também de F-actina nas regiões hipocampais (Yang, 2020), com redução da mortalidade e severidade do *SE* (Fox, 2020). Apesar dos efeitos positivos observados, alguns estudos não registraram

alterações, e houve relatos de aumento da mortalidade e lesão cerebral quando a indução foi feita via subcutânea (S.C) após o *SE* (Duffly, 2014).

No entanto, é importante ressaltar a associação dos AINEs e AIEs com efeitos adversos. Assim, apesar de sua eficácia no controle da dor e da inflamação, os AINEs apresentam limitações e riscos específicos que devem ser considerados. Como exemplo aumento do risco cardiovascular, toxicidade e insuficiência renal, sangramento gastrointestinal, infertilidade e teratogenia (Wirth *et al.*, 2024, 2025). Da mesma maneira, o uso de AIEs está associado a efeitos adversos psiquiátricos como agitação e *delirium*, hiperglicemia, taquicardia, hipertensão, imunossupressão, sangramento gastrointestinal e fraqueza muscular (De Bock; Sienaert, 2024; Haan *et al.*, 2024). Diante disso, é importante considerar as comorbidades do paciente e tempo de tratamento nos pacientes submetidos a terapia.

2.10 Uso de anti-inflamatórios na epilepsia

Estudos evidenciam que a neuroinflamação tem papel chave na epilepsia (Dey *et al.*, 2016a; Aronica *et al.*, 2017; Rana; Musto, 2018; Sanz; Serratosa, 2020). Vários mediadores inflamatórios (como citocinas, quimiocinas, prostaglandinas, fatores do complemento) são liberados por células cerebrais (principalmente pela glia ativada, algumas moléculas e também por neurônios), ou vasos cerebrais ativados, ou importados por macrófagos periféricos/neurotrófilos. A atividade epiléptica por si só é suficiente para desencadear a neuroinflamação. Essas moléculas, no entanto, podem preexistir no tecido cerebral após um desafio autoimune, infecção, lesões cerebrais ou no contexto de epilepsia ativa. Mediadores inflamatórios promovem a ativação transcricional de genes inflamatórios em células-alvo (por exemplo, glia e neurônios), perpetuando assim a cascata inflamatória. Notavelmente, essas moléculas podem ativar diretamente seus receptores expressos por neurônios para induzir alterações transcricionais e pós-traducionais nos receptores de glutamato e GABA e nos canais iônicos que afetam a excitabilidade neuronal. Isso também pode ocorrer indiretamente como consequência de disfunções da astróglia induzidas por neuroinflamação, que permitem a recorrência de convulsões. A pletora de efeitos altera a transmissão sináptica, a excitabilidade neuronal e promove a excitoxicidade, contribuindo assim para resultados patológicos como convulsões, perda de células neuronais, comorbidades, epilepsia (Vezzani *et al.*, 2023).

Considerando que (i) a epilepsia acomete quase 1% da população mundial (Feigin *et al.*, 2025), (ii) um terço dos pacientes não respondem aos tratamentos farmacológicos disponíveis (OMS, 2024; Haneef *et al.*, 2025) e (iii) têm sua qualidade de vida comprometida pela ocorrência de crises epiléticas (Scheffer *et al.*, 2017; Devinsky *et al.*, 2018; Seo *et al.*, 2020; Alejos *et al.*, 2023; Zhang *et al.*, 2023; Drapier, 2024) e a considerável taxa de descontinuidade por efeitos adversos (Alsfouk *et al.*, 2020; Barnard *et al.*, 2024), é evidente a necessidade de encontrar alternativas terapêuticas. Dessa maneira, este estudo buscou identificar a aplicabilidade de anti-inflamatórios no controle de crises epilépticas e, consequentemente, no tratamento da epilepsia. Embora vários estudos tenham avaliado o uso de anti-inflamatórios em epilepsia, nenhuma revisão sistemática foi realizada a fim de investigar os efeitos do uso de anti-inflamatórios nos modelos experimentais *in vivo* de crise tipo-convulsiva. Uma revisão sistemática que reúna o máximo de evidências disponíveis dos efeitos dos diferentes anti-inflamatórios em modelos animais com indução química de crises pode fornecer uma melhor interpretação dos mecanismos de ação, potenciais terapêuticos e limitações de uso desses fármacos servindo como base para futuros ensaios clínicos na área.

3. OBJETIVOS

3.1 Objetivo geral

Investigar através de revisão sistemática o efeito dos anti-inflamatórios esteroidais (AIEs) e não esteroidais (AINEs) em ensaios pré-clínicos em modelos animais de epilepsia de crise tipo-convulsiva com indução química.

3.2 Objetivos específicos

- Analisar quais anti-inflamatórios esteroidais e não esteroidais têm sido investigados no tratamento da epilepsia em ensaios pré-clínicos com indução química de crise tipo-convulsiva;
- Determinar quais modelos animais de indução química de epilepsia e de crise tipo-convulsiva têm sido utilizados na investigação de anti-inflamatórios esteroidais e não esteroidais;
- Avaliar os efeitos dos anti-inflamatórios esteroidais e não esteroidais na ocorrência e intensidade das crises tipo-convulsivas em ensaios pré-clínicos com indução química (frequência de cada estágio de crise tipo-convulsiva e escores manifestados);
- Identificar os mecanismos envolvidos nos efeitos dos anti-inflamatórios esteroidais e não esteroidais em modelos animais de epilepsia com indução química de crise tipo-convulsiva;
- Fornecer subsídios para ensaios clínicos envolvendo o uso de anti-inflamatórios esteroidais e não esteroidais na epilepsia.

4. MANUSCRITO

Effect of Steroidal and Non-Steroidal Anti-inflammatory Drugs in Preclinical Epilepsy Studies: a Systematic Review

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ABSTRACT

Epilepsy is one of the most disabling neurological disorders, characterized by a lasting predisposition to epileptic seizures implying significant impairment in the quality of life of affected individuals. Epileptic seizures are characterized as abnormal paroxysms of synchronized rhythmic discharges resulting from an imbalance between glutamatergic excitation and inhibitory GABAergic signaling in the brain, with a direct relationship between epilepsy and neuroinflammation. Pharmacotherapy with standardized antiepileptic drugs is the first line of treatment for epilepsy. However, more than 30% of people do not respond to usual pharmacological treatment. In this way, there has been an increasing search for pharmacological alternatives considering different targets and mechanisms of action. In this sense, there is evidence of adjuvant treatment with steroidal (SAIDs) and non-steroidal anti-inflammatory drugs (NSAIDs) in treating epileptic seizures in experimental epilepsy models. This systematic review retrieved 96 articles from the Pubmed, Web of Science, and SCIELO databases in order to investigate the effect of SAIDs and NSAIDs drugs in pre-clinical trials in animal models of epilepsy and chemically induced seizure-like crises. Among the 96 articles included, the NSAID class was the most prevalent (81.25%; n = 78). The most prevalent anti-inflammatory agents identified were indomethacin, celecoxib, and dexamethasone. Modulation of inflammatory mediators was highlighted as a primary mechanism of action. Other significant mechanisms included antioxidant activity, the involvement of COX-1 and COX-2 in neuronal homeostasis and plasticity, and the modulation of GABAergic and glutamatergic receptors. Mostly positive effects were found on convulsive behavior, as well as in detailed biochemical and histochemical analyses, favoring anti-inflammatory drugs with synergistic potential to drugs already in use, and suggesting the development of new studies in the area to improve the understanding of gaps in the mechanisms involved.

Keywords: Anti-inflammatory drugs, epilepsy, non-steroidal, COX inhibitors, preclinical trials, steroidal, seizure-like crisis, animal models, neuroinflammation.

1. INTRODUCTION

Epilepsy is one of the most disabling neurological disorders, characterized by a lasting predisposition to epileptic seizures and the neurobiological, cognitive, psychological, and social consequences of this condition (Fisher *et al.*, 2005, 2014). It is clinically defined by any of the following conditions: (i) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring within the next 10 years; (iii) diagnosis of an epilepsy syndrome (Fisher *et al.*, 2014).

Epilepsy affects almost 52 million individuals globally, making it the 72nd most common cause of death, with active epilepsy accounting for 0.7% of the global population. It has an incidence rate of 42.8 per 100,000, with 3.3 million new cases of active idiopathic epilepsy identified in 2021, and a mortality rate of 1.7 per 100,000 (Feigin *et al.*, 2025). There has been a 13.95% increase in global mortality from idiopathic epilepsy compared to previous decades (Zhang *et al.*, 2023). It's responsible for over 0.5% of the Global Burden of Morbidity (GBD) (WHO, 2019) and 0.5% of the Disability-Adjusted Life Years (DALYs) for combined idiopathic and secondary epilepsy, totaling almost 14 million DALYs (Feigin *et al.*, 2025).

Defined as a significant global public health concern, epilepsy was identified by the World Health Organization (WHO) in 2022 as a key priority in the prevention and control of non-communicable diseases during the 75th World Health Assembly. Consequently, a special intersectoral global action plan on epilepsy and other neurological disorders for 2022-2031 was established and is currently being implemented ("Intersectoral global action plan on epilepsy and other neurological disorders", 2022).

As a constantly evolving multifactorial pathology, epilepsy is determined to have structural, genetic, infectious, metabolic, immunological, and cryptogenic (unknown) causes (Scheffer *et al.*, 2017) along with a neurodegenerative association (Zelano *et al.*, 2020; Quiles *et al.*, 2025). In this context, about 7.6 out of every 1,000 people will experience epilepsy at some point in their lives (WHO, 2019). Consequently, just like with its etiology, it's crucial to consider the presence of comorbidities for each epilepsy patient at every classification stage, enabling early identification, diagnosis, and appropriate treatment (Scheffer *et al.*, 2017).

Distinctly, epileptic seizures are defined as abnormal paroxysms of synchronized rhythmic discharges resulting from an imbalance between excitatory (glutamatergic excitation) and inhibitory (GABAergic) signaling in the brain. This process involves kainate, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and N-methyl-D-aspartate (NMDA) receptors for the former, and gamma-aminobutyric acid (GABA) and its receptors for the latter. Thus, epileptogenesis defines the process of altering the cellular, molecular, and network architecture of a normal brain to produce these seizures through exposure to multiple predisposing conditions (Haneef *et al.*, 2025).

As a therapeutic approach, the first choice is pharmacological, represented by standardized medications such as valproic acid, carbamazepine, and levetiracetam (Nevitt *et al.*, 2022). Antiepileptic drugs (AEDs) reduce exacerbated neuronal firing through mechanisms of action that include the modulation of voltage-gated ion channels, the decrease of excitatory glutamatergic neurotransmission, and the potentiation of inhibitory GABAergic neurotransmission (Bialer; White, 2010). Thus, the targets of AEDs in the glutamatergic signaling pathway include voltage-gated sodium (Na^+) channels, synaptic vesicle glycoprotein 2A (SV2A), the alpha-2/delta (α2δ) subunit of voltage-gated calcium ($Ca2^+$) channels, N-methyl-D-aspartate (NMDA) receptors, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (Bialer; White, 2010) and kainite (Chen *et al.*, 2023). In contrast, in GABAergic synapses, targets include GABA type 1 transporter (GAT1), GABA transaminase (GABA-T), and $GABA_A$ receptors (Bialer; White, 2010).

Considering that epilepsy affects approximately 1% of the global population (Feigin *et al.*, 2025), and over 30% of patients do not respond to available pharmacological treatments (Haneef *et al.*, 2025), their quality of life is compromised by the occurrence of epileptic seizures (Scheffer *et al.*, 2017; Devinsky *et al.*, 2018; Seo *et al.*, 2020; Alejos *et al.*, 2023; Zhang *et al.*, 2023; Drapier, 2024) with a considerable discontinuation rate due to adverse effects (Alsfouk *et al.*, 2020; Barnard *et al.*, 2024), there's a crucial need to search for alternative pharmacological therapies with mechanisms of action or targets distinct from currently used antiepileptic drugs.

Moreover, there's a direct relationship between neuroinflammation and epilepsy. Increased neuroinflammation leads to microglial and astrocyte dysfunction, which culminates in neuronal hyperexcitability and excitotoxicity, ultimately triggering

seizures. Neuronal hyperexcitability and cell death following seizures release damage-associated molecular patterns (DAMPs) that activate microglia and astrocytes, eventually leading to the infiltration of peripheral immune cells (Sanz *et al.*, 2024). Consequently, neuronal activity during epileptic seizures involves several additional parameters of neurogenic neuroinflammation, which collectively further increase the frequency and severity of epileptic seizures (Xanthos; Sandkühler, 2014).

Modulating specific inflammatory pathways may be a therapeutic approach for epilepsy (Dey *et al.*, 2016b; Vitaliti *et al.*, 2019; Vezzani *et al.*, 2023) with new pharmacological targets being characterized (Vezzani *et al.*, 2023). Studies also provide evidence for the use of anti-inflammatory drugs as adjuncts in treating epileptic seizures in experimental epilepsy models (Vieira *et al.*, 2016; Guzzo *et al.*, 2018; Liu *et al.*, 2020; De Lima *et al.*, 2021). Other medications with established uses for different pathologies, as well as experimental drugs, are still under clinical investigation, though their actions target pathways already known to existing antiepileptic drugs (Perucca *et al.*, 2023). Therefore, considering epilepsy's high prevalence and that approximately one-third of patients don't respond to available drugs, identifying alternative treatments is crucial.

New pharmacological targets have been identified in animal models to interrupt convulsive-type seizures and improve neurological outcomes. For instance, the pharmacological blockade of interleukin-1 beta (IL-1β), interleukin-8, and arachidonic acid signals using selective drugs has proven effective in reducing seizure duration and severity, as well as improving pathological consequences like neuronal cell loss, mortality, and cognitive deficits (Vezzani *et al.*, 2023).

Steroidal anti-inflammatory drugs (SAIDs) and non-steroidal anti-inflammatory drugs (NSAIDs) are pharmacological agents capable of inhibiting eicosanoid release by acting at various points within the inflammatory cascade (Ferrer *et al*., 2019; Auger *et al*., 2024; Rang; Dale, 2025). They have a well-established use in medicine for diverse pathologies, both acute and chronic (Annane *et al*., 2025; Braïk, 2025), from the prenatal period through all other age groups, and in prophylactic or therapeutic capacities (Cheema *et al.*; 2023; Jensen; Watterberg, 2023; Jobe *et al.*, 2024). Given that cyclooxygenase enzyme isoforms are part of this aforementioned cascade, and that both COX-1 and COX-2 are expressed in brain tissue (Aïd; Bosetti, 2010; Ni *et al.*, 2023), the importance of investigating the effects of these drugs on neuroinflammation is

underscored, even considering their association with adverse effects (Domper *et al.*, 2022; Abbasi; Teakell, 2023; Arfeen *et al*., 2024).

Despite numerous studies on the use of anti-inflammatory drugs in animal models of epilepsy and convulsive-type seizures, no systematic review compiling information on these drugs was found. One literature review, among others, addresses the use of non-steroidal anti-inflammatory drugs in clinical and experimental epilepsy, including 6 clinical trials and 25 preclinical trials (Radu *et al*. 2017). This systematic review aims to identify the applicability of steroidal anti-inflammatory drugs (SAIDs) and non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of epilepsy. It gathers the maximum available evidence on the effects of different anti-inflammatory agents in animal models of epilepsy chemically induced convulsive-type seizures to provide a better interpretation of their therapeutic potentials, mechanisms of action, and limitations, thereby serving as a basis for future clinical trials in the field.

2. MATERIALS AND METHODS

2.1 Research design

This systematic review of preclinical trials investigating the use of steroidal anti-inflammatory drugs (SAIDs) and non-steroidal anti-inflammatory drugs (NSAIDs) in various chemically induced animal models of epilepsy and convulsive-type seizures began with the following research question: “What are the effects of steroidal and non-steroidal anti-inflammatory drugs in experimental models of chemically induced epilepsy and convulsive-type seizures?”.

The research question was based on the PICOS acronym (*Patient*, *Intervention*, *Comparison*, *Outcome*, *Study type*) (Santos *et al.*, 2007; Hooijmans *et al.*, 2014a). This strategy is composed of the following components: Population (**P**), which are animals (non-human); Intervention (**I**), which are anti-inflammatory drugs (NSAIDs and SAIDs); Comparator (**C**), which is the untreated group or the control group (treated with an antiepileptic drug); Outcomes (**O**), which are related to the occurrence and intensity of convulsive-type seizures (primary outcomes) as well as biomarkers (such as oxidative stress and neuroinflammation markers) and other parameters of behavioral,

electroencephalographic, or neurochemical alterations; Study type (**S**), including preclinical studies in animal models of chemically induced convulsive-type seizures.

The results were presented, and the manuscript was written following the "*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*" (PRISMA) (http://www.prisma-statement.org/PRISMAStatement) (Page *et al.*, 2021a, 2021b). The review project was included in the "*International prospective register of systematic reviews*" (PROSPERO) database with registration ID493226.

2.2 Eligibility criteria

2.2.1 Inclusion criteria

We included preclinical trials that assessed the use of NSAIDs and SAIDs in animal models of epilepsy and convulsive-type seizures, specifically those utilizing chemical induction methods. Mixed studies featuring an *in vivo* model were also included, considering all animal species, both sexes, and anti-inflammatory use at any dose, administration route, or exposure duration. Studies involving synthetic drugs still under investigation that act on the cyclooxygenase (COX) enzyme, NSAID and SAID analogues (such as pyrazole benzenesulfonamides – a celecoxib analogue), and drug metabolites (such as sodium salicylate – an aspirin metabolite) were also included. Studies with abstracts presenting an epilepsy or convulsive-type seizure model and an anti-inflammatory drug, even without specific details, were considered. The language was restricted to English, Spanish, and Portuguese, with no restriction on publication year.

2.2.2 Exclusion criteria

We excluded *in vitro* and *in silico*, studies, as well as clinical trials, cross-sectional studies, literature reviews, conference abstracts, dissertations, and theses. Studies without a control group or without a treatment group receiving the anti-inflammatory drug in isolation were also excluded. Similarly, we excluded studies involving drugs with anti-inflammatory action that are not classified as NSAIDs or SAIDs, or that are not their analogues or metabolites. Furthermore, studies with animals in the estrous cycle, pregnant rats, studies involving fetuses, prenatal induction models, or rats exposed to the drug during the prenatal period were disregarded.

Methods of physical convulsive-type seizure induction and stress/restraint models were excluded. Also excluded were models with other types of convulsive seizure induction such as multiple sclerosis, aggression, depression, and ethanol withdrawal. Models that involved convulsive-type seizures but were not models of epilepsy (theophylline), carbachol models, and post-traumatic epilepsy models like ferrous chloride ($FeCl_2$) were excluded. Non-classical epilepsy models (sarin) were excluded, as were induction models using tacrine, lithium chloride, monosodium glutamate, tetanus toxin, morphine/dango, and saikoposanin. Studies where there was a chemical induction model but only used progesterone as an anticonvulsant were excluded. Genetic models of epilepsy, including WAG/Rij rats, pre-epilepsy modifications, and knockout mice, were also excluded. Finally, studies using EP2 receptor antagonists, cortisol, hormones, non-synthetic corticosteroids, or antibiotics were excluded. Articles that could not be found, were off-site/page not found, or were inaccessible in full text, or in a language other than those specified in the inclusion criteria, were also excluded.

2.2.3 Information sources and search strategy

The electronic search was conducted on September 15, 2024, by the lead researcher, across the following databases: "*US National Library of Medicine National Institutes of Health*" (PubMed), "*Web of Science*" (WoS) and "*Scientific Electronic Library Online*" (SciELO). The search terms comprised the English keywords "*epilepsy*", "*seizure*", *status epilepticus* and "*antiinflamatory*", along with their combinations, all extracted from *Medical Subject Headings* (MeSH) metadata system. The selection of keywords was based on encompassing all possible studies related to epilepsy and anti-inflammatory drugs.

The search strategy employed was '(*((epilepsy[MeSH Terms])* OR *(seizure[MeSH Terms])*) OR (*status epilepticus[MeSH Terms])*) AND (*antiinflammatory[MeSH Terms]*)'. This search strategy was adapted for each database according to their specific requirements. For the complete strategy, please refer to Annex I in the SUPPLEMENTARY MATERIAL.

2.2.4 Selection and data collection process

The identified records were imported into the '*Rayyan*' tool (Ouzzani *et al.*, 2016; Qatar Foundation, 2024) for manual duplicate removal and subsequent screening. The initial article selection phase involved two researchers independently screening titles and abstracts, blinded to each other's choices. They considered the eligibility criteria and excluded any articles that clearly met an exclusion criterion based solely on the abstract.

The full texts of the selected articles were read in their entirety by the same researchers, who remained blinded to each other's choices when selecting articles for inclusion in the study based on the eligibility criteria. Discrepancies were resolved between the two researchers, and a third researcher was consulted if disagreements persisted. Data collection was performed by the research group, with data extracted independently by two teams using "*Microsoft Excel*" spreadsheets. Data from all studies selected in the second phase were extracted, tabulated, standardized, and included in the analyses.

2.2.5 Data extraction list

Information extracted from the studies was based on study identification, experimental details analyses and main outcomes: (1) Reference [author, publication year, digital object identifier (DOI)]; (2) Animal model (n, sex, weight, age); (3) Anesthetic [drug, dose, route of administration (admin.)]; (4) Drug induction/model (dose; route of adm.; exposure period (5); (6) Groups (control, vehicle, antiepileptic, antiinflamatory); (7) Anti-inflammatory drug (class; dose; route of adm.; period of treatment); (8) Adm. Period (pre- or post- crisis induction); (9) Evaluated parameters; (10) Crisis type; (11) Seizure-like behavior (occurrence of each seizure stage); (12) Seizure-like behavior (latency of each seizure stage); (13) Seizure-like behavior: (frequency of each seizure stage); (14) Seizure-like behavior (manifested scores); (15) Anti-inflammatory effects.

The primary outcomes analyzed will be those related to the occurrence and intensity of convulsive-type seizures. Seizure occurrence was tabulated considering, for example, the latency of the first convulsive-type seizure, their frequency, and duration. The intensity of convulsive-type seizures was assessed using the scale employed in each

study, with the Racine scale being a widely used example for this purpose (Racine, 1972; Van Erum *et al.*, 2019).

Other outcomes will also be analyzed. For biomarker tabulation, we'll note, for example, the presence in brain tissue and blood of oxidative stress markers and neuroinflammation markers such as catalase (CAT) enzyme activity, superoxide dismutase (SOD) enzyme, glutathione peroxidase, sulfhydryl groups, TLRs, COX-2, IL-1β, IL-6, IL-18, TNF-α, TGF-β, BDNF, NLRP3, and caspase. Other behavioral parameters will also be assessed, specifically the animal's cognitive/behavioral performance as relevant to the experimental animal model. For instance, studies evaluating animal locomotor and exploratory activity might include tests like "*Skinner*", "*open tank*", elevated plus-maze, and sociability tests. For aquatic animals, distance traveled, mobile time, time spent at the top, and time spent at the bottom of the apparatus will be evaluated. Other outcomes, such as neuronal death, are directly described in the data extraction list. If information is missing, ambiguous, or unclear, it will be flagged for identification.

2.2.6 Bias risk assessment of the studies

For bias risk assessment, the "*Systematic Review Center for Laboratory Animal Experimentation*" (SYRCLE) tool was used (Hooijmans *et al.*, 2014a; Hooijmans *et al.*, 2014b). This tool contains ten items related to six types of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. For selection bias: (a) "was the allocation sequence adequately generated and applied?"; (b) "were the groups similar at baseline or adjusted in the analysis?"; (c) "was allocation properly blinded?". For performance bias: (a) "were the animals randomly housed during the experiment?"; (b) "were caregivers and/or researchers blinded to the intervention received during the procedure?". Regarding detection bias: (a) "were the animals randomly selected for outcome assessment?"; (b) "was the outcome assessor blinded?". Regarding attrition bias: (a) "were incompletely addressed outcome data adequately handled?". Regarding reporting bias: (a) "are the study reports free from selective outcome reporting?". Regarding other biases: (a) "does the study appear to be free from other problems that could lead to a high risk of bias?".

These items are used to assign a risk of bias judgment as low, high, or unclear. A "yes" judgment indicates a low risk of bias, a "no" judgment indicates a high risk of bias, and insufficient details to adequately assess the risk of bias indicate an unclear judgment. This assessment was conducted by four researchers working in two independent groups, with disagreements resolved through consensus. A fifth researcher was consulted to resolve any remaining discrepancies.

The study quality was assessed using a scale adapted from the '*Collaborative Approach for Meta-Analysis and Review of Animal Data from Experimental Studies*' (CAMARADES) (Zeng *et al.*, 2015). The modified CAMARADES tool included the following criteria for in vivo studies: (1) publication in a peer-reviewed journal; (2) statement of temperature control; (3) randomization of treatment or control, with a description of the method; (4) allocation concealment; (5) blinded assessment of all outcomes; (6) use of an anesthetic without significant intrinsic neuroprotective activity; (7) use of animals with an appropriate model; (8) sample size calculation; (9) declaration of compliance with regulatory requirements; and (10) declaration about possible conflict of interests. One point will be awarded for each fulfilled criterion and zero if the information is absent, insufficient, or unclear, resulting in a final score ranging from 0 (lowest) to 10 (highest). A table containing the score of each study will be created after applying the tool. For study quality assessment, the variation and mean score among the studies will be reported.

2.2.7 Synthesis methods

The extracted data were organized into similar groups based on the main characteristics and variables obtained from each study. A narrative synthesis of the results was presented in tables, following the data collection division by main items (as described in item 2.2.5 **Data extraction list**). The results were presented according to the PRISMA guidelines (Page *et al.*, 2021a).

3. RESULTS

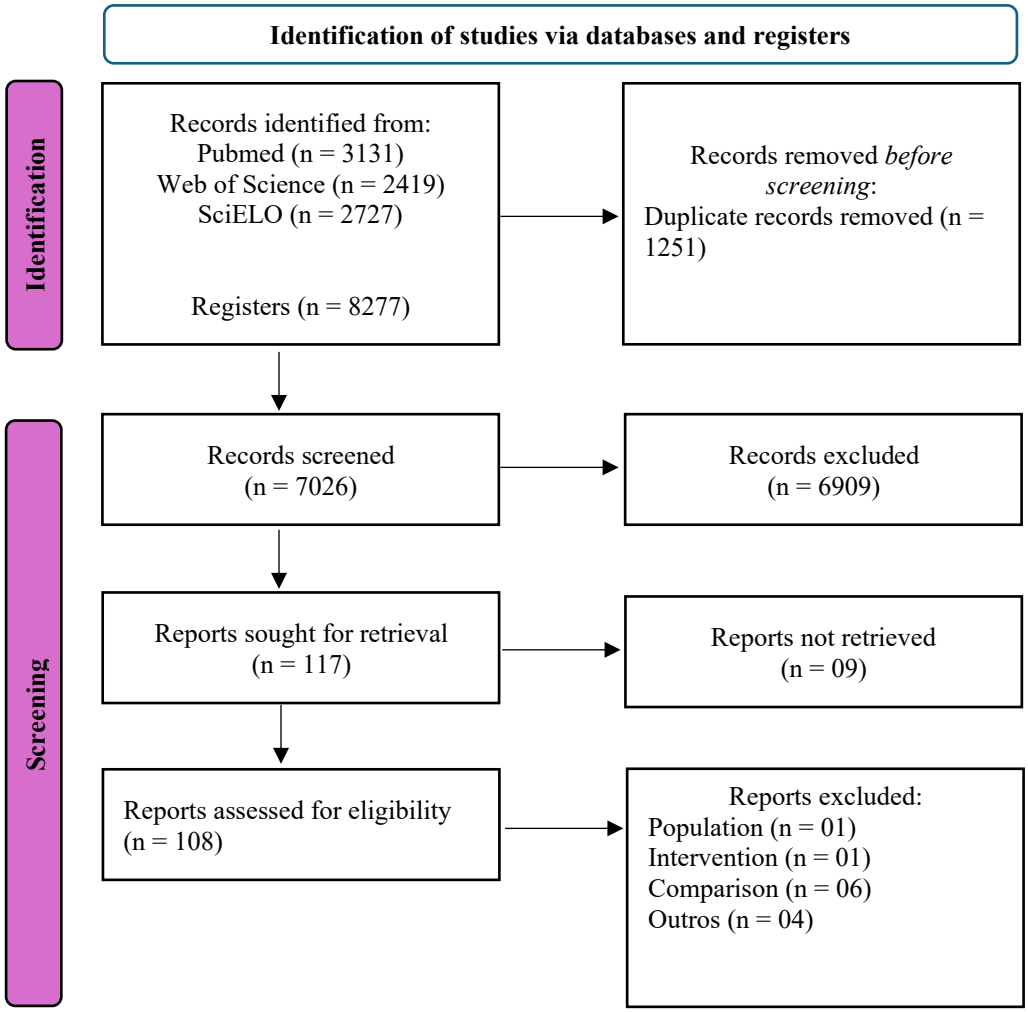
3.1 Search results

Our search across the selected databases yielded a total of 8277 records (Pubmed = 3131; WoS = 2419; SciELO = 2727). After the primary researcher manually removed

1251 duplicates, 7026 records were assessed for eligibility based on their titles and abstracts. In this initial phase, 6909 articles were excluded, leaving 117 articles eligible for full-text review. Of these, 9 articles couldn't be retrieved due to inaccessible full text (off-site hosting or restricted access to the full version and/or no response to electronic requests sent to the respective authors).

The full texts of the selected articles were read in their entirety by the same researchers, who remained blinded to each other's choices. Articles meeting the inclusion criteria were then selected for the study, totaling 96 articles for extraction. 12 articles were excluded during this second screening phase. Among them, 4 models involved physical induction and 2 used chemical induction that did not meet the inclusion criteria. Also excluded were 4 studies in Oriental languages (3 in Mandarin and 1 in Japanese), 1 study with an anti-inflammatory that didn't investigate convulsive activity, 1 study lacking a control group, and 1 study using a "*knockout*" animal model. This resulted in 96 articles for extraction. Discrepancies were resolved between the two researchers, and if disagreements persisted, a third researcher was consulted.

The flowchart illustrates the progressive selection of studies and the number of articles at each stage (Figure 1).



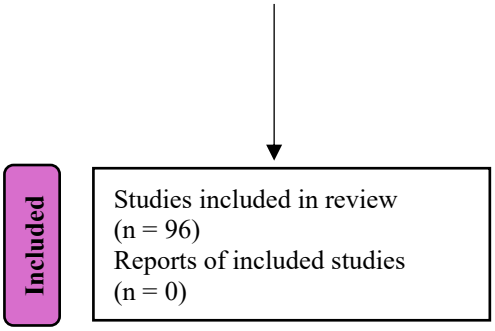


Figure 1: Flowchart diagram of the collection of studies and selection process of systematic review according to the PRISMA statement.

3.2 Characteristics of the studies

The distribution of preclinical trials by publication year is shown in Table 1, with the earliest included study dating back to 1981. Most studies were published between 2000 and 2019 (n = 59, 61,46%) while the period before 2000 accounted for the smallest portion, representing 13.54% (n = 13) of the studies included in this systematic review.

Table 1: Distribution of included studies in the systematic review by publication year.

Publication period (year)	Total studies in period (n)	Total studies in period (%)
1981 a 1999	13	13,54
2000 a 2019	59	61,46
2020 a 2024	24	25
Review total	96	100

All characteristics and data found in the studies reported below can be viewed in Table 2, along with additional information.

3.3 Characteristics of experimental details

3.3.1 Animal model

In the 96 studies included in this review, the most used animal was Winstar rats (n = 26; 27.1%), followed by Sprague-Dawley (n = 25; 26.04%) and Albino mice (n =

7; 7.3%). The non-specified models, rats and mice, corresponded to 11.4% of the studies (n = 11), the most recent being from the year 1999. The predominant sex was male (n = 77; 80.2%), followed by female (n = 7; 7.3%) (Figure 2).

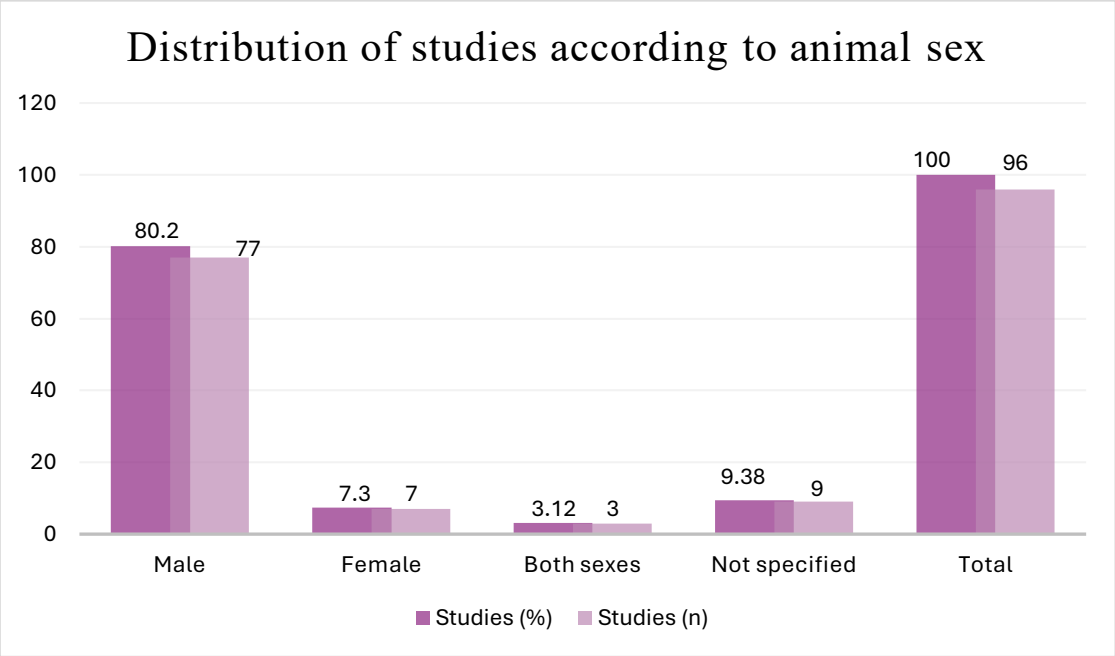


Figure 2: Sex distribution of animals in included studies, showing percentages and absolute numbers.

Only 03 studies were performed with both sexes (n = 3; 3.12%), not being accounted for in the individual count. Thus, 09 studies did not specify the sex used (n = 9; 9.38%). In mammals (n = 93; 96.9%), weight varied between 15g and 400g (Swiss albino and Sprague-Dawley, respectively) with age between 07 days and 15 weeks (Sprague-Dawley and Wistar rats) (Figure 3). It is important to highlight that there was only one study with Piglet newborn dated 1989 and without specified weight or age. In a study (Brabec, 2022), it only reports that Sprague-Dawley rat pups were separated from the mother post-natal, not making clear the lifespan, and therefore it is not possible to infer that their age is less than what was found. The other animals included in the study were of the species *Danio rerio* (zebrafish) (n = 3; 3.1%) including larvae, embryos and adults, with reported weight varying between 0.4g (+- 0.1g) to 24g in the studies (Table 2).

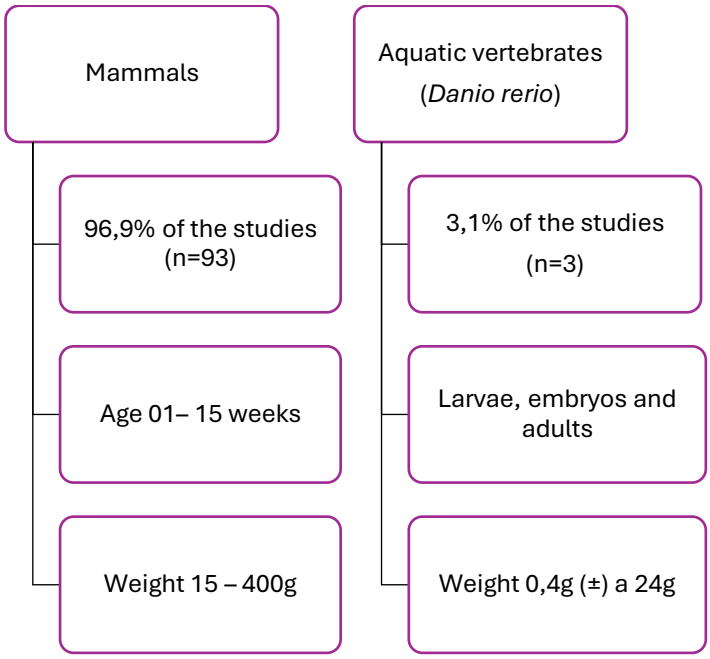


Figure 3: Characteristics of animals in the 96 studies included in the systematic review.

TABLE 2: Distribution of 96 articles chosen at the end of the screening for text evaluation.

Experimental details							Analyses	Main outcomes					
Author (year)	**Animal model (n; sex; weight; age)**	**Anesthetic (drug; dose; route of adm.)**	**Drug induction/model (dose; route of adm.; exposure period)**	**Groups**	**Anti-inflammatory drug (class; dose; route of adm.; period of treatment)**	**Adm. Period (pre- or post- crisis induction)**	**Evaluated parameters**	**Crisis type**	**Seizure-like behavior: occurrence of each seizure stage**	**Seizure-like behavior: latency of each seizure stage**	**Seizure-like behavior: frequency of each seizure stage**	**Seizure-like behavior: manifested scores**	**Anti-inflammatory effects**
de Lima (2024)	Wistar rat n=31 Male 300 g 90 days old.	N/A	PTZ 25 mg/kg I.P Administration on alternate days, starting on the second day, for 14 days.	1) Negative control group: 0.9% saline; 2) Positive control group: diazepam 2 mg/kg; 3) Test group 1: prednisolone 1 mg/kg; 4) Test group 2: prednisolone 5 mg/kg.	Prednisolone Steroidal anti-inflammatory 1 and 5 mg/kg I.P. 14 days.	Pre-induction (30 minutes before PTZ administration).	Animals were monitored for 20 minutes to assess seizure severity based on the Racine scale. Seizure latency was monitored with a stopwatch to mark the time of onset of the initial seizure. Determination of inflammatory markers (TNF-α and IL-1β; Quantification of total proteins Method: biuret method; DNA extraction from rat intestinal microbiota samples; Analysis of intestinal microbiota composition a) RISA (Ribosomal Intergenic); Analysis of microbial community structure.	The study used the picrotoxin (PIRO) kindling model and assessed seizure severity based on the Racine scale (chronic model of epileptic seizures).	Yes.	Day 1 to Day 7 Saline: ~100s Diazepam: ~300 -500 s Pred1: ~220 – 500 s Pred5: ~250 - 500 s.	N/A	N/A	↑ Latency time over several days of the protocol; Pred1: ↑ TNF-α levels Diazepam vs. Saline, Pred5 vs. Saline: → TNF-α levels; Pred1 and Pred5: ↑ IL-1β Saline and Diazepam maintained lower levels, close to each other, with no significant difference.
Gautam (2024)	Wistar rats n=48 Male 180 to 270 g 7 to 9 weeks old.	N/A	Lithium chloride 127 mg/kg I.P. (Given 22–23 h before pilocarpine). Scopolamine 1 mg/kg I.P. (Half an hour before pilocarpine). Pilocarpine 60 mg/kg I.P. (Doses repeated every 30 min, until seizure onset Time to seizure: on average 40–50 min after first dose of pilocarpine).	1) Control group (saline solution); 2) *Status Epilepticus* (*SE*) group; 3) Vehicle group (SE group treated with 0.5% DMSO; 4) Valproic acid (VPA) group 200 mg/kg; 5) 6-BIO group 2 µg/kg; 6) 6-BIO group 4 µg/kg; 7) Sulindac group 20 mg/kg; 8) Sulindac group 40 mg/kg.	1) Sulindac NSAID 20 and 40 mg/kg I.P. 2) 6-BIO GSK-3β (glycogen synthase kinase-3 beta) inhibitor; dose: 2 and 4 µg/kg I.P. 3) VPA (Sodium Valproate/Valproic Antiepileptic (broad-spectrum antiepileptic 200 mg/kg I.P. Chronic treatment started on the 35th day post-SE until the 56th day.	Post-induction of *SE*.	T-maze test; Actophotometer for locomotor activity; Rota rods for muscle coordination; Elevated plus maze (EPM) test for anxiety; Seizure behavior was assessed in 5-h sessions, but the exact duration of each seizure was not provided; Evaluation of histopathological changes in the hippocampus; Evaluation of neurogenesis (NeuN) by immunohistochemistry in the hippocampus; Evaluation of the expression of several genes (GSK-3β, β-catenin, Dvl, Bcl, Bax, Caspase) by RT-qPCR and Western Blot.	Induced seizures were of the status epilepticus type: prolonged and continuous seizures with intense convulsive activity.	Yes.	The latency to onset of spontaneous seizures was less than 7 days in all *SE* groups.	Saline: ~0 SE: ~5 Vehicle: ~5 VPA: ~5-2 BIO 2: ~4.5 – 3.5 BIO 4: ~4.5 – 3.5 Sulindac 20mg/kg: ~4.5 - ~1 Sulindac 40mg/kg: ~4.5 – ~1.5.	*SE* group: week 1: 3.5 week 8: ~3.9 Vehicle group: week 1 to week 8 ~3.5 VPA group: week 1: ~3.6 week 8: ~2.6 Sulindac 20 mg/kg group: week 1: ~3.6; week 8: ~2.1 Sulindac 40 mg/kg group: week 1: ~3.7; week 8: ~2.5. Saline group: week 1: ~0.5; week 8: ~0.	VPA and sulindac (20 mg/kg) ↓ seizure score and frequency compared with the *SE* group; The 6-BIO treatment group was ineffective in reducing the seizure score compared with sulindac; The 6-BIO (2 and 4 µg/kg), sulindac (20 mg/kg), and VPA treatment groups: ↓ locomotor behavior compared with SE rats; ↑ Motor coordination and muscle activity; ↓ Anxiety-like behavior; Improvement in memory impairment; ↓ Neuronal damage ↑ neurogenesis in the DG region of the hippocampus ↓ mRNA expression of GSK-3β; → expression of B-catenin and Dvl. Treatment with sulindac: ↓expression of Dvl and β-catenin and ↑ the expression of GSK-3β. → mRNA expression of Bcl2, Bax and caspase in the VPA, sulindac (20 and 40 mg/kg) and 6-BIO (2 and 4 µg/kg) groups.
Guzzo (2024)	Wistar rats n= 8–10 animals per group Male 250 to 300 g 8–9 weeks old.	N/A	PTZ 20 mg/kg I.P. 7 days.	1) Negative control 2) Positive control group received diazepam (2 mg/kg) 3) Piroxicam (PIRO) 0.15 mg/kg 4) PIRO 0.30 mg/kg.	Piroxicam (PIRO) NSAID 0.15 and 0.30 mg/kg I.P. 15 days.	Pre-induction (30 minutes before PTZ administration.	The animals were then placed in a transparent box and observed by two researchers for 20 minutes, to assess seizure intensity - Racine scale. Behavior test (Open field, Memory assessment – object recognition). Brain microdissection and tissue preparation. Determination of cytokines (TNF-α, IL-6 and IL-10).	Kindling model.	Yes.	N/A	N/A	Mean (± estimated) Saline: ~3.53 Diazepam: ~1.76 PIRO 0.15: ~1.83 PIRO 0.30: ~2.43.	PIRO (0.15 and 0.30 mg/kg) ↔ On the crossings, rearing, grooming and fecal boli in the open field test ↔ On memory ↓ Racine scores ↑ TNF-α (cortex) ↔ TNF-α (serum and hippocampus) ↔ IL-6 (cortex, serum and hippocampus) ↓ IL-10 (cortex and hippocampus).
Guzzo (2023)	Wistar rats n= male 250–300 g 8–9 week old.	N/A	PTZ-induced kindling Dose: 30 mg/kg I.P Subconvulsive doses on alternate days for 14 days Start of PTZ treatment: On the 2nd day of the study, 30 minutes after the other treatments Observation time after administration: 20 minutes.	1) Positive control (diazepam 2 mg/kg); 2) Negative control (sodium chloride 0.9 g%); 3) BETA Group 1 (which received doses of BETA: 0.125 mg/kg); 4) BETA Group 2 (which received doses of BETA: 0.250 mg/kg).	Betamethasone Steroidal anti-inflammatory 0.125 and 0.250 mg/kg I.P. 14 days.	Pre-induction (30 minutes before PTZ administration).	The open field test; EEG recordings for 60 min; Brain microdissection and tissue preparation; Determination of cytokine and protein levels (TNF-α, IL-1β e IL-6.	Convulsive seizures assessed using the Racine scale (progressive convulsive-like behaviors), characteristics of the PTZ-induced kindling model.	Yes.		N/A		→ Open field test ↓ Seizure scores, especially at 0.250 mg/kg, progressively ↑ Latency time ↓TNF-α and IL-1β.
Murugan (2024)	*Danio rerio* (n=90; 4 months)	Buffered tricaine overdose (500mg/L).	PTZ 10 mM I.P; per day, 5 days a week, for 4 weeks.	1) Control (E3 medium); 2) PTZ (2 h 6 mM); 3) PTZ + T1 50 µM; 4) PTZ + T1 100 µM; 5) PTZ + T1 150 µM.	Pyrazole benzenesulfonamide derivative (T1), a synthetic chemical 50, 100 and 150 µM; I.P; 24h.	Pre-induction.	Heart rate and survival rate of zebrafish embryo; Estimation of reactive oxygen species (ROS) and apoptosis; Macrophage localization assay; qPCR analysis (TNF-α, COX-2 and IL-1β; Hematoxylin and eosin staining; Immunohistochemistry (IHC) of COX-2 in brain; Behavioral analysis (open field; observation of circular movements, creases and convulsions); HPLC of GABA levels in brain.	Observation of circular movements, creases and convulsions.	Yes.	N/A	N/A	N/A	↑ Survival rates and heart rate; ↓ ROS and apoptosis; ↓ The percentage of macrophages localized in larvae pretreated with T1; ↑ BDNF; ↓COX-2, TNF-α and IL-1β; ↓ Tissue abnormalities and at 150 µM, neuron degeneration was inhibited. T1 (150 µM), circling, creasing and convulsive behaviors were significantly reduced T1 (150 µM) ↑GABA.
Ribeiro (2024)	Wistar rats n=36; Male 220 ± 20 g 13–15 weeks old.	Xylazine hydrochloride 10 mg/kg I.P. Ketamine hydrochloride 80 mg/kg I.P.	PTZ 60 mg/kg I.P Single dose.	1) Control; 2) Dexamethasone, 3) Pentylenetetrazole; 4) DEX + PTZ.	Dexametasona Steroidal anti-inflammatory 0.6 mg/kg I.P single dose.	Post-induction Single dose.	Electroencephalographic activity was recorded at 0, 24, 36 and 48 h, with readings lasting a total of 5 min. To assess the seizures: the following were observed: (i) generalized tremor; (ii) spasms of the forelimbs; (iii) isolated clonic seizures without loss of the postural reflex; (iv) generalized clonic seizures with transient loss of the postural reflex and (v) tonic-clonic seizures with total loss of the postural reflex; Histopathological alterations of the hippocampus for cerebral tissue damage (CA1, CA3, hilus and dentate gyrus regions).	Acute seizure crisis – PTZ Generalized tonic-clonic seizures with loss of postural reflex.	Yes.	Grupo PTZ: 45 – 180 s Grupo PTZ + DEX: 45 s – 200 s.	Frequency of epileptiform discharges (electrical activity on the EEG): Control and DEX group: <10 Hz; PTZ and DEX+ PTZ: up to ~40 Hz.	N/A	DEX treatment did not affect the convulsive behavior of the animals → Progression of seizures ↓ Spike wave intensity and changes in brain waves caused by PTZ. ↔ Neuronal damage in the CA3 regions of the hippocampus and hilum.

Brabec (2023)	Sprague-Dawley rat pups n = 26 Both sexes - Postnatal (P5 to P14).	Isoflurane (inhalation), used in euthanasia to collect brains two days after the last seizure.	Flurothyl Dose: 0.1 mL slowly dripped (0.05 mL/min) onto filter paper in a sealed chamber – inhalation. • Exposure time: until manifestation of tonic extension of the forelimbs and hind limbs. • Protocol: 6 daily convulsions, from postnatal day 5 to 14 (P5–P14), totaling 60 convulsive episodes per animal.	Control: no seizures, with handling and injection of vehicle • VEH (vehicle: gelatin 5%, n = 3) • ACTH (150 IU/m², n = 8) • Dexamethasone (Dex, 0.5 mg/kg, n = 3) → All groups (except Control) suffered from flurothyl-induced seizures.	ACTH (adrenocorticotropic hormone, indirect steroidal anti-inflammatory drug): 150 IU/m², subcutaneous • Dexamethasone Steroidal anti-inflammatory 0.5 mg/kg Subcutaneous 10 days (P5–P14).	Pre-induction.	Differential gene expression (RNAseq), ontological pathway (GO) enrichment, overlap of DEGs between groups, molecular effects of treatments (ACTH vs Dex), pathways associated with synaptic plasticity, trans-synaptic signaling, glial proliferation, cellular metabolism, among others.	Flurothyl-induced tonic-clonic seizures (based on tonic extension of forelimbs and hindlimbs).	Yes.	N/A	60 seizures per animal over 10 days (6 seizures/day, from P5 to P14).	N/A	ACTH (peptide hormone with anti-inflammatory and neuromodulatory action): normalized gene expression and positively influenced pathways related to synaptic plasticity and glial proliferation. - Dex (glucocorticoid): modulated more genes, but with less functional specificity for the CNS, with more systemic and nonspecific effects post-ELS.
Erdogan (2023)	Sprague–Dawley.	Ketamine 80 mg/kg I.P. Xylazine 4 mg/kg I.P.	PTZ (Group A- Electroencephalographic recordings): 35 mg/kg, I.P. (Group B - Behavioral assessments): 70 mg/kg, I.P. Seizure exposure was monitored for up to 30 minutes, after which the animals were euthanized.	Group A and B: 1) Control (no treatment); 2) Saline; 3) Diclofenac 25 mg/kg; 4) Diclofenac 50 mg/kg; 5) Diclofenac 75 mg/kg.	Diclofenac sodium NSAID 25, 50 and 75 mg/kg administered 30 minutes before PTZ administration, 1 day.	Pre-induction.	Electroencephalographic recordings (with EEG initiated 5 minutes after PTZ administration and Seizure exposure was monitored for up to 30 minutes, after which the animals were euthanized) Measurement of Brain Lipid Peroxidation (MDA); Measurement of Brain Protein Levels; Determination of Brain SOD Activity; Brain PGE2, IL-1β, TNF-α Analysis.	Myoclonic seizures (assessed by the onset of the first myoclonic jerk — FMJ). Tonic-clonic seizures (assessed by the Racine scale — RCS). EEG-recorded epileptiform activity (percentage of spike waves).	Yes.	Latency to first myoclonic jerk (FMJ): Saline: exact value not provided. Diclofenac 25 mg/kg: 93.6 s. Diclofenac 75 mg/kg: 231.7 s.	The percentage of spike waves (epileptiform activity) was: Saline: 76.8% Diclofenac 25 mg/kg: 64.1% Diclofenac 50 mg/kg: 55.9% Diclofenac 75 mg/kg: 37.8%.	Racine Scale (RCS): Saline + PTZ 70 mg/kg: mean 5.6 Diclofenac 25 mg/kg: 3.75 ± 0.2 Diclofenac 50 mg/kg: 2.8 ± 0.7 Diclofenac 75 mg/kg: 1.75 ± 0.6.	↓ Epileptiform activity in a dose-dependent ↓ Racine Scale scores; ↑ Latency to first myoclonic jerk (FMJ): ↓ MDA ↓ TNF-α ↓ IL-1β ↓ PGE2 ↑ SOD
Garcia (2023)	*Danio rerio* n = 6/group Both sexes 0,4 ± 0,1 g, 3,5 ± 0,5 cm 90 - 120 days	Ice water immersion anesthesia (1–2 s before drug application).	PTZ 7.5 mM PTZ, dissolved in water in a 250 mL beaker, exposure time not precisely specified, but behavioral assessment is immediate after exposure.	1) Negative control: DMSO 3% (20 µL, ip); 2) Positive control: Diazepam (4 mg/kg, 20 µL, ip) 3) IBUACT: 4 mg/kg, 20 mg/kg, 40 mg/kg (20 µL, ip) Flumazenil + 4) IBUACT group (for evaluation of the mechanism via GABA).	IBUACT (a formulation of ibuprofen) NSAID 4, 20 and 40 mg/kg I.P.	Pre-induction.	Acute toxicity (96 h) - Locomotor capacity (open field test - Locomotor activity was assessed based on the number of times each individual crossed the lines drawn on the Petri dishes in 5 min). - Anxious behavior (light/dark test - scototaxis). - Mechanism of action via GABA receptor (flumazenil test). - Convulsive behavior in 3 stages: • Stage I: increased swimming activity; • Stage II: whirlpool swimming; • Stage III: clonic seizure with loss of posture.	Three stages of PTZ-induced seizures: • Stage I – dramatically increased swimming activity; • Stage II – whirlpool swimming; • Stage III – clonic-like seizures with loss of posture.	Yes.	**Stage 1**: Control group: ~20 s IBUACT 4mg/kg group: ~20 s IBUACT 20 mg/kg group: ~50 s IBUACT 40 mg/kg group: ~20 s DZP group: ~40 s. **Stage 2:** Control group: ~40 s IBUACT 4mg/kg group: ~45 s IBUACT 20 mg/kg group: ~70 s IBUACT 40 mg/kg group: ~25 s DZP group: ~60 s. **Stage 3:** Control group: ~55 s IBUACT 4mg/kg group: ~50 s IBUACT 20 mg/kg group: ~140 s IBUACT 40 mg/kg group: ~60 s DZP group: ~70 s.	N/A	The behavior was classified qualitatively into three stages of severity (without numerical assignment of scores).	IBUACT (20 mg/kg) reduced locomotor activity, similar to Diazepam. - In the light/dark test, IBUACT (20 mg/kg) increased the time spent in the illuminated area (anxiolytic effect). - The anxiolytic effect was reversed by flumazenil (GABA_A antagonism), indicating GABAergic action. - IBUACT (20 mg/kg) increased the latency to the three stages of PTZ-induced seizures, with a better anticonvulsant effect than Diazepam in stage III.
Hernández-Martín (2023)	Sprague-Dawley n = 32 Male - -	Pentobarbital, 25 mg/kg I.P.	Lithium chloride: 3 mEq/kg (≈127 mg/kg), I.P. — given ~18 h before pilocarpine Pilocarpine: 25 mg/kg, I.P. — for induction of SE Methylscopolamine: 2 mg/kg, I.P. — given 30 min before pilocarpine to minimize peripheral cholinergic effects.	1) vehicle + saline 2) FLU + saline, 3) vehicle + pilocarpine; 4) FLU + pilocarpine.	FLU (Flufenamic acid or analogue) NSAID 100 mg/kg I.P 1 day = once only.	Pre-induction of *SE* Time of administration: 2 hours before methylscopolamine.	Body weight changes: Assessed daily (days 1 to 4). Onset time to *SE*: Measured in minutes after pilocarpine injection. Mortality rate: Assessed at 1 h, 24 h, and 48 h after SE; Brain glucose metabolism by [18F] FDG-PET imaging Neurodegeneration (Fluoro-Jade C) Neuronal integrity (NeuN) Reactive astrogliosis (GFAP) Histological analysis (Nissl) of the hippocampus Quantification by regions (CA1, CA3, and hilum) using Image.	*SE* seizures with generalized motor seizures.	Yes.	VEH + PILO: 39.9 ± 11.6 min FLU + PILO: 26.9 ± 5.8 min.	N/A	N/A	↓ Body weight ↑ Mortality in animals subjected to *SE* (66.6%) and even in animals that did not receive pilocarpine (33.3%) → Protective effect against brain damage induced by *SE* → Prevent neurodegeneration → NeuN → GFAP
Türel (2023)	Wistar-Albino rats, n= 8 per group; Male 200–250 g; 2 months old.	Urethane - -	Penicillin Dose: 500,000 IU (2.5 µL) I.C.V in the somatomotor cortex.	1) Epilepsy (control group, formed with penicillin), 2) Diazepam (Epilepsy + Diazepam, 3) Diclofenac Potassium, 4) Diclofenac Potassium + Diapezam.	1) Diclofenac potassium NSAID 10 mg/kg I.P 2) Diazepam Class: benzodiazepines. 0.1 mL, 5 mg/kg I.P.	Post-induction (30 min).	Electrophysiology (EEG): Frequency and peak amplitude of epileptic discharges (The recording was made for 120 minutes after the seizure was created) Serum inflammatory markers (ELISA): IL-1β, IL-6, TNF-α.	Penicillin-induced localized epileptiform activity characterized by high-frequency discharges. Peak frequency was recorded at 5-minute intervals from 30 to 125 minutes.	Yes.	N/A	Average frequency of the groups (in the interval 30 – 120 min) Epilepsy group: 185.5 spikes per interval; Diazepam group: 102.6 spikes per interval; Diclofenac potassium group: 138.9 spikes per interval; Diazepam + Diclofenac potassium group: 110.2 spikes per interval.	N/A	**Diazepam alone:** ↓ Peak frequency between 91–120 min compared to control; Diazepam was also more effective than diclofenac potassium alone at some time points (91–100 min); ↓ Amplitude at 111–125 min compared to control and diclofenac; **Diclofenac potassium + diazepam:** ↓ Peak amplitude at different time points (51–65 and 111–120 min) compared to diclofenac alone; **Diclofenac Potassium group:** ↔ changes in systemic inflammatory markers ↔ The average peak frequency measured in the first 5 minutes of epileptic activity.

Khatami (2022)	Wistar rats n= N/A Male 200–250 g, 8 weeks.	Ketamine and xylazine.	PTZ 60 mg/kg; I.P 1-2 days.	Group I (naïve group): rats that received only normal saline; Group II (control group): rats that received normal saline 30 min before the PTZ injection; Group III (VAL group): rats that received sodium valproate (100 mg/kg, I.P.) 30 min before the PTZ injection; Group IV (OXP 100 group): rats that received oxaprozin (100 mg/kg, I.P.) 30 min before the PTZ injection; Group V (OXP 200 group): rats that received oxaprozin (200 mg/kg, I.P.) 30 min before the PTZ injection; Group VI (OXP 400 group): rats receiving oxaprozin (400 mg/kg, I.P.) 30 min before the PTZ injection.	Oxaprozin; NSAID 100, 200 and 400 mg/kg; I.P. 1-2 days.	Pre-induction (30 minutes before PTZ).	Behavioral Assessment Based on the Average Racine Score; Assessment of Passive Avoidance Memory; Measurement of oxidative stress markers (GPx and MDA); qPCR of Nrf2. Hmox1.	Partial (focal) and generalized epileptic seizures based on the Racine scale.	Yes.	N/A	N/A	Average Racine scale score: Control: 0; PTZ: 4.60; VAL: 3; OXP 100: 3.60; OXP 200: 3.20; OXP 400: 2.	**OXP 400:** ↓The mean Racine score compared with that in the PTZ group. **VAL, OXP 200, and OXP 400 groups**: ↓ Memory impairment; ↑ GPx levels ↓ MDA level ↑ Hmox1 and Nrf2 gene.
Mishchenko (2022)	Male albino mice n=5 per group; 20–27 g -	N/A	Kindling + PTZ 30 mg/kg I.P 1x/day for 16 days.	Control; Pathology control (kindling without treatment); Les-6222 (100 mg/kg, intragastric route); Sodium valproate (300 mg/kg, intragastric route); Celecoxib (4 mg/kg, intragastric route).	5-[(Z)-(4-nitrobenzylidene)]-2-(thiazol-2-ylimino)-4-thiazolidinone, compared to the classical anticonvulsant sodium valproate and the NSAID Celecoxib.	Pre-induction (30 minutes before PTZ).	Day of first seizure % of animals with seizures per group Seizure-free days (13 days in the PTZ group) Biomarkers analyzed (via ELISA): COX-1, COX-2 Prostaglandins (PGE2, PGF2α, PGI2), TXB2 (thromboxane B2) 8-isoprostane (oxidative stress) NSE (neuronal injury).	PTZ-induced kindling.	Yes.	PTZ group: 4 days VPA group: 6 days Celecoxib group: 4 days Les-6222 group: 4 days.	Number of days with seizure PTZ group: 13/16 VPA group: 8/16 Celecoxib group: 13/16 Les-6222 group: 16/07.	N/A	Les-6222: ↓The incidence of seizures compared to the pathological group; ↓ COX-1 and COX-2 ↑ PGE2 and PGI2 ↓ PGF2α and TXB2 ↓ 8-isoprostano ↓ NSE Celecoxib: No anticonvulsant protective effect ↔ COX-2 ↓ COX-1 ↑ PGE2 ↓ PGF2a e TXB2 ↓ Lipid peroxidation ↔ NSE
Tsyvuin (2022)	Albino mice Female n= 6-10 animals per group weighing 20–24 g - -	N/A	kindling model + PTZ 30 mg/kg I.P 16 days.	1) Vehicle control; 2) Positive control (PC), PTZ-induced kindling without treatment; 3) PTZ-induced kindling + sodium valproate; 4) PTZ-induced kindling + digoxin; 5) PTZ-induced kindling + sodium valproate + digoxin; 6) PTZ-induced kindling + celecoxib.	Celecoxib NSAID 4 mg/kg V.O 16 days.	Pre-induction (30 minutes before PTZ).	Latency to first seizure (observation duration: 1 hour after PTZ injection per day) Number of days with and without seizures Number of mice with seizures Biochemical/molecular: COX-1, COX-2 (enzymatic markers of inflammation) Prostaglandins: PG-E2, PGF2α, PGI2 TXB2 (thromboxane B2) 8-isoprostane (oxidative stress) NSE (Neuron-specific enolase – marker of neuronal damage).	PTZ-induced tonic and clonic seizures.	Yes.	Group Latency period Control 3 days (seizures on the 4th day) Digoxin 3 days (seizures on the 4th day) Celecoxib 3 days (seizures on the 4th day) Sodium valproate 6 days (seizures on the 7th day) Valproate + Digoxin 16 days without seizures (total latency).	Control 80% Sodium valproate 50% Digoxin 30% (↓ 2.7-fold vs. control) Celecoxib 70% Valproate + Digoxin 0% (complete protective effect).	N/A	Seizures: Slight reduction in the number of animals with seizures (70%) Celecoxib showed moderate anti-inflammatory and antioxidant effects, with no evident neuroprotective effect ↓ COX-1 (for VC levels) COX-2 still elevated (1.54x vs VC) Modest changes in prostaglandins Oxidative stress: ↓ 8-isoprostane (–25.72%) Neuroprotection: Almost absent (↓ NSE of only 3.20%, not significant.
Alsaegh (2021)	Adult Wister rats, n=58 Male 150 to 200 g aged 6 to 8 weeks.	Ether, by inhalation.	Pilocarpine hydrochloride (PILO) for epilepsy induction; LPS (lipopolysaccharide) as a proinflammatory sensitizer. PILO: 380 mg/kg, IP, administered after SMB (1 mg/kg, IP, 30 min before); LPS: 1 mg/kg, IP, 6 h before PILO.	G1: Control (saline); G2: PILO + SMB; G3: LPS + SMB + PILO; G4: VPA + LPS + VPA + SMB + PILO; G5: Celecoxib + LPS + Celecoxib + SMB + PILO; G6: Celecoxib + LPS + Celecoxib + VPA + SMB + PILO.	VPA (valproic acid) anticonvulsant with anti-inflammatory action 250 mg/kg I.P. Celecoxib NSAID 10 mg/kg I.P.	Both administered prior to PILO induction. - VPA: 1st dose 1 h before LPS, 2nd dose 6 h after LPS (30 min before PILO). - Celecoxib: 1st dose 1 h before LPS, 2nd dose 6 h after LPS (30 min before PILO).	Seizure behavior (Racine scale); - Latency to onset of stage 5 (GTCS); - Biochemical biomarkers (GSH, LPO, CAT, SOD, TNF-α, IL-1β, IL-6, HMGB1); - Histopathology (H&E and toluidine blue); - Damage to the brain, liver, kidney, lung.	PILO-induced seizures, characterized on the Racine scale up to stage 5 (GTCS).	Yes.	Latency to onset of seizure according to figure 1; PILO: 5 min; PILO + LPS: 2 min; PILO + LPS + VPA: 8 min; PILO + LPS + Celecox: 15 min; PILO + LPS + VPA + Celecox: 12 min.	N/A	Racine score was significantly reduced in the groups: PILO+LPS+VPA (3) PILO+LPS+Celecoxib (2) PILO+LPS+VPA +Celecoxib (more pronounced effect - approximately 1.8 according to the graph in figure 1).	PILO+LPS+VPA+Celecoxibe ↑ GSH, SOD ↓ catalase, LPO. ↑ IL-1β, IL-6, TNF-α ↓ cytokines in the treated groups, with greater efficacy for Celecoxib (alone or combined with VPA). ↓ HMGB1 in the PILO, PILO+LPS, PILO+LPS+VPA groups (by translocation). Celecoxib (alone and in combination) inhibited HMGB1 translocation a increased its levels in the brain. It reduced seizure severity (Racine score and latency). ↑ GSH, SOD ↓ catalase, LPO ↓ cytokines Preserved histological integrity in the hippocampus, liver, kidney and lung. These effects were best observed in combination with VPA.

Demirsoy (2021)	Albino Wistar rats n = 28 sex 250 ± 22 g.	Urethane 1,25 g/kg I.P.	Penicillin 500 IU penicillin [2.5 µl, intracortical (ic)].	Group I: Control group; 500 IU of penicillin [2.5 µl, intracortical (ic)] + saline solution [1 ml, intraperitoneal (ip)], (n:7). Group II: Penicillin (500 IU/2.5 µl/ic) + DEX (5 mg/kg/1 ml/ip), (n:7). Group III: Penicillin (500 IU/2.5 µl/ic) + DEX (25 mg/kg/1 ml/ip), (n:7). Group IV: Penicillin (500 IU/2.5 µl/ic) + DEX (50 mg/kg/1 ml/ip), (n:7).	Dexketoprofen (DEX) NSAID 5, 25 and 50 mg/kg/1 ml/ I.P.	Post-induction.	Amplitude and frequency of epileptic discharges on ECoG; peak frequency and mean amplitude every 10 minutes for 180 minutes (A atividade epileptiforme atingiu seu pico em 28 ± 5 minutos após a injeção de penicilina e manteve-se estável por 3 a 5 horas.).	Bilateral synchronous epileptic discharges on ECoG.	Yes.	Biphasic spike and spike-wave activities were apparent at 4.5 ± 2 min and reached their maximum levels at 28 ± 5 min after penicillin microinjection.	Mean peak frequency (peak/min) of epileptiform activity **Control:** 0 min: 49 ± 3 40 min: 51 ± 3 60 min: 51 ± 4 180 min: 45 ± 3 **DEX (5 mg/kg)** 0 min: 48 ± 3 40 min: 40 ± 4 60 min: 35 ± 4 180 min: 26 ± 3 **DEX (25 mg/kg)** 0 min: 52 ± 6 40 min: 41 ± 4 60 min: 34 ± 5, 180 min: 23 ± 4 **DEX (50 mg/kg)** 0 min: 51 ± 5 40 min: 35 ± 6 60 min: 34 ± 5, 180 min: 19 ± 5.	N/A	↓ The frequency of penicillin-induced seizures (dose-dependent). ↔ Effect on the amplitude of epileptic discharges with either dose of DEX. **- DEX 50 mg/kg** ↓ Spike frequency to 19 ± 5/min after 180 minutes.
Kandeda (2021)	mice Mus musculus swiss n = 8 per group Male weighing 18 ± 11 g 25-40 days.	N/A	Kainic acid (*status epilepticus* model) 15 mg/kg I.P. Time to tonic-clonic seizures and *SE*: 30–80 minutes; • *SE* maintained for 2 hours. PTZ 40 mg/kg I.P. single dose.	Negative control group treated with distilled water (10 ml/kg; po); Four test groups receiving P. daemia extract (4.9, 12.3, 24.5 and 49 mg/kg; po); Two positive control groups received sodium valproate (300 mg/kg; po) or aspirin (20 mg/kg; po); One group treated with distilled water.	Aspirin NSAID 20 mg/kg V.O. *Pergularia daemia* extract (plant with supposed anti-inflammatory properties) 4.9 to 49 mg/kg V.O. Administered once daily for 14 days.	Post-induction.	Behavioral: PTZ-induced seizures: latency and duration of myoclonic, clonic, and tonic-clonic seizures; Seizure duration in the seizure group (were observed between 30 and 80 minutes after kainate injection. Mice that displayed *SE* for 2 hours were selected for the remainder of the experiment); Seizure score. Morris water maze test (spatial memory). Novel object recognition test (recognition memory). Open field test (locomotor activity). Biochemical (ELISA): In the hippocampus: GFAP, Iba-1, IL-1β, TNF-α, IL-6. In serum: IL-1β, TNF-α, IL-6. Histological: Morphology assessment of areas CA1 and CA3 of the hippocampus (H&E, ImageJ).	Generalized tonic-clonic seizures and *status epilepticus* (*SE*).	Yes.	Approximate latency time (GTCS) DW + DW: ~390 s KA + DW: ~120 s KA + VAS: ~290s KA + ASP: ~230 s KA + PD 4.9 mg/kg: ~200 s KA + PD 12.3 mg/kg: ~250 s KA + PD 24.5 mg/kg: ~310 s KA + PD 49 mg/kg: ~300 s.	DW + DW: ~1.0 (maximum score – no seizures) KA + DW (neg. control): ~0.95 (maximum seizure score) KA + VAS: ~0.45 KA + ASP: ~0.25 KA + PD 4.9 mg/kg: ~0.35 KA + PD 12.3 mg/kg: ~0.20 KA + PD 24.5 mg/kg: ~0.40 KA + PD 49 mg/kg: ~0.50.	The KA + DW group had the highest seizure score (~1.0). All groups treated with *P. daemia* (PD), or drugs (VAS and ASP) showed significant reductions in scores. The groups treated with PD at doses of 12.3 mg/kg and aspirin showed the lowest scores (~0.25), close to the sham group.	Treatment with *P. daemia* ↑ Latency to onset of seizures at all doses (maximum effect at 24.5–49 mg/kg). ↓ Seizure score especially at doses of 12.3 and 49 mg/kg. Myoclonic jerks: ↓ up to 64.5% (PD 12.3 mg/kg) Clonic seizures: ↓ up to 59.8% (PD 24.5 mg/kg) GTCS: ↓ up to 62.5% (PD 49 mg/kg), comparable to aspirin and valproate. ↑ Cognitive performance in both tests: Increased time in target quadrant and reduced latency. Increased discrimination and object recognition index. ↓GFAP ↔ Iba-1 ↓ IL-1β, IL-6 and TNF-α. maintained the integrity of neuronal cells.
Karabulut (2021)	Adult BALB-c Albino n=24 Male 35–38 g 2 months old.	N/A	PTZ 60 mg/kg; I.P. (Single dose at the last dose of the drug).	control group, healthy BALB-c mice; PTZ group, mice injected with PTZ to induce seizures; AAP-50 group, mice pretreated with 50 mg/kg AAP for 5 days; and AAP-100 group, mice pretreated with 100 mg/kg AAP for 5 days.	Acetaminophen (AAP): non-opioid analgesic, antipyretic; Dose: 50 and 100 mgkg; I.P. 5 days.	Pre-induction (30 minutes before PTZ administration).	Seizure behavior after PTZ administration was analyzed using the Racine scale and latency to initial myoclonic jerks. (30-minute observation) assessment of total oxidant status (TAS), total antioxidant status (TOS), gamma-aminobutyric acid (GABA), glutamate, nitric oxide (NO), tumor necrosis factor alpha (TNF-α), and caspase-3.	Seizure behavior after PTZ administration was analyzed using the Racine scale and latency to initial myoclonic jerks.	Yes.	Approximate average values according to figure 2: PTZ group: 80-100 s; AAP50 group: <200s; AAP100 group: 100-150.	N/A	Approximate average score according to figure 2: PTZ Group: ~5.8 AAP50 Group: >4 AAP100 Group: ~4.2.	**AAP-100** ↔ FMJ latency and RCS score ↔ TAS and TOS ↓ NO ↔ caspase-3 ↓ TNF-α ↑ GABA ↓ Glutamate **AAP-50** ↑ FMJ latency ↓RCS score ↑ TAS ↓ TOS ↓ NO ↓ caspase-3 ↓ TNF-α ↑ GABA ↓ Glutamate
Rosa (2021)	Wistar rats n = 8–10 per group Male ~300 g 2-month-old.	N/A	PTZ 25 mg/kg I.P.	1) Positive control: diazepam 2 mg/kg 2) Negative control: sodium chloride (0.9%) 3) Group prednisolone 1 mg/kg, 4) Group prednisolone 5 mg/kg.	Prednisolone NSAID 1 and 5 mg/kg I.P. 14 days.	Pre-induction.	Open field, Brain microdissection and tissue preparation; Biochemical assays (protein concentration); ELISA (cytokine levels TNF-alpha, IL-1β and IL-6).	Kindling model.	Yes.	Approximate values as shown in figure 2. Saline: ~ 3.50s Diazepam: ~3 s Prednisolone 1 mg/kg: ~2 s Prednisolone 5 mg/kg: 2.30 s.	N/A	Only in the PTZ group did the scores range from 2.5 to 3.9. The Diazepam group maintained lower and more stable scores (~1.3–2.3), with better seizure control. The Pred1 group demonstrated a more evident protective effect on days 5 and 6, with scores around 2.0 and 1.5. The Pred5 group also showed a significant reduction in scores on days 6 and 7 (~1.6 and ~1.9), with a slight effect on day 1.	Prednisolone (1 and 5 mg/kg) ↔ Number of crossings, Grooming and fecal boli deposits. ↑ Rearing (Pred5) ↓ IL-6, IL-1β and TNF-α (Hipocampus) Prednisolone ↑ IL-6 and TNF-α. (Serum).

Durankuş (2020)	Sprague-Dawley n=48 Male 200-250 g -	Ketamine 80 mg/kg Xylazine 4 mg/kg	PTZ 35 and 70 mg/kg I.P.	1) Group A1 was defined as control and did not receive any medication. 2) Group A2 received saline; 3)Group A3 received 200 mg/kg ibuprofen; 4) Group A4 received 400 mg/kg ibuprofen.	Ibuprofen NSAID 200 and 400 mg/kg I.P.	Pre-induction (30 minutes before injection with PTZ).	EEG recordings (60 min), and spike percentage was assessed; Racine Seizure Scale; Brain biochemical analysis (PGF2α levels).	Motor-type epileptic seizures, with focal seizures progressing to generalized tonic-clonic seizures.	Yes.	Control: 0 PTZ (70 mg/kg) + Saline: 62.1 ± 1.8 s PTZ + Ibuprofen (200 mg/kg): 96.2 ± 6.9 s PTZ + Ibuprofen (400 mg/kg): 137.5 ± 31.8 s.	N/A	Control: 0 PTZ (70 mg/kg) + Saline: 5.7 ± 0.2 PTZ + Ibuprofen (200 mg/kg): 4.2 ± 0.3 PTZ + Ibuprofen (400 mg/kg): 3.1 ± 0.3.	**PTZ + Ibuprofen (200 mg/kg) group:** ↓ Epileptiform activity for 55.9% ↔ PGF2α **PTZ + Ibuprofen (400 mg/kg) group** ↓ Spike percentage for 45.1% ↓ PGF2α
Elgarhi (2020)	Swiss albino n = 70 Male 15–35 g 8-week-old.	N/A	PTZ 40 mg/kg I.P. on alternate days for 17 days.	1) Control group (saline) 2) PTZ group: 3) VAL + PTZ group. 4) MEL + PTZ group. 5) DIC + PTZ group. 6) VAL + MEL group. 7) VAL + DIC group.	Sodium valproate (VAL) Class: Anticonvulsant / Antiepileptic 50 mg/kg/dia I.P 17 days. Meloxicam (MEL) NSAID 10 mg/kg/dia I.P 17 days.	Pre-induction (30 minutes before PTZ).	The mice were kept under direct observation and video recording during the experiment, and the seizure score and latency period between PTZ injection and seizure onset were recorded, the seizure duration is calculated from the onset of convulsive movements to their cessation (scoring scale: 0, no effect; 1, jerks; 2, Straub's tail; 3, clonus) Biochemical assays (TNF-α, IL-1β, MDA, GSH and PGE2).	Generalized motor seizures – clonic.	Yes.	Group PTZ: 3.7 min Group VAL + PTZ: 10.3 min MEL + PTZ group: 7.6 min DIC + PTZ group: 9.8 min VAL + MEL group: 9.9 min VAL + DIC group: 11.6 min.	N/A	PTZ Group: 5.4 VAL + PTZ Group: 2.4 MEL + PTZ group: 4 DIC + PTZ Group: 2.7 VAL + MEL group: 2 VAL + DIC group: 1.	↓ Seizure score ↑ Latency time ↓Seizure duration ↓ MDA ↑ GSH
Fox (2020)	Long-Evans rats n=15 Male - -	N/A	kainic acid (KA) 10 mg/kg I.P.	1) KA+ Dexametasona (KDK) 2) KA + PBS (KSK) 3) PBS + PBS (SSK) 4) PBS + Dexamethasone (SDK).	Dexamethasone Steroidal anti-inflammatory 1 mg/kg I.P. was administered either. 6 days or 24h. Minocycline Class: Antibiotic of the tetracycline 10 mg/kg I.P. 6 days or 24h.	Post-induction.	Behavioral seizures were observed within 30 minutes of KA injection, and persisted for 2-3 h. 0 - no response; I - behavioral arrest; II - staring, pawing, limb clonus, and head bobbing; III - clonic jerks, rearing and falling or tonic posturing and loss of balance; IV - continuous grade III seizures for longer than 30 min (status epilepticus); V - death. Seizure severity and latency to the first sign of Grade III seizures (clonic jerks, rearing and falls) were recorded. Only those animals that experienced at least grade III seizures at both P25 (first hit) and P39 (second hit) of KA were included for further examination. Weight and survival were documented daily for all animals during the week of drug therapy; Immunohistochemistry (IBA-1); In-situ end labeling; Image acquisition and quantification of immunoreactive cells.	*SE*.	Yes.	SSK: >2000 s KSK: <2000 s KDK: ~ 2000 s	SSK: 1 KSK: 5 KDK: 0	N/A	↑ Mortality rate ↔ Latency time ↓ Microglial activation ↓ Cell death
Liu R (2020)	Sprague-Dawley n=64 200-250 g 4-5 weeks old.	Isoflurane.	PTZ 35 mg/kg 29 days I.P.	1) Control group 2) IBP 30 mg/kg group (3) PTZ group; 4) IBP + PTZ group.	Ibuprofen NSAID 30 mg/kg I.P. 29 days.	Pre-induction (30 minutes before PTZ).	Behavioral observation (Seizure intensity was scored as follows: stage 0, no response; stage 1, rhythmic facial twitching, ear or facial muscle twitching; stage 2, myoclonic seizures without elevation; stage 3, forelimb clonus but not erection; stage 4, forelimb clonus with erection; stage 5, generalized clonic-tonic seizures with loss of postural control; stage 6, death. Rats with more than three consecutive stage 4 seizures were considered to have complete kindling seizures) and EEG recording; immunohistochemistry of COX-2, NLRP3, caspase-1 and IL-18; Nissl staining.	Rat Chronic Epilepsy Model.	Yes.	Group PTZ: 200 s Group IBP + PTZ: 400 s.	N/A	According to Figure 1, the initial and final score of each group was: Control: 0 to the end IBP: 0 to the end PTZ: 0-5 IBP + PTZ: 0-3.	↑ The latency time ↓ Seizure score ↓ Spike waves or epileptic sharp waves ↑ Number of Nissl positive cells ↓ COX-2 ↓ NLRP3, caspase-1 and IL-18.
Yang (2020)	ICR mice n = N/A Male weighing 22-24 g.	N/A	Methylscopolamine (0.1 mg/ml) 1 mg/kg I.P. followed by pilocarpine (30 mg/ml) 300 mg/kg I.P. 30 minutes later.	1) Control groups 2) Pilocarpine 3) Pilocarpine + dexamethasone.	Dexamethasone (DEX) Steroidal anti-inflammatory 10 mg/kg I.P. Diazepam 4 mg/kg I.P.	Post-induction.	The animals' behaviors were monitored for 2 hours, and the onset of seizures was assessed using the Racine scale (only stage 3–5 seizures were recorded and analyzed in this study) F-actin labeling, Quantification of hippocampal pyramidal cells, Labeling of pre- and postsynaptic markers Analysis of the ratio of F-actin to G-actin.	Generalized motor seizures.	Yes.	1) Pilocarpine: 10,60 min 2) Pilocarpine + dexamethasone: 16,99 min.	N/A	N/A	↑ Latency time ↔ The number and mean stage of acute seizures ↑ F-actina in the hippocampal regions CA1 and CA3 --| Depolymerization of F-actin to G-actin after *SE* → Synaptic remodeling after *SE*.

Peng (2019)	Sprague–Dawley n=60 Male 250–300 g 6–8 weeks-old.	10% chloral hydrate (0.4 ml/100 g I.P.)	PTZ 35 mg/kg I.P. all other drugs were administered 15 times on alternate days (29 days).	1) Control group: normal saline (NS) 2) PTZ group 3) 3-MA + PTZ group 4) Ibuprofen + PTZ group 5) 3 MA + Ibuprofen + PTZ group.	Ibuprofen NSAID 30 mg/kg I.P. 3-MA 10 mg/kg I.P. all other drugs were administered 15 times on alternate days (29 days).	Pre-induction (30 min before PTZ injection).	After I.P. administration of PTZ, rats were observed for 30 min, and rats with at least three epileptic seizures of grade 4 or above were considered to be fully induced. Behavioral Observation and EEG Recording Immunofluorescence (LC3 and GFAP) Western Blotting (BCA).	The seizures were graded based on the following criteria: grade 0: no seizure response; grade 1: rhythmic twitching of mouth, ear or facial muscles; grade 2: nodding with more severe twitching of facial muscles; grade 3: forelimb clonic but not with standing; grade 4: forelimb clonic accompanied by standing; grade 5: generalized tonic–clonic seizures with posture out of control.	Yes.	1) PTZ grup: 200 s 2) 3-MA + PTZ group: < 200 s 3) Ibuprofen + PTZ group: 400 s 4) 3 MA + Ibuprofen + PTZ group: ~250 s.	N/A	1) PTZ grup: 4.17 2) 3-MA + PTZ group: 4.83 3) Ibuprofen + PTZ group:2.67 4) 3 MA + Ibuprofen + PTZ group: 3.67.	**Ibuprofen + PTZ group** ↓ The mean number of fully induced seizure ↑ Latency time ↓ Duration of seizures ↓ Peaks and amplitudes of waves on the EEG ↑ LC3 ↓ GFAP
Yang (2019)	ICR mice n = 45 Male weighing 22–24 g.	Isoflurane.	Methylscopolamine (0.1 mg/ml) 1 mg/kg I.P. followed by pilocarpine (30 mg/ml) 300 mg/kg I.P. 30 minutes later.	1) Control groups 2) Pilocarpine 3) Pilocarpine + dexamethasone.	Dexamethasone (DEX) Steroidal anti-inflammatory 10 mg/kg I.P.		The animals' behaviors were monitored for 2 hours, and the onset of seizures was assessed using the Racine scale (only stage 3–5 seizures were recorded and analyzed in this study). The behavioral changes of the mice were monitored continuously for 4 weeks after *SE*. We measured the daily number of seizures and recorded the duration of each seizure. F-actin labeling, Quantification of hippocampal neuron number, Postsynaptic marker PSD95 labeling, Mossy fiber terminal marker ZNT3 labeling, Image acquisition and data analysis.	Spontaneous recurrent seizures assessed according to the Racine scale.	Yes.	N/A	Daily seizure numbers (Fig1): 2) Pilocarpine: ~18 3) Pilocarpine + dexamethasone: ~11.	N/A	↓ The duration of the seizures ↔ Number of spontaneous seizures ↑ Distribution of F-actin in subregions of CA3 stratum lucidum, CA1 stratum radiatum and the hilus of DG ↓ The loss of pyramidal neurons in CA1 and CA3 ↔ Dentate granule cells proliferation ↑ PSD95 in CA3, CA1 and hilus of DG (synaptic remodeling in hippocampal subfields) ↑ ZNT3 in subfields CA3 and hilus of DG.
Ayyildiz (2018)	Wistar rats n=28 Male 220 ± 40 g 2 – 3 months old.	Urethane 1.25 mg/kg I.P.	Penicillin G potassium 500 IU I.C. Single administration: 0.5 µL/min.	1) Baseline; 2) Penicillin; 3) Penicillin + Aspirin 150; 4) Penicillin + Aspirin 500.	Aspirin; NSAID, non-selective 150 and 500 mg/kg; I.P. single dose.	Post-induction.	Epileptiform activity.	Penicillin-induced acute epileptiform activity.	Yes.	**Penicillin** Seizure activity started about 3 – 6 min after induction, and stabilized 30 min after **Aspirin 150 mg/kg** 40 minutes to achieve anticonvulsant effect **Aspirin 500 mg/kg** 30 minutes to achieve anticonvulsant effect.	Spike frequency: **Penicillin** 37.85 ± 1.91 spike/min **Aspirin 150 mg/kg** 27.85 ± 4.62 spike/min **Aspirin 500 mg/kg** 26.15 ± 2.36 spike/min.	N/A	Aspirin ↓ the spike frequency of epileptiform activity; Aspirin 500 has a longer anticonvulsant activity than Aspirin 150.
Guzzo (2018)	Wistar rats n=50 Male 250 – 300 g 8 – 9 weeks old.	N/A.	PTZ 20 mg/kg I.P. Every other day, 30 min after treatment administration.	1) positive control group (diazepam 2 mg/kg); 2) negative control group (NaCl 0,9 g%); 3) DEX 1 mg/kg; 4) DEX 2 mg/kg; 5) DEX 4 mg/kg.	Dexamethasone Steroidal anti-inflammatory 1,2 and 4 mg/kg I.P. 15 days.	Pre-induction.	Seizure severity: Racine's adapted scale Behavioral tests – OFT: line crossing, rearing responses, grooming and fecal bolus Cytokines ELISA: TNF-α, IL-1β, IL-6.	Kindling model – PTZ.	Yes.	N/A	N/A	Approximate average score according to figure 3: Diazepam: ~ 1.5 Negative control: ~ 3.5 DEX 1: ~ 2.4 DEX 2: ~ 1.9 DEX 4: ~ 1.8	**DEX** ↓ intensity and evolution of the seizures when compared to saline; ↔ intensity of seizures between DEX and diazepam; ↔ between groups in behavioral tests; **DEX 4** ↓ levels of TNF-α in the hippocampus and serum; DEX 1 and DEX 4 ↓ levels of IL-1β in the hippocampus; **DEX 1** ↑ levels of TNF-α in the hippocampus; ↔ of IL-6 between groups; ↔ of cytokines in the cortex.

Morales-Sosa (2018)	Sprague-Dawley rats n=80 Male 20 – 25 g 10-day-old.	N/A	KA 1.4 mg/kg I.P. Every 24 h, 5 days Single dose at 30 PND.	1) SH; 2) KA; 3) CCX + KA; 4) PB + KA; 5) CCX + PB + KA.	Celecoxib NSAID 20 mg/kg E.V.	Post-induction.	Motor behavior (10, 14, 30 PND) Phase 0: No response. Phase I: Facial clonus. Phase II: Head movements and chewing. Phase III: Unilateral or bilateral clonic movements. Phase IV: Bilateral clonus with attempts to join. Phase V: Bilateral clonus with falls and attempts to join. When phase 5 was identified, the presence of *status epilepticus* (*SE*) was considered. PCR-RT: TLR-4, HMGB1 Western blot: COX-2.	Recurrent seizures induced by KA.	Yes.	Approximate average latency according to figure 1 **10 PND** 2) KA: ~10 min 3) CCX + KA: ~10 min 4) PB + KA: ~ 10 min 5) CCX + PB + KA: ~10 min **14 PND** 2) KA: ~ 3 min 3) CCX + KA: ~ 10 min 4) PB + KA: ~ 5 min 5) CCX + PB + KA: ~ 8 min **30 PND** 2) KA: ~ 10 min 3) CCX + KA: ~ 55 min 4) PB + KA: ~ 30 min 5) CCX + PB + KA: ~ 55 min.	Approximate average frequency according to table 1 **14 PND (Early time)** 2) KA: Phase 1 – 100% Phase 2 – 100% Phase 3 – 100% Phase 4 – 100% 3) CCX + KA: Phase 1 – 100% Phase 2 – 100% Phase 3 – 100% Phase 4 – 100% 4) PB + KA: Phase 1 – 100% Phase 2 – 100% Phase 3 – 100% Phase 4 – 100% 5) CCX + PB + KA: Phase 1 – 100% Phase 2 – 100% Phase 3 – 100% Phase 4 – 87.5% **30 PND (Late time)** 2) KA: Phase 1 – 100% Phase 2 – 100% Phase 3 – 100% Phase 4 – 100% 3) CCX + KA: Phase 1 – 25% Phase 2 – 25% Phase 3 – 12.5% Phase 4 – 12.5% 4) PB + KA: Phase 1 – 100% Phase 2 – 100% Phase 3 – 100% Phase 4 – 75% 5) CCX + PB + KA: Phase 1 – 62.5% Phase 2 – 62.5% Phase 3 – 62.5% Phase 4 – 50%	N/A	CCX ↓ severity of seizures; ↑ latency of KA-induced seizures; ↓ frequency of phases 2, 3, and 4; ↓ TLR4 and HMGB1 mRNA expression in the cortex and hippocampus; ↓ COX-2 expression in the cortex and hippocampus.
Suemaru (2018)	ICR mice n= N/A Male.	N/A	Acute PTZ-Induced Seizure 80 mg/kg I.P. PTZ Kindling: 40 mg/kg I.P 5 days per week for 2 weeks. Pilocarpine-Induced Seizure: 300 mg/kg I.P. (after scopolamine methyl bromide 1 mg/kg S.C.).	1) Vehicle control group; 2) Acetaminophen (various doses); 3) Valproate (various doses).	Acetaminophen: non-opioid analgesic, antipyretic; 100, 250, 300, 350, 450 and 600 mg/kg I.P. single dose, 30 min before test.	Pre-induction.	Seizure susceptibility by calculating incidence of generalized seizure, Racine's scale.	Acute clonic seizures – PTZ Chronic model – kindling, PTZ *SE* – Pilocarpine.	Yes.	N/A	N/A	Approximate average score according to figures 4 and 5: 1) Vehicle (PTZ): 4 2) Acetaminophen 250 (PTZ): 3.5 3) Acetaminophen 350 (PTZ): 1.5 4) Acetaminophen 450 (PTZ): 0.2 5) Vehicle (Pilocarpine): 5 6) Acetaminophen 300 (Pilocarpine): 5 7) Acetaminophen 600 (Pilocarpine): 5.	Acetaminophen Acute seizures: ↔ Kindling model: ↓ scores and occurrence of stages 3, 4 and 5 (in a dose-dependent manner) *SE*: ↔
Vizuete (2018)	Wistar rats n=60 Male 27-day-old.	Ketamine 75 mg/kg Xylazine 10 mg/kg	Li-pilocarpine LiCl 3mEq/kg I.P. Pilocarpine 45 mg/kg I.P. Single dose.	1) Sham + DMSO; 2) SE + DMSO; 3) SE + DEX 10 mg/kg.	Dexamethasone Steroidal anti-inflammatory 10 mg/kg I.P. 24 and 36 h after *SE*.	Post-induction.	Behavior Ocurrence of recurrent spontaneous seizures, Racine's scale Inflammatory and astrogliosis parameters (S100B, GFAP, GS, GSH, AQP-4, and Kir 4.1).	Li-Pilocarpine model of TLE.	Yes.	Approximate average latency according to additional file 2: Beginning of epileptic behavior: 2) *SE* + DMSO: ~16 days 3) *SE* + DEX: ~10 days.	N/A	Approximate average score according to additional file 2: 2) SE + DMSO: ~ 2.7 3) SE + DEX: ~ 2.5.	DEX ↔ Epileptic behavior; —| Increase of TNF-α (day 1) caused by SE; —| IL-1β increase in the hippocampus (day 56) caused by *SE*; —| PGE2 increase in the hippocampus; ↑ IL-10 in the hippocampus (day 56); ↔ COX-1 content; —| Increase of COX-2 content; —| S100B, GFAP increase; —| GSH, Kir 4.1 decrease; ↔ GS, AQP-4.
Abd-Elghafour (2017)	Albino rats n=50 Male 120 – 150 g.	Thiopental sodium 50 mg/kg	PTZ 35 mg/kg I.P. Thrice a week, 15 doses.	1) Saline 2) PTZ 3) Aspirin + PTZ	Aspirin NSAID, non-selective 20 mg/kg I.P. Daily; 35 days.	Pre-induction (treatment before PTZ daily).	Convulsive behavior: Racine scale Inflammatory markers, ELISA: LXA_4, 1L-1β and NF-κB Histopathological alterations of hippocampus: neurodegeneration.	Kindling model – PTZ.	Yes.	N/A	N/A	Approximate score according to figure 1: 2) PTZ: 3.2 3) PTZ + Aspirin: 1.7	↓ Seizure score; ↓ Cortical and hippocampal LXA_4; ↓ Hippocampal levels of 1L-1β and NF-κB; ↓ Cortico-hippocampal degenerative cells.

Ayyildiz (2017)	Wistar rats n=18 Male 300 g 12 weeks old.	Urethane 1.25 mg/kg I.P.	Penicillin G potassium 500 IU 2.5 µL I.C.	1) Penicillin; 2) Penicillin + aceclofenac 10; 3) Penicillin + aceclofenac 20.	Aceclofenac NSAID, non-selective 10 and 20 mg/kg I.P. single dose. 30 minutes after penicillin.	Post-induction.	Epileptiform activity.	Penicillin-induced acute epileptiform activity.	Yes.	N/A	Spike frequency: **Penicillin** 36.71 ± 1.54 spike/min **Aceclofenac 10 mg/kg** 41.89 ± 2.12 spike/min **Aceclofenac 20 mg/kg** 35.26 ± 2.72 spike/min	N/A	Aceclofenac 10 ↑ Epileptiform activity Aceclofenac 20 ↔ epileptiform activity.
Sairazi (2017)	Sprague-Dawley rats n=180 Male 290 ± 30 g 8 weeks.	Ketamine 90 mg/kg Xylazine 5 mg/kg I.M.	KA 15 mg/kg S.C. Single dose.	1) Control; 2) KA; 3) ASP + KA.	Aspirin NSAID, non-selective 7.5 mg/kg Orally Five times every 12h. *Diazepam 10 mg/kg was administered, I.P., after the first generalized seizure to reduce mortality.	Pre-induction.	Seizure characteristics Behavioral parameters, OFT: locomotor activity (line crossings) Antioxidant status: TBARS Histopathological parameters: neuronal loss (cresyl violet staining); degenerating neurons (Fluoro Jade C staining).	Acute seizure crisis – KA Generalized tonic-clonic seizures.	Yes.	Onset of the first generalized seizure 2) KA: 76.50 min 3) ASP + KA: 62.50 min.	N/A	N/A	↔ Onset of the first generalized seizure; ↓ Locomotor activity compared to KA; ↓ TBARS levels induced by KA; → Slight neuroprotective effect compared to KA (viable cells and FJC-positive cells.
Temp (2017)	Swiss mice n=168 Male 28 ± 3 g Adult.	N/A	PTZ 50 mg/kg I.P. Single dose	1) Vehicle 2) Nimesulide 0.2 3) Nimesulide 2 4) Nimesulide 20 5) Celecoxib 0.2 6) Celecoxib 2 7) Celecoxib 20 8) Etoricoxib 0.2 9) Etoricoxib 2 10) Etoricoxib 20.	Nimesulide Celecoxib Etoricoxib NSAIDs 0.2, 2 and 20 mg/kg P.O. single dose, 60 min before PTZ.	Pre-induction.	Convulsive behavior: Racine's scale, latency to seizure Cytokines: IL-1β, IL-6, IFN-γ, TNF-α, IL-10.	Acute seizure crisis – PTZ.	Yes.	Approximate average latency according to figures 1, 2, and 3: **Latency to myoclonic jerk (s)** Vehicle: ~ 80 s <u>Nimesulide</u> 0.2: ~80 s 2: ~80 s 20: ~80 s <u>Celecoxib</u> 0.2: ~80 s 2: ~80 s 20: ~80 s <u>Etoricoxib</u> 0.2: ~95 s 2: ~95 s 20: ~90 s **Latency to generalized tonic-clonic seizure (s)** <u>Nimesulide</u> 0.2: ~ 180 s 2: ~ 160 s 20: ~ 160 s <u>Celecoxib</u> 0.2: ~100 s 2: ~100 s 20: ~100 s <u>Etoricoxib</u> 0.2: ~120 s 2: ~100 s 20: ~100 s	N/A	Approximate average score according to figures 1, 2, and 3: 1) Vehicle: 6 2) Nimesulide (0.2, 2): 6 3) Nimesulide 20: 3.5 4) Celecoxib (0.2, 2, 20): 6 5) Etoricoxib (0.2, 2, 20): 6.	**Nimesulide** 20 mg/kg: attenuated PTZ-induced seizures by ↓ Racine's scale scores ↑ latency to myoclonic jerks and generalized tonic-clonic seizures —| increase of IL-1β, IL-6 and TNF-α; while ↑ IL-10 in the cortex; **Celecoxib** ↔ Racine scale scores —| Increase of IL-1β, IL-6 and TNF-α; while ↑ IL-10 in the cortex; **Etoricoxib** ↔ Racine scale scores ↔ latency to myoclonic jerks and generalized tonic-clonic seizures.
Zhu (2017)	Swiss mice n=56 Female 25 – 30 g.	Chloral hydrate 0.4 g/kg	Pilocarpine-Induced Seizure 300 mg/kg I.P. after methyl-scopolamine nitrate 1 mg/kg S.C.	1) Pilocarpine + saline 2) Pilocarpine + aspirin 20 3) Pilocarpine + aspirin 60 4) Pilocarpine + aspirin 80.	Aspirin NSAID, non-selective 20, 60 and 80 mg/kg 2 months after *SE*; daily; 10 weeks.	Post-induction.	Convulsive behavior: frequency and duration of stages 4 and 5; modified Racine's scale Western blot: COX-2 ELISA: PGE2, IL-6, TNF-α Hippocampal neurogenesis: BrdU proliferation marker.	Chronic TLE induced by pilocarpine.	Yes.	N/A	Saline 2.1 ± 1.48 per day Aspirin 60 mg/kg 0.48 ± 0.52 per day Aspirin 80 mg/kg 0.55 ± 0.49 per day.	Only stage 4 and 5 seizures were measured.	↓ Occurrence and duration of seizure; ↓ Frequency of spontaneous recurrent seizures; Aspirin 60 and 80 mg/kg ↓ expression of COX-2, PGE2, IL-6 and TNF-α; ↑ Hippocampal neurogenesis by BrdU labeling.
Borham (2016)	Wistar rats n=140 Male 275 ± 25 g Adult.	Ketamine hydrochloride (80 mg/kg) Xylazine hydrochloride (10 mg/kg) I.P. Ether.	LiCl 127 mg/kg I.P. Scopolamine methyl bromide (1 mg/kg) I.P. Pilocarpine hydrochloride (30 mg/kg) I.P.	1) Control (saline) 2) Li-Pilocarpine 3) Li-Pilocarpine + Celecoxib 4) Li-Pilocarpine + Dexamethasone.	Celecoxib NSAID 10 mg/kg Orally Daily, 3 weeks. Dexamethasone Steroidal anti-inflammatory 2.25 mg/kg I.P. Daily, 3 weeks. *1 h, 4 h and 8 h after SE, rats received Diazepam (15 mg/kg) I.P.	Pre-induction.	EEG: amplitude and frequency ELISA: IL-1β, IL-6, PGE2, HSP70, TGF-β2, IFN-γ.	*SE*.	N/A	N/A	N/A	Only animals who developed stages 4 – 5 were included.	**Celecoxib** ↓ Frequency and amplitude of EEG tracing; ↓ IL-6 (brain), PGE2 (serum and brain) and IFN-γ (serum) **Dexamethasone** ↔ Amplitude of EEG tracing; ↓ IL-1β, IL-6 (brain) and PGE2 (serum and brain.
Morelli (2016)	*Danio rerio* Wild-type Adults, larvae and embryos.	N/A	PTZ 15 mM Incubation 20 min. At 7 dpf.	1) Control 2) PTZ 3) Indomethacin 10 4) Indomethacin 100 5) Indomethacin 307.	Indomethacin NSAID, non-selective 10, 100 and 307 µM Incubation 24 h.	Pre-induction.	Seizure behavior: latency and occurrence Stage 1: increased swimming activity Stage 2: rapid circular "whirlpool-like" swimming; Stage 3: seizure-like activity progressing to clonus-like convulsions followed by a brief loss of posture. Gene expression: IL-1β, COX-2 and C-FOS.	Acute seizure crisis – PTZ.	Yes.	Approximate average latency according to figure 6: 2) PTZ: ~2 min 3) Indomethacin 10: ~5.5 min 4) Indomethacin 100: ~5 min 5) Indomethacin 307: ~5.4 min.	Approximate average frequency according to figure 7: Number of seizure behavior in 20 minutes of PTZ 15 mM exposure: 2) PTZ: ~40 3) Indomethacin 10: ~12 4) Indomethacin 100: ~15 5) Indomethacin 307: ~12.	NA	Indomethacin ↓ occurrence of seizure ↑ onset latency ↓ frequency of stage 3 ↓ IL-1β, COX-2 and C-FOS expression (100 and 307).

Vieira (2016)	Wistar rats n=40 Male 300 g 3-month-old.	N/A	PTZ 20 mg/kg I.P. Alternate days, 15 days.	1) Positive control (diazepam 2 mg/kg) 2) Negative control (saline) 3) Diclofenac sodium 5 4) Diclofenac sodium 10.	Diclofenac sodium NSAID, non-selective 5 mg/kg 10 mg/kg. I.P. Daily; 15 days.	Pre-induction (treatment before PTZ daily).	Severity of seizures, Racine's modified scale Behavioral parameters, OFT: line crossing, rearing, grooming and fecal bolus ELISA: IL-1β, IL-6 and TNF-α.	Kindling model – PTZ.	Yes.	N/A	N/A	Approximate average score according to figure 2: 1) Diazepam: ~ 1.7 2) Saline: ~ 3 3) Diclofenac 5: ~ 1.9 4) Diclofenac 10: ~ 1.9.	↓ Severity of seizures; Diclofenac 10 ↓ Occurrence of stages 3 and 4; ↔ Behavioral parameters; Serum: ↔ IL-1β and IL-6 levels; ↑ TNF-α; Hippocampus: ↔ IL-1β; ↓ TNF-α and IL-6.
Gupta (2015)	Wistar rats n=18 Male 150 – 250 g.	Yes. (Not specified)	PTZ 30 mg/kg I.P. Alternate days, 3 times a week, until kindling (two consecutive stage 5 seizures) One-week PTZ-free, 7th day: challenged with PTZ 30 mg/kg (day 0).	1) PTZ + DMSO 2) PTZ + ETO 1 3) PTZ + ETO 10.	Etoricoxib NSAID, COX-2 1, 10 mg/kg I.P. Day 6 to 14.	Post-induction.	Seizure severity Scoring system for PTZ kindled seizures; Stage 1 Hyperactivity, restlessness, vibrissae twitching; Stage 2 Head nodding, head clonus, myoclonic jerks; Stage 3 Unilateral or bilateral limb clonus; Stage 4 Forelimb clonic seizures; Stage 5 Generalized clonic; seizures with falling. Only animals that achieved stage 5 were included. Oxidative stress: MDA, GSH Learning and memory.	Kindling model – PTZ.	Yes.	Approximate average latency according to figure 2a: Pre-treatment 1) PTZ + DMSO: ~ 8 min 2) PTZ + ETO 1: ~ 8 min 3) PTZ + ETO 10: ~ 8 min Post-treatment 1) PTZ + DMSO: ~ 2 min 2) PTZ + ETO 1: ~ 12 min 3) PTZ + ETO 10: ~ 5 min.	N/A	N/A	**Etoricoxib 1** ↔ Seizure severity ↑ Seizure latency ↑ GSH ↔ MDA Impairment of learning and memory. **Etoricoxib 10** ↔ Seizure severity ↑ Seizure duration Impairment of learning and memory.
Payandemehr (2015)	NMRI mice n= 8 per group Male 22 – 30 g 6 – 8 weeks.	N/A	PTZ Dose: N/A I.V.	1) Vehicle 2) Licofelone 1 3) Licofelone 3 4) Licofelone 5 5) Licofelone 10 6) Licofelone 20	Licofelone COX/LOX-5 inhibitor 1, 3, 5, 10, 20 mg/kg I.P. single dose.	Pre-induction.	Clonic seizure threshold.	Acute seizure crisis – PTZ.	Yes.	N/A	N/A	N/A	↑ Seizure threshold.
Trandafir (2015)	Sprague-Dawley rats n=56 Male 250 – 400 g Adult.	Isoflurane 2%.	LiCl 127 mg/kg I.P. 18h before Pilocarpine Scopolamine bromide 1 mg/kg I.P. before Pilocarpine Pilocarpine 50 mg/kg I.P. Single dose.	1) Vehicle 2) NS-398 3) Diazepam 10 4) Diazepam + NS-398.	NS-398 NSAID, COX-2 10 mg/kg I.P. 30 minutes after first seizure, then after 6h.	Post-induction.	EEG: duration and intensity of *SE* Histopathological alterations.	*SE*.	Yes.	N/A	N/A	N/A	↔ EEG; ↓ COX-2 expression in hippocampus; ↓ Neuronal damage in the hippocampus.
Aksoy (2014)	Sprague-Dawley rats n=48 Male 200 – 250 g.	Ketamine 80 mg/kg Xylazine 4 mg/kg I.P.	PTZ 35 and 70 mg/kg I.P.	1) Control 2) PTZ + saline 3) PTZ + Dexketoprofen 20 4) PTZ + Dexketoprofen 40	Dexketoprofen NSAID, non-selective 20 mg/kg 40 mg/kg I.P. 30 min before PTZ.	Pre-induction.	Epileptiform activity: spike percentage Convulsive behavior, Racine's scale.	Acute seizure crisis – PTZ.	Yes.	Latency to first myoclonic jerk (FMJ): Control: 0 PTZ + saline: 75.1 ± 9.62 PTZ + Dexketoprofen 20: 145.8 ± 21.07 PTZ + Dexketoprofen 40: 175.1 ± 17.9.	N/A	Control: 0 PTZ + saline: 5.8 ± 0.1 PTZ + Dexketoprofen 20: 4.5 ± 0.5 PTZ + Dexketoprofen 40: 3.66 ± 0.4.	↓ Epileptiform activity ↑ Latency to FMJ ↓ Racine convulsion stage.
Duffy (2014)	Sprague-Dawley rats n=42 Male 170 – 210 g.	Isoflurane 4%.	LiCl 3meq/kg I.P. 3h before Pilocarpine Methyl scopolamine nitrate 5mg/kg I.P. 30 min before Pilocarpine Pilocarpine hydrochloride 30 mg/kg I.P.	1) Control; 2) *SE*; 3) *SE* + DEX 2; 4) *SE* + DEX 10.	Dexamethasone sodium phosphate. Steroidal anti-inflammatory 2 and 10 mg/kg. Immediately after *SE* and 24 h after. *Diazepam 10 mg/kg I.P. administered 90 and 120 min after *SE*.	Post-induction.	MRI: brain edema and hippocampal volumetry.	*SE*.	Yes.	Approximate average latency according to figure 1a: 2) *SE*: ~ 30 min; 3) *SE* + DEX 2: ~ 28 min; 4) *SE* + DEX 10: ~ 38 min.	N/A	2) *SE*: 4.3 3) *SE* + DEX 2: 4.8 4) *SE* + DEX 10: 4.3.	↑ Mortality ↑ Brain injury ↔ latency to SE onset ↔ seizure severity.
Vieira (2014)	Wistar rats n=21 Male 250 g Adult.	Yes. (Not specified)	Scopolamine methyl nitrate 1 mg/kg I.P. 30 min before Pilocarpine; Pilocarpine 350 mg/kg I.P. single dose.	1) Saline 2) Pilocarpine 3) Pilocarpine + Indomethacin.	Indomethacin NSAID, non-selective 0.5 mg/kg I.P. 30 min, 1h, 2h and 4h after *SE*.	Post-induction.	Proinflammatory molecules expression: PCR and Immunohistochemistry: kinin B1 and B2 receptors, TNF-α, and IL-1β.	*SE*.	Yes.	N/A	N/A	N/A	↓ Kinin B2 receptor, TNF-α, and IL-1β.
Yilmaz (2014)	Wistar rats n=38 Male 290 g 12 weeks old.	Urethane 1.25 g/kg I.P.	Penicillin G potassium 500 IU 2.5 µL I.C.	1) Penicillin + saline 2) Penicillin + DEX 1 3) Penicillin + DEX 3 4) Penicillin + DEX 10 5) Penicillin + PHT 6) Penicillin + LEV.	Dexamethasone Steroidal anti-inflammatory 1, 3 and 10 mg/kg I.P. 1 week.	Post-induction.	Epileptiform activity, ECoG: spike frequency, amplitude.	Penicillin-induced acute epileptiform activity.	Yes.	Onset latency of epileptiform discharges 1) Penicillin + saline: 192 ± 33 s 2) Penicillin + DEX 1: 189 ± 40 s 3) Penicillin + DEX 3: 104 ± 22 4) Penicillin + DEX 10: 142 ± 28 DEX ↔	Spike frequency of epileptiform activity. 1) Penicillin + saline: 34 ± 1 spikes/min 2) Penicillin + DEX 1: 31 ± 4 spikes/min 3) Penicillin + DEX 3: 35 ± 3 spikes/min 4) Penicillin + DEX 10: 34 ± 5 spikes/min.	N/A	DEX 3 and DEX 10 ↓ Epileptiform activity Dexamethasone ↔ onset latency of epileptiform discharges.

Chung (2013)	CD-1 Mice n= N/A sex= N/A PND 9 PND 35 PND 70.	Enflurane 2%.	KA 2, 4, 10 and 20 mg/kg I.P.	1) P9, KA 10 2) P9, KA 2 3) P9, KA 2 + Indomethacin 4) P9, KA 4 + Indomethacin 5) P35, KA 10 6) P35, KA 20 7) P35, KA 10 + Indomethacin 8) P35, KA 20 + Indomethacin.	Indomethacin NSAID, non-selective 10 mg/kg I.P. 1 h prior to KA.	Pre-induction.	Seizure behavior PND 9 0: normal 1: intermediate number of wet-dog shakes and rare focal convulsions affecting the head and extremities; 2: frequent WDS, frequent focal convulsions, and appearance of generalized convulsion with chewing/nodding and rigid posture; 3: for frequent WDS, focal convulsions, and frequent appearance of generalized convulsions with rearing, repetitive scratching, or circling; 4: frequent WDS, focal convulsions, and frequent generalized convulsions with falling, jumping, and tail upholding; 5: continuous tonic-clonic seizure or death within 2 h. PND 35 0: normal; 1: immobility; 2: frequent forelimb and/or tail extension, giving the appearance of a rigid posture; 3: repetitive scratching, circling, and frequently impaired control of balance; 4: continuous impaired balance with tonic-clonic seizure lying on one side; 5: continuous tonic–clonic seizure with bilateral limb jerks or death within 2 h. COX-2 expression.	Seizure susceptibility.	Yes.	N/A	N/A	2) P9, KA 2: 3.3 – 3.7 4) P9, KA 4: 4.5 – 4.7 5) P35, KA 10: 2.1 – 2.3 6) P35, KA 20: 2.6 – 3.2 7) P35, KA 10 + Indomethacin: 3.2 – 3.3 8) P35, KA 20 + Indomethacin: 4.6 – 4.8.	Developing brain (PND 9) is more susceptible to KA induced seizure. Indomethacin: ↑ Seizure levels.
Jeong (2013)	C57BL/6 mice n= N/A Male 8 weeks old.	15% Chloral hydrate.	Atropine methyl nitrate 2 mg/kg I.P. Terbutaline hemisulfate salt 2 mg/kg I.P. Pilocarpine hydrochloride 280 mg/kg I.P.	1) Control 2) *SE* + Vehicle 3) *SE* + Aspirin 15 4) *SE* + Aspirin 150.	Aspirin NSAID, non-selective 15 and 150 mg/kg I.P. 10 days *Diazepam (10 mg/kg I.P.) administered to terminate seizure.	3 days before SE, continuing until 6 days after *SE*.	Seizure susceptibility: onset of first seizure, *SE*, mortality; Racine's scale Histopathological alterations: neuronal cell death, glial responses.	*SE*.	Yes.	2) *SE* + Vehicle: 29.4 ± 1.8 min 3) *SE* + Aspirin 15: 25.2 ± 2.2 min 4) *SE* + Aspirin 150: 20 ± 1 min.	N/A	N/A	↓ Onset time of *SE* ↑ Mortality ↔ Cell death and glial responses.
Xing-hua (2013)	Wistar rats n=42 Male 200 – 250 g 3-month-old.	Chloral hydrate.	LiCl 127 mg/kg I.P. 18h and 30 min before Pilocarpine Methyl-scopolamine bromide 1 mg/kg I.P. before Pilocarpine Pilocarpine 80 mg/kg I.P. Every 30 minutes until *SE* onset.	1) Saline control 2) Tenidap control 3) Saline *SE* 4) Tenidap *SE*.	Tenidap COX/LOX-5 inhibitor 10 mg/kg I.P. 30 min before and daily, 14 days.	30 minutes before pilocarpine, and daily for 14 days post-*SE*.	Seizure behavior, Racine's scale: spontaneous recurrent seizures, frequency and severity Histological and immunocytochemical analyses.	TLE.	Yes.	N/A	3) Saline SE: 4.2 ± 2.2 4) Tenidap SE: 3.7 ± 2.1	N/A	↔ Seizure severity and frequency of seizures ↓COX-2 expression in the hippocampus (CA3); ↓ Neuronal damage in the CA3 area.
Al-Shorbagy *et al.,* (2012)	Wistar rats; n = 6-12 animals/group; male; 180 ± 20g; adult.	Lithium chloride; 3 mequiv/kg body mass; ip.	Pilocarpine; 150 mg/kg body mass; ip; sd.	Control (saline vehicle); Li-PIL (3 mequiv/kg+150 mg/kg); DEX 5 (5 mg/kg+ PIL 150 mg/kg); DEX 10 (10 mg/kg+ PIL 150 mg/kg); DEX 20 (20 mg/kg+ PIL 150 mg/kg).	Dexamethasone (corticosteroid); 5, 10, and 20 mg/kg body mass; ip; sd, 30 min before crisis induction.	Pre- induction.	Seizure-like: Racine scale (30 min). Cerebral damage: H&E staining. Biochemical: ELISA (TNF-α, IL-10, PGE2); MPO activity; GSH levels; LPO; NO levels.	Convulsive attacks.	Yes. Median stage seizure occurrence: Li-PIL: 5; DEX 5: 4; DEX 10: 2; DEX 20: 5.	Stage 3: Li-PIL: 5.2 min; DEX 5: 4.8 min; DEX 10: 27.3 min DEX 20: 3.0 min.	Stage 3-5 seizure incidence: Li-PIL: 100%; DEX 5: 100%; DEX 10: 16.7%; DEX 20: 100%.	0: behavioral arrest, hair raising, excitement, and rapid breathing; 1: mouth movements, vibrissae movements, and salivation; 2: head and eye clonus; 3: forelimb clonus, "wet dog shakes"; 4: clonic rearing; 5: clonic rearing with loss of postural control and uncontrollable jumping.	↑ Seizure latency (DEX 10 mg/kg); ↓ Seizure incidence and intensity (DEX 10 mg/kg); → Neuronal cell protection in CA3 area (DEX 10 mg/kg); ↓ PGE2 and TNF-α levels (DEX 10 mg/kg); ↑ IL-10 levels (DEX 10 mg/kg); ↓ MPO activity (DEX 10 mg/kg); ↑ GSH levels (DEX 10 mg/kg); ↓ TBARS (DEX 10 mg/kg); ↔ NO levels.
Ma (2012)	Sprague-Dawley rats n=80 Male 200 – 250 g Adult.	Sodium pentobarbital 50 mg/kg I.P.	LiCl 3meq/kg I.P. 18h before Pilocarpine Scopolamine methyl bromide 1 mg/kg I.P. 20 min before Pilocarpine Pilocarpine 30 mg/kg I.P.	1) Control; 2) *SE*; 3) *SE* + Aspirin 0 h; 4) *SE* + Aspirin 3 h; 5) *SE* + Aspirin 24; h.	Aspirin NSAID, non-selective 20 mg/kg I.P. Single dose after pilocarpine: 0 h 3 h 24 h. *Diazepam (10 mg/kg I.P.) administered to terminate seizure.	Post-induction. Different time-points.	Seizure behavior, Racine's scale: frequency, duration COX expression in hippocampus, immunoblots Histopathological alterations: hippocampal neuronal loss, mossy fiber sprouting, cell proliferation in the dentate gyrus.	*SE*.	Yes.	N/A	2) *SE*: 8.4 ± 0.3 seizures per day 3) *SE* + Aspirin 0 h: 1.5 ± 0.2 seizures per day 4) *SE* + Aspirin 3 h: 2.1 ± 0.2 seizures per day 5) *SE* + Aspirin 24 h: 1.2 ± 0.1 seizures per day.	N/A	↓ COX-1 and COX-2 expression in the hippocampus; ↓ Frequency and development of spontaneous seizures; Aspirin attenuated hippocampal neuronal loss, prevented aberrant migration of newly generated granule cells and formation of basilar dendrites.

Claycomb *et al.,* (2011)	CD-1 mice; n= 5-18 animals/group; male; weight N/A; 8-12 weeks.	Ketamine (120 mg/kg), Xylazine (20 mg/kg), i.p.	PTZ 0.2 mL/0.03 kg; ip. Acute paradigm: 40 and 55 mg/kg; sd. Kindling paradigm: 40 mg/kg; daily until kindled (reaching ≥stage 3 seizures for 4 consecutive days).	Acute paradigm: PTZ (40 or 55 mg/kg, sd); Rofecoxib (30 mg/kg)+PTZ (40 or 55 mg/kg, sd); Kindling Maintenance: PTZ (40 mg/kg); Rofecoxib (30 mg/kg)+PTZ (40 mg/kg).	Rofecoxib (NSAID)-containing food 180 mg/kg for a dose of 30 mg/kg/day; po; daily.	Acute and Kindling Acquisition: Pre- induction. Kindling Maintenance: Post-kindling establishment.	Seizure-like: Established scoring system (15 min). Stage 0, no behavioral change; stage 1, hypoactivity and immobility; stage 2, two or more isolated, myoclonic jerks; stage 3, generalized clonic convulsions, with preservation of righting reflex; and stage 4, generalized clonic or tonic–clonic convulsions with loss of righting reflex. Cerebral damage: Cresyl violet and FluoroJade staining. Biochemical: IHC (COX-2).	Acute convulsive seizures and kindling.	Yes. Median score seizure occurrence: PTZ (40 mg/kg): 1; PTZ (40 mg/kg)+Rofecoxib: 1; PTZ (55 mg/kg): 2.5; PTZ (55 mg/kg)+Rofecoxib: 3;	Acute paradigm: PTZ (55 mg/kg): (108 ± 31 s); PTZ (55 mg/kg)+Rofecoxib: (106 ± 77 s); Kindling acquisition: N/A; Kindling maintenance: 10 days post-kindled: PTZ 130±20 s; Rofecoxib 110±30 s; 20 days post-kindled: PTZ 120±30 s; Rofecoxib 110±30 s;	N/A	PTZ (40 mg/kg) and Rofecoxib: nonconvulsive seizure (score 2); acute and kindling seizures; PTZ (55 mg/kg) and Rofecoxib: convulsive seizure (score 3 or 4).	↔ Incidence or severity of seizures; ↔ Latency to acute convulsive seizures and kindling maintenance; ↔ Kindling development or kindled state; ↑ COX-2 expression; ↔ Neuronal cell death;
Marchi *et al.*, (2011)	Sprague-Dawley rats; n = 15 animals/group; male; 225-250g; age N/A.	Methylscopolamine; 0.5 mg/kg; ip; Isofluorane.	Pilocarpine; 340 mg/kg; ip; sd.	Pilocarpine (340 mg/kg); Dexa+Pilo (2mg/kg+340mg/kg); IL-RA+Pilo (30 µg/kg+340 mg/kg).	Dexamethasone (corticosteroid); 2mg/kg; ip; twice a day for 2 days.	Pre- induction.	Seizure-like: Racine scale and EEG (duration N/A). Cerebral damage: BBB integrity by serum S100β and brain Evan's Blue extravasation. Biochemical: FACS (CD8a-FITC, CD3-R-PE, CD4-PE-Cy5); ELISA (1L-1β). Mortality rate.	*SE*.	N/A	Latency to *SE* onset: Pilo: ~25 min; Dexa+Pilo: ~40min; IL-1RA+Pilo: ~45 min.	Time-joint frequency analysis without counting.	N/A	↑ *SE* latency; ↓ Mortality associated with SE; ↓ Seizure amplitude and frequency; ↓ *SE* severity; —| BBB damage; ↓ T-cells number; ↑ CD4/CD8 ratio; ↓ 1L-1β levels.
Jayaraman *et al.*, (2010)	Albino mice; n = 6-8 animals/group; male; 25-30g; adult.	N/A Decapitation.	PTZ; 105 mg/kg; ip; sd.	Vehicle+PTZ; Diazepam (2 mg/kg); Etoricoxib (6 mg/kg); Etoricoxib (10 mg/kg); Etoricoxib+Diazepam (6 mg/kg+2 mg/kg); Etoricoxib+Diazepam (10 mg/kg+2 mg/kg).	Etoricoxib (NSAID); 6 and 10 mg/kg; po; sd, 45 min before crisis induction.	Pre- induction.	Seizure-like: Means of chimney test (45 min) Determination of plasma levels.	Clonus-type convulsions.	N/A	PTZ: 97.38 ± 5.50s Diazepam: 338.33 ± 6.00s Etoricoxib (6 mg/kg): 301.22 ± 3.19s Etoricoxib (10 mg/kg): 309.32 ± 2.29s Etoricoxib+Diazepam (6 mg/kg+2 mg/kg): 364.16 ± 11.86s Etoricoxib+Diazepam (10 mg/kg+2 mg/kg): 429.16 ± 10.67s.	N/A	N/A	↓ Mortality (Etoricoxib 10 mg/kg + Diazepam 2mg/kg); ↓ Duration of clonic convulsions (Mortality (Etoricoxib 6 or 10 mg/kg + Diazepam 2 mg/kg); ↔ Motor coordination.
Polascheck *et al.*, (2010)	Sprague-Dawley rats; n = 8-20 animals/group; female; 200-220g; age N/A.	Chloral hydrate (360 mg/kg, ip); CO_2 and decapitation. Lithium chloride; 127 mg/kg Methylscopolamine; 1 mg/kg; ip.	Pilocarpine; 10-50 mg/kg; ip; every 30 min until onset of *SE*. Average dose of pilocarpine for inducing convulsive *SE* was 24.2±1.2 mg/kg.	Control (vehicle-NaCl); Control (parecoxib); *SE*+parecoxib; *SE*+NaCl.	Parecoxib (NSAID); 10 mg/kg; ip; twice a day for 18 days.	Post- induction.	Seizure-like: Racine scale and video/EEG monitoring (7 days). Behavior: Open field, elevated plus maze, hyperexcitability, and Morris water maze. Cerebral damage: Nissl/Thionin-staining and NeuN immunostaining. Biochemical: IHC (COX-2); ELISA (PGE2); HPLC (determination of parecoxib and valdecoxib levels).	Generalized convulsive *SE*.	Yes. Median score seizure occurrence: *SE*+NaCl: 4.5±0.049; *SE*+parecoxib: 3.89±0.051.	*SE*+NaCl: onset of SE was 67.9±3.9min. SE+parecoxib: N/A.	*SE*+NaCl: 12.1±6.5 seizures/week; SE+parecoxib: 10.9 ±4.7 seizures/week.	Majority of spontaneous seizures were generalized convulsive stage 4 or 5.	↔ Incidence and frequency of seizures; ↓ *SE* severity; → Learning improvement; ↓ Grooming frequence and duration; ↔ Mortality; — PGE2 increase levels; ↓ Neuronal damage in CA1, CA3 and piriform cortex.
van Vliet *et al.*, (2010)	Wistar Unilever rats; n = 32 animals/group; female; weight N/A; adult.	Lithium chloride; 127 mg/kg; ip. Methylscopolamine; 1 mg/kg; ip; Isoflurane. Decapitation.	Pilocarpine; 10 mg/kg; ip; every 30 min until onset of *SE*.	Control; Vehicle NS-398; NS-398+Pilocarpine; Vehicle SC-58236; SC-58236+Pilocarpine.	NS-398 (NSAID); 10 mg/kg; ip; twice a day for 3 days. SC-58236 (NSAID), 10 mg/kg; po; twice a day for 3 days.	Pre-induction.	Seizure-like behavior: N/A. Biochemical: IHC (Pgp); WB (COX-2); PGE2; BBB integrity (mannitol-induced disruption and FSC).	*SE*.	Yes. NS-398+Pilocarpine: 72%; Pilocarpine: 63%.	N/A	N/A	N/A	↔ *SE* severity; ↑ Pgp expression; ↔ COX-2 expression; ↔ PGE2 brain levels.
Zandieh *et al.*, (2010)	Swiss mice; n = 10-21 animals/group; male; 20-25g; 6-8 weeks.	N/A	PTZ; 50 or 80 mg/kg; ip; sd.	Control – Vehicle (CMC 0.5%); Celecoxib+PTZ (1 mg/kg + 80 mg/kg); Celecoxib+PTZ (2.5 mg/kg + 80 mg/kg); Celecoxib+PTZ (5 mg/kg + 80 mg/kg); L-NAME+PTZ (20 mg/kg + 80 mg/kg); L-NAME+PTZ (50 mg/kg + 80 mg/kg); L-arginine+PTZ (100 mg/kg + 80 mg/kg); L-arginine+PTZ (200 mg/kg + 80 mg/kg); L-NAME 20 mg/kg + Celecoxib 1 mg/kg – PTZ 50 mg/kg; L-arginine 100 mg/kg + Celecoxib 5 mg/kg – PTZ 50 mg/kg.	Celecoxib (NSAID); 1, 2.5, 5 mg/kg; po; 60 min before PTZ. L-NAME (NOS inhibitor); 20 and 50 mg/kg; ip; 30 min before PTZ. L-arginine (NOS substrate) 100 and 200 mg/kg; ip; 45 min before PTZ.	Pre- induction.	Seizure-like: Convulsion appearance – open field (20 min).	Generalized clonus.	Yes. Generalized convulsions following PTZ (50 mg/kg): Control: 10/19; L-NAME 20 mg/kg: 9/19; Celecoxib 1 mg/kg: 10/21; L-NAME 20 + Celecoxib 1: 4/21; L-arginine 100 mg/kg: 11/20; Celecoxib 5 mg/kg: 6/20; L-arginine 100 + Celecoxib 5: 10/21.	Latency for the first myoclonic jerk and generalized clonus increased in celecoxib groups of 2.5 and 5 mg/kg and L-NAME 50 mg/kg. L-arginine 200 mg/kg) reduced the latency for first myoclonic jerk and generalized convulsion.	N/A	Myoclonic jerks and generalized convulsions.	Celecoxib 2.5 and 5 mg/kg; L-NAME 50mg/kg: ↑ Latency; Celecoxib 1 mg/kg + L-NAME 20 mg/kg: ↓ Incidence of myoclonic jerks and generalized convulsions; L-arginine 200 mg/kg: ↓ Latency; L-arginine (100 mg/kg) —| effect of Celecoxib (5 mg/kg) in incidence of myoclonic jerks and generalized convulsions.
Zibell *et al.*, (2009)	Wistar Unilever rats; n = 75, 7-9 animals/group; female; 180-200g; age N/A.	Lithium chloride; 127 mg/kg; ip. Methylscopolamine; 1 mg/kg; ip; CO_2 and decapitation.	Pilocarpine; 10 mg/kg; ip; every 30 min until onset of *SE*.	Vehicle (10 % DMSO) – Pilocarpine (10 mg/kg); Celecoxib (20 mg/kg) – Pilocarpine (10 mg/kg);	Celecoxib (NSAID); 20 mg/kg; ip; 7 injections in 12h intervals.	Pre-induction.	Seizure-like: monitoring seizure activity (90 min). Biochemical: IHC (Pgp and COX-2). Mortality rate.	*SE*.	Yes. *SE* development: Pilocarpine: 83% (15/16); Celecoxib-treated: 94% (20/24).	N/A	N/A	N/A	↔ Incidence and severity of *SE*; —| Pgp up-regulation; ↔ COX-2 expression; ↔ Mortality.

Akula *et al.*, (2008)	Albino mice (Laka strain); n = 6-10/group; male; 22-30g; adult.	N/A	PTZ; 0.5% (w/v), i.v. infusion (constant rate 0.3 ml/min). Infusion stopped at 3 min or onset of extension phase. Seizure threshold (mg/kg of PTZ) determined for myoclonic jerks, generalized clonus, and tonic extension.	Control (vehicle). Rofecoxib (1, 2, 4 mg/kg i.p.). Adenosine (25, 50, 100, 200 mg/kg i.p.). Rofecoxib (1 mg/kg) + Adenosine (25 mg/kg). 2-Chloroadenosine (1, 2 mg/kg i.p.). Rofecoxib (1 mg/kg) + 2-Chloroadenosine (1 mg/kg). Rofecoxib (1 mg/kg) + 2-Chloroadenosine (2 mg/kg). Caffeine (100, 200 mg/kg i.p.). Rofecoxib (4 mg/kg) + Caffeine (100 mg/kg). Rofecoxib (4 mg/kg) + Caffeine (200 mg/kg). Theophylline (50, 100 mg/kg i.p.). Rofecoxib (4 mg/kg) + Theophylline (50 mg/kg). Rofecoxib (4 mg/kg) + Theophylline (100 mg/kg). Dipyridamole (5, 10, 20 mg/kg i.p.). Rofecoxib (1 mg/kg) + Dipyridamole (5 mg/kg).	Rofecoxib (NSAID); 1, 2, 4 mg/kg; i.p.; sd; 45 min before PTZ infusion.	Pre-induction.	Seizure-like: Seizure threshold (mg/kg of PTZ) for myoclonic jerks, generalized clonus, and tonic extension.	Convulsions (myoclonic jerks, generalized clonus, tonic extension).	N/A	N/A	N/A	Seizure threshold (mg/kg of PTZ) for each phase. Rofecoxib (4 mg/kg): ↑ For all phases; Rofecoxib (2 mg/kg): ↑ For myoclonic jerks and tonic extension; No effect on generalized clonus. Rofecoxib (1 mg/kg): No effect on any phase (sub-effective dose). Adenosine (50-200 mg/kg): ↑ For myoclonic jerks and generalized clonus. Adenosine (100, 200 mg/kg): ↑ For tonic extension. Rofecoxib (1 mg/kg, sub-effective) + Adenosine (25 mg/kg, sub-protective): ↑ Action for tonic extension phase. No effect on myoclonic jerks or generalized clonus. Rofecoxib (1 mg/kg, sub-effective) + 2-Chloroadenosine (1 or 2 mg/kg): ↑ For generalized clonus and tonic extension phases. No effect on myoclonic jerks. Caffeine (100, 200 mg/kg) (alone): No effect. Caffeine (100, 200 mg/kg) + Rofecoxib (4 mg/kg): Reversed the anticonvulsant effect of rofecoxib (↓ PTZ seizure threshold in all parameters tested). Theophylline (50, 100 mg/kg) (alone): No effect. Theophylline (50, 100 mg/kg) + Rofecoxib (4 mg/kg): Significantly inhibited the anticonvulsant effect of rofecoxib (↓ PTZ seizure threshold in all parameters tested). Dipyridamole (10, 20 mg/kg): ↑ For tonic extension. No effect on myoclonic jerks or generalized clonus. Dipyridamole (5 mg/kg, sub-effective) + Rofecoxib (1 mg/kg, sub-effective): ↑ Action for tonic extension phase. No effect on myoclonic jerks or generalized clonus.	↑ Seizure threshold for PTZ-induced convulsions (rofecoxib). Robecoxib effects: → by Adenosine/2-chloroadenosine; —| by caffeine and theophylline; → by dipyridamole.
Dhir *et al.*, (2008)	Albino mice (Laka strain); n = 6-10 animals/group; male; 22-30g; adult.	N/A	PTZ; 80 mg/kg; ip; sd.	Control-vehicle (0.25 %w/v CMC); Topiramate (25, 50 e 100 mg/kg); Rofecoxib (0.5, 1, 5 mg/kg); Rofecoxib (0.5 mg/kg) + Topiramate (25 mg/kg).	Rofecoxib (NSAID); 0.5, 1 and 5 mg/kg; ip; sd.	Pre-induction.	Seizure-like: Observation for 30 min after PTZ adm.	Convulsive crisis.	Yes.	See anti-inflammatory effects section.	N/A	Evaluation of the three phases of convulsions: myoclonic jerks, clonus, and extensor phases.	↑ Onset time for the three phases of convulsions (Rofecoxib 1 and 5 mg/kg; Topiramate 50 and 100 mg/kg); ↑ Onset time of clonus and extensor phase (Rofecoxib 0.5 mg/kg + Topiramate 25 mg/kg); ↔ Onset time of jerks (Rofecoxib 0.5 mg/kg + Topiramate 25 mg/kg).

Kim *et al.*, (2008)	ICR mice; n = 3-6/group; male; 35g; adult.	1.5–2% enflurane; Isoflurane; Sodium pentobarbital.	Kainic acid; 10 or 20 mg/kg; ip; sd.	COX Inhibitors: KA only (10/20mg/kg); Nimesulide (10mg/kg) + KA; Indomethacin (10mg/kg) + KA; Ketoprofen (10mg/kg) + KA; Celecoxib (10/20mg/kg) + KA. PGs & Analogues: INDO + KA; INDO + PGF2α (700ng) + KA; INDO + PGE2 (700ng) + KA; INDO + PGE2 analogue (100ng) + KA; INDO + PGD2 (700ng) + KA. FP Receptor Antagonists: KA only (10mg/kg); AL 8810 (10ng) + KA; AL 8810 (50ng) + KA. PGF2α + Celecoxib: Celecoxib + KA; Celecoxib + PGF2α (700ng) + KA; KA only (10mg/kg).	NSAID drugs: Indomethacin, nimesulide, and ketoprofen; 10 mg/kg; ip; 1h before or 10-20min after KA. Celecoxib; 10 or 20 mg/kg; po; 1h before or 15min after KA. Prostaglandin: PGF2α; 700ng/35g; ic; 20min before KA. PGE2; 700ng/35g; ic; 20min before KA. PGE2 analogue; 100ng/35g; ic; 20min before KA. PGD2; 700ng/35g; ic; 20min before KA. FP receptor antagonist: AL 8810; 10/50ng/35g; ic; 20min before KA.	Pre- & Post-induction (NSAID). Pre-induction (PGs, analogues, AL 8810).	Seizure-like: Video monitoring behavior and EGG (2h); 0 (normal) to 5 (continuous generalized seizures and death). Cerebral damage: Cresyl Violet staining. Mortality rate.	KA-induced seizure activity.	Yes.	N/A	N/A	KA (10mg/kg): score<2. COX Inhibitors (pre-/post-treatment): scores 3-4, prominent generalized seizures, jumping/falling. Nimesulide: score 5, led to death in 6/6 animals within 2h. Ketoprofen; scores 3-4. PGF2α (700ng ic): score<2. PGE2 (700ng ic): score 3-4. PGD2 (700ng ic): score 3-4. PGE2 analogue (100ng ic): score 3-4. AL 8810 (10/50ng ic): score 3-4.	↑ Seizure activity (Indomethacin, Nimesulide, Celecoxib); → Hippocampal neuronal death (Indomethacin); ↑ Mortality (Indomethacin, Nimesulide, Celecoxib); —| Neuronal death (PGF2α); ↓ Mortality (PGF2α and PGE2 analogue).
Oliveira *et al.*, (2008)	Wistar rats; n = 5-11 animals/group; male; 200-250g; adult.	Equithesin (1% phenobarbital, 2% magnesium sulphate, 4% chloral hydrate, 42% propylene glycol, 11% ethanol; 3 mL/kg, i.p.).	PTZ; 60 mg/kg for crisis induction and 20 mg/kg sub convulsive dose; ip; sd.	PTZ (60 mg/kg); Celecoxib (0.2, 2, or 20 mg/kg) + PTZ (60 mg/kg); Vehicle (carboxymethylcellulose + Tween 80) + PTZ (60 mg/kg); Anti-PGE2 (4 ug/2 ul) + PTZ (60 mg/kg); Vehicle (PBS) + PTZ (60 mg/kg); PGE2 (1; 10 or 100 ng/2 ul) + PTZ (20mg/kg); Vehicle (PBS) + PTZ (20mg/kg); Celecoxib (2mg/kg) + PTZ (20mg/kg); Vehicle (carboxymethylcellulose + Tween 80) + PTZ (20 mg/kg); PGE2 (10ng/2 ul) + PTZ (20mg/kg); Vehicle (PBS) + PTZ (20mg/kg).	Celecoxib (NSAID); 0.2, 2, 20 mg/kg; po; sd; 60 min before PTZ injection. PGE2 monoclonal antibodies (4 ug/2 ul; icv; sd; 15 min before PTZ injection.	Pre- induction.	Seizure-like: Video monitoring behavior and EGG (20 min).	Clonic and generalized convulsive episodes.	Yes.	Celecoxib 2 mg/kg: Latency increase for 1st clonic seizure and generalized convulsion of 329% and 317%, respectively. Anti-PGE2 antibodies: Latency increase for 1st clonic seizure and generalized convulsion of 205% and 181%, respectively.	N/A	Generalized convulsive episodes are characterized by generalized whole-body clonus involving all four limbs and tail, rearing, wild running and jumping, sudden loss of upright posture and autonomic signs, such as hypersalivation and defecation.	↑ Latency for 1st clonic and generalized convulsion (Celecoxib 2 mg/kg and anti-PGE2 antibodies); ↓ Duration of generalized convulsions (Celecoxib 2 mg/kg); Evidence of PGE2 inflammatory pathway involvement in celecoxib anti-inflammatory effects.
Zhang *et al.*, (2008)	Sprague-Dawley rats; n = 10-45 animals/group; male; 30-50g; immature.	Lithium chloride; 127 mg/kg; ip. Methylscopolamine; 1 mg/kg; ip. Decapitation.	Pilocarpine; 30 mg/kg; ip; sd.	Control; Epilepsy-only (Pilocarpine 30 mg/kg); Epilepsy-celecoxib (20 mg/kg).	Celecoxib (NSAID); 20 mg/kg; po; once a day for 14 or 28 days.	Pre-induction.	Seizure-like: Racine's scale (12 hours/day). Biochemical: IHC (COX-2, c-Fos, GAP-43); WB (COX-2, ERK1/2, $GABA_A$). Morbidity rate.	*SE* and SRS (Spontaneous recurrent seizures).	Yes. *SE* development: Pilocarpine: 87% (35/40); Celecoxib-treated: 56% (25/45).	Pilocarpine: 10±2 min. Latency for SRS: Pilocarpine: 15.6±2.1d Celecoxib-treated: 12.8±1.8d.	Frequency/duration of SRS: Pilocarpine: 1.9±0.58 times/day; 15.2±3.3s Celecoxib-treated: 0.6±0.3 times/day; 7.1±2.53s.	Continuous motor limbic seizures accompanied by intermittent rearing and falling.	↓ Morbidity and duration of seizures *SE*; ↔ Latent period for SRS; ↓ Frequency of SRS per day; ↓ Duration per seizure —| Neurogenesis, gliogenesis and cell proliferation; ↓ Microglia activation; ↔ Up-regulation of c-Fos positive cells; ↓ COX-2 expression (5;10;15d after *SE*); ↓ c-Fos expression (0;5d after *SE*); ↓ ERK2 expression (0;5d after *SE*); ↓ $GABA_A$ receptors expression (0;5;10;15d after *SE*).
Bauer *et al.*, (2007)	Wistar Unilever rats; n = 12-18 animals/group; female; 200-220g; adult.	Lithium chloride; 127 mg/kg; ip. Methylscopolamine; 1 mg/kg; ip. Chloral hydrate 360 mg/kg, ip.	Pilocarpine; 10 mg/kg; ip; every 30 min until onset of *SE*.	Control (vehicle); Pilocarpine; Indomethacin + Pilocarpine.	Indomethacin (NSAID); 2.5 mg/kg; ip; twice daily for 3 days.	Pre-induction.	Seizure-like: N/A Biochemical: IHC (Pgp; Glut1; NeuN). Mortality rate.	*SE*.	Yes. Vehicle: 67% (8/12); Indomethacin: 89% (16/18).	N/A	N/A	N/A	↔ SE Severity; ↔ Mortality rate; ↓ Pgp expression; —| Neurodegeneration.

Bishnoi *et al.*, (2007)	Laca mice; n = 6/group; male; 20-25g; adult.	N/A Decapitation.	Kainic acid; 50 mg/kg, i.p.; sd.	KA (50 mg/kg) Indomethacin (10 mg/kg) + KA Nimesulide (10 mg/kg) + KA Rofecoxib (10 mg/kg) + KA AKBA (100 mg/kg) + KA Indomethacin (10 mg/kg) + AKBA (100 mg/kg) + KA Nimesulide (10 mg/kg) + AKBA (100 mg/kg) + KA Rofecoxib (10 mg/kg) + AKBA (100 mg/kg) + KA.	Indomethacin, Nimesulide or Rofecoxib, (NSAID);10 mg/kg; p.o.; sd; 45 min prior to KA. AKBA (Acetyl-11-keto-β-boswellic acid): Specific 5-LOX inhibitor; 100 mg/kg; p.o.; sd; 45 min prior to KA.	Pre-induction.	Seizure-like: according to the following rating scale: 0 = normal, rare convulsions; 1 = intermediate and intense immobility with rare convulsions; 2 = frequent convulsions; 3 = progression to more serious convulsions with rearing and salivation; 4 = continuous generalized seizures (rearing and falling over), and 5 = generalized tonic-clonic seizures and death (1h). Biochemical: LPO; GSH; MPO activity; NO levels; SOD and CAT activity.	Excitotoxicity/ neurotoxicity-induced convulsions.	N/A	KA (50mg/kg): Convulsion latency 15.31 ± 1.40 min; Severe convulsion latency 21.17 ± 1.84 min. Indomethacin/Nimesulide/AKBA (per se): No significant behavioral changes (convulsion latency, severe convulsion latency). Rofecoxib (per se): 28.25 ± 0.96 min; Severe convulsion latency 40.04 ± 1.24 min. Nim (10) + AKBA (100): 32.68 ± 1.40 min; Severe convulsion latency 48.91 ± 3.48 min. Rof (10) + AKBA (100): 38.26 ± 2.26 min; Severe convulsion latency 63.26 ± 1.27 min. Ind (10) + AKBA (100): No change in behavioral parameters vs. Indomethacin *per se*.	N/A	KA (50mg/kg): 5. Indomethacin (10mg/kg) + KA: 5. Nimesulide (10mg/kg) + KA: 4. Rofecoxib (10mg/kg) + KA: 3. AKBA (100mg/kg) + KA: 4. Indomethacin (10) + AKBA (100) + KA: 5. Nim (10) + AKBA (100) + KA: 2 (↓ vs. Nimesulide per se). Rof (10) + AKBA (100) + KA: 1 (↓ vs. Rofecoxib per se, more marked effect than Nim + AKBA).	↑ Convulsion latency; ↓ Seizure severity (Rof 10 + KA; Nim 10 + AKBA 100 + KA; Rof 10 + AKBA 100 + KA). Rofecoxib per se: ↑ latency, ↓ seizure score. Nimesulide/Rofecoxib per se: attenuated ↑ LPO, ↓ GSH levels, ↓ MPO activity, ↓ NO levels, ↑ SOD, CAT. Indomethacin/AKBA per se: ↔ LPO, GSH, NO, MPO, SOD, CAT). Combinations (Nim/Rof + AKBA): protective effect ↓ LPO, ↑ GSH, ↓ MPO, ↓ NO, ↑ SOD, CAT. Rofecoxib + AKBA: protective effects ↓ LPO, ↑ GSH, ↓ MPO, ↓ NO, ↑ SOD, CAT. Indomethacin + AKBA: No behavioral or biochemical protective effects.
Dhir *et al.*, (2007)	Albino mice (Laka strain); n = 6-8/group; male; 22-30g; adult.	N/A Decapitation.	PTZ; 40 mg/kg; ip; alternate days for 15 days.	Vehicle, p.o. (daily for 15 days) + Saline, i.p. (alternate days). Vehicle, p.o. + PTZ. Nimesulide 2.5 mg/kg + Saline. Nimesulide 5 mg/kg + Saline. Nimesulide 2.5 mg/kg + PTZ. Nimesulide 5 mg/kg + PTZ.	Nimesulide (NSAID); 2.5 or 5 mg/kg; p.o.; daily for 15 days (45 min before PTZ or saline challenge).	Pre-induction.	Seizure-like: Mean kindling score (0-3 scale: 0=no seizures, 1=jerks, 2=straub's tail, 3=clonic convulsions) (10-15 min). Biochemical: LPO; MPO activity; GSH levels; NO levels.	PTZ-induced chemical kindling.	Yes.	N/A	N/A	PTZ: progressive increase in kindling score, reaching max on day 15; Nimesulide (2.5 or 5 mg/kg): significant decrease in mean kindling score.	↓ Mean kindling score; ↓ MDA levels; ↑ GSH levels; ↓ Nitrite levels; ↓ MPO activity; Nimesulide alone (2.5 or 5 mg/kg) did not show effect on biochemical parameters.
Akarsu *et al.*, (2006)	BALB/c mice, n=8-17/group; male; 28-38g, adult.	N/A	PTZ; 60 mg/kg; ip; injected at 2, 4, 8, 12, 18, 24h after LPS. LPS; 100 µg/kg; ip; sd.	LPS Time Course: Saline + PTZ (control); LPS (2h, 4h, 8h, 12h, 18h, 24h) + PTZ. COX Inhibitors alone + PTZ: Saline + PTZ; Vehicle (Tween 20) + PTZ; Valeryl salicylate (20, 40 mg/kg s.c.) + PTZ; SC-58236 (20, 40 mg/kg s.c.) + PTZ; Indomethacin (0.5 mg/kg s.c.) + PTZ; Diclofenac (1 mg/kg s.c.) + PTZ. SC-58236 on LPS-induced changes: Saline + PTZ; LPS (4h) + PTZ; LPS (4h) + SC-58236 (20, 40 mg/kg) + PTZ; LPS (18h) + PTZ; LPS (18h) + SC-58236 (20, 40 mg/kg) + PTZ.	SC-58236: Selective COX-2 inhibitor; 20 or 40 mg/kg; s.c.; sd 30 min before PTZ. Valeryl salicylate: COX-1 selective inhibitor; 20 or 40 mg/kg; s.c.; sd 30 min before PTZ. Indomethacin: NSAID; 0.5 mg/kg; s.c.; sd 30 min before PTZ. Diclofenac: NSAID; 1 mg/kg; s.c.; sd 30 min before PTZ.	LPS pre-treatment (various time points before PTZ); COX inhibitors pre-treatment (30 min before PTZ).	Seizure-like: +1: myoclonic twitches; +2:generalized tonic–clonic seizures lasting 1–15s; +3: generalized tonic–clonic seizures lasting 16–30s; +4: generalized tonic–clonic seizures lasting 31–45s; +5: generalized tonic–clonic seizures lasting 46–60s; +6: generalized tonic–clonic seizures lasting longer than 60s; +7: death in the first convulsive period (5 min). Mortality rate: up to 60 min after PTZ.	Generalized tonic-clonic seizures.	Yes.	Control (Saline + PTZ): 109 ± 8s. LPS Time-Dependency: LPS (4h) + PTZ: 87 ± 7s. LPS (18h) + PTZ: 97 ± 10s. LPS (2h, 8h, 12h, 24h) + PTZ: No significant changes compared to control. COX Inhibitors alone + PTZ: Valeryl salicylate (20 mg/kg): 102 ± 12s. Valeryl salicylate (40 mg/kg): 104 ± 9 s. SC-58236 (20 mg/kg): 126 ± 14s. SC-58236 (40 mg/kg): 93 ± 7s. Indomethacin (0.5 mg/kg): 97 ± 8s. Diclofenac (1 mg/kg): 101 ± 6s. SC-58236 on LPS-induced changes: LPS (4h) + SC-58236 (20 mg/kg) + PTZ: 121 ± 8 s. LPS (4h) + SC-58236 (40 mg/kg) + PTZ: 119 ± 6 s. LPS (18h) + SC-58236 (20 mg/kg) + PTZ: 117 ± 15 s. LPS (18h) + SC-58236 (40 mg/kg) + PTZ: 138 ± 19 s.	Incidence of seizures: Control (Saline + PTZ): 92%. LPS Time-Dependency: LPS (18h) + PTZ: 41%. LPS (4h) + PTZ: 100%. LPS (18h) + SC-58236 (20 mg/kg) + PTZ: 72%. LPS (18h) + SC-58236 (40 mg/kg) + PTZ: 67%.	Control (Saline + PTZ): 3. LPS Time-Dependency: LPS (4h) + PTZ: 4.5. LPS (18h) + PTZ: 3. Valeryl salicylate (20, 40 mg/kg): 6. SC-58236 (20, 40 mg/kg): 3. Indomethacin (0.5 mg/kg): 5. Diclofenac (1 mg/kg): 6. SC-58236 on LPS-induced changes: LPS (4h) + SC-58236 (20 mg/kg) + PTZ: 5.5. LPS (4h) + SC-58236 (40 mg/kg) + PTZ: 5. LPS (18h) + SC-58236 (20 mg/kg) + PTZ: 4. LPS (18h) + SC-58236 (40 mg/kg) + PTZ: 3.5.	LPS time-dependently effect: early proconvulsant (4h) and late anticonvulsant (18h) states; ↓ Proconvulsant changes (4h) and incidence caused by LPS (SC-58236, partially); → Valeryl salicylate itself facilitated PTZ-induced seizures; ↑ Seizure intensity and mortality (Indomethacin (0.5 mg/kg) + PTZ and Diclofenac (1 mg/kg) +PTZ.
Dhir; Kulkarni (2006)	Albino mice (Laka strain); n= 6-10/group; male; 22-30g; adult.	N/A	PTZ; 80 mg/kg; ip; sd.	Control (vehicle 0.25% CMC). Tiagabine (0.5, 1, 5, 10 mg/kg, i.p.). Rofecoxib (0.5, 1, 5 mg/kg, i.p.). Tiagabine (0.5 mg/kg, sub-protective) + Rofecoxib (0.5 mg/kg, sub-effective).	Rofecoxib, (NSAID); 0.5, 1, 5 mg/kg; ip.; sd; 45 min prior to PTZ. In combination: Rofecoxib administered 10 min before Tiagabine, then 35 min later (total 45 min after Rofecoxib) PTZ.	Pre-induction.	Seizure-like: Mean onset time of jerks, clonus, and extensor phases (30 min).	Clonic convulsions.	Yes.	Rofecoxib (1-5 mg/kg) and Tiagabine (1-10 mg/kg) : increase of mean onset time of all three phases (jerks, clonus, extensor), dose-dependently. Rofecoxib (0.5 mg/kg) and Tiagabine (0.5 mg/kg): No significant effect on onset time of any phase (chosen as sub-effective dose). Rofecoxib (0.5 mg/kg) + Tiagabine (0.5 mg/kg): increase of mean onset time of jerks, clonus, and extensor phases.	N/A	N/A	↑ Mean onset time (Rofecoxib (1-5 mg/kg) and Tiagabine (1-10 mg/kg)); → Rofecoxib 0.5 mg/kg + Tiagabine 0.5 mg/kg): Pronounced anticonvulsant effect.

Jung *et al.*, (2006)	Sprague-Dawley rats; n=9-36/group; male; 200-220g; 12 weeks-old.	N/A	Pilocarpine; 10 mg/kg; ip; sd. Lithium chloride; 127 mg/kg ip; 24h prior to pilocarpine. Methylscopolamine-bromide; 1 mg/kg ip; 30 min prior to pilocarpine.	Normal control; Epilepsy-only; Epilepsy-celecoxib.	Celecoxib (NSAID); 20 mg/kg; po; 14 or 28 days after *SE*.	Post-induction.	Seizure-like: SRS monitoring using Racine's scale (video-monitored 12h/day from 28 to 42 days after *SE*). Cerebral damage: Nissl staining. Biochemical: IHC (COX-2, OX42, BrdU), WB (COX-2).	SRS.	N/A	Mean latency of *SE* onset = 22 ± 4 min.	SRS Likelihood: Epilepsy-only: 89% of 9; Celecoxib-treated: 56% of 9; SRS Frequency: 1.92 ± 0.60 seizures/day; Celecoxib-treated: 0.68 ± 0.32 seizures/day.	Seizure Severity (Racine's scale, for *SE*): continuous motor-limbic seizures accompanied by intermittent rearing and falling. SRS Duration: Epilepsy-only: 14.82 ± 3.50 seconds/seizure. Epilepsy-celecoxib: 7.12 ± 2.82 seconds/seizure.	↓ SRS likelihood, frequency, severity and duration; —| Neuronal death → Neuroprotection ↓ Cell proliferation ↓ Ectopic neurogenesis/gliogenesis: ↓ COX-2 expression.
Kim; Jang (2006)	Sprague-Dawley rat; n=18-30 group; N/A; N/A; 7 to 10 days old.	N/A	Flurothyl; 0.1 ml flurothyl administered continuously for 10 min through a hole in an airtight box. Recurrent seizures induced 25 times (5 times a day for consecutive days).	Control rats: (n=18 total in control group, 6 for "seizure, 25 times" experiment, 12 for "COX-2 expression related to age"). Seizure control rats: (n=5 for celecoxib experiment, treated with solvent only). Seizure rats treated with Celecoxib: Celecoxib (10 mg/kg) (n=5); Celecoxib (20 mg/kg) (n=5). Recurrent seizure group: (n=6 for "seizure, 25 times" experiment, for COX-2/mPGES expression). Seizure rats for seizure frequency/COX-2 expression: (n=9).	Celecoxib: Selective cyclooxygenase-2 (COX-2) inhibitor; 10 mg/kg or 20 mg/kg; p.o.; sd; 1h before flurothyl.	Pre-induction.	Seizure-like: Time of seizure onset (s); Observation (clonic movements of four limbs, loss of posture). Cerebral damage: Histological/Pathologic findings, apoptotic cells (TUNEL staining). Biochemical: IHC and optical density (COX-2); WB (COX-2, mPGES-1/2, Cas-3).	Neonatal seizure (recurrent seizures).	Yes.	Seizure control rats (solvent only): 126 ± 37s. Celecoxib (10 mg/kg): 144 ± 39s. Celecoxib (20 mg/kg): 176 ± 42s.	N/A	Seizure attacks characterized by clonic movements of four limbs and loss of posture.	↑ Latency of seizure attacks; ↓ COX-2 expression; COX-2 expression was seizure frequency dependent (higher frequency associated with higher COX-2 expression). mPGES-2 expression was similar in both recurrent seizure and control groups. mPGES-1 was not detected. No significant pathologic findings or apoptotic cells were found in recurrent seizure rats (hippocampus) or control groups. Active subunits of caspase-3 were not found.
Yoshikawa *et al.*, (2006)	Wistar rats; n=3-16/group; male; N/A; 3-week-old.	N/A	Kainic acid; 10 mg/kg, i.p; sd.	Control (saline); KA (10 mg/kg); KA + CNQX, UBP296 or UBP301 (KA receptor antagonists) (100 nmol/rat i.c.v.); KA + NS398 or Indomethacin (10 mg/kg).	NS398 or Indomethacin; 10 mg/kg; ip; sd; 30 min before KA.	Pre-induction.	Biochemical: LC-ESI-MS/MS (PGF2α, PGD2, PGE2, TxB2, 6-keto-PGF1α, 11-HETE, 12-HETE).	Seizure (model of temporal lobe epilepsy).	N/A	N/A	N/A	N/A	NS398: ↓ Initial phase PG production; → PGF2α, PGE2, 6-keto-PGF1α inhibition; Indomethacin: → Suppressed all PG productions.
Dhir *et al.*, (2005)	Albino mice (Laka strain); n = N/A; male; 22-30g; age N/A.	N/A Euthanasia: decapitation.	PTZ; 40 mg/kg; ip; 15 days (alternate days).	Vehicle (CMC+saline); Vehicle + PTZ (40 mg/kg); PTZ+ Naproxen (7 mg/kg); PTZ+ Naproxen (14 mg/kg).	Naproxen (NSAID); 7 and 14 mg/kg; ip; 15 days (every day).	Pre- induction.	Seizure-like: Mean kindling score. 0: no effect; 1: jerks; 2: straub tail; 3: clonus (10-15 min). Behavior: locomotor activity; Mirror chamber test; Plus maze test; hyperalgesia. Biochemical (brain tissue): LPO, GSH levels; NO levels; MPO activity.	Kindling.	Yes.	N/A	N/A	Progressive increase in mean kindling score induced by PTZ.	↓ Mean kindling score; ↓ Ambulatory movements; ↓ Exploratory behavior; ↔ % retention (memory); —| Hyperalgesia; ↓ Anxiety; ↓ MDA levels; ↑ GSH levels; ↓ NO levels; ↓ MPO activity.
Kawaguchi *et al.*, (2005)	Sprague-Dawley rat; n=6-9/group; male; 275-300g; adult.	Heparin (100 U/kg, i.p.) + Chloral hydrate (500 mg/kg, i.p.) for sacrifice. N2O (67%) + O2 (30%) + Isoflurane (3%) for intubation; Pancuronium bromide (0.3 mg/kg) for paralysis; Isoflurane (1%) for maintenance. Chloral hydrate (500 mg/kg, i.p.) for sacrifice.	For COX-2 expression: Kainic acid 10 mg/kg, s.c.; tissue collected at 0, 2, 8, 18, 24 h. For neuronal death/SC58125: Kainic acid 0.6 µg (0.4 mg/ml at 0.15 µl/min for 4 min), intraventricular.	COX-2 Expression Time Course: Vehicle (s.c. saline); Kainate (10 mg/kg, s.c.). PGE2 Concentration Inhibition: Vehicle (1% methyl cellulose, p.o.); SC58125 (3 mg/kg, p.o.) + Kainate (s.c.); Vehicle (p.o.) + Kainate (s.c.). Neuronal Death/SC58125 Treatment: Vehicle (1% cellulose solution, p.o.) + Kainate (intraventricular); SC58125 (3 mg/kg, p.o.) + Kainate (intraventricular).	SC58125: Selective COX-2 inhibitor; 3 mg/kg; p.o.; 1h before KA, and again at 24 and 48 h after KA (for neuronal death study).	Pre-induction (1h before KA) and Post-induction (24h and 48h after KA) for neuronal death study. Pre-induction (1h before KA) for PGE2 study.	Seizure-like: EEG monitoring (Types I-IV activity), total duration of Type IV EEG activity. Seizure activity (not scored behaviorally in this paper). Cerebral damage: Cresyl violet staining, surviving neuron counts in CA3. Biochemical: IHC (COX-2), ELISA (PGE2).	Limbic seizures.	All animals developed Type IV EEG activity.	Seizure onset within 1 min.	N/A	Total duration of Type IV EEG activity Control group (Kainate + Vehicle): 135 ± 38 min. SC58125-treated group: 140 ± 33 min.	↔ Duration or rate of Type IV EEG activity ↓ PGE2 levels; → Survival of CA3 neurons.

Kunz *et al.*, (2005)	Sprague-Dawley rat; n=5-15/group; male; ~270g; adult.	Halothane anesthesia (for sacrifice and brain removal).	Kainic acid 10 mg/kg; i.p.; sd.	Short-term treatment - Days 0-2: Seizure Vehicle (DMSO); Seizure Rofecoxib (10 mg/kg); Non-seizure controls (saline + DMSO). Long-term treatment - Days 0-9: Seizure Vehicle (DMSO); Seizure Rofecoxib (10 mg/kg); Non-seizure controls (saline + DMSO).	Rofecoxib: Selective COX-2 inhibitor; 10 mg/kg; i.p. Short-term: Twice daily for 2 days (Day 0-2), starting 8h after KA. Long-term: Once daily for 9 days (Day 0-9), starting 8h after KA.	Post-induction.	Seizure-like: Behavioral seizure grading (Racine scale, grades 3 & 4 for inclusion – 5h). Cognitive/Behavioral: Visuospatial learning (Morris Water Maze) Cerebral damage: Hippocampal cell death (TUNEL staining).	Limbic seizures (generalized convulsions).	Yes. Only animals developing generalized convulsions (seizure grades 3 and 4) were subjected to inhibitor treatment.	Behavioral changes started ~30 min after KA (wet dog shakes, chewing, salivation, rearing, twitches, generalized convulsions).	N/A	Seizure Grades (for inclusion): Animals showed seizure grades 3 and 4 (generalized convulsions).	↔ Seizure-induced visuospatial learning deficits; ↔ Hippocampal late phase neurodegeneration.
Gobbo; O'Mara (2004)	Wistar rat; n=5-15/group; male; 250-300g; adult.	N/A Decapitation.	Kainic acid;12 mg/kg or 6 mg/kg; i.p.; sd.	KA Dose Response: Control (saline); KA (6 mg/kg); KA (12 mg/kg). Post-treatment with Celecoxib: Control (saline); KA (12 mg/kg) + Vehicle Celecoxib (DMSO); KA (12 mg/kg) + Celecoxib (6 mg/kg) (once or 5 days). Pre-treatment with Celecoxib: Control (saline); KA (12 mg/kg) + Vehicle Celecoxib (DMSO); KA (12 mg/kg) + Celecoxib (6 mg/kg) (once or 5 days).	Celecoxib: Selective COX-2 inhibitor; 6 mg/kg; i.p. Post-treatment: Once daily for 5 days, or once 2h post KA-treatment. Pre-treatment: Once daily for 5 days, or once 2h prior to KA.	Pre-induction (2h prior or 5 days prior to KA) AND Post-induction (2h post or 5 days post KA).	Seizure-like: Acute behavioral syndrome (wet dog shakes, seizures from mild forehead nodding to severe limbic convulsions with rearing and foam at the mouth). Behavioral: Morris Water Maze; Open Field; Object Exploration Task. Cerebral damage: Neuronal loss (Methylene Blue staining, cell counts in CA1, CA2, CA3 areas). Biochemical: ELISA (BDNF). Mortality rate.	Limbic seizures.	Yes.	N/A	N/A	KA induced an acute behavioral syndrome, including "wet dog shakes" and seizures from mild forehead nodding to severe limbic convulsions with rearing and foam at the mouth.	Celecoxib pre-treatment: ↔ Learning performance ↔ Hyperactivity ↔ Object exploration task ↔ BDNF expression ↑ Mortality rate Celecoxib post-treatment: ↓ Learning deficit ↓ Hyperactivity → Performance on the object exploration task → Neurodegeneration recovery ↔ Neuronal loss ↓ BDNF expression ↔ Survival.

Sayyah *et al.*, (2003)	NMRI mouse; n=10/group; male; 20-28g; 28-35 days old.	N/A	PTZ; 10 mg/ml; i.v. infusion (constant rate 0.3 ml/min). LPS (EscherIHCia coli serotype 026:B6); 0.001, 0.01, 0.1, 1, or 10 mg/kg; i.p.; sd.	LPS Dose/Time Course: Saline control; LPS (0.001, 0.01, 0.1, 1, 10 mg/kg); LPS (1 mg/kg) at 0.5, 1, 4, 8, 12, 24 h before PTZ. L-NAME + LPS: Control; L-NAME (1, 5, 10 mg/kg i.p.); LPS (1 mg/kg); L-NAME (1, 5, 10 mg/kg) + LPS (1 mg/kg) - at 1h or 8h post-LPS. Piroxicam + LPS: Control (sesame oil); Piroxicam (1, 5, 10 mg/kg i.p.); LPS (1 mg/kg); Piroxicam (1, 5, 10 mg/kg) + LPS (1 mg/kg) - at 1h or 8h post-LPS. Naloxone + LPS: Control; Naloxone (0.1, 1, 2 mg/kg i.p.); LPS (1 mg/kg); Naloxone (0.1, 1, 2 mg/kg) + LPS (1 mg/kg) - at 1h or 8h post-LPS.	Piroxicam; Cyclooxygenase inhibitor; 1, 5, 10 mg/kg; i.p.; sd; administered before LPS (interval not explicitly stated for this drug, but L-NAME/Naloxone were 0.5h before LPS).	Pre-induction (LPS administered before PTZ; L-NAME/Piroxicam /Naloxone administered before LPS).	Seizure-like: Clonic seizure threshold (mg/kg of PTZ) until onset of general clonus (loss of righting reflex). Monitored until endpoint.	Clonic seizures.	Yes.	N/A	N/A	Clonic Seizure Threshold (mg/kg of PTZ) (mean ± SEM): Control (Saline): 40.0-42.5 mg/kg (approx. from figures). LPS (dose-dependent, at 1h): LPS (0 mg/kg): ~42 mg/kg LPS (0.001 mg/kg): ~44 mg/kg LPS (0.01 mg/kg): ~36 mg/kg LPS (0.1 mg/kg): ~32 mg/kg **(**p<0.01) LPS (1 mg/kg): ~27 mg/kg **(**p<0.001) LPS (10 mg/kg): ~28 mg/kg **(**p<0.001) LPS (time-dependent, 1 mg/kg): LPS (0h): ~42 mg/kg LPS (0.5h): ~29 mg/kg **(**p<0.001) LPS (1h): ~25 mg/kg **(**p<0.001) LPS (4h): ~33 mg/kg **(**p<0.05) LPS (8h): ~28 mg/kg **(**p<0.001) LPS (12h): ~32 mg/kg **(**p<0.05) LPS (24h): ~42 mg/kg L-NAME + LPS (at 1h post-LPS): LPS (1mg/kg): ~27 mg/kg (***) L-NAME (1, 5, 10 mg/kg) alone: No effect (threshold ~40-42 mg/kg). L-NAME (1 mg/kg) + LPS (1mg/kg): ~39 mg/kg (a) L-NAME (5 mg/kg) + LPS (1mg/kg): ~40 mg/kg (b) L-NAME (10 mg/kg) + LPS (1mg/kg): ~40 mg/kg (c) L-NAME + LPS (at 8h post-LPS): LPS (1mg/kg): ~29 mg/kg (***) L-NAME (1, 5, 10 mg/kg) + LPS (1mg/kg): ~39-40 mg/kg (c) Piroxicam + LPS (at 1h post-LPS): LPS (1mg/kg): ~26 mg/kg (***) Piroxicam (1, 5, 10 mg/kg) alone: No effect (threshold ~40-42 mg/kg). Piroxicam (1 mg/kg) + LPS (1mg/kg): ~38 mg/kg (c) Piroxicam (5 mg/kg) + LPS (1mg/kg): ~43 mg/kg (c) Piroxicam (10 mg/kg) + LPS (1mg/kg): ~44 mg/kg (c) Piroxicam + LPS (at 8h post-LPS): LPS (1mg/kg): ~29 mg/kg (***) Piroxicam (1, 5, 10 mg/kg) + LPS (1mg/kg): ~41-42 mg/kg (c) Naloxone + LPS (at 1h post-LPS): LPS (1mg/kg): ~26 mg/kg (***) Naloxone (0.1, 1, 2 mg/kg) alone: No effect (threshold ~40-42 mg/kg). Naloxone (0.1, 1, 2 mg/kg) + LPS (1mg/kg): ~38-40 mg/kg (c for 1mg/kg, a for 0.1mg/kg, b for 2mg/kg)	—| Reversed the proconvulsant effect of LPS on seizure threshold.

Ciceri *et al.*, (2002)	Sprague-Dawley rat; n=5-8/group; male; 250-300g; N/A (adult).	Sodium pentobarbital (65 mg/kg) for perfusion.	Kainic acid; 10 mg/kg; s.c.; sd.	PGs & COX Activity Profile: Normal; Kainate (10 mg/kg s.c. for 24h). Dexamethasone/mRNA: Normal; Kainate (10 mg/kg s.c. for 24h); Dexamethasone (1 mg/kg p.o.) + Kainate. Celecoxib Effect on PGE2: Normal; Kainate (10 mg/kg s.c.); Celecoxib (various doses) + Kainate.	Celecoxib: Selective COX-2 inhibitor; 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10 mg/kg; po; sd 20h after KA (therapeutic). Dexamethasone: Glucocorticoid (COX-2 synthesis inhibitor); 1 mg/kg; po; 1h before and 8h after KA.	Post-induction (20h after KA for Celecoxib); Pre- & Post-induction (1h before and 8h after KA for Dexamethasone).	Seizure-like: Behavioral syndrome (wet-dog shakes, rearing, tremor of forepaws – 4h). Biochemical: IHC (COX-2), ELISA of eicosanoid content (PGE2, PGF2α, PGD2, TxB2, 6-keto-PGF1α), COX activity (PGE2 formation from arachidonic acid), PCR (COX-1, COX-2, PGE synthase, PGD synthase, WB (COX-2, PGE synthase).	Limbic seizures.	Yes.	N/A	N/A	KA-treated rats displayed a typical behavior syndrome (wet-dog shakes, rearing, tremor of the forepaws) for 30 min to 4h after injection.	Celecoxib effects: —| PGE2 synthesis (dose-dependently) ↔ COX-2 or PGE synthase mRNA levels Dexamethasone effects: ↓ COX-2 and PGE synthase mRNA levels ↓ PGE2 brain production (at 24h).
Edwards *et al.*, (2002)	Sprague-Dawley rat; n=5-15/group; male; N/A; 15-day-old (prepubertal).	Halothane 1.5% (for kindling electrode implantation).	ScMET Pentylenetetrazol (Metrazol); 85 mg/kg; s.c.; sd. Observation for 60 min. MMT Pentylenetetrazol; 150 mg/kg; s.c.; sd. Observation for 60 min.	Controls: Saline (for ACTH-treated groups); Cyclodextran (for steroid hormone-treated groups). Hormones tested: ACTH (4 IU/kg i.p.); Deoxycorticosterone (DOC) (20 mg/kg s.c.); Dihydroepiandrosterone (DHEA) (50 mg/kg s.c.); Corticosterone (CORT) (20 mg/kg s.c.); Dexamethasone (DEX) (50 mg/kg s.c.); Aldosterone (ALDO) (20 mg/kg s.c.); Progesterone (P4) (20 mg/kg s.c.).	Dexamethasone: Glucocorticoid (COX-2 synthesis inhibitor); 50 mg/kg; s.c.; single acute injection. ACTH: Peptide hormone; 4 IU/kg; i.p.; single high dose. Deoxycorticosterone (DOC): Steroid hormone; 20 mg/kg; s.c.; single high dose. Dihydroepiandrosterone (DHEA): Steroid hormone; 50 mg/kg; s.c.; single high dose. Corticosterone (CORT): Steroid hormone; 20 mg/kg; s.c.; single high dose. Aldosterone (ALDO): Steroid hormone; 20 mg/kg; s.c.; single high dose. Progesterone (P4): Steroid hormone; 20 mg/kg; s.c.; single high dose.	Pre-induction.	Seizure-like: scMET: Moshe's stage-paradigm for young rats: 1-7 scale. Latency to forelimb clonus (s). MMT: Latency to forelimb clonus (s), Latency to forelimb flexion (s). 60 min of observation.	Seizures.	Yes. MES Seizures (% Animals Exhibiting Forelimb Tonic Extension): Cyclo (control): 95%. DOC (20mg/kg): 59% (p<0.05 vs. Cyclo). DHEA (50mg/kg): 85%. CORT (20mg/kg): 90%. DEX (50mg/kg): 85%. ALDO (20mg/kg): 63%. P4 (20mg/kg): 49% (p<0.05 vs. Cyclo). Saline (control): 89%. ACTH (4IU/kg): 95%.	scMET Seizures (Latency to Forelimb Clonus in s, mean ± SE): Cyclo (control): ~970s. DOC (20mg/kg): ~3100s (p<0.05 vs. Cyclo). DHEA (50mg/kg): ~550s. CORT (20mg/kg): ~2050s (p<0.05 vs. Cyclo). DEX (50mg/kg): ~1500s. ALDO (20mg/kg): ~3300s (p<0.05 vs. Cyclo). P4 (20mg/kg): ~3250s (p<0.05 vs. Cyclo). Saline (control): ~390s. ACTH (4IU/kg): ~1600s (trend, not significant). MMT Seizures (Latency to Forelimb Clonus & Flexion in s, mean ± SE): Cyclo (control): Clonus ~120s, Flexion ~450s. DOC (20mg/kg): Clonus ~3400s (p<0.05 vs. Cyclo); Flexion ~3300s (p<0.05 vs. Cyclo). ALDO (20mg/kg): Clonus ~1100s (p<0.05 vs. Cyclo); Flexion ~1800s (p<0.05 vs. Cyclo). P4 (20mg/kg): Clonus ~3250s (p<0.05 vs. Cyclo); Flexion ~3300s (p<0.05 vs. Cyclo).	N/A	N/A	Dexamethasone ↔ Latency to forelimb clonus or flexion ACTH ↔ Latency to forelimb clonus or flexion DOC ↑ Latency to forelimb clonus and flexion DHEA ↔ No significant effect on any parameter CORT ↑ Latency to forelimb clonus (scMET) ALDO ↑ Latency to forelimb clonus and flexion P4 ↑ Latency to forelimb clonus and flexion.

Reddy; Rogawski (2002)	Sprague-Dawley, rat; n=7-8/group (PTZ threshold); male; 250-300g; N/A (adult). NIH Swiss, mouse; n=8/group (chemoconvulsants, MES, kindling); male; 25-30g; N/A (adult). Adrenalectomized mice also used.	CO_2 gas (for blood collection in mice).	Stress Model: Acute swim stress; 10 min; water at ambient temperature (22ºC); single exposure. PTZ Seizure Threshold (rat): Pentylenetetrazol (PTZ); 20 mg/ml solution; i.v. infusion (0.5 ml/min). Single infusion until myoclonic forelimb clonus. PTZ Seizure Test (mouse - all-or-none): PTZ; 85 mg/kg; s.c.; single dose. Observation for 30 min. Chemoconvulsants (mouse): Picrotoxin (3.2 mg/kg s.c.); Methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) (7.5 mg/kg s.c.); Strychnine (1.3 mg/kg s.c.); Kainic acid (32 mg/kg s.c.); 4-Aminopyridine (13.3 mg/kg s.c.); NMDA (257 mg/kg s.c.). Single dose. Observation for 30 min.	Stress & Finasteride: Naive; Stress; Naive + Finasteride (100 mg/kg); Stress + Finasteride (100 mg/kg). DOC Dose-Response (rat PTZ threshold): Control (vehicle); DOC (1.9-30 mg/kg i.p.). DOC Dose-Response (mouse PTZ test, all-or-none): DOC (0-200 mg/kg i.p.). DOC vs. Other Chemoconvulsants: DOC (various doses) + Picrotoxin/DMCM/Strychnine/KA/4-AP/NMDA. Finasteride/Indomethacin on DOC: DOC alone; DOC + Finasteride (10 mg/kg i.p.); DOC + Indomethacin (100 mg/kg i.p.). (For mouse PTZ test). DHDOC/THDOC (mouse PTZ test): DHDOC; THDOC. Finasteride/Indomethacin on DHDOC/THDOC: DHDOC; DHDOC + Finasteride; DHDOC + Indomethacin; THDOC; THDOC + Finasteride; THDOC + Indomethacin.	Indomethacin: COX inhibitor (also acts as 3α-hydroxysteroid oxidoreductase inhibitor); 100 mg/kg; i.p.; single dose 30 min before DOC. Finasteride: 5α-reductase inhibitor; 100 mg/kg (rat); 10 mg/kg (mouse); 30 mg/kg (mouse adrenalectomized); i.p.; single dose 90 min before stress/60 min before DOC. Deoxycorticosterone (DOC): Adrenal steroid (precursor to neurosteroids DHDOC, THDOC); 1.9-300 mg/kg; i.p. (rat/mouse PTZ); Administered 30 min before PTZ tests. 5α-dihydrodeoxycorticosterone (DHDOC): Neurosteroid (DOC metabolite); 26-58 mg/kg; i.p.; administered 15 min before PTZ. Allotetrahydrodeoxycorticosterone (THDOC): Neurosteroid (DOC metabolite); 19-66 mg/kg; i.p.; administered 15 min before PTZ.	Pre-induction.	Seizure-like: Seizure threshold (mg/kg PTZ), Percent Seizure Protection (all-or-none tests). Behavioral: Motor toxicity (horizontal screen test). Biochemical: Plasma THDOC levels (LC-MS/MS).	PTZ-induced clonic seizures (rat, mouse), Picrotoxin-induced seizures, DMCM-induced seizures, Strychnine-induced seizures, Kainic acid-induced seizures, 4-Aminopyridine-induced seizures, NMDA-induced seizures.	Yes.	PTZ seizure threshold (mg/kg): Stress: PTZ seizure threshold was increased (22%) (~33 mg/kg) compared to naive controls (~27 mg/kg). DOC (1.9-30 mg/kg i.p.): Dose-dependently increased PTZ seizure threshold (e.g., 1.9 mg/kg DOC: 12% elevation in seizure threshold (~29 mg/kg PTZ); 30 mg/kg DOC: ~30 mg/kg PTZ threshold).	N/A	PTZ Seizure Threshold (rat): Myoclonic forelimb clonus (endpoint). PTZ Seizure Test (mouse - all-or-none): Clonic spasms lasting >5 sec (protected if absent). Chemoconvulsants (mouse): Protection from seizures.	Indomethacin (100 mg/kg): ↔ PTZ seizure threshold; → Partially antagonized DOC's anticonvulsant effect; Finasteride (100 mg/kg rat; 10 mg/kg mouse; 30 mg/kg mouse adrenalectomized): ↓ PTZ seizure threshold in stressed animals; —| Reversed DOC's anticonvulsant effect; ↔ THDOC/DHDOC protection. *Stress modulates seizure susceptibility via neurosteroids. Deoxycorticosterone (DOC) (1.9-300 mg/kg): ↑ PTZ seizure threshold (dose-dependently); —| PTZ-induced clonic seizures; —| Picrotoxin/DMCM-induced seizures (dose-dependent); ↔ No protective activity against seizures induced by strychnine, kainic acid, 4-aminopyridine, NMDA. → Motor impairment at doses comparable with those effective in PTZ test. DHDOC (26-58 mg/kg): → Dose-dependent protective activity in PTZ-induced seizures. THDOC (19-66 mg/kg): → Dose-dependent protective activity in PTZ-induced seizures.
Kunz; Oliw (2001)	Sprague-Dawley rat; n=12/group; male; N/A; N/A (adult).	N/A	Kainic acid; 10 mg/kg; i.p.; sd.	Kainic acid + Vehicle (DMSO) Kainic acid + Rofecoxib (10 mg/kg).	Rofecoxib: Selective COX-2 inhibitor; 10 mg/kg; i.p.; twice daily for 3 days, starting 6 or 8 hours after KA injection.	Post-induction.	Seizure-like: Observation for limbic seizures (onset within 30 min, lasting ~6h). Cerebral damage: Histological staining of viable cells, TUNEL staining. Biochemical: IHC (COX-), COX-2 mRNA (in situ hybridization).	Limbic seizures.	Limbic seizures were triggered in 60% of the animals.	Seizures started within 30 min.	N/A.	N/A	↓ Cell loss in hippocampus; ↓ DNA fragmentation; ↓ Degree of cell death.

Srivastava; Gupta (2001)	Albino mouse; n=7-8/group; male; 30-40g; N/A.	N/A	PTZ; 80 mg/kg; i.p.; sd.	Control. Aspirin (50, 100, 500 mg/kg i.p.). Diazepam (0.5, 2.0, 3.0 mg/kg i.p.). Sodium Valproate (75, 150, 300 mg/kg i.p.). Diazepam (0.5 mg/kg) + Aspirin (50 mg/kg) - for PTZ. Diazepam (0.5 mg/kg) + Aspirin (100 mg/kg) - for PTZ. Diazepam (0.5 mg/kg) + Aspirin (150 mg/kg) - for PTZ. Aspirin (100 mg/kg) + Sodium Valproate (150 mg/kg) - for PTZ.	Aspirin: NSAID (prostaglandin synthesis inhibitor); 50, 100, 500 mg/kg; i.p.; sd; 45 min before PTZ challenge.	Pre-induction.	Seizure-like: Number of animals showing generalized clonic seizures with falling; Latency for generalized clonic seizures (for combination).	Generalized clonic seizures with falling.	Control: 8/8 animals convulsed (100% incidence). Aspirin: Aspirin (50 mg/kg): 6/7 (85.7%). Aspirin (100 mg/kg): 4/8 (50%). Aspirin (500 mg/kg): 2/7 (28.5%). Diazepam: Diazepam (0.5 mg/kg): 4/8 (50%). Diazepam (2.0 mg/kg): 2/7 (28.5%). Diazepam (3.0 mg/kg): 0/8 (0%). Sodium Valproate: Sodium Valproate (75 mg/kg): 8/8 (100%). Sodium Valproate (150 mg/kg): 4/8 (50%). Sodium Valproate (300 mg/kg): 2/7 (28.5%). Diazepam (0.5 mg/kg) + Aspirin (50 mg/kg): 1/7 (14.2%). Diazepam (0.5 mg/kg) + Aspirin (100 mg/kg): 2/7 (28.5%). Diazepam (0.5 mg/kg) + Aspirin (150 mg/kg): 1/7 (14.2%). Aspirin (100 mg/kg) + Sodium Valproate (150 mg/kg): 2/7 (28.5%).	Diazepam (0.5 mg/kg) + Aspirin (50 mg/kg): Increased latency to 371 s (in one animal).	N/A	N/A	Aspirin: ↓ Incidence of generalized clonic seizures (dose-dependent); Aspirin + Diazepam (sub-anticonvulsant doses): → Potentiated the anticonvulsant effect of diazepam. Aspirin + Sodium Valproate (sub-anticonvulsant doses): → Potentiated the anticonvulsant effect of sodium valproate.
Kim *et al.*, (2000)	ICR mouse; n=8-12/group; male; 25-30g; N/A (adult).	N/A Decapitation.	Kainic acid; 30 mg/kg; i.p.; sd.	Control (Saline). KA (30 mg/kg). Phenidone (various doses) + KA. Phenidone alone. Vitamin E + KA. N-acetylcysteine (NAC) + KA. Probucol + KA.	Phenidone: Dual inhibitor of cyclooxygenase/lipoxygenase pathways; 5, 10, 20 mg/kg; i.p.; sd; 30 min before KA injection.	Pre-induction.	Seizure-like: Behavioral seizure activity (endpoint: tonic-clonic convulsions; graded severity scale: 0-3 for myoclonic jerk, generalized clonic convulsion, tonic hindlimb extension). Mortality. Cerebral damage: H&E staining, viable neuron counts Biochemical: LPO (TBARS), GSH, GSSG, DNA fragmentation (gel electrophoresis), Glutamate release (HPLC), SOD, CAT.	Convulsions.	Yes. KA (30 mg/kg): Induced severe limbic seizures characterized by wet dog shakes, scratching, rearing, and generalized clonic convulsions. Mortality rate = 100% within 1.5-2 h. Phenidone (5 mg/kg): 100% mortality. Phenidone (10 mg/kg): 50% mortality. Phenidone (20 mg/kg): 0% mortality.	KA (30 mg/kg): Myoclonic jerk latency = ~15 min. Generalized clonic convulsion latency = ~20-25 min. Tonic hindlimb extension latency = ~30 min. Phenidone (5 mg/kg): Myoclonic jerk latency = ~25 min. Generalized clonic convulsion latency = ~30 min. Tonic hindlimb extension latency = ~45 min. Phenidone (10 mg/kg): Myoclonic jerk latency = ~30 min. Generalized clonic convulsion latency = ~50 min. Tonic hindlimb extension latency = ~75 min. Phenidone (20 mg/kg): Myoclonic jerk latency = ~30 min. Generalized clonic convulsion latency = ~50 min. Tonic hindlimb extension latency = >120 min.	N/A	Behavioral seizure severity scale (0-3): KA (30 mg/kg): Myoclonic jerk score = 3; Generalized clonic convulsion score = 3; Tonic hindlimb extension score = 3. Phenidone (5 mg/kg): Myoclonic jerk score = 2; Generalized clonic convulsion score = 2; Tonic hindlimb extension score = 2. Phenidone (10 mg/kg): Myoclonic jerk score = 1; Generalized clonic convulsion score = 1; Tonic hindlimb extension score = 1. Phenidone (20 mg/kg): Myoclonic jerk score = 0; Generalized clonic convulsion score = 0; Tonic hindlimb extension score = 0.	—| KA-induced neurotoxicity; ↓ Mortality (dose-dependent); ↓ Behavioral seizure activity (dose-dependent); ↑ Latency; ↓ Severity scores; —| Neuronal damage (20 mg/kg); ↓ LPO; —| KA-induced GSH depletion and GSSG accumulation; ↓ Glutamate release; ↑ SOD and CAT activities; Phenidone provided superior protection (reducing mortality and neuronal damage) compared to Vitamin E, N-acetylcysteine (NAC), and Probucol.
Najbauer *et al.*, (2000)	Sprague-Dawley rat; n=5-7/group; male; 180-250g; N/A (adult).	N/A	Kainic acid; 12 mg/kg; i.p.; sd. *SE* aborted with diazepam (10 mg/kg, i.p.) 1.5-2 h later.	KA (12 mg/kg). KA (12 mg/kg) + Sodium Salicylate (SS) (500 mg/kg). Control (PBS). Control (SS 500 mg/kg).	Sodium Salicylate (SS): Aspirin metabolite; 500 mg/kg; i.p.; administered 1h before KA, and then every 12h for 40h (total 4 doses after KA).	Pre-induction (1h before KA) and Post-induction (every 12h for 40h after KA).	Seizure-like: Electrographic activity (EEG, focal spike, poly-spike discharges, continuous ictal activity, rhythmic epileptiform discharges); Behavioral seizures (wet dog shakes, motor arrest, falling). Cerebral damage: hemorrhage (visual inspection, score 0-3), H&E, cresyl violet, NeuN, TUNEL, Fluoro-Jade B), Blood-brain barrier (BBB) integrity (Evans blue extravasation).	*SE*.	Animals developed SE. Electrographic activity in KA-treated animals showed focal spike and poly-spike discharges followed by continuous ictal activity. Behavioral observations: wet dog shakes, motor arrest, and falling during *SE*.	*SE* was aborted 1.5-2 h after its onset with diazepam.	N/A	N/A	↔ Behavioral seizure activity; → Focal cerebral hemorrhage; ↑ Neuronal cell death; ↑ BBB damage.

Baik *et al.*, (1999)	ICR, mouse; n=6-15/group; male; 25-30g; N/A (adult).	N/A Decapitation.	Kainic acid; 50 mg/kg; i.p.; sd.	Control (Saline). Kainic acid (50 mg/kg). Kainic acid + NS-398 (10 mg/kg). Kainic acid + Celecoxib (10 mg/kg). Kainic acid + Indomethacin (5 mg/kg). Kainic acid + Aspirin (10 mg/kg).	NS-398: COX-2 selective inhibitor; 10 mg/kg; i.p.; sd; 15-30 min before KA. Celecoxib: COX-2 selective inhibitor; 10 mg/kg; i.p.; sd; 15-30 min before KA. Indomethacin: Non-selective inhibitor; 5 mg/kg; i.p.; sd; 15-30 min before KA. Aspirin: Non-selective inhibitor; 10 mg/kg; i.p.; sd; 15-30 min before KA.	Pre-induction.	Seizure-like: Behavioral seizure activity (endpoint: tonic-clonic convulsions). Onset time (min), mortality (%). Cerebral damage: TUNEL staining, Cresyl violet staining for viable neurons, cell counts in hippocampus CA1, CA3a, CA3b regions. Biochemical: ELISA (PGE2).	Tonic-clonic convulsions.	KA (50 mg/kg): Evoked seizure within 15 min and led to 29% mortality within 2h.	KA (50 mg/kg): 15 min. NS-398 (10 mg/kg) + KA: 6.5 min Celecoxib (10 mg/kg) + KA: 8.3 min Indomethacin (5 mg/kg) + KA: 12.5 min. Aspirin (10 mg/kg) + KA: 13.0 min.	N/A	N/A	NS-398, Celecoxib: ↓ Latency; ↑ Severity scores; ↑ Mortality (100%); ↑ Neuronal death; ↓ PGE2 levels. Indomethacin, Aspirin: ↑ Seizure activity; (less severe vs COX-2 selective inhibitors) Mortality of 43% and 33%.
Kábová *et al.*, (1999)	N/A rat; n=5-12/group; male; N/A; 12, 18, and 60-day-old (adult).	Halothane anesthesia (for EEG electrode implantation).	N-methyl-D-aspartate (NMDA); 15-200 mg/kg; i.p.; sd.	Age-Specific NMDA Sensitivity: 12-day-old rats; 18-day-old rats; 60-day-old (adult) rats. NMDA Seizure Profile: NMDA (various doses). Drug Treatment (18-day-old rats): Hydrocortisone (5, 10, 25 mg/kg); Pyridoxine (20, 50, 250 mg/kg); Sodium Valproate (VPA) (200, 400 mg/kg); Each drug alone vs. NMDA.	Hydrocortisone: Adrenocorticosteroid (glucocorticoid); 5, 10, 25 mg/kg; s.c.; sd; 30 min before NMDA.	Pre-induction.	Seizure-like: Behavioral seizures (automatisms, emprosthotonic (hyperflexion), clonic-tonic seizures); Latency to first symptom, latency to clonic-tonic seizure, latency to death; EEG changes (spikes, high-amplitude polyspikes, electrographic seizures, isoelectric line). Behavioral: Performance in horizontal bar, rotarod, open field.	Seizures (automatisms, emprosthotonic, clonic-tonic).	NMDA (age-specific): ED50 for clonic-tonic seizures: 12-day-old rats (19.3 mg/kg), 18-day-old rats (106.8 mg/kg), 60-day-old rats (178.6 mg/kg). Hydrocortisone (in 18-day-old rats, against 150 mg/kg NMDA): Hydrocortisone (25 mg/kg) resulted in 100% clonic-tonic seizures vs. ~80% NMDA control.	NMDA (age-specific): 12-day-old rats: Latency to first symptom ~10 min. Latency to clonic-tonic seizure ~15-20 min (with 50 mg/kg NMDA). 18-day-old rats: Latency to first symptom ~5 min. Latency to clonic-tonic seizure ~10-15 min (with 150 mg/kg NMDA). 60-day-old (adult) rats: Latency to first symptom ~5 min. Latency to clonic-tonic seizure ~10-15 min (with 200 mg/kg NMDA). Hydrocortisone (in 18-day-old rats, against 150 mg/kg NMDA): Hydrocortisone (25 mg/kg) caused a clonic-tonic latency of ~8 min versus ~13 min for the NMDA control.	N/A	N/A	↑ Incidence of emprosthotonic and clonic-tonic seizures; ↓ Latency to first symptom and clonic-tonic seizures; → Proconvulsant effect; ↓ Performance In horizontal bar and rotarod; ↑ Rearing and distance travelled; → Motor and neurotoxic effects.
Cook; Persinger (1996)	Rat; n=12 total; male; N/A; N/A.	N/A	Lithium/pilocarpine; 3 mEq/kg; single systemic injection; 4h later pilocarpine 30 mg/kg; sd; Chronically epileptic (induced ~30 days before experiment began).	Chronically epileptic rats (general control for magnetic field experiment). Chronically epileptic + Gabapentin (Neurontin). Chronically epileptic + Prednisolone. Chronically epileptic + No treatment. Chronically epileptic + Magnetic fields (over right hemisphere). Chronically epileptic + Magnetic fields (over left hemisphere). Chronically epileptic + Reference conditions (no magnetic field).	Prednisolone: Adrenocorticosteroid; 0.25 mg/cc; po (water supply); administered during radial maze training (chronic administration).	Post-induction.	Seizure-like: Overt stereotyped forelimb clonus (time required to display after pilocarpine injection). Behavioral: Radial maze (learning and memory, numbers of correct trials, time to complete trials); Conditioned taste aversion.	Chronic epilepsy (seizure-induced brain injury).	Yes. Overt stereotyped forelimb clonus was observed after pilocarpine injection.	Numbers of trials per day were positively correlated with the time required to display the overt stereotyped forelimb clonus after the single pilocarpine injection.	N/A	N/A	↔ Learning memory.
Baran *et al.*, (1994)	Sprague-Dawley rat; n=7-8/group (seizure scoring), n=3-4/group (histological); male; 180-200g; N/A (adult).	Chloral hydrate (360 mg/kg, i.p.) + Sodium pentobarbital (200 mg/kg, i.p.) for perfusion prior to histology.	Kainic acid; 10 mg/kg; s.c.; sd.	Control (Saline). Kainic acid (10 mg/kg). Kainic acid + BW755C (50 mg/kg). Kainic acid + BW755C (100 mg/kg).	BW755C: Dual cyclooxygenase/lipoxygenase inhibitor; 50 or 100 mg/kg; i.p.; administered 30 min before KA injection.	Pre-induction.	Seizure-like: Behavioral seizure activity (scoring scale: 0-5; where 0=no symptoms, 5=generalized tonic-clonic seizures), mortality. Cerebral damage: assessment of surviving pyramidal cells in hippocampus CA1-CA3.	Limbic seizures.	KA (10 mg/kg): All animals developed seizures within 1 h. KA (10 mg/kg): Mortality rate = 25-50% within 24h.	KA (10 mg/kg): ~15 min. BW755C (50 mg/kg) + KA: ~45 min. BW755C (100 mg/kg) + KA: ~75 min.	N/A	KA (10 mg/kg): 4-5. BW755C (50 mg/kg) + KA: ~2-3. BW755C (100 mg/kg) + KA: ~1-2.	↑ Latency to onset; ↓ Seizure severity (dose-dependent); → Protected against KA-induced mortality; —| Neuronal damage.
Minami *et al.*, (1991)	Rat; n=varied; male; N/A; N/A.	N/A	Kainic acid; 10 mg/kg; i.p.; single systemic administration. PTZ; 60 mg/kg; i.p.; single systemic administration.	KA (10 mg/kg). PTZ (60 mg/kg). KA + Diazepam (10 mg/kg). KA + Dexamethasone (10 mg/kg).	Dexamethasone: Glucocorticoid; 10 mg/kg; i.p.; sd; 30 min before KA.	Pre-induction.	Seizure-like: Convulsions (observed behaviorally). Biochemical: IL-1β and c-fos mRNA expression (Northern blot hybridization).	Seizures.	Yes.	N/A	N/A	N/A	↔ Convulsions; —| IL-1β mRNA expression; ↔ c-fos mRNA expression.
Wallenstein (1991)	Rat; n=5-6/group; N/A; N/A; adult.	N/A	PTZ; 25 mg/kg; i.p.; administered at intervals of 4 days for 20 sessions.	Control (no NSAID pretreatment). Acetaminophen (50, 100, 200 mg/kg). Mefenamic acid (20, 60 mg/kg). Ibuprofen (10, 30, 90 mg/kg).	Acetaminophen: non-opioid analgesic, antipyretic; 50, 100, 200 mg/kg; p.o.; administered over 20 sessions (intervals of 4 days for 20 sessions). Mefenamic acid: NSAID (COX inhibitor); 20, 60 mg/kg; p.o.; administered over 20 sessions. Ibuprofen: NSAID (COX inhibitor); 10, 30, 90 mg/kg; p.o.; administered over 20 sessions.	Pre-induction.	Seizure-like: Electrocortical (EEG) spike-wave activity; Clonic convulsions; Behavioral excitation (intensity, duration); EEG spike activity.	Kindling (excitation of CNS, intensification over sessions).	Yes. Control (no NSAID): CNS excitation intensified over 20 sessions. Periods of motor arrest (concurrent with electrocortical spike-wave activity) increased to clonic convulsions (concurrent with bursts of spike activity).	N/A	N/A	N/A	Acetaminophen (50, 100, 200 mg/kg): ↓ Seizure activity (dose-dependent). Mefenamic acid (20 mg/kg): —| PTZ-induced excitation. Mefenamic acid (60 mg/kg): → PTZ-induced excitation. Ibuprofen (10, 30 mg/kg): ↔ PTZ-induced excitation. Ibuprofen (90 mg/kg): ↓ PTZ-induced excitation.

Simmet; Tippler (1990)	Rat; n=5-6/group; N/A; 150-200g; N/A (adult).	N/A	Kainic acid; 10 mg/kg; i.p.; single systemic administration.	Control (Saline). Kainic acid (10 mg/kg). Kainic acid + Indomethacin (10 mg/kg). Kainic acid + Phenidone (10 mg/kg). Kainic acid + Flunarizine (10 mg/kg). Kainic acid + Brotizolam (10 mg/kg).	Indomethacin: Cyclooxygenase inhibitor; 10 mg/kg; i.p.; sd; 30 min before KA. Phenidone: Cyclooxygenase/Lipoxygenase inhibitor; 10 mg/kg; i.p.; sd; 30 min before KA.	Pre-induction.	Seizure-like: Behavioral changes (latency to first wet dog shakes, onset of generalized seizures, and death). Mortality. Biochemical: Cysteinyl-leukotriene (LT) (immunoreactive properties and HPLC profiling), Prostaglandin F2α (PGF2α) (HPLC profiling) in various brain regions (cortex, hippocampus, midbrain, hypothalamus).	Limbic seizures.	Yes. KA (10 mg/kg): Induced limbic seizures in all animals, progressing to generalized seizures and death. Mortality rate = 83-100%.	KA (10 mg/kg): Latency to first wet dog shakes ~15 min. Latency to generalized seizures ~30 min. Latency to death ~40 min. Indomethacin (10 mg/kg) + KA: Latency to first wet dog shakes ~5 min. Latency to generalized seizures ~15 min. Latency to death ~25 min. Phenidone (10 mg/kg) + KA: Latency to first wet dog shakes ~25 min. Latency to generalized seizures ~45 min. Latency to death ~75 min.	N/A	N/A	Indomethacin (10 mg/kg): ↓ Latency to first wet dog shakes, generalized seizures, and death; —| Formation of PGF2α; ↔ Cysteinyl-LT. Phenidone (10 mg/kg): ↑ Latency to first wet dog shakes, generalized seizures, and death; ↓ Mortality; ↔ Formation of PGF2α; —| Cysteinyl-LT.
Busija; Leffler (1989)	Piglet; n=5-7/group; N/A; newborn.	Halothane anesthesia.	Bicuculline; 1.0 mg/kg; i.v.; sd.	Bicuculline seizures (Control). Bicuculline seizures + Indomethacin (5 mg/kg). Hypothermic controls (to match Indomethacin group's baseline CBF).	Indomethacin: NSAID (Cyclooxygenase inhibitor); 5 mg/kg; i.v.; sd; 30 min before bicuculline.	Pre-induction.	Seizure-like: EEG (not explicitly detailed how analyzed for parameters, but seizures induced). Biochemical: Prostanoid levels (PGE2, 6-ketoprostaglandin F1α, PGF2α, thromboxane B2) in cortical periarachnoid cerebrospinal fluid (CSF) by radioimmunoassay. Physiological: Pial arteriolar diameter (μm), Cerebral blood flow (CBF) (ml·min^{-1}·100g^{-1}) by radioactive microspheres; Body temperature (°C).	Seizures.	Bicuculline administration resulted in seizures (confirmed by EEG).	N/A	N/A	N/A	—| PGE2, 6-ketoprostaglandin F1α, PGF2α, and thromboxane B2 increased levels; ↓ Cerebral blood flow; ↓ Pial arteriolar dilation; → Hypothermia (to 35º C).
Ikonomidou-Turski *et al.*. (1988)	Rat; n=8-15/group; male; N/A; N/A.	N/A	Pilocarpine (200 mg/kg); i.p.; single systemic administration (non-convulsant dose). Pilocarpine (320 mg/kg); i.p.; single systemic administration (convulsant dose).	Control (Pilocarpine alone). Sodium Salicylate (SS) (50-400 mg/kg) + Pilocarpine (200 mg/kg). Phenylbutazone (25-100 mg/kg) + Pilocarpine (200 mg/kg). Indomethacin (1-100 mg/kg) + Pilocarpine (320 mg/kg). Ibuprofen (10-100 mg/kg) + Pilocarpine (320 mg/kg). Mefenamic acid (10-100 mg/kg) + Pilocarpine (320 mg/kg).	Sodium Salicylate (SS): NSAID; 50, 100, 200, 400 mg/kg; i.p.; sd; 30 min before pilocarpine. Phenylbutazone: NSAID; 25, 50, 100 mg/kg; i.p.; sd; 30 min before pilocarpine. Indomethacin: NSAID (COX inhibitor); 1, 3, 10, 30, 100 mg/kg; i.p.; sd; 30 min before pilocarpine. Ibuprofen: NSAID (COX inhibitor); 10, 30, 100 mg/kg; i.p.; sd; 30 min before pilocarpine. Mefenamic acid: NSAID (COX inhibitor); 10, 30, 100 mg/kg; i.p.; sd; 30 min before pilocarpine.	Pre-induction.	Seizure-like: Onset time (min), duration (min), incidence (%) of clonic-tonic seizures (grade 3, 4, or 5). Mortality (%). Cerebral damage: visual assessment of affected brain areas.	Seizures and *SE*.	Pilocarpine (200 mg/kg) alone: No clonic-tonic seizures or mortality (0% incidence). Pilocarpine (320 mg/kg) alone: 100% incidence of clonic-tonic seizures; 100% incidence of SE. Sodium Salicylate (SS) (50, 100, 200, 400 mg/kg) + Pilocarpine (200 mg/kg): Caused clonic-tonic seizures (ED50 = 103 mg/kg). Phenylbutazone (25, 50, 100 mg/kg) + Pilocarpine (200 mg/kg): Caused clonic-tonic seizures (ED50 = 59 mg/kg). Indomethacin (1-100 mg/kg) + Pilocarpine (320 mg/kg): Indomethacin (1-3 mg/kg): No effect on incidence of clonic-tonic seizures (100% incidence). Indomethacin (10-100 mg/kg): Reduced incidence of clonic-tonic seizures (e.g., 30 mg/kg: 60% incidence). Ibuprofen (10-100 mg/kg) + Pilocarpine (320 mg/kg): Ibuprofen (10 mg/kg): No effect on incidence (100%). Ibuprofen (30-100 mg/kg): Reduced incidence of clonic-tonic seizures (e.g., 100 mg/kg: 40% incidence). Mefenamic acid (10-100 mg/kg) + Pilocarpine (320 mg/kg): Mefenamic acid (10-30 mg/kg): No effect on incidence (100%). Mefenamic acid (100 mg/kg): Reduced incidence of clonic-tonic seizures (20% incidence).	See “Anti-inflammatory effects” section.	N/A	N/A	Indomethacin: ↔ Latency to clonic-tonic seizures (1-3 mg/kg); ↑ Latency to clonic-tonic seizures (10-100 mg/kg); ↓ Seizure incidence; ↓ Neuronal damage. Ibuprofen: ↔ Latency to clonic-tonic seizures (10 mg/kg); ↑ Latency to clonic-tonic seizures (30-100 mg/kg); ↓ Seizure incidence; ↓ Neuronal damage. Mefenamic acid: ↔ Latency to clonic-tonic seizures (10-30 mg/kg); ↑ Latency to clonic-tonic seizures (100 mg/kg); ↓ Seizure incidence. Sodium Salicylate (50-400 mg/kg) and Phenylbutazone (25-100 mg/kg): Converted a non-convulsant dose of pilocarpine into a convulsant one (proconvulsant effect). Induced neuronal damage.

Sztriha *et al.*, (1986)	Sprague-Dawley, rat; n=6-7/group; male; 180-200g; N/A (adult).	N/A	Kainic acid; 10 mg/kg; i.p.; single systemic administration.	Control (Saline). Kainic acid (10 mg/kg). Kainic acid + Dexamethasone (5 mg/kg).	Dexamethasone: Synthetic glucocorticoid; 5 mg/kg; i.p.; sd; 2h before KA.	Pre-induction.	Seizure-like: Behavioral seizures (observed, not explicitly quantified). Cerebral damage: Histopathological alterations (hippocampus, piriform cortex, thalamus, visual assessment); BBB damage (Evans blue extravasation). Biochemical: Water content (gravimetry), Sodium content (flame photometry), Potassium content (flame photometry).	Seizures.	KA (10 mg/kg): Led to the development of seizures, often progressing to *SE*.	N/A	N/A	N/A	↔ Development of seizures; ↓ Vasogenic edema; ↔ Cytotoxic edema; ↓ BBB damage; ↓ Neuronal damage (thalamus).
McGinley *et al.*, (1985)	Albino Swiss Webster mice; n=10/group; female; 25-30g; N/A.	N/A Decapitation.	PTZ; 100 mg/kg; i.p.; N/A.	Control. OKY-1581 (20 mg/kg). UK 38,485 (50 mg/kg). Indomethacin (10 mg/kg).	OKY-1581: Thromboxane synthetase inhibitor; 20 mg/kg; i.p.; administered 30 min before PTZ infusion. UK 38,485: Thromboxane synthetase inhibitor; 50 mg/kg; i.p.; administered 30 min before PTZ infusion. Indomethacin: Cyclooxygenase inhibitor; 10 mg/kg; i.p.; administered 30 min before PTZ infusion.	Pre-induction.	Seizure-like: Tonic seizure threshold (mg/kg). Biochemical: Thromboxane B2 (TxB2), PGE2, PGF2α, 6-keto-PGF1α production in brain (measured after 2 min of convulsive activity by radioimmunoassay).	Tonic seizures.	Yes. Tonic Seizure Threshold (mg/kg): Control: 78 ± 2.6 mg/kg. OKY-1581 (20 mg/kg): 77 ± 3.4 mg/kg. UK 38,485 (50 mg/kg): 79 ± 4.3 mg/kg. Indomethacin (10 mg/kg): 62 ± 3.7 mg/kg.	N/A	N/A	N/A	OKY-1581 (20 mg/kg) and UK 38,485 (50 mg/kg): ↔ Tonic seizure threshold; ↓ TxB2 production (>90%); ↔ PGE2, PGF2α, or 6-keto-PGF1α. Indomethacin (10 mg/kg): ↓ Tonic seizure threshold; —| TxB2 and prostaglandin production.
Förstermann *et al.*, (1982)	Mice; n=N/A; male; 25-30g; age N/A.	N/A	PTZ; 120 mg/kg; i.p.; single systemic administration.	Control (Saline). PTZ (120 mg/kg). PTZ (120 mg/kg) + Indomethacin (10 mg/kg). PTZ (120 mg/kg) + Indomethacin (20 mg/kg).	Indomethacin: Non-steroidal anti-inflammatory drug (prostaglandin synthesis inhibitor); 10 or 20 mg/kg; i.p.; sd; 30 min before PTZ.	Pre-induction.	Seizure-like: Tonic convulsions (occurrence, latency); Mortality. Biochemical: Prostanoid levels (PGD2, PGF2α, PGE2, TxB2, 6-keto-PGF1α) in whole brain homogenates by radioimmunoassay.	Tonic convulsions.	Control (Saline): No tonic convulsions. PTZ (120 mg/kg): 100% of animals showed tonic convulsions. PTZ (120 mg/kg) + Indomethacin (10 mg/kg): 100% of animals showed tonic convulsions. PTZ (120 mg/kg) + Indomethacin (20 mg/kg): 100% of animals showed tonic convulsions.	PTZ (120 mg/kg): 18.0 ± 0.6 min. PTZ (120 mg/kg) + Indomethacin (10 mg/kg): 13.1 ± 1.0 min. PTZ (120 mg/kg) + Indomethacin (20 mg/kg): 10.3 ± 0.9 min.	N/A	N/A	↓ Latency to tonic convulsions; ↔ Mortality induced by PTZ; —| Increase in brain prostanoids (10 mg/kg).
Steinhauer; Hertting (1981)	Mice; n=10; male; 27-30g; age N/A.	N/A Decapitation.	PTZ; 100 mg/kg (10 mL/kg); i.p.; single systemic administration.	Control (PTZ alone). Acetaminophen (30 mg/kg). Aspirin (100 mg/kg) Indomethacin (10 mg/kg). Flurbiprofen (10 mg/kg). Diclofenac (10 mg/kg). Ibuprofen (50 mg/kg).	Acetaminophen: non-opioid analgesic, antipyretic; 30 mg/kg; i.m.; sd; N/A. Aspirin: NSAID (prostaglandin synthetase inhibitor); 100 mg/kg; i.m.; sd; 2h before PTZ. Indomethacin: NSAID (prostaglandin synthetase inhibitor); 10 mg/kg; i.m.; sd; 2h before PTZ. Flurbiprofen: NSAID (prostaglandin synthetase inhibitor); 10 mg/kg; i.m.; sd; 2h before PTZ. Diclofenac: NSAID (prostaglandin synthetase inhibitor); 10 mg/kg; i.m.; sd; 2h before PTZ. Ibuprofen: NSAID (prostaglandin synthetase inhibitor); 50 mg/kg; i.m.; sd; 2h before PTZ.	Pre-induction.	Seizure-like: Tonic seizure onset time (min); ED50 (mg/kg) of PTZ (for tonic seizures). Biochemical: PGF2α, PGE2, TxB2 in mouse brain (measured by radioimmunoassay).	Tonic seizures.	Yes. All animals in PTZ control and NSAID+PTZ groups developed tonic seizures.	Control (PTZ alone): 243 ± 19s Acetaminophen (30 mg/kg): 255 ± 27s Aspirin (100 mg/kg): 241 ± 23s Indomethacin (10 mg/kg).: 174 ± 20s Flurbiprofen (10 mg/kg): 180 ± 12s Diclofenac (10 mg/kg): 155 ± 15s Ibuprofen (50 mg/kg): 219 ± 31s.	N/A	N/A	Indomethacin (10 mg/kg), Flurbiprofen (10 mg/kg), and Diclofenac (10 mg/kg): —| Convulsion-induced rise of PG and TxB2 levels; ↓ Latency to onset of tonic seizures; ↓ LD50 of PTZ. Ibuprofen (10 mg/kg): —| Convulsion-induced rise of PGF22α, PGE2, and TxB2; ↔ Latency to onset of tonic seizures; ↓ LD50 of PTZ. Acetaminophen (30 mg/kg) and Aspirin (100 mg/kg): ↔ PGs and TxB2 levels; ↔ Latency to onset of tonic seizures.

The sex of the animals used was computed as: males; females; not applicable (N/A) for larvae and unclear when the sex of the animals was not reported; -, was used to address missing information in the articles. The main findings were described as: ↑, higher; ↓, lower; Abbreviations: BBB: Blood-Brain Barrier; *BDNF*: Brain-Derived Neurotrophic Factor; C-FOS: Cellular FOS; Caspase-1: Casteine-dependent aspartate-directed protease-1; CAT: Catalase; COX-1: Cyclooxygenase-1; COX-2: Cyclooxygenase-2; DMSO: Dimethyl Sulfoxide; FACS: Fluorescence-Activated Cell Sorting; GABA: Gamma-Aminobutyric Acid; $GABA_A$: Gamma-Aminobutyric Acid type A receptor; GFAP: Glial Fibrillary Acidic Protein; GPx: Glutathione Peroxidase; GS: Glutamine Synthetase; GSH: Glutathione; GSSG: Glutathione Sulfhydryl Sulfhydryl Glutathione; Hmox1: Heme oxygenase 1; HMGB1: High Mobility Group Box 1; HPLC: High-Performance Liquid Chromatography; HSP70: Heat Shock Protein 70; IFN-γ: Interferon-gamma; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-18: Interleukin-18; Kir 4.1: K inward rectifier 4.1 (a type of potassium channel); LOX-5: Lipoxygenase-5; LPO: Lipid Peroxidation; LXA4: Lipoxin A4; MDA: Malondialdehyde; MPO: Myeloperoxidase; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; Nrf2: Nuclear factor erythroid 2-related factor 2; NLRP3: NLR family Pyrun domain containing 3; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PGE2: Prostaglandin E2; PGF2α: Prostaglandin F2 alpha; PGI2: Prostaglandin I2; PTZ: Pentylenetetrazol; QP-4: Aquaporin-4; qPCR: Quantitative Polymerase Chain Reaction; S100B: S100 Calcium-Binding Protein B; SOD: Superoxide Dismutase; TBARS: Thiobarbituric Acid Reactive Substances; TGF-β2: Transforming Growth Factor-beta 2; TNF-α: Tumor Necrosis Factor-alpha.

3.3.2 Anesthetic

Just over half of the studies used some anesthetic (n = 55; 57.3%), however, 02 of them (2.1%) did not specify which one. Also, 16 (16.7%) of them used more than one anesthetic. Decapitation was present in 13 (13.5%) studies, with or without the use of some adjunct substance. Three anesthetics (xylazine, isoflurane, and chloral hydrate) showed the same incidence in the studies, each corresponding to 10.4% (n = 10) of all studies. Next, ketamine appeared in fourth place (n = 9; 9.4%) corresponding to 16.4% of studies with anesthetic use, being the first record of use in a study from the year 2011. Others appeared few times, such as equithesin, enflurane, ether, and urethane.

3.3.3 Drug induction/model

The majority of studies used Pentylenetetrazol (PTZ) (n = 46, 47.91%) as a seizure-inducing drug, primarily as the sole inducer (Figure 3). It was followed by Pilocarpine (n = 26; 27.1%), kainic acid (n = 18; 18.75%), lithium (n = 10; 10.42%), and Penicillin (n = 5; 5.2%). Additionally, among the drugs utilized (either as crisis inducers or solely during induction) were Methylscopolamine (n = 4; 4.17%), Scopolamine methyl bromide (n = 3; 3.12%), lipopolysaccharide (LPS) (n = 3; 3.12%), Flurothyl (n = 2; 2.08%), and N-methyl-D-aspartate (NMDA) (n = 2; 2.08%). Furthermore, other drugs were registered on a smaller scale, such as bicuculine (n = 1; 1.04%), 4-Aminopyridine (n = 1; 1.04%), Picrotoxin (n = 1; 1.04%), Strychnine (n = 1; 1.04%), terbutaline hemisulfate salt (n = 1; 1.04%) and atropine methyl nitrate (n = 1; 1.04%). It is worth noting that 73 studies (76.04%) used only one inducing drug. The other 23 (23.95%) used drugs in association or more than one drug was evaluated in the same study (Figure 4).

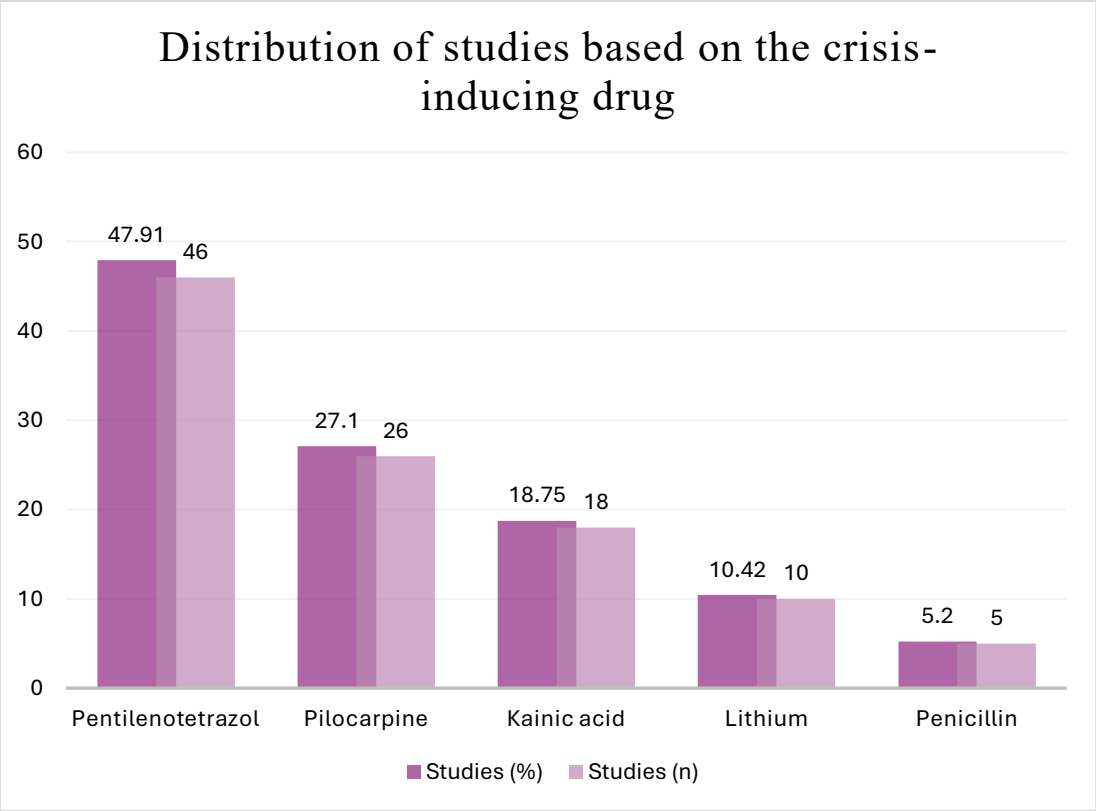


Figure 3: Distribution of studies based on the main drugs used for crisis induction (alone or in combination), in percentage (%) and absolute number (n).

The main route of drug administration was intraperitoneal (I.P.), such that 82.3% (n = 79) of the studies have at least one inducing drug with this administration present. I.P. and 17 (17.7%) without any induction via I.P., with induction routes being subcutaneous, intraventricular, inhalational, intravenous, and via immersion.

Regarding PTZ, administration was mainly via intraperitoneal (n = 39; 40.6%), in addition to intravenous (n = 3; 3.12%), subcutaneous (n = 2; 2.08%), intraventricular (n = 1; 1.04%), immersion (n = 1; 1.04%). For zebrafish, the administration routes were incubation, immersion, and intra-peritoneal, all corresponding to 1.04% (n = 1) of all studies and 33.33% of studies with *Danio rerio*. As expected, there was variation in dose and exposure time between studies and most drugs as per Table 2.

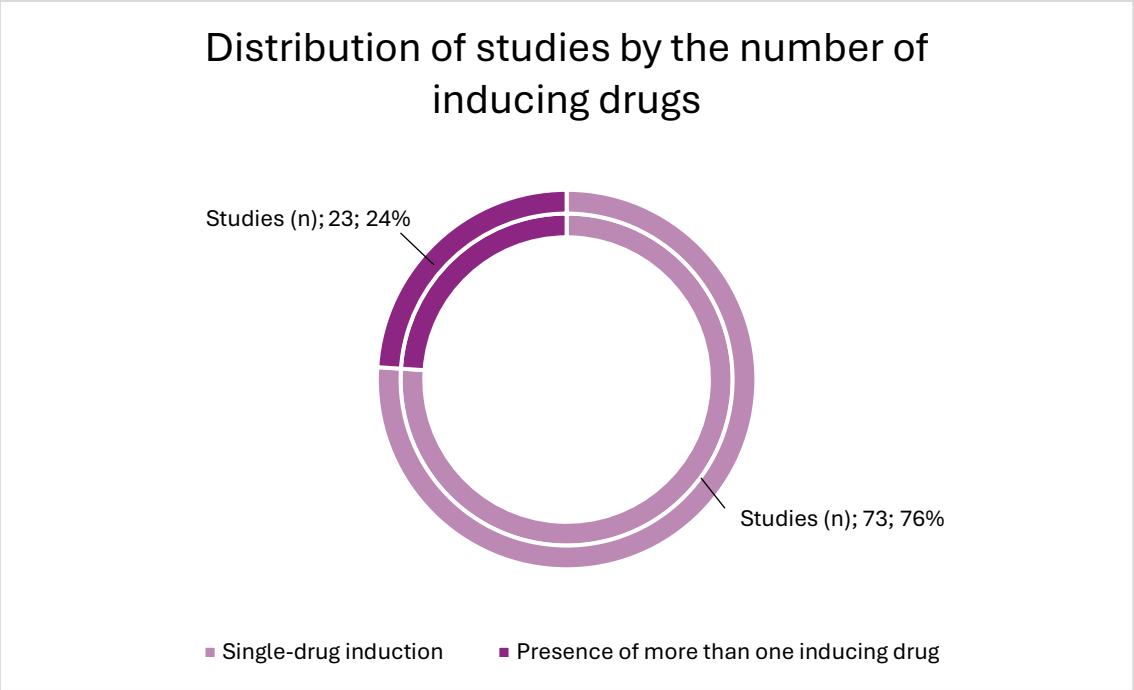


Figure 4: Distribution of included studies according to single-drug induction versus the presence of more than one drug in induction, in percentage and absolute number.

3.3.4 Groups

All studies had at least two groups including a crisis induction control (or more than one) and another anti-inflammatory treatment. Only 01 (1.04%) article with two groups, 13 (13.54%) with three groups, and 82 (85.42%) with at least four groups, including positive and negative control. 01 (1.04%) study with 15 groups and 04 (4.17%) articles with more than 10 groups in the study were identified.

3.3.5 Evaluated parameters

Convulsive behavior was determined by observational and quantitative parameters that helped evaluate and characterize the intensity/severity, occurrence, latency, and frequency of seizure-like crises. These parameters can be divided into behavioral scales, quantitative data, and complementary tests. All evaluated parameters can be visualized in Table 2.

Behavioral scales were used in 81 articles (84.4%), including the traditional or modified Racine scale, variants adapted for fish (e.g., in *Danio rerio*), or modifications

for specific *SE* models. Following this, 52 articles (52.4%) employed other forms of recording such as electroencephalogram (EEG) or electrocorticography (ECoG), video monitoring, electrophysiological spike recording, quantification of epileptiform activity, and observation with a stopwatch or continuous filming. Finally, complementary behavioral tests were utilized in 24 studies (25%), including Open Field, Elevated Plus Maze, T-maze or Y-maze, object recognition test, light/dark test (scototaxis – in fish), and forced swim.

Biochemical parameters such as inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-10), oxidative stress markers (MDA, GSH, SOD, CAT, LPO, 8-isoprostane), neurotransmitters/metabolites (GABA, NO, glutamate, COX-2, NSE, HMGB1), prostaglandins (PGE2, PGF2α, PGI2, TXB2), and gene/protein expression parameters (Caspase-3, Bax, Bcl2, GSK-3β, β-catenina, Dvl) were evaluated to varying degrees in most studies (n=74; 77.1%). Histopathological parameters were assessed in 43 studies (44.8%), for example, to evaluate neurodegeneration and neurogenesis. Various other parameters were also evaluated, varying across studies (Figure 5).

As examples of inflammatory cytokines evaluated in both brain tissue and systemically, we have TNF-α, IL-1β, IL-6, IL-10, and IFN-γ. Among the antioxidant enzymes are SOD, GPx, and Catalase. Other biochemical parameters include oxidative stress markers (MDA, 8-isoprostane), prostaglandins (PGE2, PGF2α, PGI2, TXB2), neuronal markers (NSE (neuron-specific enolase), *BDNF*), glial inflammation markers (COX-2, GFAP, IBA-1, S100B), among others like GABA, Glutamate, GSH, NO, and LC3 (autophagy).

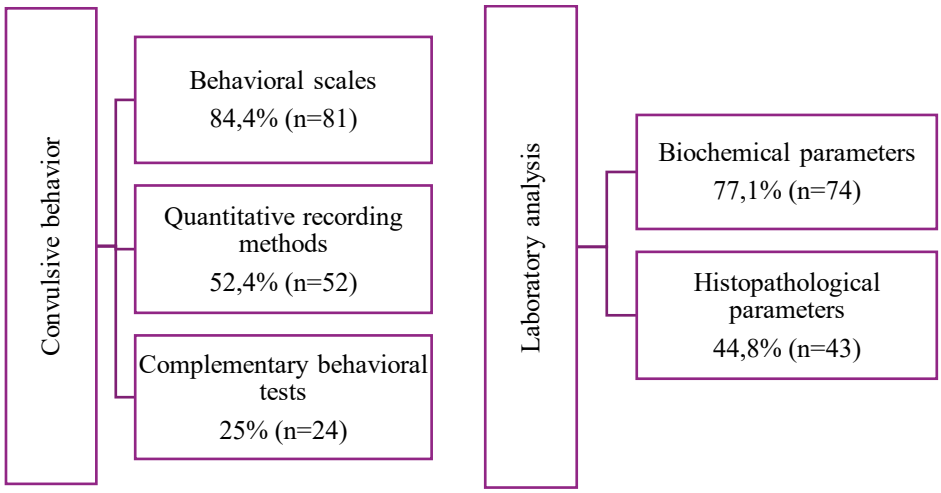


Figure 5: Representation of parameter types evaluated in percentage and absolute number, considering all studies included in the systematic review (n=96).

3.3.6 Anti-inflammatory drug

Of the anti-inflammatory drugs studied, only 21 studies (27.83%) include the class of steroidal anti-inflammatory drugs (SAIDs) (Figure 6). Among them, dexamethasone was the most prevalent, with 16 studies evidencing its use (76.19% of the SAIDs found), followed by 03 (14.29%) with prednisolone, 01 betamethasone (4.76% of studies with SAIDs) and 01 with hydrocortisone (4.76%) (Table 3). There are 78 (81.25%) articles that include non-steroidal anti-inflammatory drugs (NSAIDs) as well as drugs with action on COX under study. Highlighting that more than one anti-inflammatory drug may be present in the same study. These are described below, with the description of the quantity in relation to all studies and percentage in relation to studies with NSAIDs and drugs under investigation: indometacin (n = 16, 20.51%) and celecoxib (n = 16; 20.51%) in first place, followed by aspirin (n = 11; 14.10%), rofecoxib (n = 9; 11.54%), ibuprofen (n = 07; 8.97%), acetaminophen (n = 4, 5.13%), diclofenac (n = 4, 5.13%), nimesulide (n = 4, 5.13%), ketoprofen and its analog dexketoprofen (n = 4, 5.13%), etoricoxib (n = 3; 3.85%), NS-398 (n = 3; 3.85%), Sodium Salicylate (n = 2; 2.56%), piroxicam (n = 2; 2.56%) and SC-58236 (n = 2; 2.56%) (Table 4). Others appear in minority, with one study reported each. Thus, each corresponds to 1.28% of the 78 studies, these being BW755C, sulindac, pyrazole benzenesulfonamide derivative (T1), flufenamic acid, oxaprozin, meloxicam, aceclofenac, tenidap, naproxen, parecoxib, nixib, phenidone. In relation to the anti-inflammatory drugs present in studies with the species *Danio rerio* (3.13% of studies), the pyrazole benzenesulfonamide derivative (T1), indomethacin and ibuprofen were evidenced.

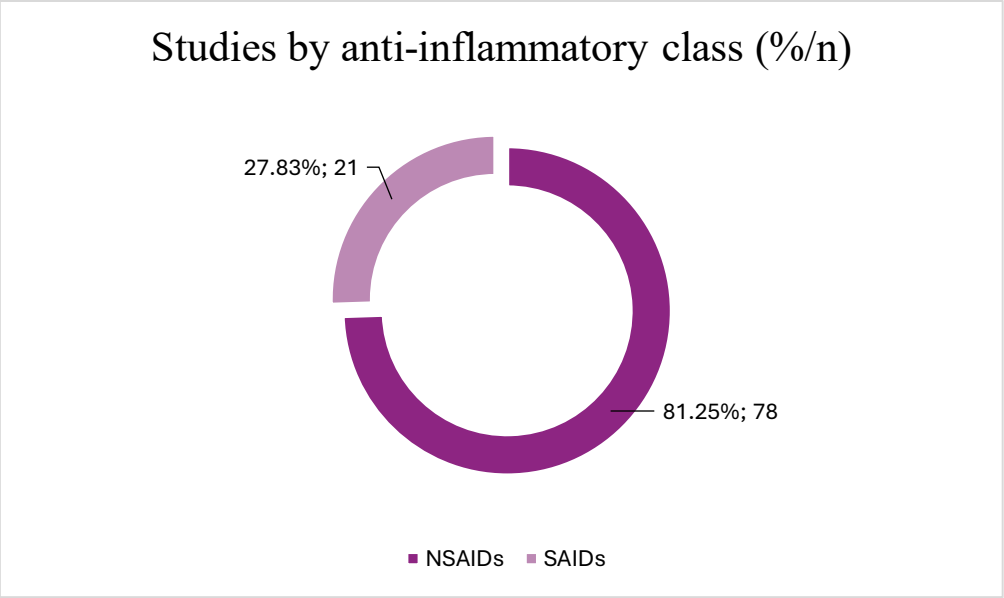


Figure 6: Distribution of studies included in the systematic review by anti-inflammatory class, presented as percentages (%) and absolute numbers (n). A single study may encompass multiple anti-inflammatory agents.

Regarding the period of anti-inflammatory drug administration, over 80% of the studies encompassed the pre-induction period (n = 81, 84.38%). Thus, only 15 (15.62%) had seizure-inducing drug administration in the post-induction period and 05 (5.21%) with evaluation of administration in both periods. Furthermore, 81 (84.38%) had occurrence of each seizure stage with varied crisis type among the studies (Figure 7).

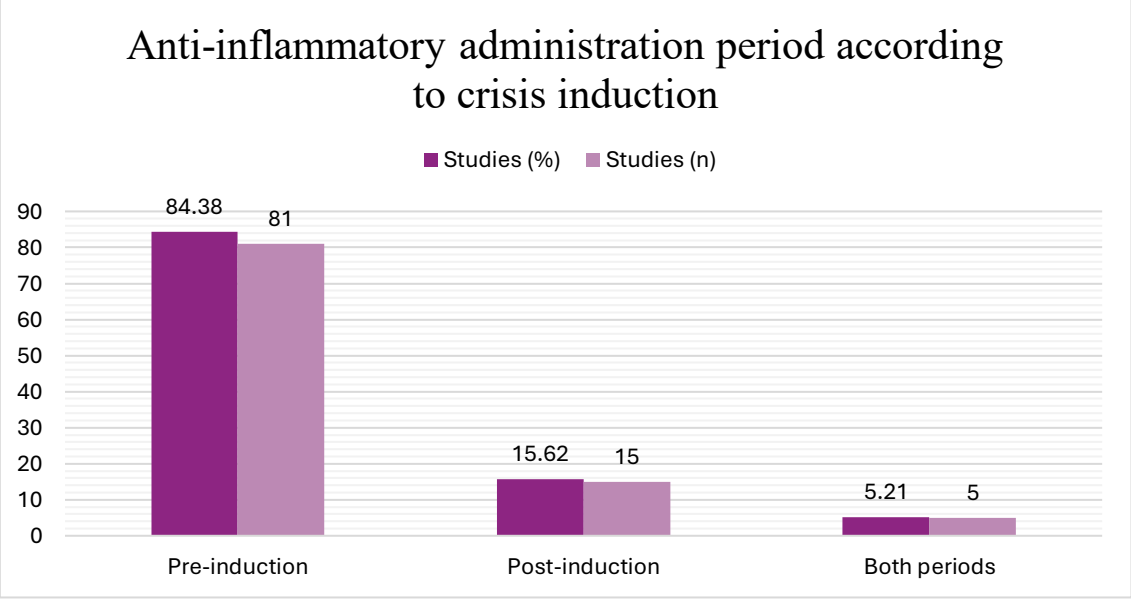


Figure 7: Distribution of included studies in the systematic review by anti-inflammatory Administration period, in percentage (%) and absolute number (n).

Table 3: Distribution of included studies in the review according to the steroidal anti-inflammatory drug (SAID) investigated, by absolute number (n) and percentage (%).

SAID	Studies (n)	Studies (%)
Dexamethasone	16	76,19
Prednisolone	03	14,29
Betamethasone	01	4,76
Hydrocortisone	01	4,76
Total	**21**	**100**

Table 4: Table 4: Distribution of Included Studies in the Review by NSAID studied, as well as Synthetic/Investigational COX Inhibitor Drugs, in Absolute Number (n) and Percentage (%). *Drug found in a *Danio rerio* study.

NSAID	Studies (n)	Studies (%)
Celecoxib	16	20,51
Indomethacin *	16	20,51
Aspirin	11	14,10
Rofecoxib	09	11,54
Ibuprofen *	07	08,97
Diclofenac	04	05,13
Acetaminophen	04	05,13
Nimesulide	04	05,13
Ketoprofen/dexketoprofen	04	05,13
Etoricoxib	03	03,84
NS-398	03	03,84
Piroxicam	02	02,56

Sodium salicylate	02	02,56
SC-58236	02	02,56
BW755C	01	1,28
Sulindac	01	1,28
Benzenesulfonamide pyrazole *	01	1,28
Flufenamic acid	01	1,28
Oxaprozin	01	1,28
Meloxicam	01	1,28
Aceclofenac	01	1,28
Tenidap	01	1,28
Naproxen	01	1,28
Parecoxib	01	1,28
Nixib	01	1,28
Phenidone	01	1,28
Total	**78**	**100**

3.3.6.1 Steroidal anti-inflammatory drugs

Regarding Dexamethasone (n = 16; 76.19%), all studies were in mammals, with the majority having administration via I.P. (n = 13; 81.25%), followed by 03 (18.75%) via subcutaneous injection (S.C.). The minimum dose administered among the studies was 0.5mg/kg (for 10 days via S.C.) and the maximum dose was 10mg/kg via I.P. single dose. As effects, considering treatment with 0.5mg/kg SC for 10 days, there was modulation of more genes less specific to the central nervous system (CNS) (in comparison to the ACTH drug). At a slightly higher dose (1mg/kg) administered in the post-induction period via I.P. for 06 days, there was a reduction in microglial activation and cell death, but with an increase in the mortality rate, while maintaining the latency time. In studies with dexamethasone at 10mg/kg via I.P. single dose, a positive effect observed was an increase in latency time and an increase in F-actin (related to synaptic plasticity and an essential component of the cytoskeleton) in the CA1 and CA3 regions, inducing synaptic remodeling after *SE*. With a lower dose of 2.25mg/kg, it maintained the amplitude of the EEG tracing and reduced inflammatory markers such as IL-1β, IL-6 (brain) and PGE2 (serum and brain).

Of the three studies encompassing prednisolone, 02 (66.66% of studies with prednisolone) had convulsive crisis induction via I.P. and one via oral (33.33%). Effects with 1 and 5mg/kg I.P. for 14 days, starting in pre-induction (30min before PTZ), increased the latency time of the crises, with an increase in TNF-α levels at lower doses, and the same levels maintained with the 5mg/kg dose (similar to diazepam). Both doses increased IL-1β. In a similar study with the same dose, induction, and route of administration, there was no effect on the number of crossings, grooming, and fecal pellets, with an increase in crossing with prednisone at the 5mg/kg dose, in addition to a reduction in inflammatory markers IL-6, IL-1β, and TNF-α (Hippocampus) and an increase in IL-6 and TNF-α in serum. The experiment performed orally was post-induction, via water supply with prednisolone concentration at 0.25 mg/cc chronically and without specification of time or effect on learning memory. Thus, it may not have had effectiveness due to the mode of administration, and we also do not know the duration of the experiment. It is noted that some effects vary with the same anti-inflammatory dose in different studies. The primary effects observed in studies utilizing steroidal anti-inflammatory drugs are presented in Table 5. Supplementary data, as well

as information on other anti-inflammatory drugs, can be found in Table 2, presented previously.

Table 5: Primary effects observed in studies included in this systematic review, grouped by steroidal anti-inflammatory drug.

SAID	Positive effects	Negative effects or no effect
Dexamethasone	↓ incidence ↓ intensity of seizures; (especially 10mg/kg) ↑ latency; ↓ IL-1β, IL-6 (brain) and PGE2 (serum and brain); Modulation of more genes; ↓ microglial activation ↓ cell death. (1mg/kg IP post-KA induction)	Less specific central nervous system (CNS) genes; (0.5 mg/kg SC pre-induction) (Brabec, 2023) ↑ mortality rate. (1mg/kg IP post-KA induction) (Fox, 2020)
	Status epilepticus (*SE*): ↑ latenty; ↑ F-actin in CA1 and CA3 regions, inducing synaptic remodeling after *SE*; ↓ neuroinflammation ↓ brain damage.	↔ seizure behavior; (0,6 mg/kg P single post-induction dose) (Ribeiro, 2024) ↔ *SE* severity or latency; ↑ mortality rate. (2, 10mg/kg IP post-pilocarpine + lithium induction) (Duffy, 2014)
Prednisolone	↑ seizure latency; (1, 5mg/kg IP) ↓ IL-6, IL-1β e TNF-α (hippocampus). (5mg/kg IP)	↑ TNF-α levels; (1, 5 mg/kg IP) (similar to diazepam) ↑ IL-1β; ↑ IL-6 and TNF-α (in serum); (5mg/kg IP) ↔ learning memory (0.25 mg/ml PO post-PILO + Li induction) (Cook; Persinger, 1996)
Betamethasone	↑ Latency time; ↓ Seizure scores, especially at 0.250 mg/kg, progressively; ↓TNF-α and IL-1β.	→ Open field test. (Guzzo, 2023)

Hydrocortisone	No positive effects identified in this study excerpt.	↓ latency; Pro-convulsant effect (converted a non-convulsant dose of NMDA into a convulsant one). (5, 10, 25mg/kg SC pre-NMDA induction) (Kábová *et al.*,1999)

3.3.6.2 Non-steroidal anti-inflammatory drugs

3.3.6.2.1 Non-selective COX-2 inhibitors

Only one study presented Sulindac, with a minimum dose of 20mg/kg and a maximum of 40mg/kg via I.P. with a duration of 21 days. The latency to the onset of spontaneous seizures was less than 7 days in all *SE* groups. The frequency in each seizure stage was ~4.5, similar with both doses in the study (drug at 20mg/kg and 40mg/kg) and the control being ~0 (saline solution). Regarding the convulsive behavioral score, both doses had a similar effect in the first week and in the eighth week, scoring Racine at ~3.6 (saline group ~0.5) in the first week (sulindac 20mg/kg) and ~2.5 in the eighth week (saline group ~0) with sulindac at 40mg/kg. The observed effects when co-administered with valproic acid (VPA) (sulindac 20 mg/kg) were a reduction in the score and frequency of seizure-like crises compared to the *SE* group, in addition to the induction of Bax (apoptosis regulator) and caspase (sulindac 20-40 mg/kg). When treated alone with sulindac, a reduction in Dvl and β-catenin expression was observed with an increase in GSK-3β expression.

The Racine scale (Racine, 1972), for example, is widely used to assess the intensity of seizure-like crises. The anti-inflammatory drug with the best action on seizure-like behavior, as evaluated by the Racine scale, was aspirin in studies (Kandeda, 2021), with a Racine score of ~0.25 (positive control ~1.0; negative control ~0.95) in the NSAID treatment group. The study was conducted with 64 male Mus musculus Swiss mice, aged between 25–40 days and weighing 18 ± 11g. The induction model was status epilepticus with kainic acid (KA) + PTZ (KA 15 mg/kg I.P. + PTZ 40 mg/kg I.P.), and the anti-inflammatory drug was administered post-induction at 20 mg/kg orally (P.O.), daily, for 14 days. The study (Zhu, 2017) also had a significant effect on

convulsive behavior, with a lower absolute value of mean frequency of spontaneous seizures at 0.48 (PILO 2.1 ± 1.48) using aspirin as an intervention at a higher dose with the same route of administration (60 mg/kg O.P.) for 10 weeks in a chronic epilepsy model induced by pilocarpine (PILO) (PILO 300 mg/kg I.P.) using 56 female Swiss mice, approximately 02 months old and weighing 25 – 30 g. Among other parameters, tonic-clonic seizures (stages 4 and 5 of the modified Racine scale) were evaluated. The reduction was similar with the 80mg/kg dose.

The only study with pyrazole benzenesulfonamide derivative (T1), conducted in *Danio rerio* with a minimum dose of 50 and maximum of 150 μM via I.P. for 24h (in pre-induction with PTZ). An increase in survival rates and heart rate was observed, in addition to a reduction in apoptosis and ROS. There was also a reduction in the percentage of macrophages located in the larva pre-treated with the anti-inflammatory. Thus, an increase in BDNF, reduction in COX-2, TNF-α, and IL-1β, as well as a reduction in tissue abnormalities with inhibition of neuronal degeneration at doses of 150μM, were evidenced. Additionally, circular, coiling, and convulsive behaviors were significantly reduced, with increased GABA (at the maximum dose).

Diclofenac was featured in 04 studies with PTZ I.P. induction. The only one with intracerebroventricular (I.C.V.) induction by penicillin was also the only study with post-induction administration. The minimum administered dose was 1mg/kg S.C. single dose and the maximum treatment time was 15 days (at varied doses). The Latency of each stage varied between 93.6 s (Diclofenac 25 mg/kg) and 231.7 s (Diclofenac 75 mg/kg). In this study, the exact value of the saline control was not described. Regarding the frequency of each seizure-like crisis stage, the percentage of spike waves (epileptiform activity) varied from 37.8% (Diclofenac 75 mg/kg) to 64.1% (Diclofenac 25 mg/kg) (saline control had 76.8%). The average frequency of the groups (in the 30 – 120 min interval) showed 138.9 peaks per interval in the potassium diclofenac group with 110.2 peaks per interval when associated with Diazepam (penicillin control of 185.5 peaks per interval). The group treated only with Diazepam had the best results, with 102.6 peaks per interval. Thus, no significant difference was seen between the diclofenac group and the Diazepam group. Regarding the effect on the Racine scale (RCS), there was a variation from 3.75 ± 0.2 (Diclofenac 25 mg/kg) to 1.75 ± 0.6 (Diclofenac 75 mg/kg), with the control group with PTZ (70 mg/kg) showing a score of 5.6. As expected, the reduction in the Racine scale was smaller with the higher dose of anti-inflammatory and with an important difference compared to the

control. Regarding the effects, diclofenac showed variations according to the doses. Thus, at the lowest dose (1 mg/kg S.C.) pre-induction, an increase in both seizure intensity and mortality was observed. In another study with a higher dose, via intramuscular (I.M.) in pre-induction, a reduction in latency, intensity, and mortality was observed. At a higher dose but via I.M. and also a single pre-induction dose, a reduction in the latency to tonic seizures was evidenced, despite reducing the LD50 (lethal dose) of PTZ.

However, doses between 5 and 10mg/kg administered via I.P. for 15 days caused a reduction in seizure severity as well as a reduction in the occurrence of stages 3 and 4, with no effect on behavioral parameters or blood levels of IL-1β and IL-6. Despite this, an increase in TNF-α was evidenced. In the Hippocampus, there was no effect on IL-1β, with a reduction in TNF-α and IL-6 levels. In a similar study, potassium diclofenac at 10mg/kg had no effect on either systemic inflammatory markers or the average peak frequency measured in the first 5 minutes of epileptic activity. Despite this, it had a beneficial effect, reducing epileptiform activity, reducing scores on the Racine scale, and increasing the latency to the first myoclonic seizure in a dose-dependent reduction. In contrast to lower doses, the effects with higher doses (25 to 75mg/kg) were mostly positive, even with a shorter treatment time (pre-induction by PTZ) with a single dose, evidencing a dose-dependent reduction in epileptiform activity, a reduction on the Racine scale, an increase in the latency to the first myoclonic jerk (FMJ), a reduction in MDA (malondialdehyde) and TNF-α, IL-1β, and PGE2, with an increase in SOD (antioxidant defense).

Regarding ibuprofen (n = 7), the predominant route of administration was I.P. (n = 6; 85.71%), with dose varying from 30mg to 400mg/kg I.P. and 4 to 40mg IP (analog – IBUACT) and 30mg to 400mg/kg I.P. The minimum treatment time was single dose and the maximum time 29 days (I.P. 30mg/kg). All studies had pre-induction administration period. Thus, the latency for crisis occurrence was minimum of 20s (stage I increased swimming activity) and maximum 400s (with ibuprofen 30mg/kg for 29 days). The frequency of each seizure stage was not evaluated in any study. The minimum score manifested was 2.67 (with ibuprofen 30mg/kg) and maximum 4.2 ± 0.3 (200 mg/kg). A lower dose of ibuprofen (10 mg/kg) I.M. single dose had no effect on the latency for the occurrence of the first tonic crisis, still, it reduced latency to onset of tonic seizures. However, it reduced convulsion-induced rise of PGF22α, PGE2, and TxB2 besides the lethal dose of PTZ (LD50).

IBUACT (ibuprofen formulation) at a 20mg/kg single dose increased latency in three stages of PTZ-induced crisis, with a better anticonvulsant effect than Diazepam in Stage III. Doses of Ibuprofen at 10 - 30 mg/kg for 04 days I.P. and 20 sessions had no effect on PTZ-induced excitation, which was only evidenced with the higher dose of 90mg/kg. Ibuprofen 30mg/kg I.P. single dose reduced the average number of fully induced convulsions, increased latency time with a reduction in seizure duration, peaks, and amplitudes of waves on EEG, in addition to reducing GFAP (gliosis indicator). The same dose with longer exposure time (ibuprofen 30mg/kg I.P. for a longer time of 29 days), as expected, also increased latency time and reduced markers COX-2, NLRP3, caspase-1, and IL-18. The highest dose (ibuprofen 200 mg/kg single dose) showed a reduction in epileptiform activity to 55.9%, but without effect on PGF2α. A higher dose of 400mg/kg was capable of reducing peak percentage to 45.1% and PGF2α.

The drug dexketoprofen was featured in 02 studies with doses ranging from 5 to 50mg/kg, both with I.P. administration. One study was post-induction without behavioral description of the convulsive crisis type, showing a reduction in the frequency of penicillin-induced crises (dose-dependent), with no effect on the amplitude of discharges with each dexketoprofen dose. The higher dose was capable of reducing the peak frequency to 19 ± 5/min, reducing epileptiform activity, and significantly increasing the latency for first myoclonic jerck (FMJ) [from 145.8 ± 21.07 (20mg/kg) to 175.1 ± 17.9 (40mg/kg), with PTZ being 75.1 ± 9.62]. Also at this dose, it reduced the score on the Racine scale [3.66 ± 0.4 (DEX 40mg/kg)] to 4.5 ± 0.5 (20mg/kg) (with PTZ being 5.8 ± 0.1).

Regarding some unique studies, oxaprozin was studied with a minimum dose of 100mg/kg and a maximum of 400 mg/kg, and a duration of 1 to 4 days. The Racine scale showed dose-dependent variation: minimum 2 (oxaprozin 400mg) and maximum 3.6 (oxaprozin 100mg/kg), with the PTZ group at 4.6, demonstrating a reduction in the Racine scale. Other effects observed from the 200mg/kg dose included reduced memory impairment, increased GPx and MDA levels, as well as increased expression of the Hmox1 and Nrf2 genes.

In the only study with flufenamic acid, an anti-inflammatory dose of 100 mg/kg I.P. single dose was observed in pre-induction with pilocarpine, which reduced the latency for each seizure stage from 39.9 ± 11.6 min (Vehicle + pilocarpine) to 26.9 ± 5.8 min (pilocarpine + flufenamic acid). Despite increasing latency, detrimental effects such as reduced body weight and increased mortality in animals subjected to SE were

observed, even in animals that did not receive pilocarpine (33.3%). There was no change in the effect against SE-induced brain damage, nor in the prevention of degeneration or GFAP. Other anti-inflammatory drugs were evaluated, with data also recorded in Table 2.

3.3.6.2.2 COX-2 Selective Inhibitors

Of the 16 studies with celecoxib, 11 (68.75%) had oral/intragastric (P.O.) administration, 04 (25%) via I.P., and 01 via intravenous (I.V.) (6.25%). The minimum dose administered was 0.003mg/kg orally and the maximum was 20mg/kg I.V., both as a single dose. The longest treatment duration was 28 days with the maximum dose (P.O. 1x/day). Piroxicam, in turn, had 02 studies in total, both with I.P. administration, with a minimum administered dose of 0.15 mg/kg for 15 days and a maximum of 10mg/kg single dose. Thus, the lower dose was given over a longer interval, and the higher dose was given via single administration. Below are the primary effects observed in studies that used NSAIDs, both non-selective and selective COX-2 inhibitors, organized by the specific anti-inflammatory (Table 6). Supplementary data, as well as information on other anti-inflammatory drugs, can be found in Table 2, presented previously.

Tabela 6: Primary effects observed in studies included in this systematic review, grouped by NSAIDs. This table considers the previously presented Table 2. Acetaminophen, although not strictly considered a NSAIDs, has been included in this table. In the "Negative effects" column, the study author is also provided to help correlate with the presented effects.

NSAID	Positive effects	Negative effects or no effect
Diclofenac	Higher doses (25-75mg/kg): ↓ epileptiform activity; ↓ Racine scores; ↑ latency to first seizures; ↓ MDA (malondialdehyde) + ↑ SOD; ↓ TNF-α, IL-1β and PGE2.	↓ latency time (10mg/kg). (IM admin. pre-PTZ induction) (Steinhauer; Hertting, 1981) Low doses (1mg/kg): ↑ seizure intensity; ↑ mortality; (SC admin. pre-induction, PTZ + LPS induction model) (Akarsu *et al.*, 2006)

Indomethacin	**Zebrafish:** ↓ incidence; ↓ seizure frequency; ↑ latency time; **Piglets:** ↓ cerebral blood flow and pial arteriolar dilation; Inhibited prostanoid production; **Mice:** ↓ PTZ lethal dose; Prevention of increased PG and TxB2 (increased thromboxane B2 is associated with inflammatory effects).	**Mice:** ↓ latency time (10mg/kg) (IP admin. pre-KA induction) (IM admin. pre-PTZ induction) (Chung, 2013; Steinhauer; Hertting, 1981) ↑ convulsive activity and mortality (10mg/kg) (IP admin. pre- and post-KA induction) (Kim *et al.*, 2008) Low dose (0,5mg/kg) ↑ convulsive activity and mortality (SC admin. pre-PTZ + LPS induction) (Akarsu *et al.*, 2006)
Aspirin	**Better action on seizure-like behavior, even in heterogeneous studies;** (Racine Scale/mean frequency of spontaneous seizures) ↓ frequency of epileptiform spikes; ↓ seizure incidence; ↓ seizure duration in mice; Potentiated the anticonvulsant effect of diazepam and sodium valproate in PTZ pre-induction; ↓ expression of COX-2, PGE2, IL-6 and TNF-α; ↑ hippocampal neurogenesis	↔ onset of the first generalized seizure in rats, although it decreased locomotor activity; (PO pre-induction, acute KA model / 7.5mg/kg) (Sayrazi, 2017) ↔ onset of tonic-clonic seizures. (IM admin. pre-PTZ induction) (Steinhauer; Hertting, 1981)
Sodium salicylate	↓ seizure scores;	Pro-convulsant effect at non-convulsive doses of pilocarpine (converted a non-convulsive dose into a convulsant one); Induced neuronal damage; (50-400mg/kg IP pre-pilocarpine induction) (Ikonomidou-Turski *et al.*, 1988) ↔ behavioral activity;

		↑ neuronal death; ↑ blood-brain barrier (BBB) damage. (500 mg/kg; IP pre-KA induction) (Najbauer *et al.*, 2000)
Celecoxib	↓ seizure severity; ↑ seizure latency; ↓ frequency and duration of spontaneous recurrent seizures; **↑ latency to the first myoclonic spasm and generalized seizure;** ↓ COX-2 expression; **Potentiated the effect of VPA, even in the presence of a pro-inflammatory sensitizer.** **Post-administration:** → recovery from neurodegeneration.	Showed no anticonvulsant effect (seen in biomarkers); **(4 mg/kg, PO pre-PTZ induction, both for 16 days)** (Mishchenko; 2022; Tsyvuin, 2022) ↓ latency; ↑ seizure severity; ↑ mortality; (Baik *et al*., 1999; Gobbo; O'Mara, 2004; Kim *et al*., 2008) **Pre-administration:** ↑ mortality rate; ↔ neuronal loss and survival. (6mg/kg IP KA induction) (Gobbo; O'Mara, 2004)
Rofecoxib	↑ seizure threshold in all phases of PTZ-induced seizures; ↑ clonic seizure latency. (in mice)	↔ incidence; ↔ seizure severity; ↑ COX-2 expression; ↔ seizure-induced neurodegeneration in rats. (30mg/kg PO pre-PTZ induction); (Claycomb *et al.*, 2011) ↔ seizure-induced neurodegeneration in rats. (10mg/kg IP post-KA induction) (Kunz *et al.*, 2005)
Oxaprozin	↓ mean Racine score; ↓ memory impairment in rats.	No negative effects or lack of effect were identified in this study excerpt.
Acetaminophen	↑ latency to the first myoclonic spasm; ↓ Racine score.	↔ latency to first seizures; ↔ Racine score.

	(50mg/kg) ↓ NO, TNF-α, IL-1β; ↓ glutamate ↑ GABA. (50 and 100mg/kg)	(100 mg/kg)
Nimesulide	**Attenuated PTZ-induced seizures;** ↓ Racine scores; ↑ latency time; Showed antioxidant effects. (mice 20 mg/kg)	↑ convulsive activity. (when administered alone, in a KA-induced model 10mg/kg IP) (Kim *et al.*, 2008)
Ibuprofen	↓ PTZ-induced excitation; (90 mg/kg) ↑ Latency to clonic-tonic seizures (30-100 mg/kg); ↓ Seizure incidence; ↓ Neuronal damage; Inhibited convulsion-induced rise of PGF22α, PGE2, and TxB2; ↓ GFAP, COX-2, NLRP3, caspase-1 e IL-18.	↔ PTZ-induced excitation; (10, 30 mg/kg I.P. pré-induction) (Wallenstein, 1991) ↔ Latency to clonic-tonic seizures; (10 mg/kg I.P. pre-induction pilocarpine) (Ikonomidou-Turski *et al.*;1988) ↔ Latency to onset of tonic seizures; (pré-induction I.M) ↓ LD50 of PTZ. (Steinhauer; Hertting, 1981)

3.3.6.2.3 Dual COX/LOX Inhibitory Anti-Inflammatories

Licofelone was presented in one study at minimum doses of 1 and maximum of 20mg/kg, via IP with a single dose in pre-induction. This study showed an increased action in raising the seizure threshold, without defined induction dose information and with several parameters not evaluated. BW755C was administered at a minimum dose of 50mg/kg and a maximum dose of 100mg/kg in pre-induction with kainic acid. Complementary information about other dual COX/LOX inhibitory anti-inflammatories is detailed in Table 2. Below are the primary effects found in studies that utilized dual COX/LOX inhibitory anti-inflammatories (Table 7). Other anti-inflammatory drugs were evaluated, with data also recorded in Table 2.

Table 7: Primary effects observed in studies included in this systematic review, grouped by dual COX-LOX inhibitory anti-inflammatory. This table considers the previously presented Table 2, where

additional details can be found. In the "Negative effects" column, the study author is also provided to help correlate with the presented effects.

Inibidores duplo COX/LOX	Positive effects	Negative effects or no effect
BW755C	↑ latency; ↓ seizure severity; Protection against mortality and neuronal damage.	No negative effects or lack of effect were identified in this study excerpt.
Pirfenidone	↑ latency; ↓ Severity scores; ↓ Mortality; ↓ Behavioral seizure activity.	No negative effects or lack of effect were identified in this study excerpt.
Licofelone and Tenidap	↑ Seizure threshold in mice; ↓ Hippocampal neuronal damage in rats.	No negative effects or lack of effect were identified in this study excerpt.

3.3.7 Risk of bias and quality assessment

In this review, we used the SYRCLE risk of bias tool for animal studies to evaluate the 96 included articles. The risk of bias assessment is presented in Figure 1. The “Low” judgment indicates that the risk of bias is low, and the “High” judgment indicates a high risk of bias. If reporting details were insufficient to assess any of the parameters, the judgment was “Unclear”. Through this analysis, it was possible to observe a lack of detail regarding the experimental design of the studies. Thus, the “Unclear” judgment is the most prevalent in the description of the results.

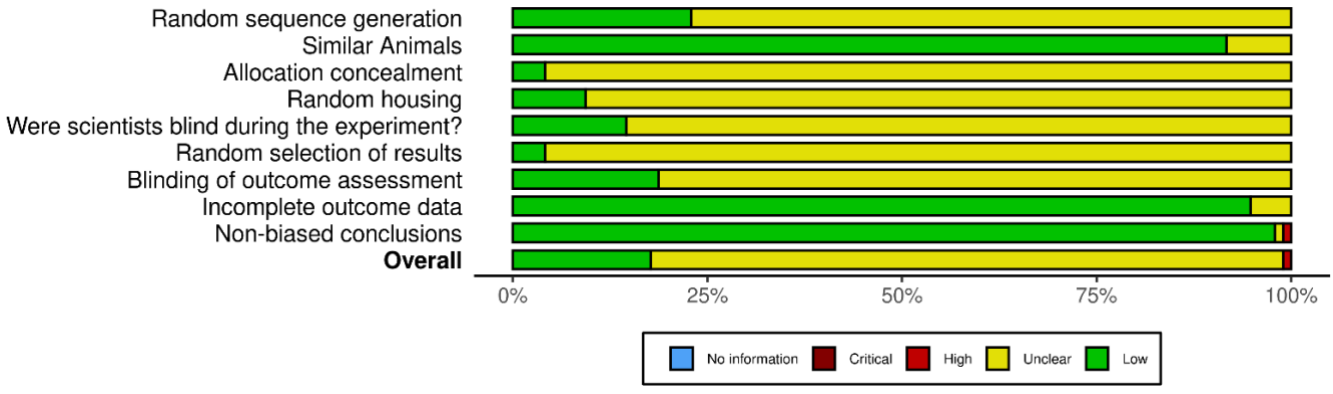


Figure 8: Risk of bias assessment for the 96 included studies. The evaluation used the SYRCLE tool, and the results indicate the results indicate the percentage of studies with a low, unclear or high risk for each of the nine methodological items.

The quality assessment of the studies was performed using the CAMARADES ten-item checklist, with some adaptations. For animal articles, scores for quality items ranged from 3 to 8, out of a total of 10 points. The average score was 5.49 out of 10 (with a median of 6), which indicates a medium methodological quality of the reports (Table 3). Despite the limitations of detail in the experimental designs of the studies, both in the risk of bias and the analyzed methodological quality, these are not factors that prevent the realization of this systematic review.

Table 8: Characteristics of included studies.

	CAMARADES CHECKLIST (adapted)	1	2	3	4	5	6	7	8	9	10	Total
1	**de Lima (2024)**	✓	✓	✓		✓	✓	✓		✓	✓	8
2	**Gautam (2024)**	✓	✓	✓				✓		✓	✓	6
3	**Guzzo (2024)**	✓	✓	✓		✓	✓	✓		✓	✓	8
4	**Guzzo (2023)**											
5	**Murugan (2024)**	✓	✓				✓	✓		✓	✓	6
6	**Ribeiro (2024)**	✓	✓	✓		✓	✓	✓		✓	✓	8
7	**Brabec (2023)**	✓	✓	✓			✓	✓		✓	✓	7
8	**Erdogan (2023)**	✓	✓	✓			✓	✓		✓	✓	7
9	**Garcia (2023)**	✓	✓	✓			✓	✓		✓	✓	7
10	**Hernández-Martín (2023)**	✓	✓				✓	✓		✓	✓	6
11	**Türel (2023)**	✓	✓					✓		✓	✓	5
12	**Khatami (2022)**	✓	✓	✓		✓	✓	✓		✓	✓	8
13	**Mishchenko (2022)**	✓	✓	✓				✓		✓	✓	6
14	**Tsyvunin (2022)**	✓	✓	✓		✓	✓	✓		✓	✓	8
15	**Alsaegh (2021)**	✓	✓				✓	✓		✓	✓	6
16	**Demirsoy (2021)**	✓	✓	✓			✓	✓		✓	✓	7
17	**Kandeda (2021)**	✓	✓				✓	✓		✓	✓	6
18	**Karabulut (2021)**	✓	✓	✓			✓	✓		✓	✓	7
19	**Rosa (2021)**	✓	✓				✓	✓		✓	✓	6
20	**Durankuş (2020)**	✓	✓	✓			✓	✓		✓	✓	7
21	**Elgarhi (2020)**	✓	✓				✓	✓		✓	✓	6
22	**Fox (2020)**	✓	✓				✓	✓		✓	✓	6
23	**Liu R (2020)**	✓	✓				✓	✓		✓	✓	6
24	**Yang (2020)**	✓	✓				✓	✓		✓	✓	6
25	**Peng (2019)**	✓	✓	✓			✓	✓		✓	✓	7
26	**Yang (2019)**	✓	✓				✓	✓		✓	✓	6
27	**Ayyildiz (2018)**	✓	✓					✓		✓	✓	5
28	**Guzzo (2018)**	✓	✓				✓	✓		✓	✓	6
29	**Morales-Sosa (2018)**	✓	✓				✓	✓			✓	5

30	**Suemaru (2018)**	✓	✓				✓	✓		✓	✓	6
31	**Vizuete (2018)**	✓	✓					✓		✓	✓	5
32	**Abd-Elghafour (2017)**	✓		✓		✓		✓		✓	✓	6
33	**Ayyildiz (2017)**	✓	✓					✓		✓	✓	5
34	**Sairazi (2017)**	✓	✓	✓		✓		✓		✓	✓	7
35	**Temp (2017)**	✓	✓				✓	✓		✓	✓	6
36	**Zhu (2017)**	✓	✓	✓		✓		✓		✓	✓	7
37	**Borham (2016)**	✓	✓					✓		✓	✓	5
38	**Morelli (2016)**	✓	✓				✓	✓		✓	✓	6
39	**Vieira (2016)**	✓	✓				✓	✓		✓	✓	6
40	**Gupta (2015)**	✓	✓			✓		✓		✓	✓	6
41	**Payandemehr (2015)**	✓	✓				✓	✓		✓	✓	6
42	**Trandafir (2015)**	✓				✓		✓		✓		4
43	**Aksoy (2014)**	✓	✓	✓		✓		✓		✓	✓	7
44	**Duffy (2014)**	✓		✓				✓		✓		4
45	**Vieira (2014)**	✓	✓					✓		✓	✓	5
46	**Yilmaz (2014)**	✓	✓					✓		✓		4
47	**Chung (2013)**	✓						✓		✓		3
48	**Jeong (2013)**	✓	✓					✓		✓		4
49	**Xing-hua (2013)**	✓	✓	✓				✓		✓	✓	6
50	**Al-Shorbagy *et al.*, (2012)**	✓	✓					✓		✓		4
51	**Ma (2012)**	✓		✓		✓		✓		✓		5
52	**Claycomb *et al.*, (2011)**	✓	✓	✓	✓	✓		✓		✓	✓	8
53	**Marchi *et al.*, (2011)**	✓	✓				✓	✓		✓	✓	6
54	**Jayaraman *et al.*, (2010)**	✓	✓					✓		✓	✓	5
55	**Polascheck *et al.*, (2010)**	✓	✓	✓		✓	✓	✓		✓		7
56	**van Vliet *et al.*, (2010)**	✓	✓				✓	✓		✓		5
57	**Zandieh *et al.*, (2010)**	✓	✓				✓	✓		✓		5
58	**Zibell *et al.*, (2009)**	✓	✓			✓	✓	✓		✓		6
59	**Akula *et al.*, (2008)**	✓		✓			✓	✓		✓		5
60	**Dhir *et al.*, (2008)**	✓	✓				✓	✓		✓	✓	6
61	**Kim *et al.*, (2008)**	✓	✓			✓	✓	✓		✓		6
62	**Oliveira *et al.*, (2008)**	✓	✓				✓	✓		✓		5
63	**Zhang *et al.*, (2008)**	✓			✓	✓	✓	✓		✓		6
64	**Bauer *et al.*, (2007)**	✓	✓			✓	✓	✓		✓		6
65	**Bishnoi *et al.*, (2007)**	✓					✓	✓		✓		4
66	**Dhir *et al.*, (2007)**	✓	✓				✓	✓		✓		5
67	**Akarsu *et al.*,**	✓	✓				✓	✓		✓		5

	2006								
68	**Dhir; Kulkarni (2006)**	✓				✓	✓	✓	4
69	**Jung *et al.*, (2006)**	✓			✓	✓	✓	✓	5
70	**Kim; Jang (2006)**	✓	✓			✓	✓	✓	5
71	**Yoshikawa *et al.*, (2006)**	✓				✓	✓	✓	4
72	**Dhir *et al.*, (2005)**	✓	✓			✓	✓	✓	5
73	**Kawaguchi *et al.*, (2005)**	✓	✓			✓	✓	✓	5
74	**Kunz *et al.*, (2005)**	✓			✓	✓	✓	✓	5
75	**Gobbo; O'Mara (2004)**	✓	✓	✓	✓	✓	✓	✓	7
76	**Sayyah *et al.*, (2003)**	✓	✓			✓	✓	✓	5
77	**Ciceri *et al.*, (2002)**	✓	✓	✓		✓	✓	✓	6
78	**Edwards *et al.*, (2002)**	✓	✓		✓	✓	✓	✓	6
79	**Reddy; Rogawski (2002)**	✓	✓			✓	✓	✓	5
80	**Kunz; Oliw (2001)**	✓			✓	✓	✓	✓	5
81	**Srivastava; Gupta (2001)**	✓				✓	✓		3
82	**Kim *et al.*, (2000)**	✓				✓	✓	✓	4
83	**Najbauer *et al.*, (2000)**	✓				✓	✓	✓	4
84	**Baik *et al.*, (1999)**	✓				✓	✓		3
85	**Kábová *et al.*, (1999)**	✓	✓			✓	✓	✓	5
86	**Cook; Persinger (1996)**	✓				✓	✓		3
87	**Baran *et al.*, (1994)**	✓				✓	✓		3
88	**Minami *et al.*, (1991)**	✓				✓	✓		3
89	**Wallenstein (1991)**	✓				✓	✓		3
90	**Simmet; Tippler (1990)**	✓				✓	✓		3
91	**Busija; Leffler (1989)**	✓	✓				✓		3
92	**Ikonomidou-Turski *et al.*, (1988)**	✓				✓	✓		3
93	**Sztriha *et al.*, (1986)**	✓				✓	✓		3
94	**McGinley *et al.*, (1985)**	✓				✓	✓		3

95	**Förstermann *et al.*, (1982)**	✓		✓	✓	3
96	**Steinhauer; Hertting (1981)**	✓		✓	✓	3

1) Publication in peer-reviewed jornal; **2)** Statement of control of temperature; **3)** Randomization of treatment or control; **4)** Allocation concealment; **5)** Blinded assessment of outcome; **6)** Avoidance of anesthetics with marked intrinsic properties; **7)** Use of animals as appropriate models for seizures; **8)** Sample size calculation; **9)** Statement of compliance with regulatory requirements; **10)** Statement regarding possible conflict of interest.

4. DISCUSSION

The behavioral and biochemical parameters in animal models of epilepsy in response to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) have been studied since the 1980s (Steinhauer & Hertting, 1981; McGinley *et al.*, 1985). Given the known relationship between neuroinflammation and epilepsy, and the critical need for new antiepileptic drugs, clinical trials on the use of steroidal anti-inflammatory agents (SAIDs) and non-steroidal anti-inflammatory agents have increased over the years. This is evidenced by a considerable rise in articles published in the last four years compared to previous periods. Therefore, we conducted a systematic review of studies involving the use of these drugs in animal models of epilepsy with chemically induced seizure-like crises. In these studies, analysis of convulsive behavior, along with biomarkers of oxidative stress, neural activity, gene expression, and inflammation markers, were frequently employed. Next, we describe some anti-inflammatory drugs included in this review and their effects, evidenced through the evaluation of different parameters such as convulsive behavior, as well as biomarkers of oxidative stress, neural activity, and inflammation markers.

In rats, potassium diclofenac has been shown to reduce the frequency of epileptic discharges in a penicillin-induced model when combined with diazepam (Türel, 2023). Other studies using sodium diclofenac in rats and mice indicated a reduction in seizure severity (Vieira, 2016) and an increase in latency (Erdogan, 2023). These studies also showed decreased inflammatory mediators like TNF-α, IL-6 (Vieira, 2016), IL-1β, and PGE2, alongside an increase in SOD (Erdogan, 2023). However, a study in mice (Akarsu *et al.*, 2006) suggested that low doses of diclofenac (1 mg/kg) might increase seizure intensity and mortality in an LPS and PTZ-induced seizure model. This particular study lacked biochemical parameter analysis, which hinders an in-depth investigation into the harmful mechanisms involved and whether they relate to the administration route or dose. This limitation also applies to indomethacin, which was subcutaneously administered at a low dose (0.5 mg/kg) in the same study, contrasting with other research (Reddy & Rogawski, 2002; Yoshikawa *et al.*, 2006) that demonstrated positive effects. Conversely, Steinhauer and Hertting (1981) observed that slightly higher doses of diclofenac (10 mg/kg) and indomethacin (10 mg/kg), administered intramuscularly (IM) before PTZ induction, were associated with a reduced latency to the onset of tonic seizures. This occurred despite already showing

positive effects in reducing the lethal dose of PTZ and preventing the increase of seizure-induced PG and TxB2 levels. This evidence supports the analysis that diclofenac, similar to other anti-inflammatories, can exhibit dose-dependent and time-dependent beneficial effects, although it can also act as an aggravating pro-inflammatory factor depending on the context.

Results considering indomethacin, however, are mixed and sometimes paradoxical. In zebrafish, indomethacin decreased the occurrence, increased the latency, and reduced the frequency of PTZ-induced seizures (Morelli, 2016). Nevertheless, in mice, indomethacin increased seizure activity and mortality (Kim *et al.*, 2008). Furthermore, in rats, indomethacin decreased the latency to the first "wet dog shakes", generalized seizures, and death in a KA-induced model (Chung, 2013). In newborn piglets, indomethacin reduced cerebral blood flow and pial arteriolar dilation during bicuculline-induced seizures, while inhibiting prostanoid production (Busija; Leffler, 1989).

Aspirin has been shown to reduce the frequency of epileptiform spikes in rats (Ayyildiz, 2018) and the incidence and duration of seizures in mice (Zhu, 2017). It also decreased seizure scores (Abd-Elghafour, 2017) and the expression of inflammatory mediators like COX-2, PGE2, IL-6, and TNF-α (Zhu, 2017). However, in an acute KA-induced seizure model, aspirin did not alter the onset of the first generalized seizure in rats, although it did reduce locomotor activity (Sairazi, 2017). In mice, lower doses of aspirin did not change the onset time of tonic convulsions (Steinhauer; Hertting, 1981). Interestingly, studies have also shown that sodium salicylate (an aspirin metabolite) and phenylbutazone can have a pro-convulsant effect at non-convulsant doses of pilocarpine, inducing neuronal damage (Ikonomidou-Turski *et al.*, 1988; Akarsu *et al.*, 2006). Conversely, other authors highlight the superior effect of aspirin at higher doses. For instance, Ayyildiz (2018) and Srivastava; Gupta (2001) demonstrated that aspirin reduced generalized clonic seizures with a dose-dependent effect. Furthermore, it potentiated the anticonvulsant effect of diazepam and sodium valproate in PTZ pre-induction.

However, celecoxib, a selective COX-2 inhibitor, presents complex results. In some studies, celecoxib reduced seizure severity, increased latency (Kim; Jang, 2006) and decreased the frequency and duration of spontaneous recurrent seizures in chronic epilepsy models (Oliveira *et al.*, 2008; Morales-Sosa, 2018). It was also associated with decreased expression of COX-2 (Kim; Jang, 2006) and neuroinflammation (Jung *et al.*,

2006; Morales-Sosa, 2018; Alsaegh, 2021). Conversely, other studies reported that celecoxib had no anticonvulsant effect (Temp, 2017; Mishchenko, 2022; Tsyvuin, 2022) or even decreased latency and increased the severity and mortality of KA-induced seizures in mice (Baik *et al.*, 1999; Gobbo; O'Mara, 2004; Kim *et al.*, 2008). In mice, celecoxib (2.5 and 5 mg/kg) increased the latency to the first myoclonic jerk and generalized convulsion (Zandieh *et al.*, 2010). In contrast, a study by Alsaegh (2021) showed that celecoxib potentiated the effect of VPA, even in the presence of a pro-inflammatory sensitizer.

Although some studies included drug administration at more than one time point (pre and post-induction of seizure-like crisis), Najbauer *et al.* (2000), Ciceri *et al.* (2002), Kawaguchi *et al.* (2005), Kim *et al.* (2008) and in only one (Gobbo; O'Mara, 2004), celecoxib treatment was evaluated in both pre- (2h prior or 5 days prior to KA 12 mg/kg I.P.) and post-induction (2h post or 5 days post KA) administration periods. It was found that celecoxib in pre-induction increased the mortality rate, unlike in post-induction, where it showed effects on the recovery of neurodegeneration, having no effects on neuronal loss and survival.

In the study by Najbauer *et al.* (2000), deleterious results were also evidenced through the administration of sodium salicylate (500mg/kg I.P.) administered 1h before KA (12mg/kg I.P.), and then every 12h for 40h (total 4 doses after KA). This showed no effect on behavioral seizure activity, with increased neuronal death and increased blood-brain barrier damage (BBB). Although this study demonstrated two time points of drug induction, it is not possible to determine if the drug administration period is solely responsible for the deleterious effect, since it does not compare the two interventions separately.

In mice, rofecoxib (another selective COX-2 inhibitor) was also tested and shown to increase the seizure threshold for all phases of PTZ-induced convulsions (Akula *et al.*, 2008) and also the onset time of clonic convulsions (Dhir; Kulkarni, 2006). However, in a kindling model (Claycomb *et al.*, 2011), rofecoxib did not alter seizure incidence or severity. Some studies indicated that rofecoxib did not affect seizure-induced neurodegeneration in rats (Kunz *et al.*, 2005; Claycomb *et al.*, 2011).

In rats, dexketoprofen increased the latency to the first myoclonic jerk and decreased the Racine score and epileptiform activity (Aksoy, 2014). Oxaprozin, on the other hand, reduced the mean Racine score and memory impairment in rats in a PTZ-induced model (Khatami, 2022). Acetaminophen (AAP) at 50 mg/kg increased the

latency to the first myoclonic jerk and decreased the Racine score. However, a dose of 100 mg/kg did not alter latency or decrease the Racine score. Both doses decreased NO, TNF-α, IL-1β, and glutamate, while increasing GABA (Karabulut, 2021). In mice, AAP dose-dependently reduced seizure scores and occurrence in the PTZ kindling model, but it had no effect on acute seizures or *status epilepticus* (Suemaru, 2018). Additionally, in mice, Nimesulide (20 mg/kg) attenuated PTZ-induced seizures by reducing Racine scores and increasing latency (Temp, 2017). It also decreased the mean kindling score and exhibited antioxidant effects (Dhir *et al.*, 2007). However, a study by Kim *et al.* (2008) indicated that nimesulide, when administered alone, might increase seizure activity in a KA-induced model.

It's also observed that the dual cyclooxygenase/lipoxygenase (COX/LOX) inhibitor BW755C increased the latency and decreased the severity of KA-induced seizures in rats, in addition to protecting against mortality and neuronal damage (Baran *et al.*, 1994). Another dual COX/LOX inhibitor, pirfenidone, significantly reduced mortality and behavioral seizure activity, increasing latency and decreasing severity scores in mice with KA-induced seizures in both rats and mice (Simmet; Tippler, 1990; Kim et al., 2000). Furthermore, the drugs Licofelone and Tenidap increased the seizure threshold in mice and decreased hippocampal neuronal damage in rats (Xing-hua, 2013; Payandemehr, 2015).

Regarding SAIDs, results with dexamethasone are extensive and, at times, inconsistent. In rats, dexamethasone did not affect convulsive behavior in a study by Ribeiro (2024). However, in other studies, it increased the latency to *status epilepticus* (*SE*) (Marchi *et al.*, 2011) and decreased seizure incidence and intensity, particularly at a dose of 10 mg/kg (Al-Shorbagy *et al.*, 2012). It also demonstrated a reduction in neuroinflammation (Borham, 2016; Guzzo, 2018) and brain damage (Sztriha *et al.*, 1986; Yang, 2019). Nevertheless, other studies reported that dexamethasone did not alter SE severity or latency (Duffy, 2014; Fox, 2020). A study in rat pups showed that while it modulated more genes, it had less functional specificity for the CNS compared to ACTH (Brabec, 2023). In mice, dexamethasone increased latency in pilocarpine-induced models (Marchi *et al.*, 2011; Al-Shorbagy *et al.*, 2012; Yang, 2020). A study in rats with NMDA-induced seizures suggested a pro-convulsant effect of hydrocortisone (Kábová *et al.*, 1999). Dexamethasone was also associated with decreased inflammatory cytokines like IL-1β and IL-6 in the brain (Marchi *et al.*, 2011; Borham, 2016).

In rats, prednisolone increased the latency of PTZ-induced seizures over several days (de Lima, 2024) and reduced inflammatory cytokine levels in the hippocampus (Rosa, 2021). However, a study on chronic epilepsy found no alteration in learning memory with prednisolone (Cook; Persinger, 1996). Meanwhile, betamethasone progressively decreased seizure scores, especially at a dose of 0.250 mg/kg, and increased latency, in addition to decreasing TNF-α and IL-1β (Guzzo, 2023).

During and after epileptic seizures, there's an increased production of reactive oxygen species. Antioxidant enzymes like SOD and catalase, along with GSH (Averill, 2023), protect neurons against this oxidative stress. Inflammation and oxidation are related but distinct processes (Biswas, 2016). Therefore, the antioxidant effects of a drug can only be precisely confirmed when specific biomarkers of oxidative stress are measured, requiring at least one marker of oxidative damage and one of antioxidant activity (Katerji, 2019). In this review, some studies in brain tissue showed a reduction in MDA (a biomarker of oxidative damage), along with an increase in CAT (Bishnoi *et al.*, 2007; Khatami, 2022), SOD, and GSH (Elgarhi, 2020; Fox, 2020; Demirsoy, 2021; Khatami, 2022; Erdogan, 2023). This evidence highlights the neuroprotective effect stemming from the anti-inflammatory drug's antioxidant action.

Inflammatory mediators can act as neuromodulators, affecting neuronal function and excitability (Ravizza; Vezzani, 2018). Thus, studies evidence the involvement of COX-1 and COX-2 (Choi, 2009; López, 2020) in neuroinflammation, homeostasis, and neuronal plasticity, with evidence of possible additional effects that may indicate non-common mechanisms in NSAIDs to enhance GABA-A receptor function (Khansari, 2012). This effect was observed in a study (Garcia, 2023) included in the systematic review, which demonstrated the GABAergic action of IBUACT (ibuprofen formulation at 20mg/kg), administered via immersion of IBUACT in pre-induction with PTZ in zebrafish. Other studies in the review found increases in GABA levels (Murigan, 2024; Karabulut, 2021), unlike the study by Zhang *et al.* (2012), which reported a reduction in the GABA receptor (Zhang *et al.*, 2012).

Many studies highlight the modulation of inflammatory mediators such as cytokines (TNF-α, IL-1β, IL-6) and prostanoids (PGE2) (Yoshikawa *et al.*, 2006; Vizuete, 2018; Alsaegh, 2021; Mishchenko, 2022; Erdogan, 2023) as a key mechanism behind the anti-inflammatory effects on seizures. The reduction of neuroinflammation appears to be a protective factor in numerous seizure models (Xing-hua, 2013; Zhu, 2017). However, the relationship between inflammation and seizure activity is complex.

Some NSAIDs, especially selective COX-2 inhibitors, have shown pro-convulsant results under certain conditions (Tsyvuin, 2022; Mishchenko, 2022; Alsaegh, 2021). This might be due to the disruption of prostanoid balance, which can have either protective or pro-convulsant effects depending on the context. Additionally, the modulation of GABAergic receptors (Garcia, 2023) and glutamatergic receptors (Karabulut, 2021), as well as oxidative stress (Elgarhi, 2020; Khatami, 2022; Erdogan, 2023) and neuronal damage (Liu, 2020; Alsaegh, 2021; Gautam, 2024), are parameters frequently affected by these drugs, contributing to their observed effects.

The timing of administration (pre- or post-seizure induction) also appears to be a crucial factor. Many studies show beneficial effects when anti-inflammatories are administered before or soon after seizure induction (Durankuş, 2020; Elgarhi, 2020; Alsaegh, 2021; Erdogan, 2023). However, chronic treatment can yield different outcomes, as observed with celecoxib (Morales-Sosa, 2018; Mishchenko, 2022; Tsyvuin, 2022). In summary, while many anti-inflammatories, both NSAIDs and SAIDs, show potential in managing seizures and epilepsy, primarily through the modulation of neuroinflammation (Elgarhi, 2020; Liu, 2020; Alsaegh, 2021; Erdogan, 2023), their effects are highly dependent on the experimental context. Optimizing the dose, timing of administration, and a deeper understanding of the underlying mechanisms are essential to translate these findings into effective clinical applications.

Another important limitation to consider in this review is that not all studies evaluated the adverse effects of anti-inflammatory administration. A systematic toxicological assessment typically includes analysis of lethality, body weight, edema, systemic biochemistry (with hepatic and renal profiles), and general clinical signs (such as piloerection and grooming). Thus, most studies did not provide a complete evaluation. In this regard, some preclinical trials mentioned lethality but did not clearly quantify it in percentages (Yang *et al.*, 2015; Vieira *et al.*, 2022) or focused only on a partial evaluation centered on inflammation (Rosa *et al.*, 2021) and neuroprotective effects.

Despite this, we were able to observe significant toxicity with ibuprofen (nearly 60% dose-related lethality) and dexamethasone (suggesting exacerbation of acute cerebral edema and brain injury) (Wallenstein, 1991; Duffy *et al.*, 2014), in addition to cognitive impairment from etoricoxib (associated with memory and learning deficits) (Gupta *et al.*, 2015). Some studies also made no mention of significant adverse effects from aspirin or celecoxib (Srivastava & Gupta, 2001; Schlichtiger *et al.*, 2010; Zhu *et*

al., 2017; Alsaegh *et al.*, 2021), and dose-related toxicity was noted for acetaminophen (Wallenstein, 1991).

Therefore, while this systematic review lists various positive and negative effects of anti-inflammatories across different parameters, it's crucial to also consider the adverse effects of these medications, especially given the possibility of chronic pharmacological use. This is because anti-inflammatories are also known for their adverse effects, making the determination of a systematic toxicological profile in preclinical trials important. Similarly, results from preclinical trials cannot be directly extrapolated, and caution is advised as doses can often be much higher than clinical doses, necessitating more realistic pharmacokinetic profiles.

In this way, performing a meta-analysis of this systematic review would represent a crucial step in defining future protocols for the replication of pre-clinical trials. This would enhance the robustness and precision in validating scientific knowledge in the field and in evaluating the influence of various experimental factors, such as animal model, dose, route of administration, and exposure time, across different studies.

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Informed Consent Statement

Not applicable.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

I – COMPLETE DATABASE SEARCH STRATEGY

Estratégia de busca: Pubmed.

"epilepsy" [MeSH Terms] OR *"epilepsies"* OR *"seizure disorder"* OR *"seizure disorders"* OR *"epilepsy, cryptogenic"* OR *"cryptogenic epilepsies"* OR *"cryptogenic epilepsy"* OR *"epilepsies, cryptogenic"* OR *"aura"* OR *"auras"* OR *"awakening epilepsy"* OR *"epilepsy, awakening"* AND *"seizure [MeSH Terms]"* OR *"Jacksonian seizure"* OR *"seizure, Jacksonian"* OR *"single seizure"* OR *"seizure, single"* OR *"single seizures"* OR *"atonic absence seizures"* OR *"atonic absence seizure"* OR *"absence seizure, atonic"* OR *"Absence seizures, atonic"* OR *"seizure, atonic absence"* OR *"seizures, focal"* OR *"focal seizure"* OR *"focal seizures"* OR *"seizure, focal"* OR *"partial seizures"* OR *"partial seizure"* OR *"seizure, partial"* OR *"seizures, generalized"* OR *"generalized seizure"* OR *"generalized seizures"* OR *"seizure, generalized"* OR *"seizures, sensory"* OR *"seizure, sensory"* OR *"sensory seizure"* OR *"sensory seizures"* OR *"seizures, auditory"* OR *"auditory seizure"* OR *"auditory seizures"* OR *"seizure, auditory"* OR *"convulsive seizures"* OR *"seizure, convulsive"* OR *"seizures, convulsive"* OR *"seizures, motor"* OR *"motor seizure"* OR *"motor seizures"* OR *"seizure, motor"* OR *"convulsive seizure"* OR *"seizures, gustatory"* OR *"gustatory seizure"* OR *"gustatory seizures"* OR *"seizure, gustatory"* OR *"seizure, olfactory"* OR *"olfactory seizures"* OR *"seizure, olfactory"* OR *"seizures, somatosensory"* OR *"seizure, somatosensory"* OR *"somatosensory seizure"* OR *"somatosensory seizures"* OR *"seizures, vertiginous"* OR *"seizure, vertiginous"* OR *"vertiginous seizure"* OR *"vertiginous seizures"* OR *"seizures, vestibular"* OR *"seizure, vestibular"* OR *"vestibular seizure"* OR *"vestibular seizures"* OR *"seizures, visual"* OR *"seizure, visual"* OR *"visual seizure"* OR *"visual seizures"* OR *"convulsion, non-epileptic"* OR *"convulsion, non epileptic"* OR *"convulsions, non-epileptic"* OR *"non-epileptic convulsion"* OR *"non-epileptic convulsions"* OR *"nonepileptic seizures"* OR *"non-epileptic seizures"* OR *"non epileptic seizures"* OR *"nonepileptic seizure"* OR *"non-epileptic seizures"* OR *"non epileptic seizures"* OR *"nonepileptic seizure"* OR *"seizure, non epileptic"* OR *"seizures, non epileptic"* OR

"non-epileptic seizure" OR *"non epileptic seizure"* OR *"seizure, non-epileptic"* OR *"complex partial seizures"* OR *"complex partial seizure"* OR *"partial seizure, complex"* OR *"partial seizures, complex"* OR *"seizure, complex partial"* OR *"epileptic seizures"* OR *"seizures, epileptic" OR "epileptic seizure"* OR *"seizure, epileptic"* OR *"generalized absence seizures"* OR *"generalized absence seizure"* OR *"Absence seizure, generalized"* OR *"Absence seizures, generalized"* OR *"seizure, generalized absence"* OR *"tonic-clonic seizures"* OR *"seizures, tonic-clonic"* OR *"generalized tonic-clonic seizures"* OR *"generalized tonic-clonic seizure"* OR *"generalized tonic clonic seizures" OR "seizure, generalized tonic-clonic"* OR *"seizures, generalized tonic-clonic"* OR *"tonic-clonic seizure, generalized"* OR *"tonic-clonic seizures, generalized"* OR *"tonic clonic seizure" OR "clonic seizures, tonic"* OR *"clonic seizure, tonic"* OR *"seizure, tonic clonic"* OR *"tonic clonic seizures"* OR *"tonic clonic seizure"* OR *"clonic seizures, tonic"* OR *"clonic seizure, tonic"* OR *"seizure, tonic clonic"* OR *"tonic clonic seizures" OR "tonic-clonic seizure"* OR *"seizure, tonic-clonic" OR "myoclonic seizures"* OR *"myoclonic seizure"* OR *"seizure, myoclonic"* OR *"clonic seizures"* OR *"seizures, clonic"* OR *"clonic seizure"* OR *"seizure, clonic"* OR *"tonic seizures"* OR *"seizures, tonic"* OR *"tonic seizure"* OR *"seizure, tonic"* OR *"atonic seizures"* OR *"atonic seizure"* OR *"seizure, atonic"* OR *"convulsions" OR "convulsion"* OR *"absence seizures"* OR *"petit mal convulsion"* OR *"convulsion, petit mal"* OR *"absence seizure"* OR *"seizure, absence"* AND *"status epilepticus"[MeSH Terms]* OR *"status epilepticus, generalized"* OR *"generalized status epileptics"* OR *"petit mal status"* OR *"status, petit mal"* OR *"absence status"* OR *"status, absence"* OR *"complex partial status epileptics"* OR *"status epilepticus, complex partial"* OR *"grand mal status epilepticus"* OR *"generalized convulsive status epilepticus"* OR *"status epilepticus, generalized convulsive"* OR *"status epilepticus, grand mal"* OR *"non-convulsive status epilepticus"* OR *"non convulsive status epilepticus"* OR *"status epilepticus, non-convulsive"* OR *"status epilepticus, non convulsive"* OR *"simple partial status epilepticus"* OR *"status epilepticus, simple partial" OR "status epilepticus, subclinical"* OR *"subclinical status epilepticus"* OR *"status epilepticus, electrographic"* OR *"electrographic status epilepticus"* AND *"anti-inflammatory"[MeSH Terms]* OR *"anti inflammatory agents"* OR *"anti-inflammatories"* OR *"anti-inflammatory agent"* OR *"agent, anti-inflammatory"* OR *"anti inflammatory agent"* OR *"antiinflammatory agent"* OR *"agent, anti-*

inflammatory" OR *"agents, anti-inflammatory"* OR *"agents, anti inflammatory"* OR *"agents, anti-inflammatory"* OR *"anti-inflammatories"* OR *"anti inflammatories"* OR *"antiinflammatory agents"*

Estratégia de busca: Web of Science:

TS = ("epilepsy" OR "epilepsies" OR "seizure disorder" OR "seizure disorders" OR "cryptogenic epilepsy" OR "cryptogenic epilepsies" OR aura OR "awakening epilepsy")

AND

TS = ("seizure" OR "Jacksonian seizure" OR "single seizure" OR "atonic absence seizure" OR "focal seizure" OR "partial seizure" OR "generalized seizure" OR "sensory seizure" OR "auditory seizure" OR "convulsive seizure" OR "motor seizure" OR "gustatory seizure" OR "olfactory seizure" OR "somatosensory seizure" OR "vertiginous seizure" OR "vestibular seizure" OR "visual seizure" OR "non-epileptic seizure" OR "complex partial seizure" OR "epileptic seizure" OR "absence seizure" OR "tonic-clonic seizure" OR "myoclonic seizure" OR "clonic seizure" OR "tonic seizure" OR "atonic seizure" OR "convulsion")

AND

TS = ("*status epilepticus*" OR "generalized *status epilepticus*" OR "petit mal *status*" OR "absence *status*" OR "complex partial *status epilepticus*" OR "grand mal *status epilepticus*" OR "non-convulsive *status epilepticus*" OR "simple partial *status epilepticus*" OR "subclinical *status epilepticus*" OR "electrographic *status epilepticus*")

AND

TS = ("anti-inflammatory" OR "anti-inflammatory agent" OR "anti-inflammatory agents" OR "anti-inflammatory agent" OR "anti-inflammatory agents" OR "anti-inflammatories")

Estratégia de busca: SCIELO

("epilepsy" OR "epilepsies" OR "seizure disorder" OR "seizure disorders" OR "cryptogenic epilepsy" OR "cryptogenic epilepsies" OR "aura" OR "awakening epilepsy")

AND

("seizure" OR "Jacksonian seizure" OR "single seizure" OR "atonic absence seizure" OR "focal seizure" OR "partial seizure" OR "generalized seizure" OR "sensory seizure" OR "auditory seizure" OR "convulsive seizure" OR "motor seizure" OR "gustatory seizure" OR "olfactory seizure" OR "somatosensory seizure" OR "vertiginous seizure" OR "vestibular seizure" OR "visual seizure" OR "non-epileptic seizure" OR "complex partial seizure" OR "epileptic seizure" OR "absence seizure" OR "tonic-clonic seizure" OR "myoclonic seizure" OR "clonic seizure" OR "tonic seizure" OR "atonic seizure" OR "convulsion")

AND

("*status epilepticus*" OR "generalized *status epilepticus*" OR "petit mal *status*" OR "absence *status*" OR "complex partial *status epilepticus*" OR "grand mal *status epilepticus*" OR "non-convulsive *status epilepticus*" OR "simple partial *status epilepticus*" OR "subclinical *status epilepticus*" OR "electrographic *status epilepticus*")

AND

("anti-inflammatory" OR "anti-inflammatory agent" OR "anti-inflammatory agents" OR "anti-inflammatory agent" OR "anti-inflammatory agents" OR "anti-inflammatories")

II – PRISM CHECKLIST

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page and manuscript
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction and manuscript
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 3 and manuscript
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2.2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 2.2.3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 2.2.4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.2.5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 2.2.5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Section 2.2.5 and Table 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 2.2.5 and Table 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.2.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5).	Section 2.2.7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing	Section

Section and Topic	Item #	Checklist item	Location where item is reported
		summary statistics, or data conversions.	2.2.7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Section 2.2.7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 2.2.7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Section 2.2.7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Section 2.2.7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section 2.2.7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Section 2.2.7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3.1/Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section 3.1
Study characteristics	17	Cite each included study and present its characteristics.	Section 3.2 and Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 3.3.7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Section 3.3.7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section 3.3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Section 3.3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Section 3.3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Section 3.3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Section 3.3.7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Section 3.3.7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4
	23b	Discuss any limitations of the evidence included in the review.	Section 4
	23c	Discuss any limitations of the review processes used.	Section 4

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Section 4
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Section 2.1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 2.1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Section 2.1
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p.84
Competing interests	26	Declare any competing interests of review authors.	p.84
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p.84

III – SYRCLE CHECKLIST

Table 2 SYRCLE's tool for assessing risk of bias

From: SYRCLE's risk of bias tool for animal studies

Item	Type of bias	Domain	Description of domain	Review authors judgment
1	Selection bias	Sequence generation	Describe the methods used, if any, to generate the allocation sequence in sufficient detail to allow an assessment whether it should produce comparable groups.	Was the allocation sequence adequately generated and applied? (*)
2	Selection bias	Baseline characteristics	Describe all the possible prognostic factors or animal characteristics, if any, that are compared in order to judge whether or not intervention and control groups were similar at the start of the experiment.	Were the groups similar at baseline or were they adjusted for confounders in the analysis?
3	Selection bias	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment.	Was the allocation adequately concealed? (*)
4	Performance bias	Random housing	Describe all measures used, if any, to house the animals randomly within the animal room.	Were the animals randomly housed during the experiment?
5	Performance bias	Blinding	Describe all measures used, if any, to blind trial caregivers and researchers from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?
6	Detection bias	Random outcome assessment	Describe whether or not animals were selected at random for outcome assessment, and which methods to select the animals, if any, were used.	Were animals selected at random for outcome assessment?
7	Detection bias	Blinding	Describe all measures used, if any, to blind outcome assessors from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	Was the outcome assessor blinded?
8	Attrition bias	Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized animals), reasons for attrition or exclusions, and any re-inclusions in analyses for the review.	Were incomplete outcome data adequately addressed? (*)
9	Reporting bias	Selective outcome reporting	State how selective outcome reporting was examined and what was found.	Are reports of the study free of selective outcome reporting? (*)
10	Other	Other sources of bias	State any important concerns about bias not covered by other domains in the tool.	Was the study apparently free of other problems that could result in high risk of bias? (*)

*Items in agreement with the items in the Cochrane Risk of Bias tool.

From: HOOIJMANS, C.R., ROVERS, M.M., DE VRIES, R.B. *et al.* SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 14, 43 (2014). https://doi.org/10.1186/1471-2288-14-43.

III – CAMARADES CHECKLIST

Pooling of Animal Experimental Data Reveals Influence of Study Design and Publication Bias

Malcolm R. Macleod, PhD; Tori O'Collins, BSci; David W. Howells, PhD; Geoffrey A. Donnan, MD

Background and Purpose—The extensive neuroprotective literature describing the efficacy of candidate drugs in focal ischemia has yet to lead to the development of effective stroke treatments. Ideally, the choice of drugs taken forward to clinical trial should be based on an unbiased assessment of all available data. Such an assessment might include not only the efficacy of a drug but also the in vivo characteristics and limits—in terms of time window, dose, species, and model of ischemia used—to that efficacy. To our knowledge, such assessments have not been made. Nicotinamide is a candidate neuroprotective drug with efficacy in experimental stroke, but the limits to and characteristics of that efficacy have not been fully described.

Methods—Systematic review and modified meta-analysis of studies of experimental stroke describing the efficacy of nicotinamide. The search strategy ensured ascertainment of studies published in full and those published in abstract only. DerSimonian and Laird random effects meta-analysis was used to account for heterogeneity between studies.

Results—Nicotinamide improved outcome by 0.287 (95% confidence interval 0.227 to 0.347); it was more effective in temporary ischemia models, after intravenous administration, in animals without comorbidities, and in studies published in full rather than in abstract. Studies scoring highly on a quality measure gave more precise estimates of the global effect.

Conclusions—Meta-analysis provides an effective technique for the aggregation of data from experimental stroke studies. We propose new standards for reporting such studies and a systematic approach to aggregating data from the neuroprotective literature. **(*Stroke*. 2004;35:1203-1208.)**

Key Words: meta-analysis ■ stroke ■ animal models ■ neuroprotection ■ nicotinamide

The failure of neuroprotective drugs in clinical trials represents a major challenge to the doctrine that animals provide a scientifically valid model for human stroke. This failure has provided the impetus for the creation of the Stroke Academic Industry Roundtable (STAIR) in an attempt to overcome the difficulties in taking animal neuroprotectants to successful clinical trial in humans.[1–3] It has been argued that for many drugs so tested, the animal data were not sufficiently robust to warrant the expectations placed on them.[4] Furthermore, the sheer volume of the published neuroprotective literature, with >4000 publications describing the neuroprotective efficacy of >700 drugs (our unpublished observations), renders it is virtually impossible for any individual to maintain an overview of the field.

Systematic review and meta-analysis have contributed greatly to the interpretation and aggregation of data in the clinical sciences. Systematic review uses a methodical approach to minimize the risk of bias in the selection of studies for inclusion, whereas meta-analysis combines results from individual studies to produce a better estimate of treatment effect. Stratified meta-analysis can then be used to explore the impact of particular study characteristics.[5]

Nicotinamide (Vitamin B3) is a precursor of nicotine adenine dinucleotide, an important cofactor in energy metabolism.[6] Nicotinamide also inhibits poly (ADP-ribose) polymerase, an enzyme activated after DNA strand breaks; animals with targeted deletions in PARP have reduced infarct volume after experimental ischemia,[7] suggesting that drugs that inhibit PARP activity may be effective in stroke.

We have investigated the characteristics of nicotinamide in experimental stroke using the techniques of systematic review, meta-analysis, and stratified meta-analysis. Specifically, we have calculated a global estimate of the efficacy of nicotinamide, and we have examined the impact of study quality and various study characteristics on the estimate of effect size.

Materials and Methods

Studies of nicotinamide in animal models of stroke were identified from Pubmed (1974 to June 2003), Embase (1980 to June 2003), and

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***Stroke* is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000125719.25853.20**

Characteristics of Included Studies

Publication	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	Score	Ref
Sun	1998	X	X	X		X	X					5	11
Ayoub	1999	X	X				X			X		4	12, 21
Ogilvy	1999						Nk					0	23
Mokudai	2000	X	X	X	X	X	X			X		7	13, 22
Sakakibara	2000	X	X		X		X			X		5	14
$Maynard_1$	2001	X	X				X			X		4	15
$Maynard_2$	2001						Nk					0	27
Shen	2001						Nk					0	25
Ayoub	2002	X	X				X			X		4	16, 26
Chang	2002	X					X			X		3	17
Sakakibara	2002	X	X			X	X	X		X		6	18
Yang	2002	X								X		2	19
Sadanaga-Akiyoshi	2003	X	X	X			X	X		X		6	20, 28
Sarhan	2003	X	X				X			X		4	24, 29

Studies fulfilling the criteria of: (1) peer reviewed publication; (2) control of temperature; (3) random allocation to treatment or control; (4) blinded induction of ischemia; (5) blinded assessment of outcome; (6) use of anesthetic without significant intrinsic neuroprotective activity; (7) animal model (aged, diabetic, or hypertensive); (8) sample size calculation; (9) compliance with animal welfare regulations; and (10) statement of potential conflict of interests. Also see supplementary material.

Ref indicates references; Nk, not known.

BIOSIS (1969 to June 2003). Our search strategy used the words [<nicotinamide> OR <Vitamin B3>] AND [<stroke> OR <ischemia>]. We also performed hand-searching of abstracts of scientific meetings, reference lists of identified publications, and requests to senior authors of identified publications for references to other studies. We included all controlled studies of the effect of nicotinamide in animal models of focal cerebral ischemia in which the outcome was measured as a volume of infarction or a neurological score.

We extracted data for mean outcome, standard deviation (SD), and number of animals per group for individual comparisons (defined as the assessment of outcome in treatment and control groups after treatment with a given dose of drug or vehicle, with treatment starting a given time before or after the induction of cerebral ischemia). Values for data expressed graphically were requested from authors. When nicotinamide was administered in multiple doses, the comparison was grouped according to the first dose at the first time it was administered.

When neurological tests were performed at different times, only the final test was included. When 1 group of animals were scored in >1 neurological domain (for instance, motor and sensory scores), or when both neurological score and infarct volume were measured, data were combined using meta-analysis (see later) to give an overall estimate of effect size and its standard error. We defined effect size as the proportional reduction in outcome (infarct volume, neurological score, or combined score) in treated animals relative to untreated ischemic controls.

Methodological quality of individual studies was assessed according to published criteria[4,8] refined in discussion between basic and clinical scientists. These criteria were: peer-reviewed publication; statement of control of temperature; random allocation to treatment or control; blinded induction of ischemia; blinded assessment of outcome; use of anesthetic without significant intrinsic neuroprotective activity; appropriate animal model (aged, diabetic, or hypertensive); sample size calculation; compliance with animal welfare regulations; and statement of potential conflict of interests. Each study was given a quality score out of a possible total of 10 points, and the group median was calculated.

For each comparison, the mean outcome for the treatment group and the SDs in treatment and control groups were expressed as a proportion of the outcome in the control group, and the effect size (the difference between the treatment and control groups) and its standard error were calculated. Data were aggregated using a weighted mean difference method; because of anticipated heterogeneity between studies, we used the random effects model of DerSimonian and Laird,[9] in which the weighting given to individual comparisons depends on the variance within those comparisons and on overall heterogeneity (see supplementary material, available online at http://stroke.ahajournals.org). This is a generally more conservative technique than fixed-effects meta-analysis.

When a control group served >1 experimental group, the number of observations in that control group was, for the purpose of the meta-analysis, divided by the number of experimental groups served.

To explore the impact of study characteristics on estimates of effect size, we then performed a stratified meta-analysis[10] with experiments grouped according to: methodological score; use of aged, diabetic, or hypertensive experimental animals; anesthetic used; whether the data had been published in full or in abstract; permanent or temporary ischemia; outcome measure; route of drug delivery; and species and gender of animal used. The significance of differences between n groups was assessed by partitioning heterogeneity and by using the χ^2 distribution with n−1 degrees of freedom (df).

Results

Electronic searching identified 157 publications, of which 14 described experiments reporting the effect of nicotinamide in focal cerebral ischemia in which the outcome was expressed as a volume of infarction or a neurological score, and hand-searching identified a further 4 publications. There were 10 full articles[11–20] and 8 abstracts.[21–28] Four abstracts described work that was also described in full articles,[21,22,26,28] and 1 further abstract has been published in full since the search was performed.[29] This meta-analysis is therefore based on data from 11 full articles and 3 abstracts.

Study characteristics are shown in the Table. No study described a sample size calculation or disclosed a potential conflict of interest, even though some studies included in

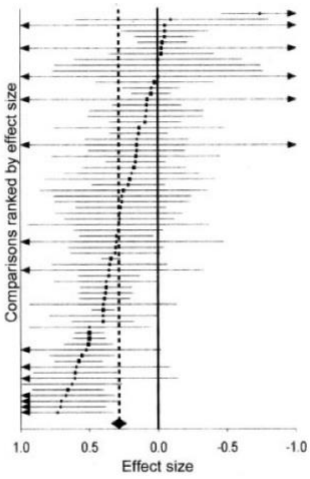

Figure 1. Point estimate and 95% confidence intervals for global estimate and each of 71 comparisons ranked by effect size. Effect size is the improvement in treated animals expressed as a proportion of the outcome in control animals. The diamond indicates the global estimate and its 95% confidence interval. The solid vertical line marks where treatment and control are equal. The size of each point reflects the weight of that comparison in the meta-analysis. For a more detailed version of this figure, see supplementary material (available online at http://stroke.ahajournals.org).

authorship individual(s) holding a patent for the use of nicotinamide in ischemic stroke. Random allocation to treatment group and blinded assessment of outcome were described in 3 studies each, and 2 studies reported that ischemia was induced by an investigator blinded to treatment allocation. The median quality score (see Methods) was 3.5 (range 0 to 7).

The global estimate of the effect of nicotinamide was 0.287 (95% confidence interval 0.227 to 0.347, $P<0.00001$), an improvement in outcome of ≈30% (Figure 1). There was substantial statistical heterogeneity ($\chi^2=207$, df=70, $P<0.00001$), consistent with substantial biological heterogeneity between the studies. Doses of nicotinamide from 100 mg/kg to 750 mg/kg were significantly protective, as were treatments beginning 90 minutes to 6 hours after the onset of ischemia (Figure 2). Although the lack of efficacy beyond 6 hours was expected, an early limit to the time window for efficacy was not. This was observed even when drug was administered before middle cerebral artery occlusion and therefore cannot be explained by a failure of drug to reach brain. This suggests that the concept that neuroprotective drugs have maximum efficacy when administered as soon as possible after stroke onset may need revised, and that some drugs may be most effective if administered later in the course of stroke.

Nicotinamide was less effective in animals with diabetes or hypertension (0.218, 0.131, to 0.304) than in healthy animals (0.300, 0.232 to 0.367; $\chi^2=7.4$, df=1, $P<0.01$). There was a nonsignificant increase in efficacy in studies using ketamine anesthesia (0.414, 0.276 to 0.553 versus 0.265, 0.200 to 0.331; $\chi^2=2.5$, df=1, $P=0.11$). Comparisons published in abstract only gave a significantly lower estimate of effect size (0.162, 0.066 to 0.258) than those subjected to peer review and published in full (0.306, 0.241 to 0.371; $\chi^2=12.2$, df=1, $P<0.001$). More generally, comparisons from studies scoring highly for methodological quality tended to give a more precise estimate of the global estimate than those from low-quality studies (Figure 3).

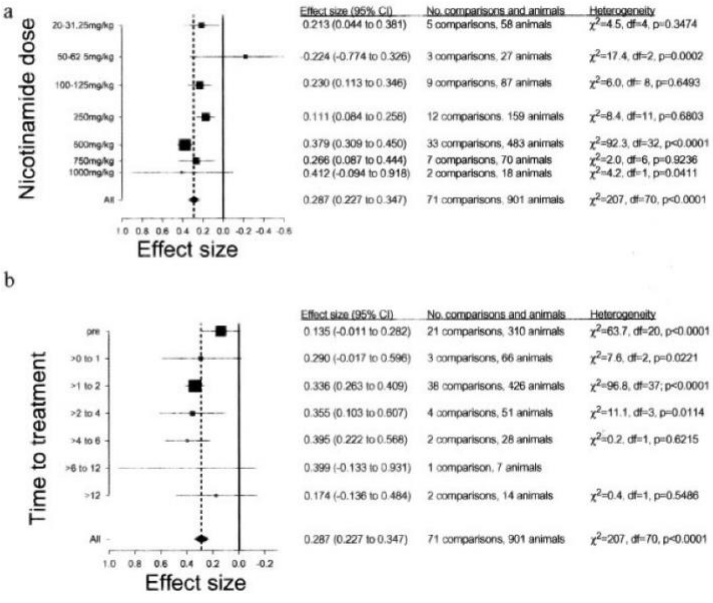

Figure 2. Point estimates and 95% confidence intervals of effect size for (a) dose and (b) time to treatment. Where the 95% confidence interval does not reach the solid vertical line, outcome is significantly different from control ($P<0.05$). The text indicates effect size and 95% confidence interval; number of comparisons and of animals contributing to each point; χ^2 test, and probability of observed heterogeneity. The size of each point reflects the weight of that comparison in the meta-analysis.

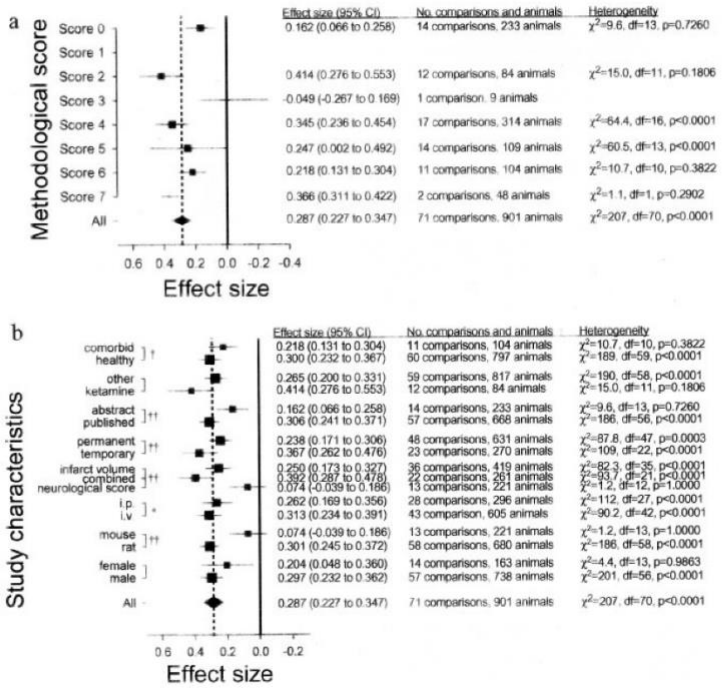

Figure 3. Point estimate of effect size and 95% confidence intervals for a stratified meta-analysis according to (a) methodological score or (b) study characteristics. For details, see Figure 2 legend. In (a), groupings are significantly different (partitioning of heterogeneity, $P<0.001$). In (b), *$P<0.05$, †$P<0.01$, and ††$P<0.001$ by partitioning of heterogeneity.

Nicotinamide was more effective when cerebral ischemia was temporary (0.367, 0.262 to 0.476) than when permanent (0.238, 0.171 to 0.306; $\chi^2=11.0$, df=1, $P<0.001$), and after intravenous (0.313, 0.234 to 0.391) rather than intraperitoneal (0.262, 0.169 to 0.356) administration ($\chi^2=4.8$, df=1, $P<0.05$). Comparisons reporting both infarct volume and neurological score gave a higher estimate of effect size (0.392, 0.287 to 0.478) than those reporting infarct volume (0.250, 0.173 to 0.327) or neurological score (0.074, −0.039 to 0.186) alone ($\chi^2=30.1$, df=2, $P<0.0001$). Nicotinamide was effective in rats (0.301, 0.245 to 0.372) but not in mice (0.074, −0.039 to 0.186) ($\chi^2=20.3$, df=1, $P<0.0001$), and although outcome in male animals (0.297, 0.232 to 0.362) was not significantly higher than that in females (0.204, 0.048 to 0.360; $\chi^2=2.4$, df=1, $P=0.12$), a biologically important effect cannot be excluded. In a post hoc analysis, stratification by animal model suggested that efficacy was greater in surgical occlusion than in photothrombotic or filament occlusion models ($\chi^2=37.3$, df=3, $P<0.0001$).

Discussion

We have shown a robust neuroprotective effect of nicotinamide in experimental stroke. Although the effect is modest compared with that reported for many other drugs in single studies, this is the first systematic meta-analysis of any neuroprotective drug in experimental stroke. No true comparison with other drugs is possible, as yet, because such rigorous assessments have not been available.

Nava-Ocampo et al[30] describe a meta-analysis of glutamate release inhibitors in experimental stroke. However, their search strategy was limited to MEDLINE. Although they, too, extracted data for individual comparisons, they excluded 17 of 47 comparisons to attain statistical heterogeneity, and they do not describe the meta-analysis technique used. The systematic review of nimodipine in experimental stroke by Horn et al[8] used a limited search strategy that would have missed 4 of our 14 studies. Because we disaggregated data into individual comparisons, we have been able to explore the effect of drug dose and time to treatment rather than simply a global effect of drug. Finally, grouping according to study characteristics has allowed, for the first time, a systematic exploration of the impact of study design on effect size.

Although the stratified meta-analyses were prespecified, results should be interpreted with caution because this is a form of subgroup analysis. Increased efficacy with temporary ischemia is biologically plausible and provides further support for the combination of neuroprotection with thrombolysis.[31,32] Experiments using healthy animals, ketamine anesthesia, or male animals may overstate effect size. Ischemic stroke generally occurs in elderly patients with associated medical problems, and our data are consistent with the work of Davis et al showing reduced efficacy for the NMDA receptor antagonist D-CPPene in aged rats.[33] Financial and ethical considerations discourage the use of aged rats, but despite the availability of spontaneously hypertensive rats, and of streptozotocin to render animals diabetic, this approach is not widespread. Most models of experimental stroke require anesthesia for the induction of ischemia; some anesthetic agents, including ketamine, have marked intrinsic neuroprotective activity, particularly when administered in

combination with other drugs,[17] and if it is necessary to use a stroke model requiring anesthesia, these anesthetics should be avoided.

The smaller effect size for studies published only in abstract demonstrates publication bias. Meta-analysis can only consider available data, and groups who have found no effect of nicotinamide may not have published their results at all, even in abstract. It is therefore likely that the impact of publication bias is even larger than we estimate here. Although journals may not favor negative studies, a medium for their publication should be found to avoid further distortion of the literature.

Using random effects meta-analysis, the weighting given to individual comparisons is derived from the variance of data within that comparison and the heterogeneity between comparisons. Alternative weighting systems based on study quality have some attractions, but these are often subjective judgements, and a weighting based on variance reflects sample size and, to a degree, the quality of the data.

Studies varied in their methodological quality score, and low-quality score was associated with less precise estimates of the overall observed effect size. We believe that the components of the score have an important bearing on study quality. However, some components are more important than others, and some important components may have been omitted; the development of more sophisticated quality scores, perhaps with weighting of different components, is an important area for future research.

Some components such as publication after peer review, randomization to treatment group, and blinded assessment of outcome are widely accepted. For the rest, we believe that it is important for ischemia to be induced blinded to treatment allocation (or for randomization to occur after the induction of ischemia) to prevent a bias in the severity of the induced infarct. Although it would be best to avoid all anesthesia, some anesthetics have much higher intrinsic neuroprotective activity, and their use is, we believe, relevant to study quality. Although there is no evidence that experiments using aged, diabetic, or hypertensive animals provide a better model of human stroke, given the prevalence of these comorbidities in human stroke, it seems likely that such models may be more relevant. Sample size calculations are uncommon in the animal literature, and most studies are underpowered. We believe that such calculations should be routinely reported. Finally, because the financial interests of authors or sponsors may lead to biased data interpretation, many journals now require a statement of any potential conflicts of interest. However, publications may predate the requirement for such disclosure and, even now, not all journals require such disclosure. This remains an important quality issue.

Despite such concerns, these studies compare favorably with others in the animal literature, although less favorably with clinical studies. There is no fundamental reason why such standards cannot be achieved in basic science. In our laboratory, we have adopted the principles of randomization to treatment group; performance of surgery blinded to treatment allocation; blinded assessment of outcome; minimization of use of anesthetics with intrinsic neuroprotective activity; increased use of hypertensive and diabetic animals; and full reporting of potential conflicts of interest. We recommend that others do the same. Journals publishing studies in experimental stroke should consider the development of guidelines similar to the CONSORT guidelines for clinical studies[34] to act as a force for quality improvement.

We have demonstrated the use of systematic review and meta-analysis in the preclinical assessment of candidate stroke drugs. Extending this approach to other putative neuroprotectants will allow a more systematic assessment of relative efficacy, will generate hypotheses for testing in further animal experiments, will provide robust information about the characteristics of individual drugs, and may provide the basis for a new classification of neuroprotective drugs based on their in vivo characteristics rather than their putative mode of action.

Given the huge number of putative neuroprotective agents, such a classification represents a considerable challenge. We propose a collaborative approach, modeled on the Cochrane Collaboration, to develop a rigorous evidence-based summary of animal experimental stroke data. This would inform the choice of drugs for clinical trial and therefore protect trial participants from exposure to potentially dangerous drugs with limited, and often overestimated, efficacy.

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5. CONSIDERAÇÕES FINAIS

Esta revisão sistemática expõe uma busca abrangente para compilar estudos sobre os efeitos de anti-inflamatórios esteroidais e não esteroidais (bem como com mecanismos similares) em modelos animais de indução química de crises tipo-convulsivas. Nosso objetivo foi resumir as informações de todos os artigos encontrados, identificando os impactos desses anti-inflamatórios nos parâmetros avaliados, e assim, estabelecer uma base para reconhecer fatores favoráveis e desfavoráveis nesses estudos.

A maioria dos anti-inflamatórios apresentou efeitos benéficos, promovendo melhorias tanto nas manifestações das crises tipo-convulsivas quanto nos marcadores inflamatórios e histopatológicos. Contudo, alguns estudos observaram efeitos negativos, que podem ter uma relação multifatorial. Houve a identificação de limitações importantes, como a grande variabilidade no delineamento experimental dos estudos e a discrepância no número de pesquisas para cada anti-inflamatório, bem como a falta da determinação de efeitos adversos.

Assim, são necessários mais estudos para comparar pontos específicos de cada anti-inflamatório, replicando ensaios pré-clínicos para confirmar os achados e aprofundar nosso conhecimento. Para isso, a realização de uma meta-análise forneceria estimativas mais precisas acerca do potencial terapêutico de cada fármaco considerando a heterogeneidade dos estudos e avaliando a consistência dos mesmos; o que seria útil para definir protocolos mais assertivos. Em suma, esta revisão sistemática evidenciou o efeito neuroprotetor dos anti-inflamatórios na maioria dos estudos, provavelmente através de vias anti-inflamatórias. Esses resultados são promissores e podem servir como base para futuros ensaios clínicos, abrindo caminho para novas abordagens terapêuticas no tratamento da epilepsia.

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