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Review article

The effectiveness of anti-inflammatory agents in reducing chemotherapy-induced cognitive impairment in preclinical models – A systematic review

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ABSTRACT

Chemotherapy-induced cognitive impairment (CICI) is a debilitating condition resulting from chemotherapy administration for cancer treatment. CICI is characterised by various cognitive impairments, including issues with learning, memory, and concentration, impacting quality of life. Several neural mechanisms are proposed to drive CICI, including inflammation, therefore, anti-inflammatory agents could ameliorate such impairments. Research is still in the preclinical stage; however, the efficacy of anti-inflammatories to reduce CICI in animal models is unknown. Therefore, a systematic review was conducted, with searches performed in PubMed, Scopus, Embase, PsycInfo and Cochrane Library. A total of 64 studies were included, and of the 50 agents identified, 41 (82%) reduced CICI. Interestingly, while non-traditional anti-inflammatory agents and natural compounds reduced impairment, the traditional agents were unsuccessful. Such results must be taken with caution due to the heterogeneity observed in terms of methods employed. Nevertheless, preliminary evidence suggests anti-inflammatory agents could be beneficial for treating CICI, although it may be critical to think beyond the use of traditional anti-inflammatories when considering which specific compounds to prioritise in development.

1. Introduction

Cancer treatment typically uses a multimodal approach, comprising surgery, radiotherapy, and chemotherapy (Mounier et al., 2020). Increased cancer survivorship has been attributed in large part to advances in chemotherapy targeting and pharmacology (Matsos and Johnston, 2019; Selamat et al., 2014). However, chemotherapy treatments induce a wide-range of toxicities which affect patient quality of life, including hair loss, nausea, fatigue, neuropathy, and an area of growing research interest, cognitive impairment (Ahles et al., 2002; Wefel et al., 2004). Cognitive impairment can occur either during chemotherapy treatment or immediately following treatment and may persist for several years post treatment (Foley et al., 2008). This impairment typically presents as deficits in memory, learning, attention, concentration, as well as slower processing speed (Boykoff et al., 2009; Foley et al., 2008). This is a condition known as chemotherapy-induced cognitive impairment (CICI), or colloquially, 'chemobrain.' CICI affects as many as 70% of cancer survivors (Dijkshoorn et al., 2021; Janelsins et al., 2014; Whittaker et al., 2021), with mild to moderate impairments shown to last anywhere between 6 months and 20 years following cessation of treatment (Collins et al., 2009; Koppelmans et al., 2012). These impairments can negatively impact quality of life for cancer survivors, as it can become harder to care for families, work, study or maintain a social life (Wefel et al., 2004). This has a profound effect on the individual, with cancer survivors emphasising the need to adjust to a "new normal," with changes in personal identity, social interactions and working life needed to be made (Henderson et al., 2019). Concerningly, in spite of suggestions that various lifestyle modifications such as exercising may help to ameliorate the condition, there are currently no recommended therapeutic treatment strategies for CICI (Nguyen and Ehrlich, 2020).

To develop an effective therapeutic strategy, it is first critical to understand the neural mechanisms that underlie cognitive changes following chemotherapy treatment. A range of potential mechanisms have been implicated in driving the central nervous system (CNS) changes leading to cognitive decline in CICI, including the ability of

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chemotherapeutic agents to alter the permeability of the blood brain barrier (BBB) (Jacobs et al., 2010; Wardill et al., 2016), promote oxidative stress, and increase inflammation (Argyriou et al., 2011; Matsos and Johnston, 2019; Ren et al., 2019). Among these, in recent years, there has been growing evidence for the role that neuroinflammation plays in the development of this condition (Vichaya et al., 2015). Neuroinflammation is a protective immune response within the brain and spinal cord that occurs in response to harmful stimuli, including pathogens, dead cells, or irritants (DiSabato et al., 2016). The anti-inflammatory response is the regular response when a harmful insult occurs, resulting in the release of cytokines, such as IL-4, IL-10 and IL-13, through the M2 anti-inflammatory phenotype (Tohidpour et al., 2017). Conversely, the pro-inflammatory response is where neuroinflammation can spiral out of control and pro-inflammatory cytokines are released, such as IL-1β and TNF-α, through the M1 proinflammatory phenotype (Santos and Pyter, 2018; Tohidpour et al., 2017). An insufficient inflammatory response can lead to the persistent infection of pathogens; therefore, some form of inflammation is required (Guo et al., 2015). However, when neuroinflammation becomes chronic, it can lead to the spread of inflammation throughout the brain, and ultimately, damage to cellular components, structural changes, and neuronal cell death (Guo et al., 2015).

It is believed that inflammatory processes in the CNS play an important role in the cell death pathway, contributing to several neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (Dheen et al., 2007). Similarly, neuroinflammation has also been shown to play a role in the development of CICI (Briones and Woods, 2014; George et al., 2021; Matsos and Johnston, 2019). For example, CICI studies have shown that treatment with various types of chemotherapeutic agents accentuates the production and release of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6 (Seruga et al., 2008). Another study investigating the use of methotrexate (MTX) chemotherapy found that microglial activation within the hippocampus was increased at one and three weeks following treatment in adult male Wistar rats (Seigers et al., 2010). Additionally, a study investigating various types of chemotherapy treatments in a breast cancer cohort found that when compared to chemotherapy-naïve or healthy patients, there was increased inflammation in the brain, which was associated with impaired cognition (Schroyen et al., 2021). This was characterised by a 20-fold higher level of NfL, a marker of axonal damage, and increased relative glial expression (Schroyen et al., 2021).

Based on this evidence for the role of neuroinflammation in CICI development, it follows that anti-inflammatory agents may be effective therapeutic options for preventing or treating CICI. Traditionally, the term anti-inflammatory agent refers to non-steroidal anti-inflammatory drugs (NSAIDs) (Vane and Botting, 1998). These agents block cyclooxygenase (COX) enzymes to reduce prostaglandins and resultant inflammation (Chaiamnuay et al., 2006). Therefore, their use in blocking the inflammation observed in CICI is promising to investigate. However, a range of other drugs or nutraceuticals may also possess anti-inflammatory properties, acting via other mechanisms to reduce neuroinflammation, and therefore may also have utility for ameliorating the cognitive deficits observed in CICI. At this point in time, however, many anti-inflammatory agents are experimental in nature or may have shown promise in other conditions affecting cognition but have yet to be repurposed for CICI. As a result, screening of these compounds in preclinical models is needed to investigate their effectiveness for the treatment of CICI, and such work is currently well underway. From here, in order to move suitable anti-inflammatory candidates from preclinical models into clinical trials, it is imperative that an assimilation of the literature is performed to provide an evidence-base for this decision.

Therefore, a systematic review of the literature was conducted to determine whether agents that exert anti-inflammatory properties or effects are able to ameliorate CICI in preclinical models. This will guide researchers towards those agents where further preclinical studies or clinical trials are warranted, with the goal of finding a therapeutic agent to target and treat CICI, to ultimately improve quality of life for those experiencing this condition.

2. Methods

An a priori protocol for this review was registered through PROSPERO (CRD42021240789). Review reporting is in accordance with the 2020 PRISMA guidelines (Page et al., 2021).

2.1. Search strategy

A comprehensive database search was performed in April 2021, with an updated search undertaken in October 2021, in MEDLINE via PubMed, EMBASE, Cochrane Library, PsychInfo and Scopus, in order to identify relevant publications. The search strategy was developed based on an initial scoping search and in consultation with a medical information specialist. The search consisted of terms such as, 'anti-inflammatory agents,' 'chemotherapy,' 'cognitive impairment,' 'pre-clinical models,' and related synonyms. Further records were sourced through citation searching. Grey literature sourced through these databases was eligible for inclusion; however, conference abstracts and review articles were excluded. See appendix A for developed search strategies.

2.2. Study selection

Following the search, identified citations were uploaded into EndNote X9.3.3 and duplicates were removed. Potentially relevant studies were retrieved in full, and their citation details imported into Covidence (Veritas Health Innovation, Melbourne, Australia). Title screening was conducted by one reviewer, whilst abstract and full text screening for assessment against the inclusion and exclusion criteria (see below) were performed by two independent reviewers. Any conflicts were resolved via discussion, and if a consensus could not be met, a third reviewer was consulted.

2.3. Inclusion criteria

The search had no restrictions on the year of publication; however, only English language publications were included. Inclusion criteria included: 1) Population: any animal model, regardless of age, sex, strain, or species, that had been administered any chemotherapeutic agent, regardless of dose and regime, with the intention of modelling CICI; 2) Intervention: animal model of CICI, as defined below, with co-administration of an anti-inflammatory agent, as defined below; 3) Comparator: groups administered chemotherapy alone as a comparison; 4) Outcome: behavioural test outcomes considered to be relevant for determining cognitive state; 5) Study design: pseudo RCT studies and observational study designs.

2.4. Exclusion criteria

Exclusion criteria included: 1) human clinical or in vitro studies, 2) non-CICI animal model, 3) no anti-inflammatory agent administered, 4) intervention may have had anti-inflammatory actions, but was not able to be administered as a substance, for example, exercise, 5) studies included no chemotherapy-alone group as a comparator, 6) studies where treatment groups did not run in parallel with a control group and, 7) outcome measures were not relevant as a direct determinant of cognition, such as molecular and histological outcomes.

2.5. Chemotherapy-induced cognitive impairment in a preclinical animal model definition

An animal receiving any chemotherapy treatment with the intention of inducing cognitive impairment, as measured through cognitive behavioural testing.

2.6. Anti-inflammatory agent definition

Any agent that is administered as a substance and has confirmed anti-inflammatory mechanisms, properties, or effects, as determined based on peer-reviewed literature. A detailed table outlining each of the included anti-inflammatory's mechanism of action can be found in appendix B.

2.7. Data extraction

Data were extracted from the included studies by two independent reviewers, with a third consulted if necessary when a consensus was not achieved. This data extraction was conducted in Covidence using a modified version of the systems extraction template (see appendix C). The data extracted included behavioural test outcomes, comprising of the test type, cognitive function measured, brain region(s) investigated and their results. Prior to this, two reviewers independently extracted data from three studies and results were discussed to ensure each assessor was uniformly extracting the data. An improvement in cognition was determined to have occurred if there was a significant difference between the groups receiving the anti-inflammatory + chemotherapy compared to the chemotherapy alone control group on a particular behavioural test.

2.8. Assessment of methodological quality

A quality assessment was conducted for each study by the same two independent reviewers using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool (Hooijmans et al., 2014). Papers were classified into a low risk of bias, high risk of bias or an unclear risk of bias based on the following characteristics, 1) random sampling, 2) sample homogeneity, 3) allocation concealment, 4) random housing, 5) trial caregivers and researcher blinding, 6) random outcome assessment, 7) outcome assessor blinding, 8) justification of incomplete outcome data, 9) non-selectivity of outcome reporting and 10) other. The review team recorded 'unclear' when no mention was made of a criterion, reserving a high risk of bias judgement for when methods reported were deemed inappropriate or were clearly not conducted. Conversely, reviewers allocated a low risk of bias when reporting of the above characteristics was mentioned. Studies were included irrespective of quality. Summary graphs were created in Review Manager (RevMan) ([Computer program], Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

2.9. Data synthesis

An initial descriptive analysis of the studies was undertaken to identify relevant subgroups where studies with similar characteristics could be combined. Studies were then grouped according to the type of anti-inflammatory agent investigated and presented accordingly in narrative format. This grouping included: Group 1) traditional anti-inflammatory agents (NSAIDs); Group 2) non-traditional agents with known anti-inflammatory properties or effects; and Group 3) natural compounds with known anti-inflammatory properties or effects. The evidence presented across all studies was also assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) summary of findings (GRADEpro GDT: GRADEpro Guideline Development Tool [software]) (Table 5).

2.10. Statistical analysis

Due to the heterogeneity of the outcomes measured, and low numbers of studies utilising the same anti-inflammatory agent, statistical combination of findings, via meta-analysis was not able to be performed.

3. Results

A total of 5254 studies were identified following database and citation searching. After the removal of duplicates, a total of 4637 remained. After title and abstract screening, a total of 891 studies remained. Following this, 86 papers were identified for full text assessment. During this assessment, 22 studies were excluded due to investigating the incorrect treatment type, such as an agent with no anti-inflammatory properties (n = 6), no animal model used (n = 2), no full text article available (n = 6), incorrect indication (i.e. measuring the efficacy of a chemotherapeutic agent rather than an anti-inflammatory agent), (n = 3), investigating the incorrect intervention (i.e. no chemotherapy treatment) (n = 2), assessing the incorrect cognitive outcomes, such as histological or molecular outcomes (n = 1), or not assessing CICI (n = 2). This resulted in a total of 64 full text papers included in the final review. Details of this process are described in the PRISMA diagram below (Fig. 1).

3.1. Study characteristics

Publication dates ranged from 2008 to 2021, with 58% published between 2019 and 2021. Studies were published across 19 countries, with approximately 21% published in the United States of America. All animal species were included in the search; however, only mouse or rat strains were identified in the included studies. Of the 64 included studies, 62.5% used rats, with 37.5% using mice. Whilst seven rat stocks/strains were investigated, Sprague-Dawley was the most common (38% of studies, with one study failing to report the strain). For mouse studies, ten strains were investigated, with the most common being the inbred C57BL/6 J strain, with 22% utilising this strain. Male animals were the most common sex used, with inclusion in 80% of rat studies and 50% of mouse studies. Only one study investigated both sexes for rats and two mouse studies failed to report the sex. The age of the animals varied, with approximately 39% not stating what age they were when the study commenced, 30% aged between 4 and 8 weeks old, 21% aged between 9 and 14 weeks old, 5% aged between 15 and 20 weeks old and one study each including animals aged 6 months, 10 months and 1 year. Sample sizes ranged from 4 to 25 per group, with seven studies failing to report sample sizes. The time points investigated ranged from 24 h to 90 days post-treatment, with twelve studies either not stating the time point investigated or it was unclear as to what time point was investigated.

Several chemotherapeutic agents were also administered, with six studies investigating the use of agents in combination with each other, one study investigating the use of two separate agents within different treatment groups, and the remainder investigating a single agent. The single agents investigated included cisplatin (CIS) (n = 13), cyclophosphamide (CYP) (n = 5), doxorubicin (DOX) (n = 21), docetaxel (n = 1), 5-flurouracil (5-FU) (n = 2), paclitaxel (PTX) (n = 4), methotrexate (MTX) (n = 6), oxaliplatin (n = 1) and temozolomide (TMZ) (n = 1). Combinations of chemotherapeutic agents included CYP + MTX + 5-FU (CMF) (n = 5), MTX + 5-FU (n = 1), DOX + CYP (n = 2), DOX + cytotoxan (n = 1) and docetaxel + DOX + CYP (DAC) (n = 2). The most common chemotherapeutic agent utilised was DOX (31.25% of included studies), administered either alone or in combination with other agents, with an intraperitoneal injection being the most common route of administration. Dose and dose frequency varied between chemotherapeutic agents and for the same agent investigated across multiple studies. Overall, a repeated dosing regime was utilised across the majority of studies for all agents except OXP. A single dose schedule was also reported for CYP (n = 1), CIS (n = 1), OXP (n = 1) and DOX (n = 1).

A total of 50 anti-inflammatory agents were identified across the 64 studies. These were divided into 3 groups, as outlined above. Group 1 was comprised of only two NSAIDs, being naproxen and aspirin. Group 2 comprised of 26 agents, with the most investigated being donepezil

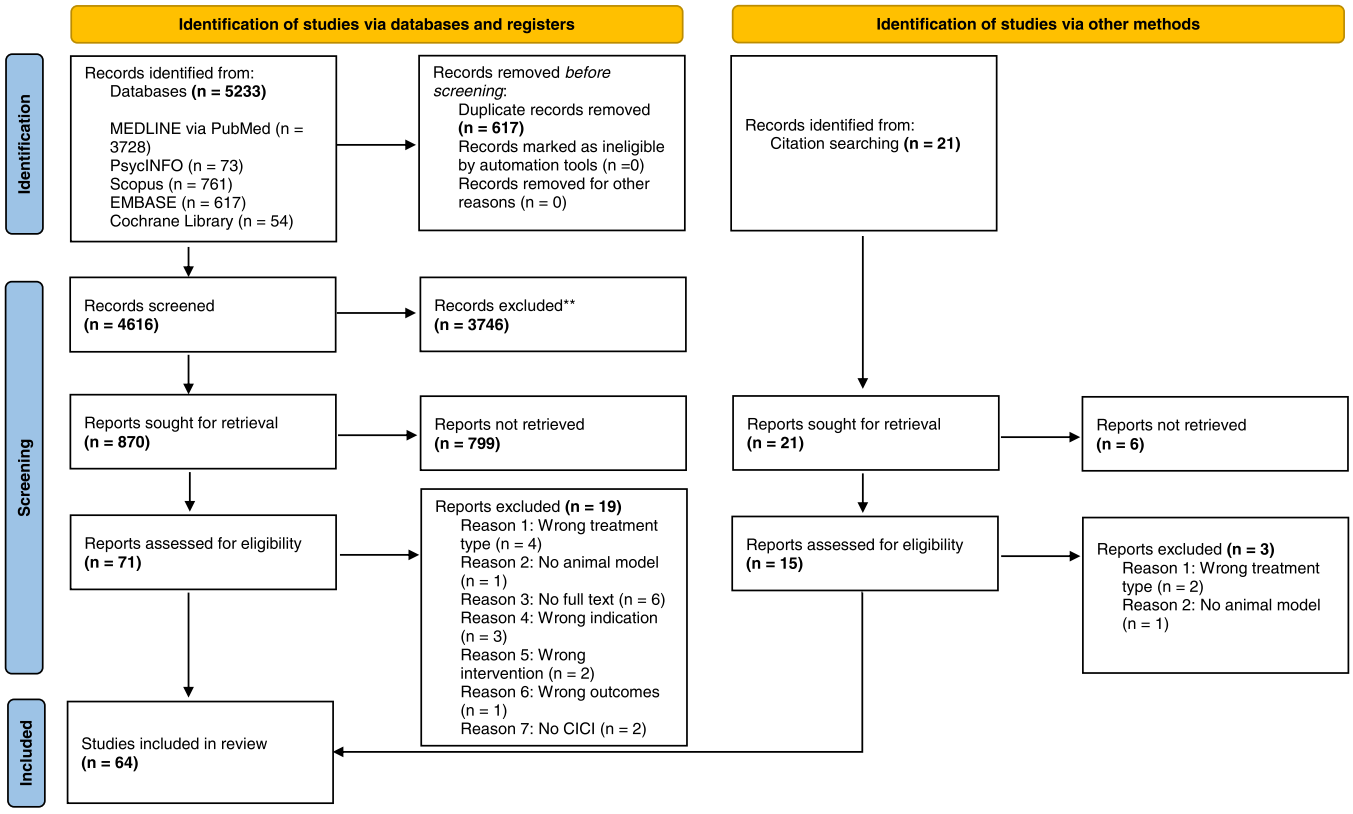

Fig. 1. PRISMA Diagram from 2020 PRISMA guidelines, indicating database searches and number of full text studies identified.

(n = 5), metformin (n = 4), N-acetylcysteine (NAC) (n = 3), lithium (n = 2), memantine (n = 2), fluoxetine (n = 2), melatonin (n = 2), 2-mercaptoethane sulfonate (MESNA) (n = 2) and ACY-1215 (n = 2). Finally, group 3 comprised of 22 agents, with the most investigated being curcumin (n = 4), resveratrol (n = 2) and rutin (n = 2). Oral administration through drinking water, food or gavage was the most common route of administration. Dose and dose frequency varied between agents and studies, but a repeated dose cycle was the most utilised regimen, with the exception of one study, where pifithrin-U was administered in a single dose.

A wide range of behavioural tests was also employed, testing various aspects of cognition. These included tests of different aspects of learning, memory, discrimination ability and problem-solving, spanning different underlying brain regions, as described in Table 1.

3.2. Group 1 – traditional anti-inflammatory agents: behavioural outcomes

Two studies investigated the oral administration of two NSAIDs, aspirin and naproxen, as summarised in Table 2. Neither agent was shown to improve cognition in either study, being unable to restore either short-term spatial memory and reference memory, investigated through the Y-maze after CYP chemotherapy administration (Pavlock et al., 2021), or recognition memory investigated through the NOR test after PTX chemotherapy administration (Chang et al., 2020). Both studies administered the chemotherapeutic agent intraperitoneally, whereas aspirin was orally administered through the animals drinking water and naproxen was orally administrated through the animals' diet.

3.3. Group 2 – non-traditional anti-inflammatories: behavioural outcomes

Of the 64 included studies, a total of 37 investigated the use of a non-traditional anti-inflammatory agent, with a total of 26 agents identified. Of these, 17 agents were investigated once, and 9 were investigated in more than one study, as summarised in Table 3. These included, donepezil (n = 5), metformin (n = 4), NAC (n = 3), lithium (n = 2), memantine (n = 2), fluoxetine (n = 2), melatonin (n = 2), MESNA (n = 2) and ACY-1215 (n = 2). Overall, of the 37 studies, an improvement in cognition was evident in 26 (70.2%). Additionally, 9 studies (24.3%) noted improvement depending on the behavioural test conducted or treatment group type, leaving only 2 studies (5.5%) with no improvements observed. A summary of the aspects of cognition investigated across the included behavioural tests for the 26 identified agents in group 2 and the direction of effect on these aspects of cognition is summarised in Fig. 2.

3.3.1. Donepezil

Five studies investigated the use of donepezil. Lim et al., observed an improvement in cognition after animals received donepezil intraperitoneally following administration of two different chemotherapeutic agents (CYP or DOX), also administered intraperitoneally. These agents were investigated using the MWM and passive avoidance tests. Additionally, cognition improved when donepezil was administered orally for 30 consecutive days, as evidenced through outcomes from the NOL and NOR tests when receiving DOX intraperitoneally (Ongnok et al., 2021). Kinra et al., also found that mice intraperitoneally injected with CMF once a week for three weeks, with concurrent oral donepezil administration, showed an improvement in cognition in the MWM. However, in the final two studies, results were more variable, with both improvements in cognition and no changes observed, depending on the behavioural test investigated, the timing of administration of donepezil and its route of administration. For example, when donepezil was administered subcutaneously 1 h after a combination of DOX and CYP, no improvement in cognition was evident in the MWM; however, when administered 1 h prior to chemotherapy, an improvement in cognition was evident in the MWM (Philpot et al., 2019). For the final study (Winocur et al., 2011), an improvement in cognition, investigated

Table 1
Description of the various behavioural tests employed across the 64 included studies, with the aspects of cognition that they test, and the primary brain region (s) involved in test performance.

Behavioural Test	Aspect of Cognition Tested	Primary Brain Regions Investigated
Y-Maze/spontaneous alternation task	Short-term spatial working and reference memory	Hippocampus, prefrontal cortex, septum, and basal forebrain (Kraeuter et al., 2019)
Object in place	Long-term recognition memory (object, place) and working memory	Hippocampus, perirhinal cortex, medial prefrontal cortex (Winters et al., 2010)
Novel object recognition	Short and long-term recognition memory (object)	Hippocampus, perirhinal cortex (Antunes and Biala, 2012)
Novel object location	Short and long-term recognition memory (place)	Hippocampus, perirhinal cortex and medial prefrontal cortex (Vogel-Ciernia and Wood, 2014)
Elevated plus maze	Anxiety related behaviour and short-term spatial working memory	Hippocampus and amygdala (Walf and Frye, 2007)
Temporal order memory task	Short and long-term recognition memory (temporal order)	Hippocampus, perirhinal cortex, medial prefrontal cortex (Barker et al., 2007)
Spatial memory task	Spatial memory	Hippocampus (Vorhees and Williams, 2014)
Non spatial test of cued memory task	Long-term stimulus response learning and cued memory	Hippocampus, caudate nucleus, and related striatal structuresMcDonald et al. (1999)
Morris water maze/ with reversal	Short and long-term spatial working memory	Hippocampus, cerebellum, prefrontal cortex, striatum and basal forebrain (D'Hooge and De Deyn, 2001)
Puzzle box	Executive function (problem solving) and short and long-term memory	Prefrontal cortex and hippocampus (acquisition), various thalamic nuclei, hypothalamus, cerebellum and limbic structures (O'Connor et al., 2014)
Non-matching to sample/Delayed non-matching to sample	Discrimination learning and working memory	Frontal lobe and hippocampus (Yhnell et al., 2016)
Contextual and cued fear conditioning	Long-term contextual memory and long-term stimulus response learning (cued fear conditioning)	Hippocampus, amygdala, frontal cortex and cingulate cortex (Curzon P and Browman, 2009)
Inhibitory avoidance task	Long-term avoidance learning	Hippocampus and amygdala (Roozendaal and McGaugh, 1996)
Step through passive avoidance task/ Step down avoidance task	Memory retention and short-term memory	Hippocampus and amygdala (Eagle et al., 2016)

through the spatial memory task and DNMTS, was evident, but not on either the cued memory task or NMTS, after receiving a combination of MTX and 5-FU intraperitoneally and oral administration of donepezil.

3.3.2. Metformin

Metformin was investigated in four studies. In two of these (Sritawan et al., 2020, 2021), metformin led to an improvement in cognition in the NOL and NOR behavioural tests. Sritawan et al. (2020) additionally demonstrated that improvement resulted when metformin was administered as a preventative treatment at 200 mg/kg/day and alongside MTX chemotherapy. Both studies utilised an IP injection for metformin, administering the same dose (200 mg/kg/day), while Sritawan et al. (2020) also utilised an IP injection for MTX, whereas Sritawan et al. (2021) differed by utilising an IV injection for MTX. Conversely, the third study by Alharbi et al., found that cognition was not improved by orally administering metformin at 3 mg/ml per day alongside DOX, when evaluated by the Y-maze, NOR and EPM tests. In the final study (Alhowail et al., 2019), results varied between behavioural tests; while no improvement in cognition was found for the NOR, an improvement was found for the Y-maze and EPM tests. Similar to the Alharbi et al., study, oral administration of metformin was investigated, but at a dose of 5 mg/ml per day alongside CYP.

3.3.3. N-acetylcysteine (NAC)

NAC was investigated across three studies and cognition was improved in all, as determined through the NOL, passive avoidance, contextual and cued fear conditioning, context object discrimination and NOR tests. Differences between these studies included the route of administration for both the anti-inflammatory and chemotherapeutic agent. For two of the studies (Kitamura et al., 2020; Lomeli et al., 2017), both NAC and the chemotherapeutic agent were administered via an IP injection, while the other (Konat et al., 2008) utilised a subcutaneous (SC) injection for NAC and an IP injection for the chemotherapeutic agent. Additionally, different chemotherapeutic agents were administered, including one study utilising DOX + CYP (Kitamura et al., 2020), another DOX + CTX (Konat et al., 2008) and the last investigating the use of CIS (Lomeli et al., 2017). Each study also administered NAC at different doses and for different periods of time. For example, Kitamura et al., utilised a 30 mg/kg dose, administered 3 times at 30 min before and 30 min and 1 h after chemotherapy treatment. Whereas Konat et al., administered a higher dose of NAC (200 mg/kg), 3 times a week for 4 weeks during chemotherapy treatment. Finally, Lomeli et al. (2017) administered an even higher dose of NAC (250 mg/kg), which was administered for 5 days, starting 2 days before each of the 4 chemotherapy injections.

3.3.4. Lithium

Lithium was evaluated in two studies (Huehnchen et al., 2017; Nguyen and Ehrlich, 2020) through an IP injection, and both studies saw an improvement in cognition after PTX administration. The behavioural tests analysed were the MWM and NOL. Differences included the fact that Huehnchen et al., administered lithium at a dose of 170 μm LI+ /kg, before PTX, 3 times a week for 4 weeks, whereas Nguyen et al., administered lithium at a dose of 12.8 mg/kg, 1 h before each chemotherapy injection.

3.3.5. Memantine

Both studies that trialled memantine through an IP injection recorded an improvement in cognition using the MWM and object placement test, in both pre- and co-treatment groups. Both studies investigated the use of two different chemotherapeutic agents, which were MTX (Cole et al., 2013) and PTX (Sung et al., 2021). Additional differences included the fact that Cole et al., administered memantine at a dose of 2.5 mg/kg, 5 times a week for 3 weeks, whereas Sung et al., administered memantine at two different doses, being either 50 mg/kg, 1 week prior to and 30 min before PTX or 10 mg/kg, daily for 6 days, concomitantly with PTX.

3.3.6. Fluoxetine

Fluoxetine improved cognition in two studies (Lyons et al., 2012, 2011) from the same laboratory group based on results from the NOL test, and when administered either before chemotherapy or throughout chemotherapy treatment. However, no improvement in cognition was evident when fluoxetine was administered after chemotherapy (Lyons et al., 2012). For the two studies, a different chemotherapeutic agent was administered, being either MTX, administered intravenously (Lyons et al., 2011) or 5-FU, administered intraperitoneally (Lyons et al., 2012). Both studies administered fluoxetine at a dose of 10 mg/kg/day through the animals drinking water, however, Lyons et al. (2011) only had one treatment group, which received fluoxetine every day for 40 days,

Table 2
Summary characteristics of the traditional anti-inflammatory agents' group (Group 1). NSAID = non-steroidal anti-inflammatory drug. — no overall improvement occurred in behavioural tests when administered an anti-inflammatory agent concurrently with a chemotherapeutic agent compared to the chemotherapy alone treatment group.

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test of Cognition Employed	Effect on Cognition
(Chang et al., 2020) Australia	Mouse BALB/C Male 13–14 weeks old	Paclitaxel (PTX) Non-tumour bearing	10 mg/kg Every 2nd day for 2 weeks Intraperitoneal	Aspirin	0.125 μg/ml Began 24 h prior to first injection of PTX and continued until the end of the experiment (26 days total) Orally through drinking water	Irreversibly inhibits both cyclooxygenase-1 and 2 (Vane and Botting, 1998). Used to reduce fever and relieve mild to moderate pain.	Began 24 h after cessation of PTX treatment and conducted for 13 days following this	Novel object/novel place recognition test	—
(Pavlock et al., 2021) United States of America	Mouse C57BL/6 Female 9–10 weeks old	Cyclophosphamide (CYP) Non-tumour bearing	100 mg/kg Every third day over a 2-week period (5 injections in total) Intraperitoneal	Naproxen	375 ppm Given one week before CYP treatment Orally through diet	Reversibly inhibits both cyclooxygenase-1 and 2 enzymes as a non-selective coxib (Duggan et al., 2010). Used to reduce fever, relieve mild to moderate pain, and relieve symptoms of arthritis.	Began 48 h after final CYP injection	Y-maze	—

Summary Characteristics: Group 1 - Traditional anti-inflammatories (NSAIDs).

starting a week prior to chemotherapy. Conversely, Lyons et al. (2012) investigated three different treatment groups, with the throughout group receiving fluoxetine for the 40-day duration of the experiment, the preventative group receiving fluoxetine for 20 days, starting a week before chemotherapy treatment and the recovery group receiving fluoxetine the day before the final chemotherapy treatment and then for 20 days after.

3.3.7. *Melatonin*

Melatonin administered intraperitoneally improved cognition in the two included studies based on results from the NOL, NOR, Y-maze and MWM tests. Differences between these were the type of chemotherapeutic agent administered, where one administered MTX intravenously (Sirichoat et al., 2019) and the other administered CIS intraperitoneally (Zakria et al., 2021). Additionally, the dose and dose regimen for melatonin differed, with Sirichoat et al., administering melatonin at a dose of 8 mg/kg/day to three treatment groups. The preventative group began receiving melatonin 15 days before and during chemotherapy treatment, the recovery group received it for 15 days after chemotherapy treatment and the throughout group received melatonin for 30 days during and after chemotherapy treatment. On the other hand, Zakria et al., administered melatonin at a higher dose of 20 mg/kg to one treatment group, for 30 days after chemotherapy treatment.

3.3.8. *MESNA*

MESNA improved cognition in two studies which used the passive avoidance (Saadati et al., 2020) and NOR (Keeney et al., 2018) tests. However, there were differences in this effect depending on the timing of administration of MESNA for the NOR test. For one of the studies (Keeney et al., 2018), an improvement was evident at 72 h after MESNA and DOX treatment, but no improvement was evident 24 h after treatment, on the NOR test. Further differences included the fact that Keeney et al., administered MESNA at 160 mg/kg intraperitoneally, 15 min before DOX treatment, as well as 3 and 6 h after, whereas Saadati et al., administered MESNA also intraperitoneally, but at a dose of 150 mg/kg/day for 4 weeks during CIS treatment.

3.3.9. *ACY-1215*

ACY-1215 led to an improvement in cognition in one study (Wang et al., 2019) utilising the NOR and MWM tests. In this study, ACY-1215 and CIS was administered via an IP injection at a dose of 50 mg/kg for ACY-1215 starting 1 h prior to each CIS injection and for 30 consecutive days following. Conversely, no improvement in cognition was found in the other study (Ma et al., 2018) investigating the Y-maze test. This study administered ACY-1215 via oral gavage and CIS via an IP injection. Additionally, this study administered ACY-1215 at a lower dose of 30 mg/kg, comprising 14 doses, starting 3 days after finishing CIS treatment.

3.3.10. *Non-traditional anti-inflammatories investigated once only*

Of the agents where only a single investigation has been performed to date, one failed to produce any improvements in cognition, which was

Table 3
Summary characteristics of the non-traditional anti-inflammatory agents with known anti-inflammatory properties or effects (group 2). [a-i]: indicated studies with multiple experiments in the one study, investigating multiple dosages, treatment groups etc. ↑ improvement in cognition occurred in the behavioural tests after the administration of an anti-inflammatory agent concurrently with a chemotherapeutic agent compared to the chemotherapy alone treatment group. — no improvement in cognition occurred in behavioural tests after the administration of an anti-inflammatory agent concurrently with a chemotherapeutic agent compared to the chemotherapy alone treatment group.

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
Metformin (n = 4)									
(Alharbi et al., 2020) Saudi Arabia	Rat Strain not stated Male Age not stated	Doxorubicin (DOX) Non-tumour bearing	4 mg/kg Once weekly for 5 weeks Intraperitoneal	Metformin	3 mg/ml Daily for 5 weeks, starting the day before DOX treatment Dissolved in drinking water	Suppresses the inflammatory response by inhibition of NFκB via AMP-activated protein kinase (AMPK)-dependent and independent pathways (Saisho, 2015). First line medication to treat type 2 diabetes mellitus.	Began one day after cessation of DOX treatment	Y-maze Novel object recognition Elevated plus maze	— — —
(Alhowail et al., 2019) Saudi Arabia	Mouse Strain not stated Sex not stated Age not stated	Cyclophosphamide (CYP) Non-tumour bearing	100 mg/kg Every 2 alternative days, 4 doses total Intraperitoneal	Metformin	5 mg/ml Began the day before CYP treatment until the end of study period (approximately 12 days total) Orally through drinking water		Tests performed for 3 consecutive days 24 h after final dose of CYP	Y-maze Novel object recognition Elevated plus maze	↑ — —
(Sritawan et al., 2020) Thailand	Rat Sprague Dawley Male 4–5 weeks old	Methotrexate (MTX) Non-tumour bearing	75 mg/kg Administered on days 7 and 14 Intraperitoneal	Metformin[g]	200 mg/kg **Preventative group:** Starting 7 days before and after first dose of MTX **Throughout group:** From 7 days before MTX treatment and for 28 days until after second MTX dose Intraperitoneal		Performed on days 1–4 before treatment and then days 31–35 after cessation of MTX treatment	Novel object location/ recognition Novel object location/ recognition	**Preventative group:** ↑ **Throughout group:** ↑
(Sritawan et al., 2021) Thailand	Rat Sprague Dawley Male 4–5 weeks old	Methotrexate (MTX) Non-tumour bearing	75 mg/kg Administered on days 7 and 14 Intravenous	Metformin	200 mg/kg Administered for 14 days starting from first MTX treatment Intraperitoneal		Began 4 days after final MTX treatment, from days 18–21 at the end of study period	Novel object location/ recognition	↑
Donepezil (n = 5) and Galantamine (n = 1)									

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
(Kinra et al., 2021) India (Also found in group 3)	Mouse Swiss Albino Male 8–10 weeks old	Combination of Cyclophosphamide, Methotrexate and 5-Fluouoracil (CMF) Non-tumour bearing	50 mg/kg, 5 mg/kg and 5 mg/kg respectively 3 cycles, once a week for 3 weeks Intraperitoneal	Donepezil	2 mg/kg Every day for 21 days during same CMF treatment period Oral – suspended in carboxymethyl cellulose	**Donepezil:** Shown to suppress IL-1β and COX-2 expression in the brain to prevent systemic inflammation (Yoshiyama et al., 2010). Used to treat Alzheimer's disease. **Galantamine:** Shown to lower plasma levels of proinflammatory cytokines, TNF and leptin and increase levels of anti-inflammatory cytokines, adiponectin, and IL-10 (Consolim-Colombo et al., 2017). Used to treat Alzheimer's disease.	Unclear	Morris water maze	↑
(Lim et al., 2016) Republic of Korea	Rat Sprague Dawley Female Age not stated	Cyclophosphamide (CYP) or doxorubicin (DOX) Non-tumour bearing	CYP 100 mg/kg or DOX 4 mg/kg Once weekly for 3 weeks Intraperitoneal	Donepezil	5 mg/kg Every day for 3 weeks during chemotherapy administration Intraperitoneal		Unclear	 Morris water maze Passive avoidance test Morris water maze Passive avoidance test	**CYP treatment group:** ↑ ↑ **DOX treatment group:** ↑ ↑
(Ongnok et al., 2021) Thailand	Rat Wistar Male 8 weeks old	Doxorubicin (DOX) Non-tumour bearing	3 mg/kg 6 doses total, first 3 doses injected every 4 days, followed by final 3 doses injected once a week Intraperitoneal	Donepezil	5 mg/kg Daily for 30 consecutive days beginning at same time as first DOX treatment Gavage		Unclear	Novel object location/ recognition	↑
(Philpot et al., 2019) United States of America	Mouse BALB/C Female 8 weeks old	Combination of Cyclophosphamide (CYP) and Doxorubicin (DOX) Non-tumour bearing	CYP 25 mg/kg and DOX 2.5 mg/kg Once per week for 4 weeks Intravenous	**Experiment 1:** Donepezil[c] **Experiment 3:** Galantamine[d]	3 mg/kg for both **Experiment 1:** Administered approximately a week after chemotherapy treatment, from days 44–71 at 1 h prior to		**Experiment 1:** From days 44–71 during donepezil or galantamine treatment **Experiment 3:** From days 16–43	Morris water maze	**Experiment 1: Donepezil** — **Galantamine**

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
					behavioural testing **Experiment 3:** Administered daily during the 4 weeks of chemotherapy treatment, from days 16–43 at 1 h prior to chemotherapy treatment or behavioural assessments Subcutaneous		during donepezil or galantamine treatment	Morris water maze Morris water maze Morris water maze	— **Experiment 3: Donepezil** ↑ **Galantamine** ↑
(Winocur et al., 2011) Canada	Mouse BALB/C Female 3 months old	Combination of Methotrexate (MTX) and 5-fluorouracil (5-FU) Non-tumour bearing	MTX 50 mg/kg and 5-FU 75 mg/kg Weekly for 4 consecutive weeks Intraperitoneal	Donepezil	3 mg/kg Every morning throughout experiment and 1 h before beginning of behavioural testing, for 4 weeks total Gavage		Testing conducted from weeks 5–10 immediately after cessation of chemotherapy treatment	Spatial memory Cued memory Non-matching to sample Delayed non-matching to sample	↑ — — ↑
N-acetylcysteine (NAC) (n = 3)									
(Kitamura et al., 2020) Japan	Rat Wistar Male Age not stated	Combination of doxorubicin (DOX) and cyclophosphamide (CYP) Non-tumour bearing	DOX 5 mg/kg and CYP 50 mg/kg Once a week for 2 weeks Intraperitoneal	N-acetylcysteine (NAC)	30 mg/kg Administered 3 times, at 30 min before, 30 min after and 1 h after CYP treatment Intraperitoneal	Shown to inhibit the inflammatory cytokines, TNF-α, IL-1β and IL-6 in LPS-activated macrophages under mild oxidative conditions (Palacio et al., 2011). Used to treat paracetamol overdose and to loosen thick mucus in chronic bronchopulmonary disorders.	Unclear	Novel object location	↑
(Konat et al., 2008) United States of America	Rat Sprague Dawley Female 10 months old	Combination of doxorubicin (DOX) and Cytoxan (CTX) Non-tumour bearing	DOX 2.5 mg/kg and CTX 25 mg/kg Once weekly for 4 weeks Intraperitoneal	N-acetylcysteine (NAC)	200 mg/kg 3 times a week for 4 weeks during chemotherapy treatment Subcutaneous injection		Unclear	Passive avoidance	↑

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
(Lomeli et al., 2017) United States of America	Rat Sprague Dawley Male Adult (age not specified)	Cisplatin (CIS) Non-tumour bearing	3 mg/kg/day One injection per week for 4 consecutive weeks Intraperitoneal	N-acetylcysteine (NAC)	250 mg/kg/day Administered for 5 days, starting 2 days before each CIS injection. On the days of CIS administration, NAC administered 4 h afterwards Intraperitoneal		Performed 5–6 weeks post cessation of CIS treatment	Fear conditioning Context object discrimination Novel object recognition	**Chronic study:** ↑ ↑ ↑
Lithium (n = 2)									
(Huehnchen et al., 2017) Germany	Mouse C57BL/6 N Male 9 weeks old	Paclitaxel (PTX) Non-tumour bearing	20 mg/kg 3 times a week for 4 weeks Intraperitoneal	Lithium	170 μm LI+ /kg Before PTX administration, 3 times a week for 4 weeks Intraperitoneal	Shown to suppress COX-2 expression, inhibit IL-1β and TNF-α production and enhance IL-2 and IL-10 synthesis (Nassar and Azab, 2014). Used as a mood stabiliser and psychiatric medication.	Unclear	Morris water maze	**Preventative experiment:** ↑
(Nguyen et al., 2021) United States of America	Mouse C57BL/6 Female 7 weeks old	Paclitaxel (PTX) Non-tumour bearing	20 mg/kg 4 pairs of injections over 8 days Intraperitoneal	Lithium chloride	12.8 mg/kg 1 h before each PTX injection Intraperitoneal		Carried out over 2 consecutive days, unclear exactly when in relation to treatment	Novel object location	↑
Memantine (n = 2)									
(Cole et al., 2013) United States of America	Rat Long Evans Male 8 weeks old	Methotrexate (MTX) Non-tumour bearing	0.5 mg/kg 4 doses within 2 weeks Transcutaneous cisternal magna puncture	Memantine	2.5 mg/kg Daily (Monday to Friday) for 3 weeks, beginning 1 day before MTX treatment Intraperitoneal	Shown to reduce microglia-associated inflammation and stimulate neurotrophic factor release from astroglia (Wu et al., 2009). Used as a neuroprotective agent to treat moderate-to-severe Alzheimer's disease.	Conducted one month after last MTX treatment	Object in place	↑
(Sung et al., 2021) Taiwan	Mouse C57BL/66NCrlB1tw Sex not stated	Paclitaxel (PTX) Non-tumour bearing	**Experiment 2:** 10 mg/kg Administered for 6 consecutive days (days 1–6)	Memantine[f]	**Experiment 2:** 50 mg/kg Administered one week prior to and 30 min before PTX		Conducted after cessation of chemotherapy and memantine treatment, for 6 days (days 7–12)	Morris water maze	**Experiment 2 – pre-treatment:** ↑ (But may cause

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
	8 weeks old		Intraperitoneal **Experiment 3:** 6 mg/kg Administered for 6 consecutive days (days 1–6) Intraperitoneal		treatment Intraperitoneal **Experiment 3:** 10 mg/kg Administered daily, concomitantly with PTX from days 1–6 Intraperitoneal			Morris water maze	depressive like symptoms) **Experiment 3 – Co-treatment:** ↑ (No depressive like symptoms)
Fluoxetine (n = 2)									
(Lyons et al., 2011) Egypt	Rat Lister Hooded Male Age not stated	Methotrexate (MTX) Non-tumour bearing	75 mg/kg 2 doses a week apart Intravenous	Fluoxetine	10 mg/kg/day Every day for 40 days, starting a week prior to the first MTX injection Orally through drinking water	Shown to inhibit the phosphorylation of mitogen activated protein kinase and activation of NF-kB (Caiaffo et al., 2016). Used to treat depression.	Carried out 6 days after cessation of fluoxetine treatment	Novel object location	↑
(Lyons et al., 2012) Egypt	Rat Lister Hooded Male Age not stated	5-fluorouracil (5-FU) Non-tumour bearing	25 mg/kg 5 doses, each 3 days apart Intraperitoneal	Fluoxetine	10 mg/kg/day **Throughout group:** Administered for the 40-day duration of the experiment **Preventative group:** Started 5 days before the first BrdU injection (BrdU administered 2 days before 5-FU administration), for 20 days **Recovery group:** Administered the day before the last 5-FU injection for 20 days Orally through drinking water		Conducted one week after fluoxetine treatment ended	Novel object location Novel object location	**Throughout and preventative groups:** ↑ **Recovery group:** —
Melatonin (n = 2)									
(Sirichoat et al., 2019)	Rat Sprague Dawley	Methotrexate (MTX) Non-tumour bearing	75 mg/kg 2 doses, 1 week apart on days 8 and 15	Melatonin[e]	8 mg/kg/day **Preventative group:** For 15 days before and	Shown to prevent the translocation of NF-kB to the nucleus and its binding to DNA, therefore reducing the	Conducted 3 days after drug treatment finished	Novel object location/	**Preventative group:**

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
Thailand	Male 4–5 weeks old		Intravenous		during MTX treatment **Recovery group:** For 15 days after MTX treatment **Throughout group:** For 30 days during and after MTX treatment Intraperitoneal	upregulation of some proinflammatory cytokines (Reiter et al., 2000). Used to treat sleep disorders.		recognition Novel object location/ recognition Novel object location/ recognition	↑ **Recovery group:** ↑ **Throughout group:** ↑
(Zakria et al., 2021) Pakistan	Mouse White Albino Male Adult (age not specified)	Cisplatin (CIS) Non-tumour bearing	2 mg/kg For 11 consecutive days (not specified when) Intraperitoneal	Melatonin	20 mg/kg For 30 days after CIS treatment Intraperitoneal		Unclear	Y-Maze Morris water maze	↑ ↑
2-mercaptoethane sulfonate (MESNA) (n = 2)									
(Keeney et al., 2018) United States of America	Mouse F1 progeny of C57BL/6 x C3H hybrids (B6C3) Male 2–3 months old	Doxorubicin (DOX) Non-tumour bearing	25 mg/kg Single injection (not specified when) Intraperitoneal	2-mercaptoethane sulfonate (MESNA)	160 mg/kg Administered 15 min before DOX treatment, as well as 3 and 6 h after single DOX injection Intraperitoneal	A sulphur-containing substance that scavenges reactive oxygen species. Has been shown to reduce DOX induced plasma oxidative stress and TNF-α levels (Aluise et al., 2011). Synthetic compound currently used in the clinic to prevent urotoxicity of some chemotherapeutic agents.	Conducted the day of treatment as a baseline measure and then one day after treatment	Novel object recognition (assessed at 24 hr and 72 hr following MESNA treatment)	**24 h:** — **72 h:** ↑
(Saadati et al., 2020) Iran	Rat Wistar Male Age not stated	Cisplatin (CIS) Non-tumour bearing	2.5 mg/kg Twice a week for 4 weeks Intraperitoneal	2-mercaptoethane sulfonate (MESNA)	150 mg/kg/day Every day for 4 weeks during CIS treatment Intraperitoneal		Unclear	Passive avoidance	↑
ACY-1215 (n = 2) and ACY-1083 (n = 1)									
(Ma et al., 2018)	Mouse	Cisplatin (CIS) Non-tumour bearing	2.3 mg/kg/day	ACY-1083 or ACY-1215	**ACY-1215:** 30 mg/kg	**ACY-1215:** First-in-class potent and selective	Conducted one week after last dose	**ACY-1083:**	**ACY-1083:**

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
United States of America	C57BL/6 J Male 8–10 weeks old		For 5 days followed by 5 days of rest and then a second round of 5 daily doses Intraperitoneal		14 doses starting 3 days after finishing CIS treatment Gavage **ACY1083:** 10 mg/kg 14 doses starting 3 days after finishing CIS treatment Intraperitoneal	HDAC6 inhibitor. Shown to decrease protein expression of TLR4 and the activation of MAPK and NF-kB signalling pathways (Zhang et al., 2018). Demonstrated antitumour effects alone or in combination with other drugs in various cancers. **ACY-1083:** Selective and brain-penetrating HDAC6 inhibitor, shown to possess anti-inflammatory effects through its effects on cell death acting through acetylation of non-histone proteins (Adcock, 2007).	of ACY-1083 or ACY-1215 treatment	Y-maze Novel object/ place recognition Puzzle box **ACY-1215:** Y-Maze	↑ ↑ ↑ **ACY-1215:** —
(Wang et al., 2019) China	Mouse C57BL/6 Male Age not stated	Cisplatin (CIS) Non-tumour bearing	2.3 mg/kg (34.5 mg/kg cumulative dose) Administered 3 cycles consisting of 5 daily injections, followed by a 5-day rest with no injections Intraperitoneal	ACY-1215	50 mg/kg Starting 1 h prior to each CIS injection for 30 consecutive days Intraperitoneal	Shown to effectively reverse chemotherapy-induced peripheral neuropathy.	Unclear	Novel object recognition Morris water maze	↑ ↑
All other agents investigated in a single study									
(Allen et al., 2019) United States of America	Mouse C57BL/6 J Male 6 months old	Adriamycin (also known as doxorubicin) Non-tumour bearing	2 mg/kg Once weekly for 4 weeks Intraperitoneal	**Experiment 1:** PLX5622 **Experiment 2:** iMG-EV	**Experiment 1 - PLX5622:** 1200 ppm 72 h after final injection of chemotherapy Orally through diet **Experiment 2 - iMG-EV:** 1.36×10^7 EV per 50 µl per injection Once weekly for 4 weeks during chemotherapy treatment Retro-orbital sinus injection	**PLX5622:** Inhibits the receptor tyrosine kinase activity of CSF1R and reduces upregulation of microglia (Ali et al., 2020b). Currently not used for treatment purposes clinically. **iMG-EV:** Human induced pluripotent stem cell derived microglia. EV's are nano-sized membrane bound vesicles that transport biomolecules between cells, maintain physiological homeostasis and influence pathogenesis. iMG-EV's transport microglia to help restore its function (Gowen et al., 2020). Currently not used for treatment purposes clinically.	**Experiment 1:** Began 4 weeks after the initiation of PLX5622 treatment, with testing spanning over 3 weeks in total **Experiment 2:** Conducted from weeks 8–9, 1 week after iMG-EV treatment	**Experiment 1:** Novel object recognition Object in place Contextual and cued fear conditioning **Experiment 2:** Novel object recognition Fear conditioning	**Experiment 1:** ↑ ↑ ↑ **Experiment 2:** ↑ ↑

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
(Briones and Woods, 2014) United States of America	Rat Sprague Dawley Female 12 months old	Combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) Non-tumour bearing	Cyclophosphamide 40 mg/kg, MTX 37.5 mg/kg and 5-FU 75 mg/kg Once a week for 4 weeks Intraperitoneal	NS-398	10 mg/kg Injected 1 h after first CMF dose and then administered daily for 4 weeks Intraperitoneal	Cyclooxygenase inhibitor that reduces the upregulation of prostaglandins that promote inflammation, pain, and fever (Futaki et al., 1994). Currently not used for treatment purposes clinically.	Unclear	Novel object recognition Object in place Temporal order memory task	— ↑ ↑
(Callaghan and O'Mara, 2015) Ireland	Rat Han Wistar Male 4–5 months old	Docetaxel Non-tumour bearing	1 mg/kg Once weekly for 4 weeks Intravenous	Rolipram	0.5 mg/kg Daily for 4 weeks during chemotherapy treatment Oral - suspended in 0.2 ml of maple syrup	Shown to suppress expression of proinflammatory cytokines and other mediators of inflammation (Zhu et al., 2001). Used to treat asthma and COPD. Experimental treatment for autoimmune disease, Alzheimer's disease, spinal cord injury and respiratory diseases.	Conducted in week 12 of experiment, 72–96 h before the end of the experiment, approximately 12 weeks after original treatment	Object exploration task	↑
(Cankara et al., 2021) Turkey	Rat Wistar Albino Male 10 weeks old	Cisplatin (CIS) Non-tumour bearing	7 mg/kg Administered once on the first day of the study Intraperitoneal	Agomelatine[a]	20 mg/kg or 40 mg/kg, Administered after first CIS treatment then for 7 days thereafter Oral – not specified how	Shown to inhibit microglial activation through the TLR4/NLRP3 signalling pathway (Chumboatong et al., 2022). Is a melatonin analogue, used for major depressive disorder and sleep disturbances.	Conducted 24 h after final CIS treatment	 Passive avoidance Novel object recognition Passive avoidance Novel object recognition	**20 mg/kg dose:** ↑ ↑ **40 mg/kg dose:** ↑ ↑
(Chiu et al., 2017) United	Mouse C57BL/6 J Male	Cisplatin (CIS) Non-tumour bearing	2.3 mg/kg Daily for 5 days, followed by 5 days rest with no injection, then	Pifithrin-u	8 mg/kg Administered 1 h prior to CIS injection	Shown to reduce the M1 response in BV2 cells, suggesting an anti-inflammatory effect on microglia is occurring (Fleiss et al., 2015).	Conducted 7 days after final CIS treatment	Novel object recognition	↑

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
States of America	Age not stated		another 5 days of injections Intraperitoneal		Intraperitoneal	Currently not used for treatment purposes clinically.		Y-Maze	↑
(Iarkov et al., 2016) Chile	Rat Wistar Female 2–4 months old	Combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) Non-tumour bearing	Cyclophosphamide 40 mg/kg, MTX 37.5 mg/kg and 5-FU 75 mg/kg Once a week for 2 weeks Intraperitoneal	Cotinine	5 mg/kg Administered 3 days after CMF treatment then daily until euthanasia Gavage	Shown to inhibit the production of cytokines associated with the NFkB system, such as TNF-α, IL-6 and IL-1β, and shifts the response to an anti-inflammatory one to be more IL-10 dominated (Bagaitkar et al., 2012). Currently being studied to treat depression, PTSD, schizophrenia, and Alzheimer's disease.	Conducted in the final week of experiment (week 5), 2 weeks after final CMF treatment	Novel object location	↑
(Jangra et al., 2016) India	Rat Wistar Male 5–6 weeks old	Cisplatin (CIS) Non-tumour bearing	5 mg/kg Once a week for 7 weeks, finishing on day 49 of the experiment Intraperitoneal	Edaravone	10 mg/kg Once a week for 7 weeks during CIS treatment Intraperitoneal	Shown to activate the Nrf2/HO-1 pathway, reducing cognitive damage, as well as acting as a defence mechanism from cell apoptosis (Cho and Shukla, 2021). Injections used to treat amyotrophic lateral sclerosis (ALS).	Conducted between days 46–50, during chemotherapy treatment	Morris water maze Novel object recognition	↑ ↑
(Johnston et al., 2017) Australia	Rat Wistar Male and female depending on experiment number (male: experiment 1, 2 and 4 and female: experiment 3) Age not stated	Oxaliplatin (OXP) Non-tumour bearing	6 mg/kg Single injection on day 0 of experiment Intraperitoneal	Ibudilast[b]	7.5 mg/kg **Experiment 1:** Administered for 6 consecutive days starting prior to OXP treatment **Experiment 2:** Administered for 3 days after OXP treatment **Experiment 3:** Pre-treatment immediately before OXP treatment **Experiment 4:** Long term reversal based on single treatment (3 days after	Non-selective phosphodiesterase inhibitor, that has been shown to suppress TNF- α production (Suzumura et al., 1999). Treatment for asthma and stroke.	**Experiment 1:** Began 8 days after OXP treatment **Experiment 2:** Began 8 days after OXP treatment **Experiment 3:** Began 10 days after OXP treatment **Experiment 4:** Began 10 days after OXP treatment	**Experiment 1:** Novel object recognition Novel object location **Experiment 2:** Novel object recognition Novel object location **Experiment 3:** Novel object recognition	**Experiment 1:** ↑ ↑ **Experiment 2:** ↑ ↑ **Experiment 3:** ↑

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
					OXP treatment). Intraperitoneal			**Experiment 4:** Novel object location Renewal of extinguished freezing	**Experiment 4:** ↑ ↑
(Li et al., 2020) China	Rat Sprague Dawley Male Age not stated	Cisplatin (CIS) Non-tumour bearing	5 mg/kg Once a week for 4 weeks Intraperitoneal	Dexmedetomidine	30 ug/kg Pre-treated 30 mins prior to CIS, then once per week for 4 weeks Route of administration not stated	Highly selective adrenergic a2 receptor agonist. Shown to reduce the level of serum inflammatory factors including IL-6, IL-8 and IL-10 (Chen et al., 2021). Used as an anxiolytic, sedative and pain medication drug.	Unclear	Morris water maze	↑
(Mounier et al., 2021) Egypt	Rat Albino Male 7–9 weeks old	Doxorubicin (DOX) Non-tumour bearing	2 mg/kg Once a week for 4 weeks Intraperitoneal	Atorvastatin	5 mg/kg/day, 10 mg/kg/day, or 20 mg/kg/day 5 days a week for 4 weeks during DOX treatment Oral – not specified how	Shown to inhibit the inflammatory response and NLRP3 inflammasome activation by inducing autophagy (Peng et al., 2018). Used to prevent cardiovascular disease and to treat abnormal lipid levels.	29 days total	 Passive avoidance Morris water maze **10 mg/kg/day dose:** Passive avoidance Morris water maze **20 mg/kg/day dose:** Passive avoidance Morris water maze	**5 mg/kg/day dose:** ↑ — ↑ ↑ ↑ ↑

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Table 3 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule (amount, regime, and route of administration)	Anti-Inflammatory Agent Investigated	Anti-Inflammatory agent Dosing Schedule (amount, regime, and route of administration)	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
(Verma et al., 2017) India	Rat Wistar Male 6–8 weeks old	Doxorubicin (DOX) Non-tumour bearing	2.5 mg/kg Once every 5 days for 10 cycles (total dosing time = 50 days) Intraperitoneal	Sodium Valproate[h]	50 mg/kg, 100 mg/kg, or 200 mg/kg 30 min prior to DOX treatment Gavage	Shown to promote expression of BDNF, protective effect against glutamate induced-NMDA mediated excitotoxicity and increase NF-kB signalling, leading to a decrease in cell death (Chuang et al., 2009). Used as an anti-epileptic drug.	Unclear	Novel object recognition Novel object recognition Novel object recognition	**50 mg/kg dose:** — **100 mg/kg dose:** — **200 mg/kg dose:** —
(Wahdan et al., 2020) Egypt	Rat Albino Male Age not stated	Doxorubicin (DOX) Non-tumour bearing	2 mg/kg/week Once weekly for 4 consecutive weeks Intraperitoneal	IFN-β-1a or Infliximab	**IFN-β-1a:** 300,000 units (1.1 ug) 3 times per week concomitantly with DOX treatment Subcutaneous **Infliximab:** 5 mg/kg/week Once a week concomitantly with DOX treatment for 4 consecutive weeks Intraperitoneal	**IFN-β-1a:** Cytokine with a wide range of immunoregulatory properties affecting cell proliferation. Shown to increase expression and concentration of anti-inflammatory cytokines, while suppressing the expression of pro inflammatory cytokines (Kieseier, 2011). Used to treat multiple sclerosis. **Infliximab:** Blocks TNF-α and reduces peripheral inflammation (Guo et al., 2013). Used to reduce symptoms of moderate-to-severely active Chron's disease and ulcerative colitis.	Conducted 1 week after final DOX treatment on day 28 of study	Step through passive avoidance Y-maze Step through passive avoidance Y-maze	**IFN-β-1a:** ↑ ↑ **Infliximab:** ↑ ↑
(Zhou and Qiu, 2019) China	Mouse ICR Female Age not stated	Cisplatin (CIS) Non-tumour bearing	2 mg/kg/day Administered for 10 consecutive days Intraperitoneal	Propofol[i]	50 mg/kg or 250 mg/kg After the mice reached the 60 s learning criterion in the behavioural test, they immediately received propofol at either dose once Intraperitoneal	Shown to have anti-inflammatory effects on the biosynthesis of TNF-α, IL-1β and IL-6 in LPS-activated macrophages (Chen et al., 2005). Used as an anaesthetic.	Conducted approximately 11 days after chemotherapy treatment ended, on day 21 of study	Inhibitory avoidance task Inhibitory avoidance task	**50 mg/kg dose:** ↑ **250 mg/kg dose:** —

Summary Characteristics: Group 2 - Non-traditional anti-inflammatories with known anti-inflammatory properties or effects.

sodium valproate (Verma et al., 2017). This agent failed to improve recognition memory in the NOR test when given via oral gavage at various doses (50 mg/kg, 100 mg/kg, or 200 mg/kg). Conversely, the agents PLX5622, iMG-EV, rolipram, agomelatine (both the 20 mg/kg dose and 40 mg/kg dose), pifithrin-U, cotinine, edaravone, ibudilast (in all 4 experiments), dexmedetomidine, ACY-1083, IFN-β-1a and infliximab were shown to improve cognition on the various behavioural tests investigated. For other agents, including NS-398, atorvastatin, galantamine and propofol, results were mixed, with improvements on some behavioural tests, but not others. Furthermore, there was dependence on the dose of the anti-inflammatory administered, the timing in which it was administered and the route of administration. See Table 3 for specific information.

3.4. Group 3 – natural compounds: behavioural outcomes

Of the 64 included studies, a total of 26 investigated various natural compounds, with 22 specific types identified, as summarised in Table 4. A summary of the aspects of cognition investigated through the various behavioural tests is presented in Fig. 3. Of the 22 agents investigated in this group, 19 were investigated in a single study, whereas curcumin, resveratrol and rutin were investigated multiple times across different studies (n = 4, n = 2 and n = 2 studies, respectively). Overall, improvements in cognition were evident in 17 out of the 26 studies (65%). Additionally, 7 studies (27%) saw improvements in cognition depending on the behavioural test or treatment group, leaving only 2 studies (8%) with no improvements observed.

3.4.1. Curcumin

Curcumin was found to improve cognition across all four studies that have investigated this compound to date (Akomolafe et al., 2020; Moretti et al., 2021; Oz et al., 2015; Yi et al., 2020). All four administered curcumin orally, utilising the Y-maze, MWM and NOR behavioural tests. One of these studies (Akomolafe et al., 2020) investigated the administration of curcumin at a dose of 20 mg/kg, both before and after chemotherapy treatment for 14 days. Improvements in cognition in the Y-maze and MWM tests were observed with both doses. Additionally, another study (Moretti et al., 2021) conducted the NOR at both 3 and 24-hours post habituation period (after treatment with both curcumin and DOX), and an improvement in cognition was evident at both time points. This study administered curcumin at a dose of 100 mg/kg/day for 28 days. The third study, (Oz et al., 2015) administered curcumin at a higher dose of 300 mg/kg every day for 5 weeks during chemotherapy treatment and found that the addition of curcumin with CIS resulted in more time spent in the target quadrant in the MWM test than animals receiving only CIS. The final study, (Yi et al., 2020) administered curcumin at a dose of 100 mg/kg, 1 h prior to chemotherapy, which consisted of 3 cycles of 5 daily injections followed by 5 days of rest. It was found that cognition was improved with the addition of curcumin in the NOR and MWM tests in this study.

3.4.2. Resveratrol

To date, the impact of oral administration of resveratrol on cognition following chemotherapy has been investigated in two studies, which found that effects were dependent on either the time point of administration, or the dose administered. One study (Moretti et al., 2021) investigated the NOR test at both 3 and 24-hours post habituation period (after treatment with both resveratrol and DOX). It was noted that resveratrol was able to improve cognition at 24-hours, but not at 3-hours. In this study resveratrol was administered via oral gavage at a dose of 19 mg/kg/day for 28 days during chemotherapy treatment. For the second study (Shi et al., 2018), two doses of resveratrol were administered also via oral gavage, being either 50 mg/kg/day or 100 mg/kg/day, commencing one week prior to DAC chemotherapy. It was observed that the 50 mg/kg/day dose did not improve cognition as evidenced in the MWM test; however, the higher 100 mg/kg/day dose did improve cognition in this test.

3.4.3. Rutin

Rutin was investigated in two studies by the same research group (Ramalingayya et al., 2017, 2019). Both studies investigated the use of DOX chemotherapy at a dose of 2.5 mg/kg, injected intraperitoneally once every five days over a 50-day period. Rutin was also administered orally for both studies, at a dose of 50 mg/kg daily, starting one week prior to DOX treatment, and continued until the end of the study. These studies differed in the fact that one used tumour bearing rats, utilising a mammary cancer model (Ramalingayya et al., 2019). This study investigated cognition through the NOR and MWM and found that the addition of rutin improved short and long-term recognition and spatial working memory. Conversely, the other study used healthy, non-tumour bearing rats and investigated the use of the NOR only, which also resulted in an improvement in short and long-term recognition memory (Ramalingayya et al., 2017).

3.4.4. Non-traditional anti-inflammatory agents investigated on one occasion

Of the other 19 anti-inflammatories that were investigated in a single study each, 5 agents led to inconsistent findings, with improvements in cognition evident in some behavioural tests, but not others. These agents included asiatic acid, compound K, chrysin, berberine and ginsenoside Rg1. Conversely, 12 of the agents improved cognition in all behavioural tests investigated, consisting of CAPE (both 10umol/kg/day and 20umol/kg/day doses), catechin, astaxanthin, MR (both 1 ml/kg and 2 ml/kg doses), ginseng X, KXS, hesperidin, dehydrozingerone, naringin, polydatin, mulmina mango (both 40 ml/kg/day and 80 ml/kg/day doses) and c-phycocyanin. Finally, only two agents, sulforopane and carnosic acid, resulted in no improvements in cognition in any of the behavioural tests investigated, which were the EPM, Y-maze and MWM with reversal tests. See Table 4 for specific details.

3.5. Risk of bias

Overall, the risk of bias of the included studies was unclear, mainly due to the general under-reporting of criteria. As evident in Fig. 4, there was generally poor conduction or reporting of randomisation, use of random housing, allocation concealment, random outcome assessment, blinding, and attrition bias. The domains of baseline characteristics of the animals, selective reporting and other bias were generally considered to be of low risk. A risk of bias summary diagram outlining each study separately can be found in Appendix D.

3.5.1. Selection bias

There was an unclear risk of bias for a majority of the included studies in terms of random sequence generation and allocation concealment reporting. However, baseline characteristics reporting was overall considered to be a low risk of bias. Random sequence generation reporting posed a low risk of bias in only four studies, as they stated the method in which they randomly allocated animals into treatment groups (Huehnchen et al., 2017; Johnston et al., 2017; Philpot et al., 2019; Yi et al., 2020). A high risk of bias was allocated to eight studies, (Chang et al., 2020; Chiu et al., 2017; Gourishetti et al., 2019; Hou et al., 2013; Kitamura et al., 2020; Konat et al., 2008; Ramalingayya et al., 2017; Shi et al., 2019) as they did not state that they randomised group allocations and an unclear risk of bias was allocated to the remaining 52 for stating that animals were randomly allocated into treatment groups, but not how this was conducted. For allocation concealment, a low risk of bias was allocated for two studies, (Huehnchen et al., 2017; Lyons et al., 2011) as they stated how they concealed the allocation process. A high risk of bias was allocated for three studies, (Gourishetti et al., 2019; Kinra et al., 2021; Ramalingayya et al., 2017) as there was no mention of concealing the allocation process and an unclear risk of bias was allocated for the remaining 59, as they failed to state how they concealed the

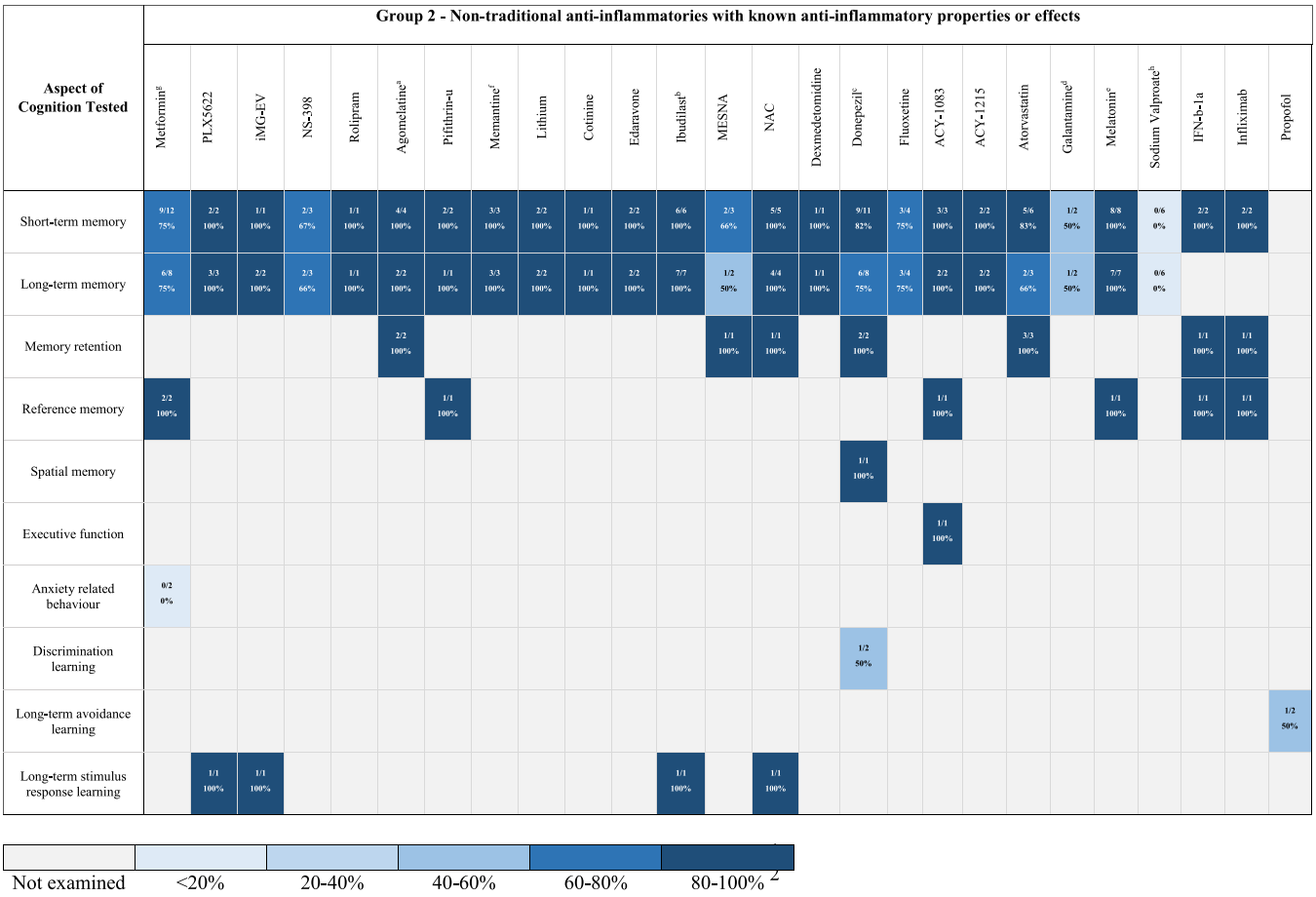

Fig. 2. Heatmap demonstrating the percentage of studies where an improvement in an aspect of cognition tested in a behavioural test was observed following the administration of a non-traditional anti-inflammatory agent. [a-i] indicates agents that have been investigated across multiple studies corresponding with Table 3. Studies were counted as more than one if they utilised multiple treatment groups or dose amounts etc. MESNA = 2-Mercaptoethane sulfonate and NAC = N-acetylcysteine.

allocation sequence. Conversely, for baseline characteristics reporting, 50 studies were deemed a low risk of bias for stating all relevant information regarding the animals at baseline, while two were a high risk of bias for not stating information such as strain, sex and weight of the animals at baseline (Alhowail et al., 2019; Gourishetti et al., 2019). The remaining 12 studies (Akomolafe et al., 2020; Alharbi et al., 2020; Ali et al., 2020a; Allen et al., 2019; Chiu et al., 2017; Huehnchen et al., 2017; Johnston et al., 2017; Kitamura et al., 2020; Mounier et al., 2021; Sritawan et al., 2021; Wahdan et al., 2020; Wang et al., 2019) were deemed an unclear risk of bias for reporting some information about the strain, sex and the age of the animals at baseline, but not all.

3.5.2. *Performance bias*

There was an unclear risk of performance bias across all included studies. For blinding of participants and personnel, 55 studies were allocated an unclear risk of bias for stating that they blinded, but not how this was conducted. Additionally, two studies were reported to be a high risk of bias for not stating whether they blinded at all (Gourishetti et al., 2019; Kinra et al., 2021) and the other 7 (Briones and Woods, 2014; Huehnchen et al., 2017; Keeney et al., 2018; Lyons et al., 2012, 2011; Ramalingayya et al., 2017; Saadati et al., 2020) were allocated a low risk of bias for stating that they blinded and how they did this. For random housing reporting only 1 study (Huehnchen et al., 2017) was allocated a low risk of bias for stating how they randomly allocated animals in the room in which they were housed. A high risk of bias was assigned to 4 studies (Allen et al., 2019; Oz et al., 2015; Ramalingayya et al., 2017; Yi et al., 2020) for not stating housing at all and the remaining 59 were allocated an unclear risk of bias for stating that they randomised the housing process, but not how this was conducted.

3.5.3. *Detection bias*

Overall, detection bias across the included studies was unclear. For reporting of blinding of outcome assessment, 7 studies (Briones and Woods, 2014; Callaghan and O'Mara, 2015; Cheruku et al., 2018; Johnston et al., 2017; Lyons et al., 2012; Saadati et al., 2020; Yi et al., 2020) were assigned a low risk of bias because they stated that they blinded the outcomes assessment process and how they did this, 3 studies (Gourishetti et al., 2019; Kinra et al., 2021; Zhou and Qiu, 2019) were assigned a high risk of bias for not stating this at all and the remaining 54 were assigned an unclear risk of bias, due to stating that they blinded outcome assessment, but not how this was conducted. For random outcome assessment, one study (Briones and Woods, 2014) was assigned a low risk of bias for stating how they randomly allocated animals for behavioural testing, two studies (Gourishetti et al., 2019; Kinra et al., 2021) was allocated a high risk of bias for not stating this and the remaining 61 were reported as an unclear risk of bias, due to stating that they randomly assessed animals, but did not state the methods in which they conducted this.

3.5.4. *Attrition bias*

For reporting of attrition of animals, 11 studies (Anderson, 2018a; b; Callaghan and O'Mara, 2015; Cankara et al., 2021; Jangra et al., 2016; Johnston et al., 2017; Kinra et al., 2021; Lomeli et al., 2017; Lyons et al., 2011; Lyu et al., 2021; Zhou and Qiu, 2019) were allocated a low risk of

Table 4
Summary characteristics of natural compounds with known anti-inflammatory properties or effects (group 3). [a-i] indicates studies with multiple experiments in the one study corresponding to Fig. 3, investigating multiple dosages, time points, treatment groups etc. ↑ improvement in cognition occurred in behavioural tests after the administration of an anti-inflammatory agent concurrently with a chemotherapeutic agent compared to chemotherapy alone treatment group. —no improvement in cognition occurred in behavioural tests after the administration of an anti-inflammatory agent concurrently with a chemotherapeutic agent compared to chemotherapy alone treatment group.

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
Curcumin (n = 4)									
(Akomolafe et al., 2020) Nigeria	Rat Wistar Male Age not stated	Cyclophosphamide (CYP) Non-tumour bearing	150 mg/kg Single injection on the first day of study Intraperitoneal	Curcumin[a]	20 mg/kg Daily for 14 days before or after CYP treatment Dissolved in DSMO and orally administered	Natural compound of turmeric that attenuates the inflammatory response of TNF-α stimulated human endothelial cells by interfering with NF-kB (Alok et al., 2015). Used to help with inflammatory diseases such as arthritis and hyperlipidaemia.	Unclear	Y-maze Morris water maze Y-maze Morris water maze	**Before CYP:** ↑ ↑ **After CYP:** ↑ ↑
(Oz et al., 2015) Turkey	Rat Wistar Albino Male Age not stated	Cisplatin (CIS) Non-tumour bearing	5 mg/kg/week Once per week for 5 weeks Intraperitoneal	Curcumin	300 mg/kg Administered once per day during CIS treatment Oral – not specified how		Conducted in week 5 of experiment (final week of chemotherapy treatment)	Morris water maze	↑
(Yi et al., 2020) China	Mouse SPF C57BL/6 Male 8 weeks old	Cisplatin (CIS) Non-tumour bearing	2.3 mg/kg (34.5 mg/kg cumulative dose) 3 cycles consisting of 5 daily injections followed by 5 days of rest Intraperitoneal	Curcumin	100 mg/kg Administered 1 h prior to CIS treatment Oral – not specified how		Unclear	Novel object recognition Morris water maze	↑ ↑
See below for curcumin investigated by Moretti et al. (2021).									
Resveratrol (n = 2)									
(Moretti et al., 2021) Brazil	Rat Wistar Male 3 months old	Doxorubicin (DOX) Non-tumour bearing	2.5 mg/kg Weekly for 4 weeks Intraperitoneal	Resveratrol[f] or Curcumin	**Curcumin:** 100 mg/kg/day Daily for 28 days during DOX treatment Gavage **Resveratrol:** 10 mg/kg/day	**Curcumin:** See above **Resveratrol:** Natural polyphenol widely existing in fruits and medicinal plants. Suppresses neuroinflammation by up-regulating the production of	Conducted 6 days following final DOX treatment on days 27 and 28 of experiment	Novel object recognition (assessed at 3 hr and 24 hr post treatment) Novel object recognition	**Resveratrol:** — 3 h ↑ 24 h **Curcumin:** ↑ ↑

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Table 4 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
					Daily for 28 days during DOX treatment Gavage	anti-inflammatory cytokines and inhibiting pro-inflammatory cytokine production (Meng et al., 2021).		(assessed at 3 hr and 24 hr post treatment)	
(Shi et al., 2018) China	Mouse C57B16/J Female Age not stated	Combination of Docetaxel, Adriamycin (DOX), and Cyclophosphamide (DAC) Non-tumour bearing	10 mg/kg, 10 mg/kg, and 40 mg/kg (Docetaxel + adriamycin + cyclophosphamide respectively) 3 injections at 2-day intervals within one week Intraperitoneal	Resveratrol[h]	50 mg/kg/day or 100 mg/kg/day Daily for 3 weeks, beginning 1 week before DAC treatment Gavage	Used for high cholesterol and heart disease.	Conducted from days 22–31 after treatment ended on day 21 of study	Morris water maze Morris water maze	**50 mg/kg/day dose:** — **100 mg/kg/day dose:** ↑
Rutin (n = 2)									
(Ramalingayya et al., 2017) India	Rat Wistar Female 12 weeks old	Doxorubicin (DOX) Non-tumour bearing	2.5 mg/kg Once in 5 days over a period of 50 days Intraperitoneal	Rutin (RUT)	50 mg/kg Daily starting 1 week before first DOX treatment and then continued thereafter until the end of the study Oral – suspended in carboxymethyl cellulose	Is a citrus flavonoid found in a wide variety of plants. Shown to suppress activity of proinflammatory cytokines by diminishing TNF-α and IL-1β production in microglia (Ganeshpurkar and Saluja, 2017). Used in alternative medicine to treat osteoarthritis and other inflammatory conditions.	Began 1 day after final chemotherapy injection (days 59–65)	Novel object recognition	↑
(Ramalingayya et al., 2019) India	Rat Sprague Dawley Female 4–5 weeks old	Doxorubicin (DOX) Tumour bearing	2.5 mg/kg Administered 10 cycles once in 5 days up to 50 days Intraperitoneal	Rutin (RUT)	50 mg/kg Pre-treatment daily for 1 week, and continued thereafter daily for 50 days Oral – not specified how		Conducted on days 59–64, one day after final chemotherapy treatment	Novel object recognition Morris water maze	↑ ↑
All other agents investigated in a single study									
(Ali et al., 2020a) Egypt	Rat Sprague Dawley Male Age not stated	Doxorubicin (DOX) Non-tumour bearing	2 mg/kg/week Administered for 4 weeks, 1 h after CAPE Intraperitoneal	Caffeic acid phenethyl ester (CAPE)[b]	10μmol/kg/day or 20μmol/kg/day Administered for 5 days per week for 4 weeks during DOX treatment Intraperitoneal	Natural phenolic chemical compound. Acts to downregulate inflammation by blocking NF-kB and inhibits arachidonic acid release from the cell membrane and therefore inhibits COX-1 and COX-2 activity (Armutcu et al., 2015).	Conducted on days 28–32 after treatment ended on day 21 of study	Morris water maze Passive Avoidance	**Group 3–10μmol/kg/day dose:** ↑ ↑

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Table 4 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
						Studied for its use in infections, cancer, and diabetes.			**Group 4–20μmol kg/ day dose:**
								Morris water maze	↑
								Passive Avoidance	↑
(Anderson, 2018a) United States of America	Mouse C57B16/J wild-type Female 4 months old	Combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) Non-tumour bearing	60 mg/kg, 4 mg/kg, and 60 mg/kg respectively Injections weekly for 4 weeks. Received a total of 4 injections on days 1, 8, 15 and 22 Intraperitoneal	Carnosic Acid	3 mg/kg Administered following CMF injections and received daily injections of carnosic acid. First injection 30 min after final CMF injection. Received a total of 7 daily injections Intraperitoneal	Is a natural benzenediol abietane diterpene found in rosemary and sage. Shown to downregulate the NF-kB transcription factor through a mechanism dependent on the activation of the Nrf2/HO-1 axis (de Oliveira et al., 2018). Studied for its use in cancer, metabolic syndrome, and arthritis.	Conducted 4 weeks post chemotherapy treatment	Elevated plus maze	—
								Y-maze	—
								Morris water maze with reversal	—
(Anderson, 2018b) United States of America	Mouse C57B16/J wild-type Female 4 months old	Combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) Non-tumour bearing	60 mg/kg, 4 mg/kg, and 60 mg/kg respectively Injections weekly for 4 weeks. Received a total of 4 injections on days 1, 8, 15 and 22 Intraperitoneal	Sulforaphane	50 mg/kg Administered first injection 30 min after final CMF treatment and received a total of 7 daily injections Intraperitoneal	Is a compound within the isothiocyanate group of organosulfur compounds, commonly found in vegetables such as broccoli. Acts by inducing the Nrf2 pathway and inhibits NF-kB (Santín-Márquez et al., 2019). Studied for its use in conditions such as autism, asthma, and COPD.	Conducted 2 weeks post final chemotherapy treatment	Elevated plus maze	—
								Y-maze	—
								Morris water maze with reversal	—
(Chaisawang et al., 2017) Thailand	Rat Sprague Dawley Male Adult (age not specified)	5-fluorouracil (5-FU) Non-tumour bearing	25 mg/kg, Administered 5 times on days 8, 11, 14, 17 and 20 Intravenous	Asiatic Acid[c]	30 mg/kg **Preventative group:** Administered for 20 days on days 1–20 **Recovery group:** Administered 1 day after final 5-FU	Triterpene compound found in Centella asiatica, reported to have neuroprotective properties. Shown to decrease nitric oxide, TNF-α and IL-1β (Huang et al., 2011). Used to treat cellulite, venous	Conducted 3 days after treatment finished	Novel object location	**Preventative group:** ↑ **Recovery group:**

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Table 4 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
					injection for 20 days, on days 21–40 **Throughout group:** Received for entire experimental period from days 1–40 Gavage	insufficiency of lower limbs and varicose veins.		Novel object location Novel object location	— **Throughout group:** ↑
(Cheruku et al., 2018) India	Rat Wistar Male 12 weeks old	Doxorubicin (DOX) Non-tumour bearing	2.5 mg/kg Administered in 10 cycles every 5 days Intraperitoneal	Catechin	100 mg/kg Administered for 57 days including one-week prior to first cycle of DOX Oral – not specified how	Is a flavan-3-ol, a type of natural phenol and antioxidant. Its anti-inflammatory effects have been shown to be activated through a variety of mechanisms including modulation of nitric oxide synthase isoforms (Sutherland et al., 2006). Eating foods high in catechin has been shown to prevent certain chronic conditions such as heart disease and diabetes.	Conducted 1 day after completion of chemotherapy treatment	Novel object recognition	↑
(El-Agamy et al., 2018) Egypt	Rat Albino Male Age not stated	Doxorubicin (DOX) Non-tumour bearing	2 mg/kg/week Once weekly for 4 weeks Intraperitoneal	Astaxanthin	25 mg/kg/day Administered 5 times a week for 4 weeks during DOX treatment Suspended in olive oil and administered orally	Naturally occurring carotenoid, shown to protect cell membranes against RONS and oxidative damage (Pereira et al., 2021). Research conducted for its use in athletic performance and muscle soreness.	Conducted 1 week post final chemotherapy treatment and 3 days post final astaxanthin treatment	Passive avoidance	↑
(Gourishetti et al., 2019) Saudi Arabia	Rat Sprague Dawley Female 8–10 weeks old	Doxorubicin (DOX) Non-tumour bearing	2.5 mg/kg For 10 cycles – not specified exactly when Route of administration not stated	Medhya Rasayana (MR)[d]	1 ml/kg/1.26 g/kg or 2 ml/kg/2.53 g/kg Regimen not stated Route of administration not stated	Is an ayurvedi formulation, reported to reduce oxidative stress, maintain good blood flow to the brain and maintain brain glucose levels, although its exact mechanisms are currently unknown (Kulkarni et al., 2012). Studies suggest it helps in the improvement of memory power.	Conducted on days 59–65 of experiment, 1 day after final treatment	Novel object recognition Novel object recognition	**1 ml/kg dose:** ↑ **2 ml/kg dose:** ↑

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Table 4 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
(Hou et al., 2013) Republic of Korea	Mouse ICR Male 8 weeks old	Cyclophosphamide (CYP) Non-tumour bearing	80 mg/kg 4 injections once weekly for 4 weeks Intraperitoneal	Compound K[e]	2.5 mg/kg, 5 mg/kg, or 10 mg/kg Administered once a week for 4 weeks, during CYP treatment Oral – not specified how	Is the intestinal metabolite of major ginsenoside Rb1. Shown to inhibit the expression of various inflammatory molecules by modulating NF-kB, AP-1 and CREB (Park et al., 2012). Studied for its use in diabetes and for various allergies.	Conducted in final week of experiment (week 4), immediately following final chemotherapy treatment	Passive avoidance Y-maze Passive avoidance Y-maze Passive avoidance Y-maze	**2.5 mg/kg dose:** — ↑ **5 mg/kg dose:** ↑ ↑ **10 mg/kg dose:** ↑ ↑
(Hussien and Yousef, 2021) Egypt	Rat Sprague Dawley Male Adult (age not specified)	Cisplatin (CIS) Non-tumour bearing	4 mg/kg Once a week for 90 days Intraperitoneal	Ginseng X	100 mg/kg Administered daily for 90 days during CIS treatment Oral – not specified how	Ginseng constituents such as ginsenosides have antioxidant, anti-inflammatory, immuno-modulatory and antifatigue properties. Shown to regulate the levels of GSH and ROS-mediated NF-kB pathway, which improves oxidative stress-mediated neurodegeneration (Makkar et al., 2020). Used to lower blood sugar in diabetes patients and for respiratory infections.	Conducted from days 85–90 of study, during treatment with both chemotherapy and ginseng X	Morris water maze	↑
(Ibrahim et al., 2021) Egypt	Rat Wistar Male 8 weeks old	Doxorubicin (DOX) Non-tumour bearing	2 mg/ml Once a week for 4 weeks Intraperitoneal	Chrysin (5,7-dihydroxyflavone)	30 mg/kg Initiated 1 h after DOX and thereafter 5 times per week for 4 weeks Prepared in DSMO and	Is a flavonoid naturally found in bee propolis and honey. Found to have anti-oxidant, anti-inflammatory, memory, and cognitive enhancing abilities, although its exact mechanisms are currently	Conducted from days 29–34 of study, 1 week following final chemotherapy treatment and 3 days following final Chrysin treatment	Y-Maze Morris water maze	— —

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Table 4 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
					corn oil and administered orally	unknown (Samarghandian et al., 2011). Used to treat anxiety, gout, and erectile dysfunction.		Step through passive avoidance	↑
(Kinra et al., 2021) India (Also found in group 2)	Mouse Swiss Albino Male 8–10 weeks old	Combination of Cyclophosphamide, Methotrexate and 5-Fluouoracil (CMF) Non-tumour bearing	50 mg/kg, 5 mg/kg and 5 mg/kg respectively 3 cycles, once a week for 3 weeks Intraperitoneal	Mulmina Mango[j]	40 ml/kg/day or 80 ml/kg/day Daily for 3 weeks during the same period as chemotherapy treatment Oral – not specified how	Consists of mangiferin, and has been shown to possess anti-inflammatory, antioxidant and neuroprotective activities, through its ability to cross the blood brain barrier (Feng et al., 2019).	Unclear	Morris water maze Morris water maze	**40 ml/kg/day dose:** ↑ **80 ml/kg/day dose:** ↑
(Lyu et al., 2021) China	Mouse BALB/C Female 6–8 weeks old	Doxorubicin (DOX) Tumour bearing	5 mg/kg Weekly for 3 weeks (finished on day 14 of study) Intraperitoneal	Kai-Xin-San (KXS)	1 g/kg Administered daily for 3 weeks beginning the first time DOX was administered Gavage	Traditional Chinese medicine prescription, composed of Ginseng Radix, Poria, Polygalae Radix, and Acori Tatarinowii Rhizoma. Shown to suppress neuronal inflammation, although its exact mechanisms are currently unknown (Cao et al., 2020). Used for the treatment of Alzheimer's disease, depression, and anxiety.	Conducted after treatment finished (after day 14 of study)	Morris water maze	↑
(Naewla et al., 2019) Thailand	Rat Sprague Dawley Male 5 weeks old	Methotrexate (MTX) Non-tumour bearing	75 mg/kg Administered on days 8 and 15 of experiment Intravenous	Hesperidin (Hsd)	100 mg/kg Administered for 21 days during MTX treatment Gavage	Is a flavonoid glycoside that has been shown to reduce inflammation through the suppression of cytokine production, NF-kB activity and oxidative stress (Xiao et al., 2018). Commonly used for blood vessel conditions such as haemorrhoids and varicose veins.	Unclear	Novel object location Novel object recognition	↑ ↑
(Pathak et al., 2020)	Rat Wistar	Temozolomide (TMZ) Tumour bearing and	18 mg/kg Once every 5 days for 7	Dehydrozingerone (DHZ)	100 mg/kg Regimen not stated	Is an unsaturated derivative of ginger rhizome and is a by-product of curcumin. Shown to	Conducted from days 21–31 of study		**Tumour bearing group:**

(*continued on next page*)

Table 4 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
India	Male 12 weeks old	non-tumour bearing groups	cycles (up until day 31 of study) Intravenous		Oral – not specified how	possess anti-depressant, anti-bacterial, anti-oxidant and anti-inflammatory properties, although its exact mechanisms are currently unknown (Profumo et al., 2016). Studied for its use as a treatment for prostate cancer.	(throughout treatment cycle)	Novel object recognition Morris water maze Novel object recognition Morris water maze	↑ ↑ **Non-tumour bearing group:** ↑ ↑
(Ramalingayya et al., 2018) India	Rat Wistar Female 10–12 weeks old	Doxorubicin (DOX) Non-tumour bearing	2.5 mg/kg Administered 10 cycles, once in 5 days up to 50 days Intraperitoneal	Naringin (NAR)	50 mg/kg Administered 1 week before DOX and continued throughout the study period Orally suspended in sodium carboxymethyl cellulose (CMC)	Is a flavanone-7-O-glycoside between the flavanone naringenin and the disaccharide neohesperidose that naturally occurs in citrus fruits. Shown to prevent the TNF-α mediated inflammatory process in tissue damage in liver and vasculature (Alam et al., 2014). Shown to be beneficial in the treatment of obesity, diabetes, hypertension, and metabolic syndrome.	Conducted from days 51–60 of study, one day following final chemotherapy treatment	Novel object recognition	↑
(Shaker et al., 2021) Egypt	Rat Albino Male 8 weeks old	Doxorubicin (DOX) Non-tumour bearing	2 mg/kg Once a week for 4 consecutive weeks Intraperitoneal	Berberine (BBR)[g]	50 mg/kg or 100 mg/kg Administered 5 times a week for 4 consecutive weeks during DOX treatment Oral – not specified how	Is a quaternary ammonium salt found in plants such as berberis. Shown to inhibit the production of IL-6, and TNF-α, which could be attributed to the inhibition of ERK1/2 activation (Zou et al., 2017). Used for diabetes and high cholesterol.	Conducted one week after final chemotherapy treatment and 3 days after final BBR treatment	Morris water maze Passive avoidance Y-maze	**50 mg/kg dose:** ↑ ↑ — **100 mg/kg dose:**

(*continued on next page*)

Table 4 (*continued*)

Author and Country of Publication	Animal Species, Strain, Sex and Age Investigated	CICI Animal Model	Chemotherapeutic Agent Dosing Schedule	Anti-Inflammatory Agent Investigated	Anti-Inflammatory Agent Dosing Schedule	Anti-inflammatory Primary Mechanism of Action and Common Use	Time of Behavioural Test Post Treatment	Behavioural Test (s) of Cognition Employed	Effect on Cognition
								Morris water maze	↑
								Passive avoidance	↑
								Y-maze	↑
(Shi et al., 2019) China	Mouse C57B16/J Female Age not stated	Combination of Docetaxel, Adriamycin (DOX), and Cyclophosphamide (DAC) Non-tumour bearing	10 mg/kg, 10 mg/kg, and 40 mg/kg (Docetaxel, Adriamycin, and cyclophosphamide respectively) 3 injections (one 10 mg/kg, one 10 mg/kg and then one 40 mg/kg) at a 2-day interval within 1 week Intraperitoneal	Ginsenoside Rg1[i]	5 mg/kg or 10 mg/kg Administered once daily and co-administered 1 week prior to DAC treatment for 3 weeks Intraperitoneal	Is a natural compound derived from ginseng. Shown to suppress pro-inflammatory cytokines (such as TNF-α, IL-1β and IL-6) as well as enzyme expression (such as iNOS and COX-2) (Im, 2020). Used to treat myocardial ischemia, long QT syndrome and atherosclerosis.	Conducted following the end of treatment (after 3 weeks)	Morris water maze Morris water maze	**5 mg/kg dose:** — **10 mg/kg dose:** ↑
(Tong et al., 2020) China	Rat Sprague Dawley Male 6 weeks old	Doxorubicin (DOX) Non-tumour bearing	2 mg/kg Once a week for 4 weeks Intraperitoneal	Polydatin	50 mg/kg Every day for 3 weeks during DOX treatment Oral – not specified how	Is an active ingredient isolated from the natural medicine polygonum cuspidatum. Shown to modulate inflammation by increasing Gli1, Ptch1 and SOD1 expression (Du et al., 2013). Has been shown to help in the treatment of cardiovascular diseases such as atherosclerosis.	States that behavioural analysis of each treatment group occurred after 28 days	Morris water maze Step-down avoidance task	↑ ↑
(Wang et al., 2020) China	Mouse C57BL/6 Male Age not stated	Doxorubicin (DOX) Non-tumour bearing	2.5 mg/kg Every 2 days for a total of 7 injections over a 2-week period Intraperitoneal	C-phycocyanin	50 mg/kg Daily for 3 weeks starting 1 week before DOX treatment. On the day of DOX treatment, C-phycocyanin was given 2 h prior Intraperitoneal	Is a protein-bound pigment soluble in water and is an accessory pigment to chlorophyll. Shown to inhibit pro inflammatory cytokine production, iNOS and COX-2 expression (Shih et al., 2009). Its neuroprotective effects have been observed in experimentally induced neurodegeneration models such as Parkinson's disease and multiple sclerosis.	Unclear	Morris water maze	↑

Summary Characteristics: Group 3 - Natural compounds with known anti-inflammatory properties or effects.

bias for reporting animal numbers at the start and throughout the paper, which either remained the same or reasons were stated for why these numbers may have changed. A high risk of bias was allocated to 11 studies (Alharbi et al., 2020; Ali et al., 2020a; Chang et al., 2020; Cole et al., 2013; Gourishetti et al., 2019; Iarkov et al., 2016; Kitamura et al., 2020; Li et al., 2020; Ongnok et al., 2021; Shaker et al., 2021; Shi et al., 2019) for not reporting sample sizes and the remaining 42 were allocated an unclear risk of bias as sample sizes may have changed from the beginning of the study to what was recorded in figures, without an explanation as to why this occurred.

3.5.5. Reporting bias

Overall, there was a low risk of bias in terms of the reporting of results. Only 1 study (Gourishetti et al., 2019) was considered a high risk of bias, as text reporting did not match with results presented in figures. An unclear risk of bias was allocated to 17 studies, (Allen et al., 2019; Anderson, 2018a; b; Chaisawang et al., 2017; Chang et al., 2020; Chiu et al., 2017; Huehnchen et al., 2017; Iarkov et al., 2016; Konat et al., 2008; Lim et al., 2016; Lomeli et al., 2017; Nguyen and Ehrlich, 2020; Pathak et al., 2020; Sritawan et al., 2020; Verma et al., 2017; Wang et al., 2019; Winocur et al., 2011) due to there being some discrepancies in reporting compared to what was mentioned in the methods and the remaining 43 were allocated a low risk of bias, as the methods and results reported corresponded with each other.

3.5.6. Other bias

The other potential risk of biases was non-disclosure of a funding or supporting body or a lack of reporting of potential conflicts of interest. A high risk of bias was allocated to 2 studies (Kinra et al., 2021; Gourishetti et al., 2019) as they either did not mention these factors or had a conflict of interest. While 20 studies (Akomolafe et al., 2020; Alharbi et al., 2020; Alhowail et al., 2019; Allen et al., 2019; Briones and Woods, 2014; Callaghan and O'Mara, 2015; Cankara et al., 2021; Chiu et al., 2017; Hou et al., 2013; Hussien and Yousef, 2021; Iarkov et al., 2016; Konat et al., 2008; Lyons et al., 2012, 2011; Ma et al., 2018; Mounier et al., 2021; Tong et al., 2020; Verma et al., 2017; Wahdan et al., 2020; Wang et al., 2019) were assigned an unclear risk of bias, due to only reporting one of the two criteria and the remaining 42 were assigned a low risk of bias for accurately reporting these.

3.6. Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used to grade the certainty of the evidence presented in the included studies (Schünemann et al., 2013, 2019). Through this, a summary of findings (SoF) table was created using the GRADEPro GDT software (McMaster University, ON, Canada) (GRADEpro GDT, 2022). The SoF presents the impact on cognition each of the three groups of anti-inflammatory agents had in a preclinical model of CICI. The SoF table can be seen in Table 5.

4. Discussion

CICI is a condition affecting cancer patients receiving chemotherapy treatment for which there are currently no therapeutic options available (Nguyen and Ehrlich, 2020). However, there are a range of agents that are used in clinical practice to treat other conditions where cognition is impaired, such as AD (Shah et al., 2008). Therefore, there is an opportunity to repurpose these agents for use in preventing or managing CICI. Since neuroinflammation has been established as a driver of pathology in CICI (Vichaya et al., 2015), anti-inflammatory agents may represent leading candidates to achieve this aim; however, research is still in the preclinical stage and many critical questions remain. This is the first systematic review to provide a comprehensive synthesis of the literature on the use of agents with anti-inflammatory properties or effects in preclinical animal models of CICI.

Overall, improvements in cognition were evident in groups 2 (non-traditional anti-inflammatory agents) and 3 (natural compounds). Specifically, 26 studies (70%) in group 2 resulted in cognitive improvements after the addition of an anti-inflammatory agent, with 17 studies (65%) in group 3 also resulting in an improvement in cognition. Conversely, group 1, comprising naproxen and aspirin, resulted in no improvements in cognition. In particular, some agents from group 2 that were investigated across multiple studies (i.e., NAC, lithium, memantine, melatonin) showed promise in their ability to reduce cognitive impairments observed after chemotherapy administration. For other non-traditional anti-inflammatory agents, including metformin, donepezil and ACY-1215, results were mixed, with cognitive improvements in some studies, but not all. Similarly, for both fluoxetine and MESNA, improvement was dependent on the timing of administration of the anti-inflammatory agent relative to chemotherapy administration. Amongst group 3, curcumin was the most effective in improving cognition, with all four studies investigating this agent, demonstrating benefits for cognition. For the other naturally-derived compound assessed in more than one study, resveratrol, effects depended on the timing of administration, or the dose administered. Across both groups 2 and 3, it was difficult to fully evaluate the benefits of multiple compounds, given that they have been assessed in only a single study to date. Additionally, while it was surprising that neither of the traditional NSAIDs in group 1 were successful in improving cognition, only a single study for each has been conducted. This suggests that significant future research remains to be conducted, in order to fully assess the benefits of anti-inflammatory agents in preclinical models of CICI.

4.1. Group 1 – traditional anti-inflammatory agents

Naproxen and aspirin are both NSAIDs designed to reduce inflammation by blocking the enzyme, cyclooxygenase (COX), which produces prostaglandins (Weissmann et al., 1987). Naproxen is used for the treatment of rheumatoid arthritis, tendinitis, and osteoarthritis (Ahmad et al., 2018) and acts by inhibiting COX-1 and COX-2 activity (Hautaniemi et al., 2012). Conversely, aspirin is used to reduce fever and relieve mild to moderate pain such as muscle aches, headaches, and the common cold (Vane and Botting, 2003). It works by irreversibly inhibiting COX-1 and modifying the enzyme activity of COX-2, which in turn suppresses the production of prostaglandins and thromboxanes (Vane and Botting, 2003). Therefore, it was assumed that NSAIDs would ameliorate cognitive impairment in preclinical models of CICI, as this condition has been shown to be driven by an inflammatory mechanism (Vichaya et al., 2015). However, there is no evidence of this in the two included studies. The study by Chang et al., investigating the use of aspirin found that there was no evidence of inflammation, as indicated by cytokine analysis in the brain, following chemotherapy administration (paclitaxel at 10 mg/kg, administered every second day for 2 weeks) (Chang et al., 2020). This is contrary to other studies that have found that neuroinflammation is increased with the use of PTX in preclinical models of CICI. For example, Loman et al., found that treatment with PTX in female BALB/c mice increased proinflammatory cytokines, such as IL-1β, TNF-α and IL-6 (Loman et al., 2019). Similarly, another study found that the expression of proinflammatory cytokines, including TNF-α and IL-1β, was increased in male Sprague-Dawley rats after receiving PTX (John et al., 2021). However, while Chang and colleagues did not observe the same increases in inflammation noted in earlier studies, they did note that treatment with PTX alone caused deficits in the NOR test, with animals spending a reduced amount of time exploring the novel object compared to control animals (Chang et al., 2020). This may indicate that cognitive impairment in this model is driven by another mechanism other than neuroinflammation. If this is the case, then it is perhaps not surprising that aspirin failed to lead to improvements in cognitive function. Nevertheless, given discrepancies with prior literature, further investigations are warranted.

Similarly, naproxen did not improve cognition following CYP

chemotherapy administration (Pavlock et al., 2021). Interestingly, while naproxen is an anti-inflammatory agent, it has been reported to produce toxic effects on organs throughout the body and therefore may also contribute to inflammation (Ahmad et al., 2018; Fiorucci et al., 2001). In this study, CYP itself caused a significant increase in the anti-inflammatory cytokine IL-10, whereas the addition of naproxen increased the anti-inflammatory cytokine IL-4, as well as pro-inflammatory cytokines; IL-1α, IL-1β, IL-2 and IL-3 (Pavlock et al., 2021). Therefore, in the case of this study, the authors found that the combination of CYP and naproxen exacerbated hippocampal inflammation, instead of helping to reduce it. This is in line with previous work investigating the genotoxicity of oral naproxen in male Wistar rats, which found that naproxen contributed to a biochemical imbalance and induced oxidative stress that contributed to cell integrity loss (Ahmad et al., 2018). It is possible that these effects may be exacerbated by the presence of the chemotherapeutic agent.

Overall, there is limited evidence to come to a conclusion on the usefulness of NSAIDs in reducing the effects of CICI, as only two studies have been conducted. Given this gap in the literature, more research is warranted.

4.2. Group 2 – non-traditional anti-inflammatory agents with known anti-inflammatory properties or effects

There are several agents used to treat a range of conditions that are not designed to have primary anti-inflammatory actions, but which have been discovered to possess anti-inflammatory properties or effects. In this group, there were a number of agents that were only investigated in a single study each. Of these agents, only one failed to improve cognition (sodium valproate), while the rest were found to improve cognition depending on the behavioural test investigated, dose received, or treatment schedule utilised. However, as these agents were only investigated once in a preclinical model of CICI, there is limited evidence as to whether there is value in these agents for treating CICI and there is a need for more research to be conducted.

Agents such as NAC, lithium, memantine and melatonin were investigated across multiple studies and demonstrated improvements in cognition across all. As multiple studies have investigated these agents, there is more robust evidence to suggest that these agents make promising candidates to continue to research into their effectiveness in treating CICI. NAC (n = 3) is often used to treat respiratory conditions and paracetamol overdose and works by providing cysteine for glutathione synthesis (Lauterburg et al., 1983). It has also been shown to be a powerful antioxidant and to have anti-inflammatory effects, reducing pro-inflammatory cytokine levels, such as IL-1β, IL-6 and TNF-α, in a rat model of colitis (Uraz et al., 2013). Additionally, a systematic review investigating the administration of NAC to treat cognitive impairment as a result of alzheimer's disease, bipolar disorder, schizophrenia and ketamine-induced psychosis, found that there were statistically significant improvements in cognition in the clinical literature (Skvarc et al., 2017), making it a promising candidate to further research for CICI treatment. Lithium (n = 2), on the other hand, is a mood stabilising drug, used to treat psychiatric conditions. Its primary mechanism of action is through stimulating the NMDA receptor, which increases glutamate availability in the post synaptic neuron (Malhi et al., 2013). It has also been shown to posess anti-inflammatory properties through its

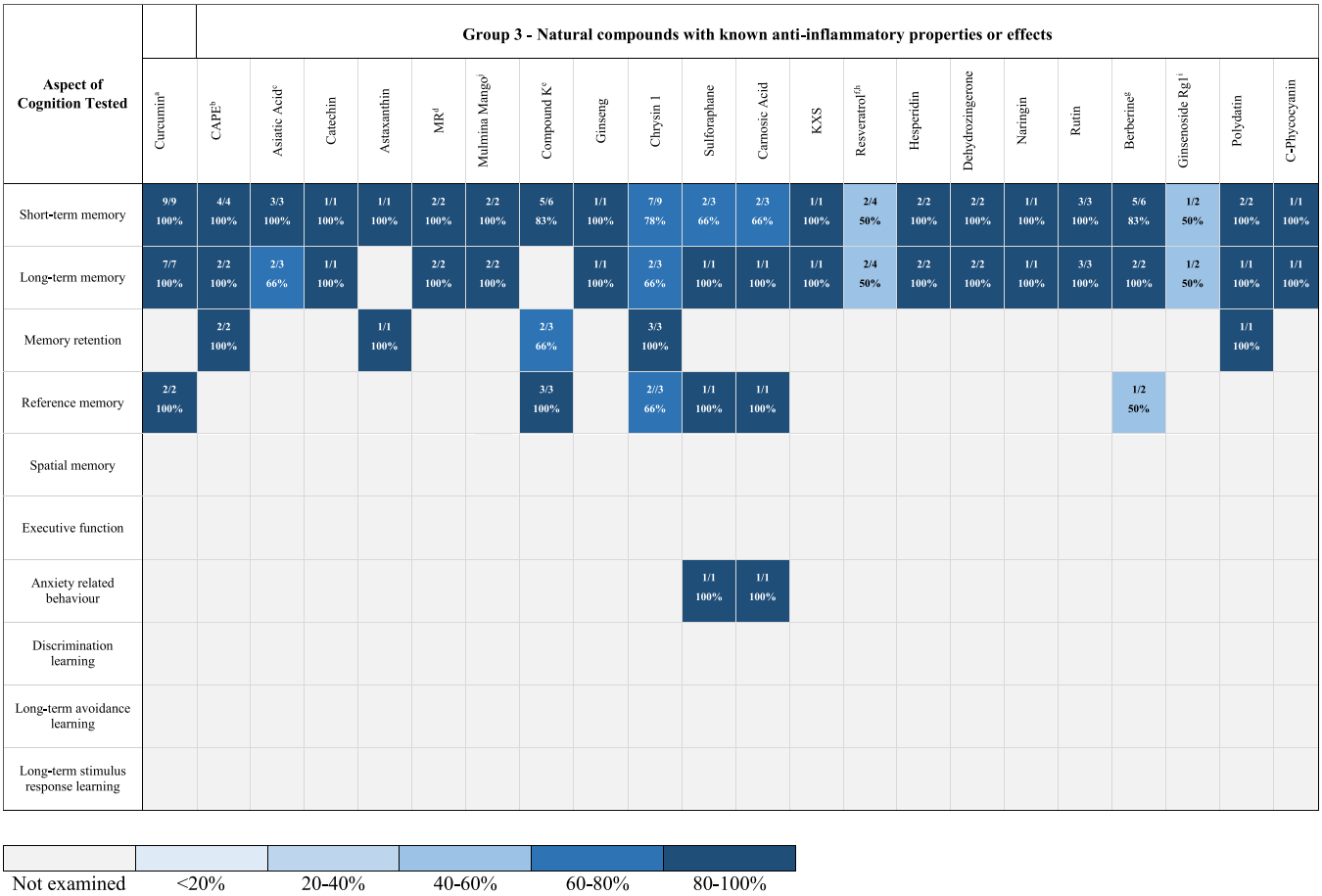

Fig. 3. Heatmap demonstrating the percentage of studies where an improvement in an aspect of cognition tested in a behavioural test was observed following the administration of a natural compound. [a-i] indicates agents that have been investigated across multiple studies, corresponding with Table 4. Studies were counted as more than one study if they utilised multiple treatment groups, dose amounts etc. CAPE = , Caffeic acid phenethyl ester MR = Medhya Rasayana, KXS = Kai-Xin-San.

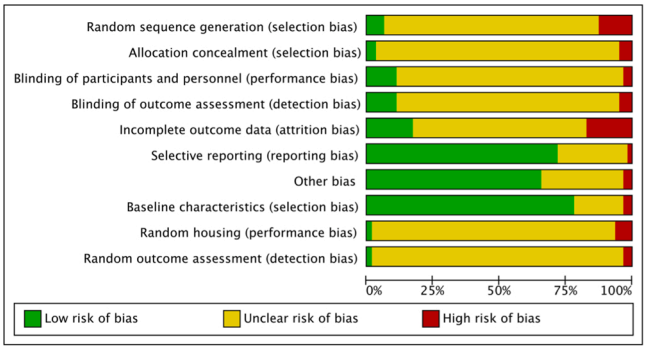

Fig. 4. Percentage of studies that achieved either a low, unclear, or high risk of bias for each domain using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool.

ability to suppress COX-2 expression, inhibit IL-1β and TNF-α production and enhance IL-2 and IL-10 synthesis (Nassar and Azab, 2014). Preclinical literature suggests that lithium is able to exert neuroprotective effects, however, there is limited evidence to suggest this in the clinical literature in bipolar disorder (Pfennig et al., 2014). Memantine (n = 2) is an antagonist of the NMDA subclass of glutamate receptors that blocks current flow through channels of these receptors and is often used to treat AD (Johnson and Kotermanski, 2006). Given its effectiveness in treating cognitive impairments observed in AD, it is logical to hypothesise that it may also have utility for CICI. In line with this, it has been shown to posess anti-inflammatory actions through its ability to reduce microglia-associated inflammation and stimulate neurotrophic factor release from astroglia, therefore warranting its use in CICI to reduce the inflammation present after chemotherapy adminstration (Wu et al., 2009). Lastly, melatonin (n = 2) is a derivative of tryptophan, which binds to melatonin receptor type 1A, which then acts on adenylate cyclase and inhibits the cAMP signal transduction pathway (Boutin et al., 2005). It is used to treat sleep disorders, and has been shown to posesses anti-inflammatory properties through its ability to prevent the translocation of NF-kB to the nucleus and its binding to DNA, therefore reducing the upregulation of some pro-inflammatory cytokines (Reiter et al., 2000). Studies have investigated its use in AD and the related cognitive impairment that occurs with this disorder and found that the ability of patients to remember previously learned items improved with the use of melatonin (Cardinali et al., 2010). Encouragingly, melatonin is also currently readily available in pharmacies, making it a particularly attractive candidate for further development.

For other non-traditional anti-inflammatory agents investigated across multiple studies, mixed results were found for donepezil (n = 5), metformin (n = 4), ACY-1215 (n = 2), fluoxetine (n = 2) and MESNA (n = 2), where it appeared that improvements in cognition were dependent on timing relative to chemotherapy administration and/or the route of administration. Of these agents, donepezil is the most promising, as it is already used as a treatment option for AD (Marucci et al., 2021). Donepezil works by selectively and reversibly inhibiting the acetylcholinesterase enzyme, which normally breaks down acetylcholine, therefore helping to enhance cholinergic transmission (Marucci

Table 5
Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Summary of Findings table for primary outcomes investigating the use of anti-inflammatory agents to improve cognitive impairment evident in CICI.

The Effects of Anti-inflammatory Agents on Cognition in Chemotherapy-Induced Cognitive Impairment			
Patient or population: Laboratory mice and rats used for research purposes **Intervention of interest:** Anti-inflammatory agents **Comparison:** No anti-inflammatory agent administered or chemotherapy only treatment groups			
Outcomes	**Impact**	**Number of Participants (Studies)**	**Certainty of the Evidence (GRADE)**
Group 1 - Traditional anti-inflammatory agents (NSAIDs), assessed with: Validated behavioural tests of cognition	The two anti-inflammatory agents investigated (aspirin and naproxen) were shown to not help improve cognition after chemotherapy treatment as tested through various behavioural tests of cognition.	(2 RCTs)	⨁◯◯◯ Very low[a,b,c,d]
Group 2 - Non-traditional anti-inflammatories, assessed with: Validated behavioural tests of cognition	There were 26 different anti-inflammatory agents investigated across 37 studies. 9 of these agents were investigated across multiple studies, while the remaining 17 were investigated in just the one study. Overall, a majority of these agents helped to improve cognition after chemotherapy treatment, as determined through various behavioural tests of cognition. However, as there is limited evidence for these agents as a majority of these were only investigated in the one study, it is hard to determine the effectiveness of them in the treatment of CICI at this stage.	(37 RCTs)*	⨁◯◯◯ Very low[b,c,d,e]
Group 3 - Natural compounds with known anti-inflammatory properties or effects, assessed with: Validated behavioural tests of cognition	There were 22 different types of anti-inflammatory agents that were investigated across 26 studies. 3 agents, being curcumin, resveratrol and rutin were investigated in more than one study, while the remaining 19 were investigated in the one study. Therefore, there is limited evidence on the effectiveness of these agents in the treatment of CICI. Curcumin, however resulted in improvements in cognition as determined by various behavioural tests in all 4 studies that investigated this agent, therefore, making it a promising agent to continue to investigate as a possible therapeutic option for CICI.	(26 RCTs)	⨁◯◯◯ Very low[b,c,d,e]

GRADE Working Group grades of evidence:
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Explanations
aRisk of Bias: As determined by the risk of bias assessment; most studies were assigned an unclear risk of bias.
bIndirectness: As these are preclinical studies, they are not currently translatable to clinical work.
cImprecision: Based on relevant outcomes and clinical significance.
dPublication Bias: Strongly suspected that there is publication bias across the studies, as determined by the risk of bias assessment.
*Extra study included due to Kinra et al., investigating two anti-inflammatory agents, one in group 2 and one in group 3.

et al., 2021). While donepezil is not traditionally an anti-inflammatory agent, it has been shown to possesses anti-inflammatory properties through its ability to suppress IL-1β and COX-2 expression in the brain to prevent systemic inflammation (Yoshiyama et al., 2010), making it a promising agent to continue to research, as it may help improve cognition in CICI. Similarly, metformin is also promising, as it is already used to treat type 2 diabetes, meaning it is already highly researched and safe to use. Metformin works by suppressing gluconeogenesis and improves glucose uptake and insulin sensitivity (Rena et al., 2017). It has been shown to act via both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms, by inhibiting mitochondrial respiration (Rena et al., 2017). It has also been shown to have anti-inflammatory properties via its ability to inhibit NF-kB via AMP-activated protein kinase (AMPK)-dependent and independent pathways (Saisho, 2015). A study investigating the use of metformin in older people with diabetes, found that they had slower cognitive decline and therefore a lower risk of developing dementia compared to those with diabetes, but not receiving metformin and those without diabetes (Samaras et al., 2020).

Overall, the evidence supports the use of non-traditional anti-inflammatory agents to improve cognitive function in preclinical models of CICI; however, more research is needed into understanding their mechanisms by which they reduce neuroinflammation in this model, as well as their optimal dosage and administration protocols.

4.3. Group 3 – natural compounds with known anti-inflammatory properties or effects

Of the 22 agents investigated in this group, only 2, being sulforaphane and carnosic acid, failed to yield cognitive improvements. These two agents were only investigated in a single study each, therefore more research is warranted to draw any conclusions. In this group, curcumin stood out as being a promising agent to treat CICI across the four separate studies that investigated this agent. Curcumin is a polyphenol and is the most active component of turmeric (Jacob et al., 2007). It has been shown to possess anti-inflammatory properties (Alok et al., 2015), perhaps due to its ability to block NFkB activation (Hewlings and Kalman, 2017), although its exact mechanisms of action are currently unknown. In line with this, curcumin is commonly used to aid in the management of oxidative and inflammatory conditions, including metabolic syndromes and arthritis (Hewlings and Kalman, 2017). Promisingly, curcumin has also been shown to lead to improvements in cognitive function in animal models of AD, although evidence from clinical studies is mixed (See review of, Voulgaropoulou et al., 2019). Nevertheless, a clinical study investigating the use of curcumin to help with cognitive function in the elderly Asian population found that those who consumed curry "often" (with curcumin in it) had a significantly better 'Mini-Mental State Examination' score, indicating preserved cognitive function, compared to those who "never" or "rarely" consumed curry (Ng et al., 2006). Taken together with the current evidence of curcumin's benefits in animal models of CICI, it suggests that this compound warrants further development. Furthermore, given that all four studies investigating curcumin used oral administration, it may represent the possibility for a safe and non-invasive therapeutic strategy to be rapidly translated clinically. Curcumin has also been shown to be safe, even at high doses, with no adverse reactions on liver and kidney function noted and is readily available in pharmacies and supermarkets (Rahmani et al., 2018).

Additionally, resveratrol was investigated across two studies, with mixed results depending on the timing of administration, route of administration, behavioural tests investigated, or dose administered. Evidence from preclinical studies with resveratrol suggests that the addition of this agent can improve memory and learning in rats and primates, however, results from the clinical literature are mixed (Evans et al., 2017). The two included studies in this review were recently published in 2018 and 2021, raising the possibility that more work is currently being conducted on this agent or will be in the future.

Importantly, other natural compounds with anti-inflammatory properties or effects that were only investigated in a single study each, were found to show improvements for some studies and not for others. More research therefore needs to be conducted on these agents, as one study does not provide sufficient evidence to draw conclusions about potential benefits.

Overall, natural compounds have shown promise throughout the literature to help improve cognitive function in different neurological and neurodegenerative disorders, particularly through their antioxidant and anti-inflammatory abilities. They are also readily available, inexpensive and generally have few detrimental side effects (Ekor, 2014). Therefore, natural compounds, particularly curcumin, should be targeted for further investigation in CICI.

4.4. Heterogeneity of results

Despite the fact that a majority of the agents investigated improved cognition in preclinical models of CICI, the results need to be taken with caution due to the heterogeneity across the studies in terms of methods employed. Animal models are an important first step to investigate the use of such agents; however, with this comes variability in models used, as there is currently no gold standard animal model utilised in CICI research (Matsos and Johnston, 2019). This review shows that several different strains of rats and mice were employed. The strain of an animal can affect research outcomes, as some are genetically different to others (Gileta et al., 2021). For example, deciding between using inbred strains or outbred stocks is important as inbred animals are usually more uniform and genetically similar, requiring fewer numbers and are easy to replicate in future research, whereas outbred animals are often used in genetic, toxicology and pharmacology research, as they are genetically heterogeneous and are therefore a more accurate representation of a clinical population (Festing, 2014). Particular animals are also more efficient at learning certain components of a behavioural test and are therefore better suited for some tests over others (Ellenbroek and Youn, 2016). For example, rats have been shown to be more superior at maze learning compared to mice, as mice can experience more stress and anxiety while doing so (Ellenbroek and Youn, 2016). It is also important to note that 61 of the 64 studies used healthy animals without cancerous tumours. Evidence suggests that a diagnosis of cancer itself can cause cognitive impairment in up to 33% of patients (Ahles et al., 2008; Janelsins et al., 2014). Therefore, the use of animal models in CICI with tumours would be more clinically relevant. However, sometimes this is not possible from an ethical or practical point of view since tumour humane endpoints are often reached before the needed timelines to investigate CICI progression. In spite of this, there is good evidence from the animal and clinical literature that chemotherapy plays a fundamental role in inducing impairments to cognition, regardless of cancer state, and thus ameliorations to cognitive impairment as a result of therapeutics can still be reliably identified in non-tumour bearing models (Foley et al., 2008; Seigers et al., 2008; Winocur et al., 2006).

Additionally, timing in relation to chemotherapy treatment also varied among studies, as well as the duration of treatment. This can have an impact on comparing results between studies, as some studies administered the anti-inflammatory agent for a longer period of time than others or at a higher dose. The challenge is knowing the time course in which chemotherapy treatment affects cognition and being able to standardise the timing of treatment in preclinical studies and then translating this to clinical studies. A systematic review investigating the prevalence of cognitive impairment following chemotherapy treatment for breast cancer patients found that cognition gradually resolved over time for many patients, but the timing in which this happens is currently not well understood (Whittaker et al., 2021). Furthermore, several behavioural tests were utilised in the included studies, each testing different aspects of cognition and different underlying brain regions. This can make it difficult to draw comparisons between studies

conducted by different groups, who may use slightly different protocols and tests. The reproducibility of behavioural tests also comes under question with differences in environmental conditions and experimenters shown to influence results (Nigri et al., 2022).

Finally, the route via which both the chemotherapeutic agent and the anti-inflammatory agent were administered varied. The route of administration needs to be carefully thought about before designing a study, in order for the substance to work most effectively. Oral administration is common throughout animal research, as it is economic, convenient, and relatively safe (Turner et al., 2011). However, it can be unreliable, especially when administered through water or food, as the amount in which the animal has received may not be accurate (Turner et al., 2011). Additionally, oral administration may result in a slower onset of action, with reduced efficacy and lack of absorption (Turner et al., 2011). For this reason, injections are often utilised, particularly intraperitoneal and subcutaneous injections, as they bypass the need for solute absorption (Turner et al., 2011). However, the route in which a substance will be most effective is dependent on the substance itself and the dose administered, which could explain the mixed results found. This variability could be minimised if researchers use allometric scaling for cross-species comparisons, and elevated dosages to account for first-pass metabolism. Across the included studies, there was no clear indication as to whether a specific route of administration was more efficacious than others in regard to improving cognitive outcomes in CICI.

Overall, it is imperative that there is a standardised animal model created for CICI research, as it can pose a threat to future progress in the area and translation of findings. In particular, the International Cancer and Cognition Task Force (ICCTF) have highlighted the need to provide recommendations on how to standardise models and research design for animal models of CICI (Winocur et al., 2018).

4.5. Methodological quality of included studies

Overall, the methodological quality of many of the included studies was poor due to the unclear risk of bias assigned to most of them. In general, reporting of time points, sample sizes, randomisation methods, blinding methods and attrition of animals was poor. This can make it hard to draw conclusions on the methods used and how effective many of these agents really are if other researchers are not able to easily replicate such findings. A major concern is the failure to report blinding. If researchers are not blinded, this will have implicit biases on the data recording process and potentially the randomisation of the study and random outcome detection, making it difficult to truly interpret results. This indicates considerable room for improvement through adherence to reporting guidelines such as the ARRIVE guidelines (George et al., 2021; Percie du Sert et al., 2020).

5. Conclusion

Taken together, we conclude that while it seems that many of the anti-inflammatory agents investigated were successful in improving cognition after chemotherapy treatment in preclinical animal models, the results should be taken with caution due to the heterogeneity observed between studies in terms of the methods employed. Additionally, many agents were only investigated in a single study, making it difficult to consider moving compounds forward into clinical assessment until further research is conducted. It is also important to note that, while this review only focused on the behavioural cognitive outcomes of these studies, other outcomes were also measured in many, including molecular and histological techniques. These outcomes are also relevant to understanding the mechanisms behind why these agents may be helping to contribute to reducing the effects of CICI through reducing inflammation. However, this information is beyond the scope of this review and could be investigated further in the future. Overall, it was concluded that agents including NAC, lithium, memantine, melatonin, donepezil and curcumin showed potential for the treatment of CICI, due to their investigation across multiple studies, and the improvements in cognition noted across a majority of these. Specifically, agents such as curcumin and melatonin, that are already readily available and safe to use, are big contenders to continue to research clinically for the treatment of CICI.

Conflict of interest

The authors declare that this review was conducted with no external funding and there are no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105120.

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