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REVIEW

The Effects and Mechanisms of Xanthones in Alzheimer's Disease: A Systematic Review

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Abstract
Xanthones are natural secondary metabolites that possess great potential as neuroprotective agents due to their prominent biological effects on Alzheimer's disease (AD). However, their underlying mechanisms in AD remain unclear. This study aimed to systematically review the effects and mechanisms of xanthones in cell culture and animal studies, gaining a better understanding of their roles in AD. A comprehensive literature search was conducted in the Medline and Scopus databases using specific keywords to identify relevant articles published up to June 2023. After removing duplicates, all articles were imported into the Rayyan software. The article titles were screened based on predefined inclusion and exclusion criteria. Relevant full-text articles were assessed for biases using the OHAT tool. The results were presented in tables. Xanthones have shown various pharmacological effects towards AD from the 21 preclinical studies included. Cell culture studies demonstrated the anti-cholinesterase activity of xanthones, which protects against the loss of acetylcholine. Xanthones exhibited neuroprotective effects by promoting cell viability, reducing the accumulation of β-amyloid and tau aggregation. The administration of xanthones in animal models resulted in a reduction in neuronal inflammation by decreasing microglial and astrocyte burden. In terms of molecular mechanisms, xanthones prevented neuroinflammation through the modulation of signaling pathways, including TLR4/TAK1/NF-κB and MAPK pathways. Mechanisms such as activation of caspase-3 and -9 and suppression of endoplasmic reticulum stress were also reported. Despite the various neuroprotective effects associated with xanthones, there are limited studies reported on their underlying mechanisms in AD. Further studies are warranted to fully understand their potential roles in AD.

Keywords Xanthone · Alzheimer's disease · Neuroinflammation · Acetylcholinesterase · Memory impairment

Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
AMPK	AMP-activated protein kinase
APP	Amyloid precursor protein
Aβ	Amyloid beta
BACE1	β-Site amyloid precursor protein cleaving enzyme 1
Bax	Bcl-2-associated X protein

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Bcl-2	B-cell lymphoma 2
BuChE	Butyrylcholinesterase
COX-2	Cyclooxygenase-2
DNA	Deoxyribonucleic acid
DPPH	2,2-Diphenyl-1-picrylhydrazyl
ERS	Endoplasmic reticulum stress
FDA	Food and Drug Administration
GSK	Glycogen synthase kinase
H_2O_2	Hydrogen peroxide
HO	Heme oxygenase
IgG1	Immunoglobulin G1
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LPO	Lipid peroxide
LPS	Lipopolysaccharide
MeSH	Medical Subject Headings
mRNA	Messenger ribonucleic acid
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
NLRP3	NLR family pyrin domain containing 3
NO	Nitric oxide
OHAT	Office of Health Assessment and Translation
PGC-1 α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PICO	Population, Intervention, Comparison and Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-SR	Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Systematic Reviews
ROS	Reactive oxygen species
SIRT1	Sirtuin 1
SOD	Superoxide dismutase
TNF-α	Tumor necrosis factor alpha
TLR4	Toll-like receptor-4

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the gradual deterioration of cognitive and behavioral functions such as memory loss, language deterioration and cognitive impairment. It becomes more prevalent affecting more than 50 million people worldwide as of 2020, particularly those aged 65 and above [1]. The incidence of AD appears to be increasing, underscoring the significant need for the development of pharmacological therapeutics agents. Despite extensive research conducted over the past century, the exact etiology of AD remains unknown. However, several factors have been proposed to contribute to its development, including acetylcholine (ACh) deficiency, oxidative stress, dyshomeostasis of biometals and amyloid beta (Aβ) peptide deposition [2, 3].

ACh is a neurotransmitter that plays a crucial role in various cognitive functions, particularly memory and learning [4]. Within the central nervous system, ACh is primarily synthesized by neurons in the basal forebrain and released into different regions, especially those involved in memory and cognition, such as the hippocampus, amygdala and prefrontal cortex [5]. The decline in ACh levels leads to impairment of the cholinergic system in the brain, particularly in the hippocampus, amygdala and prefrontal cortex, which are crucial for memory formation and retrieval. This impairment contributes to the clinical manifestation of memory deficits and cognitive decline observed in patients with AD [5]. Additionally, the cholinergic system also plays a significant role in other vital processes in the central nervous system, including neurogenesis, synaptic plasticity and cell survival [5]. The involvement of ACh in memory and cognitive processes supports the cholinergic hypothesis regarding pathogenesis of AD. Therefore, current treatments for AD primarily focus on targeting the cholinergic system to alleviate the cognitive symptoms associated with the disease.

The expanding lifespan of individuals has led to a rapid rise in the number of dementia patients, mainly those with AD, prompting extensive research focused on its treatment. Despite all arduous research efforts, the current pharmacologic treatment options have been extremely limited. Previously approved drugs only provide symptomatic improvement and fail to modify the disease progression. Acetylcholinesterase inhibitors such as tacrine, donepezil, rivastigmine and galantamine, while beneficial, are associated with gastrointestinal side effects including nausea and diarrhea which can be intolerable for elderly patients [6]. Undoubtedly, there are substantial unmet medical needs among AD patients, emphasizing the urgent need for alternative therapeutic approaches and the discovery of novel drug candidates. A crucial direction in therapy development is to explore new approaches that demonstrate improved efficacy in halting the progression of AD [7]. In recent years, the U.S. Food and Drug Administration (FDA) has approved aducanumab and lecanemab, monoclonal IgG1 antibodies that bind to Aβ fibrils or protofibrils to decrease Aβ deposition in the brain [8–10].

Xanthones are natural secondary metabolites that exhibit a broad spectrum of biological activities, which depend on the specific substituents and their positions on the core structure of xanthone. Their diverse biological activities, including anti-inflammatory, antioxidant, anticholinergic, antidiabetic, and antitumor properties, have sparked significant interest in the research field [11]. In recent years, there has been extensive study and exploration of both natural and synthetic xanthone derivatives targeting AD. Xanthones have been found to inhibit acetylcholinesterase (AChE)

and butyrylcholinesterase (BuChE), which are important biological targets in AD, along with demonstrating antioxidant activity [12]. Furthermore, these compounds have been shown to possess various pharmacological actions such as inhibiting Aβ aggregation [13], and reducing oxidative stress and neuroinflammation [14]. Therefore, this study aimed to systematically review the effects and mechanisms of action of xanthones in AD, providing a comprehensive understanding of their potential roles as new potential anti-Alzheimer drugs.

Methods

Research Question

The research question was defined and structured by using the Population, Intervention, Comparison and Outcome (PICO) framework [15]. The key concepts in the research question and search terms were identified through PICO and searched in two electronic databases, namely Medline and Scopus. The research question was structured based on the four elements in the PICO tool, in conjunction with the inclusion and exclusion criteria (Supplementary information 1).

Search Strategy

The study was conducted by systematically reviewing previous literature of xanthones in AD with a comprehensive search of two electronic databases, namely Medline and Scopus. All relevant articles published until June 2023 were identified. The search terms included Medical Subject Headings (MeSH) terms and text words that are relevant to the research questions. The following keywords were used for retrieval purposes: xanthone* [MeSH Terms], xanthone*, xanthen-9-one, alzheimer disease [MeSH Terms], dementia* [MeSH Terms], neurodegenerat* [MeSH Terms], alzheimer*, dementia*, and neurodegenerat* (Supplementary Information 2).

Selection of Articles

A total of 123 papers from Medline and 2168 papers from Scopus were identified. After removing duplicates, 2173 original papers remained for screening. Compilation and elimination of duplicates were conducted by the Rayyan referencing software [16]. During the preliminary screening, titles and abstracts were screened independently and evaluated by two reviewers (i.e. PLW and YHY). The pre-specified inclusion and exclusion criteria were used to screen full-text articles (Supplementary Information 1). Each article was labeled as either 'included', 'excluded' or 'maybe'. Articles that could not be determined eligibility (which were labelled as 'maybe') based on title and abstract were retrieved as full texts and both reviewers reached a consensus for study inclusion. The final selection of articles was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow method (Fig. 1) [17].

Data Extraction

Information on authors, year of study, cell line used or animal models, induction method if applicable, study findings and data of significant statistical value were extracted using designated tables. Any discrepancy in extracted data was discussed among the reviewers until a consensus was reached. The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Systematic Reviews (PRISMA-SR) was used as a checklist in documenting the rationale, methodology and findings of the systematic review (Supplementary Information 3) [17].

Bias Assessment

The articles included were subjected to bias assessment by using the Office of Health Assessment and Translation (OHAT) risk of bias tool [18]. The OHAT risk of bias tool was applied to assess the risk of articles included based on six types of bias including selection bias, confounding bias, performance bias, attrition or exclusion bias, detection bias and selective reporting bias that may cause potential threats to the internal validity of the study. A series of risk of bias questions were used to categorize the judgment for each bias type into 'definitely low risk of bias', 'probably low risk of bias', 'probably high risk of bias' and 'definitely high risk of bias'. The full-text articles were reviewed independently and evaluated by two reviewers (i.e. PLW and YHY). Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion with an independent reviewer, SH. A summary of the bias assessment risks was presented in Supplementary Information 4.

Results

The review included a total of 21 papers, of which 13 were in vitro studies, four were in vivo studies and four studied both in vitro and in vivo studies. Table 1 summarizes the included papers reporting on respective xanthones, study design, assay and parameters used.

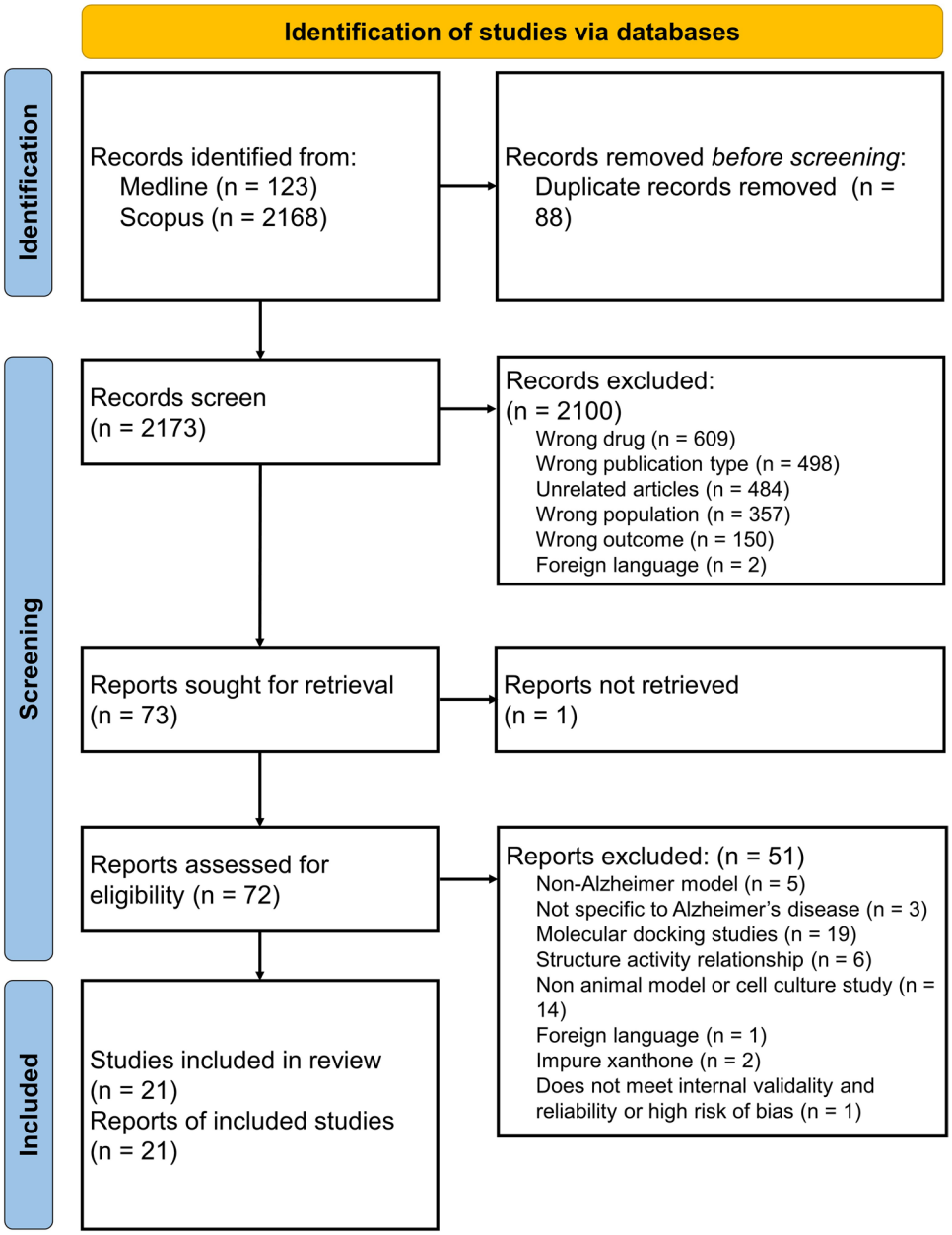

Fig. 1 PRISMA flow diagram of the selection process and search strategy for systematic review

Antioxidant Activity

Mangiferin has been shown its antioxidant effects by reversing the elevated levels of brain thio barbituric acid reactive substance and decreasing the level of brain glutathione level induced by scopolamine. These results indicate its potential in reducing oxidative stress [20]. The study by conducted Alberdi et al. further supports the antioxidant properties of mangiferin as it was found to reduce the levels of reactive oxygen species (ROS) in a concentration of 1 µM [31]. Additionally, mangiferin restored the decrease in catalase and superoxide dismutase (SOD) levels [31]. These findings are congruent with the results from a rodent study by Du et al., where both low (100 mg/kg/day) and high (200 mg/kg/day) doses of mangiferin significantly increased the levels of total SOD and glutathione peroxidase, while high dose of mangiferin led to a reduction in lipid peroxidase levels [21]. Similarly, a recent study demonstrated that 250 µM mangiferin significantly reversed the ROS production induced by formaldehyde in HT22 cells [23].

A study conducted by Reyes-Fermin et al. revealed that α-mangostin has the ability to reduce the production of ROS induced by iodoacetate in a concentration-dependent manner. Apart from α-mangostin, other xanthones such as γ-mangostin, garcinone C, gartanin and mangostanaxanthone IV were also found to possess antioxidant properties

Table 1 The characteristics of included articles

Xanthone	Study design	Assay/test	Parameters	References
Mangiferin	In vitro & in vivo	Passive avoidance test, Morris water maze test, acetylcholine assay, immunoblot assay of NF-κB activation	Animal behavioral performance, acetylcholine level, TNF-α level	[19]
	In vivo	Elevated plus maze, passive shock avoidance, brain AChE activity assay, brain biogenic amines, antioxidant studies, H&E staining	Animal behavioral performance, brain AChE activity, emission spectra of dopamine and noradrenaline, brain thio barbituric acid, glutathione level, histology of hippocampus	[20]
	In vivo	Morris water maze, H&E and immunohistochemical staining, total SOD, GSH-Px, MDA enzymatic assays	Animal behavioral performance, histology of hippocampus, APP and Aβ proteins, SOD, GSH-Px and MDA activities	[21]
	In vitro	MTT, NO assay, ELISA, RTPCR, Western blot, Immunofluorescence staining	Cell viability, NO production, mRNA and protein expression of iNOS and COX-2, protein expression of IL-1β, IL-6, and TNF-α, nuclear translocation of NF-κB p65, NLRP3, ASC and caspase 1	[22]
	In vitro & in vivo	Cell viability assay, DCFH-DA assay, Western blot, Y-maze test, novel object recognition test, calcium concentration determination	Cell viability, mitochondrial function, ROS production, protein expression of tau, GSK-3β, CaMKII, GRP78, CHOP, animal behavioral performance	[23]
α-Mangostin	In vitro	Cell viability assay, neurite outgrowth assay, molecular docking and dynamics simulations, dot blot assay, Western blot, ThT fluorescence assay	Cell viability, total neurite length, interaction between α-mangostin and Aβ, protein expression of Aβ oligomers, morphologies of Aβ fibrils	[13]
	In vitro	MTT assay, fluorescent probes dihydroethidium and carboxy-DHFDA assay, Western blot	Cell viability, ROS production, HO-1 protein level, HO activity	[24]
	In vitro	ELISA, RTPCR, Western blot, secretase activity assay, β-secretase activity assay, molecular docking	$A\beta_{40}$ and $A\beta_{42}$ levels, expression of enzymes involved in non- and amyloidogenic pathways and APP maturation, β-secretase activity, γ-secretase activity, BACE1 activity	[25]
	In vitro & in vivo	Cell viability assay, wound healing migration assay, phagocytosis assay, ELISA, Western blot, immunofluorescence staining, open filed test, Morris water maze	Cell viability, microglial migration and phagocytosis, TNF-α, IL-6 level, NO production, iNOS protein level, protein expression of phosphorylated p65, TLR4, MyD88 and phosphorylated TAK1, MAP2-immunoreactivity, animal behavioral performance	[26]
	In vivo	Open field test, Morris water maze, Western blot	Animal behavioral performance, protein expression of BDNF and CaMKII	[27]
	In vitro	MTT assay, DCFDA assay, Annexin V apoptosis and caspase-3/7 activation assays, Western blot	Cell viability, ROS production, apoptosis, protein expression of BAX, BCL-2, SIRT1, SIRT3, FOXO3a, CAT, SOD2	[28]
α-Mangostin, 8-deoxygartanin, gartanin, garciniafuran, garcinone C, garcinone D, and γ-mangostin	In vitro	ThT fluorescence assay, assay of BACE1 inhibitory activity, DPPH radical scavenging activity, copper chelating activity assay, in vitro BBB permeation assay, MTT assay, non-fluorescent dye carboxy H_2DCF-DA assay, Western blot	Aβ aggregation inhibitory activity, BACE1 activity, antioxidant capacity, metal chelating properties, BBB penetration, cell viability, ROS production, HO-1 protein level	[29]

Table 1 (continued)

Xanthone	Study design	Assay/test	Parameters	References
α-Mangostin, and its analogues	In vitro	ThT fluorescence assay, ELISA, cell viability assay, immunofluorescence staining	Aβ fibrils formation, Aβ uptake and degradation assay, expression of IL-6 and TNF-α, cell viability, BBB permeability	[30]
Mangiferin & morin	In vitro	LDH viability assay, immunocytochemistry assay, Western blot, antioxidant assay, mitochondrial membrane potential analysis	Cell viability, propidium iodide uptake, quantification of fluorescence intensity, protein expression of DNP, ROS production, total carbonyl content, catalase and SOD activity, mitochondrial potential, calcium concentration and respiratory state of mitochondria	[31]
α- and γ-Mangostins	In vitro & in vivo	MTT assay, DCFH-DA assay, TUNEL assay, Western blot, DPPH radical scavenging activity, lipid peroxidation assay, in vitro β-secretase activity assay, passive avoidance test	Cell viability, ROS production, microscopic images, protein expression of caspases 3 and 9, DPPH formation, lipid peroxide formation, β-secretase activity, animal behavioral performance	[32]
γ-Mangostin	In vitro	Cell viability assays, RTPCR, ELISA, NO assay, ROS assay, Western blot	Cell viability, expression of IL-1β, IL-6, TNF-α, iNOS and COX-2, NO & ROS production, protein expression of JNK, ERK and p38 MAPK	[33]
Toxyloxanthone B	In vitro	Griess reaction assay, MTT assay	NO inhibitory activity, cell viability	[34]
Gartanin	In vitro	MTT assay, flow cytometry, H_2DCF-DA assay, mitochondrial membrane potential analysis, Western blot, transfection and luciferase reporter assay	Cell viability, apoptosis, ROS production, mitochondrial membrane potential, protein expression of Bcl-2, Bax, HO-1, pAMPKa, SIRT1 and PGC-1α	[35]
Thioxanthenone-based derivatives	In vitro	ThT fluorescence assay, cell viability assay	Tau and Aβ aggregation, cell viability	[36]
3-*O*-β-D-Glucopyranosyloxy-1,6-dihydroxy-2,5,7-trimethoxyxanthone and 1,3,6-trihydroxy-2,5,7-trimethoxyxanthone	In vitro	ThT fluorescence assay, MTT assay, immunohistochemical evaluation	Aβ fibrils formation, cell viability, cell morphology, immunoreactivity of tau, Aβ and α-synuclein	[37]
Mangostanaxanthone IV	In vivo	Morris water maze, ELISA, Western blot, histopathological examination	Animal behavioral performance, expression of GSH, MDA, H_2O_2, TNF-α, IL-6, and NADPH oxidase, protein expression of tau, PI3K, Akt and GSK-3β, quantification of amyloid plaques	[38]

AMPK AMP-activated protein kinase, *APP* amyloid precursor protein, *ASC* apoptosis-associated speck-like protein containing a CARD, *Aβ* amyloid beta, *BACE1* β-site amyloid precursor protein cleaving enzyme 1, *BBB* blood brain barrier, *BDNF* brain-derived neurotrophic factor, *CaMKII* calmodulin-dependent protein kinase II, *carboxy-DCFDA* sarboxy-2′,7′-dichlorofluorescein diacetate, *COX-2* cyclooxygenase-2, *DCFH-DA* dichloro-dihydro-fluorescein diacetate, *DNP* antidinitrophenyl, *DPPH* 2,2-diphenyl-1-picrylhydrazyl, *ELISA* enzyme-linked immunosorbent assay, *GSK* glycogen synthase kinase, *GSH-Px* glutathione peroxidase, *H&E* hematoxylin and eosin, *H2DCF-DA* 2′,7′-dichlorodihydrofluorescein diacetate, *H_2O_2* hydrogen peroxide, *HO-1* heme oxygenase-1, *AChE* acetylcholinesterase, *IL-1β* interleukin 1 beta, *IL-6* interleukin 6, *iNOS* inducible nitric oxide synthase, *LDH* lactate dehydrogenase, *LOX* lipoxygenase, *MAPK* mitogen-activated protein kinase, *MDA* malondialdehyde, *MTT* 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, *MyD88* myeloid differentiation primary response 88, *NF-κB* nuclear factor kappa light chain enhancer of activated B cells, *NLRP3* NLR family pyrin domain containing 3, *NO* nitric oxide, *PGC-1α* peroxisome proliferator-activated receptor gamma coactivator 1-alpha, *ROS* reactive oxygen species, *RT-PCR* real-time polymerase chain reaction, *SIRT1* sirtuin 1, *SOD* superoxide dismutase, *TAK1* transforming growth factor-β (TGF-β)-activated kinase 1, *ThT* thioflavin T, *TLR4* toll-like receptor-4, *TNF-α* tumor necrosis factor alpha, *TUNEL* terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate (dUTP) nick end-labeling

[24, 33, 35, 38]. The authors proposed that the stress-repressing capacity of α-mangostin, gartanin, garcinone C and γ-mangostin was directly correlated to their ability to scavenge oxygen peroxide [29]. Consistent results were also observed for α-mangostin in a series of in vitro and in vivo assays [28, 32]. Ruankham et al. reported that the ROS suppressor activity of α-mangostin is associated with its ability to restore antioxidant enzyme activities, notably catalase (CAT) and superoxide dismutase (SOD) during oxidative stress [28]. Interestingly, in contrast to previous literature, α-mangostin did not exhibit DPPH radical scavenging activity and had no effect on reducing ROS production at any of the tested concentrations, whereas γ-mangostin displayed both of these effects [32]. The ability to suppress lipid peroxide (LPO) induced by Fe^{2+} and L-ascorbic acid in rat brain homogenates was also evaluated. The findings showed that γ-mangostin significantly suppressed LPO formation at high concentrations of 10 and 30 μM, but not at a lower concentration. However, α-mangostin exhibited only slight inhibition compared to γ-mangostin [32]. The antioxidant effects of xanthones are tabulated in Table 2.

Neuroprotective Effects

Table 3 presents an overview of the neuroprotective effects of xanthones focusing on cell viability and apoptosis, neuroinflammation, nerve growth and mitochondrial cascade. Several studies have reported on the anti-neurotoxic effect of α-mangostin by reversing the decreased cell viability due to neurotoxicity induced by Aβ oligomers or other neurotoxins [13, 24, 28, 30]. However, it should be noted that some studies demonstrated contradicting findings by suggesting that α-mangostin lacks of neuroprotective effect [26, 29, 32]. Interestingly, other xanthones extracted from the pericarp of mangosteen have shown significant protective effects against cell death. These xanthones include gartanin [29, 35], garcinone C [29] and γ-mangostin [29, 32, 33]. Ruankham et al. and Gao et al. also discovered that xanthones exert an anti-apoptotic effect by up-regulating the expression of Bcl-2 protein, an antioxidant protein, in a time-dependent manner [28, 35]. By conserving the levels of anti-apoptotic Bcl-2 protein that had been down-regulated by neurotoxin, xanthones shifted the balance between pro- and anti-apoptotic factors towards cell survival [28, 35]. Moreover, Lee et al. also elucidated the neuroprotective role of α- and γ-mangostin in preventing H_2O_2-induced apoptosis [32]. Notably, only γ-mangostin (at concentration of 10 μM) remarkably inhibited the DNA fragmentation and activation of caspase-3 and -9 induced by H_2O_2, whereas no significant effects were observed for α-mangostin [32]. Other compounds such as mangiferin, toxyloxanthone B and synthetic xanthones have also exhibited a significant inhibitory effect against neurotoxicity [22, 23, 31, 34, 36, 37].

Some studies highlighted the ability of selective xanthone to enhance heme oxygenase (HO) activity by increasing the protein expression of HO-1, including α-mangostin [24, 29] and gartanin [35], however, an opposing effect was reported for γ-mangostin and garcinone C [29]. The exact mechanism responsible for this effect remains unclear for these xanthones. Nevertheless, Gao et al. have proven that the protein expression of HO-1 increased by gartanin was independent of Nrf-2 activation. However, they revealed that this neuroprotective effect was partially mediated through the AMP-activated protein kinase (AMPK) pathway as the protein levels of pAMPKα, and its two regulators, SIRT1 and PGC-1α were increased remarkably after gartanin treatment [35]. Consistently, a recent study demonstrated that α-mangostin modulates oxidative stress-induced neuronal cells through the SIRT1/3-FOXO3a pathway [28]. This finding provides further insights into the mechanisms by which α-mangostin exerts its neuroprotective effects in relation to oxidative stress and neuronal cell function.

On the other hand, inducible nitric oxide synthase (iNOS) was also found to be suppressed by α-, γ-mangostin [26, 33] and mangiferin [22]. Xiong et al. also reported potent nitric oxide (NO) inhibitory activity for toxyloxanthone B [34]. Additionally, Lei et al. also showed that mangiferin not only suppressed the mRNA and protein expression of iNOS but also the levels of cyclooxygenase-2 (COX-2) induced by lipopolysaccharide (LPS) in a murine microglial cell line called BV-2 [22]. Similarly, a recent study also demonstrated γ-mangostin decreased the mRNA expression of COX-2 induced by Aβ oligomers in the same cell line [33]. The authors evidenced that the neuroprotective role of γ-mangostin can be attributed to its ability to suppress the Aβ-mediated p38 MAPK and JNK activation, although this effect is independent of the ERK pathway.

Similarly, several studies also revealed that mangiferin [19, 22], mangostanaxanthone IV [38], γ-mangostin [33], α-mangostin [26, 30] and its synthetic analogues [30] exert anti-inflammatory effects. These compounds reduced the release of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6 and IL-1β. Jung et al. reported that mangiferin inhibited the activation of nuclear factor kappa light chain enhancer of activated B cells (NF-κB) stimulated by TNF-α or scopolamine [19]. This finding is congruent with the results reported by Lei et al., where mangiferin significantly inhibited the nuclear translocation of NF-κB p65 from the cytosol to the nucleus [22]. Whereas Guan et al. showed that α-mangostin exerted an inhibitory effect on the activation of NF-κB p65 [26]. They further elucidated that α-mangostin exerted its anti-inflammatory effects by inhibiting the activation of TLR4/TAK1/NF-κB signaling pathway induced by LPS in microglial and neuronal cells [26]. Lei et al. also concluded that mangiferin modulated the LPS-induced

Table 2 Xanthones and antioxidant activity

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
Mangiferin	3 months old of 22–28 g and aged 14 months old 35-52 g Swiss albino mice	Scopolamine treatment (IP 3 mg/kg)	Glutathione colorimetric assay	Dose of 40, 20 and 10 mg/kg significantly reversed both scopolamine-induced and aging-induced increase in brain thio barbituric acid reactive substance levels and decrease in brain glutathione levels	0.001, 0.01, 0.05	[20]
	Senescence-accelerated mouse prone 8 (SAMP8) mouse model, 6 months old	–	Total SOD, GSH-Px and MDA enzymatic assays	Low dose (100 mg/kg/day) and high dose of mangiferin (200 mg/kg/day) significantly increased the total SOD and GSH-px and high dose of mangeferin reduced LPO levels	$<0.01, <0.01, <0.01$	[21]
	Cortical neurons of E18 Sprague–Dawley rat embryos	5 μM Aβ oligomers	CM-H_2DCFD assay	Mangiferin 1 μM reduced ROS levels	<0.05	[31]
			Colourimetric assay for catalase and SOD activity	Mangiferin significantly restored the decreased catalase and SOD levels	$<0.001, <0.001$	
	HT22 cells	0.5 mM formaldehyde	DCFH-DA assay	Mangiferin 250 μM reversed the increase of ROS induced by formaldehyde	0.0052	[23]
α-M	Primary cultures of cerebellar granule neurons were prepared from 7-day old neonatal Wistar rats	18 μM IAA	Fluorescent probes dihydroethidium and carboxy-H_2DCF-DA assays	8, 12, 14 μM α-M were able to prevent the increase in ROS production induced by IAA	<0.05, 0.01, 0.01	[24]
	SH-SY5Y neuroblastoma cell	H_2O_2	H_2DCF-DA assay	α-M (1 μM) decreased H_2O_2-induced ROS generation	<0.01	[28]
			Western blot	α-M rescued the protein expressions of CAT and SOD2	$<0.01, <0.01$	
α-M, 8-deoxygartanin, gartanin, garciniafuran, garcinone C, garcinone D, and γ-M	HT22 murine hippocampal neuronal cells	–	DPPH radical scavenging activity	γ-M, garcinone C and gartanin exhibited DPPH radical scavenging capacity of $23.7 \pm 2.7\%$, $48.7 \pm 0.5\%$, $50.7 \pm 1.4\%$, respectively	NA	[29]
		2 mM glutamate	DCFH-DA fluorescent probe assay	α-M, gartanin, garcinone C and γ-M showed a protective effect on ROS production		

Table 2 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
α- and γ-M	Primary culture of rat cerebrocortical cells containing neuronal and nonneuronal cells	–	DPPH radical scavenging activity assay	γ-M considerably attenuated the formation of DPPH radicals at 3 μM, 10 μM and 30 μM concentrations	<0.05	[32]
				α-M showed no effect	>0.05	
		Fe^{2+} (10 μM) and L-ascorbic acid (100 μM)	Lipid peroxidation assay	γ-M showed effective inhibition of LPO formation in concentration-dependent manner at 10 and 30 μM, but showed no significant effect at 0.3, 1 and 3 μM	<0.05	
				α-M has mininal lipid peroxidation inhibition effect at 10 and 30 μM concentration. Other concentration showed no significant effect	<0.05	
		H_2O_2- or X/XO	DCFH-DA assay	γ-M showed a significant reduction in ROS generation induced by X/XO at 3 and 10 μM and ROS induced by H_2O_2 at 3–10 μM	$<0.05, <0.05$	
				α-M showed no effect	>0.05	
γ-M	Murine microglial cells BV-2	$A\beta_{42}$ oligomers	NO assay	Pretreatment with 1 and 5 μM γ-MG reduced the NO release by 34.15%and 42.25%, respectively, compared with the $A\beta_{42}$ oligomer-treated cells	0.0358, 0.0134	[33]
			DCFH-DA assay	Pretreatment with 1 and 5 μM γ-MG reduced the ROS production induced by $A\beta_{42}$ oligomers	<0.0001 for all variables	
Gartanin	HT22 cell line	2 mM glutamate	H_2DCF-DA assay	Gartanin significantly decreased glutamate-induced ROS	<0.001	[35]

Table 2 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
MX-IV	Adult male Swiss albino mice, 3–4 months	ICV 3 mg/kg streptozotocin	ELISA	Treatment with MX-IV diminished streptozotocin-induced oxidative stress with increased GSH content in contrast to decreased MDA and H_2O_2 contents and reduced NADPH oxidase activity	<0.05 for all variables	[38]

Aβ amyloid beta, *CM-H2DCFD* chloromethyl derivative of H2DCFDA, *DCFH-DA* dichloro-dihydro-fluorescein diacetate, *DCFH-DA* dichlorodihydrofluoresceine diacetate, *DPPH* 2,2-diphenyl-1-picrylhydrazyl, *GSH-Px* glutathione peroxidase, *H2DCF-DA* 2′,7′-dichlorodihydrofluorescein diacetate, H_2O_2 hydrogen peroxide, *IAA* iodoacetate, *ICV* intracereboventricular, *LPO* lipid peroxidase, *MDA* malondialdehyde, *NA* not available, *NO* nitric oxide, *NADPH* nicotinamide adenine dinucleotide phosphate, *ROS* reactive oxygen species, *SOD* superoxide dismutase, *XXO* xanthine/xanthine oxidase, *α-M* α-mangostin, *γ-M* γ-mangostin, *MX-IV* mangostanaxanthone IV

inflammation by inhibiting NF-κB and NLR family pyrin domain containing 3 (NLRP3) inflammasome in microglia [22]. Furthermore, α-mangostin has been evidenced to suppress microglial migration and phagocytic events in LPS-treated microglial cells [26]. Another study concluded that the protective effect of mangostanaxanthone IV in neuroinflammation was medicated by its ability in upregulating phosphorylation of P13K, Akt and glycogen synthase kinase (GSK)-3β [38].

In terms of nerve growth, Wang et al. revealed that α-mangostin significantly increased the number of living primary rat cerebral cortical neurons, indicating its role in neuronal injury [13]. It significantly reversed neuronal damage induced by $A\beta_{1-40}$ and $A\beta_{1-42}$ by increasing total neurite length and branch point counts [13]. However, α-mangostin was demonstrated to have no role in modulating the brain-derived neurotrophic factor and calmodulin-dependent protein kinase II protein expressions in the hippocampus, which indicates that it does not influence the synaptic plasticity in the hippocampus, yet it could possibly act on the other regions of the brain [27]. In addition, mangiferin and gartanin also associated with the reduction in mitochondrial dysfunction by preventing the mitochondrial depolarization induced by neurotoxins [23, 31, 35]. In addition, endoplasmic reticulum stress (ERS) which is key to initiate mitochondrial apoptotic program. Mangiferin was found to decreased the expression of ERS biomarkers, GRP78 and CHOP in a dose-dependent manner after induced by formaldehyde in both in vitro and in vivo studies [23].

Cholinergic Neurotransmission

Jung et al. showed that mangiferin improved scopolamine-induced memory impairment in the mice and this was suggested to be related to the effect of mangiferin in reversing ACh reduction induced by scopolamine and this effect was comparable to the positive control, tacrine even though inhibition of mangiferin on AChE was less potent than tacrine [19]. The authors explained that the observed differences could be attributed to the differences in absorption or bioavailability of tacrine and mangiferin in the blood or brain or cholinergic receptor stimulation [19]. Consistently, Birader et al. also demonstrated that mangiferin increased the AChE activity in the brain through a dose-dependent manner with the greatest effect at 40 mg/kg, followed by 20 and 10 mg/kg [20]. In terms of the effect of mangiferin on other neurotransmissions, Biradar et al. showed insignificant differences in dopamine and noradrenaline after mangiferin treatment [20]. The effects of xanthones on neurotransmission are presented in Table 4.

Table 3 The neuroprotective effects and mechanisms of xanthones

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
Cell viability and apoptosis						
α-M	Primary rat cerebral cortical neurons	Aβ oligomers	Cell viability assay with CCK-8	Co-incubation of $A\beta_{(1-40)}$ oligomers with 0.5, 5 and 50 nM α-M significantly increased the cell viability to 86.30 ± 6.03%, 86.79 ± 3.93% and 91.98 ± 5.02%, respectively. The EC_{50} value is 3.89 nM	< 0.05, < 0.01, < 0.01	[13]
				Co-incubation of $A\beta_{(1-42)}$ oligomers with 0.5, 5 and 50 nM α-M significantly increased the cell viability to 75.44 ± 2.39%, 86.41 ± 3.82% and 83.85 ± 5.47%, respectively. The EC_{50} value is 4.14 nM	< 0.01, < 0.01, < 0.05	
	Primary cultures of cerebellar granule neurons	8 μM IAA	MTT assay	α-M protected cell death induced by IAA in a concentration-dependent manner. The highest concentration used (14 μM) prevented about 60% of the IAA-induced cell death	< 0.05	[24]
	Murine microglial cell line BV-2	100 ng/mL LPS	Cell viability assay with CCK-8	No obvious cytotoxicity after 24 h α-M treatment at concentrations of 50–1000 nM (data not shown) and no effect on cell viability in the presence of LPS	NA	[26]
	SH-SY5Y neuroblastoma cell	H_2O_2	MTT assay	α-M (1 and 5 μM) significantly retained viability in H_2O_2-induced cell death	< 0.01 for all variables	[28]
			Annexin V apoptosis and caspase-3/7 activation assays	The pretreatment of α-M (1 μM) decreased apoptotic-like cells (23.29%) and caspase-3/7 activation (13.41%) due to H_2O_2 treatment	< 0.01 for all variables	
			Western blot	α-M showed an ability to protect neuronal cells against H_2O_2 treatment by reducing BAX and inducing BCL-2	< 0.01, < 0.05	
α-M, and its analogues	Primary mouse cerebral cortical neurons (C57BL/6 mice)	Aβ oligomers	Cell viability assay with CCK-8	Co-incubation of $A\beta_{(1-42)}$ oligomers with 5 and 50 nM α-M significantly reversed cell viability to 80.27 ± 1.69% and 83.02 ± 5.54%, respectively. The EC_{50} value is 0.70 nM	< 0.05 for all variables	[30]
				5 and 50 nM $C_{24}H_{30}O_{10}$ significantly reversed cell vianility to 84.50 ± 3.13% and 84.61 ± 5.79%, respectively	< 0.01 for all variables	
α-M, 8-deoxygartanin, gartanin, garciniafuran, garcinone C, garcinone D, and γ-M	HT22 murine hippocampal neuronal cells	2 mM glutamate	MTT assay	Gartanin, garcinone C and γ-M were effective even at the lowest tested concentration (1 μM) and were able to totally reverse glutamate-induced damage at 10 μM; 1, 3 and 10 μM of gartanin, garcinone C and γ-M increased its viability in a dose-dependent manner	< 0.001 (all 3 doses)	[29]

Table 3 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
α- and γ-M	Primary culture of rat cerebrocortical cells containing neuronal and nonneuronal cells	NA	MTT assay	No cytotoxicity was found with 0.3–10 μM of α- or γ-M	> 0.05	[32]
		H_2O_2	Fluorescence microscopy	The reduced viability of the H_2O_2-treated cells was completely reversed by γ-M at the concentration of 10 μM	< 0.05	
		X/XO		The decreased viability of the X/XO-treated cells was reversed by γ-M at the concentration of 10 μM	< 0.05	
		H_2O_2	TUNEL assay	H_2O_2-induced DNA fragmentation was remarkably inhibited by γ-M at 10 μM; γ-M significantly attenuated the H_2O_2-induced activation of both caspases 3 and 9 at concentrations of 3 and 10 μM	< 0.05 for all variables	
γ-M	Murine microglial cells BV-2	NA	LDH viability assay	No significant impact on cell viability at 1, 2 and 5 μM, but 10 μM showed mild toxicity	> 0.05, > 0.05, > 0.05, < 0.0001	[33]
			Cell viability assay with CCK-8	No significant impact on cell viability at 1, 2 and 5 μM, but 10 μM showed mild toxicity	> 0.05, > 0.05, > 0.05; 0.0098	
	N2a and SH-SY5Y neuroblastoma cell	BV2 cells treated with $A\beta_{42}$ oligomers	LDH viability assay	The conditioned medium pretreated with 1 or 5 μM γ-MG reversed the cytotoxicity on the SH-SY5Y cells; all concentrations (1, 2, or 5 μM) reversed the cytotoxicity on N2a cells	< 0.05, < 0.0001; < 0.001, < 0.05, < 0.0001	
	N2a and SH-SY5Y neuroblastoma cell	BV2 cells treated with $A\beta_{42}$ oligomers	Cell viability assay with CCK-8	The conditioned medium pretreated with 1, 2, or 5 μM γ-MG reversed the cytotoxicity on the SH-SY5Y cells and N2a cells, respectively	< 0.05, < 0.01, < 0.01; < 0.01, < 0.01, < 0.0001	
Gartanin	HT 22 cell line	2 mM glutamate	MTT assay	1, 3 and 10 μM gartanin significantly attenuated the reduced effect of cell viability by glutamate with greatest effect on 3 μM	< 0.001, < 0.001, < 0.001	[35]
			Flow cytometry	Decreased glutamate-induced HT22 cell apoptosis	< 0.001	
			Western blot	Increased the ratio of Bcl-2/Bax expression	< 0.01	
Mangiferin	Cortical neurons of E18 Sprague–Dawley rat embryos	5 μM Aβ oligomers	LDH viability assay	Greatly reduced significantly the Aβ induced cell death; reduced the increase in propidium iodide uptake by damaged cells induced by Aβ	< 0.05, < 0.001	[31]
	Murine microglial cell line BV-2	0.5 μg/mL LPS	MTT assay	No cytotoxicity of mangiferin (50–150 μg/mL) was observed, but it significantly inhibited the effect of LPS on the survival rate for 100 and 150 μg/mL	< 0.01	[22]
	HT22 cells	0.5 mM formaldehyde	Cell viability assay with CCK-8	Mangiferin dose-dependently protected cells from formaldehyde-induced cytotoxicity at 100–250 μM	< 0.01, < 0.01, < 0.001	[23]

Table 3 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
Toxyloxanthone B	SH-SY5Y neuroblastoma cells	$A\beta_{25-35}$	MTT assay	Significant increased cell viability (22.31%) at 10 μM	< 0.01	[34]
Thioxanthenone-based derivatives	SH-SY5Y neuroblastoma cell	Okadaic acid-induced tau toxicity	MTT assay	1 compound (0.1 and 1 μM) demonstrated ability to restore cell viability counteracting tau-induced toxicity	< 0.001, < 0.1	[36]
3-*O*-β-D-Glucopyranosyloxy-1,6-dihydroxy-2,5,7-trimethoxyxanthone and 1,3,6-trihydroxy-2,5,7-trimethoxyxanthone	SKNAS neuroblastoma cell and in vitro AD model cells	$A\beta_{25-35}$ oligomers	MTT assay	100 μM of both compounds were more effective for neuroprotection at 48 h in both SKNAS and in vitro AD model cells	NA	[37]
Neuroinflammation						
α-M	Primary cultures of cerebellar granule neurons	8 μM IAA	Western blot	12, 14 μM α-M increased HO-1 protein level; 8, 12 and 14 μM α-M increases HO activity	< 0.01; < 0.01	[24]
	Murine microglial cell line BV-2	100 ng/mL LPS	Wound healing migration assay & phagocytosis assay	α-M suppressed microglial migration. α-M reduced phagocytosis events significantly in LPS-stimulated cells	< 0.01; < 0.001	[26]
			ELISA	TNF-α, IL-6, NO and iNOS protein levels significantly reduced by α-M in a dose-dependent manner at 100, 200 and 500 nM with the highest inhibition rate at 500 nM	< 0.05 for all variables	
			Western blot	α-M inhibited LPS-induced TNF-α, IL-6 and TLR4 levels; α-M showed inhibitory effect to LPS-induced high protein level of MyD88 and phosphorylation of TAK1 and activation of NF-κB p65	< 0.001, < 0.001, < 0.001; < 0.001, < 0.001, < 0.01	
	Primary hippocampal neuron culture (in vivo)	IP 2 mg/kg LPS	ELISA	α-M significantly repressed TNF-α and IL-6 level in hippocampus and cerebral cortex	< 0.01, < 0.001, < 0.001	
			Western blot	α-M suppressed protein level of iNOS in hippocampus and cerebral cortex tissues; α-M inhibited the upregulation of TLR4 and MyD88 expression and phosphorylation of TAK1 and NF-κB p65 induced by LPS in hippocampus and cerebral cortex	< 0.05 for all variables	
	SH-SY5Y neuroblastoma cell	H_2O_2	Western blot	α-M rescued the protein expressions of SIRT1, SIRT3, FOXO3a	< 0.05, < 0.05, < 0.01	[28]

Table 3 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
α-M, and its analogues	Murine microglial cells BV-2	100 ng/mL LPS	ELISA	TNF-α and IL-6 protein levels significantly reduced by α-M (250 nM) and its analogues: $C_{24}H_{28}O_8$, $C_{24}H_{30}O_{10}$, $C_{24}H_{30}O_8$, $C_{21}H_{22}O_9$ (100 nM)	$<0.0001, <0.01, <0.001, <0.0001, <0.0001; <0.05, <0.001, <0.01, <0.001; >0.05$	[30]
α-M, 8-deoxygartanin, gartanin, garciniafuran, garcinone C, garcinone D, and γ-M	HT22 murine hippocampal neuronal cells	NA	Western blot	α-M, gartanin, garciniafuran, garcinone D effectively increased the HO-1 protein level; garcinone C and γ-M decreased the HO-1 protein level at the concentration of 10 μM	$<0.001, <0.001, <0.01, <0.01; <0.05, <0.05$	[29]
γ-M	Murine microglial cells BV-2	$A\beta_{42}$ oligomers	ELISA	Pretreated with 5 μM γ-M decreased mRNA expression of TNF-α, IL-1β, and IL-6 by 36.75%, 44.34%, and 51.64%, respectively, compared to those exposed to the $A\beta_{42}$ oligomers only	0.0005, 0.0007, 0.0002	[33]
			RTPCR	Pretreated with 5 μM γ-M decreased mRNA expression of iNOS and COX-2 by 48.70% and 25.72%, respectively, compared to those exposed to the $A\beta_{42}$ oligomer-treated cells	0.0001, 0.0376	
			Western blot	5 μM γ-MG decreased phosphorylation expression of JNK and p38 MAPK decreased by 29.08% and 22.52%, respectively, compared with the Aβ42 oligomer-treated cells; JNK phosphorylation was decreased by 23.36% when pretreated with 1 μM γ-M	0.0082, 0.0152; 0.0247	
Gartanin	HT22 cell line	2 mM glutamate	Western blot	0.3, 1, 3 and 10 μM increased HO-1 protein expression but no effect on Nrf-2	$<0.05, <0.001, <0.001; <0.001$	[35]
				3 μM gartanin increased pAMPKα (Thr172), SIRT1 and PGC-1α protein level	$<0.01, <0.01, <0.001$	

Table 3 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
Mangiferin	Murine microglial cell line BV-2	0.5 μg/mL LPS	Griess reaction assay	Mangiferin inhibited LPS-stimulated NO production in a dose-dependent manner, with significant inhibition at 150 μg/mL	< 0.001	[22]
			RT-PCR	50, 100 and 150 μg/mL mangiferin treatment suppressed LPS-induced mRNA expression of COX-2 levels; 100 and 150 μg/mL mangiferin treatment suppressed LPS-induced mRNA expression of iNOS levels	COX-2: < 0.01; < 0.001; < 0.001 iNOS: < 0.01; < 0.001	
			Western blot	100 and 150 μg/mL mangiferin treatment suppressed LPS-induced protein expression of COX-2 levels; 50, 100 and 150 μg/mL mangiferin treatment suppressed LPS-induced protein expression of iNOS levels; 50, 100 and 150 μg/mL mangiferin reduced the protein expression of NLRP3 in LPS-activated BV2 cells. 100 and 150 μg/mL mangiferin reduced the protein expression of ASC and caspase-1 p20 in LPS-activated BV2 cells	COX-2: < 0.01; < 0.001 iNOS: < 0.01; < 0.01; < 0.001 NLRP3: < 0.01; < 0.001; < 0.001 ASC: < 0.01; < 0.01 Caspase-1 p20: < 0.01; < 0.001	
			ELISA	50, 100 and 150 μg/mL mangiferin suppressed the expression of IL-1β, IL-6, and TNF-α and stimulated the secretion of IL-10	IL-6: < 0.001; < 0.001; < 0001 IL-1β: < 0.01; < 0.001; < 0.001 TNF-α: ≥ 0.05; < 0.01; < 0.001 IL- 10: < 0.01; < 0.001; < 0.001	
			Immunoblot assay of NF-κB activation	150 μg/mL mangiferin treatment significantly inhibited the nuclear translocation of NF-κB p65 from the cytosol to nucleus	Cytosol: < 0.001, Nucleus: < 0.01	
	Murine microglial cell line BV-2	Scopolamine	Immunoblot assay of NK-κB activation	Significantly reduced the TNF-α level induced by scopolamine by 82% with 20 mg/kg of mangiferin	< 0.05	[19]
				Inhibited NF-κB activation in BV-2 cells stimulated with TNF-α or scopolamine	NA	
	HT22 cells	0.5 mM formaldehyde	Western blot	Mangiferin (≥ 100 μM) restored formaldehyde-induced expression of GSK-3β and CaMKII in a dose-dependent manner; mangiferin (≥ 200 μM) significantly decreased the expression of GRP78 and CHOP in a dose-dependent manner	< 0.0001, 0.0133; 0.0013, 0.0001	[23]
	Male C57/BL6 mice, 8 weeks old	3.8% methanol aqueous	Western blot	Mangiferin restored formaldehyde-induced expression of GSK-3β, CaMKII, GRP78 in a dose-dependent manner	< 0.05 for all variables	

Table 3 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
Toxyloxanthone B	Murine microglial cell line BV-2	–	Griess reaction assay	Potent NO inhibitory activity with $IC_{50} = 12.4$ μM	< 0.01	[34]
MX-IV	Adult male Swiss albino mice, 3–4 months	ICV 3 mg/kg streptozotocin	ELISA	Treatment with MX-IV ameliorated neuroinflammation associated with streptozotocin with decreased TNF-α and IL-6 contents	< 0.05 for all variables	[38]
			Western blot	Treatment with MX-IV reversed streptozotocin-induced deleterious effects with upregulation of p-PI3K, p-Akt, and p-GSK-3β	< 0.05 for all variables	
Nerve growth						
α-M	Primary rat cerebral cortical neurons	Neurotoxicity induced by Aβ oligomers	Neurite outgrowth assay	$A\beta_{(1-40)}$: 5 nM α-M increased neuronal cells and decrease non neuronal cells, increased total neurite growth and branch point counts; $A\beta_{(1-42)}$: 5 nM α-M increased neuronal cells and decrease non neuronal cells	< 0.01, < 0.05, < 0.05; < 0.05 , < 0.05	[13]
α-M	Male Sprague Dawley rat 250–300 g	Permanent bilateral occlusion of common carotid arteries (2VO) in rats (ventral midline incision was made in the neck of the rats)	Western blot	Sub-acute treatment of α-MG (50 mg/kg) showed no significant changes in BDNF and CaMKII protein in hippocampus	≥ 0.05; ≥ 0.05	[27]
Mitochondrial cascade						
Mangiferin	Cortical neurons of E18 Sprague–Dawley rat embryos	5 μM Aβ oligomers	Ca^{2+} imaging and immunocytochemistry assay	1 μM mangiferin increased Ca^{2+} overload in cytosolic of neurons to 2 to 2.3-fold; mangiferin prevented the loss of mitochondrial membrane potential and of cytochrome c release to cytosol and induced by Aβ oligomers	< 0.05; < 0.05	[31]
	HT22 cells	0.5 mM formaldehyde	Calcium concentration determination	Mangiferin 250 μM increased intracellular mitochondrial fluorescence intensity, indicating a reduced mitochondrial damage and dose-dependently (≥ 25 μM) reduced formaldehyde-induced calcium overload	0.0057; 0.002	[23]
Gartanin	HT22 cell line	2 mM glutamate	Mitochondrial membrane potential analysis	3 and 10 μM significantly reduced the mitochondrial membrane depolarization induced by glutamate	< 0.001; < 0.001	[35]

AD Alzheimer's disease, *AMPK* AMP-activated protein kinase, *ASC* apoptosis-associated speck-like protein containing a CARD, *Aβ* amyloid beta, *BDNF* brain-derived neurotrophic factor, *CaMKII* calmodulin-dependent protein kinase II, *CCK-8* Cell Counting Kit 8, *COX-2* cyclooxygenase-2, EC_{50} half maximal effective concentration, *ELISA* enzyme-linked immunosorbent assay, *GSK* glycogen synthase kinase, H_2O_2 hydrogen peroxide, *HO-1* heme oxygenase-1, *IAA* iodoacetate, IC_{50} half-maximal inhibitory concentration, *ICV* intracerebroventricular, *IL* interleukin, *iNOS* inducible nitric oxide synthase, *IP* intraperitoneal, *LDH* lactate dehydrogenase, *LPS* lipopolysaccharide, *MTT* 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide, *MyD88* myeloid differentiation primary response 88, *NA* not available, *NF-κB* nuclear factor kappa light chain enhancer of activated B cells, *NLRP3* NLR family pyrin domain containing 3, *NO* nitric oxide, *Nrf-2* nuclear factor erythroid 2-related factor 2, *PGC-1 α* peroxisome proliferator-activated receptor gamma coactivator 1-alpha, *RT-PCR* real-time polymerase chain reaction, *SIRT1* sirtuin 1, *TAK1* transforming growth factor-β (TGF-β)-activated kinase 1, *TNF-α* tumor necrosis factor alpha, *TLR4* toll-like receptor-4, *TUNEL* terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate (dUTP) nick end-labeling, *X/XO* xanthine/xanthine oxidase, *α-M* α-mangostin, *γ-M* γ-mangostin, *MX-IV* mangostanaxanthone IV

Table 4 The effects of xanthones on neurotransmission

Xanthone	Animal model	Method of induction	Assay	Findings	P value	References
Mangiferin	Male ICR mice 28–30 g	IP 1 mg/kg scopolamine	ACh assay	20 mg/kg recovered the reduced ACh level by 74.9%	< 0.05	[19]
			AChE activity assay	Inhibited AChE activity in a dose-dependent manner, with an IC_{50} value of 62.8 μM	NA	
Mangiferin	3 months old of 22–29 g and 14 months old 35–52 g Swiss albino mice	IP 3 mg/kg scopolamine	Brain AChE activity assay	Increased brain AChE activity was reversed in dose-dependent manner: 40 mg/kg, 20 mg/kg, 10 mg/kg which were administered chronically for 14 days	< 0.001;0.01; 0.05	[20]
			Brain biogenic amines analysis	Insignificant decreased in the height intensity of emitted spectra of dopamine and noradrenaline in young normal animals and insignificant reversal of increased height intensity of dopamine and noradrenaline in natural aged animals	> 0.05; > 0.05	

ACh acetylcholine, A*ChE* acetylcholinesterase, IC_{50} half-maximal inhibitory concentration, *IP* intraperitoneal

Effects on Amyloid-Dependent Cascade

Some xanthones play a role in reducing the Aβ formation, including α-mangostin [13, 25, 30], γ-mangostin [29], mangiferin [21], gartanin [29], mangostanaxanthone IV [38] and synthetic xanthones [30, 36]. However, it is worth noting that α-mangostin did not change the mRNA and protein expression of α-, β- and γ-secretase despite reducing the activities of β- and γ-secretases [25]. Therefore, they concluded that α-mangostin does not decrease the Aβ through modulation of the amyloidogenic pathway, but rather by inhibiting β- and γ-secretase. This finding is consistent with other studies that have reported the inhibition of β-secretase activity by both α- and γ-mangostin [29, 32]. On the other hand, mangiferin has demonstrated effectiveness in reducing the aggregation of $A\beta_{1-40}$ and $A\beta_{1-42}$, supporting its potential effect in ameliorating Aβ formation although the amyloid precursor protein (APP) remained unchanged [21]. The effects of xanthones on amyloidogenic activity and tau aggregation are represented in Table 5.

Interestingly, recent investigations involving synthetic xanthones, mangiferin and mangostanaxanthone IV have revealed that their significant protective roles in tau aggregation or hyperphosphorylation [23, 37, 38]. Abdallah et al. explained that the protective effect of mangostanaxanthone IV was likely to be mediated by PI3K/Akt/GSK-3 pathway, leading to enhance neuronal survival and cognition [38].

Effects on Cognition and Behavior

The effects of xanthones on cognition and behavior are summarized in Table 6. Numerous studies have demonstrated the role of mangiferin in improving memory impairment induced by neurotoxin or in naturally occurring ageing animal models using different recognition tests, including passive avoidance test [19, 20], Morris water maze test [19, 21], elevated plus maze [20], Y-maze test and novel object recognition test [23]. Nevertheless, the effective doses reported across these studies are varied from 20 to 200 mg/kg/day.

Similarly, α-mangostin also significantly restored the neurotoxin-induced memory impairment in Morris water maze test [26, 27], although no significant role was reported in the passive avoidance test [32]. In addition, Tiang et al. reported that α-mangostin did not alter the locomotor activity and explorative behavior of the animals in an open field

Table 5 The effects of xanthones on amyloid-dependent cascade

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
α-M	Primary rat cerebral cortical neurons	Aβ oligomers ($A\beta_{1-40}$ and $A\beta_{1-42}$)	ThT fluorescence assay	Decreased fibrils formation to 72.10 ± 2.91% for $A\beta_{(1-40)}$ and 72.32 ± 1.33% for $A\beta_{(1-42)}$ of that without co-incubation with α-M	< 0.001, 0.001	[13]
	Primary rat cerebral cortical neurons	Aβ oligomers ($A\beta_{1-40}$ and $A\beta_{1-42}$)	ELISA	6.25, 12.5 and 25 nmol/L α-M decreased $A\beta_{40}$ reaching its maximum effect at 25 nmol/L; 6.25, 12.5 and 25 nmol/L α-M decreased $A\beta_{42}$ reaching its maximum effect at 25 nmol/L	< 0.01 (all 3 doses); < 0.05, < 0.01, < 0.01	[25]
			RT-PCR	No significant change in mRNA expressions of α-secretase ADAM9, ADAM10, ADAM17, β-secretase BACE1 and γ-secretase PS1	> 0.05 (for variables)	
			Western blot	No significant change in protein expressions of APP, IDE, BACE1 and PS1	> 0.05 (for all variables)	
			Secretase activity assay	12.5 and 25 nmol/L α-M reduced β-secretase activities to 95.31 ± 6.58%, 80.31 ± 6.58% and 64.24 ± 5.26%; 6.25, 12.5 and 25 nmol/L α-M reduced γ-secretase activities to 64.86 ± 15.26, 60.38 ± 16.41% and 43.70 ± 25.89%; IC_{50} for β- and γ-secretases = 13.22 nmol/L, 16.98 nmol/L	< 0.01 (all variables)	
			In vitro β-secretase activity assay	α-M dose responsively inhibited BACE1 activity with IC_{50} = 12.63 nmol/L	NA	

Table 5 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
α-M, and its analogues	Primary mouse cerebral cortical neurons (C57BL/6 mice)	Aβ oligomers	ThT fluorescence assay	Decreased fibrils formation to 54.32%, 19.86% and 54.58% respectively after co-incubated with α-M and its analogues ($C_{24}H_{28}O_8$, $C_{24}H_{30}O_{10}$)	$<0.0001, <0.001, <0.0001$	[30]
	Murine microglial cells BV-2	Aβ oligomers	ELISA	Both α-M and $C_{24}H_{30}O_{10}$ promoted the $A\beta_{(1–42)}$ uptake and degradation efficiency of BV-2 by 22.70% and 24.30%, respectively	<0.05 for all variables	
α-M, 8-deoxygartanin, gartanin, garciniafuran, garcinone C, garcinone D, and γ-M	HT22 murine hippocampal neuronal cells	2 mM glutamate	ThT fluorescence assay	Gartanin, garciniafuran, garcinone C, garcinone D and γ-M exhibited high inhibition of $A\beta_{42}$ aggregation (63.5%, 50.7%, 83.7%, 34.9%, 47.8%)	NA	[29]
			Assay of BACE1 inhibitory activity	α-M, gartanin, garciniafuran, garcinone D and γ-M showed modest potency against BACE1 at the concentration of 100 μM (60.3%, 39.8%, 36.3%, 62.7%, 42.1%)	NA	
α-M and γ-M	Primary culture of rat cerebrocortical cells containing neuronal and nonneuronal cells	–	In vitro β-secretase activity assay	Both α- and γ-M showed significant β-secretase inhibitory effect at 3 μM	<0.05	[32]
Mangiferin	Senescence-accelerated mouse prone 8 (SAMP8) mouse model, 6 months old	–	Immuno-histochemical staining	Low and high dose of mangiferin (100 and 200 mg/kg/day) reduced the protein expression of $A\beta_{(1–40)}$ and $A\beta_{(1–42)}$ but APP levels remain unchanged	<0.01 (for both doses)	[21]
	HT22 cells	0.5 mM formaldehyde	Western blot	Mangiferin (≥ 100 μM) restored formaldehyde-induced phosphorylation of tau in a dose-dependent manner	0.0003	[23]
	Male C57/BL6 mice, 8 weeks old	3.8% methanol aqueous	Western blot	Mangiferin restored formaldehyde-induced phosphorylation of tau	<0.05	

Table 5 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
Thioxanthenone-based derivatives	*Escherichia coli* competent cells BL21 (DE3)	Aβ oligomers	ThT fluorescence assay	8 compounds inhibited the $A\beta_{40}$ aggregation with $IC_{50} < 10$ μM	NA	[36]
		PHF6	ThT fluorescence assay	3 compounds inhibited PHF6 aggregation, with > 80% inhibition at 10 μM	NA	
3-*O*-β-D-Glucopyranosyloxy-1,6-dihydroxy-2,5,7-trimethoxyxanthone and 1,3,6-trihydroxy-2,5,7-trimethoxyxanthone	SKNAS neuroblastoma cell and in vitro AD model cells	$A\beta_{25\text{-}35}$ oligomers	Immuno-histochemical evaluation	Tau immunoreactivities were not significantly different between compound-treated and control SKNAS cells; For in vitro AD cell model, immunoreactivities of tau were significantly lower in 1,3,6-trihydroxy-2,5,7-trimethoxyxanthone-treated group; Immunoreactivities of α-synuclein were significantly lower in compound-treated group in both SKNAS and in vitro AD model cells	> 0.05; 0.0001; 0.0015, 0.0005	[37]
MX-IV	Adult male Swiss albino mice, 3–4 months	ICV 3 mg/kg streptozotocin	Western blot	Treatment with MX-IV reversed streptozotocin-induced deleterious effects with decreased expression of p-tau proteins	< 0.05	[38]
			Histo-pathological examination	Administration of MX-IV resulted in a noticeable decline in the number and size of amyloid plaques in the brain tissue	< 0.05	

AD Alzheimer's disease, *APP* amyloid precursor protein, *Aβ* amyloid beta, *BACE1* β-site amyloid precursor protein cleaving enzyme 1, *ELISA* enzyme-linked immunosorbent assay, IC_{50} half-maximal inhibitory concentration, *ICV* intracerebroventricular, *IDE* insulin-degrading enzyme, *NA* not available, *PHF6* paired helical fragments, *PS1* presenilin 1, *RT-PCR* real-time polymerase chain reaction, *ThT* Thioflavin T, *α-M* α-mangostin, *γ-M* γ-mangostin, *MX-IV* mangostanaxanthone IV

Table 6 The effects of xanthones on cognition and behavior

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
Mangiferin	Male ICR mice 28–30 g	IP 1 mg/kg scopolamine	Passive avoidance test	Significantly increased this scopolamine-induced reduction in step-through latency by 44% (10 mg/kg), 65% (20 mg/kg), and 59% (40 mg/kg)	< 0.05 (all 3 doses)	[19]
			Morris water maze test	Significantly shortened escape latency with 20 mg/kg of mangiferin; significantly ameliorated the decreased swimming time in the platform quadrant induced by scopolamine during the training time and probe trial with 20 mg/kg	< 0.05; < 0.05	
	3 months old of 22–29 g and 14 months old 35–52 g Swiss albino mice	IP 3 mg/kg scopolamine	Elevated plus maze	40, 20, 10 mg/kg mangiferin reversed the scopolamine and aging induced memory deficits by decreasing the transfer latencies	< 0.001, < 0.01, < 0.05	[20]
			Passive shock avoidance (step down) paradigm	40, 20, 10 mg/kg mangiferin reversed the scopolamine and aging induced memory deficits by increasing the step-down latencies	< 0.001, < 0.001, < 0.01	
	Senescence-accelerated mouse prone 8 (SAMP8) mouse model, 6 months old	–	Morris water maze test	High dose of mangiferin (200 mg/kg/day) decreased the escape latencies and increased the seek times (time to find the platform), cross platform times and time interval spending on swimming toward the maze platform	< 0.01 (for all variables)	[21]
	Male C57/BL6 mice, 8 weeks old	3.8% methanol aqueous	Y-maze test	Mangiferin (20 and 40 mg/kg) dose-dependently increased the time spent exploring the novel arm	0.0428; 0.0011	[23]
			Novel object recognition test	Mangiferin (40 mg/kg) dose-dependently increased the discrimination index	0.008	
α- and γ-M	Timed-pregnant Sprague–Dawley (SD) rats and 6 weeks old ICR mice 28–30 g	IP 3 mg/kg scopolamine	Passive avoidance test	γ-M (10 and 30 mg/kg) significantly restored the scopolamine induced decrease in time latency	< 0.05	[32]

Table 6 (continued)

Xanthone	Cell line/animal model	Method of induction	Assay	Findings	P value	References
α-M	Male C57BL/6 mice (20–25 g)	IP 2 mg/kg LPS	Morris water maze test	Decreased escape latencies on day 4 and 5, the number of platform crossings and increased time spent and the distance travelled in the target quadrant	< 0.05 (for all variables)	[26]
	Male Sprague Dawley rat 250–300 g	Permanent bilateral occlusion of common carotid arteries (2VO) in rats (ventral midline incision was made in the neck of the rats)	Open field test	No significant difference in locomotor activity, total distance travelled, average travelling speed, time spent in centre zone and number of centre entries	≥ 0.05 (for all variables)	[27]
			Morris water maze	50 mg/kg α-M showed shorter escape latency and increased exploration in the target quadrant	< 0.001, < 0.01	
MX-IV	Adult male Swiss albino mice, 3–4 months	ICV 3 mg/kg streptozotocin	Morris water maze	MX-IV (30 mg/kg/day, oral) showed enhancement in time consumed in the target quadrant	< 0.05	[38]

ICV intracerebroventricular, *IP* intraperitoneal, *LPS* lipopolysaccharide, *α-M* α-mangostin, *γ-M* γ-mangostin, *MX-IV* mangostanaxanthone IV

test, suggesting it may not have any effect on anxiety-related behavior [27]. On the other hand, other studies have reported that γ-mangostin and mangostanaxanthone IV significantly reversed the memory impairment induced by neurotoxins [32, 38].

Bias Assessment

The bias assessment was reviewed by PLW and YHY according to the OHAT assessment tool. The majority of the studies included (63.7%) had been classified as Tier 1, rated as 'Definitely low risk of bias' and 'Probably low risk of bias' for all key elements. Seven studies have been rated 'probably high risk of bias' on selection and confounding bias elements. Studies that are associated with bias are due to several reasons including poorly reported study procedure (e.g. inadequate randomization and failure to specify the concentration of diluent used) or lack of control group. One study was rated as 'Definitely high risk of bias' in other bias domains because it did not conduct any statistical analysis for in vitro study and only statistically analyzed the results of the animal study [39]. Hence, this paper is excluded from the review. Moreover, one study had been rated as 'Probably high risk of bias' in other bias domains due to reasons for not reporting statistical results for some variables. Overall, the studies included in this review fulfilled most of the internal validity criteria in controlling the bias.

Discussion

Apart from the pharmacological treatments available in the market, natural products are emerging as potential drug candidates for the treatment of AD. Among these natural products, xanthones have shown promising neuroprotective effects against the hallmarks of AD. Xanthones are the naturally occurring secondary metabolites in various plant families, mainly Gentianaceae and Clusiaceae [40]. They are potential therapeutic agents to treat AD due to their anti-inflammatory and antioxidative properties, with positive effects on improving memory and learning abilities [41]. Among the xanthones, mangiferin, α-, γ-mangostin and gartanin have been extensively studied for their anti-Alzheimer properties.

Oxidative stress is closely associated with various chronic neurodegenerative diseases including AD [42]. Excessive production of ROS disrupts the redox balance, leading to oxidative damage of biomolecules such as DNA, proteins and lipids, particularly within mitochondria, which in turn impairs normal cellular function [43]. Persistent oxidative stress can result in axonal degeneration and neuronal apoptosis, which leads to structural damage in the brain [44]. Mangiferin has been reported to possess significant antioxidant

properties by reducing ROS and brain glutathione levels, and reversing the decrease in catalase, SOD and glutathione peroxidase levels. For α-mangostin, there are contradictory findings on its antioxidant activities [24, 29, 32]. These discrepancies could potentially be attributed to variations in the cell lines used and the methods of induction, which limits the generalization of the results from these studies. Further investigations are warranted to clarify and confirm the antioxidant effects of α-mangostin.

Various studies have explored the potential ability of xanthones in reversing neurotoxicity in cell death or apoptosis. Among the xanthones, mangiferin, γ-mangostin and gartanin have demonstrated some potential role in this neuroprotective effect [22, 29, 31, 32, 35]. However, α-mangostin, in contrast, appears to be lacking this neuroprotective effect, as recent studies reported that it has no role in restoring cell death due to neurotoxicity [26, 29, 32]. Only two studies have explored the underlying mechanism pertaining to the anti-apoptotic effects of xanthones, notably gartanin [35], α- [28] and γ-mangostin [32]. Some studies have reported that the anti-apoptotic effect of selected xanthones, such as gartanin and α-mangostin is associated with their ability to conserve Bcl-2 protein levels and preserve the mitochondrial membrane potential, thus preventing apoptosis [28, 35]. Whereas γ-mangostin was elucidated to exert its anti-apoptotic effect by inhibiting the activation of caspases, particularly caspase-3 and -9, which are the crucial mediators of apoptosis [32].

Among the diverse pathophysiological factors involved in the onset and development of AD, neuroinflammation plays a key role in neuronal cell death. Among the redox-sensitive inducible enzymes, HO-1 protects neurons against acute insults and stress conditions due to its antioxidant abilities and anti-inflammatory properties [45]. α-Mangostin and gartanin have been shown to promote HO activity by regulating the expression of HO-1 protein [24, 29, 35]. Gao et al. proposed that the increase in HO-1 protein expressions by gartanin was mediated through the AMPK pathway [35]. However, the exact mechanism by which α-mangostin regulates HO activity remains unknown. On the other hand, α- [26], γ-mangostin [33] and mangiferin [22] also demonstrated modulatory effect on iNOS, a key mediator of immune activation and inflammation that produces NO. Interestingly, the neuroprotective effects of xanthone have been found to be associated to sirtuins, which are NAD^+-dependent histone deacetylases that regulate important metabolic pathways involved in neuronal survival, mitochondrial homeostasis, DNA repair and cell metabolism [46]. This suggests a novel target of these xanthones in SIRT1/3-FOXO3a pathway, highlighting their potential in modulating cellular processes related to neuroprotection.

Microglia, the predominant immune cells, play a crucial role in maintaining brain homeostasis. They reside in the brain as phagocytes. Persistent activation of microglial can be detrimental to neurons and contributes to the pathogenesis of neurodegenerative diseases including AD [47]. LPS interacts with microglial through toll-like receptor-4 (TLR4) to trigger neuroinflammatory responses and impair cognitive function, which ultimately leads to the progression of neurodegenerative disorders [48]. Activation of the TLR4 receptor initiates downstream signaling pathways, including NF-κB, resulting in the release of pro-inflammatory cytokines such as TNF-α and IL-6 [49]. Besides, increased expression of TLR4 has been observed in the brain of AD patients [50]. Thus, targeting the TLR4 signaling pathway is an important approach to controling microglial activation in attenuating AD. The anti-inflammatory effect of α-mangostin has been attributed to its inhibition of the TLR4/TAK1/NF-κB signaling pathway induced by LPS in microglial and neuronal cells [26], Similarly, mangiferin modulated the LPS-induced inflammation by inhibiting NF-κB and NLRP3 inflammasome in microglia [22]. Therefore, the potential role of xanthones in neuroinflammation could be explained by their mechanism in regulating the TLR4/TAK1/NF-κB signaling pathway. Furthermore, γ-mangostin has been reported to modulate the mitogen-activated protein kinase (MAPK) signaling pathway to ameliorate Aß-induced neuroinflammation [33]. MAPK cascades can be activated by various stimuli, including pro-inflammatory cytokines and contribute to inflammation, cell survival, apoptosis and metabolism [51]. Another study has shown that mangostanaxanthone IV has a role in up-regulating the phosphorylation of P13K, Akt and glycogen synthase kinase (GSK)-3β, implying its protective effect in neuroinflammation [38]. Considering the limited studies exploring the molecular mechanisms of xanthones, further investigation is warranted to gain better understanding of the mechanisms of action of other xanthones.

The cognitive decline and development of AD are associated with the dysfunction of cholinergic neurotransmission [52]. Scopolamine, an anticholinergic agent is commonly used in neuroscience research to induce cognitive deficiency in experimental animals because it is readily cross the blood–brain barrier. This mimics the loss of cholinergic function and impaired central cholinergic functioning seen in AD. The effects of scopolamine in AD include cholinergic dysfunction and an increase in Aβ deposition, both of which are the major hallmarks of AD [53]. Several studies have evaluated the effects of xanthones on scopolamine-induced animal models [19, 20, 32]. Surprisingly, only two studies examined the effect of mangiferin in modulating cholinergic neurotransmission [19, 20]. The role of mangiferin in restoring ACh reduction has been proven to be closely related to its functional ability in improving memory impairment in AD animal models [19, 20]. Nevertheless, the role of

other xanthones in cholinergic neurotransmission remains unexplored.

Deposition of amyloid plaques remains the main hallmark of AD and various studies on xanthones have been conducted to target this key target [13, 21, 25, 29]. BACE1, a type 1 transmembrane aspartyl protein is widely expressed in the brain, particularly in neurons, oligodendrocytes and astrocytes [54]. BACE1 acts as the β-secretase enzyme by cleaving the transmembrane APP into Aβ oligomers. It is referred to as the rate-limiting catalytic step for the synthesis of Aβ [55]. BACE1 concentration and rates of activity are relatively high in the brains of AD patients, supporting the theory that BACE1 plays a key role in the pathophysiology of AD. Therefore, BACE1 could be a promising therapeutic target for Aβ reduction in early AD [54]. Limited studies explored the mechanism of xanthones in modulating the amyloidogenic or tau aggregation pathway [21, 25]. α-Mangostin inhibited β-and γ-secretase to decrease the Aβ formation without modulating the amyloidogenic pathway [25]. Contradicted findings were reported for mangiferin in modulating amyloid pathology [21]. Another microscopic feature associated to AD is the intraneuronal neurofibrillary tangles as a results from tau hyperphosphorylation, Tau protein involved in microtubule stabilization and is predominantly found in axons in the brain [56]. Recent studies highlight the protective role of xanthones in tau aggregation [23, 37, 38]. Although studies reported that various xanthones reduce the Aβ formation [13, 21, 25, 29] and tau aggregation [37, 38], the underlying mechanisms of these xanthones in amyloidogenic and tau aggregation pathways are not fully understood.

Due to the cytotoxic properties and relatively low potency of xanthone, the use of naturally occurring xanthone in AD is limited [41]. Modification of the chemical structure of xanthone could be an approach to increase its therapeutic potential towards AD. Thus, the xanthone derivatives have been receiving attention in recent years [30, 36, 37]. A series of the compound with mannich bases of 1,3-dihyoxyxanthone analogues with alkoxy and alkenoxy substituted at position 3 of xanthone, and dialkylamine methyl substituted at position 2 were synthesized using xanthone as the building block, and their effects against AChE and BuChE were examined [57]. The structure analysis reported that the alkoxy or alkenoxy substituent at position 3 of xanthone has a beneficial influence on the inhibitory potency while the dialkylamine methyl at position 2 affects cholinesterase activity and selectivity towards both enzymes [57]. In addition, the kinetic analysis revealed that the compound possesses mixed-type interaction with cholinesterases, which could mean they simultaneously interact with both the active site and peripheral active site of both enzymes [57]. In addition, Chen et al. reported that α-mangostin carbamates derivatives could prevent $A\beta_{25-35}$ oligomer induced Aβ deposition in rat cerebral hippocampal neurons while simultaneously enhancing learning and memory function and reducing neuronal damage by scavenging Aβ in the hippocampus of the AD rodent model [41]. A study by Zhang et al. revealed that xanthone conjugated with alkylbenzylamine with alkyl linker demonstrated strong blood–brain barrier penetration and free radical scavenging [58]. Importantly, it was discovered that the compound might enhance memory function in scopolamine-induced amnesia rats [58]. In short, the xanthone derivatives will be a promising compound with the potential for future development for the research of AD. However, this is not the focus of this review.

Although a number of narrative reviews have been done on xanthones, there is lacking systematic review on these natural compounds. Thus, this review is being conducted in accordance with the proper protocols of a systematic review and the papers included are being assessed with the risk of bias tool. This is to ensure that the findings and data in this review are accurate with minimal risk of bias. This review included a small number of articles due to the inclusion criteria where papers included was inclusive of only purified extract in order to ensure that the review focused on the effects that were exhibited by the xanthone itself, without any effects from other compounds. Since only those English articles were included, any papers in other foreign languages being excluded may have been attributed to publication bias. Different cell lines and animal models were employed in different studies; hence, it is difficult to conclude the effects on xanthones. Nevertheless, this review provides insights for researchers to have a better understanding of the pharmacological effects and underlying mechanisms of xanthones and highlights the research gaps for these compounds. This would be important in the drug discovery and medication development process. Although xanthones are widely available in the market, their uses are mainly limited to dietary supplements and their uses for medical purposes are not approved by the FDA. A clinical trial (NCT04151641) is currently being completed on xanthones from mangosteen extract in Spain to compare the pharmacokinetics and bioavailability of the xanthones, yet no results were updated.

Despite the small number of papers, this review reveals the therapeutic effects of xanthones, and its underlying mechanisms tested on in vitro and in vivo models. To the best of our knowledge, this is the first systematic review reported on the effects and mechanisms of xanthone in AD. Therefore, with appropriate application of the data from this review, it provides the researchers a fundamental understanding of this potential neuroprotective agent in developing and discovering new agents.

Conclusion

This study reviewed the various effects and mechanisms of xanthones in AD. The xanthones are found to have therapeutic effects ranging from antioxidant, neuroprotective effects towards cell death and neuroinflammation, anticholinesterase, improvement on learning and memory impairment and anti-amyloidogenic effects. Several mechanisms reported on the neuroprotective effects of xanthones, however, there is no accepted theory to explain the mechanisms involved. Thus, further research and studies are required to understand thoroughly this potential anti-Alzheimer agent. A deeper knowledge of the involvement of xanthones in the regulation of AD pathogenesis is required as this could pave the way for developing new therapeutic strategies in the future.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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