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Review

Neuroprotective, Anti-Inflammatory and Antifibrillogenic Offerings by Emodin against Alzheimer's Dementia: A Systematic Review

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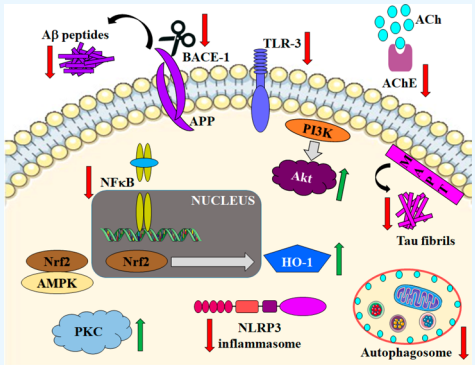
ABSTRACT: Background: Alzheimer's disease (AD) is among the major causes of dementia in the elderly and exerts tremendous clinical, psychological and socio-economic constraints. Currently, there are no effective disease-modifying/retarding anti-AD agents. Emodin is a bioactive phytochemical with potent multimodal anti-inflammatory, antioxidant, and antifibrillogenic properties. In particular, emodin may result in significant repression of the pathogenic mechanisms underlying AD. The purpose of this review is to accumulate and summarize all the primary research data evaluating the therapeutic actions of emodin in AD pathogenesis. **Methodology**: The search, selection, and retrieval of pertinent primary research articles were systematically performed using a methodically designed approach. A variety of keyword combinations were employed on online scholarly web-databases. Strict preset inclusion and exclusion criteria were used to select the retrieved studies. Data from the individual studies were summarized and compiled into different sections, based upon their findings. **Results**: Cellular and animal research indicates that emodin exerts robust multimodal neuroprotection in AD. While emodin effectively prevents tau and amyloid-beta (Aβ) oligomerization, it also mitigates their neurotoxicity by attenuating neuroinflammatory, oxidative, and bioenergetic defects. Evidences for emodin-mediated enhancements in memory, learning, and cognition were also found in the literature. **Conclusion**: Emodin is a potential anti-AD dietary supplement; however, further studies are warrantied to thoroughly understand its target players and mechanisms. Moreover, human clinical data on emodin-mediated amelioration of AD phenotype is largely lacking, and must be addressed in the future. Lastly, the safety of exogenously supplemented emodin must be thoroughly evaluated.



1. INTRODUCTION

Alzheimer's dementia/disease (AD) is one of the most prevalent dementias in the aged population, across the globe, after cardiovascular diseases and cancers.[1] AD is characterized by various behavioral deficits such as cognitive decline, memory loss, sleep disturbances, and neuropsychiatric issues.[2] AD has a multimodal origin and progression of the disease is dependent on a plethora of environmental and genetic factors. For example, age is the most significant risk factor for the development of sporadic AD, the major type of AD. Familial AD, however, represents a significant minority of AD clinical cases and is thought to be associated with deleterious mutations in amyloid precursor protein (APP) and presenilin 1 (PS1). In the molecular perspective, histo-pathological hallmarks of AD involve formation of extracellular senile plaques composed of misfolded and aberrantly accumulated amyloid-beta (Aβ) peptides, and intracellular neurofibrillary tangles (NFTs) composed of abnormal depositions of misfolded microtubule associated protein-tau (MAP-T) species.[3] However, recent studies indicate that the actual pathogenic species are the soluble oligomers of Aβ and tau, the levels of both of which elicit prodromal elevations, decades before the onset of the classical behavioral phenotypes of AD.[4] Several pathways have been implicated as the initiators and regulators of amyloid and tau pathology, chief among them are synaptic (e.g., glutamatergic and cholinergic) deficits, abnormal activation of neuroinflammatory pathways, oxidative stress, and mitochondrial dysfunction.[5−7]

Unfortunately, no effective disease-modifying therapies are available against AD. Most approved drugs are symptomatic, acting to relieve the subjects from the AD-related symptoms and as such only elicit moderate effects. An example is memantine, an *N*-methyl-D-aspartate (NMDA) antagonist.[8] Recently, there has been a renewed interest in therapeutic phytochemicals (e.g., rosmarinic acid[9]) as potential neuroprotective agents because these are safe and can be easily supplemented in diet. In this respect, emodin is emerging as yet another suitable candidate, particularly against AD. This

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Table 1. Plant Sources of Emodin

plant species	family
Rhamnus pubescens, R. alaternus, R. sphaerosperma	Rhamnaceae
Ventilago leiocarpa	Rhamnaceae
Cassia obtusifolia, C. occidentalis, C. siamea	Fabaceae
Polygonum cuspidatum, P. multiflorum	Polygonaceae
Rheum emodi, R. officinale, R. australe, R. acuminatum	Polygonaceae
Rumex confertus, R. chinensis	Polygonaceae
Hypericum hirsutum, H. tetrapterum, H. attenuatum, H. maculatum	Hypericaceae
Alvaradoa subovata	Picramniaceae
Picramnia sellowii	Picramniaceae
Momordica charantia	Cucurbitaceae
Thevetia peruviana	Apocynaceae
Glossostemon bruguieri	Malvaceae

bioactive compound occurs naturally and is present in numerous medicinal herbs, particularly those belonging to the *Rhamnaceae*, *Fabaceae* (*Leguminoceae*), and *Polygonaceae* plant families (Table 1). Well-known sources of emodin include *Rheum palmatum*,[10] *Polygonum cuspidatum*,[11] *Aloe vera*,[12] *Polygonum multifarum*,[13] and *Casia obtusofolia*.[14] Emodin elicits significant anti-inflammatory, antioxidant, antimutagenic, antiapoptotic, and antiallergic properties, among many other benefits.[15] Unsurprisingly, emodin has been proposed to have multiple therapeutic functions against diabetes, asthma, osteoporosis, cancers, liver and kidney dysfunctions, and cardiovascular diseases.[16] In recent years, several studies have advocated for a robust neuroprotective function of emodin.[17] Moreover, the beneficial effects of emodin in amelioration of the pathogenic mechanisms of Alzheimer's disease are only beginning to be realized. The purpose of this systematic review is to accumulate and summarize all relevant data evaluating the ameliorative potential of emodin against AD.

2. METHODS

2.1. Focused Research Objectives. The major aims of this review article were developed to accumulate and summarize primary research published on the themes of its ameliorative potential against neuroinflammation and AD pathogenesis. The focus was on discussing the known molecular players and mechanisms underlying emodin-mediated neuroprotection specifically with regards to Alzheimer's dementia. In addition, the review also sheds light on the pharmacokinetic and safety aspects of emodin. The study was performed in accordance with the guidelines of the PRISMA 2020 checklist (Supporting Information file).

2.2. Research Study Search. Identification and retrieval of relevant research articles dealing with the mechanisms of emodin-induced attenuation of AD phenotypes was undertaken methodically employing a well-structured approach for literature search. Multiple keyword combinations were employed for the literature search on widely used online scholarly web-databases; PubMed/Medline, Google Scholar, and Web of Science. The keywords used were {("emodin") AND ("Alzheimer's disease" OR "neuroinflammation" OR "dementia" OR "amyloid-beta" OR "tau", etc.)}. A few more keywords were used, such as "pharmacokinetics", "safety", etc. The studies were included according to the relevance to the topic, irrespective of the date of publication. Further, the retrieved studies were chosen for assessment only after evaluation of their titles and abstracts, which were verified for relevance with regards to the specific aims of the systematic review; i.e., emodin-mediated neuroprotection in AD. Additionally, apart from the retrieval of the pertinent primary researches from the online web-databases, the references listed in and articles citing the retrieved articles were carefully evaluated to select any relevant research studies that may have been overlooked during the initial searches.

2.3. Inclusion and Exclusion Criteria. Only original research articles that were published in various English language peer-reviewed journals and indexed in reputable databases were included for the systematic review of the primary data evaluating the ameliorative effects of emodin in AD pathology. Strict preset inclusion and exclusion criteria were employed for the selection of the individual primary studies for the purpose of drawing appropriate conclusions. The following are the exclusion criteria: (i) publication of the primary study in a language other than English, (ii) employment of a plant extract containing emodin as a bioactive component, as opposed exclusive use of emodin as the therapeutic agent, (iii) use of glucuronidated or other conjugated forms of emodin, (iv) usage of an inappropriate cellular or animal model of AD, and (v) duplicate studies, abstract and conference proceedings. Here, the authors would like to point out that the language bias for the selection of primary studies for this systematic review was because of our innate inability to read, comprehend, and assimilate languages other than English. In the past, our attempts of employing even the best platforms for translation/transliteration have yielded unfruitful results. This is a definite limitation on our part, and in no way or form, should suggest inferiority of studies published in languages other than English. Figure 1 summarizes the retrieval and selection methodology for the relevant studies for this systematic review. All selected studies included for the systematic review were original research articles evaluating the therapeutic effects of emodin against AD pathology.

2.4. Literature Search Strategy. The methodological strategy for literature search was as follows. One investigator, P.S., independently evaluated the titles and the abstracts of the articles selected at different levels of the sequential search conducted on the different scholarly online databases. Relevance of the primary data reported in the retrieved studies was confirmed by examination of their full-texts. This was followed by a systematic and independent appraisal of the suitability of the retrieved data by the second investigator, F.A. The inclusion and exclusion criteria for the study selection were thoroughly followed by the investigators while selecting

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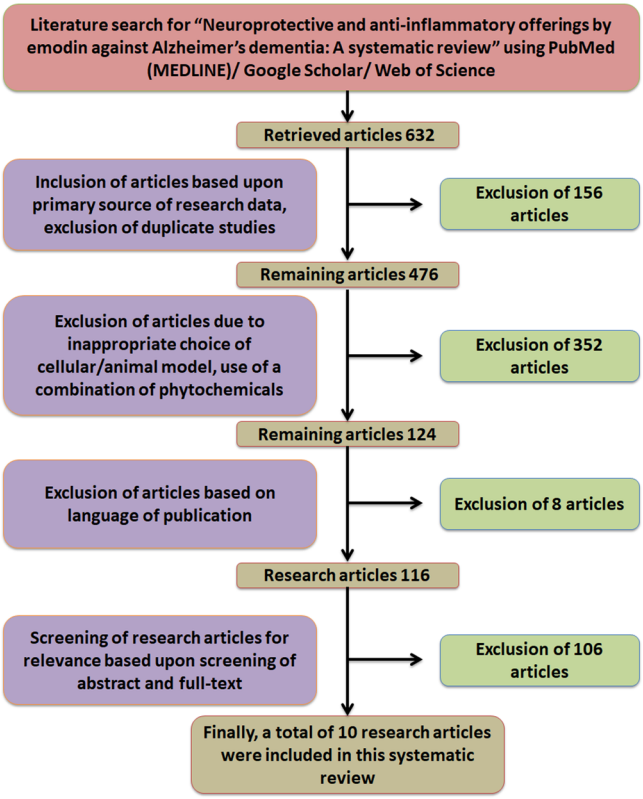

Figure 1. Strategy and outcome of the retrieval of primary studies. Study selection process and iterative steps used in the systematic selection of the pertinent studies for this article.

the retrieved primary research articles. After finalization of the study-set, the investigators summarized the relevant data from the screened articles. Conflicts occurring between the investigators during the study selection and data abstraction processes were resolved with logical debate.

3. RESULTS

3.1. Retrieval of Primary Studies. Initially, 632 articles were retrieved from the online search over PubMed/Medline, Google Scholar, and Web of Science databases. Strict application of the preset exclusion and inclusion criteria resulted in curtailment of the retrieved publications to 124 primary research articles. Finally, screening of these articles based upon their titles, abstracts, and full-texts allowed the selection of a final set of 10 primary research studies. The study selection (preset criteria of study inclusion−exclusion) process and iterative steps applied in this systematic review are depicted as a flowchart in Figure 1.

3.2. Data Abstraction. The investigators P.S. and F.A. performed the quality assessment of the data retrieved from all the primary research studies included in the systematic review. The data fetched from the included studies were summarized with the following information: year of publication and the country of origin of the study, type of AD model employed, dose, route, frequency, and time frame of emodin treatment, nature of and mechanisms underlying the therapeutic effects of emodin in AD pathophysiology, and the first author name along with the citation (Table 2).

In addition to the summarization of the primary data for above-mentioned aspect, other relevant studies discussing the general themes such as neuroinflammatory pathways in AD, emodin's anti-inflammatory effects, and its pharmacokinetics and safety aspects were also included according to their relevance.

4. CHEMICAL NATURE OF EMODIN

Chemically, emodin can be described as a trihydroxy-derivative of methylanthraquinone. The chemical name of this planar phytochemical hence is 1,3,8-trihydroxy-6-methylanthraquinone and the IUPAC name is 1,3,8-trihydroxy-6-methylanthracene-9,10-dione (Figure 2). As a derivative of quinone, emodin has an anthracene ring structure (three aromatic rings condensed together). Like other anthraquinones (e.g., rhein and aloe-emodin), emodin is a polyphenolic secondary metabolite that is produced in fungi, plants and some insects. In higher plants, emodin can occur both freely and in glycosylated forms, where it elicits significant protective functions against abiotic and biotic stressors.[30]

Emodin and other anthraquinones are targets for nucleophilic attacks by various chemical groups, such as thiols, hydroxyls and amines, which are abundantly present in proteins because of the widespread occurrence of amino acids cysteine, serine, and lysine, respectively. This actually constitutes the physiological basis for the bioactivity of emodin and other plant-derived anthraquinones.[31]

5. PHARMACOKINETICS OF EMODIN

Pharmacokinetics is the study of bioavailability of an exogenous drug and how it is distributed in the body over a period of time, following its supplementation via multiple routes. It encompasses the processes of absorption, metabolism/biotransformation, and excretion.[32] Multiple studies have evaluated the pharmacokinetic behavior of emodin in experimental animals, both alone and as part of a medicinal plant extract. Since the topic has been reviewed recently in detail (see for e.g., refs 30,33) we will merely discuss the major findings in brief in the present review.

Studies in rats suggest that orally administered emodin is mainly absorbed from the stomach,[34] although intestinal absorption also contributes to its pharmacokinetics. However, the primary route of excretion is through renal excretion urine.[35] Bioavailability of exogenously administered emodin suffers from some issues, including its weak intestinal absorption, high rate of elimination, and first-pass metabolism.[33] First-pass metabolism (mainly glucuronidation) of emodin in particular, seems to be a major concern for the bioavailability of emodin. Thus, upon intravenous and oral administration in rats, emodin has been illustrated to be rapidly converted into its glucoronide adduct forms, omega hydroxyemodin (ω-OHE) and its sulfated form.[36] Interestingly, bioavailability of orally supplemented emodin may show appreciable dependence on gender, given that there are four times higher plasma levels of emodin in male rats, compared to females after a single oral dosing of emodin at 8 mg/kg body weight. Nevertheless, the gender effects in bioavailability of emodin do not elicit when it is administered intravenously at 4 mg/kg body weight.[37] In concurrence, female mice were reported to elicit significantly increased clearance of emodin both upon its intraperitoneal and oral supplementation.[38]

There are some strategies which likely increase emodin bioavailability. For example, pretreatment with stilbene glucosides from *Radix Polygoni Multiflori* prevents glucuronidation of emodin, and increases its plasma concentration upon oral

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Table 2. Summary of the Systematically Selected Primary Studies Evaluating the Neuroprotective Actions of Emodin against Pathogenic Mechanisms of AD

experimental model of AD	dose, duration and route of emodin treatment	summary of major findings	first author of the primary study	country of origin of the primary study	reference
in vitro studies					
in vitro aggregation and heparin-induced PHF formation for multiple forms of tau (10 μM), and disassembly assay for preformed tau PHFs	various concentrations (10 pM to 200 μM)	70−90% inhibition of PHF formation for different tau forms at 60 μM concentration, and strong disassembly activity for preformed PHFs	Pickhardt, Marcus	Germany	18
in vitro spectrophotometry-based activity assay of recombinant human AChE	various concentrations of emodin for determination of IC_{50}	potent in vitro inhibition of AChE (IC_{50} of 21.8 μM), in addition to amelioration of H_2O_2-induced oxidative damage in PC12 cells	Wang, Yan	Hong Kong	19
spontaneous aggregation of Aβ_{1-42} (100 μM) at 37 °C for 48 h	sodium salts of emodin at various concentrations	increased solubility of Na salts of emodin compared to emodin itself, in addition to their more potent antifibrillogenic actions, with IC_{50} values of EM-1Na and EM-2Na being 18.4 and 29.1 μM, respectively	Li, Yaping	China	20
in vitro fluorescence resonance energy transfer (FRET) and spectrophotometry-based activity assay of recombinant human BACE-1 and AChE, respectively; and assessment of kinetic parameters for BACE-1 inhibition	multiple concentration of emodin (0−100 μM for kinetic assays for BACE-1 inhibition)	potent inhibition of the activities of BACE-1 (IC_{50} of 4.5 μM) and AChE (IC_{50} of 9.7 μM); and strong and mixed-type inhibition for BACE-1 (K_i of 20 μM) in kinetic studies	Jung, Hyun Ah	Republic of Korea	21
in vitro human AChE activity assay	various concentrations of emodin for determination of IC_{50}	inhibition of AChE (IC_{50} of 15.2 μM)	Augustin, Ntemafack	India	22
in vitro Aβ_{1-42} aggregation (20 μM) at 37 °C for 24 h	co-incubation with multiple concentrations of emodin (1:0.3, 1:1 and 1:3 molar ratios)	antifibrillogenic activity resulting in 80% reduction in Aβ aggregation as assessed by ThT-fluorescence, TEM and CD analyses	Wang, Lichun	China	23
cellular models of AD					
neuroblastoma N2A cells overexpressing K18ΔK280 tau	15 μM for 7 days	high antiaggregation activity as assessed by sarkosyl extraction and ThS staining, without affecting tau expression	Pickhardt, Marcus	Germany	18
primary cortical rat neurons treated with 30 μM Aβ_{25-35} for24 h	20 μM (24 h pre- and 24 h cotreatment)	attenuation of membrane disintegrity, apoptosis and neurotoxicity in a PI3K/Akt1-dependent manner	Liu, Tao	China	24
PC12 cells exposed to 10 μM Aβ_{25-35} for 24 h	10 μM (1 h pre- and 24 h cotreatment)	stimulation of the PI3K/beclin-1/Bcl-2 pathway resulting in beneficial effects on membrane integrity and mediators of autophagy, apoptosis and cellular toxicity	Sun, Yan-ping	China	25
hippocampal HT-22 cells challenged with 5 μM Aβ_{1-42} for 24 h	10 and 20 μM (1 h pre- and 24 h cotreatment)	increased cell survival and viability	Du, Changwang	China	26
U251 astroglioma cells exposed to 15 μM Aβ_{1-42} for 24 h	50 μM (3 h pre- and 24 h cotreatment)	activation of endogenous antioxidant mechanisms and reversal of Aβ-induced mitochondrial dysfunction, apoptotic induction, and cell damage and toxicity	Li, Zhiping	China	27
SH-SY5Y cells treated with 1 μM Aβ_{1-42} for 48 h	Treatment with Aβ_{1-42} monomers coincubated with various concentrations (0.25−2 μM) of emodin, before treatment of cells	Attenuation of cytotoxicity (MTT assay) and apoptotic damage (Annexin V-FITC-based assay)	Wang, Lichun	China	23
animal models of AD					
9 months old APP/PS1 mice with 10 nM Aβ_{25-35} (intracerebroventricular injection)	50 mg/kg/day for 7 days (oral administration)	Inhibition of autophagic (LC3-II and beclin-1) and stimulation of antiapoptotic (Bcl-2) pathways	Sun, Yan-ping	China	25
7−8 months old APP/PS1 mice	5, 10, and 20 mg/kg for 70 days (intraperitoneal injection)	amelioration of fear-conditioning and spatial memories, mediated via PKC signaling	Du, Changwang	China	26
chemical model of hyperhomocysteinemia-induced dementia in rats	80 mg/kg/day for 2 weeks (intragastric administration)	repression of the levels of BACE-1, Aβ species and phosphorylated-tau, stimulation of CREB signaling, preservation of neuronal numbers, synaptic proteins and cerebral microvasculature, and improvements in object recognition and spatial memories	Zeng, Peng	China	28
8 months old APP/PS1 mice	10 or 20 mg/kg/day for 8 weeks (oral administration)	downregulation of Aβ and phosphorylated-tau levels, reduced oxidative damage and 4-HNE levels, and amelioration of behavioral deficits (anxiety-like phenotype and deficits in spatial memory)	Li, Zhiping	China	27
transgenic Aβ-expressing *Caenorhabditis elegans*	37 and 74 μM for 3−5 days	inhibition of Aβ-induced paralysis, possibly via induction of metallothioneins (MT-1 and 2), metal detoxifying enzymes	Pretsch, Dagmar	Austria	29

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Table 2. continued

experimental model of AD	dose, duration and route of emodin treatment	summary of major findings	first author of the primary study	country of origin of the primary study	reference
animal models of AD					
8 months old APP/PS1 mice	6.25 mg/kg/day for 2 months (oral administration)	60−70% stimulation of short-term (Y-maze) and long-term spatial memory, concomitantly with 50−70% decrease in hippocampal and cortical amyloid plaque load	Wang, Lichun	China	23

Figure 2. Ball and stick model of emodin. The 3-D structural model for emodin (1,3,8-trihydroxy-6-methylanthracene-9,10-dione) is taken from the National Center for Biotechnology Information (2023); PubChem Compound Summary for CID 3220, Emodin (https://pubchem.ncbi.nlm.nih.gov/compound/Emodin#section=3D-Conformer). Carbon and oxygen atoms are depicted as gray and red balls, while the white balls represent hydrogen atoms.

administration.[39] Similarly, cotreatment with piperine was also found to inhibit glucuronide formation of orally administered emodin, while increasing the bioavailability of its free form.[40] Interestingly, cocrystallization of emodin with berberine chloride has been found to improve emodin bioavailability in rats with reference to administration of emodin alone.[41] Nanoformulations are another potential strategy for increasing the bioavailability of emodin, and may also serve to aid its directed delivery to specific tissues/cells (Table 3). Nano-emulsification may also decreses the clearance of orally administered emodin, while increasing its brain distribution and bioavailability. In fact, when supplemented in nano-emulsified form, the clearance time of emodin in the brain was found to be reduced by as much as 2-fold compared to other tissues.[42] Lastly, treatment of emodin with sodium hydroxide to form its sodium salt may represent another strategy for improving the solubility and bioavailability of emodin.[20] Importantly, Na salt formation does not influence the antifibrillogenic actions of emodin against Aβ species (section 8.1).

6. SAFETY OF EMODIN SUPPLEMENTATION

According to data from experimental animal studies, emodin is a relatively safe drug. For example, a recent study indicates no significant deleterious effects of subchronic (12 weeks) emodin treatment at a maximum dose of 80 mg/kg body weight (orally, in diet) or 40 mg/kg body weight (intraperitoneal). There were no toxic hepatic, colonic, intestinal, or cardiovascular repercussions in mice of both sexes.[38] Higher doses (500−1500 mg/kg body weight) of emodin supplementation may however result in toxicity including inflammation and hepatotoxicity.[71,72] Some studies have also reported toxic effects of emodin in in vitro systems.[73,74] In addition, spermatoxicity[75] and genototoxicity[76] of emodin have also been reported.

It should however be noted that most of the reports of emodin toxicity have been proposed in in vitro models, or upon excessive (much greater than the required therapeutic doses) dosing. Hence, thorough analyses of the toxic effects of exogenous supplementation of therapeutic doses of emodin are required, both in experimental animals and humans.

7. PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE (AD)

7.1. Pathogenic Species. As mentioned previously, the central pathogenic mechanisms in AD pathology revolve around Aβ peptides and tau species. Aβ is a proteolytic

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Table 3. Summarization of Nanoformulations Used for Emodin Delivery In Vitro and In Vivo

nanoformulations	species/model used	pathological conditions	beneficial effects	reference
emodin-loaded 1,2-dimyristol-*sn*-glycero-3-phosphocholine liposomal nanoparticles embedded in silk fibroin-chitosan scaffolds	GILM-2 breast cancer cells, and orthotopic tumor in nude mice	breast cancer	reduced tumor load	43
emodin-encapsulated solid stearic acid—based lipidaceous nanoemulsions	human breast cancer MCF-7 and MDA-MB-231 cells	breast cancers	enhanced toxicity and arrest at the G2/M cell cycle phase cell cycle of tumor cells	44
emodin encapsulated in nanoparticles made of catechol conjugated to low molecular weight chitosan	mice with unilateral ureter obstruction	renal fibrosis	attenuation of renal injury and fibrotic lesions	45
emodin-loaded magnesium silicate hollow nanospheres	retinal capillary endothelial cells, human umbilical vein endothelial cells, and fertilized chicken eggs	oscular neovascularization	significant inhibition of angiogenesis in a vascular endothelial growth factor (VEGF)-dependent manner	46
emodin-containing pH-sensitive phenylboronic acid nanoparticles	hepatocellular carcinoma Hep G2 cells	hepatocellular carcinoma	accelerated emodin release under low pH conditions (pH 5), increased toxicity against cancer cells	47
emodin-containing polylactic-*co*-glycolic acid-D/α-tocopheryl polyethylene glycol 1000 succinate (PLGA/TPGS) and *N*-acetylaminogalactosyl (GalNAc)-PLGA-TPGS nanoparticles	hepatocellular carcinoma Hep G2 and Hca-F cells, and diethylnitrosamine-induced mouse model of primary hepatocarcinoma	primary liver cancer	reduced tumor cell viability and suppression of tumorigenesis	48−50
mesoporous silica-based SBA-15 nanoformulation carrying emodin	larvae of brown moth *Euproctis chrysorrhea*	*E. chrysorrhea* is a pest of multiple plant species	feeding the larvae with emodin-SBA-15 nanoparticles induced their endogenous antioxidant enzyme systems	51
emodin-containing colloidal Ag nanoparticles on nanostructured porous silicon prepared	cecal ligation and puncture-induced mouse model of sepsis	sepsis	antimicrobial actions, and attenuation of sepsis-associated hyperactivated immune	52
emodin-containing poly(ethylene glycol) methyl ether methacrylate- 2-(dimethylamino)ethyl methacrylate-methyl azoxy methanol (PEGMA-DMAEMA-MAM) nanocomposites	streptozocin- and high calorie diet-induced type 2 diabetes mellitus rat model	diabetic neuropathic pain	reduced mechanical and thermal hyperalgesia, possibly in a purin 2 × 3 receptor-reliant manner	53
gelatin-cyclodextrin based nanocomposites containing emodin	*Streptococcus suis* biofilm	bacterial infection	enhanced antibiofilm actions in vitro	54
emodin-encapsulated nanocomposites made of bovine serum albumin and functionalized with folic acid	breast cancer MCF7, and prostate cancer PC3 cell lines	breast and prostate cancers	enhanced cytotoxicity of cancer cells, presumably via induction of immune and macrophage actions	55
emodin-incorporated monomethoxy-poly(ethylene glycol)-poly(lactic acid)-chitosan-2-mercaptobenzimidazole (mPEG-PLA-Chi-MBI) nanoparticles	5/6 nephrectomized rats	chronic kidney disease	beneficial alterations in the gut microbial homeostasis, mitigation of systemic inflammation and renal injury, and enhancement of renal functions	56
emodin carrying PLGA nanocomposites	human breast cancer MCF-7 cells, and ectopic tumor expressing nude mice	breast cancer	enhanced toxicity and death of MCF-7 cells in vivo and in vitro	57
emodin-containing propylamine functionalized mesoporous silica nanomaterial surface-modified with *N*-methyl isatoic anhydride	human colon carcinoma HT-29 cells	colon cancer	enhanced apoptosis of cancer cells	58
ultrasound-sensitive emodin-containing lecithin-based nanoformulations	squamous cell carcinoma FaDu and CAL-27 cells	neck squamous cell carcinoma	sonodynamic therapy-based beneficial actions of emodin in enhancing cytotoxicity of cancerous cells by activating oxidative stress and apoptotic pathways	59
ultrasound-sensitive emodin-containing nanoformulations	in vitro bacterial biofilms composed of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*	infections of burn wounds	robust destruction of bacterial biofilms, and repression of biofilm formation	60
polyethylene glycol-coated magnetic Fe_3O_4 nanoparticles containing emodin	human pancreatic cancer BxPC3 cells, and mice with pancreatic tumor xenografts	pancreatic cancer	robust in vitro and in vivo antitumorigenic actions against pancreatic cancer cells	61
liquid nanoparticles containing emodin-enriched extract from *Rhamnus cathartica*	mice infected with malarial parasite *Plasmodium bergbei* NICD	malaria	significant inhibition of parasitic growth	62
emodin-containing deoxycholic acid-chitosan coated nanosized liposomes, and in situ colonic gel and microcapsules containing emodin nanoemulsions	rats with unilateral ureter obstruction	renal fibrosis	restoration of gut mricobiota dysbiosis and rescue of renal fibrosis	63,64
multiple types of photo- and/or ultrasound-sensitive emodin nanocomposites	*Streptococcus mutans* and *Enterococcus faecalis* biofilms, and *acrylic resin discs*	dental caries, root canal and demineralization of enamel	sono- and photodynamic therapy based on antimicrobial and antibiofilm actions of emodin	65−68
lactoferrin-functionalized emodin containing nanoparticles loaded onto oral delivery platforms composed of β-1,3-D-glucan, and emodin-borate nanocomposites loaded onto microgels made of oligomeric mannitol	dextran sodium sulfate-induced mouse model of ulcerative colitis	ulcerative colitis	enhanced biotargeting of emodin to lesion sites, mitigation of inflammation, rescue of intestinal mucosal damage and gut barrier dysfunction, and deliverance from stool inconsistencies	69,70

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fragment of APP formed via the latter's amyloidogenic processing mediated by β and γ secretases. Imbalances in the production of Aβ peptide species are thought to promote their aggregation, resulting in the formation of soluble oligomers, protofibrils, and fibrils.[77] Tau pathology, though not specific for Alzheimer's disease, is also a critical propagator of AD pathogenesis. Several deleterious posttranslational modifications (such as phosphorylation, truncation, and acetylation) are known to stimulate fibrillization and the formation of soluble toxic oligomers and fibrils.[78] Soluble oligomers of both Aβ and tau may act synergistically to induce severe deficits in cellular mechanisms of synaptic signaling and plasticity, neuroinflammation, bioenergetic functions, and redox and calcium homeostasis.[79,80]

7.2. Neuroinflammation in AD. Gliosis and hyperactivation of neuroinflammatory signaling is a primary feature of multiple neurological diseases, including neurodegenerative conditions such as AD (see detailed reviews[81,82]). Pathogenic Aβ and tau species can robustly induce microglial and astrocytic activation, resulting in aberrant pro-inflammatory signaling.[83] Recent studies suggest that Aβ oligomers can interact with microglia via multiple receptors on the latter's cell membrane, including cluster of differentiation receptors (CD-14, -36, and -47) and toll-like receptors (TLR-4 and -6).[84−86] Toxic tau oligomers are also known to deleteriously activate pro-inflammatory signaling in the brain.[87,88] Activated glial cells in AD elicit altered expression of both anti-inflammatory mediators such as transforming growth factor-β1 (TGF-β1[89]) and triggering receptor expressed on myeloid cells 2 (TREM-2[90]); and pro-inflammatory cytokines including interleukins (IL-1β, -6, and -8[91,92]), and tumor necrosis factor-alfa (TNF-α[93]). The end result is reduced clearance of soluble oligomeric species of Aβ and tau, aggravation of amyloid and tau pathology, and consequent induction of neuronal synaptic and bioenergetic deficits, oxidative stress and damage, and cellular apoptotic pathways. In this regard, NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammosome is widely recognized to be one of the most critical mediators linking amyloid and tau dysfunctions to neuroinflammation in AD pathogenesis. Indeed, altered activation of NLRP3 inflammasome in AD is thought to contribute to the disease progression via multiple mechanisms and biotargets (reviewed in refs 94,95).

8. NEUROPROTECTION MEDIATED BY EMODIN IN AD

Because of its multimodal beneficial effects on a plethora of molecular and cellular pathways, emodin may serve as a potent plant-based anti-AD agent (Figure 3). Multiple studies have advocated a range of ameliorative effects mediated by emodin in AD pathogenesis (Table 2).

8.1. Antifibrillogenic Effects. As discussed, oligomerization and fibrillization of Aβ and tau species are the two principle mechanisms of AD pathogenesis. As opposed to the moderately acting drugs aimed at merely minimizing the phenotypic manifestations of AD, recent research has proposed the evaluation of therapies/agents which can halt or retard the progression of AD pathogenesis. In this regard, bioactives such as those derived from plant sources which target the mechanisms regulating Aβ and tau aggregation have emerged as prime candidates.[96,97]

Emodin is a particularly interesting phytochemical with the capability to both prevent the formation of Aβ and tau

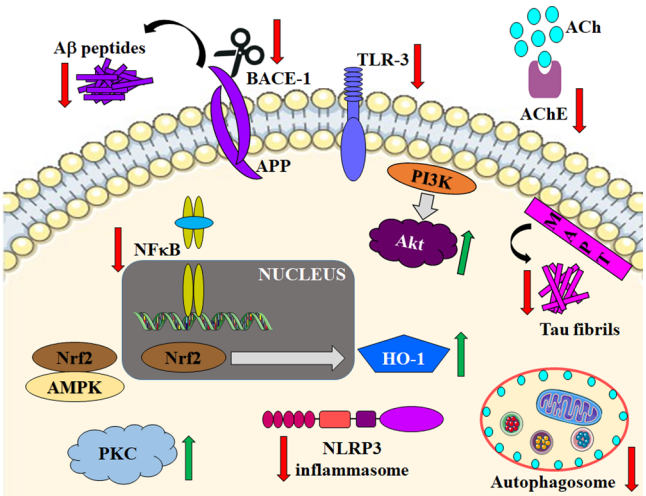

Figure 3. Cellular and molecular targets of emodin-mediated neuroprotection in AD. Emodin elicits multimodal therapeutic effects in AD pathogenesis, from inhibition of amyloidogenic pathway and repression of Aβ and tau aggregation, to inhibition of pro-inflammatory, oxidative, autophagic, and apoptotic pathways and promotion of cholinergic, antioxidant, and cell survival pathways. Consequently, emodin has modulatory effects on a plethora of endogenous targets and pathways which are known to be defunct in AD. ACh: acetylcholine, AChE: acetylcholinesterase, AMPK: AMP-activated protein kinase, BACE-1: β-site amyloid precursor protein (APP) cleaving enzyme 1, HO-1: heme oxygenase-1, MAPT: microtubule-associated protein tau, NFκB: nuclear factor kappa B, NLRP3: NOD-, LRR- and pyrin domain-containing protein 3, Nrf2: nuclear factor erythroid 2-related factor 2, PI3K: phosphoinositide 3-kinase, PKC: protein kinase C, and TLR-3: toll-like receptor 3.

aggregates and to attenuate their toxic effects at multiple levels, including neuroinflammatory, bioenergetic, and redox signaling. In fact, emodin's antifibrillogenic effects in amyloidogenesis may be even more potent than that of curcumin. It should be noted here that curcumin is regarded as among the strongest plant-based inhibitors of Aβ aggregation.[98,99] Thus, Wang and colleagues reported robust antifibrillogenic properties of emodin against Aβ_{1-42} in in vitro systems as assessed by transmission electron microscope (TEM) and fluorescence-based Thioflavin T (ThT) assays, possibly by inhibiting the formation of β-sheet-rich structure required for Aβ oligomerization. Based upon in silico molecular docking analyses and circular dichroism (CD) spectroscopy, they identified Leu-17−Gly-33 as the critical sequence in Aβ for the physical interaction between Aβ and emodin. Further, they confirmed Val-18 and Phe-19 as the focal binding points for emodin-mediated anti-Aβ oligomerization using mutational analyses.[23] Amyloidogenic aggregation of Aβ is known to be exacerbated in the presence of metal ions such as zinc (Zn^{2+}; section 8.4). Using a transgenic Aβ overexpressing *C. elegans* model, Pretsch and co-workers observed significant attenuation of Aβ-induced toxicity and paralysis, possibly via prolonged activation of metallothionein (MT[29]). It should be noted here that Na salt formation of emodin (emodin-1Na or $C_{15}H_8O_5^{2-}\bullet Na^+$ and emodin-2Na or $C_{15}H_8O_5^{2-}\bullet 2Na^+$) for improvement of its solubility and hence the bioavailability has been shown to preserve its inhibitory actions on Aβ_{1-42} aggregation,[20] indicating the utility of this strategy for enhancing the pharmacokinetic (section 5) and therefore, the therapeutic properties of emodin.

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In addition to its antifibrillogenic effects, emodin may also be involved in inhibition of the amyloidogenic pathway of Aβ species by inhibition of β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE-1; EC: 3.4.23.46). In fact, emodin has been shown to harbor excellent BACE-1 inhibitory activity (IC_{50} = 4.5 μg/mL) in in vitro studies. Kinetic analyses of emodin's inhibition of BACE-1 suggested a strong affinity with an inhibition constant (K_i) of 20 μM. Using molecular docking analyses, the authors further proposed that the methyl groups in emodin take part in hydrophobic interactions with Ala-39, Val-69, Trp-76, Phe-108, and Ile-118 for the emodin-BACE1 complex formation. In addition, the hydroxyl group at C-9 in emodin is involved in hydrogen bonding with the Asp-32 residue of BACE-1, contributing to the high-affinity (with a binding energy of −6.89 kcal/mol) interaction with BACE-1.[21]

Repression of tau oligomerization by emodin has also been proposed in in vitro studies. For example, heparin-induced paired helical filament (PHF) formation of human tau isoforms hTau-23 and 24 was significantly repressed by emodin, as measured by thioflavin S (ThS)- and tryptophan-based fluorescence spectroscopy assays as well as by electron microscopy-based visualization. Moreover, emodin was found to have a potent capacity for disassembly of PHFs, without affecting its physiologically relevant interactions with microtubules. In fact, the robustness of emodin as an antifibrillogenic agent can be comprehended from low its half-maximal inhibitory concentration (IC_{50} = 1−5 μM) and half-maximal degradation concentration (DC_{50} = 2−4 μM) against heparin-induced tau aggregation.[18] It should be however be noted that repressive effects of emodin on tau oligomerization may be significantly lowered when it is induced by arachidonic acid, instead of heparin.[100] Pickhardt et al.[18] also provided evidence for in vivo antifibrillogenic potency of emodin (15 μM) in neuroblastoma N2A cells overexpressing a mutant K18ΔK280 tau with a high susceptibility for aggregation, as assessed by both ThS staining and sarkosyl solubilization followed by immunoblotting-based assessment of the levels of soluble and aggregated tau species.

8.2. Attenuation of Cytotoxicity Induced by Aβ and Tau. Studies have reported various ameliorative effects of emodin against Aβ- and tau-induced neurotoxicity by targeting a plethora of underlying molecular players and mechanisms. For example, Liu and co-workers examined the outcome of emodin treatment in primary rat cortical neurons challenged with Aβ_{25-35} (30 μM for 24 h). They reported signification protection against Aβ_{25-35}-induced neurotoxicity elicited by emodin (20 μM) pretreatment as measured by 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide (MTT) reduction and lactate dehydrogenase (LDH) release assays. The results were confirmed by flow cytometry-based Annexin V-FITC apoptosis assay as well as by nuclear Hoechst33258 staining. Use of pharmacological antagonists indicated the activation of Akt kinase and repression of Jun-*N*-terminal kinase (JNK) as the underlying mechanism of emodin-mediated neuroprotection.[24] Similar emodin (10 μM)-mediated protective effects were observed in PC12 cells upon Aβ_{25-35} (10 μM for 24 h)-induced toxicity,[25] in HT-22 mouse hippocampal neuronal cell-line after their treatment with Aβ_{1-42} (5 μM for 24 h),[26] as well as in human neuroblastoma SH-SY5Y cells exposed to Aβ_{1-42} (1 μM for 48 h).[23] In an interesting study performed in human astrogliomal U251 cells, emodin pre and cotreatment (50 μM) significantly attenuated Aβ_{1-42} (15 μM for 24 h)-induced apoptotic activation, as indicated by MTT reduction, LDH release, Annexin V, propidium iodide, and proapoptic caspases activation assays. In addition, emodin supplementation was associated with attenuation of Aβ-induced alterations in mitochondrial membrane potential (MMP) and generation of reactive oxygen species (ROS), possibly via its beneficial effects on the expression levels of antioxidation mediator, nuclear factor erythroid 2-related factor 2 (Nrf2), and its downstream effectors, heme oxygenase-1 (HO-1), superoxide dismutase 1 (SOD-1), and catalase.[27]

Therapeutic efficiency of emodin in animal models of AD has also been evaluated. Sun and Liu, for example, orally supplemented emodin (at 50 mg/kg body weight daily for 7 days), and observed robust repression of autophagic pathways, as deduced from decreases in the conversion of microtubule-associated protein 1A/1B-light chain 3-I (LC3-I) to LC3-II and beclin-1 levels, as well as from upregulation of the protein levels of B-cell lymphoma 2 (Bcl-2).[25]

8.3. Inhibition of Acetylcholinesterase (AChE). Cholinergic signaling has long been known to be altered in AD pathogenesis, and acetylcholinesterase (AChE; EC 3.1.1.7), an enzyme which degrades the neurotransmitter acetylcholine (ACh), is acknowledged to be one of the key biotargets for anti-AD therapies.[101] Multiple studies have shown that emodin elicits moderate to strong inhibition of AChE. For example, emodin was identified among the top human AChE inhibitor in molecular docking screening of a number of phytochemicals, with an IC_{50} of 21.8 μM and equilibrium dissociation constant (K_D) of −8. The interaction possibly relied on hydrogen binding interactions with amino acids Tyr-133, Tyr-337, and Glu-202; and $\pi-\pi$ interactions with Trp-86.[19] Indeed, the proposed anti-AD therapeutic activity of the dried seeds of the medicinal herb *Cassia obtusifolia*[102] may rely on the presence of emodin as one of the principle chemical constituents, as demonstrated by in vitro studies supporting the latter's ability to robustly inhibit the enzyme activities of AChE (IC_{50} = 9.2 μg/mL). In addition, emodin was found to weakly inhibit the activity of butyrylcholinesterase (BChE; IC_{50} = 157 μg/mL), another enzyme implicated in AD pathology.[21] More recently, Augustin et al.[72] identified emodin as one of the four bioactive components in the ethanolic fraction of the medicinal plant *Rumex abyssinicus* Jacq with moderate in vitro inhibition of AChE activity and a moderate IC_{50} of 15.21 μM. Lastly, Xie and co-workers[103] have also confirmed the strong binding and inhibitory actions of emodin both in its free form and as a component of a memory-enhancing (section 8.6) plant extract.

8.4. Regulation of Neuroinflammation. Neuroinflammation is key pathogenic pathway in AD (section 7.2) and emodin is known to elicit robust anti-inflammatory actions in several pathologies of the nervous system. Although not proven in cellular or animal models of AD, it is likely that emodin mitigates dysregulations in inflammatory signaling by modulating multiple interlinked molecular players and pathways. Signaling through the NLRP3 inflammasome is an important regulatory hub in AD pathology. Emodin elicits strong attenuation of NLRP3 inflammosome activation induced by lipopolysaccharide (LPS; a bacterial endotoxin which is often used for hyperactivation of pro-inflammatory signaling in in vivo and in vitro models) in mice, thereby preventing secretion of pro-inflammatory mediators such as IL-1β.[104] Of note cardiovascular factors are closely implicated in AD pathology and emodin seems to harbor appreciable protective potential against LPS-induced pyroptotic and apoptotic damage to

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ACS Omega 2024, 9, 7296−7309

murine microglial BV-2 and hippocampal HT-22 cells by inhibiting hyperactivation of NLRP3 inflammosome and the consequent reduction in the production of proinflammatory cytokines, IL-18, IL-1β, and TNF-α.[105] Similar findings of emodin-mediated regulation of the NLRP3 inflammasome have been proposed in a cellular model of sepsis brain injury composed of human astrocytic 1321N1 cells treated with LPS. In this study, emodin was found to significantly reduce inflammatory and pyroptotic signaling via its actions on multiple effectors by inhibiting the NLRP3 pathway in a methyltransferase-like 3 (METTL-3)-dependent manner.[106]

Another example of regulatory target of emodin is the nuclear factor kappa B (NF-$\kappa\beta$) signaling, which has been shown to be beneficially regulated by it in LPS-challenged macrophage-like, Abelson leukemia virus-transformed RAW 264.7 cells,[107] and in an rat model of LPS-induced keratitis.[108] Along similar lines, emodin has been shown to have significant therapeutic effects against multiple sclerosis in a mouse model of experimental autoimmune encephalomyelitis (EAE). In silico and biochemical analyses demonstrated that emodin's effects relied on attenuation of NF-$\kappa\beta$ signaling, in addition to the modulation of the activation status of cell survival phosphoinositide 3-kinase (PI3K)/Akt1 pathway, concomitantly with M1 (proinflammatory) to M2 (anti-inflammatory) phenotypic conversion of microglia.[109] Lastly, the anti-inflammatory and antiapoptotic activities of Geijigadaehwang-tang, a traditional Chinese medicine concoction of extracts from various herbs, and containing emodin as one of the major bioactive component have recently been evaluated in trimethyltin (TMT)-induced hippocampal degeneration, which is one of the features of AD pathology. TMT treatment in both BV-2 cells and in in vivo mice was associated with deleterious alterations in redox, inflammatory and apoptotic pathways. Emodin-containing Geijigadaehwang-tang elicited a significant protection against TMT cytotoxicity in both in vitro and in vivo in a multimodal fashion. The ameliorative actions of Geijigadaehwang-tang included reduction in neuroinflammation markers, ionized calcium-binding adapter molecule 1 (IBA1) and glial fibrillary acidic protein (GFAP), possibly via inhibition of the NFκB/iNOS/TNF-α as well as NLRP3/apoptosis-associated speck-like protein (ASC)/caspase-1 signaling. In addition, the authors reported that Geijigadaehwang-tang elicited antioxidant actions by stimulating the Nrf2/HO-1 axis.[110] In another study, emodin-containing ethanolic extract from the traditional medicinal plant, *Polygonum multiflorum* Thunb was found to increase healthy lifespan of *C. elegans*, via its beneficial actions on endogenous antioxidant pathways and mitochondrial membrane potential and ATP generation functions in an insulin/insulin growth factor 1 (IGF-1) pathway- and a PI3K/Akt signaling-dependent manner. Interestingly, the authors also reported the ameliorative actions of this plant extract against chemotaxic deficiency and paralysis in an Aβ-overexpressing transgenic strain of *C. elegans*, concomitantly with significant reduction in the Aβ load (section 8.1).[111]

Another target of anti-inflammatory mediation elicited by emodin is the TLR-3 signaling, which is significantly repressed by it in mice exposed to coxsackie-virus B3m which is associated with several infectious diseases such as encephalitis, meningitis, and respiratory illness.[112] Inhibition of TLR-3 signaling has also been reported as the underlying mechanism for emodin-mediated therapeutic effects in herpes virus encephalitis.[113] Induction of anti-inflammatory signaling mediated by the AMP-activated protein kinase (AMPK)/Nrf2 pathway in response to oxidative stress and astroglial activation has also been proposed as a mechanism of emodin-mediated neuroprotection. Thus, in LPS-challenged microglia, emodin may manifest significant activation of AMPK/Nrf2 pathway, consequently resulting in downregulation of pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, IL-6, NFκB inhibitor of nuclear factor kappa B, alpha (IκBα), and stimulation of endogenous antioxidant signaling cascades involving HO-1 and NAD(P)H quinone dehydrogenase 1 (NQO-1).[114]

In conclusion, it appears that emodin has the capability to reduce astrogliosis and neuroinflammation during the pathogenesis of AD by its ameliorative effects of several interacting biotargets (e.g., AMPK/Nrf2, NLRP3 inflammasome, TLR-3, and NF-$\kappa\beta$); however, direct evidence from appropriate disease models of amyloid and tau pathology are needed to confirm this.

8.5. Countering Metal (Zinc) Dyshomeostasis. It has been known for some time now that deregulation of the levels of metal ions stimulates the pathogeneses of neurodegenerative states, such as AD.[115] Alterations in the levels of zinc (Zn) in particular is closely implicated in AD pathology, via multiple mechanisms such as promotion of amyloidogenesis and Aβ deposition, induction of dysfunction of synaptic signaling and plasticity, and activation of oxidative, neuroinflammatory, and apoptotic signaling (reviewed in[116,117]).

Emodin (20 μM) has been shown to elicit robust ameliorative effects against Zn (200 μM $ZnSO_4$; 1 h)-induced toxicity in SH-SY5Y cells by preventing cell membrane damage and apoptotic induction. Emodin pretreatment essentially reduced the entry of Zn^{2+} ions inside the cells by attenuating Zn-mediated increase in the expression of zinc transporter, zinc transporter-1 (ZnT-1). In addition, emodin abrogated the reductions in the levels of metabolic markers, ATP and NAD+, and the elevations in ROS and ER-stress response elements induced by high Zn. Using immunoblotting analyses, the authors proposed that these therapeutic effects of emodin likely stem from its regulatory actions on AMPK-acetyl-CoA carboxylase (AMPK-ACC) signaling.[118] Induction of the activity of metallothionein (MT), an endogenous metal ion chelator and detoxifier, by emodin in *C. elegans*[29] potentially aids in the latter's protective effects against Zn-induced toxicity.

8.6. Memory- and Cognition-Enhancement. Studies have indicated at the cognition-enhancement properties of emodin as a complex mixture of phytochemicals in form of extracts of traditional medicinal plants. Ning et al.[90] demonstrated the memory-improving therapeutic action of emodin-enriched extracts of Chinese traditional medicinal plants, *Polygonum multiflorum* and *Acorus tatarinowii* in scopolamine-challenged mice. These behavioral effects were associated with attenuation of scopolamine-induced alterations in neurotransmitter levels, and augmentation of synaptic signaling-related proteins, including brain-derived neurotrophic factor (BDNF), cAMP response element binding protein (CREB), and postsynaptic density 95 (PSD-95).[119] In a recent follow-up study, the authors have also implicated stimulation of cholinergic signaling as the mechanistic basis of the ameliorative action of this emodin-enriched plant extract. Thus, they reported recovery of scopolamine-induced alterations in the expression and activity levels of proteins central to

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cholinergic signaling, such as AChE (section 8.3), vesicular acetylcholine transporter (VAChT), and high-affinity choline transporter (CHT-1).[103]

Emodin as a singular therapeutic agent has also been shown to elicit multiple cognitive attributes. For instance, Zeng et al.[24] evaluated the efficiency of emodin (intragastric administration at 80 mg/kg body weight; daily for 2 weeks) against homocysteine-induced behavioral deficits in rats, and found appreciable beneficial effects in the performance of the animals in open field, novel object recognition, and Morris water maze tests. In addition, emodin attenuated Aβ (both Aβ_{1-40} and Aβ_{1-42}) production and tau hyperphosphorylation (at Ser-214, Thr-231, and Ser-396) induced by hyperhomocysteinemia, concomitantly with attenuation of microglial activation and neuroinflammation, microvasculature damage, and redox and DNA methylation impairments; and resulted in significant protection of hippocampal neurons, as assessed by Nissl staining.[28] Following intraperitoneal injection in APP/PS1 mice at doses of 5, 10, and 20 mg/kg body weight for ca. 2 months, emodin elicited significant improvements in fear-motivated associative learning (passive avoidance tasks) and spatial memory (Morris water maze) compared to untreated mice at all doses tested. The authors implicated emodin-induced stimulation of the activity of protein kinase C (PKC), an important memory-related protein, as the basis for its anti-AD effects in APP/PS1 mice,[26] however a direct evidence was not provided. In concurrence with these results, Li et al.[22] have also reported significant reductions in the latency to find the hidden platform in the water maze in APP/PS1 mice, indicating their improvements in spatial memory and learning upon oral supplementation of emodin at a dose of 20 mg/kg body weight, daily for 8 weeks. Moreover, the authors demonstrated significant anxiolytic effects of emodin in these AD mice, as assessed by the open field tests. The anxiolytic and memory-enhancing capabilities of emodin in APP/PS1 mice were associated with repressed depositions of Aβ_{1-42} and phosphorylated (Ser-396) tau species, in conjugation with elevations in the levels of antiapoptotic mediator, Bcl-2 and demotions in Bcl-2-associated X protein (Bax; a apoptosis inducing protein) levels. Further, emodin enhanced Nrf2-HO-1 axis, SOD-1 and catalase activation and consequently lowered the levels of oxidative damage marker, 4-hydroxy-2-nonenal (4-HNE).[27]

Similar amelioration of water maze-associated spatial memory was observed in APP/PS1 mice supplemented with 6.25 mg/kg body weight of emodin via intragastric administration daily for 2 months. In addition, short-term spatial working memory as assessed by Y-maze was also reported to be considerably improved, concomitantly with significant reduction in the cortical and hippocampal plaque load.[23]

9. CONCLUSIONS AND FUTURE DIRECTIONS

Absence of an effective and potent ameliorative cognition-enhancing and disease-modifying and retarding agent/strategy for AD has been lacking. Most therapeutics used currently against AD are symptomatic and function merely to reduce the symptoms, without affecting the underlying molecular mechanisms and players involved in its pathogenesis. Strategies/agents for preventing or retarding the pathogeneses of amyloidogenic and tau pathologies in AD by inhibiting Aβ and tau aggregation and preventing their neurotoxic effects have been the focus of attention as they constitute a much more effective and relevant target of anti-AD therapy.

Phytotherapy or the employment of bioactives present in traditional medicinal plants is currently being evaluated as an inexpensive, safe, biologically relevant, and effective alternative for controlling the progression of multiple CNS disorders, such as AD. One such potentially beneficial phytochemical is emodin which has long been used as an ingredient in traditional herbal medicinal preparations. While its therapeutic potential is known in many human diseases such as diabetes, cancer, and cardiovascular conditions, it is only recently that it has been started to be envisioned as an antifibrillogenic, antineuroinflammatory, and neuroprotective agent. In this systematic review, we have summarized the various studies which have evaluated the therapeutic potential of emodin against AD at the molecular level. Our strict inclusion and exclusion criteria for the systematic selection of meaningful and relevant primary research studies and their subsequent analyses suggest that emodin may elicit multimodal ameliorative effects during AD pathogenesis, targeting multiple interlinked molecular targets and pathways. In particular, emodin elicits significant inhibition of both Aβ and tau aggregation and oligomer formation. In addition, it prevents the neurotoxic effects induced by both these pathogenic species which are central to AD development. The implications of emodin as a memory and cognition enhancing agent are also apparent.

In spite of the positive data from the recent studies, the anti-AD potential of exogenous emodin supplementation is yet to be concretely established. Hence, more research studies are warrantied to confirm and establish emodin as an efficient and relevant neurotherapeutic, particularly against AD. Indeed, the mechanisms underlying emodin-mediated anti-AD effects require thorough investigation using suitable model systems. Additionally, clinical trials must be initiated in order to assess the benefits of emodin supplementation in human cases of AD and mild cognitive impairment (MCI), which is considered an early stage of AD by many. Another issue is the toxicity concerns of emodin. Studies have reported varied, often inconclusive and contrasting results in this regard. Hence, this aspect of emodin therapy also needs careful and exhaustive evaluation.

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