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REVIEW ARTICLE

Effects of Mulberry on The Central Nervous System: A Literature Review

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Abstract: ***Background*:** Mulberry, including several species belonging to genus *Morus,* has been widely used as a traditional medicine for a long time. Extracts and active components of mulberry have many positive neurological and biological effects and can become potential candidates in the search for new drugs for neurological disorders.

***Objectives*:** We aimed to systematically review the medical literature for evidence of mulberry effects on the central nervous system.

***Methods*:** We conducted a systematic search in nine databases. We included all *in vivo* studies investigating the effect of mulberry on the central nervous system with no restrictions.

***Results*:** We finally included 47 articles for quality synthesis. Our findings showed that mulberry and its components possessed an antioxidant effect, showed a reduction in the cerebral infarct volume after stroke. They also improved the cognitive function, learning process, and reduced memory impairment in many animal models. *M. alba* and its extracts ameliorated Parkinson's disease-like behaviors, limited the complications of diabetes mellitus on the central nervous system, possessed anti-convulsant, anti-depressive, and anxiolytic effects.

***Conclusion*:** Mulberry species proved beneficial to many neurological functions in animal models. The active ingredients of each species, especially *M. alba*, should be deeper studied for screening potential candidates for future treatments.

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1. INTRODUCTION

Mulberry is the generic name of species in the genus *Morus* of the Moraceae family. These plants are mostly found in Asia, Europe, America, and Africa. They grow in various conditions of climate, topography, and type of soil [1]. For a long time, mulberry was widely used in Chinese as a medicinal herbal treating several disorders, and several studies determined certainly its health benefits afterward [2, 3]. Some studies recorded the presence of phenolics, flavonoids, anthocyanins, and carotenoids in deeply colored mulberry, which might be responsible for its several potential effects [4-7]. Amongst these, *M. indica* root, *M. lhou* Koidz and flavonoids from these plants could be active compounds causing antioxidant and anti-inflammatory effects, as mice consumed these interventions saw a reduction of oedema and writhing response [8, 9]. Besides, many benefits of mulberry were also reported such as the protection against obesity, diabetic, neurotoxicity and hepatotoxicity [3, 10].

With regards to the neuroprotective effects, polyphenols, anthocyanin, and other phenolic compounds might be attrib-

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uted to the protection against oxidative damage in the brain resulting in the improvement of brain functions, for example, improving the learning ability *via* the protection against neurotoxicity and the increase in neuron cells [11]. Nevertheless, the evidence seemed to be inconclusive with the limit of evidence of possible mechanisms of action *in vivo* models. For instance, the aged-related memory impairment in mice was improved by *M. alba* fruit powder but this fruit did not entirely show their positive effect in alcoholic mice [12, 13]. Other reports revealed that *M. alba* leaves possessed the anxiolytic-like activity in mice assessed by elevated plus maze (EPM) and hole-board test *via* the histaminergic system [14]. Notably, specific compounds that were responsible for these bioactivities have not been presented. This issue led to the arguments about mulberry's efficiency and its application for potential treatments in the future.

Neurodegenerative diseases are a burden on both human health and finance. Since human has had greater longevity than ever, the numbers of patients with Alzheimer diseases (AD) and Parkinson disease (PD) are sharply increasing. Notably, it is estimated that over 100 million AD patients globally in 2050 [15]. Similarly, the total number of PD patients in 2030 could be doubled compared with their number in 2005 [16]. Unfortunately, there is no cure for both diseases. Besides, pharmacotherapy for AD can only focus on relieving the symptoms [17]. Therefore, it is beneficial to neurodegenerative patients, especially the elderly, to use supplementary food, which can help to enhance their brain activity apart from pharmacological treatments. Interestingly, mulberry is becoming a candidate for the treatment of both AD and PD through improving their symptoms and preventing age-related neurodegeneration. For example, some motor deficits related to PD in mice were improved by consuming *M. alba* extract [18]. Additionally, artoindonesianin O, mulberrofuran G (MG), albanol B and kuwanon isolated from *M. alba* were predicted to prevent the amyloid β (Aβ)-peptide plaque *via* the inihibition of phospho-extracellular signal-regulated protein kinases 1 and 2 (p-ERK1/2) or *via* the inhibition of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) *in vitro* models [19, 20].

Although several papers reported the advantages of various species, there is no review of their therapeutic activities on the brain. We conducted a systematic review including papers showing reliable evidence to show a thorough insight into the advantages of mulberry, confirm the effects of the mulberry extract on the brain and nervous system, and suggest the active compounds which can be investigated for further studies of mulberry applications.

2. MATERIALS AND METHODS

2.1. Protocol Registration

We followed the Recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to conduct this systematic review, as shown in the PRISMA checklist (Table **1**). The protocol could be accessed at PROSPERO (CRD42015026620).

2.2. Selection Criteria

Our inclusion criteria were (1) studies showing neurological effects of the mulberry genus *Morus*, (2) only including studies of the genus *Morus,* (3) studies dealing with humans or animals, and (4) no restriction on language, country, gender, age or study design. Exclusion criteria were: (1) unreliably extracted data, (2) overlapped data sets, (3) *in vitro* studies, (4) articles without available full-text and (5) theses, book chapters, editorials, author responses, conference papers, reviews, posters, letters, and patents.

2.3. Search Strategy

We performed our search in nine electronic databases including MEDLINE (PubMed), Scopus, Google Scholar, ISI Web of Science, POPLINE, the System for Information on Grey Literature in Europe (SIGLE), Global Health Library (GHL), Virtual Health Library (VHL), and the New York Academy of Medicine Grey Literature Report (NYAM) for studies published up to September 18, 2017. Details of the search terms for each database are presented in Table **2**. A manual search was also performed by screening the reference of the included studies, the similar studies proposed by PubMed, Google Scholar on the first page, and the references of reviews relevant to our topic.

The search results were then imported into Endnote X7 (Thomson Reuters, USA) software to remove duplications. The references were screened based on the title and abstract with specified criteria by three independent reviewers. The full-texts of the remained papers were downloaded and separately screened for eligibility. We translated the articles in foreign languages into English. Discussions between reviewers and, if necessary, the consultation from the supervisor (NTH) resolved all discrepancies during the screening phases

2.4. Data Extraction

Randomly included studies were used to develop a pilot extraction sheet. Three independent reviewers extracted all data, and the supervisor (NTH) resolved any disagreement related to the data. We extracted articles' essential characteristics (first author, year of publication, study design) along with essential characteristics of patient/animal characteristics (race, gender, age). Also, information including species, plants, compound, solvent for extraction, the dosage of each experiment were concomitantly retrieved. Additionally, tests of measuring the neurological effect of the mulberry species, as well as their outcomes and times of evaluation, were also reported.

2.5. Quality Assessment

Three independent reviewers assessed the quality of each paper based on SYRCLE tools, which were developed to assess methodological quality in animal experiments [21].

We consecutively evaluated ten domains, including sequence generation, baseline characteristics, allocation concealments, random housing, performance bias blinding,

Table 1. PRISMA checklist.

Section/Topic	Checklist Item	Reported on Page #
TITLE		
Title	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT		
Structured summary	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION		
Rationale	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	Provide an explicit statement of questions being addressed concerning participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS		
Protocol and registration	Indicate if a review protocol exists, if and where it can be accessed (*e.g*., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	Specify study characteristics (*e.g*., PICOS, length of follow-up), and report characteristics (*e.g*., years considered, language, publication status) used as criteria for eligibility, giving a rationale.	2
Information sources	Describe all information sources (*e.g*., databases with dates of coverage, contact with study authors to identify additional studies) in the search, and date last searched.	2
Search	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	State the process for selecting studies (*i.e*., screening, eligibility, included in a systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	Describe the method of data extraction from reports (*e.g*., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	List and define all variables for which data were sought (*e.g*., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2
Summary measures	State the principal summary measures (*e.g*., risk ratio, the difference in means).	2
Synthesis of results	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (*e.g*., I^2) for each meta-analysis.	NA
Risk of bias across studies	Specify any assessment of the risk of bias that may affect the cumulative evidence (*e.g*., publication bias, selective reporting within studies).	N/A
Additional analyses	Describe methods of additional analyses (*e.g*., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS		
Study selection	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	For each study, present characteristics for which data were extracted (*e.g*., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	Present data on the risk of bias of each study and, if available, any outcome-level assessment (see item 12).	5
Results of individual studies	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-22

(Table 1) contd….

Section/Topic	Checklist Item	Reported on Page #
RESULTS		
Synthesis of results	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	Present results of any assessment of the risk of bias across studies (see Item 15).	NA
Additional analysis	Give results of additional analyses, if done (*e.g*., sensitivity or subgroup analyses, meta-regression	NA
DISCUSSION		
Summary of evidence	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (*e.g*., healthcare providers, users, and policy makers).	22-23
Limitations	Discuss limitations at study and outcome level (*e.g*., risk of bias), and at review-level (*e.g*., incomplete retrieval of identified research, reporting bias).	23
Conclusions	Provide a general interpretation of the results in the context of other evidence and implications for future research.	24
FUNDING		
Funding	Describe sources of funding for the systematic review and other support (*e.g*., the supply of data); the role of funders for the systematic review.	25

Table 2. Detailed search strategy for nine database searches.

No.	Databases (Total 9)	Search Terms	Results Total = 1187
1	PubMed	(mulberry OR Morus) AND (neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system)	118
2	Scopus	(TITLE-ABS-KEY (mulberry OR Morus) AND TITLE-ABS-KEY (neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system)	203
3	ISI (WOS)	(mulberry OR Morus) AND (neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system)	610
4	WHO GHL	(mulberry OR Morus) AND (neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system)	97
5	VHL	(mulberry OR Morus) AND (neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system)	93
6	POPLINE	(mulberry OR Morus) AND (neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system)	0
7	SIGLE	(mulberry OR Morus) AND (neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system)	1

(Table 2) contd….

No.	Databases (Total 9)	Search Terms	Results Total = 1187
8	Google Scholar	(1) with all of the words: mulberry with at least one of the words: neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system) where words occur: title of the article	44
		(2) with all of the words: Morus with at least one of the words: neurotoxicity OR neurotoxic OR Neuroprotection OR neuroinflammation OR neurodegenerative OR Alzheimer OR Parkinson OR dementia OR Neuroprotective OR neurodegeneration OR Huntington OR memory OR cognitive OR cognition OR learning OR perception OR intelligence OR brain OR CNS OR (central nervous system) where words occur title of the article	21
9	NYAM	(1) Mulberry (2) Morus	0

random outcome assessment, detection bias blinding, incomplete outcome data, selective outcome reporting and other sources of bias. We categorized the judgment of each reviewer on each domain as "low risk," "high risk," or "unclear risk" of bias. Any disagreement was resolved by discussions between reviewers and by consultation from a supervisor (NTH) to reach a consensus.

3. RESULTS

3.1. Search Results

Our search retrieved 1187 studies. We performed title and abstract screening removed duplicates, screened full texts for inclusion according to our inclusion and exclusion criteria. After that, we performed a manual search in the reference of included studies, and we included 47 studies in the qualitative synthesis. We excluded the rest of the studies with reasons in the PRISMA flow diagram (Fig. **1**).

3.2. Baseline Characteristics Of Included Studies

A summary of the included studies is presented in Table **3**. All included studies are *in vivo*, no clinical trial on humans was found. There was a variety of mulberry species used, amongst which *M. alba* was the most popular one (33 studies). Other species such as *M. nigra*, *M. atropurpurea*, *M. laevigata,* and *M. rubra* were reported randomly. Methanol and ethanol extractions were the most regularly used solvents for extraction. The used doses of mulberry used and its active ingredients for neuroprotective effects varied considerably among the included studies from 0.2 mg/kg/day up to 10 g/kg twice a day. The administration was mostly *via* oral, except ten study treated animals *via* intraperitoneal injection (i.p). The treatments of mulberry fruits often saw positive effects including cognitive function improvement, antioxidant, anxiolytic, anti-depressant, and anti-ischemic activities. Multiple tests consisting of infarct volume measurement, cell viability, Morris water maze, Hole-Board Test, Horizontal Wire Test, Open Field Test, Forced swim test, *etc*. were performed to support the statements and findings of each study.

3.3. Quality Assessments

We evaluated almost all included studies (44/47) as a high risk of bias *via* SYRCLE tools evaluation. The three categories of selection bias, performance bias, and detection bias were frequently determined as high risk. In particular, all studies did not report a method to randomly divide animals into groups and pick them for assessing outcomes. Only six studies performed the blinding of caregivers and researchers [22-27]. Two studies stating the observators were blind in assessing the outcomes were considered low bias for blinding of detection bias [22, 26].

Additionally, 43 among 47 studies reporting the results of all experiments are rated with the low bias of selective outcome reporting. Table **4** represents the details of each item evaluation.

3.4. Phytochemical Screening Of Studied Extracts

The methanol extract of *M. alba* leaves contains a wide range of phytochemical groups, including phenolic, flavonoid, tannin, sterol, alkaloid, saponin, anthocyanin, anthraquinone, carbohydrate, protein, and amino acid [22, 23, 28, 29]. From this extract, it could be found the presence of tannins, alkaloids, glycosides, and flavonoids in the ethyl acetate soluble fraction (EASF) [30]. Extracting its leaves with nonpolar solvents such as petroleum ether or chloroform, we could observe the presence of steroids and glycosides [29]. However, the petroleum ether leaves extract had saponins, flavonoids and tannins while chloroform leaves extract showed terpenoids, alkaloids and carbohydrates. The EASF of *M. alba* methanol root extract had fewer phytochemical groups compared to the leaves extract, as only phenolics, flavonoids and alkaloids were reported [31]. For *M. alba* fruit powder, phenolics and anthocyanidins were found [12]. Extracting *M. alba* fruit with ethanol, we could obtain a high amount of anthocyanins, a smaller quantity of flavonoids, and phenolics [32].

M. nigra leaves extract mainly contains phenolics [24, 33]. However, the major compound of hot water extract is syringic acid (80.57%), while the methanol extract only has

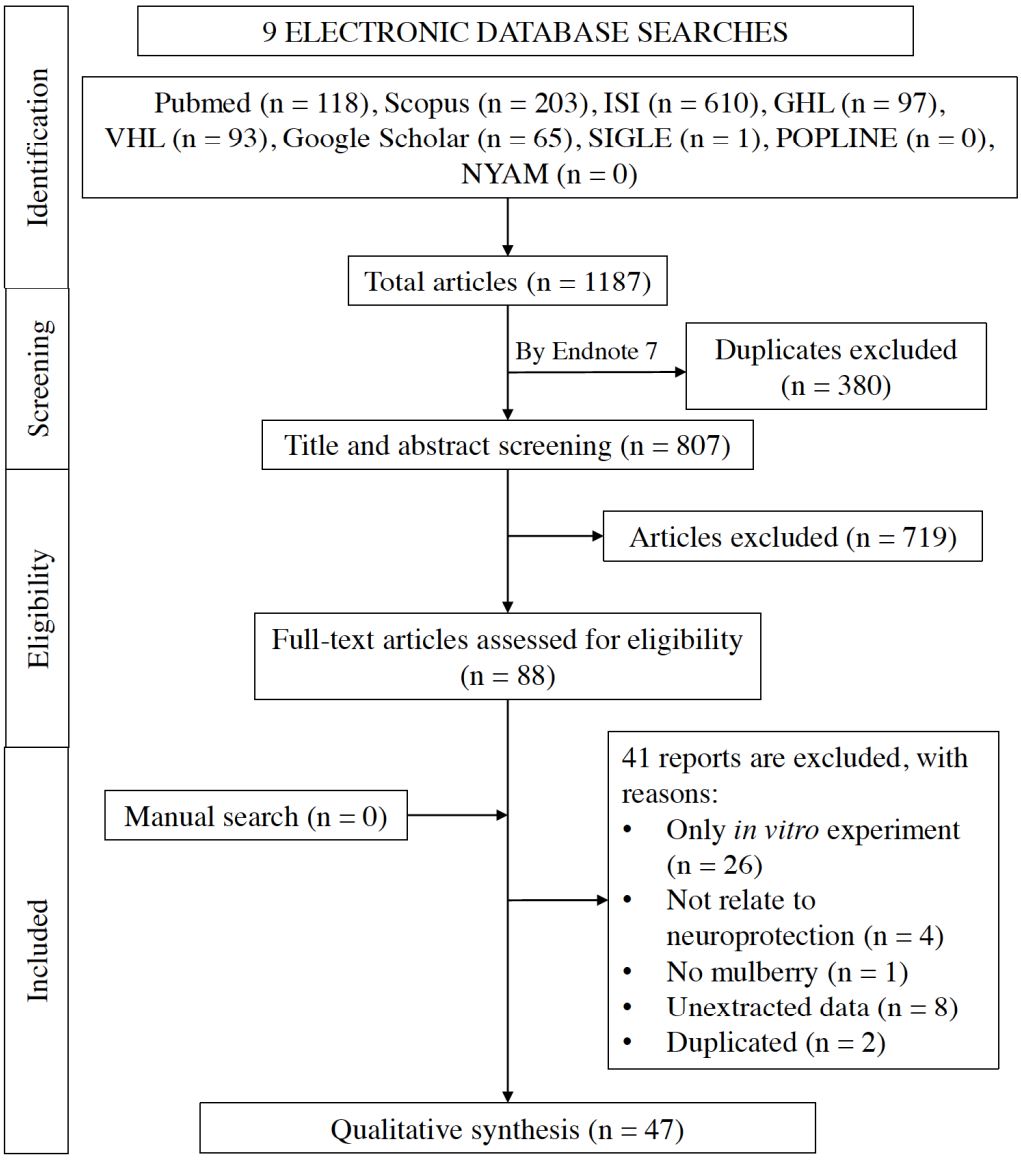

Fig. (1). PRISMA flow diagram of the included studies. ISI: Web of Science, SIGLE: The System for Information on Grey Literature in Europe, GHL: Global Health Library, VHL: Virtual Health Library, NYAM; The New York Academy of Medicine Grey Literature Report. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

a small concentration of this compound. Instead, the methanol leaves extract of *M. nigra* has a significant quantity of vanillic acid and chlorogenic acid [33]. Other phenolic acid are gallic, protocatechuic, p-hydroxybenzoic, caffeic, p-coumaric, ferulic, o-coumaric, rosmarinic, and trans-cinnamic acids.

The constituents of *M. laevigata* leaves were also varied [29]. The methanol extract consists of steroids, terpenoids, saponins, alkaloids, flavonoids, tannins, carbohydrates, proteins and amino acids. In the chloroform extract, there are steroids, terpenoids, alkaloids and carbohydrates while the petroleum ether extract has saponins, flavonoids, tannins, and carbohydrates.

In the wine made from *M. rubra* fruit, they determined the presence of flavonoids and phenolics, in which several polyphenols were determined namely gallic acid, gallocatechin, catechin, caffeic acid, ferulic acid, p-coumaric acid, cinnamic acid, trans-resveratrol, trans-piceid, cis-resveratrol, cis-piceid [34].

Some purified compounds that showed positive effects in this review could be extracted from mulberry as followed. Sanggenon G was extracted from root or root bark of *M. alba* by methanol, then fractionalized the parent extract by ethyl acetate [35, 36]. Its concentration was indicated of 0.446 ± 0.007 mg/g. An anthocyanin, cyanidin-3-O-β-D-glucopyranoside (C3G), could be extracted from *M. alba* fruit by the isolation from 1% HCl-Methanol extract [37]. Oxyresveratrol (a hydroxystilbene) was obtained from *M. alba* wood after several steps [38]. First, the *M. alba* wood was extracted with 96% ethanol, then purified by a mixture of chloroform-methanol *via* a silica vacuum liquid

Table 3. Baseline characteristics of included studies.

Author/Year	Plant/ Compounds	Solvent for Extraction	Dose	Positive Control	Study Design	Effect	Tests
Nade/2010 [22]	*M. alba* leaves	Methanol	100 - 300 mg/kg	N/A	Haloperidol-induced oxidative stress in mice	Antidopaminergic effect Antioxidant effect	Behavioral testing Biochemical analysis
Bauomy/2014 [42]	*M. alba* leaves	70% ethanol	200; 400; 800 mg/kg	N/A	Mice infected with *S. mansoni*	Antioxidant effect Neuroprotection against damage from *S. mansoni*	Biochemical analysis
Rebai/2017 [44]	*M. alba* leaves	70% acetone	100 µg/mL/kg	N/A	Glyphosate-induced toxicity in brain mice	Antioxidant effect	Biochemical analysis
Choi/2000 [47]	*M. alba* leaves	NA	100 and 300mg/kg	N/A	Healthy rats	Anti-oxidant effect	Biochemical analysis
Choi/2000 [46]	*M. alba* leaves	NA	100 - 300 mg/kg	N/A	Healthy rats	Antioxidant effect	Oxygen radical formation
Kang/2006 [49]	*M. alba* leaves	85% Methanol	1, 10, 50 mg/ml	N/A	MCAO mice	Protection against ischemia	Infarct volume measure-ment Cells viability
Tamtaj/2016 [51]	*M. alba* leaves	Alcoholic	100, 200, 400 mg/kg	N/A	Healthy rats	Improve cognitive function	Morris water maze test
Nade/2015 [30]	*M. alba* leaves	methanol	25, 50, 100 mg/kg	Ondansetron	Scopolamine-induced cognitive deficits mice	Improve cognitive function	Elevated plus maze Morris water maze task
Sattayasai/2008 [55]	*M. alba* leaves	NA	100, 200, 500 or 1000 mg/kg	Desipramine, diazepam	Healthy mice	Antidepressant- without an anxiolytic-like effect	The chronic forced swim-ming test The elevated plus-maze The climbing test The coordination test The rota-rod test Sieve test.
Yadav/2008 [28]	*M. alba* leaves	Methanol	50, 100, 200 mg/kg	Diazepam	Healthy mice	Anxiolytic effect	Hole-Board Test Elevated plus maze test Open Field Test
Lee/2013 [14]	*M. alba* leaves	85% Methanol	200 or 400 mg/kg	Diazepam	Healthy mice	Anxiolytic effect	Elevated plus maze test Hole-Board Test Horizontal Wire Test Open Field Test,
Yadav/2008 [23]	*M. alba* leaves	Methanol	50, 100, 200 mg/kg	N/A	Catalepsy model	Anti-dopaminergic effect	Footshock-induced aggression Sleeping time
Kim/2003 [52]	*M. alba* leaves	NA	10 mg/kg and 100 mg/kg	N/A	Healthy mice	Recovery from the central nervous system complica-tions of diabetes mellitus.	New cell formation
Nade/2010 [41]	*M. alba* root	Methanol	25, 50 and 100mg/kg	Diazepam	Mice suffered chronic restraint stress	Anti-stress Antioxidant effect	Passive shock avoidance test Elevated plus maze Open field test Biochemical analysis

(Table 3) contd….

Author/Year	Plant/ Compounds	Solvent for Extraction	Dose	Positive Control	Study Design	Effect	Tests
Nade/2009 [31]	*M. alba* root	Methanol	25, 50, 100 mg/kg	Diazepam	Healthy mice	Adaptogenic activity Anti-stress activity Antioxidant	Elevated plus maze Biochemical analysis
Lee/2013 [56]	*M. alba* root	NA	50, 100, and 200 mg/kg	RU486 (mifepristone)	Healthy mice	Antidepressant-like effects	Forced swim test Tail suspension test
Lim/2014 [26]	*M. alba* root bark	NA	30 and 100 mg/kg	RU486 (mifepristone)	Healthy mice	Antidepressant-like effects	Forced swim test
Ye/2017 [57]	*M. alba* root bark	NA	10 g/kg	N/A	Diabetes mice	Antidepressant-like effects	Forced swim test Open-field test Locomotor activity assessment
Wattanathorn/2012 [12]	*M. alba* fruit	NA	2, 10, 50 mg/kg	Donepezil	Cholinotoxin-induced cognitive decline in mice	Improve cognitive function Neuroprotection	Morris water maze
Kaewkaen/2012 [25]	*M. alba* fruit	Ethyl alcohol	2, 10, 50 mg/kg	Vitamin C, Donepezil	MCAO mice	Improve cognitive function Neuroprotection	Morris water maze
Kaewkaen/2012 [50]	*M. alba* fruits	NA	2, 10, 50 mg/kg	Vitamin C	MCAO mice	Improve cognitive function Neuroprotection	Morris water maze Hot plate test
Wattanathorn/2012 [13]	*M. alba* fruit	NA	2, 10, 50 mg/kg	Vitamin C, Donepezil	Alcoholic mice	Improve cognitive function Neuroprotection	Morris water maze
Kaewkaen/2012 [32]	*M. alba* fruit	Ethyl alcohol	2, 10, 50 mg/kg	Donepezil	MCAO mice	Improve cognitive function Neuroprotection	Morris water maze
Kim/2013 [52]	*M. alba* fruit	Ethanol	20, 100, 500 mg/kg	Donepezil	Healthy mice	Improve cognitive function	Object recognition test Step-through passive avoidance test
Kim/2015 [53]	*M. alba fruit*	Ethanol	0.1, 1, 10, 100 microgram/ml	N/A	Alzheimer disease-like models	Improve cognitive function	Novel object recognition test Y maze test
Gu/2017 [18]	*M. alba* fruit	70% ethanol	250 mg/kg	N/A	Parkinson disease model	Protection against PD-like symptoms	Olfactory test Pole test Open filed test
Kim/2010 [61]	*M. alba* fruit	70% ethanol	500 mg/kg	N/A	Parkinson disease model	Protection against PD-like symptoms	Behavioral test
Hwang/2004 [63]	*M. alba* fruit	Not reported	Not reported	N/A	Healthy mice	MAO activity modulation	Biochemical analysis
Khan/2015 [59]	*M. alba* stem bark	Methanol	100, 200, 250, 500 mg/kg	Diazepam	Healthy mice	Sedative effect	Open field test Hole cross test
Kim/2015 [54]	*M. alba* leaves and fruit mixture	Ethanol	0.2, 0.5, 1 g/kg/day	N/A	Obese mice	Improve cognitive function	Novel object recognition test
Turgut/2015 [33]	*M. nigra* leaves	Methanol	50, 100 mg/kg	N/A	D-galactose-induced aging mice	Improve cognitive function	Morris water maze
Dalmagro/2017 [24]	*M. nigra* leaves	Hot water	3–100 mg/kg	Fluoxetine	Healthy mice	Antidepressant-like effects	Forced swim test Tail suspension test Biochemical analysis
	Syringic acid		0.1 – 10 mg/kg				

(Table 3) contd….

Author/Year	Plant/ Compounds	Solvent for Extraction	Dose	Positive Control	Study Design	Effect	Tests
Shih/2010 [43]	*M. atropurpurea* fruit	Methanol	NA	N/A	Aging mice	Improve cognitive function Antioxidant effect	Avoidance response tests. Oxidant status assays
Srikanta/2016 [34]	*M. rubra* fruit	NA	20 mg/kg	Resveratrol	Streptozotocin-induced diabetic rats	Antioxidant effect	Physicochemical analysis Antioxidant Status
Tubaş/2017 [60]	*M. rubra* fruit	Not reported	5, 10 mg/kg	N/A	Penicillin-induced epileptiform mice	Anti-epileptic activity	Electrocorticogram records
Barman/1980 [9]	*M. indica* leaves	Methanol	200 mg/kg	N/A	Healthy mice	Sedative effect	Spontaneous activity Anti-convulsant effect
Samuel/2016 [48]	Mulberry variety AR-14 leaves	NA	100 mg/kg p.o.	Resveratrol	MCAO mice	Protection against focal cerebral ischemia	Neurobehavioral test Histological studies
Samuel/2016 [40]	Nine varieties of *M. alba* and *M. indica*	Water	100 mg/kg	N/A	Rotenone- induced oxidative stress	Antioxidant effect	Biochemical analysis
El-baz/2016 [45]	*M. alba* fruit *M. rubra* fruit	Ethanol	300 mg /Kg	Donepezil	Alzheimer induced rats	Neuroprotection against Alzheimer disease	8-OHdG/2-dG ratio DHCR24 and FKBP1B genes ROS level Apoptotic related enzymes
Aditya Rao/2012 [29]	*M. alba* leaves *M. laevigata* leaves	Petroleum, ether, chloroform, methanol	200 and 400 mg/kg	N/A	Healthy mice	Sedative effect	Locomotor activity
Hong/2017 [39]	Mulberrofuran G the root bark of *M. bombycis*	NA	0.2, 1, and 5 mg/kg	N/A	MCAO mice	Protection against ischemia	Infarct volume measurement
Kang/2006 [37]	Cyanidin-3-O-beta-D-glucopyranoside from *M. alba*	1% HCl–MeOH	10, 20, 30 μg/ml	N/A	MCAO mice	Protection against ischemia	Infarct volume measurement Cells viability
Andrabi/2004 [38]	Oxyresveratrol from mulberry wood	NA	2, 10, 20 and 30 mg/kg	N/A	MCAO mice	Protection against ischemia	Infarct volume measurement Histological analysis
Lim/2016 [35]	Sanggenon G isolated from the root bark of *M. alba*	Ethyl acetate	5, 10 and 20 mg/kg	Yohimbine	Healthy mice	Antidepressant-like effects	Forced swim test Open-field test
Lim/2015 [36]	Sanggenon G isolated from the root bark of *M. alba*	Ethyl acetate	30 mg/kg	Imipramine	Healthy mice	Antidepressant-like effects	Forced swim test
Gupta/2014 [58]	Morusin from *M. alba* stem bark	NA	5, 10 mg/kg	Diazepam	Healthy mice	Sedative effect Anticonvulsant activity	Convulsion model Locomotor activity
Ma/2014 [27]	Mulberry flavonoid from *M. alba* leaves	NA	0.3 g/kg	Methycobal	Alloxan-induced diabetic rats	Recovery of peripheral nerve injury in diabetic rats	Histopathological examination

MCAO: Middle Cerebral Artery Occlusion, N/A: Not applied.

Table 4. Quality assessment of included studies by using SYRCLE tool.

Author/ Year	Selection Bias			Performance Bias		Detection Bias		Attrition Bias		Other	Overall Assessment
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	
Nade/2010 [22]	+	+	+	+	-	+	-	-	-	-	High risk
Samuel/2016 [40]	+	+	+	+	+	+	+	-	-	?	High risk
Nade/2010 [41]	+	+	+	+	+	+	+	-	-	-	High risk
Turgut/2015 [33]	+	-	+	+	+	+	+	+	?	?	High risk
Bauomy/2014 [42]	+	+	+	+	+	+	+	-	-	?	High risk
Shih/2010 [43]	+	-	+	+	?	+	+	?	-	-	High risk
Rebai/2017 [44]	+	-	+	-	+	+	+	-	-	?	High risk
El-baz/2016 [45]	+	+	+	+	+	+	+	-	-	?	High risk
Wattanathorn/2012 [12]	+	+	+	+	?	+	+	?	?	?	High risk
Kaewkaen/2012 [25]	+	+	+	+	-	+	+	-	-	-	High risk
Choi/2000 [47]	+	+	+	+	+	+	+	-	-	-	High risk
Choi/2000 [46]	+	+	+	+	+	+	+	-	-	-	High risk
Srikanta/2016 [34]	+	-	+	+	+	+	+	+	-	?	High risk
Dalmagro/2017 [24]	+	-	+	+	-	+	+	+	+	-	High risk
Hong/2017 [39]	+	-	+	+	+	+	+	-	-	?	High risk
Samuel/2016 [48]	+	-	+	+	+	+	+	-	-	?	High risk
Kang/2006 [49]	+	+	?	+	?	+	+	+	-	?	High risk
Kang/2006 [37]	+	+	+	+	+	+	+	+	-	?	High risk
Andrabi/2004 [38]	+	-	?	+	?	+	+	+	-	?	High risk
Kaewkaen/2012 [50]	+	+	+	+	+	+	+	?	-	?	High risk
Wattanathorn/2012 [13]	+	+	+	+	+	+	+	-	-	-	High risk
Kaewkaen/2012 [32]	+	-	+	+	?	+	+	?	-	-	High risk
Tamtaj/2016 [51]	+	-	+	?	+	-	+	+	-	-	High risk
Nade/2015 [30]	+	+	+	+	+	+	+	-	-	-	High risk
Nade/2009 [31]	+	+	+	+	+	+	+	-	-	-	High risk
Kim/2013 [52]	+	+	+	+	?	+	+	?	-	-	High risk
Kim/2015 [53]	+	+	+	+	?	+	+	-	-	-	High risk
Kim/2015 [54]	+	+	+	+	?	+	+	-	-	-	High risk
Sattayasai/2008 [55]	+	+	+	+	+	+	+	?	-	?	High risk
Lim/2016 [35]	+	+	+	+	+	+	+	+	?	-	High risk
Lee/2013 [56]	+	+	+	+	?	+	+	?	-	-	High risk
Lim/2014 [26]	+	+	-	?	-	+	-	-	-	-	Low risk

(Table 4) contd….

Author/ Year	Selection Bias			Performance Bias		Detection Bias		Attrition Bias		Other	Overall Assessment
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	
Lim/2015 [36]	+	-	+	+	+	+	+	-	-	+	High risk
Ye/2017 [57]	+	-	+	+	+	+	+	?	-	-	High risk
Yadav/2008 [28]	+	+	+	+	+	+	+	-	-	-	High risk
Lee/2013 [14]	+	+	+	+	+	+	+	+	-	-	High risk
Gupta/2014 [58]	+	+	+	+	+	+	+	-	-	?	High risk
Aditya Rao/2012 [29]	+	-	+	+	+	+	+	-	-	-	High risk
Khan/2015 [59]	+	+	+	+	+	+	+	-	-	?	High risk
Barman/1980 [9]	+	+	+	+	+	+	+	?	-	?	High risk
Tubaş/2017 [60]	+	-	+	?	+	+	+	+	-	-	High risk
Yadav/2008 [23]	+	+	+	+	-	+	+	-	-	-	High risk
Gu/2017 [18]	+	-	+	+	+	+	+	?	-	-	High risk
Kim/2010 [61]	+	+	+	+	+	+	+	?	-	-	High risk
Kim/2003 [52]	+	+	+	+	+	+	+	?	-	?	High risk
Ma/2014 [27]	+	-	?	+	-	+	+	-	-	-	Low risk
Hwang/2004 [63]	+	+	+	+	+	+	+	?	-	?	High risk

+: high risk. -: low risk. ?: unclear.

chromatography column, and finally the residual resin was extracted with chloroform (yield = 0.34% of the wood weight). Finally, MG (a prenylated flavonoid) was isolated from the methanol extract of dried root bark of *M. bombycis* [39]. The purified process involved in varied solvents including n-hexane, chloroform, and ethyl acetate, then fractionalized by methanol *via* a chromatography column. Detail of constituents of the extracts in this review is presented in Table **5**.

3.5. The Anti-Oxidant Effect In The Brain

Different extracts from all parts of types of mulberry (*M. alba*, *M. nigra*, *M. rubra* and *M. atropurpurea*) showed their antioxidant effect on a wide range of animal models (Table **6**).

Our study showed that mulberry reversed the disorder of redox system in brain caused by rotenone [40], chronic stress [41], haloperidol [22], D-galactose [33], *Schistosoma mansoni* infection [42], aging [43], glyphosate [44], Alzheimer [45], and cholinotoxins [12]. These triggers led to the decrease in levels of antioxidant enzymes in the body including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GST), glutathione reductase (GRd), and the contents of reduced glutathione (GSH). Also, they increased lactate dehydrogenase (LDH) activity, nitrite (NO), and malonyldialdehyde (MDA) levels, which are formed by the oxidation. There was an exception that SOD, CAT, and peroxidase activities increased in order to respond to stress [41], and the neurotoxicity caused by glyphosate [44]. However, all those changes were almost normalized by the acute or subchronic consumption of mulberry except the case of GRd activity reported by Shih *et al.* [43]. This study indicated that methanol extract of *M. alba* fruit insignificantly increased that enzyme even at a high dose (500 mg/kg/day after 12 weeks of treatment). Besides, 10 days of treatment at all doses of *M. alba* leaves extract improved total antioxidant capacity (TAC) in mice after 46 days infected with *S. mansoni* [42].

In the model of vascular dementia, mice were pretreated with the ethanol extract of *M. alba* fruit at 10 and 50 mg/kg 7 days before and 21 after occlusion of the right middle cerebral artery (MCAO). The results showed the enhanced activities of SOD, CAT, and GPx, although this elevation of CAT activity was not remarkable [32]. Interestingly, the antioxidant effect of mulberry was also observed in normal mice. Choi *et al.* [46, 47] demonstrated that treating 100 and 300 mg/kg/day after 6 weeks of methanol extract of *M. alba* leaves could reduce hydroxyl radical, superoxide radical, lipid peroxide, basal and induced oxygen levels in both mitochondrial and microsome in the brain. Moreover, the results from this group of authors clarified that *M. alba* leaves extract rose the activities of both Mn-SOD in brain mitochondrial and Cu/Zn-SOD in brain cytosol [46].

Table 5. Phytochemical analysis in studied extracts.

Refs.	Species	Part Used	Solvent	Phytochemical Analysis												
				Phe	Fla	Ster	Tan	Alk	Sap	Antho	Anthra	CH	Proteins	Amino Acids	Terp	Gly
[22, 23, 28, 29]	*M. alba*	Leaves	Methanol	+	+	+	+	+	+	+	+	+	+	+		
[30]	*M. alba*	Leaves	Methanol/ EASF		+		+	+								+
[29]	*M. alba*	Leaves	Petroleum ether		+	+	+		+							+
[29]	*M. alba*	Leaves	Chloroform			+		+				+			+	+
[31]	*M. alba*	Root	Methanol/ EASF	+	+			+								
[12]	*M. alba*	Fruit	N/A	+						+						
[32]	*M. alba*	Fruit	Ethanol	+	+					+						
[24, 33]	*M. nigra*	Leaves	Hot water	+												
[24, 33]	*M. nigra*	Leaves	Methanol	+												
[29]	*M. laevigata*	Leaves	Methanol		+	+	+	+	+			+	+	+	+	
[29]	*M. laevigata*	Leaves	Chloroform			+		+				+			+	
[29]	*M. laevigata*	Leaves	Petroleum ether		+		+		+			+				
[34]	*M. rubra*	Fruit	N/A	+	+											

Alk: alkaloids, Antho: anthocyanins, Anthra: anthraquinones, EASF: ethyl acetate soluble fraction, Fla: flavonoids, Gly: glycosides, N/A: Not applied, Phe: phenolics, Sap: saponins, Ster: steroids, Tan: tannins, Terp: terpenoids.

There were only two studies that did not show the positive antioxidant effect of mulberry in the brain. Srikanta *et al.* [34] observed that 6 weeks of the treatment of wine made from *M. rubra* fruit did not improve the total antioxidant capacity after the oxidation caused by streptozotocin in diabetic mice. Similarly, Dalmagro *et al.* [24] also reported that almost all dose of the aqueous extract of *M. nigra* did not dramatically influence the contents of oxidant markers in the brain, like protein carbonyl (PC), non-protein thiol groups (NPSH), thiobarbituric acid reactive substances (TBARS), and NO level compared to normal mice. The subacute treatment of its primary compound - syringic acid (SA) acted as a pro-oxidant compound illustrated by the downgrade of NO level in the brain.

3.6. Protection Against Ischemia

M. alba leaves and the riched gamma-aminobutyric acid (GABA) leaves, *M. alba* fruit extract (MLE) are positive candidates to screen for the prevention of ischemic injury.

Regarding the neuroprotective effect of mulberry against ischemia, Samuel *et al.* [48] compared the strength between MLE-AR-14, a freeze-dried solid leaf extracted from the mulberry variety AR-14, and resveratrol. Using doses of 50 and 100 mg/kg of MLE- AR-14 orally one hour before middle cerebral artery occlusion/reperfusion (MCAO/R) induced a similar reduction of infarct size in mice compared to 50 and 100 mg of resveratrol (34%, 65% vs. 55%, 76%, respectively). This study also pointed out a notable active effect of those two interventions, even on a post-ischemic injury. Namely, after 6 hours of ischemic injury, treatment with MLE-AR-14 (50 mg and 100 mg) provided a neuroprotective effect of about 28% and 54%, respectively; whereas the percentage of ischemic brain reduction was a bit higher, by 53% and 68% for doses of 50 mg and 100 mg by resveratrol, respectively. The effect against neural cell death induced by cerebral ischemia was hypothesized to be involved in the free radical scavenging activity. The authors observed the attenuation of MDA level (an oxidative stress marker) and the upregulation of glutathione levels (an endogenous antioxidant) in the blood in the presence of MLE-AR-14 or resveratrol, although resveratrol showed significantly more effective.

However, Kang *et al*. reported that oral treatment of methanol *M. alba* leaves extract (200 mg/kg) 30 minutes after the MCAO did not reduce the infarct volume of the mice brain. The neuroprotective effect against MCAO- induced mice was only enhanced when conducting the accumulation of GABA in *M. alba* leaves (GAML). GAML shortened the cerebral injury size by 31% using a dose of 200 mg/kg orally compared with the control group [49].

Table 6. Antioxidant effect of *Morus* on brain.

Refs.	Species	Part Used	Solvent	Dose* (Administration)	Positive Control	Animal Model	Model	Test Duration	Main Results
Nade *et al.* [22]	*M. alba*	Leaves	Methanol	100-300 mg/kg/day (p.o)	N/A	Male Wistar strain rats, 170–220g	Haloperidol-induced oxidative stress	21 days	↑ CAT and SOD levels ↓ LPO and NO levels
Choi *et al.* [47]	*M. alba*	Leaves	Methanol	100-300 mg/kg/day (p.o)	N/A	Male Sprague Dawley, 160±10g	Healthy rats	6 weeks	↓ BORs levels by 25.1%, IORs levels by 16.5%, LPO levels by 18.1% and OP levels by 14.2%.
Choi *et al.* [46]	*M. alba*	Leaves	Methanol	100-300 mg/kg/day (p.o)	N/A	Male Sprague Dawley, 260±20g	Healthy rats	6 weeks	↓ Hydroxyl radical by 21.1%, superoxide radical by 12%, LPO by 12.26%, and OP levels by 13.77%. ↑ Mn-SOD activity by 18.6%, Cu/Zn-SOD activity by 17.7%, and GPx activity by 23.9%.
Bauomy *et al.* [42]	*M. alba*	Leaves	Methanol	200, 400, 800 mg/kg/day (p.o)	N/A	9-11 weeks male Swiss albino mice	Mice infected with *Schistosoma mansoni*	10 days	↑GSH and CAT levels in normal and infected mice in a dose-dependent manner. ↑ TAC in infected mice.
Rebai *et al.* [44]	*M. alba*	leaves	Cold acetone	100 µg/kg/day (i.p)	N/A	Female Wistar rats, 180–240g	Glyphosate-induced toxicity in brain mice	15 days	↓ LDH activity, PC and MDA levels ↑ SOD activity
Nade *et al.*. [41]	*M. alba*	root	methanol	25, 50 and 100mg/kg/day (p.o)	Diazepam	Male Wistar rats, 150–180g	Chronic restraint stress	10 days	↑ CAT, GSH, SOD level ↓ LPO level
Kaewkaen *et al.* [32]	*M. alba*	fruits	Ethanol	2, 10 and 50 mg/kg/day (p.o)	Donepezil	8 weeks male Wistar rats, 300–350g	Vascular dementia	28 days	↓MDA level and ↑ SOD and GSH-Px activity. ↑ CAT insignificantly
Wattanathorn *et al.* [12]	*M. alba*	fruits	N/A	2, 10 and 50 mg/kg/day (p.o)	Donepezil	Male Wistar rats, 180-200g	Cholinotoxin-induced cognitive decline in mice	2 weeks	↓MDA level
Turgut *et al.* [33]	*M. nigra*	leaves	methanol	50,100 mg/kg/day (p.o)	N/A	8 weeks male BALB/c mice	D-galactose-induced aging mice	5 days	↓ MDA levels, and ↑SOD, GPx and CAT activities
Dalmagro *et al.* [24]	*M. nigra*	leaves	Water	3, 10, 30, 100 mg/kg/day (p.o)	Fluoxetine	Male Swiss mice, 30-40g	Healthy mice	Acute: 1 day Chronic: 7 days	Acute and chronic treatment did not change the levels of TBARS, NPHS levels. ↓ PC level only at 30 mg/kg. ↓ NO level in the brain at 30 and 100 mg/kg with subchronic treatment.
	Syringic acid from *M. nigra*	N/A	N/A	0.1, 1, 10, 100 mg/kg/day (p.o)					↑ TBARS in the brain ↓ PC and NO levels in the brain
El-baz *et al.* [45]	*M. alba* *M. rubra*	Fruit	Ethanol	300 mg/kg/day (p.o)	Donepezil	Male Albino rats, 180-200 g	Alzheimer induced rats	6 weeks	↑109.54 – 118.09% of LPO levels and 55.17 – 54.6% of GSH levels compared with AD-induced mice

(Table 6) contd….

Refs.	Species	Part Used	Solvent	Dose* (Administration)	Positive Control	Animal Model	Model	Test Duration	Main Results
Srikanta *et al.* [34]	Wine made from *M. rubra*	fruit	N/A	20 mg/kg/day (p.o)	Resveratrol	8 weeks male Wistar rats, 200g	Streptozotocin-induced diabetic rats	6 weeks	No insignificant change of antioxidant capacity in the brain of diabetic rats
Shih *et al.* [43]	*M. atropurpurea*	fruit	Methanol	100; 500 mg/kg/day (p.o)	N/A	6 months male SAMR1 and SAMP8 mice	Senescence-accelerated mice	12 weeks	↑ GST and CAT levels at 100 mg/kg, and further GPx level at 500 mg/kg No significant improvement of GRd was observed
Samuel *et al.* [40]	Nine varieties of *M. alba* and *M. indica*	leaves	Water	100 mg/kg/day (p.o)	N/A	Male Sprague Dawley rats, 200±10g	Rotenone-induced oxidative stress	1 hours (pre-treatment)	↓ MDA levels by 50.49% and 41.36% when treating with S-146 and BR-2 extract, respectively ↓ SOD level by 54.01 % and 40.18% when treating with S-146 and AR-14 extract

BOR: basal oxygen radical, CAT: catalase, GPx: glutathione peroxidase, GRd: glutathione reductase, GSH: glutathione, GST: glutathione S-transferase, IOR: Induced oxygen radical, i.p.: intraperitoneal injection, LDH: lactate dehydrogenase, LPO: lipid peroxide, MDA: malonyldialdehyde, N/A: not applied, NPHS: non-protein sulfhydryls, NO: Nitrite, PC: Protein carbonyl, p.o: per oral, TAC: total antioxidant capacity, TBARS: thiobarbituric acid reactive substance. *weight of extract per body weight of the animal.

This result was quite similar to the effect of positive control (5 mg/kg intravenously injected edaravone). The mulberry fruit extracted with 1% HCl-MeOH also reduced the ischemic brain volume by 26% [37].

Additionally, purified compounds extracted from *M. alba* fruit (C3G), *M. alba* fruit (oxyresveratrol), and *M. bombycis* root bark (MG) showed neuroprotective effects against cerebral ischemia [37]. Treatment of C3G 30 minutes after MCAO (10 mg/kg per orally), successfully reduced the ischemic brain volume by 18%. Similarly, intraperitoneally injecting 10 and 20 mg/kg of oxyresveratrol (twice: before and after MCAO) decreased the injured brain volume at days 3 after stroke by 54% and 63%, respectively [38]. The intraperitoneal administration of MG (0.2, 1, and 5 mg/kg) 30 minutes before MCAO/R showed a similar effective impact on the reduction of injured brain zone in mice compared to carnosine (25, 50, and 75 mg/kg, i.p.) [39]. The injured brain zone was 39.0 ± 6.4%, 26.0 ± 7.4%, and 19.0 ± 4.3% by the dose of 0.2, 1, and 5 mg/kg, respectively, in MG group; and the cerebral infarct size was 50.6 ± 6.2%, 40.0 ± 6.5%, and 19.6 ± 4.2% at dose 25, 50, and 75 mg/kg, respectively, in carnosine group.

Regarding their probable mechanism, these compounds protected the brain cells after MCAO *via* varied pathways. C3G and MLE prevented the polymorphonuclear leukocytes from infiltrating into cerebral focal ischemic tissue after stroke, which might be helpful for cell survival [37]. Meanwhile, oxyresveratrol prevented the cell death *via* the inactivation of apoptotic markers including cytosolic cytochrome c release and caspase-3 [38], and MG potentially inhibited the reactive oxygen species (ROS) generation *via* the decrease in nicotinamide adenine dinucleotide phosphate oxidase (NOX) enzyme activation and NOX4 protein expression [39].

3.7. Effect On Cognitive Functions

Fourteen articles reported the therapeutic activities of mulberry on cognitive impairment using various models, including the Morris water maze test, object recognition test, passive or active avoidance test, and elevated plus-maze model. Various forms of mulberry such as ethanol extracts of *M. alba* leaves and fruit, methanol extract of *M. alba* leaves, *M. nigra* leaves and *M. atropurpurea* fruit, *M. alba* fruit powders and a mixture of *M. alba* leaves and fruit (2:1) showed their effect on memory improvement at a wide range of dosages (Table **7**).

M. alba fruit powder and *M. alba* ethanol fruit extract at 2, 10 mg/kg enhanced the learning and memory process in models of MCAO, alcohol intoxication-induced memory impairment, or age-related cognitive impairment induced by cholinotoxin [12, 13, 25, 32, 50]. Almost all results showed that mice using mulberry spent less time to reach the hidden platform, and spent more time in the target quadrant (retention time) in Moris Maze Test. Only alcoholic rats consuming mulberry powder, and MCAO mice consuming mulberry ethanol extract had no change of retention time. The healthy mice also enhanced their retention memory when consuming these forms of mulberry [25, 50].

Several leaves' extracts from *M. alba* and *M. nigra* proved their efficacy on improving retention memory *via* Moris Maze Test. This was reflected by the reduction of time to find the target quadrant and of time for escape latency as well as by the increase in retention time and times that mice came across the platform location [30, 33, 51].

These improvements were in a dose-dependent manner and differed according to the mulberry form. For instance, in stroke condition, mulberry fruit powder at the high dose of 50 mg/kg exhibited no positive effects on retention time,

Table 7. The activities of mulberry on learning and memory.

Refs.	Species	Part Used	Solvent	Dose* (Administration)	Positive Control	Animal Model	Model of Study (Duration)	Main Results	Conclusion
Wattanathorn *et al.* [12]	*M. alba*	Fruit	N/A	2,10, 50 mg/kg/day (p.o) x 2 weeks	Donepezil	Male Wistar rats, 180-200g	MMT (4 days)	↓ Escape latency time at all doses ↑ Retention time at 2, 50 mg/kg	Enhancing memory in ageing mice.
Wattanathorn *et al.* [13]	*M. alba*	Fruits	N/A	2,10, 50 mg/kg/day (p.o) x 2 weeks	Vitamin C Donepezil	8 weeks male Wistar rats, 180-220g	MMT (14 days)	↓ Escape latency at all doses in single-dose administration and on days 7, 14 No significant change of retention time	Enhance spatial memory in alcoholic mice.
Kaewkaen *et al.* [50]	*M. alba*	Fruit	N/A	2, 10, 50 mg/kg/day (p.o) x 2 weeks	Vitamin C	8 weeks Male Wistar rats, 300-350g	MMT (14 days)	↓ Escape latency time at 2, 10 mg/kg in a healthy condition in a single dose and after 7 days. No changes in retention time. ↑Retention time at 2, 10 mg/kg in stroke condition 14 days after stroke. No changes in escape latency.	Protect against memory impairment in MCAO mice and improve neuron density in the hippocampus.
Kaewkaen *et al.* [25]	*M. alba*	Fruits	Ethanol	2,10 and 50 mg/kg/day (p.o) x 28 days	Vitamin C Donepezil	8 weeks male Wistar rats, 300-350g	MMT (21 days)	↓ Escape latency time at 50 mg/ kg in single-dose administration in healthy/stroke condition 7 days after stroke ↑ Retention time at 2, 10 mg/kg on a single dose in healthy condition ↑ Retention time at 2, 10, 50 mg/kg stroke condition after days 7 and 14. No change observed in 21 days.	Enhance cognitive functions in the MCAO rats.
Kaewkaen *et al.* [32]	*M. alba*	Fruit	Ethanol	2, 10, 50 mg/kg/day (p.o) x 28 days	Donepezil	8 weeks male Wistar rats, 300-350g	MMT (21 days)	↓ Escape latency time at 5 and 10 mg/kg after 21 days. No change in retention time	Enhance memory of MCAO mice
Kim *et al.* [52]	*M. alba*	Fruit	Ethanol	20, 100 and 500 mg/kg/day (p.o) x 7 days	N/A	6 weeks male ICR mice, 25–28 g	PAT	↑ Retention time at 100 and 500 mg/kg	Enhance memory *via* up-regulating nerve growth factor.
							ORT	↑ Recognition time at 100 and 500 mg/kg	
Kim *et al.* [53]	*M. alba*	Fruit	70% Ethanol	20, 100, and 500 mg/kg/day (p.o) x 14 days	N/A	6 weeks male ICR mice, 25–28 g	NORT	↑ Novel object recognition index in a dose-dependent manner	Protect cognitive function and survival neurons in Alzheimer disease-like models.
							Y-maze test (14 days)	↑ Spontaneous alteration	

(Table 7) contd….

Refs.	Species	Part Used	Solvent	Dose* (Administration)	Positive Control	Animal Model	Model of Study (Duration)	Main Results	Conclusion
Tamtaj *et al.* [51]	*M. alba*	Leaves	Ethanol	100, 200, 400 mg/kg/day (p.o) x 1 month	N/A	Male Wistar rats, 250 g	MMT (4 days)	↓ Time to find the hidden platform at all doses in the learning stage ↓ Time to find the hidden platform at 400 mg/kg in rehearsal stage	Improve the learning process at all dose Improve spatial memory at 400 mg/kg
Kim *et al.* [54]	*M. alba*	Leaves and fruits	70% Ethanol	1 g/kg/day (p.o) x 12 weeks	N/A	4 weeks male C57BL/6 mice, 23-25 g	NORT	↑ Memory index by 78.63%	Recover memory function in obese mice.
Nade *et al.* [31]	*M. alba*	Root	Methanol/ Ethyl acetate	25, 50 and 100 mg/kg/day (p.o) x 21 days	Diazepam	Male Wistar rats, 150-180g	EPM (21 days)	↓ Transfer latency on days 7, 10, 21 at all doses	Recover cognitive function in mice suffering chronic footshock stress
Nade *et al.* [41]	*M. alba*	Root	Methanol/ Ethyl acetate	25, 50 and 100 mg/kg/day (p.o) x 10 days	Diazepam	Male Wistar rats, 150-180g	EPM (5 and 10 days)	↓ Transfer latency on days 5, 10 at all doses	Recover cognitive function in mice suffering chronic restraint stress
Nade *et al.* [30]	*M. alba*	Leaves	Methanol/ Ethyl acetate	25, 50 and 100 mg/kg/day (p.o) x 9 days	Ondansetron	Male Swiss albino mice, 22 - 25 g and male Wistar rats, 120-150 g	ORT	↑ Discrimination index	Improve learning and memory in scopolamine-induced cognitive deficits mice
							EPM (4 days)	↓ Transfer latency	
							MMT (4 days)	↑Swimming time in the target quadrant	
Shih *et al.* [43]	*M. atropurpurea*	Fruit	Methanol	100, 500 mg/kg/day (p.o) x 12 weeks	N/A	6 months male SAMR1 and SAMP8 mice	PAT (7 days)	↑ Latency time on days 3, 7 at 500 mg/kg	Improve memory in aging mice
							AAT (7 days)	↑ Latency time on days 2, 3, 4 at all doses	
Turgut *et al.* [33]	*M. nigra*	Leaves	Methanol	50, 100 mg/kg/day (p.o) x 8 weeks	N/A	8 weeks male BALB/c mice	MMT (4 days)	↓ Time for escape latency ↑ Time spent to find the target quadrant ↑ Time swimming in the target quadrant ↑ Times crossed the platform location	Improve cognitive deficits in aging mice induce by D-galactose.

AAT: Active avoidance test, EPM: Elevated plus maze, MCAO: Middle Cerebral Artery Occlusion, MMT: Moris Maze Test, N/A: Not applied, NORT: Novel object recognition test, OTR: Object recognition test, PAT: Passive avoidance test, p.o: per oral. *weight of extract per body weight of the animal.

whereas it was still active in another model [12, 50]. Also, all doses of *M. alba* fruit extract increased retention time 14 days after stroke, but 50 mg/kg of *M. alba* fruit powder failed to show that effect [25, 50].

Apart from Moris Maze test, Nade *et al.* [30, 31, 41] emphasized the memory enhancement of ethyl acetate soluble fraction (EASF) of *M. alba* methanol extract by the increase in discrimination index *via* object recognition test, and by the

reduction of transfer latency in EPM test on days 7, 14, 21. The extract might be effective than diazepam against chronic footshock stress, as this drug only showed improvement on the 1st day [31].

In a similar designed model, Kim *et al.* [52-54] showed that ethanol extract of *M. alba* fruit and mixture extract of *M. alba* leaves and fruit (2:1) improved the time spent to discover the novel object in healthy mice, in obese mice, and $A\beta_{25-35}$-injected mice. Particularly, *M. alba* fruit extract at 100 and 500 mg/kg could increase time spent on a novel object by 66.88 ± 72.57%, and 69.14 ± 72.84%, respectively, compared with $A\beta_{25-35}$-injected mice [53]. There was a significant improvement in memory of obese mice by 78.63% as well [54].

Finally, the latency time mice spent to avoid the electrical foot shock in both passive and active avoidance test was raised by treating with EASF of *M. alba* methanol root extract, *M. alba* ethanol fruit extract and *M. atropurpurea* methanol fruit extract showing that the learning process of memory-impaired mice, was improved [41, 43, 52].

The positive effect on the cognitive functions might be chronic with the duration of mulberry exposure ranging from 9 days – 12 weeks. In addition, memory and learning improvement resulted from mulberry activities were associated with neuroprotection. This was shown in the increase of antioxidant capacity in the body [13, 32, 33, 41], the increase in density and differentiation of survival hippocampal cells [12, 13, 50, 52, 54], the inhibition of acetylcholinesterase (AchE) [13, 25], the increase in the cholinergic neuron and the acetylcholine formation [32], and the reduction of apoptotic markers in the hippocampus [32, 53].

There was a suggestion that the molecule mechanism of the anti-apoptotic activity of mulberry *in vivo* relating to the reduction of glycogen synthase kinase-3β (GSK-3β) pathway-mediated tau phosphorylation. This metabolite resulted in the formation of the neurofibrillary tangles [53] as well as the increase in B-cell lymphoma 2 (Bcl-2) expression in the hippocampus which led to the amplification of signals of apoptotic cascade such as cytochrome c release and the activation of caspase-3 [32, 53]. Therefore, preventing this reaction caused the reduction of apoptosis and the protection of brain cells [53]. Nerve growth factor (NGF) content in the hippocampus was also enhanced in a dose-dependent manner after the treatment of mulberry resulting in the induction of neurite and synapse formation, *via* the promoting extracellular-signal-regulated kinase (ERK) and cyclic AMP response element-binding protein (CREB) phosphorylation as well as pre- and post-synapse markers formation [52]. As a result, new cells generation caused memory improvement effect.

3.8. Antidepressant, Anxiolytic And Sedative Effects

Previous studies have reported the antidepressant-like effects of mulberry extracts such as sanggenon G from root bark, methanolic extract from leaves, ethyl acetate fraction, and n-butanol fraction from methanol extract of *M. alba* root, and alcohol extract of *M. alba* root (Table **8**).

In general, all parts of mulberry (*M. alba* leaves green tea, *M. alba* root bark, *M. nigra* leaves, sanggenon G and syringic acid extracted from mulberry) could decrease the immobility time that mice spent in forced swim test (FST) [24, 26, 31, 35, 36, 55-57], and in tail suspension test (TST) [24, 56]. These indicated that mulberry possessed an antidepressant-like effect. The antidepressant-like effect of *M. alba* green tea extract at 200 mg/kg was even comparable with 10 mg/kg of desipramine [55]. The antidepressant-like effect of mulberry could be acute (measured 30 – 60 minutes after administration) or subchronic (measured after 7 days of administration) or chronic (measured after 28 days). The doses of extracts ranged from 3 mg per day to 10 g twice a day orally, or 3 – 100 mg/day by intraperitoneal injection. Sanggenon G showed effective antidepression at higher doses (20 and 30 mg/kg, i.p.), whereas syringic acid was better at average doses (1 and 10 mg/kg, p.o.) The modulation of the limbic hypothalamic–pituitary–adrenocortical (HPA) axis, which reported by few studies, clarified this effect [26, 31, 36, 56]. Accordingly, ethyl acetate fraction of *M. alba* methanol root bark extract, sanggenon G extract from the root bark, and ethanol extract of Cortex Mori Radicis (CMR) prevented the promotion of corticosterone response and c-fos immunoreactivity in the dentate gyrus or hippocampus under FST-induced depressive condition. These could be associated with the increase in glucocorticoid receptors (GR) expression in the hippocampus through the promotion of phosphorylation at S232 and S246 of GR [56]. Moreover, the anti-depressive effect of sanggenon G might be mediated by an interaction with the serotonergic system as well, as Lim *et al.* indicated pretreating with a selective 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor antagonist could reserve this positive effect [36].

Apart from that, several other effects related to antidepressive like effects were observed. Lim *et al.* indicated that the practical impact of sanggenon G at 5 - 10 mg/kg was also promoted by the presence of the α_2-antagonist (yohimbine) [35]. Otherwise, *M. alba* root bark extraction could reserve the depressive-like behaviors in diabetic mice assessed *via* FST [57].

The anxiolytic effect of mulberry had controversial results *via* different experiments. Additionally, mulberry could show the acute anxiolytic effect after 30 – 60 minutes of administration, regardless of oral administration or intraperitoneally injection. In open field test (OFT), two extracts of *M. alba* (*M. alba* leaves methanol extract and *M. alba* root methanol extract) decreased the latency time to enter the main area and increased the number of squares crossed as well as the number of rearings in both standards and stressed mice indicating that mulberry extracts had an anxiolytic effect [14, 28, 41]. However, only Lee *et al.* showed no change in the frequencies of rearing observed in mice treated with *M. alba* methanol leaves extract [14]. Mulberry extracts also showed their anxiolytic effect *via* the EPM test, light/dark exploration test, and hold board test. In the EPM test, more time was spent in the open arms along with the short transfer latency to the closed arms [14, 28, 41]. For instance, methanol extract of *M. alba* leaves increased up to 49.9 ± 3.1% of time spent on the open arms and 63.3 ± 1.3% of the number of entries into open arms compared with the control group [14]. Additionally, mulberry enhanced the exploratory head-dipping behaviors and time spent in lightbox in hold board test,

Table 8. Anti-depression, anxiolytic, anti-stress effects of mulberry

Refs.	Species	Part Used	Solvent	Dose* (Administration)	Positive Control	Animal Model	Model of Study	Main Results	Conclusion
Ye *et al.* [57]	*M. alba*	Root bark	N/A	10 g/kg twice daily (p.o) x 4 weeks	N/A	2 months male Sprague-Dawley rats	OFT	↑ Number of rearing ↑ Number of line crossing insignificantly	Reserve depressant behaviors in diabetes mice
							LAT	↑ Locomotor activity insignificantly	
							FST	↓Immobility time	
Lee *et al.* [56]	*M. alba*	Root bark	Ethanol	50, 100, 200 mg/kg/day (p.o) (p.o) x 5 days	RU486 (mifepristone)	Male Wistar rats, 180–220g	FST	↓Immobility time at 100 and 200 mg/kg ↑Climbing time at 200 mg/kg. No significant change of swimming time	Antidepressant-like effects
							TST	↓Immobility time at 100 mg/kg	
Lim *et al.* [26]	*M. alba*	Root bark	Methanol/ EtOAc Methanol/ n-butanol	30, 100 mg/kg/day (p.o) x 7 days	RU486 (mifepristone)	8 weeks Male Wistar rats, 180–210g	FST	↓Immobility time, ↑climbing time, ↑swimming time at 100 mg/kg of EtOAc fraction No change observed with an n-butanol fraction	Antidepressant-like effects
Nade *et al.* [41]	*M. alba*	Root	Methanol/ EtOAc	25, 50, 100 mg/kg/day (p.o) x 10 days	Diazepam	Male Wistar rats, 150-180g	OFT	↑ Number of squares crossed at all doses on day 10 ↓ Latency at all doses ↑ Number of rearings at 50 and 100 mg/kg	Anxiolytic effect
Nade *et al.* [31]	*M. alba*	Root	Methanol	25, 50, 100 mg/kg/day (p.o) x 28 days	Diazepam	Male Wistar rats, 150-180g	DST (21 days)	↓ Immobility time at day 1, 14, 21	Antidepressant-like effects
Khan *et al.* [59]	*M. alba*	Stem bark	Methanol	250, 500 mg/kg/day (p.o)	Diazepam	4 weeks male and female Swiss albino mice, 40-45 g	OFT	↓ Number of movement at all dose after 120 minutes of administration	Sedative effect
							HCT	↓ Locomotor activity at high dose	
Lee *et al.* [14]	*M. alba*	Leaves	Methanol	50, 100, 200, 400 mg/kg (p.o)	Diazepam	5 weeks male ICR mice, 23–25 g	LAT	No alternation in locomotor activities or rearing frequencies after 1 hour of administration	Anxiolytic effect
							EPM	↑ Time spent in the open arms after 1 hour of administration ↑ Entries into open arms after 1 hour of administration	
							HBT	↑ Head-dips at doses of 200 and 400 mg/kg after 1 hour of administration	
Aditya Rao *et al.* [29]	*M. alba* *M. laevigata*	Leaves	Petroleum ether, chloroform, methanol	200 and 400 mg/kg/day (p.o)	N/A	Male and female albino mice, 25-30 g	LAT (5 mins)	↓ Locomotor activity after 1 hour of administration	Sedative effect

(Table 8) contd….

Refs.	Species	Part Used	Solvent	Dose* (Administration)	Positive Control	Animal Model	Model of Study	Main Results	Conclusion
Sattayasai *et al.* [55]	*M. alba*	Leaves	Boiling water	100, 200, 500, 1000 mg/kg (i.p.)	Desipramine, diazepam	Male IRC mice	FST	↓ Immobility time at 100 and 200 mg/kg after 30 minutes of administration	Antidepressant-like effect at low dose (100, 200 mg/kg) Sedative effect at high dose (500, 1000 mg/kg)
							CT	↓ Climbing activity at 500 and 100 mg/kg after 30 minutes of administration	
							OFT	↓ Time spent in open arms and the number of entry at 500 and 100 mg/kg after 30 minutes of administration	
							RRT	↓ Time spent on the rod after 30 minutes of administration	
Yadav *et al.* [28]	*M. alba*	Leaves	Methanol	50, 100, 200 mg/kg/day (i.p.)	Diazepam	Male Swiss albino mice, 18-22 g	OFT	↑Square traversed at all doses after 30 minutes of administration ↑Rearing and self-rearing at 100 and 200 mg/kg after 30 minutes of administration	Anxiolytic effect
							HBT	↑ The number of a head poking at 100 and 200 mg/kg after 30 minutes of administration ↑Duration of a head poking at all doses after 30 minutes of administration	
							EPM	↑Time spent in open arms at 100 and 200 mg/kg after 30 minutes of administration ↓ Time spent in closed arms and ↑ The entries to open arms at 200 mg/kg after 30 minutes of administration	
							LDP	↑Time spent in lightboxes and ↓the time spent in dark boxes at 100 and 200 mg/kg after 30 minutes of administration No change of crossings and transfer latency.	
Dalmagro *et al.* [24]	*M. nigra,*	Leaves	Water	3–100 mg/kg/day (p.o) x 1 day (for acute test, and x 7 days for subchronic test	Fluoxetine	Male Swiss mice, 30–40 g	FST	↓ Immobility time at all doses in acute test	The antidepressant-like property might occur due to syringic acid
							TST	↓ Immobility time at 3, 10, 30 mg/kg in acute test, and at 3, 10, 30, 100 mg/kg in subchronic test	
							OFT	No significant changes in the number of crossings, rearing, and fecal boluses in both tests	
	Syringic acid	N/A	N/A	0.1 – 100 mg/kg/day (p.o)			TST	↓ Immobility time at 1, 10 mg/kg in both acute and subchronic tests	
							OFT	No significant changes in the number of crossings, rearing, and fecal boluses in both tests	
Barman *et al.* [9]	*M. indica*	Root	Methanol	200 mg/kg/day (i.p.)	N/A	Male adult albino rats (150-165 g)	SAT	↓ Spontaneous activity by 72.78% after 30 minutes of administration	Sedative effect

(Table 8) contd….

Refs.	Species	Part Used	Solvent	Dose* (Administration)	Positive Control	Animal Model	Model of Study	Main Results	Conclusion
Gupta *et al.* [58]	Morusin	N/A	N/A	5, 10 mg/kg (i.p.)	Diazepam	Wistar albino rats (150–200 g)	LAT	↓ Locomotor activity by 48.82% and 70.20% at 5 and 10 mg/kg, respectively after 30 minutes of administration	Sedative effect
Lim *et al.* [36]	Sanggenon G	N/A	N/A	3, 10, 30 mg/kg/day (i.p.)	Imipramine	8 weeks male Sprague Dawley rats, 180–210g	FST	↓ immobility time at 30 mg/kg after 60 minutes of administration ↑ swimming time at all dose after 60 minutes of administration No change of climbing time	Antidepressant-like effects mediated serotonergic system.
Lim *et al.* [35]	Sanggenon G	N/A	N/A	5, 10, 20 mg/kg/day (i.p.)	Yohimbine	8 weeks male Sprague–Dawley rats, 180–210g	FST (6 mins)	↓ Immobility time at 20 mg/kg after 60 minutes of administration	Antidepressant-like effect

CT: Climbing test, DST: Despair swim test, EPM: Elevated plus maze, EtOAc: Ethyl acetate, FST: forced swimming test, HCT: Hole cross test, HBT: Hold board test, HWT: Horizontal Wire Test, i.p.: intraperitoneal injection, LAT: locomotor activity test, LDP: Light/dark paradigm, N/A: Not applied, OFT: Open field test, p.o: per oral, RRT: Rota-rod test, SAT: Spontaneous activity test, TST: Tail suspension test. * weight of extract per body weight of the animal.

and light/dark exploration test, respectively [14, 28]. However, *M. alba* root bark only tended to improve the results in diabetic mice insignificantly, and the aqueous extract of *M. alba* leaves showed no anxiolytic effect at 100 - 200 mg/kg [55, 57]. Lee *et al.* suggested that the anxiolytic activity might relate to the histaminergic system in the central nervous system, as a histamine H_3 receptor antagonist abolished this effect [14].

The decreased movement of mice in the locomotor activity test showed that *M. alba* leaves and stem bark methanol extract, *M. alba* steam bark morusin, several extracts of *M. laevigata* possessed sedative effect [28, 29, 58, 59]. The methanol extract of *M. indica* root bark at 1000 mg/kg also showed the same effect, as it decreased the spontaneous motility up to 72.78% [9]. As same as the anxiolytic effect, the sedative effect of mulberry was acute. These outcomes above were observed after 30 – 60 minutes of administration.

On the other hand, the anxiolytic and sedative effects of mulberry were in a dose-dependent manner. No significant anxiolytic effect was shown by *M. alba* leaves methanol extract at a low dose (below 100 mg/kg) [14, 28, 52], and aqueous extract of *M. alba* leaves only had a sedative effect at high dose (over 500 mg/kg) [55]. The petroleum ether, chloroform and methanol fractions obtained from aqueous extract of both *M. alba* and *M. laevigata* leaves decreased over 50% of locomotor activity. Nevertheless, the petroleum ether fractions exhibited stronger effect compared to methanol fractions, then followed by chloroform fraction in both cases, indicating that solvents for extraction affected the effectiveness of mulberry [29].

3.9. Other Effects

Two studies also evaluated the anticonvulsant effect of mulberry. Tubas *et al.* showed that intraperitoneal treatment of *M. ruba* fruit extract at 10 mg/kg significantly decreased the spike frequencies of convulsions in penicillin-induced epileptiform mice from the 80th minute observed during 120 minutes tested although no change of the amplitude was observed [60]. This result was reflected in the study of Gupta *et al.* [58] who showed that morusin – a compound extract from *M. alba* dramatically increased the onset of convulsive time caused by isoniazid, from 306.16 ± 22.16 (s) to 491.42 ± 29.07 (s) (at 5 mg/kg) and 659.10 ± 31.28 (s) (at 10 mg/kg). There was a significant reduction in the duration of convulsions and the percentage of mortality as well. In maximal electroshock-induced convulsion rats, morusin intraperitoneal injected administration at 5 mg/kg led to a decrease in the duration of tonic hind limb extension (seconds) whereas 10 mg/kg of this compound even abolished this reaction. Regarding the mechanism of action, the anticonvulsant effect results from the reduction of MDA levels in erythrocytes and plasma, and the preservation of GABA in the brain [58, 60]. These anticonvulsant effects were acute observed after 30 minutes of treatments. However, a report of Barman *et al.* showed a different result, as *M. indica* root failed to stop pentylene tetrazole-induced convulsion in mice [9].

Besides, mulberry also showed its effect on sleep medicines, and this effect was dose-dependent. The sleeping time caused by two barbiturates (pentobarbitone and phenobarbitone) was extended by pretreating (i.p.) with *M. indica* root and *M. alba* leaves at 200 mg/kg 30 minutes prior the barbiturates treatments [9, 23]. This extension, however, was not significant when pretreating with *M. alba* leaves at the dose of 100 mg/kg. On the other hand, the use of 100 and 200 mg/kg of *M. alba* leaves also reduced the onset time of sleeping while there was no change with 50 mg/kg of this extract.

Regarding PD, Gu *et al.* [18] studied the effect of 70% ethanol extract of mulberry (*M. alba*) fruit against PD-like symptoms caused by 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine/probenecid (MPTP/p), which is a neurotoxic agent. They found that the extract at the dose of 250 mg/kg/day inhibited the motor deficits in mice after 38 days of treatment, that proved by longer staying of mice on the rod in the rotarod test, less locomotor activity time when

mice descended to the floor in the pole test and thus, improved bradykinesia and increased locomotor activity in the open field test. Also, non-motor deficits were improved, as pellet retrieval time was shortened in the olfactory test in the treated group. This result was concordant with the report of Kim *et al.* [61] who also showed the improvement of bradykinesia in behavioral tests in mice intraperitoneally administrated 500 mg/kg/day of 70% ethanol extract of *M. alba* fruit during 15 days period. This protection against bradykinesia was hypothesized to be associated with the protection of dopamine neurons in the substantia nigra pars compacta and striatum through the inhibition of Bax protein (an apoptotic protein) or α-synuclein and ubiquitin levels (factors killed dopaminergic cells), in PD models.

Regarding the protection against diabetes mellitus complications on the central nervous system, Kim *et al.* reported an increase in new cell proliferation in the dentate gyrus in both normal and diabetic rats after 3 days of intraperitoneal treatments with 100 mg/kg of heat-extracted leaves of *M. alba* [62]. The increased expression of neuropeptide Y, which relates to the cell division, most likely mediated this effect. Additionally, another study showed that 0.3 g/kg of flavonoids extracted from *M. alba* in 8 weeks period could chronically recover a severe peripheral nerve injury in diabetic rats. Accordingly, the oral administration of these compounds led to an increase in the myelin sheath area and the myelinated fiber cross-sectional area. The study demonstrated that the extramedullary fiber number, the onion-bulb type myelin destruction, and the degeneration of mitochondria and Schwann cells reduced remarkably [27].

Another effect shown is the effect on catalepsy induced by antidopaminergic agents [23]. Haloperidol (a non-selective D_2 dopamine antagonist) and metoclopramide (dopaminergic blocking agent) inhibited dopamine transmission by blocking its receptor in the striatum, causing catalepsy. The authors showed that there was an increase in catalepsy score at 100 mg/kg of *M. alba* leaves extract after 28 days treatment period. On the other hand, footshock-induced aggression, which was associated with the increase in dopamine level in the brain, was also attenuated with the use of 50, 100 and 200 mg/kg of mulberry leaves extract proved by the increase in latency to fight and the decrease in fighting attacks. These results indicated that *M. alba* leaves extract might possess antidopaminergic activity.

Hwang *et al.* [63] suggested that 5 consecutive days of treatment of *M. alba* fruit extract caused modulation of MAO (monoamine oxidase) in mice brain after physical stress. The study indicated that there was a recovery of the decreased MAO-A level and the increased MAO-B level to their normal levels after 30 minutes of swimming.

Finally, several abnormalities in the brain that caused by *S. mansoni* infection in the form of a disturbance in the antioxidant system, the attenuation of GABA level and AchE activity returned to normal levels when treated with 200 – 800 mg/kg of 70% methanol extract of *M. alba* leaves after 10 exposed days. Also, these extracts induced normal brain parenchymal cells from histological view with fewer abnormalities of neuronal architecture compared to the control group [42]. Regarding neuro-amelioration against AD, El-baz *et al.*

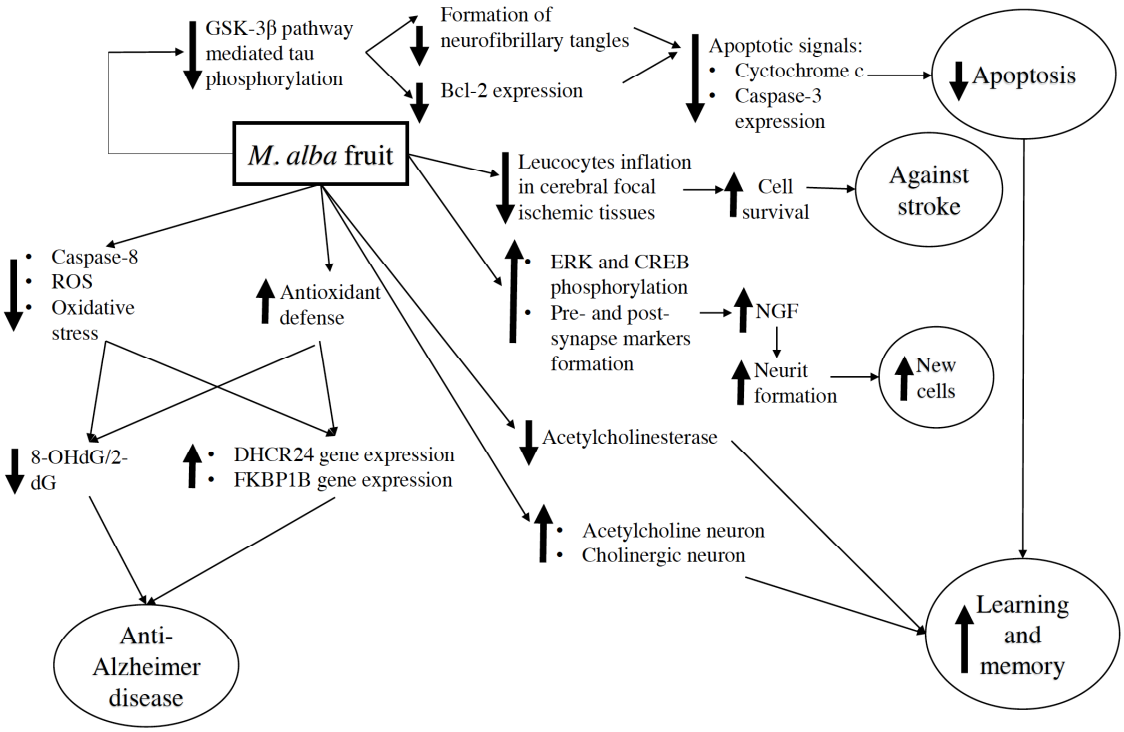

Fig. (2). Mechanism of positive effects of *Morusalba* fruit in brain functions Bcl-2: B-cell lymphoma 2, CREB: cyclic AMP response element-binding protein, ERK: extracellular-signal-regulated kinase, GSK: glycogen synthase kinase-3β, ROS: reactive oxygen species. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

[45] realized that there was an increase in the ratio of 8-OHdG/2-dG, pointing out the DNA damage, and a decrease in levels of the expression of DHCR24 and FKBP1B genes which play an essential role in degenerative disorders in AD mice. These expressions turned to the normal levels compared to mice of the control group by consuming 300 mg/kg of *M. alba* or *M. ruba* for six weeks. The authors suggested that these effects were associated with the inhibition of reactive oxygen species (ROS) as well as the apoptotic marker (caspases-8), and the promotion of antioxidant enzyme activity (such as GSH).

The mechanism of activities of *M. alba* fruit is shown in Fig. (**2**).

4. DISCUSSION

Varied types of mulberry have exhibited their protection of brain functions through *in vivo* models. *M. alba* was the most popular tested plant for varied effects. This plant showed the antioxidant effect in the brain, cognitive function improvements, antidepressant effect, sedative effect, antidopaminergic effect, anti-PD-like symptoms effect, MAO modulation, prevention of AD and the complications of central nervous in diabetic mice. Meanwhile, *M. nigra* was only tested for antioxidant effect, antidepressant effect and memory improvement. M. *indica* and M. *laevigata* had a sedative effect at the high doses. Besides, *M. indica* and *M. atropurpurea* could inhibit oxidative stress. Also, *M. atropurpurea* enhanced the memory of aging mice. Especially, ethanol fruit extract of *M. rubra* could promote the antioxidant defense whereas wine made from this plant had no positive affection on the antioxidant system. Additionally, *M. rubra* was the sole plant that had the anticonvulsant effect in this review. Almost all these effects were subchronic or chronic with the duration of treatments ranging from 5 days to 12 weeks. Exceptionally, the anticonvulsant effect and antidepressant, anxiolytic and sedative effects were acute which showed their protection against the triggers when pretreating with the plants 30 – 60 minutes before the tests.

Our review recorded large ranges of used doses across included studies. *M. alba* extracts showed their activities at the doses ranging from 5 mg/kg to 1 g/kg per day per oral, and at 100 μg/kg – 1000/kg mg *via* intraperitoneal injection. *M. nigra* had the used doses between 3 – 100 mg/kg. Similarly, *M. atropurpurea, M. indica,* and *M. laevigata* were examined at 100 – 500 mg/kg/day while *M. rubra* was intraperitoneally injected at 10 mg/kg for anticonvulsant effect, and 20 – 300 mg/kg per oral for antioxidant effect. This raised a challenge for further studies because the doses have not been standardized. It appeared that the authors randomly chose the ranges of doses for testing, although they conducted the same experiments with similar plant characteristics. For the small doses (2 – 10 mg/kg) or very high doses (1 or 10 g/kg), we might need more studies to confirm the efficacy of the extracts with these doses because it is quite hard for the active ingredients in the extract with small doses reaching the active concentrations in the body after they undergo the absorption and metabolism process. Besides, if an extract only showed their effect at very high doses (1 or 10 g/kg), it is impossible to apply these extracts in human studies as there is a need for a large number of plants to obtain the sufficient extracts for chronic interventions. C3G showed its efficacy at 10 mg/kg/day per oral in mice. However, its absorption in the body is quite low; thus, this point must be considered in further studies in humans [64]. Turn back to specific effects, mulberry contains the high concentrations of polyphenol, anthocyanin, phenolic, and flavonoid compounds that might be the source of their antioxidant effect [12, 13, 32, 33]. The results obtained were slightly inconsistent might be due to the variation of the compositions extracted from different species or used solvents. For illustration, most of the extracts of *M. alba* increased antioxidant enzymes' levels. However, wine from *M. rubra* and aqueous leaves extract of *M. nigra* failed to improve to the antioxidant capacity in mice, whereas methanol leaves extract of *M. nigra* significantly altered the levels of CAT, SOD and GPx [24, 33, 34]. The content of syringic acid might be a reason. This ingredient, which played a role as a pro-oxidant compound, was the primary phenolic compound in aqueous extract of *M. nigra* while its concentration was minor in methanol extract of this plant [24, 33]. Instead, the major phenolic acids determined in methanol extract of *M. nigra* were vanillic acid and chlorogenic acid, and syringic acid only existed with a minor percent [33]. Also, the different efficiency might be attributed to the used doses. Wine from *M. rubra* in this experiment was only 20 mg/kg whereas *M. rubra* methanol extract showed the antioxidant effect at 300 mg/kg. However, we can generally see the fact that mulberry had a positive effect on keeping antioxidant enzymes' activities and the concentration of brain oxygen radicals in balance. This activity might result in other effects such as improving memory [13, 32] or protecting against ischemia [13, 48] and brain cells [27, 44].

Regarding the result of Srikanta *et al.* [34], they hypothesized that the negative effect of *M. nigra* on antioxidant capacity might also be due to the poor bioavailability of antioxidant compounds as phenolics, or their inadequate consumption into tissues. In a clinical trial, Goldberg *et al.* found that the bioavailability of three prevalent phenolics (catechin, quercetin, and resveratrol) was too low compared to experimental concentrations to cause a positive effect in the *in vitro* studies [65]. However, we found that the main phenolics compounds of mulberry were syringic acid, vanillic acid, chlorogenic acid. The extracts of mulberry also had benefits in the *in vivo* studies. Therefore, we suggest that the effect of individual compounds on antioxidant enzymes should be investigated in the future to confirm whether they are active compounds. Also, the bioavailability could be studied to predict their realistic efficiency.

The lack of oxygen, glucose, and blood to the brain cell is the main caution of cerebral ischemia [66]. The oxygen-glucose deprivation, therefore, is a popular model to study ischemic cell deaths. *Via* this model, the pre-treatment with C3G and MG increased the percent of cell viability of PC12 cells and SH-SY5Y cells comparing to the control group [37, 39]. The study found that these positive results in the *in vitro* experiments promised satisfactory results of protection against ischemia in the *in vivo* study. In our review, we found that mulberry extracts and their compositions signifi-

cantly decreased the infarct volume in MCAO mice, asserting their effect on the *in vivo* studies. Besides, the connection between antioxidant effect and the protection against stroke became quite clear. Free radicals such as H_2O_2 could cause the death of brain cells [67]. The results of Kang *et al.* confirmed this by showing that PC12 cells exposure to H_2O_2 had lower cell viability than the vehicle group [37, 49]. However, pre-treatments of these cells with C3G and GAML enhanced more survival cells showing that free radicals scavenging could protect cell apoptosis [37, 49]. In this case, oxyresveratrol might be a potential candidate for the protection against stroke, as it had a strong antioxidant effect and could inhibit the apoptotic cascades [38, 68]. More important, oxyresveratrol could cross the blood-brain barrier where it could directly show its effects [69].

Besides, the increase in NOX4 expressions could result in ROS generation after cerebral ischemia [70]. Thus, the inhibition of the expressions of this protein by MG *in vitro* was predicted to prevent excessive ROS expression [39]. MG was also demonstrated to suppress the expression of factors involving the apoptotic cascade, namely poly (ADP-ribose) polymerase, caspase-9, and caspase-3, which could be active *in vivo* and protect against brain cells death [39]. From our results in this review, there was an actual downgrade of these expressions in MCAO mice implying the activity of MG *via* the ROS scavenging and the prevention of apoptotic signals. Nevertheless, we must emphasize that MG was intraperitoneally administrated at 0.2 – 5 mg/kg in this study. This is a challenge for its application in the future because it could be hard to reach these concentrations in the body *via* the oral admistration. We recommend pharmacokinetics studies of MG to predict its effect in clinical in the future.

Regarding the protection against the cognitive deficit, included studies showed that different parts and preparations of mulberry could improve the learning ability and memory impairment. There were studies reported that stress oxidant, hippocampal damage, and GSK-3β activation were associated with downgraded brain functions *via* neural cell death [71, 72]. Therefore, the hippocampal protection and antioxidant could be a critical factor against these affections. Otherwise, the enhancement of ACh in the brain, which plays a role in encoding and retrieval of spatial memory in the hippocampus, could lead to memory improvement [73]. Our study presented the evidence that was concordant with these theories, as the memory and learning process of mice was improved following by the increase in survival brain cells in several hippocampal areas, the elevation of the acetylcholine levels as well as the suppression of MDA level. These findings reinforced the potential effect of several species of *Morus* genus with an insight into mechanisms of action.

GABA plays a primary role in the transmission in the brain, which mediates the depolarization through K^+ and Ca^{2+} channels, which is vital for the differentiation of brain cells and the development of the brain [74]. The $GABA_A$ defects might cause idiopathic epilepsy, which correlated with the mutation in genes of voltage-channels and ligand-gated ion-channels [75]. Hence, GABAergic inhibitory transmission is an essential element in the mechanism of both anxiolytic and anticonvulsant effects [76]. Moreover, the decrease in dopaminergic transmission relates to the enhancement of GABA transmission as well [77]. In our study, we found that mulberry extract increased GABA levels in the brain and might possess antidopaminergic activity through dopamine D_2 receptors [23, 58]. These results provided strong evidence of mulberry's therapeutic potentials relating to GABA receptor and GABA inhibitory transmission. Moreover, flavones are known to bind with the GABAA receptor [77] strongly. In our review, flavonoids could be found in various parts of *M. alba* (leaves, root, and fruit). From these results, we can see that the GABA receptor and flavones might be clues for the mechanism of anxiolytic and anticonvulsant activities shown in this review, which should be more investigated.

The loss of dopaminergic neurons is well known to be the leading cause of the core motor symptoms in PD patients [78]. In this review, we found that consistent results are showing that ethanol extract of mulberry fruit protected dopaminergic neurons against some neurotoxicity and improved PD-like symptoms in rats [18, 61]. The regulation of ROS generation and some apoptotic signals as Bcl2, Bax protein, or caspase-3 to normal levels indicated that the protection of dopaminergic cells might be related to the modulation of oxidative stress and the apoptosis [61]. These outcomes seem to be incompatible with the antidopaminergic activity of this plant because the dopaminergic blocking could worsen the PD symptoms. That conflict could be attributed to the different used solvents and used parts, as the antidopaminergic activity might result from the presence of flavonoids, tannins, and saponins in mulberry leaves whereas the major compounds of mulberry fruit which improved PD-like behaviors were phenolics, flavonoids and anthocyanins [18, 23, 32]. On top of that, antidopaminergic agents had their adverse reactions in mental health [79]. For example, mulberry treatment enhanced the haloperidol-induced catalepsy as shown in our review [23]. further studies should investigate the compounds in these extracts and their bioactivities to elucidate the active ingredients for each activity to use to suitable intervention and minimize the risk of unexpected effects.

One of our limitations was that we could not compare different species of genus *Morus* to clarify which species were more beneficial. However, from the general perspective, we realized that many parts from *M. alba* showed a stronger antioxidant effect than other species. The antioxidant effect of *M. nigra* depended on used parts and the extracted solvents. Almost all parts of different species of mulberry showed a positive effect on cognitive function improvement, while root bark extract might be responsible for anti-depressive activities. The variable compositions in different extracts could cause a controversial effect, like antidopaminergic action and PD-like behavior improvement. Although there are many studies investigating the effects of mulberry *in vivo*, there are still no more profound studies investigating the pharmacokinetics of their active ingredients, leading to its limited application in human studies. The doses of these extracts should be considered and standardized to have optimized options for further studies. Finally, we did not include and report the systemic toxicology of

mulberry because of our strategy. Other studies should consider this point when conducting their researches with high doses of mulberry extract (1 g or 10 g/kg).

Furthermore, most of the included studies carried out experiments on the whole extracts, but only very few studies identified which compounds were used. In specific cases, MG (a prenylated flavonoid), C3G (an aglycone of anthocyanin) and oxyresveratrol (a stilbenoid) decreased the brain infarct volume. Through these studies, we can only assert that the protection against the stroke caused by these compounds was due to the antioxidant activities and the prevention of the apoptosis suggesting that there would be many compounds that possess this activity. Sanggenon G was the only specific compound that was investigated and showed a useful anti-depressive effect. No active ingredients were used for investigating other activities as an antioxidant effect, PD, and AD-like behavior improvement. It narrows the number of active compounds that further studies should focus on. Instead, we need more studies finding out the active ingredients in specific extracts, making the comparison to determine the most effective candidates. Nevertheless, our study contributes to elucidating the potential activities of the plant-based on evidence, which can promote its application. We recommend further studies to concentrate on investigating compounds from active extracts to provide stronger evidence.

CONCLUSION

Mulberry species proved beneficial to many neurological functions in animal models. *M. alba* leaves methanol extract; ethyl acetate fraction and n-butanol fraction from methanol extract of *M. alba* root; and alcohol extract of *M. alba* root possessed anti-depressant-like effect. The methanol extraction of both *M. alba* root and *M. alba* leaves had an anxiolytic effect. Plus, *M. laevigata* leaves, *M. alba* methanol extract of leaves and stem bark, as well as its morusin showed the sedative effects at high doses. Varied species exhibited their ability to improve the memory and learning process, including *M. alba* leaves and fruit, *M. nigra* leaves, *M. atropurpurea* fruit. Some specific compounds extracted from mulberry namely MG, oxyresveratrol, and C3G could prevent ischemia in the brain either before or after stroke. Interestingly, *M. rubra* fruit and morusin increased the onset of convulsive time as well as reduced the convulsive duration. The antioxidant activity is still inconsistent and might be associated with the specific species, solvent for extraction, route of administration, doses, and the main constituents. Anti-Alzheimer disease and anti-Parkinson's disease activities are intriguing, as the symptoms in mice were improved and the mechanisms were also suggested. However, we need more studies to confirm them. The active ingredients of each species, especially *M. alba*, should be deeper studied for screening potential candidates for future treatments.

LIST OF ABBREVIATIONS

5-HT_{1A}	=	5-hydroxytryptamine$_{1A}$
AchE	=	Acetylcholinesterase
AD	=	Alzheimer diseases
C3G	=	Cyanidin-3-O-b-D-glucopyranoside
CAT	=	Catalase
CMR	=	Cortex mori radicis
CREB	=	Cyclic AMP response element-binding protein
EASF	=	Ethyl acetate soluble fraction
EPM	=	Elevated plus-maze
ERK	=	Extracellular-signal-regulated kinase
GABA	=	Gamma-aminobutyric acid
GAML	=	GABA in mulberry leaves
GHL	=	Global health library
GPx	=	Glutathione peroxidase
GR	=	Glucocorticoid receptors
GRd	=	Glutathione reductase
GSH	=	Glutathione
GST	=	Glutathione S-transferase
GSK-3β	=	Glycogen synthase kinase-3β
FST	=	Forced swim test
HPA	=	Hypothalamic–pituitary–adrenocortical
LDH	=	Lactate dehydrogenase
MAO	=	Monoamine oxidase
MCAO/R	=	Middle cerebral artery occlusion/reperfusion
MDA	=	Malonyldialdehyde
MG	=	Mulberrofuran G
MLE	=	Mulberry fruit extract
MLE-AR-14	=	Mulberry leaf extracted variety AR-14
MPO	=	Myeloperoxidase
MPTP/p	=	1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine/probenecid
NO	=	Nitrite
NOX	=	Nicotinamide adenine dinucleotide phosphate oxidase
NPSH	=	Non-protein thiol groups
NYAM	=	the New York Academy of Medicine Grey Literature Report
OFT	=	Open field test
ROS	=	Reactive oxygen species
PC	=	Protein carbonyl
PD	=	Parkinson disease

PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SA	=	Syringic acid
SIGLE	=	the System for Information on Grey Literature in Europe
SOD	=	Superoxide dismutase
SYRCLE	=	The Systematic Review Centre for Laboratory Animal Experimentation
TAC	=	Total antioxidant capacity
TBARS	=	Thiobarbituric acid reactive substances
TST	=	Tail suspension test
VHL	=	Virtual health library

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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