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MORUS (MULBERRY) AND ITS BRAIN-RELATED PROTECTIVE ACTIVITIES. LITERATURE UPDATE

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ABSTRACT

Morus genus (mulberry) plants that are globally known as important fruiting trees. But in addition to their very high nutritional and economic values, they were used for medicinal purposes for thousands of years. Numerous research and review articles were published about their medicinal properties-activities. Yes, although many of these research publications are related to brain, very few review article summarized these results. In this review, an up-to-date presentation of these studies will be presented. Major focus will be on neuroprotection, Alzheimer's disease (AD), Parkinson's disease (PD), memory protection and enhancement, and general cognitive wellbeing. Major active natural products will be shown in figures and some of these compounds will be extensively discussed in the discussion section. In addition, since *Morus* trees have a very large number of ethnobotanical and ethnomedicinal uses, in this review article we will present only those uses that are brain-related. Finally, in the conclusions section, some future research recommendations will be proposed.

KEYWORDS: *Morus*, *Morus alba*, Alzheimer's disease, Parkinson disease, neuroprotective, aging, cognition, memory, anticonvulsant, antidepressant.

Abbreviations: Ahc and her/his colleagues, AChE acetylcholine esterase, AD Alzheimer's disease, BACE1 β-site amyloid precursor protein cleaving enzyme 1, BuChE butyrylcholine esterase, DPPH 2,2-Diphenyl-1-picrylhydrazyl, DCM dichloromethane, GABA γ-amino butyric acid, GSK-3β glycogen synthase kinase-3β, GSH glutathione, HPLC high performance liquid chromatography, LPS lipopolysaccharide, MAO monoamine oxidase, MDA malondialdehyde, NOX nicotinamide adenine dinucleotide phosphate oxidase, PD Parkinson's disease, PE petroleum ether, SOD superoxide dismutase, STZ streptozotocin,

TEAC Trolox equivalent antioxidant capacity, TLC thin layer chromatography, TPC total phenolic content,

1) INTRODUCTION

Taxonomy, Archeology and Previous Review Article

The *Morus* genus (Mulberry) is part of the Moraceae family, which consists of 37 genera and more than 1100 species.[1] The exact number of *Morus* species is very debated: it ranges from 12 to 150, where the higher number includes hybrid species. Most researchers agree that there are around 40 *Morus* species.[2] Except for the two poles, *Morus* trees are globally widespread[3], and there are evidences that they originated in China and were domesticated more than 5000 years ago.[4] Outside of China, archeological evidences showed that *Morus alba* was used to treat infections of the lower respiratory tract more than 2500 years ago[5], and surprisingly, *Morus nigra* was used in Belgium more than 3400 years ago.[6]

As we mentioned earlier, numerous review articles were published about medicinal and other properties-activities of *Morus* genus and specific species, mostly *Morus alba*. For example, we published a review article about the superb antidiabetic activity and the outstanding nutritional value of these trees.[7] But for our surprise, we found only two review articles that have major focus on brain-related properties-activities of this genus. O. Rebai ahc reviewed the antioxidant and neuroprotective activities of *Morus* ssp.[8] In addition to being a very short review article, structures of active natural products were not presented and some brain-related activities (cognitive) were not discussed. A more recent and way more comprehensive review article was published by D.N. Tam ahc.[9] Despite the long introduction of work methods, this review article is very detailed and the information is highly organized. It lacks only more information about active natural products and their structures.

2) Brain-Related Ethnobotany and Ethnomedicine of *Morus*

To the best of our knowledge and literature search, traditional, ethnomedicinal and ethnobotanical uses of the *Morus* species were published in more than 150 research and review articles. Most of these publications discuss *Morus alba* and to much smaller extend, *Morus nigra*. For example, S. Yadav ahc published a comprehensive review article about the ethnobotany, phytochemistry and phytopharmacology of this genus.[10]

Interestingly, very few of these articles presented brain-related activities of the *Morus* species, and when mentioned, it is a minor property. A summary of these publications in presented in **Table 1**.

Table 1: Brain-Related Ethnobotany and Ethnomedicine of *Morus*.

Species	Country	Uses, Reference
M. alba	India	Unspecified plant part, no more details, brain tonic[11]
M. alba	Iran	Fruits, leaves, twigs; insomnia[12]
M. mesozygia	Nigeria	Unspecified plant part, no more details, sedative[13]

3) Published Brain-Related Activities-Properties of *Morus*

The genus *Morus* is one of the most studied plant genera, and research and review articles were published about its species in thousands. Anticancer and antidiabetic are among its most important properties-activities, but many others were published less frequently. But while *Morus alba* was published and reviewed in hundreds of articles leaving behind *Morus nigra* with a large gap, the latter have significant publication gap over others. Up-to-date, some of the species like *Morus japonica* and a few other species, were never published for any property-activity. And when brain-related activities-properties are concerned, the list of published species is even mush shorter, but *Morus alba* is expectedly still topping it. A summary of these activities-properties is presented in **Table 2**.

Table 2: Published Brain-Related Activities-Properties of *Morus*.

Activity-Property, Testing Method(s), Result(s), Reference
Morus alba
Leaves were separately extracted with *n*-hexane, 70% aqueous acetone (see note after table) 30% aqueous ethanol and ethanol. Extracts were tested for lifespan increase in nematode of *Caenorhabditis elegans*, where ethanolic extract had an effect of 17.4 % increase. The standard drug in this study was ethosuximide (antiseizures in humans) which increased the lifespan by 35%.[14]
Leaves 80% aqueous methanolic extract was used to treat PC-12 cells, and several biomarkers were tested to measure the effect of this treatment, especially oxidant-antioxidant. Clear effect was measured, and it was compared with 6-hydroxydopamine and dextromethorphan. Researchers concluded that this extract can be used for treating neurodegenerative diseases like PD, Schizophrenia and antiaging.[15]
Leaves methanolic extract inhibited formation of amyloid β-peptide (1-42) and protected hippocampal neurons isolated from rats.[16]
A follow-up of the research cited in reference 16: leaves methanolic extract was tested for amyloid β-peptide (1-42) destabilization resulting around 74% (average).[17]
Leaves 50% aqueous methanolic extract inhibited AChE in serum albumin. This activity was referred to well-known phenolics that this extract contains: myricetin, luteolin and kaempferol.[18]
Encapsulated dry leaves were supplied to women with mild AD resulting positive cognitive

effect.[19]

Fruits 70% aqueous ethanolic extract was successively partitioned with several solvents including chloroform, and this fraction was chromatographed to afford artoindonesianin O (**Figure 1A**). This compound was tested against neurotoxicity of Aβ42, N-methyl-D-aspartate and okadaic-acid, showing positive effect in these tests.[20]

Roots methanolic extract was successively fractionized with water, DCM, ethyl acetate and *n*-butanol. The extract was chromatographed yielding mulberrofuran G, albanol B and kuwanon G (**Figure 1A**). Extract, fractions and the three compounds were tested for inhibition of AChE, BuChE and BACE1, showing significant activities. Molecular docking was performed for the inhibition activity of the three compounds.[21]

Roots 95% aqueous ethanolic extract was partitioned with PE, ethyl acetate and *n*-butanol. The ethyl acetate fraction was analyzed yielding ten Diels-Alder type adducts, where one of them was new. These compounds were subjected to 11 tests of anti-AD activities (mainly enzymes inhibition), anti-neuroinflammation, antioxidant and neuroprotective. Results showed that mulberrofuran K was most active, and its structure is presented in **Figure 1A** along with the new compound inethermulberrofuran.[22]

Roots methanolic extract was partitioned with water, *n*-hexane, DCM and ethyl acetate. The DCM fraction was chromatographed affording five arylbenzofurans: mulberrofuran D, mulberrofuran D2, mulberrofuran H, morusalfuran B and sanggenofuran A (**Figure 1B**). These compounds had significant inhibition activities of AChE, BuChE, BACE1, and GSK-3β enzymes. Molecular docking was performed for these activities.[23]

Fruits ethanolic extract had positive effect in genetically modified mice for AD model. This effect was measured behavioral and biochemical parameters. Donepezil was reference drug in this study.[24]

Fruits aqueous extracts of 27 cultivars were analyzed for TPC, total cyanins and for single phenolics yielding three known compounds. Extracts were tested for antioxidant (DPPH method) and enzyme inhibition (AChE, BuChE and BACE1) activities, and found clear correlation between them.[25]

Leaves 50% aqueous methanolic extract had positive effect against convulsions induced by pentylenetetrazole or maximal electric shock methods in rats, and improved GABA levels. Diazepam was positive control in this research.[26]

Stem bark 70% aqueous ethanolic extract was analyzed yielding morusin (**Figure 1B**), which had positive effect against convulsions induced by isoniazid or maximal electric shock methods in rats, and improved GABA levels. Diazepam and phenytoin were positive control in this research.[27]

Leaves 90% aqueous ethanolic extract had positive effect against seizures induced by pentylenetetrazole or maximal electric shock in rats.[28]

Leaves tea was supplemented to mice and had antidepressant and anxiolytic effects in the following tests: climbing, coordination, muscle strength, thermal tail-flick, chronic forced swimming and elevated plus-maze. Desipramine and diazepam were positive controls.[29]

Root bark (Cortex Mori Radicis) ethanolic extract was administered to rats to test its effect in forced swimming and tail suspension tests. Clear positive effects (several behavioral and biochemical parameters) were measured and consequently, a mechanism of action is proposed. RU486 (mifepristone) was positive control in this research.[30]

Root bark 80% aqueous methanolic extract was fractionized with ethyl acetate and other solvents. The ethyl acetate fraction had antidepressant effect in forced swimming test, measure with several biochemical parameters. Mechanism of action is presented and RU486 was positive control in this study.[31]

Follow-up studies of previous study: root bark 80% aqueous methanolic extract was fractionized with ethyl acetate and other solvents, and this fraction was chromatographed

affording sanggenon G (**Figure 1B**). This compound had antidepressant effect in forced swimming test, measure with several biochemical parameters. Mechanism of action is presented, and imipramine was positive control in this study.[32,33]

Leaves aqueous extract had antidepressant effect in tail suspension and forced swimming tests in mice. Imipramine was positive control in this research.[34]

Root bark was included in the diet of high fat-, STZ-induced diabetic rats. Comparing to control group, antidepressant effect was observed in animals of test group in three behavioral tests: open field, locomotor activity and forced swimming. Several biomarkers were measured (including blood glucose and fat) and a mechanism of action is proposed.[35]

Leaves were successively extracted with PE, ethanol and methanol, but only ethanolic extract was used for tests. These were done in mice, tail suspension and forced swimming, resulting antidepressant effect. Analysis of this extract (HPLC) showed high content of well-known phenolic acids, chlorogenic and gallic, and authors refer this activity to these compounds (see **Discussion**).[36]

Bark 90% aqueous ethanolic extract had antidepressant activity in hole cross and open field tests in mice. GCC is presented.[37]

Commercial anthocyanin-rich "milk" of this plant was supplemented to healthy human volunteers resulting anxiolytic and antidepressant activities, detected by a questionnaire.[38]

Leaves were defatted with PE and extracted with methanol. This extract was tested for behavioral effect in mice in the following tests: haloperidol and metoclopramide induced catalepsy, foot shock-induced aggression, amphetamine-induced stereotyped behaviour and phenobarbitone induced sleeping. In all these tests, positive effect was observed especially aggression reduction and elongation of sleep. In addition, the extract had anti-dopaminergic effect in isolated rat vas deferens.[39]

Leaves were sequentially extracted with PE, methanol and ethyl acetate, and the combined extract, in combination with clozapine, was used to treat lithium sulphate-induced psychosis (causes serotonin blockage from serotonergic neurons). It was also used to treat 5-hydroxytryptophan potentiating.[40] [a]

Leaves 90% aqueous ethanolic extract was used to treat haloperidol-induced catalepsy psychosis model in rats.[41]

Fruits ethyl acetate and methanolic extracts were tested for MAO inhibition, *in vitro* and *in vivo*. In the *in vitro* tests, ethyl acetate inhibited MAO-A activity with serotonin and benzylamine as substrates. In the *in vivo* tests (rats), ethyl acetate extract inhibited both MAO-A and MAO-B, while the methanolic extract increased the activity of MAO-A and inhibited MAO-B.[42]

A follow-up of previous study where inhibition activity was measured in rats after forced physical activity (stress), resulting very significant effect.[43]

Another follow-up of previous studies but in this case and in addition to MAO inhibition, the concentrations of lactate dehydrogenase were measured as an index of the intensity of physical activity.[44]

Roots were defatted with PE, extracted with methanol and fractionized with ethyl acetate. Stress was induced in rats by intense, forced physical activity, and the animals were treated with the ethyl acetate fraction, showing clear positive effect which was measured with behavioral and biochemical parameters (SOD activity and lipid peroxidation). Diazepam was reference drug in this study.[45]

Leaves extract [b] was used to treat stress in rats that was induced by chronic immobilization and epinephrine. Positive effect was measured with serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase and bilirubin.[46]

Leaves were defatted with PE and extracted with methanol. This extract had anxiolytic effect in mice in the following tests: head poking in the hole-board, elevated plus-maze, open field

test and spontaneous locomotor activity count. Diazepam was standard in this study.[47]
Leaves 85% aqueous methanolic extract had anxiolytic activity in mice in five anxiety-inducing tests. The effect of the extract was abolished by thioperamide, suggesting involvement of H_3 histamine receptor in the mechanism of action of the extract.[48]
Leaves 90% aqueous ethanolic extract was used to treat phenobarbitone-induced sleep and intense physical activity-induced anxiety in rats. In both cases positive effects were recorded with diazepam as a reference.[49]
Leaves aqueous extract was supplemented to human volunteers resulting improvement of memory and cognition, where effects were measured with biochemical parameters and questionnaires.[50]
Commercial morin (**Figure 1B**, see **Discussion**) had positive effect on transgenic preexisting model of AD in mice. This effect was measured with behavioral and biochemical tests (four) which clearly showed improvement of memory and cognitive state.[51]
Fruits aqueous and ethanolic extracts were tested for nootropic activity in rats using two methods: conditioned avoidance response and AChE activity after administration of scopolamine butyl bromide. Positive effect was detected in both tests.[52]
Fruits ethanolic extract alleviate focal cerebral ischemia-induced dementia in rats. Effect was measured with water maze test and AChE concentrations. Ascorbic acid and donepezil were positive controls in this study.[53]
A follow-up of previous study with special focus on antioxidant properties of the fruits extract and its relationship with memory protection and dementia amelioration.[54]
Another publication by the same group that tested the effect of fruits powder on rats memory after induction of dementia with chronic ethanol intake. Effect was measured by AChE concentrations and oxidant-antioxidant biomarkers.[55]
Fruits 70% aqueous ethanolic extract had memory enhancement effect in mice tested with two behavioral tests (passive avoidance, object recognition) and histochemical parameters, mainly nerve growth factor. A mechanism of action is proposed.[56]
Leaves were defatted with PE, extracted with methanol and the extract was partitioned with ethyl acetate. This fraction had protective effect against scopolamine-induced memory damage in mice. Effect was measured with water maze and object recognition tests. It also had positive effect on serotonin-induced contractions of isolated rat fundus.[57]
Leaves ethanolic extract enhanced spatial memory in healthy rats. Effect was measured with water maze test.[58]
Leaves ethanolic extract had protective effect against scopolamine-induced learning memory damages in rats.[59]
Fruits ethanolic extract had protective effect against STZ-induced memory deficit in mice. Effect was measured with water maze test and eight biomarkers. A mechanism of action is proposed.[60,61]
Leaves were treated with molecular nitrogen to increase the GABA content, then extracted with 85% aqueous methanol. The extract had enhanced antioxidant and neuroprotective activities *in vitro* (PC12 cells) and *in vivo* (rat brain against ischemic damage). Activities were measure with several biomarkers.[62]
A follow-up of the previous study using cyanidin-3-*O*-β-D-glucopyranoside (**Figure 1B**) isolated from fruits of the tree. Enhanced activities were indicated.[63]
Defatted (PE) leaves methanolic extract had protective effect against haloperidol-induced orofacial dyskinesia (behavioral parameters) and oxidative stress (four biomarkers).[64]
Donated leaves aqueous extract was supplemented (in food, 21 days) to rats with sciatic nerve crush injury. Positive effect was measured in sensory and behavioral tests.[65]
Follow-up research of the study cited in reference 63: DIV 7, 9 and 11 cells were used for *in vitro* study of neuroprotective and antioxidant effects after oxygen-glucose deprivation. The

cyanidin-3-*O*-β-D-glucoside fraction had clear positive activities.[66]

Root bark 95% aqueous ethanolic extract was chromatographed affording morusalbanol A (**Figure 1C**) that showed notable neuroprotection against hydrogen peroxide-induced cell (type is not indicated) damage.[67]

Leaves 70% aqueous methanolic extract ameliorated damages in rat brain infected with *Schistosoma mansoni*. Effect was measured by oxidant-antioxidant biomarkers.[68]

Commercial flavonoid-rich leave extract fraction had protective effect on sciatic nerve in alloxan-induced diabetic rats. Effect was measured with three biomarkers.[69]

Fruits were successively extracted with ethanol, 70% aqueous ethanol, ethyl acetate and *n*-butanol, then chromatographed yielding seven compounds that were tested for protective activity on glutamate-induced oxidative injury in HT22 hippocampal cells. Two of these compounds were notably active: artoindonesianin O (**Figure 1A**) and morachalcone A (**Figure 1C**).[70]

Leaves 70% aqueous ethanolic extract ameliorated manganese (MnO_2) neurotoxicity in rats by reducing the concentrations of this element in the brain and the blood, and increasing the concentrations of GSH.[71]

Leaves aqueous extract reversed the damages to STZ-induced diabetic rats brains, expressed by eight biomarkers, mainly of oxidant-antioxidant type.[72]

Commercial herbal mixture of the tree (Cortex Mori Radicis) was extracted with 50% aqueous ethanol and the extract was analyzed affording 18 compounds, where four of them were new benzofuran-type stilbene glycosides, all four are derivatives of moracin. Testing all 18 compounds for neuroprotective activity against glutamate-induced cell death in SK-N-SH cells, revealed that three previously known compounds were significantly active: moracins O, R and P (**Figure 1C**). Molecular docking was performed and a mechanism of action is proposed.[73]

Leaves 70% aqueous acetone extract was active against glyphosate-induced neurotoxicity in rats brain. Effect was measured with five biomarkers.[74]

Leaves 95% aqueous ethanolic extract was chromatographed yielding five neuroprotective compounds (**Figure 1C**) against PC12 cell damage caused by serum deprivation and against PC12 cell damage caused by nicouline. Four of these compounds were new, including moralsin.[75]

Leaves were successively extracted with *n*-hexane, PE, ethyl acetate, methanol and water. The final extract had neuroprotective activities *in vitro* (against H_2O_2 -induced oxidative damage in U87MG cells. Effect was measured with five biomarkers) and *in vivo* (against AlF_3 toxicity in rats. Effect was measured with Barnes maze test of spatial and learning memory.[76]

Follow-up of the study cited in reference 21 using mulberrofuran G, kuwanon G and albanol B (**Figure 1A**), to inhibit MAO via modulation of four dopaminergic receptors. Molecular docking is presented.[77]

Fruits aqueous extract had ameliorative activity against formaldehyde neurotoxicity in zebrafish. Effect was measured with forced swimming test.[78]

Fruits and leaves were separately extracted with 50% and 95% aqueous ethanol (four extracts). These extracts were tested separately and in combinations against hydrogen peroxide-induced neurotoxicity in SH-SY5Y Cells. Effect was measured with several biomarkers, mainly oxidant-antioxidant.[79]

Fruits 70% aqueous ethanolic extract had protective effect (measured with TPC and antioxidant biomarkers) against $AlCl_3$ -induced neurotoxicity in rats, as AD model.[80]

Fruits 70% aqueous ethanolic extract had protective effect against PD-model neurotoxicity *in vitro* and *in vivo*. In SH-SY5Y cells stressed with 6-hydroxydopamine or 1-methyl-4-phenylpyridinium (measured with several biomarkers), and in mice against 1-methyl-4-

phenyl-1,2,3,6-tetrahydropyridine (effect measured with behavioral tests).[81] Fruits 70% aqueous ethanolic extract increased contractions in human intestinal tissue and in mice, suggesting increasing both myogenic and neurogenic contractions.[82] Fruits aqueous extract had positive effect on cognitive functions and had anxiolytic and antidepressant-like effects, indicated in behavioral tests in mice.[83] Leaves/fruits ethanolic extract improved sleep in mice by around 33-35%. Effect was caused mainly due to polyphenolics and phytosterols content that increased the release of serotonin and GABA.[84,85] a) Strangely enough, authors conclude that "both Morus Alba and clozapine can be used to treat psychosis induced by amphetamine", even though amphetamine was not mentioned anywhere else in this article. b) It is not clear which extract was prepared/used. Section 2.3 is titled "collection & preparation of ethanolic extract", which was not mentioned even once more. The text beneath this title stars with "aquas leaf extract of *M. Alba* was administered ...".
Morus atropurpurea Fruits anthocyanin-rich aqueous extract was fed to mice resulting decrease of biomarkers associated with aging: serum aspartate aminotransferase, alanine aminotransferase, triglyceride and total cholesterol.[86] Fruits from four different ripening stages (May 2015) were ultrasonically extracted with methanol (contained 1% formic acid) and this extract was applied to A$\beta_{25\text{-}35}$-treated PC12 cells (AD model). Results showed direct positive link between high polyphenolic content and neuroprotective activity.[87]
Morus bombycis A follow-up of the research cited in reference 16: leaves methanolic extract was tested for amyloid β-peptide (1-42) destabilization resulting 72% (average).[17] Bark was ultrasonically extracted with methanol and this extract was analyzed affording kuwanon V (**Figure 2**). This compound increased the production of neuronal stem cells. A mechanism of action is proposed.[88] Mulberrofuran G (**Figure 1A**) was isolated from the root bark of the tree after several extraction and fractionation steps. It inhibited inhibited NOX enzyme activity and oxygen–glucose deprivation/reoxygenation (OGD/R)-induced NOX4 protein expression in SH-SY5Y cells. The enzymes are associated with cerebral ischemia.[89]
Morus latifolia A follow-up of the research cited in reference 16: leaves methanolic extract was tested for amyloid β-peptide (1-42) destabilization resulting around 73% (average).[17]
Morus lhou Bark methanolic extract was analyzed yielding eight prenylated flavones that were tested for inhibition of β-secretase (BACE-1). All compounds were active but two of them, kuwanon A and kuwanon C (**Figure 3**) had notably higher activities. Morin (**Figure 1B**) was standard reference in this research.[90] Follow-up of previous study where nine compounds were isolated: 5'-geranyl-4'-methoxy-5,7,2'-trihydroxyflavone (new), 5'-geranyl-5,7,2',4'-tetrahydroxyflavone, kuwanon U, kuwanon E, morusinol, cyclomorusin, neocyclomorusin (**Figure 3**), morusin (**Figure 1B**) and kuwanon C (**Figure 3**). All compounds apart from morusinol inhibited AChE and BuChE enzymes.[91]
Morus macroura Fruits and leaves were separately extracted with 80% aqueous ethanol and these extracts were analyzed yielding mainly polyphenols and phytosterols. Anti-AD molecular docking was performed for the pure compounds resulting four promising leads: ferulic acid, chrysin, resveratrol and moracin D (**Figure 4**). Four enzyme inhibition tests were also done for the

pure compounds.[92]
Leaves of *M. alba*, *M. indica*, *M. macroura* and *M. nigra* were separately extracted with 70% aqueous methanol. The four extracts were tested for activity in LPS-induced AD model in mice resulting highest activity for *M. macroura*. Effect was measured with several behavioral and biochemical parameters. All extracts were analyzed for chemical composition affording many active compounds where several of these were new, such as moranoline di-*O*-hexoside (1-deoxynojirimycin di-*O*-hexoside, 1-DNJ di-*O*-hexoside **Figure 4**).[93]
Leaves and stem branches were separately extracted with 80% aqueous ethanol and both extracts were partitioned with DCM and ethyl acetate. DCM fractions were tested for antidepressant activity on post myocardial infarction depression induced by isoprenaline, in rats. Effect was measured with several behavioral and biochemical parameters. DCM fractions were TLC-analyzed resulting nine active compounds, where the most active was "lupeol palmitate" (wrong name, see notice below, **Figure 4**).[94]*
Follow-up of previous study but in this research the ethyl acetate fraction was used for biological tests and analyzed for chemical composition, which is presented in a very detailed table.[95]
* In this article, "compound 6" is named more than once "lupeol palmitate" but the structure that is shown for it, also more than once, does not match this name. Palmitic, is C16:0 (saturated) fatty acid while the structure shown, even with GC-MS fragmentation, is that of lupeol palmitoleate (derivative of palmitoleic acid, C16:1, with a *Z* double bond). In addition, in "Figure 1" in the article, the stereochemistry of double bond of fatty chain is *Z* which is correct, and in "Figure 2" of the GC-MS fragmentation, the double bond is *E* which is incorrect.

Morus mesozygia
Stem bark 80% aqueous methanolic extract was prepared and partitioned with PE and ethyl acetate. Crude extract and fractions were tested for antidepressant activity in rats, using forced swimming and tail suspension methods. In all cases positive results were recorded, compared with impramine as a standard drug.[96]
Leaves 50% aqueous ethanolic extract was tested for antidepressant activity in mice, using forced swimming and tail suspension methods, compared with impramine as a standard drug. By using reserpine test, it was concluded that monoamine transporter is involved in the mechanism of action.[97]
Leaves 50% aqueous ethanolic extract was supplemented to mice before performing two depression methods: forced swimming and sucrose preference. Results showed decrease of nitrite and MDA concentrations in the brains of animals, while concentration of GSH was elevated.[98]

Morus nigra
Leaves were extracted by electrophoresis and the resulting extract was used to treat cognitive impairment and oxidative stress status of D-galactose-induced aging mice. Positive effect was recorded in water maze test and by measurement of oxidant-antioxidant biomarkers. Several antioxidant compound concentrations were determined in the extract.[99]
Fruits 80% ethanolic extract was used to treat CO_2 -induced aging damages in rats. Positive effect was recorded using behavioral tests (water maze, passive avoidance) and biochemical parameters (decrease of oxidant enzyme concentrations and increase of GABAergic interneurons).[100]
Fruits were treated with ethanol-water mixture to obtain antioxidant phenolic-rich extract. This extract inhibited β-amyloid toxicity in PC12 neuronal cells and in *Drosophila melanogaster* AD model.[101]
Fruits aqueous extract had protective effect against Aβ protein in transgenic *Caenorhabditis elegans*. Mechanistic study showed that effect was achieved by activating insulin DAF-16

(gene) signaling pathway.[102]
A slight improvement of cognitive function was recorded after 12 weeks consumption of fruits as part of their diet.[103]
Leaves aqueous extract had antidepressant and neuroprotective activities in mice. Effects were measured with three behavioral tests (forced swimming, tail suspension, open field); biochemical parameters (lipid peroxidation, protein carbonyl assay, nitrite determination, non-protein thiols); and cerebral cortex slices incubated with glutamate. Authors refer these activities to the high antioxidant capacity of the extract major component, syringic acid (**Figure 5**).[104]
Follow-up of previous study: mechanistic investigation revealed involvement of PI3K/Akt/GSK-3β signaling pathway against glutamatergic excitotoxicity.[105]
Another follow-up of the research cited in reference[104] but in this research, the hippocampal damage was induced by corticosterone.[106]
Leaves 70% aqueous ethanolic extract had antidepressant effect (and improved glucose tolerance) in ovariectomized female rats, measured with three behavioral tests.[107]
Another follow-up of the research cited in reference[104] but in this research, the role of quercetin and rutin is highlighted, in addition to syringic acid.[108]
Fruits methanolic extract had protective activity against strychnine-induced seizures (frequency and duration) in mice.[109]
Commercial fruits aqueous extract was supplemented to human healthy young adults, in combination with powders of raw sunflower and pumpkin seeds. Results showed positive effect on cognitive tasks (visual forward digit span, visual backward digit span, auditory forward digit span, auditory backward digit span, Corsi block task, working memory test); and biochemical parameters (concentrations of glucocorticoid receptor-α, glutamate dehydrogenase and brain-derived neurotrophic factor).[110]
Leaves 50% aqueous methanolic extract had protective effect against acrylamide-induced neurotoxicity in zebrafish (*Danio rerio*). Effect was measured with oxidant-antioxidant biomarkers concentrations.[111,112]
Fruits were extracted with microwave hydro-diffusion and gravity extraction and the resulting extract was tested for neuroprotective activity both *in vitro* (several models) and *in vivo* (*Caenorhabditis elegans*, several tests). Positive effects were indicated in all these tests and authors refer this to high antioxidant capacity of the extract, which was tested separately (FRAP method).[113]
Leaves aqueous extract ameliorated 6-hydroxydopamine-induced PD-like in mice. Effect was measured with three biomarkers (angiotensin converting enzyme, protein oxidation and lipid peroxidation) with captopril as a reference drug.[114,115]
PD was induced in mice using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, and after four days dyskinesia was induced using L-dopa (7 days). Then these animals were treated with fruits whole juice resulting alleviation of disease symptoms, mainly abnormal involuntary movements and cylinder behavioral test.[116]

Morus rubra

Fruits 70% aqueous extract had protective effect (measured with TPC and antioxidant biomarkers) against $AlCl_3$ -induced neurotoxicity in rats, as AD model.[80]
Leaves aqueous extract had ameliorating effect on rats subjected to physical and emotional overloads. Effect was measured with three methods: forced swimming, open field tested and water maze test.[117]

* Unless indicated otherwise, solvent mixtures are volume/volume, v/v.

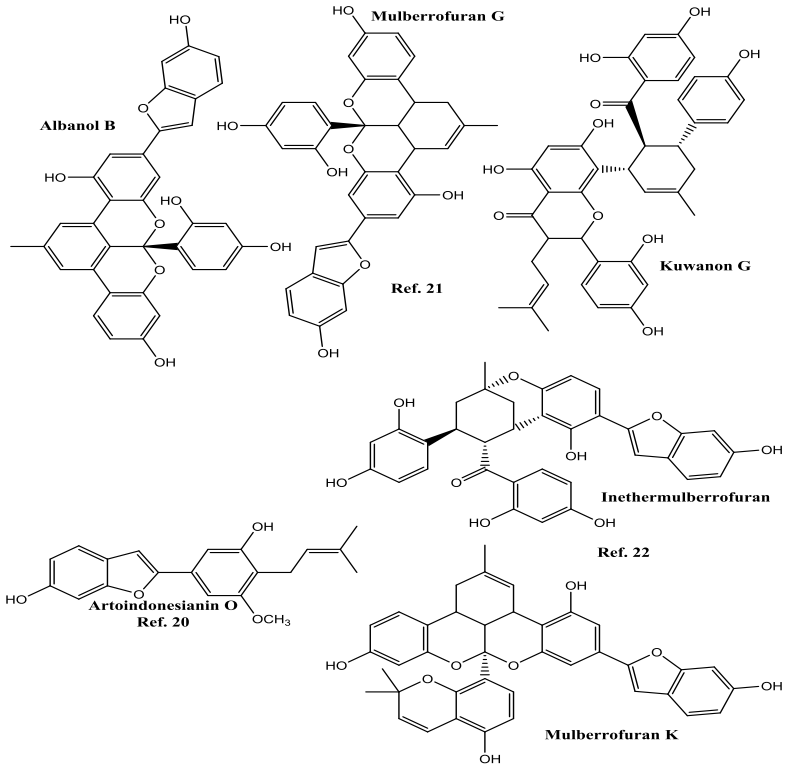

Figure 1A: Brain-Related Active Natural products isolated from *Morus alba.*

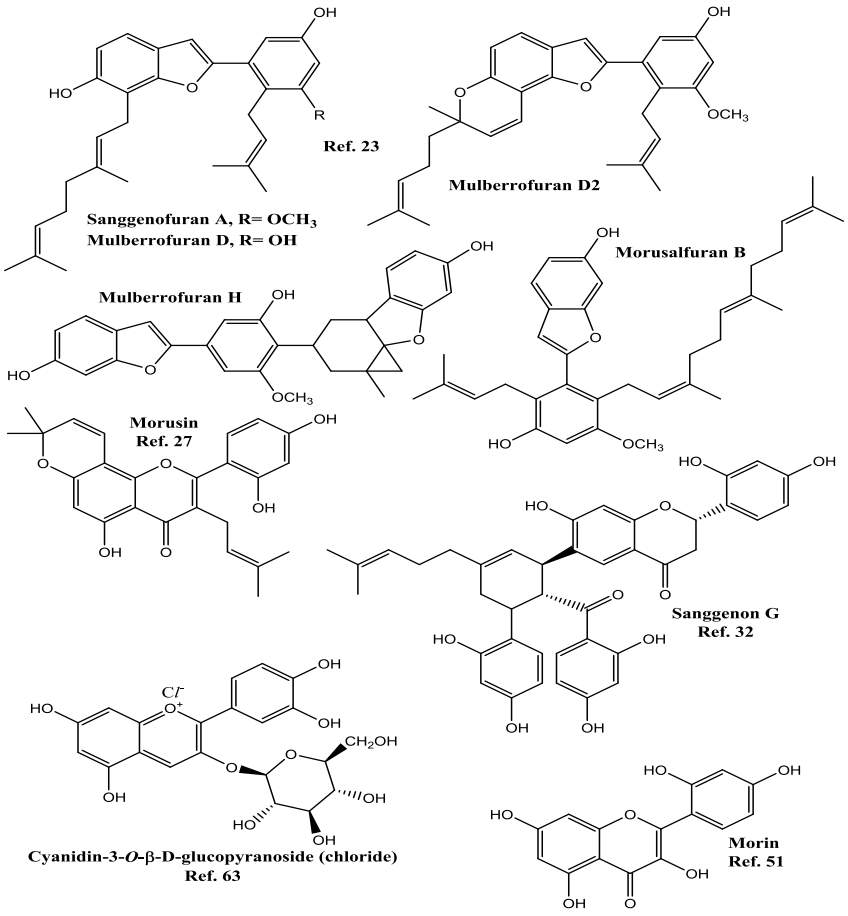

Figure 1B: Brain-Related Active Natural products isolated from *Morus alba.*

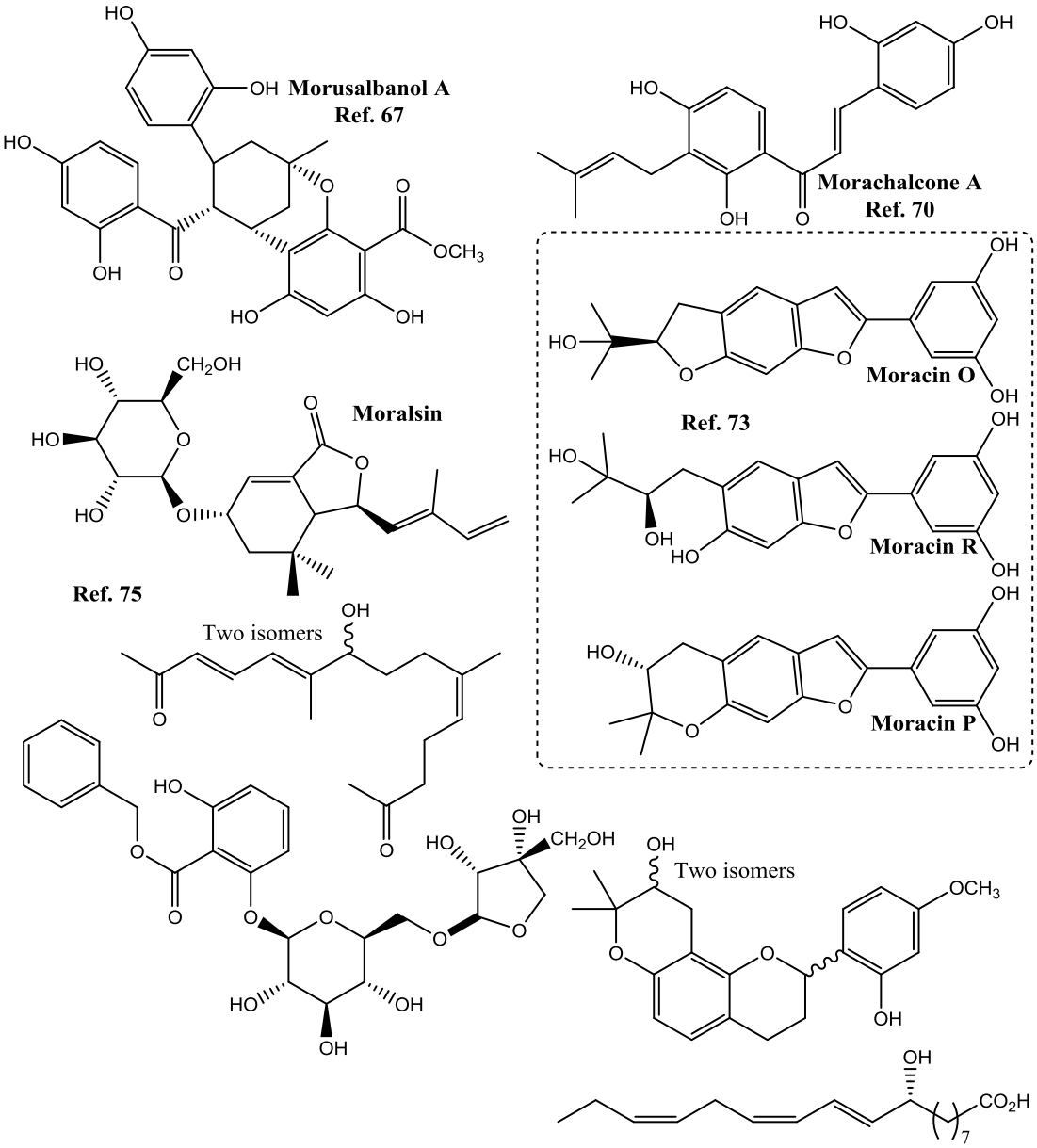

Figure 1C: Brain-Related Active Natural products isolated from *Morus alba.*

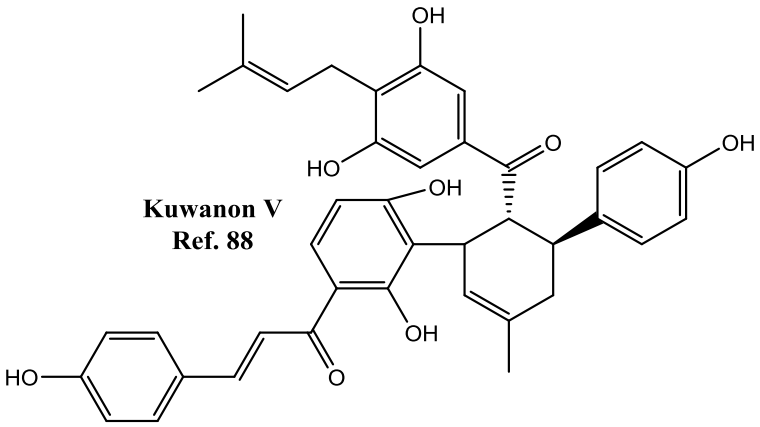

Figure 2: Brain-Related Active Natural products isolated from *Morus bombycis.*

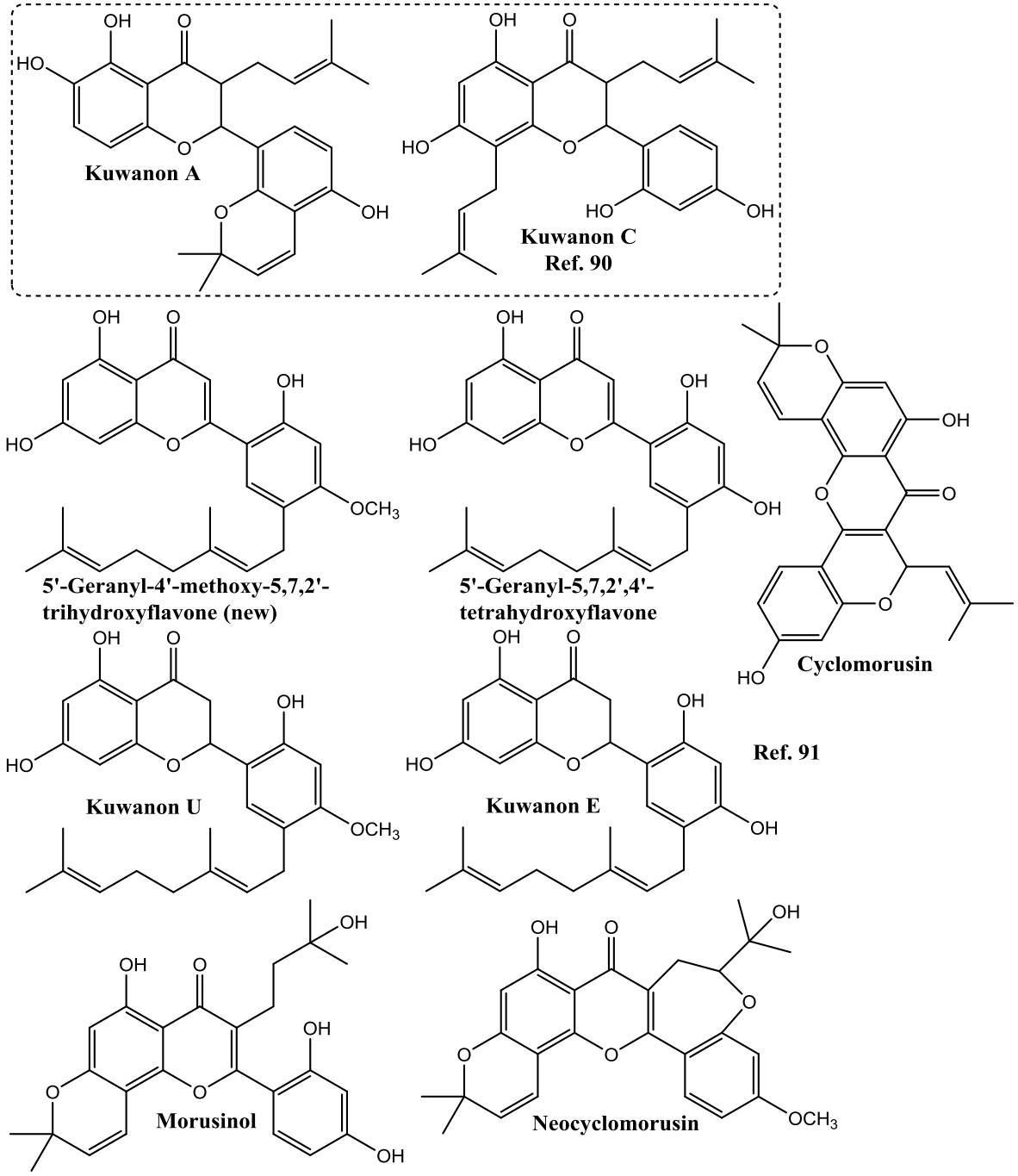

Figure 3. Brain-Related Active Natural products isolated from *Morus lhou*.

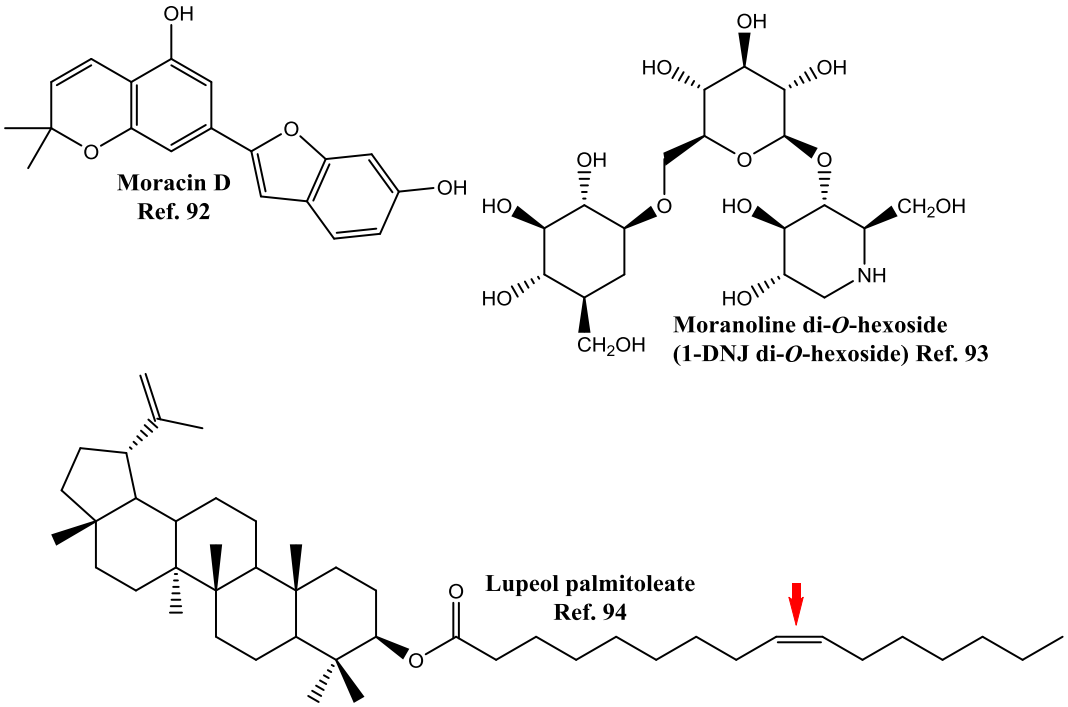

Figure 4: Brain-Related Active Natural products isolated from *Morus macroura.*

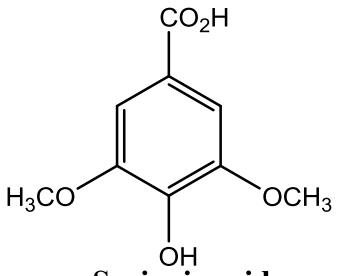

Figure 5: Brain-Related Active Natural products isolated from *Morus nigra.*

4) DISCUSSION

Numerous publications and reports indicate that he prevalence of brain-related health disorders is expanding in a worrisome fashion over the last few decades. Among those, neurodegenerative like Alzheimer's (AD) and Parkinson (PD) diseases are most widespread, and consequently, most damaging. For example, A.S. Abdul Manap ahc stated that by 2024 there were 35 million people worldwide that suffered AD, and it is expected that this number will reach around 140 million.[118] As for PD, in 2021 the total worldwide number of cases was around 11.3 million and predicted to reach around 25.2 million in 2050, according to D. Su ahc.[119] But these numbers are highly debated, at least for AD: J. Zhang ahc estimated that 55.2 million people are globally affected by dementia, and this number will reach 78 million

people by 2030, five years from now[120]! And to conclude this introduction, it is worthwhile citing some startling statistics from the review article of Q. Jiang ahc.[121] They state that the number of elderly (aging) people aged 60 and over will rise from 1 to 2.1 billion. The global costs of dementia are expected to increase from around USD 1 trillion in 2015 to around USD 9.12 trillion in 2050.

These shocking statistics have caught the attention of decision makers and there a trend of awareness and efforts to prepare for the coming decades. Major part of these preparations involves medicinal plants and their derived natural products, which some of them, have long and proven history of neurodegenerative disorders amelioration. For example, the very well-known phenolic acids, chlorogenic and gallic (**Figure 6**), and this activity is strongly related to their superb antioxidant capacity.[36,122,123]

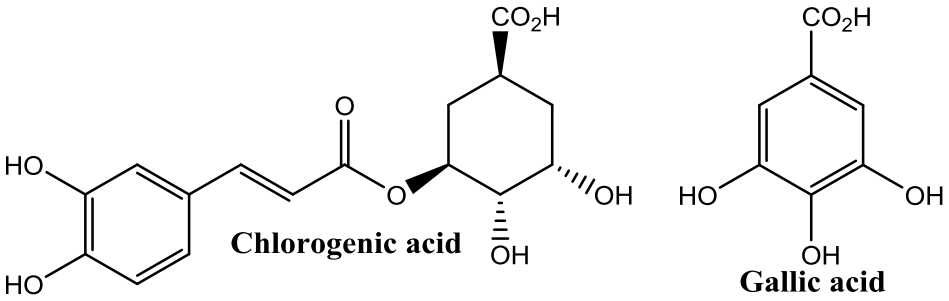

Figure 6: Chlorogenic and gallic acids. Neuroprotective natural products.[36,122,123]

One of the natural products that is clearly associated with *Morus* trees is morin (**Figure 1B**), which we presented through the publications of Y. Du ahc [in *Morus alba*, 51] and J.K., Cho [in *Morus lhou*,[90] Among the compounds that were isolated from *Morus* trees, it is one of the most studied.

H. Hlasiwetz, and L. Pfaundler reported the first isolation and characterization of this compound as early as 1863[124], but it was not significantly investigated for medicinal properties until the early 2010's. J.Y. Yang and H.S. Lee reported its isolation from *M. alba* along with its antioxidant and antibacterial activities[125], and S.A. Rajput ahc published one of the significant review articles about its activities.[126] In addition to the two publications that we cited earlier about the brain-related activities of this compound, several more articles were published, focusing mainly on neuroprotection and PD: Z.T. Zhang ahc[127], D.G. Hong ahc[128], Z. Wang ahc[129], S. Banaeeyeh ahc[130], and some others.

A comprehensive literature survey about *Morus* species that we made revealed more than 3000 research and review articles, where more than half of them discuss *Morus alba*, that seems to be the most used species. According to Y. Wang ahc, "in traditional Chinese medicine, *M. alba* L. is regarded as a treasure due to the rich active ingredients and modern activities of its different parts".[131] This "dominance" is very clear also according to **Table 2**.

A. Paul ahc performed computerized simulation (molecular docking) for some of the anti-AD (inhibition of AChE and glycogen synthase kinase-3β) components of *M. alba* and discovered clear synergistic relationships.[132] This finding puts a challenge in front of scientists concerning the use of pure natural products vs whole extracts and other non-chromatographed plant products. One of these interesting pure natural products is GABA. *Morus alba* extracts and pure natural compounds contained in these extracts have clear positive effect on brain GABA [G. Gupta ahc, 26,27 and other references]. But *Morus alba* plant materials contain GABA in significant concentrations, and this compound was extracted from leaves and proved to have notable anti-fatigue activity in mice.[133]

In **Table 1** we presented several reports of the memory enhancement by *Morus alba* extracts and pure compounds [J. Wattanathorn ahc 50, Y. Du ahc 51, and other references]. J. Wattanathorn ahc reported another research on this type where they combined the extracts of *Morus alba* and *Polygonum odoratum* to produce quercetin-rich formulation.[134] This product has notable memory enhancement activity in humans. One of the major components of *Morus alba* that has clear positive on memory is morin, which we thoroughly presented and discussed in this article. H. Martínez-Coria ahc investigated the effect of pure commercial morin on memory of mice, and results indicated significant positive effect.[135] And since using commercial plant-derived pure compounds and extracts is very common [See for example, P. Rangseekajee ahc, 38, S-T., Ma ahc, 69, and other references], for *Morus alba* and numerous plants, for scientific research, medicine and nutrition; it is highly important to ensure the quality of these commercial products. In this context, the work of M. Polumackanycz ahc that tested the phenolic composition (and some biological activities including AChE inhibition) of *Morus alba* commercial products, is highly important.[136]

Pure compounds isolated from *Morus alba* play key role in inhibition of monoamine oxidase (MAO) [K.H. Hwang ahc, 43, P. Paudel ahc, 77, and several other references]. This enzyme is responsible for many health disorders, especially of neurodegenerative nature.[137] It

oxidizes primary and secondary amine entities (conjugated acids), and the general scope of its mechanism of action is shown below in **Figure 7** [R. Aljanabi ahc.[138]

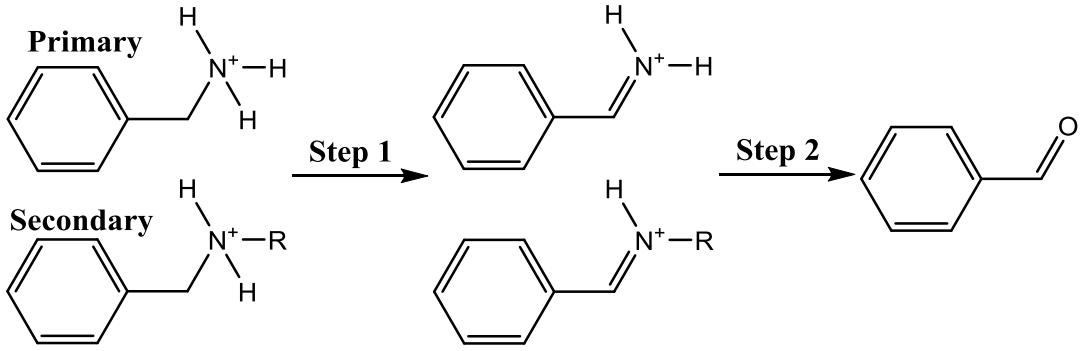

Figure 7: Oxidation of primary and secondary amines (conjugated acids) by MAO.[138]

In the last few years, several comprehensive review articles about plant derived MAO inhibitors were published, and natural products of *Morus alba* are included. The strength of the review of T. Das ahc is the presentation of structure-activity-relationships, but its weakness is poor presentation of some structure.[139] The article of N.D. Chaurasiya has no weaknesses: its very comprehensive and detailed, natural products are presented properly, it presents mechanisms of action, and its major strength from the point of view of our article, is that if focuses on brain-related activities.[140]

To conclude this part of the discussion about *Morus alba*, it is worth mentioning the concerns about the safety/toxicity of this species. Several studies were conducted to evaluate this safety/toxicity, and we will cite three of them that concluded that the fruits of *Morus alba* and their extracts are very safe, up to 2000 mg/kg in mice/rats: A. Paul ahc[141], P. Sood ahc[142] and A. Fauzi ahc.[143]

D.W. Lim ahc prepared extracts of root bark of *Morus alba* and found that these extracts had antidepressant activity.[31] In two follow-up works, they analyzed these extracts for active compounds and discovered that sanggenon G (**Figure 1B**) was the major antidepressant.[32,33] T. Fukai ahc reported in 1998 the isolation of five new sanggenols (sanggenol J is shown in **Figure 8**) from the root bark of *Morus cathayana* collected.[144] Authors stated that these sanggenols have geranyl groups and same skeleton as sanggenons A-E. Y. They also isolated sanggenons A, C, D, L and M. Qin ahc reported that commercial sanggenon C (that can also be isolated from *Morus alba*, **Figure 8**) had antidepressant activity in rats.[145]

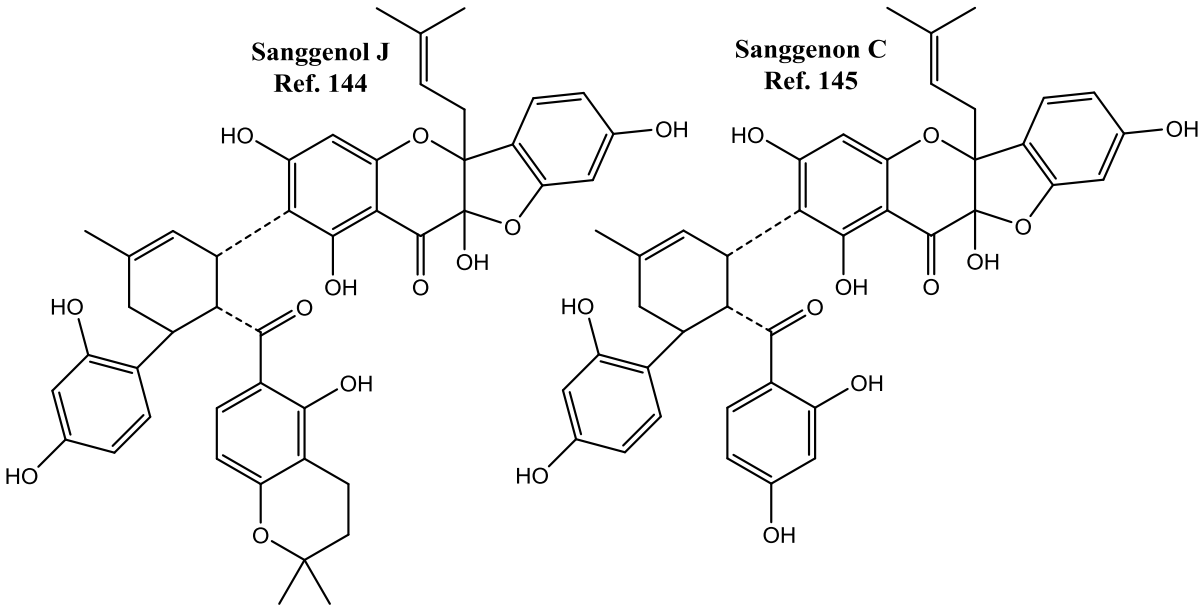

Figure 8: Structures of Sanggenol F and Sanggenon C.

1-Deoxynojirimycin (DNJ, 1-DNJ, duvoglustat, moranolin or moranoline; we will use 1-DNJ) is (2R, 3R, 4R, 5S)-2-hydroxymeth yl-3, 4, 5-trihydroxypiperidine (**Figure 9**).

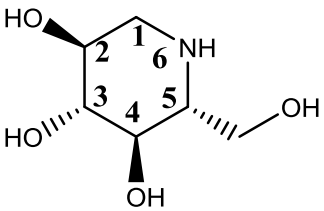

Figure 9: Structure of 1-Deoxynojirimycin (1-DNJ).

It was isolated for the first time from *Morus alba* by M. Yagi ahc in 1976[146], and it is best known for its strong α-glucosidase inhibition, and thus, being highly antidiabetic.[147] Due to its many medicinal activities, several special methods were developed to determine its content in plant materials, such as the work of J-W. Kim ahc.[148] In addition, several unique methods were developed to enhance its content in *Morus* species, and as a result, its biological activities. Among these, the work of J.H. Jeong ahc[149] and Y-G. Jiang[150], are of special significance.

The proposed biosynthesis of 1-DNG was studied and published by D. Wang ahc in a very detailed and comprehensive research article[151]: it comprises eleven steps. Y.R. Esti Wulandari ahc developed a method for determination of 1-DND, and it is adapted to the

seasonal content of this compound according to maturity stage.[152] And C. Liu ahc developed an efficient method for determination and extraction of 1-DNJ *Morus alba* tea.[153]

1-DNJ was tested for brain-related activities that match our review article, where results indicate significant activities. G-H. Chen ahc reported antiaging activity[154], I.S. Parida ahc published anti-AD activity in insulin resistance conditions with proposed mechanism of action[155], W. Chen ahc published neuroprotective activity against cognitive impairment, β-amyloid deposition, and neuroinflammation[156] and TC Costa ahc used 1-DNJ in combination with ibuprofen for neuroprotection against microglial activation, phagocytosis and dopaminergic degeneration.[157] Toxicity issues of 1-DNJ were studied and published by several groups. T.K. Marx ahc tested *Morus alba* aqueous extract, standardized with 5% 1-DNJ.[158] They supplemented this extract to rats for 28 days resulting no toxicity up to very high dose of 4000 mg/kg.

Morus nigra is one of the three most widespread of this genus (the others are *Morus alba* and *Morus rubra*).[159] It is probably also the tastiest. E.M. Tousson and B. Al-Behhehani report a unique use of its fruits dark color: a natural dye for nervous tissues staining.[160]

A research group lead by A.L. Bertarello Zeni published four articles about the brain-related activities of *Morus nigra* with special focus on "major phenolic, syringic acid" as the major active compound in antidepressant activity.[104-106,108] We have presented the structure of this acid in **Figure 5**. In the second publication,[105] a mechanistic study revealed involvement of PI3K/Akt/GSK-3β signaling pathway against glutamatergic excitotoxicity. Ö. Güzelad ahc studies the anti-PD (induced by 6-Hydroxydopamine) mechanism of syringic acid in rat model.[161] They discovered that antioxidant capacity of this compound enables the anti-PD activity.

To finalize this part of the discussion about *Morus nigra*, we want to shed light on the publication of X. Hu ahc, where they isolated and characterized ten new isoprenylated flavonoids, nigrasins A-J, where two of them (nigrasins H, I) had significant adipogenesis promoting activity.[162] All these nigrasins have close structures to active compounds that we presented in previous figures. To the best of our knowledge, nigrasins have never been tested for brain-related activities. In **Figure 10** the structures of nigrasins H, I are presented.

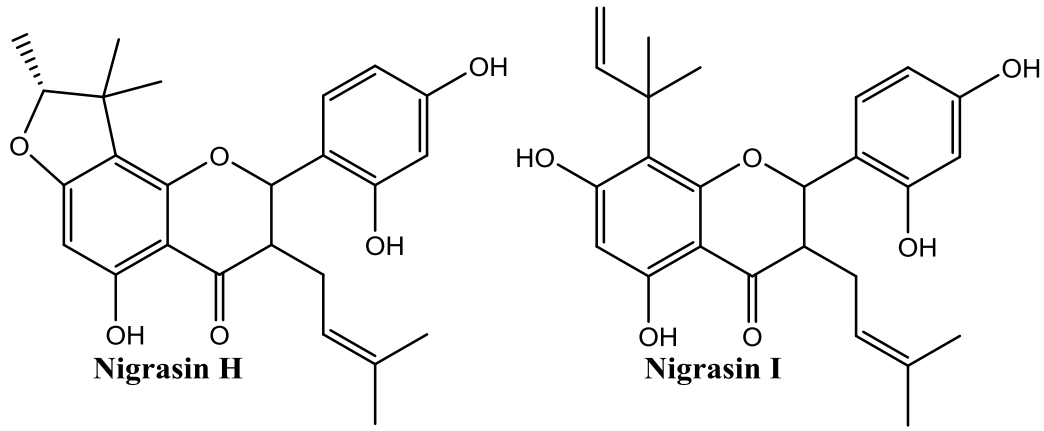

Figure 10: Structures of nigrasins H, I isolated from *Morus nigra*.[162]

Oxyresveratrol is one of the most active and health beneficial natural products. It was published in hundreds of research and review articles, where the review article of K. Likhitwitayawuid: it is comprehensive, detailed and presents sources, production, biological activities, pharmacokinetics and delivery systems.[163] Its biosynthesis in *Morus alba* was recently published by A. Santiago ahc[164], and its structure with the structure of resveratrol are shown in **Figure 11**.

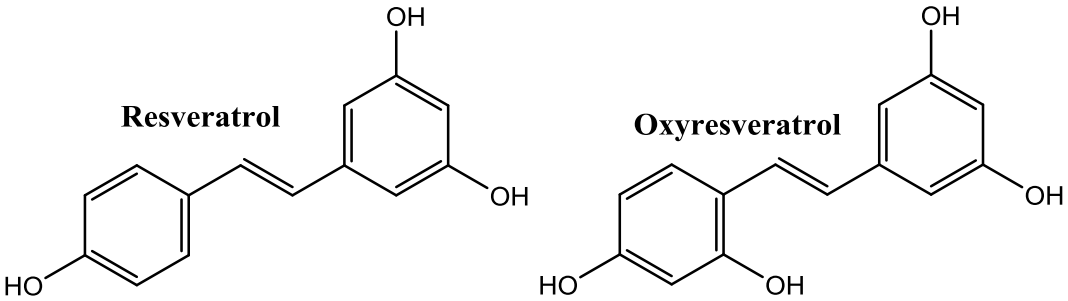

Figure 11: Structures of Resveratrol and Oxyresveratrol.[164]

Finally, J.T. Weber ahc reported neuroprotective effects of oxyresveratrol against traumatic injury, *in vitro*.[165]

5) CONCLUSIONS

1) *Morus* trees possess great potential for treatment brain-related disorders.

2) *Morus alba* was sufficiently investigated for these activities but other *Morus* species were either partially studied or not at all.

3) It is very important to expand research to maximum number of *Morus* species.

4) Some structurally very interesting natural products isolated from *Morus* species were never studied for brain-related disorders, and this should be done.

5) It is highly important to encourage people worldwide to consume foods from *Morus* trees.

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