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REVIEW ARTICLE

Potential of Medicinal Plants as Neuroprotective and Therapeutic Properties Against Amyloid-β-Related Toxicity, and Glutamate-Induced Excitotoxicity in Human Neural Cells

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Abstract: Alzheimer's disease (AD) and Parkinson's disease (PD) are notorious neurodegenerative diseases amongst the general population. Being age-associated diseases, the prevalence of AD and PD is forecasted to rapidly escalate with the progressive aging population of the world. These diseases are complex and multifactorial. Among different events, amyloid β peptide (Aβ) induced toxicity is a well-established pathway of neuronal cell death, which plays a vital function in AD. Glutamate, the major excitatory transmitter, acts as a neurotoxin when present in excess at the synapses; this latter mechanism is termed excitotoxicity. It is hypothesised that glutamate-induced excitotoxicity contributes to the pathogenesis of AD and PD. No cure for AD and PD is currently available and the currently approved drugs available to treat these diseases have limited effectiveness and pose adverse effects. Indeed, plants have been a major source for the discovery of novel pharmacologically active compounds for distinct pathological conditions. Diverse plant species employed for brain-related disorders in traditional medicine are being explored to determine the scientific rationale behind their uses. Herein, we present a comprehensive review of plants and their constituents that have shown promise in reversing the (i) amyloid-β -related toxicity in AD models and (ii) glutamate-induced excitotoxicity in AD and PD models. This review summarizes information regarding the phytochemistry, biological and cellular activities, and clinical trials of several plant species in view to provide adequate scientific baseline information that could be used in the drug development process, thereby providing effective leads for AD and PD.

Keywords: Alzheimer's disease, beta-amyloid, Parkinson disease, glutamate excitotoxicity, plant derived-compounds, neurodegenerative diseases (NDS).

1. INTRODUCTION

Neurodegenerative diseases (NDs) form part of the leading causes of morbidity and mortality, especially among the elderly [1]. Globally, 50 million people have dementia and the two main causes are Alzheimer's disease (AD) which corresponds up to 70% of cases and Parkinson's disease (PD) [2]. Moreover, an estimation in 2016 revealed that 5.4 million Americans suffer from AD while it is estimated that in 2020, around 900,000 Americans could be living with PD [3]. Dementia does not pose an ill health and economic burden for the patient solely but also for the patient's family, carers and society at large [2]. Generally, NDs are on the rise worldwide [4].

Some of the prime factors that have contributed to an escalation in NDs cases worldwide relates directly to the increase in modern man's life expectancy, the complexity of NDs as well as the lack of an adequate cure for NDs [5, 6]. Given an increase in the elderly population, NDs remain important for scientists to efficiently tackle [7]. Generally, NDs induce cognitive and memory deterioration that interfere with the person's ability to breathe, move and speak. Hence,

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given the distress that NDs induce, effective treatments are warranted to improve the daily living of patients [5]. Concretely, AD is hallmarked by two main characteristics: (i) the synthesis and subsequent accumulation of the extracellular amyloid-beta (Aβ) plaques and (ii) deposition of the intracellular hyperphosphorylated tau proteins/neurofibrillary tangles in the brain [8]. On the other hand, PD is marked by a diminution of pigmented neurons in the substantia nigra pars compacta region of the brain as well as in the Lewy body or neurite that results in a reduction in the neurotransmitter dopamine [9, 10]. This results in post accumulation of misfolded α-synuclein, which is the main protein marker in PD [11]. Clinical symptoms of PD are characterized by akinesia/bradykinesia, postural instability, rigidity and tremor [12]. Interestingly, biochemical, genetic and molecular studies have concluded that there are several shared mechanisms among both AD and PD pathogenesis. These relate to the involvement of *α*-synuclein protein, genes, iron, locus coeruleus, mitochondrial dysfunction, oxidative stress, and tau protein in the progression of both diseases. Research on these factors should be encouraged to unveil approaches that might prove beneficial in NDs therapy [13].

Medication use is a crucial resource for people living with NDs [14]. Alike, treatment with levodopa is considered one of the main approaches in PD. Nonetheless, with time, patients become dependent on the drug and symptoms exacerbate [15]. In PD rat models, dorsal column stimulation, alongside 6-hydroxydopamine administration, resulted in richer dopaminergic innervation in the striatum as well as a higher number of neurons in the substantia nigra pars compacta. Therefore, the dorsal column stimulation model has been proposed as an additional therapeutic approach that can be adopted in PD patients [16]. Given that existing therapies can only focus on addressing the symptoms of NDs and that NDs are directly related to aging, there is a dire need for the development of therapies that can retard the development of the disease [17]. In addition, existing therapies are costly and accompanied by major side effects [1]. Deep brain stimulation therapy is also available but is reserved only for those patients who fulfill a number of criteria [16].

The following biological processes are involved in the pathogenesis of NDs including apoptosis, excitotoxicity, inflammation, mitochondrial dysfunction, oxidative stress, and protein misfolding [18]. In fact, botanicals such as fruits and vegetables are rich in polyphenols that can neutralize oxidative stress, chelate heavy metal ions, protect cells, act as anti-inflammatory agents as well as enzyme (cholinesterase and β-secretase) inhibitors and hence ward the body against NDs [4, 19, 20]. Alongside, phytochemicals can preserve neutrophins levels, which in turn play a crucial role in maintaining and keeping alive neural cells [4]. On the other hand, phytochemicals such as astragaloside IV from *Astragalus membranaceus* (Fisch.) Bge, bearing anti: apoptotic, inflammatory and oxidant properties can improve motor deficits and neurochemical activity [21].

Given that reviews that highlight the potential of medicinal plants on NDs, particularly AD and PD are limited, the aim of this review is to use the latest available literature sources to focus on the most pertinent prospective plants as well as their corresponding metabolites that have potential prospect to be developed as therapeutic candidates for NDs. Research on plants against NDs has prompted increase consumption of neuroprotective phytochemicals [4]. Concomitantly, it is also a sustainable effort towards the research and development of low side effects and better cost-effective medicinal agents to uplift the quality of life of NDs sufferers [22].

2. AMYLOID-β-RELATED TOXICITY THE PATHOGENESIS OF AD

The current AD pathogenesis theory, the amyloid hypothesis, indicates that the build-up of pathological forms of amyloid beta (Aβ) due to an increase in the formation and/or reduced elimination is the chief pathological process implicated in AD [23]. Aβ is a short peptide (4.2 kDa) consisting of 40-42 amino acids produced by the intracellular break down of the amyloid precursor protein (APP) *via* subsequent action of β- and γ-secretase two proteolytic enzymes. The neuropathological events taking place in AD patients are likely to result from the toxicity of Aβ aggregated forms such as amyloid oligomers and fibrils instead of its monomeric form. The polymeric forms of Aβ activate alterations in biomolecules and activities in brain cells, causing numerous neuropathological anomalies linked to AD symptoms [24]. Besides, Aβ aggregation and deposits outside neurons in the brain tissues of individuals having AD, cause neuritic plaques to be formed, also referred to as senile or amyloid plaques. The occurrence of these neuritic plaques represents the key pathological feature of AD. Thus, Aβ peptide, the major component of these plaques, plays a fundamental role in AD and is considered as the cause of disease's progress [24].

As a result of Aβ accumulation, the amyloid level is controlled by the body *via* numerous mechanisms. The APP controls the concentration of Aβ peptide and influx into the brain across the blood-brain barrier (BBB), chiefly through the receptor for advanced glycation end products (RAGE), and by elimination from the brain *via* the low-density lipoprotein receptor-related protein-1 (LRP1), as well as enzymatic degradation within the brain [25-27]. Therefore, disturbance in these mechanisms results in the build-up and deposit of excess levels of Aβ peptide in AD brain [24]. Additionally, numerous studies have reported Aβ toxic properties to be mediated by a number of key mechanisms, including oxidative stress, mitochondrial diffusion, changes in membrane permeability, synaptic dysfunction, inflammation, and excitotoxicity through its interaction with some neurotransmitters receptors, amongst others [28-32].

It has been suggested that oxidative stress, an overproduction of free radicals or a diminution of free radical scavenging capacity compared to those of cognitively aged-matched controls, is extensively acknowledged as a crucial factor in the pathogenesis and development of AD [33]. Oxidative stress may trigger changes in Aβ metabolism and the activation of stress responsive kinases, which can then lead to neuronal degeneration and thus AD pathology. In fact, various studies have highlighted the beneficial effects of antioxidants against Aβ toxicity or AD pathology in animal or cell-based models of AD [34].

NADPH oxidase (NOX) is one of the main enzymes implicated in the process of oxidative stress. Its overexpression is brought about particularly by microglial activation in the brain in both chronic and acute conditions. NOX seems to play a role in AD, especially by the action of NOX2, which is upregulated in the brain of AD patients. NOX2 expression is induced by the presence of Aβ plaques that cause the activation of microglial NOX leading to superoxide formation, which in turn leads to mitochondrial dysfunction, cleavage of nucleic acids, and proteolysis [35]. A direct association between cognitive impairment in AD patients and the increase of NOX activity has also been reported [36].

Besides, it has been suggested that Aβ disturbs the oxidative balance and increases oxidative stress by causing mitochondrial dysfunction and lipid peroxidation. Furthermore, the methionine at 35 position of Aβ is thought to be critical for Aβ-induced oxidative stress and neurotoxicity, and the presence of methionine sulfoxide reductase might play an antioxidant role in AD [37].

The abnormal tau hyperphosphorylation is a characteristic of AD and other associated neurodegenerative conditions, called tauopathies. In healthy neurons, tau, a phosphoprotein potentially having 80 serine/threonine and 5 tyrosine phosphorylation sites, is a vital constituent of microtubules, which are the internal support structures for transporting vesicles, mitochondria, chromosomes and nutrients from the cell body to the ends of the axon and back. Besides, microtubules stabilize growing axons crucial for the growth and development of neurites. In a normal brain, tau contains 2-3 moles of phosphate per mole of the protein, however, in AD brain, the phosphoprotein is unusually hyperphosphorylated to a stoichiometry of at least three times greater than normal tau, and in this changed state, it is aggregated into paired helical filaments giving way to neurofibrillary tangles (NFTs). The density of NFTs in the neocortex is linked with dementia and is considered a potential therapeutic target and an area of growing research interest [38, 39].

The therapeutic approach in the management and treatment of AD is to decrease amyloid levels, prevent amyloid aggregation/toxicity, as well as tau phosphorylation/ aggregation [40]. There are four types of treatments for AD that have effectively progressed to advanced phases in clinical trials, namely (1) immunotherapies, (2) secretase inhibitors, (3) selective $A\beta_{42}$-lowering agents (SALAs), and (4) anti-Aβ aggregation agents [41].

Immunotherapy triggers the host immune system to detect and attack Aβ or produces antibodies that improve the clearance of Aβ oligomers or plaques, thereby inhibiting the accumulation of plaque. Active or passive Aβ immunization prevents Aβ to oligomerize, which explains why antibodies to Aβ can be utilized to lower cerebral plaque levels. This reduction is brought about by promoting microglial clearance and redistribution of the peptide from the brain to the systemic circulation. Several antigenic determinants of Aβ are exposed and accessible for antibody capture of the soluble peptides, whereas others are available for antibodies to attach with oligomers [42]. Several anti-Aβ antibodies have been tested in clinical trials, notably, bapineuzumab, gantenerumab, solanezumab, crenezumab, and ponezumab, among others [43].

Aβ is formed through the sequential endoproteolysis of APP by the enzymes β-secretase and γ-secretase. β-secretase cuts first at the N-terminus of Aβ; γ-secretase cleaves only after that to make the C-terminus of Aβ. Aβ is then secreted from neurons to produce amyloid plaques in the AD brain. For that reason, inhibition of β-secretase could consequently diminish the production of Aβ, the pathogenic form of the peptide [44].

BACE1 is the β-secretase enzyme that cleaves the transmembrane APP and, along with γ-secretase, generates Aβ species that in AD produce increasingly bigger and conformationally complex soluble regionally deposited brain aggregates. Cleavage of BACE1 is the rate-limiting step for the formation of Aβ [45]. In fact, BACE1 has been comprehensively inspected in the context of brain amyloid genesis and was shown to be directly involved in the production of Aβ according to *in vivo* studies [46-48]. BACE1 inhibitors can be classified into two major categories, peptidomimetics and nonpeptidics, and further sub-classification can be made based on the core functional groups that interact with the catalytic dyad [49]. Furthermore, BACE1 has been pharmacologically targeted, with several inhibiting compounds making it to clinical development and trials, efficiently reducing levels of Aβ in humans [45].

Furthermore, hyperphosphorylation leads to solubility loss and results in the development of paired helical filaments (PHFs), which further aggregate to NFTs [50-52]. Tau protein hyperphosphorylation arises due to an imbalance of tau phosphorylation and dephosphorylation. Thus, several kinases acknowledged being imperative for the pathological tau hyperphosphorylation have been the focus of drug discovery and screening approaches [53].

Other post-translational alterations of tau, like proteolytic truncation [54] and acetylation [55], are also taken into consideration as part of the pathogenic mechanism of tau in neurodegeneration and as possible targets for therapeutic intervention. Inhibition of tau aggregation could be valuable given that selective, potent, and brain-penetrant compounds could be established, but this has proved to be quite difficult. The detachment of abnormal, hyperphosphorylated tau from microtubules in AD neurons has led to the development of microtubule stabilizers to avoid any loss of normal tau function that could lead to AD [56]. Nonetheless, such compounds need to stabilize microtubules without overstabilizing them, given that the dynamic assembly and disassembly of microtubules is vital for their normal function, such as in replication of cells and axonal transport.

Aggregation of Aβ protein is regarded as one of the contributors in AD development. Numerous investigations have established the significance of non-steroidal anti-inflammatory drugs (NSAIDs) as Aβ aggregation inhibitors [57]. Laboratory experiments have even suggested that NSAIDs can decrease AD pathology by hindering microglial activation or deposits of Aβ peptide [58-60].

There are two principal isoforms of Aβ, the 42-residue (Aβ42) and the 40-residue (Aβ40). The single difference

between these two is that Aβ42 has two additional residues at the C-terminus. The amyloid plaques in AD brains consist mostly of Aβ42 and some plaques include only Aβ42, although Aβ40 level is several-fold higher than Aβ42 [61, 62]. A subset of NSAIDs seems to modify γ-secretase cleavage away from the more fibrillogenic $A\beta_{42}$ species towards peptides such as $A\beta_{40}$ and $A\beta_{38}$ [63, 64]. These findings suggested that this γ-secretase effect is key to NSAIDs' apparent capacity to protect against AD, with the subset of NSAIDs referred to as "selective $A\beta_{42}$-lowering agents" being responsible for the lowered AD risk with NSAIDs overall [65]. In fact, earlier epidemiologic studies have also shown that the use of NSAIDs can provide a protective effect against the development of AD [66-68]. Amid the multiple mechanisms that have been proposed, NSAIDs could serve as a barrier to cyclooxygenase, leading to reduced levels of prostacyclins, prostaglandins, and thromboxanes, which are essential substances in AD pathogenesis [69-71].

Examples of other agents that are regarded as neuroprotectants are activity-dependent neurotrophic factor (ADNF) and humanin, which have demonstrated their capacity to suppress amyloid toxicity. Nevertheless, these compounds possess certain constraints; for instance, ADNF seems to lose its protective effects at high concentrations and humanin has a relatively low bioavailability since it is susceptible to degradation. Nevertheless, a 'hybrid peptide', colivelin, appears to be promising. Colivelin is a synthetic peptide arising from the combination of ADNF to a derivative of humanin; which was observed to exhibit significantly strong protective effects against amyloid toxicity at low concentrations (100 fM), protects against memory deficiency, and has the capability to cross the BBB [72].

3. GLUTAMATE EXCITOTOXICITY IN THE PATHOGENESIS OF PD

The primary clinical manifestations of PD comprise resting tremor, muscle rigidity, bradykinesia, impaired postural reflexes, and varying magnitude of autonomic dysfunction. The characteristic pathological changes in PD consist of the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) of the rostral midbrain that project to the striatum (nigrostriatal pathway), including the existence of intracytoplasmic inclusions (Lewy bodies) in these neurons. The exact cause of PD remains unknown, although a number of toxic mechanisms implicated in neuronal damage have been suggested, such as oxidative stress, mitochondrial dysfunction, protein misfolding and aggregation, and excitotoxic injury mediated by altered glutamate neurotransmission [73].

Glutamate, a major excitatory amino acid neurotransmitter in the brain [74], plays essential roles under physiological conditions in nerve cell function and brain plasticity by activating glutamate receptors. However, the excessive activation of glutamate receptors during neurological conditions can result in loss of nerve cell function and lead to death of cells by a process called excitotoxicity. Glutamate-mediated excitotoxicity is set off by the build-up of excess glutamate in the extracellular space that triggers the overactivation of glutamate receptors, thereby disturbing the cell membrane permeability, as well as causing the downstream activation of signalling cascades implicated in the loss of nerve cell function, cell damage and death [75].

Excitotoxicity is associated with many neurodegenerative disorders such as AD, Huntington's disease, lateral amyotrophic sclerosis, stroke or traumatic brain injury, including PD. Glutamate in both neurons and glial cells is synthesized through the tricarboxylic acid cycle and also in neurons by the glutamate-glutamine cycle, where it is accumulated in vesicles for future discharge [76]. Glutamate-mediated neurotransmission occurs *via* particular receptors. There are two families of glutamate receptors positioned on the plasma membrane of neurons, namely ionotropic glutamate receptors (iGluR), acting as ion channels and metabotropic glutamate receptors (mGluR), which are allied to intracellular second messenger systems [77]. mGluRs are G-protein-coupled membrane receptors that mediate their actions through GTP (guanosine 5'-triphosphate)-binding protein-dependent mechanisms linked to phospholipase C and phosphoinositide turnover that mobilise internal Ca^{2+} stores. mGluR subtypes have been found to cause the downregulation of K^+ channels and upregulation of non-selective cation channels, restrain GABA (gamma-aminobutyric acid) receptor activity, as well as potentiate iGluR function, causing improved neuronal excitability. Consequently, these receptors have a pivotal function in mediating neuronal plasticity, pain, nociception, and in some cases, neurodegeneration. iGluRs play a vital part in mediating the synaptic plasticity that is involved in our capability to learn and create memories. The ionotropic family of receptors can be separated into pharmacologically different subfamilies with respect to their affinity for N-methyl-D-aspartate (NMDA), a-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) or kainite. iGluRs are composed of ligand-gated ion channels displaying permeability to Na^+, K^+ and Ca^{2+} ions [78, 79]. However, NMDA receptors exhibit a superior permeability for Ca^{2+} than do AMPA or Kainic acid receptors and possess a higher capacity for inducing intracellular Ca^{2+} overload and initiating the degenerative cascade [80].

Under pathological stimuli, glutamate release is excessive; glutamate receptors overactivation follows, resulting in an amplified intracellular Ca^{2+} influx (Fig. **1**). This elevated intracellular Ca^{2+} concentration disturbs calcium homeostasis and starts off a cascade of signalling pathways, leading to the upregulation of neuronal nitric oxide synthase, mitochondria dysfunction, and deregulated oxidative phosphorylation, ROS formation, ER stress, and discharge of lysosomal enzymes. The excessive Ca^{2+} concentration is the key mediator of glutamate toxicity through overactivation of ionotropic and metabotropic receptors. Glutamate build-up can hinder cystine uptake as well, by causing the reversal of the action of the cystine/glutamate antiporter (Xc^-) which then strengthens the aforementioned events by exhausting neurons of cystine and eventually glutathione, leading to the accumulation of free radicals. During the absence of glutamate receptors, glutamate toxicity concurs through this antiporter, encouraging a Ca^{2+} independent, non-receptor mediated oxidative glutamate toxicity. Glutamate exhibits its toxic effects through molecular pathways, leading to neurodegeneration and cell death [76].

The dysregulation of the homeostatic mechanisms of mitochondrial maintenance (mitochondrial fission, fusion, transport, biogenesis, and degradation referred to as mitochondrial dynamics) has been greatly linked to neurodegeneration and PD neuropathology. Mutation of the E3 ubiquitin ligase parkin, which causes familial autosomal-recessive juvenile-onset PD, is related to the maintenance of mitochondrial dynamics. Parkin has been chiefly linked to mitochondrial quality control; whereby damaged and depolarized mitochondria are targeted for autophagic degradation (mitophagy). In this pathway, parkin translocate to depolarized mitochondria *via* a PINK1-dependent mechanism, identifying them for mitophagic degradation. This pathway has been suggested to be crucial in PD as the regulation of mitochondrial homeostasis is vital for neuronal survival, and accumulation of damaged mitochondria could be deleterious, even though it is unclear if the loss of Parkin function could give way to a selective loss of PD-affected neurons [82]. In fact, the potential role of excitotoxic processes in PD has been reinforced by the observations that there seems to be a mitochondrially encoded defect in complex I activity of the electron transport chain and an eventual impairment of oxidative phosphorylation increases susceptibility to excitotoxicity [83].

Studies have also shown parkin regulates the function and stability of excitatory glutamatergic synapses. Postsynaptic expression of parkin dampens excitatory synaptic transmission and induces a striking loss of excitatory synapses in hippocampal neurons. However, the knockdown of endogenous parkin or expression of PD-linked parkin mutants deeply improves synaptic efficiency and stimulates the proliferation of glutamatergic synapses, which is associated with increased susceptibility to synaptic excitotoxicity. Therefore, parkin negatively modulates the quantity and potency of excitatory synapses. Accordingly, an increase in excitatory drive generated by the disruption of parkin may add to the pathophysiology of PD [84].

It is generally acknowledged that the N-Methyl-D-aspartic acid receptor (NMDAR) family plays an important function in glutamate toxicity due to their elevated Ca^{2+} permeability. Activation of NMDAR causes Na^{+} influx that moderate osmotic swelling of the cell body and dendritic spines, and calcium ions are responsible for neuronal degen-

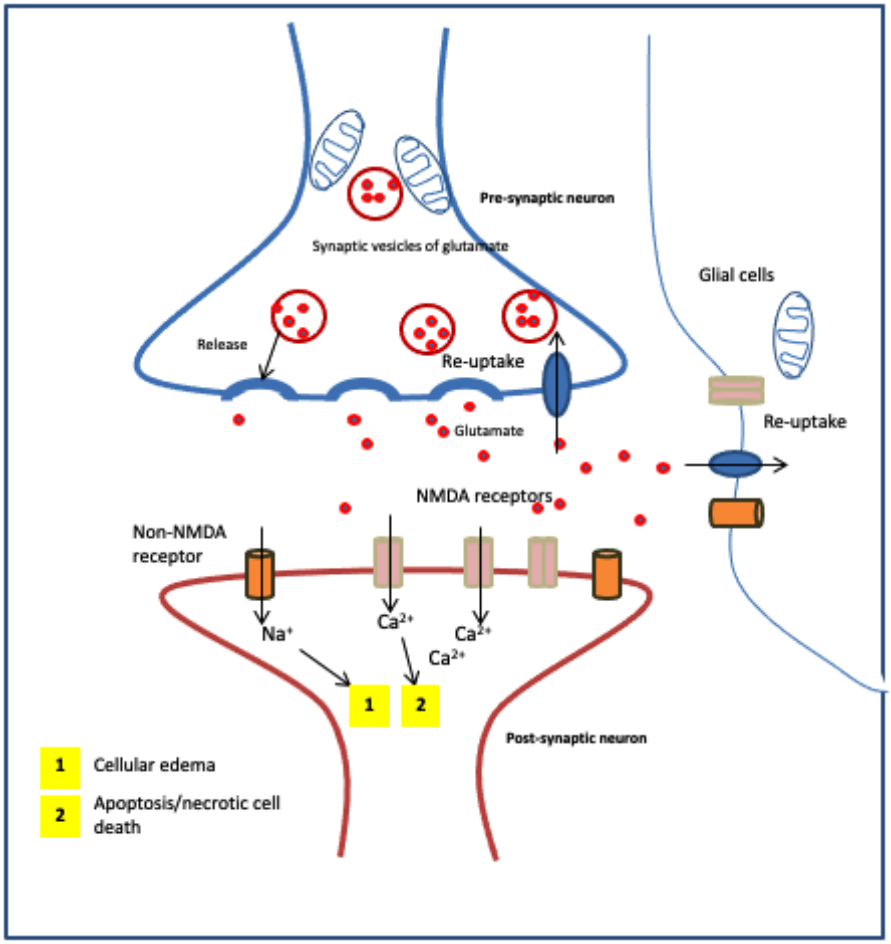


Fig. (1). Mechanisms of glutamate excitotoxicity in the neuron glial unit. Glutamate is released from the presynaptic terminal of neuronal axons into the synaptic cleft and acts as a neurotransmitter. The reuptake of extracellular glutamate occurs at the presynaptic terminals and adjacent glial cells. Mitochondria provide energy for the reuptake of glutamate. The excess binding of glutamate to NMDA receptors allows entrance of Ca^{2+} into the postsynaptic neuron, resulting into necrotic cell death/apoptosis, while the excessive glutamate binding to non-NMDA receptors allowing Na^{+} to enter into the postsynaptic neuron, cause cytotoxic oedema [81].

eration [78] (Fig. **1**). The entry of Ca^{2+} through NMDARs is of significant importance owing to the exceptional potential of these receptors to gate high concentrations of Ca^{2+} influx. As a result, the focus of several laboratory and clinical studies on a number of diseases in which glutamate induced excitotoxicity is thought to play a role has been on NMDAR antagonists. Therefore, while impeding NMDAR activity caused by overstimulation may be a valuable mechanism to counteract excitotoxicity, this must be achieved without significantly interfering with the normal synaptic function [85].

For example, memantine has the capacity to obstruct the excitotoxic effects of NMDAR overactivation without changing normal synaptic transmission as it is a low-affinity, uncompetitive, open-channel blocker and has a fairly rapid off-rate from the channel. At resting membrane potentials under normal conditions, NMDARs are blocked by extracellular Mg^{2+} occupying the channel. In excitotoxic conditions, depolarization of the cells occur and the Mg^{2+} is repelled, opening the channel to Ca^{2+} influx [85]. The fast off-rate prevents memantine from building up in NMDAR-operated channels, thereby preventing interference with physiological neurotransmission [86]. Memantine has been found to be less voltage-dependent than Mg^{2+}, therefore enabling it to maintain blockage of the channels under relatively depolarized conditions [87]. The activation of synaptic NMDARs induces pro-survival events, whereas the activation of extrasynaptic NMDARs may overrule these normal pathways, eliciting the many detrimental pathways that eventually cause cell death [88]. Besides, memantine is able to preferentially obstruct extrasynaptic NMDAR channels while sparing normal synaptic activity, which could explain the restricted adverse effects observed in patients taking memantine as treatment [85].

Since the increased glutamatergic transmission in the basal ganglia is believed to contribute to the motor symptoms of PD and AMPA receptors mediate glutamatergic neurotransmission, obstruction of AMPA receptors has also been proposed as a promising therapeutic strategy [89]. AMPA receptors are postsynaptic ion channels that control most of the fast-excitatory amino acid neurotransmitters present in the brain. They are cation-selective heterooligomers found in several combinations of the subunits GluR1, -2, -3, and -4. AMPA receptor subunits are expressed in large quantities and are situated in various sites inside neuronal cell bodies and processed in the cerebral cortex, basal ganglia, limbic system, thalamus, cerebellum, and brainstem, with precise patterns in various regions of the brain [90]. Compared to NMDA receptors, AMPA receptors are slightly permeable to external Ca^{2+}. When gates are opened by synaptically released glutamate, AMPA receptors mediate the inflow of Na^{+} (and in some cases Ca^{2+}) into neurons, while they cause K^{+} efflux. Even though the ion channels assembled by the homomeric or heteromeric combinations of GluR1 and GluR3 show substantial permeability to Ca^{2+}, the integration of a GIuR2 subunit restrains Ca^{2+} permeability [91]. Besides, it was revealed that activation of AMPA receptors boosts the influx of extracellular Zn^{2+} into nigral dopaminergic neurons, leading to movement disorder [92]. Hence, implicating that Ca^{2+} and Zn^{2+}-permeable GluR2-lacking AMPA receptors are predominantly significant for treatment of PD [93].

4. MEDICINAL PLANTS AND THEIR ISOLATED PHYTOCHEMICALS IN MANAGING NEURODEGENERATIVE DISEASES

The existing synthetic drugs available in the market possessed undesirable side effects. For this reason, searching for novel treatment approaches based on natural resources especially medicinal plants, has been an area of current focus [94]. In the past recent years, there has been a growing interest in screening medicinal plants to discover novel drug leads with the ability to cure neurological dysfunctions, including AD. Despite the availability of modern methods such as molecular modelling, combinatorial chemistry and other synthetic chemistry techniques applied by pharmaceutical industries and funding organizations, medicinal plants are still the focal point of most scientists since plants remain an important reservoir of novel drugs drug leads and chemical entities. Furthermore, traditional medicinal plants with reliable ethnopharmacological propensities have proved to exhibit promising neurotrophic and neuroprotective activities, which could be helpful in hindering the death of nerve cells in neurodegenerative and neuroinflammatory disorders [95, 96]. In the following subsections, existing literature on potential plants and phytochemicals able to prevent or disrupt β amyloid aggregation and also demonstrating promising glutamate receptor inhibitory effects will be summarized.

4.1. Plants and Plant-Derived Products with β Amyloid Aggregation Inhibitory Activity

It is suspected that the accumulation of Aβ peptides in the brain is predominantly a pathological process. Hence, suppressing the early phases of Aβ aggregation with biomolecules could be a promising treatment strategy for AD [94]. In particular, the aggregation of Aβ peptides has been exclusively studied in recent decades [97]. The amino-terminal end of the Aβ peptide in amyloid fibrils is susceptible to possible interaction with other surrounding biomolecules. The middle part of the peptide and the carboxyl-terminal end is instead involved in inter- and intra-molecular interactions that can occur between different molecules of Aβ [98]. Several phytochemicals belonging to different classes have been studied in former reports as non-covalent binding partners of Aβ peptides. As representative examples, phenolic compounds such as oleuropein **(1)** and oleocanthal **(2)** present in olives, resveratrol **(3)** in fruits, curcumin **(4)** in turmeric, cinnamaldehyde **(5)** in cinnamon, myricetin **(6)** and epigallocatechin-3-gallate **(7)** in green tea are known to reduce proteins misfolding. These compounds pose a few advantages such as they are easily available worldwide, cost-effective and less toxic. Also, these compounds are highly specific as their mode of action involves direct interaction with the protein aggregates [99]. Anti-aggregation inhibitors work by forming covalent and non-covalent bonds (*i.e*. pi-pi interactions, hydrogen bonding, charge-charge interactions) with the target protein that may disturb the initial or all steps involved in an aggregation process. However, it is of paramount importance to highlight that the amyloid inhibitory

activity of most components has not been verified yet *in vivo* [99].

Amyloid molecules assemble into fibrils and oligomers can bind with thioflavin T **(8)**. On the other hand, amyloid monomers do not interact with the aforementioned compound. The excitation spectra of thioflavin T (3 μM in potassium phosphate buffer (50 mM)) revealed a signal with high intensity at 450 nm in the presence of Aβ (1-28) and Aβ (1-40). However, in the absence of the amyloid molecules, a low intensity signal was observed at the same wavelength. The emission spectra also showed a maximum at 482 nm when Aβ (1-28) and Aβ (1-40) are combined with thioflavin T, but no signal was observed with thioflavin T alone at the same recorded wavelength [100]. Despite the interplay between amyloid fibrils and thioflavin T has not been fully elucidated, it is thus speculated that thioflavin T binds to the β-sheet *via* the interaction of the sequences (17-42) belonging to several Aβ (1-42) molecules [101]. In a study carried by Porzoor *et al*. (2015), a group of 21 phenolic compounds related to the Chinese herbal medicine danshen (*Salvia miltiorrhiza* Bunge) was investigated for Aβ42 oligomerization inhibitory activity. Since the number and position of hydroxyl substituents attached to phenyl groups in benzoic **(9)** and cinnamic **(10)** acids are unpredictable, the influence of the hydroxyl groups in amyloid inhibition of such polyphenols was investigated. Results showed that when thioflavin T are incubated for 24h in the presence of Aβ42, five compounds namely rosmarinic acid **(11)**, gentisic acid **(12)**, epigallocatechin-3-gallate **(7)**, caffeic acid **(13)**, gallic acid **(14)**, and salvianolic acid B **(15)** significantly decreased thioflavin T fluorescence indicating their anti-amyloidogenic activities. Transmission electron microscope (TEM) and immunoblotting analysis also demonstrated that these five compounds could hinder the formation of amyloid fibrils even after a prolonged incubation time [102]. In a recent analysis, gallic acid, a naturally occurring organic compound, was showed to attenuate the cognitive decline of APP/PS1 transgenic mouse *via* the decrease of Aβ42 aggregation and neurotoxicity. The study also showed that oral administration of gallic acid not only improves the memory of 4-month old APP/PS1 mice but also enhances spatial learning, working and reference memory of 9-month old APP/PS1 mice. Results obtained from atomic force microscopy, dynamic light scattering and thioflavin T fluorescence densitometry analyses demonstrated that gallic acid substantially prevents Aβ42 aggregation both *in vivo* and *in vitro* [103].

Consuming tea is considered as a complementary treatment for neurodegenerative complications, as carefully detailed in a review compiled by Polito *et al*. (2018) [104]. A study mentioned that green tea catechins and black tea theaflavins are positively associated with improved language and verbal memory of patients [105]. Misfolded Aβ assemble themselves into high order oligomers responsible to affect integrity of membranes, causing synaptic degradation and neural cell death. The aim of a study carried out by Gauci *et al*., (2011) was to determine whether small biomolecules and extract of black tea could prevent Aβ aggregates from disrupting phospholipid membranes. Findings listed in the study reported that black tea extract, the flavones, apigenin **(16)**, baicalein **(17),** and the stilbene, nordihydroguaiaretic acid **(18)** were able to antagonize liposome permeabilization by Aβ42 oligomers [106].

Numerous neurodegenerative conditions, including AD are related to glycation which potentiates the accumulation and enhances toxicity of Aβ. Published data reported that fruits rich in polyphenol (for example, anthocyanin) possess anti-glycation activity and neuroprotective properties. Ma *et al*. (2018) therefore evaluated the anthocyanin extracted from a number of berries namely blackberry, blueberry, cranberry, black raspberry, red raspberry, and strawberry for its antioxidant, anti-glycation, anti-Aβ aggregation and neuroprotection features. At a concentration of 100 μg/ml, anthocyanin-enriched berry extracts exhibited potent free radical quenching, anti-glycation, reactive carbonyl trapping, anti-Aβ fibrillation, and microglial neuroprotective activities. These *in vitro* findings of the tested berries prompt further *in vivo* studies to assess the neuroprotective potentials against AD [107]. *Uncaria rhynchophylla* (Miq.) Miq. Ex Havil. has long been traditionally used to manage NDs. Shin *et al*. (2018) tested if *U. rhynchophylla* could prevent Aβ aggregation and adult hippocampal neurogenesis in the brain of 5XFAD mice. Indeed, results obtained from thioflavin T and amyloid staining assays have shown that *U. rhynchophylla* can efficiently inhibit Aβ aggregation and accumulation in the cortex and subiculum parts of the brain of mice under investigation and can improve damaged adult hippocampal neurogenesis. The authors concluded the potency of *U. rhynchophylla* on inhibiting Aβ deposition and Aβ-mediated neuropathology in mice brain can be used as a therapeutic and preventive therapy for AD [108].

Centella asiatica (L.) Urb. is a valuable medicinal plant used to treat cognitive ailments and disorders related to mental health. Studies mentioned that the plant can act as a neuroprotectant since it possesses anti-inflammatory, anti-anxiety, anti-depressive effects, neuron regenerative ability and has the ability to attenuate oxidative stress and neurotoxicity (for reviews, see [109] and [110]). Reports stated that D-galactose (D-gal) promotes oxidative stress and acetylcholinesterase (AChE) activity in the brain of rats. D-gal interrupts the normal activity of hippocampal and cortical cells leading to a degeneration of various parts of the brain. Interestingly, recent analysis has demonstrated that the ethanolic extract of *C. asiatica* substantially suppresses oxidative stress and AChE activity in the brain caused by D-gal, and preserves a normal cellular architecture in hippocampal and cortical areas. The authors of the study concluded that *C. asiatica* protects the brain from the side effects of D-gal, such as memory loss [111].

The traditional plant *Rhodiola crenulata* (Hook.f. & Thomson) H.Ohba has been widely consumed as a healthy food in China for several years as antidepressant and antifatigue. Findings presented by Zhang *et al*. (2019) showed that *R. crenulata* markedly increased the level of acetylcholine and choline acetyl transferase activity. The plant extract also repaired damaged hippocampus neurons and averted Aβ deposition in the hippocampus of Aβ (1-42) injected rats [112]. Another medicinal plant used in China for managing mental health issues is *Cistanche tubulosa* (Schenk) Wight.

A study conducted by Wu *et al*. (2014) revealed that echinacoside **(19)** and acteoside **(20)** present in the extract of *C. tubulosa* improved cognitive dysfunction by blocking amyloid deposition and reversing cholinergic and hippocampal dopaminergic neuronal function [113].

The insignificant toxicity of natural compounds compared to synthesized chemicals showed that natural products could open the door for the potential discovery and development of efficient natural protein misfolding inhibitors that may be beneficial in treating numerous incurable pathological complications [114]. Using PubMed, ScienceDirect and other important databases, a thorough literature search was conducted in order to list all possible medicinal plants and phytochemicals possessing inhibitory effects against β amyloid aggregation as presented above and further detailed in Table **1** with more examples. The following subchapters are dedicated to some secondary metabolites commonly present in medicinal plants exhibiting β amyloid fibrillogenesis.

4.2. Some Common Compounds from Medicinal Plants Inhibiting β Amyloid Fibrillogenesis

4.2.1. Gallic Acid

Gallic acid (GA) **(14)** is a naturally occurring hydroxybenzoic acid present in grape seeds, black tea, black radish, onions and red fruits. Several publications have reported that GA exhibit good anti-amyloidogenic activity against Aβ peptides and can be characterized as an anti-aggregation compound [115]. Gallic acid works by suppressing the formation of amyloids, hindering the formation of mature fibrils and favours instead of forming short amorphous aggregates. The mode of action is believed to be *via* a short and direct interaction between the compound and unfolded monomeric species, which then stabilizes the latter [116]. A study assessed the ability of GA to hinder Aβ fibril formation using the thioflavin T assay by incubating GA in a solution of 50 μM Aβ (1-40) for 10h. Data suggested that GA at a concentration of 100 μM prevented the production of fluorescence when thioflavin T molecules are bound to Aβ (1-40) fibrils [117]. In another study, Aβ (1-42) fibrillization was determined by thioflavin T test both in the absence and presence of GA (100 μM). Despite results obtained from the thioflavin T test reported a decrease in fluorescence when Aβ (1-42) was incubated with GA, TEM, on the other hand, indicated that fibrils formation was present, and GA may interact with Aβ [118]. Yu *et al*., (2019) reported that a solution concentration of 20 μM Aβ (1-42) fibrils incubated with 2-fold molar excess GA undergone disaggregation [103].

Ban *et al*. (2008) reported that GA isolated from *Sanguisorbae* radix of *Sanguisorba officinalis* L. prevent damage caused by Aβ (25-35) fibrils. The phenolic compound decreased the Aβ (25-35)-induced $[Ca^{2+}]_c$ upsurge, which as a result suppresses apoptotic death in rat cortical neurons. The authors suggested that the obtained result might be attributed, if not fully, to GA [119]. 1,2,3,4,6-penta-O-galloyl-β-d-glucopyranose (PGG) **(21)** is a gallotannin (a hydrolysable tannin derived from GA) of high molecular weight isolated from *Paeonia sufruticosa* Andrews, a medicinal plant with anti-inflammatory property. A study indicated that PGG prevented formation of Aβ fibrils and destabilized preformation of Aβ fibrils both *in vivo* and *in vitro* models. It was observed that when the compound was administered orally to AD mice, deposition of Aβ40 and Aβ42 was reduced without any toxic effects reported [120]. However, the high molecular weight and hydrophilicity of PGG may cause a problem for brain delivery due to low blood-brain barrier permeability [114]. Taken together, these findings pointed to the fact that the size of Aβ aggregates decreased when incubated with GA, even though the mode of action remains uncertain and may have prevented the formation the plaque in the brain. All the evidence supports the notion that in the future GA could become a potential multi-targeted pharmacological compound used to treat AD [121].

4.2.2. Rosmarinic Acid

Rosmarinic acid (RA) **(11)** is a polyphenol present in common culinary herbs such as oregano, sage, thyme, and peppermint. This compound prevents formation of oligomers and fibrils by amyloids in a concentration-dependent manner and disrupts preformed aggregates *in vitro* [122]. Data collected from *in vivo* assays showed that the oral administration of RA exerts favourable effects on the learning process of mice affected by AD and cerebral amyloid angiopathy and impedes the development of AD-associated complications [114]. This phenolic compound also prevents the new generation of small oligomers *via* a mechanism that involves suppression of the β-sheet conversion, decreasing associated synaptotoxicity [123]. Rong *et al*., (2018) showed that RA could hamper Aβ-induced cellular reactive oxygen species generation and lipid hydroperoxides [124]. A RA solution prepared at a concentration 20 μM was incubated in Aβ (1-42) for 24h and analysed using thioflavin T assay. A low intensity fluorescence was recorded in contrast to the peptide incubated in the vehicle buffer [102]. Similar findings were reported by Sun *et al*., (2019) with 1, 10 and 100 μM RA solution [125]. Hamaguchi *et al*., (2009) conducted an interesting *in vivo* experimental test in which mice of five-month-old were fed with RA for 10 months. Beta amyloid deposition was markedly decreased in mice brain. These findings demonstrated that RA taken orally could hinder the development of AD neuropathology by disrupting different pathways of Aβ aggregation *in vivo*. Although these data seem promising, clinical trials should be conducted to confirm these effects and to ensure safety in humans [126].

4.2.3. Resveratrol

Resveratrol **(3)** is a phytoalexin stilbenoid polyphenolic natural product produced by plants when attacked by pathogens including bacteria and fungi and is present in abundance in grapes, soybeans, peanuts, and red wine. Resveratrol has been cited as a 'miracle drug' in a recent systematic review and meta-analysis compiled by Khorshidi *et al*. (2020) [127]. Nevertheless, depending on the dose of the phytoalexin and the cell type, it has also been observed that resveratrol can exert pro-oxidant properties, resulting in oxidative breakage of cellular DNA in the presence of transition metal ions such as copper [128]. Several lines of evidence have highlighted the neuroprotective and anti-aggregation properties of resveratrol against various amyloids. As a representative example, data gathered from a recent analysis demonstrated that the interaction of resveratrol with Aβ (1-42)

Table 1. Plants and plant-derived compounds with β amyloid aggregation inhibitory activity.

Plant Name (Family)	Plant Part /Crude Extracts/Isolated Compounds	Method	Findings/Mode of Actions	Refs.
Salvia officinalis L. (Lamiaceae)	Hydroalcoholic extract of leaves	*In-vitro*: Pre-treating PC12 cells with Aβ (1-42) for 24 h in the presence of rosmarinic acid	DNA fragmentation was markedly reduced	[144]
Dipsacus asper Wall. ex DC. (Dipsacaceae)	Aqueous extract: Akebia saponin D, Loganic acid ethyl ester, Chlorogenic acid, Caffeic acid, Loganin, Cantleyoside, Syringaresinol-4′, 4″-O-bis-β-Dglucoside	*In-vitro*: Pre-treating PC12 cells with Aβ (25-35)	Akebia saponin D **(23)** blocked Ab-induced Ca^{2+} influx	[145]
Withania somnifera (L.) Dunal (Solanaceae)	Methanolic extract of seeds: Withanamides A (WA) **(24)** and C (WC) **(25)**	*In-vitro*: Pre-incubated PC12 cells with WA and WC for 48h in the presence of Aβ (10 µg/ml)	Cells were completely protected by both WA and WC from damage caused by Aβ	[146]
Angelica sinensis (Oliv.) Diels (Apiaceae)	Methanolic extract of roots	*In-vitro*: Pre-treating PC12 cells with Aβ (1-40) at two concentrations: 4 µM and 10 µM	A dose dependent prevention of PC-12 cells from Aβ (1-40) toxicity	[147]
Salvia miltiorrhiza Bunge (Lamiaceae)	Salvianolic acid B **(15)**	*In-vivo*: Salvianolic acid B was administered in male mice	Cognitive dysfunctions were generated by a cholinergic blockade and memory impairments caused by Aβ (25-35) peptides	[148]
	Cryptotanshinone (CTS)	*In-vivo*: Mice were administered with CTS at a dose of 15 mg/kg/day for a period of four months to assess whether CTS could improve memory of mice *In-vitro*: Aβ (40-42) in conditioned media and lysate of cortical neural cells containing amyloid precursor proteins were tested to determine the effect of CTS on the level of the amyloids	Memory was significantly ameliorated with CTS Levels of both extra- and intracellular Aβ were dose-dependently decreased by 2.5-10 µM CTS treatment for 18 h	[149]
Curcuma longa L. (Zingiberaceae)	Calebin-A 1,7-bis(4-hydroxy-3 methoxyphenyl)-1,4,6-heptatrien-3-one, curcumin, demethoxycurcumin, bisdemethoxycurcumin, 1-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-6-heptene-3,5-dione, 1,7-bis(4-hydroxyphenyl)-1-heptene-3,5-dione, 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one, 1,5-bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadien-3-one	*In-vitro*: Pre-incubated PC12 cells with the listed compounds in the presence of Aβ (1-42) at 5 µg/ml and Aβ (25-35) at 1 µg/ml	Compounds calebin-A **(27),** curcumin **(4)**, demethoxycurcumin **(28)**, bisdemethoxycurcumin **(29)**, and 1,7-bis(4-hydroxyphenyl)-1-heptene-3,5-dione **(30)** could effectively protect PC12 cells from Aβ damage ED50 =0.5-10 µg/ml) in contrast to the positive control, Congo red (ED50 = 37-39 µg/ml)	[150]
Elsholtzia rugulosa Hemsl. (Labiatae)	Luteolin **(22)**	*In-vitro*: Aβ protein precursor was determined by indirect immunofluorescence assay	Suppression of Aβ protein expression and lowered the production of Aβ (1-42)	[151]
Magnolia officinalis Rehder & E.H.Wilson (Magnoliaceae)	Ethanolic extract of bark: 4-O-methylhonokiol **(31)**	*In-vivo*: Mice was injected with Aβ (1-42) (200 µg/ml) at a rate of 0.2 µl/s	Aβ aggregation was prevented	[152]
Polygala tenuifolia (Willd.) (Polygalaceae)	Ethanolic extract	*In-vitro:* Pre-treatment of cortical neurons with extract for 12 h followed by the addition of Aβ oligomeric (1-42) solution (20 µM)	Oligomeric Aβ-induced neurotoxicity was reduced	[153]

(Table 1) contd….

Plant Name (Family)	Plant Part /Crude Extracts/Isolated Compounds	Method	Findings/Mode of Actions	Refs.
Punica granatum L. (Lythraceae)	Ethanolic extract	*In-vivo:* Mice were fed with food containing the extract. The mice then were injected with Aβ (1-42) (410 pmol)	Mice exhibited attenuated Ab1-24-induced impairment of passive avoidance performance in a concentration-dependent manner	[154]
Scutellaria baicalensis Georgi (Lamiaceae)	Baicalein **(32)** and baicalin **(33)**	*In-vitro:* Pre-treating PC12 cells with Aβ (1-42)	Aβ defibrillation was noted	[103]
	Stem leaves	*In-vivo:* Male rats were administered with (50 and 100 mg/kg) once daily. On day 8, Aβ (25-35) (10 μg) was injected into the brain of rats	Neuronal apoptosis caused by Aβ (25-35) was reduced	[155]
Eragrostis ferruginea (Thunb.) P.Beauv. (Poaceae)	Tricin **(34)**	*In-vitro*: Pre-treating PC12 cells with Aβ (1-42)	The compound exhibited neuroprotective activity with ED50 20.3 μM against Aβ (1-42) in PC12 cells	[156]
Schisandra chinensis (Turz.) Baill. (Schisandraceae)	Stems	NG	Possess anti-neuroinflammatory properties in Aβ (1-42)-induced microglia cells	[157]
Callistemon lanceolatus (Sm.) Sweet (Myritaceae)	4',5-dihydroxy-6,8-dimethyl-7 methoxyflavanone **(35)**	*In-vitro*: Pre-treating PC12 cells with Aβ (1-42)	The compound exhibited neuroprotective activity with ED50 6.7 μM against Aβ (1-42) in PC12 cells	[158]

Aβ: beta-amyloid; PC12: Pheochromocytoma12; NG: Not given.

peptides leads to the degradation of the latter into smaller fragments. Results from atomic force microscopy showed that the amyloids aggregate into proteinaceous deposits under normal conditions, while an absence of these deposits was noted when Aβ (1-42) peptides were incubated with resveratrol. In the same study, shorter peptides were recorded after the amyloids were incubated with resveratrol for 10 days [129].

Interestingly, PC12 cells were found to be protected by resveratrol and catechin from Aβ insult due to a synergistic effect caused by the two polyphenols [130]. It is hypothesized that since resveratrol is an important activator of AMP-activated protein kinase (AMPK) in neuronal cell lines, the polyphenol might have beneficial effects against AD. For this reason, Chiang *et al*. (2018) attempted to confirm this hypothesis. Results collected in the study showed that the Aβ-mediated activities in human neural stem cells were substantially abolished when co-treated with resveratrol and that the activation of AMPK-dependent signalling by resveratrol prevented Aβ-mediated neurotoxicity in the neural stem cells. Collectively, the authors of the study concluded that the findings can be served as baseline information for the development of therapies or ameliorate clinical results among patients suffering from AD [131]. In 2018, Sciacca *et al*. conjugated resveratrol with a phosphoryl moiety (4′-O-PR) to improve its solubility and pharmacological activities. Evidence from the study showed that this derivative hindered amyloid formation and prevented membrane damage [132]. However, in the study conducted by Feng *et al*. it was observed that although resveratrol inhibited Aβ oligomeric cytotoxicity, resveratrol could not prevent the formation of oligomers [133]. Treating murine models diagnosed with AD with resveratrol reduced amyloid plaque formation without disturbing amyloid protein precursor processing, improved cognitive skills, protected integrity of blood-brain barrier, reduced microgliosis and reactive oxygen species [114].

4.2.4. Luteolin

Luteolin **(22)** is a tetrahydroxyflavone with four hydroxy groups at position 3', 4', 5 and 7 belonging to the flavonoid group and is present abundantly in plants. According to published literature, luteolin demonstrated anti-amnesic activity against Aβ-induced neurotoxicity. Liu *et al*., (2009) injected mice with Aβ (25-35) peptides to evaluate the anti-amnesic and neuroprotective effects of luteolin on them. After oral administration of luteolin for eight days, spatial learning and memory capabilities ameliorated, an increase in the values of the regional cerebral blood flow was noted, reactive oxygen species were cleared and the brain-derived neurotrophic factor level was increased [134]. Using thioflavin T assay, a solution of 100 μM luteolin incubated with Aβ (1-42) showed a drop-in fluorescence [135]. A similar result was obtained when a lower concentration of luteolin was used (40 μM) [136]. Preclinical examinations showed that luteolin significantly reduces amyloidogenesis and traumatic brain injury in mice models diagnosed with AD [137]. Intraperitoneal therapy with luteolin (20 mg/kg/day) for 30 days in Tg2576 mice markedly reduced cognitive deficits and inhibition of soluble Aβ (1-40) and Aβ (1-42) deposition by 25% and 49% was detected in an ELISA assay. A selective inactivation of glycogen synthase kinase 3α is the most probable mechanism behind the drop in Aβ aggregation essential for both PSEN1 processing/phosphorylation and interaction between amyloid protein precursor and PSEN1 [138].

4.2.5. Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) **(7)** is one of the major active components of green tea leaves and is the ester of gallic acid and epigallocatechin. The compound showed promising results on the defibrillation and toxicity of numerous proteins involved in protein misfolding disorders. Nonetheless, the mode of action remains unanswered and is believed to be *via* the adjustment of multiple pathways [114]. Reports mentioned that this ester might have direct a interaction with misfolded proteins in a non-specific manner during the initial phases of aggregation [139]. EGCG may also interact with monomers, intermediates and mature fibrils of amyloid protein precursor *via* hydrogen bonding which as a result inhibit amyloid fibrillation [140]. It was found to suppress the deposition of oligomeric Aβ dose-dependently by promoting the development of larger fragments [141]. When the amyloid peptides were incubated with EGCG, a decrease of less than 20% of the fibrillization process for Aβ (1-42) was noted [103]. Similar outcomes were recorded when EGCG was incubated with a Aβ (1-42) peptide solution of 20 μM mixed in a molar ratio of 1:1 [142]. In a clinical trial, patients with amyloid light chain amyloidosis (ALCA), a bone marrow disorder where misfolded immunoglobulins deposit in different organs, including the heart-were given green tea to consume on a regular basis. Findings revealed that amelioration in their cardiac condition was observed in contrast to patients who did not drink green tea. This study suggested that EGCG-rich beverages could provide beneficial effects for preventing ALCA [143].

Table **1** tends to gather further existing information on plants/isolated compounds inhibiting β amyloid aggregation and Fig. **2** illustrates the chemical structures of the compounds.

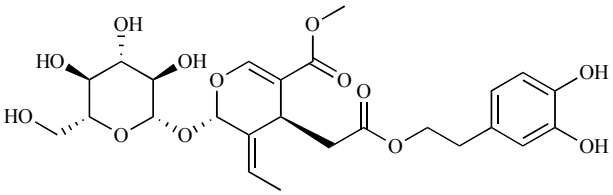
4.2. Plants and their Phytochemicals as Promising Agents Against Glutamate-Induced Excitotoxicity

A number of plants or plant-derived compounds have proved to be effective against glutamate excitotoxicity in Alzheimer's and Parkinson's models (Table **2** and Fig. **3**). Ma *et al*. (2009) have performed activity-guided isolation of the dichloromethane fraction of the bark of *Machilus thunbergia* Sieb. Et Zucc (family: Lauraceae), which is widely used in Korean folk medicine. At a concentration 0.1μM to 10.0 μM, the eight isolated compounds [(+)-9′-hydroxygalbelgin **(36)**, (7S,8S,8′R)-3′,4′-dimethoxy-3,4,-methylenedioxylignan-7-ol **(37)**, isogalcatin B **(38),** 5,7-dimethoxy-3′,4′-methylenedioxyflavan-3-ol **(39)**, 1-hydroxy-7-hydroxymethyl-6-methoxyxanthone **(40)**, (+) -(3S,4S,6R)-3,6-dihydroxypiperitone **(41)**, tyrosol **(42)** and protocatechuic acid methyl ester **(43)**] have showed significant protective effects against toxicity induced by glutamate, in primary cultures of rat cortical cells. At a dose of 10.0 μM, tyrosol has shown activity (70.2 % protection) similar to MK-801 or CNQX (79.3 % and 69.5 % protection, respectively), widely known inhibitors of glutamate receptor [159].

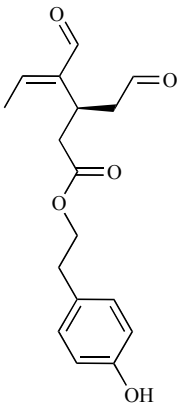
Boswellia serrata Roxb. ex Colebr. (Family: Burseraceae) is a plant which is widely employed as folk remedy for several chronic inflammatory ailments such as arthritis and osteoarthritis. Several reports have documented pharmacological actions of *B. serrata*, including its neuroprotective effect [160-162]. In 2016, Rajabian *et al*., (2016) evaluated the protective ability of oleo-gum extract of *B. serrata* (BSE) and 3-acetyl-11-keto-β-boswellic acid (AKBA) **(44)**, a triterpenoid, isolated from BSE, against glutamate-induced neurotoxicity in PC12 and N2a cell lines. Co- and pre-treatment with 25-100 mg/mL BSE or 5 mM AKBA have significantly mitigated glutamate-induced (8 mM) production of ROS in PC12 and N2a cell lines. For instance, pre-treatment with 100 mg/mL with BSE has reduced glutamate-induced excessive ROS generation in PC12 (138.7%) and N2a (151.3%) as compared to glutamate-treated group (232.4% and 234.6% of control), respectively. It was observed that there was constant suppression of ROS formation by BSE and AKBA treatment have led to significant decrease in lipid peroxidation, DNA damage, and reinstating the superoxide dimutase activity [163]. Rahimi *et al*. (2017) have documented on the neuroprotective effect of the ethanolic of *B. serrata* oleo-gum resin on OLN-93 cells against glutamate and quinolinic acid-induced neurotoxicity. The extract was observed to improved cell viability by 40 %-50% as compared by glutamate group and 75%-80% as compared to quinolinic acid group [164]. Lately, Lu *et al*., (2020) have reported that 11-keto-β-boswellic acid **(45)** hindered 4-aminopyridine-evoked glutamate release from hippocampal synaptosomes by decreasing the voltage-dependent calcium channel and protein kinase A activity [165].

Sharma and Kaur (2018) have reported on the neuroprotective and neuroregenerative effects of butanol extract of *Tinospora cordifolia* (Wild.) Miers in primary cerebellar neuronal cultures. The results suggested that the *T. cordifolia* extract exerts its effect by regulating different pathways, for example, neuronal differentiation, inflammation, oxidative stress and apoptosis. Hippocampus, a part of limbic system, is essential for learning and memory processes. The toxic effect of glutamate on neuronal population of forebrain, especially hippocampus led to a decline in memory [166]. Therefore, Sharma and co-researcher attempted to assess further the neuroprotective potential of *T. cordifolia* butanol extract using primary hippocampal neurons and experimental animal models. It was found that the tested extract exerted protective effects against glutamate-induced toxicity by maintaining MAP-2 expression in the cells to near control levels and improves cognitive impairments resulted from glutamate-induced neurotoxicity in Wistar strain albino rats models by targeting downstream NMDAR, ERK, PI3K/Akt pathways of synaptic plasticity. Tinosporicide **(45)** was isolated from the extract, which was potent under *in-vitro* condition, at a low dose (25 ng/mL) as compared to crude extract (20 μg/mL) [167].

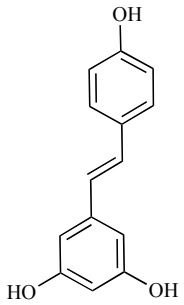
Acanthus ebracteatus Vahl. belongs to Acanthaceae family and is a medicinally important mangrove plant. A study by Prasansuklab and Tencomnao (2018) have showed that ethanol extract of *A. ebracteatus* leaves was effective against toxicity caused by glutamate insult (5 mM), in which at a dose of 50 μg/mL, the extract has fully reinstated the viability of HT-22 hippocampal neuronal cells exposed to glutamate. This neuroprotective effect of *A. ebracteatu* extract was possibly due to the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant system, resulting to a decreased



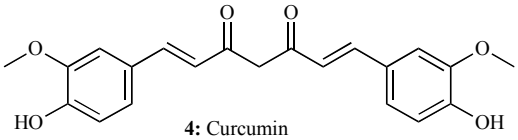
1: Oleuropein



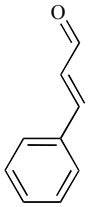
2: Oleocanthral



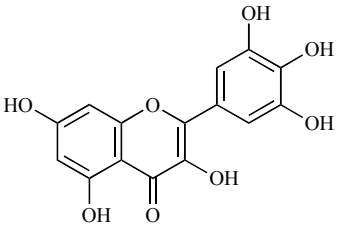
3: Revesratrol



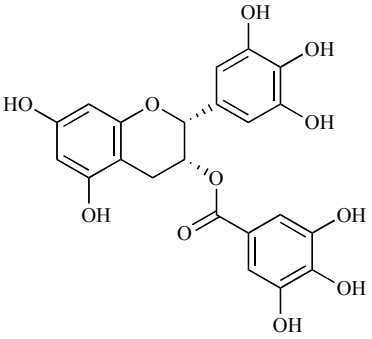
4: Curcumin



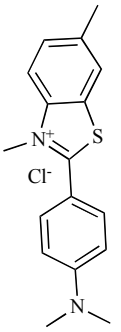
5: Cinnamaldehyde



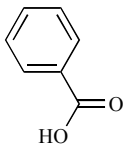
6: Myricetin



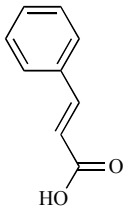
7: Epigallocatechin-3-gallate



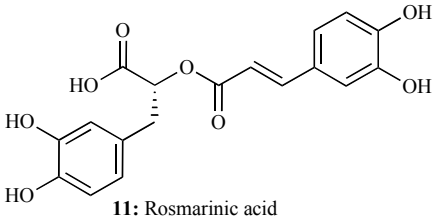
8: Thioflavin T



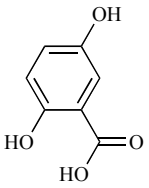
9: Benzoic acid



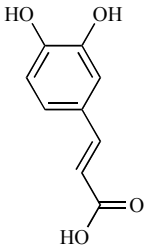
10: Cinnamic acid



11: Rosmarinic acid



12: Gentisic acid



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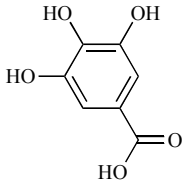
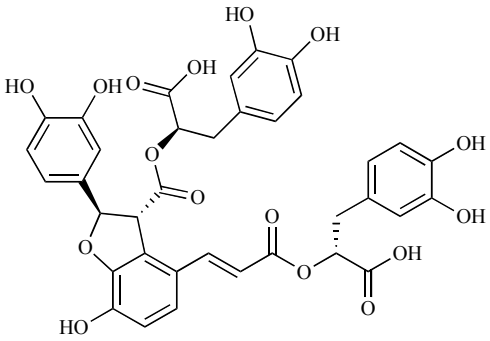
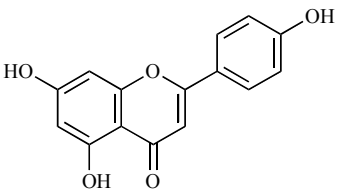


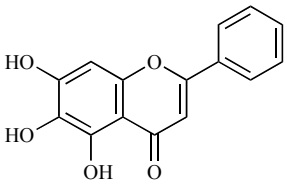
14: Gallic acid



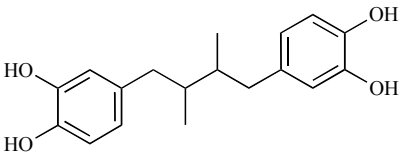
15: Salvianolic acid B



16: Apigenin

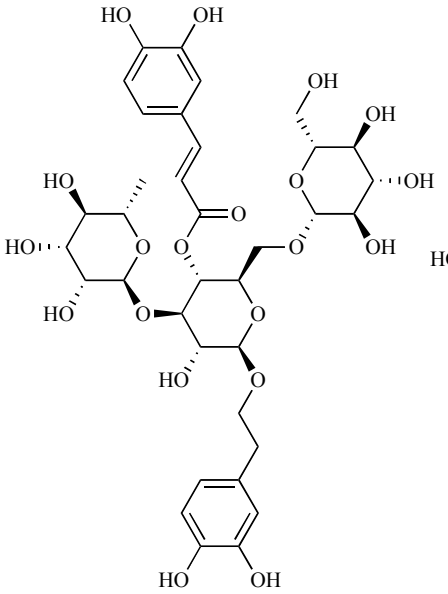


17: Baicalein

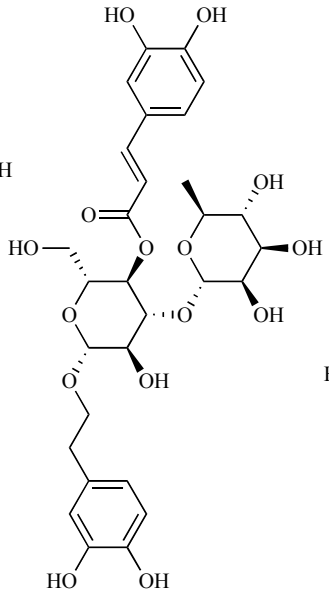


18: Nordihydroguaiaretic acid

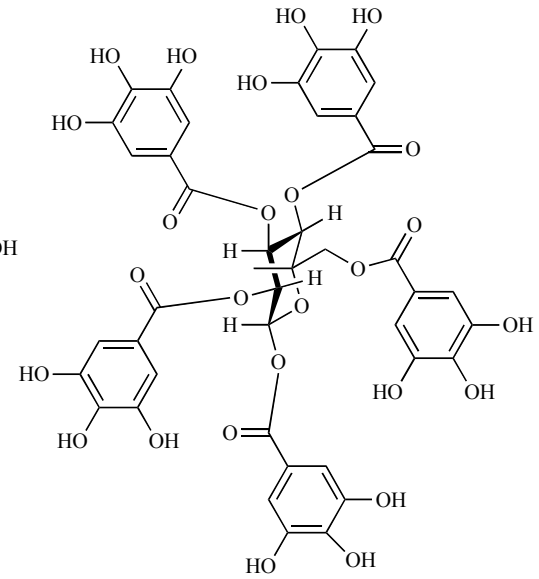
Fig. (2). contd….



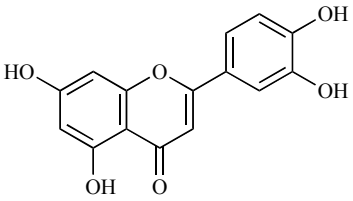
19: Echinacoside



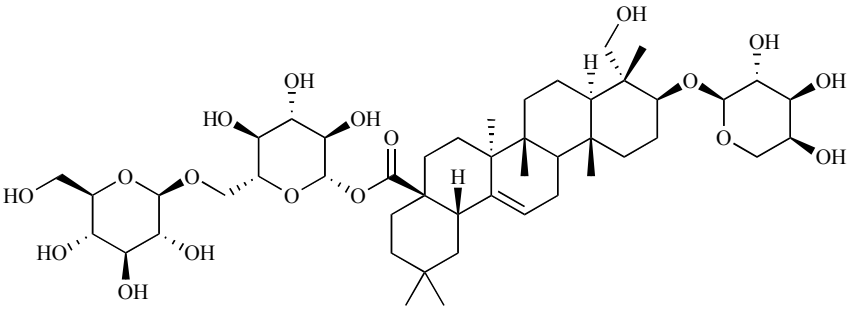
20: Acteoside



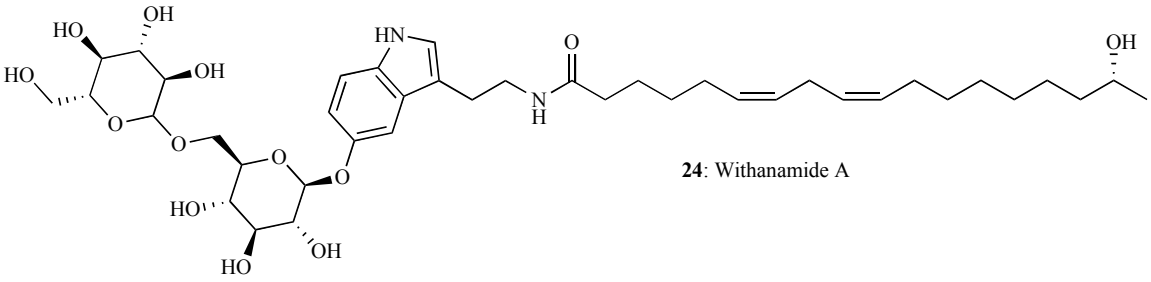
21: 1, 2, 3, 4, 6-penta-O-galloyl-b-D-glucopyranose



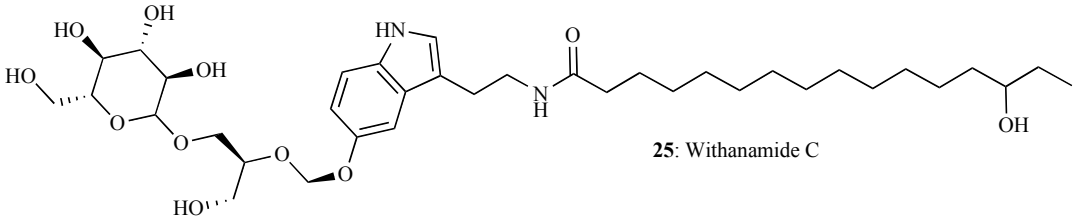
22: Luteolin



23: Akebia saponin D



24: Withanamide A



25: Withanamide C

Fig. (2). contd….

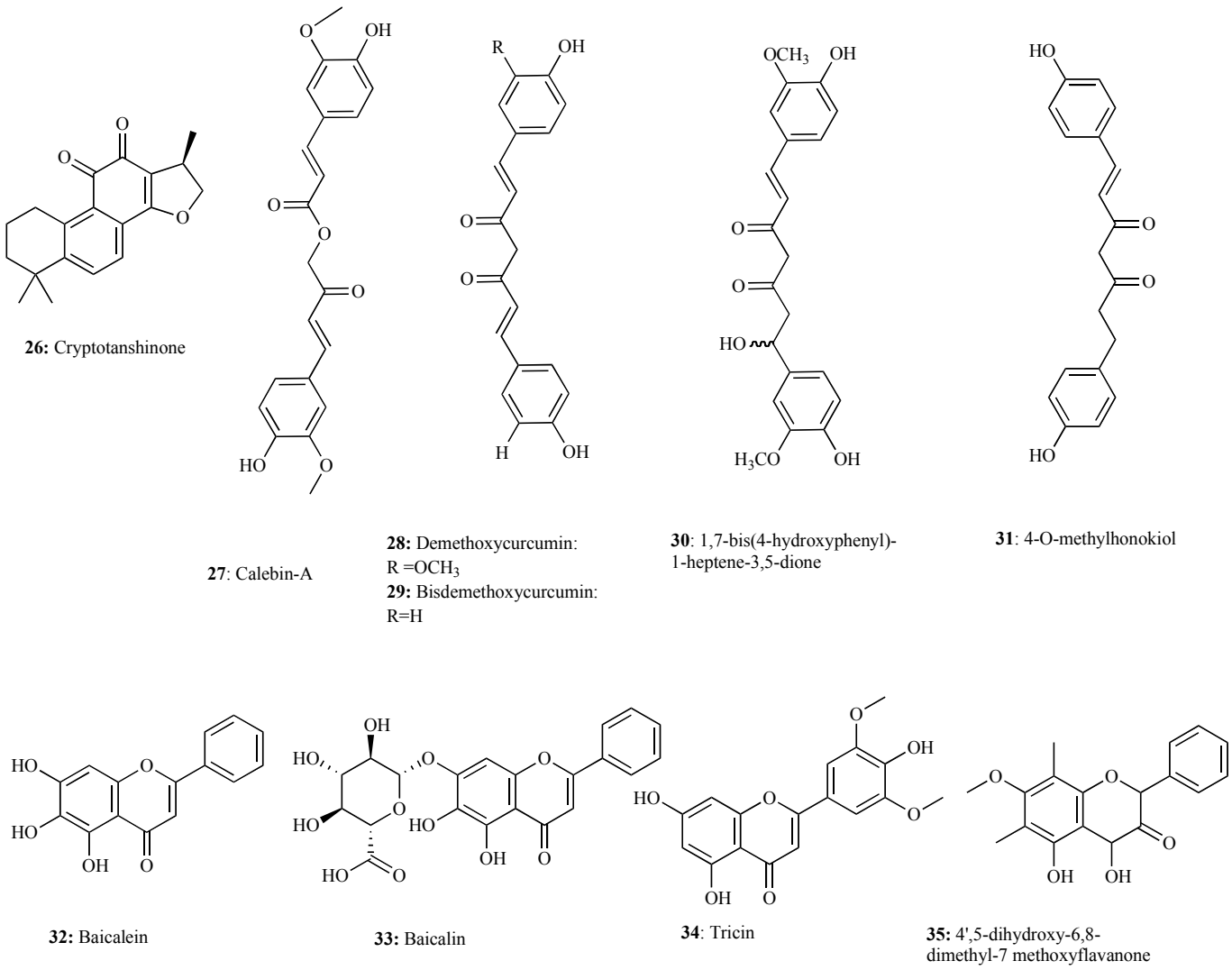


Fig. (2). Chemical structures of compounds with β amyloid inhibitory aggregation activity.

ROS level and, thus downregulation of the AIF-mediated apoptotic pathway [168]. *Cleistocalyx nervosum* var. paniala (Family: Myrtaceae) is a berry plant, native to the northern provinces of Thailand. The fruits are widely consumed by the local people. In 2017, Sukprasansap *et al*., (2017) reported that pre-treatment (24 h) of HT22 mouse hippocampal neuronal cells with 0.05-1 μg/mL aqueous fruit extract of *C. nervosum* var. *paniala* has considerably protected the cells against glutamate-induced neurotoxicity. It was noted that glutamate trigger apoptosis in cells by augmenting the protein expression of ER stress-apoptotic markers, for instance, cleaved caspase-12, calpain, and C/EBP homologous proteins (CHOP), which was considerably hindered by pretreatment of cells with tested *C. nervosum* var. *paniala* extracts [169].

The study carried by Prasansuklab *et al*. (2017) have demonstrated the neuroprotective potential of ethanol leaves extract of *Streblus asper* Lour., a medicinal plant from family Moraceae against toxicity caused by glutamate in HT22 hippocampal neuronal cells. It was suggested that these cells were protected *via* the suppression of ROS accumulation caused by glutamate, apoptotic-inducing factor (AIF) nuclear translocation, and elevation in Nrf2 signalling. Further to this, the tested extract (50 μg/mL) was found to prolong the lifetime of *Caenorhabditis elegans* at L1 larval stage as compared to control group, supporting its therapeutic potential for treating age-associated NDs [170]. In a similar study, Brimson *et al*., (2020) have found that the hexane extract of *Bacopa monnieri* (L.) wettst. (Family Plantaginaceae) was effective at protecting HT22 hippocampal neuronal cells against glutamate excitotoxicity, increasing lifespan and reducing aging in *C. elegans.* It was suggested that the tested extract exhibited neuroprotective effects by reducing ROS accumulation caused by glutamate and preventing mitochondrial stress. Bacoside A **(46)** compounds were identified in the hexane extract, which could possibly contribute to the neuroprotective property of *B. monnieri* [171].

The sesquiterpene, 9-Hydroxy epinootkatol **(47),** isolated from the Chinese medicinal plant, *Alpinia oxyphylla* Miquel (family Zingiberaceae), have been reported to protect cortical

Table 2. The protective effects of plants extract or plant-derived compounds on glutamate-induced neurotoxicity.

Plant Name (Family)	Plant Part /Crude Extracts/Isolated Compounds	Method	Findings/Mode of Actions	Refs.
Acanthus ebracteatus Vahl (Acanthaceae)	Hexane extract and ethanolic extract of leaves	*In-vitro*: Co-treatment of mouse hippocampal HT22 cell with 5 mM glutamate and extracts (3.125-50 µg/mL) for 24 h.	Restored cell viability dose-dependently. 50 µg/mL was used for subsequent assays: The extract exerted its effect by suppressing glutamate-induced apoptosis and glutamate-induced AIF nuclear translocation and oxidative stress.	[168]
Amburana cearensis (Allemao) A.C.Sm (Leguminosae)	Dichloromethane, ethyl acetate ethanolic and hexane extracts of seeds; Presence of isoflavone coumarin	*In vitro:* Pre-treatment of PC12 cells with glutamate (1 mM) for 6 h, following exposure to varied concentrations of the extract (0.1-1000 µg/ml)	Reduce neuronal cell death by up to 30% and anti-oxidant activity was noted.	[189]
Angelica gigas Nakai (Apiaceae)	Decursinol (55) and decursin (56) isolated from roots	*In-vitro:* Pre-treatment of cultured rat cortical cells with 0.1% of the compounds, followed by exposure to 100 µM L-glutamate.	Attenuated glutamate-induced neuronal cell death. 1.0 μM of Decursinol have showed 67.1 % protection, while at dose of 10 μM decursin have showed 65.5 % protection. Improved cellular anti-oxidative defence system and decreased of glutamate-induced Ca^{2+} influx.	[190]
Aronia melanocarpa (Michx.) Elliott (Rosaceae)	Ethanolic extract of berries	*In vitro:* Co-treatment of HT22 cells with the extract (10-100 µg/ml) and glutamate (2 mM) for 24 h.	Reduce glutamate-induced death of HT22 cells by 16.81-35.38% by decreasing ROS level and intracellular Ca^{2+} and increasing anti-oxidant enzymes.	[191]
Callicarpa dichotoma (Lour.) K.Koch (Lamiaceae)	Acteoside and its aglycones isolated from the leaves	*In-vitro*: Pre-treatment of primary cortical cells with the compounds (1.0 to 10.0 µM) for 1 h, followed by 24 h exposure to 100 µM glutamate.	Protective against glutamate-induced neurotoxicity (40- 75 % protection for 10.0 µM compounds) by modulating oxidative stress. The compounds have controlled the NO level comparable to control level (control: 18.2 ± 1.2 nM, glutamate: 64.9 ± 7.9 nM, acteoside: 19.3 ± 3.9 nM, caffeic acid: 17.1 ± 1.3 nM, 3′,4′- DHPE: 20.4 ± 4.4 nM). Acteoside (57) was more potent than Caffeic acid (13) and 3′,4′-dihydroxylphenylethanol (58).	[192]
Calendula officinalis L. (Compositae)	Methanolic (70%) of flowers	*In vivo:* The animal models have received oral extracts (100 and 200 mg/kg), 1 h after administration of monosodium glutamate for 7 days.	A decrease in oxidative stress, hippocampal damage, and improvement in behavioural changes was observed.	[193]
Citrus × *aurantium* L. (Rutaceae)	Ethanolic extracts of peels and seeds	*In vitro:* Pre-treating PC12 cells with the extracts at doses from 6 to 200 µg/ml) for 2 h, followed by an exposure to 8mM glutamate mM for 24 h.	Increase in % cell viability: 61.4-80 % for peel extract and 63-70 % for seed extract. Reduced glutamate-induced toxicity by decreasing ROS level, malondialdehyde level and apoptotic cells.	[194]
Ferula gummosa Boiss (Apiaceae)	Hydroalcoholic extract of roots	*In vitro:* Pre-treating rat adrenal pheochromocytoma (PC12) and mouse neuroblastoma (N2a) cells with extract (25200 µg/ml) for 2 h and then exposed to glutamate for 24 h	Increase in cell viability *via* reduction of intracellular ROS level. Extract at tested concentrations was able to reduce ROS levels in PC12, to 227 ± 6.1%-172 ± 5.7%, as compared to control group (260 ± 7.8%). In N2a, at doses of 50200 µg/ml, the decrease was 168 ± 4.5%-133 ± 4.8%, as compared to control (210.7 ± 11%).	[195]

(Table 2) contd….

Plant Name (Family)	Plant Part /Crude Extracts/Isolated Compounds	Method	Findings/Mode of Actions	Refs.
Lonicera japonica Thunb. (Caprifoliaceae)	Methanol extract of flower	*In vitro*: Pre-treatment of primary rat cortical cells with 10, 50 and 100 µg/ml of extract for 2 h, followed by exposure to 200 µM L-glutamate for 24 h.	At tested dose (0.03-1%), the extracts were effective and has restored cell viability by 100%. A decrease calcium influx was noted The extracts inhibited overproduction of NOS, ROS and peroxide and preserved cellular activity of superoxide dismutase.	[196]
Pueraria candollei var. *mirifica* (Airy Shaw & Suvat.) Niyomdham (Leguminosae)	Ethyl acetate and ethanol extract	*In-vitro*: Co-treating HT22 cells with the extracts (10 and 50 µg/mL) and glutamate (3.5 mM) for 24 h.	Provided protection against glutamate toxicity, possibly mediated through reducing ROS accumulation.	[197]
Rhinacanthus nasutus (L.) Kurz (Acanthaceae)	Ethanol extract of root; lupeol (59), stigmasterol (60) and β-sitosterol (61) was identified in the extract.	*In-vitro*: Treatment of HT22 cells with extract (0.1, 1 and 10 µg/ml) and glutamate (5 mM) for 18 h	Increase in cell viability *via* modulation of oxidative stress. Ethanol extract: protective EC50 = 1.7 $\mu g \cdot mL^{-1}$ for trypan blue exclusion assay; EC50 = 0.63 $\mu g \cdot mL^{-1}$ for the LDH assay.	[198]
Rhodiola rosea L. (Crassulaceae)	Salidroside (62)	*In vitro:* Pre-treatment of hippocampal neurons with salidroside (30, 60, or 120 µM) for 24 h and treatment with exposure to 125 µM glutamate with 10 µM of glycine	Protected hippocampal neurons against glutamate-induced apoptotic cell death in dose-dependently by hindering increase in caspase-3-like activity and uncontrolled Ca2+ influx prompted by glutamate.	[199]
Sanguisorba officinalis L. (Rosaceae)	Sanguiin H-11 **(63)** from dried roots (also known as Sanguisorbae radix)	*In vitro:* Co-treatment of HT22 cells with glutamate (5 mM) and Sanguiin H-11 (10 or 20 µM) for 24 h.	Prevented glutamate-induced death in HT22 cells, dose-dependently. Suppressed oxidative stress-mediated mitogen-activated protein kinases (MAPK) activation.	[200]
Sophora flavescens Aiton (Leguminose)	(2S)-2'-methoxykurarinone (a), sophoraflavanone G (b), leachianone A (c), and (-)-kurarinone (d) isolated from the roots.	*In vitro*: Pre-treating HT22 cells with the compounds (10-40 µM) in the absence or presence of the inhibitor of HO activity, SnPP, for one 1 h, followed by exposure to 5 mM glutamate for 12 h.	(2S)-2'-methoxykurarinone (64) and kurarinone (65) protected HT22 cells from glutamate exitotoxicity in a dose-dependently *via* modulation of oxidative stress.	[201]
Uncaria sinensis (Oliv.) Havil (Rubiaceae)	Hexane extract of dried hooks and stems	*In vitro:* Pre-treatment of primary rat cortical cells with 0.1-10 μg of extract for 24 h and then exposed to 200 µM glutamate for 6 h	Significantly reduction in glutamate-induced neurotoxicity and lactate dehydrogenase, dose-dependently. Decreased apoptosis by inhibiting expression of death receptor (DR)4 and expression of anti-apoptotic proteins XIAP and Bcl-2 Pre-treatment with the extract ended activation of caspases-8, -9 and -3.	[202]
	1-methoxyoctadecan-1-ol (MOD) (66)	*In vitro:* Pre-treatment of HT22 cells with MOD (0.01 to 1 µg/ml for 24 h) and then co-treatment with 5 mM glutamate and MOD for 24 h	Increased cell viability significantly Elevated mature brain-derived neurotrophic factor (BDNF), and subsequent phosphorylated p38 mitogen-activated protein kinases (p38 MAPK) and dephosphorylated phosphatidylinositol-3 kinase (PI3K)-mediated CREB signalling.	[203]
	Corynoxeine, rhynchophylline, isorhynchophylline isocorynoxeine geissoschizine methyl ether, hirsuteine and hirsutine, isolated from the hooks and stems of the plants	*In vitro:* Treatment of cerebellar granule cells with the isolated compounds (10^{-5}±10^{-3}M).	Rhynchophylline (10^{-3}M- 85.2% protection) (67), isorhynchophylline (10^{-4}-10^{-3} M, 55.7%-97.0% protection) (68), isocorynoxeine (10^{-4}-10^{-3} M, 56.8%-84.3% protection) (69), hirsuteine (10^{-4}-3 x 10^{-4} M, 53. 4%-63.7%) (70) and hirsutine (10^{-4}-3 x 10^{-4} M, 49-9%- 61.0%) (71) have increased cell viability significantly. An increased inCa^{2+} influx was noted.	[204, 205]

(Table 2) contd….

Plant Name (Family)	Plant Part /Crude Extracts/Isolated Compounds	Method	Findings/Mode of Actions	Refs.
Withania somnifera (L.) Dunal (Solanaceae)	Water extract of leaves	*In-vitro:* Pre-treating of rat glioma (C6) and human neuroblastoma (IMR-32) cells with 0.05% and 0.1% extract, followed by exposure to glutamate (0.06 mM-10 mM)	0.1 % extract have inhibited of glutamate excitotoxicity.	[206]
	Withanolide A (72)	*In-vitro:* Pre-treatment of retinoic acid differentiated Neuro2a neuroblastoma cells with withanolide-A (2.5, 5, 10, and 20 μM) and exposure to glutamate (10 mM) for 2 h	Increase in % cell viability: 74.50 % for MK-801 (specific NMDA receptor antagonist), 70.21% for 2.5 μM, 71.15% for 5 μM and 69.9% for 10 μM withanolide-A in MTT assay. A significant decline in the glutamate-induced influx of intracellular Ca^{2+} and excessive ROS generation was noted Normalisation of pro-apoptotic and anti-apoptotic proteins levels that influenced by glutamate treatment.	[207]

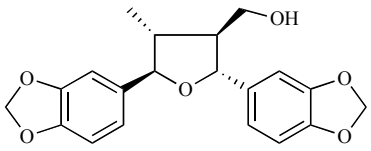
EC_{50}: Half maximal effective concentration.

neurons from glutamate-induced neuronal apoptosis. Co-treatment with glutamate and 40 μM 9-Hydroxy epinootkatol, has caused a decrease in the proportion of apoptotic nuclei by 28%. 9-Hydroxy epinootkatol has exerted its effect by hindering glutamate-induced activation of caspase-3, formation of NO and ROS and down-regulating glutamate-induced neuronal nitric oxide synthase (nNOS) expression. The results of the study support that *A. oxyphylla* might serve as potential therapeutic for NDs, which is in accordance with its traditional usage for enhancing mentality [145, 172]. Chen *et al*. (2018) have documented the potential of a novel Tetramethylpyrazine derivative, a well-known active component from traditional Chinese medicine Chuanxiong, to prevent glutamate-induced neuronal damage in the primary culture of rat cerebellar granule neurons. The compound was suggested to exert its effect *via* regulation of PGC1α/Nrf2 and PI3K/Akt pathways [173]. Another herb from Chinese Traditional Medicine which has been reported to potent against glutamate-induced neurotoxicity is *Coelogloss*um *viride* var. *Bracteatum*. The results suggested that the protective effect of *C. viride* var. *Bracteatum* extract (0.1, 1 and 10 mg/ml) was mediated by Akt and its downstream target Bcl-2 and regulation of the protein kinase C (PKC)-GluA2 axis. While the extract has improved immune function in sub-acute aging mice models, and hindered the loss of dopaminergic neurons in PD mouse model, induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a neurotoxin [174].

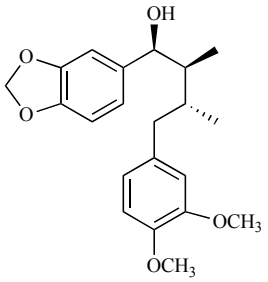
Carsonic acid **(48)**, a diterpene which presents many plants, for example, *Rosmarinus officinalis* L. and *Salvia officinalis* L., is well documented to be Nrf2 inducer and a mitochondrial protective agent. In 2019, de Oliveria *et al*. attempted to evaluate the ability of carnosic acid to protect mitochondria of neuronal cells against glutamate-induced excitotoxicity. Treatment of human neuroblastoma SH-SY5Y cells with 1 μM carnosic acid for 12 h prior to the exposure to glutamate for 24 h have induced mitochondrial protection in the cells treated with glutamate by decreasing the generation of ROS and apoptosis. The experimental data suggested that carsonic acid mediated its protective effects through the involvement in a mechanism associated with Nrf2 [175]. Similarly, ß-caryophyllene **(49),** a bicyclic sesquiterpene which is commonly found in essential oils of different plants including *Piper nigrum Cinnamomum* spp., has been shown to protect the C6 glioma cells against glutamate-induced toxicity *via* involvement in the Nrf2 pathway [176].

Thymoquinone (TQ) **(50),** the active ingredient of the essential oil of *Nigella sativa* seeds have been widely documented for its therapeutic effects, including antioxidant and antiapoptotic [177-179]. In a study by Al Mamun *et al*. (2015), treatment with thymoquinone (0.1-3 μM) for 18 h, followed by exposure to glutamate (8 mM) for 8 h, have shown to attenuate attenuated glutamate neurotoxicity by reducting ROS production and apoptosis [180]. Faoud *et al*., (2018) reported that administration of thymoquinone (2.5 and 10 mg/kg) enhance spatial memory and cognitive function in neurobehavioral tests in experimental animal models. Thymoquinone-treated group was found to show a decrease in the level of Caspase-3, lactate dehydrogenase, Aβ-42, and cytochrome c gene expression as compared to the group treated with glutamate [181]. Likewise, in a placebo-controlled clinical trial, treatment with *N. sativa* seed capsule (500 mg), twice a day for a period of 9 weeks was found to enhance cognitive function, memory and attention in elderly participants [182]. Hence, *N. sativa*, especially its component, thymoquinone, could serve as a promising therapeutic for treating NDs. Atractylenolide III **(51)** isolated from the medicinal Chinese herb, *Atractylodes macrocephala* Koidz. (Family Compositae) by means of bioactivity-guided fractionation have significantly reduced neuronal apoptosis induced by glutamate *via* suppressing caspase signalling pathway [183].

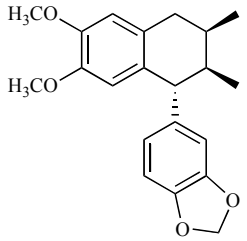
Phenolic compounds, in particular, have been the focus of many investigations because of their antioxidant activities, which could be directly associated with neuroprotective property. In this context, Rabai *et al*. (2017) performed a study to investigate the mode of actions of chlorogenic acid **(52)** and its main hydrolysates, caffeic **(13)** and quinic acid **(53)** in the protective potential against glutamate-toxicity.



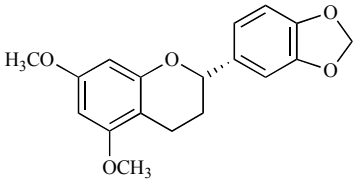
36: (+)-9'-hydroxygalbelgin



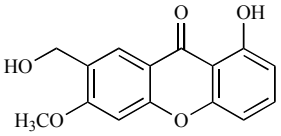
37: (7S,8S,8'R)-3',4'-dimethoxy-3,4,
-methylenedioxylignan-7-ol



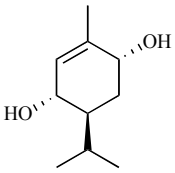
38: Isogalcatin B



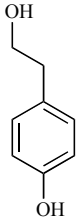
39: 5,7-dimethoxy-3',4'-methylenedioxyflavan-3-ol



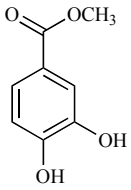
40: 1-hydroxy-7-hydroxymethyl-6-methoxyxanthone



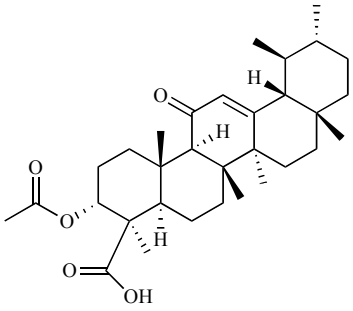
41: (+)-(3S,4S,6R)-3,6-dihydroxypiperitone



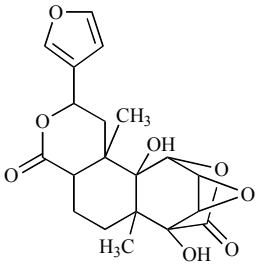
42: tyrosol



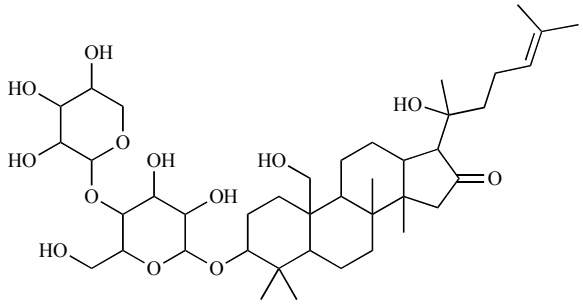
43: Protocatechuic acid methyl ester



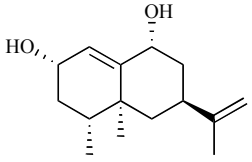
43: R=AcO; 3-acetyl-11-keto-β-boswellic acid
44: R =HO; 11-keto-β-boswellic acid



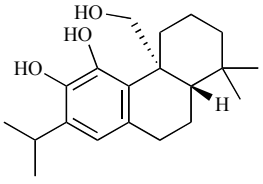
45: Tinosporicide



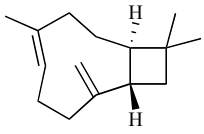
46: Bacoside A



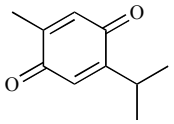
47: 9- Hydroxy epinootkatol



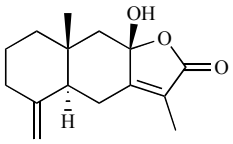
48: Carsonic acid



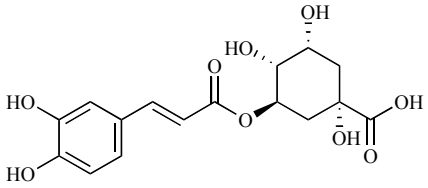
49: b-caryophyllene



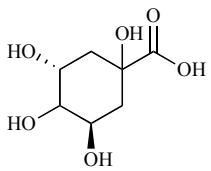
50: Thymoquinone



51: Atractylenolide III



52: Chlorogenic acid



53: Quinic acid

Fig. (3). contd….

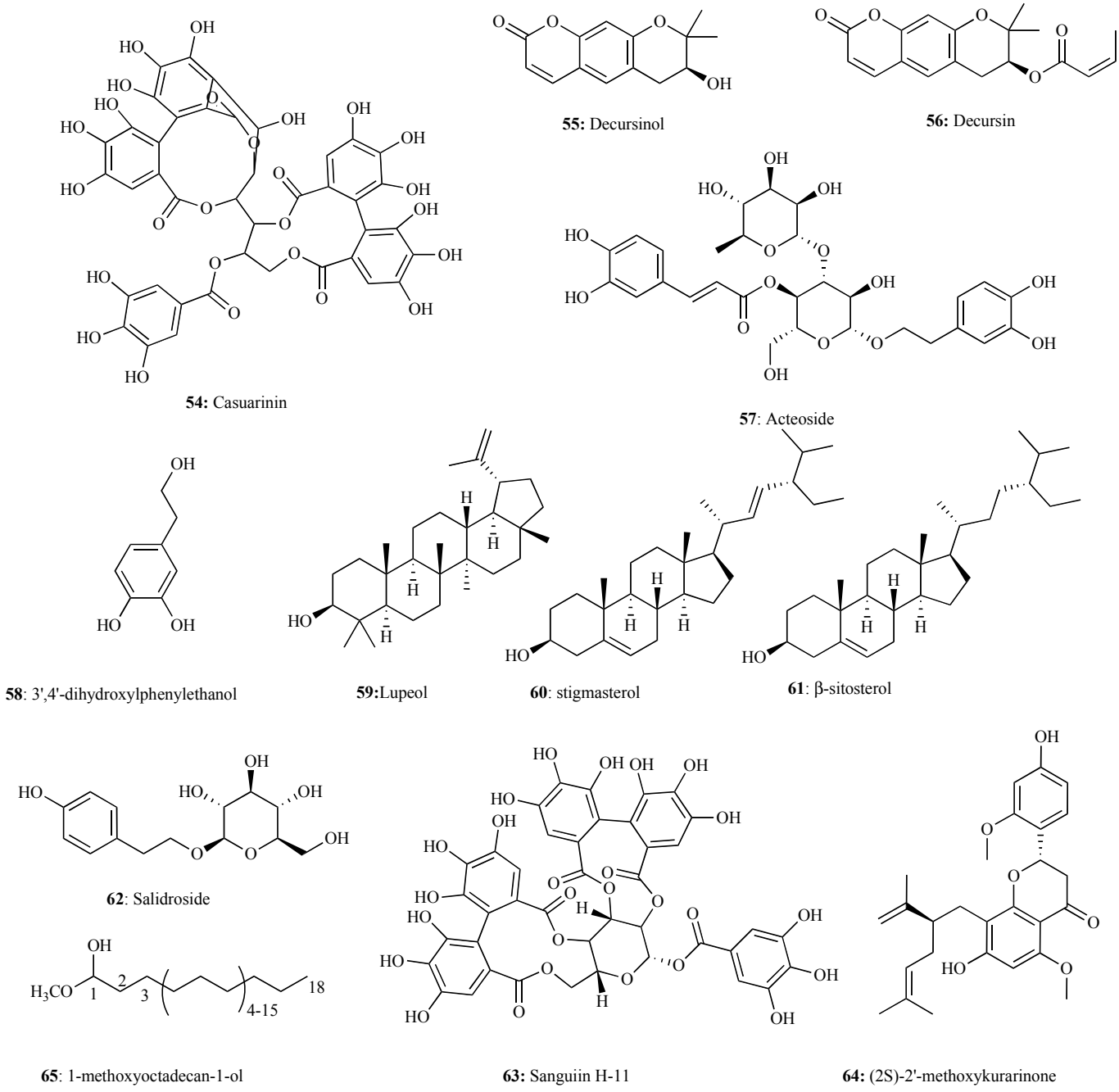


Fig. (3). Chemical structures of compounds that show neuroprotection against glutamate-induced excitotoxicity.

At concentrations of 10-100 μM, the tested compounds have inhibited cell death stimulated by glutamate in rat cortical neurons, with quinic acid was less potent. Results from the study have indicated that chlorogenic acid acts a neuroprotective agent against glutamate-induced injury by inhibiting endogenous ROS accumulation and reinstating mitochondrial membrane potential, elevating superoxide dismutase (SOD) activity and the intracellular Ca^{2+} level. Interestingly, chlorogenic acid and caffeic acid also displayed anti-apoptotic activity against glutamate-induced cleaved activation of caspase 1, 8 and 9 and calpain. Casuarinin **(54)**, a C-glycosidic ellagitannin, have been documented to decrease cell death in HT22 murine hippocampal neuronal, induced by glutamate by suppressing ROS generation decreasing chromatin condensation, and hindering oxidative stress-mediated MAPK phosphorylation [184]. The study by dos Santos Souza *et al*., (2018) have shown that *Agathisflavone*, a flavonoid isolated from *Poincianella pyramidalis* (Tul.) L.P.Queiroz is an effective neuroprotectant against glutamate excitotoxicity by exerting anti-inflammatory effects on microglia and augmenting expression of neuroprotective cytokines (NFα, IL1β and IL6) and trophic factors (BDNF, NGF, NT4 and GDNF) [185]. Curcumin, the main polyphenolic compound found in the turmeric (*Curcuma longa* L.) has been documented to possess properties that can prevent or ameliorate pathological processes related to NDs. Curcumin

(4) has been presented beneficial effects against glutamate excitotoxicity [21, 186, 187] in different cellular models. For example, Chang *et al*., (2014) have demonstrated that curcumin-protected PC12 cells against glutamate excitotoxicity by mediating the glutathione-dependent NO/ROS pathway and the mitochondria-dependent NO/ROS pathway [188].

CONCLUSION

A significant number of people rely on herbal medicines not only because they are considered safe and effective, but the costs associated with modern medicines are beyond the reach of many people, especially in low-resources countries. The rising incidence of complex metabolic and NDs in developed countries that have no drugs for cure support the fact that medicinal plants could still be exploited as a valuable reservoir of lead compounds as has been done throughout the history of mankind. Indeed, medicinal plants have been linked to a plethora of mechanisms which target neurodegenerative disorders retardation and neuroprotection. The main mechanisms through which medicinal plants act include prevention of protein misfolding, antioxidant, anti-glycation, anti-Aβ aggregation activity, suppression of oxidative stress and AChE activity in the brain caused by D-gal, reversing cholinergic and hippocampal dopaminergic neuronal function, suppressing the biosynthesis of mature fibrils and favour instead the formation of short amorphous aggregates among a plethora of other mechanisms. Nonetheless, most of these mechanisms have been noted solely *in vitro* and further investigations need to be performed to validate these effects *in vivo* and clinically. In furtherance, studies should gear at enhancing the bioavailability of promising medicinal plant compounds against NDs as well as their ability to cross the blood brain barrier should be validated to confirm their potential utility in NDs therapy. Once these factors are validated, extended research focused on standardized dosing of the promising medicinal plants against neurodegenerative disorders in human beings to validate the therapeutic dose and to prevent any unwanted effects.

LIST OF ABBREVIATIONS

AChE	=	Acetylcholinesterase
AD	=	Alzheimer's disease
ADNF	=	Activity-dependent neurotrophic factor
AIF	=	Apoptotic-inducing factor
AKBA	=	3-acetyl-11-keto-β-boswellic acid
ALCA	=	Amyloid light chain amyloidosis
AMPA	=	A-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid
AMPK	=	AMP-activated protein kinase
APP	=	Amyloid precursor protein
Aβ	=	Amyloid-β
BACE1	=	Beta-site amyloid precursor protein cleaving enzyme 1
BBB	=	Blood-brain barrier
BDNF	=	Brain-derived neurotrophic factor
COX	=	Cyclooxygenase
CREB	=	cAMP Response Element Binding protein
CTS	=	Cryptotanshinone
D-gal	=	D-galactose
ED50	=	median effective dose
EGCG	=	Epigallocatechin-3-gallate
ER	=	Endoplasmic reticulum
GA	=	Gallic acid
GABA	=	Gamma-aminobutyric acid
iGluR	=	Ionotropic glutamate receptors
LRP1	=	Low-density lipoprotein receptor-related protein-1
mGluR	=	Metabotropic glutamate receptors
ND	=	Neurodegenerative diseases
NFTs	=	Neurofibrillary tangles
NMDA	=	N-methyl-D-aspartate
NMDAR	=	N-Methyl-D-aspartic acid receptor
nNOS	=	Neuronal nitric oxide synthase
Nrf2	=	Nuclear factor erythroid 2-related factor 2
NSAIDs	=	Non-steroidal anti-inflammatory drugs
p38 MAPK	=	phosphorylated p38 mitogen-activated protein kinases
PD	=	Parkinson's disease
PGG	=	1,2,3,4,6-penta-O-galloyl-β-d-glucopyranose
PHFs	=	Paired helical filaments
PI3K	=	phosphatidylinositol-3 kinase
PKC	=	Protein kinase C
RA	=	Rosmarinic acid
RAGE	=	Receptor for advanced glycation end products
ROS	=	Reactive oxygen species
SALAs	=	Aβ42-lowering agents
TEM	=	Transmission electron microscope
WA	=	Withanamides A
WC	=	Withanamides C
Xc-	=	Cystine/glutamate antiporter

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise

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