Trop J Nat Prod Res, July 2022; 6(7):1019-1046 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

Pharmacological Actions of Phytoconstituents on Neurodegenerative Disorders

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ARTICLE INFO

Article history:
Received 28 August 2021
Revised 17 June 2022
Accepted 17 July 2022
Published online 03 August 2022

ABSTRACT

Neurodegenerative diseases (NDs) have over the years become a growing cause for concern and it is increasingly becoming a major health problem associated with impairment, ageing of the brain and other neuropathological conditions. These include Parkinson's disease, Dementia, Huntington's disease, Alzheimer disease, and Depression. Due to increase in prevalence of various NDs over the years, there is growing need to provide suitable means by which the disease can be mitigated. Various pharmacological agents are being researched on to investigate the most suitable and effective means to curb these diseases. This review was aimed at perusing therapeutic potentials of various pharmacological agents in the treatment of NDs. Over a hundred research papers, from Pubmed, NCBI, BMC med, Neurosci etc published on NDs treatments via phytochemicals within the past two decades were analysed. This review will help guide research on pharmacological agents with a wider range treatment options for NDs. Curcumins were most frequently studied for all NDs management. Other commonly used pharmacological agents are resveratrol, epigallocatechin n-gallate (ECGC) and l-theanine. In the management of NDs, curcumin is found to normalize altered mechanisms associated with caspase-3 level, TNF-α, COX-2, NO, iNOS, PGE2, IL-6, Glial fibrillary acidic protein (GFAP), IL-1β, insulin-degrading enzymes, apoptosis, inflammation, mitochondria dysfunction, inhibitory activity of AChE, and cell viability. It was surmised from the study that curcumin, resveratrol, ECGC and L-theanine are the most common and effective classes of phytochemicals for a wide range of NDs management.

***Keywords*:** Neurodegenerative disease, pharmacological agents, phytochemicals, curcumin, resveratrol.

Introduction

The human brain is the most complex organ of the body. It possesses a vast array of billions of neurons which work intricately to carry out various vital functions. Such functions include receiving and sending nerve impulses. It also functions in ensuring optimum neuron functioning by providing support for glial cells. By carrying out all these functions it is able to perform behavioural and cognitive activity. Once there is alteration in the normal functioning of the brain, this will lead to disease that could affect the normal way of life of an individual.[1] This alteration could be due to inability to maintain a constant energy supply required for the brain to perform its function. It could also be as a result of damage to the supporting glia cells. Any of these can lead to brain dysfunction and also result in behavioural lapse. Any disease as a result of this is referred to as Neurodegenerative disease which includes Parkinson's disease, Alzheimer's disease (AD), seizure disorders, dementia and depression. Neurodegenerative disease has been a prominent cause of concern when it comes to neuropathological conditions and also brain ageing. It has a death rate of about 10% and has been identified as a prominent cause of death worldwide.[1]

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Citation: Kayode AAA, Kayode OT, Rotimi DE. Pharmacological Actions of Phytoconstituents on Neurodegenerative Disorders. Trop J Nat Prod Res. 2022; 6(7):1019-1046. doi.org/10.26538/tjnpr/v6i7.2

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Neurodegenerative diseases have been a major health problem involved in brain ageing and neuropathological conditions. They have been noted as a prominent cause of death worldwide, with a death rate of about 10%.[2] Some common examples of cognitive dysfunction and neurodegenerative disorders include Parkinson disease, Alzheimer's Disease (AD), seizure disorders, dementia and depression.[3] This brings about the need for neuroprotection. Neuroprotection are ways or mechanisms by which the brain can be protected from neuronal injury due to neurodegenerative disorders and also ensure viability and optimum functioning of the brain.[4]

The need for neuroprotection has led to research in prospective candidates that could provide protection for the brain. Plants are one of the investigated candidates for neuroprotection. Plants have been an essential need for humans as they are not only important as food source alone but also serves as medicines. Previously, there have been intense interests in plant or herbal medicines in response to various health problems. Significant health benefits have been associated to vegetables and fruits rich diets as they boost the functionality of the body and brain due to the presence of phytochemicals present in them.[5] Studies revealed that these phytochemicals can decrease the risk and symptoms of diseases including cancers, stroke, cardiovascular disease and neurodegenerative diseases.[6,7] Over time, the intrinsic antioxidant properties of the phytochemical have been attributed to their therapeutic effects due to the fact that oxidative stress causes most of the chronic age-related diseases.[5]

These phytochemicals when consumed in adequate amount has been shown to have beneficial effects on health. This also can be applied to neurodegenerative diseases. Therefore, the risk of neuronal dysfunction can be reduced by the increased consumption of vegetables and fruits.[8,9]

Parkinson's Disease

Parkinson's disease (PD) is the commonest neurodegenerative disease after Alzheimer disease and affects over 5.7 million people worldwide majorly aged adults.[10] Parkinson's disease causes impairment of the cognitive function and motor skills due to the progressive deterioration of dopaminergic neurons of the substantia nigra (SN) pars compacta and of nerve fibres projecting to the striatum, significantly decreases the level of the neurotransmitter responsible for neural modulation which is dopamine.[11] Some symptoms associated with PD disorder include autonomic dysfunction, anxiety, resting tremor, bradykinesia, postural instability, cognitive dysfunction rigidity and depression.[12] Several pathogenic mechanisms that mediates damages to dopaminergic neurons include oxidative stress, inflammation, apoptosis, mitochondrial dysfunction and transition metal accumulation.[11,13]

Till date, despite the effort to manage PD, the therapeutic approaches administrated are just able to alleviate symptoms. The pharmacological therapy for PD is dopamine replacement treatment which is effective for approximately 10 years and reduces efficiently depression, pain and motor symptoms. Although the long-term effect of the drug results in toxic metabolites and Reactive Oxygen Species (ROS) accumulation resulting from dopamine metabolism. Moreover, the disease progression cannot be slowed or halted by the drugs.[14,15]

Although, the etiology of PD is unknown, numerous studies have revealed different risk factors associated with PD either through interaction or independently, they include environmental factors (pesticides, heavy metals, and herbicides) and genetic factors (leucine-rich repeat kinase 2, parkin and mutations in the α-synuclein).[16] Studies about the neuropathology revealed that the two stages of the disease are dopamine reduction in the SN due to the development of Lewy neuritis (LNs) and Lewy bodies (LBs) and the selective death of dopaminergic neurons in the SN pars compacta.[17] The pathogenesis of PD has been attributed to enhanced oxidative stress and mitochondria dysfunction.[16] Mitochondrial respiratory chain activities are inhibited by oxidative stress resulting in overproduction of aggregated α syn and ultimately increase ROS levels and mitochondrial dysfunction.[18] A study showed that PD development can be reduced by promoting autophagy which is facilitated by placing aggregates of α syn into the autophagic vesicle and then degrading it.[16] Previous PD animal and *in vitro* models showed that pathogenesis of PD are linked with the apoptosis pathways. Also, it has been observed that the apoptosis process of PD involves significantly the p53/Bcl-2 family members. The promotion of p53-dependent apoptosis activates p38 and c-Jun NH2-terminal kinase (JNK) by suppressing the anti-apoptotic agents (Bcl-2) and activating the caspase pathway which result in neurodegeneration of the disease.[19]

Different phytochemicals have been effective in cell and animal models of PD (tables 1 and 2). Some of these phytochemicals with already established anti-parkinsonian effects include polyphenols such as phenols, phenolic acids, flavonoids, flavones, stilbenes, and lignanes as well as terpenes. Others include alkaloids, amino acids, carbohydrates, cinnamates and fatty acid amides and they all had therapeutic effects in PD treatment. Different investigations revealed that majority of the compounds suppressed apoptosis and elevates the cell viability by reducing Bax/Bcl-2 ratio, caspase-3 level and accumulation of α-syn and expression of proinflammatory cytokines (such as NF-κB, IL-6, IL-1*β*, NO, TNF-*α*, PGE 2) and intracellular transduction and transcription pathways (SIRT and Nrf) and modulation of cellular and nuclear inflammatory signaling. In addition, there are increases in neurotrophic factors, protection of mitochondrial respiratory chain, improvement of antioxidant enzyme, increase in GSH level and decrease in ROS formation and lipid peroxidation, are cellular phytochemicals mechanisms of anti-parkinsonian. In animal-induced PD, therapeutic effect of numerous phytochemicals includes suppression of the apoptosis process and expression and decrease in dopaminergic neuronal loss and depletion of DA. Neuronal inflammation was reduced in TNF-*α*, iNOS, IL-1*β* and COX-2 while increases in CAT, SOD and GPx and oxidative stress were reduced via decrease in lipid peroxidation, MDA and ROS.

Table 1: *in vitro* anti-parkinson activity of different phytochemicals[20]

Authors	***In vitro* model**	**Phytochemical name**	**Mechanism**
Chao *et al*.[21]	Rotenone and dieldrin were exposed to SH-SY5Y neuroblastoma cells	L-theanine	↓ caspase-3 activity; ↓ nuclear damage; ↑ Cell viability; ↑ GDNF and BDNF
Kumar *et al*.[22]	MPTP was exposed to SH-SY5Y neuroblastoma cells	Gastrodin	↓ ROS; ↑ Cell viability; ↓ PARP proteolysis ↓ Bax/Bcl-2;
Du *et al*.[23]	MPTP was exposed to MES23.5 cells	Rosmarinic acid	↑ caspase-3 activity ↑ C ell viability; ↑ Bcl-2/Bax; ↓ ROS;
Qualls *et al*.[14]	salsolinol and rotenone was exposed to SH-SY5Y neuroblastoma cells	Curcumin	↓ caspase-3 level ↑ Cell viability;
Ham *et al*.[24]	SH-SY5Y neuroblastoma cells	Moracenin D	↓ α-syn mRNA
Kim *et al*.[25]	MPTP was exposed torat mesencephalic cells	Acacetin	↓ TNF-α, PGE2 and NO
Mu *et al*.[26]	6-OHDA was exposed to PC12 cells and SH-SY5Y neuroblastoma cells	Baicalein SH-	Improved morphological properties in PC12 cells ↑ cell viability SH-SY5Y cells; ↓ Apoptosis in

Li *et al*.[27]	rotenone was exposed to PC12 cells	Bu-7	↑ Cell viability; ↓ cleaved caspase-3 ↓ p53;
Tai and Truong [28]	DDT was exposed to SH-SY5Y neuroblastoma cells	Epigallocatechin 3-Gallate (EGCG)	↑ Cell viability
Tamilselvam *et al*.[29]	Rotenone was exposed to SK-N-SH neuroblastoma cells	Hesperidin	↑ Cell viability; ↑ Bcl-2 ↓ caspase-3 and -9; ↓ cytochrome c release; ↓ Bax; ↑ antiapoptotic performance: protection of MMP; ↑ GSH; ↑ antioxidant performance: ↓LPO; ↓ ROS
Filomeni *et al*.[30]	SH-SY5Y neuroblastoma exposed to Rotenone	Kaempferol	↓ ROS and mitochondrial carbonyls;
Lee *et al*.[31]	Primary cultured neurons exposed to MPTP	Silibinin	no antioxidant effect; ↑ Cell viability; protection of MMP
Park *et al*.[32]	MPTP was exposed to rat mesencephalic cells	6-Shogaol	↓ TNF-α and NO; ↑ Cell viability
Leal *et al*. [33]	6-OHDA was exposed to rat mesencephalic cells	Amburoside A	↓ nitrite; ↓ LPO; ↑ Cell viability
Wang and Xu[34]	MPTP was exposed to SH-SY5Y neuroblastoma cells	Salvianic acid A	↑ Cell viability; ↓ caspase-3 activity ↓ Cytochrome c release; ↓ Bax/ Bcl-2; ↓ nuclear damage; ↓ ROS; ↓ apoptosis;
Chao *et al*.[35]	6-OHDA was exposed to SH-SY5Y neuroblastoma cells	Resveratrol	↓ caspase-3 activity ↓ LDH;
Chen *et al*.[36]	6-OHDA was exposed to SH-SY5Y neuroblastoma cells	Carnosic acid	↓ cleaved caspase-3 and PARP; ↓ ROS; ↑ Cell viability; ↓ nuclear damage; ↑ Nrf2; ↑ GSH; ↓ JNK and p38 phosphorylation;

Dementia

Dementia is principally an age-related irreversible disease which progressively reduces cognitive functions by reducing the ability to perform daily activities, especially in millions of elderly people suffering from dementia and Alzheimer's disease (AD).[37] It has been recorded that there is a new case of dementia every 4 second and 8 million cases documented annually and about 50 million patients worldwide. Dementia is a multifactorial disease (Figure 1) and has been connected to aging and environmental impacts.[38]

According to National Institute of Health, the different classification of dementia is Alzheimer's disease (AD), frontotemporal dementia (FTD), vascular dementia (VaD), mixed dementias and dementia with Lewy bodies (DLB).[39] The commonest dementia worldwide is AD and it accounts for roughly 55-60% of dementia cases, followed by vascular dementia (VaD) (20%), then dementia with Lewy bodies (DLB) at almost 10% and frontotemporal dementia (FTD) at 2% .[40]

Alzheimer's disease is described as a progressive deterioration of the cholinergic neurons in the cortex and hippocampus areas thereby resulting in damage to the cognitive function and results in symptoms including depression, mental deterioration, memory loss and impaired judgement. The pathological mechanism of Alzheimer's disease are senile plaques, resulting from the amyloid beta (Aβ) protein accumulation, aggregated Tau protein and the neurofibrillary tangles (NFTs).[41] Oxidative stress and inflammation are events that results from accumulation of Aβ.[42] In addition, Aβ activates microglia by releasing Reactive Oxygen Species (ROS) and pro-inflammatory cytokines which leads to excitotoxic neuronal death. Typical treatment options for AD are primarily symptomatic among which are

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

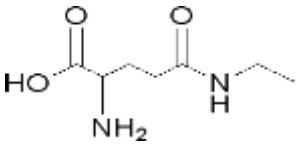
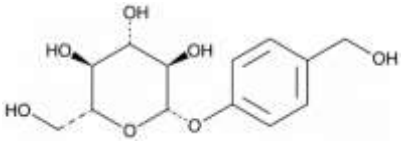
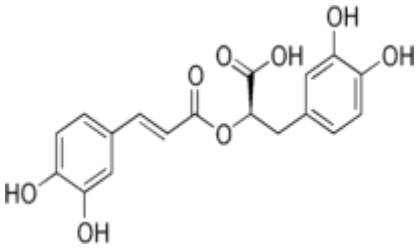
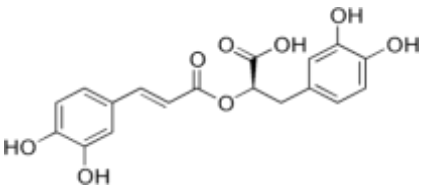
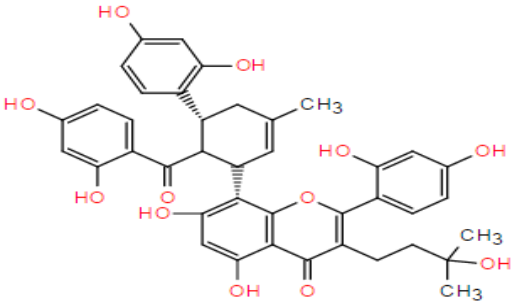
rivastigmine (RIV, galantamine (GAL, Reminyl®), donepezil (Aricept®) and Exelon®). These treatments consist of acetylcholinesterase inhibitors (AChEIs) which enhances cholinergic transmission and improved cognition functioning [43]. Other drug that have proven beneficial effects is memantine (Namenda®), acts as N-methyl-D-aspartate (NMDA) receptor's antagonist.[44] The VaD is a condition characterized by a cerebrovascular etiology (stroke) of a whole spectrum of cognitive dysfunctions. There have been reported cases of cholinergic deficits in VaD patients and cholinergic treatment shows therapeutic effects on cognitive function.[45] Treatment options for VaD are aimed at averting further vascular injury by reducing its risk factors such as diabetes mellitus and hypertension.[46]

The DLB is characterized by the abnormal α-synuclein (α-Syn) protein aggregation in Lewy bodies (neuronal cells).[47] The DLB pathogenetic mechanisms are multifactorial, although formation of Lewy bodies implicates the genetic mutations in the α-Syn family genes.[48] It is clinically characterized by slowed movements, sleep disturbances, recurrent visual hallucinations, tremors (Parkinsonism), stiff limbs, and fluctuations in alertness and cognition. Neurodegeneration can be caused by accumulation of α-Syn and therefore results in mitochondrial degeneration which induces oxidative stress.[49, 50]

The FTD is characterized by progressive atrophy in the temporal or frontal lobes which causes a gradual decline in behavior. It is pathologically and genetically heterogeneous. So far, no therapy has been found but the symptoms can be managed using antipsychotics or antidepressants.[51]

In preclinical studies, phytochemicals such as polyphenols have displayed properties including anti-oxidative, anti-inflammatory and anti-amyloidogenic properties in dementia treatment (table 3).

Table 2: Chemical structures of phytochemicals with anti-parkinson activity

Photochemical name	Category	Structure
L-theanine	Amino acid	
Gastrodin	Benzyl alcohol	
Rosmarinic acid	Cinnamate	
Curcumin	Diarylheptanoid	
Moracenin D	Flavone	

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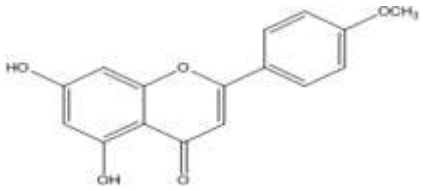
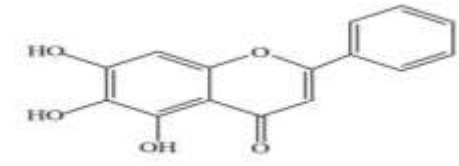
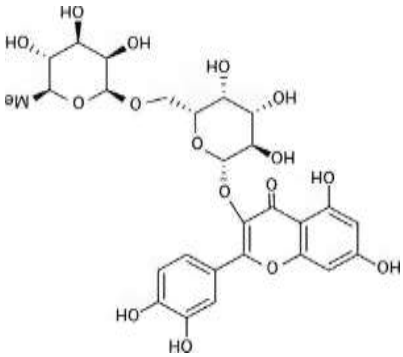
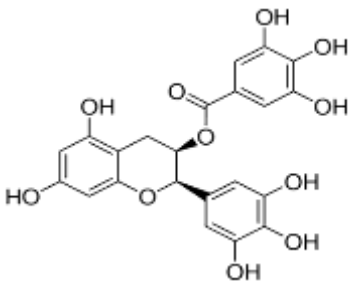
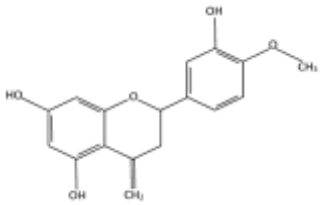
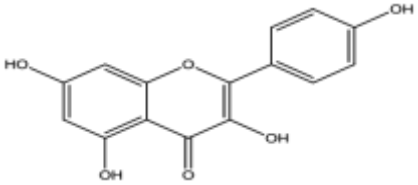
Acacetin	Flavonoid	
Baicalein SH-		
Bu-7		
Epigallocatechin 3-Gallate (EGCG)		
Hesperidin		
Kaempferol		

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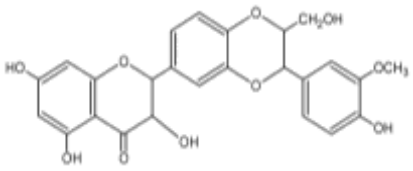
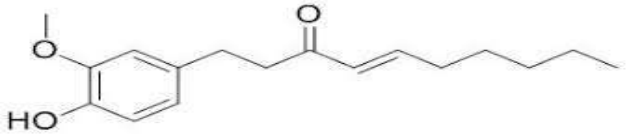
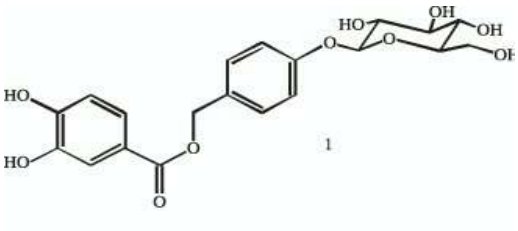
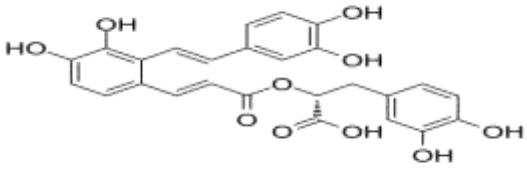
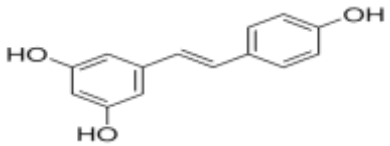
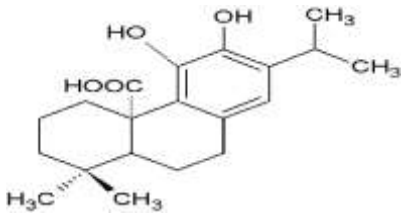
Silibinin		
6-Shogaol	Phenol	
Amburoside A	Phenol glucoside	
Salvianic acid A	Phenolic acid	
Resveratrol	Stilbene	
Carnosic acid	Terpene	

Table 3: Neuroprotective effects of phytochemicals on dementia in preclinical studies.[52]

Phytochemical	Model	Proposed Mechanisms Involved (*In vitro*/*In vivo*)	Mediated Protective Effects	References
Curcumin	LPS-stimulated rat BV2 microglia	TNF-α, COX-2, IL-1β, NO, iNOS, PGE2, IL-6	antioxidative, anti-inflammatory	Jin *et al.*[53]
	Mutant APPswe over expression in SH-SY5Y		anti-amyloidogenic	Durairajan *et al.*[54]
	Tg2576 mice expressing mutant APP	GFAP, IL-1β, amyloid plaques	anti-inflammatory, anti-amyloidogenic	Lim *et al.*[55]
	PS1/APP double transgenic AD mice	insulin-degrading enzymes	anti-amyloidogenic	Wang *et al.*[56]
Resveratrol	Aβ-induced rat C6 glioma cells	iNOS, PGE2, COX-2, NO	anti-inflammatory	Debprasad *et al*[57]

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	Aβ-induced rat PC12 cells	JNK, Bax, ROS, NFκB	anti-apoptotic anti-inflammatory	Jang and Surh[58]
	Healthy rats	MDA, SOD and CAT	Anti-oxidative	Mokni *et al.*[59]
	PS1/APP double transgenic AD mice	SIRT-1, AMPK	Anti-oxidative, anti-amyloidogenic	Porquet *et al.*[60]
	CCH rats	CREB phosphorylation and PKA	spatial learning and memory improvement	Lonze and Ginty[61]
EGCG	IL-1β/Aβ exposed U373MG cells	MAPK, COX2, VEGF, IL-8, PGE, IL-6, NFκB, JNK	anti-inflammatory	(Kim *et al.*[62]
	icv-STZ rats	AChE, ROS	anti-amyloidogenic anti-oxidative	Biasibetti *et al.*[63]

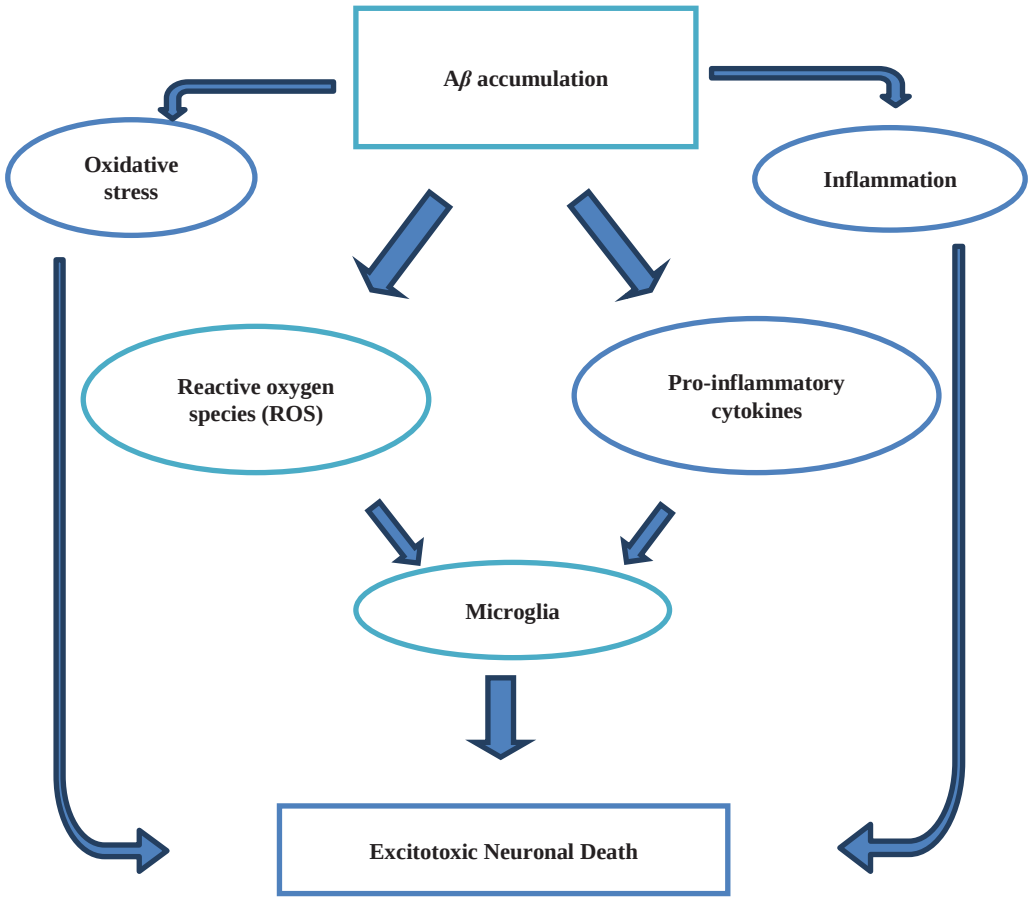


Figure 1: Mechanisms of action of dementia as it relates to inflammation and oxidative stress

Huntington's disease

Huntington's disease (HD) was first described by an Ohio physician, George Huntington. The HD also known as Huntington's chorea is an inherited autosomal dominant neurodegenerative disorder characterized by progressive motor dysfunction affecting motor ataxia, muscle coordination leading to chorea and dystonia, cognitive decline, emotional disturbances, memory, and weight loss.[64, 65] The pathological alterations mainly involves enkephalin neurons of basal ganglia in HD, GABA loss, N-methyl-D-aspartate (NMDA) receptors modification and the Medium Spiny Neurons (MSNs) of striatum, and cortex.[66]. Out of 100, 000 persons worldwide, HD occur in about 3-6 persons and approximately 20 persons as carriers.[67] Death of the patients usually occurs 16-20 years after the symptoms appear, these symptoms usually develop between the ages of 37 and 50 in humans.[68, 69] So far, there has not been a known treatment procedure to check progressive neuronal dysfunction; symptom management has been through conventional therapeutic approach.[70] Presently, non-pharmacological treatments of HD involve palliative care and gene therapy.[68]

Early symptoms management reported as efficacious are mood stabilizers and Selective Serotonin Reuptake Inhibitors (SSRIs).[66, 65] Series of cellular and animal models have been used to mimic this condition. According to WHO, there is reported over-dependence on traditional medicine. It has been popularized due to its lower cost, reported therapeutic efficacy against a number of ailments, its availability and lesser side effects.[71] Characterization of active constituents of these herbs may bring about new drug discoveries.[71, 72] Recently, considerable attention has been given to the use of herbs to treat neurodegenerative diseases. Some of the effective phytochemicals that may ameliorate the condition are listed in table 4 and there structures are shown in table 5.

However, further investigation is required to understand the safety, efficacy and tolerability of many herbal formulations.[73]

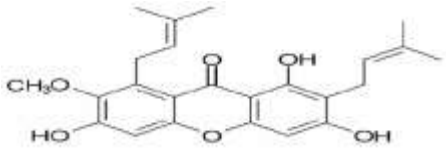
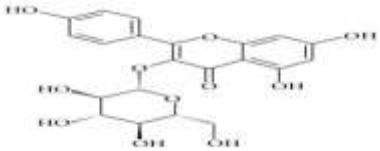
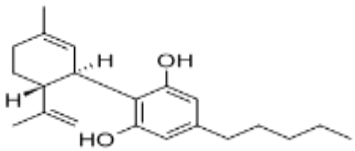
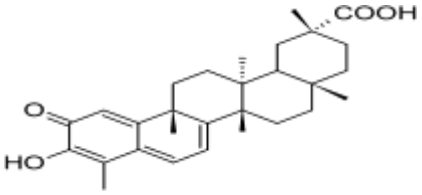
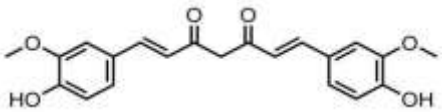
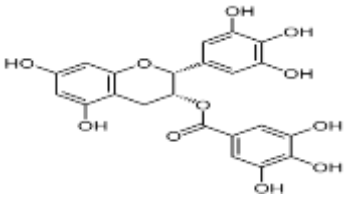
Table 4: Phytochemicals with anti-HD activity

Authors	Models	Plant source	Compound	Mechanism of action
Pedraza Chaverrí *et al*.[74]	3-NP, CGNs	*Garcinia mangostana* L.	α-mangostin	Enhanced antioxidant activities, ↓ROS production
Zhang *et al*.[75]	mutant poly Q, *C. elegans*	*Astragalus membranaceus*	astragalan	↑adult lifespan, ↑lifespan of daf-2 and age-↓polyQ aggregation
Sagredo *et al*.[76]	3-NP, rats	*Cannabissativa* L.	cannabidiol	antioxidant, ↓striatal atrophy
Zhang and Sarge[77]	mutant polyQ, HeLa and PC12 cells	*Tripterygium wilfordii*	celastrol	Modulation of HSP
Sandhir *et al*.[78]	3-NP, rats	*Curcuma longa* L.	curcumin encapsulated solid lipid nanoparticles (C-SLNs)	↓mitochondrial dysfunction
Ehrnhoefer *et al*.[79]	polyQ-mediated htt protein, HD yeast;	*Camellia sinensis (L.) Kuntze*	(-)-epigallocatehin-gallate	↓photoreceptor degeneration, ↓cytotoxicity ↑motor function ↓mutant Httex1 protein aggregation
Maher *et al*.[80]	PC12 cells expressing mutant Httex1	*Many plants*	fisetin	↑ERK activation ↓mHtt,
Park *et al*.[81]	3-NP, rats	*Galanthus sp.*	galantamine	↓striatal lesion, nAChR modulation, anti-apoptotic
Wu *et al*.[82]	Striatal MSNs from YAC128 HD mouse	*Panax ginseng C.A.*	ginsenosides (Rb1, Rc, and Rg5)	↓glutamate-induced Ca(2+) responses
Menze *et al*.[83]	3-NP, rats	*citrus fruits*	hesperidin	↑cortical, striatal and hippocampal MDA levels, antioxidant, anti-inflammatory, prevented change in locomotor activity
Lagoa *et al*.[84]	3-NP, rats	*many plants*	kaempferol	↓striatal lesions, antioxidant ↓mortality, ↓motor deficit,
Binawade and Jagtap[85]	3-NP, rats	*many plants*	lutein	↑neurobehavioral improvement, ↑body weight, ↑mitochondrial enzymes complex activities, antioxidant
Kumar *et al*.[86]	3-NP, rats	*tomatoes, other red fruits and vegetables*	lycopene	NO modulation, ↑behavioral and biochemical activities
Túnez *et al*. [87]	3-NP, rats	*many plants*	melatonin	antioxidant
Kumar and Kumar[88]	3-NP, rats	*citrus fruits and others*	naringin	↓mitochondrial enzymes complex dysfunction, antioxidant, NO modulation ↓behavioral alterations,
Tariq *et al*.[89]	3-NP, rats	*Nicotiana tabacum L.*	nicotine	↓depletion of striatal DA and GSH
Wu *et al*.[90]	mHtt, PC12 cells	*Radix Polygalae*	onjisaponin B	↑autophagy via the AMPK-mTOR signaling
Sandhir and Mehrotra[91]	3-NP, rats	*many plants*	quercetin	↓oxidative stress, ↓neurobehavioral deficits ↓mitochondrial dysfunctions,
Maher *et al*.[80]	PC12 cells	*red grapes*	resveratrol	↑ERK activation

	expressing mutant Httex1;	*and others*		
Pérez-De La Cruz *et al.*[92]	3-NP, rat brain	*Allium sativum L.*	S-allylcysteine	↓mitochondrial dysfunction, ↓lipid peroxidation, antioxidant
Lam and Ko[93]	3-NP, rat PC12 cells	*Schisandra chinensis*	(-)schisandrin B	anti-apoptotic, anti-necrotic
Kumar *et al.*[94]	3-NP, rats	*Sesamum indicum, L.*	sesamol	antioxidant, ↑free radical scavenging activity
Sarkar *et al.*[95]	COS-7 and PC12 cells expressing	*many plants*	trehalose	↑autophagy against mHtt

↑: increased/improved/enhanced ↓: decreased/declined/attenuated

Table 5: Chemical structures of phytochemicals with anti-HD activity

Compound	
α-mangostin	
Astragalan	
Cannabidiol	
Celastrol	
Curcumin	
epigallocatechin n-gallate	

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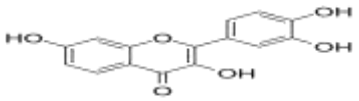
Fisetin



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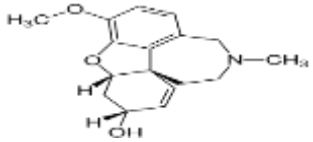
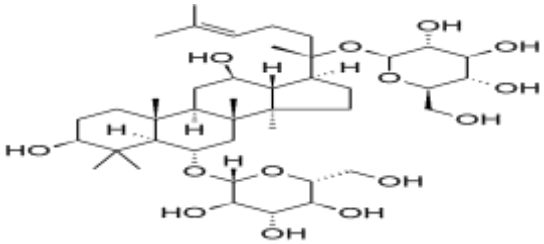
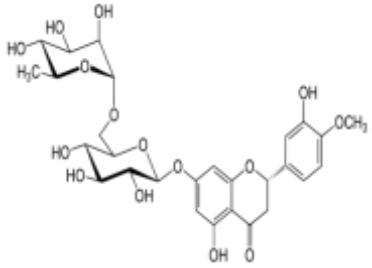


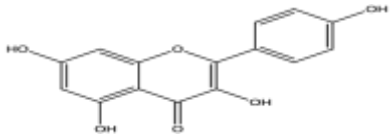
ginsenosides



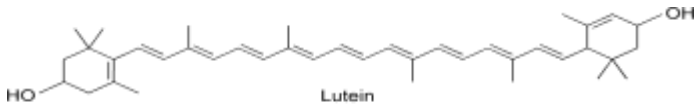
Hesperidin



kaempferol



Lutein



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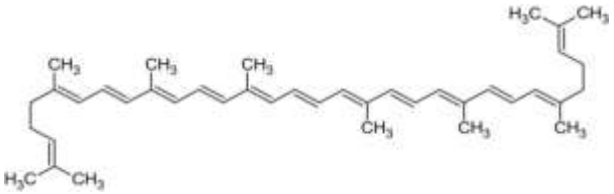

melatonin

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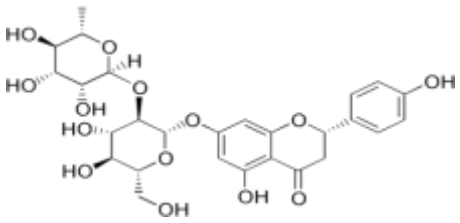
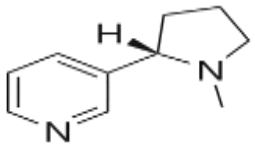
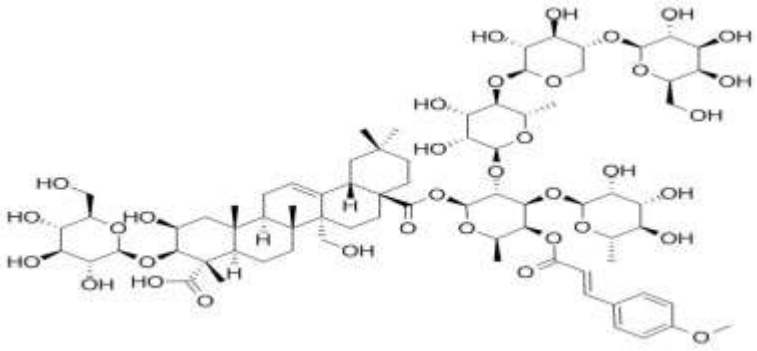
naringin



nicotine



onjisaponin B



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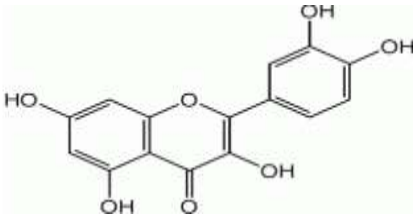
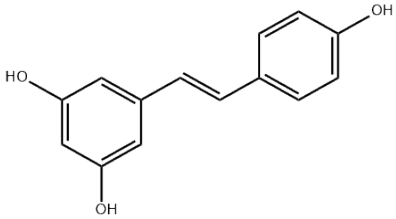
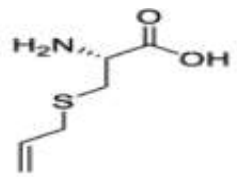


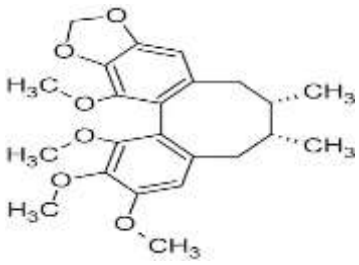
resveratrol



S-allylcysteine



(-)schisandrin B



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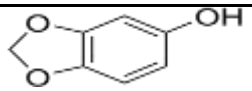
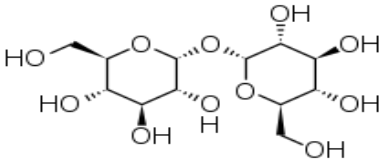
sesamol	
trehalose	

Alzheimer disease

Alzheimer's disease (AD) is a complicated and severe neurodegenerative disease characterized by impairment of cognitive function and memory.[96] In 1906, a German physician named Alois Alzheimer was the first to describe and diagnose Alzheimer's disease.[97] According to a worldwide consensus, neurodegenerative diseases prevalence is on the increase.[98] It is commonly associated with dementia in aged people (> 65 years) and account for up to 70% cases of chronic dementia around the world.[99] The chances of AD occurrence after the age of 65 has been understood to double every five years.[100] Different epidemiological studies of AD also revealed that women over the age of 85 have a higher rate of developing AD than the men.[101]

It has three clinical phases categorized as dementia phase, pre-dementia phase and pre-symptomatic phase.[102] Symptoms experienced include difficulty in word fluency, delusional symptoms, loss of short term memory and decreasing level of vocabulary along with urinary incontinence[103, 104]

So far, AD is still irremediable but present treatment option only offers symptomatic relief by reducing cognitive impairment associated with AD through temporary palliative therapy.[105, 1-6] Enzyme inhibition of acetylcholinesterase (AChE) is a major therapeutic approaches providing symptomatic effects and in advanced stages of AD, Memantine can be successfully combined as treatment.[107] Although this combined treatment has been approved as anti-AD drugs but there are adverse side effects.[99] Lack of extensive knowledge on pathogenesis of AD, restricted therapeutic approaches and AD heterogeneity open up new searches for anti-AD treatment effective on AD.[108] Common conventional therapy include vitamin therapy and antioxidant, hormonal therapy, use of NSAIDs and selective phosphodiesterase (PDE) inhibitors.[109-111]

Plants have been proven to be enhancers and promoters of cognitive functions as they act as neuroprotectants either as phytochemicals or in crude extracts[112] Presently, rivastigmine and galantamine are plants products licensed as anti-AD drugs. Phytochemicals have been sources of anti-AD treatment and also candidates for synthetic drugs. Some phytochemicals that exhibited anti-AD properties such as MAO inhibitors and antioxidants[113] include resveratrol, curcumin and catechins (Table 6 & 7) and their activity is due to their anti-inflammatory, anti-oxidative and anti-amyloidogenic properties; by triggering neurohormesis[99] (Figure 2)

Table 6: Phytochemicals with Anti-AD properties

Authors	Models	Source plant	Phytochemical Compound	Mode of action
Elgorashi *et al.*[114]	AChE inhibition	Amaryllidaceae family members	1-O-acetyllycorine	↑ inhibitory activity of AChE
Heo *et al.*[115]	Aβ-induced PC12 cells	*Artemisia asiatica*	4',5-dihydroxy-3',6,7-trimethoxyflavone	↓oxidative stress ↓ Aβ toxicity
Park *et al.*[116]	Aβ (1-42)-induced BV-2 murine microglia cell lines and murine primary microglia	*Schisandra chinensis* (Turcz.) Baill. (Schisandraceae) fruit	*α* -iso-cubebenol	↓neuroinflammation ↓NF-κB/inhibitor of κBα and MAPK
Orhan *et al.*[117]	AChE inhibition	*Lycopodium clavatum* L	α-onocerin (atriterpenoid)	↑ inhibitory activity of AChE
Wang *et al.*[118]	Aβ (25-35)- induced SHSY5Y cells	many plants	Acteoside (phenylethanoid glycoside)	↓ROS ↓Aβ toxicity,
Zhao *et al.*[119]	PS1/APP double transgenic AD mice	many plants	apigenin (flavone)	↓oxidative stress ↓Aβ burden, ↑ERK/CREB/BDNF pathway ↑learning and memory,
Wei *et al.*[120]	PC12 cells and AβPP/PS1 mice	an active component of the Acorigramineirhizome (AGR)	*β*-asarone	↑CaMKII-α/p CREB/Bcl-2 pathway ↓apoptosis,
Heo *et al.*[121]	Aβ-induced PC12 cells	*Scutellaria baicalensis* (Lamiaceae)	baicalein and baicalin (flavonoids)	↓Aβ-induced toxicity
Urbain *et al.*[122]	AChE inhibition	*Gentiana campestris* L. (Gentianaceae)	bellidifolin, bellidin	↑ inhibitory activity of AChE
Jiang *et al.*[123]	Aβ (1-42)-induced cortical neuron-glia cultures	*Rehmannia glutinosa*	catalpol (iridoid glycoside)	↓ Aβ toxicity
Mei *et al.*[124]	Aβ42-insulted SH-SY5Y cells	*Salvia miltiorrhiza*	cryptotanshinone (diterpene)	↓ apoptosis ↓ cytotoxicity
Durairajan	Aβ40 and Aβ42 in N2a	root of *Salvia*	cryptotanshinone	↓production of Aβ,

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et al.[125]	mouse neuroblastoma cells	*miltiorrhiza*		↑activation and translocation of a disintegrin and metalloproteinase-10 (ADAM10)
Park and Kim[126]	Aβ-induced PC12 cells	*Curcuma longa* L. (Zingiberaceae)	curcumin, calebin-A, demethoxycurcumin, 1,7-bis (4-hydroxyphenyl)-1-heptene-3,5-dione	↓ Aβ toxicity
Wang *et al.*[127]	Aβ (1-40)-induced rats	*Curcuma longa* L. (Zingiberaceae)	curcumin (a diarylheptanoid)	↑GFAP (Glial fibrillary acidic protein) ↑spatial memory
Ahmed and Gilani[128]	**ex vivo** and **in-vitro** (hippocampus and frontal cortex)	*Curcuma longa* L. (Zingiberaceae)	curcuminoids	↑ inhibitory activity of AChE ↑memory
Ahmed and Gilani[129]	Aβ (1-40) + IBA-infused rat model	*Curcuma longa* L. (Zingiberaceae)	demethoxycurcumin, curcuminoid mixture and demethoxycurcumin	↓ apoptosis ↓inflammation,
Lee *et al.*[130]	AChE inhibition, scopolamine induced mice	*Cynanchum atratum* (Apocynaceae)	cynatroside B	↑anti-amnesic activities ↑anti-AChE,
Yan *et al.*[131]	A*β* (1-40)-induced mice	*Angelica gigas*	decursinol, a coumarin	↓ impairment of memory
Li *et al.* [132]	A*β* (25-35)-induced PC12 cells	*Angelica gigas* Nakai	Decursinol	↓Aβ-induced toxicity ↑MAPK signal, ↑Nrf2 activation ↑free radical scavenging activity,
Aronson et al.[133]	patients with AD	*Galanthus* sp.	galantamine (hydrobromide), alkaloid	↑efficacious against AD
Suh *et al.*[134]	Korean population with mild to moderate AD	*Galanthus* sp.	galantamine (hydrobromide), alkaloid	↑behavioral symptoms ↑cognitive function
Zeng *et al.*[135]	Aβ (25-35)-induced cultured hippocampal neurons	*Glycine max* (L.) Merr. (Fabaceae)	genistein (isoflavone)	↓ apotosis, ↑antioxidation
Bate *et al.*[136]	amyloid-beta1-42 induced SH SY5Y neuroblastoma cells	EGb 761 extract from *Ginkgo biloba* L. leave	ginkgolides A or B	↓neurotoxicity ↓caspase-3 ↓prostaglandin E2
Wang *et al.*[137]	Aβ (25-35)-induced PC12 cells	*Valeriana amurensis* P.	heishuixiecaoline A-C	↓Aβ-induced toxicity
Xiao *et al.*[138]	Aβ (25-35)-induced cells	*Huperzia serrata*	huperzine A (sesquiterpene	↓caspase-3, ↓ apotosis, ↓ROS,
Zeng *et al.*[139]	Aβ (25-35)-induced PC12 cells	*Epimedium brevicornum Maxim*	icariin (flavonoid)	↓GSK-3β,↑PI3K/Akt, ↓tau protein hyperphosphorylation
Xian *et al.*[140]	Aβ (25-35)-induced rats	*Uncaria rhynchophylla*	isorhynchophylline	↓tau protein hyperphosphorylation ↓apoptosis, and ↑phosphorylation of phosphatidylinositol 3-kinase

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				(PI3K) substrate Akt (PI3K/Akt) ↓glycogen synthase kinase 3β (GSK-3β) activity,
Kim *et al.*[141]	Aβ (1-42)-induced mice	*Camellia sinensis (L.)*	l-theanine (an amino acid)	↓Aβ toxicity, ↓ERK, ↓ NF-κB ↓p38
Zheng *et al.*[142]	SH-SY5Y cells	*many plants*	luteolin (bioflavonoid)	↓BACE1 expression
Heo *et al.*[143]	Aβ induced PC12 cells, scopolamine induced mice	*Citrus junos*	naringenin (flavanone)	↑antiamnestic activity, ↑antioxidation ↓oxidative stress, ↓ Aβ toxicity,
Ma *et al.*[144]	PC12 neuronal cells incubated with Aβ(25-35)	*Panax notoginseng*	notoginsenoside R1	↑cell viability, ↓apoptosis, ↓ MAPK signaling ↑ mitochondrial membrane potential,
Kim *et al.*[145]	Aβ-induced PC12 cells	many plants	piceatannol	↑antioxidation, ↓PARP cleavage ↓activation of caspase-3 ↓DNA fragmentation ↑anti apoptotic
Yoon *et al.*[146]	Aβ (25-35)-induced PC12 cells	*Cornus officinalis*	p-coumaric acid	↓NF-κB activity ↓ c-Jun N terminal kinase (JNK) phosphorylation, ↓ERK1/2
Chonpathompikunlert *et al.*[147]	AD rat models induced by AF64A	*Piper nigrum* L. (Piperaceae)	piperine (alkaloid)	↑neurotrophic effect ↓lipid peroxidation, ↑anti-AChE
Li *et al.*[148]	fAβ 1-40 insultedm hBMECs	many plants	quercetin (flavonoid)	↑cell viability, ↑SOD, ↓LDH, ↓ROS
Zhang *et al.*[149]	Aβ (25-35)-induced SH SY5Y human neuroblastoma cells	*Rhodiola rosea* L. (Crassulaceae)	salidroside (a glucoside of tyrosol)	↓phosphorylation of JNK and p38 MAPK ↑antioxidant enzymes, ↓oxidative stress, ↓Bax, ↑Bcl-X(L), ↑ MMP
Peng *et al.*[150]	Aβ (25-35)- induced PC12 cells	*Allium sativum* L. (Amaryllidaceae)	s-allyl cysteine (SAC)	↓Aβ toxicity ↓caspase-3, ↓ROS, ↓PARP cleavage, ↓memory impairments
Chauhan[151]	AD transgenic Swedish double mutant mouse model Tg2576	*Allium sativum* L.	di-allyl-disulfide (DADS) and s-allyl-cysteine (SAC)	↑anti-amyloidogenic, ↑antiinflammatory, ↑anti-tangle
Lu *et al.*[152]	Aβ (25-35)-induced mice	*Silybum marianum* (L.)	silibinin (flavonoid)	↓overexpression of iNOS and TNF-α mRNA ↓oxidative stress ↑memory, ↑anti-inflammatory
Ingkaninan *et al.*[153]	AChE inhibition	*Stephania venosa*	stepharanine, cyclanoline and N methyl stepholidine	↑ inhibitory activity of AChE
Urbain *et al.*[154]	AChE inhibition	*Gentianella amarelle*	triptexanthoside C and other xanthones	↑ inhibitory activity of AChE
Pan *et al.*[155]	Aβ (1-42)-induced microglial cells	*Tripterygium wilfordii Hook.F*	tripchlorolide (T4), an extract	↓neuroinflammation, NF-kappaB and JNK modulation
Hong *et al.*[156]	Aβ(25-35)-induced PC12 cell.	*Cornus officinalis*	gallic acid, p coumaric acid, and ursolic acid	↑anti apoptotic ↓DNA fragmentation ↑antioxidation,
Chi *et al.*[157]	Aβ (25-35)-induced SHSY5Y cells	*Xanthoceras sorbifolia*	xanthoceraside (triterpene)	↓caspase-3 activity ↓ROS, ↓apoptosis
Yu *et al.*[158]	Aβ-induced SH	*Itoa orientalis*	xylocoside G (XG)	↓Aβ-

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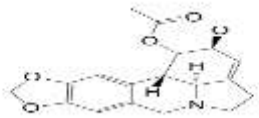
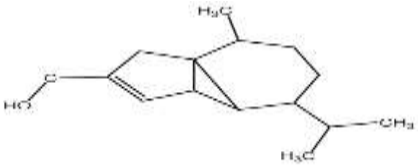
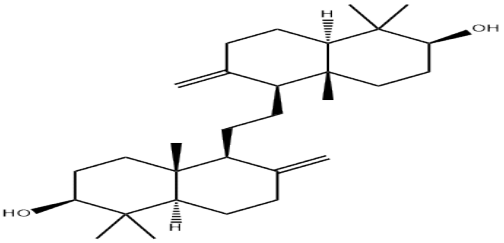
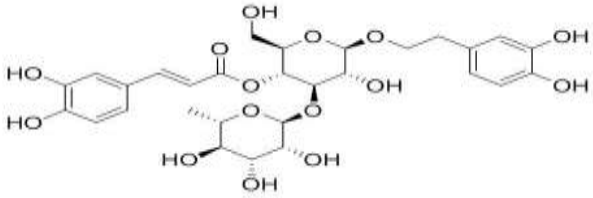
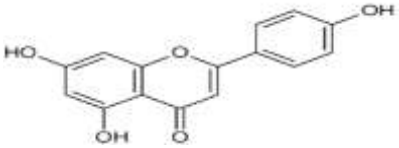
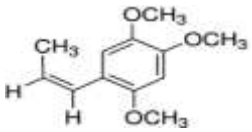
	SY5Y cells	*Hemsl.*		induced NF-κB p65 translocation, ↓prostaglandin E2 ↓interleukin-1β, ↓TNF-α, ↓JNK phosphorylation
Heo *et al*.[159]	AChE inhibition in PC12 cells	*Fiatoua villosa*	zeatin	↑anti-AChE

↑: increased/improved/enhanced ↓: decreased/declined/attenuated

Table 7: Chemical structures of phytochemicals with Anti-AD properties

Phytochemical Compound	Chemical structure
1-O-acetyllycorine	
α-iso-cubebenol	
α-onocerin (a triterpenoid)	
acteoside (phenylethanoid glycoside)	
apigenin (flavone)	
β-asarone	

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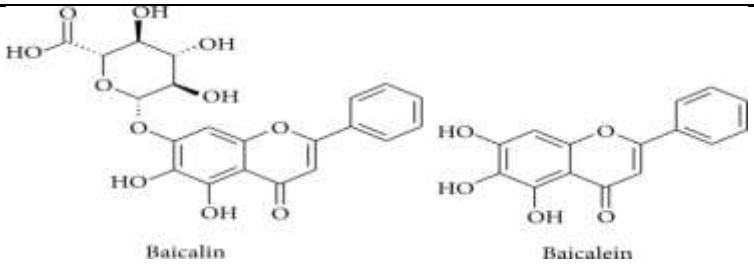
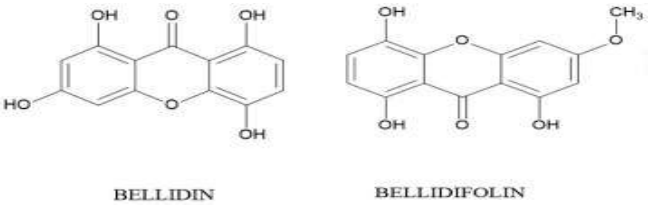
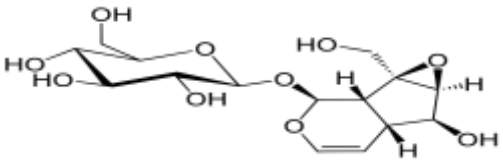
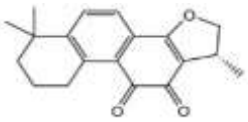
baicalein and baicalin (flavonoids)	 Baicalin Baicalein
bellidifolin, bellidin	 BELLIDIN BELLIDIFOLIN
catalpol (iridoid glycoside)	
cryptotanshinone (diterpene)	
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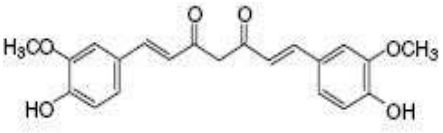
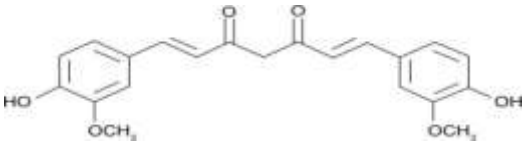
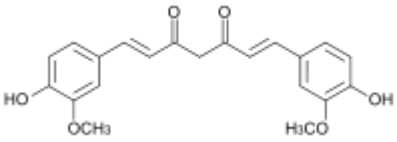
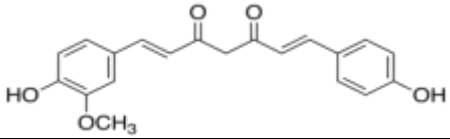
curcumin, calebin-A, demethoxycurcumin, 1,7-bis (4-hydroxyphenyl)-1-heptene-3,5 dione	
curcumin (a diarylheptanoid)	
curcuminoids	
demethoxycurcumin, curcuminoid mixture and demethoxycurcumin	

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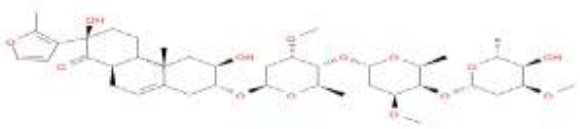
cynatroside B



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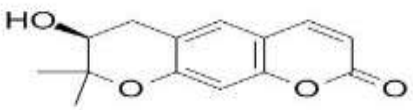
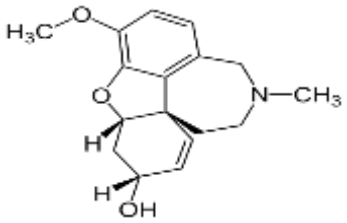
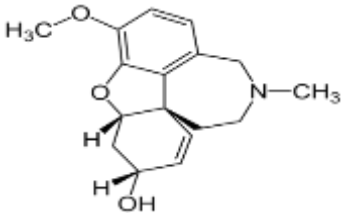


Galantamine (hydrobromide), alkaloid



Galantamine (hydrobromide), alkaloid



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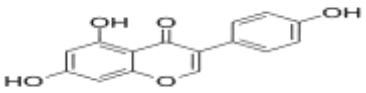
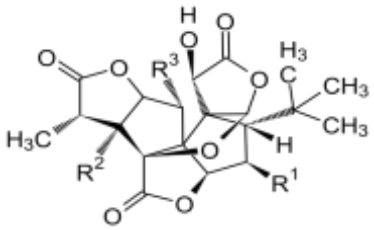
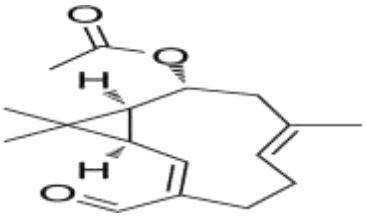


ginkgolides A or B



heishuixiecaoline A-C



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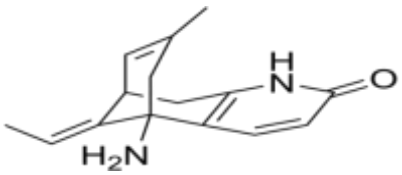
huperzine A
(sesquiterpene



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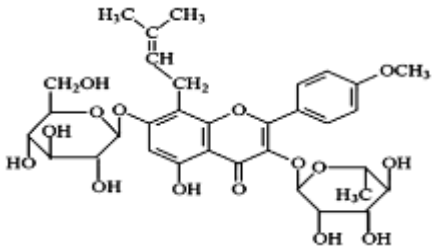
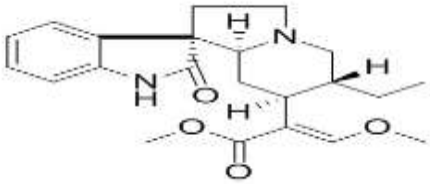


isorhynchophylline



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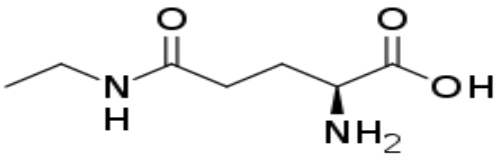
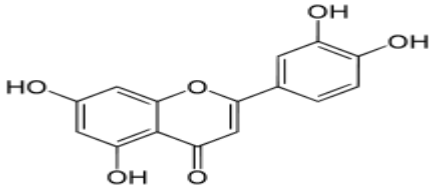
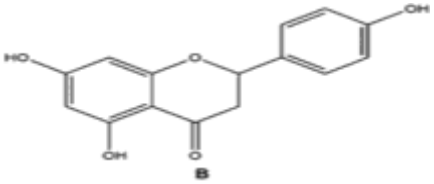


Luteolin (bioflavonoid)



Naringenin (flavanone)



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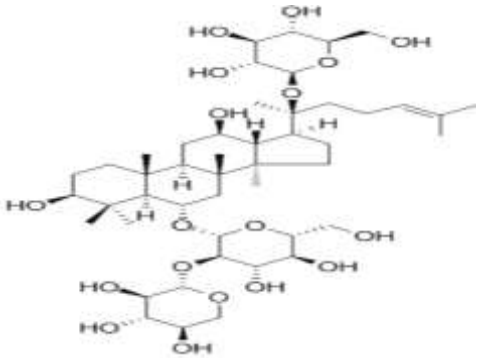

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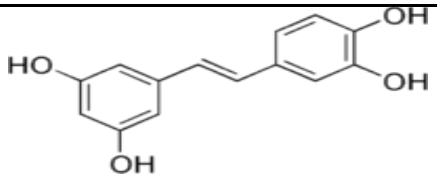
piceatannol



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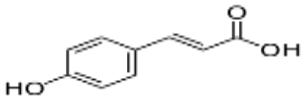

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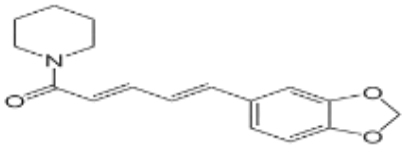
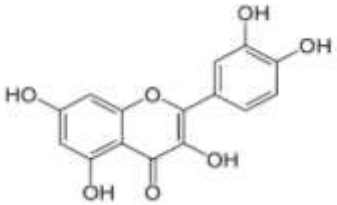
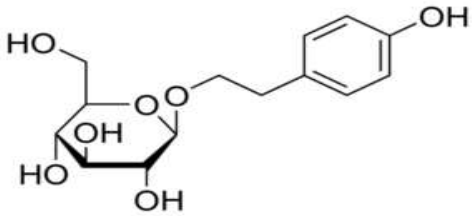


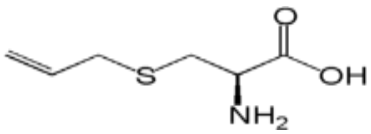
quercetin (flavonoid)



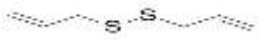
salidroside (aglucoside of tyrosol)



s-allyl cysteine (SAC)



di-allyl-disulfide (DADS) and s-allyl-cysteine (SAC)



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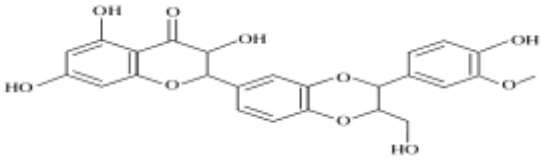
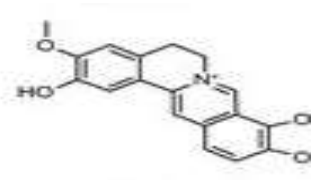


stepharanine, cyclanoline and N methyl stepholidine



Cyclanoline

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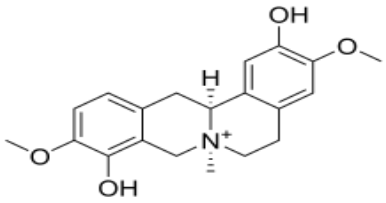
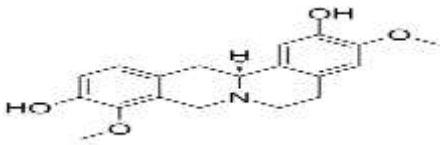
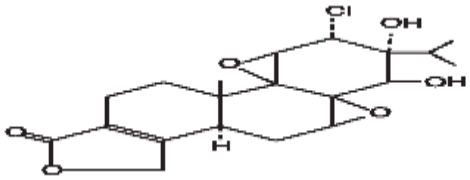
N-methyl stepholidine



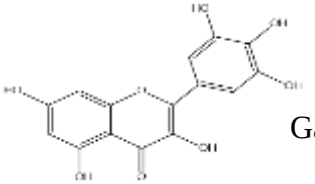


triptexanthoside C
and other xanthones

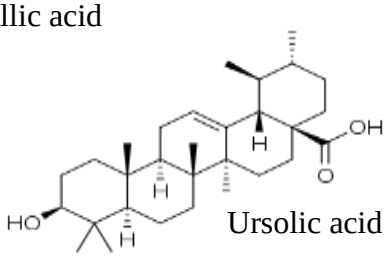
tripchlorolide (T4), an extract



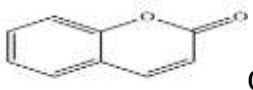
gallic acid,
coumaric acid,
and ursolic acid



Gallic acid

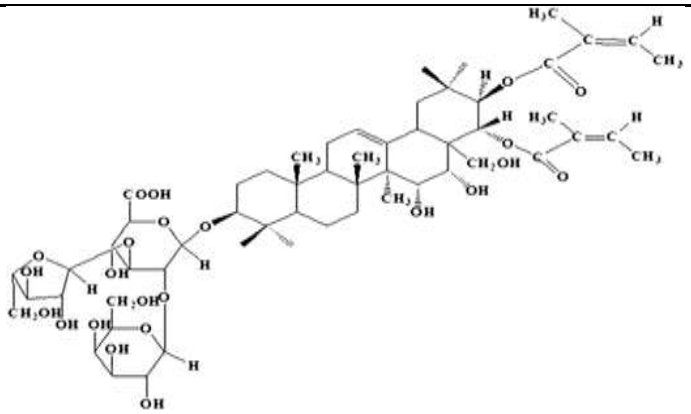


Ursolic acid

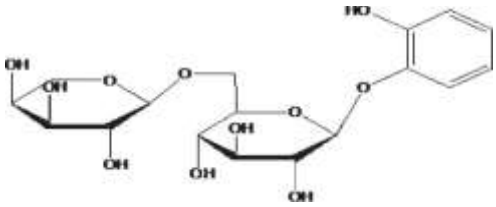


Coumaric acid

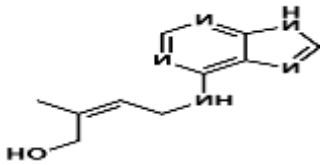
xanthoceraside (triterpene)



xylocoside G (XG)



zeatin



Depression

Depression is a severe and recurrent mental ailment connected to anorexia, insomnia, incessant sadness, and loss of interest in activities.[160]

The etiology of depression involves several factors such as psychological, environmental, social, genetic and biochemical factors. Environment and gene interaction jointly project a person at a greater risk. Common risk factors include trauma and viral infections[161] Monoamine hypothesis of depression in which decrease in the brain neurotransmitters level (norepinephrine and serotonin) is assumed as the leading cause of depression; however, recently, the pathophysiology of the disease has now been associated with multiple hormonal and neuronal systems. In general, depression incidence is about 3–10% but higher in patients with chronic disorders.[162]

World Health Organization ranked depression as the fourth leading cause of disability.[163] Women are twice more probable to suffer from depression during their lifetime. There are three different main therapeutic agents for the disease: monoamine oxidase inhibitors, second-generation and tricyclic antidepressants. Monoamine oxidase (MAO) inhibitors inhibit the enzymatic activities of monoamine oxidase. Phenelzine, isocarboxazid, tranylcypromine and moclobemide are examples of MAO that act as first-line therapy.[164] MAO inhibitors block neurotransmitter's transporter which increase the level of synaptic c and thus enhances neurotransmission.[165]

Tricyclic antidepressants are however being replaced by novel antidepressants with fewer adverse effects. Norepinephrine reuptake inhibitors, the selective serotonin reuptake inhibitors, and the serotonin norepinephrine reuptake inhibitors, are examples of new second-generation antidepressants. Despite the development of these conventional drugs, depression treatment still fails to achieve clinical remission in lots of cases.[166]

Moreover, many patients still display intolerant or refractory responses with these drugs.[167] Indeed, use of these agents is limited by unexpected side effects and some of them show contradictive outcomes.[168, 169] On the other hand, conventional antidepressants have a long list of side effects, categorized into sexual dysfunction, central nervous system disorders (fatigue, headaches, sedation, agitation, insomnia), serotonin syndrome, parkinsonism, postural hypotension, blurred vision, gastrointestinal (vomiting and nausea), and weight gain, which cause poor patient compliance that could result in treatment failure.[170-173] The risk of neurodegenerative diseases and other disorders like autoimmune and cardiovascular diseases have been decreased significantly by the use of phytochemicals obtained from herbs overtime (Table 8). Phytochemicals that showed potent anti-inflammatory and antioxidant properties such as curcumin, carvacrol, ferulic acid, L-Teanine quercetin, proanthocyanidin, and resveratrol have demonstrated their neuroprotective effects thereby improving the symptoms of depression.

Table 8: Phytochemicals effective against Depression

Phytochemical	Treatment	Study design	Effects and mechanisms	Reference
Carvacrol	12.5–50 mg/kg	Oral administration in mice	Induce antidepressant effects that seem to be dependent on an interaction with the dopaminergic brain pathways	Melo *et al.*[174]
	12.5 mg/kg	Oral administration in rats	Raise 5-HT and dopamine ranges in the hippocampus and prefrontal cortex Influence neuronal activity through modulation of neurotransmitters	Zotti *et al.*[175]

Curcumin *(Curcuma longa)*	1.25–10 mg/kg	Oral administration in rats	Reduce immobility time in the forced swimming test Reverse bilateral olfactory bulbectomy-induced hyperactivity in the open feld and defcits in step-down passive avoidance	Xu *et al*.[176]
	20–40 mg/kg	Intraperitoneal injection in mice	Restore biochemical and behavioral changes induced by the chronic stress Reverse the decreased immobility period and MAO activity induced chronic stress	Bhutani *et al*.[177]
	10 mg/kg	Oral administration in mice	Reduce duration of immobility in forced swimming test May be associated with 5-$HT_{1A/1B}$ and 5-HT_{2C} subtypes	Wang *et al*.[178]
	10–20 mg/kg	Oral administration in rats	Attenuate the stress-induced hippocampus 5-HT_{1A} mRNA	Xu *et al*.[179]
Ferulic acid	100–250 mg/kg	Oral administration in mice	Attenuate stress-induced behavior Increase CREB phosphorylation and brain-derived neurotropic factor mRNA level in the hippocampus	Yabe *et al*.[180]
L-Theanine (*Camellia sinensis*)	1–20 mg/kg	Oral administration in mice	Reduce immobility time in the forced swimming test and tail suspension test without ambulation in the open field test Antagonize reserpine-induced ptosis and hypothermia	Yin *et al*.[181]
Proanthocyanidin	25–50 mg/kg	Oral administration in mice	Reduce immobility period in the forced swimming test and tail suspension test Enhance 5-HT levels in hypothalamus, hypothalamus, and frontal cortex	Xu *et al*.[182]
Quercetin	20–40 mg/kg	Oral administration in mice	Prevent hyperactivation of the HPA axis	(Bhutada *et al*.[183]
Resveratrol	20–80 mg/kg	Oral administration in mice	Decrease immobility period in the despair tests without influence on locomotor activity Enhance 5-HT and noradrenaline concentrations in the brain	Xu *et al*.[182]
	40–80 mg/kg	Oral administration in rats	Reverse less weight gain, reduce sucrose preference and defcits in the shuttle box Raise 5-HT, dopamine, and noradrenaline concentrations in brain Reduce MAO activity	Yu *et al*.[184]

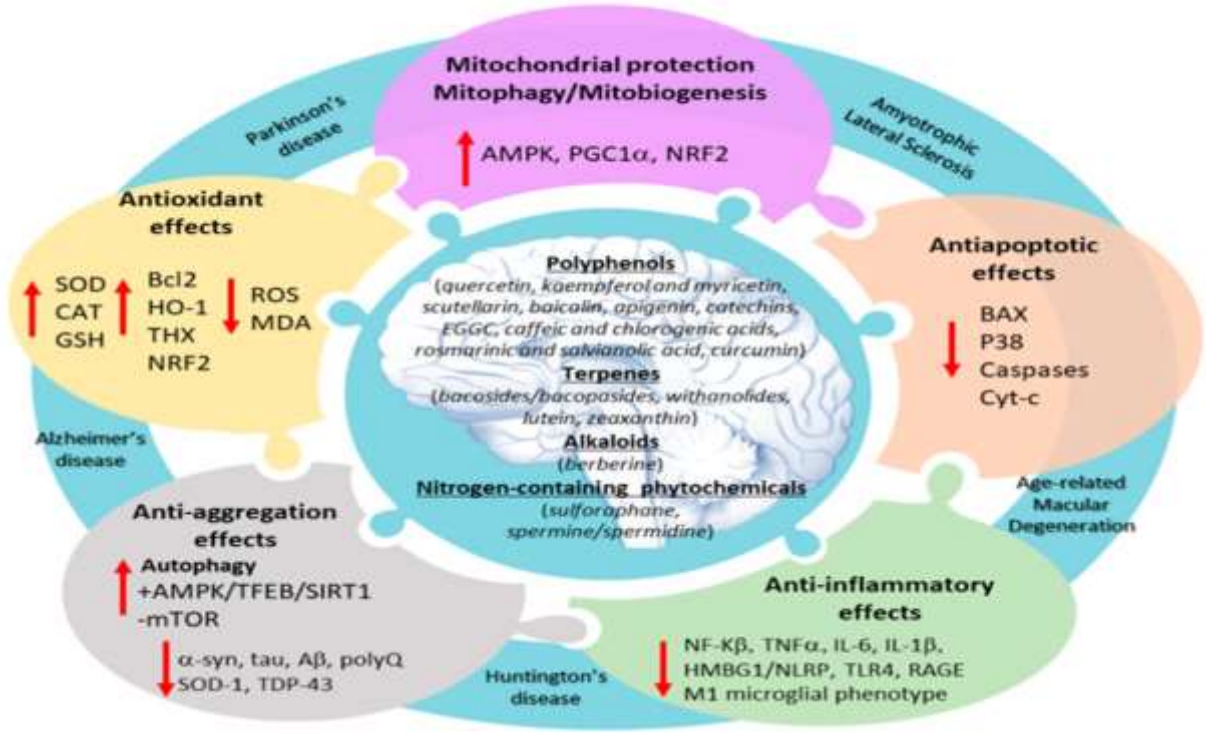


Figure 2: Mechanism of action of phytochemical constituents' interactions with Huntington's disease and other neurodegenerative disorders[185]

Conclusion

In this review, it can be deduced that certain phytochemicals possess ameliorative effect towards the NDs management. From this study, curcumin was observed to be effective in the management of a wider range of NDs, normalizing altered mechanisms associated with caspase-3 level, TNF-*α*, COX-2, IL-1β, NO, iNOS, PGE2, IL-6, Tau hyperphosphorylation, APP and GSK3β activity, Glial fibrillary acidic protein (GFAP), IL-1*β*, amyloid plaques, insulin-degrading enzymes, apoptosis, inflammation, mitochondria dysfunction, inhibitory activity of AChE, and cell viability. Curcumins, resveratrol, ECGC and L-theanine are found to be the most common and effective classes of phytochemicals for a wide range of NDs management. However, gap in knowledge abound in extensive elucidation of rate-limiting and protein conformational studies of the use of these phytochemicals in NDs management. Therefore it is highly imperative that these promising phytochemicals be researched on extensively in order to come up with more effective treatment for these neurodegenerative diseases.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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