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A review: *In vivo* studies of Phytochemicals acting on Neurological Disorders

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Abstract
Seven to ten million people worldwide suffering with Parkinson's disease (PD).it is most prevalent neurodegenerative condition. Substantia Nigra (SNc) is hallmark of PD, increasing loss of dopaminergic neurons in the substantia Nigra pars compacta (SNc). The symptoms motor functions, such as resting tremor, stiffness, bradykinesia, and postural instability, are caused by the nigrostriatal pathway. According to research data a number of molecular mechanisms, including as oxidative stress, neuro inflammation, and α-synuclein (α-syn) aggregation and crucial in the pathogenesis of PD. Over the year, neuroinflammation and oxidative stress have been found in the etiology of this disease. Due to this research, recently focused on identifying and analysing novel natural molecules in order to create potential effect on PD. Natural polyphenols have lots of interest in this content because of their therapeutic effects. In this review we plan to summarise pertinent *in vivo* research, mechanism and chemical constituents on the possible therapeutic value of natural polyphenols and alkaloids in PD.

Keywords: SNc, Syn, polyphenols, Parkinson's disease, inflammation, oxidative stress

Introduction
The secondary metabolites are analogous to phytochemicals like Terpenoids, Flavonoids, and Alkaloids that are present in plants which are physiologically active substances. Many studies proof similar association between consuming a diet which is high in antioxidant phytochemicals have beneficial effect on health. Many scientific data revealed that interaction allying consuming a nutrient based food which are having antioxidant potential showed better health outcomes, such as a reduced probability of occurrence of neurodegenerative disorders [1].

Last past ten years, high-efficacy disease-modifying medicines (DMTs) have enabled more successful treatment of relapsing-remitting multiple sclerosis (RRMS). Alemtuzumab, Natalizumab, Fingolimod, Ocrelizumab, and Cladribine are used in parkinsonism (PD) and Alzheimer's disease (AD) but are not particularly effective. These medications are also impacted by factors like age, illness severity, treatment history, cost, duration of the disease, and others [2].

Researchers then turn to natural plants based on traditional knowledge and therapeutics because they have less side effects and are abundant in secondary metabolites, which are better at treating neurodegenerative diseases.

Cerebral infraction, Subarachnoid Hemorrhage, Subdural Hematoma, and Extradural Hemorrhage are all examples of Transient Ischemic Attack (TIAs). Peripheral neuropathy is few examples of nervous system disorders like meningitis, polio, epidural abscess, encephalitis, carpal tunnel syndrome, cervical spondylosis, brain or spinal cord injury, bell's palsy etc. [3].

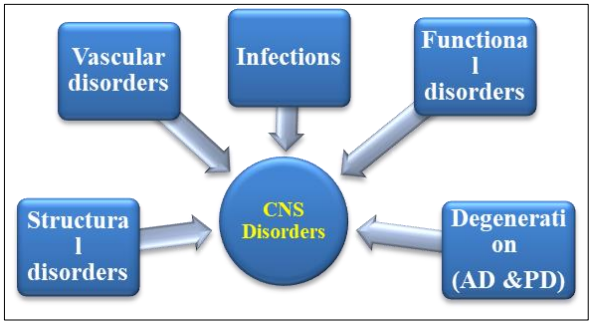


Fig 1: Type of CNS disorders

Parkinson disorders (PD)

Parkinson's disorder is the second most prevalent neurological condition worldwide. New instances without a cure are increasing with rising prevalence. By 2030, the prevalence of PD will be greatly increasing and replicating [4]. 1-2% of adults over 60 years are affected with neurological dysfunctions, which is describing by a decline in dopamine neurotransmitter in nucleus of substantia nigra [5]. The primary neuropathological correlates of motor dysfunction in Parkinson's disease (PD) are striatal dopamine depletion and continually degrading dopamine, which results in the creation of Lewy bodies affected by dopaminergic nucleus located in mid brain. Among the symptoms include stiffness, bradykinesia, resting tremor, trouble walking, behavioral problems and postural instability [6]. Non-motor signs include anxiety, depression, hormonal changes, empirical decline, sleeping problems, and anosmia. Parkinson's disease is treated with carbidopa-levodopa a fixed dose combination, and monoamine oxidase inhibitors [1].

It is a complicated condition from a pathological standpoint, with an unknown cause. Age, sex, and environmental pollutants (pesticides and herbicides) all contribute to the aetiology of disease in addition to gene mutation. Compared to women, men are more prone to this disorder. It is ascribed to chronic Loss of dopaminergic neurons in mid brain, inflammation regarding nervous system, mitochondrial damage, and oxidative stress. Neurons are not well understood. Synuclein glycation is the main factor causing synuclein to aggregate and develop a Lewy structure, which leads to neuronal cell death during Parkinson's disease (PD) [1].

Presenile dementia

Presenile dementia is one of the prevalent types of neurodegenerative disorder like dementia and Alzheimer's disease (AD). This has a unique characteristic that it is progressive in nature and causes deterioration of cognition and social ability. The amyloid hypothesis is best suited treatment regimen in clinical setup. This is based on pathophysiology of AD which include target proteins as amyloid beta and tau protein.

However, since there is currently no cure, scientists are focusing on components of Alzheimer's disorder other than the Amyloid-β and tau proteins. In addition to these, epidemiological studies reveals that particular environmental factors cause dementia and the findings highlight that etiology of dementia tends to be diverse. On novel risk factors or putative aetiologies, substantial study has been done in recent decades. Several fresh findings in epidemiologic and clinical studies on sleep, hypoxia, food, gut flora, and hearing loss are presented [7].

Many healing, Mucuna pruriens, Vicia faba, Nigella sativa, and Castanea sativus are examples appropriate to such species function largely by lowering oxidative stress and neuro-inflammation, which causes Parkinson's illnesses to be induced [8]. These plants can inhibit MAOs and alter the amount of dopamine, norepinephrine, and serotonin, in mid brain [9].

According to several studies, flavonoids maintain their potential neuroprotective action by attaching to several crucial targets for Parkinson's disease. The flavonoids like aspalathin, and norartocarpetin have the shown to be effective in Alzheimer's disease treatment, while the flavonoids like europinidin, capensinidin, and rosinidin have been proven to be effective against Parkinson's disease.

It was observed that these flavonoid derivatives were more engage more with hydrophobic areas of the binding sites in protein of interest when coupled with hydrophobic hydroxyl groups [10].

Many therapeutic plants, such as *M. Pruriens*, and *C. Sativus*, primarily function by reducing oxidative stress and neuro-inflammation, which causes PD to be induced. 8 These plants have the potential to inhibit MAOs and change the way essential neurotransmitters like dopamine, 5-HT and norepinephrine are stored in central brain specifically the substantia nigra [9].

The use of herbal remedies to treat or prevent Parkinson's disease has recently attracted a spike of interest. The main objective is to give future references for critical and clinical research as well as to summarize and analyze the herbal remedies evaluated in PD models [11].

Table 1: Showing few examples of Plants that have anti-Parkinson's activity

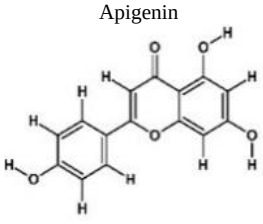
Scientific name	Common name	Plant part	Chemical Constituent	Common uses	Reference
Eleutherococcus senticocus Family-Araliaceae	Siberian ginseng	Dried root and rhizome or stem	Isofraxidin syringin (Eleuthero side B) leutheroside E	Inflammation, fatigue, and cancer	(Lau *et al*., 2019)
Centella asiatica Family-umbellifere	Gota kola, kodavan, Indian pennywort and Asiatic pennywort	Whole plant	Tannins, β-chariophylen, trans -beta - pharenesen and germachrene D), Phytosterols (campesterol, sitosterol, stigmasterol, free aminoacids, flavonoids (derivatives of chercetin, kempferol) and alkaloid (hydrochotine), fatty acids.	Minor wounds, contact dermatitis, skin irritation, drowsiness, sedative and anxiolytic, antidepressant, antiepileptic, cognitive and antioxidant, gastric ulcer, antinociceptive and anti-inflammatory.	(Intari *et al*., 2018)
Citrus sps. Family-rutaceae	Orange pomelos, limes, tangelos mandarins, lemons, kamquats, grapefruits.	Fruits and leaves	Flavonones-naringin, natirutin, hesperidine Flavones-rhoifolin,vitexin, diaosmin Polymethoxyflavones-nobiletin, tangeretin,5-demethylnobiletin Flavonols-quercetin, rutin, kaemferol Antrocyanidins- cyanidine 3-glycoside, cyanidine3-(6-malonyl) glycoside, peonidin 3-(6- malonyl) glycoside.	Neuroprotective, hepatoprotective, anti-microbial, anti-allergic, anti-melanogenesis	(Lv *et al*., 2015)
Mucuna pruriens	Velvet bean	Legume seed, leaves, whole	Protein (gp Muc), tannins, alkaloids, L-dopa, amino acids, isoquinolines, cyclitols,	anti-microbial, neuroprotective, anti-	(Lampariello *et al*., 2012)

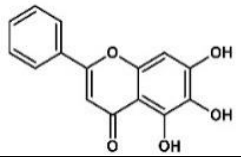
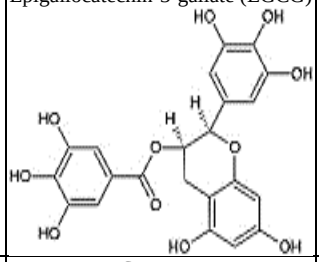
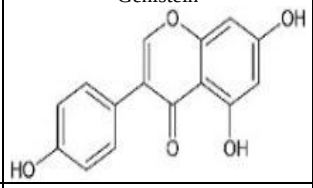
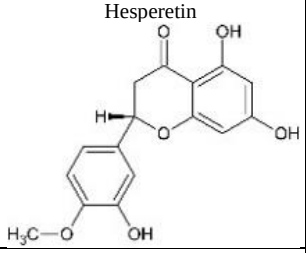
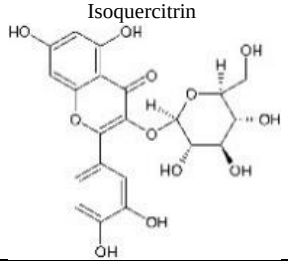
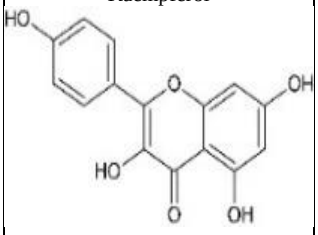
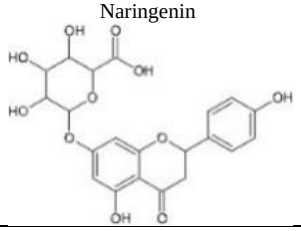
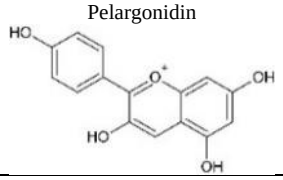
Family-Fabaceae		plant	oligosaccharides, phenols	diabetic, anti-oxidant, Anti-venom,	
Withania somnifera Family- solanaceae	Ashwagandha, winter cherry, Indian ginseng	Roots and leaves	Withanine, withaniol, somnirol, somnitol, withanic acid, phytosterol, iprunol, somniferine, somnine, somniferine, withamine, pseudowithamine, withanmine and withanamone.	Cardioprotective, anti-depressant, anti-cancer, antioxidant, anti - bacterial, anti-gungal, anti- inflammatory, hepatoprotective, hypoglycemic, male inferitility, obessive compulsive disorder, anti-anxiety, hypolipidemic, bone and muscle strengthening potential.	(Saleem *et al*., 2020)
Morus alba Family- moracea	White mulberry, silk warm mulberry	Leaves, bark, twings, Fruits, stem	1-deoxynojirimycine, p-caumaric acid, morucin, mulberroside A, moracin M, rutin, umbelliferone, norartocarpetin, 4-hydroxybenzoic acid, isoquercetin, oxyresveratrol.	Antidiabetic, immunomodulator. Anoxidant, hypocholesterolemic, an helmintic, anxiolytic, antimicrobial, hepatoprotective, antidopaminergic, anti-mutagenic activity, malonin biosynthesis inhibitor, anticancer, nephroprotective	(Hussain *et al*., 2017)
Psoralea carylifolia	*Bemchi, sitavari, kalameshi,babchi*	Whole plant	Angelicin, aryl caumarin, astragalin, bakuchiol, bavachinin, carylifols, dadzin, dadzein, genistein, xanthoangelol, psoralidin	Anti-Alzheimer, carboxylesterase inhibitors, osteoblast, antiprotozoal, antibacterial, anti-oxidant, anticancer, psoriasis, anti-diabetic, anti-depressant.	(Alam *et al*., 2018)
Sida cardifolia Family- malvaceae	*Bala, heartleaf, Indian chikana, khariti, silky white mallow*	Whole plant	Beta-phenethylamines, vasicine, vasicinone, 5,7-dihydroxyvasicine, cryptolepine, essential oil, sidasterone, 20- hydroxyecdysone, malvalic acid, sterculic acid	Anti-Parkinson's activity, lipid peroxidase inhibitor, anti-inflammatory, analgesis, antipyretic, antioxidant, hypotensive, antidiabetic, sedative effect, and CNS depressant	(Galal *et al*., 2014)

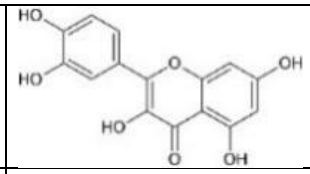
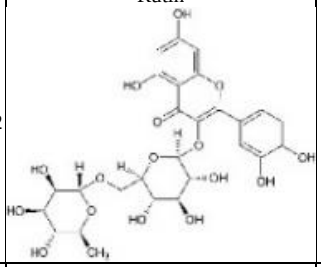
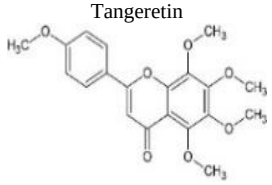
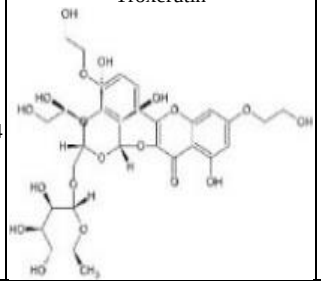
Alzheimer's Disorders (AD)

This is a neurodegenerative disorder that causes dementia and is most prevalent. It is characterized by decrease in cognition and social interactions in progressive manner. The treatment modalities of clinical management of AD are based on amyloid hypothesis which has proteins named amyloid beta and tau as biomarkers in pathophysiology of AD. Researchers are concentrating on features of AD other than Amyloid beta and tau proteins because it is observed that there is currently no viable treatment for the disease. In addition, the studies of epidemiology show that development of dementia is affected by many environmental factors and that the etiology of dementia is probably varied. Researchers in recent decades are focusing on new risk factors or probable aetiologies, thus these new risk factors are studied extensively in recent times. We go over several recent advances in epidemiologic and clinical research related to sleep, hypoxia, food, gut microbiome, and hearing loss [7].

Table 2: Showing flavonoids that possess Anti-Parkinson's and Anti-Alzheimer's activity

Sr No	Name and Structure	Molecular formula and Molecular mass (Dalton)	Pharmacokinetics	References
1	Apigenin 	$C_{10}H_{10}O_5$ and 270.05	Apigenin has a low oral bioavailability; apigenin when administered through oral route is excreted as such no absorption or metabolism occurs of the little quantity absorbed. Apigenin is absorbed as glucuronide, sulphate conjugates, or luteolin in the bloodstream and tissues. An accumulation in tissues appears to be possible due to its slow elimination. Apigenin has been claimed to have tendency to cause drug-drug interactions, these interactions are based on literature which suggest Apigenin inhibit P-gp and CYP3A4. Compound, apigenin is primarily excreted in the urine. Apigenin levels in urine and faeces were 51.0% and 12.0%, respectively, after a single oral dose.	12
2	Baicalein	$C_{21}H_{18}O_{11}$ and 446.4	The conc. of baicalein peaked in intestine follows oral administration. The baicalein in the small and large intestine after 60 mins, 8 h, 12 h accounted for 87%,	13

			45% and 20% of initial dose administered respectively. The primary metabolites were glucuronidation, sulfation, and methylation. The metabolism of Baicalein in the small and large intestine, the conc. of metabolites was found to be more in large intestine.	
4	Epigallocatechin-3-gallate (EGCG) 	$C_{22}H_{18}O_{10}$ and 442.4	$T_{1/2}$ Elimination of EGCG Intravenous(i.v) (10 mg/kg) = 62 +/- 11mins oral (100 mg/kg) = 48 +/- 13 min, each. According to a PK studies, oral BA of EGCG in healthy rats was approximately 4.95%.	14
5	Genistein 	$C_{15}H_9O_5$ and 269.23	Genistein was converted to glucuronides FVB mice were administered with sulfates after i.v. and p.o. When sulfates in FVB mice administered after intravenous treatments at 20 mg/kg, with genistein aglycone having an absolute bioavailability of 23.4%. Genistein revealed a relatively extended $t_{1/2}$ (46 hr) in living body following oral treatment, implying that *In vivo*, genistein has a significant or unknown mechanism of removal.	15
6	Hesperetin 	$C_{16}H_{14}O_6$ and 302.28	Hesperetin was readily engrossed, with plasma conc. peaking 20 minutes after dosage and lasting 4 h and 3.5 hrs, separately. The mean C(max) hesperetin= (2731.8+/-1358.4 nmol/l) mean AUC(0-infinity) = 4846.20+/-1675.99 ng/ml. Hesperetin's elimination $T_{1/2}$ = 3.05+/-0.91 h. The mean peak of plasma conc. = 825.78+/-410.63 ng/ml and respectively 2009.51+/-770.82 ng/ml (7386.6+/-2833.4 nmol/l) and 4846.20+/- 1675.99 ng/ml for the mean AUC(0-infinity) values. Hesperetin's elimination half-life was found to be 3.05+/- 0.91 hours.	16
7	Isoquercitrin 	$C_{21}H_{20}O_{12}$ and 464.4	*In Vitro* and *in vivo*, Isoquercitrin is more bioavailable than quercetin has a multitude of chemoprotective properties against oxidative stress. All possibilities of Cancer, cardiovascular disease, diabetes, and allergic responses are examples of stress-related conditions. Even though modest quantities of intact. Isoquercitrin have been reported to be present in blood plasma and body tissues after oral administration, and extensive metabolism have been observed of this phyto-molecule in the body. On metabolism in liver and intestine of Isoquercitrin involves de-glycosylation and formation of quercetin derivatives either breakdown to phenolic acids and CO_2.	14
8	Kaempferol 	$C_{15}H_{10}O_6$ and 286.24	Intravenous (IV) kaempferol (10, 25 mg/kg) orally collected portal data revealed gastrointestinal first pass effects. After taking kaempferol orally blood 100 mg/kg Pharmacokinetic parameters were measured by blood. noncompartmental analysis were acquired with WinNonlin Following IV injection, in the plasma The conc.-time value for 10 and 25 mg/kg matched the high clearance (3 lt/h/kg). And a very huge distribution volume (8-12 lt/kg). The quantity was distinguished by a inoperable 3-4 hour $t_{1/2}$ value. The plasma conc.-time value after orally given indicated rather quick absorption (tmax 1-2 hr). The values of the area under the curve (AUC)after IV and oral dosages, the dose rose proportionally. Bioavailability (F) was low at 2%.	17
9	Naringenin 	$C_{15}H_{12}O_5$ and 272.25	naringenin were readily absorbed, with plasma concentrations peaking 20 minutes after dosage and lasting 3.5 hours. C(max) = 2009.51+/-770.82 ng/ml (7386.6+/-2833.4 nmol/l) AUC (0-infinity) = 4846.20+/-1675.99 ng $T_{1/2}$ elimination = 2.31+/-0.40 h. urine excretion = 5.81+/-0.81%.	16
10	Pelargonidin 	$C_{15}H_{11}O_5$ and 271.24	C_{max} =175.38 ± 55.95 nM at 60 min. Plasma investigation revealed 3 metabolites were present which includes: 1. Pg3Rmonoglucuronide (m/z 755.2046), 2. Pg3R-hydroxylated (m/z 595.1644), 3. Pg3R-demethylated (m/z 565.1569) metabolites. The bioavailability of Pg3R = 1.13% Pg3G =0.28%	18
11	Quercetin	$C_{15}H_{10}O_7$ and 302.236	Through oral administration Absorption = 59.1% BA = 5.3% Metabolism = 93.3% enterohepatic recirculation was not seen	19

				
12	Rutin 	$C_{27}H_{30}O_{16}$ and 610.517	Absorption = Intestine 1.35 to 0.37 microg/mL in terms of distribution The metabolites 3,4-dihydroxyphenylacetic acid, m-hydroxyphenylacetic acid, and homovanillic acid are produced during metabolism. Excretion = Through urine is about 10% and remaining 90% by feces	20
13	Tangeretin 	$C_{20}H_{20}O_7$ and 372.37	Cmax = 0.87 ±0.33 mg/mL Tmax = 340.00± 48.99 min, The calculated absolute oral bioavailability was 27.11%. Maximum tissue distribution Tangeretin concentrations in vital organs were found 4 or 8 hours after oral administration. The kidney, lung, and liver accumulated the most targeting followed by the spleen and heart	21
14	Troxerutin 	$C_{33}H_{42}O_{19}$ and 742.68	Cmax = 0.75 ± 0.31 ng mL-1 at 0.90 ± 0.20 h, t1/2 = 2.35 ± 1.14 h and the area under the plasma concentration–time curve (AUC0–24h) 3.60 ± 1.76 ng h mL^{-1}.	22

Mechanism of Flavonoids

Flavonoids work through a variety of pathways that are connected to brain ageing and neurodegenerative disorders. In order to treat neurodegenerative illnesses, they can function as multi-factorial therapies [23]. The mechanisms involved in flavonoids activity in brain cells like neurons are

1. Reduce stress due to free radicles (Oxidative)
2. Enhancing pathway of neurotrophic factor
3. Reducing processing of proteins
4. Reducing alteration of synaptic functions
5. Preventing triggering signals of inflammations.

Moreover, flavonoids might enhance memory and learning performance and lessen behavioural problems [4].

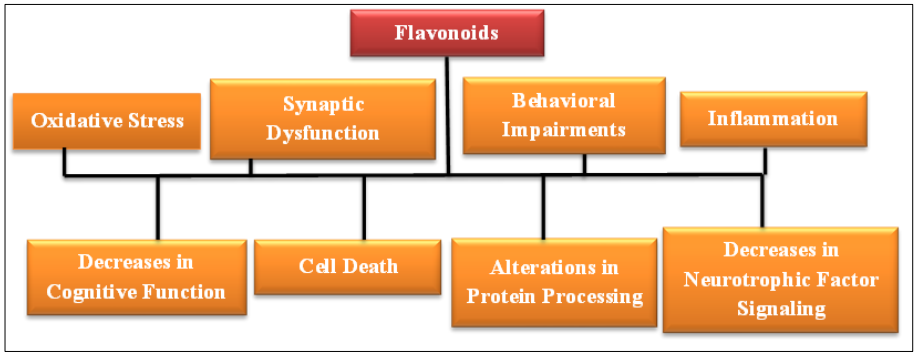


Fig 2: Mechanism of Flavonoids

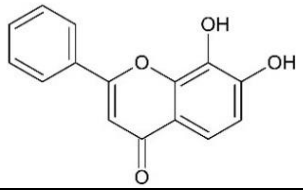
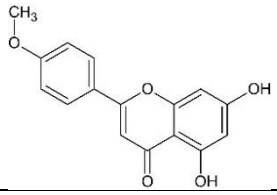
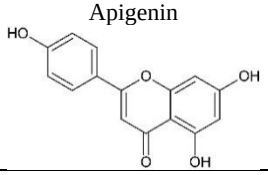
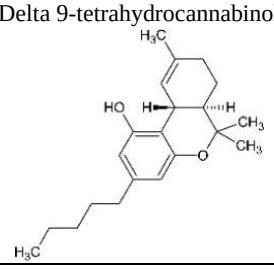
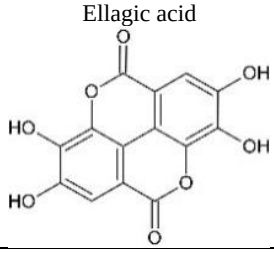
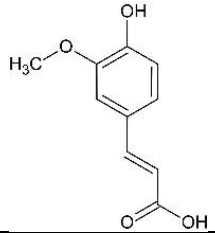
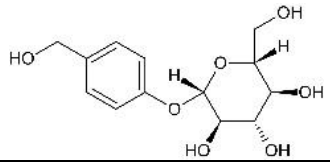
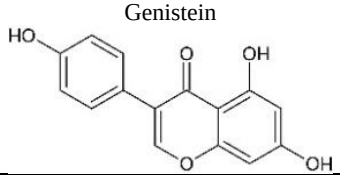
Polyphenols

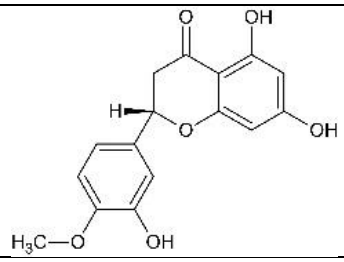
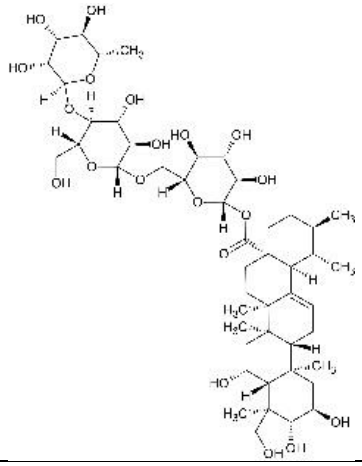
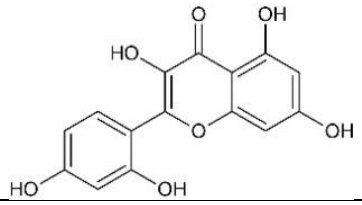
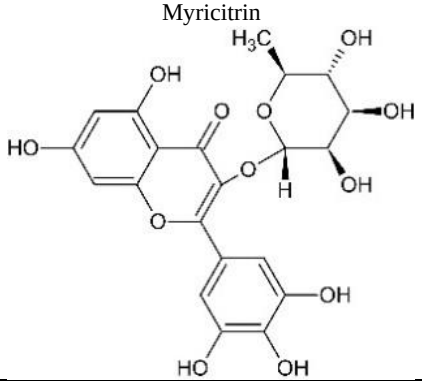
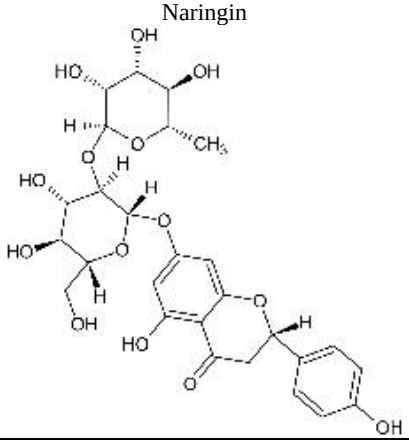
According to recent studies, oxidative stress, inflammation, and aberrant mitochondrial activity are the root causes of neurodegenerative disorders. To prevent and treat any illness certain genes and proteins are targeted. These genes and proteins are the best hit for the novel approach of drug treatment. Polyphenols have potential to control oxygen free radicles, channels regulating ions movements and neurotransmitters which play crucial role in disease management. Polyphenols have antioxidant potential. Resveratrol, quercetin, and other polyphenols with neuroprotective qualities include EGCG. Several studies have demonstrated that polyphenols activate antioxidant pathways like Nrf2. The inhibition of proinflammatory cytokines like tissue necrosis factor and interferons that activates immune response are regulated by polyphenols. Hence, polyphenols having these unique characteristics has been experimented to be neuroprotective in action. These studies showed that phytochemicals like polyphenols protect the neurons [1].

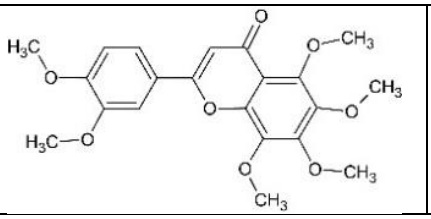
Many polyphenols have an impact on neurodegenerative diseases. Several studies have reported their pharmacokinetics using various methods and animal models. A brief summary of the pharmacokinetics of various substances is included in table 2 belong.

Many medicinal and pharmacological uses exist for polyphenols. They can be discovered in many different fruits and nutritional foods. Several polyphenols have been investigated for their possible contribution to the treatment of neurodegenerative conditions as Multiple sclerosis, Alzheimer's, and Parkinson's disease [24].

Table 3: Showing Polyphenols with their Molecular formula and molecular weight as well as pharmacokinetics parameters.

Sr. No	Name and Structure	Molecular formula And Molecular weight (Dalton)	Pharmacokinetics
1	7,8-dihydroxyflavone 	$C_{15}H_{10}O_4$ and 254.238	Cmax = 1554.9 ng/ml Tmax = 0.28 h $T_{1/2}$ = 2.32 h oral bioavailability =18%.
2	Acacetin 	$C_{16}H_{12}O_5$ and 284.26	Solubility = ≤119 ng/mL (Poor) in phosphate buffer of pH 7 Stability = 27.5-62.0% when observed in 24 hrs Absorption is very less from GIT Oral bioavailability = 2.34%. Plasma clearance = 199 mL/min/kg
3	Apigenin 	$C_{15}H_{10}O_5$ and 270.240	1-5 µmol/L concentration 30% bioavailability, (Cmax) and (Tmax) 0.5-2.5h
4	Delta 9-tetrahydrocannabinol 	$C_{21}H_{30}O_2$ and 314.45	Plasma concentrations was unstable huge variations observed in subjects. Cmax = 1.42-4.57 ng/mL Tmax = 67-92 min incase of trail subjects that achieved Cmax in 2hrs.
5	Ellagic acid 	$C_{14}H_6O_8$ and 302.197	Cmax =203 ng/ml on oral administration after 0.54 hours. $T_{1/2}$ = 5.0 h.
6	Ferulic acid 	$C_{10}H_{10}O_4$ and 194.18	Tmax = 0.03 h. Cmax = 8174.55 ng/L AUC = 2594.45 ng/mL These datas are on oral administration of drug.
7	Gastrodin 	$C_{13}H_{18}O_7$ and 286.27	LLoQ = 0.5 ng/ml for gastrodin Calibration curves was linear in concentration between 0.5-5000 ng/mL with r = 0.995.
8	Genistein 	$C_{15}H_{10}O_5$ and 270.241	absolute bioavailability = 23.4% of genistein $t_{1/2}$ = 46 hours
9	Hesperetin	$C_{16}H_{14}O_6$ and 302.27	$T_{1/2}$ = 3.05+/-0.91 h elimination.

			Hesperetin – mean urinary excretion = 3.26 % Naringenin - mean urinary excretion = 5.81%
10	Madecassoside 	$C_{48}H_{78}O_{20}$ and 975.1	Excretion rates Bile = 7.16% Urine = 0.25% Faeces = 24.68%
11	Morin 	$C_{15}H_{10}O_7$ and 302.2357	oral administration of Morin= 15 mg/kg AUC = 45.8% Cmax = 32.0% absolute bioavailability = 35.9%
12	Myricitrin 	$C_{21}H_{20}O_{12}$ and 464.37	Bioavailability = 9.62 for 50 mg/kg PO Bioavailability = 9.74 for 100 mg/kg PO Cmax and AUC showed dose dependent increase on oral administartion
13	Naringin 	$C_{27}H_{32}O_{14}$ and 580.541	Cmax = 2.56 ± 0.77 Tmax = 0.67 ± 0.20 h AUC0-t = 3.23 ± 0.54 $t_{½}$ = 4.1 ± 0.8h
14	Nobiletin	$C_{21}H_{22}O_8$ and 402.39	Cmax = 1.78 g/ml (Plasma) Cmax = 4.20 g/ml (Brain) AUC0-t = 7.49 gh/mL (Plasma) AUC0-t = 20.66 gh/mL (Brain) $t_{1/2}$ = 1.80 hours, elimination (Plasma) $t_{1/2}$ = 11.42 hours, elimination (Brain)

Mechanism of polyphenols

Through many investigations of polyphenols as neuroprotective agents, it has been reveled that these phyto-molecules have antioxidant potential to overcome oxidative stress, management of iron at cellular level to reduce oxygen free radicles, mediators that cause inflammation in neurons are regulated and controlled. By these overall phenomenon polyphenols protect the dopaminergic neurons and hence, maintain level of dopamine. Thus, these molecules are one of the major part of scientific investigations as a key target to develop a preventive regimen for Parkinson's disease.10

Polyphenols that have been studied in PD models as neuroprotective:

1. Quercetin have been studied on Sprague Dawley rats. In this study male rats were treated with rotenone to induce PD. The observations were increase in rotational behavior, tyrosine hydroxylase-positive neurons and Dopamine. The antioxidant parameters also showed the positive response. This molecule was shown to have potential to prevent PD.
2. Piceid have also been studied on Sprague Dawley rats. The male rats were challenged with rotenone to induce PD. This molecule also increased tyrosine hydroxylase-positive neurons. The antioxidant parameters showed positive response. Apart from this the inflammatory mediators were reduced by piceid like decrease in IL-1β, tissue necrosis factor-α and COX-2.
3. Apigenin experiments were performed on Swiss-albino mice. The male mice were treated with MPTP/p to induce PD. Apigenin increased the Locomotor activity, and tyrosine hydroxylase-positive neurons. The antioxidant potential showed significant action and inflammatory mediators like tissue necrosis factor along with monoamine oxidase enzyme activity was found to reduce.
4. Ellagic acid were studied on wistar rats. The male rats were challenged with 6-OHDA to induce PD. Ellagic acid was found to significantly decrease the inflammatory mediators like interleukin -1β and tissue necrosis factor-α.
5. Delta 9-tetrahydrocannabinol studied on Sprague-Dawley rats. The male rats were treated with 6-OHDA to induce PD. This molecule increased the dopamine levels in brain and tyrosine hydroxylase mRNA activity.
6. Baicalein study was performed on C57BL/6 mice. The male mice were treated with MPTP. The increase in motor co-ordination was observed, further glutamate receptor pathway showed upregulation of glutamate receptor and neurotransmitter glutamate was released in abundance.
7. Acacetin study against PD was performed on C57BL/6 mice. The male mice were treated with MPTP to induce PD. The drug showed beneficial effects on PD by decreasing damage to dopaminergic cells and increasing dopamine. Further, tyrosine hydroxylase-positive neurons were also increased with decrease in inflammatory mediators like COX-2
8. Tangeretin was the drug, studied against PD on C57BL/6 mice. In this study male mice were used and to induce PD the toxicant used was MPTP. There was increase in tyrosine hydroxylase-positive neurons, dopamine levels and GRP-78 protein.
9. Nobiletin, this molecule was studied by using Sprague Dawley (SD) rats. The rats chosen in this experiment were females and animal model used to induce PD was MPTP. There was increase in tyrosine hydroxylase-positive neurons, dopamine levels and interlukin-1β protein.
10. Quercetin, this phytomolecule has been studied in many disorders and C57BL/6 mice were used for PD model. In this experiment male mice and MPTP model was used. There was increase in motor balance, dopamine levels, antioxidant parameters and anticholinergic activity was seemed to increase.
11. Morin was studied on B57/BL male mice and MPTP mice model to induce PD was used. There was decrease in cataleptic time and increase in counts of steps (drag test), dopamine level and tyrosine hydroxylase-positive neurons.

The secondary metabolites like flavonoids and alkaloids from plants have been reported to have potential to act against parkinsonism model. These molecules are reported with their probable mechanism which is described in figure 3.

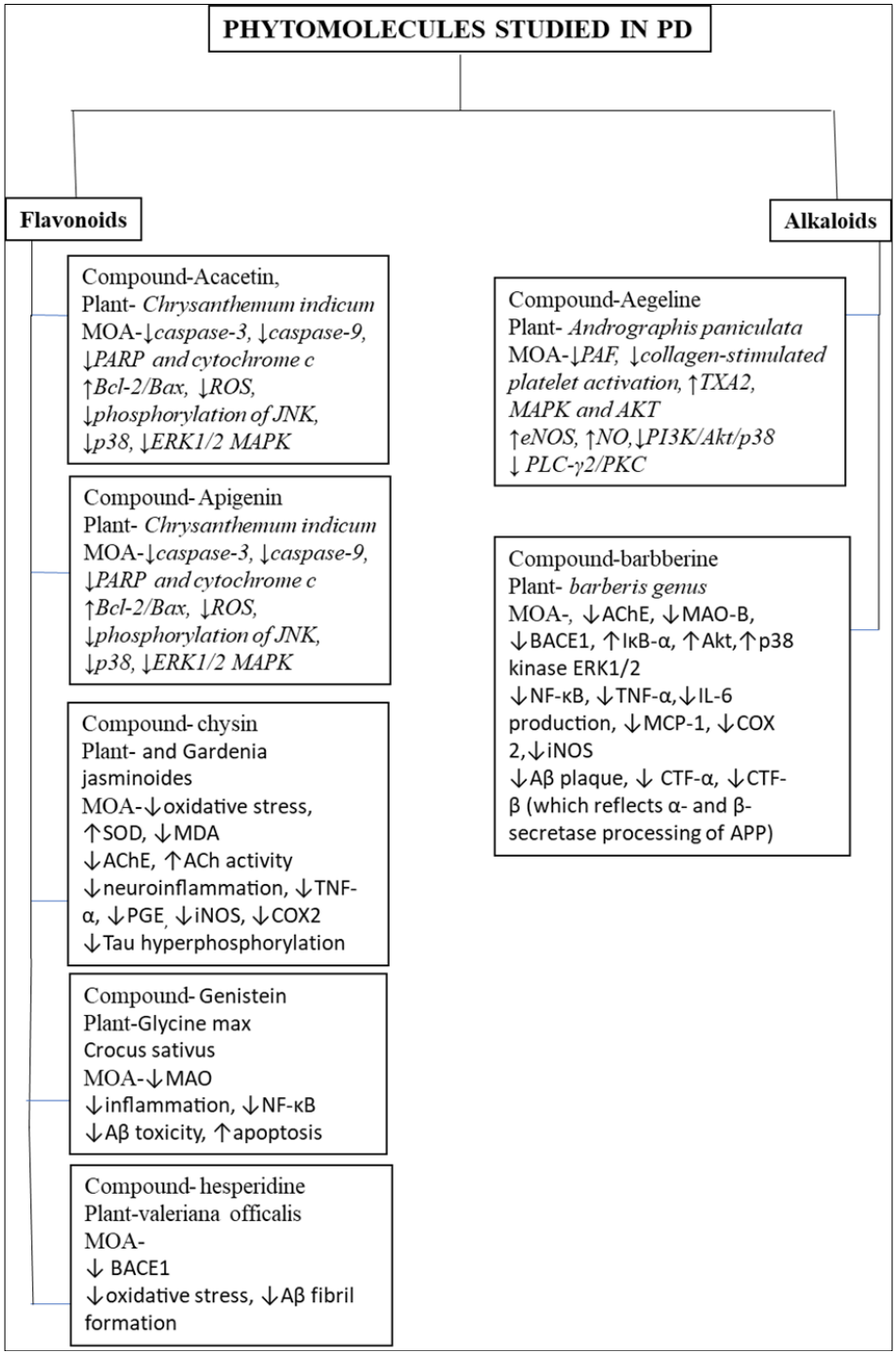


Fig 3: Few examples of Flavonoids and Alkaloids with reported mechanism of actions against Parkinsonism model of *in-vitro* and *in-vivo* models

Abbreviations

↓-reduce
↑-increase
MPTP-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MAO-A-Monoamine oxidase A
Aβ- Amyloid β protein
LPS-lipopolysaccharide
NF-κB- nuclear factor
TNFα-tumor necrosis factor-α
6-OHDA-6-hydroxydopamine
LDH-Lactate dehydrogenase
AChE-Acetylcholinesterase
SOD-superoxide dismutase
CAT- catalase
GPX-glutathione peroxidase
p75 NTR- p75 neurotrophin receptor
MAPK-mitogen-activated protein kinase JNK-c-Jun N-terminal kinase
p38 mitogen-activated protein kinase (p38 MAPK)
BDRF-brain-derived neurotrophic factor
LC3- microtubule-associated protein 1 light chain 3

Conclusion

The most popular occurring phytochemicals like alkaloids and polyphenols that can be used to trat neurodegenerative disorders are included in this overview. These phytochemicals defends against neuronal injury, and this review describes the numerous mechanism, kinetics, common uses by which they do so. Although many more studies have been done on the possible health benefits of these phytochemicals, more research is still required to determine the long -term impacts and effectiveness of utilising phytochemicals as treatment for neurodegenerative diseases.

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