Review Article

Beneficial Effects of Sesamol, Hesperidin, Quercetin and Phloroglucinol in Parkinson's Disease Models- A Review

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ABSTRACT

Parkinson's disease is the progressive degeneration of dopaminergic neurons that constitute motor deficits. Current Parkinson's disease therapies deal with the symptoms and do not halt the disease progression. The interest on bioactive compounds for the treatment of Parkinson's disease is mounting now. Treatments for Parkinson's disease to be included with prevention of brain cell dysfunction and death. Hence, we attempted to study the bioactive compounds (sesamol, hesperidin, quercetin and phloroglucinol) in Parkinson's disease induced models. This article reviews the *in vitro*, *in vivo* and *in silico* approach of these four compounds. These four bioactive compounds have been reported to exert neuroprotective effects in various experimental models of Parkinson's disease.

Key words: Parkinson's disease, antioxidants, sesamol, hesperidin, quercetin, phloroglucinol

INTRODUCTION

Contemporary life style habits increase the risk towards stress every day. Stress affects various parts of the body including the central nervous system, which is the midpoint of regulatory processes. The metabolic rate of brain and its reduced capacity for cellular regeneration increases its risk towards reactive oxygen species. [1] Neurodegenerative diseases are fatal all over the world. Age is a dominant factor in stimulating neurodegenerative diseases even in optimally healthy people. Neurodegeneration is characterized by accumulative damage of neurons that results in neurological deficits and loss.

Parkinson's disease is the second most common neurodegenerative disorder which affects the standard of life. [2] Epidemiological studies estimated that over one million people in United States are analysed with Parkinson's disease. [3] Parkinson's disease not only affects the nigrostriatal dopaminergic pathway but also make changes in glutamatergic, noradrenergic, serotonergic, GABAergic and cholinergic systems. [4] Recent research have reported that the etiology of Parkinson's disease could be environmental, genetic, advanced age, family history, reduced estrogen levels, pesticides, folate deficiency and head trauma. Biochemical anomalies have been detected in the affected brain region in Parkinson's disease that provides clues to how genetic or environmental factors may induce cell death. [5] Interestingly, the downstream mechanisms triggered by mitochondrial dysfunction, complex I (NADH coenzyme Q oxidoreductase) of the respiratory chain in the basal ganglia leads to Parkinson's disease. [6,7] Boveris and Navarro [8] studied

the involvement of oxidative damage in Parkinson's disease patients by postmortem analysis and proved that increased level of oxidative stress was viewed in the substantia nigra pars compacta. Evidently, critical battery of studies reported that the loss of tyrosine hydroxylase in the striatum and substantia nigra may increase the Parkinson's disease progression. [9,10]

In the beginning, Parkinson's disease is diagnosed with the pathological confirmation of lewy bodies during autopsy. [11] Later, Tolosa, *et al*. [12] observed that misdiagnosis could be possible with patients suffering from Alzheimer's disease and vascular parkinsonism. Jankovic [13] reviewed the diagnosis of Parkinson's disease where Parkinsonian disorders have been classified into four types: primary parkinsonism (idiopathic), secondary parkinsonism (acquired, symptomatic), here do degenerative parkinsonism and multiple system degeneration (parkinsonism plus syndromes). Many neurotoxins and pharmacological agents such as rotenone, 6-hydroxy dopamine, paraquat, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and Maneb are the classic models whereas genetic manipulations (alpha synuclein, DJ-1, PINK1, Parkin, etc) or selectively disrupting nigrostiatal neurons (MitoPark, Pitx3, Nurr1, etc) are employed to mimic Parkinson's disease model. [14]

Farooqui and Farooqui [15] validated that 60% degeneration of pigmented dopamine containing neurons in the pars compacta of substantia nigra results in typical motor signs. The hallmark of basal ganglia disorder is bradykinesia which includes difficulties in planning, initiating, movement and in performing sequential and immediate tasks. [16] Other complications such as sleep disorders, mood fluctuations, postural instability, tremor, muscular stiffness, rigidity, psychosis, depression, and dementia are also identified in Parkinson's disease patients. [17,18]

Selikhova, *et al*. [19] observed the two main subtypes of Parkinson's disease which involves the clinical observations based on the age of onset and the other is the evolution/progression of the disease. Mutations in specific genes linked with mitochondrial proteins are involved in the familial forms of Parkinson's disease. [20] Biskup, *et al*. [21] reported that genes of mitochondrial (alpha-synuclein, parkin, PINK1), lysosomal (alpha-synuclein, ATP13A2), developmental regulation (UCHL1, LRRK2) and their localization at the synapse (synphilin, LRRK2) also plays a role in the sporadic form of Parkinson's disease. Marios Politis, *et al*. [22] findings suggest that Parkinson's disease patients perceive lack of response.

Neuroscientists are making attempts to understand the disease and provide the best treatments for the Parkinson's disease patients. Parkinson's disease treatments currently focus on alleviating the symptoms and do not arrest the neurodegeneration. Roberto, *et al*. [23] have studied the modern pre-levodopa era in Parkinson's disease and its associations with motor complications. Deep brain stimulation causes stimulation of subthalamic nucleus or globus pallidus and may improve symptoms like tremor. [24] Ives, *et al*. [25] observed that monamine oxidase B inhibitors such as selegiline and rasagiline have been employed for Parkinson's disease treatment. Pallidotomy is also employed in few cases.

Antioxidants in Parkinson's Disease

Sen Li, et al. [26] reported that external environment results in free radical production in human body and this leads to oxidative damage and finally gene mutation. In general, the free radicals are the culprits for manipulating various diseases. Stanley Fahn and Gerald Cohen [27] reported that oxidative stress can cause cell damage due to chain reactions of membrane lipids and the evidences show that oxidative stress causes loss of monoaminergic neurons in patients with Parkinson's disease. Hence, to maintain the homeostasis and to prevent diseases, intake of foods rich in antioxidants are essential. Antioxidants rich food not only involved in the treatment of diseases but also can avoid the severe effects on

health. Antioxidants have an extensive opportunity to sequester metal ions involved in neuronal plaque formation to inhibit oxidative stress. [28] Yossi, *et al*. [29] noted that to treat neurodegenerative diseases induced by oxidative stress requires antioxidants that can penetrate the blood brain barrier. Hence, the therapeutic uses of natural compounds are limited since a few of them do not penetrate the blood brain barrier. Alteration of the thiol-reducing agent glutathione in the dopaminergic neurons of substantia nigra is observed in Parkinson's disease conditions. [30,31] Jha, *et al*. [32] observed that glutathione exhaustion in PC12 results in selective inhibition of mitochondrial complex I activity.
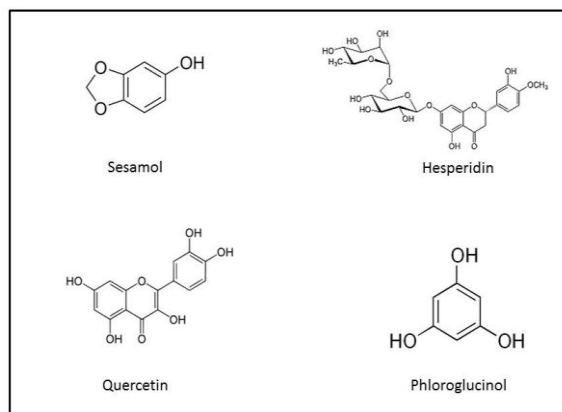
Natural Compounds in Parkinson's Disease

Figure 1: Molecular structures of sesamol, hesperidin, quercetin and phloroglucinol
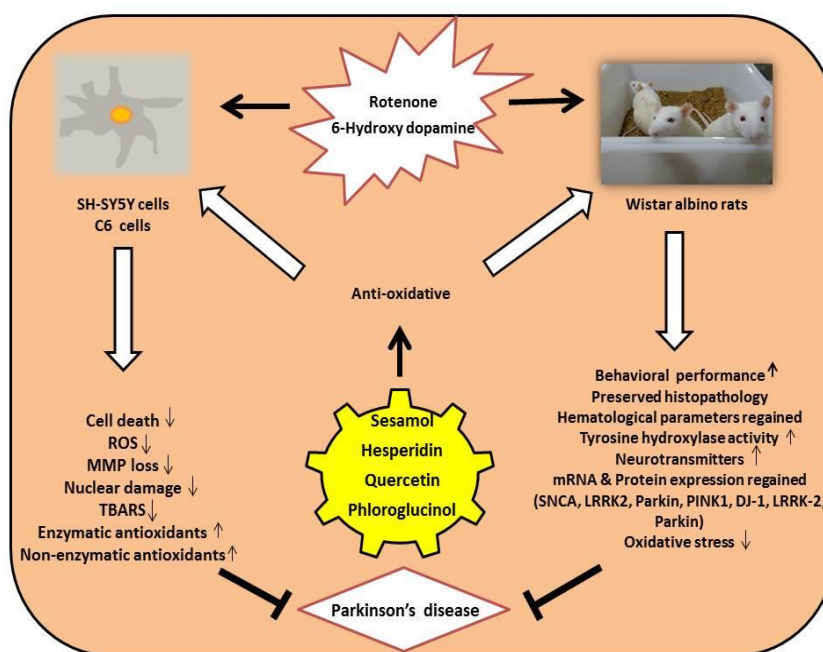en.wikipedia.org [33]

Figure 2: The neuroprotective properties of sesamol, hesperidin, quercetin and phloroglucinol- *In vitro* **and** *In vivo* **approaches**

The molecular structures of sesamol, hesperidin, quercetin and phloroglucinolare shown in Figure 1. The purpose of the article is to review the role of natural compounds (sesamol, hesperidin, quercetin and phloroglucinol) which haveneuroprotective properties (Figure 2) and the mechanisms that protect the neuronal cells against Parkinson's disease.

Sesamol

Sesamum indicum seeds contains enormous amount of sesamol (5-hydroxyl-1,3-benzodioxole or 3,4-methylenedioxyphenol) which provides resistant to oxidative deterioration. [34] *Sesamum indicum* is considered to have nutritional values with medicinal effects. Sesamol is reported to be liberated during the refining of oil from roasted sesame seeds. [35] It is used as an efficient Chinese medicine to prevent aging. [36] Among other edible oils, sesame seed oil is unique due to

its oxidative stability. [37] Sesame seeds and its oil are employed in treating burns and wounds. [38] Zhekang, *et al*. [39] reported that sesame lignans exerts important vascular protective effects in the model of atherosclerosis. Sesamol, sesamolin and sesaminol are the major constituents present in sesame seed oil. [40]

Accumulating evidences report that sesamol is a powerful antioxidant with neuroprotective properties. [41-46] Sesamol is a phenolic derivative with a methylenedioxy group with beneficial health effects of antioxidation, [47,48] anti-inflammatory, [49] chemoprevention, [50] anti-hepatotoxic, [51] photo-protection [52] and anti-mutagenic. [53] Abdul Enein [54] observed the scavenging effects of phenolic compounds on reactive oxygen species. Sesamol has the ability to penetrate the blood brain barrier and through the hepatobiliary excretion, where it is incorporated into liver and transported to other tissues and excreted. [55] In iron-intoxicated mice, sesamol is said to provide protection against systemic oxidative stress and hepatic dysfunction. [56] In cultured astrocytes, sesamol was able to attenuate the production of nitric oxide, [57] hydrogen peroxide and also reduced the monoamine oxidase activity. [58] Chao, *et al*. [59] reported the novel role of sesamol in inhibiting NF-κB mediated signaling in platelet activation. Therefore, sesamol was found to play a potent role in treating thromboembolic disorders. Sesamol is also used to remove wrinkles when applying during facial massage. [60] Sesamol can enhance the vascular fibrinolytic capacity by regulating the plasminogen activator and nitric oxide release in endothelial cells. [61,62] The protective effect of sesamol against myocardial infarction was also observed by Vennila and Pugalendi. [63] Hayes, *et al*. [64] demonstrated the role of sesamol on lipid peroxidation and oxymyoglobin oxidation in bovine and porcine muscle model systems. The ameliorative effect of sesamol against seizures, cognitive impairment and oxidative stress was studied by Hassanzadeh, *et al*. [65] The data generated

from Moiz.*et al*, [66] clearly reports the antifungal nature of sesamol that exploited for improving the therapeutic strategies. Cellular, biochemical and neurochemical evidence in 6-hydroxy dopamine induced neurotoxicity in mice model reveals the neuroprotective property of sesame seed oil. [67] Kumar, *et al*. [68] reported that sesamol is effective in treating Huntington's disease. Chandrasekaran, *et al*, [69] observed the protective effect of sesamol against mitochondrial oxidative stress and hepatic injury in acetaminophen-overdosed rats. Kumar, *et al*. [44] also detected the neuro psychopharmacological effect of sesamol in depression. Sesamol has shown to suppress the ferric nitrilotriacetate-induced renal damage in mice. [70] Sesamol reduces oxidative stress and shields organ from injury in animal model of sepsis. [71,72]

KhadiraSereen and Vijayalakshmi [42] studied the antioxidant potential of sesamol using free radicals such as DPPH (2,2-diphenyl-1-picrylhydrazyl), superoxide anion, nitric oxide, hydroxyl radical, hydrogen peroxide and the reducing capacity of sesamol. In DPPH free radical scavenging activity, the IC_{50} value of sesamol was 5.9μg/ml. In superoxide anion radical scavenging activity, IC_{50} value of sesamol was 42.4μg/ml. IC_{50} value of sesamol in nitric oxide radical scavenging activity was 41.4μg/ml whereas in hydroxyl radical scavenging radical activity, the IC_{50} value of sesamol was 31.4μg/ml. In hydrogen peroxide scavenging activity, the IC_{50} value of sesamol was 10.1μg/ml. The reducing activity of sesamol was greater than the standard ascorbic acid and the IC_{50} was 6.2μg/ml.

Khadira Sereen, *et al*. [73] investigated the effect of sesamol and folic acid on behavioral activity and antioxidant profile of rats in 6-hydroxy dopamine induced Parkinson's disease model. In this study, the behavioral tests such as apomorphine induced rotational test, grip test and ladder climbing test were performed. Disability was observed in the behavior of rats induced with 6-hydroxy

dopamine whereas it was recovered by the administration of sesamol + folic acid. The activity of superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase and the levels of glutathione, vitamin C, vitamin E, thiobarbituric acid reactive substances, nitric oxide were estimated in the brain tissue. The activities and the levels of biochemical parameters were significantly altered with 6-hydroxy dopamine whereas in sesamol + folic acid treated groups their levels were near normal.

KhadiraSereen, *et al.* [74] reported the effect of sesamol and folic acid on the biochemical, neurochemical and histopathological changes in rats induced with 6-hydroxy dopamine. The levels of glucose, triglycerides and protein were altered in 6-hydroxy dopamine (p<0.001) induced rats. Their levels were restored by sesamol + folic acid (p<0.001) treatment which showed good results among the treatment groups. There was significant decrease in the activities of enzymatic (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase) and non-enzymatic antioxidants (glutathione, vitamin C, vitamin E) when induced with 6-hydroxy dopamine (p<0.001) whereas sesamol + folic acid (p<0.001) treated rats showed increased enzymatic and non-enzymatic antioxidants activities. TBARS (thiobarbituric acid reactive substances) level were significantly elevated in the 6-hydroxy dopamine (p<0.001) induced rats which was reduced after the treatment with sesamol + folic acid (p<0.001). The levels of neurotransmitters such as dopamine, nor-epinephrine, DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid) were significantly reduced (p<0.001) in the striatum of rats induced with 6-hydroxy dopamine. Sesamol + folic acid treated group showed increased level of neurotransmitters which was highly significant (p<0.001) when compared with the Parkinson's disease induced rats. The histopathological changes of striatum of experimental rats were also noted. The 6-hydroxy dopamine induced rats showed

cellular inflammation, vascular degeneration and cytoplasmic vacuolation in striatum. Sesamol + folic acid treated groups showed better architecture of striatum similar to that of control rats.

KhadiraSereen and Vijayalakshmi [75] have observed the anti-parkinson effect of sesamol in association with folic acid in 6-hydroxy dopamine induced model by regulating PARK genes. The dopamine level in striatum of 6-hydroxy dopamine rats were significantly reduced (p<0.001) and it was restored by the treatment of sesamol + folic acid (p<0.001). The tyrosine hydroxylase (TH +ve) cells were depleted in the right striatum of 6-hydroxy dopamine rats. In contrast, sesamol + folic acid treated rats showed improved TH +ve cells and restored the normal architecture of neurons. The gene and protein expression of DJ-1, LRRK-2 and Parkin in right striatum were analysed. In 6-hydroxy dopamine-induced rats, the mRNA and protein expression of DJ-1 and Parkin were down regulated whereas LRRK-2 was over expressed. Sesamol + folic acid treated rats showed a significant regulation of these genes and proteins in the right striatum.

Rohini and Vijayalakshmi [76] observed the neuroprotective effect of sesamol against rotenone-induced cell death in SH-SY5Y cells associated with Parkinsonism. Rotenone (20μM) significantly decreased (p<0.001) the cell viability in SH-SY5Y cells. In contrast, sesamol (50μM) significantly increased the cell viability. Sesamol ameliorated the rotenone-induced reactive oxygen species generation, loss of mitochondrial membrane potential and nuclear damage.SH-SY5Y cells exposed to rotenone showed significant increase in DCF fluorescence whereas sesamol treated cells showed decreased fluorescence. Rotenone-induced cells were viewed under microscope showed decreased fluorescence intensity which represented the drop in mitochondrial membrane potential whereas sesamol treatment prevented it. Rotenone-induced cells were detected for nuclear damage

which was ameliorated by sesamol. Sesamol also reduced TBARS level and increased the activities of catalase, superoxide dismutase, glutathione peroxidase and increased the levels of glutathione in rotenone-induced SH-SY5Y cells.

Rohini and Vijayalakshmi [77] have investigated the ameliorative effect of sesamol in rotenone-induced rat model of Parkinson's disease. Body weight and behavioral test such as pole test, ladder climbing test and open field test were assessed. The rotenone-induced rats showed significant decline (P<0.001) in the body weight whereas significant reversal was noted in groups treated with SES (p<0.001), SES + L-DOPA combination (p<0.001). Administration of rotenone significantly (P<0.001) caused impaired ability in movement. In contrast, Sesamol + L-DOPA treated rats showed maximal restoration (P<0.001) in behavioral changes.

Rohini and Vijayalakshmi [78] observed that sesamol increased the cell viability in rotenone-induced C6 cells. Sesamol also reduced rotenone-induced reactive oxygen species generation, mitochondrial membrane potential impairment and nuclear damage in C6 cells. Histopathological evidences in the mid brain revealed that sesamol attenuated the injury caused by rotenone.

Hesperidin

Hesperidin is present in citrus fruits and is a flavanone glycoside, which belongs to the flavonoid family. The main fruit crop in the world is citrus which has a total production of 122 million tons. [79] Intake of fresh oranges increased at an annual rate of 2.8%. [80] Citrus are enriched with nutrients and minerals like vitamin C, folate, etc that potentially protects health. [81] Amir and Fatemeh [82] observed the antioxidative capacity of Iranian *Citrus sinensis* Var. *Valencia* peels with anti-hydroxyl radical and anti-superoxide effect. Ji and Min [83] obtained results showed the mixture of hesperidin, naringin, hesperetin, neohesperitin, neohesperedine and rutin were found in citrus juice processing waste where hesperidin and neohesperidin were predominantly present. In plants, hesperidin has a protective role against fungal and microbial infections. [84] Yamada, *et al*. [85] detected the bioavailability of hesperidin in rats where the hesperidin proceed to the colon and the gut microbes liberate it as aglycone hesperetin which was further absorbed and degraded.

Garg, *et al*. [86] reported that hesperidin to have biological effects like anti-oxidative, anti-inflammatory, anti-microbial and anti-carcinogenic. Bonina, *et al*. [87] have demonstrated that flavonoids are protective agents against photo-oxidative skin injury. Kiran Mishra [88] studied the structure-activity of anti-oxidative property of hesperidin which exhibited a strong reducing power, chelating activity on Fe^{2+}, free radical-scavenging, hydroxyl radical and hydrogen peroxide scavenging effects. The flavonoid hesperidin was studied to inhibit the lipopolysaccharide stimulated COX-2 expression which suggests hesperidin to be an anti-inflammatory compound. [89] The spectrophotometric determinations of hesperidin were carried out by scientists to observe the ability for chelating metal ions. [90-92] Hesperidin has the capacity to modulate the hepatic biotransformation of enzymes and can enhance the intrinsic antioxidants. [93]

Hosseinimehr and Nemati [94] demonstrated that hesperidin has powerful effects against DNA damage and showed its radio-protective effect in mouse bone marrow cells. Cho [95] has demonstrated that hesperidin and hesperitin have the antioxidant property and protect the neurons from various types of insults linked with neurodegeneration. Kamisli, *et al*. [96] studied that hesperidin treatment could attenuate the reactive oxygen species generation by reducing the TBARS levels and increasing the antioxidants activities in brain injured by cisplatin. By modulating nitergic pathway, hesperidin was able to ameliorate the stress-induced behavioral and biochemical alterations and mitochondrial dysfunction in mice. [97] Another study on

hesperidin protected the neurons from reactive oxygen species-mediated injury by activation of Akt and ERK1/2 pathways that underlie the anti-apoptotic effects. [98] One more study showed that hesperidin therapy could reduce the cerebral damage in rat brain due to stroke induced free radicals formations and neuroinflammation. [99]A study, reported that hesperidin, a plant flavanone on rotenone-induced oxidative stress and apoptosis in SK-N-SH neuroblastoma cell line. [100]

Priya and Vijayalakshmi [101] investigated the antioxidant activity of the flavonoid hesperidin. In this study, the scavenging activity of DPPH, nitric oxide, superoxide, hydrogen peroxide, hydroxyl radicals and reducing activity of hesperidin was observed. The IC_{50} values of hesperidin for DPPH radical (438µg/ml), nitric oxide (431µg/ml), superoxide (323µg/ml), hydrogen peroxide (442µg/ml), hydroxyl radical (421µg/ml) and reducing activity (486µg/ml) was noted.

Priya, *et al*. [102] observed the role of hesperidin in the body weight, movement co-ordination and biochemical parameters in 6-hydroxy dopamine induced Parkinson's disease model. It has been studied that the body weight has been decreased due to the systemic administration of 6-hydroxy dopamine (146±1.89) when compared to control animal (158.16±1.16). Significant reversal of body weight was noted in treatment groups such as hesperidin (154.50±1.04), hesperidin + L-DOPA (158.0±0.89), L-DOPA (156.50±1.37).The movement co-ordination was assessed by grip test, rotation test, swing test and catalepsy test.The 6-hydroxy dopamine induced animals showed reduced behavioral activities($P<0.001$). The hesperidin + L-DOPA ($P<0.001$) treated group showed the maximal decrease in the behavioral changes. The biochemical parameters such as glucose, triglycerides and proteins were also evaluated in this study. 6-hydroxy dopamine induced animals showed changes in biochemical parameters ($P<0.001$) whereas hesperidin + L-DOPA ($P<0.001$) treated

group modified the alterations caused by 6-OHDA.

Priya and Vijayalakshmi [103] investigated the role of hesperidin, a bioflavonoid in the expression levels of SNCA, LRRK2, Parkin and PINK1 in brain striatal tissue of rats. The upregulation of genes and proteins like SNCA and LRRK2 was observed in 6-hydroxy dopamine induced Parkinson's disease rats whereas hesperidin treated rats showed mild downregulation, hesperidin + L-DOPA treated rats showed significant down regulation of mRNA and protein expression patterns of SNCA and LRRK2. Downregulation of parkin and PINK1 were observed in 6-hydroxy dopamine induced rats. Hesperidin treated rats showed slight upregulation, hesperidin + L-DOPA treated rats showed significant upregulation of mRNA and protein expression patterns of parkin and PINK1.

Priya and Vijayalakshmi [104] demonstrated the *in silico*docking of target proteins like alpha synuclein, monoamine oxidase B, COMT (catechol-O-methyltransferase), ubiquitin carboxyl-terminal esterase L-1with hesperidin and L-DOPA using Auto Dock version 4.2.The docking energy of hesperidin with alpha synuclein (-1.0kcal/mol), monoamine oxidase B(-6.26kcal/mol), COMT (-2.47kcal/mol), ubiquitin carboxyl-terminal esterase L-1(-6.08kcal/mol) was examined. Indicating that hesperidin has similar binding sites and interactions with the target proteins compared to the standard drug L-DOPA.

Priya and Vijayalakshmi [105] studied the anti-Parkinson effect of hesperidin in 6-hydroxy dopamine model by neurochemical, histopathological and immunohistochemical analysis. Neurochemicals such as dopamine, epinephrine, nor-epinephrine and serotonin levels were significantly reduced ($p<0.001$) in Parkinson's disease induced rats. Rats treated with hesperidin + L-DOPA showed significant increase in their levels. Histopathological studies of striatum in 6-

hydroxy dopamine rats showed changes like neuronal loss with cytoplasmic vacuolation whereas hesperidin + L-DOPA treated rats showed reduction in the abnormalities. Histopathological studies of mid brain in 6-hydroxy dopamine rats showed changes like degeneration of cells and large cytoplasmic vacuolation whereas hesperidin + L-DOPA treated rats showed reduction in these abnormalities. Tyrosine hydroxylase immunostaining pattern in the striatum and mid brain were also studied. Decrease in the number of cells was investigated in 6-hydroxy dopamine rats. In contrast, the treatment with hesperidin + L-DOPA resulted in comparative increase in the number of dopaminergic neurons.

Quercetin

Quercetin (3,3',4',5,7-pentahydroxy-flavanone) is a polyphenol present in vegetables (onions, broccoli) and fruits (apples). Quercetin is found to possess various beneficial effects which includes antioxidant, anti-inflammation, anti-cancer properties. [106-108] Heijnen, *et al.* [109] demonstrated that quercetin is an antioxidant with free radicals scavenging effect with ability to scavenge hydroxyl groups. Quercetin is also found to involve in chelating and free radical scavenging mechanisms in lipid peroxidation. [110] Quercetin is a powerful antioxidant and reverse the decrease in the antioxidant defense mechanism (glutathione peroxidase, catalase, superoxide dismutase) induced by ultraviolet A light. [111]

Srimathi Priyanga and Vijayalakshmi [112] reported the antioxidant potential of quercetin in scavenging free radicals. In this study, the scavenging activity of DPPH, superoxide, nitric oxide, hydroxyl radical, hydrogen peroxide, and reducing activity of quercetin was observed. Quercetin was noted to possess efficient free radical scavenging capacity. Hence, it may be helpful in the treatment of neurodegenerative diseases related to oxidative stress.

Quercetin was rapidly metabolized by gastrointestinal tissues which were studied by Graf,*et al.* [113] After oral intake of quercetin, no glycine form is detectable in human plasma. [114] The half-life of quercetin and its metabolites in humans was about 17 hr and its plasma concentration increases after repeated oral intake. [115] Fiorani, *et al.* [116] demonstrated that quercetin has the capacity to prevent the glutathione depletion in rabbit red blood cells. In *in situ* model, it was observed that quercetin, a flavonoid was able to penetrate the blood brain barrier which is the essential property of a compound to treat neurodegenerative diseases. [117]

Cho, *et al.* [118] observed that quercetin, a natural flavonoid was said to provide protective role against neuronal damage caused by transient global cerebral ischemia. Napatr, *et al.* [119] reported that quercetin, a substance possessing antioxidant effect was able to reduce the cognitive impairment in 6-hydroxy dopamine induced rats. In addition, the levels of antioxidant enzymes were increased. Quercetin enhanced spatial memory by decreasing the oxidative damage in neurons. Quercetin also plays an important role in protecting neurons from oxidative stress-induced neuro degeneration. [120] Quercetin was also found to alleviate oxidative stress in streptozotocin-induced diabetic rats by decreasing lipid peroxidation and improving the activities of enzymatic antioxidants. [121] The herbal medicine *Ginkgo biloba* with high levels of quercetin exhibited neuro protection against oxidative damage caused by Parkinson's disease. [122] Pu, *et al.* [123] suggested that quercetin plays a vital role in improving spatial memory in cerebral ischemia rats.

Rajat and Arpit [124] investigated that supplementation of Quercetin was effective in improving mitochondrial dysfunction in Huntington's disease. Where the ATP levels were restored and it prevented lipid peroxidation and mitochondrial swelling. Oxidative stress-induced by 6-hydroxy dopamine was reduced in the rat striatum and thus quercetin emphasized its neuroprotective role against Parkinson's

disease. [125] Quercetin also exerted neuroprotective effect through inhibition of iNOS/NO system and pro-inflammation gene expression in PC12 cell line and zebra fish model. [126] Quercetin was proved to highlight its neuroprotective capacity by modulating the markers of apoptotic death in dopaminergic neurons. [127] Mehdizadeh, *et al*. [128] demonstrated that the flavonoid quercetin administration could safe guard the neurons present in the substantia nigra pars compacta against 6-hydroxy dopamine toxicity.

Phloroglucinol

Phloroglucinol is asymmetrically tri-hydroxylated benzene derivative which is more commonly available in brown algae and terrestrial pants. [129] Phloroglucinol is a transient metabolite of enormous edible polyphenolics. [130] To reduce oxidative stress by scavenging reactive oxygen species, the polyphenols are employed. [131] The secondary metabolites of phloroglucinol found in plants of the families Guttiferae, Rutaceae, Lauraceae, Compositae, Aspidiaceae, Fagaceae, Euphorbiaceae, Rosaceae, Crassulaceae, Cannabinaceae. [132] The half-life of phloroglucinol in plasma was studied in healthy volunteers. [133] Kang, *et al*. [134] observed the cytoprotective effect of phloroglucinol on oxidative stress induced cell damage via the activation of the enzymatic antioxidant catalase. Recent research has observed that phloroglucinol exerts several pharmacological effects such as antithrombotic, profibrinolytic and anti-inflammatory.

In vitro and cell culture studies, it was proved that phloroglucinol has a strong and concentration dependent free radical (nitric oxide, superoxide anions and hydroxyl) scavenging effects in LLC-PK1 renal epithelial cells. [135] In the study, phloroglucinol was found to attenuate the oxidative stress, increase the cell viability, decreased lipid peroxidation and this suggests that aging process could be delayed by phloroglucinol treatment. Agus Hadian Rahim, *et al*. [132] have studied the regulation

of Nrf2/Maf-mediated expression of antioxidant enzymes and inhibition of osteoclastogenesis by phloroglucinol.

Phloroglucinol has also attenuated the motor functional deficits in Parkinson's disease model by enhancing Nrf2 activity. [136] Warrington, *et al*. [137] have also studied the activity of cytochrome P450 3A4 with phloroglucinol. In lung fibroblast cells, phloroglucinol has reduced the cell damage caused by hydrogen peroxide induced oxidative stress by its antioxidant mechanism. [138] Kim, *et al*. [139] explored that phloroglucinol has the tendency to attenuate the cytotoxicity of hydrogen peroxide in SH-SY5Y cells. Where the pretreatment of phloroglucinol significantly reduced the reactive oxygen species generation and also found to down regulate the levels of 8-isoprostane, protein carbonylation and 8-hydroxy deoxyguanine formed due to hydrogen peroxide. Hence, the study has demonstrated that phloroglucinol possessed neuroprotective activity.

Yang, *et al*. [140] investigated that phloroglucinol has neuroprotective effect on Alzheimer's disease. Phloroglucinol reduced oxidative stress induced by oligomeric $A\beta1$-42 in the HT-22, hippocampal cell line and also in rat primary hippocampal neuron cultures. It was also observed that cognitive deficits in Alzheimer's disease model have been attenuated by phloroglucinolas reported by Morris water maze and T-maze tests.

Concluding Remarks

In conclusion, we observed that sesamol, hesperidin, quercetin and phloroglucinol were capable of ameliorating the damage caused by Parkinson's disease. This review provides strong evidence that natural compounds may be potentially therapeutic for the Parkinson's disease. Given the benefits of these natural compounds, the main "take home message" of this review article expresses the neuroprotective properties (*in vivo*, *in vitro* and *in silico* models). Possibly in the future, the usage of these natural compounds in

clinical studies could contribute the novel therapy to Parkinson's disease pathogenesis and symptoms.

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