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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

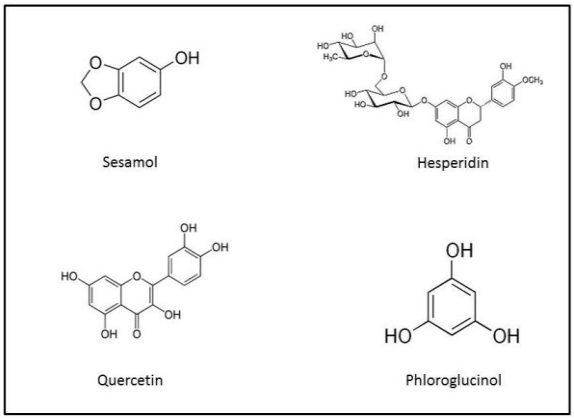

Figure 1: Molecular structures of sesamol, hesperidin, quercetin and phloroglucinol
en.wikipedia.org [33]

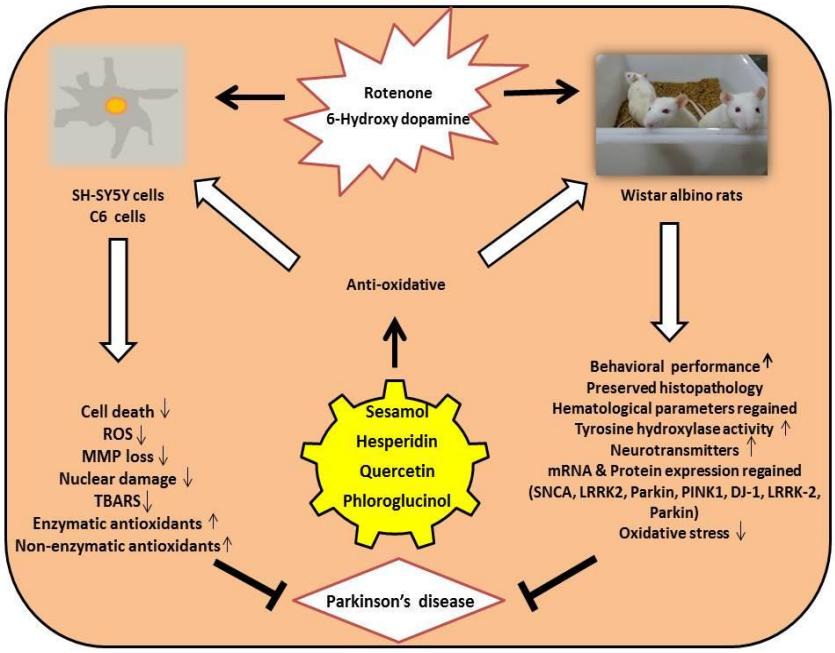

Figure 2: The neuroprotective properties of sesamol, hesperidin, quercetin and phloroglucinol- *In vitro* and *In vivo* approaches

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 Alzehimer's disease. Phloroglucinol reduced oxidative stress induced by oligomeric Aβ1-42 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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REFERENCES

1. Julie A. (2004). Oxidative stress in neurodegeneration: cause or consequence? Nat Med. Doi: 10.1038/nm1434.
2. Robert AF, Kenneth H. (2002). Oxidative stress in brain aging: Implications for the therapeutics of neurodegenerative disease. Neurobiol Aging. 23, 795-807.
3. Fahn S, Przedborski S. (2000). Parkinsonism. In: Merritt's neurology (Rowland LP, ed), New York: Lippincott Williams and Williams, Ed 10, 679-93.
4. Brichta L, Greengard P, Flajolet M. (2013). Advances in the pharmacological treatment of Parkinson's disease: targeting neurotransmitter systems. Trends Neurosci. 36, 543-54.
5. Schapira AH, Jenner P. (2011). Etiology and pathogenesis of Parkinson's disesase. MovDisord. 26, 1049-55.
6. Gubellini P, Picconi B, Di FM, Calabresi P. (2010). Downstream mechanisms triggered by mitochondrial dysfunction in the basal ganglia: from experimental models to neurodegenerative disease. BiochimBiophysActa. 1802, 151-61.
7. Dawson TM, Dawson VL. (2003). Molecular pathways of neurodegeneration in Parkinson's disease. Science. 302, 819-22.
8. Boveris A, Navarro. (2008). Brain mitochondrial dysfunction in aging. Life. 60, 308-14.
9. Snyder GL, Keller RW, Zigmond MJ. (1990). Dopamine efflux from striatal slices after intracerebral 6-hydroxydopamine: evidence for compensatory hyperactivity of residual terminals. J Pharm ExpTher. 253, 867-76.
10. Drolet RE, Behrouz B, Lookingland KJ, Goudreau JL. (2006). Substrate-mediated enhancement of phosphorylated tyrosine hydroxylase in nigrostriatal dopamine neurons: evidence for a role of alpha-synuclein. J Neurochem. 96, 950-9.
11. Gibb WR. Lees AJ. (1988). The relevance of the lewy body to the pathogenesis of idiopathic Parkinson's disease. J NeurolNeurosurg Psychiatry. 51, 745-52.
12. Tolosa E, Wenning G, Poewe W. (2006). The diagnosis of Parkinson's disease. Lancet Neurol. 5, 75-86.
13. Jankovic J. (2008). Parkinson's disease: clinical features and diagnosis. J Neurol Psychiatry. 79, 368-76.
14. Gubellini P, Kachidian P. (2015). Animal models of Parkinson's disease: an updated overview. Revue Neurologique. 171, 750-61.
15. Farooqui T, Farooqui A. (2011). Lipid-mediated oxidative stress and inflammation in the pathogenesis of Parkinson's disease. Parkinons Dis. Doi: 10.4061/2011/247467.
16. Berardelli A, Rothwell JC, Thonpson PD, Hallett M. (2001). Pathophysiology of bradykinesia in Parkinson's disease. Brain. 124, 2131-46.
17. Hindle JV. (2008). Parkinson's disease in the older patient. Neuropsychiatr Dis Treat. 4, 835-45.
18. Divya S, Kavimani S, Sudha Rani S, Subashree S, Praveen Kumar S, Mahalakshmi S, et al. (2014). Parkinson's disease: a phytochemical approach. Int J Pharm Rev Res. 4, 111-9.
19. Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ. (2009). A clinicopathological study of subtypes in Parkinson's disease. Brain. 132, 2947-57.
20. Bueler H. (2009). Impaired mitochondrial dynamics and function in the pathogenesis of Parkinson's disesase. Exp Neurol. 218, 235-47.
21. Biskup S, Gerlach M, Kupsch A, Reichmann H, Riederer P, Vieregge P, et al. (2008). Genes associated with Parkinson syndrome. J Neurol. 255, 8-17.
22. Marios P, Kit Wu, Sophie M, Peter GB, Ray C, Paola P. (2010). Parkinson's disease symptoms: the patient's perspective. MovDisord. 25, 1646-51.
23. Roberto C, Albert A, Fred SS, Momodou C, Marianna A, Emanuele C, et al. (2014). The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain. 137, 2731-42.
24. Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, et al. (1988). Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 339, 1105-11.
25. Ives NJ, Stowe RL, Marro J, Counsell C, Macleod A, Clarke CE, et al. (2004).

Monamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. BMJ. Doi: 10.1136/bmj.38184.606169.
26. Sen L, Guowei C, Chao Z, Man W, Shuyan W, Qing L. (2014). Research progress of natural antioxidants in food for the treatment of diseases. Food Science and Human Wellness. 3, 110-16.
27. Stanley Fahn, Gerald Cohen. (1992). The oxidant stress hypothesis in Parkinson's disease: evidence supporting it. Ann Neurol. 32, 804-12.
28. Uttara B, Singh AV, Zamboni P, Mahajan RT. (2009). Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. CurrNeuropharmacol. 7, 65-74.
29. Yossi GS, Eldad M, Daniel O. (2001). Oxidative stress induced-neurodegenerative disease: the need for antioxidants that penetrate the blood brain barrier. Neuropharmacology. 40, 959-75.
30. Perry TL, Yong VW. (1986). Idiopathic Parkinson's disease, progressive supranuclear palsy and glutathione metabolism in the substabtia nigra of patients. Neurosci. 67, 269-74.
31. Pearce RK, Owen A, Daniel S, Jenner P, Marsden CD. (1997). Alterations in the distribution of glutathione in the substantianigra in Parkinson's disease. J Neural Transm. 104, 661-7.
32. Jha N, Jurma O, Lalli G, Liu Y, Pettus EH, Greenamyre JT, et al. (2000). Glutathione depletion in PC12 results in selective inhibition of mitochondrial complex I activity. Implications for Parkinson's disease. J Biol Chem. 275, 26096-101.
33. en.wikipedia.org
34. Parihar VK, Prabhakar KR, Veerapur VP, Kumar MS, Reddy YR, Joshi R, et al. (2006). Effect of sesamol on radiation-induced cytotoxicity in Swiss albino mice. Mutat Res. 611, 9-16.
35. Fukuda Y, Nagata M, Osawa T, Namiki M. (1986). Chemical aspects of the antioxidative activity of roasted sesame seed oil and the effect of using the oil for frying. AgricBiol Chem. 50, 857-62.
36. Namiki M, Kobayashi T. (1989). Goma no Kagaku (Science of Sesame). Asakura Shoten, Tokyo, 1-2.
37. Kamal Edlin A, Appelqvist LA. (1994). Variation of fatty acid composition of the different acyl lipids in seed oils from four sesame species. J Am Oil Chem Soc. 71, 135-9.
38. Kiran K, Asad M. (2008). Wound healing activity of Sesamum indicum L seed and oil in rats. Indian J Exp Biol. 46, 777-82.
39. Zhekang Y, Nisharahmed K, Thomas K, Georgeta M, Orlando S, Rajagopal D, et al. (2011). A modified sesamol derivative inhibits progression of atherosclerosis. Atherioscler ThrombVasc Biol. 31, 536-42.
40. Isshiki S, Umezaki T. (1997). Genetic variations of isoenzymes in cultivated sesame (Sesamum indicum L.). Euphytica. 93, 375-77.
41. Prasad NR, Mahesh T, Menon VP, Jeevanram RK, Pugalendi KV. (2005). Photoprotective effect of sesamol on UVB-radiation induced oxidative stress in human blood lymphocytes in vitro. Environ ToxicolPharmacol. 20, 1-5.
42. KhadiraSereen A, Vijayalakshmi K. (2013). Antioxidant potential and reducing activity of sesamol. IJPRBS. 2, 465-74.
43. Kuhad A, Chopra K. (2008). Effect of sesamol on diabetes-associated cognitive decline in rats. Exp Brain Res. 185, 411-20.
44. Kumar B, Kuhad A, Chopra K. (2011). Neuropsychopharmacological effect of sesamol in unpredictable chronic mild stress model of depression: behavioral and biochemical evidences. Psychopharmacology. 214, 819-28.
45. Suja KP, Jayalekshmy A, Arumughan C. (2004). Free radical scavenging behavior of antioxidant compounds of sesame (Sesamumindicum L.) in DPHH(*) system. J Agric Food Chem. 52, 912-5.
46. Thiraviam G, Bhandari R, Kaur IP. (2009). Sesamol: an efficient antioxidant with potential therapeutic benefits. Med Chem. 5, 367-71.
47. Joshi R. Kumar MS, Satyamoorthy K, Unnikrisnan MK, Mukherjee T. (2005). Free radical reactions and antioxidant activities of sesamol: pulse radiolytic and biochemical studies. J Agric Food Chem. 53, 2696-703.
48. Uchida M, Nakajn S, Toyoshima M. (1996). Antioxidative effect of sesamol and related compounds on lipid peroxidation. Biol Pharm Bull. 19, 623-6.

49. Hsu DZ, Chu PY, Lin MY. (2009). The non-peptide chemical 3,4-methylenedioxyphenol blocked lipopolysaccharide from binding to LPS-binding protein and inhibited pro-inflammatory cytokines. Innate Immun. 15, 380-5.
50. Kapadia GJ, Azuine MA, Tokuda H, Takasaki M, Mukainaka T, Konoshima T, et al. (2002). Chemopreventive effect of resveratrol, sesamol, sesame oil and sunflower oil in the Epstein Barr virus early antigen activation assay and the mouse skin two-stage carcinogenesis. Pharmacol Res. 45, 499-505.
51. Chandrasekaran VR, Hsu DZ, Liu MY. (2009). The protective effect of sesamol against mitochondrial oxidative stress and hepatic injury in acetaminophen-overdosed rats. Shock. 32, 89-93.
52. Sharma S, Kaur IP. (2005). Development and evaluation of sesamol as an antiaging agent. Int J Dermatol. 45, 200-8.
53. Kaur IP, Saini A. (2000). Sesamol exhibits antimutagenic activity against oxygen species mediated mutagenicity. Mutat Res. 470, 71-6.
54. AboulEnein HY, Kruk I, Kladna A, Licgszteld K, Michalska T. (2007). Scavenging effects of phenolic compounds on reactive oxygen species. Biopolymers. 86, 222-30.
55. Jan KC, Ho CT, Hwang LS. (2008). Bioavailability and tissue distribution of sesamol in rat. J Agric Food Chem. 56, 7032-7.
56. Hsu DZ, Chien SP, Chen KT, Liu MY. (2007). The effect of sesamol on systemic oxidative stress and hepatic dysfunction in acutely iron-intoxicated mice. Shock. 28, 596-601.
57. Chen Y, Vartiainen NE, Ying W, Chan PH, Koistinaho J, Swanson RA. (2001). Astrocytes protect neurons from nitric oxide toxicity by a glutathione-dependent mechanism. J Neurochem. 77, 1601-10.
58. Mazzio EA, Harris N, Soliman KF. (1998). Food constituents attenuate monoamine oxidase activity and peroxide levels in C6 astrocytic cells. Plant Med. 64, 603-6.
59. Chao CC, Wan JL, Eng TO, Cheng WC, Song CL, Shih YH, Joen RS. (2011). A novel role of sesamol in inhibiting NF-κB mediated signaling in platelet activation. J Biomed Sci. Doi: 10.1186/1423-0127-18-93.
60. Sharma S, Kaur IP. (2006). Development and evaluation of sesamol as an antiaging agent. Int J Dermatol. 45, 200-8.
61. Chen PR, Lee CC, Chang H, Tsai CE. (2005). Sesamol regulates plasminogen activator gene expression in cultured endothelial cells: a potential effect on the fibrinolytic system. J NutrBiochem. 16, 59-64.
62. Chen PR, Tsai CE, Chang H, Liu TL, Lee CC. (2005). Sesamol induces nitric oxide release from human umbilical vein endothelial cells. Lipids. 40, 955-61.
63. Vennila L, Pugalendi KV. (2010). Protective effect of sesamol against myocardial infarction caused by isoproterenol in Wistar rats. Redox Rep. 15, 1-7.
64. Hayes JE, Stepanyan VV, Allen PP, O'Grady MN, O'Brein NM, Kerry JP. (2009). The effect of lutein, sesamol, ellagic acid and olive leaf extract on lipid oxidation and oxymyoglobin oxidation in bovine and porcine muscle model systems. Meat Sci. 83, 201-8.
65. Hassanzadeh P, Arbabi E, Rostami F. (2014). The ameliorative effects of sesamol against seizures, cognitive impairment and oxidative stress in the experimental model of epilepsy. Iran J Basic Med Sci. 17, 100-7.
66. Moiz AA, Zeeshan F, Staif H. (2014). Sesamol: a natural phenolic compound with promising anticandidal potential. J Pathog. Doi: 10.1155/2014/895193.
67. Ahmad S, Khan MB, Hoda MN, Bhatia K, Haque R, Fazlil IS, Jamal A, Khan JS, katare DP. (2012). Neuroprotective effect of sesame seed oil in 6-hydroxydopamine induced neurotoxicity in mice model: cellular, biochemical and neurochemical evidence. Neurochem Res. 37, 516-26.
68. Kumar P, Kalonia H, Kumar A. (2009). Sesamol attenuate 3-nitropropionic acid-induced Huntington-like behavioral, biochemical and cellular alterations in rats. J Asian Nat Prod Res. 11, 439-50.
69. Chandrasekaran VR, Chien SP, Hsu DZ, Liu MY. (2011). Antihepatotoxic effects of 3,4-methlenedioxyphenol and N-acetylcysteine in acutely acetaminophen-overdosed mice. Hum ExpToxicol. 30, 1609-15.

70. Hsu DZ, Wan CH, Hsu HF, Lin YM, Lin MY. (2008). The prophylactic protective effect of sesamol against ferric-nitrilotriacetate-induced acute renal injury in mice. Food ChemToxicol. Doi:10.1016/j.fct.2008.04.029.
71. Hsu DZ, Chen KT, Li YH, Chuang YC and Liu MY. (2006). Sesamol delays mortality and attenuates hepatic injury after cecal ligation and puncture in rats: role of oxidative stress. Shock. 25, 528-32.
72. Hsu DZ, Li YH, Chu PY, Chien SP, Chuang YC, Liu MY. (2006). Attenuation of endotoxin-induced oxidative stress and multiple organ injury by 3,4-methylenedioxyphenol in rats. Shock. 25, 300-5.
73. KhadiraSereen A, Priya N, Vijayalakshmi K. (2014-15). Effect of sesamol and folic acid on behavioural activity and antioxidant profile of rats induced with 6-hydroxydopamine. Int J Res Pharm Sci. 6, 930-5.
74. Khadira S, Vijayalakshmi, Nagappan P, Balima S. (2014). Effect of sesamol on association with folic acid on 6-OHDA induced parkinsonian animals- biochemical, neurochemical and histopathological evidence. Int J Res Pharm Sci. 5, 16-20.
75. KhadiraSereen A, Vijayalakshmi K. (2015). Sesamol in association with folic acid shows anti-parkinson effect on 6-OHDA induced Parkinsonian animal by regulating the PARK genes. Int J Pharm Bio Sci. 6, 346-54.
76. Rohini D, Vijayalakshmi K. (2016). Sesamol antagonizes rotenone-induced cell death in SH-SY5Y neuronal cells. Int J Pharm Sci. 8, 72-7.
77. Rohini D, Vijayalakshmi K. (2017). Sesamol ameliorates the motor behavior in rotenone- induced rat model of Parkinson's disease. Int J Pharm Bio Sci. 8, 330-7.
78. Rohini D, Vijayalakshmi K. (2018).Protective effect of sesamol on rotenone-induced C6 cell line and rat brain. European journal of molecular biology and biochemistry. 5, 1-8.
79. Food and Agriculture Organisation of the United Nations. http://www.fao.org/corp/topics/en.
80. Nations FaAOotu. (2010). Citrus fruit fresh and processed. Annual statistics.
81. Raymond HB. (1968). Enrichment of fruit products and fruit juices. J Agric Food Chem. 16, 177-83.
82. Amir S, Fatemeh J. (2016). The antioxidative capacity of Iranian Citrus sinensis Var. Valenica peels from Iran. IJPPR. 8, 1944-50.
83. Ji HK, Min YK. (2016). The potential use of citrus juice waste as sources of natural phenolic antioxidants. J App Pharm Sci. 6, 202-5.
84. Del Rio JA, Gomez P, Baidez AG, Arcas MC, Botia JM, Ortuno A. (2004). Changes in the levels of polymethoxyflavones and flavanones as part of the defense mechanism of citrus sinensis (cv. Valenica Late) fruits against Phytophthoracitrophthora. J Agric Food Chem. 52, 1913-7.
85. Yamada M, Tanabe F, Arai N, Mitsuzumi H, Miwa Y, Kubota M, et al. (2006). Bioavailability of glycosyl hesperidin in rats. BiosciBiotechnolBiochem. 70, 1386-94.
86. Garg A, Garg S, Zaneveled JD, Singla AK. (2001). Chemistry and pharmacology of the citrus bioflavonoid hesperidin. Phytotherapy Res. 15, 655-69.
87. Bonina F, Lanza M, Montenegro L, Puglisi C, Tomaino A, Trombetta D, et al. (1996). Flavonoids as potential protective agents against photooxidative skin damage. Int J Pharm. 145, 87-94.
88. Kiran Mishra. (2013). Structure-activity relationship of antioxidative property of hesperidin. IJPE. 2, 40-53.
89. Atsusi H, Yukio M, Masao S, Yoshinori K, Seiichiro F. (2005). Kinetics of radica-scavenging activity of hesperidin and their inhibitory activity on COX-2 expression. Anticancer Res. 25, 3367-74.
90. Malesev D, Radovi Z, Kunti V, Kosani M. (1997). Spectrophotometric determination of hesperidin by Al(III)- hesperidin complex in water-methanol solution. Annal Letters. 30, 917-26.
91. Kunti V, Blagojevi S, Malesev D, Radovi Z. (1999). Spectrophotometric investigation of Cu(II)- hesperidin complex in 50% ethanol. Pharmazie. 54, 548-9.
92. Kunti V, Kosani M, Malesev D, Radovi Z, Mio U. (1988). Spectrophotometric investigation of uranil(II)- hesperidin complex in 70% methanol. J Serb Chem Soc. 63, 565-72.

93. Nandakumar N, Balasubramanian MP. (2012). Hesperidin a citrus bioflavonoid modulates hepatic biotransformation enzymes and enhances intrinsic antioxidants in experimental breast cancer rats challenged with 7,12-dimethylbenz (a) anthracene. J ExpTherOncol. 9, 321-5.
94. Hosseinimehr SJ, Nemati A. (2006). Radioprotective effects of hesperidin against gamma irradiation in mouse bone marrow cells. Br J Radiol. 79, 415-8.
95. Cho J. (2006). Antioxidant and neuroprotective effects of hesperidin and its aglyconehesperetin. Archives of Pharmacal Research. 29, 699-706.
96. Kamisli S, Ciftci O, Kaya K, Cetin A, Kamisli O, Ozcan C. (2013). Hesperidin protects brain and sciatic nerve tissues against cisplatin-induced oxidative, histological and electromyographical side effects in rats. ToxicolInd Health. 31, 841-51
97. Viswanatha GL, Shylaja H, SandeepRao KS, Santhosh Kumar VR, Jagadeesh M. (2012). Hesperidin ameliorates immobilization-stress-induced behavioral and biochemical alterations and mitochondrial dysfunction in mice by modulating nitrergic pathways. ISRN Pharmacology. Doi: 10.5402/2012/479570.
98. Vauzour D, Vafeiadou K, Rice-Evans C, Williams RJ, Spencer JPE. (2007). Activation of pro-survival Akt and ERK1/2 signalling pathways underlie the anti-apoptotic effects of flavanones in cortical neurons. J Neurochem. 103, 1355-67.
99. Raza SS, Khan MM, Ahmad A, Ashafaq M, Khuwafa G, Tabassum R, et al. (2011). Hesperidin ameliorates functional and histological outcome and reduces neuroinflammation in experimental stroke. Brain Res. 1420, 93-105.
100. Kuppusamy T, Nady B, Thamilarasan M, Musthafa ME, Nagarajan RP, Subburayan K, et al. (2013). Neuroprotective effects of hesperidin, a plant flavanone, on rotenone-induced oxidative stress and apoptosis in a cellular model of Parkinson's disease. Oxid Med Cell Longev. Doi: 10.1155/2013/102741.
101. PriyaNagappan, Vijayalakshmi Krishnamoorthy. (2014). IC_{50} value of hesperidin against free radicals: an invitrostudy. The journal of free radicals and antioxidants. Photon. 140, 271-7.
102. Priya N, Vijayalakshmi K, Khadira S. (2014). Investigation on the neuroprotective effects of hesperidin on behavioural activities in 6-OHDA induced Parkinson model. Int J Pharm Bio Sci. 5, 570-7.
103. Priya N, Vijayalakshmi K. (2015). Hesperidin a bioflavonoid modulates the expression levels of SNCA and PARKIN in 6-hydroxydopamine induced neurotoxicity in rats. Int J Pharm. 5, 219-224.
104. Priya N, Vijayalakshmi K. (2015). Structural prediction and comparative molecular docking studies of hesperidin and L-DOPA on alpha-symuclein, MAO-B, COMT and UCHL-1 inhibitors. IJPCR. 7, 221-5.
105. Priya N, Vijayalakshmi K. (2016). Anti-Parkinson effect of hesperidin in combination with L-DOPA on 6-OHDA induced Parkinsonism in Wistar rats- a neurochemical, histopathological and immunohistochemical analysis. IJPRIF. 9, 266-73.
106. Takahama U. (1988). Scavenging of active oxygen by flavonoids, TanpakushitsuKakusanKoso. Protein, nuclei acid, enzyme. 33, 2994-9.
107. Rogerio AP, Kanashiro A, Fontanari C, da Silva EV, LucisanoValim EV, Soares EG, et al. (2007). Antiinflammatory activity of quercetin and isoquercetin in experimental murine allergic asthma. Inflamm Res. 56, 402-8.
108. Lamson DW, Bringall MS. (2000). Antioxidants and cancer III: quercetin. Altern Med Rev. 5, 196-208.
109. Heijnen CGM, Haenen GRMM, Van Acker FAA, Van Der Vijgh JF, Bast A. (2001). Flavonoids as peroxynitrite scavengers: the role of the hydroxyl groups. ToxicolIn Vitro. 15, 3-6.
110. Afanas'ev IB, Dorozhko AI, Brodskii AV, Kostyuk VA, Potapovitch AI. (1989). Chelating and free radical scavenging mechanisms of inhibitory action of rutin and quercetin in lipid peroxidation. Biochem Pharmacol. 38, 1763-9.
111. ErdenInlal M, Kahraman A, Koken T. (2001). Beneficial effects of quercetin on oxidative stress induced by ultraviolet A. Clin Exp Dermatol. 26, 536-9.
112. SrimathiPriyanga, Vijayalakshmi K. (2017). Investigation of antioxidant potential of quercetin and hesperidin: an

invitro approach. Asian J Pharm Clin Res.11,83-6..

113. Graf BA, Ameho C, Dolnikowski GG, Milbury PE, Chen CY, Blumberg JB. (2006). Rat gastrointestinal tissues metabolize quercetin. J Nutr. 136, 39-44.
114. Graefe EU, Witting J, Mueller S, Riethling AK, Uehleke B, Drewrlow B, et al. (2001). Pharmacokinetics and bioavailability of quercetin glycosides in human. J ClinPharmacol. 41, 492-9.
115. Egert S, Wolffram S, BosyWestphal A, BoeschSaadatmandi C, Wagner AE, Frank J, et al. (2008). Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. J Nutr. 138, 1615-21.
116. Fiorani M, De Sanctis R, Menghinello P, Cucchiarini L, Cellini B, Dacha M. (2001). Quercetin prevents glutathione depletion induced by dehydroascorbic acid in rabbit red blood cells. Free Radic Res. 34, 639-48.
117. Youndin KA, Qaiser MZ, Begley DJ, Rice Evans CA, Abbott NJ. (2004). Flavonoid permeability across an in situ model of the blood brain barrier. Free RadicBiol Med 36, 592-604.
118. Cho JY, Kim IS, Jang YH, Kim AR, Lee SR. (2006). Protective effect of quercetin, a natural flavonoid against neuronal damage after transient global cerebral ischemia. NeurosciLett. 404, 330-5.
119. Napatr S, Jintanaporn W, Supaporn M, Somsak T, Kamoltip B, Kowit C. (2012). Cognitive-enhancing effect of quercetin in a rat model of Parkinson's disease induced by 6-hydroxydopamine. Evid Based Complement Alternat Med. Doi: 10.1155/2012/823206.
120. Heo HJ, Lee CY. (2004). Protective effects of quercetin and vitamin C against oxidative stress-induced neurodegeneration. J Agric Food Chem. 52, 7514-7.
121. Mahesh T, Menon VP. (2004). Quercetin alleviates oxidative stress in streptozotocin-induced diabetic rats. Phytother Res. 18, 123-7.
122. Kim MS, Lee JI, Lee WY, Kim SE. (2004). Neuroprotective effect of Ginkgo bilobaL. extract in a rat model of Parkinson's disease. Phytother Res.18, 663-6.
123. Pu F, Mishima K, Irie K, Motohashi K, Tanaka Y, Orito K, et al. (2007). Neuroprotective effects of quercetin and rutin on spatial memory impairment in an 8-arm radial maze task and neuronal death induced by repeated cerebral ischemia in rats. J Pharmacol Sci. 104, 329-34.
124. Rajat S, Arpit M. (2013). Quercetin supplementation is effective in improving mitochondrial dysfunctions induced by 3-nitropropionic acid: Implications in Huntington's disease. BiochimBiophysActa. 1832, 421-30.
125. Haleagrahara N, Siew CJ, Mitra NK, Kumari M. (2011). Neuroprotective effect of bioflavonoid quercetin in 6-hydroxydopamine-induced oxidative stress biomarkers in the rat striatum. NeurosciLett. 15, 139-43.
126. Zhang ZJ, Cheang LCV, Wang ME, Yuen Lee SM. (2011). Quercetin exerts a neuroprotective effect through inhibition of the iNOS system and pro-inflammation gene expression in PC12 cells and in zebrafish. Int J Mol Med. 27, 195-203.
127. Bournival J, Quessy P, Martinoli MG. (2009). Protective effects of resveratrol and quercetin against MPP+-induced oxidative stress act by modulating markers of apoptotic death in dopaminergic neurons. Cell MolNeurobiol. 29, 1169-80.
128. Mehdizadeh M, Mohammad TJ, Maliheh N, Roya A. (2009). Neuroprotective effect of quercetin in a model of Parkinson's disease in rat: a histochemical analysis. BCN. 1, 3- 6.
129. Binod KR, Anshul S, Ajit KT, Shyam SC, Vikas K. (2015). Anti-stress activity of phloroglucinol: atransient metabolite of some plant polyphenolics. Pharmacologia. 6, 21-30.
130. Vissiennon C, Nieber K, Kelber O, Butterweck V. (2012). Route of administration determines the anxiolytic activity of the flavonolskaempferol, quercetin and myricetin: are they prodrugs? J NutrBiochem. 23, 733-40.
131. Rah DK, Han DW, Baek HS, Hyon SH, Park JC. (2005). Prevention of reactive oxygen species-induced oxidative stress in human microvascular endothelial cells by green tea polyphenol. ToxicolLett. 155, 269-75.
132. Agus HR, Bambang S, Firli RPD, Zairin N. (2015). Regulation by phloroglucinol of Nrf2/Maf-mediated expression of antioxidant enzymes and inhibition of

osteoclastogenesis via the RANKL/RANK signaling pathway: in silico study. Acta Inform Med. 23, 228-32.

133. Li XQ, Wang RT, Wang QH, Tang XL, Lu CT, Gong HG, et al. (2017). Determination of phloroglucinol by HPLC-MS/MS and its application to a bioequivalence study in healthy volunteers. Eur Rev Med Pharmacol Sci. 21, 1990-8.
134. Kang KA, Lee KH, Chae S, Zhang R, Jung MS, Ham YM, et al. (2006). Cytoprotective effect of phloroglucinol on oxidative stress induced cell damage via catalase activation. J Cell Biochem. 97, 609-20.
135. Mi Jung So, EunJu Cho. (2014). Phloroglucinol attenuates free radical-induced oxidative stress. Nutr Food Sci. 19, 129-35.
136. Ryu J, Zhang R, Hong BH, Yang EJ, Kang KA, Choi M et al. (2013). Phloroglucinol attenuates motor functional deficits in an animal model of Parkinson's disease by enhancing Nrf2 activity. Plos one. Doi: 10.1371/journal.pone.0071178.
137. Warrington JS, Shader RI, Von Moltke LL, Greenblatt DJ. (2000). In vitro biotransformation of sildenafil (Viagra): identification of human cytochromes and potential drug interactions. Drug MetabDispos. 28, 392- 7.
138. Kang KA, Zhang R, Chae S, Lee SJ, Kim J, Kim J, et al. (2010). Phloroglucinol (1,3,5-trihydroxybenzene) protects against ionizing radiation-induced cell damage through inhibition of oxidative stress in vitro and in vivo. ChemBiol Interact. 185, 215-26.
139. Kim HS, Lee K, Kang KA, Lee NH, Hyun JW, Kim HS. (2012). Phloroglucinol exerts protective effects against oxidative stress-induced cell damage in SH-SY5Y cells. J Pharmacol Sci. 119, 186-92.
140. Yang EJ, Ahn S, Ryu J, Choi MS, Choi S, Chong YH, et al. (2015). Phloroglucinol attenuates the cognitive deficits of the 5XFAD mouse model of Alzheimer's disease. Plos one. Doi: 10.137/journal.pone.0135686.

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