ROLE OF HESPERETIN & PYRIDOXINE PROTECT IN THE NIGROSTRIATAL DOPAMINERGIC PROJECTION IN A NEUROTOXIN MODEL OF PARKINSON’S DISEASE

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INTRODUCTION
Parkinson’s disease (PD) as described by James Parkinson in 1817 is the second most frequent Neurodegenerative disease among elderly people after Alzheimer disease, affecting six million people worldwide13. The major motor symptoms of Parkinson’s disease are mainly bradikinesia, rigidity, akinesia, postural abnormalities, and tremor which are associated with the loss of nigral dopaminergic cells in the substantia nigra pars compacta (SNpc).3, 4, 5 and a decline in caudate-putamen dopamine content that led to the introduction of dopamine replacement therapy.1, 2, 9 These dopaminergic neurons project to the medium spiny neurons of the striatum, where dopamine is released onto dopamine D1 and D2 receptor subtypes, resulting in modulation of complex downstream pathways.6, 7, 8 However, recent advances have emphasized that PD is a multisystem disorder which affects not only the dopaminergic neurons in the SNpc but also other neurotransmitter systems.9, 10, 11

EPIDEMIOLOGY
Parkinson’s is a 2nd commonest neurodegenerative disease.13 It was estimated that the no. of people with PD will rise from 4.1 to 4.6 million in 2005.14, 15 Six of the most populous countries are in Asia (China, India, Pakistan, Japan) are expected to increase from 2.757 million in 2005 to 6.17 million in 2030.

ETIOLOGY
Pathogenesis of Parkinson’s disease is not clearly known.3, 6, 8 The main mechanism of toxicity that is received in the pathogenesis of the Parkinson’s is damage of cell from oxiradicals.

Dopamine has ability to generate free radicals from autooxidation and from the metabolism of MAO.10, 13, 14 Several anti oxidative mechanism are present inside and outside of the neurons to limit any damage that might be produced by the attack of free radical but one possibility is that this production is overwhelmed and damaged in Parkinson’s. Chronic infection, programmed cell death and excitotoxicity are also the etiology of Parkinson’s.11 Neurotoxins can also damage the Substantia nigra like MPTP, Cyanide, Manganese13, 14, 15

ABSTRACT
Parkinson’s is a neurodegenerative disease. It is characterized mainly by the movement disorders like bradikinesia, postural instability, rigidity and resting tremors and an impairment of postural balance. It is a progressive condition causing degeneration of Dopaminergic neurons in the substantia nigra resulting in the progressive loss of dopamine containing neurons which is a common signs of aging, so it is a problem which is started commonly at the age of 60. It has been suggested that oxidative stress plays a role in the etiology and progression of PD. For instance, low levels of endogenous antioxidants, increased reactive species, augmented dopamine oxidation, and high iron levels have been found in brains from PD patients. In laboratory the parkinsonism is induced by chemicals (MPTP, Mangnese, Cyanide, Reserpine, Carbon mono oxide) and neuroleptic drugs. Flavonoids (Hesperidins, Quercitin and Hesperetin) are the phenolic constituents obtained from plant origin having potential antioxidant property have been suggested to play an important role in the prevention of neurodegenerative diseases, including Parkinson’s and Alzheimer’s diseases. Many vitamins like A, B, C, E have also shown protective effects against oxidative-induced neuronal death. In this paper, we have reviewed about the mechanisms by which Hesperetin and Vitamin B6 antioxidants can produce protection in PD.

KEYWORDS: PD, Flavonoids, Substantia nigra, Antioxidant.
PATHOPHYSIOLOGY
The primary defect in the Parkinson's is the loss of the neurons present in the Substantia nigra pars compacta which provide dopaminergic innervations to the striatum (putamen and caudate). In this stage there is about 80% loss of dopamine present in striatal. This will lead to loss of neuron from the Substantia nigra which lead to replacement to dopamine could restore its function. Dopamine is a catecholamine which is synthesised in the terminal of Dopaminergic neuron. Tyrosine is firstly 3 hydroxylated and then decarboxylated to form Dopamine. Then dopamine is beta hydroxylated to form Norepinephrine which is n-methylated in chromaffin to form Epinephrine. Dopamine is stored in vesicles, this storage decreases intraneuronal metabolism of these transmitters and their leakage outside the cell. The vesicular amine transporter (VMAT2) mainly appears to be driven by pH and potential gradients that are established by an ATP-dependent proton translocase. For every molecule of amine taken up, two H⁺ ions are extruded. Monoamine transporters are relatively promiscuous and transport dopamine, Norepinephrine, epinephrine, and serotonin; Reserpine inhibits monoamine transport into storage vesicles and ultimately leads to decrease of catecholamine from sympathetic nerve endings and in the brain. Several vesicular transport cDNAs have been cloned; these cDNAs reveal open reading frames predictive of proteins with 12 transmembrane domains. There are mainly two neuronal membrane transporters for catecholamines, The Norepinephrine transporter (NET) mentioned earlier and the dopamine transporter (DAT); The NET is also present in the adrenal medulla, the liver and the placenta, whereas the DAT is present in the stomach, pancreas and kidney. Dopamine is release by the opening of voltage gated calcium channel.

Two enzymes are responsible for metabolism of Dopamine- Mono amino oxidase (MAO) and Catechol-O-methyl transferase (COMT). Catabolism is the main Mechanism for deactivation of Dopamine. It involves multiple pathways like oxidative deamination by MAO and COMT and conjugation by sulfotransferase and glucuronidase.

Neural Mechanism of Parkinsonism
The loss of dopaminergic input to the neurons of the neostriatum gives rise to the clinical features of PD. The basal ganglia can be viewed as a modulatory side loop that regulates the flow of information from the cerebral cortex to the motor neurons of the spinal cord. The neostriatum is the principal input structure of the basal ganglia and receives excitatory glutamatergic input from many areas of the cortex. Most neurons within the striatum are projection neurons that innervate other basal ganglia structures. A small but important subgroup of straital neurons consists of interneuron that connects neurons within the striatum but do not project beyond its borders. Acetylcholine and neuropeptides are used as transmitters by this straital interneuron. The outflow of the striatum proceeds along two distinct routes, termed the direct and indirect pathways. The direct pathway is formed by neurons in the striatum that project directly to the output stages of the basal ganglia, the substantia nigra pars reticulate and the globus pallidus interna these, in turn, relay to the ventroanterior and ventrolateral thalamus, which provides excitatory input to the cortex. The neurotransmitter of both links of the direct pathway is Gama amino butyric acid (GABA), which is inhibitory, so that the net effect of stimulation of the direct pathway at the level of the striatum is to increase the excitatory outflow from the thalamus to the cortex. The indirect pathway is composed of straital neurons that project to the globus pallidus externa. This structure, in turn, innervates the sub thalamic nucleus (STN), which provides outflow to the SNpr and GPe output stage. As in the direct pathway, the first two links the projections from striatum to GPe and GPe to STN use the inhibitory transmitter GABA; however, the final link the projection from STN to SNpr and GPe is an excitatory glutamatergic pathway. Thus the net effect of stimulating the indirect pathway at the level of the striatum is to reduce the excitatory outflow from the thalamus to the cerebral cortex.

TREATMENT
Drugs which are used in the Parkinson's disease are known as Antiparkinson's drug. The main drugs which are used in Parkinson's are:
- **DOPAMINE PRECURSOR**- Levodopa.
- **PERIPHERAL DECARBOXLASE INHIBITOR**- Carbidopa, Benserazide.
- **DOPAMINE RECEPTOR AGONIST**- Bromocriptine, Pergolide, Ropinirol, Pramipixoole.
- **SELECTIVE MAO-B INHIBITOR**- Salagilnine, Rasagiline.
- **CATECHOL-O-METHYL TRANSFRASE INHIBITOR**- Tolcapone, Entacapone.
- **ANTIMUSCARINIC AGENT**- Benzotropine, Procyclidine, Biperiden.
- **DOPAMINE FACILATOR**- Amantadine.

HESPERETIN IN THE TREATMENT OF PARKINSONS
Hesperetin is a Flavonoids. Flavonoids are a group of polyphenolic compounds of low molecular weight (200–600g/mol) that present a common benzo-g-pyrene structure. They are further sub-categorized into various subclasses including flavones, flavonols, flavanones, isoflavonones, anthocyanidins and catechins. The average human diet contains a considerable amount of flavonoids mainly consumed through ingestion of fruits and vegetables (i.e. onion, broccoli, green pepper and tomato), soybeans and different herbs. Among the classes of flavonoids, flavanones have been defined as citrus flavonoids due to their almost unique presence in citrus fruits. They are powerful antioxidants against free radicals and are described as...
free-radical scavengers. This activity is attributed to their hydrogen-donating ability. Indeed, the phenolic groups of flavonoids serve as a source of a readily available “H” atoms such that the subsequent radicals produced can be delocalized over the flavonoid structure. Free radical scavenging capacity is primarily attributed to high reactivities of hydroxyl substituents that participate in the reaction as shown below.\[^{25, 26}\]

\[
F\text{-OH+R} \rightarrow F\text{-O} + RH
\]

Flavonoids inhibit lipid peroxidation in vitro at an early stage by acting as scavengers of superoxide anion and hydroxyl radicals.\[^{26, 29}\] They terminate chain radical reaction by donating hydrogen atom to a peroxy radical, thus, forming flavonoids radical, which, further reacts with free radicals thus terminating propagating chain. So Hesperetin reduce the autooxidation in the brain which is a beneficial effect in the PD. It may protect the breakdown of dopamine in the Nigrostriatal area of the brain.\[^{30, 31}\]

**PYRIDOXINE IN THE TREATMENT OF PARKINSONS**\[^{32, 33}\]

Vitamin B6 (pyridoxine) is required for the synthesis of neurotransmitters serotonin and norepinephrine and for myelin formation.\[^{32}\]

Pyridoxine deficiency in adults principally affects the peripheral nerves, skin, mucous membranes, and the blood cell system. In children\[^{33}\], the central nervous system (CNS) is also affected. Deficiency can occur in people with uremia, alcoholism, cirrhosis, hyperthyroidism\[^{34, 35, 36}\], malabsorption syndromes, congestive heart failure (CHF), and in those taking certain medications.\[^{31, 37}\]

Mild deficiency of vitamin B6 is common. Major sources of vitamin B6 include: cereal grains, legumes, vegetables (carrots, spinach, peas), potatoes, milk, cheese, eggs, fish, liver, meat, and flour.\[^{32, 36}\] Pyridoxine is frequently used in combination with other B vitamins in vitamin B complex formulations.\[^{36, 37}\]

Vitamin B6 is a water-soluble vitamin that exists in three major chemical forms: pyridoxine, pyridoxal, and pyridoxamine. It performs a wide variety of functions in your body and is essential for your good health.

**Vitamin B6 helps the body**

- Build protein
- Make antibodies, which is a key to a strong immune system
- Make hormones
- Make red blood cells and keep nerve tissue healthy.\[^{37, 38}\]

**Vitamin B6** in physiologically active form is the prerequisite for the production of dopamine. Deficiencies and disorders in B vitamin and folate metabolism have thus been implicated in many neurological disorders, including PD and studies as early as the 1970’s were directed at demonstrating the effects of supplementation—initially with discouraging results.\[^{39, 40}\]

As our understanding of the role of the toxic amino acid homocysteine grew, however, more targeted and mechanism-based studies became possible. Homocysteine levels are closely related to folate, vitamin B6, and vitamin B12 status and elevated homocysteine is found in cardiovascular disease and a variety of neurological and psychiatric disturbances, including PD. Paradoxically, levodopa treatment of PD can itself lead to elevations in homocysteine, potentially worsening the condition. This has prompted researchers to recommend B complex supplements in those taking the drug.\[^{32, 41}\]

**CONCLUSION**

Hesperetin and Pyridoxine both are potent antioxidant. Hesperetin inhibit the oxidation in the brain areas and as well as protect the breakdown of Dopamine and Pyridoxine is required for the synthesis of Neurotransmitter and also required for the synthesis of dopamine. So by using the Hesperetin and Pyridoxine in combination we can minimize the symptoms and risks in PD and this may show a beneficial treatment in the PD.

**REFERENCES**


