Ethnopharmacological aspects of *Psiduim guajava* And *Madhuca Indica*

Mudita Mishra[1], Santosh Kumar Verma[2],

Faculty of Pharmaceutical Sciences, Motherhood University[1]

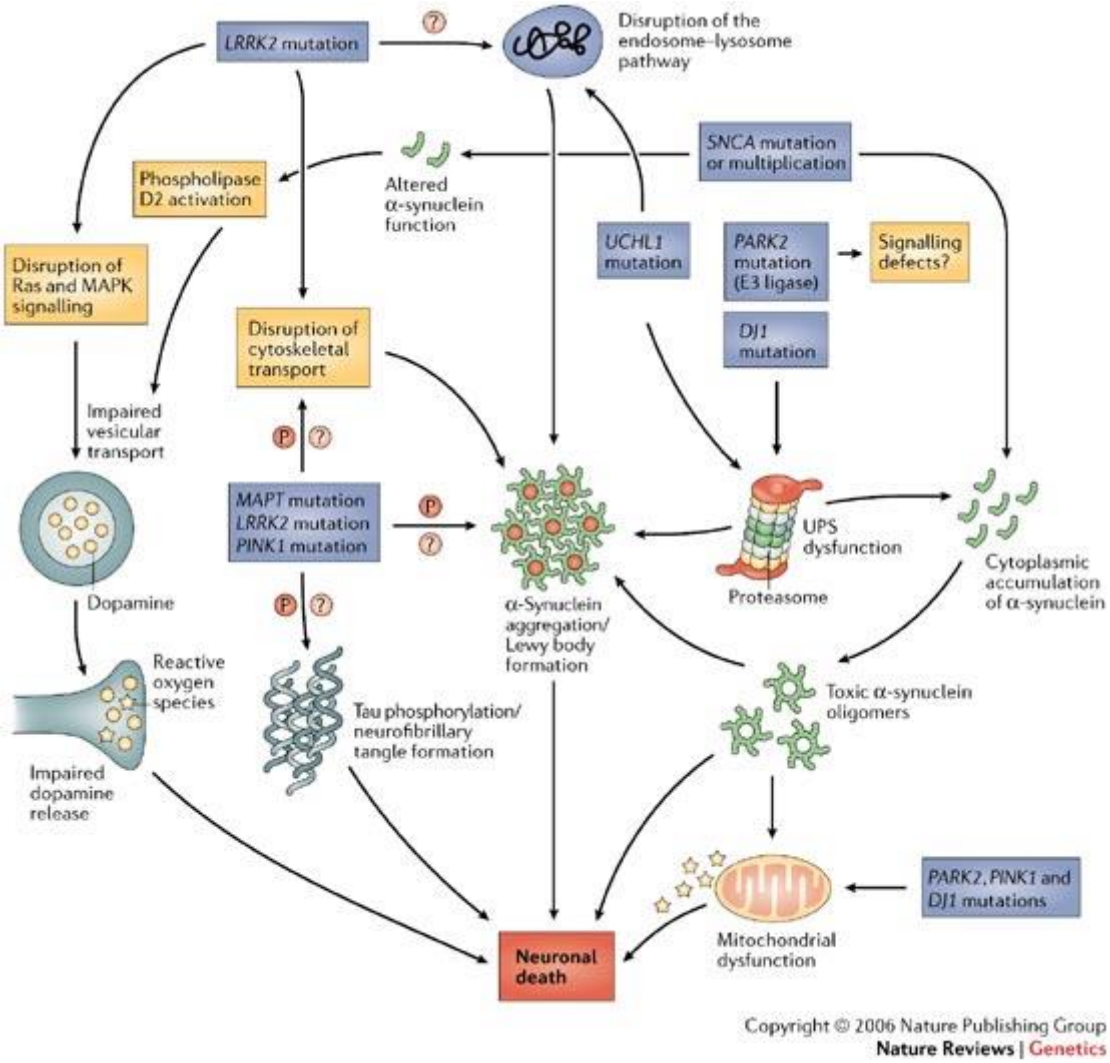
Abstract- Parkinson disease is one of the major movement related disoreder in elderly patients. The symptoms are rigidity, tremor, bradykinesia followed by akinesia and postural abnormality. The current scenario of synthetic drug treatment gives symptomatic relief and the patient's quality of life gets increased. Amphetamine and methamphetamine are the metabolite of Selegeline (MAO B inhibitor) causes side effect like Anxiety and Insomnia and number of side effect like hallucinations, Diarrhoea, postural hypotension. The drug *Madhuca indiaca* has property to inhibit (neuronal NOS) nitric oxidase synthase inhibitor, one of the major enzyme to produce oxidative stress by the mechanism of apoptosis, it also suppress MDA level, a marker of oxidative stress, while *Psiduim guajava* have polyphenolic compounds that has important role to suppress oxidative stress, that has key role in the Pathogenesis of Parkinson Disease. This review suggests the opinion of different authors on ethanopharmacology of *Psiduim guajava* and *Madhuca indica.* It has protective role in pathogenesis of Parkinson's Disease.

Keywords- PD- Parkinson Disease, Nnos-Neuronal nitric Oxide Synthase, MAO- Mono Amino Oxidase, MDA –Malonaldialehyde.

1.1 Introduction

Parkinson disease is one of the major life style affecting disorder in which there is imbalance between dopaminergic and cholinergic neuron in substantia nigra and Pars Compacta region of brain, which is responsible for movement and control of the body. The symptoms are shown when 50% of nigral dompamiergic neuron and 50% of straital neurons are lost.[1] The term Parkinson Disease was first described by James Parkinson in 1817 as "Shaking Palsy".[2] It has been widely reported that oxidative stress plays a pivotal role in the neurodegeneration associated with PD.[3] The neuronal inflammation induces glial cell activity in SN of the brain which is a well known characteristic of PD pathology. Oxidative stress is known to damage lipids, proteins and DNA along with decreased superoxide dismutase (SOD), catalase, and glutathione levels. Oxidative stress and inflammatory pathways ultimately leads to neuronal death. The etiology of PD results from defect in mitochondrial function, dysregulation of brain iron, inflammatory responses and abnormalities of energy metabolism.[4] The life expectancy of adequately treated patient increases and good functional mobility can be maintained for many years.[5] The existing drug treatment for Parkinson disease like Seligeline (MAOB inhibitor) causes anxiety and insomnia due formation of metabolites amphetamine, methamphetamine,The quality of life of patients may be increase and only symptomatic relief may be found.[6] Parkinson disease is believed to be caused mainly by environmental factors. The neuronal damage is caused by-

Protein misfolding and aggregation, Excitotoxicity, Oxidative stress and Apoptosis. About 1million Americans have Parkinson's disease. The total cost investment to be estimated nearly $ 25 billion/ year for treatment of Parkinson disease. About one million Americans have Parkinson's disease. [7]



Pathogenesis of Parkinson's disease [8]

1.1.1 Protein misfolding and aggregation

Misfolding means the adoption of abnormal conformations, by certain normally expressed proteins such that they tend to form large insoluble aggregates. The misfolding often means that hydrophobic residues that would normally be buried in the core of the protein misfolded conformations can be generated spontaneously at a low rate throughout life, so that aggregates accumulate gradually with age. In the nervous system, the aggregates often form distinct structures, generally known as *amyloid deposits*, that are visible under the microscope and are characteristics of neurodegenerative disease.[9] Although the mechanisms are not clear, such aggregates, or the misfolded protein precursors, lead to neuronal death. The brain possesses a variety of protective mechanisms that limit the accumulation of such protein aggregates.[10] The main ones are the production of '*chaperone*' proteins, which bind to newly synthesised or misfolded

proteins and encourage them to fold correctly, and the '*ubiquitination*' reaction, which prepares proteins for destruction within the cell.[11]

Excitotoxicity

Glutamate is highly toxic to neurons. Calcium overload is the essential factor in excitotoxicity. Glutamate activates NMDA, AMPA and metabotropic receptors. Activation of AMPA receptors depolarises the cell, which unblocks the NMDA channels, permitting calcium ion entry.[12] Depolarisation also opens voltage-activated calcium channels releasing more glutamate. Metabotropic receptors cause the release of intracellular Calcium ion from the endoplasmic reticulum. Sodium ion entry further contributes to calcium ion entry by stimulating calcium and sodium ion exchange. Depolarisation inhibits or reverses glutamate uptake thus increasing the extracellular glutamate concentration.[13]

1 . 1 . 2 Oxidative stress

The brain has high energy needs, which are met almost entirely by mitochondrial oxidative phosphorylation, generating ATP at the same time as reducing molecular oxygen to dihydrogen oxide. Under certain conditions, highly reactive oxygen species, i.e. hydroxyl free radicals and hydrogen peroxide, may be generated as side products of this process.[14] Oxidative stress is the result of excessive production of these reactive species. They can also be produced as a by-product of other biochemical pathways, including nitric oxide synthesis and arachidonic acid metabolism. Defence mechanisms are in the form of enzymes such as *superoxide dismutase* (SOD) and *catalase*, as well as antioxidants such as ascorbic acid, glutathione and α-tocopherol (vitamin E), which normally keep these reactive species in checks.[15]

1.1.3 Apoptosis

Apoptosis can be initiated by various cell surface signals. The cell is systematically dismantled, and the shrunken remnants are removed by macrophages without causing inflammation. Many different signalling pathways can result in apoptosis, but in all cases the final pathway resulting in cell death is the activation of a family of proteases. [16]

Table 1.2 Some major anti Parkinson drugs with their mode of action, site of action and their biological effects.[17]

S. no.	Compound	Mode of action	Site of action	Effects
1	Apigenin	Free radical scavenging property	Substantia nigra of brain Region	Increase SOD, CAT & GSH.
2	Luteolin	Neuroprotection	Substantia nigra of brain region	NF-KB inhibitor, Reduce oxidative stress cause inflammation & apoptotic protein
3	Pramipexole	Dopamine agonist	Striatal dopamine receptor	D3 receptor agonist
4	Rasagaline	Selective MAO- B inhibitor	triatal region of brain	lectively and irreversibly inhibit MAO B
5	Tolcapone	COMT inhibitor	Presynaptic brain region	hibit central and peripheral conversion of COMT
6	Levodopa	Dopamine precursor	Presynaptic terminal of dopaminergic neuron in straitum	Conversion of levodopa to dopamine by decarboxylation
7	7- Nitroindazole	Neuronal NOS-inhibitor	Nigrostriatal pathway of striatal neurons	Phosphorylation of DARPP-32 which involved in neuronal activation.

1.2.1 *Psidium guajava* (Myrtaceae) is a small evergreen sub deciduous tree. It is found in tropical and subtropical areas. Guava is rich in tannin, phenols, flavanoids, saponins, carotenoids, vitamins, fiber and fatty acids. Guava fruit is rich in Vitamin-C. **The leaves specially contain polyphenolic compound having ability to reduce pathways involved to generate oxidative stress, that play a key role in pathogenesis of Parkinson disease**. The leaves contain essential oil with the main components viz *α*-pinene, *β*-pinene, limonene, menthol, terpenyl acetate, isopropyl alcohol, longicyclene, caryophyllene, *β*-bisabolene, caryophyllene oxide, *β*-selinene, cardinene and curcumene. Curcumene has anti-inflammatory effect that reduce neuroinflammation a key factor in pathogenesis of PD.

1.2. 2 Plant Profile of *Psidium gvajava*[18]

Common name: Guava, Amruud.

Family plant: Myrtaceae.

Related species: *P. acutangulum*; *P. densiconum*; *P. guianense.*

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Plant parts used: The leaves are mainly used, sometimes the unripe fruit, bark or roots.

Active ingredients: Numerous tannins and other phenolic compounds have been identified from *P. guajava*, of which **amritoside** is of particular importance. Amritoside is a glycoside (gentiobioside) of ellagic acid. Another biologically interesting compound in the plant is guiajaverin, a glycoside (arabinopyroside) of **quercetin**. The leaves also contain essential oils and **triterpenoids.**[19]

Pharmacological effects: Ellagic acid is a known intestinal astringent and haemostatic which explains the therapeutic value of the plant against diarrhoea and dysentery. The tannins are generally of value because of their vasoconstricting effects and their ability to form a protective layer on the skin and mucosa. These effects, together with proven antibacterial and antifungal activity, result in effective treatment of both internal and external infections. **Quercetin** (and its glycosides) undoubtedly also contribute to the efficacy of the medicine, because it is a known **antioxidant with anticarcinogenic**, **anti-HIV and antibiotic effects**. Hypoglycaemic effects have been documented.[20]

Medicinal use: Guava leaves are commonly used in South Africa as a remedy for diarrhoea. The leaves are also used for several other ailments, including diabetes, fever, cough, ulcers, boils, and wounds.

1.2.3 CNS activity: The leaves of the guava tree in decoction is used for spasms, cerebral affections. The plant extracts exhibited mostly dose-dependent antinociceptive effects in chemical and thermal tests of analgesia. The extracts also produced dose-dependent prolongation of pentobarbitone-induced sleeping time. Tincture is also used for rubbing into the spine of children suffering from convulsions. It has also been used as a tonic in psychiatry CNS-depressant activity was exhibited by the extract which potentiated the phenobarbitone sleeping time in mice.[21]

1.3.1 *Madhuca indica* (Sapotaceae) used to treat nerve disorder, cough and burning sensation. The bark of trunk contain lupeol acetate, quericitin, dihydroquericitin,beta amyrin acetate, alpha-spinasterol. The **bark of**

drug show DPPH (1,1-diphenyl,2-picryl hydrazyl) radical scavenging activity, nitric oxide radical scavenging activity, super oxide anion radical scavenging activity, inhibition of hydroxy radical, and lipid peroxidation activity.[22]

1.3.2 Plant profile of *Madhuca indica*

Madhuca indica a plant of Indian origin having tremendous therapeutic and potential use but due to unawareness of people it is not fully utilized. It is hidden from the eyes of the researchers and other botanist.

Local names: English (Indian butter tree), Hindi (Mahua, Mohwa, mauwa),

Habitat and Distribution

The Madhuca Indica commonly known as Mahua is an important economic plant growing throughout the subtropical region of the indo-Pakistan subcontinent. Large numbers of Mahua trees are found in the state of **Dehradun,** Saharanpur, Chota Nagpur, Siwaliks, Uttar Pradesh, Madhya Pradesh, Orissa, Chhattisgarh, Jharkhand, Gujarat, Andhra Pradesh, Maharashtra, Bihar, West Bengal, Deccan and Karnataka.[23]

Botanical Description and Identification Features

The bark thick dark colored cracked, inner bark dark red, milk, trunk short, branches numerous ridges are found.

Active constituent present in different parts of madhuca indica are **bark contain Flavonoids,** Triterpene, Sterol Latex Soluble Resin, Insoluble Resin Leaf contain Moisture, Organic Matter, Minerals, Potash, Phosphoric Acid, Silica, Alkaloids, Flavonoids, Protobasic Acid. Flower contains Carotene, Ascobic acid, Thiamine, Riboflavine, Niacine, Folic Acid, Biotine, Inositole. Ripe Fruit contain Protein, Fat, Carbohydrates, Minerals, Calcium, Phosphoras, iron, Carotene, Ascorbic Acid.

Parts vise use of *Madhuca indica*

Medicinal Properties Leaf are Ecezyma, Wound Healing, Anti Burns, Bone Fracture Oil Emollient, Skin Disease, Rheumatism, Headache, laxative, Piles, Hemorrhoids, Emetics, Anti Earth worm. Fruit are sweet and used as Refrigerant, Aphrodisic, Tonic, Bronchitis, Astringent, Anti Ulcer, Acute and Chronic Tonsillitis, Pharyngitis. Bark is used in Rheumatism, Ulcer, Inflammation, Bleeding, Spongy Gums, Tonsillitis, Diabetic, Stomach Ache, Anti Snake Poisoning, Astringent, Emollient. Fruits are used in preparation of Liquor, Jelly, Sweet Syrup, Expectorant Increase the production of milk in woman, Stimulant, Diuretics, Anthelmentic, Strangury, Verminosis, Hepatoprotective. Gastropathy.[24]

1.3.3 Antioxidant Activity: Oxidative stress is produced during normal metabolic process in the body as well as induced by a Varity of environmental and chemical factor, which cause a generation of a various reactive free radical. [25]

and subsequent change in DNA and lipids. The property of ethanolic bark extract of *Madhuca Indica* implies that it is capable of donating hydrogen atom in a dose dependent manner. The high content of phenolic compounds in the extract may be a contributing factor towards antioxidant activity because the phenol compounds are known to have direct antioxidant property due to the presence of hydroxyl groups, which can function as hydrogen donor**. The reducing capacity of oxidative stress may serve as a significant**

indicator of its potential antioxidant activity. The anti oxidant potency of any drug depends upon the two mechanism first to prevent the oxidation by oxidizing itself or second by creating a layer of protection over the neuron.[26] Patel *et al* **(2019)** suggested that the water extract prepared by Microwave Assisted Extraction method has better anti-infective activity, and its activity was further compared with hydroalcoholic extract prepared using the same extraction method against five different pathogenic bacteria. Both these extracts could attenuate virulence of *P. aeruginosa*, *S. aureus*, *Serratia marcescens*, and *Chromobacterium violaceum*, towards *C. elegans*.[27] Borah *et al*. **(2019)** reported that, total of twenty seven compounds were identified in the leaf essential oil. The major compounds were α-terpinyl acetate (23.57 %), trans-caryophyllene (17.65 %), nerolidol (12.16 %), α-cadinol (6.71 %), α-copaene (6.5 %) and minor compounds identified were α-humulene (3.92 %) and (-)-caryphyllene oxide (3.66 %) were found.[28] Vasconcelos A. G. *et al.* **(2017)** suggested that lycopene-rich extract from red guava has beneficial effect on acute inflammation, offering protection against the consequences of oxidative stress by downregulating inflammatory mediators and inhibiting gene expression involved in inflammation,[29] while Kumar D. *et al.* **(2016)** reported synergistic effect of a polyherbal formulation (PHF) of *Allium sativum* , *Eugenia jambolana, Momordica charantia* , *Ocimum sanctum*, and *Psidium guajava* on p-glycoprotein (Pgp) of intestine. PHF pretreatment downregulated the expression of intestinal Pgp and this downregulated intestinal Pgp would result in decreased functional activity. In addition, this downregulated Pgp expression might affect the bioavailability of antidiabetic Pgp substrate drugs.[30] Hydroalcholic extracts of *Psidium guajava* leaves prepared by three different extraction methods were compared with respect to their anti-infective activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* in the nematode host *Caenorhabditis elegans*.[31] Joseph L. *et al*. **(2016)** isolated the active principles by column chromatography and characterize the isolated compound by chemical tests and IR spectroscopy. The phytochemical investigation identified the presence of glycosides, flavanoids, alkaloids, saponins, and vitamin, tannins, which showed phytoconstituents in various proportions in aqueous and alcoholic extracts of seeds, fruit pulp and leaves of ***Psidium guajava***.[32] The review of *Smeeta M. et al. **(2016)*** reported that *Madhuca indica* (Sapotaceae) has shown antioxidant, anti-inflammatory, analgesic, anti-diabetic and hepatoprotective potential. It has been traditionally used as laxative, tonic, anti-burn, anti-earthworm, wound healing and in headache.[33] Apart from this Ojha Shreesh *et al.* **(2015)** suggested that Rotenone cause significant reduction in antioxidants compounds like, catalase, superoxide dismutase, glutathione. It also raises MDA level by lipid peroxidation. Apart from it neruroinflammatory mediators like cylooxygenase-2 NOs (nitric oxide synthase) also raises.[34] Ojha. *et al.* **(2015)** also revealed ROT injection causes loss of dopamine level and increases number of activated microglia and astrocytes in substantia nigra pars compacta region of brain.[35] Wang F. *et al.* **(2014)** suggested that the budding leaves of *Psidium guajava* contained huge amounts of soluble polyphenolics (qurectin) and having antioxidant property by scavenging DPPH free radical,[36] while *Jamal F. et al.* **(2014)** describes the purification of a bioinsecticidal trypsin inhibitor from *Madhuca indica* seeds and its effect on developmental physiology of the polyphagous insect *H. armigera* through a series of *in vitro* and *in vivo* experiments.[37] Akshatha K. N. *et al.* **(2013)** suggested that Ethnomedical uses having significant antipyretic, hepatoprotective, anti-inflammatory, analgesic, antitumor,

anti-progestational, anti-estrogenic and wound healing activity.[38] Traditionally *M. longifolia* bark is used in rheumatism, ulcers, bleedings and tonsillitis. Chen Xin *et al.* **(2012)** suggested that rotenone model cause significant decrease in substantia nigral dopaminergic neuron and microglial activation.[39] There is also enhanced *tnf alpha* (tumor necrosis factor) and *interlukin-1beta* that cause degeneration of substantial nigral region of brain that has important role in movement.[40] Nor and Yatim *et al.* **(2011)** reported that *Pink* guava puree supplementation can decrease lipid peroxidation and increase antioxidant enzyme activity such as catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase in spontaneous hypertensive rat's blood. Shekhwat N. *et al* **(2010)** also evaluated anti-inflammatory, analgesic and anti-pyretic properties of *Madhuca indica* by using methanolic extract the phytochemicals flavonoids, cardiac glycosides,saponins, steroids, tannins and terpenes.[41] Abubakar *et al*. **(2009)** suggested antimicrobial especially antibacterial effect of crude leaves extract. The gram negative bacteria were less susceptible to the effect of crude drug.[42] Jankovic J. *et al* **(2007)** suggested the clinical characteristics of PD with emphasis on those feature that differentiate the disease from other parkinsonian disorder. The genetic mutation, neuroimaging abnormalities and other test are potential biomarker by which quality of diagnosistical procedure and indetification of person at risk of PD.[43]

Conclusion-

The Parkinson disease is resulting from imbalance between cholinergic and dopaminergic neuron in substantia nigra pars compacta region of brain. The PD manifestation should be essential to study on broad spectrum. There is no definitive test for diagnosis of PD. Neuroimaging abnormalities, genetic mutation or variants and other potential biomarker helpful to identify PD. The conventional approach for the drug discovery and development procedure is costly, time consuming, beside it a large number of volunteers are required for clinical trial. On contrary isolation of active compound from natural sources is comparatively easier, less time consuming in comparison to synthesis of drug in laboratory. Curcumin, flavonoid rich products like blueberries, green tea, jasmine tea red wine containing anthocyne lowers the risk of PD. Phytochemical sources have been popular, partly because of their low cost and minimal side effects. This review article suggests the opinion of different authors on ethanopharmacology of *Psiduim guajava* and *Madhuca indica.* On the basis of chemical constituents present in both plants has protective role in pathogenesis of Parkinson's Disease. In order to establish these predictions their exhaustive study like In vivo and vitro study will be need.

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