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Review for Herbal Design in Treatment of Parkinsons Disease"

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Abstract: *Parkinson's disease (PD) is an age-related neurodegenerative disorder that pathological feature is basically related on the progressive degradation of dopamine production in substantia nigra. The clinical manifestation includes bradykinesia (especially having difficulties in initiating movement), hypokinesia (lose of facial expression), rigidity, rest tremor (pill-rolling movement of the forearm) and non-motor features including depression, psychosis autonomic dysfunction .[1].*

Keywords: Parkinson's

I. INTRODUCTION

Parkinson's disease (PD) is an age-related neurodegenerative disorder that pathological feature is basically related on the progressive degradation of dopamine production in substantia nigra. The clinical manifestation includes bradykinesia (especially having difficulties in initiating movement), hypokinesia (lose of facial expression), rigidity, rest tremor (pill-rolling movement of the forearm) and non-motor features including depression, psychosis autonomic dysfunction .[1]

Parkinson's disease (PD) is a neurodegenerative disease with prominent motor impairments that include resting tremor, rigidity, bradykinesia and postural abnormality. Epidemiological studies show that the prevalence of PD in industrialized countries is usually estimated at 0.3% of the whole population and at ~1% in people over 60 years of age[2]

On the contrary, prevalence rate and incidence rate is slightly lower in Asian countries. It was reported that a standardized all-age prevalence of was 51.3 to 176.9 per 100,000 and the standardized incidence rates were 8.7 per 100,000 person-years[3]

The prevalence increases progressively along with the age. According to the cross-sectional study of United Kingdom in 2000, the prevalence was only 20/100,000 in below 50 years old, but 342/100,000 in sixties and 1265/100,000 in over eighties[4]

Because of diversity of the studies with different population and methodology, the prevalence rate and incidence varies broadly in difference studies. In the European countries, crude prevalence rate estimates ranged from 65.6 per 100,000 to 12,500 per 100,000 and annual incidence estimates ranged from 5 per 100,000 to 26 per 100,000[5]

A previous study of the Chinese population in Hong Kong reported that the prevalence among those aged ≥55 years was 0.5% [6]

Despite various advances in the understanding of PD, pharmacological treatment of PD by Western medicine is mainly for symptom management. Among different pharmacological treatments, levodopa remains the most efficacious and is still the mainstay of therapy.[7]

(TCM) has been used for centuries to treat conditions such as trembling of hands and shaking of head that correspond to the modern term "PD". Up to the present, Chinese herbal medicine remains very popular for management of PD in Asian countries such as China, Korea and Japan. In a study done by Rajendran et al., it was observed that 40% of patients with PD use at least one form of alternative therapy[8]

Parkinson's disease (PD) is a common, chronic, and progressive neurodegenerative disorder resulting from the death of the dopamine containing cells in substantia nigra and can cause significant disability and decreased quality of life.[9]

However, China faces the largest number of patients with PD because it has one-fifth of the world's population (1.34 billion in 2011). Therefore, the burden of PD prevention and treatment in China is much higher than that in the developed countries. Fortunately, there is one important characteristic of China's national medical system, that is,

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traditional Chinese medicine (TCM) and western medicine complement and cooperate with each other, being responsible for the health care of Chinese people together[10]

With the use of a standard 10-herb formula, the investigators demonstrated a significant reduction in tremor in patients. Unlike Western medicine, TCM diagnoses of PD fall into different categories according to the patient's fundamental constitution. According to TCM theory, PD is a condition that represents a depletion of energy, especially in the spleen and stomach. Herbal drugs have therefore been used in the treatment of PD under the general guideline of "strengthening the spleen and regulating the stomach". "Jia Wei Liu Jun Zi Tang" (JWLJZT) is an ancient formulation developed by a TCM doctor Zhang Lu in 1695 AD, with the specific function of tonifying the energy (Qi) of spleen and stomach; it has been used to treat symptoms that are now defined as PD In this study, we determined the effect of this formulation of Chinese herbal medicine on the symptoms and quality of life of patients with idiopathic PD[11]

In modern time, TCM therapy is still widely used for PD treatment, and the application covers about three-fourths of the areas in China. In the past decades, several compressive and systematic reviews have focused on TCM for PD treatment [8–10]. However, there is still a lack of reliable scientific evidences for the application of TCM therapy on PD. Recently, some high-quality trials have been published in China[12]

Parkinson's disease is a chronic midbrain Substantia nigra neurological disorder. Dopaminergic neuron is gradually degenerated and causes reduction of the dopaminergic level in Striatum. Tremor, dyskinesia, myotonia and so on are the signs Watched mostly in the individual suffering from the disease[13]

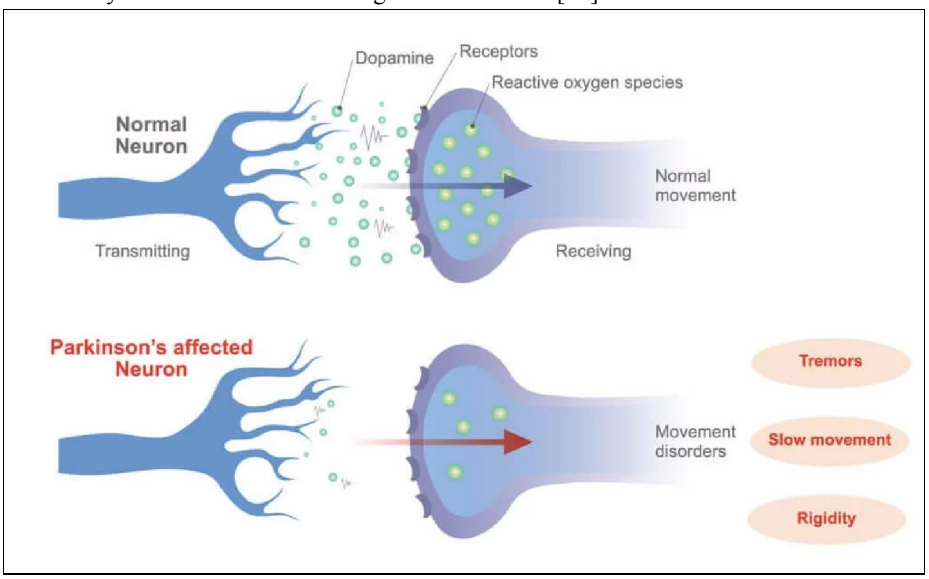

Fig no-01

Parkinson's disease (PD) is a progressive age-dependent neurodegenerative syndrome, characterized by four main symptoms: tremor, rigidity, bradykinesia and impairment of balance. The classical pathological findings are the presence of Lewy bodies in the substantia nigra, and loss of nerve cells in portions of its ventral tier (Calne, 2001). The selective depletion of dopaminergic inputs to the striatum is the most important neurochemical characteristic of the PD (Ehringer and Hornykiewiez, 1998.The objective of the present paper is to review the scientific information on medicinal plants and their bioactive compounds with potential for PD treatment. A systematic review was carried out through a recent database, the Natural Products Alert (NAPRALERT-SM) besides the following other sources: Biological Abstracts, MEDLINE and WEB of SCIENCE.The current therapeutic approach consists mainly on either increasing the dopaminergic neurons activity or inhibiting the cholinergic effects to the striatum. Protective and/or rescuing treatments have also been proposed trying to suppress the possible causes of dopaminergic neurons apoptosis such as: oxidative stress, age dependent mitochondrial dysfunction, neurotoxins, decrease of neurotrophic factors, excitotoxicity, disturbances of calcium homeostasis, immunologic and infectious mechanisms (Naoi and Maruyama, 2001). Among these, oxidative stress has been suggested as playing a major role. Various factors have been recognized to increase oxidative stress in nigral dopaminergic neurons such as dopamine oxidation generating reactive oxygen

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species (ROS) and cytotoxic dopamine quinone; increased iron deposition; and reduced antioxidative capacity (Gotz et al., 1990). [14-17]

AIM & OBJECTIVE

AIM:-To Study the Herbal drug in treatment of Parkinson's disease

OBJECTIVE:-

- To study Antioxidant effects Herbal drugs with antioxidant properties can help reduce oxidative stress in the brain, which is associated with Parkinson's disease
- To study Anti-inflammatory effects Herbal remedies may target inflammation in the brain, which is believed to play a role in the development and progression of Parkinson's disease
- To study Side effect management: Herbal drugs may be used to manage side effects of conventional Parkinson's medications, such as dyskinesias or gastrointestinal issues.
- To study Herbal drugs may aim to alleviate the motor symptoms of Parkinson's disease, such as tremors, bradykinesia, and rigidity.
- To study Some herbal compounds may have neuroprotective properties, potentially slowing down the progression of the disease or protecting against further damage to dopaminergic neurons

COMMON SYMPTOMS[18-22]

- Gradual loss of automatic movement, which may lead to decreased blinking, decreased frequency of swallowing and drooling
- A stooped, flexed posture with bending at the elbows, knees and hips
- Unsteady walk or balance
- Depression or dementia
- Muscle rigidity or stiffness of the limbs – most common in the arms, shoulders or neck
- Gradual loss of spontaneous movement, which often leads to decreased mental skill or reaction time, voice changes, decreased facial expression, etc.

Fig no-02

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PATHOPHYSIOLOGY[23-25]

Parkinson's disease is characterized by a loss of dopaminergic neurones in the substantia nigra of the basal ganglia.3 A decrease in dopamine production results in facilitation of the indirect pathway because of a lack of D1 facilitation of the direct pathway and of D2 inhibition of the indirect pathway. This dopamine is associated with increased activity of inhibitory nuclei in the basal ganglia (using the neurotransmitter g-aminobutyric acid (GABA)), eventually leading to excessive inhibition, and effectively to a shutdown, of the thalamic and brainstem nuclei that receive from the basal ganglia. Excessive thalamic inhibition results in suppression of the cortical motor system with akinesia, rigidity and tremor, while inhibition of brainstem locomotor areas may contribute to abnormalities of posture and gait.

Oxidative stress is thought to be the common underlying mechanism that leads to cellular dysfunction and demise. In Parkinson disease, oxidative stress induced by free radicals damages neuronal membrane lipids, proteins and other components of brain tissues and may cause dopaminergic degeneration in the substantia nigra. Antioxidant helps cells to copewith oxidative stress by effectively quenching free radicals. Antioxidants are generally regarded as safe – vitamin E, beta-carotene and lipoic acid.

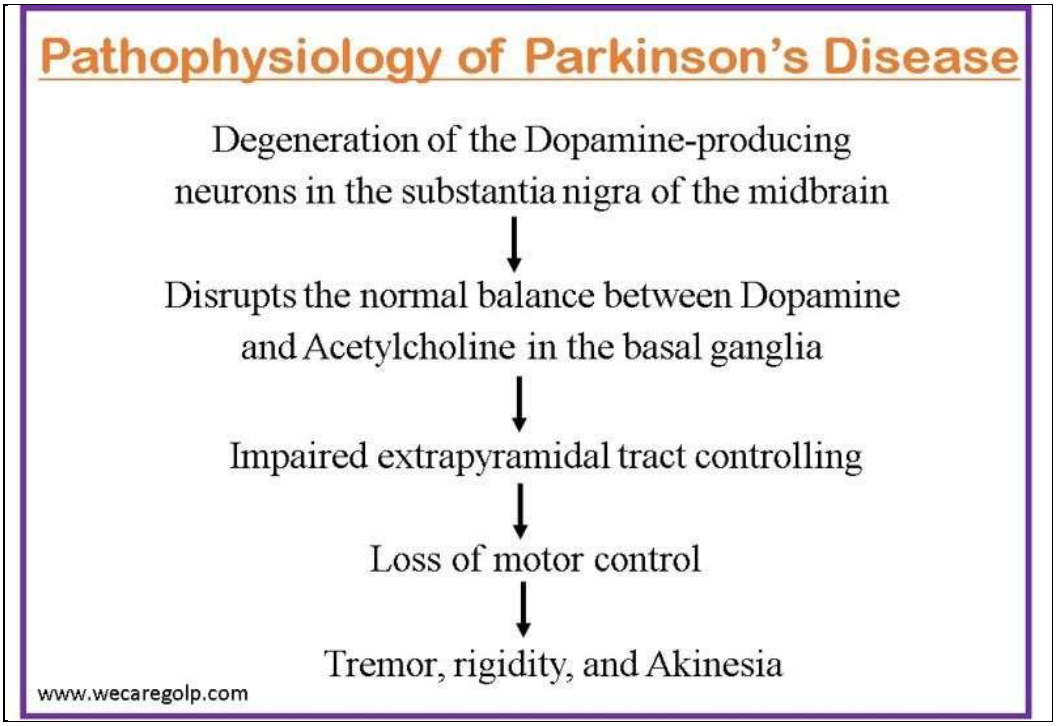

Fig no-03

CAUSES OF PARKINSON'S DISEASE[26]

Neurotransmitter Death

The brain's substansia nigra produce dopamine. If the dopaminergic neurons that secrete dopamine begin to die rapidly, the amount of dopamine in the body declines, resulting in Parkinson's symptoms.

Gene Abnormality

The much more similar inherited cause of Parkinson's disease is a single genetic mutation in the LRRK2 gene.

Environmental Cause

Some chemicals and metals have been related to Parkinsonism, according to recent study. Herbicides, insecticides, and fungicides used in crops, and also metals used in factories like spur, manganese, and trichloroethylene, all could cause the disease.

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CLASSIFICATION OF PARKINSONISM[29-35]

1. Idiopathic PD (Primary Parkinsonism)

Idiopathic PD usually presents in patients over age 60, and age is considered the most common risk factor for developing idiopathic PD; however, approximately 5% of patients begin before age 40 years. Genetic mutations are likely to be the cause of idiopathic PD for these young-onset patients. The widely recognized cardinal motor features of idiopathic PD include rigidity, asymmetric resting tremor, postural instability and bradykinesia. Of the essential motor features; asymmetric tremors are most often reported by patients as the first symptom. In fact, lack of asymmetry suggests a differential diagnosis.

2. Secondary Parkinsonism

Drug-induced Parkinsonism (DIP)

DIP is the second most widespread etiology of Parkinsonism after idiopathic PD in the elderly. Because of the clinical features of DIP and PD are indistinguishable, many cases with DIP may be misdiagnosed with PD.16 Typical antipsychotics (neuroleptics) including, haloperidol, chlorpromazine and fluphenazine are the most common DIP due to blockage of DA receptors in the striatal region leading to alterations in the basal ganglia motor circuit.17 Parkinsonism most often appears days to weeks after treatment with antipsychotics, however in some cases the onset may be take several months. 16 Aging is the most evident risk factor for DIP, supposedly explained by low number of striatal DA receptor. However, some studies reported the occurrence of DIP in younger patients. 18 The female gender, cognitive dysfunction and possibly a genetic predisposition are considered as individual risk factors for DIP.19 Other drugs such as dopamine depleting drugs (reserpine), anti-emetic (metoclopramide), calcium channel blockers (flunarizine, cinnarizine, diltiazem and verapamil), amiodarone, lithium and alpha-methyldopa are considered as DIP.

Vascular Parkinsonism

Ischemic cerebrovascular disease is the main cause of vascular Parkinsonism; therefore, it is categorized as secondary Parkinsonism, and it is known as arteriosclerotic Parkinsonism.Vascular Parkinsonism is typically bilaterally symmetrical Parkinsonism, affecting the lower limbs greater than the upper limbs and termed as lower-body Parkinsonism, with the lack of resting tremors. There are usually additional features, such as early dementia, speech disturbance and pseudobulbar palsy.

Other causes for secondary Parkinsonism

Hypoxia, hydrocephalus, trauma and infection such as encephalitis may also produce secondary parkinsonism.

3. Parkinsonism plus syndrome

Parkinsonism plus syndrome is a group of heterogeneous degenerative neurological disorders, which differ from the classical idiopathic PD in certain associated clinical features and poor response to Ldopa. Progressive supranuclear palsy, dementia with lewy body disease and Shy-Drager syndrome are commoner disorders.

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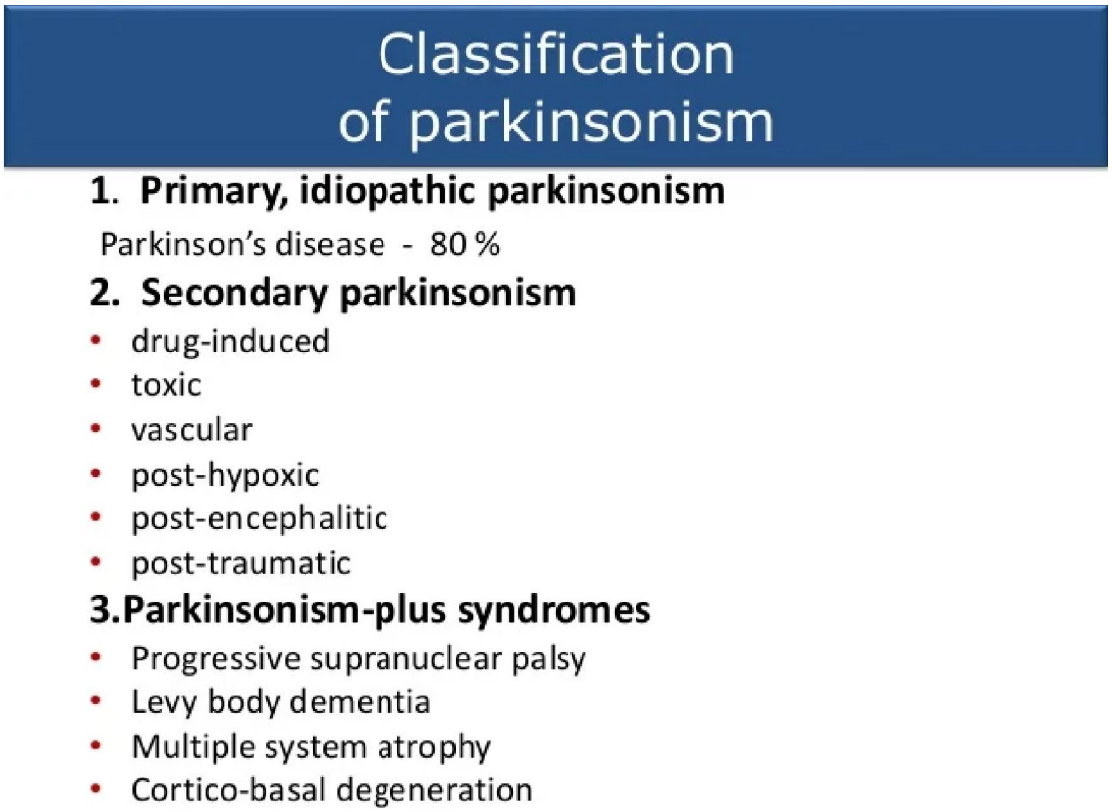

Fig no-04

INTRODUCTION TO HERBAL MEDICINE:[27,28]

Herbal medicine Herbal medicine (HM) is the fulcrum of complementary and alternative medicine, which in recent times is increasingly gaining widespread popularity all over the world and gradually streaming toward integration into the mainstream healthcare systems.

The use of HM cuts across gender, social and racial classes in both developing and developed countries of the world.

Due to the increasing popularity of HM, stakes in the world markets (local and international) are also rapidly increasing and the annual sale is rapidly approaching US $62 billion.

An important driver in this upsurge in patronage and use includes low cost, the wide acceptance due to its status of being a natural product with the acclaim of low toxicity, efficacy in certain challenging diseases, flexibility in its accessibility, preparation and use. HM includes preparations of biologically active natural products that consist largely of herbs or herbal materials some recipes may contain materials such as fungal and bee products, as well as minerals (kaolin, bentonite), ash, shells, insects and animal parts, and are used for the maintenance of health and management of various diseases.

HMs can elicit numerous benefits just as some can cause adverse effects. The pharmacologic and most of the toxic effects that are elicited by HMs have been linked to the activities of the secondary metabolites. In many instances, HMs have been appropriately used, misused and sometimes misunderstood. The benefits of HMs as a means of healthcare depends largely on the correct and adequate knowledge, and experiences while misuse as well as misunderstanding have been tracked to the knowledge gap on herbal medicines especially as it relates to their benefits and potential drawbacks by the primary healthcare professionals: doctors, pharmacists, nurses and the public.

The attraction to herbal medicine will continue to increase across the globe for various reasons, hence the urgent need for appropriate and enough information on HM especially that which highlights on important topics such as benefits,

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efficacy, safety, toxicity, research and development, formulation, regulation, analytical techniques, quality control, economic © 2018 The Author(s).

ROLE OF NATURAL PRODUCTS[54-60]

HERBAL PRODUCTS

Baicalein

Baicalein is a chemical compound derived from the dried root of the Scutellariabaicalensis plant (Labiatae). Baicalein prevented the buildup of ROS, apoptosis, ATP depletion and mitochondrial membrane rupture in PC12 cells when tested for rotenone-induced neurotoxicity. Baicalein treatment prevents Dopamine levels in the basal ganglia from dropping and boosts Dopamine and 5-hydroxytryptamine levels. In Hela and SH-SY5Y cells, Baicalein inhibited the aggregation of α-synuclein and the production of α-synuclein oligomers.

Erythrina velutina

The ethanol extract of this plant (Fabaceae) has a neuroprotective effect. It has been shown to reduce the neurotoxicity caused by 6-OHDA in SH-SY5Y cells and to get rid of free radicals, which suggests it could be used to treat Parkinson's disease.

Resveratrol

Resveratrol is a polyphenolic compound present in a variety of plants, including grapes and berries. Resveratrol has been found to help with motor deficits, oxidative stress, and the loss of TH neurons in animal models of Parkinson Disease. Resveratrol inhibits mitochondrial enlargement and chromatin condensation while also lowering COX-2 and TNF-α gene expression.

Peganum harmala

Peganum harmala (Nitrariaceae) made muscles less stiff, stopped oxidation of fats and proteins in the brain and stopped dopaminergic neurons from dying . It is thought that this herb's neuroprotective properties come from its ability to reduce the activity of angiotensin II. This reduces oxidative stress and protects dopaminergic neurons.

Curcuma longa

Curcuma longa (Zingiberaceae) has been shown to have anti-inflammatory, chemotherapeutic, anti-oxidant, woundhealing, anti-proliferative and antiparasitic properties. The active component polyphenolic fraction, curcumin, is probably to blame. Curcumin protects MPTP-induced loss of TH-positive neurons and DA depletion in the striatum of MPTP-induced mouse models, as well as a reduction in cytokines, total nitrite, and inflammatory markers such inducible nitric oxide synthase.

Carthamus tinctorius L. (Safflower)

Safflower (Asteraceae) has been discovered to contain flavonoids and is widely used as a conventional treatment for cerebrovascular disorders in China. It increased DA transporter and DJ-1 protein expression as well as DA levels. Overexpression or aggregation of α-synuclein, as well as reactive astrogliosis, may be inhibited by safflower.

Pueraria lobata

Puerarin (Fabaceae) has been shown to inhibit proteasomal malfunction as well as the buildup of ubiquitin-conjugated proteins and other potentially hazardous proteins. On the other handPuerarin, lowers the ratio of bcl-2/bax and caspase-3 activity. Puerarin protects tyrosine hydroxylase (TH)-positive neurons from 6- OHDA-mediated injury, recovers DA and its metabolites

Juglandis semen

The neuroprotective effects of aqueous Juglandis semen (walnut) extract have been demonstrated. The walnut extract was reported to reduce reactive oxygen species (ROS) and nitric oxide (NO) formation as well as restrict the depletion of striatal DA and its metabolites, resulting in a considerable improvement in PD movement abnormalities in a mouse model of Parkinson's disease. Walnut is thought to have neuroprotective effects because it can block the monoamine oxidase B (MAO-B) enzyme, which increases oxidative stress in people with Parkinson's disease. Walnut also has antioxidant and mitochondrial protection properties.

Ginkgo biloba

Ginkgo biloba (Ginkgoaceae) is a Chinese tree that has long been used to treat symptoms related to heart and lung problems. Flavonoids, ginkgolic acid and terpenoids are three of the most common constituents in G. Biloba. In a PD

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rat model treated with 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP), long-term use of EGb761 prevented the loss of dopaminergic nerve terminals caused by MPTP. EGb761 was shown to protect against dopaminergic neurotoxicity caused by MPTP whether it was given before or after the treatment . Also, EGb761 decreased the neurotoxicity of levodopa in the 6-hydroxydopamine (6-OHDA) Parkinson's disease (PD) model. This suggests that levodopa is neurotoxic and that EGb761 may reduce this toxicity

Ginseng

Ginsenosides (Araliaceae) Rb1 and Rg1 are regarded to be the primary molecules responsible for ginseng's therapeutic properties. A previous study found that the ginsenosides Rb1 and Rg1 both decreased MPTP-induced cell death in SN K-SH cells (a neuroblastoma cell line) (Rudakewich et al., 2001). Rg1 protects cells against apoptosis caused by MPTP by increasing Bcl-2 and Bcl-xl expression, decreasing Bax and iNOS expression and blocking caspase-3 activation (Chen et al., 2002). Ginsenosides protect by lowering intracellular reactive oxygen species (ROS), boosting antioxidant activity, maintaining complex I activity, and raising intracellular Adenosine triphosphate (ATP) levels, according to research. Mice given 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) had better motor function and more dopaminergic neurons in the substantia nigra (SN) and striatum when they were given Rg1. In addition, the ginsenoside Rb1 has the ability to disaggregate fibrils and inhibit α-synuclein polymerization.

Drugs use in Parkinson;s disease

PLANT NAME	FAMILY	COMMON NAME	PLANT PART USE	CHEMICAL CONSTITUENTS
Blepharis Maderaspatensis	Acanthaceae	Nethirs poondu	Dry Seed	Steroids-gomisin-D
Smilax perfoliata	Smilacaceae	Ram damtena	Dry root	Steroidal Sapogenins
Smilax zeylanica	Smilacaceae	Rough blind weed,hill lotus	Dry root	Alpha, beta hydroxy acids
Plantago ovata	plantaginaceae	Flax seed	Husk fiber	Mucilage, cyano genetic glycocydes-linamarin lotaustralin

Fig.Herbal drugs used in Parkinson's disease

Fig no-05

HERBAL EXTRACT AND ACTIVE COMPONENT WITH ANTI-PARKINSONIAN[38-41]

The herbal medicines were listed in table 1, which, according to their families, species and part of the plant used in treatment, have been shown to be effective on PD.

ACANTHOPANAX:-

Acanthopanax from A. Senticosus Harms protects C57BL/6 mice against dopaminergic MPTP-induced neuronal damage. B-side Eleuthero, a part of A. Senticosus Harms protects the PC12 cells from MPP (+) damage 2. Sesamin, a part of A. Senticosus Harms has a protective impact on the behavioral instability of rotenone-induced rat model and picomolar concentrations of sesamine-induced neuronal PC12 cells from cell deathinduced MPP+ 3. Stem bark extract is successful in raising DA and nor-adrenaline rates in the MPTP-induced PD rat model[35]

CHRYSANTHEMUM :-

The indicum Chrysanthemum L. The extract is protective against lipopolysaccharideinduced cytotoxicity in SH-SY5Y cellular model and BV-2 microglial cells of Parkinson's disease and 1-methyl-4-phenylpyridinium ion 5. Inhibits the

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mitochondrial apoptotic process, suppresses ROS aggregation, greatly increases the ratio elevation of Bax / Bcl-2 in SH-SY5Y cells and decreases SH-SY5Y cell death.

WITHANIA SOMNIFERA:-

Withaniasomnifera is commonly used as the Ashwagandha ginseng, Indian. Ashwagandha mitigates the Alterations of movement output and inflammatory neuronal biomarkers in a paraquat-induced rat model of Parkinson's disease

DRUG PROFILE[42-53]

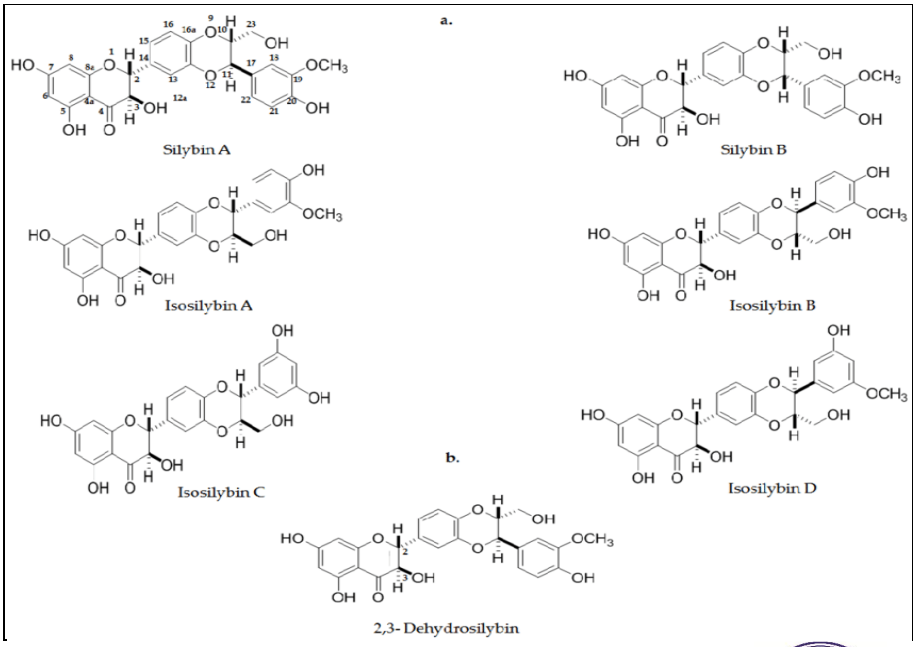
SILYMARIN

SOURCE OF SILYMARIN:-

Silymarin is a pharmacologically active phytochemical extracted from seeds and fruits of S. marianum, commonly known as milk thistle . Marianum is an annual or biennial plant and is a member of plant family Asteraceae. The genus Silybum contains two species that are S. marianum and Silybum eburneum. Geographically this plant distributes around the globe. It is cultivated in the Mediterranean region, Sinai, and Afghanistan, and has been neutralized in other parts of the world . It has been used from ancient times where Theophrastus (4th century B.C.) was probably first to describe it under the name Pternix. The initial use of S. marianum was reported by Dioscorides for treatment of serpent bites. In 1898, the use of herb to relieve obstructions of the liver was documented by British herbalist Culpepp.

CHEMISTRY OF SILYMARIN:-

Silymarin is a mixture containing isomer flavonolignans (silybin, isosilybin, and silychristin), small number of flavonoids (taxifolin), fatty acids, and other polyphenolic compounds. It is a lipophilic agent extracted from seeds of S. marianum. Silybin comprises 50–70% of silymarin having greatest degree of biological activity Seeds of S. marianum also contain other flavonolignans including isosilybin, dehydrosilybin, desoxysilychristin, desoxysilydianin, silandrin, silybinome, silyhermin, and neosilyhermin. Flavonolignans present in the mixture of silymarin contain flavonoid moiety links to a molecule of lignin moiety (coniferyl alcohol). It has been documented that silybin is a mixture of diastereo-isomers namely silybin A and silybin B. Silybin also known as silibinin contains 1,4-dioxane ring in addition to flavonoid moiety and is a most active anti-hepatotoxic agent. It has been reported that the presence of 2,3-double bond in the C-ring of flavonoid structure results in increasing antioxidant activity of silybin.



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NEUROPROTECTIVE POTENTIAL OF SILYMARIN

Silymarin is a polyphenolic flavonoid with strong antioxidant activities and is in clinical practice for management of hepatic disorders. Free radicals scavenging, elevating cellular glutathione level, and improving activity of superoxide dismutase are key mechanisms attributed to antioxidant activities of silymarin. Through inhibition of oxidative stress, silymarin possesses neuroprotective effects and it can be used in the management of neurodegenerative disorders including Alzheimer's disease, PD stroke, and traumatic brain Injury.

SAFETY PROFILE OF SILYMARIN

Being a phytochemical Silymarin generally possesses favorable safety profile, although allergic reactions including anaphylactic reactions have been reported. Other ADRs include mild laxative effects, nausea, epigastric discomfort, arthralgia, pruritus, urticaria, and headache. Silymarin also leads to inhibition of cytochrome P450 system and thus affecting the clearance of other drugs including chemotherapeutic agents.

LOW SOLUBILITY OF SILYMARIN

Low solubility of silymarin has been documented, i.e., 0.04 mg/ml and this is one of the basic reason of low oral bioavailability of silymarin from GIT. Studies also reflect that, however, silymarin has low aqueous solubility, it possesses lipophilic properties.

ANTI-PARKINSON'S TARGETS OF SILYMARIN

As stated earlier in this review that neuro-inflammation is a consequence or a cause of nigral cell loss and thus plays one of the most crucial roles in pathophysiology of PD. Beside antioxidant properties silymarin also inhibits neuro-inflammation by several mechanisms. Silymarin exerts its anti-inflammatory activities mainly by inhibiting microglia activation. It reduces the production of inflammatory mediators such as TNF-α, IL-1β, and NO, and protects dopaminergic neurons against degeneration. However, studies also suggest that silymarin induces many features of apoptosis in Candida albicans such as disruption of calcium homeostasis, loss of MMP, DNA fragmentation, and caspase activation. It needs further research whether these effects have a link with neurological actions of silymarin. It inhibits the activation of NF-kB by decreasing phosphorylation of p65 subunit which is responsible for strong transcription activating potential of NF-kB.

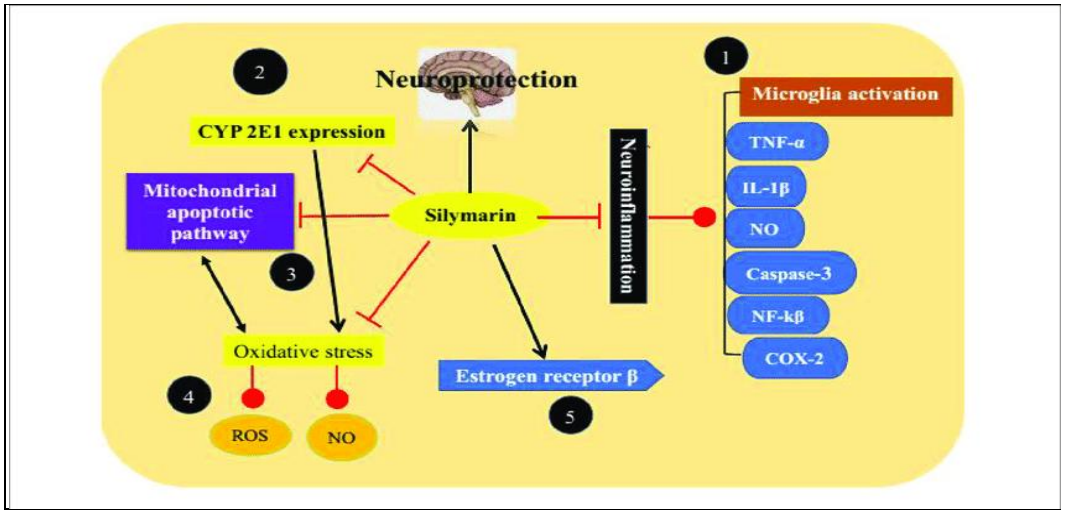

Fig no-06

Lipopolysaccharide (LPS) is most widely used as neurotoxic agent in vitro models of PD. It protects dopaminergic neurons from LPS-induced neurotoxicity by inhibiting activation of microglia reflecting its anti-inflammatory actions. Silymarin regulates NF-κB 100 times betterthan aspirin. Several kinases regulate NF-κB that belong to mitogen-activated protein kinase (MAPK) family and C-Jun N-terminal kinase (JNK). Silymarin inhibits these kinases without

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posing any threat to the cell. It has been documented from in vitro studies that silymarin also reduces superoxide and TNF-α production while inhibiting inducible NOsynthase.

DIAGNOSIS

The absence of other neurological signs upon examination
No history of other possible causes of parkinsonism, such as the use of tranquilizer medications, head trauma or stroke
Responsiveness to Parkinson's medications, such as levodopa
Presently, the diagnosis of Parkinson's is primarily based on the common symptoms outlined above. There is no X-ray or blood test that can confirm the disease. However, noninvasive diagnostic imaging, such as positron emission tomography (PET) can support a doctor's diagnosis. Conventional methods for diagnosis include
The presence of two of the three primary symptoms

TREATMENT OF PARKINSON'S DISEASES[36,37]

Pharmacologic treatments for Parkinson's disease motor symptoms are primarily dopamine based. Levodopa preparations, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors are useful initial therapies. For young individuals with prominent tremors, anticholinergic agents (e.g., trihexyphenidyl) are useful, but caution is required because of the potential for adverse events, particularly relating to cognition.
More than 40% of individuals treated with oral dopamine agonists (ropinirole, pramipexole) experience impulse control disorders (e.g., gambling, compulsive spending, abnormal sexual and eating behaviors, compulsive medication use, and lobbyism). Individuals who discontinue the use of dopamine agonists, often due to impulse control disorders, experience withdrawal symptoms (e.g., anxiety, panic attacks, irritability, diaphoresis, pain, and drug cravings) 15% to 20% of the time. Due to this, sometimes the dopamine agonist cannot be discontinued despite serious associated adverse events such as impulse control disorders.

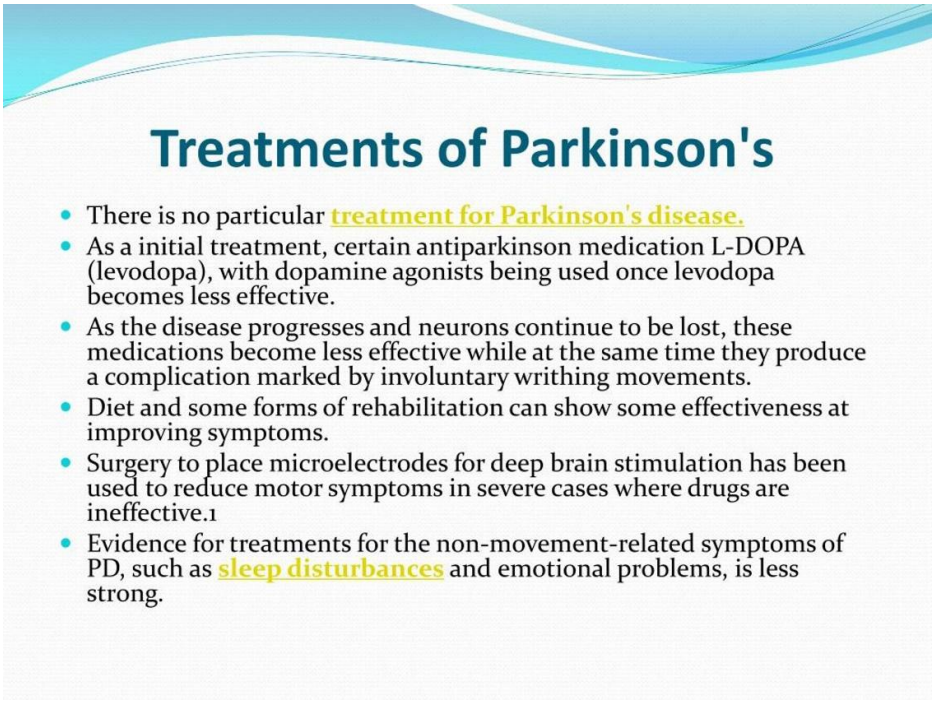

Fig no-07

Selecting the optimal strategy for starting treatment of Parkinson's disease requires shared decision-making with the patient to consider benefits and risks. Levodopa use results in more functional improvements but has increased dyskinesia risks, particularly with higher doses. Severe dyskinesias are uncommon. MAO-B inhibitors and dopamine agonists are associated with less robust symptom relief but lower dyskinesia risk; dopamine agonists are associated with

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a higher overall risk of adverse events. Ultimately, most individuals with Parkinson's disease use medications from multiple classes to attain complementary benefits while limiting high medication doses and dose-related adverse events.

II. CONCLUSION

Parkinson's disease (PD) is a complex neurodegenerative disease, manifested by the progressive functional impairment of the midbrain nigral dopaminergic neurons. Due to the unclear underlying pathogenesis, disease-modifying drugs for PD remain elusive. In Asia, such as in China and India, herbal medicines have been used in the treatment of neurodegenerative disease for thousands of years, which recently attracted considerable attention because of the development of curative drugs for PD. In this review, we first specified the potential targets of the bioactive compounds or extractions of herbs in view of the signaling pathways such as PI3K, NF-κB, and AMPK which are implicated in oxidative and inflammatory stress in neurons. We consider that this knowledge of herbal medicines or their bioactive components can be favorable for the development of disease-modifying drugs for PD.Alsosummarized the pathogenic factors of PD including protein aggregation, mitochondrial dysfunction, ion accumulation, neuroinflammation, and oxidative stress, and the related recent advances. Secondly, we summarized 32 Chinese herbal medicines (belonging to 24 genera, such as Acanthopanax, Alpinia, and Astragalus), 22 Chinese traditional herbal formulations, and 3 Indian herbal medicines, of which the ethanol/water extraction or main bioactive compounds have been extensively investigated on PD models both in vitro and in vivo. We elaborately provided pictures of the representative herbs and the structural formula of the bioactive components (such as leutheroside B and astragaloside IV) of the herbal medicines.

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