EFFECT OF L-LINALOOL ON PRIMARY SYMPTOMS AGAINST RESERPINE INDUCED PARKINSON'S DISORDER IN WISTAR ALBINO RAT MODELS

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Submitted by

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled **"EFFECT OF L-LINALOOL ON PRIMARY SYMPTOMS AGAINST RESERPINE INDUCED PARKINSON'S DISORDER IN WISTAR ALBINO RAT MODELS"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, was carried out by **Mr.SAKTHISUNDARAM.S.** Department of Pharmacology, Nandha College of Pharmacy, Erode for the partial fulfillment for the degree of **MASTER OF PHARMACY** in Pharmacology under the supervision of **Dr. S.HAJASHERIEF, M.Pharm., Ph.D.,** Professor, Department of Pharmacology, Nandha College of Pharmacy, Erode.

The work is original and has not been previously formed the basis for the award of any other Degree, Diploma, Associateship, Fellowship or any other similar title and the dissertation represent entirely an independent work on the part of the candidate.

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This work is original and has not been submitted in part or full for any other degree or diploma of any university.

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DECLARATION CERTIFICATE

The work presented in this thesis entitled **"Effect of L-Linalool on Primary Symptoms Against Reserpine Induced Parkinson's Disorder in Wistar Albino Rat Models"** was carried out by me in the Department of Pharmacology, Nandha College of Pharmacy, Erode under the supervision and guidance of **Dr. S. Haja Sherief M.Pharm., Ph.D.,** Professor, Department of Pharmacology, Nandha College of Pharmacy, Erode.

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This is to certify that the project **Proposal No: NCP/IAEC/2021-22/03** entitled **"Effect of L-linalool on primary symptoms against (MPTP) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced Parkinson's disorder in Wistar albino rat model."** submitted by Dr./Mr./Ms **S. Sakthisundaram** has been approved/recommended by the IAEC of Nandha College of Pharmacy in its meeting held on 12/08/2021 and **Wistar Albino Rat : 24** (Number and Species of animals) have been sanctioned under this.

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ABBREVIATIONS

Abbreviation	Explanation
CNS	Central Nervous System
AD	Alzheimer's Disease
PD	Parkinson's Disease
Ach	Acetylcholine
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP+	1-methyl-4-phenylpyridinium
α-synuclein	Alpha synuclein
UCHL-1	Ubiquitin carboxy-terminal hydrolase L-1
SNCA	α-synuclein gene
LRRK2	Leucine-rich repeat kinase 2
ROS	Reactive oxygen species
SNpc	Substantia Nigra pars compacta
RAS	Renin-angiotensin system
UPS	Ubiquitin-proteasome system
CMA	Chaperone-mediated autophagy
PET	Positron emission tomography
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicity
HLA	Human leucocyte antigen

CAT	Catalase
COMT	Catechol O-methyltransferase
ANOVA	Analysis of Variance
DA	Dopamine
DOPAC	3,4-Dihydroxyphenylacetic acid
HVA	Homovanillic acid
HPLC	High performance liquid chromatography

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INTRODUCTION

Introduction

Parkinson's disease (PD), is a long-term degenerative disorder of the central nervous system that mainly affects the motor system of the body. The symptoms usually arise slowly, and as the disease worsens, non-motor symptoms become more common. The most evident early symptoms are tremor, rigidity, slowness of movement, and difficulty with walking. Cognitive and behavioral problems may also occur with depression, anxiety, and apathy takes place in many people with Parkinson's disease. Dementia becomes common within the advanced stages of the disease. Those with Parkinson's also can have problems with their sleep and sensory systems. The motor symptoms of the disease results from the death of cells in the substantia nigra of the midbrain, leading to a dopamine deficit. The explanation for this necrobiosis is poorly understood, but involves the build-up of misfolded proteins into Lewy bodies within the neurons. Collectively, the most of the motor symptoms also are referred to as Parkinsonism. [1]

The explanation for Parkinson's disease is unknown, with both inherited and enviromental factors being believed to play a task. Those with a family member affected by Parkinson's disease are at a high risk of getting the disease, with certain genes known to be inheritable risk factors. Other risk factors are those that are exposed to certain pesticides and who have prior head injuries. Tobacco smokers and coffee, tea drinkers are at reduced risk. [2]

No cure for Parkinson's disease is known; treatment aims to scale back the consequences of the symptoms. Initial treatment is usually with the medications levodopa (L-DOPA), MAO-B inhibitors, or dopamine agonists.

Because of the disease progresses, these medications subsided effective, while at an equivalent time producing a side effect marked by involuntary muscle movements.

At that point, medications could also be utilized in combination and doses could also be increased. Diet and certain sorts of rehabilitation have shown some effectiveness at improving symptoms. Surgery to put microelectrodes for deep brain stimulation has been wont to reduce motor symptoms in severe cases where drugs are ineffective.

Evidence of treatments for the no movement-related symptoms of Parkinson's disease, such as sleep disturbances and emotional problems, is less strong. [3]

The disease is known as after English doctor Parkinson, who published the primary detailed description in An Essay on the paralysis agitans, in 1817. Public awareness campaigns include World Parkinson's Day (on the birthday of Parkinson, 11 April) and therefore the use of a red tulip because the symbol of the disease. [4]

Etiology

Parkinson's disease is a multifactorial disease, with both genetic and environmental factors playing a role. Age is the biggest risk factor for Parkinson's disease, with the median age of onset being 60 years of age. The incidence of the disease raises with age to 93.1 (per 100,000 person-years) in age groups between 70 and 79 years.

Additionally, there are cross-cultural variations, with higher prevalence reported in Europe, North America, and South America compared with African, Asian and Arabic countries. [5]

Cigarette smoking

Cigarette smoking has been extensively studied with respect to Parkinson's disease, with mostly consistent results. Most of the epidemiological reports are case-control studies showing a reduced risk of developing Parkinson's disease, with larger cohort studies also in agreement. A large meta-analysis including 44 case-control studies and 8 cohort studies from 20 countries showed an inverse correlation between smoking and Parkinson's disease, with a pooled relative risk of 0.39 for current smokers. Two other meta-analyses also reported an inverse correlation between smoking and Parkinson's disease, with a pooled odds ratio ranging from 0.23 to 0.70, indicating a protective mechanism against Parkinson's disease. They also reported an inverse correlation between the number of pack years, the number of years smoking and the risk of Parkinson's disease, with the risk of developing Parkinson's disease being significantly reduced in heavy or long-term smokers compared with nonsmokers. [6, 7]

The reasons underlying with this associated reduced risk are not fully understood. Activation of nicotinic acetylcholine receptors on dopaminergic neurons by nicotine or selective agonists has been shown to be neuro-protective in experimental models of Parkinson's disease. Nevertheless, nicotine can also stimulate the release of dopamine, which is involved in the reward mechanisms; it is therefore difficult to confirm whether smoking prevents Parkinson's disease or whether Parkinson's disease helps prevent the habitual use of cigarettes. As a result of a reduction in dopamine in patients with Parkinson's disease, patients may be less prone to addictive behaviors, and thus less likely to smoke.

This hypothesis is supported by the fact that patients with prodromal Parkinson's disease and Parkinson's disease were able to give up smoking much easier than controls, suggesting this association could be due to the decreased responsiveness to nicotine. [8-10]

Caffeine

Several studies have investigated the effect of caffeine on the development of Parkinson's disease and reported a reduced risk of developing Parkinson's disease among coffee drinkers. Caffeine is an adenosine A_{2A} receptor antagonist, which is believed to be protective in Parkinson's disease and has been shown to be neuroprotective in a mouse model of Parkinson's disease. It has been previously reported that there is a 25% risk reduction in developing Parkinson's disease among coffee drinkers. Two large prospective epidemiological studies (27, 29), as well as multiple retrospective studies, have also shown a reduced risk of developing Parkinson's disease with a relative risk ranging from 0.45 to 0.80 in coffee drinkers versus non-coffee drinkers.

A meta-analysis including eight case-control studies and five cohort studies also showed a significantly reduced risk of developing Parkinson's disease in coffee drinkers (RR 0.69) . Regular tea drinkers also have been reported to have a lower risk of developing Parkinson's disease.

As with smoking, the causative role of caffeine in preventing Parkinson's disease remains to be established. Furthermore, there were differences noted between studies with respect to gender. In two cohort studies, there was a strong inverse correlation between coffee and the development of Parkinson's disease in men, whereas in women this association was weaker.

As estrogen competitively inhibits caffeine metabolism, interactions between estrogen and caffeine may explain in part why Parkinson's disease risk is dependent on hormone replacement therapy in post-menopausal women. [11, 12]

Pesticides, herbicides, and heavy metals

In 1983, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was first discovered to be associated with nigrostriatal degeneration when several people developed typical Parkinson's disease signs after injecting themselves with a drug contaminated with MPTP.

MPTP is metabolized into the neurotoxin, MPP+ (1-methyl-4-phenylpyridinium), which is a mitochondrial complex-I inhibitor that selectively damages dopaminergic cells in the substantia nigra. The identification of MPTP as a cause of nigral degeneration led to the idea that Parkinson's disease could be caused by an environmental toxin. Since then, several studies have shown an association between pesticides and Parkinson's disease, with one case-control study showing an increased association with professional pesticide exposure in men and late-onset Parkinson's disease (odds ratio [OR] 2.2).

Paraquat (a herbicide which is structurally very similar to MPP+) and rotenone (a pesticide) are also selective complex-I inhibitors and induce dopaminergic depletion in animal models of Parkinson's disease. The relationship between exposure to these chemicals and the risk of developing Parkinson's disease has been investigated in other epidemiological studies. It has also led to the study of surrogate markers, including the association of farming, drinking well water, and living in rural areas with Parkinson's disease risk. Welding and heavy metal exposure (e.g., iron, copper, lead, aluminum, and zinc) have also been investigated, but the relationship between these and Parkinson's disease remains inconclusive. [13]

Genetics

Although Parkinson's disease is generally an idiopathic disorder, there is a minority of cases (10–15%) that report a family history, and about 5% have Mendelian inheritance. Furthermore, an individual's risk of Parkinson's disease is partially the product of as-yet poorly defined polygenic risk factors.

The genes that have been found to potentially cause Parkinson's disease are assigned a "PARK" name in the order they were identified. To date, 23 PARK genes have been linked to Parkinson's disease. Mutations in the PARK genes demonstrate either autosomal dominant (e.g., *SCNA*, *LRRK2*, and *VPS32*) or autosomal recessive inheritance (e.g., *PRKN*, *PINK1*, and *DJ-1*).

The involvement of some of these genes has not been conclusively confirmed (PARK5, PARK11, PARK13, PARK18, PARK21, and PARK23), while others are considered risk factors (PARK3, PARK10, PARK12, PARK16, and PARK22). The numerically most important genetic risk factors predisposing to Parkinson's disease are mutations in *GBA1*, a gene encoding β-glucocerebrosidase a lysosomal enzyme responsible for the hydrolysis of glucocerebrosides. *GBA1* mutations are known to cause Gaucher disease, which is the most common lysosomal storage disorder).

Other genetic risk factors include the major histocompatibility complex, class II (HLA-DQB1) and the gene encoding the protein tau, *MAPT*, among others. [14, 15]

Autosomal dominant Parkinson's disease

The first type of familial Parkinson's disease caused by a point mutation in the α-synuclein gene (*SNCA*) was discovered in 1997. Four additional point mutations, as well as gene duplication or triplication, have now been linked to autosomal dominant Parkinson's disease. However, these mutations are relatively rare.

The most frequent autosomal dominant monogenic Parkinson's disease is caused by mutations in the gene encoding leucine-rich repeat kinase 2 (*LRRK2*). Six *LRRK2* mutations have been confirmed as pathogenic, the most common of which is p.G2019S, estimated to account for 1% of sporadic and 4% of familial Parkinson's disease worldwide. More recent

genetic studies have led to the discovery of additional mutations in other genes responsible for autosomal dominant Parkinson's disease, including *VPS35*. [16-20]

Autosomal recessive Parkinson's disease

Autosomal recessive forms of Parkinson's disease typically present with an earlier onset than classical Parkinson's disease. Three of the PARK-designated genes causing autosomal recessive Parkinson's disease have been linked to mitochondrial homeostasis (*PRKN*, *PINK1*, and *DJ-1*). Specifically, the proteins PINK1 and parkin (encoded by the *PRKN* gene) are both involved in the same mitochondrial quality control pathway, with PINK1 recruiting parkin to dysfunctional mitochondria and thus initiating mitophagy. Mutations in *PRKN* are the most common cause of autosomal recessive familial Parkinson's disease occurring in up to 50% of all early-onset cases. Finally, several of the autosomal recessive genes have been linked to atypical Parkinsonism with variable features.[21]

Epidemiology and risk factors

In industrialized countries the estimated prevalence of Parkinson's disease is 0.3% in the general population, 1.0% in people older than 60 years and 3.0% in people older than 80 years; incidence rates of Parkinson's disease are estimated to range between 8 and 18 per 100 000 persons per years. Estimated prevalence and incidence rates for Parkinson's disease range between 65 and 12,500 per 100 000 and between 5 and 346 per 100000 person per years respectively. Age is the most important risk factor for the disease; male gender confers a moderate risk. Some environmental factors have been linked to the risk of Parkinson's disease, including certain pesticides and rural living.

It is of interest that some substances such as 1-methyl-4-phenyl tetrahydropyridine (MPTP) and annonacin can cause nigrostriatal cell death and a form of atypical Parkinsonism. Exposure to toxic levels of manganese, trichloroethylene, carbon monoxide and other agents

can likewise sometimes lead to a type of Parkinsonism, but with clinical and pathological features distinct from Parkinson's disease. β2-adrenoreceptor antagonists have been linked to an increased risk for Parkinson's disease, whilst in contrast β2-adrenoreceptor agonists seem to reduce it. Conversely, there is an inverse association between the risk of Parkinson's disease and cigarette smoking, coffee drinking calcium channel blockers and statins, whilst contrasting evidence is available regarding the use of nonsteroidal anti-inflammatory drugs and uric acid levels or gout.

Family history is a risk factor for Parkinson's disease and the relative risk in first-degree relatives of Parkinson's disease cases increases by approximately two to three fold compared to controls. [22]

Pathophysiology of Parkinson's disease

A number of mechanisms have been implicated in Parkinson's disease pathogenesis, with α-synuclein aggregation central to the development of the disease. Multiple other processes are thought to be involved with several studies suggesting that abnormal protein clearance, mitochondrial dysfunction, and neuro inflammation play a role in the onset and progression of Parkinson's disease. However, the relationship between these pathways remains unclear.

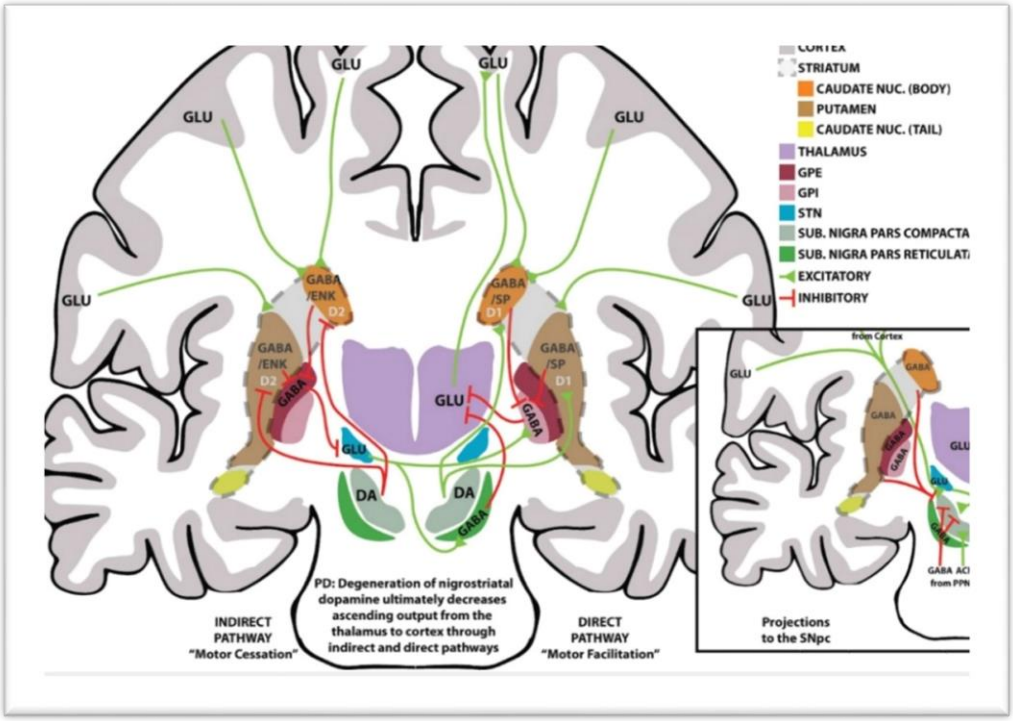


Figure No. 1: Mechanism of causing Parkinson's disease

α-synuclein misfolding and aggregation

Native α-synuclein in the brain is mostly unfolded without a defined tertiary structure, although in aqueous solutions it can be present in stable tetramers that resist aggregation. Upon interaction with negatively charged lipids, such as the phospholipids that make up cell membranes, α-synuclein folds into α-helical structures through its N-terminal.

In Parkinson's disease, it is an α-synuclein adopts a β-sheet-rich amyloid-like structure that is prone to aggregate. Indeed, misfolded α-synuclein is found within LBs as 5–10 nm long filaments.

Several mechanisms have been proposed for the conformational changes that lead to abnormal α-synuclein aggregation, including serine 129 phosphorylation, ubiquitination, and the C-terminal truncation.

Hence, different species of α-synuclein are found in the Parkinson's disease brain, including unfolded monomers, soluble oligomers, protofibrils, and high molecular weight insoluble fibrils. Recent studies in rodents indicated that the most neurotoxic α-synuclein species is the early oligomeric form, rather than the mature insoluble fibrils.

The increased toxicity of these oligomers, as opposed to the fibrillary α-synuclein, was validated in cell-based assays. The oligomeric species of α-synuclein are capable of "seeding" and accelerating abnormal protein aggregation. [23, 24]

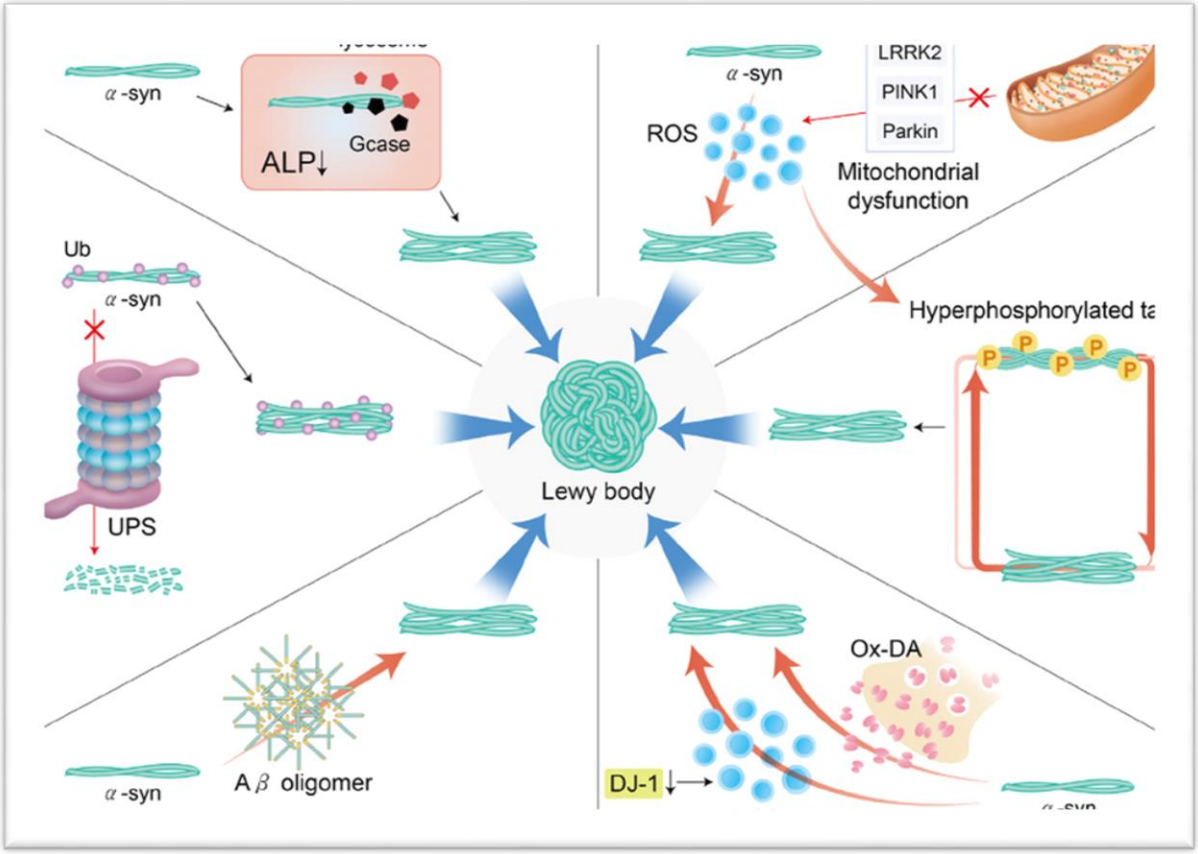


Figure No. 2 : α- Synuclein activity in the formation of lewy body in brain

Mitochondrial dysfunction

Mitochondrial dysfunction is considered a key element in the pathogenesis of both idiopathic and familial Parkinson's disease. Early postmortem studies in the SNpc of Parkinson's disease brains reported a deficiency of the mitochondrial complex-I, which is a vital component of the electron transport chain. These data provided one of the first direct links between mitochondrial dysfunction and Parkinson's disease.

Complex-I deficiency was also found in skeletal muscle and platelets of Parkinson's disease patients compared to healthy subjects.

Further evidence arose by the discovery that abuse of the substance MPTP caused permanent Parkinsonian symptoms, with postmortem examination revealing dopaminergic cell loss. Follow-up studies showed that MPTP when oxidized is taken up by DA neurons and leads to complex-I inhibition. Other toxins and pesticides that impair mitochondrial complex-I activity, like rotenone and paraquat, also cause a Parkinsonian phenotype and DA cell loss in animals, and potentially in humans. Defects in the mitochondrial complex-I may be crucial in driving DA cell death due to energy depletion.

Another major clue pointing to the role of mitochondria in Parkinson's disease pathogenesis is that many of the known genes that cause familial Parkinson's disease play a role in mitochondrial homeostasis. One example is the involvement of PINK1 and parkin (PARK2 and PARK6, respectively), both of which are vital components of the pathway that regulates the removal of dysfunctional mitochondria, a process called mitophagy. Loss-of-function mutations in either gene lead to impaired mitochondrial quality control and cause autosomal recessive Parkinson's disease.

Finally, α-synuclein by itself is known to interfere with mitochondrial function. For instance, α-synuclein can interact with the mitochondrial membrane and accumulate inside the

organelles. This leads to the damage of complex-I activity, ultimately resulting in mitochondrial dysfunction and increased oxidative stress. A more recent study reported an interaction between oligomeric (but not monomeric or fibrillar) α-synuclein and the mitochondrial receptor TOM20. This interaction resulted in impairment of the mitochondrial protein import machinery, reduced respiration, and led to excessive production of reactive oxygen species (ROS). [25, 26]

Dysfunctional protein clearance systems

There are two central protein clearance systems within cells responsible for the removal of dysfunctional proteins: the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway. The UPS is primarily responsible for breaking down abnormal proteins, and it does so by "tagging" them with ubiquitin and transporting them to the proteasome for degradation.

The autophagy-lysosome pathway is divided into three constituents: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Briefly, in macroautophagy, intracellular components, including cytosolic proteins, are engulfed by the autophagosome, which then fuses with the lysosome, leading to the breakdown of its contents. On the other hand, in microautophagy, the lysosome alone engulfs and destroys cytoplasmic components. CMA is a more selective process, whereby molecular chaperones target specific proteins and transport them to the lysosome for degradation.

Monomeric α-synuclein is generally cleared by both the UPS and the autophagy-lysosome pathway and damage in either of their machineries is implicated in the pathogenesis of Parkinson's disease by contributing to the accumulation of defective proteins, in particular soluble misfolded α-synuclein. [27]

Ubiquitin-proteasome system

Proteasomal abnormalities are a shared feature among many proteinopathies, that is, neurodegenerative diseases characterized by abnormal protein accumulation. Evidence of such abnormalities in Parkinson's disease was first provided by postmortem studies in the SNpc, where the catalytic activity of the UPS was found substantially reduced compared to healthy brains.

The same findings were later reported in peripheral blood mononuclear cells of Parkinson's disease but not in healthy individuals. Apart from diminished activity, a lower expression of different proteasomal components has also been identified in the SNpc of Parkinson's disease brains. Specifically, the 20S proteasome α-subunit and other molecules involved in the normal function of the UPS, like PA700 and PA28 (proteasome activators), are reduced. Additional evidence is provided from genetic studies and the discovery that two of the PARK genes linked to monogenic Parkinson's disease encode proteins involved in UPS function, namely, parkin (PARK2; E3 ubiquitin ligase) and UCH-L1 (PARK5; Ubiquitin C-terminal hydrolase).

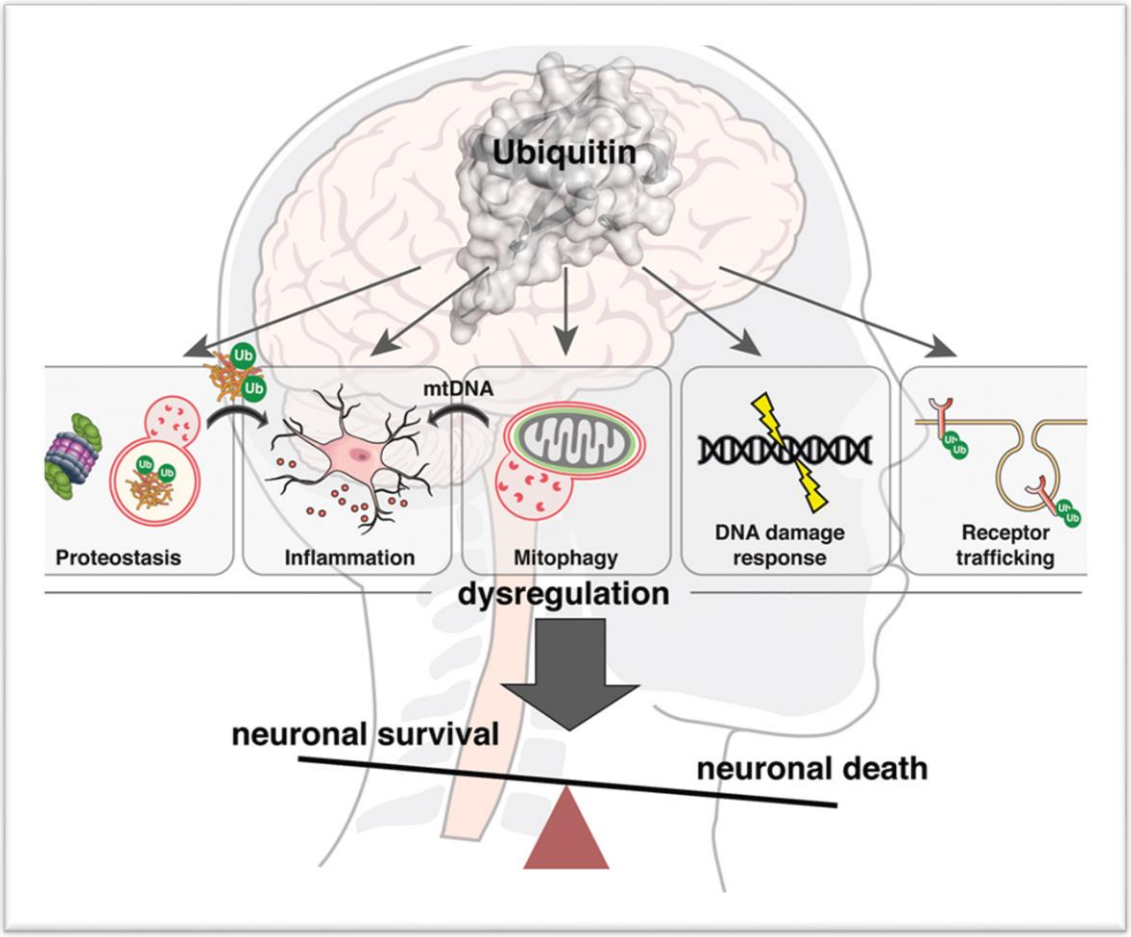


Figure No. 3: Ubiquitin Proteasome systems action on neuron

Following on from findings in human Parkinson's disease, altered proteasome activity was observed in different disease models. Marmosets injected with the toxin MPTP had diminished enzyme activity in the UPS, in addition to decreased levels of the 26S subunit components. In a second set of experiments, the same group showed that pharmacological inhibition of the proteasome in wild-type rats leads to dopaminergic cell death. Similarly, Bedford and colleagues using transgenic mice with proteasomal defects (knockout for 26S proteasome regulatory subunit 4) showed dopaminergic cell degeneration and observed LB-like inclusions in the brain, which however lacked the dense core of classical human LBs, and it is unclear whether they contained aggregated α-synuclein.

Nevertheless, all these studies show that dysfunction of protein turnover can result in neuronal cell death, thus providing a potential pathogenic mechanism for Parkinson's disease. [28, 29]

Autophagy- lysosome system

Similar to findings in the UPS system, numerous lysosomal and autophagy-related components are malfunctioning or differentially expressed in Parkinson's disease. In nigral neurons of Parkinson's disease brains, the levels of the autophagosome marker LC3-II were increased, suggesting an accumulation of autophagic vacuoles. In contrast, vital proteins of lysosomal membranes (LAMP1 and LAMP2A), and several molecular chaperones from the heat shock protein family (such as hsc70 and hsp35) were found to be decreased at postmortem examination. Furthermore, of particular note is the discovery of a point mutation in the gene of the lysosomal protein ATP13A2 (PARK9), leading to an autosomal recessive atypical Parkinsonian syndrome, referred to as Kufor–Rakeb syndrome.

Point mutations in two more PARK genes impair the function of either parkin (PARK2) or PINK1 (PARK6), both of which are involved in the autophagic turnover of mitochondria. Additionally, the emergence of *GBA1* mutations, which result in dysfunction of the lysosome-autophagy system, as a strong genetic risk factor for Parkinson's disease adds weight to the idea that this system is important in the development of Parkinson's disease.

These studies lend support to the hypothesis that malfunction in the autophagy-lysosome pathway may be contributing to the pathogenesis of Parkinson's disease. [30]

Neuro inflammation

Postmortem brain studies have described microglial and complement activation, T-lymphocyte infiltration, and increased concentration of pro-inflammatory cytokines in the

SNpc and striatum of Parkinson's disease patients compared to healthy individuals. Furthermore, positron emission tomography (PET) neuroimaging with the [^{11}C]-PK11195 radio ligand has demonstrated increased microglial activation early on in Parkinson's disease in the brainstem, basal ganglia, and frontotemporal cortices, with added involvement of the parietal and occipital cortices in patients with Parkinson's disease dementia, compared to healthy subjects.

While initially thought to be a secondary phenomenon, there is now evidence that inflammatory responses can by themselves contribute to disease pathogenesis. It has been demonstrated in early studies with rodent models of Parkinson's disease (6-hydroxydopamine and MPTP) that inhibition of microglial activation with minocycline pre- and post-neurotoxic insult led to a significant attenuation of dopamine cell death in the SNpc, suggesting that microglia-induced inflammatory processes may be contributing to the degeneration of these cells.

There is also a plethora of evidence suggesting that α-synuclein can directly trigger microglial activation and initiate inflammatory processes. For instance, in primary cultures, an a α-synuclein mediates a dose-dependent activation of microglia.

Genetic clues suggesting that immune activation might contribute etiologically in Parkinson's disease come from the identification of a strong association between the human leucocyte antigen (HLA) class II region (a key molecule of the immune system) and the risk of developing Parkinson's disease - a finding that was later confirmed in genome-wide association studies.

Additionally, extensive epidemiological studies suggest a decreased Parkinson's disease risk with regular use of the nonsteroidal anti-inflammatory drug ibuprofen. Finally, recent data showed that in Parkinson's disease patients at diagnosis a more 'pro-inflammatory'

immune marker profile in the serum is associated with a faster motor symptom progression and more impaired cognitive function.

Regardless of whether neuro inflammatory responses are a direct trigger of neurodegeneration in Parkinson's disease or are activated as a response to neuronal damage, it is now becoming clear that the engagement of the immune system can initiate a vicious cycle, thereby exacerbating neuronal dysfunction. Hence, manipulation of the immune system remains a promising topic for disease-modifying therapies. [30]

Symptoms

Parkinson's disease signs and symptoms can be different for everyone. Early signs may be mild and go unnoticed. Symptoms often begin on one side of body and usually remain worse on that side, even after symptoms begin to affect both sides.

Parkinson's signs and symptoms may include:

Tremor: A tremor, or shaking, usually begins in a limb, often hand or fingers. May rub thumb and forefinger back and forth, known as a pill-rolling tremor. Hand may tremble when it's at rest.

Slowed movement (bradykinesia): Over time, Parkinson's disease may slower the movement, making simple tasks difficult and time-consuming. Steps may become shorter when walk. It may be difficult to get out of a chair.

Rigid muscles: Muscle stiffness may occur in any part of the body. The stiff muscles can be painful and limit range of motion.

Impaired posture and balance: Posture become stooped, or balance problems as a result of Parkinson's disease.

Loss of automatic movements: Decreased ability to perform unconscious movements, including blinking, smiling or swinging arms while walking.

Speech changes: Speak softly, quickly, slur or hesitate before talking. Speech may be more of a monotone rather than have the usual inflections.

Writing changes. It become hard to write, and writing appear small. [31]

Complications

Parkinson's disease is often accompanied by these additional problems, which may be treatable:

Thinking difficulties: People may experience cognitive problems (dementia) and thinking difficulties. These usually occur in the later stages of Parkinson's disease. Such cognitive problems aren't very responsive to medications.

Depression and emotional changes: Experience depression, sometimes in the very early stages. Receiving treatment for depression can make it easier to handle the other challenges of Parkinson's disease. May also experience other emotional changes, such as fear, anxiety or loss of motivation.

Swallowing problems: May develop difficulties with swallowing as condition progresses. Saliva may accumulate in mouth due to slowed swallowing, leading to drooling.

Chewing and eating problems: Late-stage Parkinson's disease affects the muscles in mouth, making chewing difficult. This can lead to choking and poor nutrition.

Sleep problems and sleep disorders: People with Parkinson's disease often have sleep problems, including waking up frequently throughout the night, waking up early or falling asleep during the day. People may also experience rapid eye movement sleep behavior disorder, which involves acting out your dreams. Medications may help your sleep problems.

Bladder problems: Parkinson's disease may cause bladder problems, including being unable to control urine or having difficulty urinating.

Constipation: Many people with Parkinson's disease develop constipation, mainly due to a slower digestive tract.

Blood pressure changes: May feel dizzy or lightheaded when stand due to a sudden drop in blood pressure (orthostatic hypotension).

Smell dysfunction: May experience problems with sense of smell. May also have difficulty identifying certain odors or the difference between odors.

Fatigue: Many people with Parkinson's disease lose energy and experience fatigue, especially later in the day. The cause isn't always known.

Pain: Some people with Parkinson's disease experience pain, either in specific areas of their bodies or throughout their bodies.

Sexual dysfunction: Some people with Parkinson's disease notice a decrease in sexual desire or performance. [31, 32]

Treatment

Parkinson's disease can't be cured, but medications can help control symptoms, often dramatically. In some more advanced cases, surgery may be advised. Doctor may also

recommend lifestyle changes, especially ongoing aerobic exercise. In some cases, physical therapy that focuses on balance and stretching also is important. A speech-language pathologist may help improve speech problems.

Medications

Medications may help to manage problems with walking, movement and tremor. These medications increase or substitute for dopamine. People with Parkinson's disease have low brain dopamine concentrations. However, dopamine can't be given directly, as it can't enter your brain. Significant improvement of symptoms may takes place after beginning Parkinson's disease treatment. Over time, however, the benefits of drugs frequently diminish or become less consistent.

Carbidopa-levodopa: Levodopa, the most effective Parkinson's disease medication, is a natural chemical that passes into brain and is converted to dopamine.

- Levodopa is combined with carbidopa (Lodosyn), which protects levodopa from early conversion to dopamine outside brain. This prevents or lessens side effects such as nausea.
- Side effects may include nausea or lightheadedness (orthostatic hypotension).
- After years, as disease progresses, the benefit from levodopa may become less stable, with a tendency to wax and wane ("wearing off").
- Also, may experience involuntary movements (dyskinesia) after taking higher doses of levodopa. Doctor may lessen dose or adjust the times of doses to control these effects. [37]

Inhaled carbidopa-levodopa: Inbrija is a new brand-name drug delivering carbidopa-levodopa in an inhaled form. It may be helpful in managing symptoms that arise when oral medications suddenly stop working during the day.

Carbidopa-levodopa infusion: Duopa is a brand-name medication made up of carbidopa and levodopa. However, it's administered through a feeding tube that delivers the medication in a gel form directly to the small intestine.

- Duopa is for patients with more-advanced Parkinson's who still respond to carbidopa-levodopa, but who have a lot of fluctuations in their response. Because Duopa is continually infused, blood levels of the two drugs remain constant.
- Placement of the tube requires a small surgical procedure. Risks associated with having the tube include the tube falling out or infections at the infusion site.

Dopamine agonists: Unlike levodopa, dopamine agonists don't change into dopamine. Instead, they mimic dopamine effects in your brain.

- They aren't as effective as levodopa in treating your symptoms. However, they last longer and may be used with levodopa to smooth the sometimes off-and-on effect of levodopa.
- Dopamine agonists include pramipexole (Mirapex), ropinirole (Requip) and rotigotine (Neupro, given as a patch). Apomorphine (Apokyn) is a short-acting injectable dopamine agonist used for quick relief.
- Some of the side effects of dopamine agonists are similar to the side effects of carbidopa and levodopa. But they can also include hallucinations, sleepiness and compulsive behaviors such as hypersexuality, gambling and eating.

MAO B inhibitors: These medications include selegiline (Zelapar), rasagiline (Azilect) and safinamide (Xadago). They help prevent the breakdown of brain dopamine by inhibiting the

brain enzyme monoamine oxidase B (MAO B). This enzyme metabolizes brain dopamine. Selegiline given with levodopa may help prevent wearing-off.

- Side effects of MAO B inhibitors may include headaches, nausea or insomnia. When added to carbidopa-levodopa, these medications increase the risk of hallucinations.
- These medications are not often used in combination with most antidepressants or certain narcotics due to potentially serious but rare reactions.

Catechol O-methyltransferase (COMT) inhibitors: Entacapone (Comtan) and opicapone (Ongentys) are the primary medications from this class. This medication mildly prolongs the effect of levodopa therapy by blocking an enzyme that breaks down dopamine.

- Side effects, including an increased risk of involuntary movements (dyskinesia), mainly result from an enhanced levodopa effect. Other side effects include diarrhea, nausea or vomiting.
- Tolcapone (Tasmar) is another COMT inhibitor that is rarely prescribed due to a risk of serious liver damage and liver failure.

Anticholinergics: These medications were used for many years to help control the tremor associated with Parkinson's disease. Several anticholinergic medications are available, including benztropine (Cogentin) or trihexyphenidyl.

- However, their modest benefits are often offset by side effects such as impaired memory, confusion, hallucinations, constipation, dry mouth and impaired urination.

Amantadine: Amantadine alone to provide short-term relief of symptoms of mild, early-stage Parkinson's disease. It may also be given with carbidopa-levodopa therapy during the later stages of Parkinson's disease to control involuntary movements (dyskinesia) induced by

carbidopa-levodopa.Side effects may include a purple mottling of the skin, ankle swelling or hallucinations. [37-39]

Surgical procedures

Deep brain stimulation open pop-up dialog box

Deep brain stimulation. In deep brain stimulation (DBS), surgeons implant electrodes into a specific part of your brain. The electrodes are connected to a generator implanted in your chest near collarbone that sends electrical pulses to brain and may reduce Parkinson's disease symptoms.

Doctor may adjust settings as necessary to treat your condition. Surgery involves risks, including infections, strokes or brain hemorrhage. Some people experience problems with the DBS system or have complications due to stimulation, and doctor may need to adjust or replace some parts of the system.

Deep brain stimulation is most often offered to people with advanced Parkinson's disease who have unstable medication (levodopa) responses. DBS can stabilize medication fluctuations, reduce or halt involuntary movements (dyskinesia), reduce tremor, reduce rigidity, and improve slowing of movement. DBS is effective in controlling erratic and fluctuating responses to levodopa or for controlling dyskinesia that doesn't improve with medication adjustments.

However, DBS isn't helpful for problems that don't respond to levodopa therapy apart from a tremor. A tremor may be controlled by DBS even if the tremor isn't very responsive to levodopa. Although DBS may provide sustained benefit for Parkinson's symptoms, it doesn't keep Parkinson's disease from progressing. [39]

VARIOUS IN-VIVO MODELS FOR PARKINSON'S DISEASE:-

Animal models are valuable tools for studying the biology and genetics of human Parkinson as well as for preclinical investigation of anti-Parkinson therapeutics and Parkinson preventive studies. Various animal models have been generated by genetic engineering, graft transplantation, and viral/physical/chemical induction. Studies from animal models of Parkinson have been utilized for preclinical investigation of therapeutic efficacy and toxicity of chemicals and biologicals. Tremendous advances have been made in the generation of animal models of Parkinson, which have become increasingly sophisticated by application of new technologies and integration of clinical information from patients. The goals are to faithfully recapitulate the human Parkinson diseases in the animal models and apply them as preclinical tools, with the hope of successfully translating the basic knowledge into treatment and prevention of Parkinson in humans. The mouse has been the traditional animal model for basic and preclinical studies of Parkinson, and other organisms including zebrafish play important and complimentary roles as models of Parkinson research.

Genetically engineered mouse models of Parkinson have been generated by a variety of interventions such as chemical or physical mutagenesis, viral infection, insertion of transgenes, homologous recombination, and the recently developed gene edition.

MPTP induced Parkinson's diseases :

1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), is a potent neurotoxin & highly lipophilic. After systemic administration it rapidly crosses the blood-brain barrier, enters astrocytes and is metabolized to its active metabolite MPP+ by monoamine oxidase-B (MAO-B). MPP+ is able to inhibit complex 1 of the mitochondrial electron transport chain, resulting in the formation of ROS & leading to reduced ATP production.

Neuroprotection suggests preventing or slowing disease progression. Nevertheless, despite advances toward this goal, all current treatments are symptomatic; none halt or retard dopaminergic neuron degeneration. L-dopa treatment produces many distressing side effects, and its possible that metabolism of excess dopamine by the monoamine oxidase enzymes in the brain produces too much H_2O_2. An initial good response to symptomatic pharmacological treatment declines with time, and severe side effects develop and later on surgical interventions are to be used. The progressive neurodegeneration in Parkinson's disease is not arrested by the currently used drug therapies. Hence, recent researches are focusing on finding therapies, preferentially herbal drugs [33, 34]

6-OHDA lesioned rats

6-OHDA is a neurotoxin, which, when directly injected into the medial forebrain bundle, striatum or SN, induces nigrostriatal DA neuronal degeneration. Although 6-OHDA leads to clear apoptosis of nigrostriatal dopaminergic cells, evidence indicates that the toxic effects of 6-OHDA are in part mediated through the activation of microglia. Direct administration of 6-OHDA into the SN of mice activates microglia and increases the number of activated microglia in the SN with the subsequent loss of dopaminergic neurons after 1 week. Furthermore, 6-OHDA-lesioned rats have been demonstrated to have increased levels of TNF-a in both SN and striatum. [35, 36]

ROTENONE induced Parkinson's disease:

Parkinson's disease can be induced with mitochondrial complex I inhibitors such as the environmental toxins rotenone. Rotenone, a commonly used natural pesticide prepared from the roots of tropical plants, such as Derris elliptica, can freely cross cell and mitochondrial membranes. In vitro, rotenone has been shown to promote the accumulation and aggregation

of alpha-synuclein and ubiquitin, cause oxidative damage, and endoplasmic reticulum stress, and lead to cell death.

In vivo, chronic exposure of rats to rotenone induces Parkinson's disease -like symptoms, including dopaminergic neurodegeneration and the occurrence of cytoplasmic inclusions similar to Lewy bodies. Recent studies show that chronic exposure of Drosophila to rotenone recapitulates key features of Parkinsonism, including selective loss of dopaminergic neurons and locomotor deficits.[figure-3] Although there are also study showing contradictory results, most of the evidences are consistent and suggesting that rotenone exposure contributes to Parkinson's disease -like symptom and that rotenone-based Parkinson's disease models can be used to test potential compounds for Parkinson's disease intervention. [33]

Tremorine and Oxotremorine Antagonism:

The muscarinic agonist's tremorine and oxotremorine induce parkinsonism-like signs such as tremor, ataxia, spasticity, salivation, lacrimation and hypothermia. These signs are antagonized by anticholinergic drugs. The oxotremorine antagonism has been proven to be a reliable method for testing central anticholinergic activity. The overt isomorphism between the animal model and the symptoms of Parkinson's disease recommend this test for screening of anti-Parkinson drugs. However, the model measures only central anticholinergic activity. [33]

Reserpine Antagonism:

Reserpine induces depletion of central catecholamine stores. The sedative effect can be observed in mice shortly after injection, followed by signs of eyelid ptosis, hypokinesia, rigidity, catatonia, and immobility. These phenomena can be antagonized by dopamine agonists. Locomotor activity and grooming scores of drug treated animals are compared with controls treated with reserpine and vehicle only by analysis of variance. [33]

Purpose of this study:

The existing conventional strategies that target Parkinson's disease are associated with numerous side effects and possess an economic burden. In recent years, there has been a growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants. A natural product is a chemical compound or substance produced by a living organism that is, found in nature. In the broadest sense, natural products include any substance produced by life. The compositional of C. sativum. Linalool (60–80%), geraniol (1.2%–4.6%), terpinen-4-ol (3%), a-terpineol (0.5%) Hydrocarbons- g-terpinene (1–8%), r-cymene (3.5%), limonene (0.5%–4.0%), a-pinene (0.2%–8.5%), camphene (1.4%), myrcene (0.2%–2.0%) Camphor (0.9%–4.9%) Esters Geranyl acetate (0.1%–4.7%), linalyl acetate (0%–2.7%) [40]

Coriandrum sativum is also a natural product commonly known as coriander and belonging to the Apiaceae family is cultivated throughout the world known for its nutritional value. In traditional medicine, coriander is recommended for the relief of pain, anxiety, flatulence, loss of appetite and convulsions. [42]

Remarkably, L-linalool which has been efficacious in treating neurological issues has already been reported has found to the more exciting treatment. This product possesses neuroprotective property, Anti-oxidative, Anti-inflammatory, nootropic, Anti-depressant, Anti-convulsant, Anti-alzheimer properties. It is commonly used in traditional medicine for memory enhancing and various other mental disorders from centuries and is known not to produce any toxic or adverse effect in human but probably there is no scientific evidence available on toxicity till date. [41]

Based on this present study has been designed to evaluate the anti-parkinsonism effect of L-linalool and its ability to prevent early symptoms such as olfactory discrimination and short-term memory impairments in Parkinson's. And evaluate its effect on different bio amine associated with Parkinson's.

LITERATURE REVIEW

Rossana Migheli et al., **(2021)** aimed at investigating the hypothesis that LIN's neuroprotective, antinociceptive and anti-inflammatory properties descend from its ability to act as antioxidant. The study challenges this hypothesis by verifying whether LIN may counteract hydrogen peroxide (H_2O_2)-induced oxidative stress in PC12 cells. Results indicate that LIN protects PC12 cells from H_2O_2 -induced oxidative stress. This mechanism could justify the neuroprotective, anti-nociceptive and anti-inflammatory effects of this compound and suggest LIN as a potential therapeutic agent for the management oxidative stress-mediated pain. [43]

Chunyu Yuan et al., **(2021)** studied that linalool intake increased the survival of the AD model flies during development in a dose dependent manner, while the survival of wild-type flies was not affected even at high linalool concentrations. Linalool also decreases Aβ-induced apoptosis in eye discs as well as the larval brain. Moreover, linalool intake was found to reduce neurodegeneration in the brain of adult AD model flies. However, linalool did not affect the total amount of Aβ42 protein or Aβ42 aggregation. Rather, linalool decreased Aβ-induced ROS levels, oxidative stress, and inflammatory response in the brains of AD model flies. Furthermore, linalool attenuated the induction of oxidative stress and gliosis by Aβ1-42 treatment in the rat hippocampus. Taken together, our data suggest that linalool exerts its beneficial effects on AD by reducing Aβ42-induced oxidative stress and inflammatory reactions. [44]

***Lucia Caputo et al.,* (2020**) investigated neuroprotective effect of lavender and coriander essential oils (EOs) and their main active constituent linalool, against the neurotoxicity elicited by Aβ1-42 oligomers, a key molecular factor in the neurodegeneration of AD. Lavender and coriander EOs and linalool also showed to counteract the increase of intracellular reactive oxygen species production and the activation of the pro-apoptotic enzyme caspase-3 induced by Aβ1-42 oligomers. Our findings provide further evidence that these EOs and their main constituent linalool could be natural agents of therapeutic interest against Aβ1-42-induced neurotoxicity. [45]

***Jalles Dantas de Lucena et al.,* (2020)** studied the neuroprotective effects of LIN on a model of Parkinson's disease. For that, maleWistar rats were divided into groups. Then the animals were subjected to behavioral tests. Then, the animals were euthanized, and the striatum, hippocampus, and prefrontal cortex were processed for neurochemistry. Results showed that LIN significantly prevented the reduction in TH and DAT expressions demonstrated in the right 6-OHDA-lesioned striatum. All these data strongly suggest that LIN presents a neuroprotective action in hemiparkinsonian rats, probably related to the drug anti-inflammatory and antioxidant activities. [46]

***Joon Min Cha et al.,* (2020)** investigated the MeOH extract of the aerial parts of Coriandrum sativum Linn. An extended phytochemical investigation of the aerial parts of C. sativum led to the isolation and identification of seven compounds (1–7) including two new isocoumarin glycosides (1–2) and a new phenolic glycoside (5). The chemical structures of the new compounds (1, 2, and 5) were elucidated by analysis of 1D and 2D NMR (1H and 13C NMR, COSY, HSQC, and HMBC) and HRESIMS data as well as by using chemical methods. Compounds 1–3 and 7 were stimulants of NGF release, with levels of NGF stimulated at 127.23 ± 1.89%, 128.22 ± 5.45%, 121.23 ± 6.66%, and 120.94 ± 3.97%, respectively. Furthermore, the aglycones of 1 and 2 (1a and 2a) showed more potent NGF secretion activity and anti-neuroinflammatory effect than did their glycosides (1a : 130.81 ± 5.45% and 2a : 134.44 ± 5.45%).[47]

***Keuri Eleutério Rodrigues et al*., (2019)** aimed to investigate the effects of Coriandrum sativum aqueous extract (CSAE) on the rat progeny of mothers exposed to methylmercury (MeHg). Based on the behavioral tests, which detected large locomotor, balance, and coordination improvements, as well as a reduction in oxidative stress, we conclude that CSAE had positive functional results in the offspring of rats exposed to MeHg. [48]

***Cecilia Raccagni1 et al.,* (2018)** aimed to identify quantitative gait parameter differences in Parkinson's disease and a Parkinson's disease patients using sensor-based gait analysis and to correlate gait parameters with clinical rating scales. Findings suggest that patients with a Parkinson's disease had more severely impaired gait parameters than Parkinson's disease patients despite similar disease severity. Instrumented gait analysis provides complementary rater independent, quantitative parameters that can be exploited for clinical trials and care. [49]

***Józef A Opara et al.,* (2017)** reviewed the presents possibilities of motor assessment in Parkinson`s disease. Motor assessment of Parkinson`s Disease can be divided into clinimetrics, assessment of balance and posture, arm and hand function, and gait/walking. These are many clinimetric scales used in Parkinson`s Disease, the most popular being the Hoehn and Yahr stages of progression of the disease and Unified Parkinson's disease Rating Scale. Balance and posture can be assessed by clinimetric scales like the Berg BS, Tinetti, Brunel BA, and Timed Up and Go Test, or measured by posturometric platforms. Among skill tests, the best known are: the Purdue Pegboard Test, Nine-Hole Peg Test, Jebsen and Taylor test, Pig- Tail Test, Frenchay Arm Test, Action Research Arm Test, Wolf FMT and Finger-Tapping Test. Among motricity scales. Recently, the most popular is three-dimensional analysis of movement. [50]

***Quan Feng Liu et al.,* (2016)** investigated the neuroprotective effects of an ethanol extract of Coriandrum sativum (C. sativum) leaves on Aβ cytotoxicity and examined the molecular mechanisms underlying the beneficial effects. Although recent studies have shown the benefits of the inhalation of C. sativum oil in an animal model of AD, the detailed molecular mechanisms by which C. sativum exerts its neuroprotective effects are unclear. Here, we found that treatment with C. sativum extract increased the survival of both Aβ-treated mammalian cells and Ab42- expressing flies. Moreover, C. sativum extract intake suppressed Aβ42-induced cell death in the larval imaginal disc and brain without affecting Aβ42 expression and accumulation. These results suggest that C. sativum leaves have antioxidant, anti-inflammatory, and ERK signaling inhibitory properties that are beneficial for patients with AD.[51]

***Hyeon Park et al.,* (2016)** aimed to assess neuroprotective effects of (-)-linalool against oxygenglucose Deprivation/reoxygenation (OGD/R)-induced cortical neuronal injury, an in vitro model of ischemic stroke. (-)- Linalool significantly attenuated OGD/R-evoked cortical neuronal injury/death, although it did not inhibit N-methyl-Daspartate (NMDA)-induced excitotoxicity. Linalool significantly reduced intracellular oxidative stress during OGD/R-induced injury, as well as scavenging peroxyl radicals (Trolox equivalents or TE = 3.8). This anti-oxidant effect was found to correlate with the restoration of OGD/Rinduced decreases in the activities of SOD and catalase. In addition, (-)-linalool inhibited microglial migration induced by monocyte-chemoattractant protein-1 (MCP-1), a chemokine released by OGD/R. These findings show that (-)-linalool has neuroprotective effects against OGD/R-induced neuronal injury, which may be due to its anti-oxidant and anti-inflammatory activities. [53]

***José-Luis Ríos et al.,* (2016)** review compiled with the data on the principal medicinal plants and natural products as potential antiparkinsonian agents. They act by different mechanisms, such as the inhibition of α-synuclein condensation, reduction of oxidative stress and neuro-inflammation, increase of dopaminergic neurons survival, or the blockade of the A2A receptor. [52]

***Ka Young Kim et al.,* (2015)** investigated whether (-)-linalool and linalyl acetate, the major components of lavender, can protect SH-SY5Y cells against sodium nitroprusside (SNP)-induced cytotoxicity. Findings, showing that (-)-linalool protected SH-SY5Y cells against SNP-induced cytotoxicity by decreasing the production of NO, suggested that (L)-linalool has anti-oxidant activity in the central nervous system and may be a potential therapeutic drug in patients with neurodegenerative diseases. [54]

***Soghra Mehri et al.,* (2014)** evaluated the possible effects of linalool which is a naturally enantiomer monoterpene compound. Linalool has shown antioxidant properties in several studies. Male Wistar rats were treated with ACR (50 mg/kg ip) alone or with linalool (12.5, 25, 50 and 100 mg/kg ip) for 11 days. In another 2 groups rats were treated with linalool (12.5 mg/kg ip) 3 days after and before ACR administration. Then behavior index (gait score) was examined for rats. After that, rats were sacrified and molondialdehyde (MDA) as a marker of lipid peroxidation and glutathione (GSH) content were determined in brain tissue. Exposure to ACR led to severe gait abnormalities and treatment with linalool significantly reduced abnormalities. ACR reduced GSH content and increased level of MDA in cerebral cortex. Linalool increased GSH content while decreased ACR-induced lipid peroxidation in rat brain tissue and the best protocols were initiation of supplementation before or simultaneous with ACR administration. [55]

***Oana Cioanca et al.,* (2014)** analyzed the possible anxiolytic, antidepressant and antioxidant proprieties of inhaled coriander volatile oil extracted from Coriandrum sativum var. microcarpum in beta-amyloid (1–42) rat model of Alzheimer's disease The beta-amyloid (1–42)-treated rats exhibited the following: decrease of the locomotor activity, the percentage of the time spent and the number of entries in the open arm within elevated plus-maze test and decrease of swimming and immobility times within forced swimming test. Exposure to coriander volatile oil significantly improved these parameters, suggesting anxiolytic- and antidepressant-like effects. Moreover, coriander volatile oil decreased catalase activity and increased glutathione level in the hippocampus. Our results suggest that multiple exposures to coriander volatile oil can be useful as a mean to counteract anxiety depression and oxidative stress in Alzheimer's disease conditions. [56]

***Oana Cioanca et al.,* (2013**) studied the effects of inhaled coriander volatile oil (1% and 3%, daily, for 21 days) extracted from C. sativum var. microcarpum on spatial memory performance were assessed in an Aβ(1–42) rat model of Alzheimer's disease and the results suggest that exposure to coriander volatile oil ameliorates Aβ(1–42)-induced spatial memory impairment by attenuation of the oxidative stress in the rat hippocampus.[57]

***Adalberto A. Castro et al.,* (2012)** demonstrated that rodents treated intranasally with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) display time-dependent impairments in olfactory, emotional, cognitive and motor functions associated with disruption of dopaminergic neurotransmission in different brain structures conceivably analogous to those observed during different stages of Parkinson's disease (PD) and results provide new insights in experimental models of Parkinson's disease, indicating that Li and VPA may represent new therapeutic tools for the management of olfactory and cognitive symptoms associated to early preclinical phases of Parkinson's disease, together with their neuroprotective potential demonstrated in previous research. [58]

***G Park et al.,* (2012)** examined the protective effects of a standardized CS leaf extract against oxidative stress in human HaCaT keratinocytes. Oxidative defense factors, including nuclear factor erythroid-derived 2-related factor 2 (Nrf2), are centrally involved in repairing skin cells or protecting them from oxidative damage. Results suggest that CS protects human keratinocytes from H_2O_2-induced oxidative stress through antioxidant effects. [60]

***Kotisree Lahiri et al.,* (2012)** reported the protocol for plant regeneration through callus morphogenesis in four strains belonging to two different varieties of Mucuna pruriens. Friable, soft and nodular callus was induced from nodal and internodal segments of in vitro-grown seedlings on modified Murashige and Skoog's (MS) medium supplemented with 2,4-dichlorophenoxyacetic acid (2,4-D), α- naphthaleneacetic acid (NAA) and 6-benzylaminopurine (BAP). The regenerated shoots were rooted in vitro in half-strength of liquid MS medium supplemented with various levels of NAA. The regenerates were acclimatized for 2–3 weeks and showed about 80 % survival rate after transferring to the field. Cytological analysis revealed chromosome number stability of all the regenerates with complete absence of aneuploidy. Random Amplified Polymorphic DNA (Parkinson's disease) and Inter Simple Sequence Repeat (ISSR) analyses of total genomic DNA supported stability at the molecular level among Alzheimer's disease (AD), the most common neurodegenerative disease, has a complex and widespread pathology that is all the clones of these strains when compared with their mother plants. [59]

***Vinod Nair et al.,* (2012)** evaluated the anti-inflammatory and anti-granuloma activities of Coriandrum sativum hydroalcoholic extract (CSHE) in experimental models. CSHE at the highest dose tested (32 mg/kg) produced a significant reduction (P>0.05) in paw edema after carrageenan administration. CSHE treatment also reduced dry granuloma weight in all treated animals. Serum IL-6 and IL-1 levels were significantly (P>0.05) lower in the CSHE (32 mg/kg)-treated group as compared to control. Although there was an increase in serum TNF-α level in the CSHE-treated group as compared to control, TNF-R1 expression on peritoneal macrophages was found to be reduced. Conclusion: Thus, the result of this study demonstrates the anti-inflammatory and anti-granuloma activities of CSHE in experimental models, and validates its traditional use for the management of arthritis and other inflammatory disorders. [61]

***Fabio Blandini et al.*, (2011)** reveiwed the pathogenesis and pathophysiology of this neurodegenerative disorder. These models have been classically based on the systemic or local (intracerebral) administration of neutoxins that are able to replicate most of the pathological and phenotypic features of PARKINSON'S DISEASE in mammals (i.e. rodents or primates). If a substantial and reproducible nigrostriatal lesion is required (e.g. for testing therapeutic interventions aimed at counteracting Parkinson's disease -related cell death), a classic toxic model such as one based on the administration of 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine or 6-hydroxydopamine will adequately serve the purpose. On the other hand, if selected molecular mechanisms of Parkinson's disease pathogenesis must be investigated, transgenic models will offer invaluable insights. Therefore, until the 'perfect' model is developed, indications to use one model or another will depend on the specific objectives that are being pursued. [62]

***Richard L Doty et al.*, (2011)** reviewed the olfactory dysfunction in an early 'pre-clinical' sign of Parkinson's disease (PD). The olfactory bulb is implicated in the dysfunction, since only those syndrome with olfactory bulb pathology exhibit significant smell loss. The role of dopamine in the production of olfactory system pathology is enigmatic, as overexpression of dopaminergic cells within the bulb's glomerular layer is a common feature of PARKINSON'S DISEASE and most animal models of PARKINSON'S DISEASE. Damage to cholinergic, serotonergic, and noradrenergic systems is likely involved, since such damage is most marked in those diseases with the most smell loss. [63]

***Muralikrishnan Dhanasekaran et al*., (2008)** demonstrated the antioxidant activity of *Mucuna pruriens* was by its ability to scavenge DPPH radicals, ABTS radicals and reactive oxygen species. *Mucuna pruriens* significantly inhibited the oxidation of lipids and deoxyribose sugar. *Mucuna pruriens* exhibited divalent iron chelating activity and did not show any genotoxic/mutagenic effect on the plasmid DNA. These results suggest that the neuroprotective and neurorestorative effect of *Mucuna pruriens* may be related to its antioxidant activity independent of the symptomatic effect. In addition, the drug appears to be therapeutically safe in the treatment of patients with Parkinson's disease. [64]

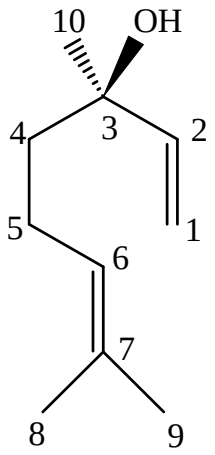
***Masoumeh Emamghoreishi et al.,* (2004)** aimed to study the aqueous extract of *Coriandrum sativum* seed and its anxiolytic effect in mice. Additionally, its effect on spontaneous activity and neuromuscular coordination were evaluated. The results showed that the aqueous extract of *Coriandrum sativum* seed has anxiolytic effect and may have potential sedative and muscle relaxant effects. [65]

***Bala V. Manyam et al.,* (2004)** evaluated the neurorestorative effect of Mucuna pruriens cotyledon powder on the nigrostriatal tract of 6-OHDA lesioned rats. Mucuna pruriens cotyledon powder significantly increased the brain mitochondrial complex-I activity but did not affect the total monoamine oxidase activity (in vitro). Unlike synthetic levodopa treatment, Mucuna pruriens cotyledon powder treatment significantly restored the endogenous levodopa, dopamine, norepinephrine and serotonin content in the substantia nigra. This additional finding of a neurorestorative benefit by Mucuna pruriens cotyledon powder on the degenerating dopaminergic neurons in the substantia nigra may be due to increased complex-I activity and the presence of NADH and coenzyme Q-10. [66]

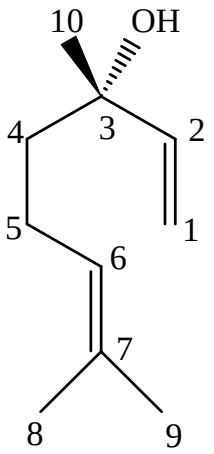
DRUG PROFILE

L-LINALOOL [68]

Structure:



3R-(-)-Linalool



3S-(+)-Linalool

Chemical names **:** Linalool, Linalol, linalyl alcohol

IUPAC name **:** 3, 7-dimethylocta-1, 6-dien-3-ol

Chemical formula **:** C10H18O

Molecular weight **:** 154.25

Appearance **:** Colorless to pale yellow liquid

Odour **:** Pleasant floral or woody scent, with a touch of spiciness; Similar to bergamot oil and French lavender

Taste **:** Spicy, citrus taste

Density **:** 0.865 at 15 °C

Boiling point **:** 197.5 °C

Melting point **:** <25°C

Solubility **:** Soluble in alcohol, ether, fixed oils, and propylene glycol; insoluble in glycerin

Octanol/water partition co-eNfficient : log K o/w = 2.97

Log P **:** 2.97

H Bond donor **:** 1

H Bond acceptor **:** 1

Pharmacological properties

Metabolism:

Linalool when administered orally, or by aerosol, to rats produce a significant increase in the activities of cytochrome P-450-dependent mono-oxygenase, as well as the level of cytochrome P450. Furthermore, it was observed that along with cytochrome P-450, cytochrome b, was also induced to a considerable extent and the percentage increase in drug metabolizing enzyme activities paralleled the flavoprotein reductase activity. [67]

Therapeutic uses:

Neuroprotective Property, Anti-Oxidative, Anti-Inflammatory, Nootropic, Anti-depressant, Anti-convulsant, Anti-alzheimer. [41]

AIM AND OBJECTIVES

AIM

The aim of the study is to evaluate the prevention of primary symptoms of Parkinson's disease using Reserpine induced Parkinson model.

OBJECTIVES

Our study is mainly focusing on the effect of L-linalool in the treatment of early symptoms of Parkinson's disease such as olfactory discrimination and short- term memory impairments.

Coriandrum sativum commonly known as coriander and belonging to the Apiaceae family is cultivated throughout the world known for its nutritional value. In traditional medicine, coriander is recommended for the relief of pain, anxiety, flatulence, loss of appetite and convulsions. [42]

Linalool (60–80%) is the main constituent of *Coriandrum sativum.* L-linalool which has been efficacious in treating neurological issues has already been reported has found to the more exciting treatment. This product possesses neuroprotective property, anti-oxidative, anti-inflammatory, nootropic, anti-depressant, Anti-convulsant, Anti-alzheimer properties. It is commonly used in traditional medicine for memory enhancing and various other mental disorders from centuries and is known not to produce any toxic or adverse effect in human but probably there is no scientific evidence available on toxicity till date. [41] Hence based on the observation, the main objective of the study is,

To evaluate the Anti-Parkinson's activity of the L-linalool in treatment of early symptoms Parkinson's using

- *In-vivo* Reserpine induced Parkinson model.

PLAN OF WORK

PHARMACOLOGICAL EVALUATION

In-vivo Study

In-vivo Reserpine induced Parkinson model.

Parameters:-

Behavioral tests:

- Evalution of Tremor and Akinesia
  - **Locomotor activity**: Actophotometer , Open field exploratory behavior apparatus
- Grip strength: Rotarod Apparatus
- Anti-depressive effect: Forced swim test

Estimation of Neurotransmitters

1. Neurochemical assays Determination of dopamine (DA) by HPLC
2. Neurochemical assays Determination of 3,4-Dihydroxyphenylacetic acid (DOPAC) by HPLC
3. Neurochemical assays Determination of homovanillic acid (HVA) contents in the rat striatum by HPLC

Statistical analysis

The data were analyzed using one way analysis of variance (ANOVA) followed by Dunnett's "*t*" test. $P<0.05$ was considered as significant.

MATERIALS AND METHODS

DRUGS AND CHEMICALS USED

L-linalool are natural constituent which is purchased from (Sigma Aldrich) Bangalore. Reserpine was obtained from (Sigma Aldrich) Bangalore. All other chemicals and reagents used in the study were of analytical grade.

ETHICAL CONSIDERATIONS

Experimental protocols (Proposal number: NCP/IAEC/2021-22/03) and procedures used in this study were in accordance of the guidelines of CPCSEA and was approved by Institutional Animal Ethics Committee of Nandha College of Pharmacy, Erode. (Reg.No:688/PO/Re/S/02/CPCSEA)

EXPERIMENTAL ANIMALS

Wistar Albino rats and Juvenile male wistar rats were procured from the Animal house, Kerala Veterinary and Animal Sciences University, Mannuthy, Kerala. The procured animals were placed in quarantine area for 1 week before experiment. Animals were grouped and marked with picric acid for identification. The experimental animals were housed under ambient temperature (21±2˚C) and relative humidity (55±5%) with fixed 12h light and 12h dark cycle. The animals were used after an acclimatization period of five days in propylene cage in the laboratory environment. During acclimatization period animal was provided with standard pellet diet (Hindustan Lever Pvt Ltd., Bangalore) and clean drinking water *ad libitum*.

EXPERIMENTAL DESIGNS

IN-VIVO STUDY

IN-VIVO RESERPINE INDUCED PARKINSON MODEL [58]

The animals were divided into four groups consists of 6 animals each group. L-linalool was administered at a dose of 25mg and 50mg/kg. Reserpine was given to all groups at the dose of 5 mg/kg (i.p) once in a day for 5 days consecutively. The drug treatment was given for 5 days and observations were made after 24 hours of the last treatment of reserpine. All the groups have undergone behavioral and biochemical tests.

BEHAVIORAL TESTS [59-64]

1. EVALUTION OF TREMOR AND AKINESIA

After 24 h of last treatment animals were tested for induction of severity of tremors by giving the scores as follows: No tremors-0, Occasional twitches-1, Moderate or Intermittent twitches-2, Continues tremors-3. The number of tremors was counted for 5 min. If animals were not showing tremors then the score is 0, if animals showed 1 or 2 tremors then score is 1 if animals showed 3 or 5 tremors in 5 mins, then the score is 2 and for 6 or more tremors, score is 3.

Akinesia was determined by holding the tail of animal and putting the front paws on the platform and let the animal to walk while holding (number of steps taken with forelimbs of animal was counted for 3 min). [65-67]

2. LOCOMOTOR ACTIVITY

Actophotometer:

The spontaneous locomotor behavior of the animals was recorded individually for 5 min using a digital actophotometer. The apparatus consist of photoelectric cells, which are connected in circuit with a counter. When the beam of light falling on the photocell is cut off by the animal, a count was recorded for 10 min.

Figure No. 4: Actophotometer

Open-field exploratory behavior apparatus:

The open-field box was a cubic chamber (60×60×40 cm), with a white floor divided into 16 equal squares. It was placed in a quiet room with dim light. Rats were delivered to the testing room, 30 min prior to the experiment. Each animal was gently placed in the center of the box and allowed to move freely over a 5-min period. The number of lines crossed by four paws in the open field apparatus was recorded. The apparatus was cleaned before each trial. [68-70]

Figure No. 5: Open-field exploratory behavior apparatus

3. GRIP STRENGTH

Rotarod Apparatus:

The rotarod test was performed to evaluate the motor coordination of animals. Briefly, one day before the test, animals were pre-trained on the rotarod apparatus twice at 15 rpm speed for at least 5 min, until they reached a stable baseline performance. On the day of the experiment, animals were evaluated on the rod rotating at an accelerating speed (from 4 to 40 rpm), over five min. The time taken for the falling of the rat (latency time) from the rotating rod, was recorded and the mean value of time (seconds on the rod) from the two or three testing trials was then calculated. [71-75]

Figure No. 6: Rotarod apparatus

4. ANTI-DEPRESSIVE EFFECT

Forced swim test: In forced swim test the rats were individually forced to swim in a transparent vertical glass cylinder (45 cm high, 20 cm in diameter) filled with 27°C water to a depth of 20 cm. The duration of immobility of the animals (in sec) were measured for 6 min. 'Immobility' was defined as floating and treading water just enough to keep the nose above water. The water was changed for each animal. [77]

Figure No. 7: Forced swimming Test

ESTIMATION OF NEUROTRANSMITTERS

I. **Neurochemical assays Determination of dopamine (DA) by HPLC**

II. **Neurochemical assays Determination of 3,4-Dihydroxyphenylacetic acid (DOPAC) by HPLC**

III. **Neurochemical assays Determination of Homovanillic acid (HVA) by HPLC**

Procedure

The striatal contents of DA, DOPAC, and HVA were determined by HPLC. Homogenates were prepared in 10% $HclO_4$, sonicated for 30 s and centrifuged at 4 °C (15,000 rpm, 15 min). Then, the supernatant was filtered (0.2 μm, Millipore), and a 20 μL sample was injected into a high performance liquid chromatography (HPLC) column. For that, an electrochemical detector (model L-ECD-6A from Shimadzu, Japan) coupled to a column (Shim-Pak CLCODS, 25 cm) with a flux of 0.6 mL/min was employed. A mobile phase was prepared with monohydrated citric acid (150 mM), sodium octyl sulfate (67 mM), 2% tetrahydrofuran, and 4% acetonitrile in deionized water. The mobile phase pH was adjusted to 3.0 with NaOH (10 mM). Monoamines were quantified by comparison with DA, DOPAC, and HVA standards, processed the same manner as the samples. The results are expressed as ng/g tissue. [78]

STATISTICAL ANALYSIS

ANOVA (Analysis of Variance)

The data were analysed using One way ANOVA followed by Dunnett's test $p<0.05^{*}$, $p<0.01^{**}$, $p<0.001^{***}$ were considered as significant, more significant, most significant respectively.

RESULTS

IN-VIVO STUDY OF RESERPINE INDUCED PARKINSON MODEL

BEHAVIORAL TESTS

EVALUTION OF TREMOR AND AKINESIA

Table No. 1: Effect of L-linalool on tremor in reserpine-induced motor defects

S.NO	GROUPS	TREMOR (Score)
1	Normal control (Vehicle)	0.0±0.00***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	2.6±0.15
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	1.6±0.03*
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	1.0±0.01**

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, & *P<0.05 Vs Reserpine induced control.

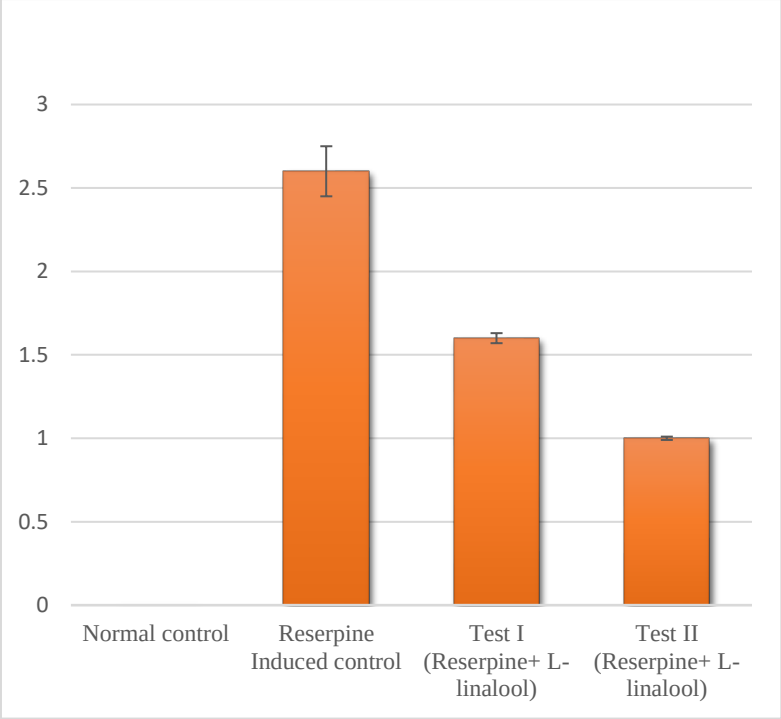


Figure No. 8: Effect of L-linalool on tremors in reserpine-induced motor defects

Effect of L-linalool on tremor induced by reserpine was analyzed in the different groups of rat Figure no 8. Score of tremor in normal control group was 0. Where as Reserpine induced non drug treated group score was 2.6±0.15.

Linalool at a dose (25mg/kg) treated animal showed a significant ($P<0.01$) reduction in tremor score (1.6±0.03) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a moderate significant ($P<0.001$) reduction in tremor score (1.0±0.01) when compared to reserpine control.

From the above finding it shows that L-linalool effectively prevent the tremor production.

Table No.2 : Effect of L-linalool on akinesia in reserpine-induced motor defects

S.NO	GROUPS	AKINESIA (No. Of steps taken with forelimbs)
1	Normal control (Vehicle)	38.1±1.61***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	22.1±0.98
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	29.5±0.83**
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	35.8±0.75***

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, &*P<0.05 Vs Reserpine induced control

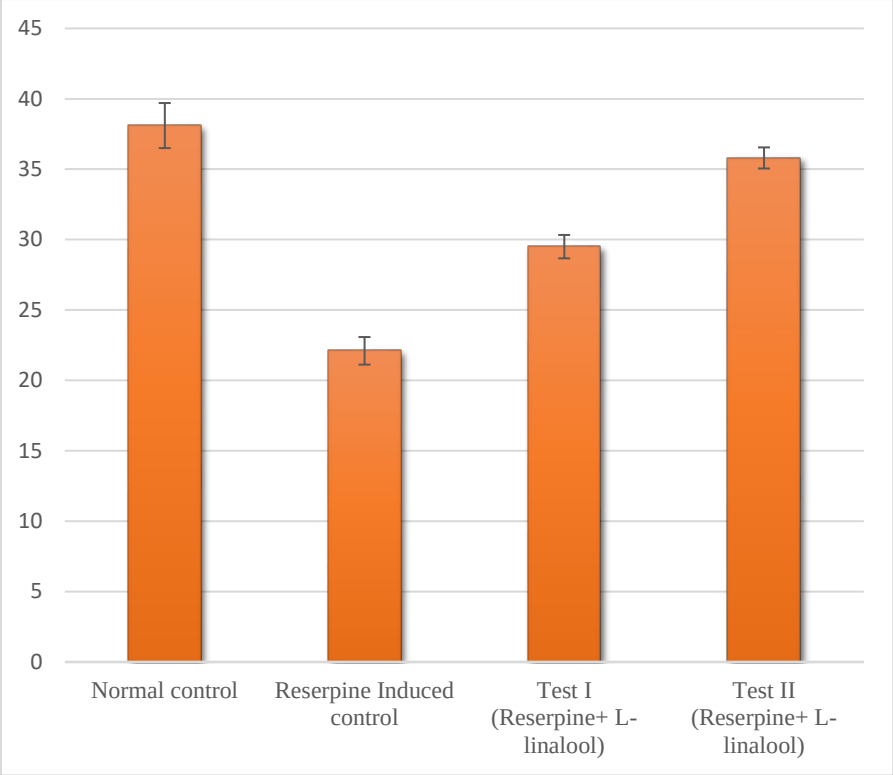


Figure No. 9: Effect of L-linalool on akinesia in reserpine-induced motor defects

Effect of L-linalool on akinesia induced by reserpine was analyzed in the different groups of rat Figure no 9. Number of steps taken by normal control group was 38.1±1.61 (P< 0.001). But in reserpine induced non drug treated group number steps was reduced 22.1±0.98.

Linalool at a dose (25mg/kg) treated animal showed a moderate significant (P<0.01) reduction in number of steps taken (29.5±0.83) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a more significant (P<0.001) reduction in number of steps taken (35.8±0.75) when compared to reserpine control.

From the above finding it shows that L-linalool effectively prevent the akinesia induced by reserpine.

LOCOMOTOR ACTIVITY

Table No. 3: Effect of L-linalool on locomotor activity by actophotomer in reserpine-induced motor defects.

S.NO	GROUPS	LOCOMOTOR ACTIVITY (In 10 minutes)
1	Normal control (Vehicle)	78.3±1.63***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	29.6±1.03
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	60±1.41**
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	70±0.63***

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, & *P<0.05 Vs Reserpine induced control.

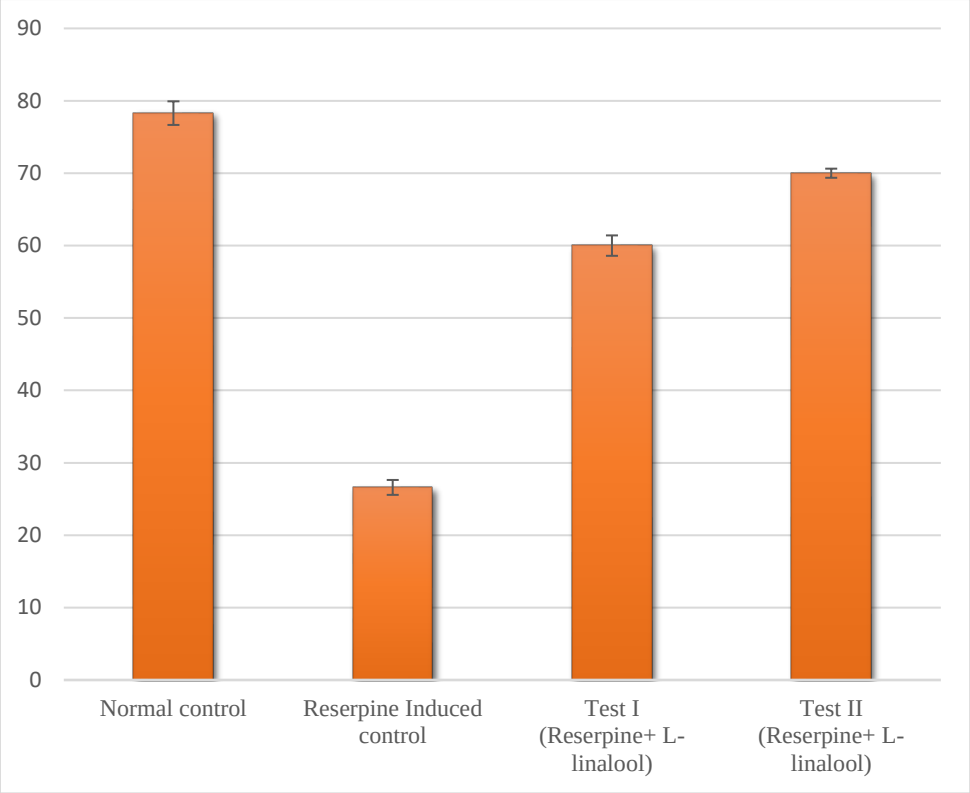


Figure No. 10: Effect of L-linalool on locomotor activity by actophotomer in reserpine-induced motor defects

Effect of L-linalool on Locomotor activity in reserpine induced animals was analyzed in the different groups of rat using Actophotometer Figure no 10. Locomotor activity in normal control group was 78.3±1.63 ($P< 0.001$). But in reserpine induced non drug treated group locomotor activity was reduced 29.6±1.03.

Linalool at a dose (25mg/kg) treated animal showed a moderate significant ($P<0.01$) increased the locomotor activity (60±1.41) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a more significant ($P<0.001$) increased the locomotor activity (70±0.63) when compared to reserpine control.

From the above finding it shows that L-linalool effectively increase the locomotor activity in reserpine induced groups.

Table No.4: Effect of L-linalool on locomotor activity by Open field in reserpine-induced motor defects

S.NO	GROUPS	LOCOMOTOR ACTIVITY (No. of crossing)
1	Normal control (Vehicle)	30.6±0.81***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	20.6±0.81
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	24.16±0.75**
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	27.16±0.75***

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, & *P<0.05 Vs Reserpine induced control

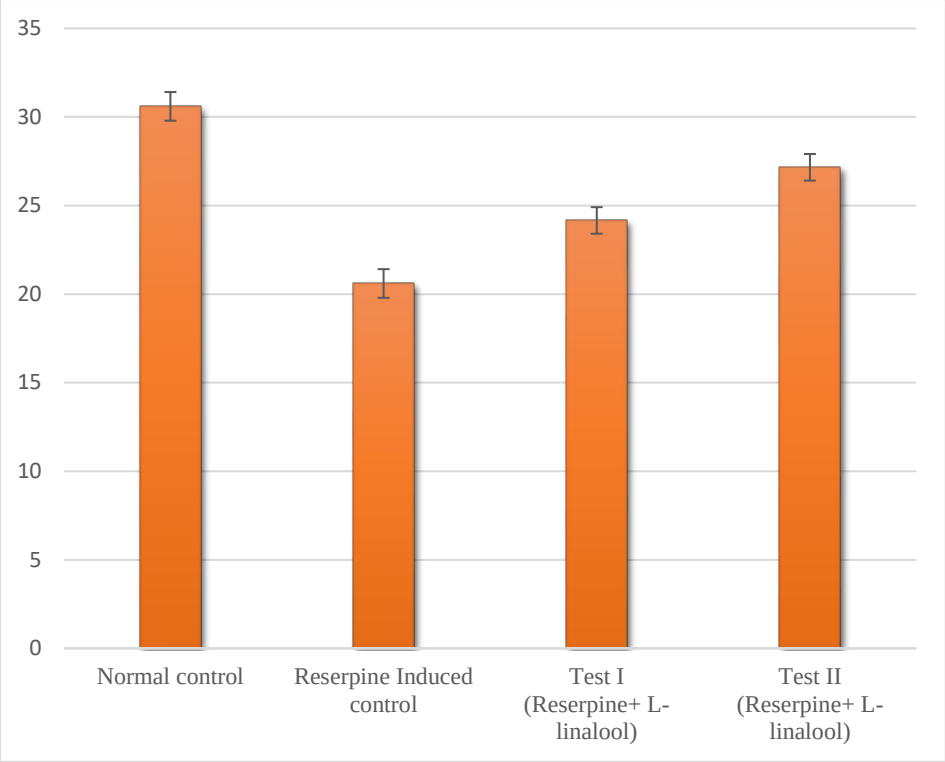


Figure No. 11: Effect of L-linalool on locomotor activity by Open field in reserpine-induced motor defects

Effect of L-linalool on Locomotor activity in reserpine induced animals was analyzed in the different groups of rat using open field method Figure no 11. Locomotor activity in normal control group was 30.6±0.81 (P< 0.001). But in reserpine induced non drug treated group locomotor activity was reduced 20.6±0.81.

Linalool at a dose (25mg/kg) treated animal showed a moderate significant (P<0.01) increased the locomotor activity (24.16±0.75) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a more significant (P<0.001) increased the locomotor activity (27.16±0.75) when compared to reserpine control.

From the above finding it shows that L-linalool effectively increase the locomotor activity in reserpine induced groups.

GRIP STRENGTH

Table No. 5: Effect of L-linalool on grip strength by rotarod apparatus in reserpine-induced motor defects

S.NO	GROUPS	GRIP STRENGTH (Latency to fall in sec)
1	Normal control (Vehicle)	31.3±1.03***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	15.83±1.16
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	26.5±0.54**
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	28±0.89***

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, & *P<0.05 Vs Reserpine induced control

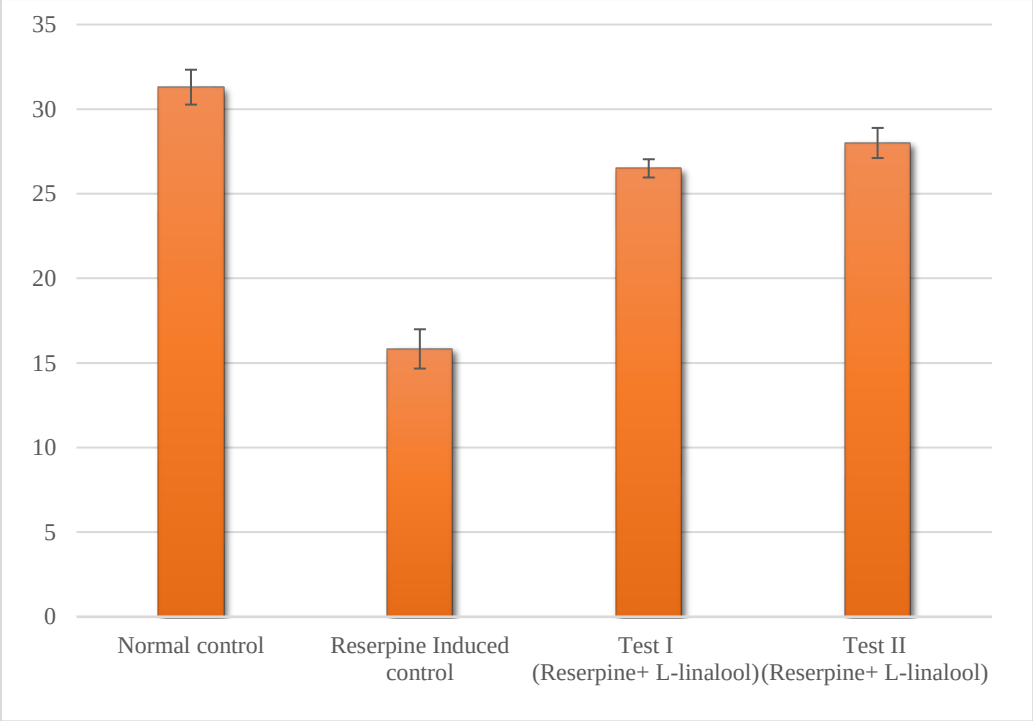


Figure No. 12: Effect of L-linalool on grip strength by rotarod apparatus in reserpine induced motor defects

Effect of L-linalool on grip strength in reserpine induced animals was analyzed in the different groups of rat Figure no 12. Latency to fall by normal control group was 31.3±1.03 (P< 0.001). But in reserpine induced non drug treated group grip strength was reduced hence lantency to fall is increased 15.83±1.16.

Linalool at a dose (25mg/kg) treated animal showed a moderate significant (P<0.01) increased the grip strength (26.5±0.54) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a more significant (P<0.001) increased the grip strength (28±0.89) when compared to reserpine control.

From the above finding it shows that L-linalool effectively increase the grip strength in reserpine induced Parkinson rats.

ANTI-DEPRESSIVE EFFECT

Table No.6: Effect of L-linalool on depressive effect by forced swim test in reserpine-induced motor defects

S.NO	GROUPS	ANTIDEPPRESSIVE EFFECT (Time of immobilization)
1	Normal control (Vehicle)	148.5±1.76***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	204.4±3.61
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	132.6±2.12**
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	121.5±1.64***

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, & *P<0.05 Vs Reserpine induced control

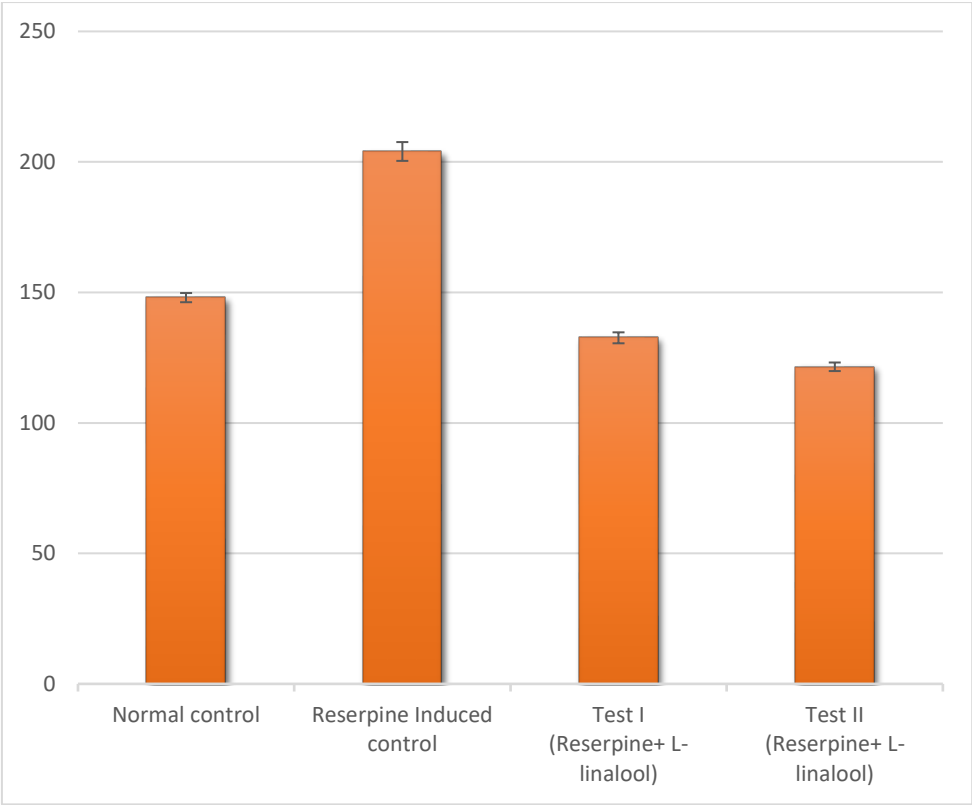


Figure No. 13: Effect of L-linalool on depressive effect by forced swim test in reserpine-induced motor defects

Effect of L-linalool on depressive effect in reserpine induced animals was analyzed in the different groups of rat Figure no 13. Time of immobilization in normal control group was 148.5±1.76 (P< 0.001). But in reserpine induced non drug treated group time of immobility was increased 204±3.6.

Linalool at a dose (25mg/kg) treated animal showed a moderate significant (P<0.01) decreased the time of immobility (132.6±2.12) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a more significant (P<0.001) decreased the time of immobility (121.5±1.64) when compared to reserpine control.

From the above finding it shows that L-linalool effectively decreases the time of immobility in reserpine induced groups. Which shows the anti-depressive effect of L-linalool.

ESTIMATION OF NEUROTRANSMITTERS

ESTIMATION OF DOPAMINE

Table No. 7: Effect of L-linalool in the level of dopamine in striatum

S.NO	GROUPS	DOPAMINE (µg/g)
1	Normal control (Vehicle)	3.08±0.26***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	0.76±0.2
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	2.4±0.1**
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	3.2±0.1***

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, &*P<0.05 Vs Reserpine induced control.

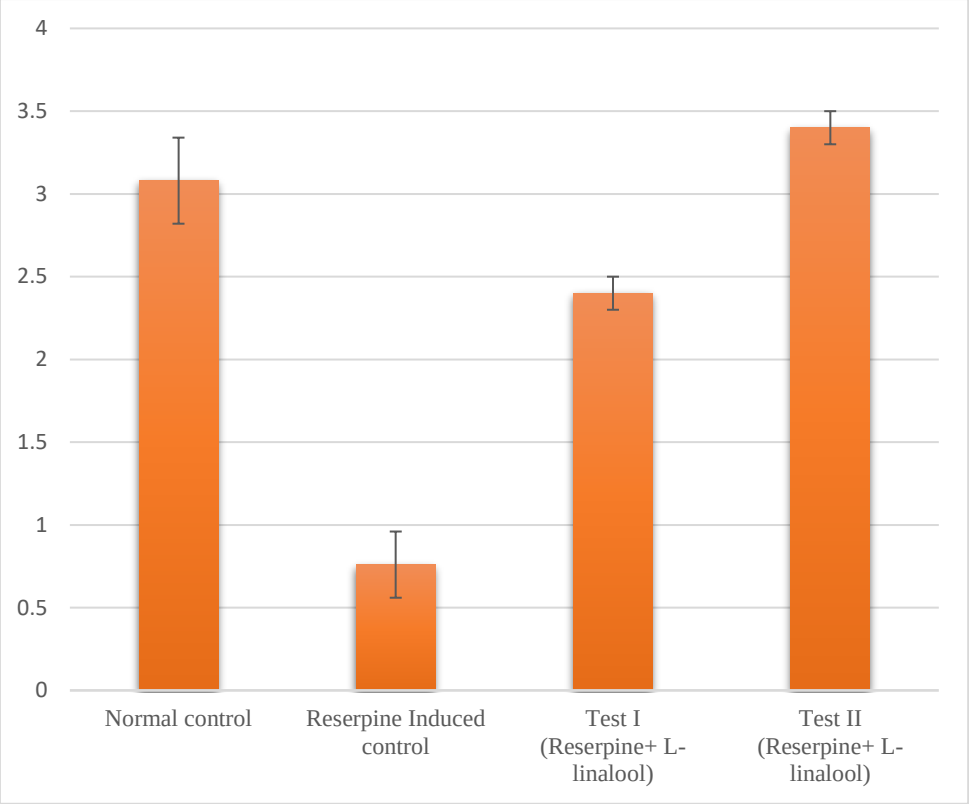


Figure No. 14: Effect of L-linalool in the level of dopamine in striatum

Effect of L-linalool on Level of dopamine in striatum was analyzed in the different groups of rat Figure no 14. Level of dopamine in striatum of normal control group was 3.08 µg/g ± 0.26 (P< 0.001). But in reserpine induced non drug treated group level of dopamine in striatum was reduced to 0.76 µg/g ± 0.2

Linalool at a dose (25mg/kg) treated animal showed a moderate significant (P<0.01) increased the level of dopamine in striatum (2.4±0.1) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a more significant (P<0.001) increased the level of dopamine in striatum (3.2±0.1) when compared to reserpine control.

From the above finding it shows that L-linalool effectively increase level of dopamine in striatum in reserpine induced groups.

Estimation of 3,4-Dihydroxyphenylacetic acid (DOPAC)

Table No. 8: Effect of L-linalool in the level of 3,4-Dihydroxyphenylacetic acid (DOPAC) in striatum

S.NO	GROUPS	DOPAC (µg/g)
1	Normal control (Vehicle)	4.1±0.15***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	1.26±0.23
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	2.7±0.3**
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	3.8±0.2***

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, &*P<0.05 Vs Reserpine induced control.

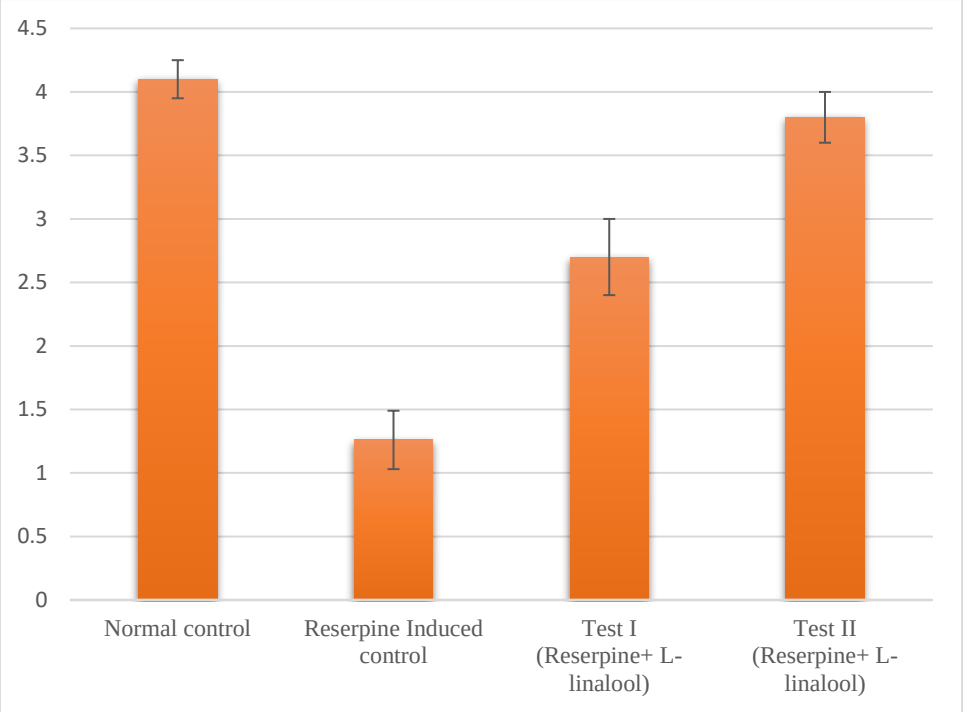


Figure No. 15: Effect of L-linalool in the level of 3, 4-Dihydroxyphenylacetic acid (DOPAC) in striatum

Effect of L-linalool on Level of 3, 4-Dihydroxyphenylacetic acid (DOPAC) in striatum was analyzed in the different groups of rat Figure no 15. Level of 3, 4-Dihydroxyphenylacetic acid (DOPAC) in striatum of normal control group was 4.1 µg/g ± 0.15 (P< 0.001). But in reserpine induced non drug treated group level of 3, 4-Dihydroxyphenylacetic acid (DOPAC) in striatum was reduced to 1.26 µg/g ± 0.23

Linalool at a dose (25mg/kg) treated animal showed a moderate significant (P<0.01) increased the level of dopamine in striatum (2.7±0.3) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a more significant (P<0.001) increased the level of 3, 4-Dihydroxyphenylacetic acid (DOPAC) in striatum (3.8±0.2) when compared to reserpine control.

From the above finding it shows that L-linalool effectively increase level of 3, 4-Dihydroxyphenylacetic acid (DOPAC) in striatum in reserpine induced groups.

Estimation of homovanillic acid (HVA)

Table No. 9: Effect of L-linalool in the level of homovanillic acid (HVA) in striatum

S.NO	GROUPS	HVA (ng/g)
1	Normal control (Vehicle)	573.2±14.8***
2	Parkinson's control (Reserpine) 5mg/kg. p.o	212.6±13.2
3	Test I (5mg/kg (p.o) Reserpine + 25mg/kg (p.o) L-linalool)	446.5±22.9**
4	Test II (5mg/kg (p.o) Reserpine + 50mg/kg (p.o) L-linalool)	525.1±26.7***

Values are mean ± SEM. Statistical analysis are done by using one way ANOVA followed by Dunnett's '*t*' test***P<0.001, **P<0.01, &*P<0.05 Vs Reserpine induced control.

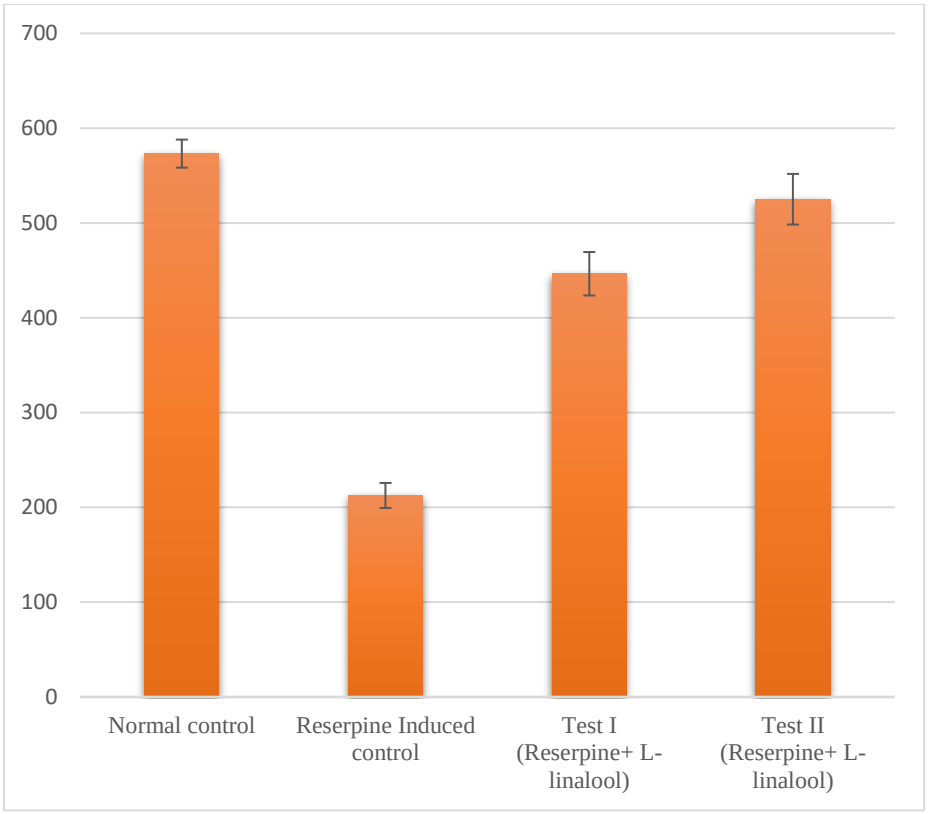


Figure No.16: Effect of L-linalool in the level of homovanillic acid (HVA) in striatum

Effect of L-linalool on Level of homovanillic acid (HVA) in striatum was analyzed in the different groups of rat Figure no 16. Level of homovanillic acid (HVA) in striatum of normal control group was 573 ng/g ±14.8 ($P< 0.001$). But in reserpine induced non drug treated group level of homovanillic acid (HVA) in striatum was reduced to 212.6 ng/g ± 13.2.

Linalool at a dose (25mg/kg) treated animal showed a moderate significant ($P<0.01$) increased the level of homovanillic acid (HVA) in striatum (446.5±22.9) when compared to reserpine control.

Linalool at a dose (50mg/kg) treated animal showed a more significant ($P<0.001$) increased the level of homovanillic acid (HVA) in striatum (525±26.7) when compared to reserpine control.

From the above finding it shows that L-linalool effectively increase level of homovanillic acid (HVA) in striatum in reserpine induced groups.

DISCUSSION

Parkinson Disease is a disorder of the central nervous system, involving primarily a degeneration of certain nerve cells in deep parts of the brain called the basal ganglia, and in particular a loss of nerve cells (or neurons) in a part of the brainstem called the substantia nigra. These cells make the neurochemical messenger dopamine, which is partly responsible for starting a circuit of messages that coordinate normal movement.

The dopamine is an important neurotransmitter that plays a critical role in a number of bodily functions, such as movement and coordination. As such, low dopamine levels can cause problems with movement.

Dopamine is the chemical messenger that transmits signals between the substantia nigra and the corpus striatum. Researchers may refer to this as the nigrostriatal pathway. Both the substantia nigra and corpus striatum form part of the basal ganglia. Which is a group of structures in the brain that help facilitate movement.

Low levels of dopamine may disrupt the nigrostriatal pathway and cause abnormal nerve firing patterns, which can result in movement problems. Evidence suggests that most people with PD lose 60–80% or more of dopamine-producing cells in the substantia nigra by the time they present symptoms like tremor, akinesia, muscle rigidity etc. In the present work, we demonstrated the neuroprotective property activity of L-linalool (LIN), in primary Parkinson induced rats. L-Linalool is a monoterpene found as the major component of essential oils of several aromatic species. For that, the rats were subjected to a model of Parkinson's disease which is induced by reserpine. Although the L-Linalool neuroprotective activity against acrylamide-induced neurotoxicity has been already detected [79].

The authors explored only its action against oxidative stress (GSH and lipid peroxidation measurements), in rat brain tissue. In addition, neuroprotective effects of nerolidol, a sesquiterpene alcohol, were observed on a rotenone-induced experimental model of PD. [80]

However, the present study is the first one focusing on the neuroprotective effects of L-Linalool, on a model of neurodegenerative disease, as Parkinson's disease (PD). [81] Others showed the neuroprotective effects of L-Linalool on the cortical neuronal injury induced by oxygen-glucose deprivation, which is an in vitro model of ischemic stroke. These authors concluded that LIN has neuroprotective effects, which may be due to its antioxidant and anti-inflammatory activities. Interestingly, the neuroprotective effects of L-Linalool were also demonstrated for neuropathological and amyloid-beta-induced cognitive deficits, in animal models of AD in mice .In both studies, L-Linalool antioxidant and antiinflammatory effects were also implicated with the drug neuroprotection. But in this study we were analyzed its neuroprotective activity towards Parkinson. [82]

Tremor occurs due to lower levels of dopamine in the brain, which cause problems with movement. It differs from other types of tremors as it commonly occurs when at rest and may present with characteristic pill rolling in the hands. L-linalool at the dose of (25 and 50 mg/kg, p.o.) produced a significant reduction of tremor in rats, which is induced by reserpine.

Akinesia and muscle rigidity also caused as a result of a lack of dopamine. Your brain produces dopamine and passes it along into your body by neurons. Due the damage of neuron. Dopamine levels are thought to disrupt the balance between the muscles which extend and relax for each movement, resulting in rigidity and no movement situation. L-linalool was also able to increase the locomotor activity and grip strength in rats. Reserpine induced motor defect

was significantly reversed by L-linalool. Amelioration of symptoms of reserpine by L-linalool demonstrates its Anti-Parkinson's activity.

Depression is one of the problems of Parkinson's disease. The challenges of Parkinson's disease are enough to cause depression. But the scientists also believes that depression in Parkinson's might also come from change of certain chemical like dopamine. L-linalool showed the antidepressant effect which was found by using swimming test. L-linalool at the dose of (25 and 50 mg/kg, p.o.) produced a significant reduction of depression in rat.

Biochemical estimation of dopamine, 3, 4-Dihydroxyphenylacetic acid (DOPAC) homovanillic acid (HVA), showed L-Linalool at a dose (25 and 50 mg/kg, p.o.) significantly increased the level of dopamine, 3, 4-Dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), in striatum. Which shows the activity of L-Linalool on increasing catecholamine level at nerve terminals.

So, the above behavioral and biochemical results suggest that L-Linalool has the ability to improve symptoms of Parkinsonism, in part, by the restoring the level of dopamine, and by the preventing the muscular and motor symptoms. Thus, by considering it neuroprotective activities may be responsible for anti parkinsons effect. Hence, L-Linalool useful as a neuroprotective agent in the treatment of PD.

SUMMARY

Majority of the Central nervous system diseases are life threatening. When there is are cognition of the sign and symptoms of this disease it will help the patient to acquire instant treatment and which will lead to recovery easily and faster. Many neurodegenerative diseases- including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease- occur as a result of neurodegenerative processes.

Parkinson's disease is the second most common neurodegenerative disease and manifests as bradykinesia, rigidity, resting, tremor and posture instability. Parkinson's disease is a degenerative disorder of the central nervous system. It results from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain; the cause of cell death is unknown.

L-Linalool was used in this research work as the test compound against the treatment of Parkinson. It was analyzed using the *In-vivo* reserpine induced Parkinson in rat. The effect of L-Linalool were evaluated with different behavioral and biochemical parameter.

L-linalool at the dose of (25 and 50 mg/kg, p.o.) produced a significant reduction of tremor in rats, which is induced by reserpine

L-linalool was also able to increase the locomotor activity and grip strength in rats. Reserpine induced motor defect was significantly reversed by L-linalool. Amelioration of symptoms of reserpine by L-linalool demonstrates its Anti-Parkinson's activity.

L-linalool showed the antidepressant effect which was found by using swimming test. L-linalool at the dose of (25 and 50 mg/kg, p.o.) produced a significant reduction of depression in rat.

Biochemical estimation of dopamine, 3, 4-Dihydroxyphenylacetic acid (DOPAC) homovanillic acid (HVA), showed Linalool at a dose (25 and 50 mg/kg, p.o.) significantly increased the level of dopamine.

Above behavioral and biochemical study showed the effect of L-Linalool on treatment of primary symptoms of Parkinson. And it proves to improve the dopamine level in the striatum.

CONCLUSION

Parkinson disease is a chronic, progressive, neurodegenerative disorder with multiple pharmacological treatments. The drugs employed clinically in treatment and management of Parkinson was associated with multiple other adverse effect which additionally make its treatment more difficult thus this research was aimed at examining L-Linalool a natural constituent in the treatment of Parkinson and open new vistas in treatment and management of this disease. So, the results indicated the protective effect of L-Linalool against Parkinson disease induced by reserpine model test of wistar rats. The drug can therefore offer an alternative approach in Parkinson state. Conclusively additional investigation is required on other animal models to obtain a dependable oversight of the outcome of L-Linalool on Parkinson in actual clinical scenario.

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