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NEUROPROTECTIVE EFFECT OF LITCHI CHINENSIS SONN IN HALOPERIDOL INDUCED NEURODEGENERATION IN RAT MODELS

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ABSTRACT:

Using a rat model of haloperidol-induced catalepsy, the antioxidant and anticataleptic properties of litchi chinensis Sonn's methanolic seed extract were examined by the measurement of several behavioral and biochemical parameters. Haloperidol (1 mg/kg, ip) was given to a female albino rat in order to cause catalepsy. All drug-treated groups showed a substantial decrease in cataleptic ratings wcompared to the haloperidol-treated group; the group that received Nelumbo nuciferi (200 and 400 mg/kg body weight) saw the largest decrease. In the brain, biochemical markers such as dopamine (DA), reduced glutathione (GSH), catalase (CAT), thiobirbituric acid reactive substances (TBARS), and catalase and superoxide bismutise (SOD) were measured. When haloperidol was administered, the levels of SOD and catalase decreased and the production of TBARS and dopamine rose. This study found that in rats with haloperidol-induced catalepsy, therapy with Litchi chinensis Sonn restored the levels of TBARS, catalase, and SOD.

1. INTRODUCTION:

1.1. Parts of the brain and their function

In the human body, the brain is the most complex and important organ. This article aims to introduce you to the many parts of the brain and their functions rather than to provide a detailed review of all the brain research that has been done. The brain is merely three pounds in weight, but it can sense, interpret, and trigger bodily activity in addition to controlling behavior. It is the source of cognition within our bodies, housed in a shell made of bone and protected by cerebral fluid. The origin of every trait that makes us uniquely human is the brain.

1.1.1. Cerebrum

The cerebrum of the human brain comprises the bulk of the organ. Often called the cortex, it carries out a multitude of essential brain functions, such as processing thought and action. The cerebrum is divided into four separate areas. We refer to these lobes as the frontal, occipital, parietal, and temporal lobes.

Frontal Lobe: The frontal lobe is involved in higher level cognitive processes, expressive language, reasoning, motor skills, and other functions. In the brain, it is found in the frontal lobe. Any damage to it could lead to changes in attention spans, sociability, sexual preferences, and other activities.

Parietal Lobe: The information that the tactile senses—pain, pressure, and touch—send to the brain is processed by the parietal lobe. The brain's core is where it is located. Any harm to it may result in issues with verbal memory, eye control, and language.

Occipital Lobe: The job of the occipital lobe is to interpret the information sent to the brain from the eyes. It is located at the back of the brain. If it is damaged, it affects your visual ability, such as not being able to recognize colors, words and objects.

Temporal Lobe: The temporal lobe is responsible for forming memories and processing sounds recorded by the ears. It is located in the lower part of the brain. Any damage to it can cause problems with language ability, speech perception and memory.

Cerebellum

The cerebellum is known as the cerebellum and resembles the brain in that its surface is strongly folded and divided into two hemispheres. This part of the brain is responsible for functions such as balance, posture and coordination of movements. It contains more neurons than the entire brain itself. Located at the back of the brainstem and on the pons.

1.1.2. Limbic System

The limbic system is located within the brain. It is sometimes called the emotional brain. The four different parts that make up the limbic system are.

Thalamus: The thalamus is an important part of the gray matter located deep in the forebrain. It performs motor and sensory functions. All sensory information sent to the brain, with the exception of the sense of smell, travels to the thalamus and from there neurons send it to the cerebral cortex.

Hypothalamus: The hypothalamus is involved in functions such as circadian rhythms, homeostasis, hunger, emotions and thirst. In addition to these functions, it is also responsible for controlling the pituitary gland, which is responsible for the production of hormones. The hypothalamus is located in the abdomen relative to the thalamus and is part of the diaphragm..

Amygdala: The amygdala, as part of the telencephalon, is located in the temporal lobe and is associated with fear, memory and emotions. It is located below the anterior and medial part of the temporal lobe.

Hippocampus: The hippocampus helps with learning and memory development. There, short-term memories become permanent. In addition, the hippocampus also helps us remember spatial relationships in the world. It is located in the basomedial part of the temporal lobe.

Brain Stem

The brainstem is located below the limbic system. This part of the brain is responsible for controlling important functions such as blood pressure, breathing and heartbeat. The brainstem organizes reflexes and coordinates fine movements of the face and limbs. It consists of the midbrain, eyes and medulla.

Midbrain: The midbrain is located at the mouth of the brainstem and consists of the tegmentum and tectum. It controls functions such as body movement, hearing, vision and eye movement. The brainstem is located in the anterior part of the midbrain.

Pons: The eye is responsible for performing sensory analysis and controlling motor functions, and the information coming from the ears to the brain reaches the eyes first. It is responsible for maintaining sleep and level of consciousness. Some of its parts are connected to the cerebellum and are thus involved in posture and movements.

Medulla: The medulla is located between the spinal cord and the pons. It is the back end of the brainstem and is responsible for controlling vital body functions such as heart rate and breathing.

1.2. Motor cortex

The motor cortex is the area of the brain involved in planning, controlling and executing intentional movements. Classically, the motor cortex is a region of the frontal lobe located in the dorsal precentral gyrus just anterior to the central sulcus.

Components of the motor cortex

The motor cortex can be divided into three areas:

1. The primary motor cortex is the main factor in the generation of nerve impulses that travel along the spinal cord and control the execution of movements. It is located on the medial surface in the anterior paracentral lobe.

2. The premotor cortex is responsible for certain aspects of motor control, including preparation for movement, sensory control of movement, spatial control of reach, or direct control of certain movements, with an emphasis on control of proximal and trunk muscles. The body. Located in front of the primary motor cortex.

3. There are numerous postulated uses for the supplementary motor area, often known as SMA, including internally generated movement planning, movement sequence planning, and bilateral body coordination, such as bi-manual coordination. positioned anterior to the primary motor cortex on the hemisphere's midline surface.

The cerebellum, the basal ganglia, the pedunculopontine nucleus, the thered nucleus, and other subcortical motor nuclei are among the other brain regions that are also crucial to proper motor function.

1.2.2. The premotor cortex

There was only one cortical area identified in the early studies of the motor cortex that was involved in motor control. It was first proposed by Alfred Walter Campbell that the motor cortex might be divided into two fields: the "primary" motor cortex and the "intermediate precentral" motor cortex. "Betz cells"—large cell bodies found in certain cells—are found in the primary motor cortex. It was once believed that these cells were the primary outputs from the cortex, sending fibers to the spinal cord [1].

A primary motor cortex (area 4, in accordance with Brodmann's [4] naming scheme) and a higher-order motor cortex (area 6, according to Korbinian Brodmann) are the two divisions proposed by other researchers, including Vogt and Vogt [2] and Otfrid Foerster [3]. In stark contrast, Wilder Penfield [5][6] opined that there was no functional differentiation between region 4 and area 6. Woolsey [7], who investigated the monkey motor map, concurred that primary motor and premotor functions were interchangeable.

Nowadays, there are four main regions of the premotor cortex [8,9, 10]. The role that PMDc plays in directing reaching is a topic of frequent research [11, 12, 13].

Studying PMVc, also known as F4, is common when it comes to its function in sensory-guided movement. These neurons respond to auditory, visual, and tactile stimuli [14,15,16,17]. It is common research to examine PMVr, or F5, in relation to how it shapes the hand during grasping and how the hand and mouth interact [18, 19].

1.2.3. The supplementary motor cortex

Penfield [20] described a cortical motor area, the supplementary motor area (SMA), in the upper or dorsal part of the cerebral cortex. Each SMA neuron can affect many muscles, many parts of the body and both sides of the body [21,22,23].

1.2.4. The motor cortex map

Most motor cortex neurons that project to spinal synapses in spinal interneuron circuits do not directly project to a motoneuron [24]. One suggestion is that direct cortico-motoneuron projections are a specialization that allows fine-tuning of the fingers [24][25].

1.3. Introduction for neurodegenerative disease

Ayurveda, recorded in ancient scriptures, has been passed down from generation to generation and developed over 6,000 years. This time-tested holistic system of medicine states that good health exists when body, mind, spirit and environment are in perfect harmony. This global awareness of all things natural is the biggest challenge for the Indian pharmacist in developing newer technologies. The World Health Organization (WHO) currently encourages, recommends and promotes traditional herbal medicines in national theater programmes. The NAPALERT database documents ethnomedicinal use alone for 9,200 of 33,000 species of monocots, dicots, lichens, mosses and lichens, suggesting that 28% of the country's plants were used in ethnomedicine [26].

During the last decade, the scientific community has done a lot of work focusing [27]• on the levels and chemical structure of antioxidant phenols in various plant foods, aromatic plants and various plant materials.

• The probable role of plant. phenols in various diseases related to oxidative stress, such as cardiovascular vascular and neurodegenerative diseases in the prevention of degenerative diseases and cancer.

• The ability of plant polyphenols to change enzyme activity, the biological effect is not yet known.

• certain. classes of plant phenols, such as flavonoids (also called polyphenols), bind to proteins. Flavonol protein binding, such as binding to cell receptors and transporters, involves mechanisms of polyphenols that are not only related to their direct antioxidant effects.

1.4. PARKINSON'S DISEASE

1.4.1. Introduction

Akanthisia (inability to sit still) and pill-rolling tremors are two of the symptoms of Parkinson's disease (PD), a neurodegenerative illness that progresses slowly. Strictness, Kinesis (dyskinesia, akinesia) a hunched-over, unstable position Absent arm movements in time with leg movements, Nervous depression, oculogyric crises (holding the eyes open for a variable period of time), sialorrhoea, irreversible tremors, Masked expression and seborrhea. While Parkinson's disease, also known as paralysis agitans, is limited to primary or idiopathic parkinsonism, the term parkinsonism is used to describe any disease state with similar symptoms [28].

1.4.2. Classification of Parkinsonism:

A) Primary (idiopathic) parkinsonism

1) Parkinson's disease

B) Secondary (symptomatic) parkinsonism

1) Drug induced:

a) Phenothiazines

b) Butyrophenones

c) Metoclopramide

d) Reserpine

e) Alpha methyl dopa

2) Infectious:

a) Post encephalitic

b) Syphilis

3) Metabolic

a) Hepatocerabral degeneration

b) Hypoxia

c) Parathyroid dysfunction

4) Structural

a) Brain fever

b) Hydrocephalus

c) Trauma

5) Toxin

a) Carbon monoxide

b) Carbon disulphide

c) Cyanide

d) Manganese

e) MPTP

6) Vascular

C) Parkinson-plus syndromes

1) Cortical- basal ganglionic degeneration.

2) Hemi parkinsonism- hemi atrophy

3) Dementia syndromes, Alzheimer's disease, Diffuselewy body disease.

4) Multiple system atrophy, parkinsonism- amyotrophy, shy- Drager syndrome, sporadic olivoponto cerebellar degeneration, striatonigral degeneration.

5) Progressive supranuclear palsy.

D) Hereditary degenerative disease

1) Autosomal-dominant cerebellar ataxias (includes Machodojoseph disease).

2) Hallervorden-spate disease.

3) Huntington's disease.

4) Mitochondriopathies

5) Wilson's disease

1.4.3. Symptoms

1. Motor symptoms

A) Cardinal symptoms

- Tremor
- Rigidity

- Bradykinesia/akinesia
- Postural instability

B) Other motor symptoms

1. Gait and posture disturbance

2. Shuffling.

3. Decreased arm swing.

4. Difficulty in turning head.

5. Stopped, forward - flexed posture.

6. Festination - combination of stooped posture, imbalance.

7. Dystonia (In about 20% of cases)- Abnormal, sustain, painful twisting muscle contractions, usually affecting the foot and ankle.

8. Speech and swallowing disturbances:

9. Hypophonia - soft speech.

10. Festinating speech-excessive rapid, poorly intelligible speech.

11. Speech/language disturbance- less verbal fluency, cognitive disturbance.

12. Dysphagia -impaired ability to swallow.

13. Fatigue (up to 50% cases).

14. Masked faces, with infrequent blinking.

15. Difficulty rolling in bed or raising from seated position.

16. Micrographia(small, cramped hand writing).

17. Impaired motor coordination.

18. Poverty of movement.

II. Non-motor systems

1. Mood disturbances:

2. Depression (20-80% cases).

3. Anxiety.

4. Cognitive disturbance:

5. Slowered reaction time.

6. Executive dysfunction.

7. Dementia.

8. Short term memory loss.

9. Sleep disturbances:

10. Daytime somnolence.

11. Disturbances in REM sleep.

12. Sensational disturbances:

13. Impaired visual contrast sensitivity.

1.4.4. Etiological Factors

a. Aging

b. Environmental Factors

c. Genetic Factors

1.4.5. Diagnosis

The main clinical tool used to help with diagnosis and assess the severity of Parkinson's disease (PD) is called "the unified parkinson's disease rating scale." At autopsy, only 75% of PD cases with a clinical diagnosis are confirmed.19. PD's obvious symptoms and indicators are occasionally written off as the result of aging processes. Before it becomes clear that the symptoms are persistent, the doctor may need to keep an eye on the patient for some time.

Clinical stages

There are five clinical stages.

Phase 1: PD Hoehn and Yahr's (1967) staging approach states that individuals exhibiting unilateral signs, which are typically tremor and rigidity, are in stage 1 illness.

Stage 2: When gait or balance issues are absent, the condition is characterized by bilateral symptoms and indications.

Stage 3: A patient is diagnosed with Parkinson's disease when they exhibit unsteadiness in their walk or falling.

Step 4: Patients in Stage 4 need help getting around (a cane, walker, or another person).

5. step - patients are either in a wheelchair or bedridden is part of the step [29].

1.4.8. Pathogenesis of PD

The pathogenic factors include

- Alpha-synuclein
- Iron
- Oxidative stress
- Mitochondial dysfunction
- Calcium cytotoxicity

1.4.9. Pharmacological management of PD

Classification of antiparkinsonian drugs

1) Drugs affecting brain dopamine systems:

a) Dopamine precursor: Levodopa (DA does not cross BBB)

b) Peripheral decarboxylase inhibitors: Carbidopa, Benserazide.

Dopaminergic agonist: Bromocriptine, Pergolide, Piribedi, Ropinirole, Pramipexole.

d) MAO-B inhibitors: Seligiline.

e) COMT inhibitors: Entacopone, Tolcapone.

f) Dopamine facilator: Amantadine.

2)Drugs affecting brain cholinergic system:

a) Central anticholinergics: Trihexyphenidyl, Procyclidine, Biperiden.

b) Antihistaminics: Ophenadrine, Promethazine [30].

2. PLANT PROFILE

Plant	-	Lychee
Botanical name	-	Litchi chinensis Sonn
Synonym	-	Lychee, lichi, litchi
Family	-	Sapindaceae

Taxonomical classification:

Kingdom	:	Plantae
Sub kingdom	:	Tracheo binote
Order	:	Sapindales
Family	:	Sapindaceae
Sub family	:	Sapindoideae
Genus	:	Litchi Sonn
Species	:	L-chinensis

Relatives: Spanish lime (mamoncillo, kinep; Melicoccus bijugatus), longan (Dimocarpus longan Lour), akee (Blighia sapida Koenig), and rambutan (Nephelium lappaceum L)

Other common names: litchi, leechee, mamoncillo chino (Spanish), lichi

3.AIM AND OBJECTIVE:

The ethanolic extract of Litchi chinensis Sonn peel extract's anti-parkinsonianism efficacy in albino rats given haloperidol.

Experimental protocol and plan of work

Here are the steps that are used to carry out the scheduled work:
1) Compliance with the obligation of the ethics committee
2) Plant material identified as possibly having polyphenolic properties

3) Preparing plant extract with ethanol as a solvent
4) Chemical tests are used to filter the extract for contaminants in order to determine its composition.
5) Biochemical studies
6) Study design
7) Examining Data Using Statistics

4.PLAN OF WORK

Meterials And Methods

4.1. Animals

The study employed female Wistar rats. Under usual settings (27+2°C, 44-56% relative humidity), the animals were housed in groups of six. The rats were fed a standard rat chow and given access to unlimited amounts of chlorinated drinking water for one week prior to and during the trials. A time-controlled lighting system was employed to maintain a regular daily illumination cycle. The Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA Reg No. 1523/PO/a/11/CPCSEA), Ministry of Social Justice and Empowerment, Government of India, granted permission for all experiments and protocols described in this study. These committees and the Southern Institute of Medical Sciences, College of Pharmacy, Mangaladas nagar, Guntur, Institutional Animal Ethical Committee (IAEC) approval.

4.2. Drugs And Chemicals

Haloperidol, Levodopa (Sigma-Aldrich, Hyderabad, India.)

solution

4.3 Instruments

Tissue homogenizer (H. L. Scientific Industries, Ambala, India), centrifuge (Remi, model no: CM-8 Plus, Mumbai, India), electronic balance (Shimadzu Corp., Japan, model no: AUY-220), and UV-visible spectrophotometer (PG Instruments Ltd., U.K., model No: T-60).

4.4 Plant Material

4.4.1. Preparation of Litchi chinensis Sonn ethonolic extract by soxhlet apparatus

The fruits of the Litchi chinensis Sonn plant were gathered at the New Delhi fruit market. Dr. B. Sandhya from the Southern Institute of Medical Sciences in Guntur's Department of Life Sciences recognized and authenticated them. The entire dried plant was ground into coarse granules after the peel was shade-dried. Petroleum ether was used to continuously extract hot material from the coarse powder in a Soxhlet system. Through distillation at low pressure, the solvent was eliminated, leaving behind a sticky, greenish residue that yielded 10%w/w of dried plant material. For future research, the concentrated crude extract was kept in storage.

4.4.2. Preparation of dilution

The residue was utilized to dose the animals orally using a cavage needle after being diluted in purified water to the necessary concentration of 200,400 mg/kg body weight.

4.5. Phytochemical screening

The extract was then subjected for the phytochemical screening

Table.4 Preliminary phytochemical Screening

Chemical Test	**Inference**
Alkaloids	
Mayer's Test	Alkaloids are present
Wagner's Test	Alkaloids are present
Dragendroff's reagent	Alkaloids are present
Phytosterols	
1ml acetic anhydride + 2ml H_2SO_4	Presents of steroids
1ml conc. H_2SO_4	Presents of steroids
Glycosides	
Shaken in graduated cylinder for 15min	Presence of saponins
1ml NH_3 + 1ml lead acetate	Prescence of saponins

Borntrager's test for anthraquinone glycoside	Prescence of glycosides
Shinoda test for flavonoids	Prescence of flavonoids
Tannins and phenolic compounds	
1ml 5% $FeCl_3$ solution	Presents of phenols and tannins
1ml 10% lead acetate solution	Presents of phenols and tannins
1ml of 10% potassium hydroxide + dichromate solution	Presents of phenols and tannins

5. STATISTICAL ANALYSIS

The mean ± SEM was used to express all the data. Using a one-way ANOVA and a computer-based fitting tool (Graph Pad Prism 5), the Dunnett's test was used to determine whether there was statistical significance between more than two groups. P less than 0.01 was considered statistically significant.

6.RESULTS

Treatment	SOD Nmol/mg Protein	CATALASE Nmol-1min-1mg-1	GSH µmol/g	TBAR Nmol/mg Protein	DOPAMINE Nmol/mg Protein
Positive Control	37.82± 0.0928	39.16±0.0928	94.86± 0.02333	66.56± 0.02028	59±0.09905
Negative Control	33.72± 0.01764	79.41±0.2074	92.56± 0.1167	72.21± 0.01155	71.58±0.109
Standard	45.08± 0.02082	98.41±0.07965	95.73± 0.0895	69.14± 0.0809	43.56±0.05859
Test-1	32.82± 0.165	95.48±0.08083	93.35± 0.1309	75.41± 0.1071	64.11±0.02082
Test-2	16.12± 0.02517	71.42±0.07371	98.34± 0.07	78.4± 0.1387	66.66±0.1848

7.DISCUSSION

Blocking dopamine receptors is how neuroleptics work [33]. This kind of obstruction raises dopamine turnover, which raises hydrogen peroxide generation and causes oxidative stress [31,32]. In animal models with bilateral lesions, the swim test is an effective way to assess motor injury and evaluate motor impairment directly [34].

Additionally, auto-oxidation of dopamine produces superoxide radical during metabolism. The hydroxyl radical, the most hazardous free radical, can be created by hydrogen peroxide interacting with iron or copper ions. The overproduction of these potentially harmful free radicals may result from neuroleptics' increased dopamine turnover [35]. According to reports, oxygen free radicals also impair the function of the dopamine transporter, which raises the levels of dopamine outside of cells.

When taken over an extended period of time, the neuroleptic haloperidol induces oxidative stress due to changes in the mitochondrial electron transport chain, which contributes to its neurotoxicity [36,37].

It is possible that the presence of phenols in EEIC is what causes the neuroprotective effect. It has been suggested that the antipsychotic impact of haloperidol is directly related to the antagonistic action of dopamine D2 receptors, as evidenced by the suppression of dopaminergic transmission in rats. Neuroleptics such as haloperitol affect dopaminergic signaling in many ways, resulting in behavioral abnormalities and catalepsy related to dopamine. The balance of transmitters in the basal ganglia is mostly regulated by glutamate receptors. Stimulation of N-

methyl-D-aspartate (NMDA) receptors in the striatum has a behaviorally depressive effect. stimulatory actions of antagonists of these receptors. All of the NMDA receptor antagonists work in concert with L-DOPA to alleviate parkinsonian symptoms in animal models of the disease.

The results of this study suggest that an ethanolic extract of Litchi chinensis Sonn. may help rats with catalepsy caused by haloperidol. EELC may increase the bioavailability of circulatory dopamine by upregulating dopaminergic signaling, and it may increase the bioavailability of L-DOPA by inhibiting DOPA-decarboxylase activity similar to that of carbidopa [38,39]. These mechanisms may be responsible for the amelioration.

Ageratum conyzoides L. is a well-known herb with several documented applications that is utilized in Indian traditional medicine. However, it is unknown how this entire plant's ethanolic extract might help treat some conditions connected to the central nervous system. It is therefore important to investigate the impact of this plant's ethanolic extract on rats that have been given haloperidol-induced catalepsy. The current study examined how EELC affected extrapyramidal symptoms, which include depression, stiffness, and poor motor coordination. These symptoms are important indicators of Parkinson's disease. At a dose of 400 mg/kg, EELC demonstrated notable anticataleptic efficacy in catalepsy produced by haloperidol. The anticataleptic properties of EELC were similar to those of the common medication L-DOPA. At 400 mg/kg, EELC dramatically restored the locomotor activity that had been reduced by haloperidol. The conventional medications L-DOPA considerably restored the motor activity inhibition caused by haloperidol. Rats treated with haloperidol exhibit considerably more exploratory behaviors, such as head dipping and line crossing, when exposed to 400 mg/kg of EELC. When rats were given haloperidol, the usual medication L-DOPA considerably boosted their exploratory behavior.

8. CONCLUS ION

According to the findings of the aforementioned research, it is possible that the protective effect of EELC against Parkinson's disease symptoms, such as catalepsy, is caused by the regulation of neurotransmitters like glutamate, serotonin, and dopamine, which are known to have antioxidant and catalepsy-prevention effects. To find out how the plant's separated principles and different extracts affect other CNS illnesses, more research must be done on these subjects.

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