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Neuroprotective Potential of Pergularia Daemia Constituents in Frontotemporal Dementia

P. N. Prakash[1*]; V. Divya[2]; S. Hemalatha[2]; P. Karthikeyan[2]; M. Nekitha[2]; S. Rachana[2]

[1]Assistant Professor, Department of Pharmaceutical Chemistry, Shree Venkateshwara College of Paramedical Science, Gobi-638455, Erode (DT), Tamil Nadu, India.
[2]Department of Pharmaceutical Chemistry, Shree Venkateshwara College of Paramedical Science Gobi-638455, Erode (DT), Tamil Nadu, India.

Corresponding Author: P. N. Prakash[1*]

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Abstract: Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder characterized by behavioral alterations, language impairment, and cognitive decline resulting from degeneration of the frontal and temporal lobes of the brain. The disease involves multiple pathological mechanisms, including oxidative stress, neuroinflammation, abnormal protein accumulation, and neuronal loss. Despite advancements in understanding its pathology, effective disease-modifying therapies for FTD remain limited. Pergularia daemia, a medicinal climbing plant widely used in traditional systems of medicine, is known to possess a wide range of bioactive phytochemicals such as flavonoids, alkaloids, terpenoids, tannins, and glycosides. Key constituents including quercetin, kaempferol, β-sitosterol, and lupeol exhibit notable antioxidant and anti-inflammatory activities. These compounds may contribute to neuroprotection by reducing oxidative damage, modulating inflammatory responses, and preventing neuronal degeneration. Thus, Pergularia daemia demonstrates promising potential as a natural source for developing neuroprotective agents in the management of frontotemporal dementia. However, further in vitro, in vivo, and clinical investigations are necessary to confirm its therapeutic efficacy and safety.

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I. INTRODUCTION

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder characterized by prominent alterations in behavior, personality, and social functioning, along with impairments in language and cognition. These clinical features arise due to the gradual degeneration of the frontal and temporal lobes of the brain, which play a critical role in emotional regulation, decision-making, and communication. The pattern of neurodegeneration often determines the specific clinical presentation of the disorder.

FTD represents a group of related conditions rather than a single disease entity. It is broadly classified into two major forms: the behavioral variant of FTD (bvFTD), which primarily affects personality and social conduct, and primary progressive aphasia (PPA), which mainly impairs language abilities. PPA is further subdivided into semantic dementia and progressive non-fluent aphasia based on the nature of language dysfunction. In addition, overlap syndromes are increasingly recognized, where FTD coexists with other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) and progressive supranuclear palsy (PSP).

The behavioral symptoms of FTD are often associated with deficits in social cognition, which includes the ability to perceive, interpret, and respond appropriately to social and emotional cues. Key components of social cognition include emotion recognition, empathy, and theory of mind. Impairment in these domains leads to difficulties in understanding others' emotions, reduced emotional responsiveness, and inappropriate social behavior.

II. CLINICAL CHARACTERISTICS

Based on the intensity of symptoms, frontotemporal dementia (FTD) is typically divided into early, middle, and late stages. The main feature of FTD is progressive neurodegeneration of the frontal and temporal lobes of the brain, which results in noticeable alterations in behavior, personality, language, and cognitive function.

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➢ *Symptoms Related to Behavior and Cognition*

Patients with FTD frequently show notable behavioral and personality changes in the during the early stages of the disease. Disinhibition, apathy, lack of empathy, compulsive behaviors, and poor judgment are a few examples. People may exhibit inappropriate social behavior, diminished emotional responsiveness, and trouble organizing or planning daily tasks.

Executive functions, including decision-making, problem-solving, and attention, are primarily impacted by cognitive impairment in FTD. In contrast to certain other dementias, memory may be largely intact at first but progressively deteriorates as the illness worsens.

➢ *Disruptions in Language*

Patients with some types of FTD, especially primary progressive aphasia, see a gradual decline in their language skills. Word finding difficulties, decreased speech fluency, poor comprehension, and issues naming objects are some of the symptoms. Communication becomes more challenging as the illness progresses.

➢ *Motor Symptoms*

Although FTD primarily affects behavior and cognition, motor abnormalities may appear in some patients during later stages. These may include muscle weakness, rigidity, tremors, or movement disorders, particularly when FTD overlaps with conditions such as amyotrophic lateral sclerosis (ALS) or parkinsonian syndromes.

➢ *Psychiatric Manifestations*

Psychiatric symptoms are also common in FTD and may include depression, anxiety, irritability, emotional blunting, and impulsivity. Changes in eating habits, repetitive behaviors, and reduced social awareness are frequently observed. These behavioral and psychiatric disturbances often become more pronounced as the disease progresses.

III. PATHOPHYSIOLOGY

➢ *Frontotemporal Dementia (FTD) and Oxidative Stress:*

The pathophysiology of several neurodegenerative disorders, including frontotemporal dementia (FTD), is strongly influenced by oxidative stress. Oxidative stress arises from an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense mechanisms of the body. Excessive ROS production leads to neuronal damage through lipid peroxidation, protein oxidation, and oxidative DNA damage.

Studies have reported elevated levels of oxidative stress markers in patients with FTD. Increased concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a biomarker of oxidative DNA damage, have been observed in the frontal and temporal cortices. In addition, higher levels of protein oxidation markers such as 3-nitrotyrosine and lipid peroxidation products like malondialdehyde (MDA) have been identified in brain tissues.

Oxidative stress also contributes to the misfolding and aggregation of pathological proteins, including tau, TAR DNA-binding protein 43 (TDP-43), and fused in sarcoma (FUS), which are key features of FTD. The accumulation of these abnormal proteins disrupts neuronal function and promotes progressive neurodegeneration. Furthermore, excessive ROS production impairs mitochondrial function, reduces ATP synthesis, and ultimately leads to neuronal cell death in the affected brain regions.

➢ *Frontotemporal Dementia: Involvement of Excitotoxicity*

Another mechanism linked to neuronal degeneration in FTD is excitotoxicity. It involves overstimulation of glutamate receptors, especially NMDA receptors, which is brought on by either increased sensitivity of postsynaptic neurons or poor glutamate clearance by astrocytes.

Proteolytic enzyme activation, aberrant intracellular calcium accumulation, mitochondrial dysfunction, and neuronal damage are all caused by overactivation of glutamate receptors. Neurons in the frontal and temporal brain regions, which are in charge of behavior, language, and executive functions, gradually degenerate as a result of this excitotoxic mechanism.

➢ *Metabolic Dysfunction and Mitochondrial Impairment*

Mitochondrial dysfunction is also considered a significant contributor to the pathogenesis of frontotemporal dementia. Mitochondria are responsible for ATP production and regulation of intracellular calcium homeostasis. In FTD, mitochondrial abnormalities lead to reduced energy production, impaired glucose metabolism, and increased oxidative damage.

Patients with FTD show hypometabolism in the frontal and temporal lobes, according to neuroimaging and biochemical research. Neuronal vulnerability and degeneration are exacerbated by mitochondrial dysfunction, which also increases oxidative stress. Impaired cellular respiration and energy metabolism in impacted brain regions are indicated by elevated lactate levels and disturbed metabolic pathways.

➢ *Herbs and Secondary Metabolites' Neuroprotective Potential in FTD*

It has long been known that natural products are a significant source of therapeutic agents for neurodegenerative diseases. The antioxidant, anti-inflammatory, anti-apoptotic properties, and neuroprotective qualities of many medicinal plants and their secondary metabolites may help combat the pathological mechanisms of FTD.

Polyphenols, flavonoids, alkaloids, and terpenoids are examples of phytochemicals that have been shown to lower oxidative stress, control calcium homeostasis, prevent aberrant protein aggregation, and shield neuronal cells from apoptosis. These characteristics make substances derived from plants attractive options for the creation of therapeutic and preventive measures against frontotemporal dementia.

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IV. PLANT PROFILE

➢ *Plant Profile: Pergularia Daemia*

- *Classification and Distribution*

✓ Family: Apocynaceae, formerly known as Asclepiadaceae
✓ Common names: Uttamani, Trellis-vine, and Veliparuthi
✓ Origin and Distribution: Pergularia daemia is widely distributed in tropical and subtropical regions of Asia and Africa. In India, it commonly grows in hedges, wastelands, roadsides, and dry fields. The plant has been extensively used in Ayurvedic and traditional medicine for the treatment of respiratory disorders, neurological conditions, and inflammatory diseases.

➢ *Phytoconstituents and Biological Activities*

- *Polyphenols and Antioxidants*

Gallic acid, catechins, and derivatives of chlorogenic acid are among the phenolic compounds found in Pergularia daemia, according to phytochemical studies. In tests like DPPH and ABTS, these substances exhibit potent free-radical scavenging activity, suggesting substantial antioxidant potential. One of the main pathological mechanisms underlying neurodegenerative diseases like frontotemporal dementia is oxidative stress, which antioxidant compounds aid in reducing.

- *Flavonoids and Tannins*

Tannins and flavonoids, including derivatives of quercetin and myricetin, are found in leaves and other plant parts. These substances have neuroprotective, analgesic, antimicrobial, and anti-inflammatory properties. Neuronal cells may be shielded from inflammatory damage linked to neurodegenerative diseases by their anti-inflammatory properties.

- *Alkaloids, Saponins, and Steroidal Compounds*

Alkaloids, saponins, cardiac glycosides, steroids, and triterpenoids have been found in Pergularia daemia through phytochemical screening. The pharmacological characteristics of the plant, such as central nervous system activity, antioxidant effects, and possible neuroprotective advantages, are influenced by these bioactive molecules.

- *Other Bioactive Components*

The pharmacological activities of Pergularia daemia, including its anti-inflammatory, hepatoprotective, antimicrobial, and antioxidant properties, are attributed to the presence of bioactive constituents such as glycosides, terpenoids, and phenolic acids. Owing to these biological activities, Pergularia daemia represents a promising candidate for neuroprotective research and therapeutic exploration in neurodegenerative diseases.

V. EXTRACTION OVERVIEW

➢ *Extraction Overview – Pergularia daemia*

- *Solvent and Technique Selection*

✓ Leaves and Whole Plant: 80% methanol or ethanol are frequently used as solvents for extraction. To increase yield, methods like Soxhlet extraction, magnetic stirring, and ultrasound-assisted extraction are used. The phytochemicals found in these extracts, such as flavonoids, phenolic compounds, alkaloids, and saponins, these constituents support antibacterial, anti-inflammatory, and antioxidant properties of the plant.
✓ Roots and Aerial Parts: Because they contain bioactive components like quercetin, rutin, and other phenolic compounds, extracts made with methanol, ethanol, or petroleum ether have demonstrated notable antioxidant, analgesic, and central nervous system (CNS) depressant activity.

- *Standard Extraction Protocol for Pergularia Daemia*

✓ Fresh leaves of Pergularia daemia were collected and thoroughly washed with distilled water to remove dust and other contaminants. The cleaned plant material was then shade-dried at room temperature for several days to eliminate residual moisture.
✓ The dried leaves were pulverized into a fine powder using a mechanical grinder and stored in airtight containers until further use.
✓ The powdered plant material was subjected to extraction with 80% methanol to obtain the crude extract, using either magnetic stirring for 6–8 hours at room temperature or ultrasonic-assisted extraction for 30–60 minutes.
✓ The extract was filtered through Whatman No. 1 filter paper to remove plant debris and obtain a clear filtrate.
✓ The filtrate was concentrated under reduced pressure using a rotary evaporator to remove the solvent and yield the crude methanolic extract.
✓ The yield of the crude extract from Pergularia daemia leaves typically ranged from 15–30%, depending on the extraction conditions and the nature of the plant material.
✓ The obtained extract was subsequently used for phytochemical screening, antioxidant assays, and pharmacological evaluations.

- *Key Phytoconstituents Relevant to Frontotemporal Dementia (FTD)*

✓ *Flavonoids (Kaempferol, Quercetin):*

Flavonoids present in Pergularia daemia exhibit potent anti-inflammatory and antioxidant properties. As oxidative stress and neuroinflammation are key pathological factors associated with frontotemporal dementia, these compounds may contribute to neuroprotection by preserving neuronal integrity and improving cognitive function.

✓ *Heart Glycosides (Calotropin, Pergularoside):*

Pergularia daemia contains steroidal glycosides that exhibit significant biological activities, including

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neuroprotective and anti-inflammatory effects. In neurodegenerative conditions such as frontotemporal dementia (FTD), these compounds may help reduce neuronal degeneration and promote neuronal survival.

✓ *Phenolic Substances:*

The plant's phenolic components have potent free-radical scavenging activity (DPPH assay). These substances lessen oxidative damage in brain cells linked to frontotemporal dementia by neutralizing reactive oxygen species (ROS).

✓ *Alkaloids and Terpenoids:*

These secondary metabolites contribute to antioxidant and anti-inflammatory activities. Their presence in Pergularia daemia may help regulate neuronal signaling pathways and protect neurons from degeneration.

✓ *Leaf Extracts:*

Methanolic and ethanolic extracts of Pergularia daemia leaves have demonstrated significant antioxidant activity through DPPH and hydrogen peroxide scavenging assays, suggesting potential neuroprotective effects that may be beneficial in managing frontotemporal dementia.

➢ *Yields of Extraction and Phytochemical Characteristics by Pergularia daemia Plant Part (Related to Frontotemporal Dementia)*

- *Plant Part, Extraction Method, Yield, and Phytochemical Content (Leaves):*

Leaves of Pergularia daemia were subjected to 80% methanolic extraction using magnetic stirring or ultrasonic-assisted extraction. The extraction yield ranged from approximately 18–35%. The total phenolic content (TPC) was estimated to be about 10–45 mg GAE/g of extract, while the total flavonoid content (TFC) ranged from 3–18 mg QE/g of extract. Phytochemical analysis revealed the presence of flavonoids, phenolic acids, and terpenoids, which exhibit strong antioxidant activity and may contribute to neuroprotection against oxidative stress associated with frontotemporal dementia.

Whole Plant/Aerial Parts 70% Ethanol extraction by room temperature maceration for 24 to 48 hours Yield of extract: 15–30%. Alkaloids, flavonoids, tannins, saponins, and cardiac glycosides are among the phytochemicals found. These substances have anti-inflammatory and free-radical scavenging properties that could lessen frontotemporal dementia-related neuronal degeneration.

Leaves / Roots Hydro-ethanolic extraction (60–70% ethanol) followed by filtration and concentration.

Antioxidant activity reported with DPPH $IC_{50} \approx 20–90$ µg/mL and hydroxyl radical scavenging activity. Extracts also show central nervous system protective effects, suggesting potential therapeutic relevance for neurodegenerative diseases such as frontotemporal dementia.

- *Relevance to Frontotemporal Dementia*

Flavonoids, phenolic compounds, and terpenoids are among the bioactive phytochemicals found in Pergularia daemia extracts that exhibit anti-inflammatory and antioxidant properties. The pathophysiology of frontotemporal dementia is significantly influenced by oxidative stress and neuroinflammation. Thus, by lowering oxidative damage and enhancing neuronal survival, the phytochemical components of Pergularia daemia may contribute to neuroprotective effects, indicating possible therapeutic value for the treatment of frontotemporal dementia.

VI. ANTIOXIDANT SCREENING

➢ *In Vitro Assays*

- *DPPH Radical Scavenging Activity:*

A volume of 0.5 mL of the extract at various concentrations was mixed with 2 mL of DPPH solution (25 µg/mL in methanol). The reaction mixture was vortexed and incubated in the dark at room temperature for 30 minutes. The absorbance was then measured at 517 nm using a spectrophotometer. A decrease in absorbance indicated an increase in free radical scavenging activity.

- *Total Antioxidant Capacity (Phosphomolybdenum Method):*

To 1 mL of the extract at different concentrations, 1 mL of reagent solution containing 0.6 mM sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate was added in an Eppendorf tube. The tubes were sealed and incubated at 95 °C for 90 minutes in a thermal block. After cooling to room temperature, the absorbance was measured at 695 nm against a blank. Ascorbic acid was used as the reference standard.

- *Hydrogen Peroxide (H_2O_2) Scavenging Assay:*

A reaction mixture containing 1 mL of the sample, 3 mL of phosphate buffer, and 1 mL of hydrogen peroxide solution was prepared (total volume: 5 mL). The mixture was incubated at 37 °C for 10 minutes. The absorbance was then measured at 230 nm. Ascorbic acid was used as the positive control and standard antioxidant.

➢ *Frontotemporal Dementia (FTD) Relevance*

The pathophysiology of frontotemporal dementia is significantly influenced by oxidative stress and neuroinflammation. Overproduction of reactive oxygen species (ROS), mitochondrial dysfunction, and impaired antioxidant defense systems are associated with neuronal degeneration in the frontal and temporal lobes. The results of these assays indicate that Manilkara zapota extracts possess the ability to scavenge reactive oxygen species and enhance antioxidant defenses, thereby suggesting potential neuroprotective effects in preventing or delaying the progression of frontotemporal dementia.

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VII. RECOMMENDED IN VITRO FTD ASSAY DESIGN

- Pre-treatment: M. zapota extracts were cultured with neural cell lines, such as SH-SY5Y and PC12.
- Stress Induction: When cells are exposed to oxidative or inflammatory stimuli (such as hydrogen peroxide, glutamate, or lipopolysaccharide).
- Evaluations:

- *In Vitro Cellular Assays:*

✓ Intracellular reactive oxygen species (ROS) levels were measured using the DCFDA fluorescent probe.
✓ Cell viability was assessed using MTT or LDH assays.
✓ Cellular markers associated with frontotemporal dementia (FTD) were evaluated, including:

- Mitochondrial membrane potential (ΔΨm) using JC-1 staining
- Caspase-3 activation as a marker of apoptosis
- Expression of TDP-43 protein and tau protein aggregation, which are key pathological hallmarks of FTD
- In vivo Neurobehavioral and Biochemical Studies:

- *A Cognitive and Behavioral Assessment in Animal Models:*

Frontotemporal dementia-related cognitive and behavioral deficits may improve in animal models given 200–400 mg/kg of M. zapota ethanolic fruit extract.

- *Behavioral Tests may Include:*

✓ The Morris Water Maze test was employed to evaluate spatial learning and memory.
✓ The Elevated Plus Maze was used to assess anxiety-related behavior.
✓ Working memory and recognition memory were evaluated using the Y-Maze and Novel Object Recognition tests.

Biochemically, the extract may exert neuroprotective effects by reducing lipid peroxidation and enhancing the levels of endogenous antioxidant enzymes, including glutathione (GSH), catalase, and superoxide dismutase (SOD).

VIII. CONCLUSION

Pergularia daemia contains a diverse range of phytoconstituents, including flavonoids, phenolic compounds, alkaloids, and terpenoids, which exhibit significant antioxidant and anti-inflammatory properties. These bioactive compounds may help mitigate oxidative stress and neuroinflammation, two major pathological factors implicated in frontotemporal dementia (FTD). Although specific studies evaluating Pergularia daemia in FTD are limited, its phytochemical profile suggests potential neuroprotective effects. Therefore, Pergularia daemia may serve as a promising natural source for the development of therapeutic strategies for FTD; however, further experimental and clinical studies are required to substantiate its efficacy.

➢ *Key Supporting Evidence:*

- According to in vitro research, the bioactive components of Pergularia daemia, including flavonoids, phenolic compounds, and terpenoids, have potent antioxidant activity and offer substantial cellular defense against oxidative stress-induced brain damage.
- Treatment with extracts containing these phytoconstituents has been shown to improve cognitive function, enhance motor coordination, and restore biochemical markers associated with neurodegeneration in in vivo experimental models.

Collectively, these findings suggest that the phytochemical constituents of Pergularia daemia, particularly those rich in polyphenolic compounds, possess significant potential as neuroprotective agents for the management of neurodegenerative disorders such as frontotemporal dementia. These bioactive components may exert neuroprotective effects by reducing oxidative stress, neuronal degeneration, and behavioral impairments associated with the disease.

However, further studies employing FTD-specific cellular and animal models, along with detailed investigations of underlying molecular signaling pathways and isolation of active bioactive compounds, are necessary to validate this therapeutic potential. Such studies may facilitate the development of novel neuroprotective drugs or adjunct therapeutic strategies for the treatment of frontotemporal dementia.

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