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Review Article

From Ancient Remedies to Modern Neuroscience: The Potential of *Citrus Medica* Linn. Essential Oil for Cognitive Health

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ABSTRACT

Citrus medica Linn. essential oil (CMEO) is gaining recognition as a potential neurotherapeutic agent that effectively connects traditional herbal practices with modern neuroscience. Enriched with active compounds such as limonene, citral, and β -pinene, CMEO exhibits a broad spectrum of neuroprotective actions. These include the inhibition of amyloid- β aggregation, prevention of tau protein hyperphosphorylation, and mitigation of neuroinflammatory and oxidative stress pathways hallmarks of Alzheimer's and Parkinson's diseases. Due to its lipophilic nature, CMEO components readily cross the blood-brain barrier, and its efficacy is further enhanced through intranasal delivery, enabling direct transport to the brain. Preclinical data indicate that CMEO supports cognitive function by enhancing cholinergic activity, regulating glutamatergic transmission, and stimulating neurogenesis via upregulation of brain-derived neurotrophic factor (BDNF). Additionally, CMEO possesses antiviral and antimicrobial properties, with computational studies suggesting limonene may inhibit SARS-CoV-2 protease and experimental findings showing efficacy against biofilm-producing bacteria such as *Staphylococcus aureus*. Novel formulations like nano-emulsions and nasal sprays offer promising strategies to improve their bioavailability. While in vitro and animal studies validate its pharmacological potential, clinical trials are essential to confirm its therapeutic value and safety profile. As the prevalence of neurodegenerative diseases continues to grow,

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CMEO stands out as a versatile, natural compound with the potential to fill critical gaps in neuroprotective and cognitive health interventions.

INTRODUCTION

Citron (*Citrus medica* L.): Botanical Characteristics and Historical Importance: The citron (*Citrus medica* L.), a member of the Rutaceae family, represents one of the most ancient cultivated citrus species. This slow-growing evergreen tree or shrub exhibits distinctive morphological features, including large oblong-ovate leaves with serrated margins, fragrant white to purplish blossoms, and notably large fruits (15-30 cm) characterized by a thick, irregularly textured rind and minimal acidic pulp [1,2]. Unlike its juicy citrus relatives, citron is primarily valued for its aromatic peel, which has been significant in its historical utilization [2,3]. The species holds remarkable cultural and historical significance, tracing back to northeastern India or Southeast Asia before spreading westward. Historical records indicate its introduction to Mediterranean regions circa 300 BCE, where it became an important cultivated species in Greek and Roman societies [3,4]. Beyond its horticultural importance, citron has maintained profound religious significance in Judaism, where its cultivar 'etrog' serves as an essential ritual object during Sukkot celebrations [4]. Ancient medical practitioners, including Theophrastus and Dioscorides, documented its therapeutic applications, particularly for digestive disorders and as a detoxifying agent [3]. The fruit's rarity and distinctive fragrance further elevated its status as a luxury commodity in ancient Rome, reflecting its socioeconomic importance in classical antiquity [3,4].

Therapeutic Applications of Essential Oils in Traditional Medical Systems: An Intercultural

Perspective: The essential oils have constituted a fundamental component of ethnopharmacological practices across major traditional medicine systems, demonstrating remarkable convergence in their therapeutic applications while maintaining distinct philosophical frameworks. Within **Ayurvedic medicine**, volatile phytoconstituents derived from sacred botanicals such as tulsi (*Ocimum sanctum* L.) and sandalwood (*Santalum album* L.) are systematically employed to modulate the tridosha system, particularly for managing respiratory disorders and cognitive enhancement through their adaptogenic properties [5]. The **Unani tradition**, grounded in humoral theory, strategically incorporates rose (*Rosa damascena* Mill.) and saffron (*Crocus sativus* L.) essential oils for their cardioprotective and temperament-balancing (Mizaj) activities, reflecting a sophisticated understanding of aromatics in systemic health maintenance [6]. **Traditional Chinese Medicine (TCM)** pharmacopeia utilizes camphoraceous oils, including *Cinnamomum camphora* (L.) J. Presl and *Mentha × piperita* L. to regulate Qi flow and alleviate musculoskeletal pain, often synergistically combined with acupuncture modalities [7]. Contemporary phytochemical analyses have validated many traditional claims, revealing these volatile fractions possess significant antimicrobial, anti-inflammatory, and neuro-modulatory capacities that bridge empirical traditional knowledge with evidence-based phytotherapy [8].

❖ Citrus Medica Essential Oil: Bioactive Composition, Extraction Dynamics, And Comparative Analysis:

- 1. Major Bioactive Constituents:** The phytochemicals present in *C. medica* can be categorized into two groups: nutrient compounds, including vitamins, essential and



non-essential amino acids, and minerals, and non-nutritive compounds, such as flavonoids, alkaloids, terpenes, and coumarins. The metabolic profile of *C. medica*, as illustrated in the diagram, highlights the

distribution of these compound classes based on existing research. This section provides a detailed examination of the plant's nutritional content and chemical makeup, along with an evaluation of the extraction.

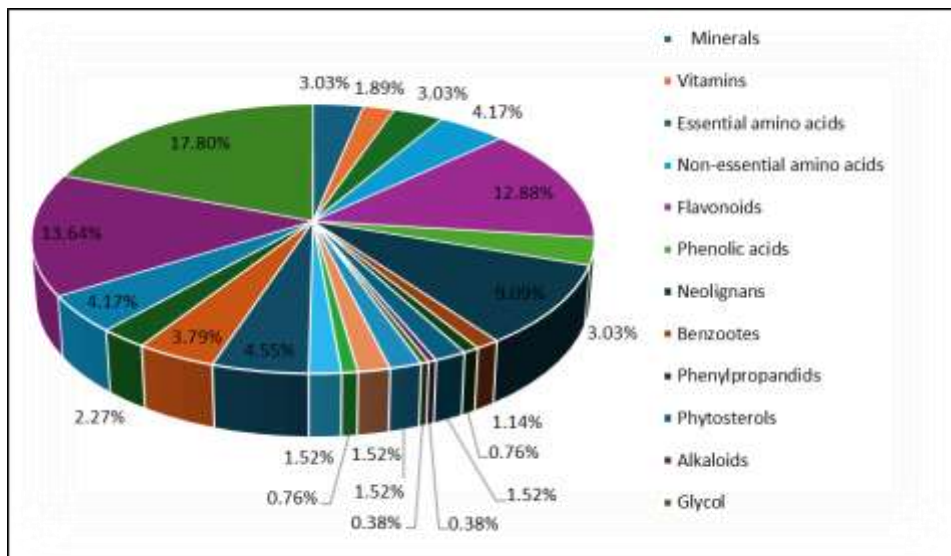


Fig.1-Metabolic Profile of *Citrus medica* L.:

The classification of compounds in *C. medica* based on their percentage ranges within the plant. Compounds present in amounts less than 1.8% are categorized under 'Other Compounds.'

techniques employed in relevant studies [9].

The citrus medica essential oil (CMEO) is characterized by a diverse array of bioactive phytochemicals, with limonene, citral (a mixture

of neral and geranial), β -pinene, γ -terpinene, and linalool representing its principal components [10]. These monoterpenoid compounds collectively contribute to the oil's demonstrated pharmacological activities, including notable antioxidant capacity, antimicrobial effects, and anti-inflammatory properties [11]. The specific combination and ratios of these constituents are responsible for CMEO's unique therapeutic profile.

Table No.1-Major constituents of peel essential oil from *Citrus medica* L. [12]

S. No.	Name of constituents	%
1.	Isolimonene	39.37
2.	Citral	23.12
3.	Limonene	21.78
4.	β -Myrcene	2.70
5.	Neryl acetate	2.51
6.	Neryl Alcohol	2.25

1. Variation Based on Extraction Methods:

The phytochemical composition of CMEO

exhibits significant variation depending on extraction methodology [13]. Cold-pressing

techniques tend to preserve higher concentrations of oxygenated compounds like citral and maintain limonene content, while steam distillation methods may alter the relative proportions of monoterpene

hydrocarbons and aldehydes [14]. These extraction-induced variations directly influence the oil's bioactive potential, as different compound profiles exhibit distinct mechanisms of action.

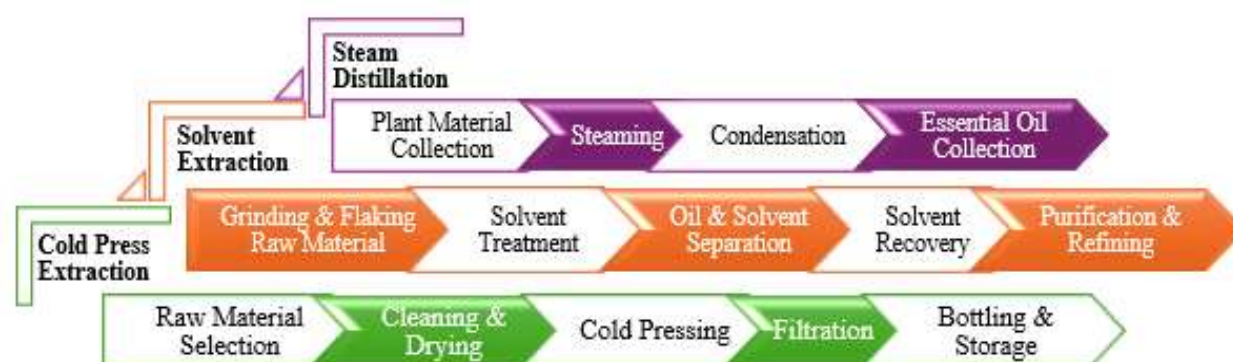


Fig.2-Essential Oil Extraction Techniques: A Comparative Study of Three Major Methods.

2. Comparative Analysis with Related Citrus Oils: When compared to essential oils from related Citrus species such as *C. limon* (lemon) and *C. bergamia* (bergamot), CMEO demonstrates a characteristically distinct neuroactive profile [15]. Particularly noteworthy is its elevated citral content, which has been associated with both anxiolytic properties and cognitive-enhancing effects in preclinical studies [16]. This unique phytochemical signature positions CMEO as an up-and-coming candidate for neurological applications among citrus essential oils.

❖ Molecular and Cellular Drivers of Cognitive Impairment: A Pathological Perspective:

Multifactorial Neuropathological Processes Underlying Cognitive Impairment:

A. Proteostasis Failure in Neurodegeneration: Molecular Mechanisms of Pathogenic Protein Aggregation:

1. The Role of Amyloid- β ($A\beta$) Plaque Formation in Disease Pathophysiology: The amyloid- β ($A\beta$) plaques represent a defining pathological feature of Alzheimer's disease (AD) and are integral to its pathogenesis. These extracellular deposits arise from the aberrant processing of amyloid precursor protein (APP) by the sequential actions of β -secretase (BACE1) and γ -secretase, culminating in the generation of insoluble $A\beta$ peptides particularly $A\beta_{42}$ which readily form toxic oligomers and fibrillar aggregates [17]. The accumulation of $A\beta$ disrupts synaptic integrity, activates microglia, and fosters a state of chronic neuroinflammation, collectively driving widespread neuronal damage and loss [18]. $A\beta$ pathology is also linked to increased oxidative stress, mitochondrial dysfunction, and the promotion of tau protein hyperphosphorylation, which contributes to neurofibrillary tangle formation [19]. Genetic mutations in APP, PSEN1, and PSEN2, commonly associated with early-onset familial AD, directly modulate $A\beta$ synthesis and aggregation dynamics [20]. In addition,

the presence of the APOE $\epsilon 4$ allele a well-established risk factor for sporadic, late-onset AD compromises A β clearance, thereby exacerbating its cerebral deposition [21]. Together, these genetic and molecular processes interact to drive the neurodegenerative cascade underlying AD progression.

2. **Deciphering the Pathogenic Cascade: Tau Hyperphosphorylation to Neurofibrillary Tangles in AD:** Tau hyperphosphorylation and the subsequent formation of neurofibrillary tangles (NFTs) are hallmark pathological features of Alzheimer's disease (AD), strongly associated with neuronal dysfunction and cognitive impairment. Tau, a microtubule-associated protein essential for maintaining neuronal cytoskeletal stability, undergoes abnormal hyperphosphorylation in AD, primarily mediated by kinases such as glycogen synthase kinase-3 β (GSK3 β) and cyclin-dependent kinase 5 (CDK5), which diminish its affinity for microtubules [22]. This post-translational modification leads to tau misfolding and its aggregation into paired helical filaments (PHFs), which accumulate intracellularly as NFTs, thereby disrupting axonal transport, impairing synaptic function, and ultimately triggering neuronal degeneration [23]. The propagation of pathological tau across different brain regions follows a characteristic trajectory that correlates closely with disease progression and clinical severity [24]. While mutations in the MAPT gene, which encodes tau, are primarily linked to frontotemporal dementia and parkinsonism associated with chromosome 17 (FTDP-17), they highlight tau's pathogenic potential, despite not being a direct cause of AD [25]. Moreover, genetic factors such as the APOE $\epsilon 4$ allele may indirectly exacerbate tau

pathology by increasing amyloid- β accumulation, which in turn facilitates tau hyperphosphorylation and aggregation [26]. Together, these molecular mechanisms contribute to the neurodegenerative processes underlying AD.

3. **α -Synuclein Aggregation and Neurodegeneration: Molecular Pathways in Parkinson's Disease & Dementia:**

The aggregation of α -synuclein is a hallmark of Parkinson's disease dementia (PDD) and also plays a contributory role in Alzheimer's disease (AD) pathology. Misfolded α -synuclein accumulates to form Lewy bodies, which impair synaptic function, induce oxidative stress, and trigger neuroinflammatory responses, ultimately leading to neurodegeneration [27]. In AD, α -synuclein interacts with amyloid- β and tau, facilitating amyloid plaque formation and promoting tau hyperphosphorylation [28]. Genetic mutations in SNCA, the gene encoding α -synuclein, enhance its propensity to aggregate and are associated with familial Parkinson's disease and Lewy body dementia [29]. Furthermore, the APOE $\epsilon 4$ allele, a well-established genetic risk factor for AD, has been implicated in exacerbating α -synuclein pathology, reinforcing the molecular link between these neurodegenerative disorders [30].

B. **Microglial Hyperactivation and Astrocytic Dysfunction: Dual Pathways Driving Neuroinflammatory Synaptopathy:**

1. **Microglial Overactivation and Chronic Neuroinflammation:** The excessive activation of microglia results in the heightened production of pro-inflammatory cytokines such as IL-1 β and TNF- α , along with the stimulation of the NF- κ B signaling

pathway, leading to sustained neuroinflammation. This prolonged immune response induces oxidative stress, disrupts the blood-brain barrier, and contributes to neuronal damage, thereby exacerbating neurodegenerative conditions like Alzheimer's and Parkinson's disease [31].

2. **Astrocyte Dysfunction and Synaptic Impairment:**

The dysfunctional astrocytes compromise synaptic homeostasis, leading to impaired neurotransmitter regulation and diminished neurotrophic support. In their reactive state, astrocytes can also secrete pro-inflammatory factors, further exacerbating neuronal injury and synaptic loss-key pathological hallmarks of neurodegenerative disorders [32].

C. **Oxidative Stress & Mitochondrial Dysfunction: Stealth Mediators of Cellular Decline and Disease:**

1. **Impact of Reactive Oxygen Species (ROS) Accumulation on Neuronal Integrity:**

The neurons are highly vulnerable to oxidative damage due to their high metabolic demand and limited regenerative capacity. Excess ROS, primarily generated by dysfunctional mitochondria, can damage lipids, proteins, and nucleic acids, leading to synaptic dysfunction and eventual cell death. Mitochondrial DNA is especially susceptible, and its damage can further impair electron transport, creating a vicious cycle of ROS production and neuronal injury. These mechanisms are strongly implicated in the pathogenesis of neurodegenerative diseases such as Alzheimer's and Parkinson's disease [33,34].

2. **Reduced Antioxidant Defenses (SOD, GSH Depletion):**

The endogenous antioxidants like superoxide dismutase (SOD) and glutathione

(GSH) are critical in neutralizing ROS. In pathological conditions, the depletion of GSH or mutation/dysfunction in antioxidant enzymes (e.g., SOD1 in ALS) diminishes the cell's ability to mitigate oxidative damage. In diseases such as Parkinson's, reduced GSH levels have been observed in affected brain regions, indicating compromised antioxidant defense and increased oxidative stress burden [35,36].

D. **Dysregulation of Synaptic Transmission and Neurotransmitter Signaling:**

1. **Cholinergic Dysfunction (Reduced Acetylcholine and Elevated AChE Activity):**

The cholinergic system is essential for regulating cognitive functions such as memory, attention, and learning. In Alzheimer's disease and related neurodegenerative disorders, a pronounced reduction in acetylcholine (ACh) levels occurs, primarily due to the degeneration of cholinergic neurons in the basal forebrain. Compounding this deficit is the increased activity of acetylcholinesterase (AChE), which hastens ACh degradation and further diminishes its synaptic availability. This cholinergic impairment is strongly associated with cognitive deterioration. To counteract this, AChE inhibitors such as donepezil and rivastigmine are widely used to enhance cholinergic signaling in dementia patients [37].

2. **Glutamatergic Excitotoxicity (NMDA Receptor Overactivation):**

The glutamate serves as the principal excitatory neurotransmitter in the central nervous system. Under pathological conditions, excessive glutamate release or insufficient clearance can lead to sustained activation of NMDA receptors. This prolonged stimulation triggers intracellular calcium overload, disrupts



mitochondrial function, and ultimately induces neuronal cell death a process known as excitotoxicity. This mechanism plays a central role in the pathophysiology of several neurological disorders, including stroke, ALS, and Alzheimer's disease. Pharmacological agents such as NMDA receptor antagonists (e.g., memantine) are employed to mitigate this excitotoxic stress [38].

3. Imbalances in Dopaminergic and Serotonergic Systems (Mood-Cognition Interaction):

The dopamine and serotonin are critical neuromodulators involved in regulating mood, cognition, and behavior. Disruptions in dopaminergic signaling particularly within the mesocortical and nigrostriatal pathways are associated with disorders such as Parkinson's disease and schizophrenia, affecting both cognitive performance and motor function. Similarly, serotonergic dysregulation is implicated in mood disorders like depression and anxiety, and also contributes to cognitive impairment observed in aging and neurodegeneration. The complex interaction between these neurotransmitter systems underscores the intrinsic link between affective and cognitive domains [39,40].

E. Impaired Neurogenesis and Synaptic Plasticity:

1. **Reduced Brain-Derived Neurotrophic Factor (BDNF) and Cognitive Decline:** The BDNF plays a critical role in supporting neuronal health, facilitating synaptic plasticity, and enabling memory processes. A reduction in BDNF expression has been consistently associated with cognitive dysfunction in neurodegenerative conditions such as Alzheimer's disease. This decline disrupts synaptic communication and promotes

neuronal degeneration, ultimately manifesting as memory impairment [41].

2. Hippocampal Atrophy in Neurodegenerative and Mood Disorders:

The hippocampus is a key structure involved in memory formation and emotional regulation and is notably susceptible to damage in both Alzheimer's disease and major depressive disorder. Its atrophy is frequently linked to diminished BDNF levels, impaired neurogenesis, and chronic stress exposure. This structural deterioration is strongly correlated with both cognitive deficits and affective disturbances [42].

F. Blood-brain barrier (BBB) Dysfunction:

1. **Entry of Neurotoxic Agents (e.g., Amyloid- β , Inflammatory Cytokines):** The compromise of the BBB permits the infiltration of neurotoxic molecules, including amyloid- β peptides and proinflammatory cytokines, into the brain tissue. This breach fosters a neuroinflammatory environment that accelerates neuronal injury and is implicated in the progression of Alzheimer's disease [43].
 2. **Disrupted Nutrient Transport and Neuronal Energy Deficiency:** The BBB is essential for the regulated transport of nutrients such as glucose and amino acids to the brain. When its function is disrupted, the resultant nutrient deprivation leads to energy deficits within neurons, impairing synaptic function and cellular survival. Such metabolic insufficiency is increasingly recognized as a contributing factor to cognitive decline in neurodegenerative conditions [44].
- ❖ **Deciphering the BBB Crossing Ability of Citrus Medica Essential Oil:**



The blood-brain barrier (BBB) serves as a selective filter, restricting the passage of molecules into the brain. However, several components of *Citrus medica* essential oil (EO) have demonstrated the ability to cross the BBB through various mechanisms:

- 1. Lipid-Mediated Passive Diffusion:** Terpenes present in *Citrus medica* EO, such as limonene, γ -terpinene, and p-cymene, are small and lipophilic, which facilitates their passive diffusion across the lipid-rich BBB [45].
- 2. Carrier-Mediated Transport:** Certain monoterpenes in *Citrus medica* EO may interact with transporters, including P-

glycoprotein, that regulate the entry of xenobiotics into the brain [46].

- 3. Modulation of Tight Junctions (Limited Evidence):** Some terpenes, particularly α -pinene, have been suggested to transiently modulate tight junction proteins, potentially enhancing BBB permeability under certain conditions [47].
- 4. Nasal Route (Direct Nose-to-Brain Delivery via Olfactory Pathway):** Inhalation of volatile compounds from *Citrus medica* EO may facilitate direct delivery to the brain by bypassing the BBB through the trigeminal and olfactory nerve pathways [48].

Table No.2-Routes of Administration for Citrus medica Essential Oil.

Sr. No.	Route	Advantages	Limitations	Evidence for Citrus medica EO
1	Inhalation (Aromatherapy)	Rapid brain uptake via olfactory pathway	Short duration of effects	Shown to modulate CNS activity in animal models [49]
2	Oral Ingestion	Systemic absorption via gut	First-pass metabolism reduces bioavailability	Limited studies; terpenes may be metabolized [50]
3	Topical (Transdermal)	Slow release, avoids first-pass effect	Variable absorption rates	Some terpenes (e.g., limonene) penetrate skin [51]
4	Sublingual	Fast absorption, avoids GI degradation	Limited volume capacity	No direct studies on Citrus medica EO
5	Intranasal (Spray/Drops)	Direct nose-to-brain delivery	Mucosal irritation possible	Promising for neuroactive EOs [52]

❖ Neurocognitive Modulation by Citrus Medica Essential Oil: An Evolutionary-Inspired Neuroscience Investigation:

Neuroprotective Potential of Citrus Medica Essential Oil: Modulation of Key Pathological Mechanisms in Cognitive Disorders: Citrus Medica Linn. essential oil (EO) contains a variety

of bioactive compounds, particularly neuroactive terpenes and flavonoids, that influence critical molecular and cellular mechanisms associated with cognitive disorders like Alzheimer's, Parkinson's, and vascular dementia. The key phytochemicals present in the

EO include:

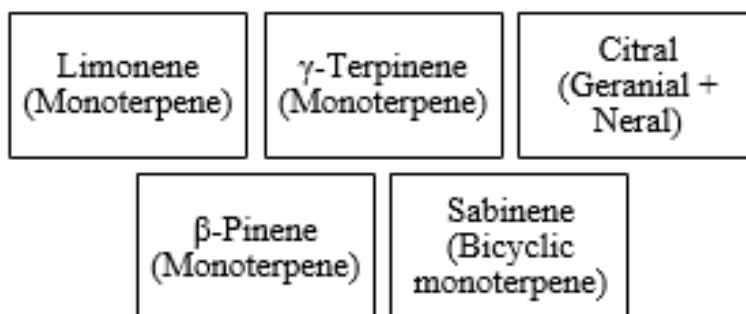


Fig.3-These compounds interact with various pathological pathways to potentially offer neuroprotective effects in cognitive decline.

Table No.3-Mechanistic Insights into the Cognitive Benefits of Citrus medica Essential Oil

Sr. No.	Cognitive Pathology	Molecular/Cellular Target	Relevant EO Compound	Mechanism of Action	Evaluation Method
1	Amyloid- β (A β) Aggregation	BACE1, A β fibrils	Limonene, Citral	Inhibits β -secretase (BACE1), prevents A β plaque formation	Thioflavin T assay, Western blot (A β 40/42)
2	Tau Hyperphosphorylation	GSK-3 β , p-tau	Limonene, β -Pinene	Suppresses GSK-3 β $\rightarrow$ reduces tau tangles	Immunohistochemistry (AT8 antibody)
3	Neuroinflammation	NF- κ B, TNF- α , IL-6	γ -Terpinene, Linalool	Downregulates pro-inflammatory cytokines	ELISA (TNF- α , IL-6), qPCR
4	Oxidative Stress	ROS, SOD, GSH	Limonene, Citral	Scavenges free radicals, boosts antioxidant enzymes	DCFH-DA assay, SOD/GSH activity
5	Cholinergic Dysfunction	Acetylcholinesterase (AChE)	Citral, β -Pinene	AChE inhibition $\rightarrow$ $\uparrow$ Acetylcholine	Ellman's assay, HPLC (ACh levels)
6	Glutamate Excitotoxicity	NMDA receptors	Linalool	Blocks excessive Ca ²⁺ influx $\rightarrow$ prevents neuron death	Calcium imaging, electrophysiology
7	Neurogenesis Decline	BDNF, TrkB	Limonene, Linalool	$\uparrow$ BDNF secretion $\rightarrow$ supports neuron growth	Western blot (BDNF), BrdU staining
8	Blood-Brain Barrier (BBB) Leakage	Tight junction proteins (Claudin-5, ZO-1)	γ -Terpinene	Strengthens BBB integrity	Evans blue assay, TEM imaging
9	Synaptic Plasticity Loss	PSD-95, Synaptophysin	Citral, Limonene	Enhances synaptic protein expression	Immunofluorescence, WB (PSD-95)

The *Citrus medica* Linn. essential oil (EO) exhibits notable neuroprotective potential, attributed to its rich profile of bioactive compounds including limonene, citral, γ -terpinene, β -pinene, and

linalool. These constituents modulate critical pathological processes involved in cognitive disorders. Limonene and citral inhibit BACE1, reducing amyloid- β (A β) plaque formation, while

tau hyperphosphorylation is attenuated via GSK-3 β inhibition by limonene and β -pinene. [53,54] Neuroinflammation is suppressed by γ -terpinene and linalool through downregulation of NF- κ B, TNF- α , and IL-6. Oxidative stress is mitigated as limonene and citral enhance antioxidant defenses such as SOD and GSH. Citral and β -pinene also improve cholinergic transmission by inhibiting acetylcholinesterase (AChE), preserving acetylcholine levels. [55,56] Linalool protects against glutamate excitotoxicity by modulating NMDA receptor-mediated calcium influx. Neurogenesis is supported through BDNF and TrkB upregulation by limonene and linalool. γ -Terpinene enhances blood-brain barrier (BBB) integrity via regulation of tight junction proteins like Claudin-5. Additionally, citral and limonene promote synaptic plasticity by increasing expression of PSD-95 and synaptophysin. [57] These mechanisms have been validated using techniques such as Western blot, ELISA, qPCR, calcium imaging, and immunofluorescence, highlighting the therapeutic promise of *Citrus medica* EO in managing neurodegenerative diseases.

❖ Recent Advances in Neuroscientific Assessment Techniques:

A. Behavioral and Cognitive Assessments:

- 1. Morris Water Maze (MWM) – Spatial Memory:** The MWM is employed to evaluate spatial learning and memory in rodents by requiring them to locate a hidden platform submerged in a water maze using surrounding visual cues. This task predominantly assesses hippocampal-dependent spatial navigation and memory consolidation processes [58].
- 2. Y-Maze Spontaneous Alternation – Working Memory:** This test measures spatial working memory based on the rodent's natural

inclination to explore a novel arm of a Y-shaped maze. The frequency of spontaneous alternation, or choosing a previously unvisited arm, reflects the integrity of working memory function [59].

- 3. Novel Object Recognition Test (NORT) – Recognition Memory:** The NORT is designed to assess recognition memory by exposing rodents to both familiar and novel objects. A preference for interacting with the novel object indicates preserved recognition memory capacity [60].
- 4. Passive Avoidance Test – Fear-Associated Memory:** This task evaluates associative learning and memory retention by conditioning rodents to avoid an environment where they previously encountered an aversive stimulus. The latency to re-enter the aversive compartment serves as an indicator of fear-based memory retention [61].
- 5. Elevated Plus Maze (EPM) & Open Field Test (OFT) – Anxiety and Exploratory Behavior:** The EPM measures anxiety by recording rodents' willingness to explore open versus enclosed arms of a plus-shaped apparatus. The OFT assesses both anxiety and exploratory behavior based on movement patterns in an open arena [62,63].

B. Neuroimaging and Electrophysiological Techniques:

- 1. MRI/fMRI – Structural and Functional Brain Analysis:** Magnetic Resonance Imaging (MRI) provides high-resolution images to assess structural attributes such as hippocampal volume. Functional MRI (fMRI), on the other hand, evaluates neural activity and inter-regional connectivity by detecting



hemodynamic changes associated with neuronal function [64].

2. PET Imaging – Amyloid Deposition and Metabolic Activity: Positron Emission Tomography (PET) uses radiolabeled tracers to visualize biological processes. In neuroscience, it is particularly useful for detecting amyloid-beta accumulation and evaluating cerebral glucose metabolism, key markers in neurodegenerative disorders [65,66].

3. EEG/MEG – Neural Oscillations and Processing Speed: Electroencephalography (EEG) and Magnetoencephalography (MEG) measure electrical and magnetic brain activity, respectively. These modalities are instrumental in examining neural oscillatory patterns and assessing cognitive processing dynamics [67].

C. In Vitro and Animal-Based Models:

1. SH-SY5Y Neuronal Cells – Amyloid Toxicity and Oxidative Stress: The SH-SY5Y human neuroblastoma cell line is extensively used to model neuronal responses to amyloid-beta toxicity and oxidative stress, facilitating the study of cellular mechanisms underlying neurodegeneration [68].

2. BV-2 Microglial Cells – Inflammation Studies: The BV-2 cells, a murine microglial model, are widely utilized to investigate neuroinflammatory responses and the efficacy of anti-inflammatory interventions in central nervous system disorders [69].

3. Transgenic Alzheimer's Disease Mice (APP/PS1, 3xTg) – Pathological Hallmarks: The Genetically modified mouse models such as APP/PS1 and 3xTg exhibit amyloid plaque

and tau tangle formation, simulating key pathological features of Alzheimer's disease. These models are critical for studying disease progression and evaluating therapeutic strategies [70].

4. Scopolamine-Induced Amnesia-(Cholinergic Dysfunction Modeling): The Administration of scopolamine, a muscarinic receptor antagonist, induces temporary cognitive impairment in animals, serving as a pharmacological model for studying cholinergic deficits associated with Alzheimer's disease [71].

D. Clinical Assessments in Human Studies:

1. Cognitive Evaluation Tools: MMSE, MoCA, ADAS-Cog:

- *Mini-Mental State Examination (MMSE):* A 30-point scale assessing orientation, memory, attention, and language to detect cognitive deficits [72].
- *Montreal Cognitive Assessment (MoCA):* A comprehensive screening tool for mild cognitive impairment, examining executive functions, attention, memory, and language [73].
- *Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog):* Specifically designed to quantify cognitive dysfunction in Alzheimer's disease, focusing on domains like memory, language, and praxis [74].

2. Biomarker Profiling-(CSF A β 42, Phosphorylated Tau, Plasma NfL): Biomarkers such as cerebrospinal fluid amyloid-beta 42 (A β 42), phosphorylated tau (p-tau), and plasma neurofilament light chain (NfL) are essential in diagnosing and tracking the progression of neurodegenerative diseases [75].



3. Neuropsychological Testing: Digit Span, Trail Making Test (TMT):

- *Digit Span*: Measures attention span and working memory through forward and backward number sequence recall [76].
- *Trail Making Test (TMT)*: Evaluates visual attention, cognitive flexibility, and executive function by requiring participants to connect alternating numeric and alphabetic sequences [77].

E. Advanced Neuroscientific Methods:

1. Optogenetics-Precision Control of Neural Circuits: Optogenetics enables the manipulation of specific neuronal populations using light-activated proteins, providing unparalleled precision in studying neural circuitry and associated behaviors [78].

2. Two-Photon Microscopy-Deep Tissue Imaging: This advanced imaging technique allows for high-resolution visualization of neuronal structures and activity in live animals, enabling longitudinal studies with minimal phototoxic effects [79].

❖ Future Perspectives: The Expanding Role of Citrus Medica Essential Oil in Cognitive Disorders and Neuroprotection:

A. Cognitive Disorders:

1. Alzheimer's Disease: Citrus *medica* essential oil (EO) is being explored in clinical trials as a supportive agent to traditional AChE inhibitors (like donepezil), potentially enhancing effects on amyloid and tau pathology. [80] Advanced delivery systems such as lipid-based nanoencapsulation may improve brain targeting. [81]

2. Parkinson's Dementia: Combining L-DOPA with EOs could help reduce oxidative stress and neuroinflammation. [82] Inhalation delivery methods are being considered for faster central nervous system action. [83]

3. Vascular Cognitive Impairment: Prophylactic EO use in hypertension models may help protect the blood-brain barrier (BBB).[84] MRI imaging techniques can be used to assess improvements in cerebral perfusion.[85]

4. Age-Related Memory Decline: Long-term EO supplementation is under investigation in elderly groups, with enhanced efficacy expected when combined with omega-3 fatty acids to promote BDNF levels. [86,87]

B. Other Neurological Applications:

1. Depression & Anxiety: EO compounds such as limonene interact with serotonin and GABA receptors, showing potential to balance mood and reduce anxiety symptoms. [88]

C. Systemic & Physical Health Applications:

1. Metabolic Disorders: EOs may enhance insulin sensitivity by promoting GLUT4 movement in skeletal muscle cells. [89]

2. Cardiovascular Health: EOs contribute to vasodilation via the nitric oxide (NO)/cGMP pathway and help prevent atherosclerosis by decreasing LDL oxidation and LOX-1 expression. [90,91]

D. Antimicrobial & Antiviral Effects: The Molecular docking suggests limonene binds to SARS-CoV-2 main protease (COVID-19), showing potential antiviral activity. Additionally, EOs can disrupt biofilm formation in *Staphylococcus aureus*,



highlighting their antibacterial potential. [91,92]

❖ CONCLUSION:

Citrus medica Linn. essential oil (CMEO) exemplifies the evolution from traditional botanical remedy to a promising modern neurotherapeutic agent. Rich in bioactive constituents such as limonene, citral, β -pinene, and linalool, CMEO exhibits multifaceted neuroprotective effects, including the disruption of amyloid- β aggregation, attenuation of tau pathology, suppression of neuroinflammatory cascades, and enhancement of the brain's antioxidant defense systems. Its capacity to penetrate the blood-brain barrier (BBB) through both passive diffusion and olfactory routes supports its therapeutic relevance in Alzheimer's disease, Parkinson's dementia, and vascular cognitive impairment. Beyond cognitive health, CMEO's broad-spectrum antiviral potential has garnered attention, particularly in the context of COVID-19. Computational docking studies indicate that limonene may inhibit the SARS-CoV-2 main protease, suggesting its utility as a potential adjunct in antiviral strategies. The COVID-19 pandemic has spotlighted the relationship between neuroinflammation, oxidative stress, and cognitive dysfunction, often referred to as "brain fog." CMEO's anti-inflammatory and neurorestorative properties may offer protection against such long-term post-viral complications. In parallel, CMEO has demonstrated significant antimicrobial activity, notably in impairing biofilm formation by pathogens like *Staphylococcus aureus* a critical attribute in combating antibiotic-resistant infections. Advancements in drug delivery technologies, such as nano-emulsions, intranasal sprays, and transdermal systems, offer promising avenues to improve CMEO's bioavailability and

CNS targeting. Looking ahead, rigorous clinical trials are essential to substantiate CMEO's efficacy, establish safe and effective dosing parameters, and assess its synergy with standard treatments like acetylcholinesterase inhibitors and NMDA receptor antagonists. In the face of rising neurodegenerative disorders and an aging global population, *Citrus medica* essential oil emerges as a compelling candidate bridging traditional wisdom and contemporary science, with the potential to serve as a multi-target, sustainable therapeutic agent for brain health in the modern era.

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