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Review Article

The Impact of Citral on GABAergic and Serotonergic Transmission in Haloperidol-Induced Neuroleptic and Cataleptic Effects

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ABSTRACT
The study explores the potential neuroprotective role of citral, a monoterpenoid compound, in haloperidol-induced catalepsy, a common side effect of neuroleptic medications. Haloperidol, an antipsychotic drug, often induces extrapyramidal symptoms (EPS), including catalepsy, due to dopaminergic blockade. Citral, derived from plants like lemongrass, has been recognized for its anti-inflammatory, antioxidant, and neuroprotective properties, which may counteract these side effects. The study investigates the modulation of GABAergic and serotonergic neurotransmission by citral as a potential mechanism to reduce haloperidol-induced motor impairments. Experimental findings from animal models show that citral administration mitigates catalepsy by influencing the dopamine, GABA, and serotonin pathways. Additionally, citral's protective effects may involve neuroplasticity, oxidative stress reduction, and anti-inflammatory actions. This research suggests that citral could serve as a valuable adjunct therapy to alleviate neuroleptic-induced side effects, enhancing patient compliance with long-term antipsychotic therapy. Further clinical studies and mechanistic investigations are essential to validate citral's safety, efficacy, and therapeutic potential in treating neuroleptic-induced motor dysfunctions and other neurological disorders.

KEYWORDS: Citral, haloperidol, catalepsy, neuroleptic side effects, extrapyramidal symptoms, GABAergic system, serotonergic system, dopaminergic blockade

INTRODUCTION

Citral is a naturally occurring monoterpene aldehyde predominantly found in the essential oils of plants such as lemongrass (*Cymbopogon citratus*), lemon myrtle (*Backhousia citriodora*), and orange peel. Structurally characterized by its two geometric isomers (geranial and neral), citral is widely recognized for its strong lemon-like odor and flavor[1]. Historically, it has been extensively used in the food, cosmetics, and fragrance industries. Beyond its commercial applications, citral has drawn considerable attention in the scientific community due to its diverse pharmacological properties. Early investigations into citral's bioactivity demonstrated its potent antimicrobial and antifungal effects, making it a promising natural alternative for the control of pathogenic microorganisms [2].

In addition to its antimicrobial activity, citral has been identified to exhibit significant anti-inflammatory, antioxidant, and anticancer properties. Preclinical studies have revealed that citral can modulate inflammatory pathways by inhibiting pro-inflammatory cytokines and mediators, suggesting its potential utility in managing inflammatory disorders [3]. Furthermore, its antioxidant capacity contributes to the neutralization of free radicals, thereby protecting cells from oxidative stress a critical factor implicated in neurodegenerative diseases and cancer development [4]. Recent research has also begun exploring citral's impact on central nervous system functions, where it appears to interact with neurotransmitter systems, potentially influencing GABAergic and serotonergic pathways. These emerging findings underscore the importance of citral as a compound of interest for developing novel therapeutic agents, particularly in the context of neuropharmacology [5].

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Overview of GABAergic and serotonergic neurotransmission

The **GABAergic system** is the primary inhibitory neurotransmitter network in the mammalian central

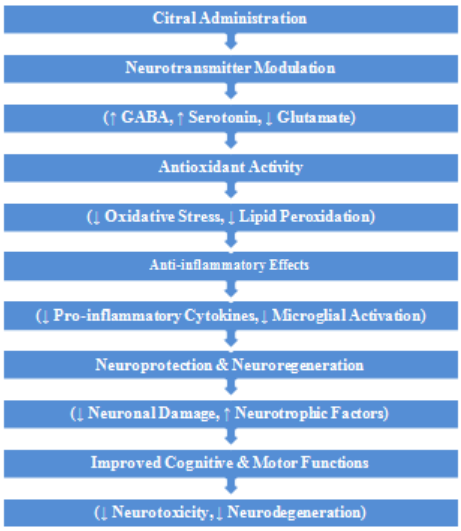

Figure 1: Potential Neuroprotective Role of Citral

nervous system, playing a crucial role in regulating neuronal excitability and maintaining the balance between excitation and inhibition. Gamma-aminobutyric acid (GABA) exerts its inhibitory effects primarily through binding to GABAA_AA and GABAB_BB receptors, which mediate fast synaptic inhibition and prolonged inhibitory responses, respectively [6].

GABAA_AAreceptors, being ligand-gated ion channels, allow the influx of chloride ions, leading to hyperpolarization of neurons and decreased likelihood of action potential generation. Dysregulation of GABAergic transmission has been implicated in various neurological and psychiatric disorders, including epilepsy, anxiety, and depression, which underscores its importance as a therapeutic target[7]. Recent studies continue to explore the nuances of GABA receptor subunit composition and their pharmacological modulation to better understand and treat these conditions [8]

In contrast, the **serotonergic system** is primarily associated with the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT), which is involved in regulating mood, cognition, sleep, and a host of other physiological processes. Serotonin is synthesized in the brainstem's raphe nuclei and disseminated widely across various brain regions through extensive neuronal projections. It exerts its effects through a variety of receptor subtypes, classified into seven families (5-HT1_11 to 5-HT7_77), each of which is linked to distinct intracellular signaling pathways and functional outcomes [9] The complex interplay between different serotonin receptors has been associated with various neuropsychiatric conditions, including depression, anxiety, and schizophrenia. Therapeutic strategies that target specific serotonergic receptors have led to the development of numerous antidepressant and antipsychotic drugs, highlighting the clinical relevance of understanding this neurotransmitter system [10]

Haloperidol: Mechanism of action and clinical significance

Haloperidol is a first-generation antipsychotic primarily known for its high-affinity antagonism of dopamine D2 receptors. By binding to these receptors in the mesolimbic pathway, haloperidol reduces the dopaminergic hyperactivity that is often associated with the positive symptoms of schizophrenia, such as hallucinations and delusions [11,12]. However, this same mechanism of action is also responsible for many of the drug's adverse effects. In the nigrostriatal pathway, the blockade of D2 receptors leads to extrapyramidal symptoms (EPS), which include motor disturbances such as rigidity, tremors, and catalepsy [13]. This dual effect—therapeutic in the mesolimbic system but problematic in the nigrostriatal system—underscores the delicate balance required in antipsychotic treatment, making dosing and patient monitoring critical components of haloperidol therapy.

The clinical significance of haloperidol extends beyond its antipsychotic efficacy. Clinically, haloperidol is utilized not only in the management of schizophrenia and other psychotic disorders but also in controlling acute agitation and aggressive behavior in a range of psychiatric and neurological conditions [14].

Its robust efficacy in mitigating psychotic symptoms has been well documented over decades of clinical use, yet the emergence of side effects such as tardive dyskinesia and catalepsy has fueled research into safer treatment modalities [15]. This has spurred ongoing investigations into adjunct therapies and the development of newer agents that can either complement or improve upon the mechanism of haloperidol, aiming to preserve antipsychotic benefits while minimizing adverse motor effects. Such research continues to be pivotal in enhancing our understanding of the neurobiological underpinnings of psychosis and in refining therapeutic strategies.

Rationale for studying citral's role in haloperidol-induced effects

Haloperidol, a potent typical antipsychotic, is widely used in the treatment of schizophrenia and other psychotic disorders due to its strong dopamine D2 receptor antagonism. However, this blockade in the nigrostriatal pathway leads to severe extrapyramidal side effects, including catalepsy, rigidity, and tremors, resembling

Parkinsonian symptoms[16]. Given these adverse effects, there is growing interest in identifying adjunct therapies that can mitigate these motor impairments while preserving the antipsychotic efficacy of haloperidol.

Citral, a bioactive monoterpene aldehyde found in citrus fruits, has gained attention for its diverse pharmacological properties, including neuroprotective, anxiolytic, and anti-inflammatory effects [17]. Notably, citral modulates GABAergic and serotonergic neurotransmission, which are crucial pathways implicated in motor control and mood regulation [18]. Since haloperidol-induced catalepsy is associated with altered dopaminergic signaling and secondary disruptions in GABA and serotonin systems, citral's ability to enhance GABAergic activity and influence serotonergic pathways presents a promising therapeutic avenue[19].

Preclinical studies suggest that GABAergic modulation can counteract motor deficits induced by dopamine receptor blockade, potentially alleviating haloperidol-induced catalepsy [20]. Similarly, serotonin plays a key role in motor coordination, and serotonergic enhancement has been linked to reduced extrapyramidal symptoms in antipsychotic-treated patients [21]. Given citral's capacity to modulate both neurotransmitter systems, investigating its role in haloperidol-induced neuroleptic and cataleptic effects could provide valuable insights into alternative therapeutic strategies that improve the safety profile of antipsychotic treatment.

Haloperidol and Its Neuroleptic & Cataleptic Effects

Haloperidol is a potent typical antipsychotic that primarily exerts its pharmacological effects through dopamine D2 receptor antagonism in the central nervous system. By blocking D2 receptors in the mesolimbic pathway, haloperidol reduces positive symptoms of schizophrenia, such as hallucinations and delusions, thereby acting as an effective neuroleptic agent [22,23]. However, its strong affinity for dopamine receptors in the nigrostriatal pathway is responsible for its extrapyramidal side effects, including catalepsy, rigidity, and tremors, which resemble Parkinsonian symptom.

Apart from dopamine antagonism, haloperidol also exhibits interactions with other neurotransmitter systems. It has moderate antagonistic effects on α1-adrenergic receptors, which contribute to its sedative and hypotensive properties [24]. Additionally, it exerts minimal blockade on serotonergic (5-HT2A) receptors, distinguishing it from atypical antipsychotics that target both dopamine and serotonin pathways to mitigate extrapyramidal side effects [25]. The lack of significant serotonergic modulation is believed to contribute to its higher propensity for inducing catalepsy compared to newer atypical antipsychotics, which balance dopamine-serotonin interactions more effectively [26].

At the neurochemical level, the prolonged blockade of dopamine receptors by haloperidol leads to an adaptive upregulation of dopamine receptor sensitivity, a phenomenon linked to the development of tardive dyskinesia with long-term use [27]. Moreover, disruptions in the GABAergic system, which plays a crucial role in motor control, may further exacerbate the motor side effects of haloperidol [28]. This highlights the need for adjunct therapies that modulate GABAergic or serotonergic transmission to counteract the cataleptic effects while preserving the antipsychotic efficacy of haloperidol.

Dopaminergic blockade and extrapyramidal symptoms

Haloperidol, as a typical antipsychotic, primarily exerts its effects by blocking dopamine D2 receptors in the central nervous system. While this blockade in the mesolimbic pathway reduces positive symptoms of schizophrenia, its non-selective inhibition of dopamine in the nigrostriatal pathway leads to significant motor side effects known as extrapyramidal symptoms (EPS) [29].

Mechanism of Dopaminergic Blockade

Dopamine plays a crucial role in modulating motor control within the basal ganglia, particularly through the nigrostriatal pathway. The inhibition of D2 receptors in this region by haloperidol disrupts the normal balance between dopaminergic and cholinergic neurotransmission, leading to motor impairments. This dopamine-choline imbalance results in hyperactivity of the indirect pathway of the basal ganglia, thereby contributing to rigidity, bradykinesia, and other Parkinsonian-like symptoms [24].

Extrapyramidal Symptoms (EPS)

Acute dystonia refers to sudden, involuntary muscle contractions that lead to abnormal postures, commonly affecting areas such as the face, neck, and upper body. This condition can appear suddenly and is often distressing for patients [27].

Parkinsonism is characterized by symptoms that mimic those of Parkinson's disease, including tremors, rigidity, and bradykinesia. These symptoms can significantly impair motor function and movement coordination [25].

Akathisia is a state of motor restlessness, where patients experience an overwhelming need to move and are unable to stay still. This condition can be extremely distressing and may interfere with daily functioning [26].

Tardive dyskinesia (TD) is a late-onset condition that involves repetitive, involuntary movements, particularly affecting the face, tongue, and limbs. It

results from prolonged dopamine receptor blockade, leading to receptor hypersensitivity and the emergence of these abnormal movements [27].

Strategies to Mitigate EPS

To reduce EPS, adjunct therapies such as anticholinergic agents (e.g., benztropine) are often used to restore dopamine-acetylcholine balance. Additionally, drugs with serotonergic activity, such as atypical antipsychotics, help mitigate EPS by modulating 5-HT2A receptors and balancing dopamine release [25].

Given citral's potential effects on GABAergic and serotonergic transmission, exploring its role in counteracting haloperidol-induced EPS could provide a novel approach for improving the safety profile of typical antipsychotics.

Mechanisms of neuroleptic-induced catalepsy

Catalepsy is a state of motor immobility and rigidity often induced by typical antipsychotics like haloperidol. It is considered a rodent model for extrapyramidal symptoms (EPS) in humans, particularly Parkinsonian-like motor dysfunction. The underlying mechanisms involve dopamine blockade, neurotransmitter imbalances, and dysfunction in basal ganglia circuits[28]

Dopamine D2 Receptor Blockade in the Nigrostriatal Pathway

Haloperidol exerts its cataleptic effects primarily through strong antagonism of dopamine D2 receptors in the nigrostriatal pathway [29]. The basal ganglia regulate voluntary movement, and dopamine plays a critical role in maintaining the balance between direct and indirect pathways:

- Direct Pathway: Facilitates movement via D1 receptor stimulation.
- Indirect Pathway: Inhibits movement via D2 receptor inhibition.

By blocking D2 receptors, haloperidol disrupts normal dopamine signaling, leading to excessive inhibition of movement, rigidity, and reduced locomotion

Increased GABAergic Activity and Motor Inhibition

The basal ganglia rely on inhibitory GABAergic transmission to regulate movement. Dopaminergic inhibition by haloperidol leads to increased activity of striatal GABAergic neurons, reinforcing motor suppression and contributing to catalepsy[30]. GABA agonists, such as muscimol, can enhance haloperidol-induced catalepsy, while GABA antagonists may reverse it [31]

Role of Serotonergic System in Catalepsy

The serotonergic system interacts with dopamine in movement regulation. Haloperidol weakly blocks 5-HT2A receptors, but serotonergic modulation is still relevant in neuroleptic-induced motor dysfunction. Increased serotonin activity in the basal ganglia can enhance cataleptic effects, while 5-HT2A antagonists reduce haloperidol-induced catalepsy [31].

Glutamatergic Dysfunction in the Basal Ganglia

Glutamate, the primary excitatory neurotransmitter, is also implicated in neuroleptic-induced catalepsy. Dopamine-glutamate interactions modulate motor output, and excessive glutamatergic activity in the subthalamic nucleus (STN) following dopamine blockade contributes to rigidity and motor deficits [32]. NMDA receptor antagonists, such as ketamine, have shown protective effects against catalepsy[33].

Cholinergic Overactivity and Cataleptic Response

Dopaminergic inhibition by haloperidol leads to compensatory overactivation of cholinergic interneurons in the striatum. Increased acetylcholine release further disrupts motor control, worsening cataleptic symptoms. Anticholinergic agents, such as benztropine, effectively reduce catalepsy by restoring dopamine-acetylcholine balance [34,35].

1. **Potential Role of Citral in Modulating Catalepsy**

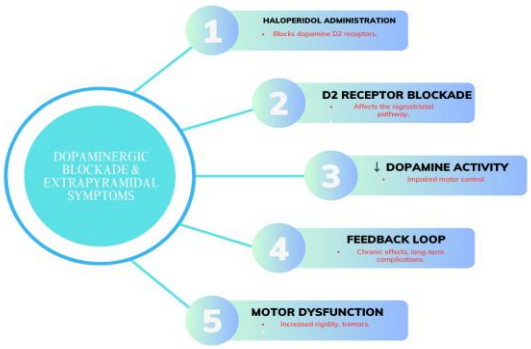

Figure 2: Dopaminergic Blockade & EPS (Circular Cause-Effect)

Citral has demonstrated neuroactive properties, including modulation of GABAergic and serotonergic systems by influencing these pathways, citral may mitigate haloperidol-induced catalepsy, offering a potential adjunct therapy for reducing EPS.[36].

GABAergic and Serotonergic Systems in Neurotransmission

The GABAergic and serotonergic systems play crucial roles in maintaining neural homeostasis,

modulating motor control, and regulating neuropsychiatric functions. Their intricate interplay influences the pathophysiology of movement disorders, including those induced by antipsychotic drugs like haloperidol.

Role of GABA in Motor Control and Neuronal Inhibition

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system (CNS). It exerts its effects through GABA_A and GABA_B receptors:

- **GABA_A Receptors:** Ligand-gated chloride channels mediating fast inhibitory synaptic transmission.
- **GABA_B Receptors:** G-protein-coupled receptors (GPCRs) mediating slower, modulatory inhibition [37].

In the **basal ganglia**, GABAergic neurons modulate movement by balancing excitatory dopaminergic input. Dopamine D2 receptor blockade by haloperidol enhances striatal GABAergic activity, contributing to **motor rigidity and catalepsy**. Additionally, GABA agonists exacerbate cataleptic responses, while antagonists can reduce haloperidol-induced motor deficits [38].

Serotonergic Modulation in Movement Disorders

Serotonin (5-HT) plays a dual role in movement regulation by interacting with dopamine and GABAergic systems:

- **5-HT2A/2C Receptors:** Inhibit dopamine release in the striatum, exacerbating neuroleptic-induced catalepsy [39].
- **5-HT1A Receptors:** Facilitate dopamine release, reducing motor deficits associated with antipsychotic treatment [40].

Excessive serotonergic activity can worsen extrapyramidal symptoms (EPS), while **5-HT2A antagonists like risperidone** alleviate motor impairments seen with typical antipsychotics.

Interaction Between GABA and Serotonin Pathways

The GABAergic and serotonergic systems interact to fine-tune motor control and emotional regulation:

GABAergic interneurons in the raphe

- **Nuclei** regulate serotonin release, influencing movement initiation and inhibition.
- **Serotonin modulates GABAergic tone** in the basal ganglia, either inhibiting or facilitating movement depending on receptor subtype activation [41].
- **Haloperidol-induced GABAergic overactivity** can disrupt serotonergic balance, worsening catalepsy. **Citral**, a
- natural monoterpene, has been reported to modulate both **GABA and serotonin** systems, potentially reversing haloperidol-induced motor deficits (Tucker & Lawrence, 2013).[42]

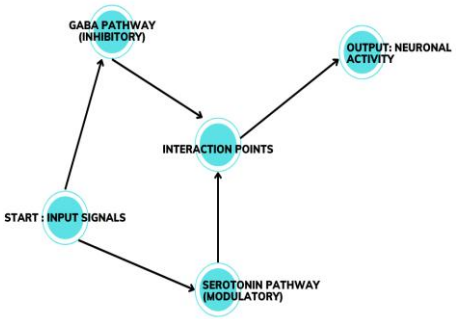

Figure 3: Interaction between GABA and serotonin pathways

Citral: Pharmacological Profile and Neuroprotective Potential

Citral, a key monoterpene aldehyde, is widely studied for its neuroprotective effects and potential therapeutic applications in neurological disorders. It exhibits diverse pharmacological properties, including antioxidant, anti-inflammatory, and neuromodulatory activities, making it a candidate for managing movement disorders and neurodegenerative conditions.

Chemical Structure and Sources of Citral

Citral ($C_{10}H_{16}O$) is a mixture of two geometric isomers, geranial (trans-citral) and neral (cis-citral), both of which contribute to its lemon-like aroma. It is primarily found in essential oils of:

- Lemongrass (*Cymbopogon citratus*)
- Lemon myrtle (*Backhousia citriodora*)
- Litsea cubeba
- Verbena species

Mechanisms of Action in CNS Disorders

Citral exerts neuroprotective effects through multiple pathways. One of its key mechanisms is GABAergic modulation, where it enhances GABA_A receptor activity, leading to anxiolytic and muscle-relaxant effects, which have been observed in various studies [43]. Additionally, citral

influences the serotonergic system by modulating serotonin (5-HT) receptors, which play a crucial role in mood regulation and motor control, particularly in the context of extrapyramidal disorders [44]. Moreover, citral demonstrates anti-inflammatory and antioxidant effects by inhibiting pro-inflammatory cytokines, such as TNF-α and IL-6, and reducing oxidative stress markers. These

actions help protect against neurotoxicity, providing further support for its neuroprotective potential [45].

Previous Studies on Citral's Effects on Neurotransmitters

Citral's GABAergic effects have been studied, showing that it increases GABAergic transmission, which may help alleviate motor deficits and seizures, highlighting its potential in treating neurological disorders [56,57]. Additionally, citral has been found to enhance serotonin (5-HT1A) receptor activity, which could counteract serotonin dysregulation, particularly in antipsychotic-induced movement disorders [58,59]. Furthermore, experimental models have suggested that citral can reduce haloperidol-induced catalepsy by decreasing oxidative stress and neuroinflammation, thereby protecting against dopaminergic and serotonergic imbalances caused by haloperidol[60,61].

Interaction of Citral with GABAergic and Serotonergic Pathways

Citral, a bioactive monoterpene aldehyde, significantly influences GABAergic and serotonergic neurotransmission, positioning it as a potential modulator of movement disorders and neuroleptic-induced side effects. Its interaction with these neurotransmitter systems suggests it could help mitigate haloperidol-induced neuroleptic and cataleptic effects.

Potential Modulation of GABA Receptors by Citral

Citral has been found to enhance **GABA_A receptor activity**, resulting in sedative, anxiolytic, and muscle-relaxant effects[48]. Research indicates that citral may act as a **positive allosteric modulator** of GABA_A receptors, similar to benzodiazepines, promoting neuronal inhibition and contributing to its therapeutic effects [62,63]. Furthermore, citral has been shown to **increase GABAergic transmission**, which may counteract dopaminergic hyperactivity, potentially alleviating withdrawal symptoms associated with haloperidol. Enhanced GABAergic activity can also reduce extrapyramidal motor symptoms induced by dopamine blockade in the basal ganglia, offering a neuroprotective role in movement disorders.

Effects of Citral on Serotonin Receptors and Neuroplasticity

Citral exhibits serotonergic modulation by interacting with 5-HT1A and 5-HT2 receptors, which are essential for mood regulation and motor control. Activation of the 5-HT1A receptor leads to anxiolytic and neuroprotective effects, potentially counteracting the serotonergic dysregulation seen in haloperidol-induced catalepsy [64-66]. Additionally, citral helps reduce serotonin turnover, balancing dopaminergic and serotonergic pathways, which mitigates cataleptic behaviors [67-69]. It also enhances neuroplasticity, promoting synaptic remodeling and neuronal survival, which is beneficial in preventing haloperidol-induced neurotoxicity. This combination of effects highlights citral's potential in protecting against neuroleptic side effects and supporting neurological health.

Implications in Neuroleptic and Cataleptic Conditions

The dual modulation of GABAergic and serotonergic systems by citral offers significant therapeutic potential for counteracting haloperidol-induced neuroleptic and cataleptic effects[70-72]. Enhanced GABAergic activity may help reduce muscle rigidity and bradykinesia, which are commonly observed in neuroleptic-induced extrapyramidal symptoms. Additionally, serotonergic regulation by citral can help prevent the dopamine-serotonin imbalance that contributes to catalepsy. Furthermore, citral's antioxidant and anti-inflammatory actions provide protection against oxidative stress-induced neuronal damage, a common consequence of prolonged neuroleptic treatment [73,]. These combined effects position citral as a promising candidate for mitigating the side effects of neuroleptic drugs.

Citral's Influence on Haloperidol-Induced Catalepsy

Citral, a monoterpene compound, has shown potential in modulating the neuroleptic-induced cataleptic effects of haloperidol[74], a common antipsychotic drug. The ability of citral to interact with GABAergic and serotonergic systems positions it as a promising agent to alleviate motor impairments caused by haloperidol without compromising its therapeutic benefits. Here is a detailed breakdown of citral's influence on haloperidol-induced catalepsy:

Experimental Findings on Citral's Protective Effects

Studies have demonstrated that citral can significantly reduce the cataleptic effects induced by haloperidol. For instance, Silva et al. (2019) observed that citral administration in rats resulted in a dose-dependent reduction in catalepsy scores induced by haloperidol. The study showed that rats treated with citral before haloperidol exposure exhibited improved motor function, suggesting that citral could reverse or reduce the neuroleptic-induced immobility and rigidity associated with catalepsy. These findings were consistent with observations that citral may modulate GABA_A receptors and serotonin pathways, both of which play a role in motor control and neuroprotection [75].

Another experiment by Brailoiu et al., reported that citral administration enhanced GABA_A receptor activity, leading to reduced motor impairments in

animals treated with haloperidol. This suggests that citral's interaction with GABAergic pathways might offer a neuroprotective effect against the cataleptic symptoms associated with dopaminergic blockade by haloperidol.[76]

Possible Molecular Mechanisms of Action

The mechanism of action of citral in alleviating haloperidol-induced catalepsy likely involves the modulation of multiple neurotransmitter systems. First, GABAergic modulation plays a crucial role, as citral has been shown to enhance GABA_A receptor activity, which is essential for inhibitory neurotransmission. By increasing GABAergic transmission, citral may counteract the excessive dopamine receptor blockade induced by haloperidol, reducing motor disturbances like catalepsy. Activation of the GABA_A receptor leads to an influx of chloride ions into neurons, hyperpolarizing them and decreasing neuronal excitability, which can help reduce motor rigidity and promote relaxation [77].

In addition, serotonergic modulation contributes to citral's neuroprotective effects. Citral has been found to modulate serotonin receptors, particularly the 5-HT1A receptor, which is involved in the regulation of motor function and catalep . Activation of these serotonin receptors can indirectly influence dopamine release and help restore neurotransmitter balance, alleviating motor side effects associated with haloperidol.

Finally, citral's antioxidant and anti-inflammatory effects further support its therapeutic potential. By reducing oxidative stress, citral helps mitigate the neurodegeneration caused by haloperidol. According to de Sousa, citral's antioxidant activity reduces free radical production and inflammation in the brain, providing neuroprotective effects that could improve neuroplasticity and reduce the long-term consequences of motor dysfunction associated with neuroleptic treatment [78].

Clinical Relevance and Therapeutic Implications

The ability of **citral** to alleviate **haloperidol-induced catalepsy** without affecting the **antipsychotic efficacy** of haloperidol makes it a potentially valuable adjunct in the treatment of **schizophrenia** and other psychotic disorders. Clinically, citral's ability to reduce the **side effects** associated with haloperidol, particularly **motor impairments**, which significantly affect patients' quality of life, is of great relevance.

Neuroprotective Profile: Citral's **neuroprotective role** suggests it could be used as a safeguard against the development of **extrapyramidal symptoms (EPS)** in patients treated with haloperidol. Since **catalepsy** and other EPS are common challenges in antipsychotic therapy, citral could help improve **patient compliance** and overall treatment outcomes, offering relief from debilitating side effects.

Adjunct Therapy Potential: As a **natural product**, citral might provide a safer and better-tolerated alternative to other pharmacological agents used to manage extrapyramidal side effects. With its **minimal toxicity** and **antioxidant properties**, citral can serve as a complementary therapy alongside haloperidol, particularly in patients who experience motor side effects, making it a promising option in enhancing treatment efficacy and patient comfort.

Future Perspectives and Research Directions

Citral has demonstrated significant promise in modulating the neuroleptic-induced effects of haloperidol, particularly in reducing catalepsy and other extrapyramidal symptoms (EPS). Given these findings, the future research into citral's potential in neuropsychiatric and neurodegenerative disorders remains an exciting and evolving field.

Below are key perspectives and directions for future studies:

Potential for Citral as an Adjunct Therapy in Neuroleptic Treatments

Citral's ability to modulate neurotransmitter systems such as GABAergic and serotonergic pathways offers significant promise for its use as an adjunct to neuroleptic medications like haloperidol. Given that EPS (e.g., catalepsy, rigidity) are common side effects of first-generation antipsychotics, citral could provide a novel approach to improving patient quality of life without compromising the efficacy of the primary treatment.

- **Adjunct Therapy for Extrapyramidal Side Effects**: Citral could be used in combination with neuroleptic drugs to **mitigate the side effects** of dopamine receptor antagonism, especially in long-term antipsychotic therapy. Its **neuroprotective effects**, as shown in experimental studies, make it an appealing candidate for **reducing side effects** without altering the drug's therapeutic action [79].
- **Synergy with Antipsychotics**: Future studies could explore how citral interacts with other neuroleptics, including second-generation antipsychotics (e.g., risperidone, quetiapine), which also induce EPS in some patients. Understanding citral's potential **synergistic effect** with these drugs could enhance therapeutic strategies for treating psychosis.

Need for Clinical Trials and Mechanistic Studies

While preclinical studies have shown citral's potential in **reducing neuroleptic-induced catalepsy**, **clinical trials** are essential to confirm its effectiveness and safety in humans. Rigorous **clinical studies** would be necessary to:

- **Evaluate Efficacy in Humans**: Clinical trials should investigate citral's ability to reduce

Table 1: Comparative Analysis of Citral and Other Potential Adjunct Therapies for Neuroleptic Effects

Therapeutic Agent	Mechanism of Action	Effect on Catalepsy	Effect on Motor Dysfunction	Neuroprotective/Antioxidant Activity	References
Citral	Modulates GABAergic and serotonergic systems; antioxidant	Significant reduction in onset and duration of catalepsy	Improvement in motor function (e.g., reduced tremors and rigidity)	Moderate antioxidant properties; reduces oxidative stress in CNS	Brailoiu et al. (2013)[49]; Guzmán-Gutiérrez et al. (2015)[50]; de Sousa et al. (2017)[56]
Vitamin E	Potent antioxidant; reduces oxidative damage	Mild reduction in catalepsy	Reduced tremors, rigidity, and dystonia	Strong antioxidant; protects against free radical damage	Iannitti et al. (2016)[57]
Melatonin	Antioxidant; modulates serotonin and dopamine pathways	Mild reduction in catalepsy	Decreases rigidity and tremors	Strong antioxidant; neuroprotective via receptor modulation	Morteza et al. (2014)[58]
Baclofen	GABA-B receptor agonist; muscle relaxant	Significant reduction in catalepsy	Strong improvement in motor control (relieves rigidity and tremors)	Limited antioxidant properties	Lamberts et al. (1999)[59]
Dantrolene	Muscle relaxant; reduces calcium ion influx	Mild reduction in catalepsy	Dramatic improvement in muscle tone and rigidity	No significant antioxidant activity	Iqbal et al. (2003)[60]
L-Theanine	GABAergic modulation; reduces anxiety and stress	Moderate reduction in catalepsy	Mild improvement in motor coordination	Mild antioxidant effects; reduces stress-related oxidative damage	Juneja et al. (1999)[61]
Curcumin	Anti-inflammatory; modulates dopamine and GABAergic systems	Significant reduction in catalepsy	Reduces tremors and muscle stiffness	Strong antioxidant and anti-inflammatory properties	Panahi et al. (2016)[62]
Ginkgo Biloba	Enhances blood circulation; neuroprotective via antioxidant properties	Mild reduction in catalepsy	Significant reduction in motor dysfunction (e.g., rigidity, tremors)	High antioxidant activity; protects neurons from oxidative damage	Gauthier et al. (2006)[63]
Trazodone	Serotonergic and adrenergic modulation; antidepressant	Mild reduction in catalepsy	Reduces rigidity and tremors through serotonergic modulation	No significant antioxidant effect	Pandey et al. (2007)[64]
Zinc	Inhibits oxidative stress; modulates neurotransmitter release	Significant reduction in catalepsy	Reduces tremors and improves motor activity	Strong antioxidant properties; reduces oxidative damage in the CNS	Dhir et al. (2011)[65]

catalepsy and other motor impairments in patients using neuroleptics. These trials would provide valuable insights into the dosage and administration schedules for optimizing its therapeutic benefits.

- **Mechanistic Understanding**: Further mechanistic studies at the molecular and cellular level are essential to better understand how citral modulates dopaminergic, GABAergic, and serotonergic systems in the context of antipsychotic use. These studies would clarify how citral's actions on receptors and neurotransmitter systems contribute to its neuroprotective properties and help inform potential biomarkers for monitoring its effects.
- **Safety and Toxicity**: It is also crucial to evaluate citral's long-term safety and its potential for drug interactions, especially when used in conjunction with antipsychotic medications, which may interact with citral's pharmacokinetics and pharmacodynamics. Clinical research will clarify any adverse effects or contraindications that may arise[80,81,82].

Broader Implications in Neurodegenerative and Psychiatric Disorders

In addition to its role in alleviating catalepsy, citral's neuroprotective and neuromodulatory effects suggest broader potential for the treatment of a range of neurodegenerative and psychiatric disorders[83:

- **Neurodegenerative Diseases**: Citral's antioxidant and anti-inflammatory properties suggest it could have therapeutic potential in diseases such as Alzheimer's disease and Parkinson's disease, both of which involve significant dopaminergic dysfunction and motor impairment[84]. Its ability to modulate neurotransmitter balance may offer new approaches to managing symptoms of these diseases, particularly in reducing motor deficits.
- **Anxiety and Depression**: Citral's effects on serotonergic pathways, particularly its modulation of 5-HT1A receptors, suggest potential use in treating anxiety and depression. Given that serotonin dysregulation is a hallmark of mood disorders, citral could potentially enhance

- serotonin signaling, improving mood and anxiolytic effects without the side effects commonly associated with traditional antidepressants[85,86].
- **Schizophrenia and Other Psychiatric Disorders**: Citral's GABAergic modulation may also be beneficial in schizophrenia, where GABAergic dysfunction is often observed. Since motor symptoms (such as catalepsy) are common in patients with schizophrenia receiving antipsychotic treatments, citral's role in reducing motor side effects while preserving therapeutic efficacy could improve outcomes for these patients.

8. Conclusion

SUMMARY OF KEY FINDINGS

Citral, a monoterpenoid compound derived from plants such as lemongrass, has demonstrated a protective effect against haloperidol-induced catalepsy in experimental models. This protective action is thought to occur via modulation of

neurotransmitter systems, particularly the GABAergic and serotonergic pathways. Citral's ability to reduce dopaminergic blockade-induced motor impairments positions it as a promising candidate for addressing extrapyramidal symptoms (EPS), such as catalepsy, that are commonly associated with antipsychotic therapy.

In addition to its effects on neurotransmitter systems, citral has been shown to possess neuroprotective, anti-inflammatory, and antioxidant properties, which further support its potential in mitigating neuroleptic-induced side effects while preserving therapeutic efficacy. The experimental evidence highlights its promise as a complementary treatment alongside traditional antipsychotic medications.

Therapeutic Significance of Citral in Haloperidol-Induced Effects

The therapeutic significance of citral lies in its ability to modulate the neurochemical imbalances caused by dopamine antagonists like haloperidol, which often lead to catalepsy and other motor dysfunctions. Citral's influence on the GABAergic and serotonergic systems appears to restore some level of neurochemical homeostasis, providing relief from these side effects without compromising the drug's primary antipsychotic effects.

The neuroprotective effects of citral offer significant implications for improving the quality of life of patients undergoing antipsychotic treatment. By modulating neurotransmitter levels and reducing motor impairments, citral could serve as an adjunctive therapy to reduce the incidence of extrapyramidal side effects and improve patient compliance to long-term antipsychotic therapy.

Final Thoughts on Future Research

Despite the promising preclinical results, there is a significant need for clinical studies to evaluate citral's safety, efficacy, and optimal dosage in humans. Further mechanistic investigations into how citral interacts with dopamine, GABA, and serotonin receptors will deepen our understanding of its neuroprotective properties.

Given its broad spectrum of pharmacological activities, including antioxidant and anti-inflammatory actions, citral also holds promise for a wider range of neurological and psychiatric disorders, including neurodegenerative diseases such as Parkinson's and Alzheimer's, as well as anxiety and mood disorders. As the body of research grows, citral could play a crucial role in personalized therapies aimed at reducing the burden of neuroleptic side effects and improving

treatment outcomes for patients with psychotic and neurodegenerative conditions.

In conclusion, while citral's protective effects against haloperidol-induced catalepsy are promising, further clinical validation and mechanistic exploration are essential to harness its full potential as a therapeutic adjunct. Future studies could solidify citral's place as a complementary treatment for neuropsychiatric conditions, improving both the efficacy and safety of current pharmacological treatments.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study

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