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Mechanistic Insights and Therapeutic Potential of Curcuminoids and Sinapic Acid in Depression: A Review centred on the Olfactory Bulbectomy Model of Mouse.

Chetan Patel[1], Dr. Shikha Jaiswal[2], Prof. Dr. Sudha Vengurlekar[3]
[1] *PG Student, University Institute of Pharmacy, Oriental university, Indore, MP*
[2] *Associate Professor, University Institute of Pharmacy, Oriental university, Indore, MP*
[3] *Principal, University Institute of Pharmacy, Oriental university, Indore, MP*

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ABSTRACT: Major depressive disorder (MDD) is a debilitating mental illness marked by persistent sadness, anhedonia, cognitive decline, and disruptions in sleep and appetite. Phytochemicals such as curcuminoids and sinapic acid are known for their antioxidant, anti-inflammatory, neuroprotective, and neurotransmission-modulating properties. It is also addressing in neurobiological mechanisms underlying depression. Current antidepressant treatments often have delayed onset, incomplete symptom remission, and adverse effects; so, highlighting the need for novel therapeutic agents. This article aims to establish an olfactory bulbectomy (OBX) mouse model to simulate key features of human depression, including behavioral deficits, oxidative stress, neuroinflammation, and neuronal damage. It can systematically evaluate and compares the antidepressant-like effects of curcuminoids and sinapic acid through behavioral, biochemical, and histological assessments. Findings will elucidate the neuroprotective potential and mechanistic pathways of these phytochemicals, offering evidence-based insights into their therapeutic relevance for MDD. This comparative approach addresses a significant gap by integrating pharmacokinetic and mechanistic data to clarify their antidepressant efficacy in a standardized experimental framework.

KEYWORDS: Olfactory bulbectomy (OBX) mouse model, antioxidant, anti-inflammatory, neuroprotective, Curcuminoids, Sinapic acids, etc.

I. INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent mental illnesses worldwide. It is characterized by persistent sadness, loss of pleasure, cognitive impairment, and issues with sleep and food consumption. According to global estimates, hundreds of millions of people are affected by this disease. Depression is a major cause of disability and socioeconomic stress. Although many types of antidepressants are available, such as selective serotonin receptor agonists (SSRIs) and monoamine oxidase (MAO) inhibitors, many patients do not achieve full recovery, have a delayed initiation of therapeutic activity, or have undesired side effects (Fried et al., 2022; Rush et al., 2016). These limitations have fuelled interest in safer, plant-derived compounds capable of multiple neurobiological mechanisms linked to depressive disorders. (World Health Organization, 2021; Malhi and Mann, 2018).

Scientists are interested in naturally occurring phytochemicals, such as polyphenols and hydroxycinnamic acids (curcuminoids and sinapic acid), because they have been shown to have antioxidant, anti-inflammatory, neuroprotective, and neurotransmission-regulating effects. Fried et al. (2022), Chen et al. (2020).

Curcuminoids derived from Curcuma longa, particularly curcumin, enhances neurotrophic signals, suppress inflammatory mediators, and modify monoaminergic pathways associated with mood regulation. However, their pharmacological activity can be limited by low bioavailability, which means they need to be taken with absorption enhancers such as Piperine. (Chen et al., 2020).

Sinapic acid (SA), a hydroxycinnamic acid derivative found in many fruits, grains, and plants, has been studied as a neuroprotective agent. According to experimental research, it may affect oxidative balance, inflammatory signals, and neurotransmitter metabolism, making it mechanistically relevant to diseases linked to depression. (Chen et al., 2020).

Animal models that mimic the important biological aspects of human depression are crucial for researching new treatment approaches. So, A well-known mouse model useful that is olfactory bulbectomy (OBX) for behavioral, biochemical, inflammatory, endocrine, and oxidative modifications similar to those observed in human depression. (Harkin et al., 2021). Hyperlocomotion, increased despair-like behavior, cognitive impairment, neuroinflammation, oxidative stress, and

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dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis are common symptoms in animals exposed to OBX. The model has excellent construct and predictive validity because such variances react to long-term treatment with clinically effective antidepressants. (Song & Leonard, 2005; Hellweg et al., 2007).

Although curcuminoids and sinapic acid have demonstrated antidepressant-like effects in other studies, their effects have not been directly compared within the OBX model. Since both medicines affect overlapping biological pathways and have different pharmacokinetic properties and mechanistic strengths, a thorough comparative study could provide a clearer explanation of their therapeutic potential. Such a study may also reveal which substance or associated biochemical pathway provides more potent control of the behavioral and molecular abnormalities associated with depression. (Hewlings & Kalman, 2017; Lopresti, 2020).

II. SCIENTIFIC BASIS AND RATIONALE

Numerous molecular systems, including monoamine signalling, neuroinflammatory activity, oxidative stress, neuroplasticity, and the HPA axis, are dysregulated in depression. Alternative or supplemental medicines with broader mechanistic actions are required because conventional antidepressants primarily act on monoaminergic pathways and have limitations in terms of onset of action, effectiveness, and side effect profiles.

Curcuminoids and Sinapic acid is natural phytochemicals with neuroprotective, anti-inflammatory, and antioxidant properties. Curcuminoids, primarily curcumin from Curcuma longa, exhibit potent anti-inflammatory and antioxidant properties, as well as antidepressant-like effects in various preclinical animal models. Curcumin suppresses NF-κB, modifies monoaminergic neurotransmission, reduces proinflammatory cytokine levels, and increases neurotrophic signaling, including Brain Derived Neurotrophic Factor (BDNF) (Hewlings & Kalman, 2017; Ramaholimihaso et al., 2020; Lopresti, 2020). Curcumin has been shown to restore behavioral and biochemical deficits in the olfactory bulbectomy (OBX) model, which is characterized by hyperactivity, neurotransmitter depletion, oxidative stress, and decreased BDNF levels (Xu et al., 2005; Rinwa et al., 2013).

Sinapic acid has shown a neuroprotective activity. It affects neurotransmitter systems involved in mood regulation and has potent antioxidant, anti-inflammatory, anti-apoptotic, and monoamine oxidase-inhibitory properties (Chen et al., 2020; Pandi et al., 2021). Act by lowering oxidative damage, regulating cytokine levels, and reestablishing monoaminergic and cholinergic activities, sinapic acid has shown antidepressant-like efficacy in stress-induced and neurodegenerative models (Verma et al., 2020; Bansal & Dhingra, 2023). Despite these encouraging characteristics, its effectiveness has not yet been assessed in the OBX model, which more fully reflects oxidative damage, structural degeneration, and chronic neuroinflammation than stress models.

According to Harkin et al. (2021) and Song & Leonard (2005), the olfactory bulbectomy (OBX) rodent model is a validated paradigm for studying depression-like states that reflect key characteristics of human MDD, such as behavioral hyperactivity, cognitive deficits, dysregulation of the HPA axis, oxidative stress, and increased neuroinflammation. Additionally, OBX consistently reacts to long-term but not short-term administration of traditional antidepressants, enabling mechanistic evaluation using behavioral tests, biochemical indicators (such as monoamines, cytokines, and oxidative stress parameters), and histological assessments of neuronal integrity (Hellweg et al., 2007).

These studies in the OBX models are scientifically justifiable because curcuminoids and sinapic acid act through different but overlapping neuroprotective mechanisms. Such a comparison can shed light on the relative effectiveness of treating the behavioral and physiological problems by OBX. But its needful to describe the molecular distinctions between the high antioxidant and MAO-inhibitory activities of sinapic acid and the stronger neurotrophic and anti-inflammatory properties of curcuminoids. Also Educate on formulation and dosage tactics, especially considering curcumin's low bioavailability. Top prospects should be prioritized for additional preclinical research or combined therapy trials.The suitability of the OBX model for integrative behavioral, biochemical, and mechanistic evaluation.

III. USE OF OBX METHOD

Curcuminoids and sinapic acid have shown antioxidant, anti-inflammatory, and neuroprotective qualities pertinent to the pathophysiology of depression (Chen et al., 2020; Hewlings & Kalman, 2017), their relative antidepressant potential has not been thoroughly examined in a validated experimental model. It is difficult to determine which molecule exhibits superior behavioral and

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biochemical efficacy in depression-like situations because of the lack of comparative preclinical data.

The independent neuroprotective and antidepressant-like effects of curcuminoids and sinapic acid have been widely documented in the literature; however, no study has compared these compounds head-to-head in the olfactory bulbectomized (OBX) mouse model, a well-established model that mimics the behavioral, neuroinflammatory, oxidative, and neurochemical characteristics of depression in humans (Harkin et al.; 2021 Rinwa et al., 2013, Pandi et al., 2021; Ramaholimihaso, 2020). PMC+1 Furthermore, compared with smaller phenolic compounds, such as sinapic acid, the limited absorption and inconsistent pharmacokinetics of curcuminoids raise concerns regarding their translational dependability (Lopresti, 2020). Pharmacokinetic bridging: Many studies report behavioral efficacy without matching brain exposure; without PK/brain AUC data, comparable findings are affected. (Jahromi et al., 2025; Poyraz et al., 2024). American Chemical Society Publications +1. The knowledge of the distinct processes and therapeutic advantages of these two phytochemicals is restricted by the lack of comparative behavioral, biochemical, and histopathological data. This research gap highlights the necessity of targeted preclinical investigations to determine which chemicals provide better mechanistic benefits and antidepressant efficacy in the OBX model.

These studies providing mechanistic and efficacy-based evidence that can help prioritize natural chemicals for future antidepressant development by using curcuminoids and sinapic acid in a validated depression model. Determining the drug based behavioral enhancement, decrease in oxidative stress, attenuation of neuroinflammation, and neuroprotective benefits could direct to formulation strategies, dosage choices, and development into clinical research strategies. Furthermore, expanding field of phytochemical-based treatments, which may be safer and have fewer adverse effects than traditional antidepressants (Hewlings & Kalman, 2017). The results may enhance the scientific knowledge of natural neuroprotective drugs by elucidating the effects of polyphenols on the biochemical pathways linked to depression. Overall, this study will close a significant gap, encourage the selection of plant-derived antidepressant candidates based on data, and aid in the development of more potent and well-tolerated depression medicines. (Pandi et al., 2021; Ramaholimihaso et al., 2020). PMC+1

The olfactory bulbectomy (OBX) model is a well-known and predictive model of depression. OBX (rodent removal of the olfactory bulbs) results in hyperactivity in open-field tests, mental retardation, altered appetitive behavior, and neurochemical changes (altered BDNF and decreased serotonergic turnover) that are responsive to long-term antidepressants. OBX is frequently used to assess neuroprotective mechanisms and antidepressant potential, but it necessitates thorough behavioral panels (open field, forced swim, sucrose preference, passive avoidance) and suitable post-surgical timing for acute versus chronic drug testing. (Hellweg et al., 2007; Song & Leonard, 2005; Coppola et al., re-evaluation/recent reviews). ScienceDirect+2PubMed+2

Evidence of curcuminoids in OBX and other depression models: There is strong preclinical evidence for curcumin in several depression models. In addition to improving behavioral endpoints and lowering neuroinflammatory and apoptotic signaling in OBX animals, chronic administration reversed depression-like behaviors in forced swim, Chronic Unpredictable Mild Stress (CUMS), and corticosterone models, and most notably provided neuroprotection (Curcumin + Piperine in OBX). Increased hippocampal BDNF, restoration of serotonin levels, suppression of NF-κB-mediated inflammation, antioxidant activity, and potential MAO-A/B inhibition at pharmacologically relevant dosages have all been suggested by mechanistic studies. The effects of curcumin on OBX have been documented in rats (Xu et al., 2005), and subsequent mechanistic OBX research (Rinwa et al., 2013) supports apoptotic regulation and oxidative/nitrosative stress as important pathways. (Rinwa et al., 2013; Ramaholimihaso, 2020; Xu et al., 2005). PubMed+2PLOS+2

Evidence of Sinapic acid as antidepressant & neuroprotective: A naturally occurring derivative of cinnamic acid (sinapic acid) has been shown to have neuroprotective, anti-inflammatory, anti-cholinesterase, and antioxidant qualities in a CNS models. Preclinical research has demonstrated the effectiveness of SA in models of neurodegeneration, stress-induced depression paradigms (e.g., unpredictable mild stress and Streptozotocin induced depression models), and cognitive impairment models (Scopolamine and intracerebroventricular Streptozotocin induced depression models). These models frequently show reductions in oxidative stress markers and inflammatory cytokines and restoration of cholinergic/BDNF signaling. Additionally, some studies indicate that cinnamic compounds, such as trans-sinapic acid, may block MAO in comparable scenarios. This mechanistic profile may be relevant to OBX pathogenesis, notwithstanding the absence of SA investigations in OBX specifically (Bais et al.,

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2017/2018; Lee et al., 2023; Bansal & Dhingra, 2023; Pandi et al., 2021; Verma et al., 2020). RJPT+4PubMed+4MDPI+4

Mechanistic of Curcuminoids and Sinapic acid

Several studies have confirmed the following common mechanisms:

1. Anti-inflammatory and antioxidant properties: Curcumin and SA lower Reactive Oxygen Species (ROS) levels and downregulate inflammatory mediators (NF-κB, TNF-α, and IL-1β), which are pathways closely associated with depression symptoms. (Pandi et al., 2021; Correia et al., 2023; Rinwa et al., 2013). PLOS+2MDPI+2
2. BDNF/CREB (cAMP Response Element Binding protein) neurotrophic signaling in CUMS and corticosterone models: Curcumin more consistently demonstrates elevation of hippocampal BDNF and CREB signaling in cognitive models, SA exhibits effects on neuroprotection and some reports showing restored cholinergic indications and potential BDNF modulation. OBX lacks direct comparative quantification methods. (Verma et al., 2020; Wu et al., 2021; Huang et al., 2011). ScienceDirect+2PMC+2
3. MAO inhibition and monoaminergic regulation: Few direct head-to-head potency comparisons of cinnamic acid derivatives such as SA and related compounds have been reported to exhibit MAO activity in some studies; suggesting a shared potential to influence monoaminergic tone. Curcumin has demonstrated MAO-A/B inhibitory activity in vitro and in vivo at certain doses and may increase monoamine availability. (Zhang et al., 2019; Bais et al., 2017; Khatri et al., 2016). PMC+2Wiley Online Library+2
4. Bioavailability and Pharmacokinetics: One important practical distinction is that SA usually exhibits superior solubility and has also been synthesized in nanoparticles, whereas curcumin has a low bioavailability and is frequently co-administered with Piperine or supplied as nano formulations. The assessment of comparative efficacy between OBX and dosing strategies will be significantly impacted by differences in bioavailability. (Poyraz et al., 2024; Jahromi et al., 2025; Rinwa et al., 2013). PLOS + 2 American Chemical Society Publications + 2

Behavioral and biochemical endpoints

Studies on curcumin OBX has shown benefits in passive avoidance, locomotor/hyperactivity, oxidative/nitrosative stress, and apoptotic indicators (caspase-3, Bax/Bcl-2 balance). And all studied in SA research in stress or metabolic models has shown effects in Tail suspension, sucrose preference, raised plus maze, forced swim, and measurements of oxidative markers, inflammatory cytokines, acetylcholine/ChAT levels, and cholinesterase activity. A behavioral battery (open field, sucrose preference, forced swim/immobility, passive avoidance), biochemical panels (serotonin turnover, BDNF, pro-inflammatory cytokines, oxidative stress enzymes), and histopathology are recommended for a thorough comparative OBX investigation. (Rinwa et al., 2013; Verma et al., 2020; Bansal & Dhingra, 2023; Xu et al., 2005). RJPT+3PubMed+3PLOS+3

Dosing, administration routes, and formulation

To achieve CNS exposure, curcumin has been studied in OBX/rodent depression models using chronic oral doses (different mg/kg), frequently with enhancers (Piperine) or nanoforms. Some SA studies have examined intracerebroventricular (ICV) or nanoparticle formulations, while other SA research has used oral doses in CUMS and other paradigms. Matching systemic exposure (pharmacokinetic bridging) is essential for comparative preclinical work: either utilize standardized mg/kg regimens plus bioavailability enhancers with measurement of brain/tissue drug levels or consider pharmacokinetic studies to choose dosages producing equivalent brain Area Under Concentrations (AUCs). (Rinwa et al., 2013; Poyraz et al., 2024; Bais et al., 2017; Xu et al., 2005). PubMed+3PubMed+3PLOS+3

IV. RESULTS AND RECOMMENDATIONS

1. Model and groups: Adult male (and preferably female) mice were randomly assigned to one of four groups: Sham, OBX+Vehicle, OBX+Curcuminoid (Curcumin; oral with/without Piperine and/or nanoform), OBX+sinapic acid (SA; oral and/or nanoform), and Positive Control (e.g. chronic Fluoxetine). For behavioral and molecular endpoints, use n-powered (power calculations based on previous OBX effect sizes). (Hellweg et al., 2007; Song & Leonard, 2005). ScienceDirect+1
2. PK bridging: To select doses that result in overlapping brain exposures or record differences for interpretation, conduct a pilot

pharmacokinetic study that measures the plasma and brain concentrations of curcumin (and metabolites) and SA. (Poyraz et al., 2024). American Chemical Society Publications

3. Behavioral battery and timing: At predetermined post OBX time points (acute vs. chronic treatment), locomotion/open field, sucrose preference, forced swim/TST, and passive avoidance were evaluated. Incorporate tests to differentiate between hyperactivity and anhedonia. (Fattore et al.; Coppola et al.). PMC+1
4. Biochemical and histological endpoints: Where possible, measure BDNF, serotonin turnover, MAO-A/B activity, oxidative stress markers (Superoxide Dismutase, Malondialdehyde), inflammatory cytokines (IL-1β, TNF-α), apoptotic markers, and neurogenesis markers in the hippocampal and prefrontal cortex. Immunohistochemistry should be considered for neural integrity. (Hellweg et al., 2007; Correia et al., 2023; Rinwa et al., 2013). PLOS+2PubMed+2

V. PROBABLE FUTURISTIC STUDIES

1. Differential Mechanistic Insights of curcuminoids and sinapic acid have similarities as anti-inflammatory and antioxidant properties, their molecular targets, bioavailability, and neurotrophic effects. A comparative analysis may reveal different or similar mechanisms of action relevant to depression treatment.
2. Therapeutic Prioritization: Future medication development or phytopharmaceutical formulation can be guided by determining which molecule produces greater behavioral and neurochemical improvements in the OBX model through a head-to-head comparison.
3. Closing Pharmacokinetic and Pharmacodynamic Gaps: Sinapic acid is more soluble than curcumin; curcumin has poor bioavailability. Translational significance of study depends on whether enhanced efficacy is related to pharmacokinetics or pharmacodynamics.
4. Novelty and Knowledge Gap: Despite the model's significance in depression-associated neurodegeneration, no preclinical investigation has directly compared sinapic acid and curcuminoids in an OBX model. Closing this gap will benefit neuropsychiatric medication discovery and phytochemical studies.
5. Translational Potential: Either molecule may be a candidate for clinical testing or the creation of synergistic polyphenolic formulations; if it exhibits potent antidepressant action along with favourable safety and mechanistic profiles.

V. CONCLUSION

Through overlapping mechanisms and Preclinical evidences of curcuminoids and sinapic acid exhibits the promising benefits. SA has promising antidepressant-like effects in stress and metabolic models with significant antioxidant and neuroprotective effects in OBX model specific. While Curcumin has direct OBX-model data and a greater literature on BDNF and anti-inflammatory benefits in depression models. To allow mechanistic and translationally useful insights, a thorough comparative OBX study should incorporate the Pharmacokinetic bridging thorough behavioral and molecular endpoints; and precisely matched formulations in Depression animal model.

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