

INSILICO AND PHARMACEUTICAL CHARACTERIZATION OF
PICEATANNOL IN LPS INDUCED DEPRESSION

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Abstract

Depression is a prevalent neuropsychiatric disorder in which neuroinflammation, impaired neuroplasticity, and synaptic dysfunction contribute to disease progression. The present study investigated the antidepressant and neuroprotective potential of piceatannol and piceatannol-loaded PLGA nanoparticles (PN-PLGA NPs) in an LPS-induced depression model. In-silico ADMET and molecular docking analyses were performed to evaluate the pharmacokinetic properties and target interactions of piceatannol. PN-PLGA NPs were characterized for particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency (EE%), and drug loading (DL%). Mice received piceatannol (20 mg/kg) or an equivalent PN-PLGA NP formulation for 14 days, followed by LPS (0.83 mg/kg, i.p.) challenge. BDNF and synaptophysin mRNA expression were evaluated using qRT-PCR. Piceatannol demonstrated favorable predicted pharmacokinetic characteristics and exhibited binding energies of -8.0 and -5.6 kcal/mol against D1 and D2 receptors, respectively. PN-PLGA NPs showed a particle size of 162.4 ± 4.7 nm, PDI of 0.148 ± 0.009 , zeta potential of -24.3 ± 1.4 mV, EE% of $84.67 \pm 2.31\%$, and DL% of $17.28 \pm 0.58\%$. Both free piceatannol and PN-PLGA NPs improved BDNF and synaptophysin expression, with the nanoparticle formulation producing a greater restoration. Overall, these findings suggest that piceatannol possesses promising antidepressant and neuroprotective potential, while PLGA nanoencapsulation may enhance its therapeutic efficacy against inflammation-associated depression.

Introduction

Depression is a common and disabling neuropsychiatric disorder characterized by persistent sadness, loss of interest or pleasure, fatigue, sleep and appetite disturbances, cognitive impairment, and reduced social and occupational functioning. Its pathogenesis is

multifactorial and involves genetic susceptibility, chronic stress, psychosocial adversity, hypothalamic-pituitary-adrenal axis dysfunction, oxidative stress, neuroinflammation, altered neurotransmission, and impaired neuroplasticity (Gutiérrez-Rojas et al., 2020). Major risk factors include genetic

predisposition, childhood trauma, chronic psychological stress, social isolation, adverse life events, female sex, socioeconomic difficulties, and chronic medical or psychiatric disorders. Globally, depression affects hundreds of millions of people and represents a major contributor to disability and reduced quality of life (WHO, 2025). Increasing evidence suggests that neuroinflammation plays an important role in depression. Lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, is widely used to establish inflammation-associated depression-like behavior in experimental animals. LPS activates Toll-like receptor 4 (TLR4), leading to NF- κ B activation, microglial stimulation, oxidative stress, and increased production of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. These inflammatory changes can impair neuronal function, synaptic plasticity, and neurotrophic signaling, resulting in depression-like behavioral abnormalities (Yin et al., 2023). Currently available antidepressant drugs include selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, escitalopram, and paroxetine; serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine; and other agents including bupropion, mirtazapine, trazodone, and vortioxetine. Although these drugs are clinically useful, delayed therapeutic effects, adverse effects, relapse, and treatment resistance remain important limitations, highlighting the need for novel therapeutic approaches.

Piceatannol (Figure 1) is a naturally occurring hydroxylated stilbene and structural analogue of resveratrol. It is reported to possess antioxidant,

anti-inflammatory, anticancer, cardioprotective, and neuroprotective activities. Piceatannol can modulate oxidative stress and inflammatory signaling, including NF- κ B-related pathways, and may influence cellular survival and neuroplasticity (Piotrowska et al., 2012). Recent experimental evidence has also demonstrated that piceatannol attenuates stress-induced neurobehavioral abnormalities through modulation of neuroinflammation, oxidative stress, and neurotransmitter imbalance, supporting its potential antidepressant-like activity (Kaur et al., 2025). However, poor solubility and limited bioavailability may restrict the therapeutic application of piceatannol. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles are biodegradable and biocompatible drug-delivery systems that can improve drug stability, solubility, controlled release, and bioavailability. Although piceatannol has been investigated in different formulations and nanoparticle systems, the specific application of piceatannol-loaded PLGA nanoparticles in LPS-induced depression has not yet been reported. Therefore, evaluation of piceatannol-loaded PLGA nanoparticles in an LPS-induced depression model may provide a novel strategy for targeting inflammation, oxidative stress, and neurobehavioral abnormalities associated with depression.

SDG Statement: This study contributes to the United Nations Sustainable Development Goal 3 (Good Health and Well-being) by improving health outcome, reducing disease burden, and supporting evidence-based healthcare interventions.

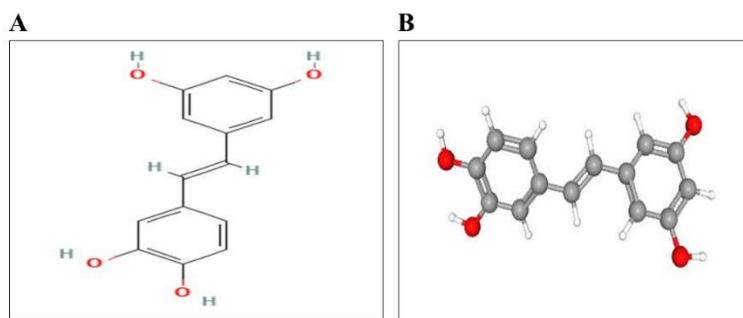


Figure 1: A and B represent 2D and 3D structures of piceatannol.

Materials and Methods

Chemicals

Piceatannol of analytical grade and lipopolysaccharide (LPS) were purchased from a certified supplier based in Shanghai, China. Other required chemicals, including chloroform, formalin, and normal saline, were procured from an authorized local supplier. All chemicals and reagents were used as received, without any additional purification or modification, to maintain consistency and reliability throughout the experimental procedures.

Animals

Healthy adult mice weighing 25–30 g were obtained from the National Institutes of Health (NIH), Islamabad, Pakistan. Before the experimental procedures, the animals were allowed an acclimatization period in the animal facility to adapt to the laboratory environment. The mice were housed in polypropylene cages, with five animals per cage, under controlled environmental conditions of $25 \pm 1^\circ\text{C}$ temperature, $50 \pm 10\%$ relative humidity, and a 12-hour light/dark cycle. Standard pellet diet and drinking water were provided ad libitum throughout the experimental period.

pkCSM Study

The pharmacokinetic and toxicity properties of piceatannol were predicted using the pkCSM online platform. The canonical SMILES structure of piceatannol was entered into the server to evaluate its absorption, distribution, metabolism, excretion, and toxicity (ADMET)

characteristics. Predicted parameters included intestinal absorption, blood–brain barrier (BBB) permeability, CYP450 interactions, renal clearance, and hepatotoxicity. The predictions obtained were used to assess the drug-like and pharmacokinetic suitability of piceatannol. These in-silico ADMET predictions provided preliminary information regarding its potential behavior and safety before further experimental evaluation (Udrea et al., 2018).

In Silico Study

The three-dimensional structure of the ligand was obtained and its molecular geometry was examined using BIOVIA Discovery Studio Visualizer. Depression-associated target proteins, dopamine D1 receptor (PDB ID: 7LJD) and dopamine D2 receptor (PDB ID: 6CM4), were retrieved from the RCSB Protein Data Bank. Before docking, the protein structures were prepared by removing water molecules and co-crystallized ligands, followed by the addition of polar hydrogen atoms. Molecular docking was performed using PyRx with AutoDock to investigate the binding affinity and orientation of the ligand within the target binding sites. The binding energies were expressed in kcal/mol, and the docking pose with the lowest binding energy was selected for further analysis of the ligand–protein interactions using 2D and 3D visualization (Narkhede et al., 2020).

Physicochemical Characterization of Piceatannol-Loaded PLGA Nanoparticles

The prepared piceatannol-loaded PLGA nanoparticles (PN-PLGA NPs) were characterized for particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency (EE%), and drug loading (DL%). Particle size and PDI were determined by dynamic light scattering (DLS) at $25 \pm 1^\circ\text{C}$ after appropriate dilution of the nanoparticle dispersion with filtered deionized water, and measurements were performed in triplicate. Zeta potential was evaluated by electrophoretic light scattering under the same experimental conditions. The amount of piceatannol was quantified by UV-visible spectrophotometry at its maximum absorption wavelength of 306 nm, using a previously prepared calibration curve. For determination of EE%, the amount of unencapsulated piceatannol present in the supernatant was quantified and the percentage of encapsulated drug was calculated relative to the initial amount of piceatannol added. Drug loading was calculated as the percentage of encapsulated piceatannol relative to the total weight of the recovered nanoparticles. All measurements were performed in triplicate and expressed as mean $\pm$ SD. These characterization procedures were performed in accordance with established approaches reported for PLGA nanoparticle systems (Derman et al., 2015)

***In Vivo* Model**

Adult mice were randomly divided into experimental groups, including saline control, LPS-induced disease, piceatannol-treated, and piceatannol-loaded PLGA nanoparticle-treated groups. Piceatannol was administered at 20 mg/kg, while the corresponding dose of piceatannol was incorporated into the PLGA nanoparticle formulation. The treatment groups received their respective formulations for 14 consecutive days, whereas the saline and disease groups received the corresponding vehicle. On the final day, depression-like behavior was induced in the disease and treatment groups by

administration of LPS (0.83 mg/kg, i.p.) (Yin et al., 2023).

Real Time Polymerase Chain Reaction

Total RNA was isolated from the collected tissue samples using a commercially available RNA extraction kit following the manufacturer's instructions. The extracted RNA was subsequently converted into complementary DNA (cDNA) through reverse transcription. Quantitative real-time PCR (qRT-PCR) was then carried out using a real-time PCR system with SYBR Green Master Mix and gene-specific primers. β -actin was used as the housekeeping gene for normalization of target gene expression. Relative changes in gene expression were determined using the comparative $2^{-\Delta\Delta\text{CT}}$ method (Bachman et al., 2013).

Statistical Analysis

The data were presented as mean $\pm$ SD for three independent observations ($n = 3$). Statistical differences among the experimental groups were assessed using one-way analysis of variance (ANOVA) followed by LSD post-hoc multiple comparison testing in IBM SPSS Statistics version 25. Graphical representations were prepared using GraphPad Prism version 9.5.0. A p -value < 0.05 was considered statistically significant.

Results**ADMET Analysis**

The pkCSM analysis indicated that piceatannol possesses favorable predicted pharmacokinetic properties, including good intestinal absorption. The compound showed predicted ability to cross the blood-brain barrier, supporting its potential central nervous system activity. The predicted CYP450 profile suggested limited interaction with major drug-metabolizing enzymes. Piceatannol also demonstrated acceptable predicted clearance and toxicity characteristics in the computational assessment. Overall, the pkCSM findings support the potential drug-like and CNS-relevant properties of piceatannol and provide a basis for its further experimental evaluation (Figure 2).

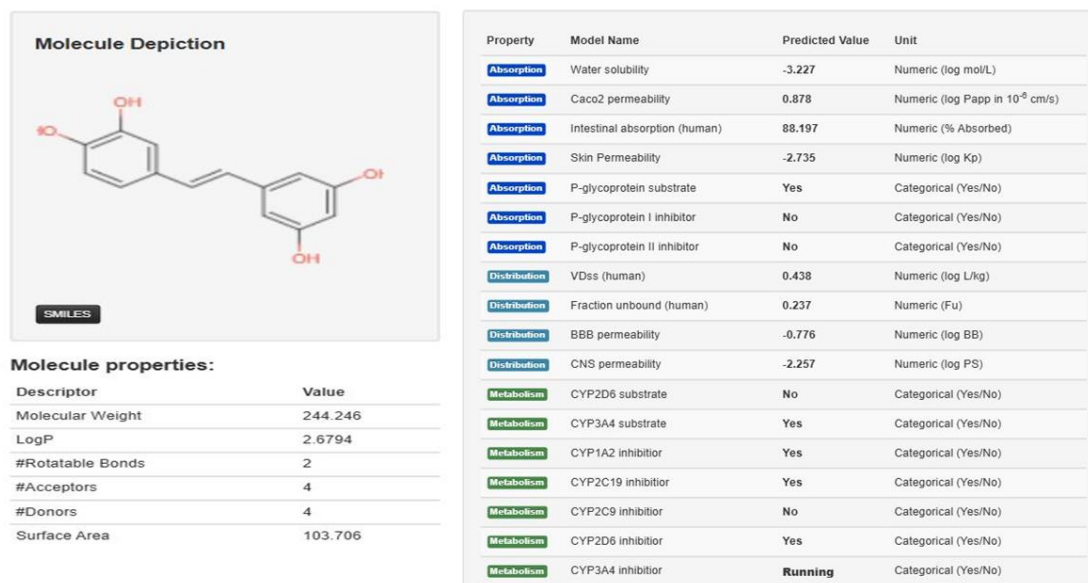


Figure 2: pkCSM analysis of piceatannol.

Computational Evaluation

Molecular docking was performed to investigate the interaction of piceatannol with depression-associated protein targets. Piceatannol exhibited favorable binding energies of -8.0 kcal/mol with D1 and -5.6 kcal/mol with D2, indicating appreciable binding affinity toward both targets (Table 1). Analysis of the docked conformations revealed that piceatannol was stabilized within the respective binding pockets through

hydrogen bonding and hydrophobic interactions (Figures 3 and 4). These interactions indicate favorable structural and chemical complementarity between piceatannol and the selected targets. Overall, the docking findings suggest that piceatannol may interact effectively with D1 and D2 receptors and could potentially influence their associated signaling pathways.

Table 1: Binding interactions of piceatannol with selected receptors.

Receptor	PDB ID	Compound	Energy Values Kcal/mol
D1	7LJD	Piceatannol	-8.0
D2	6CM4	Piceatannol	-5.6

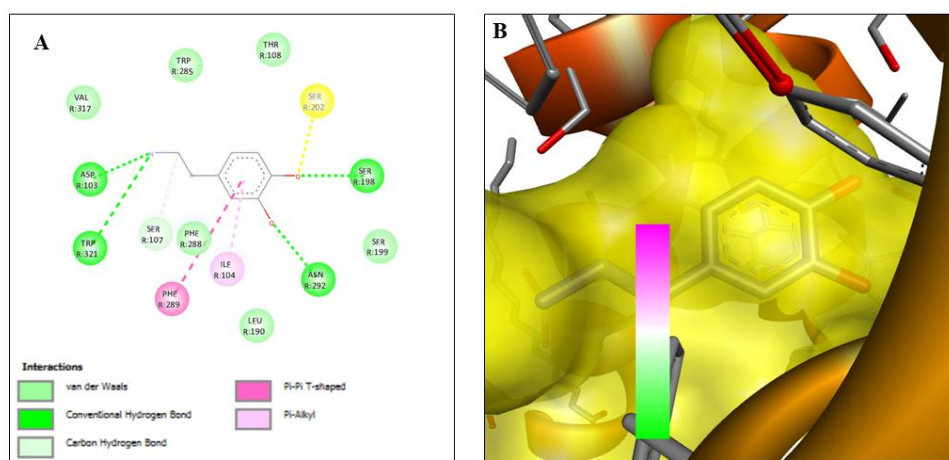


Figure 3: A and B represent 2D and 3D interactions of piceatannol with dopamine (D1).

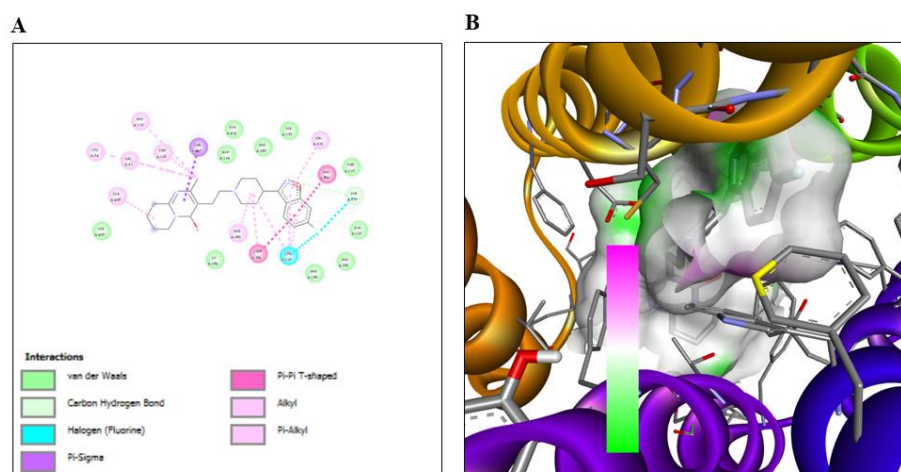


Figure 4: A and B represent 2D and 3D interactions of piceatannol with dopamine (D2).

Particle Size and PDI

The PN-PLGA NPs showed a mean particle size of 162.4 ± 4.7 nm. The PDI was 0.148 ± 0.009 , indicating a narrow and relatively uniform particle-size distribution. The nanoscale size suggests successful formation of the PLGA nanoparticle formulation. Overall, the low PDI indicates good formulation homogeneity.

Zeta Potential

The nanoparticles exhibited a zeta potential of -24.3 ± 1.4 mV.

The negative surface charge indicates the presence of negatively charged groups on the nanoparticle surface. This surface potential suggests sufficient electrostatic repulsion between particles. The observed zeta potential therefore indicates reasonable colloidal stability of the PN-PLGA NPs.

Encapsulation Efficiency (EE%)

The encapsulation efficiency of piceatannol was found to be $84.67 \pm 2.31\%$. Of the initial 10 mg of piceatannol,

approximately 8.467 ± 0.068 mg was successfully encapsulated. Only 1.533 ± 0.068 mg of piceatannol remained unencapsulated in the supernatant. The high EE% indicates efficient incorporation of piceatannol into the PLGA nanoparticle matrix.

Drug Loading (DL%)

The drug-loading capacity of the PN-PLGA NPs was $17.28 \pm 0.58\%$.

The nanoparticles had a total recovered weight of approximately 49.00 ± 0.41 mg. The obtained DL% indicates that a considerable proportion of the nanoparticle mass consisted of encapsulated piceatannol. These findings demonstrate successful preparation of a piceatannol-loaded PLGA nanoparticle formulation (Figure 5).

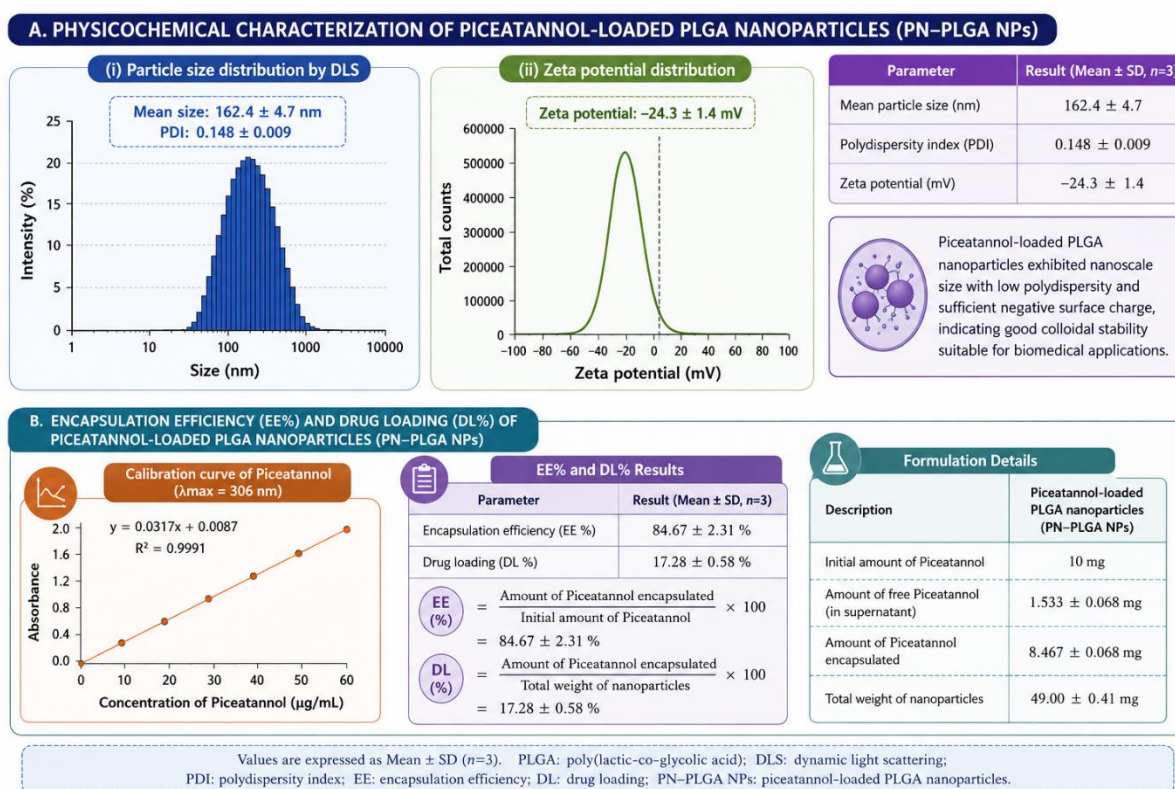


Figure 5: Characterization of piceatannol nanoparticles

Gene Expression

RT-PCR analysis revealed a significant alteration in BDNF and synaptophysin mRNA expression in the LPS-induced disease group compared with saline-treated controls. Treatment with free piceatannol (20 mg/kg) significantly improved the expression of both BDNF and synaptophysin. Notably, piceatannol-loaded

PLGA nanoparticles produced a more pronounced restoration of these genes compared with free piceatannol. These findings suggest that PLGA-based nanoencapsulation may enhance the therapeutic efficacy of piceatannol in restoring neurotrophic and synaptic function (Figure 6).

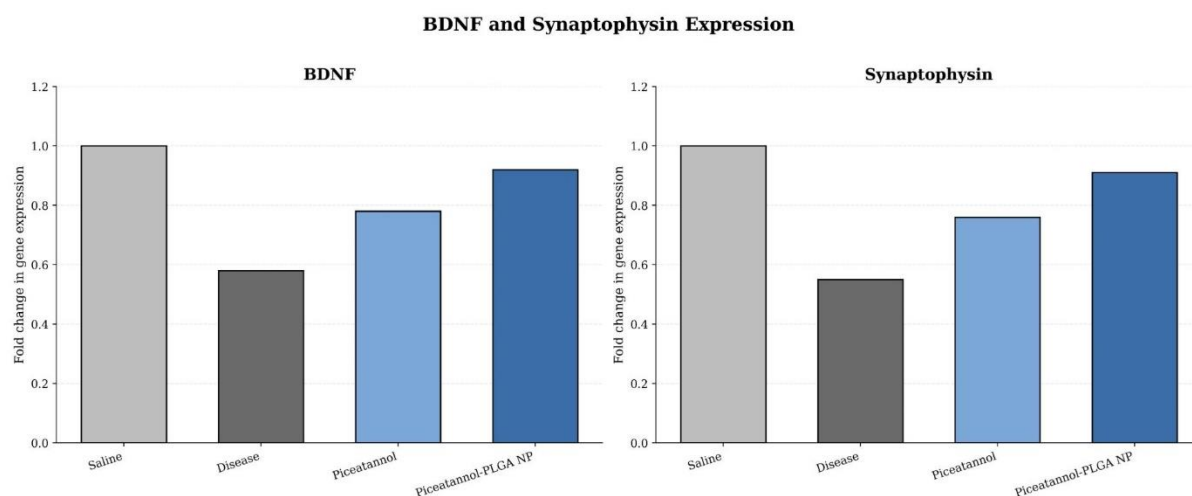


Figure 6: mRNA expression of selected genes evaluated through RT-PCR analysis

Discussion

The present study investigated the potential antidepressant-like and neuroprotective effects of piceatannol and piceatannol-loaded PLGA nanoparticles in an LPS-induced model of depression, supported by in-silico ADMET prediction, molecular docking, nanoparticle characterization, and gene-expression analysis. The major findings demonstrated that piceatannol possessed favorable predicted pharmacokinetic characteristics, showed appreciable binding interactions with the selected dopamine D1 and D2 targets, and was successfully incorporated into PLGA nanoparticles with suitable physicochemical properties. Furthermore, treatment with free piceatannol at 20 mg/kg improved the expression of the neurotrophic and synaptic genes BDNF and synaptophysin, while the piceatannol-loaded PLGA formulation produced a comparatively greater restoration. Collectively, these findings suggest that piceatannol may exert beneficial effects against inflammation-associated depressive pathology and that nanoencapsulation may improve its pharmacological performance. Depression is increasingly recognized as a disorder involving interactions among neurotransmitter imbalance, neuroinflammation, oxidative stress, impaired neuroplasticity, and altered neurotrophic signaling rather than being exclusively a disorder of monoaminergic transmission. The neuroinflammatory hypothesis is particularly relevant to the present

study because administration of LPS provides an experimental approach for producing inflammation-associated depression-like abnormalities. LPS activates innate immune signaling primarily through TLR4 and promotes downstream inflammatory responses, including activation of NF- κ B and production of pro-inflammatory mediators. Peripheral inflammatory signals can subsequently influence the central nervous system and activate microglia, thereby producing neuroinflammatory and behavioral changes. A systematic meta-analysis of LPS-induced depression-like models confirmed that LPS is widely used to investigate inflammation-associated depressive phenotypes and demonstrated that experimental outcomes are influenced by factors including mouse strain, route, dose, and behavioral assessment (Yin et al., 2023). The use of LPS in the present work is therefore mechanistically relevant to investigating the anti-inflammatory and neuroprotective potential of piceatannol. Previous experimental evidence has demonstrated that inflammatory activation can produce synaptic abnormalities together with depressive-like behavior. In particular, LPS-induced neuroinflammation has been associated with reductions in BDNF and synaptic proteins, while pharmacological inhibition of inflammatory signaling can restore these alterations. Ibrutinib, for example, was reported to reduce LPS-induced neuroinflammation and depressive-like behavior while restoring BDNF

and synaptic markers, including PSD95, SNAP25, and synaptophysin, in the hippocampus (Zhang et al., 2020). These findings provide a strong mechanistic basis for examining BDNF and synaptophysin as molecular indicators of neurotrophic and synaptic responses in the present study. The *in-silico* ADMET findings further provided preliminary support for the pharmacological suitability of piceatannol. The predicted favorable intestinal absorption and CNS-related pharmacokinetic characteristics suggest that piceatannol may possess properties compatible with activity within the central nervous system. Although computational predictions cannot substitute for experimental pharmacokinetic measurements, they are useful for preliminary assessment of drug-like characteristics and can guide subsequent biological investigations. The predicted pharmacokinetic profile observed in the present study therefore provides supportive evidence for continuing the experimental evaluation of piceatannol in a depression model. Molecular docking additionally demonstrated favorable interactions between piceatannol and the selected dopamine D1 and D2 targets, with binding energies of -8.0 and -5.6 kcal/mol, respectively. The observed hydrogen bonds and hydrophobic contacts suggest that piceatannol can be accommodated within the respective binding pockets through complementary chemical interactions. These findings should be interpreted as evidence of predicted binding compatibility rather than direct proof of receptor activation or inhibition. Nevertheless, the docking results provide a mechanistic hypothesis that piceatannol may influence dopaminergic signaling, which is relevant because dopamine participates in reward, motivation, locomotor activity, and affective regulation. The docking observations are also consistent with recent experimental work demonstrating that piceatannol can influence neurotransmitter-related abnormalities in an animal model of depression. Importantly, Kaur et al. (2025) recently reported that piceatannol at 10 and 20 mg/kg attenuated chronic unpredictable stress-induced neurobehavioral abnormalities in mice. Their study demonstrated reductions in oxidative stress and neuroinflammation together with alterations in

neurotransmitters, and implicated SIRT1 signaling in the neuroprotective effects of piceatannol. The use of 20 mg/kg piceatannol in the present study is therefore supported by this recent experimental evidence. Although the present investigation used an LPS-induced inflammatory model rather than chronic unpredictable stress, the findings from both models collectively support the potential of piceatannol to act across different pathological mechanisms associated with depression. Piceatannol is a hydroxylated stilbene structurally related to resveratrol and has previously been investigated for antioxidant and anti-inflammatory activities. Its multiple phenolic hydroxyl groups may contribute to its ability to interact with reactive species and cellular signaling pathways. Piotrowska et al. (2012) reviewed the biological activities of piceatannol and highlighted its broad pharmacological potential, including antioxidant, anti-inflammatory, and anticancer effects. These properties are particularly relevant to depression because excessive inflammatory signaling and oxidative imbalance can adversely affect neuronal function and synaptic plasticity. Thus, the biological profile of piceatannol provides a rational basis for its evaluation in an inflammation-associated model of depression. The physicochemical characterization confirmed successful preparation of the piceatannol-loaded PLGA nanoparticles. The mean particle size was 162.4 ± 4.7 nm, with a PDI of 0.148 ± 0.009 . The relatively small particle size and low PDI indicate a comparatively homogeneous nanoscale formulation. Nanoparticle size is an important determinant of drug-delivery behavior because it can influence dispersion, cellular uptake, biodistribution, and interaction with biological barriers. The observed PDI further suggests that the formulation had a relatively narrow size distribution rather than extensive particle aggregation. These characteristics are favorable for a nanoparticle-based delivery system. The zeta potential of the formulation was -24.3 ± 1.4 mV, indicating a moderately negative surface charge. Surface charge influences particle-particle interactions and colloidal behavior, with electrostatic repulsion helping to minimize aggregation. Although zeta potential alone

cannot establish long-term physical stability, the combination of a low PDI and negative surface potential provides supportive evidence of a reasonably stable nanoparticle dispersion. Previous literature has emphasized the utility of PLGA nanoparticles as biodegradable and biocompatible carriers capable of improving drug solubility, protecting encapsulated molecules, and enhancing cellular delivery, particularly for neuroprotective compounds (Gagliardi et al., 2021). The formulation also demonstrated a high encapsulation efficiency of $84.67 \pm 2.31\%$, with approximately 8.467 mg of the initial 10 mg piceatannol incorporated into the nanoparticles. This high encapsulation efficiency indicates effective incorporation of piceatannol into the PLGA matrix. The drug-loading value of $17.28 \pm 0.58\%$ further indicates that the formulation contained a substantial amount of piceatannol relative to the total nanoparticle mass. Together, these findings demonstrate successful formulation of PN-PLGA NPs and provide an important foundation for comparing free piceatannol with its nanoencapsulated form in vivo. The superior molecular response observed with piceatannol-loaded PLGA nanoparticles compared with free piceatannol is particularly important. Although both treatments improved BDNF and synaptophysin expression, the nanoparticle formulation produced a more pronounced restoration. This observation may be explained by the ability of PLGA nanoparticles to improve the physicochemical and delivery characteristics of an encapsulated compound. PLGA is biodegradable and has been extensively investigated as a carrier for CNS-active compounds. A review by Gagliardi et al. (2021) described the potential of PLGA nanoparticles to improve drug solubility, protect drugs from degradation, enhance cellular internalization, and facilitate delivery of neuroprotective compounds. Evidence from antidepressant nanoparticle studies further supports this interpretation. Venlafaxine-loaded PLGA nanoparticles have been investigated for brain delivery, and experimental biodistribution studies demonstrated that PLGA nanoparticles can reach the brain following intranasal administration (Gagliardi et al., 2019). Similarly, desvenlafaxine-loaded PLGA-chitosan

nanoparticles have been developed with the objective of improving brain delivery and antidepressant efficacy. More recently, venlafaxine-loaded PLGA nanoparticles were reported to produce antidepressant effects with rapid onset in an animal model of depression. These studies do not establish that the present piceatannol formulation reaches the brain more efficiently, because brain biodistribution was not directly measured in the current study; however, they provide supporting evidence that PLGA-based nanocarriers can be useful for delivery of CNS-active compounds. The restoration of BDNF expression observed after piceatannol treatment is particularly relevant to the neuroplasticity hypothesis of depression. BDNF is an important regulator of neuronal survival, synaptic plasticity, dendritic remodeling, and neurogenesis, and impaired BDNF signaling has been associated with depressive pathology. A review of preclinical and clinical studies reported that BDNF is closely associated with depression and that antidepressant treatments frequently increase BDNF-related signaling and neuroplasticity (Molendijk et al., 2023). Furthermore, experimental studies specifically examining inflammation-induced depression have demonstrated that LPS can alter BDNF signaling and that modulation of BDNF/TrkB signaling can influence LPS-associated depressive-like behavior (Liu et al., 2015). The present findings are also supported by evidence that BDNF deficiency increases vulnerability to inflammation-induced behavioral abnormalities. BDNF-deficient mice have been shown to develop more pronounced LPS-induced anhedonia, accompanied by exaggerated inflammatory and kynurenine-pathway responses (Dantzer et al., 2021). Thus, restoration of BDNF expression following piceatannol treatment may represent an important component of its neuroprotective response in the present model. It is plausible that the antioxidant and anti-inflammatory properties of piceatannol reduce inflammatory stress, thereby permitting recovery of neurotrophic signaling; however, because inflammatory markers and BDNF protein levels were not directly evaluated in the present experiment, this proposed mechanism should be

regarded as a plausible interpretation rather than a definitive mechanistic conclusion.

Synaptophysin provides complementary information regarding synaptic integrity. It is a presynaptic vesicle-associated protein involved in neurotransmitter vesicle function and is commonly used as a marker of synaptic density and neuronal connectivity. The simultaneous improvement of BDNF and synaptophysin expression observed in the piceatannol-treated groups therefore suggests that the beneficial effect of treatment may extend beyond inflammatory modulation to preservation or restoration of synaptic function. This interpretation is consistent with previous LPS studies in which neuroinflammation was associated with reductions in synaptic markers, including synaptophysin, and anti-inflammatory treatment restored these abnormalities (Zhang et al., 2020). The more pronounced restoration produced by PN-PLGA NPs compared with free piceatannol is therefore of particular interest. Nanoencapsulation may improve the effective exposure of piceatannol to biological tissues by protecting the compound from premature degradation and modifying its release and distribution. The relatively small particle size observed in the present formulation may also favor cellular interaction. Nevertheless, the present findings do not allow a definitive conclusion that the nanoparticles improved BBB penetration or brain accumulation because these parameters were not directly measured. Rather, the stronger molecular response provides pharmacodynamic evidence that the formulated compound produced greater biological activity under the experimental conditions used.

Overall, the findings integrate several complementary levels of evidence. Computational studies indicated favorable predicted ADMET characteristics and binding interactions with dopamine-related targets; physicochemical characterization confirmed successful formation of piceatannol-loaded PLGA nanoparticles with nanoscale size, low PDI, appropriate surface charge, high encapsulation efficiency, and appreciable drug loading and the in-vivo molecular findings demonstrated restoration of BDNF and synaptophysin expression following treatment.

The stronger response observed with PN-PLGA NPs compared with free piceatannol suggests that nanoencapsulation may enhance the pharmacological effectiveness of piceatannol against inflammation-associated neuronal and synaptic disturbances.

Conclusion

The present study provides preliminary experimental evidence supporting piceatannol as a promising natural compound for investigation in inflammation-associated depression and demonstrates the potential advantage of PLGA-based nanoencapsulation. The findings are consistent with emerging evidence that piceatannol can reduce stress-associated neurobehavioral and inflammatory abnormalities and extend this literature by evaluating a piceatannol-loaded PLGA formulation in an LPS-induced model. Future studies incorporating direct measurements of inflammatory cytokines, NF- κ B/NLRP3 signaling, oxidative stress, BDNF protein, TrkB signaling, synaptic morphology, pharmacokinetics, and brain biodistribution would be valuable for establishing the precise mechanisms responsible for the enhanced effect of nanoparticle formulation.

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