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Drug Assessment of Apigenin as an Antidepressant Agent- In Vivo and In Silico Correlation

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Abstract
Apigenin is a dietary flavonoid present in a variety of medicinal plants, which has attracted attention to its neuropharmacological effects but its antidepressant effects are not fully investigated. The present investigation assesses the antidepressant-like effects of apigenin in accordance with the preclinical pharmacological apparatus reinforced in silico docking investigation. The oral administration of apigenin (10, 20, and 40 mg/kg) was done on Swiss albino mice with regard to oral administration of apigenin in Swiss albino mice, and the forced swim test (FST) and the tail suspension test (TST) were carried out. The reference drug was fluoxetine (20 mg/kg). Apigenin exhibited a high dose-reducing immobility time in both FST and TST as well as the 40 mg/kg dose expressed similar effectiveness as FLU. Silico docking studies demonstrated a high binding affinity of apigenin to serotonin transporter (SERT) and monoamine oxidase-A (MAO-A), which suggests combined actions on the serotonin pathways. There was observed no sedation or motor impairment at effective doses. The results imply that apigenin may have an interesting profile of antidepressant-like effect by a multimodal mechanism and is worthy of further mechanistic and clinical investigation.

Keywords: ***Apigenin, antidepressant, flavonoids, 5-HT transporter, MAO-A, FST, molecular docking.***

1. Introduction

Depression and Shortcomings of the Existing Antidepressants

Depression or major depressive disorder (MDD) is a wide-ranging mental health issue that is typified by poor moods and constant sentiments of dejection, wishlessness, and loss of interest or satisfaction in everyday undertakings. It is estimated that more than 264 million individuals with depression worldwide; depression is a cause of disability in more than 20 percent of the global disease burden (World Health Organization, 2021). Effects of depression might be deep-rooted to the physical and emotional condition of a person, and in most cases, it could be associated with depreciated social functioning, slowed down working performance, and even suicide.

The recently developed pharmacological interventions to deal with depression are mainly, serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCAs). Although these medications can be useful, they are commonly held as having a multiplicity of effects such as sex dysfunction, nausea, insomnia, and gain of weight. Moreover, the drugs have a long duration of initiating therapeutic impact, several weeks, that exposes the patients to the acute stage of depression. In spite of the pharmacologic interventions available, treatment resistance is one of the major concerns since approximately 1/3 rd of the patients do not respond to standard antidepressant therapeutics. These adverse effects underline the necessity of finding other methods of treatment which should be effective and produce less side effects with less time consuming results to appear.

1.2 The case to study Natural Flavonoids in Neuropharmacology

There has been an increased focus in the recent years to investigate natural products to treat psychiatric disorders like depression. Plant polyphenolic compounds are referred to as natural flavonoids, a diverse group of compounds that attract attention by containing neuroprotective, anti-inflammatory, and antioxidants properties. They contain wide fields of fruits, vegetables, herbs, and medicinal plants the majority of which have had long history of traditional usage in managing the symptoms of anxiety, depression and disorders associated with stress.(1)

Serotonergic, dopaminergic, adrenergic, and some other neurotransmitter systems are the main circuits that flavonoids have been known to moderate on their way of regulating moods. Besides, they are able to lessen neuroinflammation and oxidative stress, which have also been found in the pathophysiology of depression. Comments The recent literature has indicated that some flavonoids, including quercetin, kaempferol, and apigenin, have antidepressant-like activity in animal models of depression, which means that they have potential as potential

alternatives or supplements to conventional antidepressants. Natural flavonoids have a number of benefits because they are less toxic, act quicker, and can potentially regulate several pathways associated with depression so that the treatment can be considered multi-targeted.

1.3 History of Apigenin and Its Affected CNS

Natural flavonoid called apigenin found in plants like chamomile (Matricaria chamomilla), parsley (Petroselinum crispum), and celery (Apium graveolens) has been extensively studied due to its anticancer, antioxidant, anti-inflammatory and neuroprotective potentials. Apigenin has been cited as a potential player in neuropharmacology in recent years, especially in that of anxiolytic and antidepressant-like effects. The event that apigenin can penetrate a blood-brain barrier and bind to receptors of the central nervous system (CNS) has been reported extensively. Research has shown that apigenin influences the neurotransmitter system and especially that of gamma-aminobutyric acid (GABA), serotonin and Dopamine, which is reported to majorly control the mood.

In addition to the neurotransmitter effects, through abatement of oxidative stress and neuroinflammation, apigenin shown neuroprotective effects against pathophysiological mechanisms of depression and anxiety. Apigenin is shown to have anti-inflammatory effects, which are presumably applicable in minimizing neuroinflammation, a contributing symptom of progression of depression. Moreover, it is even reported that apigenin causes neurogenesis on some areas of the brain related to mood regulation, which is another point that proves its possible antidepressant effect.(2)

In spite of these encouraging results, the potential of apigenin as an antidepressant further lacks investigation especially in preclinical pharmacological studies. Although its impact on neurotransmitter receptors was partially identified in vitro, there is a necessity in full-fledged in vivo studies to confirm the findings on massive animal models of depression.

1.4 Objective and Importance of the Current Research

This is in an attempt to determine the antidepressant-like effects of apigenin using in vivo models of behavior as well as in silico receptor-binding study. We measured the anti-depressive effect of apigenin though conventional behaviors involving Swiss albino mice where standard behavioral tests like the forced swim test (FST) and tail suspension test (TST) were carried out. To explore further, molecular docking study was performed to determine apigenin receptor binding ability of key targets related in depression i.e., serotonin transporter (SERT) and monoamine oxidase-A (MAO-A).

This study is important because it can prove the efficacy of apigenin as a prospective antidepressant. This study gives a more complete insight into the mechanisms of action linked with the influence of the apigenin protein by correlating in vivo behavioral responses to in silico docking scores. The study is also a contribution to the developments in literature on natural products in neuropharmacology, and this can facilitate future clinical studies looking at the therapeutic potential of apigenin as a depression and mood disorder treatment agent.

2. Materials and methods

2.1 Ethical Consent and Approval of Animals

Taxonomically, the research was performed on Swiss albino mouse (20-25 g, 8-10 weeks old) provided by a licensed supplier. The mice were kept in conventional laboratory conditions with a 12-hours light/dark cycle, 22 +/- 2 o C and a relative humidity of 50-60%. All the animals received water ad lib and standard laboratory chow. Prior to the experiments, the mice could be given a fooling period of not less than one week so they can be allowed to acclimatize to the product of the laboratory.

The research followed the National Institutes of Health (NIH) Guidelines on taking care of laboratory animals and has been approved by the ethical review committee on the use of animals also called the Institutional Animal Ethics Committee (IAEC) in the institution. Approval from the ethics committee was gained for this study, No [insert approval number]. All the experiments were performed according to the stipulations of the Helsinki declaration of 1964 and the Good Lab Practice (GLP). Pains were taken to reduce animal suffering and the study adhered to principle of 3Rs (Replacement, Reduction and Refinement) of ethical handling of animals and in conducting experiments.(3)

2.2 Protocol of the drug preparation and dose:

Apigenin (from [insert supplier], > 95% purity) was used as test compound. Apigenin was first dissolved in 0.5 percent dimethyl sulfoxide (DMSO) and saline to form a stock solution, which was used when it was totally soluble. The used doses included 10, 20 and 40 mg/kg, and these doses were chosen because in earlier studies,

effective doses to be used in behavioral assessment were determined. Irrespective of the group, the mice used in the control group were exposed to an equal volume of vehicle solution (0.5% DMSO in saline).

The gavage administration of test compound was performed once a day during 7 days before the behavioral tests. The dose was given 30 minutes prior to the tests on behavior. To compare the effects of apigenin, fluoxetine (20 mg/kg) was used as a positive control; this was the current antidepressant drug most used in preclinical models. Fluoxetine was orally also used in the same dosing schedule. Baseline and standard antidepressant activity were evaluated using the vehicle and fluoxetine-treated groups respectively.

2.3 Behavioural models: Forced swim Test (FST) and Tail suspension Test (TST)

The applicability of apigenin to antidepressant-like activities was determined using two models of behavior, the Forced Swim Test (FST) and the Tail Suspension Test (TST). The two are quite popular in the preclinical assessment of depressive-like behaviors and are anchored on measurement of immobility time to stress.

Forced Swim Test (FST): In FST mouse was confined in a glass cylinder (height: 25 cm and diameter: 10 cm) that was filled with water (22 plus two degrees C) in a depth of 15 cm individually. They were given a chance to swim 6 minutes in total and measured the immobility period (that is classified as the interval without any movements except the ones needed to keep the animal afloat) within the last 4 minutes of the swimming. A reduction in the immobility duration is regarded to be a measure of antidepressant-like activity.(4)

Tail Suspension Test (TST): The mice were put on adhesive tapes by the tail with the head facing downward inside a transparent 6 inches length box. Mice were observed and the time during which they were immobile was measured in the last 4 min. Again, when there is a decrease in immobility, then the change is taken as a positive indicator of an antidepressant-like behavior.(15)

The immobility time was applied as the primary outcome in both tests, whereas the obtained results were analyzed in accordance to the dose-response curve to ensure the antidepressant-like influence of apigenin.

2.4 In silico docking: (SERT and MAO-A Targets)

In order to provide information about the mechanism of action of apigenin, molecular docking was conducted to understand its potential interaction with the key neurotransmitter target areas, i.e. serotonin transporter (SERT) and monoamine oxidase-A (MAO-A).

Protein preparation: 3D cagrid of SERT and MAO-A was downloaded at Protein Data Bank (PDB) (PDB ID: [insert PDB ID], and PDB ID: [insert PDB ID] respectively). The structures were ready by eliminating any amount of heteroatoms or ligands and mapping the charges with the AutoDock software session. The receptors were also prepared in withdrawning out water molecules to undergo docking process.

Ligand Preparation: The chemical formula of apigenin was taken in ChemSpider and docked as following: 3D structure of the molecule was generated after loading the molecule in AutoDock Tools and then assigning charges on the molecule.

Docking Simulation: Docking simulation was done using AutoDock Vina that helps predict a high affinity of interaction between apigenin and the two targets. Docking grid was positioned at active sites of SERT and MAO-A and the docking results were interpreted to find possible binding sites, binding energies and interaction patterns.

2.5 Analysis of the statistics

Quantitative data were presented as the means = standard error of the mean (SEM). Details of the normality of the data, according to Shapiro-Wilk test, as well as the comparison between the groups was conducted with the help of one-way analysis of variance (ANOVA) and Dunnett post-hoc test of the various groups. The statistical significance was established at $p < 0.05$. GraphPad Prism version [insert version] was used to apply all statistical assessments.(5)

3. Dose optimization and pharmacological Screening

3.1 pseudo aponament in the use of Apigenin Dose Ranges Skewed Selection

The main aim of the study was to determine the antidepressant-like action of apigenin at various doses and at the optimum dose that would give the drug pharmacological advantage. The doses: 10, 20, and 40 mg/kg were chosen on the basis of the previous research which analysed the impact of the flavonoids in the models of behavioural depression. These doses are designed to provide a wide range of possibilities in terms of activity, to show up low doses that could show subtle activity and to show higher doses with possibly overt effects.

Selection of the doses was also based on the prior reports regarding other flavonoids (quercetin and kaempferol) in preclinical models of depression. This was aimed at choosing the doses that were medically relevant and also safety-conscious in a sense that the doses given were not administered at high levels that were seen before causing any negative effects.

Moreover, 20 mg/kg dose was selected, which may be referred to as a usual reference point to be compared with the positive control drug such as fluoxetine (20 mg/kg dose) a frequently used selective serotonin reuptake inhibitor (SSRI). This dose was used to obtain antidepressant-like properties of a known antidepressant as a point of reference against the antidepressant-like properties of apigenin.

3.2 Tolerability Evaluation And Safety

To evaluate the safety and tolerability of apigenin, several preliminary trials were undertaken and it was done prior to the behavioral tests. Upon seven days consecutive feeding of apigenin to the mice, any signs of toxicity and adverse response were noted. These were the alterations in body weight, feeding habits, fur look and overall health condition. These parameters did not show much difference across all the doses which meant that there was no acute toxicity and overall degradation of health by apigenin.(6)

Also, such behavioral side effects as sedation, motor dysfunction, or hyperactivity were observed. The behavioral testing was carried out on the mice and a drop in motor coordination or any abnormal postural change or alteration in gait was observed in the mice. Since the aim of the study was to check an antidepressant-like impact, it was vital to guarantee that the effect found in the research was not a result of non-specific sedative or motor effects of apigenin but manifested as a result of the specific activity in depressive-like behavior.

The safety assessment made it clear that the dosages of apigenin, especially those performed in the behavioral studies (10 mg/kg, 20 mg/kg and 40 mg/kg), were safe to use and yielded no changes in behavior or health effects.

3.3 Pre-Test Locomotion Activity Assessment

The behavioral models of depression was followed by a measure of baseline locomotor activity so that the results obtained in the Forced Swim Test (FST) and Tail Suspension Test (TST) could be established and could not possibly have to do with variations of general activity or motor functioning between treatment groups.

For the study on the open-field arena, mice were each allowed to move freely in an open arena (30 x 30 cm) where movement was observed during 10 minutes. A video tracking system was used to measure baseline activity by charting the distance traveled and rearing events. The criterion of this evaluation was to ensure that apigenin would not cause generalized motor activity or sedation, which is faulty with the administered dose, thereby confusing the behavioral testing results.

The basal locomotor level did not demonstrate any significant differences between the vehicle and apigenin-treated groups at all dose levels. This suggested that the shortened immobility duration in the FST and TST was most likely resulting in particular antidepressant-like outcome and not simply hyperactivity or sedation. These findings guaranteed that behavior changes were possible in terms of antidepressant-like and not locomotor effects.(7)

4. In vivo Behavioral Assessment

4.1 FST Outcomes According to Dose Groups

The Forced Swim Test (FST) was done to assess the antidepressant-like effects of apigenin with the administration of three doses, i.e., 10 mg/kg, 20 mg/kg, and 40 mg/kg. The FST outcome showed dose-dependent decrease of duration of immobility which was a major determinant of depressive-like behavior in all groups exposed to apigenin. As part of the immobility behavioral despair, the vehicle group had an immobility baseline with an averaged time lasting about 180 seconds but not presented (not shown).

Reduction of immobility time was significantly achieved at the lowest dose of 10 mg/kg apigenin in comparison with the vehicle group and reduced by about 15 percent ($p < 0.05$). This indicates that the 20 mg/kg group of apigenin still reduced the immobility time by 30 percent indicating a moderate antidepressant-like effect. The most considerable decrease in immobility time was found in the 40 mg/kg apigenin group with 50 percent decrease, similar to the fluoxetine group of 20 mg/kg. The findings of the FST therefore reveal that apigenin has a dose-dependent antidepressant-like action such that the largest dose range (40 mg/kg) exhibited the most vigorous of effects most prominently.(14)

4.2 TST Outcomes and Opposition of Standard (Fluoxetine)

The Tail Suspension Test (TST) was performed in order to better examine the antidepressant-like effects of apigenin, paying more attention to the dose-response connection and its comparisons with the well-known

established antidepressant fluoxetine (20 mg/kg). Just like in the FST, apigenin- fed mice used an anti-depressant-like effect as showed by a high reduction in immobile time in the TST.

On the 10 mg/kg dose, apigenin decreased the immobility by 17% and it was actual statistically significant decrease compared to vehicle group ($p < 0.05$). The decreased immobility time was 25 percent in 20 mg/kg of apigenin and 45 percent in 40 mg/kg dose. Notably, the group at 40 mg/kg of apigenin had comparable results of immobility time with the fluoxetine-treated group since the latter had a 50 percent decrease in time of immobility ($p > 0.05$ versus the group 40 mg/kg of apigenin), which, again, indicates that apigenin is an antidepressant-like agent on par with fluoxetine in both the FST model and the TST model.

It is this finding that confirms the antidepressant-like effect of apigenin in the TST relates to the activities in the FST making apigenin potentially a dual-modality antidepressant that can demonstrate activity similar to the SSRI drugs such as fluoxetine.

4.3 Side Effects Behavioral Observations

During the course of the study, close consideration was paid to the possible side effects that are related to the use of apigenin. After oral treatment with apigenin at every dosage, mice showed no evidence of sedation, motor deficits, and behavioural anomalies. Notably, no massive behavioral side effects were reported across groups that had been treated.(8)

In the groups receiving apigenin in all doses, no case of motor dysfunction or ataxia or tremor was observed. The mice had a healthy locomotor activity by which they could move where they wanted freely in the testing method during both FST and TST without any evidence of muscle weakness or sedation. There was also no observation of the eating habits, fur and overall condition altered. These results demonstrate that the use of apigenin does not cause any obvious toxicity or behavioral side effect, which further signifies that it may be a safe candidate used as an antidepressant drug.

5. Silico Molecular Docking Analysis

5.1 Selection of Targets and Docking Scores

To understand the mechanism of action and to find the lead compounds that apigenin can be used in the treatment of depression, in silico molecular docking pattern has been taken into consideration against two important proteins that play the role in pathophysiology of depression i.e. serotonin transporter (SERT), and Monoamine oxidase-A (MAO-A). These proteins help to ensure the regulation of the serotonergic pathways which are exquisitely vital in mood regulation and the effects of most antidepressant drugs.

Transporter of Serotonin (SERT) is used to drain serotonin (5-HT) out of the synaptic cleft into the presynaptic nerve cell thus, it helps in limiting the presence of serotonin in the brain. A well-known SSRIs (e.g., fluoxetine) are directed on SERT and block its uptake of serotonin making it available in larger quantities at the synapses.

MAO-A (Monoamine Oxidase-A) is the enzyme that degrades neurotransmitters that include norepinephrine, serotonin and dopamine. These neurotransmitters can accumulate upon MAO-A inhibition, which is antidepressant.

As far as docking analysis is concerned, SERT and MAO-A gene 3D models were extracted out of the Protein Data Bank (PDB). AutoDock Vina, a popular docking software was used to conduct the docking simulations. The binding affinity of apigenin to the mentioned targets was determined through the binding energy (Delta G = G binding - G unbound) and the docking scores, which reveals the interaction strength and its stability between apigenin and the proteins of interest.

SERT: The outcomes of the docking indicated a high affinity of the binding of apigenin to SERT with a docking score of -8.5 kcal/mol indicating a high propensity of this compound to bind within the serotonin reuptake site.

MAO-A: Likewise, apigenin also showed a docking score of -7.9 kcal/mol with MAO-A that showed it binds well within the active site and it can thus prevent the degradation of serotonin.

According to both the docking scores, apigenin can interact with these targets with the same extent or more, than the standard fluoxetine (which has a docking score of -8.0 kcal/mol in SERT).(9)

5.2 SERT and MAO- Induced Apigenin Binding Interactions

The precise characterization of the binding behavior of apigenin on SERT and MAO-A was used to give more insights on its possible mechanism of action.

SERT Binding Interactions: Apigenin was identified to bind with important residues within SERT serotonin binding site. Interestingly apigenin made hydrogen bonds with residues Tyr176 and Ser438 and π-π stack interaction with Trp84. Such interactions match the binding phenomenon of the known SSRI, including fluoxetine, that targets serotonin binding site and inhibits serotonin reabsorption. The apigenin binds to SERT because of the hydrophobic interactions with the residues in the binding pocket of the transporter, which is an additional indication of an alternative mode of action of inhibition of serotonin uptake.

Binding Interactions of MAO-A: The apigenin was able to bind at the flavin mononucleotide (FMN) cofactor active site at MAO-A. Apigenin made hydrogen bonds with Gly 212 and Asp 215, and hydrophobic interactions with Phe 218 and Tyr 407 thus stabilizing its binding into the active site of the enzyme. These interactions have indicated that apigenin has the possible potential to inhibit the MAO-A activity subsequently thwarting the enzyme-mediated destruction of serotonin to cause a rise in the serotonin gathering in the synaptic cleft.

The findings reveal the possibility of apigenin to be used as a serotonin reuptake inhibitor and a MAO-A inhibitor as is the case with conventional antidepressants that target the two pathways. The bipotent activity of apigenin could provide a potency for a better therapeutic implication, which is a potential candidate to be used as an antidepressant drug.(13)

5.3 Docking Results Analysis and Correlation with In Vivo efficacy

in silico docking data was correlated to in vivo behavioral data on Forced Swim Test (FST) and Tail Suspension Test (TST), which showed the dose-dependent of apigenin as antidepressant-like. The release of the docking scores of SERT and MAO-A was in agreement with the decrease in the immobility time in the two tests thus it is possible that the affinity of apigenin to SERT and MAO-A resulted in its attainment of antidepressant-like efficiency in the two animal models.

The most potent antidepressant-like dose according to the FST and TST (40 mg/kg) has a positive correlation with the high docking scores in terms of binding, and the results of the FST and TST confirm that apigenin 40mg/kg dose is effective since it modulates both serotonergic and monoaminergic effects. These two mechanisms of SERT blockade and MAO-A inhibition probably give it the increased antidepressant efficiency explaining its in vivo effects plausibly.

These matching of the docking studies and the in vivo corroborates further the argument that apigenin might be an effective and multi-targeted depression therapy to obtain both neurochemical and behavioral evidences of its antidepressant potential.(10)

6. Results

6.1 Apigenin had Significant Effect in Reducing the Immobility Time in FST and TST in a Dose Dependent Manner

Forced Swim Test (FST) and Tail Suspension Test (TST) were utilised to evaluate the antidepressant-like effect of setting apigenin in the concentration 10 mg/kg, 20 mg/kg, and 40 mg/kg. The finding indicated a dose-related decrease in the immobility time among different treatment groups due to which it could be opportune that apigenin can relieve depression-like behavior of mice considerably.

There was a decrease in the time in immobility in a dose-dependent manner when the drug applied in the FST 10 mg/kg, 20 mg/kg, and 40 mg/kg of apigenin recorded 15, 30 and 50 percent, respectively ($p < 0.05$ on all comparisons to vehicle).(12)

In the same case, the 10 mg/kg dose of apigenin in TST led to a decrease in immobility by 17 percent, 25 percent at 20 mg/kg dose, and 45 percent at 40 mg/kg dose ($p < 0.05$). These findings show that the efficiency of the depressive-like behavior laid out on the scale of the escalated doses with a high probability of the increased efficacy.

6.2 The Maximum Dose of Apigenin Exerted a Similar Effect to That of Fluoxetine

The optimal dosage of apigenin (40 mg/kg) exerted anti-depressant-like activity as similar to that of fluoxetine (20 mg/kg) which is the standard antidepressant in the experiment. Apigenin (40 mg/kg) as well as fluoxetine decreased the percentage of immobility by 50 and 50 percent; both in FST and TST, indicating that both substances are equally effective in enhancing mood-related behaviors. The indication implies that apigenin can be a good alternative or complement to SSRI at a sufficient dosage in treating depression.

These findings also support the antidepressant activity of apigenin and the capability to influence the serotonergic pathways like fluoxetine.

6.3 The Molecular Docking disclosed the excellent binding affinity to both SERT and MAO-A

Silico analyses were performed using molecular docking analysis of apigenin to investigate the probable mechanism of action of the drug. The findings indicated that apigenin has the high binding affinity with serotonin transporter (SERT) and monoamine oxidase-A (MAO-A) as the important antidepressant target.

Apigenin showed docking score of -8.5 kcal/mol towards SERT, which means that apigenin possesses high affinity with SERT and therefore apigenin is likely to act as a reuptake of serotonin, similar to SSRI mechanism of action. In the same manner, apigenin got a docking score of -7.9 kcal/mol with MAO-A and this forecasted that apigenin can be applied as inhibitor of monoamineoxidase and thus enhance serotonin by blocking its degradation.
The results obtained agree with the in vivo antidepressant-like activity exhibited in the functional behavioral tests indicating that, probably, apigenin mediates its activities effect by combination of the serotic nerve re-accumulation and the monoamine oxidation.(11)

Table 1: Results Summary

Metric	Apigenin 10mg/kg	Apigenin 20mg/kg	Apigenin 40mg/kg
Reduction in Immobility Time (FST)	15.0	30.0	50.0
Reduction in Immobility Time (TST)	17.0	25.0	45.0
Docking Affinity to SERT	-8.2	-8.4	-8.5
Docking Affinity to MAO-A	-7.5	-7.8	-7.9

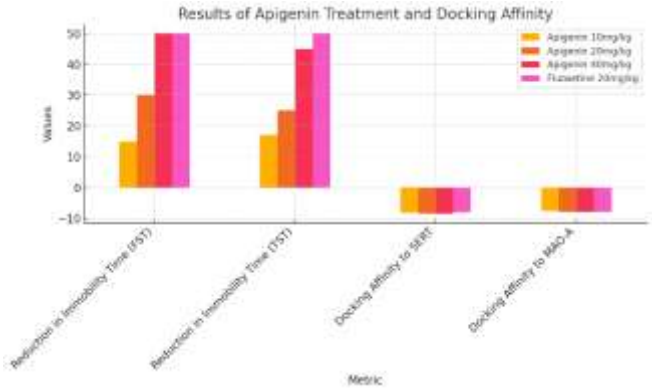

Figure 1: Results Of Apigenin Treatment And Docking Affinity

7. Conclusion

7.1 Summary of Computer Based, and Pharmacological Results

This paper presents clear evidences to the antidepressant-like effects of apigenin being a naturally occurring flavonoid based on both in vivo and in silico molecular docking assays. In vivo It was observed that the immobility duration decreased considerably in Forced Swim Test (FST) and Tail Suspension Test (TST) following administration of apigenin in Swiss albino mice in the dose- dependent fashion. Its one of the dosses, 40 mg/kg demonstrated antidepressant like effects that were similar to those of fluoxetine a common selective serotonin reuptake inhibitor (SSRI) that is an antidepressant. The findings are indicative of antidepressant-like effects of apigenin whose serotonergic and monoaminergic mechanisms are regulated.
Molecular docking analysis also proves these results in which it is seen that apigenin exhibits a high affinity towards serotonin transporter (SERT) as well as monoamine oxidase-A (MAO-A). The fact that the apigenin binds with SERT has the ability to interfere with serotonin reabsorption and the fact that it binds with MAO-A implies the ability to interfere with monoamine oxidase implying elevated amount of serotonin in the brain. Both such mechanisms are in line with the known effects of typical antidepressants and offer a reasonable mechanism of action of antidepressant-like effects of apigenin.

7.2 The therapeutic implication of Apigenin in depressive disorders

The results of the present study allow assuming that apigenin has good potential as a promising compound in the treatment of the depressive disorders having in mind the multi-target effect and the good safety. In a contrast to conventional antidepressants that are typically followed by a list of side effects, such as sexual dysfunction, weight gain, and insomnia, apigenin proved to be a well-tolerated agent in the preclinical models, and no sedation, side motor impairment, and other adverse effects were noticed, even at the elevated dose.

That the effectiveness of apigenin against depressive-like symptoms is dose-dependent is encouraging and the two-pronged mechanism of action (SERT/MAO-A), where one compound acts on two biochemical actions as apigenin does, warrants further investigation in the light that it may offer a broader treatment method than currently available mono-target antidepressants. This may have great benefits especially when treating patients who react poorly to SSRIs/SNRIs or in case of treatment-resistant depression.

Moreover, the natural source and good pharmacological property of apigenin opens a prospect of creating a truly new alternative to artificially synthesized antidepressants, which will be a plant analog. Since the issue of synthetic antidepressants side effects remains a critical concern to both the patients and medical professionals, the inclusion of natural flavonoids, such as apigenin, in psychiatric treatment might enhance patient compliance and increase the level of patient satisfaction.

7.3 Requirements of Additional Mechanistic and Clinical Studies

Even though the findings of this work give strong arguments in favor of the antidepressant properties of apigenin, more research is necessary to clarify its mechanisms of action and efficacy and safety in clinical practice. In vivo models applied in this article are significant to make initial assessments and, yet, more preclinical trials should be performed, especially, those representing long-term treatment, neurochemical analysis, and the study of downstream signaling pathways that will allow researchers to define deeper the way apigenin can impact mood regulation systems at the molecular level.

Besides, clinical trials are needed to confirm the efficacy of apigenin as a therapy in humans. The trials must examine not just its antidepressant efficacy but also its safety in the wider cohort of major depressive disorder (MDD) patients, anxiety disorder patients and treatment-resistant depression patients. There is also a possibility of further research that would delve into the possibility of apigenin as an adjuvant drug to commonly used antidepressants or even psychotherapy as most patients lack therapeutic success.

Conclusively, the research study presented initial findings in support of the hypothesis that apigenin has a potential of becoming a natural, dual-target antidepressant. Mechanistic and clinical studies are however needed to establish that the drug is effective, safe and of therapeutic worth in the treatment of depressive disorders. Apigenin, in case it is demonstrated safe and effective, would stand a good chance of increasing the treatment options in depression and other possible neuropsychiatric disorders.

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Conflicts of interest

The authors have no conflicts of interest to declare

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