RESEARCH ARTICLE

Evaluation of Antidepressant Effect of *Garcinia indica* Fruit Rind Juice in Combination with Gallic Acid: *In-silico and In-vivo* Studies

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ABSTRACT
Depression is a widespread neuropsychiatric disorder that significantly impairs quality of life and remains a global health concern. While conventional antidepressants are effective, their limitations, such as delayed onset and adverse effects, necessitate the exploration of alternative therapies. *Garcinia indica* (Kokum), traditionally used in Indian medicine, possesses antioxidant and neuroprotective properties, largely attributed to its rich content of polyphenols. The present study aims to evaluate the antidepressant potential of *Garcinia indica* fruit rind juice, both alone and in combination with gallic acid, using *in-vivo* models and molecular docking. The molecular docking (PyRx) study conducted against the MAO-A enzyme, a bioactive constituent from *Garcinia indica,* Gartanin, exhibited the highest binding affinity (-8.8 kcal/mol) in comparison with fluoxetine (-7.2 kcal/mol) and gallic acid (-6.3 kcal/mol). *In-vivo* antidepressant models, Tail Suspension Test (Group I to V), Forced Swim Test (Groups IA to VA), and biochemical estimation of MAO-A in both *in-vivo* models showed highly significant reduction ($^{***}p < 0.001$) in the immobility period and MAO-A levels for the group treated with Gallic acid (Group IV and Group IVA, 60mg/kg p.o.) along with *Garcinia indica* fruit rind juice (5 ml/kg p.o.) and Gallic acid (Group V and Group VA, 60mg/kg p.o.) along with *Garcinia indica* fruit rind juice (10 ml/kg p.o.). This integrated approach has validated the synergistic antidepressant potential of *Garcinia indica* fruit and gallic acid, offering a promising, plant-based adjunct to current antidepressant therapies with reduced side effects.

Keywords: Antidepressant, *Garcinia indica,* Gallic Acid, *In-silico* studies, *In-vivo* model, MAO-A
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INTRODUCTION

Depression is a major worldwide problem, affecting approximately 280 million people throughout the world as of 2023[1]. When depression is at its worst, it can lead to suicidal inclinations, hence ranking as the second most prevalent cause of death among those aged 15–29[2]. Conventional antidepressant therapies, such fluoxetine and other selective serotonin reuptake inhibitors (SSRIs), are extensively used, however prolonged use frequently results with negative effects such weight gain, nausea, and emotional blunting. So, there is a need to explore natural adjuvant therapy with fewer adverse effects while maintaining therapeutic efficacy[3,4].

The *Garcinia indica* (Kokum), a medicinal plant high in polyphenols, xanthones, and benzophenones, has long been recognised due to its anti-inflammatory, neuroprotective, and antioxidant activities[5,6]. As per previous literature, the fruit rind of *Garcinia indica* contains bioactive compounds such as Hydroxycitric Acid (HCA), Garcinol, Isogarcinol, Maclurin, α-Mangostin, β-Mangostin, and Gartanin, which may exhibit antidepressant effects through mechanisms like monoamine oxidase (MAO) inhibition, serotonin modulation, and neuroprotection[7-10]. Gallic acid, another potent antioxidant, has demonstrated MAO-A inhibitory activity, further enhancing the antidepressant potential of *Garcinia indica*. While *Garcinia indica* has shown neuroprotective properties, its combination with gallic acid has not been evaluated for antidepressant activity in validated models[11].

This study aims to evaluate and compare the antidepressant efficacy of *Garcinia indica* fruit rind juice with gallic acid to fluoxetine using behavioural, biochemical, and *in-silico* models[12]. Furthermore, experiments using molecular docking were carried out against MAO-A to forecast the essential phytochemicals' binding affinities[13]. This study will establish *Garcinia indica* fruit rind juice with gallic acid as a potential adjuvant in antidepressant therapy, offering a natural approach to managing depression[14].

MATERIALS AND METHODS

Collection and Authentication of Garcinia indica Fruit

Garcinia indica fruit was collected from a local vendor in Nashik. *Garcinia indica* fruit was authenticated by the Head of the Department of Botany of Pravara Rural Education Society, Padmashree Vikhe Patil College, Loni, Rahata, Ahilyanagar 413713. The authentication certificate (Ref

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No-PRES/PVP/DOB/2024/101, Specimen No. 10312 dated 02/01/2024) confirmed the sample to be *Garcinia indica* fruit, belonging to the family *Clusiaceae.*

Experimental Animals

The antidepressant activity was assessed in healthy 60 albino mice (20–30 g) of either sex. Water and food were freely available to the animals. The animals were housed and quarantined for 8-10 days in cages prior to the start of the experimental protocol. A 12-hour light and dark cycle, a temperature of 25±1°C, and a humidity range of 50–65% were all applied to each animal. The experimental protocol was approved by the Institutional Animal Ethics Committee of PRES's College of Pharmacy (For Women), Nashik (Reg. No. 1345/PO/Re/S/10/CPCSEA), and all experiments were conducted at the same institution[15,16].

Preparation of Experimental Solutions

A 0.25% (w/v) solution of Gallic Acid (99%) was prepared in distilled water and procured from Yucca Enterprises, Wadala, Mumbai 400037[17]. Fluoxetine (99%) solution, 1% (w/v) of was prepared in distilled water, which was procured from Cadila Pharmaceuticals Limited, Gujarat[18]. Isoflurane (99%) was purchased from HCX Pharmaceuticals LLP, Surat. *Garcinia indica* fruit rind was ground by a mixer, and using Whatman filter No. 42, it was

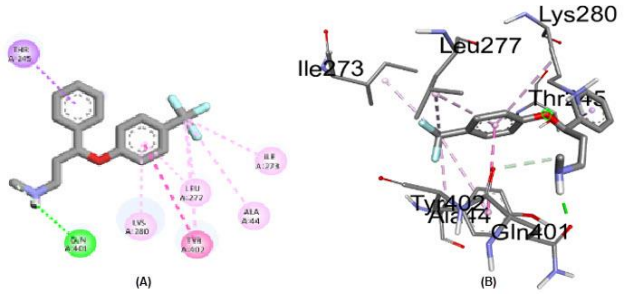

Figure 1: The 2D (A) and 3D (B) interaction of Fluoxetine with MAO-A Enzyme

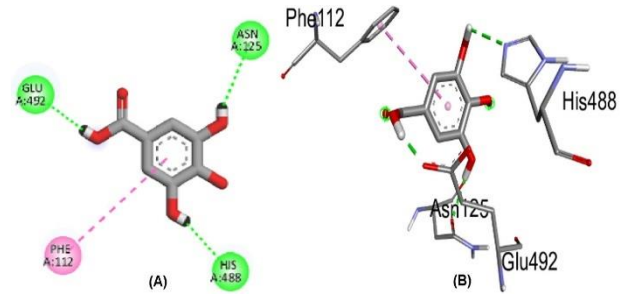

Figure 2: The 2D (A) and 3D (B) interaction of Gallic Acid with MAO-A Enzyme

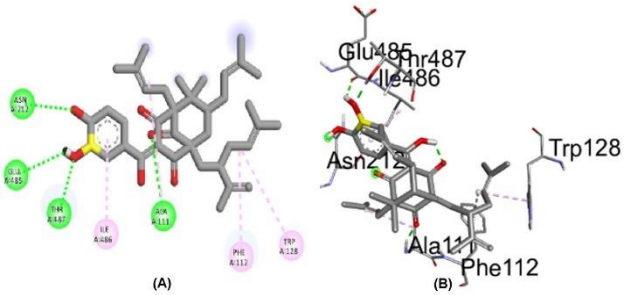

Figure 3: The 2D (A) and 3D (B) interaction of Garcinol with MAO-A Enzyme

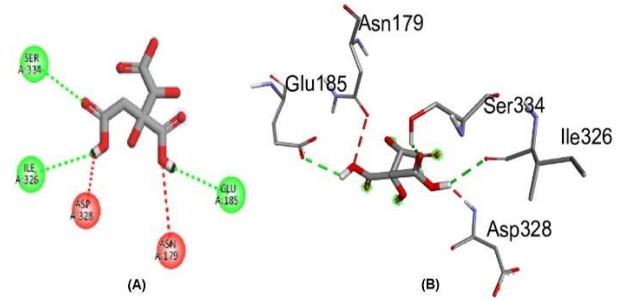

Figure 4: The 2D (A) and 3D (B) interaction of Gartanin with MAO-A Enzyme

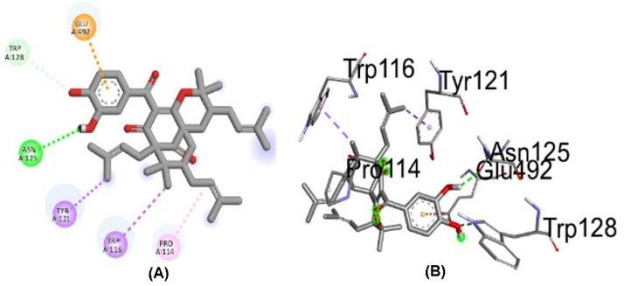

Figure 5: The 2D (A) and 3D (B) interaction of Hydroxycitric acid with MAO-A Enzyme

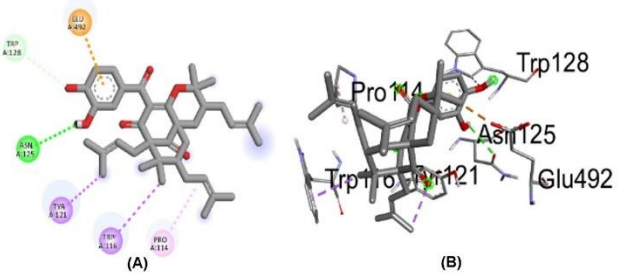

Figure 6: The 2D (A) and 3D (B) interaction of Isogarcinol with MAO-A Enzyme

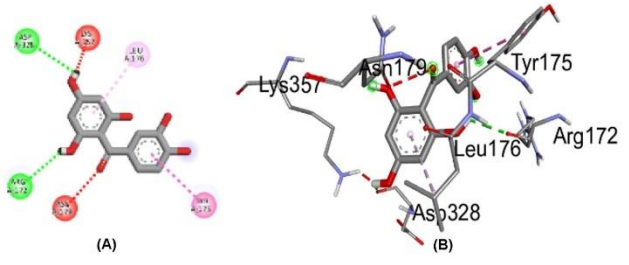

Figure 7: The 2D (A) and 3D (B) interaction of Maclurin with MAO-A Enzyme

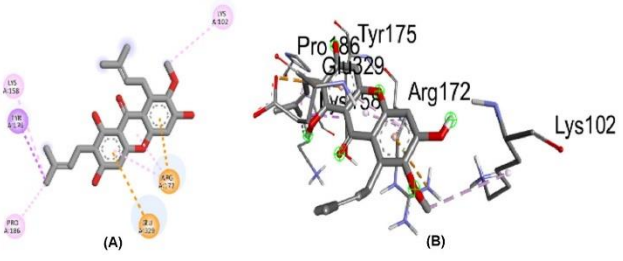

Figure 8: The 2D (A) and 3D (B) interaction of Mangostin with MAO-A Enzyme

filtered, which was then dried and stored in an airtight container.

Molecular Docking

Based on a literature review, the MAO-A protein structure (PDB ID: 2Z5X) was retrieved from the Protein Data Bank (PDB) for studying its role in antidepressant effects[19]. Ligand preparation was done using ChemDraw software (Professional 16.0). Protein preparation and optimisation were carried out using Discovery Studio Visualizer (v24.1.0.23298). Docking simulations were conducted in PyRx (Python Prescription 0.8), utilising AutoDock Vina for docking score calculations. Additionally, Discovery Studio Visualizer was used to conduct 2D and 3D interaction evaluations of the docked complexes to evaluate binding affinities and interaction types[20,21].

In-vivo Experimental Methods

Tail Suspension Test (TST)

Healthy mice were divided into five groups (I to V, n=6) based on similar prior studies. Group I was treated as vehicle control, i.e. distilled water; Group II was treated with the standard drug fluoxetine (20mg/kg p.o.); Group III was treated with test drug gallic acid (60mg /kg p.o.); Group IV was treated with gallic acid (60mg/kg p.o.) along with *Garcinia indica* fruit rind juice (5ml/kg p.o.) and Group V treated with gallic acid (60mg/kg p.o.) along with *Garcinia indica* fruit rind juice (10ml/kg p.o.). All treatments were given daily for 14 days. TST was performed on day 1 and day 14, and an immobility period was observed. The mice were suspended by their tail at a height of 58 cm above the top by using adhesive tape from an aluminium wire strung between two strands. The movements of mice were observed. The final four minutes of the six-minute test period were used to measure the overall amount of time spent immobile, which is defined as hanging still without any struggling movements[22-24].

Forced Swim Test (FST)

Healthy mice were divided into five groups (IA to VA, n=6) based on similar prior studies. Test drugs were administered once daily for a continuous 14 days by oral route. Group I was treated as vehicle control, i.e. distilled water; Group II was treated with the standard drug fluoxetine (20mg/kg p.o.); Group III was treated with test drug gallic acid (60mg /kg p.o.); Group IV was treated with gallic acid (60mg/kg p.o.) along with *Garcinia indica* fruit rind juice 5ml/kg p.o., and Group V was treated with gallic acid (60mg/kg p.o.) along with *Garcinia indica* fruit rind juice 10ml/kg p.o. FST was performed on day 1 and day 14, and an immobility period was observed. The container was filled with 25 °C tap water, and the water depth was adjusted based on the mouse's size to prevent its hind legs from touching the container's bottom. Every mouse was left in the container with water for six minutes.

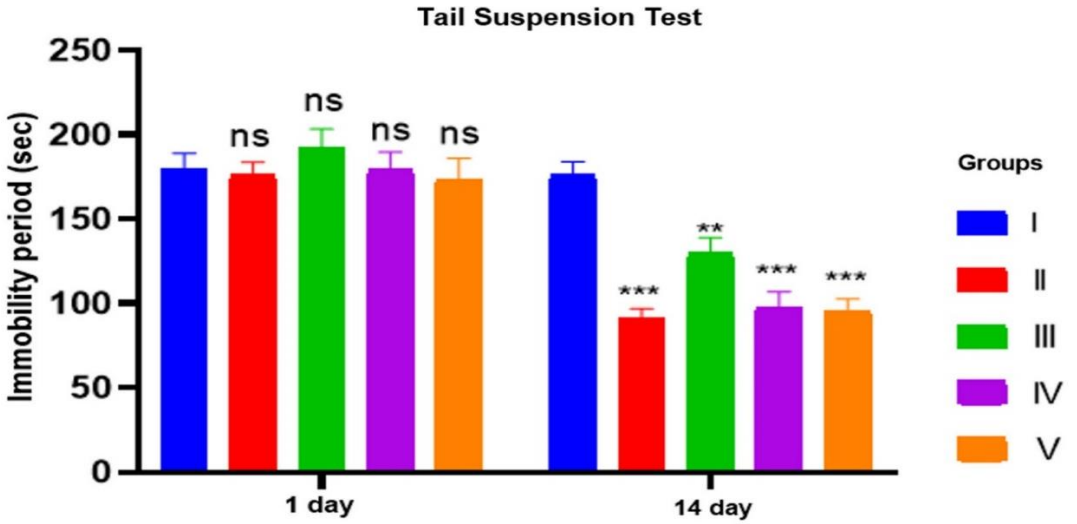

Figure 9: The graph of the immobility period of mice in the TST

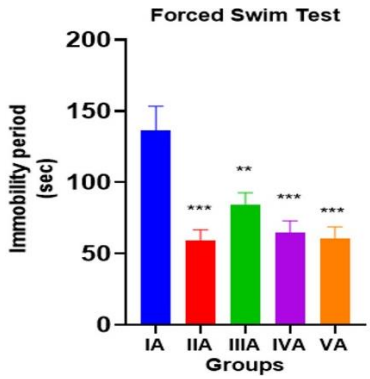

Figure 10: The graph of the immobility period of mice in the FST

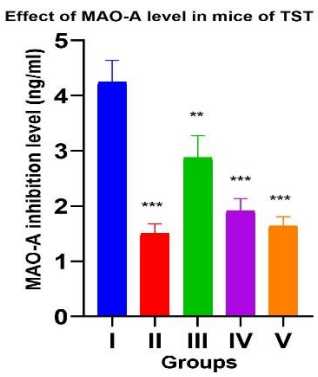

Figure 11: The graph of estimation of MAO-A level in mice of the TST model

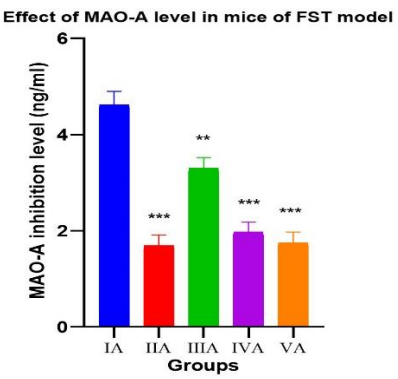

Figure 12: The graph of estimation of MAO-A level in mice of the FST model

Table 1: Results of Molecular Docking against MAO-A Enzyme

Name of Compound	Interacting with Amino Acids	Types of Bonds	Binding Affinity (kcal/mol)
Fluoxetine	GLN401, THR245, TYR402, ALA44, ILE273, LEU277, TYR402, LYS280	Hydrophobic & Hydrogen Bond	-7.2
Gallic Acid	GLU492, ASN125, HIS488, PHE112	Hydrophobic & Hydrogen Bond	-6.3
Garcinol	ALA111, ASN212, THR487, GLU485, PHE112, TRP128, ILE486	Hydrophobic & Hydrogen Bond	-8.5
Gartanin	SER334, ILE326, GLU185	Hydrophobic & Hydrogen Bond	-8.8
Hydroxycitric acid	ASN125, TRP128, GLU492, TRP116, TYR121, PRO114	Hydrophobic & Hydrogen Bond	-5.6
Isogarcinol	ASN125, TRP128, GLU492, TRP116, TYR121, PRO114	Hydrophobic & Hydrogen Bond	-7.7
Maclurin	ARG172, ASP328, TYR175, LEU176	Hydrophobic & Hydrogen Bond	-7.2
Mangostin	ARG172, GLU329, TYR175, LYS102, LYS158, PRO186, ARG172	Hydrophobic & Hydrogen Bond	-7.8

The mouse was taken out of the container and put in the temporary drying cage after six minutes had passed. The final four minutes of the six-minute test session were used to record the overall amount of time spent immobile. When mice failed to struggle and remained still in the water, with their head just above the water's surface and a little hunch, but maintaining their upright posture, they were immobile[25-27].

Biochemical Estimation of Monoamine Oxidase (MAO-A)

Mice were anaesthetised at the end of the experiment by inhalation of 1% isoflurane, and a capillary tube was used to remove 0.5–1 ml of blood from the retro-orbital sinus. Blood was transferred into EDTA K3 Tubes (Labcare) and mixed for 20 minutes. The plasma was separated by centrifuging the closed blood collection tubes (Labcare, LBCM08) for 10 minutes at 3000 rpm. To estimation of MAO-A in plasma was done as per the standard protocol of commercial kits (GENLISA ELISA)[28].

Statistical Analysis

Data is expressed as mean ± SEM (n=6). Data analysis was performed using GraphPad Prism (8.0) software. ANOVA was performed, followed by Dunnett's multiple comparison test. $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ are considered significant and $^{ns}p> 0.05$ is considered non-significant compared with control group.

RESULTS

Molecular Docking Results

Immobility Period of Mice in TST

On the 14th day, Group IV (Gallic acid 60mg/kg p.o. + *Garcinia indica* fruit rind juice 5ml/kg p.o.), Group V (Gallic acid 60mg/kg p.o. with *Garcinia indica* fruit rind juice 10ml/kg p.o.) and Group II (Fluoxetine 20mg/kg p.o.) showed a highly significant decrease in the immobility duration ($^{***}p <0.001$) as compared to the control, as shown in Figure 9. Mice treated with Gallic acid (60mg/kg *p.o.*) showed a slight decrease in immobility ($^{**}p<0.01$) when compared with the control.

Immobility Period of Mice in FST

On the 14th day, Group IVA (Gallic acid 60mg/kg *p.o.* + *Garcinia indica* fruit rind juice 5ml/kg *p.o.*), Group VA (Gallic acid 60mg/kg *p.o.* with *Garcinia indica* fruit rind juice 10ml/kg *p.o.*) and Group IIA (Fluoxetine 20mg/kg *p.o.*) showed a highly significant reduction in immobility period with ($^{***}p <0.001$) as compared to the control group, as shown in Figure 10. Group IIIA (Gallic acid 60mg/kg *p.o.*) showed a slight decrease in immobility ($^{**}p <0.01$) when compared with the control.

Estimation of MAO-A Level in Mice of the TST Model

Group IV (Gallic acid 60mg/kg *p.o.* + *Garcinia indica* fruit rind juice 5ml/kg *p.o.*), Group V (Gallic acid 60mg/kg *p.o.* with *Garcinia indica* fruit rind juice 10ml/kg *p.o.*) and Group II (Fluoxetine 20mg/kg *p.o.*) showed highly significantly ($^{***}p<0.001$) inhibition of MAO-A level as compared to control Group I ($^{ns}p>0.05$), as shown in Figure 11. Otherwise, Gallic acid alone showed significant (**p<0.01) inhibition of MAO-A level as compared to the control.

Estimation of MAO-A Level in Mice of the FST Model

Group IVA (Gallic acid 60mg/kg *p.o.* + *Garcinia indica* fruit rind juice 5ml/kg *p.o.*), Group VA (Gallic acid 60mg/kg *p.o.* with *Garcinia indica* fruit rind juice 10ml/kg *p.o.*) and Group IIA (Fluoxetine 20mg/kg *p.o.*) showed highly significantly ($^{***}p<0.001$) inhibition of MAO-A level as compared to control Group IA ($^{ns}p>0.05$), as shown in Figure 12. Otherwise, Group IVA (Gallic acid 60mg/kg *p.o*) alone showed significant ($^{**}p<0.01$) inhibition of MAO-A level as compared to the control.

DISCUSSION

Depression is a chronic illness that impacts thoughts, mood, and body health conditions, leading to low mood, lack of energy, sadness, not being able to sleep, and inability to take pleasure in life[29]. There are several medications available to treat depression, but to avoid the side effects of allopathic medicine, they can reduce the dose by using supplements or nutraceuticals[30].

In the present study, *Garcinia indica* fruit rind juice was screened for the antidepressant activity using two widely accepted and commonly used behavioural *in-vivo* models, namely the TST and the FST in mice, along with the estimation of MAO-A enzyme levels, which play a crucial role in the antidepressant activity[21,24,27]. Furthermore, an *in-silico* investigation was conducted to analyse the interaction of the reported compounds in *Garcinia indica* fruit with the MAO-A enzyme.

The molecular docking study conducted against the MAO-A enzyme offers insightful information into the binding affinity and 2D, 3D interaction patterns of various compounds (Table 1, Figure1-8). Out of six bioactive compounds from *Garcinia indica* fruit, Gartanin showed the maximum binding affinity of -8.8 kcal/mol (Table 1, Figure 4), followed closely by Garcinol -8.5 kcal/mol (Table 1, Figure 3), and Mangostin -7.8 kcal/mol (Table 1, Figure 8). The strong binding affinity of these compounds suggests their potential as effective MAO-A inhibitors. Fluoxetine, a well-known MAO-A inhibitor, displayed a binding affinity of -7.2 kcal/mol (Table 1, Figure 1). Gallic Acid (Table 1, Figure 2) and Hydroxycitric Acid (Table 1, Figure 5) demonstrated lower binding affinities of -6.3 kcal/mol and -5.6 kcal/mol, respectively. Isogarcinol and Maclurin (Table 1, Figure 6-7) exhibited moderate binding affinities (-7.7 kcal/mol and -7.2 kcal/mol, respectively).

The TST and FST *in-vivo* model is a well-characterised behavioural model to investigate the antidepressant activity of the drug. In both TST and FST, gallic acid alone (Group III and Group IIIA) has shown a moderately significant reduction in immobility period (**p-value < 0.01) compared to the control group. But gallic acid in combination with *Garcinia indica* fruit rind juice (Group IV to V and Group IVA to VA) has shown a very highly significant reduction in immobility period ($^{***}p < 0.001$).

Depressive disorders are majorly associated with oxidative stress, implicated in the breaking of the balance of reactive species. The fruit rind juice of *Garcinia indica* has shown activity, which may be because of its content of garcinol, a polyisoprenylated benzophenone with antioxidant activity[31]. The study demonstrated here further enhances the stance that antioxidants are crucial in the symptom reduction of depression.

Gallic acid (Group IV and Group IVA, 60mg/kg *p.o.*), along with *Garcinia indica* fruit rind juice (5 ml/kg *p.o.*), Gallic acid (Group V and Group VA, 60mg/kg *p.o.*), along with *Garcinia indica* fruit rind juice (10 ml/kg *p.o.*) and fluoxetine (Group II and Group IIA, 20mg/kg *p.o.*) demonstrated highly significant inhibition of MAO-A levels ($^{***}p < 0.001$) as compared to control. However, gallic acid (Group III and Group IIIA, 60mg/kg *p.o.*) alone showed a moderately significant ($^{**}p<0.01$) inhibition of MAO-A compared to the control (Figure 11 and Figure 12). This suggests that gallic acid, along with *Garcinia indica* fruit rind juice and fluoxetine, showed almost comparable effects. MAO inhibitors are an important class of antidepressants that work by inhibiting monoamine oxidase, leading to an increase in neuronal monoamine levels and consequently producing antidepressant effects[32]. Gallic acid exhibits antidepressant effects in mice due to its antioxidant properties and suppression of MAO-A[33].

In this regard, *Garcinia indica* fruit rind juice can be included as an adjunct therapy in patients, which will probably reduce the dose of conventional antidepressants and reduce their side effects.

CONCLUSION

The findings indicate that Gallic acid, along with *Garcinia indica* fruit rind juice, had a significant antidepressant effect as compared to the control. This has reduced immobility periods in TST and FST and decreased MAO-A levels. Otherwise, Gallic acid alone showed a slight decrease in the immobility period and MAO-A level as compared to the control. Therefore, *Garcinia indica* fruit rind juice may be used as a supplementary remedy in individuals undergoing long-term treatment with allopathic antidepressant drugs.

Acknowledgements

The authors express their gratitude to Yucca Enterprises, Mumbai providing a gallic acid sample for the study.

Abbreviations

FST – Forced Swim Test; TST – Tail Suspension Test; mg/kg – Milligrams per kilogram; hrs- Hours; min – Minutes; ANOVA – Analysis of Variance; SEM – Standard Error of Mean

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