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# EVALUATION OF ANTIDEPRESSANT ACTIVITY OF *CHENOPODIUM ALBUM* EXTRACTS AND FRACTIONS IN MICE

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**Keywords:**

Antidepressant, Antioxidant, *Chenopodium album*, ethylacetate fraction

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**ABSTRACT:** Traditional systems of medicine emphasize the importance of life-style, including dietary habits, for maintaining holistic health. Ayurveda recommends the use of fruits and vegetables in our diet for maintaining mental health. *Chenopodium album* is one such popular green vegetable. This plant is rich in phenolic compounds – compounds that are valued for their antioxidant activity and potential for management of CNS disorders. In this study, n-hexane, chloroform, methanol, and aqueous extracts of *C. album* leaves were prepared and standardized on the basis of total phenol content, total flavonoid content, and antioxidant potential (DPPH assay). *In-vivo* antidepressant activity of chloroform and methanol extracts was evaluated using Forced Swim Test (FST) and Open Field Test (OFT) models in mice. The bioactive methanol extract was fractionated into n-hexane, ethylacetate, and remaining aqueous fractions, followed by standardization and in-vivo evaluation of fractions. EAF had highest TPC (121.16 ± 9.31 mg GAE/g), TFC (55.42 ± 8.12 mg QE/g) and antioxidant potential (42.67 ± 2.25 µg/mL). EAF (40 mg/kg) showed significant antidepressant action without impairing the motor activity of animals. Comparative TLC fingerprint profiles confirmed the presence of ferulic acid in ME and EAF. The content of ferulic acid in *C. album* leaves, using an HPTLC method, was found to be 0.0030 ± 0.0002% w/w with respect to air-dried plant material. The antidepressant potential of *C. album* might be attributed to ferulic acid acting alone or in combination with other constituents present in *C. album* EAF.

**INTRODUCTION:** Mental health is a state of well-being in which an individual is well adjusted with self and others and contributes to society as well [1]. The present-day lifestyle has led to a surge in the occurrence of mental and emotional disorders like anxiety, depression, *etc.* [2]

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Depression is a heterogeneous syndrome 3 characterized by varying signs and symptoms including sad mood, irritable behaviour, insomnia, anorexia, suicidal tendency, *etc.* [4]

It is considered a highly prominent disease with a significant influence on quality of life, leading to impairment in person's ability to perform everyday activities [5, 6]. Depression is more prevalent among women (10-15%) as compared to men (5-10%). In India, its prevalence rate is estimated to be 15.9% [7, 8, 9]. A large number of medications are available for the treatment of depression, but these treatments provide relief to only 50-60% patients [10].

Moreover, most of the medications have adverse effects and are generally slow to produce the required therapeutic effect. To overcome these shortcomings of the synthetic medicines, people are focusing on herbal remedies to treat depression. Large numbers of plants have been evaluated for their anti-depressant effects using the animal models [11]. Traditional literature states that a proper diet may help to promote well-being. Various studies provide evidence that intake of a diet containing fruits and vegetables can enhance mental health [12]. A common green vegetable *Chenopodium album* L. (family Chenopodiaceae; common name Bathua) is one such vegetable [13, 14, 15].

The curative importance of *C. album* is mentioned in folklore literature, and its medicinal values are well established. The plant is reported to have anthelmintic, laxative, diuretic action and is used in the treatment of abdominal pain, eye disease, throat troubles, piles, diseases of the blood, heart, and spleen, and biliousness. The plant is rich in phenols and flavonoids and has demonstrated good antioxidant potential [16, 17, 18]. Literature reports suggest that plants rich in polyphenols, which possess marked antioxidant property are potential candidates for the management of various CNS disorders, including depression [19]. Thus it was thought worthwhile to evaluate the antidepressant activity of *C. album* extracts and fractions.

## MATERIALS AND METHODS:

**Plant Material:** *C. album* was sown in Punjabi University Patiala (PUP) area in the last week of October 2014, and the leaves were collected during the month of January 2015. The identity of leaves was confirmed by Mrs. Sunita Garg, National Institute of Science Communication and Information Resources (NISCAIR). (Specimen no: NISCAIR/RHMD/Consult 2015-16/122178/184)).

**Chemicals:** Chemicals and solvents used during the study were of analytical grade.

**Preparation of Extracts and Fractions:** The leaves of *C. album* were dried in the shade and reduced to a coarse powder. The powdered material (600 g) was sequentially extracted with n-hexane, chloroform, and methanol by exhaustive soxhlation to form 3 extracts, namely n-hexane extract (HE), chloroform extract (CE), and methanol extract (ME). Finally, the marc was boiled using distilled water on a hot plate to yield the aqueous extract (AE). The prepared extracts were concentrated, and the percentage yield was calculated with respect to the air-dried drug. Bioactive ME (20g) was fractionated by solvent-solvent partitioning using hexane and ethyl acetate in a successive manner (100 ml × 10) by heating at 50 °C for 30 min along with the continuous stirring.

The solvent from each separated layer was pooled and concentrated under reduced pressure to get 3 fractions, namely n-hexane fraction (HF), ethyl acetate fraction (EAF), and remaining aqueous extract (RE). The obtained fractions were dried on a water bath, and their percentage yield was calculated on an air-dried basis.

**Phytochemical Screening of Extracts and Fractions:** The prepared extracts and fractions were tested for the presence of various constituents [20, 21]. The extracts and fraction were standardized with respect to the total phenol content (TPC), total flavonoid content (TFC), and antioxidant capacity using 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay.

**Total Phenol Content:** The total phenol content (TPC) was determined by Folin- Ciocalteu method [22]. A standard plot (absorbance versus concentration) of gallic acid was prepared. The quantification was done on the basis of the standard curve, and the results were expressed as mg GAE/g dried extract/fraction.

All measurements were made in triplicate. *C. album* extracts (50 mg) were dissolved in 10 ml of distilled water, respectively, and the stock solution (5 mg/ml) of each extract was prepared.

One ml of extract, nine ml of distilled water, and 1.5 ml of Folin Ciocalteu reagent were added to the tubes and incubated for 5 min at room temperature. Further, four ml of 20% (w/v) $Na_2CO_3$ was added to each tube, and the volume was made up to 25 ml with distilled water. The mixture was stirred and allowed to stand at room temperature. Following 30 min of incubation, the absorbance was measured at 765 nm using a UV-Vis spectrophotometer. Distilled water was taken as blank.

**Total Flavonoid Content:** Colorimetric aluminium chloride method was used for flavonoid determination [23]. Total flavonoid content (TFC) was determined from the calibration curve of the quercetin and expressed as mg quercetin /g dry plant extract/fraction. All the measurements were done in triplicate. Stock solutions (10 mg/ml) of the extracts were prepared in methanol (80%) and diluted to obtain working solutions having 1 mg/ml concentration. Further, 1ml of the test sample was taken and mixed with aluminium chloride (10%) 0.1 ml, 0.1 ml of 1 M potassium acetate, and 2.8 ml of distilled water. After incubation at room temperature for 30 min, the absorbance of the mixture was noted at 415 nm using UV/ Visible spectrophotometer. The amount of aluminium chloride (10%) was substituted by the same amount of the distilled water in the blank.

**Antioxidant Activity:** DPPH free radical scavenging activity was evaluated as described by24 with slight modifications. Methanolic solution of DPPH (0.1 mmol/l) was freshly prepared. The assay was carried out by adding 1 ml of different concentrations of various samples prepared in methanol to 1 ml of DPPH solution. The reaction mixture was vigorously shaken and incubated at 30 °C for 30 min. The absorbance of the resulting mixture was measured at 517 nm using a UV / Vis spectrophotometer, using a separate blank for each concentration. All experiments were carried out in triplicate. The $IC_{50}$ values were determined using a linear regression equation. DPPH radical scavenging activity was expressed as the percentage inhibition calculated using the following equation

% inhibition = (Abs control – Abs sample) / Abs control × 100

Abs control = absorbance of the control, Abs sample = absorbance of the sample.

***In-vivo* Studies:**

**Animals:** The experimental animals (Swiss albino mice 20-30 g) were procured from Lala Lajpat Rai University of Veterinary and Animal Science, Hisar in the month of May 2018. They were housed in standard cages under controlled conditions with free excess to standard food and water during the study period. Experimental procedures were carried out according to guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, India (CPCSEA) and were approved by the Institutional Animal Ethics Committee. (Approval no: 107/GO/ReBi/S/99/ CPCSEA/2018-03)

**Experimental Groups:** The various experimental groups used in the study are given below:

**Group 1:** Vehicle group (Carboxy methyl cellulose sodium: 10 ml/kg)

**Group 2:** Standard group (Fluoxetine: 20 mg/kg)

**Group 3:** *Chenopodium album* chloroform extract (200 mg/kg)

**Group 4:** *Chenopodium album* chloroform extract (400 mg/kg)

**Group 5:** *Chenopodium album* methanol extracts (200 mg/kg)

**Group 6:** *Chenopodium album* methanol extracts (400 mg/kg)

**Group 7:** Hexane fraction (2 mg/kg)

**Group 8:** Hexane fraction (4 mg/kg)

**Group 9:** Ethyl acetate fraction (20 mg/kg)

**Group 10:** Ethyl acetate fraction (40 mg/kg)

**Group 11:** Remaining aqueous extract (173 mg/kg)

**Group 12:** Remaining aqueous extract (346 mg/kg)

The animals were given various treatments once daily, orally for 7 days. On 7$^{th}$ day, FST and OFT were performed to evaluate the antidepressant-like activity. All the extracts and fractions were administrated as a suspension in 0.5% carboxymethyl cellulose sodium.

**Behavioural Studies:**

**Forced Swim Test (FST):** The forced swim test was conducted as described by 25 with slight modifications. The mice were forced to swim individually in an open cylindrical container (diameter 14 cm, height 20 cm) filled with water up to a depth of 15 cm, and temperature was maintained at 25 ± 1 ° C. The immobility shown by mice when they are exposed to unavoidable and

inescapable stress conditions reflects behavioural despair signifying depressive disorder similar in humans. The duration of immobility was measured at the end of the procedure for 4 min in the total 6 min protocol.

**Open Field Test (OFT):** Open field test (OFT) was done to rule out any possibility of a non-specific locomotor effect of extracts or fractions. An increase in locomotor activity is considered as an index of false-positive results. The open field proves to be a better index of the animal's emotional state. As locomotor activity is a measure of the level of CNS excitability, any decrease in spontaneous motor activity can be attributed due to the sedative effect of the extract or fraction.

The behaviour parameters in the open-field test were assessed as described previously by 26. It comprises of open field arena, a wooden box measuring 40 × 60 × 50 cm with the floor divided into 12 equal squares. At the start of each trial, a mouse was placed in the centre of the field and allowed to move freely in the arena. The number of crossings (squares crossed with all paws) was recorded as a sign of locomotor activity. The movement was registered during a period of 5 min. The arena floor was cleaned with 10% ethanol after each trial [27].

**Estimation of Ferulic Acid in ME:** ME (20 mg/ml, 10 µl) was applied on pre-coated TLC plates (5 × 10 cm) in triplicate. The plate was developed using the solvent system – chloroform: methanol (9:1), in a chamber saturated for 10 min, to a distance of 8 cm. The developed plate was dried and scanned at 254 nm in a TLC scanner, and the AUC of the peak corresponding to the ferulic acid was recorded. The content of ferulic acid was determined from the standard plot and reported as a percentage with respect to air-dried plant material. The analytical method developed for estimation of marker compound in *C. album* leaves was validated as per ICH guidelines [28, 29].

## RESULTS AND DISCUSSION:

**Extraction Yields:** The % yields of the extracts were HE: 2.4 %w/w, CE: 1.98 %w/w, ME: 12.70 %w/w and AE: 11.10 %w/w and yields of fractions were HF: 86.5 %w/w, EAF: 10.1 %w/w and RE: 1.2 %w/w, respectively.

**Standardization of Extracts and Fractions:** Phytochemical screening showed the presence of phenols and flavonoids in all the extracts and fractions except HE and HF.

Therefore, the extracts and fractions (except HE and HF) were standardized on the basis of TPC and TFC. The standard plots of gallic acid and quercetin were prepared in **Fig. 1** and **2**.

The results of TPC and TFC are presented in **Table 1**. Among the extracts, ME was found to contain the highest amount of phenols and flavonoids, followed by CE and AE, whereas amongst the fractions, EAF had a higher amount of phenols and flavonoids than RE.

The results of the present study showed similar trends as reported in literature [16, 18, 30]. However, the absolute values may show variation due to different extraction methods, geographical locations, and cultivation conditions.

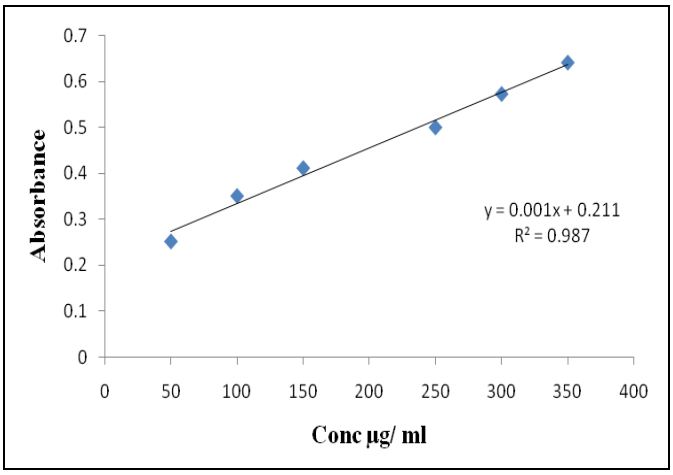


**FIG. 1: STANDARD PLOT OF GALLIC ACID**

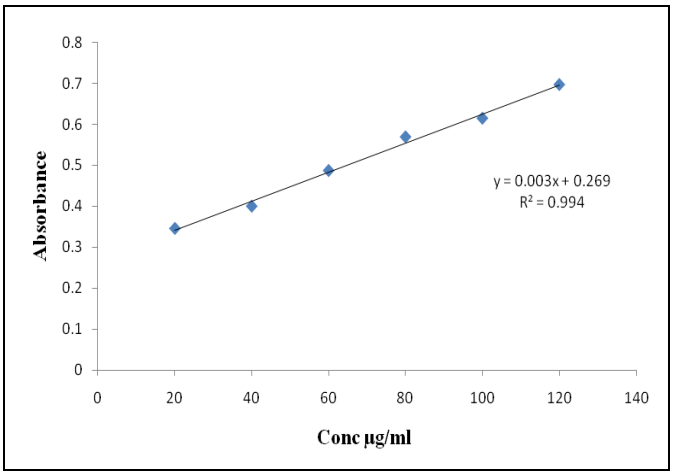


**FIG. 2: STANDARD PLOT OF QUERCETIN**

**TABLE 1: TOTAL PHENOLIC & TOTAL FLAVONOID CONTENT OF VARIOUS EXTRACTS AND FRACTIONS**

| Extract / Fraction | TPC mg GAE/g of extract (Mean$^n$ ± S.D) | TFC mg QE/g of extract (Mean$^n$ ± S.D) |
|---|---|---|
| CE | 48.34 ± 4.21 | 14.50 ±1.31 |
| ME | 101.53 ± 5.45 | 52.80 ± 4.39 |
| AE | 10.71 ± 1.31 | 3.20 ± 1.65 |
| EAF | 121.16 ± 9.31 | 55.42 ± 8.12 |
| RE | 21.32± 1.41 | 11.30± 1.86 |

Data is presented as Mean ± SD; n=3. GAE- gallic acid equivalent, QE- quercetin equivalent

***In-vitro* determination of Antioxidant Potential of Extracts and Fractions:** Literature shows that the generation of reactive oxygen species causes damage to lipids, proteins, and DNA, ultimately leading to cell death and decreased neurogenesis [31, 32]. Oxidative stress plays an important role in the pathogenesis of depression.

Hence, plants with an antioxidant profile may prove to be effective agents for the treatment of depression. Antioxidant potential of various extracts and fractions was determined using DPPH assay. Ascorbic acid was used as standard, and the results are presented in **Table 2**. EAF exhibited the highest antioxidant potential, followed by ME, RE, CE and AE.

**TABLE 2: $IC_{50}$ VALUES OF ANTIOXIDANT POTENTIAL OF EXTRACTS AND FRACTIONS IN DPPH ASSAY**

| Extract/Fraction | $IC_{50}$ value µg/ml (Mean$^n$ ± S.D) |
|---|---|
| CE | 296.34 ± 8.58* |
| ME | 152.67± 4.25* |
| AE | 850.83 ± 11.23* |
| EAF | 42.67 ± 2.25* |
| RE | 250.89 ± 4.23* |
| Ascorbic acid | 6.02 ± 0.02 |

Data is presented as Mean ± SD; n=3. The data was statically analysed by one way ANOVA followed by Tukey's multiple comparisons test, *p <0.05 *vs.* standard.

***In-vivo* Studies:** According to Guan and Liu 19 phenols and flavonoids show antidepressant activity due to their antioxidant potential. Therefore, only those extracts which possessed high amounts of phenols and flavonoids and demonstrated good antioxidant activity were selected for further studies. Amongst the extracts, CE & ME showed higher TPC, TFC, and antioxidant abilities. Therefore, CE & ME were selected for the animal studies.

**Behavioural Studies:** To explore the anti-depressant potential of extracts (CE, ME) behavioural studies were carried out using animal models. Forced swim test (FST) and open field test (OFT) were employed in the present study. Extracts were evaluated at 2 dose levels *i.e.* 200 & 400 mg/kg. The test doses ($1/20^{th}$, $1/10^{th,}$ and $1/5^{th}$ dose) were selected on the basis of acute toxicity data reported in literature [33, 34]. Dose selection for the standard drug fluoxetine was made on the basis of literature reports [35, 36]. The test doses of fractions were selected on the basis of percentage yield with respect to active extract. In FST, the duration of immobility of animals under unavoidable stress conditions reflects a state of despair, showing a depressive state of the animals. There are various advantages of this model *viz.* it is cheap, does not require any specialized instrument for carrying out the test, and no preliminary training to mice is required before conducting the test. OFT was conducted to check any changes in the locomotor activity and to rule out the possibility of false-positive result, which is associated with drugs that increase the locomotor activity.

**Effect on Immobility:** Oral administration of standard drug fluoxetine (20 mg/kg) for 7 days showed a significant decrease in duration of immobility as compared to the vehicle group. Significant reduction in immobility was also observed after administration of CE & ME at dose levels of 200 mg/kg & 400 mg/kg (p.o.). ME at the dose of 400 mg/kg (p.o.) showed the best antidepressant activity, which was statistically similar to the effects produced by the standard drug **Fig. 3**. Oral administration of HF (4 mg/kg), EAF (20 and 40 mg/kg), and RAF (173 and 346 mg/kg) resulted in decrease in the immobility period when compared to the vehicle-treated group. The most pronounced antidepressant effect was produced by EAF, which was comparable to standard **Fig. 4**.

**Effect on Locomotor Activity:** The number of line crossings in all the treatment groups was found to be similar, which signifies that extracts and fractions do not alter the locomotor activity **Fig. 5** & **6**. Based on the results of the FST and OFT it can be concluded that EAF showed the most significant antidepressant action without impairing motor activity.

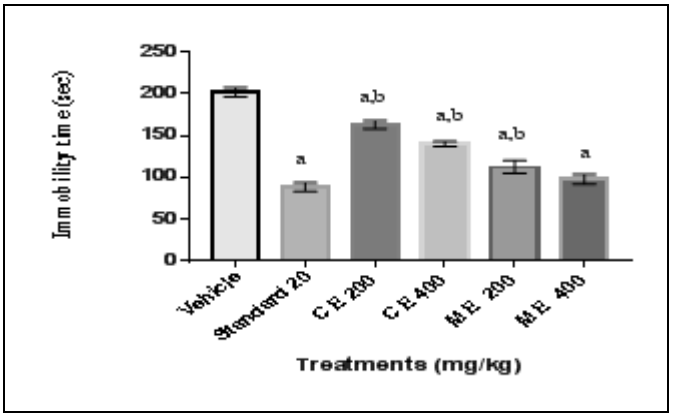


**FIG. 3: EFFECT OF EXTRACT TREATMENTS ON IMMOBILITY TIME IN FST.** All the values were presented as Mean ± SD, n=6. Data was analyzed by one way ANOVA followed by Tukey's multiple comparisons test, ap < 0.05 as compared to vehicle control, bp < 0.05 as compared to standard. CE – chloroform extract; ME – methanol extract

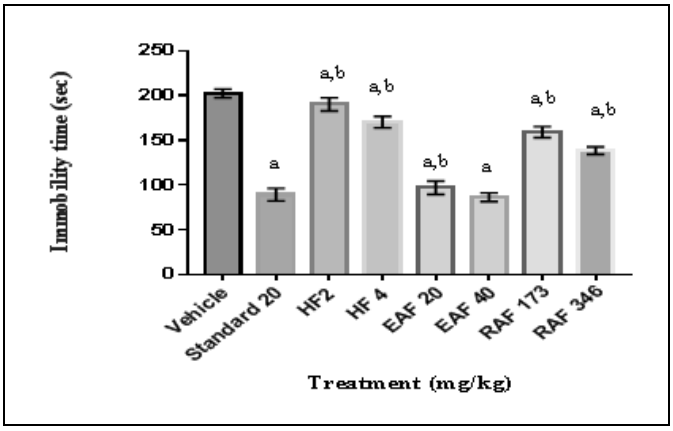


**FIG. 4: EFFECT OF FRACTION TREATMENTS ON IMMOBILITY TIME IN FST.** All the values were presented as Mean ± SD, n=6. Data was analyzed by one way ANOVA followed by Tukey's multiple comparisons test. ap < 0.05 as compared to vehicle control, bp < 0.05 as compared to standard. HF-hexane fraction; EAF-ethyl acetate fraction; RAF-remaining aqueous fraction

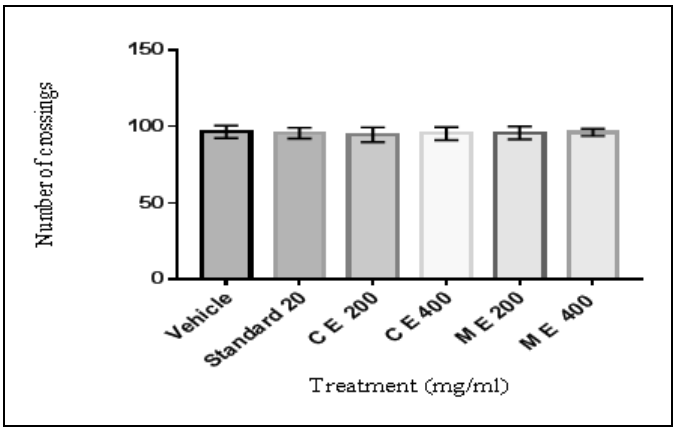


**FIG. 5: EFFECT OF EXTRACT TREATMENTS ON LOCOMOTOR ACTIVITY IN OFT** All the values were presented as Mean ± SD, n=6. Data were analyzed by one-way ANOVA followed by Tukey's multiple comparisons tests. CE – chloroform extract; ME – methanol extract

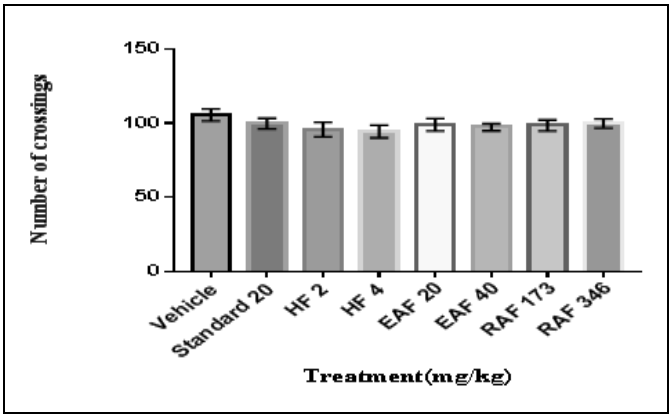


**FIG. 6: EFFECT OF FRACTION TREATMENTS ON LOCOMOTOR ACTIVITY IN OFT.** All the values were presented as Mean ± SD, n=6. Data was analyzed by one way ANOVA followed by Tukey's multiple comparison test. HF-hexane fraction; EAF-ethyl acetate fraction; RAF-remaining aqueous fraction


**FIG. 7: COMPARATIVE TLC FINGERPRINT PROFILE OF FERULIC ACID (1), ME (2) AND EAF (3) OF *C. ALBUM* VISUALIZED UNDER ULTRAVIOLET LIGHT AT 254 NM**

**TLC Fingerprinting Profile of ME and EAF of *C. album* Leaves:** Chromatographic profiling of ME and EAF was carried out by TLC using an array of standard phenolic acids, namely, m-coumaric acid, p-coumaric acid, vanillic acid, cinnamic acid, ferulic acid, sinapic acid, which were selected on the basis of literature review [30, 37, 38]. Comparative TLC fingerprint profiles confirmed the presence of ferulic acid in ME and EAF **Fig. 7**. Our findings corroborated with those of 30, 37 who reported ferulic acid in *C. album* leaves. Thus, ferulic acid was taken as a chemical marker to standardize *C. album* leaves using TLC densitometeric method. Available literature data suggest that ferulic acid is a strong antioxidant with significant antidepressant activity. In a study by [39], ferulic acid reduced levels of lipid peroxidation in the liver microsomal membrane of rats and

production of ROS in the cultured fibroblast cells. Further, Zeni [40] demonstrated that ferulic acid (0.01-1 mg/kg) decreased immobility time in animal models (FST and OFT) and also produced synergistic effects with the conventional antidepressants.

Moreover, treatment of mice with Chaihu-Sugan san extract (containing 19% FA) caused a reduction in immobility time, indicating antidepressant effect of the extract [41]. Furthermore, ferulic acid (20, 40 mg/kg) reversed Chronic Unpredictable Mild Stress Model (CUMS) induced depressive behaviour and upregulated the BDNF signaling while promoting the synaptic protein levels [42]. As ferulic acid is one of the major constituents present in *C. album*, the antidepressant-like effect produced by *C. album* might be attributed to this phenolic acid alone or in combination with other constituents.

**Estimation of Ferulic Acid in *C. album* Leaves by using TLC Densitometry**: TLC densitometry is a sophisticated instrumental technique that is used for the analysis of various constituents. This method offers various advantages, such as lower cost as compared to other methods like HPLC. The most interesting feature is that it allows simultaneous processing of both standard and sample on the same plate providing better accuracy and precision.

Nowadays, TLC densitometric methods are useful for qualitative and quantitative analysis of a wide variety of natural extracts [43]. **Fig. 8** presents the standard plot of ferulic acid. TLC densitometric chromatogram and spectra overlay of ferulic acid and ME are presented in **Fig. 9** and **10**.

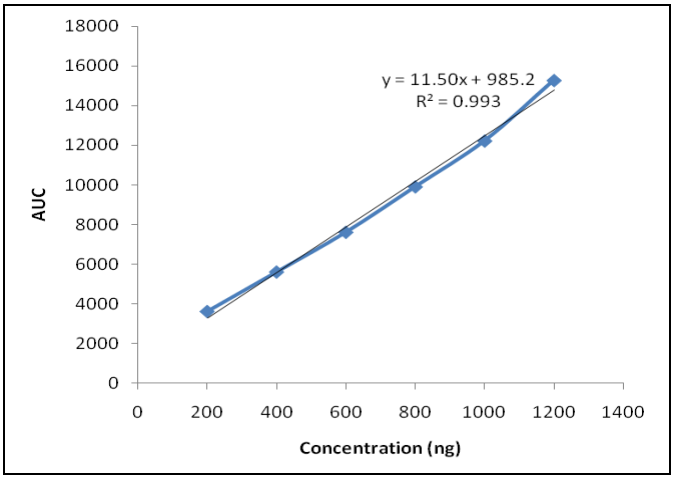


**FIG. 8: STANDARD PLOT OF FERULIC ACID**

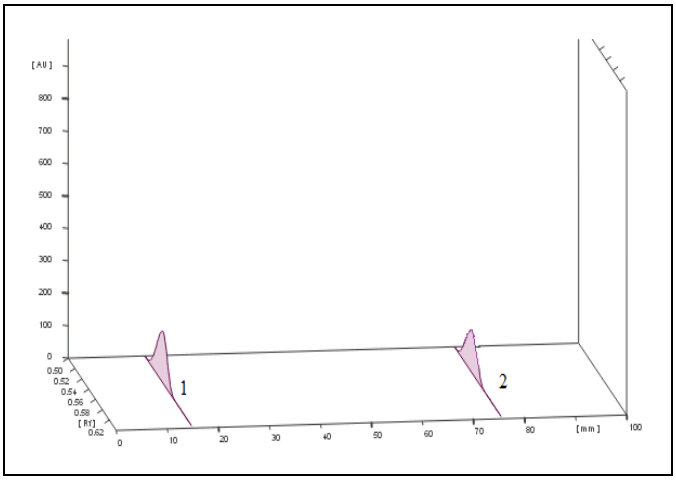


**FIG. 9: TLC DENSITOMETRIC CHROMATOGRAM OF 1) FERULIC ACID AND (2) ME (20 MG/ML) OF *C. ALBUM* SCANNED AT 254 NM**

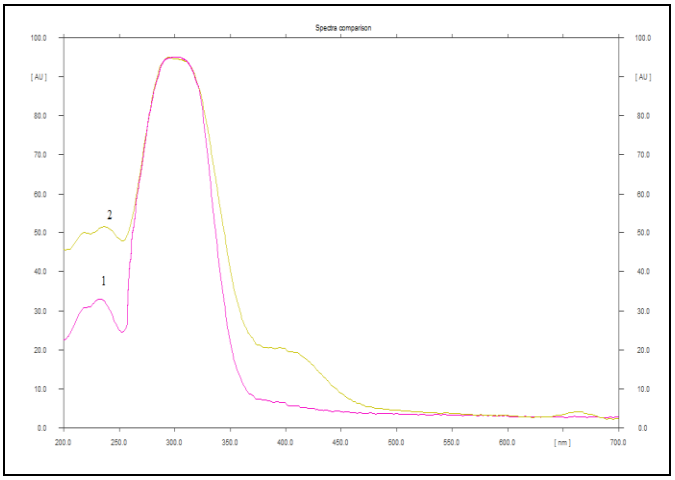


**FIG. 10: SPECTRA OVERLAY OF (1) FERULIC ACID AND (2) ME (20 MG/ML) OF *C. ALBUM* SCANNED AT 254 NM**

**TABLE 3: METHOD VALIDATION PARAMETERS FOR HPTLC METHOD**

| Parameter | Values |
|---|---|
| Instrumental precision (%CV, n-= 7) | 1.21 |
| Intra-day precision (%CV, n= 9) | 0.94 |
| Inter-day precision (%CV, n= 9) | 1.2 |
| Linearity (coefficient of correlation) | 0.994 |
| Range (ng) | 200-1400 |
| LOD (ng) | 11 |
| LOQ (ng) | 30 |
| Repeatability (%CV, n= 5) | 0.79 |
| Specificity | Specific |

The content of ferulic acid in *C. album* leaves was found to be 0.0030 ± 0.0002% w/w with respect to air-dried plant material.

The method developed for estimating ferulic acid in *C. album* leaves was validated as per ICH guidelines, and the results are presented in **Table 3**.

The results reveal that the developed method was found to be accurate, precise, and specific.

**CONCLUSION:** The findings of our study reveal that EAF of *C. album* exhibits significant antidepressant activity, which may be manifested through antioxidant pathway. The antidepressant potential of *C. album* might be attributed to ferulic acid acting alone or in combination with other constituents present in *C. album* EAF. Future studies are required to isolate the constituent/s responsible for the antidepressant activity of *C. album*.

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**CONFLICTS OF INTEREST:** Authors declared that no conflict of interest

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