

## The effective study of aqueous extract of *Crocus sativus* Linn.(Saffron) in depressed mice

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**Abstract: Objectives:** To evaluate the anti-depressant activity of *Crocus sativus* linn. aqueous extract in mice. To compare the anti depressant t activity of crocus sativus linn. with fluoxetine.

**Methods:** After obtaining Institutional Ethical Committee approval, swiss albino mice (20-25g) of either sex were randomly divided into 8 groups of 6 animals each. Dried powder of crocus sativus linn. was boiled with distilled water, cooled, filtered, placed on hotplate for complete evaporation, finally weighed and stored. The control group, test group and standard drugs group received saline, crocus sativus linn.extract (15 & 30 mg/kg), Fluoxetine (20 mg/kg) respectively by oral feeding. The anti-depressant effect was assessed by Force Swimming Test(FST) & Tail Suspension Test (TST) in mice.

**Results:** In anti-depressant models it implies that saffron with 15 mg/kg and 30 mg/kg significantly (\*\*-p<0.01) decrease the immobility period compared to that of control group.

**Conclusion:** The current study demonstrates statistically significant anti-depressant activity of crocus sativus linn.

**Key words:** *Crocus sativus* linn, anti-depressant, FST & TST.

### Introduction:

*Crocus sativus* L. (Iridaceae), commonly known as saffron<sup>1</sup>. In Ayurveda, saffron is used to treat epilepsy, chronic diseases such as asthma and arthritis, depressant, cold and coughs. Ayurvedic medicines containing saffron are used to treat acne and several skin diseases. A paste of the spice can be used as a dressing for bruises and superficial sores. Ancient texts on Ayurveda have information about the herb's use as an aphrodisiac. It is largely used as an indigenous medicine across India<sup>2-3</sup>.Recent pharmacological studies has demonstrated that saffron extract has hypolipidemic effect as well as learning or memory-improving properties<sup>4-5</sup>. In view of the need for safe and effective herbal antiepileptic and anti depressant, the present study was undertaken to evaluate the anti depressant effect of aqueous extract of crocus sativus linn.

Chemical studies have shown that *Crocus sativus* contains constituents such as crocin, crocetin safranal and picrocrocin<sup>6-8</sup>. Among the constituents of saffron extract, crocetin is mainly responsible for the above pharmacological activities.

**Phytochemistry**<sup>9,10-11</sup>

Saffron contains more than 150 volatile and aroma-yielding compounds. It also has many nonvolatile active components, many of which are carotenoids, including zeaxanthin, lycopene, and various  $\alpha$ - and  $\beta$ -carotenes.

Saffron has golden yellow-orange colour is primarily the result of  $\alpha$ -crocin. This crocin is trans-crocetin di-( $\beta$ -D-gentiobiosyl) ester (systematic (IUPAC) name:8,8-diapo-8,8-carotenoic acid). Its formula is C<sub>44</sub>H<sub>70</sub>O<sub>28</sub>. Crocin with weak bases it is converted into crocetin (C<sub>34</sub>H<sub>46</sub>O<sub>9</sub>), peculiar sugar not quite identical with dextrose, hence called crocose. The resultant  $\alpha$ -crocin is a carotenoid pigment that may comprise more than 10% of dry saffron's mass. A second element underlying saffron's aroma is 2-hydroxy-4,4,6-trimethyl-2,5-cyclohexadien-1-one, the scent of which has been described as "saffron, dried hay like". The flavouring property of saffron is due to the bitter glycoside picrocrocin chemically it is 4-( $\beta$ -D-glucopyranosyloxy)-2,6,6-trimethylcyclohex-1-ene-1-carboxaldehyde. (Chemical formula- C<sub>16</sub>H<sub>26</sub>O<sub>7</sub>). Safranal is less bitter than picrocrocin and may comprise up to 70% of dry saffron's volatile fraction in some samples<sup>12-13</sup>. It gives saffron much of its distinctive aroma. When saffron is dried after its harvest, the heat, combined with enzymatic action, splits picrocrocin to yield D-glucose and a free safranal molecule. Dry saffron is highly sensitive to fluctuating pH levels, and rapidly breaks down chemically in the presence of light and oxidizing agents. Analysis of Saffron is shown in Table No. 1 & 2.

**Table No. 1**

Component	Mass percentage
Carbohydrates	12.0-15.0
H <sub>2</sub> O	19.0-14.0
Polypeptides	11.0-14.0
Cellulose	4.0-7.0
Lipids	3.0-8.0
Minerals	1.0-1.5
Miscellaneous	40.0
Non-nitrogenous	

**Table No. 2**

Component	Mass percentage
Water soluble components	53.0
Gums	10.0
Pentosans	8.0
Pectins	6.0
Starch	6.0
$\alpha$ - Crocin	2.0
Carotenoids	1.0
Lipids	12.0
Non volatile oils	6.0
Volatile oils	1.0
Protein	12.0
Inorganic matter ("ash")	6.0
HCl soluble ash	0.5
Water	10.0
Fiber (crude)	5.0

Figure No. 1

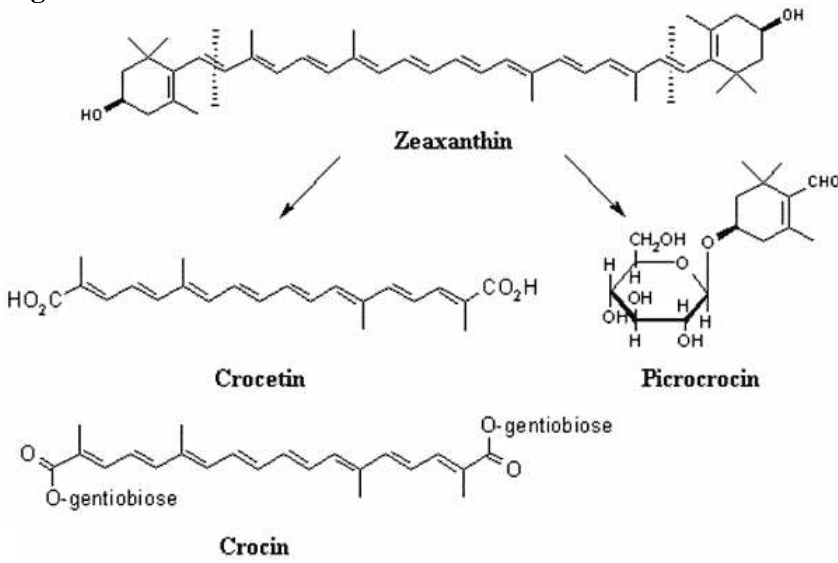
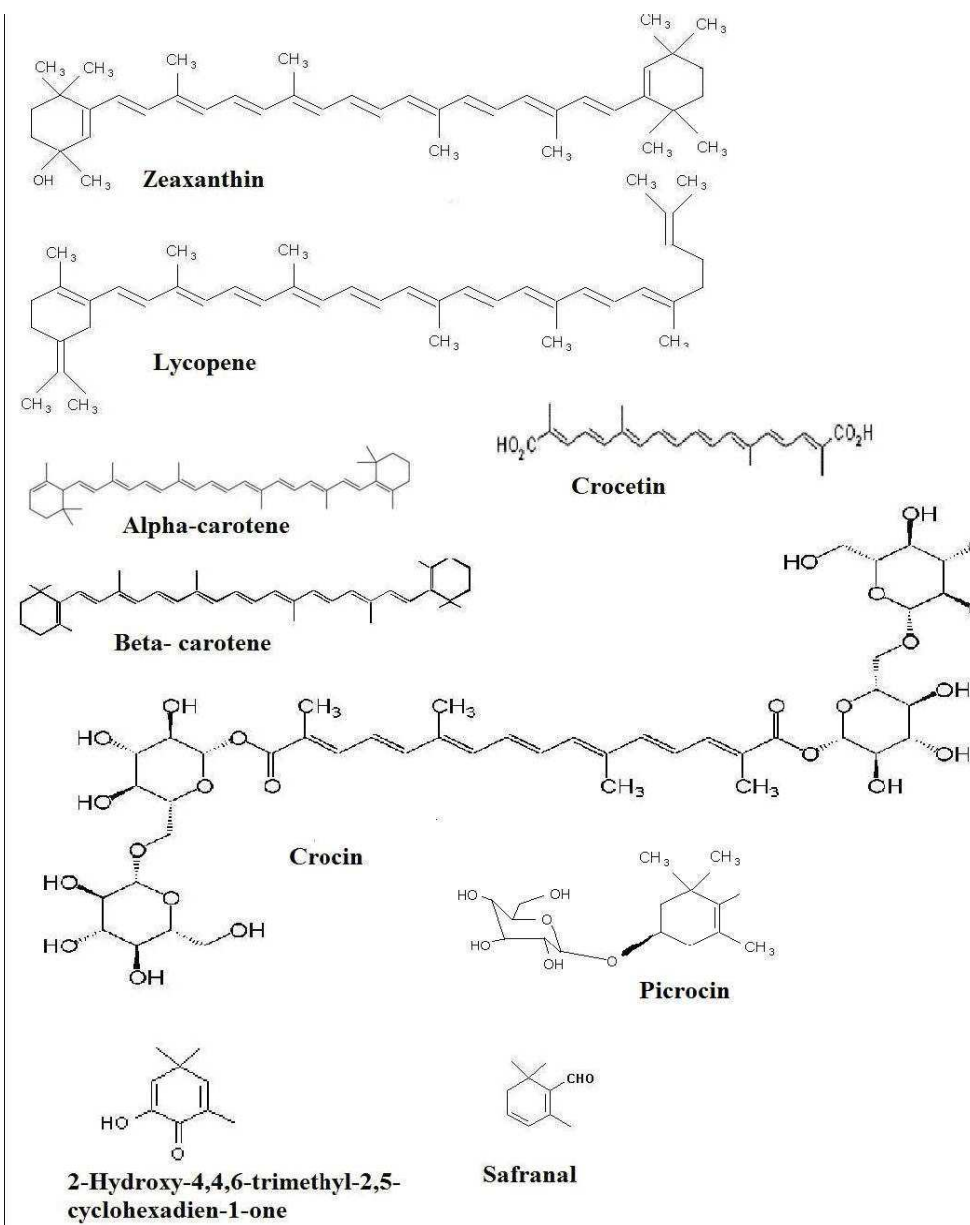


Figure No. 2



**Figure No. 3****Figure No. 4**

### **Evaluation Tablet assay**<sup>14</sup>

C.sativus stigma tablets were evaluated for short-term safety and tolerability in healthy adult volunteers. The study was a double-blind, placebo-controlled design consisting of a 1-week treatment of saffron tablets. Volunteers were divided into three groups of 10 each (five males and five females). Group 1 received placebo; groups 2 and 3 received 200 and 400 mg saffron tablets, respectively, for 7 days. General measures of health were recorded during the study such as hematological, biochemical, and electrocardiographic parameters done in pre- and post-treatment periods. Saffron with higher dose (400 mg) decreased standing systolic blood pressure and mean arterial pressures significantly. Saffron decreased slightly some hematological parameters such as red blood cells, hemoglobin, hematocrit, and platelets. Saffron increased sodium, blood urea nitrogen, and creatinine. This study showed that saffron tablets may change some hematological and biochemical parameters.

### **Quantitative structure-retention relationship**<sup>15</sup>

Quantitative structure-retention relationship (QSRR) studies were performed for predicting the retention times of 43 constituents of saffron aroma, which were analyzed by solid-phase micro-extraction gas chromatography-mass spectrometry (SPME-GC-MS). The chemical descriptors were calculated from the molecular structures of the constituents of saffron aroma alone, and the linear and non-linear QSRR modes were constructed using the best-multi-linear regression (BMLR) and pursuit regression (PPR) methods. The predicted results of the two approaches were in agreement with the experimental data. The coefficients of determination



( $R^2$ ) of the linear BMLR model were 0.9434 and 0.8725 for the training and test sets, respectively. The other non-linear PPR model gave a more accurate prediction with  $R^2$  values of 0.9806 (training set) and 0.9456 (test set). The proposed models could also identify and provide some insights into the structural features that may play a role on the retention behaviors of the constituents of saffron aroma in the SPME-GC-MS system. This study affords a simple but efficient approach for studying the retention behaviors of other similar plants and herbs.

### Chromatography and spectral analysis<sup>16-17</sup>

A variety of analytical methods, for example, TLC, HPLC, HPTLC, have been developed for analytical separation and qualitative studies of crocins; quantitative methods for crocins have recently been reported. Methods reported for preparative chromatography of crocins include aluminum oxide column chromatography,<sup>18</sup> TLC, gel column chromatography, and multi-layer coil counter current chromatography, with silica gel, aluminum oxide, Sephadex LH-20 as stationary phases. By use of these methods, the yellow pigments have been separated into seven fractions at most. A preparative HPLC method for saffron has also been reported; high purity crocins have not, however, been obtained. Eleven certified saffron samples (*C. sativus* L.), one each from Azerbaijan, China, Greece, France, India, Iran, Italy, New Zealand, Spain, Turkey, and the Sigma Chemical Company, were analyzed by using an HPLC photodiode array detection method. This analysis quantified the 10 major saffron compounds in each sample and their concentration was analyzed at three different wavelengths. Result indicated that the Greek Indian, New Zealand, and Spanish saffron extracts possessed the highest concentrations of water-soluble glycosidic carotenoids ( $\geq 8.0\%$ ) suggesting that they could be a good source of this type of metabolite for further biological evaluation.<sup>19</sup>

Thermal desorption-gas chromatography was applied to samples of saffron to quantify the safranal content that is responsible for the distinctive aroma. Safranal constituted 72% of the volatile fraction. Using  $\beta$ -cyclocitral as internal standard and submitting the sample to a temperature of 70°C for 8 min, 83% of the total was determined with the first desorption's, and 100% with three consecutive desorption's.<sup>20</sup>

### Materials and Methods

**Preparation of Aqueous Extract:** Stigmas were collected from KING INDO AGRO PRODUCTS PVT.LTD, from Srinagar Kashmir, dried in shadow, and subsequently grounded. The plant was authenticated for their correct botanical identity by the chief botanist. For the preparation of the aqueous extract, In the maceration method, 3g of stigma was macerated in 400ml of distil water (80%, v/v) for 3 days. The mixture will be subsequently filtered and concentrated at 35°C. The extract was preserved in deep freezer in air tight container.

**Animals:** Swiss albino mice (20-25g) of either sex were procured from the central animal house of the Institute. They were housed in standard polypropylene cages and were kept under controlled room temperature at 25±2°C in a 12h light /dark cycle. Animals were given dry pellets and water ad libitum. The animals were accustomed during the day time to new environment for atleast 2 days prior to the experiment. Institutional Animal Ethics Committee approval was taken prior to the start of study. The ethical guidelines for the investigation of animals used in experiments were followed in all tests.

**To evaluate antidepressant activity of crocus sativus linn. two animal models were used.**

#### 1. Forced swimming test

#### 2. Tail suspension test

#### Forced swimming test (FST)<sup>20-21</sup>

Albino mice of either sex weighing from 25 to 30g were used in this study. These were acclimatized to their environment for one week prior to experimentation. The animals were randomly distributed into four different groups. Each experimental group consisted of a 6 animals. Each group is caged separately after recording its body weight and the animals are marked with marker for identification.

**Drugs** — Crocus sativus Linn (15, 30 mg/kg – i.p)

Fluoxetine – (20mg/kg – i.p)

Saline – (0.5ml – i.p)

**Equipment** – Glass chamber, stop watch

### Principle

When an animal is forced to swim, it tries to escape by making rigorous movements. When it cannot escape from the glass chamber, the animal surrenders to the situation and floats making very little or no movements (immobility) in glass chamber. Thus forced swimming – induced immobility is considered as helplessness or a state of depression in animals. Antidepressant drugs reverse or reduce immobility period.

### Procedure

Normal saline, fluoxetine in the dose of 20 mg/kg and *Crocus sativus* Linn was administered at two different doses (15 and 30 mg/kg, IP) to mice of either sex. forced swimming test was conducted after 1hr of drug administration. Mice were allowed individually to swim inside the glass chamber (25-12-25cm) containing water up to 15cm height for 360 sec (6 min) at room temperature (25<sup>0</sup>-27<sup>0</sup>c). After initial struggle to escape for 120 sec (2 min), the animal became immobile or had little movements to keep floating in the water. Total immobility period is measured during the next 240 sec (4 min) in all groups. Later immobility period is compared in all groups.

### Tail suspension test <sup>21-22</sup>

Albino mice of either sex weighing from 25 to 30g used in this study. These were acclimatized to their environment for one week prior to experimentation. The animals were randomly distributed into four different groups. Each experimental group consisted of a 6 animals. Each group was caged separately after recording its body weight, and the animals are marked with marker for identification.

### Drugs –

*Crocus sativus* Linn – (15, 30 mg/kg i.p )

Fluoxetine – (20mg/kg i.p )

Saline – (0.5ml i.p )

**Equipment** - Adhesive tape, stop watch

**Principle**-When animal is suspended upside down leads to a characteristic behavior of immobility after initial movement struggle. This behavior reflects a state of depression which can reduce by antidepressant drugs.

### Procedure

Normal saline, fluoxetine in the dose of 20 mg/kg and *Crocus sativus* Linn were administered at two different doses (15 and 30 mg/kg, I.P) to mice of either sex. Tail suspension test was conducted after 1hr of drug administration. Mice were suspended on the edge of a table 50cm above the floor by using adhesive tape placed approximately 1cm from the tip of the tail. Immobility time recorded during 360 sec (6 min) period. Animal considered to be immobile when it did not show any movement of body and hanged passively. After initial struggle to escape for 120 sec (2 min), the animal became immobile. Total duration of immobility time recorded during the next 240 sec (6 min) in all groups. Later we compared immobile period of all groups.

### Statistical Analysis

The data was collected in case record forms. Then they are entered into excel spreadsheet 2007. Statistical analysis was performed using Microsoft Excel-2007 and Sigma Graph pad prism version-4 USA. Data was described as Mean  $\pm$  Standard deviation, and Percentages. Percentage change as compared to control was analyzed. ANOVA followed by Tukeys multiple comparison tests was used for analysis of data between the four. For all inferential statistical tests a two tailed P value of 0.05 considered significant.

**Results**

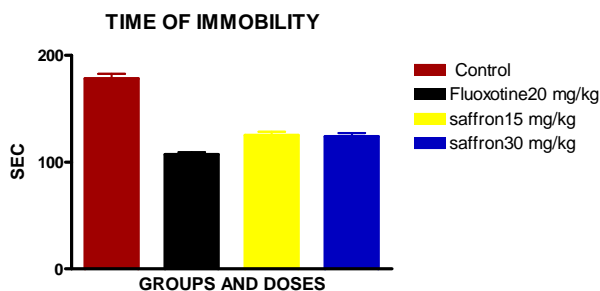
**Table ‘3’:** Shows the effect of saffron on Forced Swimming Test (FST) in mice (n = 6).

S.NO	Group & Dose (mg/kg i.p)	Immobile Period in sec Mean(SD)
1.	Group I : Control (NS)	178(4.68)
2.	GroupII:StandardFluoxetine20 mg/kg	107(2.34)***
3.	Group III : saffron15 mg/kg	125(3.60)**
4.	Group IV : saffron30 mg/kg	124(3.31)**

\*p<0.01\*\*, p<0.001 compared to control group One way ANOVA followed by Newman-Keuls comparison test

The immobility period in the control (group I) was 178(4.68) sec. whereas saffron in the doses of 15 mg/kg (groupIII), and saffron 30 mg/kg (groupIV) .The mean immobility period is 125(3.60) sec and 124(3.31)sec respectively. While fluoxetine 20 mg/kg ( groupII) the mean immobility period is 107(2.34)sec.Saffron with 15 mg/kg and 30 mg/kg significantly (\*\* - p<0.01) decrease the immobility period compared to that of control group.

**Fig‘3’:** Shows the effect of saffron on Forced Swimming Test (FST) in mice. (As per table 3)



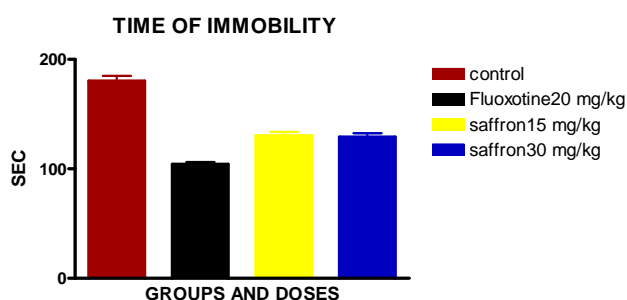
**Table ‘4’:** Shows the effect of saffron on Tail Suspension Test (TST) in mice. (n=6)

S.NO	Group & Dose (mg/kg i.p)	Immobile Period in sec Mean(SD)
1.	Group I : Control (NS)	180(4.88)
2.	GroupII:StandardFluoxetine20 mg/kg	104(2.09)***
3.	Group III : saffron15 mg/kg	130(3.69)**
4.	Group IV : saffron30 mg/kg	129(3.62)**

\*p<0.01\*\*, p<0.001 compared to control group One way ANOVA followed by Newman-Keuls comparison test

The immobility period in the control (group I) was 180(4.88) sec. whereas saffron in the doses of 15 mg/kg (groupIII), and saffron 30 mg/kg(groupIV). The mean immobility period was 130(3.69) sec and 129(3.62) sec respectively. While fluoxetine 20 mg/kg( groupII) mean immobility period was 104(2.09) sec. Saffron 15 mg/kg and 30 mg/kg significantly (\*\* p<0.01) decrease the immobility period compared to that of control group.

**Fig ‘4’:** Shows the effect of saffron on Tail Suspension Test (TST) in mice. (as per table 4)



## Discussion

The present study was aimed at evaluating the anti depressant properties of saffron in comparison with standard drugs using animal models.

Saffron is a perennial stem less herb, indigenous ingredients of ayurvedic medicine. It is mainly used for its memory enhancing property, as anticonvulsant, anti anxiety, anti depressant and for treatment of insomnia.

In the present study saffron was used in a dose of 15 & 30 mg/kg for antidepressant activity. In these doses saffron decreased the immobility period of mice as compared to control in a dose depended manner

FST & TST are the best suitable tests for evaluating anti-depressant properties of drugs, because it is the best-validated preclinical tests that predict drugs effective against depressant.

In our study, saffron showed significant anti depressant activity with 15 and 30 mg/kg compared to control group but has less activity when compared to that of standard drug fluoxetine.

### Forced swimming test (FST) in mice

Porsolt's Forced Swimming Test (Porsolt et al., 1977) is the animal model used in mice to check antidepressant properties. In this model immobility period was considered as a state of depression in mice. Porsolt et al proposed this behavioral model for the screening of new antidepressant compounds, concluded that the immobility time observed in the test reflected a state of lowered mood or hopelessness in animals, thus, this animal model is the most widely used tool for preclinical screening of putative antidepressant agents (Cryan et al., 2002, 2005).

Studies have reported that saffron have some antidepressant property, therefore the present study also includes the evaluation of antidepressant activity of saffron. We used Forced swimming test (FST) in mice for the evaluation of antidepressant property. In this model decreases the immobility period after giving the drug indicates that drug is having antidepressant activity. Present study showed that saffron has significant ( $P < 0.001$ ) anti depressant activity in comparison with control in a dose dependent manner. Saffron in a dose of 15mg and 30mg/kg treated groups significantly decreases the immobility period as compared to control.

Our study was supported by moshiri E et al<sup>21</sup>. They showed that saffron demonstrated a significant anti depressant activity in mice the immobility period is decreased. So saffron having a component of crocin may act on dopamine, serotonin and noradrenaline reuptake inhibitor<sup>22</sup>.

Akhozadeh basti A et al<sup>22</sup>, showed antidepressant activity of saffron in rats using forced swimming test. They proposed that increase in serotonin levels and inhibition of reuptake of serotonin levels in brain might be the responsible for antidepressant activity<sup>22</sup>.

Akhozadeh basti. A et al<sup>22</sup>, done research on out patients. A pilot double – blind randomized trial on depressant patients, treatment with saffron along with the fluoxetine twice daily. One group of patients (n=25) received fluoxetine at dose of 45 mg/kg and second group of patients (n=25) received fluoxetine along with saffron with a dose of 30 mg/kg. After the period of 30 days group I patients received same dose where as group II patients reduced the dose of fluoxetine to 30 mg/kg. They showed that the dose of fluoxetine required to produce anti depressant effect is decreased<sup>23-24</sup>.

### Tail suspension test (TST) in mice

The total duration of immobility induced by tail suspension was measured according to the methods described by Steru et al (1985).

Studies have reported that saffron have some antidepressant property, therefore the present study also includes the evaluation of antidepressant activity of saffron. We used tail suspension test (TST) in mice for the evaluation of antidepressant property. In this model decreases the immobility period after giving the drug indicates that drug is having antidepressant activity. Present study showed that saffron has significant ( $P < 0.001$ ) anti depressant activity in comparison with control in a dose dependent manner. Saffron in a dose of 15mg and 30mg/kg treated groups significantly decreases the immobility period as compared to control.

Our study was supported by Akhondzadeh et al (2004). They showed that saffron demonstrated a significant anti depressant activity in mice the immobility period is decreased in TST. The active principle



involved in showing antidepressant activity is crocine. Increase in mono amine neurotransmitters is the probable reason for anti depressant activity. But it needs further experimental evidences<sup>23-24</sup>.

Saffron showed anti depressant activity probably by increase in monoamine neuro transmitters in brain. The present findings suggest that the bioactive factors present in extracts of CA has antidepressant activity thus may be helpful in the treatment of depression.

The anti-depressant activity of saffron is well proved in the present study and also in the studies mentioned above. The acute toxicity studies did not revealed any toxic manifestations even at higher doses (4g/kg body wt). So, saffron being non-toxic and already in use for multi-disease cure in ayurvedic practice, the same can be used along with the standard anti-depressant drugs, thereby reducing the dose of standard anti-depressant drugs and limiting their adverse and toxic effects.

It still needs further evaluation in isolating the active components present in the plant and testing those compounds for stability, pharmacokinetics and pharmacodynamics, efficacy and other actions including adverse drug reactions.

### Conclusion:

Thus, the preliminary data of the present investigation provide some evidence for the effectiveness of saffron in the treatment of depression claimed in the Ayurvedic system of medicine.

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