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The Effects of S-adenosyl Methionine and Safflower Extract on the Withdrawal Symptoms and Relapse Following Antidepressants Discontinuation in Rats

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INTRODUCTION

Depression is a disease with a high prevalence affecting 10% of the Saudi population and 300 million people worldwide [1-2]. The class of first-line medications for treating this disease is selective serotonin reuptake inhibitors (SSRIs) including paroxetine and fluoxetine among many others. SSRIs require 2-4 weeks of continuous treatment to produce therapeutic effect which prolongs the period of depression, and their abrupt stoppage may cause withdrawal symptoms [3-5]. Herbal medicine is now becoming a form of healthcare with increasing popularity especially considering how the use of plants for healing reasons predates human history and forms the origin of much of modern medicine [6-7]. Among those means of complementary and herbal medicine is *Carthamus tinctorius* L., known also as safflower. Safflower is used in traditional middle eastern medicine to treat a variety of conditions including mental health related uses [8].

Another naturally occurring compound usually seen in the treatment of depression with its first description of antidepressant activity dating back to the 1970s is S-adenosylmethionine (SAMe). Deficiencies in B12 and folate could result in low SAMe concentrations in cerebrospinal fluid (CSF) which have been linked to depressive disorders, Parkinson's disease, and Alzheimer's dementia [9-10].

OBJECTIVES

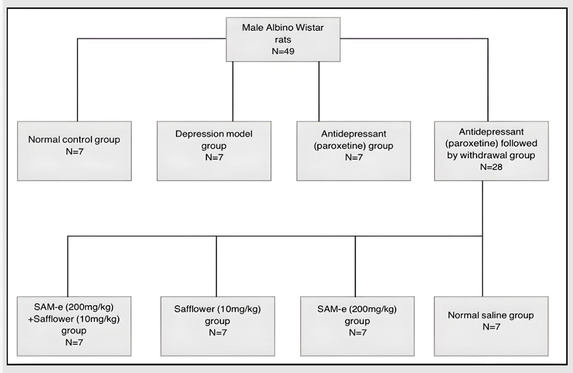
To examine the effectiveness of S-adenosyl methionine (SAMe) and safflower extract alone and in combination in the treatment of SSRIs discontinuation syndrome caused by the abrupt stoppage of the use of SSRIs.

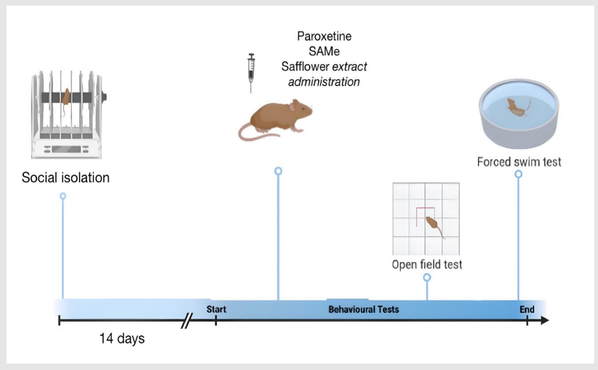
METHODS

1-Treatment preparation

SAMe was purchased in a tablets form. Tablets were powdered in a mortar and dissolved in distilled water. Safflower petals were washed and soaked in a distilled water and heated. The supernatant were collected and lyophilized in a freeze dryer, then the dried safflower water extract powder was dissolved in a distilled water.

2-Study design and behavioral tests





3-Tissue preparation

After performing behavioral tests, animals were sacrificed by decapitation. The brain was rapidly removed, the hippocampus and other brain sections were separated and frozen to be used for determination of oxidative stress markers.

4-Assay of lipid peroxidation

The process of lipid peroxidation results in the formation of malondialdehyde (MDA) as a product in the sequence of oxidation. The levels of MDA were determined using thiobarbituric acid (TBA) reagent. The absorbance of the produced pink color was measured at 535 nm against reagent blank to determine the degree of oxidative stress [15].

5-Histological examination

After fixation of hippocampus tissue, samples was dehydrated, embedded in paraffin, and processed. The fixations were later used for observational analysis of the damage and differences between the groups.

6-Statistical Analysis

The data were analyzed by GraphPad Prism 9.0 using one-way ANOVA followed by Tukey-Kramer test. All data were expressed as mean ± SEM. $P<0.05$ was considered statistically significant.

RESULTS

1- Histological examination:

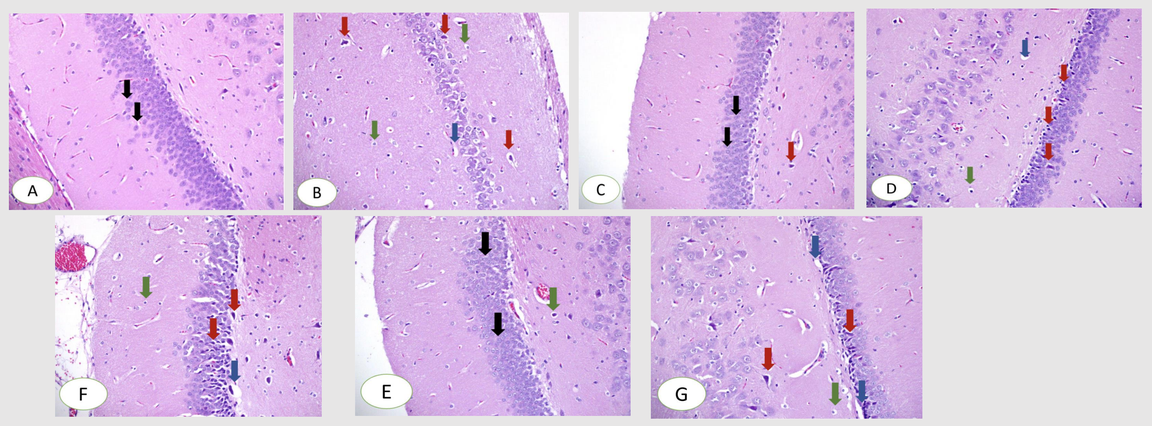


Figure 1 H&E-stained sections of the rats' hippocampus: (A) Section from normal control shows normal histological architecture, compact, thick, and well-arranged cells layer (**black** arrows). (B) Section from social isolation (SI)-induced depression group shows decreased thickness of the cells layer with hyperchromatic degenerated neurons (red arrows), apoptotic (red arrows) and inflammatory neurons (green arrows), with edematous neurons (blue arrows). (C) Section from paroxetine treated group shows more compact and thicker cells layer with less abnormal cells. (D) Section from withdrawal group shows an increase in apoptotic neurons, shrunken and hyperchromatic neurons (red arrows). (E) Section from withdrawal group treated with safflower shows more compact and thicker cells layer with less abnormal cells than withdrawal group. (F) & (G) Sections from withdrawal groups treated with SAMe & combination show more degenerated, apoptotic (red arrows) and inflammatory neurons (green arrows), with edematous neurons (blue arrows).

2- Behavioral tests

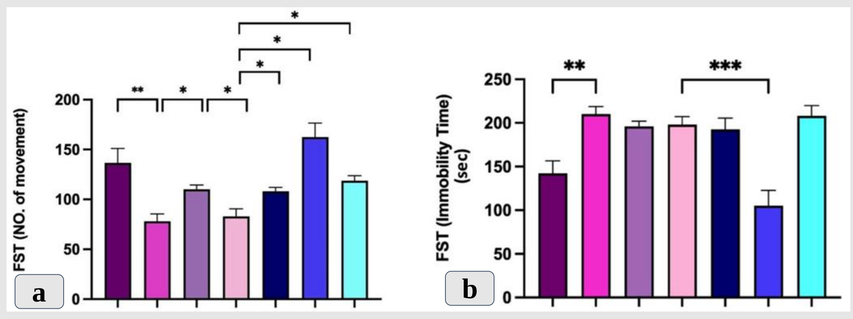


Figure 2: Effect of safflower, SAMe, and their combination on the number of movements (a) and immobility time (b) in Forced Swimming Test (FST) following paroxetine (PTX) withdrawal. Values are expressed as mean ±SEM. No. of movements were significantly reduced in both depression model and PTX withdrawal groups compared to the control and PTX groups, respectively. Safflower, SAMe, and their combination significantly ameliorates these elevated levels compared to PTX withdrawal group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

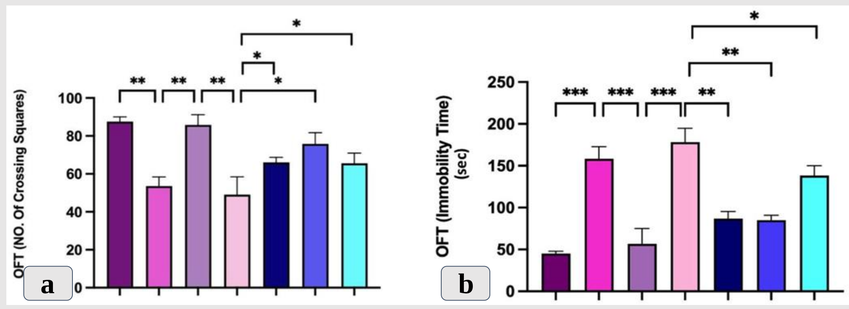


Figure 3: Effect of safflower, SAMe, and their combination on the number of crossed squares (a) and immobility time (b) in Open Field Test (OFT) following paroxetine (PTX) withdrawal. Values are expressed as mean ±SEM. No. of crossed squares were significantly reduced, while immobility time was significantly increased in both depression model and PTX withdrawal groups compared to the control and PTX groups, respectively. Safflower, SAMe, and their combination significantly ameliorates these deviations compared to PTX withdrawal group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

3- Lipid peroxidation

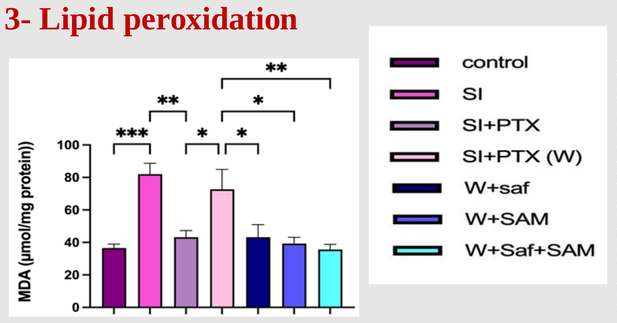


Figure 4: Effect of safflower, SAMe, and their combination on hippocampus levels of malondialdehyde (MDA; the marker of lipid peroxidation) following paroxetine (PTX) withdrawal. Values are expressed as mean ±SEM. MDA was significantly higher in both depression model and PTX withdrawal groups compared to the control and PTX groups, respectively. Safflower, SAMe, and their combination significantly ameliorates these elevated levels compared to PTX withdrawal group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

DISCUSSION &CONCLUSIONS

Complementary medicine has been gaining increasing popularity in the past decades due to the belief of it producing noticeably fewer side effects compared to conventional medicine. Our results showed possible benefits of adding safflower and SAMe supplementation to the treatment plan and could potentially ameliorate withdrawal and relapse associated with SSRIs use. However, further studies with larger number of subjects and longer duration of treatment are needed.

REFERENCES

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