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Basic Study

Antidepressant-like potential of silymarin and silymarin-sertraline combination in mice: Highlighting effects on behaviour, oxidative stress, and neuroinflammation

Onaolapo AY *et al*. Antidepressant-like potential of silymarin/silymarin-sertraline combination

Abstract

BACKGROUND

Currently, there is increasing advocacy for the use of diet, dietary supplements, and herbal remedies in depression management.

AIM

To determine the antidepressant effects of standardized extract silymarin either as a sole agent or as an adjunct in depression therapy.

METHODS

Adult mice were assigned into three main groups based on the neurobehavioural models; and each main group had ten treatment groups of 10 mice each. Treatment groups were: Vehicle control, sertraline {oral SERT} group, two groups fed Silymarin {SILY}-supplemented diet (140 and 280 mg/kg of feed), Dexamethasone (*i.p.* DEX) group, DEX/SERT group, two groups {DEX/SILY} (SILY at 140 and 280 mg/kg of feed respectively), and another two groups {SERT/DEX/SILY} (SILY at 140 and 280 mg/kg of feed respectively plus *i.p.* DEX plus SERT). Duration of the study was 7 wk, and treatments were administered daily.

RESULTS

Silymarin (alone) increased body weight, open field locomotor activity, rearing, and grooming; it also enhanced spatial working memory while decreasing anxiety-related behaviours and behavioural despair. Silymarin also improved antioxidant status, while decreasing lipid peroxidation, acetylcholinesterase activity, and inflammatory markers. Neuronal integrity of the cerebral cortex and hippocampus were preserved. Overall, when administered alone or with sertraline, silymarin counteracted dexamethasone-induced behavioural and biochemical changes while preserving neuromorphological integrity.

CONCLUSION

In conclusion, silymarin is beneficial in mitigating dexamethasone-induced central nervous system and other related changes in mice.

Key Words: Behavioural despair; Depression; Mental Health; Neurobehaviour; Neuromorphology

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Core Tip: Depression is a neuropsychiatric disorder that has in recent times become a leading cause of disability and a major contributor to global disease burden and suicide. In recent times there has been increasing advocacy for the use of dietary supplements and herbal remedies in depression management. While antidepressant effects of extracts of Silybum marianum seeds have been reported, there is a dearth of scientific information on the possible effect of its standardized extract silymarin either as a sole agent or as an adjunct in depression therapy. Hence this study.

INTRODUCTION

Depression is a neuropsychiatric disorder that has in recent times become a leading cause of disability and a major contributor to global disease burden and suicide[1]. It is characterised by the presence of anhedonia and/or evidence of alterations in mood including irritability, sadness, or emptiness[2-6]. In the last decade or more, the global prevalence of depression has continued to rise[1,7], with depression accounting for approximately 12% of hospital admissions, 50% of mental health consultations, and 4% of suicides[6,8,9]. In addition to a high socioeconomic burden and significant morbidity/mortality, depression has been ranked as the single largest contributor to global disability and suicide deaths[3,5,10-13]. Scientific evidence[14,15] of the critical role of serotonin in the pathogenesis of depression was instrumental to the development of some of the current antidepressant drugs (fluoxetine and setraline) that selectively inhibit the reuptake of serotonin at serotonin transporters, and thereby increase serotonin concentration within the synaptic cleft[15,16]. While significant strides have been made in developing newer drugs for the management of depression, the obvious advantages of more tolerable, less-toxic, and more- affordable treatment options continue to spur researchers to do more.

In recent times, the impact of diet, dietary supplements, and herbal remedies in the maintenance of mental health, as well as the aetiology, progression, and management of mental illness are becoming important areas of research[17-19]. Specifically, the search for modifiable factors in depression has led to the study of the possible associations between the development of depressive illness and dietary patterns. A number of studies have been successful in demonstrating the value of diet and/or dietary supplements including selenium, zinc, vitamins B, C, and K in the prevention, pathogenesis, or outcome of depression[20-25]. The antidepressant effects of extracts of parts of plants such as the *Silybum marianum* seed have also been reported[26].

Silymarin is a polyphenolic antioxidant complex which is derived from the fruit and seeds of the 'milk-thistle' plant known as *Silybum marianum*. While this ancient medicinal

plant has been used for centuries for hepatoprotection (or the management of hepatic disorders), the production of standardised fractions of the plant has allowed for a widespread research of its medicinal potential[27-29]. The antifibrotic, antioxidative, immunomodulatory, anti-inflammatory and antinociceptive properties of silymarin have been documented[30-33], and at pharmacological doses, it has been reported to be non-toxic[30,34]. A number of studies have also reported the neuroprotective effects of silymarin in different animal models[26-28,35-37]. While there have been suggestions of the possible antidepressant effects of *Silybum marianum* extracts, there is a dearth of scientific information on the possible antidepressant effects of standardised formulations of silymarin used alone or as an adjunct. Therefore, this study evaluated the effects of dietary supplementation with silymarin alone, or in combination with sertraline on body weight, food intake, neurobehaviour, oxidative stress parameters, inflammatory markers and acetylcholinesterase levels in a dexamethasone model of depression in mice.

MATERIALS AND METHODS

Drugs and chemicals

Silymarin (Silybon-70® Micronova Pharmaceutical industries Ltd, Lagos Nigeria), Sertraline capsules (Zoloft® 50 mg Sertraline as sertraline hydrochloride, Pfizer Inc. Lagos, Nigeria), and Dexamethasone phosphate injection (4 mg/mL, Vixa Pharmaceutical Co. Ltd, Lagos, Nigeria). Assay kits for lipid peroxidation (malondialdehyde assay kit), glutathione peroxidase, reduced glutathione, superoxide dismutase and catalase (Biovision Inc. Milpitas, CA, United States) were obtained and refrigerated until used. All other chemicals were analytical grade.

Animals

Adult male Swiss mice (Empire Breeders, Osogbo, Osun State, Nigeria) weighing between 18-25 g each were used for this study. Mice were housed singly in cages located in temperature-controlled quarters (22-25 degrees Celsius) with lights on at 7.00 a.m. daily. Animal diet was commercially sourced (TOP® feeds) standard rodent chow (29%

protein, 13% fat, and 58% carbohydrate). Mice had access to food and water *ad libitum,* except during the behavioural tests. All procedures were conducted in accordance with the approved protocols of the Ladoke Akintola University of Technology and within the provisions for animal care and use prescribed in the scientific procedures on living animals European Council Directive (EU2010/63).

Feed

Animals were fed commercially available rodent diet [(standard diet (SD)] sourced from Top Feeds Ltd, Ibadan Nigeria). Silymarin was incorporated into standard rodent diet at 140 and 280 (mg/kg of feed respectively.

Experimental method

Adult male mice were randomly assigned into three main groups (1-3) based on the neurobehavioural models. Group 1 animals were exposed to the elevated plus maze and tail-suspension paradigm, group 2 were exposed to the Y-maze and forced-swim paradigm, while mice in group 3 were exposed to the Open-field arena and radial arm maze. Animals in the main groups were subsequently assigned into ten treatment groups of 10 mice each. Treatment groups are: Vehicle control (fed standard diet (SD), and given intraperitoneal (*ip*) saline plus oral saline), sertraline (SERT) group (fed SD and given *ip* saline plus oral SERT), two groups fed Silymarin (SILY)-supplemented diet (at 140 and 280 mg/kg of feed respectively), and given *ip* saline plus oral saline, Dexamethasone (DEX) group (fed SD, and given *ip* DEX plus oral saline), DEX/SERT group (fed SD, and given *ip* DEX plus oral SERT), two groups (DEX/SILY) fed SILY-supplemented diet (at 140 and 280 mg/kg of feed respectively) and given *ip* DEX plus oral saline, and another two groups (SERT/DEX/SILY) fed SILY-supplemented diet (at 140 and 280 mg/kg of feed respectively) and given *ip* DEX plus oral SERT. SERT was administered at 5 mg/kg[38], while DEX was administered at 4 mg/kg[39-41]. Total duration of the study was 7 wk, and all treatments were administered daily. Mice in all groups were weighed weekly (7.00 am, before feeding) and food intake was measured as previously

described[42-44] using a weighing balance (Mettler Toledo Type BD6000, Greifensee, Switzerland). Food changes occurred daily at 8.00 am. Food-hoppers that contained pre-weighed quantities of food were provided daily to the mice; a thin plastic sheet was placed beneath the cages to catch food spillage. Total food consumption was then measured as the difference between the pre-weighed standard chow and the weight of chow in hopper daily. Crumbs in the plastic sheets were weighed and accounted for in the measurement of total food consumed during the 24-h period[42]. At the end of the experimental period, animals were exposed to the respective paradigms. Twenty-four hours after the last behavioural test, animals in the open field and radial arm maze group were euthanised by cervical dislocation. Blood was taken for assessment of oxidative stress parameters and inflammatory markers (Tumor necrosis factor (TNF)–α and interleukin-10). The hippocampus and cerebral cortex were excised, and either homogenised for the assessment of inflammatory markers, antioxidant status and acetylcholinesterase activity or processed for general histological examination.

Assessment of body weight and food intake

Body weight of animals in all groups were measured weekly using electronic weighing balance (Mettler Toledo Type BD6000, Switzerland) while the amount of food consumed was measured daily. Relative change in body weight or food intake was calculated for each animal using the equation below following which results for all animals where computed to find the statistical mean.

Behavioural tests

Mice were transported in their home cages to the behavioural testing laboratory and allowed to acclimatise (10 min) before exposure to paradigms. Each animal was placed in the apparatus following which behaviours were recorded. On completion of the tests, each mouse was removed from the maze and returned to the respective home cages. The interior surfaces of the mazes were then cleaned with 70% ethanol and wiped dry to

remove traces of conspecific odour. Behavioural parameters were then scored manually by independent observers who were blind to the groupings.

Anxiety model: elevated plus maze

The elevated plus-maze (EPM) is a plus-shaped apparatus with four arms placed at right angles to each other. The EPM used in the study and the procedure are as previously described[42,45,46].

Open field

Ten minutes of locomotion, rearing, and grooming were observed in the open field, and scored as previously described[47,48].

Tail suspension test

The tail suspension test (a measure of behavioural despair) was carried out according to the method described by Steru *et al*[49], Młyniec and Nowak[50], and Onaolapo *et al*[51]. Mice were securely fastened (using a medical adhesive tape) by the tip of their tail to a flat platform and suspended for 6 minutes approximately 30 cm below the platform. The total time of immobility was measured during the 6-minute period of the testing session. Immobility, which was defined as the period the animal hung passively without limb movement, was scored[40].

Forced swim test

The forced swim test is a measure of behavioural despair in mice. The test was carried out according to the method described by Porsolt *et al*[52], Kroczka *et al*[53], and Onaolapo *et al*[51]. Mice were dropped individually into glass cylinders which had a height of 25 cm, a diameter of 10 cm, were filled with 10 cm of water (water level was marked to ensure uniformity), and maintained at a temperature of 23-25°C. The dimensions of the glass cylinder ensured that the mouse was unable to touch the bottom of the cylinders either with their feet or their tails, during the test. The height also prevented mice from escaping

from the cylinder. Animals were then returned (they were dried with paper towels to prevent hypothermia) to their home cages after 15 min in water. They were reintroduced into the cylinders 24 h later. Mice were exposed to the forced swim paradigm for 6 minutes. The total duration of immobility was measured during the last 4 min of the forced swim test. The mouse was considered immobile when it had remained floating passively in the water.

Memory tests

The Y- and the radial arm maze were used to assess and score spatial working memory as previously described[54,55]. The Y-maze has three arms (41 cm long and 15 cm high, 5 cm wide at an angle of 120°), while the radial arm maze apparatus has 8 arms measuring 33 cm long spaced equidistantly from each other.

Blood collection

Blood collected from each mouse *via* cardiac puncture was used for the estimation of lipid peroxidation, reduced glutathione, superoxide dismutase, and glutathione peroxidase. Samples were collected into unheparinised bottles and processed as previously described[56,57].

Brain Homogenization

Within 24 h of the completion of the behavioural tests, animals in all groups were euthanised by cervical dislocation post-anaesthesia with diethyl ether. Homogenates of the hippocampus and cerebral cortex were prepared in ice-cold phosphate buffered saline, using a Teflon-glass homogeniser. The homogenate was centrifuged at 5000 rev/min, 4°C, for 15 minutes. The supernatant obtained was then used for estimation of lipid peroxidation levels and antioxidant status.

Biochemical assays

Estimation of MDA content (Lipid peroxidation): Lipid peroxidation level was measured as MDA content as previously described[58]. Change in colour was measured at 532 nm. The malondialdehyde kit used had a detection range of 7.813-500 ng/mL and a sensitivity < 4.688 ng/mL. The Intra-Assay: Coefficient of variability was < 7%, and the Inter-Assay coefficient of variability was < 9%.

Antioxidant activity

Superoxide dismutase activity was determined using commercially available assay kit. Colour changes were measured at an absorbance of 560 nm as described previously[29,58]. The activity of SOD was expressed as units/mL.

Level of reduced glutathione (GSH) was determined following the instructions of the manufacturer. A yellow-coloured complex which can be measured at an absorbance of 412 nm is formed by reduced glutathione form when it reacts with Ellmans reagent (DTNB) Levels of GSH was expressed as nmol/mL.

Glutathione peroxidase (GPx) is an enzyme that catalyses the reduction of hydroperoxides, such as hydrogen peroxide. Glutathione peroxidase activity was determined as previously described[29]. The activity of GPX was expressed in units/mL.

Tumour necrosis factor-α and Interleukin (IL) -10

Tumour necrosis factor-α and interleukin (IL)-10 were measured using enzyme-linked immunosorbent assay (ELISA) techniques with commercially available kits (Enzo Life Sciences Inc. NY, United States) designed to measure the 'total' (bound and unbound) amount of the respective cytokines.

Acetylcholinesterase activity

Brain acetylcholinesterase activity (Biovision, United States) was determined using commercially available assay kits following the instructions of the manufacturer.

Tissue histology

Sections of the cerebral cortex and hippocampus were fixed in 10 % formol saline for 24 h, processed for paraffin wax embedding, dehydration, clearing, infiltration sectioned and then mounted following which they were processed for general histological staining using haematoxylin and eosin as previously described[40].

Statistical analysis

Data were analysed using Chris Rorden's ANOVA for windows, version 0.98. Data analysis was by Two-way analysis of variance (ANOVA), post-hoc test (Tukey HSD) was used for within and between group comparisons. Results were expressed as mean ± SEM, $P < 0.05$ was taken as the accepted level of significant difference from control or standards.

RESULTS

Effect of silymarin on body weight

Figure 1 shows the effect of silymarin (SILY) on the change in body weight. There was a significant [$F(9, 90) = 48.1$, $P < 0.001$] decrease in body weight in the groups administered sertraline (SERT), dexamethasone (DEX), dexamethasone with sertraline (DEX/SERT) and dexamethasone with silymarin (DEX/SILY) at 140 mg/kg of feed, while an increase in body weight was observed in groups administered SILY at 140 and 280 mg/kg, DEX/SILY at 280 mg/kg of feed and those administered *ip* dexamethasone, oral sertraline, and diet supplemented with silymarin (DEX/SERT/SILY) at 140 and 280 mg/kg of feed respectively compared to control. Compared to SERT alone, there was a significant increase in body weight with SILY at 280 mg/kg of feed. While compared to DEX control, body weight increased significantly with DEX/SILY at 280 mg/kg and DEX/SERT/SILY at 140 and 280 mg/kg of feed. Compared with the group administered DEX/SERT, body weight increased significantly with DEX/SILY at 280 mg/kg, and DEX/SERT/SILY at 140 and 280 mg/kg. Overall, the results showed that silymarin administered alone increased body weight compared to control or sertraline. Silymarin when administered alone (at 280 mg/kg) reversed dexamethasone induced changes in

body weight. When co-administered with sertraline, silymarin at both concentrations reversed the changes in body weight induced by dexamethasone.

Effect of silymarin on food intake

Figure 2 shows the effect of silymarin (SILY) on the change in food intake. There was a significant [F (9, 90) = 513, $P < 0.001$] decrease in food intake with DEX, DEX/SERT and DEX/SILY at 140 and 280 mg/kg of feed, while an increase in food intake was observed with DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively compared to control. Compared to SERT alone, there was no significant difference in food intake in any of the SILY alone groups. While compared to DEX control, food intake increased significantly with DEX/SERT/SILY at 140 and 280 mg/kg of feed. Compared with the group administered DEX/SERT, food intake increased significantly with DEX/SERT/SILY at 140 and 280 mg/kg. Overall, the results showed that silymarin administered alone did not significantly alter food intake compared to control, sertraline or dexamethasone; although, co-administration of silymarin with sertraline was associated with an increase in food intake compared to control, dexamethasone, or dexamethasone with sertraline.

Effect of silymarin on locomotor and rearing activity

Figure 3 shows the effect of silymarin (SILY) on locomotor activity (upper panel) and rearing (lower panel). There was a significant [F (9, 90) = 26.5, $P < 0.001$] increase in locomotor activity with SILY at 140 mg/kg, DEX/SILY at 140 and 280 mg/kg of feed respectively, and a decrease in locomotor activity with DEX compared to control. Compared to SERT alone, there was a significant increase in locomotor activity with SILY at 140 mg/kg of feed. While compared to DEX control, locomotor activity increased significantly with DEX/SERT, DEX/SILY at 140 and 280 mg/kg, and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, locomotor activity increased significantly with DEX/SILY at 280 mg/kg. Overall, the results showed that silymarin (administered alone) concentration-dependently increased locomotor activity compared to control and sertraline. Silymarin

alone or co-administered with sertraline also mitigated the decrease in locomotor activity induced by dexamethasone.

Rearing activity decreased significantly [F (9, 90) = 6.20, $P < 0.001$] with DEX and increased with DEX/SILY at 140 and 280 mg/kg of feed respectively, compared to control. Compared to SERT alone, there was a significant increase in rearing activity with SILY at 140 mg/kg of feed. While compared to DEX control, rearing activity increased significantly with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared to DEX/SERT, the rearing activity increased significantly with DEX/SILY at 280 mg/kg. Overall, results showed that silymarin alone or co-administered with sertraline also mitigated the decrease in rearing activity induced by dexamethasone.

Effect of silymarin on grooming behaviour

Figure 4 shows the effect of silymarin (SILY) on self-grooming behaviour. There was a significant [F (9, 90) = 5.24, $P < 0.001$] increase in self-grooming with SILY, DEX/SILY, and DEX/SERT/SILY at 140 mg/kg of feed respectively, while a decrease in self-grooming was observed with DEX and DEX/SERT compared to control. Compared to SERT alone, there was a significant increase in self-grooming with SILY at 140 mg/kg of feed. While compared to DEX control, self-grooming behaviour increased significantly with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, self-grooming increased significantly with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Overall, the results showed that silymarin administered alone concentration-dependently increased self-grooming behaviour compared to control and sertraline. Silymarin alone or co-administered with sertraline also mitigated the decrease in self-grooming behaviour induced by dexamethasone.

Effect of silymarin on spatial working memory in the Y-and radial arm maze

Figure 5 shows the effect of SILY on radial arm (upper panel) and Y- (lower panel) maze spatial working memory tasks. There was a significant [$F(9, 90) = 9.20$, $P < 0.001$] increase in working memory with SILY at 140 and 280 mg/kg, DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively, while a decrease in memory was observed with DEX compared to control. Compared to SERT alone, there was a significant increase in working memory with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, working memory increased significantly with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 and 280 mg/kg of feed. Compared with the group administered DEX/SERT, working memory increased significantly with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg. Overall, the results showed that silymarin administered alone increased spatial working memory scores in the radial arm maze, compared to control and sertraline. Silymarin alone or co-administered with sertraline also counteracted the decrease in spatial working memory score induced by dexamethasone.

Y maze spatial working memory increased significantly [$F(9, 90) = 16.04$, $P < 0.001$] with SILY at 140 and 280 mg/kg, DEX/SILY(280 mg/kg) and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively and decreased with DEX compared to control. Compared to SERT alone, there was no significant difference in working memory in any of the groups fed SILY alone. While compared to DEX control, working memory increased significantly with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared to DEX/SERT, working memory increased significantly with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg. Overall, the results showed that silymarin administered alone improved spatial working memory scores in the Y-maze compared to controls. Silymarin alone or co-administered with sertraline also counteracted the decrease in spatial working memory induced by dexamethasone.

Effect of silymarin on anxiety-related behaviours

Figure 6 shows the effect of SILY on the time spent in the open (upper panel) and closed (lower panel) arms of the elevated plus maze. There was a significant [F (9, 90) = 15.11, $P < 0.001$] increase in open arm time with SERT, SILY at 140 and 280 mg/kg, DEX.SERT, DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively, while a decrease was observed with DEX compared to control. Compared to SERT alone, there was a significant increase in open arm time with SILY at 280 mg/kg of feed. While compared to DEX control, open arm time increased significantly with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 and 280 mg/kg, respectively. Compared with the group administered DEX/SERT, open arm time increased significantly with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg, respectively. Overall, the results showed that silymarin administered alone increased the time spent in the open arm of the EPM compared to controls. Silymarin alone or co-administered with sertraline also mitigated the decrease in open arm time induced by dexamethasone.

Time spent in the closed decreased significantly [F (9, 90) = 8.21, $P < 0.001$] with SERT, SILY at 140 and 280 mg/kg, DEX/SERT, DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively, and increased with DEX compared to control. Compared to SERT alone, there was no significant difference in closed arm time in any of the groups fed SILY alone. While compared to DEX control, closed arm time decreased significantly with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with DEX/SERT, the time spent in the closed arm decreased significantly with DEX/SERT/SILY at 280 mg/kg. Overall, the results showed that silymarin administered alone decreased time spent in the closed arm compared to control. Silymarin alone or co-administered with sertraline also decreased time spent in the closed arm compared to dexamethasone.

Effect of silymarin on behavioural despair

Figure 7 shows the effect of silymarin on immobility time in the tail suspension (upper panel) and forced swim (lower panel) tests. There was a significant [F (9, 90) = 26.9, $P <$ 0.001] decrease in immobility time with SILY at 140 and 280 mg/kg, DEX/SERT and

DEX/SERT/SILY at 140 and 280 mg/kg of feed while an increase was observed with SERT, DEX and DEX/SILY at 140 and 280 mg/kg of feed compared to control. Compared to SERT alone, there was a significant decrease in immobility time with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, the immobility time decreased significantly with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 and 280 mg/kg, respectively. Compared with the group administered DEX/SERT, the immobility time decreased significantly with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg, respectively. Overall, the results showed that silymarin administered alone decreased immobility time compared to control and sertraline. Silymarin alone or co-administered with sertraline also mitigated the increase in immobility time induced by dexamethasone.

Immobility time in the forced swim test decreased significantly [F (9, 90) = 24.0, $p < 0.001$] with SERT, SILY at 140 and 280 mg/kg, DEX/SERT, DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively, and increased with DEX, compared to control. Compared to SERT alone, there was a significant decrease in immobility time with SILY at 140 mg/kg of feed. While compared to DEX control, the immobility time decreased significantly with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 mg/kg, respectively. Compared to DEX/SERT, the immobility time decreased significantly with DEX/SILY at 280 mg/kg and with DEX/SERT/SILY at 140 and 280 mg/kg, respectively. Overall, the results showed that silymarin administered alone decreased immobility time compared to control and sertraline. Silymarin alone or co-administered with sertraline also mitigated the increase in immobility time induced by dexamethasone.

Effect of silymarin on serum lipid peroxidation, antioxidant status

Table 1 shows the effect of silymarin (SILY) on serum lipid peroxidation and antioxidant status. Superoxide dismutase [F (9, 90) = 13.11, $P < 0.001$], increased significantly with SILY (at 140 and 280 mg/kg) and DEX/SILY (at 280 mg/kg of feed), while a decrease was observed with DEX, DEX/SERT and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively compared to control. Compared to SERT alone, there was a significant

increase with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was an increase with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively and decrease with DEX/SERT. Compared to DEX/SERT, there was an increase in Superoxide dismutase activity with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Catalase [$F\ (9, 90) = 25.32$, $P < 0.001$], increased significantly with SILY (at 140 and 280 mg/kg) and DEX/SILY (at 280 mg/kg of feed), while a decrease was observed with DEX, DEX/SERT and DEX/SERT/SILY at 140 mg/kg of feed compared to control. Compared to SERT alone, there was a significant increase with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was an increase with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared to DEX/SERT, there was an increase in catalase activity with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively.

Reduced glutathione [$F\ (9, 90) = 9.23$, $P < 0.001$] increased significantly with SILY (at 140 and 280 mg/kg) DEX/SILY and DEX/SERT/SILY at 280 mg/kg of feed, while a decrease was observed with DEX, DEX/SERT at 140 mg/kg of feed compared to control. Compared to SERT alone, there was a significant increase with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was an increase with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared to DEX/SERT, there was an increase in reduced glutathione levels with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively.

Glutathione peroxidase activity [$F\ (9, 90) = 10.32$, $P < 0.001$] increased significantly with SILY (at 140 and 280 mg/kg) and decreased with DEX, and DEX/SERT compared to control. Compared to SERT alone, there was a significant increase with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was an increase with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared to DEX/SERT, there was an increase in glutathione peroxidase levels with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively.

Overall, the results showed that silymarin administered alone or co-administered with sertraline had a mixed response with regards to antioxidant status.

Lipid peroxidation measured as malondialdehyde (MDA) levels decreased significantly [F (9, 90) = 6.19, $P < 0.001$] with SILY (at 140 and 280 mg/kg), DEX/SILY (at 280 mg/kg) and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively, while an increase was observed with DEX, DEX/SERT and DEX/SILY at 140 mg/kg of feed compared to control. Compared to SERT alone, there was a significant decrease in MDA levels with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was a decrease with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, there was a decrease in MDA levels with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Overall, the results showed that silymarin administered alone or co-administered with sertraline decreased lipid peroxidation levels.

Effect of silymarin on brain levels of inflammatory markers, acetylcholinesterase activity, lipid peroxidation, and antioxidant status

Table 2 shows the effect of silymarin (SILY) on brain (hippocampus and cerebral cortex) levels of inflammatory markers (TNF-αIL-10), acetylcholinesterase activity, lipid peroxidation, and antioxidant status. Brain (hippocampus and cerebral cortex) levels of TNF-α [F (9, 90) = 65.12, $P < 0.001$] decreased significantly with SERT, SILY (at 140 and 280 mg/kg), DEX, DEX/SERT, DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively compared to control. Compared to SERT alone, there was a significant increase with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was an increase in brain (hippocampus and cerebral cortex) levels of TNF-α with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, there was an increase in brain levels of TNF-α with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Overall, the results showed that silymarin administered alone decreased TNF-α levels, and when given alone or co-administered with sertraline, it mitigated dexamethasone induced alterations in TNF-α levels.

Brain (hippocampus and cerebral cortex) levels of IL-10 [F (9, 90) = 22.36, $P < 0.001$] decreased significantly with SERT, DEX, DEX/SERT, DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively compared to control. Compared to SERT alone, there was a significant increase with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was an increase in brain levels of IL-10 with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, there was an increase in brain levels of IL-10 with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Overall, results showed that silymarin increased IL-10 Levels; alone or co-administered with sertraline, it mitigated dexamethasone induced alteration in IL-10 Levels.

Brain (hippocampus and cerebral cortex) acetylcholinesterase activity decreased significantly [F (9, 90) = 10.21, $P < 0.001$] with SERT, SILY (at 140 and 280 mg/kg), DEX/SILY (at 280 mg/kg) and DEX/SERT/SILY (at 140 and 280 mg/kg of feed), and increased acetylcholinesterase activity with DEX and DEX/SERT compared to control. Compared to SERT alone, there was a significant decrease in brain acetylcholinesterase activity with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, a significant decrease in brain acetylcholinesterase activity was observed with DEX/SERT, DEX/SILY, and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, there was a decrease in brain acetylcholinesterase activity with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Overall, results showed that silymarin decreased acetylcholinesterase activity; alone or co-administered with sertraline. it mitigated dexamethasone induced alteration in acetylcholinesterase activity.

Brain (hippocampus and cerebral cortex) MDA levels decreased significantly [F (9, 90) = 10.21, $P < 0.001$] with SILY (at 140 and 280 mg/kg), DEX/SILY and DEX/SERT/SILY (at 140 and 280 mg/kg of feed), and increased with DEX and DEX/SERT compared to control. Compared to SERT alone, there was a significant decrease with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was a decrease in brain MDA levels with DEX/SILY and DEX/SERT/SILY at 140 and

280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, there was a decrease in MDA levels with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Overall, results showed that silymarin decreased MDA levels; alone or co-administered with sertraline, it mitigated dexamethasone induced alteration in MDA levels.

Brain (hippocampus and cerebral cortex) levels reduced glutathione (GSH) [$F(9, 90) = 5.12$, $P < 0.001$] increased significantly with SILY (at 140 and 280 mg/kg), DEX/SILY (at 280 mg/kg) and DEX/SERT/SILY (at 140 and 280 mg/kg) of feed and decreased with DEX, DEX/SERT, DEX/SILY at 140 mg/kg of feed compared to control. Compared to SERT alone, there was a significant increase with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was an increase with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, there was an increase in GSH with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Glutathione peroxidase (GPX) activity [$F(9, 90) = 6.27$, $P < 0.001$] increased significantly with SILY at 140 and 280 mg/kg of feed and decreased with DEX, DEX/SERT, DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed respectively compared to control. Compared to SERT alone, there was a significant increase with SILY at 140 and 280 mg/kg of feed. While compared to DEX control, there was a decrease with DEX/SERT and an increase with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Compared with the group administered DEX/SERT, there was an increase in GPX with DEX/SILY and DEX/SERT/SILY at 140 and 280 mg/kg of feed, respectively. Overall, results showed that silymarin increased GPX and GSH activity; alone or co-administered with sertraline, it mitigated dexamethasone induced alterations in GPX and GSH activity.

Effect of silymarin on cerebral cortex and hippocampal morphology

Figure 8 shows representative photomicrographs of haematoxylin and eosin stained slides of the mouse cerebral cortex. Examination of the cerebral cortex slides of mice in the control group (VEH) revealed characteristic architecture of the mouse cerebral cortex

showing multipolar shaped pyramidal cells with rounded vesicular nuclei, granule cells visible as circular shaped neurons with large open-face nuclei, prominent nucleoli, and scanty cytoplasm and small round-vesicular shaped glial neurons interspersed within a pink-staining neuropil; features which are in keeping with normal cerebral cortex histology. Examination of the cerebral cortex slides of the groups sertraline (SERT), silymarin at 140 mg/kg (SILY 140) and at 280 mg/kg (SILY 140) revealed features that were in keeping with normal histology. In the group administered dexamethasone (DEX), there was evidence of normal pyramidal cells with deeply stained nuclei, interspersed between degenerating pyramidal cells with pale edges, shrunken and pale staining nuclei. There was also evidence of degenerating granule cells with pale staining pyknotic nuclei. These features are in keeping with neuronal injury.

Examination of slides from groups administered dexamethasone with sertraline (DEX+ SERT), dexamethasone with silymarin at 140 (DEX+ SILY 140) and dexamethasone with silymarin at 280 mg/kg (DEX+ SILY 280) revealed presence of normal looking cells, and few degenerating pyramidal/granule cells. The features are in keeping with varying degrees of protection against the development of dexamethasone-induced neuronal injury. In the groups administered dexamethasone with sertraline and silymarin at 140 (DEX+ SERT+SILY 140) and 280 mg/kg (DEX+ SERT+SILY 280), the features were in keeping with normal cerebral cortex histology.

Figure 9A-J shows representative photomicrographs of haematoxylin and eosin stained slides of the dentate gyrus of the mouse hippocampus. Examination of the dentate gyrus region of the hippocampus in the control group (VEH) revealed characteristic architecture of the mouse hippocampus with a few large multipolar pyramidal cells of the cornus ammonis 4 (CA4) region projecting into the concavity of the dentate gyrus. Also observed were well-compacted small granule cells with vesicular nuclei in the ascending and descending arms of the dentate gyrus. Also obvious are astrocytes and microglia, neuronal processes, and nerve cells scattered throughout the molecular layer, that is, lying between the compact zones of the cornus ammonis and dentate gyrus regions. All features are in keeping with normal hippocampal dentate gyrus histology.

Examination of the hippocampal dentate gyrus slides of groups fed sertraline (SERT), silymarin at 140 mg/kg (SILY 140) and at 280 mg/kg (SILY 280) revealed features that were also in keeping with normal histology. In the group administered dexamethasone (DEX), there are a few normal small pyramidal neurons interspersed between few degenerating pyramidal cells with pale edges, there is also a paucity of cells in the molecular layer and loss of compactness of the granule cells in the dentate gyrus. Also observed are a few degenerating granule cells with pale staining nuclei; the features are in keeping with some neuronal injury.

Examination of slides from groups administered dexamethasone with sertraline (DEX+ SERT), dexamethasone with silymarin at 140 (DEX+SILY 140) and dexamethasone with silymarin at 280 mg/kg (DEX+ SILY 280) revealed presence of normal looking cells, few degenerating granule cells features which are in keeping with varying degrees of protection against the development of dexamethasone-induced neuronal injury. In the groups administered dexamethasone with sertraline and silymarin at 140 (DEX+ SERT+SILY 140) and 280 mg/kg of feed (DEX+ SERT+SILY 280) the features were in keeping with normal dentate gyrus histology.

DISCUSSION

This study examined the antidepressant-like effects of silymarin and silymarin/sertraline combination in mice. This was with a view to ascertaining the role of silymarin either alone or as an adjunct to setraline in mitigating dexamethasone-induced behavioural and morphological changes in mice. Results showed that silymarin administered alone increased body weight without altering food intake, increased open field locomotor activity, rearing, and grooming; enhanced spatial working memory, and decreased both anxiety-related behaviours and behavioural despair (immobility time in the forced swim and tail suspension tests). This was accompanied by an improvement in antioxidant status; and a decrease in lipid peroxidation, acetylcholinesterase activity, and inflammatory markers. Also, when administered alone or co-administered with

sertraline, silymarin mitigated dexamethasone-induced behavioural, biochemical and morphological changes in relation to the cerebral cortex and hippocampus.

The impact of body weight and food intake on health, wellbeing, and disease has been reported severally[59,60]. In this study, administration of dexamethasone was associated with significant weight loss and decreased food intake. While depression is generally associated with excessive weight gain, which has been linked to bingeing on food, according to the *Diagnostic and Statistical Manual of Mental Disorders,* both weight gain and weight loss are symptoms of depression at all ages[2,61]. Similarly, the choice of dexamethasone as a model of depression is centred on its ability to cause dose-dependent weight changes[62,63]. At doses similar to those used in this study, dexamethasone had been associated with weight loss[63], corroborating the results of this study. The result of a study by Poggioli *et al*[64] revealed that chronic administration of dexamethasone was associated with decreased weight gain, which was attributed to its ability to accelerate fatty acid oxidation, and decrease brown adipose tissue thermogenesis and the activity of uncoupling protein-1 mRNA[64]. Weight loss could also be attributed to decreased feed intake which could be secondary to early satiety. The administration of sertraline to healthy mice caused a decreased in weight gain without impacting feed intake when compared to mice in the control group, while increased weight loss was observed in the group of animals administered sertraline with dexamethasone. While there is a dearth of scientific information on the impact of sertraline in healthy subjects, it is however, generally believed that selective serotonin re-uptake inhibitors like sertraline are associated with weight gain. The results of a few studies have linked weight gain mainly to long-term use of sertraline[65,66], however, some clinical studies have reported reduced weight gain or weight loss following acute use of sertraline in persons with depression[67]. The results of a preclinical study that examined the effect of sertraline on body weight parameters in monkeys administered sertraline over an 18 mo period using a placebo-controlled, longitudinal, randomized study design showed that while the body weight and body fat composition of the placebo group increased; a decrease in body weight and fat composition was observed in the sertraline treatment group[68]. In the groups of mice

fed silymarin alone, an increase in weight with no change in food intake was observed compared to mice in the control group. Also, in mice fed silymarin with dexamethasone; a reversal of dexamethasone-induced weight loss was observed. Information from the current literature reveals that the vast majority of studies evaluating the effects of silymarin on body weight have administered it in a background of disease or disorder[28,32,69-71]. The results of these studies have shown that administration of silymarin could be associated with either weight loss or weight gain[28,32,69-71] depending on the disease model used. This would suggest that silymarin effects on body weight are mainly modulatory or adaptogenic, having the ability to return the body back to baseline. The administration of silymarin with sertraline was also associated with a reversal of weight loss due to dexamethasone-induced depressive symptoms, suggesting that compared to sertraline, silymarin could be beneficial in modulating the effects of sertraline on body weight. However, the co-administration of sertraline with silymarin also in in a background of dexamethasone was associated with increased food intake compared to either silymarin or sertraline.

In this study, neurobehavioural tests revealed that administration of dexamethasone was associated with a decrease in horizontal locomotion, rearing, and grooming behaviour; consistent with the observations of Falade *et al*[40]; the chronic unpredictable stress model was also associated with similar neurobehavioural changes[55]. The decrease in locomotor activity, rearing, and grooming is reflective of a central nervous system depressant response to dexamethasone administration. Treatment with sertraline was associated with a mitigation of the central depressant effect induced by dexamethasone; although when administered to healthy mice, sertraline did not significantly alter horizontal locomotion, rearing or grooming, which is similar to the response observed by Pereira-Figueiredo *et al*[72]. In healthy mice fed a silymarin diet, a central excitatory response was observed at 140 mg/kg. Silymarin alone or silymarin co-administered with sertraline reduced the changes in locomotor activity, rearing, and grooming observed in mice administered dexamethasone alone. The concentration-dependent increase in locomotor activity, rearing, and grooming that occurred in healthy and dexamethasone-

treated mice could be linked to its ability to increase brain levels of serotonin, dopamine and norepinephrine, neurotransmitters that modulate central excitatory response in the brain[73-76]. Also, the co-administration of silymarin with sertraline was associated with a significant decrease in line crossing, an increase in grooming, with no significant difference in rearing behaviour compared with mice administered sertraline alone, suggesting that silymarin could amplify the effects of sertraline.

The neuroprotective effect of silymarin have been reported severally[28,29,77-79] with a number of studies reporting its ability to reverse cognitive deficits and anxiety-related behaviours[79]. In this study, dexamethasone was associated with spatial working memory deficits (Y-maze and radial arm maze) and anxiogenic response in the elevated plus maze paradigm. In times, past, cognitive deficits were not considered an important part of depression symptomatology, so little or no attention was paid to cognitive disorders associated with depression. However, in the light of recent knowledge, researchers now know that cognitive symptoms could significantly impact general functioning and quality of life, and risk of recurrence of depression in these individuals[80]. The results of this study demonstrated that while sertraline administration was associated with anxiolysis when administered alone or to dexamethasone-treated mice, it showed no nootropic ability in healthy mice. Although it counteracted dexamethasone-induced spatial memory deficits. The results observed with sertraline in healthy mice corroborate the reports of a study by Siepmann *et al*[81] that showed that in healthy humans, sertraline was not associated with cognitive deficits or improvements in cognition. Although sertraline reversed memory deficits in dexamethasone-treated mice, studies in humans have reported that a selective serotonin reuptake inhibitor such as sertraline was associated with memory loss and anxiety in persons with depression[82]. In groups fed silymarin supplemented diet alone, memory enhancing, and anxiolytic effects were observed in both healthy and dexamethasone-treated mice. This effect is similar to that observed by Yön *et al*[79] in diabetic rats. A number of other studies have also reported silymarin's ability to reverse cognitive deficits following scopolamine-induced amnesia[83] or mild traumatic brain injury[84], these

beneficial effects have been linked to its ability to decrease oxidative stress, inflammatory markers and brain glutamate level; as well as increase antioxidant status and brain-derived neurotrophic factor in rodents[83,84]. Although compared to sertraline, the administration of silymarin to dexamethasone treated mice was associated within reversal of memory deficits suggesting that as a sole or replacement therapy it could provide some benefits however large clinical studies would be required to confirm these in humans. When co-administered with sertraline, memory and anxiolytic effects improved significantly compared to dexamethasone-treated group administered sertraline, these would suggest that silymarin could also be beneficial as an adjunct with setraline in depression management.

In this study, administration of sertraline or silymarin supplemented diet was associated with a decrease in immobility time in the behavioural despair paradigm in healthy animals, while dexamethasone caused increased immobility time compared to healthy controls. Several studies have reported that chronic administration of dexamethasone in humans and experimental animals was associated with the development of mood disorders including psychosis and depression[40,85,86]. The ability of dexamethasone to increase immobility time has also been reported by other studies[40,87,88]. However, there is an increasing need for animal models of depression other than the currently available models of behavioural despair (forced swim test and tail suspension test). Animal models such as the one employed in this study supports the glucocorticoid hypothesis of depression[89] would be valuable in the testing of novel drugs for the management of depression. In this study, chronic dexamethasone administration was associated with weight loss, decreased in food intake, locomotor retardation, cognitive deficits, anxiety and behavioural despair; a number of these symptoms and signs are necessary for the diagnosis of depression in humans. The mitigation of a number of features by sertraline (a conventional antidepressant) supports the face- and predictive validity for its possible use as a preliminary method for studying novel pharmacologic agents with possible antidepressant effects. A limitation of this study would be our inability to assess plasma or brain glucocorticoid levels. Silymarin

supplementation alone or co-administered with sertraline in this study was associated with the reversal of dexamethasone induced behavioural despair. The antidepressant effect of silymarin have been reported especially in studies that used acute restraint stress[76], the chronic unpredictable stress model of depression[90] or posttraumatic stress disorder[91]. In both behavioural despair paradigms The antidepressant effects of setraline increased significantly with silymarin at a concentration of 280 mg/kg of feed, although it decreased at 140 mg/kg of feed, suggesting that high concentrations of silymarin was could elicit an additive beneficial effect.

The antidepressant, memory enhancing, and anxiolytic effects of silymarin have been attributed to its ability to decrease oxidative stress, improve antioxidant status, and increase antiinflammatory markers[76,90]. In this study, dietary silymarin supplementation was associated with a mitigation of dexamethasone-induced changes in brain oxidative stress, antioxidant status, and inflammatory markers. It also counteracted dexamethasone induced increase in acetylcholinesterase activity which could also be responsible for the memory enhancing effects of silymarin. Co-administered with setraline, we observed significant improvements in the oxidant antioxidant balance, and an antiinflammatory response over the effects observed with sertraline alone, also reinforcing our opinion that silymarin when examined in a rodent model of depression exhibited both adjunctive and sole therapeutic benefits.

Structural and morphological changes have been reported in humans with depression[92,93]. In this study, the administration of dexamethasone resulted in neuronal injury in the cerebral cortex and hippocampal dentate gyrus, two regions of the brain which have been implicated in depression[92-94]. In this study, sertraline and silymarin supplemented diet at both concentrations mitigated the structural changes induced by dexamethasone. The co-administration of sertraline with silymarin showed marked mitigation of these changes, suggesting that silymarin was not only beneficial when administered alone, but it also possibly accentuated the effects of setraline. While our knowledge of the structural and morphological changes in depression and how they impact pathogenesis and treatment are still evolving, it is important to realise that the use

of supplements such as silymarin that have validated adaptogenic, antioxidant, antiinflammatory, cognitive enhancing, anxiolytic and neuroprotective effects could be valuable in depression management, although clinical studies and trials would be necessary to verify its usability in humans.

CONCLUSION

Silymarin's ability to modulate behaviour, oxidative stress, and neuroinflammation makes it a possible monotherapeutic agent or an adjunct in the management of dexamethasone induced depression. In an era, when clinical management of depression has continued to be challenging, the discovery and application of such an agent is likely to be of benefit in at least a certain subset of patients. The value of an agent such as silymarin is likely to rest in the fact that it can employ mechanisms of action that go beyond neurotransmitter modulation.

ARTICLE HIGHLIGHTS

Research background

Depression is a neuropsychiatric disorder that has in recent times become a leading cause of disability and a major contributor to global disease burden and suicide.

Research motivation

There is increasing advocacy for the use of herbal supplements in depression management.

Research objectives

To determine the effect of silymarin dietary supplements alone or in combination with sertraline in a mouse model of depression.

Research methods

Preclinical study.

Research results

Silymarin mitigated dexamethasone-induced central nervous system changes in mice.

Research conclusions

Silymarin could have a place in the management of depression in humans.

Research perspectives

To examine its possible effects in humans with depression.

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