IJPSR (2017), Volume 8, Issue 12 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 June, 2017; received in revised form, 16 November, 2017; accepted, 22 November, 2017; published 01 December, 2017

EVALUATION OF THE ANTIDEPRESSANT ACTIVITY OF *TRIBULUS TERRISTRIS* IN DIABETIC DEPRESSION IN RAT MODEL

Rupasri Dutt-Roy[*1], E. Kayalvizhi [2] and M. Chandrasekhar [2]

Department of Physiology [1], Sathyabama University Dental College and Hospital, Chennai - 600119, Tamil Nadu, India.
Department of Physiology [2], Meenakshi Medical College and Research Institute, Enathur, Kanchipuram - 631552, Tamil Nadu, India.

Keywords:

TT, PCPA,
Fluoxietin, FST, STZ

Correspondence to Author:
Rupasri Dutt-Roy

Department of Physiology, Sathyabama University Dental College and Hospital, Chennai - 600119, Tamil Nadu, India

E-mail: 26rupasri@gmail.com

ABSTRACT: *Tribulus terristris* is a well known medicinal plant as anti-inflammatory, antimicrobial and nephroprotective *etc*. It is a very good drug for urinogenital problems, hepatic problems, oxidative stress *etc*. The aim of the study is to compare the depression induced by PCPA and STZ treated diabetic depression in mice and which could be restored by the ethanolic exact of fruits of *Tribulus terristris* in 21 days. **Method:** Depression was created in animals by PCPA (100 mg/k.b.w i.p. for 4 days) and STZ (25 mg/k.b.w i.p for 4 days) induced diabetic depression. Then that depression was restored by ethanolic extract of fruits of *Tribulus terristris* in a dose of 400 mg/k. b.w/day for 21 days. Fluoxietin kept as standard (5 mg/k.b.w) and continued for 21 days. Depression accessed by forced swimming test and measured the selected antioxidants level in brain homogenate and blood serum. **Result:** *Tribulus terristris* (TT) showed significant decrease in immobility in forced swim test and restored the antioxidant levels in animals as fluoxietin does, at the dose of 400 mg/k.b.w. **Conclusion:** Hence the result proposed that *Tribulus terristris* has antidepressant and antioxidant properties in chronic treatment of 400mg /k.b.w.

INTRODUCTION: Depression is a neuropsychiatric disorder with altered mood and persistent anxiety [1] which interfere everyday life. The important symptoms are feeling of emptiness, guilt, loss of confidence and lack of interest in favourite activities. Depression leads to various health problems [2]. Its Symptoms might be loss of appetite or overeating, insomnia or too much sleep and decision making problems etc. It is a very common but serious illness. In elderly people most of the times it leads to diabetes [3]. Diabetes and depression are linked to each other.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(12).5392-99

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8(12).5392-99

Diabetes Mellitus is steadily increasing everywhere in the world. According to WHO (2014) 422 million adults were living with diabetes compared to 108 million in 1980. Diabetes Mellitus, the endocrine disorder was the seventh leading cause of death [4]. Analyzed the death certificates of death due to diabetes from 2002 to 2012 in Songjiang District of Shanghai because China is one of the leading diabetic countries likse India.

Among four people, at least 1or 2 people are suffering from clinically significant depression in type II diabetes [5]. This diabetes often leads to depression due to neurotransmitter imbalance which increases the risk of morbidity, mortality and suicidal tendency in depressed population [6]. According to pharmacological reports, hyperglycemia increases oxidative stress which leads to depression [7, 8]. *Tribulus terristris* is a familiar medicinal plant of Zygophyllaceae family.

It is being used as a single component and part of combination like Rasayana Ghana. All parts are having medicinal property but thorny and stout fruits are more promising [9]. It is used since Vedic period in Ayurved, Unani and Homeopathy as diuretic [10], hepatoprotective [11] and nephroprotective *etc* [12]. The study was conducted to evaluate the antidepressant activity in diabetic depression and depression induced by PCPA in animal model through forced swimming test and by measuring the anti-oxidant levels in blood serum and brain homogenate.

MATERIAL AND METHODS:

Site of Experiments : The experiment were carried out in the department of Physiology at Meenakshi Medical College and Research Institute, Kanchi-puram with due ethical committee clearance (IAEC NO. 009/2015) on male Swiss albino rat 120 -200 g of body weight and caged in a healthy environment. (22 ± 1 ^{O}C, 12 h day and night cycle) were fed with pellet and water *ad libitum* by using male wister albino rats.

Collection of Plant Material: The dry medicinal plant was collected from, Mr. Netai pal (Thirty years experience in Herbal trading) Herbal trading Co. Ltd. College Street. Kolkata, West Bengal, India and authenticated by Dr. D. Aravind, MD (S), M.Sc of National Institute of Siddha, Ministry of AYUSH (Government of India). The authentication certificate no.:NISMB2952017.

Preparation of Plant Extract: The plants were made into powder using a normal mixy grinder. The fine powder got after using iron net and then 250 g powder was mixed with 2500 ml of 70 % ethanol which is more capable than pure ethanol to extract alkaloids and polyphenols from plant. It was kept for 48 hours on electrical gyratory shaker under constant shaking. Then filtered the solution and got golden brown fluid. The residue was re-extracted once again with 2000 ml of ethanol and the combined extracts were concentrated under vacuum and dried using a rotary flash evaporator. The dry weight of the plant was 6.7 %. Dry plant mixed with distilled water freshly every day.

Drug's Information: The analytical grade of PCPA (Para-chlorophynyl-alanine) and STZ (streptozoto-cin) bought from Sigma Chemical Company Inc. St Louis, Mo, USA. Prozac, the brand name and the generic name is fluoxietin, purchased from the Pharmacy of the Meenakshi Medical College.

Solvent of PCPA and STZ: PCPA dissolved in tween 80 is miscible in water (0.1 ml/ml) and produced a hazy light yellow colour solution. Appropriate concentration of STZ was made *i.e*. 7mg/ml in citrate buffer with pH 4.5. Always STZ should mix at the time of injection to prevent STZ's degradation in citrate buffer. TT mixed with distilled water in requisite amount every day for drug delivery by orally.

Animals Grouping and Dosing: Animals were allowed to acclimatize in new peer groups. Standard environment maintained in the cages. All the rats were divided into 7 groups with 6 animals in each cage. 3 groups were treated by PCPA (100 mg/k. b.w. i.p) and 3 groups for STZ (25 mg/k. b.w. i.p) administered once daily for 4 days. Chronic low dose was chosen for 4 days to prevent death of STZ administration from previous experiences. 4 hours fasting in animals is enough to create diabetes in animals.

First group kept for normal control treated with distilled water. On 4th day glucose level was measured by glucometer through pricking needle at 1 cm away from the cloacae on ventral side of the tail of the animals. Among 3 PCPA groups, 1 group was kept for PCPA control and other 2 groups were treated with standard antidepressant drug fluoxietin (3 mg/k.w) for 21 days and TT (400 mg/k. b.w) for 21 days respectively. Among STZ groups one group kept for diabetic control, another 2 groups further treated by TT (400 mg/k. b.w, once daily for 21 days.) and standard antidepressant drug fluoxietin (3mg/k. b.w, once daily for 21 days).

Chronic Administration of *Tibullus terestris* and Fluoxietin: *Tribullus teristris* 400 mg/k. b.w [13] and Fluox-5 mg/k. b.w [14] once daily p.o. for 21 days.

Study design: Order

1. Control: (6 animals) Distilled water (10 ml/k. b.w)

2. PCPA Control: (6 animals)100 mg/k. b.w i.p.

3. Diabetic Control: (6 animals)25 mg/kg. b.w. i.p

4. PCPA + Fluoxietine: (6 animals)5 mg/k. b.w. p.o.*21 days

5. PCPA + TT: (6 animals) 400/k. b.w for p.o.*21 days

6. STZ + Fluoxietine: (6 animals) 5mg/k. b.w p.o. *21 days

7. STZ + TT: (6 animals) 5mg/k. b.w p.o.*21days

Force Swimming Test Selected for Accessing the Depression: The test discovered by Porsolt RD 1997 [15] selected in this study. All groups were subjected to do forced swimming test in a glass cylinder of 18 cm diameter, 40 cm height filled with water height of 15 cm. Maintained the water temp of 25 ± 2 ^{O}C. Measured the immobility time the last 4 mins of 6 mins duration [16] of swimming. In each test fresh water was provided [17].

Forced Swimming Test Performed on 4th day and Repeated on 21st day of Drug Treatment: Forced swimming test performed on 4th day, 1 hour after the last dose of PCPA and STZ, again repeated 1 hour after the last dose on 21st days of treatment by TT and standard fluoxietin.

Biochemical Analysis:

Glucose Estimation: Fasting blood glucose level was measured on 4th day of treatment by PCPA and STZ in animals by using glucometer from the ventral side of the tail, 1cm away from the cloacae. 2 % lidocain was used for every pricking to reduce the pain [18].

Antioxidants Estimation: Antioxidants like CAT assayed by the method of Sinha (1972) [19] while SOD used by the method of Kakkar *et al.*, 1984 [20] and MDA determined by the method of Satoh K, 1978 [21] in blood serum and brain homogenate. The absorbance of catalase was measured at 530 nm. The result was expressed by the consumption of H_20_2 (µM /min/mg protein). In SOD the butanol layer was measured at 560 nm in spectro-photometer .The enzyme activity was expressed as units/mg protein. At the end for MDA estimation, the supernatant was measured at 540 nm in spectrophotometer. The level of lipid peroxides was expressed as n moles of MDA formed/mg protein. Brains were removed from sacrificed animals (isoflurane) by keeping on ice slab, then immediately put into nitrogen refrigerator for 10 min after that, prefrontal area and hippocampus separated from each brain. The cut area approximately should have the same weight (w/v). Tissue was homogenized with phosphate buffer (0.1M, with pH 7.4). The clear supernatant were considered after centrifugation for due estimation. Homogenate was centrifuged in 3000 rpm for 15 min.

Statistical Analysis: All the values were expressed as mean ± S.E.M and analyzed by one-way ANOVA followed by Dunnet's multiple comparison test were P< 0.05 was considered to be statistically significant.

RESULTS:

Contribution of Phytochemical in Depression, Diabetes and Oxidative Stress: Fig. 1, compared the depression level between PCPA and STZ treated animals through forced swimming test.

Each group is compared with normal control (6 animals) which is p<.001in. Performed Dennett's test values are displayed as mean ± SEM, each treated group contains 18 animals. Hence P values are statistically significant

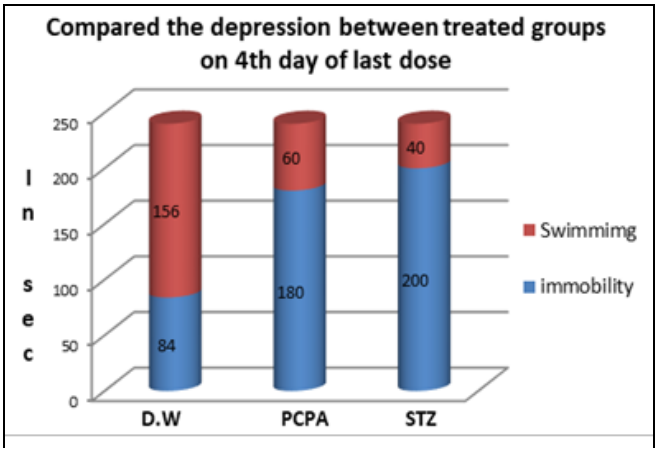

FIG. 1: COMPARED THE DEPRESSION LEVEL BETWEEN PCPA AND STZ TREATED ANIMALS THROUGH FORCED SWIMMING TEST

Fig. 2, is showing the effect of PCPA and STZ on blood glucose level.

PCPA did not showed any alteration in blood glucose level, whereas streptozotocin treated groups showed increased fasting blood sugar level of 290 mg/dl in animals considered to be diabetic. Values are expressed in standard error of mean (± SEM) of 18 animals in each treated group. Performed Dunnet-*t*-test, showed P<.001which is significant.

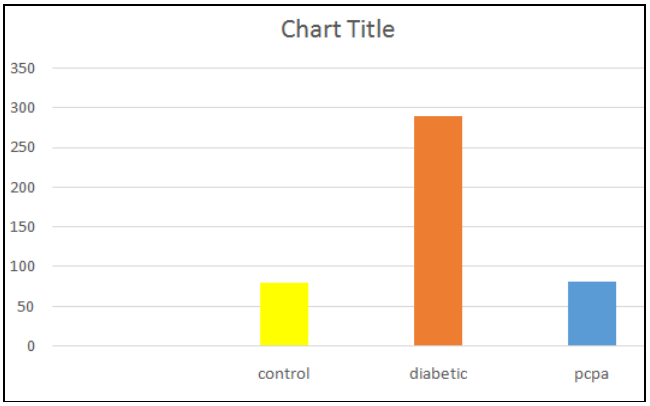

FIG. 2: IS SHOWING THE EFFECT OF PCPA AND STZ ON BLOOD GLUCOSE LEVEL

Fig. 3, is showing effect of antidepressant activity of TT on forced swimming test.

Chronic administration of TT at the dose of 400/k. b.w for 21 days showed significant reduction in immobility in PCPA and STZ treated diabetic groups compared with standard antidepressant fluoxietin (5 mg/k. b.w)and normal control. Values are expressed as mean (± SEM).Computed one-way Anova followed by Dunnett's test showed very much significant (p<.001).

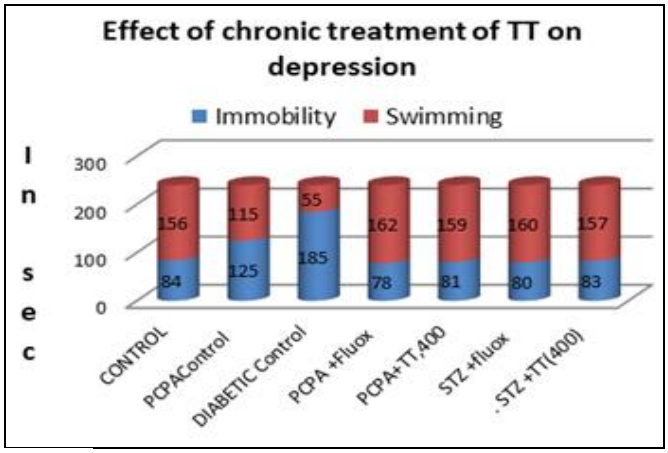

FIG. 3: IS SHOWING EFFECT OF ANTIDEPRESSANT ACTIVITY OF TT ON FORCED SWIMMING TEST

Effect of Antioxidants: Fig. 4 and **Fig. 5** chronically treated groups by TT (400 mg) and fluoxietin in **Fig. 4** and **Fig. 5** the catalase and superoxide dismutase antioxidants level increased significantly (p<.05) in blood serum and brain homogenate compared to positive controls of PCPA and STZ. In each case performed Dunnet's test.

Effect of MDA in Experiment: Fig. 6 MDA concentration is significantly higher in blood serum and brain homogenate of depressed group created by PCPA and STZ, this concentration went down as normal after treating with TT (400 mg) for 21 days. This restoration is significant (p<.001). Performed two ways Anova followed by Dunnett's test.

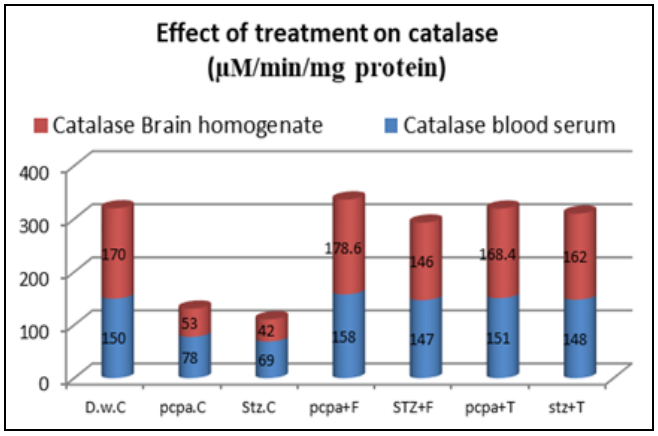

FIG. 4: EFFECT OF TREATMENT ON CATALASE

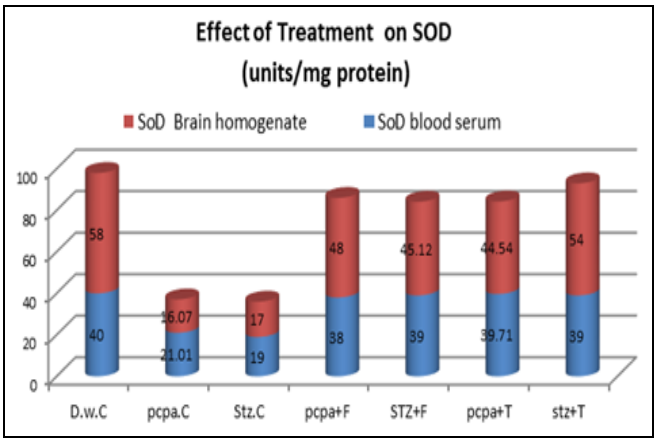

FIG. 5: EFFECT OF TREATMENT ON SOD

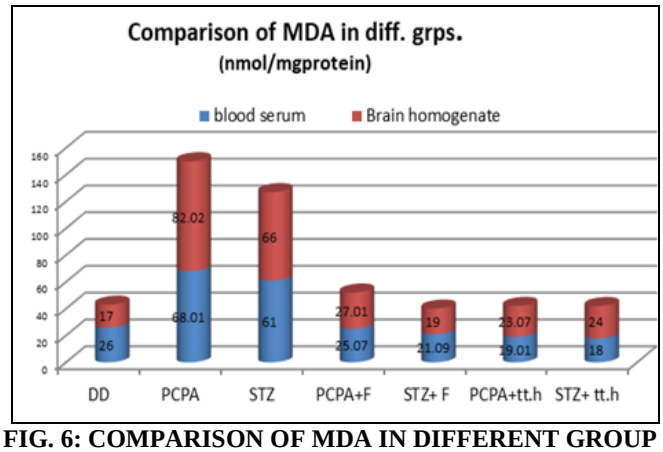

FIG. 6: COMPARISON OF MDA IN DIFFERENT GROUP

DISCUSSION: Depression is a kind of mood disorder with persistent feelings of sadness. It affects our feelings, decision making capabilities and certain behaviours. Gradually they became a burden of society. The available treatment of

depression is not satisfactory. Hence, herbal medicines are gaining popularity in every field because of short comings in synthetic antidepressant medicines like delayed onset of activity and side effects.TT is a renowned medicinal plant since long back due to its potential pharmacological activities. Diabetes is an endocrine disorder with high blood sugar level with other associate symptoms. The abnormal high blood sugar level is due to malfunction of either insulin secretion or insulin action in the body [22]. Scientists have already explored that one of the co-morbid symptoms of diabetes is depression [23]. In comparison to non diabetic community, depression is 2 - 3 times more in diabetic world population [23]. Mostly untreated diabetes leads to depression [24]. It is an established fact that diabetes significantly increases the possibility of depression [25].

The underlying pathophysiology of depression is error in neurotransmitters [26]. Mostly serotonin, nor-adrenalin and small amounts of dopamine are directly involved in depression [27]. We know that serotonin (5-hydroxytryptamine) which is known as happy hormone controls all kinds of human behaviour like mood, memory, attention, focus, sexuality, anger and aggression [28]. To study the experiment, force swimming test was selected which provides the speedy and dependable screening test for antidepressant activity of medicinal plants [29]. Immobility is the core symptom of depression which was considered in forced swimming test for assessment of depression.

In depression, the approved antidepressants are classified as selective serotonin reuptake inhibitors (SSRI), MAO-inhibitors or miscellaneous anti-depressants. But each drug has 40 % failure rate. In this experiment, depression induced in animals by PCPA and STZ was evidenced by forced swimming test in **Fig. 1** and antioxidants level. PCPA created depression [30] could be due to inhibition of MAO specifically 5-HTP which is the intermediate precursor of serotonin in synapse due to its selective and irreversible inhibitor of tryptophan hydroxylase. This is the rate-limiting enzyme in the biosynthesis of serotonin [31].The Graph II indicates no alteration of blood glucose level in case of PCPA treated groups, whereas STZ treated groups increased the fasting blood sugar level and confirmed diabetes.

STZ created diabetes leads to depression in experimental animal [32]. Similar depression found in diabetic and psychiatric patients [33]. Hence, it is proved that depression and diabetes is interlinked [34].This depression in diabetes might be due to the altered level of 5HT in hippocampus region or due to neural cell death [35]. Fluoxietin was selected for positive control to ensure the antidepressant activity of TT in depression in serotonergic pathway. Fluoxietin is selective serotonin reuptake inhibitor (SSRI) which is a great choice of drug for clinician in case of major depressive disorder and its trade name is Prozac. This is the first line of defence for the treatment of major depressive disorder [36]. In **Fig. 3** Chronic administration of TT (400 mg) for 21 days restored depression in PCPA treated groups and diabetic groups by increasing mobility in forced swimming test.

Depression is further confirmed by biochemical analysis of antioxidants in blood serum and brain homogenate in all groups. Recent studies suggested that any kind of stress induced oxidative damage due to decreased level of antioxidants and increased level of reactive oxygen species [37]. The catalase, superoxide dismutase and especially malondealdehyde enzymes are trait markers of depression for oxidative stress. The treated groups of PCPA and STZ showed the significant decrease of catalase and superoxide dismutase and increased level of MDA in blood serum and brain homogenate in **Fig. 4**, **Fig. 5** and **Fig. 6**. Hence the oxidant and antioxidant defence systems are getting deranged in depression [38] and diabetes [39].

Clinical depression is associated with a 30 % increase of inflammation in the brain, according to a new study published in JAMA Psychiatry. A study conducted by researchers in patients experienced cumulative depressive episodes with high level of c-reactive proteins which is the indicator of inflammation at Duke University Medical Center in 2012. The inflammation is an integral part of the stress response [40]. Inflammatory cells induced oxidative stress by secreting some hydrolyzing enzymes and ROS (hydrogen peroxide, superoxide, hydroxyl radical *etc*). This creates imbalance between oxidant and antioxidant enzyme system in the animal. Hence neuro-inflammation are involved in the pathophysiology of depression and anxiety [41].

In diabetes, several studies have shown that elevated extra and intra cellular glucose concentrations directly increase the reactive oxygen species generation in the cell [42]. This causes membrane lipid peroxidation. As a result, it may alter neurotransmission, neuronal function and overall brain activity [43]. Hence oxidative stress might have contribution in the pathogenesis of depression.

In the study, the depressed groups when treated by TT and fluoxietin chronically for 21 days. TT showed similar results like fluoxietin in restoration of antioxidants like catalase, superoxide dismutase and malondealdehyde. This indicates that the medicinal plants could work like synthetic drug fluoxietin due to having duel and triple therapeutic actions in animals [44]. It was studied that steroids, tritepenoidsetc have potential role in alloxan-induced diabetic rats. Similarly methanol and aqueous extract of its fruit pulp have neuro-protective activities *in-vivo* [45]. Claimed that Phenolic, flavonoids in *Phaseolus vulgaris* are helpful in preventing depression as well as having the ability to remove ROS [46].

The secondary metabolites reach the brain tissues *via* blood brain barrier [47] to work on central nervous system as potential neuroprotectants. Earlier reports showed that herbs containing flavonoids, tannins and phenolic compounds were found to possess antioxidant property and attenuated cell death induced by oxidative stress Schroeter H2000. It has observed that glycosides possess both antioxidant and antidiabetic effects [48]. The diverse activity of same phytochemical is studied by various scientists in various diseases. The isolated alkaloids showed antidiabetic and antioxidant potential *in-vitro* study [49]. Sadia Perviz *et al*., 2016 [50] reviewed the anti-depressant activity of β carboline alkaloid, a monoamine oxidase inhibitor in plants.

This theory was supported by Deole YS *et al*., 2011 [51]. They claimed that the anti-depressant and anxiolytic activity of Rasayana Ghana Tablet in ayurved is due to presence of β carboline alkaloid of TT which is the main contributor among 3 medicinal plants of Rasayana Tablet. It is observed that steroid phytochemical is responsible for hypoglycaemic activity in diabetic rats in *C. papaya* leaves [52].

This is further explained by Isela E. Juarez-Rojopa *et al*., 2014 that steroids hamper the glucose absorption by inhibiting the hydrolyzing enzymes and that helped in hypoglycaemic activity [53]. Saponins of bitter melon also showed hypoglycemic activity in alloxan-induced hyperglycemic mice which increased the mass of β cells in the pancreas and insulin production studied by scientists [54].

According to certain researchers, phenols are highly reactive as antioxidant. This scavenging effect is carried out by the O-dihydroxy group of phenolic components of radical. Phenols are not only antioxidants they are anti-diabetic too [55]. Pradeep 2013 [56] reported that the anti-diabetic activity of the ethanolic extracts of the leaves of *Strobilanthes asperrimus* plant is possible due to the presence of tannins, flavonoids, and alkaloids. Rajasree *et al*., 2016 [57] revealed that the presence of flavonoids and phenolic compounds have multiple biological effects in Central nervous system disorders. The different pharmacological activities of bioactive components of TT were explored by various scientists. In 2011, A. D Sathisha *et al*., [58] examined the antioxidant quality of TT through DPPH radical scavenging activity *in vitro*. The antidiabetic activity of saponin of TT was explored by Chu S *et al*., in 2003 [59]. The depression was restored when the experimental groups were chronically treated by TT (400 mg/ k.b.w, once daily orally). It is concluded that photochemical of medicinal plants having tremendous therapeutic potential in curing various disorders and diseases compared to the synthetic drugs with minimum side effects.

CONCLUSION: The restoration of depression and diabetic depression might be due to synergistic effect of various secondary metabolites like alkaloids, steroids, glycosides, saponins, flavonoids, phenols, tannins due to their antioxidant, anti-diabetic and antidepressant activities.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Demily C and Sedel F: Psychiatric manifestations of treatable hereditary metabolic disorders in adults. Ann Gen Psychiatry 2014; 13-27.

2. McLachlan EM: depression associated with chronic illness. InnovAiT 2011; 4(5): 272-277.
3. Jones LC, Clay OJ, Ovalle F, Cherrington A and Crowe M: Correlates of depressive symptoms in older adults with diabetes. Journal of Diabetes Research 2016; 2016: 1-8.
4. Zhu M, Li J, Li Z, Luo W, Dai D, Weaver SR, Stauber C, Luo R and Fu H: Mortality rates and the causes of death related to diabetes mellitus in Shanghai Songjiang District: an 11-year retrospective analysis of death certify-cates. BMC Endocr Disord 2015; 15-45.
5. Holt RIG, de Groot M and Golden SH: Diabetes and depression. Curr Diab Rep 2014; 14(6): 491:1-15
6. Campayo A, Gomez-Bielch and Lobo A: Diabetes and depression. Curr Psychiatry Rep 2011; 13(1): 26-30. Pubmed.
7. Chung CP, Schmidt D, Stein CM, Morrow JD and Salomon RM: Increased oxidative stress in patients with depression and its relationship to treatment. Psychiatry Res. 2013; 206(0): 213-216.
8. Mazloom Z, Ekramzadeh M, Hejazi N: Efficacy of supplementary Vitamins C and E on anxiety, depression and stress in type 2 diabetic patients: a randomized, single-blind, placebo-controlled trial. Pak J Biol Sci 2013; 16 (22): 1597-600.
9. Chatra S, Nesari T, Somani G, Kanchan D and Sathaye S: Phytopharmacological overview of *Tribulus terristris.* Pharmacogn Rev 2014; 8(15): 45-51.
10. Fatima L, Sultana A, Ahmed S and Sultana S: Pharma-cological activities of *Tribulus terrestris* Linn: a systemic review. World Journal of Pharmacy and Pharmaceutical Sciences 2014; 4(02): 136-150.
11. Sugunavarman T and Jagadeesan G: hepatoprotective activity of *Tribulus terrestris* on experimental liver damage in mice. International Journal of Modern Research and Reviews2013; 1(1): 20-23.
12. Abdel-Kader MS, Al-Qutaym A, Saeedan ASB, Hamad AM and Alkharfy KM: Nephroprotective and hepato-protective effects of *Tribulus terrestris* L. growing in Saudi Arabia. Journal of Pharmacy and Pharmacognosy Research 2016; 4 (4): 144-152.
13. Borran M, Minaiyan M, Zolfaghari B and Mahzouni P: Protective effect of *Tribulus terrestris* L. fruit extract on cerulein-induced acute pancreatitis in mice. Avicenna J Phytomed 2017; 7(3): 250-260.
14. Daniele G. Machado. Mauricio P. Cunha.Vivian B. Neis. Grasiela O. Balen. André Colla. Jaine Grando. Patricia S. Brocardo. Luis E. B. Juliano C: Fluoxetine reverses depressive-like behaviors and increases hippocampal acetyl cholinesterase activity induced by olfactory bulbectomy. Pharmacology Biochemistry and Behavior 2012; 103(2): 220-229.
15. Yankelevitch-Yahav R, Franko M, Huly A and Doron R: The forced swim test as a model of depressive-like behavior. J Vis Exp 2015; 97: e52587:1-7.
16. Chen ML, Gao J, He XR and Chen Q: Involvement of the cerebral monoamine neurotransmitters system in anti-depressant-like effects of a Chinese herbal decoction, Baihe Dihuang Tang, in mice model. Evidence-Based Complementary and Alternative Medicine2012; 2012: 1-6.
17. Lakshmi A and Devi PS: Phytochemical and anti-depressant activities of *Celastrus paniculatus* Willd J. J Pharmacol 2017; 2(1): 5-9.
18. Azari O, Molaei MM and Roshani H: Caudal epidural analgesia using lidocaine alone and in combination with tramadol in dromedary camels. Iranian Journal of Veterinary Surgery 2014; 9(2): 1-21.
19. Starlin T and Gopalakrishnan VK: Enzymatic and non-enzymatic anti-oxidant properties of *Tylophora pauciflora* Wight and Arn. - An *in-vitro* study. Asian J Pharm Clin Res. 2013; 6(4): 68-71.
20. Jagathambal M and Padma PR: Comparison of enzymic and non-enzymic antioxidant status in the leaves of five selected plants from Apiaceae Family. IJPPR. Human 2016; 6(3): 1-13.
21. Kyznetsova MY, Makieieva OM, Lavrovska DO, Tymoshenko MO, Sheverova DP, Halenova TI, Savchuk OM and Ostapchenko LI: Effect of aqueous extract from *Phaseolus vulgaris* pods on lipid peroxidation and antioxidant enzymes activity in the liver and kidney of diabetic rats. Journal of Applied Pharmaceutical Science 2015: 5(05): 001-006.
22. Sharma VK, Kumar S, Patel HJ and Hugar S: Hypo-glycemic activity of *Ficus glomerata* in alloxan induced diabetic rats. International Journal of Pharmaceutical Sciences Review and Research 2010; 1(2): 18-27.
23. Badescu SV, Tataru C, Kobylinska L, Georgescu EL, Zahiu DM, Zagrean AM and Zagrean L: The association between Diabetes mellitus and depression. J Med Life. 2016; 9(2): 120-125.
24. Wojciechowski P and Cukrzycy EW: Raport dia-betologiczny 2015; 1: 18-42.
25. Bogner HR and McClintock HFDV: Costs of coexisting depression and diabetes. J Gen Intern Med 2016; 31(6): 594-5.
26. Miller AH and Raison CL: The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature Reviews Immunology 2016; 16: 22-34.
27. Mansari ME, Guiard BP, Chernoloz O, Ghanbari R, Katz N and Blier P: Relevance of norepinephrine-dopamine interactions in the treatment of major depressive disorder. CNS Neurosci Ther 2010; 16(3): e1-e17.
28. Baixauli E: Happiness: Role of dopamine and serotonin on mood and negative emotions. Emerg Med (Los Angel) 2017; 7(2): 350:1-2.
29. Kumari E, Agrawal A, Ilango K, Singh GPI and Dubey GP: Evaluation of the antidepressant activity of a novel polyherbal formulation. Autism Open Access 2016; 6(5): 1-8
30. Cassani J, Dorantes-Barron AM, Novales LM, Real GA and Estrada-Reyes R: Anti-depressant-like effect of kaempferitrin isolated from *Justicia spicigera* Schltdl (Acanthaceae) in two behavior models in mice: Evidence for the Involvement of the Serotonergic System. Molecules 2014; 19: 21442-21461.
31. Welford RWD, Vercauteren M, Trebaul A, Cattaneo C, Eckert D, Garzotti M, Sieber P, Segrestaa J, Studer R, Groenen PMA and Nayler O: Serotonin biosynthesis as a predictive marker of serotonin pharmacodynamics and disease induced dysregulation. Scientific Reports 2016; 6: 30059:1-9. Nature.
32. Siegel JZ and Crockett MJ: How serotonin shapes moral judgment and behavior. Ann N Y Acad Sci 2013; 1299(1): 42-51.
33. Mosienko V, Bert B, Beis D, Matthes S, Fink H and Alenina N: Exaggerated aggression and decreased anxiety in mice deficient in brain serotonin. Transl Psychiatry 2012; 2: e122:1-9.
34. Han X, Tao YL, Deng YP, Yu JW, Cai J, Ren GF and Sun YN and Jiang GJ: Metformin ameliorates insulitis in STZ-induced diabetic mice. PeerJ 2017; 5: e3155: 1-13.

35. Sun N, Lou P, Shang Y, Zhang P, Wang J, Chang G and Shi C: Prevalence and determinants of depressive and anxiety symptoms in adults with type 2 diabetes in China: a cross-sectional study. BMJ Open 2016; 6:e012540: 1-8.
36. Bickett A and Tapp H: Anxiety and diabetes: Innovative approaches to management in primary care. 2016; 241(15): 1-6.
37. Chen C, Wang Y, Zhang J, Ma L, Gu and Guyu Ho: Contribution of neural cell death to depressive phenotypes of streptozotocin-induced diabetic mice. Dis Model Mech 2014; 7(6): 723-730.
38. Jia Y, Zhu H and Leung S**:** Comparative efficacy of selective serotonin reuptake inhibitors (SSRI) in treating major depressive disorder: a protocol for network meta-analysis of randomised controlled trials. BMJ Open 2016; 6(6): e010142: 1-6.
39. Nita M and Grzybowski A: The role of the reactive oxygen species and oxidative stress in the patho-mechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. Oxidative Medicine and Cellular Longevity 2016; 2016: 1-23.
40. Vavakova M, Durackova Z and Trebaticka J: Markers of oxidative stress and neuroprogression in depression disorder. Oxidative Medicine and Cellular Longevity 2015; 2015:1-12.
41. Matough FA, Budin SB, Hamid ZA, Alwahaibi N and Mohamed J: The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ Med J. 2012; 12(1): 5-18.
42. Schieber M and Chandel NS: ROS function in redox signaling and oxidative stress. Curr Biol 2014; 24(10): 453-462.
43. Miller AH and Raison CL: The role of inflammation in depression: from evolutionary imperative to modern treatment target .Nature Reviews immunology 2016; 16: 22-34.
44. Matough FA, Budin SB, Hamid ZA, Alwahaibi N and Mohamed J: The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ Med J 2012; 12(1): 5-18. NCBI.
45. Ceylan MF, Guney E, Alisik M, Ergin M, Dinc GS, Goker Z, Eker S, Kizilgun M and Erel O: Lipid peroxidation markersin children with anxiety disorders and their diagnostic implications. Redox Report. 2014; 19(2): 92-96.
46. Talukdar SN and Hossain MN: Phytochemical, phytothera -peutical and pharmacological study of *Momordica dioica*. Evidence-Based Complementary and Alternative Medicine 2014; 2014: 1-11.
47. Zhu W, Du Y, Meng H, Dong Y and Li L: A: Review of traditional pharmacological uses, phytochemistry, and pharmacological activities of *Tribulus terrestris* .Chem Cent J 2017; 11(60): 1-16. Springer.
48. Devi M and Sharma R: Antidepressant activity of aqueous extract of *Phaseolus vulgaris* (black bean) in rodent models of depression 2014; 4(2): 118-124.
49. Cardoso FL, Brites D and Brito MA: Looking at the blood-brain barrier: Molecular anatomy and possible invest-tigation approaches. Brain. Res. Rev. 2010; 64(2): 328-363.
50. Gaikwad SB, Mohan GK and Rani MS: Phytochemicals for Diabetes Management. Pharmaceutical Crops 2014; 5(S-1: M2): 11-28.
51. Ghareeb DA, ElAhwany AMD, El-mallawany SM and Saif AA: *In-vitro* screening for anti-acetylcholiesterase, anti-oxidant, anti-glucosidase, anti-inflammatory and anti-bacterial effect of three traditional medicinal plants. Biotechnol Biotechnol Equip 2014; 28(6): 1155-1164.
52. Perviz S, Khan H and Pervaiz A: Plant alkaloids as an emerging therapeutic alternative for the treatment of depression. Front Pharmacol. 2016; 7: 28.
53. Deole YS, Chavan SS, Ashok BK, Ravishankar B, Thakar AB, Chandola HM: Evaluation of anti-depressant and anxiolytic activity of Rasayana Ghana Tablet (A compound Ayurvedic formulation) in albino mice. Ayu 2011; 32(3): 375-9.
54. Saidu AN and Nweri CG: Hytochemical screening and effects of methanol extract of *Carica papaya* stem bark in alloxan induced diabetic rats. Journal of Emerging Trends in Engineering and Applied Sciences (JETEAS). 2013; 4(6): 819-822.
55. Juarez-Rojopa IE, Tovilla-Zarateb CA, Aguilar-Domin gueza DE, Roa-de la Fuentec LF, Lobato-Garciac CE, Ble-Castilloa JL, Lopez-Merazd L, Diaz-Zagoyae JC and Bermudez-Ocanab DY. Phytochemical screening and hypoglycemic activity of *Carica papaya* leaf in streptozotocin-induced diabetic rats. Rev Bras Farmacogn 2014; 24: 341-347.
56. Barky ARE, Hussein SA, Eldeen AAA, Hafez YA and Mohamed TM: Saponins and their potential role in diabetes mellitus. Diabetes Manag. 2017; 7(1): 148-158.
57. Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP and Li HB: Antioxidant phytochemicals for the prevention and treatment of chronic diseases. Molecules 2015; 20(12): 21138-21156.
58. Samal PK: Antidiabetic and antioxidant activity of *Strobilanthes asperrimus* in rats. Journal of Global Trends in Pharmaceutical Sciences 2013; 4(2): 1067-1072.
59. Rajasree RS, Sibi PI, Francis F and William H: Phyto-chemicals of Cucurbitaceae Family - A review. Inter-national Journal of Pharmacognosy and Phytochemical Research. 2016; 8(1): 113-123.
60. Sathisha D, Lingaraju HB and Prasad KS: Evaluation of antioxidant activity of medicinal plant extracts produced for commercial purpose. E-Journal of Chemistry 2011; 8(2): 882-886.
61. Chu S, Su W, Sun B and Huang X: Effect of saponins from *Tribulus terristris* on hyperlipidemea, Zhong Yao Cai. Article in chinese 2003; 26(5): 341-4. PubMed.

How to cite this article:
Dutt-Roy R, Kayalvizhi E and Chandrasekhar M: Evaluation of the antidepressant activity of *Tribulus terristris* in diabetic depression in rat model. Int J Pharm Sci Res 2017; 8(12): 5392-99.doi: 10.13040/IJPSR.0975-8232.8(12).5392-99.