JOURNAL OF COMPLEMENTARY MEDICINE RESEARCH

RESEARCH ARTICLE

Effect of herbal formulation Sharbat Ahmad Shahi on serum BDNF level in mild to moderate cases of depressive disorder

MOHAMMED YASIR[1], AHMAD ALI [2], IRFAN AHMAD[3], NILOFAR KHAN[4], MOHAMMAD ZAHID ASHRAF[5*]

[1]Dept. Biotechnology, Jamia Millia Islamia, & Assistant Professor, Aligarh Muslim University, Aligarh, India. E-mail: yasirm7@gmail.com

[2]Assistant Professor, Dept. Life sciences, University of Mumbai, India, E-mail: ahmadali@mu.ac.in

[3]Research Officer (U), Regional Research Institute of Unani Medicine, Mumbai, India, E-mail: irfanmumbai8@gmail.com

[4]Defence Institute of Physiology & Allied Sciences, New Delhi, India.

[5]Professor, Dept. Biotechnology, Jamia Millia Islamia, New Delhi, India, E-mail: zashraf@jmi.ac.in

**Corresponding Author*

ABSTRACT

Background: Depressive disorder is a common psychiatric condition where suicidal tendency, adverse events of conventional drugs prompt us to find safer yet effective alternative solutions. Traditional Unani formulation Sharbat Ahmad Shahi is used as an antidepressant but needs to be validated along with its scientific mechanism of action. Serum Brain Derived Neurotrophic Factor (BDNF) level is nowadays considered an important biomarker of depression. Hence, we conducted a clinical study to evaluate the effect of Unani formulation in mild to moderate cases of depressive disorders.

Methods: 20 diagnosed cases of depressive disorders (on DSM-V criteria) of mild to moderate intensity having Hamilton Depression Rating Scale score 8-18, were enrolled after informed consent procedure and given Sharbat Ahmad Shahi 20 ml twice daily for 6 weeks during the year 2019. Baseline and post treatment assessments were done using Hamilton Depression Rating Scale, Serum BDNF level and safety parameters.

Result: Highly significant difference was observed between baseline and post treatment Hamilton Depression Rating scale scores and serum BDNF values ($p<0.001$). However, no significant correlation was observed between these two parameters. Serum BDNF Level was significantly better in cases with full remission in comparison to those who did not remit completely ($p<0.05$). No serious clinical adverse event was observed in study cases and safety parameters.

Conclusion: Sharbat Ahmad Shahi is a safe and effective antidepressant that improves the serum BDNF level reversing the pathophysiology and hence it may be used as an alternative drug in mild to moderate depressive disorders.

KEYWORDS:
Depressive disorders; Serum BDNF; antidepressant; Unani medicine; Sharbat Ahmad Shahi

ARTICLE HISTORY:
Received Oct 02, 2021
Accepted Nov 13,2021
Published Dec 04, 2021

DOI:
10.5455/ jcmr.2021.12.04.39

VOLUME: 12
ISSUE: 4
ISSN: 2146-8397

1. INTRODUCTION

Depressive disorder is a common mental health problem occurring in about half of medical inpatients (Davidson, 2010). Depressed mood daily for a minimum 2 weeks duration is termed as major depressive disorder. Sadness, apathy, indifference, or irritability are characteristic features of depressive episode and is often associated with changes in appetite, weight and sleep patterns, fatigue, motor retardation or agitation, impaired concentration and difficulty in making decision, feelings of guilt and even thoughts of death. A major depressive episode is experienced at some point in life by almost 15% of the population and 6-8% of all outpatients in primary care centres fulfil the diagnostic criteria for the disorder (Longo, 2013). It was the third leading cause of disability in 2015 (Anniappan Arvind et al., 2019) and is contributing a major role to increase the overall global burden of disease. If left untreated, it may lead to suicide and is responsible for over 700,000 deaths every year 4-5. Although several synthetic drugs such as tricyclic antidepressants and selective serotonin reuptake inhibitors are being used as effective treatment for clinically depressed patients, the

possible adverse effects associated with these antidepressant medications like constipation, dryness of mouth, urinary hesitancy, blurred vision, fatigue, anxiety agitation, sexual dysfunction, drowsiness, and cardiac arrhythmias could not be ignored. The Monoamine Oxidase Inhibitors are very effective in atypical depression, but common side effects include weight gain, orthostatic hypotension, sleeplessness, and loss of libido. Risk of an overdose in patients of suicidal tendency, no effect of medication in one third cases, abstaining from medicines due to adverse effects and drug interactions are further disadvantages of conventional pharmacotherapy (Dhingra & Sharma, 2006; Longo, 2013). These issues demand the need for an alternative treatment approach to treat depressive disorders effectively in a safer manner and now scientists are shifting their attention towards indigenous systems of medicine to unravel and develop anti-depressant drugs from plants and their metabolites. Polyherbal Unani syrup Sharbat Ahmad Shahi is a well-known remedy for all types of depression and anxiety.(M. A. Khan, 1904) It is formulated following the Unani pharmacotherapy principles. It evacuates abnormal morbid matters, restores normal temperament and potentiates the brain functions (S. Khan, 2005). Experimental studies on rats demonstrated its antidepressant and anxiolytic effects by increasing availability of neurochemicals (tryptophan and serotonin) and decreasing the serotonin turnover rate (Ahmed & Azmat, 2017).

Various biomarkers are being studied to understand the mechanism and severity of depression and treatment outcomes as well. Brain-derived neurotrophic factor (BDNF) is one of such biomarkers, required in the regulation of several neuronal functions, as manifested by a large number of human genetics studies and animal experiments. BDNF is found in the brain as well as in circulating platelets. As BDNF is released from platelets during the process of blood coagulation, its levels can be quickly measured in serum. These levels are associated with diseases like depression, Alzheimer's disease and Huntington's disease etc. (Naegelin et al., 2018). Apart from its important role in cell survival and neural development, BDNF is believed to be essential in mechanisms of synaptic plasticity. In the central nervous system, basic activity-related changes are thought to be dependent on modification of synaptic transmission by BDNF, especially in the neocortex and hippocampus (Binder & Scharfman, 2004). There is increasing evidence that serum BDNF levels are low in patients with major depressive disorder and an association is observed in some studies with the severity of MDD (Naegelin et al., 2018). BDNF serum levels are also altered by use of antidepressant medications (Molendijk et al., 2011)(Ladea & Bran, 2013). The neurotrophin hypothesis of depression suggests that deficiency of central BDNF causes depressive disorders and that antidepressants work via restoration of this central BDNF level. The hypothesis is further supported by the fact that intracerebroventricular and intra-hippocampal injection of BDNF induces antidepressant-like effects in animal models of depression. Other studies demonstrated that BDNF could be involved in the mechanism of action of some specific antidepressants. Existing treatments for depression are considered to act primarily by increasing endogenous serotonergic and nor-adrenergic synaptic transmission, but recent studies have revealed that antidepressants that increase BDNF mRNA and protein are more effective (Altar et al., 2003)(Binder & Scharfman, 2004). Like other standard conventional antidepressants, we hypothesize that Sharbat Ahmad Shahi (SAS) improve the depressed state by increasing the serum BDNF level. Thus, for the purpose of objective assessment we evaluated the serum BDNF levels in cases of the depressive disorder before and after intervention along with their assessment on Hamilton Depression rating scale (HAM-D).

2. METHODS

Mild to moderate cases having major depressive disorders (HAM-D score 8-18) fulfilling DSMV diagnostic criteria, between ages 18 to 60 years of either gender, were screened for enrolment in the study from the outpatient department of Regional Research Institute of Unani Medicine (RRIUM), JJ Hospital campus, Mumbai during the year 2019. Patients with active drug or alcohol abuse, bipolar disorder, schizophrenia, those taking any other antidepressant drug, patients with suicidal tendency, pregnant and lactating mothers, patients with diabetes mellitus, cardiovascular diseases, uncontrolled hypertension, renal insufficiency, any other major chronic illness and patients with terminal medical conditions such as AIDS, cancer etc. were excluded from the study.

20 patients were enrolled in the study after taking their voluntary consent and thorough clinical examination. Venous blood samples of all patients were collected for serum BDNF assessment and safety parameters. All patients have been given the test drug Sharbat Ahmad Shahi 20 ml twice daily orally for 6 weeks. Patients were asked to follow up every two weeks, i.e. On 14th, 28th and 42nd day. After 6 weeks venous blood samples were again collected for safety parameters and serum BDNF assessment. Safety parameter investigations were done at Regional Research Institute of Unani Medicine, Mumbai. Pre and post treatment serum samples for BDNF assessment, collected at the pathological laboratory of RRIUM, Mumbai by centrifugation technique, stored at –20-degree Celsius freezer in Department of Life Sciences, Mumbai University, Kalina, Mumbai. BDNF assessment was done in ≤ 2 months of sample collection at School of Biotechnology & Bioinformatics, D Y Patil University, Navi Mumbai through a solid-phase, sandwich, two-site, enzyme-linked immunoassay (ELISA), using BDNF Human ELISA Kit (SEA011Hu, Cloud-Clone Corp. USA which had an excellent specificity and high sensitivity that can detect less than 11.3pg/mL), in accordance with the manufacturer's instructions given in its manual (Instruction Manual ELISA Kit for BDNF, n.d.). All samples were assayed in duplicate and the mean of measured Optical density (O.D.) was calculated. A standard curve was plotted using the mean O.D. and concentration for each standard with BDNF concentration on the Y-axis and absorbance on the X-axis in Microsoft Excel and unknown concentrations are calculated

using the graph formula. All patients were also evaluated on Hamilton Depression Rating Scale (17 points) at baseline and 6 weeks for the severity of their disease by a qualified physician trained by psychiatrist (Reynolds & Kobak, 1995).

This study was conducted following Declaration of Helsinki after obtaining approval from Institutional Ethics Committee and prospective registration in Clinical Trial Registry of India (CTRI/2019/09/021096).

In statistical analyses, categorical variables were presented in frequency and percentage, while continuous variables using mean and standard deviation (SD). Serum BDNF values were converted from pg/mL to ng/ mL to maintain uniformity with previous studies. Statistical analyses of Serum BDNF values and Hamilton Depression Rating Scale were done using paired 't' test. We considered $p \leq 0.05$ as statistically significant. All statistical analyses were done using SPSS, and Microsoft excel.

3. RESULTS

The demographic data and clinical characteristics of 20 patients are given in Table 1. 18 patients were having history of stress events in their family or workplace. No history of any mental stress was found in 2 cases. Baseline and post treatment scores of Hamilton Depression Rating Scale were found extremely significant ($p<0.001$) (Figure 1, Table 2). Mean (SD) of serum BDNF level was compared with baseline characteristics like age group, gender, diseases severity, smoking addiction, sleep pattern and physical activity (Table 3). A significant correlation was observed between serum BDNF levels of mild and moderate cases at baseline ($p<0.05$). After the intervention, serum BDNF level was increased in all patients except one (Figure 2). Highly significant difference was observed between pre-treatment and post-treatment serum BDNF levels ($p<0.001$). Significantly better outcome was observed in patients with history of sound sleep in comparison to those with disturbed sleep at baseline ($p<0.05$). All cases showed improvement in Hamilton Depression Rating Scale scores with complete remission in 9 cases. No significant correlation was found between HAM-D scores and serum BDNF levels but BDNF is significantly improved in cases with complete remission compared to non-remittent cases ($p<0.05$). No significant difference or adverse change was observed in safety parameters. Two patients reported mild symptoms after use of test drug which were resolved spontaneously without any intervention.

Table 1: Demographic Data and Baseline Clinical Characteristics (N=20)

Particulars		**Values**
Age in years: Mean (SD)		40.6 (10.6)
Gender	Female; n (%)	7 (35)
	Male; n (%)	13 (65)
Marital status	Married; n (%)	15 (75)
	Unmarried; n (%)	5 (25)
Duration of illness in months: Mean (SD)		34 (15.2)
Disease Severity	Mild; n (%)	8 (40)
	Moderate; n (%)	12 (60)
Smoking/ Tobacco addiction	Yes; n (%)	9 (45)
	No; n (%)	11 (55)
Sleep Pattern	Disturbed; n (%)	13 (65)
	Sound; n (%)	7 (35)
Physical Activities	Mild; n (%)	3 (15)
	Moderate; n (%)	14 (70)
	Hard; n (%)	3 (15)

Table 2: Baseline and Post treatment values of Serum BDNF and HAM-D Rating scores

Parameters	**Baseline Mean (SD)**	**Post treatment Mean (SD)**	**Difference Mean (SD)**
Serum BDNF ng/ml	0.54 (0.12)	0.78 (0.22)	0.24 (0.21) a
HAM-D Scores	14.35 (2.78)	7.45 (3.66)	6.9 (2.10) a

a: Highly significant difference was observed in both the parameters using paired t test. BDNF: Brain Derived Neurotrophic Factor, HAM-D: Hamilton Depression Rating Scale

Table 3: Serum BDNF levels according to different variables (N=20)

Variables		**Baseline Mean (SD)**	**After treatment Mean (SD)**	**Difference Mean (SD)**	**Remark**
Age in years	18-40	0.49 (0.07)	0.75 (0.18)	0.26 (0.15)	Better outcome
	41-60	0.59 (0.13)	0.81 (0.26)	0.23 (0.28)	Higher baseline
Gender	Female	0.49 (0.07)	0.78 (0.20)	0.29 (0.17)	Better outcome
	Male	0.57 (0.12)	0.78 (0.24)	0.21 (0.24)	Higher baseline
Disease Severity at baseline	Mild	0.62 (0.14)	0.87 (0.30)	0.25 (0.32)	Higher baseline* Better outcome
	Moderate	0.49 (0.06)	0.73 (0.15)	0.23 (0.17)	
Smoking/ Tobacco addiction	Yes	0.57 (0.15)	0.71 (0.25)	0.14 (0.28)	Higher baseline
	No	0.53 (0.10)	0.84 (0.20)	0.30 (0.15)	Better outcome
Sleep	Disturbed	0.55 (0.12)	0.72 (0.18)	0.17 (0.22)	Higher baseline
	Sound	0.53 (0.12)	0.90 (0.26)	0.37 (0.16)	Better outcome*
Physical Activities	Mild	0.49 (0.07)	0.68 (0.12)	0.19 (0.05)	

	Moderate	0.54 (0.12)	0.77 (0.22)	0.23 (0.25)	
	Hard	0.62 (0.15)	0.96 (0.29)	0.35 (0.16)	Higher baseline Better outcome

* Statistically significant difference is observed

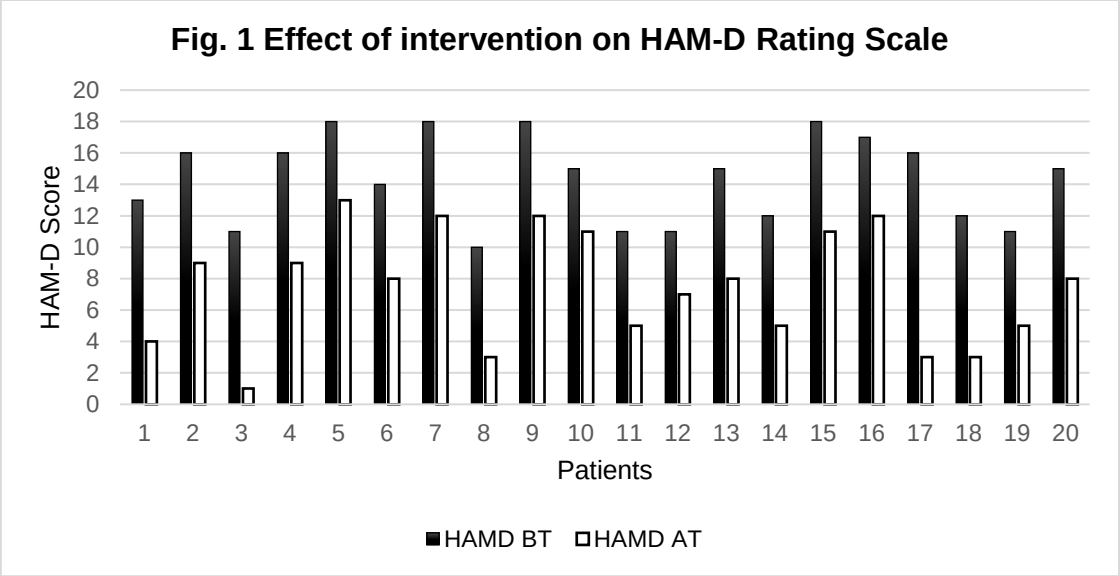

Fig.1: Effect of intervention on HAM-D Rating Scale

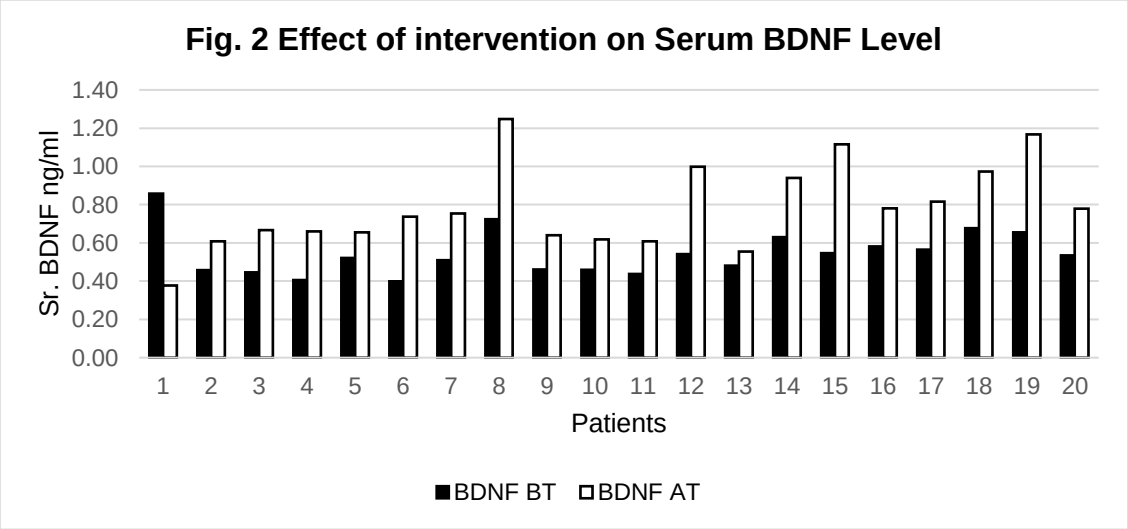

Fig.2: Effect of intervention on Serum BDNF Level

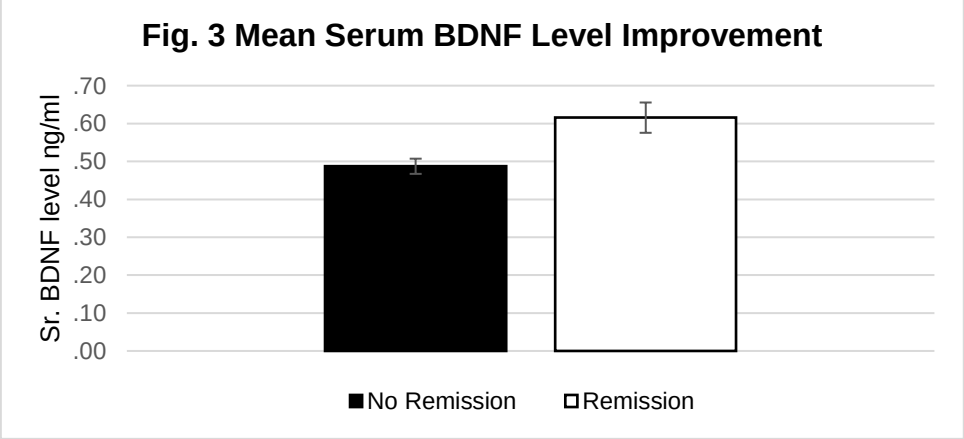

Fig.3: Mean Serum BDNF Level Improvement

4. DISCUSSION

Neuronal cells in the hippocampus produce neurotransmitter serotonin which plays a major role in mood regulation. Decreasing BDNF levels causes a decrease in the survival capability of neuronal cells affecting their neuroplasticity. This causes a reduction in the ability of neuronal cells to produce serotonin that causes an alteration in mood, anhedonia and feeling of guilt leading to depressive disorder. Effective antidepressant treatment should normalize this whole pathological process. Like other conventional antidepressants, Sharbat Ahmad Shahi improved the depressed condition, assessed by Hamilton Depression Rating Scale as well as serum BDNF level. This study generates evidence for the efficacy of Sharbat Ahmad Shahi which is advised based on holistic Unani medical principles. There is a growing need to scientifically evaluate and validate the medical concept of traditional medicine. Depression is improved in all cases to a variable degree and none reported reduction of the score while a decrease in serum BDNF level was noted in one patient unlike improvement in other 19 cases. In cases with full remission of disease, we found better improvement in BDNF level that correlates with the essential role of BDNF in remitting towards a normal state. Experimental study demonstrated the antidepressant effect of Sharbat Ahmad Shahi is modulated by the increased availability of neurochemicals (tryptophan and serotonin) and decreased serotonin turnover rate (Ahmed & Azmat, 2017). Hence, this polyherbal Unani formulation is possibly helpful in reversing the overall pathophysiological process of depressive disorders to the normal state. Earlier experimental and clinical studies reported normalization of Serum BDNF levels with some other known botanicals (Sangiovanni et al., 2017). Large scale study is needed to establish the correlation between the extent of antidepressant effect of Sharbat Ahmad Shahi and serum BDNF levels. Along with efficacy, the safety of test drug is also validated as no adverse change is observed in safety parameters and no serious clinical event appeared in any patient.

Higher baseline BDNF values with better outcome observed in patients doing hard physical activity is consistent with previous studies where it is observed that exercise increases serum BDNF level and sedentary activity may lead to lower BDNF levels (Chan et al., 2021; Kurdi & Flora, 2019). An increase in BDNF level was also proportionate to physical activity as improvement is higher in hard workers and lesser in mild workers. Mean baseline serum BDNF level was more in cases of mild depression in comparison to moderate one. This evidence supports an inverse relation of serum BDNF level with the severity of depressive disorders. This observation is in favour of serum BDNF level as a marker of disease activity although the previous study has contradictory findings (Molendijk et al., 2011)(Zheng et al., 2020). Although the normal level of BDNF is not standardized, BDNF is known to vary according to age, gender, and race (Naegelin et al., 2018). A weak association of higher baseline BDNF level was observed with male gender and age group 41 to 60 years. Smoking was found to be associated with high serum BDNF level in previous studies which is in line with our observation (Jamal et al., 2015). Improvement in BDNF level was found better in the age group 18-40 years, in females, in patients with no history of smoking or tobacco and those getting sound sleep. However, our sample size is too small to predict the strong relationship between all these variables.

As BDNF is associated with the pathological process of many diseases due to its essential role in neural development, cell survival and neuroplasticity, test drug may also be studied for its efficacy in neurodegenerative diseases, cognitive disorders and post stroke disabilities (Binder & Scharfman, 2004). Very limited clinical trials on humans are conducted for neurotrophic evaluation of herbal drugs in neuropsychiatric disorders including depression (Sangiovanni et al., 2017). This study emphasizes shifting the focus on human studies of herbs in this area that may explore better therapeutic alternatives to conventional antidepressants. Moreover, given the complexity of the BDNF mechanism, further refined analyses of the different elements are needed. It was a single-arm study as placebo control was not allowed by IEC and standard controlled study was difficult because of non-compliance of our Unani Medicine OPD for conventional antidepressant drugs.

5. CONCLUSION

We found a significant antidepressant effect of Sharbat Ahmad Shahi in mild to moderate cases of depressive disorders that supports the traditional claim of age-old Unani medicine of safe and effective treatment. We also found that Sharbat Ahmad Shahi increases the serum BDNF level significantly in depressed patients that could be considered the recovery mechanism behind the antidepressant effect. Further large-scale controlled clinical trials are needed to prove it as a better alternative to conventional antidepressants.

Acknowledgements

We are thankful to Department of Biotechnology, Jamia Millia Islamia, New Delhi and Central Council for Research in Unani Medicine, New Delhi for their support in overall research work

Conflict of interests

The authors declare no conflict of interest.

Source of Funding

Authors self-financed the study without involvement of any funding agency.

Authors Contribution

Conceptualization: MY, MZA. Methodology: MY, MZA, AA. Validation: MY, MZA and AA. Formal analysis: MY. Investigation: MY, AA, IA. Resources: MY, MZA, AA, IA. Data curation: MY. Writing – Original Draft: MY. Writing – Review & Editing: MY, MZA, AA. Supervision: MZA. Funding acquisition: MY, MZA.

REFERENCES

1. Ahmed, M., & Azmat, A. (2017). Decreased brain serotonin turnover rate following administration of Sharbat-e-Ahmed Shah produces antidepressant and anxiolytic effect in rats. Metabolic Brain Disease, 32(6), 1785–1790. https://doi.org/10.1007/s11011-017-0065-6
2. Altar, C. A., Whitehead, R. E., Chen, R., Wörtwein, G., & Madsen, T. M. (2003). Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. Biological Psychiatry, 54(7), 703–709. https://doi.org/10.1016/S0006-3223(03)00073-8
3. Anniappan Arvind, B., Gururaj, G., Loganathan, S., Amudhan, S., Varghese, M., Benegal, V., Rao, G. N., Mahadeo Kokane, A., S, C. B., K, D. P., Ram, D., Pathak, K., Singh K, L. R., Kumar Singh, L., Sharma, P., Kumar Saha, P., & Mehta, R. Y. (2019). Prevalence and socioeconomic impact of depressive disorders in India: multisite population-based cross-sectional study. BMJ Open, 9, 27250. https://doi.org/10.1136/bmjopen-2018-027250
4. Binder, D. K., & Scharfman, H. E. (2004). Brain derived neurotrophic factor. Growth Factors, 22(3), 123–131. https://doi.org/10.1016/B978-008055232-3.61338-8
5. Chan, G., Rosic, T., Pasyk, S., Dehghan, M., & Samaan, Z. (2021). Exploring the impact of modifiable factors on serum BDNF in psychiatric patients and community controls. Neuropsychiatric Disease and Treatment, 17, 545–554. https://doi.org/10.2147/NDT.S295026
6. Davidson, S. S. (2010). Davidson's principles and practice of Medicine. In Davidson's principles and practice of medicine (21st ed.). Churchill Livingstone.
7. Depression. (n.d.). WHO Website. Retrieved May 31, 2021, from https://www.who.int/news-room/fact-sheets/detail/depression
8. Dhingra, D., & Sharma, A. (2006). A review on antidepressant plants. Indian Journal of Natural Products and Resources, 5(2), 144–152.
9. Instruction manual ELISA Kit for BDNF. (n.d.). Cloud-Clone Corp. https://www.cloud-clone.us/manual/ELISA-Kit-for-Brain-Derived-Neurotrophic-Factor-(BDNF)-SEA011Hu.pdf
10. Jamal, M., Van der Does, W., Elzinga, B. M., Molendijk, M. L., & Penninx, B. W. J. H. (2015). Association Between Smoking, Nicotine Dependence, and BDNF Val66Met Polymorphism with BDNF Concentrations in Serum. Nicotine & Tobacco Research, 17(3), 323–329. https://doi.org/10.1093/NTR/NTU151
11. Khan, M. A. (1904). Qarabadeen Azam. Matba Siddiqui.
12. Khan, S. (2005). Ilajul Amraz (M. H. Hasan (Ed.); 2nd ed.). CCRUM.
13. Kurdi, F. N., & Flora, R. (2019). Physical exercise increased brain-derived neurotrophic factor in elderly population with depression. Open Access Macedonian Journal of Medical Sciences, 7(13), 2057–2061. https://doi.org/10.3889/oamjms.2019.574
14. Ladea, M., & Bran, M. (2013). Brain Derived Neurotrophic Factor (Bdnf) Levels In Depressed Women Treated With Open-Label Escitalopram. Psychiatria Danubina, 25(2), 128–132.
15. Longo, D. L. (2013). Harrison's Manual of Internal Medicine (18th ed.). McGraw-Hill.
16. Molendijk, M. L., Bus, B., Spinhoven, P., Penninx, B., Kenis, G., Prickaerts, J., Oude Voshaar, R. C., & Elzinga, B. M. (2011). Serum levels of brain-derived neurotrophic factor in major depressive disorder: state–trait issues, clinical features and pharmacological treatment. Molecular Psychiatry, 16, 1088–1095. https://doi.org/10.1038/mp.2010.98
17. Naegelin, Y., Dingsdale, H., Säuberli, K., Schädelin, S., Kappos, L., & Barde, Y. A. (2018). Measuring and validating the levels of brain-derived neurotrophic factor in human serum. ENeuro, 5(2). https://doi.org/10.1523/ENEURO.0419-17.2018
18. Reynolds, W. M., & Kobak, K. A. (1995). Reliability and validity of the Hamilton Depression Inventory: A paper-and-pencil version of the Hamilton Depression Rating Scale clinical interview. Psychological Assessment, 7(4), 472–483. https://doi.org/10.1037/1040-3590.7.4.472
19. Sagar, R., Dandona, R., Gururaj, G., Dhaliwal, R. S., Singh, A., Ferrari, A., Dua, T., Ganguli, A., Varghese, M., Chakma, J. K., Anil Kumar, G., Shaji, K. S., Ambekar, A., Rangaswamy, T., Vijayakumar, L., Agarwal, V., Krishnankutty, R. P., Bhatia, R., Charlson, F., … State-Level Disease Burden Initiative Mental Disorders Collaborators, I. (2019). The burden of mental disorders across the states of India: the Global Burden of Disease Study 1990-2017. The Lancet Psychiatry, 7, 148–161. https://doi.org/10.1016/S2215-0366(19)30475-4
20. Sangiovanni, E., Brivio, P., Dell'Agli, M., & Calabrese, F. (2017). Botanicals as Modulators of Neuroplasticity: Focus on BDNF. Neural Plasticity, 2017. https://doi.org/10.1155/2017/5965371
21. Zheng, W., Jiang, M. L., He, H. B., Li, R. P., Li, Q. L., Zhang, C. P., Zhou, S. M., Yan, S., Ning, Y. P., & Huang, X. (2020). Serum BDNF levels are not associated with the antidepressant effects of nonconvulsive electrotherapy. Neuropsychiatric Disease and Treatment, 16, 1555–1560. https://doi.org/10.2147/NDT.S256278