OPEN ACCESS

Middle East Research Journal of Pharmaceutical Sciences
ISSN 2789-7702 (Print) & ISSN 2958-213X (Online)
Frequency: Bi-Monthly
DOI: 10.36348/merjps.2023.v03i02.003

KUWAIT SCHOLARS PUBLISHER
Website: http://www.kspublisher.com/
Email: office@kspublisher.com

Molecular Mechanistic Insight Spirulina as Anti-stress Agent

Priyank Mishra[1*], Sunil Kumar[1], Jitender K. Malik[1]
[1]Institutes of Pharmacy, P. K. University, Shivpuri (M.P.), India

Abstract: When under stress, our body reacts by releasing hormones and triggering the nervous system. The hypothalamic-pituitary-adrenal axis, which transmits the stress response, is in charge of the neuroendocrine adaptation of the stress response. Corticotrophin releasing hormone neurons control hypothalamic-pituitary-adrenal function Increased. Many metabolic and neurological problems linked to stress are associated with the synthesis of corticotrophin releasing hormone. Gamma-aminobutyric acid (GABA) and GABAergic inhibition both play a significant role in controlling the activity of CRH neurons. Several synthetic medicines that target the GABAa receptor and activate GABAa activity are used to lessen the effects of stress. These treatments have relaxing effects but also come with a variety of negative effects. As they have no adverse effects and are harmless, anti-stress herbs are utilised as an alternative therapy to help the adrenal system. *Spirulina platensis* (commonly referred to as 'Spirulina'), are well for their Immune system modulation; anti-viral activity; cancer preventive properties, and cardiovascular benefits. In present work an attempt had been made to evaluate the anti-stress potential of active constituent of spirulina by molecular docking.

Keywords: *Spirulina platensis*, Phycocyanin, Serotonin receptor and docking.

Review Paper

***Corresponding Author:**
Priyank Mishra
Institutes of Pharmacy, P. K. University, Shivpuri (M.P.), India

How to cite this paper:
Priyank Mishra *et al* (2023). Molecular Mechanistic Insight Spirulina as Anti-stress Agent. *Middle East Res J. Pharm. Sci*, *3*(2): 25-30.

Article History:
| Submit: 07.03.2023 |
| Accepted: 20.04.2023 |
| Published: 22.04.2023 |

INTRODUCTION

Although there is no clear definition of stress, it is frequently referred to as a state of worry or anxiety brought on by perceptions of external obligations. Stress affects a very wide range of body systems. Different organs, emotions, feelings, and behaviours can all be impacted by different body parts in diverse ways. Unmanaged stress can eventually result in a number of medical and emotional conditions, including headaches, stomachaches, high blood pressure, chest pain, and heart disease [1]. The brain's hypothalamus is in charge of controlling various stress reactions. The pituitary gland and the adrenal medulla receive signals from the hypothalamus when a stress response is initiated. The pituitary gland is stimulated by the active brain to release adrenocorticotropic hormone [2]. The corticosteroid hormone, including cortisol, is stimulated to be produced by the adrenal gland as it travels via the bloodstream to the adrenal cortex. The body can maintain constant blood sugar levels thanks to the stress hormone cortisol. A person can deal with long-term stress better and their body can recover from it when their blood sugar levels are adequate and stable (Glover *et al*., 2010). Corticotrophin releasing hormone neurons control these stress reactions. These neurons' activity is substantially regulated by powerful Gamma-aminobutyric acid (GABA) mediated inhibition. The inhibitory neurotransmitter with the greatest distribution in the central nervous system is GABA. GABA affects our mood by lowering high levels of the chemicals dopamine, adrenalin, and noradrenalin [3]. Because to the wide variety and high concentration of nutrients it contains, spirulina is now frequently referred to as a superfood. It is the most nutrient-dense, entire food source that can be found in nature. Spirulina is sold all over the world as a dietary supplement or as a component in drinks and meals that have functional properties. It is widely accepted for the health advantages it offers consumers in Europe, North America, some regions of Asia, and Oceania. For people of all ages and lifestyles, spirulina is the perfect food supplement due to its concentrated nutrition [4]. Spirulina contains all nine essential amino acids and is a nearly 60% complete, highly digestible protein. Spirulina is the best whole food source of gamma linolenic acid (GLA), contains more beta-carotene than any other food, is high in B vitamins, minerals, trace elements, chlorophyll, and enzymes, and contains a variety of other nutrients like carotenoids, sulfolipids, glycolipids, phycocyanin, superoxide dismutase, RNA, and DNA [5].

Spirulina

In present work an attempt had been made to evaluate the anti-stress potential of active constituent of spirulina by molecular docking.

Experimental works

Molecular docking studies

Ligand Preparation:

2D Structure of ligand (phycocyanin) was drawn using ChemSketch [6], the two-dimensional structure of was converted into 3-D structure and optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structure of ligand (phycocyanin) is given below:

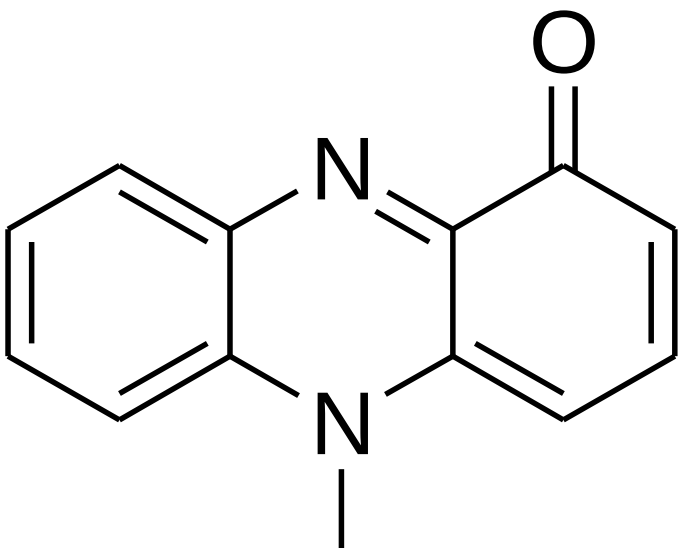


Figure 1: 2D structure of phycocyanin

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.375 Å and No. of points considered are 46, 44 and 46 points in the x, y, and z dimensions and 102.141, 115.111 and 108.423 as x, y, z centers [7, 8].

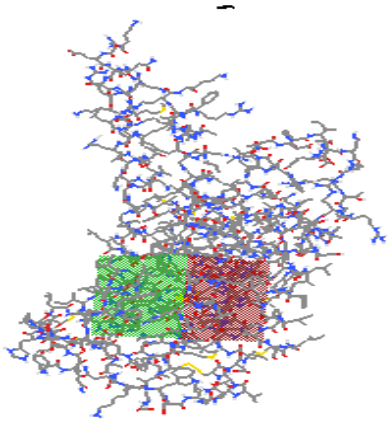


Figure 2: Grid box covering all active sites in receptor

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [3-5].

Docking of human 5HT1A receptor with Phycocyanin

Crystal structure

The crystal structure of the protein consisting of receptor associated with bound ligand serotonin is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (7e2y.pdb) registered in the Protein data bank was used. The bound ligand serotonin is found within the receptor [9, 10].

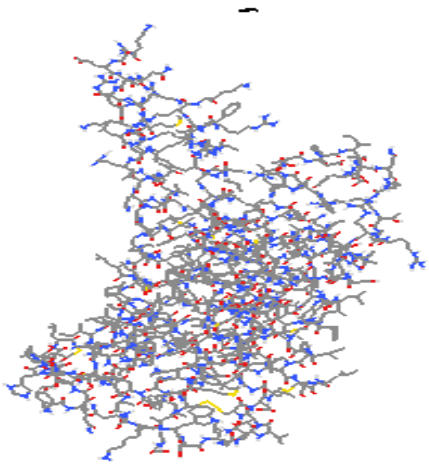


Figure 3: Crystal structure of human 5HT1A receptor with bound serotonin (PDB ID-7e2y)

Processing of Protein

The downloaded receptor protein is having two chains, i.e. chain A, B, C and R. Out of these four chains, chain R was selected for experimental purpose and other chains were removed from it. The bound ligand serotonin was separated from the macromolecular complex by using software Chimera [11].

Molecular Docking Simulation Studies

Docking of phycocyanin ligand on human COX-2 enzyme was performed by Autodock. All the

bonds of ligand were kept flexible, while no residues in receptor were made flexible [12].

Toxicity & ADME-T Studies

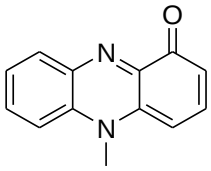
The modified lead molecules are studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [13-17].

RESULTS AND DISCUSSION

As per literature survey it has been found that phycocyanin is a photosynthetic pigment found in photosynthetic cyanobacteria, cryptophytes, and red algae. A new two-stage cultivation method to maximize the quantitative content and purity of phycocyanin obtained from Spirulina platensis was reported by Lee SH *et al*., 2016. So Phycocyanin was taken as lead molecular ligand for determination of anti-stress efficacy of *Spirulina platensis***.**

Serotonin receptors are found throughout central and peripheral nervous systems in the brain, mainly in regions involved in the neurobiology of anxiety and depression. There are 7 families of 5-HT receptors (5-HT1–5-HT7), which are further subdivided into 14 distinct receptor subtypes. Except for the 5-HT3 receptor, which is a ligand-gated ion channel, all known 5-HT receptors are G-protein coupled. One of the most important and extensively studied 5-HT1 subtypes is the 5-HT1A receptor due to its implication in the pathophysiology of several neuropsychiatric disorders including anxiety and MDD. The 5-HT1A receptors are distributed in the limbic, cortical, and dorsal and median raphe nucleus. The 5-HT1A receptors couple to the Gi/Go pathways, inhibiting the adenylyl cyclase to reduce cyclic adenosine monophosphate (cAMP) level and activating the G-protein inward rectifying potassium (GIRK) channels. 5-HT1A function as presynaptic auto receptors and postsynaptic heteroreceptors and signal to diverse and sometimes opposing pathways. Identifying biased 5-HT1A ligands that preferentially activate one pathway over another may offer novel strategies for depression treatment (Małgorzata Jaro ´nczyk *et al*., 2022). The phycocyanin was docked and the binding energy was found to be -7.21 kcal/mol and KI 5.16(table 1).Binding mode of phycocyanin with active site of receptor showed in fig. 4 &5. Interaction of lead molecule with ligand showed in fig.6, which revealed that active compound interacted with ligand by Pi-Pi stranded, alkyl & Pi-alkyl having CH- bond and Vander wall forces. Phycocyanin binds activity at Gly-R389, Cys-R-120, Val R-117,Ala R-203, Phen R-361 & Tyr R-39. The pharmacokinetic profile of phycocyanin revealed that it is having good pharmacokinetic profile without presence of any major toxic effects. The pharmacokinetic and toxicity profiling results of phycocyanin were shown in Figure 7.

Table 1: Results of docking of phycocyanin against human 5HT1A receptor.

S. No	Compound Name	Structure	Binding Energy	KI
1.	Phycocyanin		-7.21	5.16

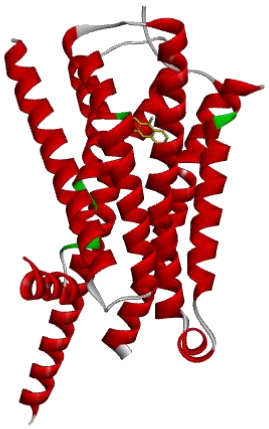


Figure 4: Binding mode of phycocyanin within the active site of serotonin Receptor

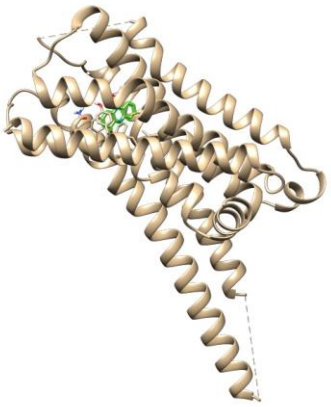


Figure 5: Binding mode of phycocyanin within the active site of serotonin Receptor

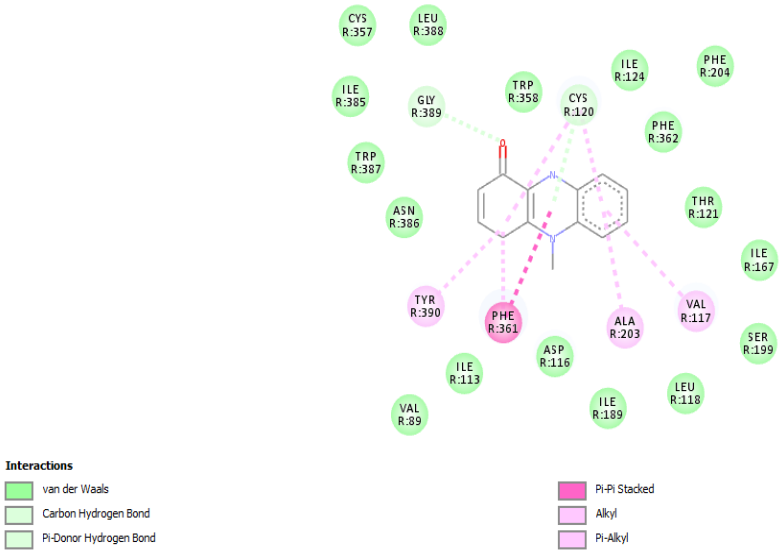


Figure 6: Interaction of Lead molecule with target ligand

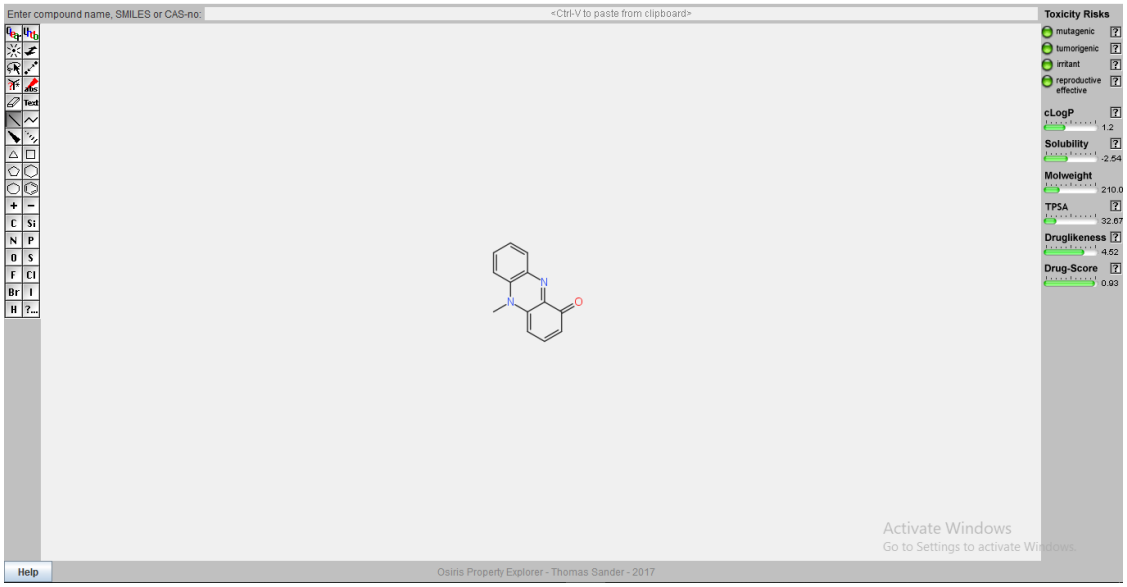


Figure 7: Pharmacokinetic and toxicity profiling of phycocyanin

CONCLUSION

According to the current research, spirulina has strong anti-stress properties. The most crucial step is relating the drug's pharmacological activity to the activation of various signaling pathways, which allows researchers to better understand the part played by particular signaling pathways in the pathogenesis of stress. According to a literature review, phycocyanin, a photosynthetic pigment found in spirulina, was chosen as the lead molecule targeted to the 5-HT1A receptors. As a result, the 5-HT1A receptors couple to the Gi/Go pathways, inhibiting adenylyl cyclase to lower cyclic adenosine monophosphate (cAMP) levels and activating the G-protein inward rectifying potassium (GIRRK) channels was determined as molecular insight the spirulina as anti-stress agent.

REFERENCE

1. Lotankar, A. R., Wankhede, S., Sharma, J. B., & Momin, A. J. (2016). Anti-Stress Activity of Flavonoids Rutin and Quercetin Isolated from the Leaves of Ficusbenghalensis. *Int J Phar Pharmac Res*, *5*(4), 5-19.
2. Sahley, B. J. (2006). GABA: The Brain and How it Affects Our Behavior, *Pain Stress Publ*.
3. Lee, M. S., Kim, Y. H., Lee, B. R., Kwon, S. H., Moon, W. J., Hong, K. S., ... & Her, S. (2014). Novel antidepressant-like activity of caffeic acid phenethyl ester is mediated by enhanced glucocorticoid receptor function in the hippocampus. *Evidence-Based Complementary and Alternative Medicine*, *2014*, 1-10.
4. Li, B., Gao, M. H., Zhang, X. C., & Chu, X. M. (2006). Molecular immune mechanism of C-phycocyanin from Spirulina platensis induces apoptosis in HeLa cells in vitro. *Biotechnology and applied biochemistry*, *43*(3), 155-164.
5. Li, B., Zhang, X., Gao, M., & Chu, X. (2005). Effects of CD59 on antitumoral activities of phycocyanin from Spirulina platensis. *Biomedicine & Pharmacotherapy*, *59*(10), 551-560.
6. Soni, H., & Malik, J. (2022). Isolation, characterization and radical scavenging activities of rutin isolated from leaves of Annona squamosa. *Journal of Pharmacognosy and Phytochemistry*, *11*(2), 222-228.
7. Fabbrini, G., Abbruzzese, G., Marconi, S., & Zappia, M. (2012). Selegiline: a reappraisal of its role in Parkinson disease. *Clinical neuropharmacology*, *35*(3), 134-140.
8. Pålhagen, S., Heinonen, E., Hägglund, J., Kaugesaar, T., Mäki-Ikola, O., Palm, R., & Swedish Parkinson Study Group. (2006). Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology*, *66*(8), 1200-1206.
9. Yang, L., Li, C. L., & Tsai, T. H. Preclinical Herb-Drug Pharmacokinetic Interaction of *Panax ginseng* Extract and Selegiline in Freely Moving Rats. ACS Omega. Kapoor LD. Hand of ayurvedic medicinal plants. CRC Press, 88, 10.
10. Henchcliffe, C., Schumacher, H. C., & Burgut, F. T. (2005). Recent advances in Parkinson's disease therapy: use of monoamine oxidase inhibitors. *Expert review of neurotherapeutics*, *5*(6), 811-821.
11. Lew, M. F. (2005). Selegiline orally disintegrating tablets for the treatment of Parkinson's disease. *Expert Review of Neurotherapeutics*, *5*(6), 705-712.
12. Malik, J. K., Soni, H., Sharma, S., & Sarankar, S. (2020). Hydroxychloroquine as potent inhibitor of COVID-19 main protease: Grid based docking approach. *Eurasian Journal of Medicine and Oncology*, *4*(3), 219-226.
13. Soni, H., Gautam, D., Sharma, S., & Malik, J. (2020). Rifampicin as potent inhibitor of COVID-19 main protease: In-silico docking approach. *Saudi Journal of Medical and Pharmaceutical Sciences*, *6*(9), 588-593.
14. Soni, H., Mishra, S., Mishra, R. K., & Mishra, S. R. (2022). Silibin as Potent Inhibitor of COVID-19 Main Protease: In-Silico Docking Approach. *Journal of Molecular Pharmaceuticals and Regulatory Affairs*, 4(1), 1-7.
15. Soni, S., Malik, J. K., Sarankar, S. K., & Soni, H. (2019). Rutin as a potent inhibitor of dihydrofolate reductase: A computational design and docking. *EAS J. Pharm. Pharmacol*, *1(6)*, 130-134.
16. Soni, N., Pardasani, K. R., & Mujwar, S. (2015). Insilico analysis of dietary agents as hepatoprotective inhibitors of insulin like growth factor 1 receptor (IGF1R), *J Pharm Pharm Sci*, 7, 191-196.
17. Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., & Ferrin, T. E. (2004). UCSF Chimera—a visualization system for exploratory research and analysis. *Journal of computational chemistry*, *25*(13), 1605-1612.