

Spirulina platensis (Blue-green algae): A miracle from sea combats the oxidative stress and improves behavioral deficits in an animal model of Schizophrenia

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Abstract: *Spirulina platensis* (blue-green algae) is a nutritional supplement. It constitutes of high content of protein, antioxidants, various phytopigments and possesses neuroprotective activities. Schizophrenia (SZ) is recognized as a neuropsychiatric disorder in humans with a reduced lifespan followed with impairments in social as well as vocational functioning. Major psychotic symptoms of SZ cluster into three categories: positive, negative and cognitive dysfunctions. Dizocilpine recognized as one of the best drugs to mimic full spectrum of SZ can develop an animal model of the disorder. Various antipsychotics are considered as approved treatment therapy for the psychotic symptoms of SZ but they also exert adverse effects. Thus, there is an excessive need for novel treatment(s) with negligible adverse effects. Present study was designed to evaluate the neuroprotective effects of spirulina in ameliorating the psychosis-like symptoms in dizocilpine-induced rat model of SZ. Spirulina was tested at the dose of 180 mg/kg. Results showed that administration of spirulina improved behavioral deficits and combated the oxidative damage evident by a significant reduction in lipid peroxidation and increase in antioxidant level. Thus, from present findings it may be suggested that spirulina can be used as a therapy for preventive or therapeutic measures.

Keywords: Schizophrenia, dizocilpine, psychosis, oxidative stress, blue-green algae.

INTRODUCTION

Spirulina platensis (blue-green algae) is recognized as a photosynthetic, multicellular edible microbe with a filamentous spiral-shaped structure (Abdel-Daim *et al.*, 2013). It is now represented as one of the richest and most complete source of nutrition from nature. Spirulina constitutes a range of prophylactic and therapeutic nutrients such as vitamins: B-complex and E, minerals, essential amino acids, bulk amount of protein, fatty acids in which gamma-linolenic acid are quite significant. It also contains potent anti-oxidant plant pigments such as carotenoids (beta-carotene), phycocyanin and a great number of bioactive compounds which are still unexplored (Ismail *et al.*, 2015). Moreover, spirulina also has been reported to possess various activities such as potent antioxidant, anti-diabetic, anti-inflammatory, anti-cancer, anti-viral, anti-hyperlipidemic, immunomodulatory and plethora of beneficial functions (Finamore *et al.*, 2017). Furthermore, this blue-green algae is considered as one of the best supplements and

alternative treatment therapy in 21st century (Seyidoglu *et al.*, 2017). National Institutes of Health (NIH) recommended this blue-green alga for nervous system treatment and other systemic diseases like obesity, diabetes mellitus and for hypercholesterolemia (Soni *et al.*, 2015).

Schizophrenia (SZ) is recognized as a chronic debilitating neuropsychiatric disorder in humans with a reduced lifespan followed with impairments in social as well as vocational functioning (Yan *et al.*, 2019). It has been estimated to affect approximately one percent of the population worldwide (Jones *et al.*, 2011). Although, the clinical use of various antipsychotics (typical or atypical) are being considered as the approved treatment therapy for the psychotic symptoms of SZ but along with that they also exert adverse effects such as extrapyramidal symptoms. Moreover, these antipsychotics also has negligible efficacy in treatment of negative and cognitive deficits of SZ (Miyamoto *et al.*, 2005). Therefore, there is a need for ongoing research based on novel treatment(s) with more efficacy and low adverse effects in treatment of

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negative symptoms as well as core persistent cognitive dysfunction of SZ. Accordingly, the objective of present study was same; it was attempted to identify a new supplement from natural herbal materials for the preventive as well as therapeutic treatment of SZ with more nutritious and negligible adverse effects. Previous studies have reported this blue-green alga as an effective supplementation against systemic diseases such as chronic obstructive pulmonary disease (Ismail *et al.*, 2015), cardiovascular disease, nonalcoholic fatty liver disease (Mazokopakis *et al.*, 2014), HIV and other viral diseases (Ngo-Matip *et al.*, 2015). Moreover, it has also been demonstrated to have neuroprotective effects in α -synuclein and 6-OHDA induced animal model of Parkinson's disease (Pabon *et al.*, 2012; Lima *et al.*, 2017) and also provide protection against haloperidol-induced tardive dyskinesia and oxidative stress (Thaakur and Jyothi, 2007). However, to the best of our knowledge none of the previous study reported the protective effects of spirulina against psychiatric disorders. Taking into consideration all the reported studies of spirulina, it can be hypothesized that this blue-green alga could have effective preventive or therapeutic treatment potential against schizophrenia and can be considered for the treatment of positive, negative and cognitive symptoms of SZ by combating oxidative stress induced in SZ condition.

MATERIALS AND METHODS

In this study, forty young male albino Wistar rats of locally bred (100-150g) were used in the present study. Before the start of experimental work, rats were acclimatized for four days with an open access to a standard rodent diet and tap water. *Spirulina platensis* was obtained from Kausar Medicos, Karachi, Pakistan, as an available supplement manufactured by Puritan's Pride, Inc. USA. Spirulina was dissolved in water and given per body weight of the animal. Rats (n=40) were randomly categorized and divided into five major groups (n=8); control group treated with 0.9% saline, model group was intraperitoneally injected with dizocilpine (0.3 mg/kg) for eight days, Spirulina group was orally administered with spirulina dissolved in water (180 mg/kg) for two weeks, Pre-Sp+Dizo group was treated with spirulina for two weeks followed by the administration of dizocilpine for eight days, and Post-Sp+Dizo group was first administrated with dizocilpine for eight days and then treated with spirulina for two weeks. After this, behavioral assessments were performed in a balance design to avoid any error regarding order and time (as depicted in fig. 1). Rats were then decapitated to collect the brain samples. The brain samples were processed to isolate pre-frontal cortex (PFC). PFC and rest of the brain were used for the biochemical estimations. All experimental work regarding animals approved by the Advanced Studies and Research Board of Institute (ASRB/02926/Sc.) and were conducted

in accordance with the rules and regulations of National Institute of Health Guide for Care and Use of Laboratory Animals with Publication no. 85-23, revised in 2011 and Scientific Procedures by UK animals (Act 1986).

Behavioral assessments

Stereotyped behavior

Stereotyped behaviors are described as types of abnormal movements and core features of psychotic disorders such as SZ and obsessive compulsive disorder (Ridley, 1994). Positive symptoms were analyzed by stereotyped behavior. It was conducted in an acrylic activity box (40×40×40 cm). The stereotyped behaviors that were examined were enlisted as: biting, chewing behavior (sawdust or unintended chewing), lifting of the forepaws (to the mouth or face), licking, grooming, shaking behavior (head or paw), cage climbing and rearing. If any of the above mentioned behavior lasted for more than 5 seconds and occurred repeatedly, then it was counted as a stereotyped behavior during 5 min cut-off time.

Sucrose preference test (SPT)

Anhedonia is regarded as an important component of depressive symptoms represented by absence of preference of sweetened water in comparison with regular tap water (Mazarati *et al.*, 2007). In order to evaluate negative symptoms, SPT was conducted and % of sucrose intake was monitored for three consecutive days. The experimental method was same as described previously (Shahzad *et al.*, 2017).

Novel object recognition test (NORT)

NOR is used for the assessment of cognitive functions in terms of recognition memory by a simple test in which the potential of rats to differentiate between two distinct objects is observed (Ennaceur and Delacour, 1988). The testing protocol followed was same as described by us previously (Haider *et al.*, 2016). Preference index (PI) was calculated by taking the ratio of time in exploration of novel object over exploration of total time in novel along with familiar object.

Biochemical estimations

Determination of oxidative status

Oxidative status was analyzed in terms of lipid peroxidation (LPO) by determining malondialdehyde (MDA) content. Whereas reduced glutathione (GSH) levels were measured to determine the antioxidant status by procedure described earlier (Haider *et al.*, 2016). MDA levels were represented as $\mu\text{mol/g}$ of brain tissue while GSH was represented as nmol/g .

STATISTICAL ANALYSIS

Experimental data were illustrated as mean \pm SD (n=8). Results were analyzed by One-way ANOVA followed by Tukey's test using SPSS version 20. Values of p less than 0.05 were taken as statistically significant.

RESULTS

Effect of spirulina on positive symptoms of SZ

Positive-like symptoms were analyzed via stereotyped behavior. One-way ANOVA showed significant changes between treatment groups [F (4, 39) = 128.688, $p < 0.01$]. Post-hoc analysis revealed significant ($p < 0.01$) increase in stereotypic interactions in dizocilpine administered rats as compared to its respective control group. Preventive and therapeutic treatment with blue-green algae revealed significant ($p < 0.01$) decrease in these stereotyped interactions as compared to model group (fig. 2).

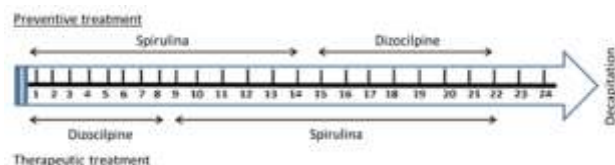


Fig.1: Schematic representation of experimental protocol of preventive and therapeutic administration of *Spirulina platensis* on dizocilpine induced psychotic behaviors.

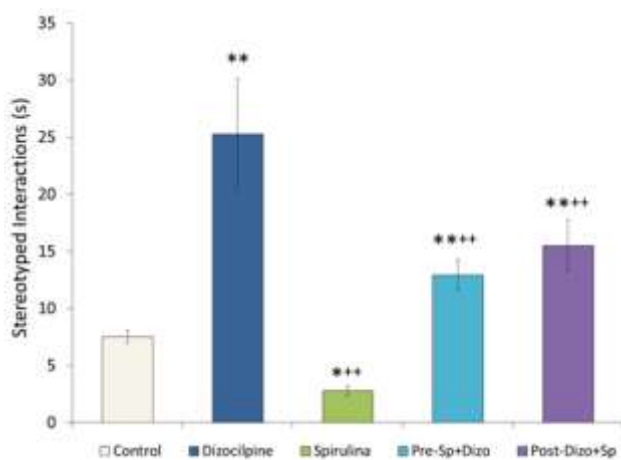


Fig. 2: Effects of preventive and therapeutic treatment of spirulina on stereotyped behavior induced by dizocilpine. Values are represented as mean \pm SD ($n=8$). Significant differences were taken by one-way ANOVA followed by Tukey's test. * $p < 0.05$, ** $p < 0.01$ as compared to controls and ++ $p < 0.01$ as compared to dizocilpine group.

Effect of spirulina on negative symptoms of SZ

Anhedonia which is one of the negative symptoms of SZ was evaluated by SPT (fig. 3). One-way ANOVA results showed significant ($p < 0.01$) differences between groups after 24h [F (4, 39) = 275.959], 48h [F (4, 39) = 30.715] and 72h [F (4, 39) = 20.667] of sucrose consumption. Post-hoc analysis depicted that dizocilpine treated rats exhibited significantly ($p < 0.01$) decreased %sucrose consumption monitored after 24h, 48h and 72h. However, spirulina as a preventive treatment significantly increased sucrose consumption after 24h ($p < 0.01$), 48h ($p < 0.01$) and 72h ($p < 0.05$) as compared to dizocilpine treated group. Therapeutic treatment with blue-green algae also

significantly enhanced sucrose consumption after 24h ($p < 0.05$), 48h ($p < 0.05$) and 72h ($p < 0.01$) as compared to dizocilpine treated group.

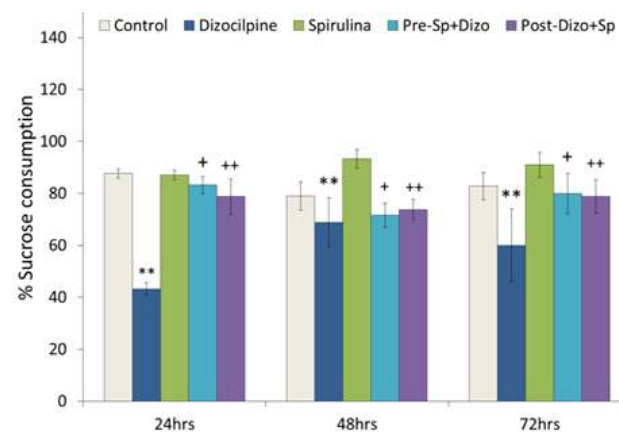


Fig. 3: Anhedonia-like state was analyzed by SPT. Effects of preventive and therapeutic treatment of spirulina on SPT evaluated by by Tukey's test showed significant differences. Values are represented as mean \pm SD ($n=8$). Significant differences were analyzed by one-way ANOVA followed by Tukey's test. * $p < 0.05$, ** $p < 0.01$ as compared to controls and ++ $p < 0.01$ as compared to dizocilpine.

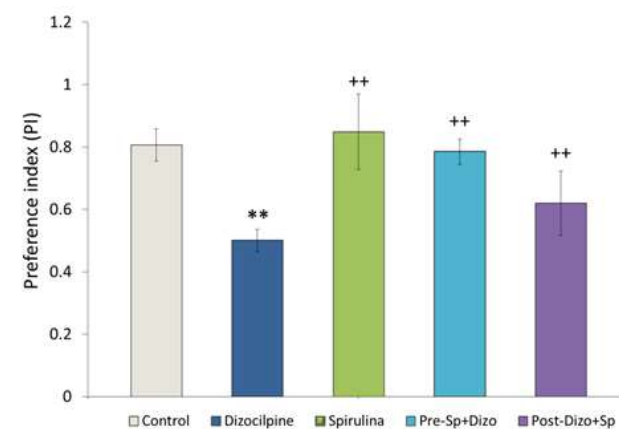


Fig. 4: Effects of preventive and therapeutic administration of spirulina on dizocilpine-induced cognitive impairment showed significant differences as evaluated by preference index (PI). Values are mean \pm SD ($n=8$). Data was analyzed by conducting one-way ANOVA test followed by Tukey's post-hoc analysis. Mean values were significantly different from control group (** $p < 0.01$) and dizocilpine administered rats (++) $p < 0.01$.

Effect of spirulina on cognitive deficits SZ

Recognition memory was also assessed in present study by NORT (fig. 4). Results analyzed by one-way ANOVA showed significant effects of treatment on PI [F (4, 39) = 39.115, $p < 0.01$]. Post-hoc comparison done by Tukey's test depicted that dizocilpine administered rats showed

significantly ($p < 0.01$) decreased PI as compared to respective control. While spirulina preventive as well as therapeutic treatment significantly ($p < 0.01$) increased PI when compared with dizocilpine administered rats.

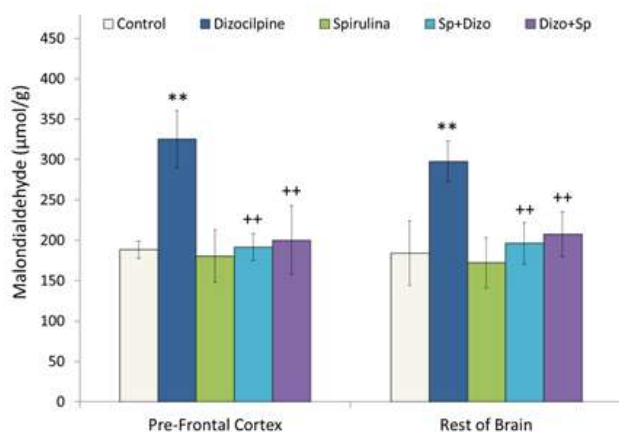


Fig. 5: Effects of preventive and therapeutic treatment with spirulina on oxidative stress induced by dizocilpine were assessed by MDA ($\mu\text{mol/g}$ of brain tissue) in PFC and rest of the brain. Values are mean \pm SD ($n=8$). Significant differences were evaluated by one-way ANOVA following Tukey's test. ** $p < 0.01$ versus control and ++ $p < 0.01$ versus dizocilpine injected group.

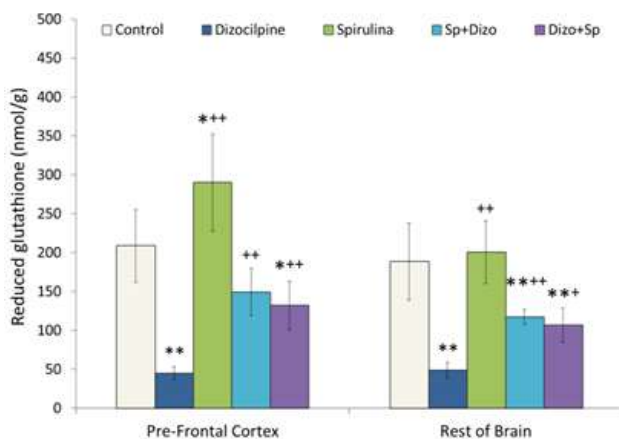


Fig. 6: Effects of preventive and therapeutic treatment with spirulina as an antioxidant on oxidative stress induced by dizocilpine on GSH (nmol/g of brain tissue) levels in PFC and rest of the brain. Values are mean \pm SD ($n=8$). Significant differences obtained from Tukey's test. * $p < 0.05$, ** $p < 0.01$ versus controls and ++ $p < 0.01$ versus dizocilpine injected group.

Effect of spirulina on oxidative status

Oxidative stress is another expected cause of psychosis in SZ. LPO was estimated in terms of MDA levels in PFC [F (4, 39) = 46.379] as well as rest of the brain [F (4, 39) = 29.742] and analyzed by one-way ANOVA which showed significant ($p < 0.01$) effects of treatment. Dizocilpine treated rats exhibited significantly ($p < 0.01$) increased MDA levels in PFC as well as in remaining part of the

brain. While preventive as well as therapeutic treatment with spirulina significantly decreased MDA levels in PFC ($p < 0.01$) and rest of the brain ($p < 0.01$) when compared with model group (fig. 5).

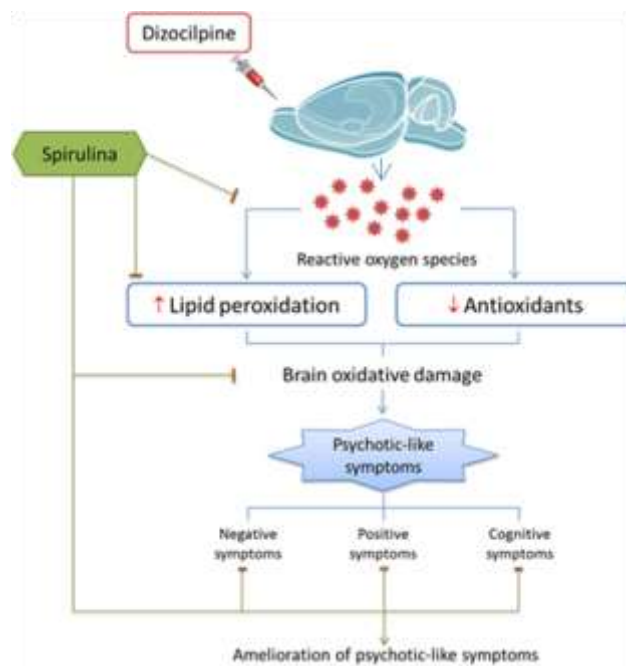


Fig. 7: Diagrammatic illustration of the current findings of preventive and therapeutic effects of spirulina on oxidative damage by dizocilpine-induced SZ psychosis animal model.

Results of GSH estimation in PFC [F (4, 39) = 57.426] and rest of the brain [F (4, 39) = 45.800] revealed significant ($p < 0.01$) differences among groups (fig. 6). Post-hoc analysis demonstrated rats that treated with dizocilpine exhibited significantly decreased GSH levels ($p < 0.01$) in PFC as well as in rest of the brain as compared to controls. Whereas, preventive ($p < 0.01$) as well as therapeutic ($p < 0.01$), ($p < 0.05$) treatment showed significant increase in GSH levels as compared to model group in brain region (PFC) as well as in rest part of the brain.

DISCUSSION

As there is no availability of any current 'gold standard' antipsychotic to treat all the symptoms of SZ except positive symptoms. Therefore, there is extensive need for novel compounds with increased efficacy to treat negative and cognitive dysfunction (Jones *et al.*, 2011). Full spectrum of SZ is mainly categorized into three major domains enlisted as positive, negative and cognitive dysfunction (Roegner *et al.*, 2012). Stereotyped behaviors are described as a number of types of abnormal movements and they are the core features of psychotic disorders such as SZ and obsessive-compulsive disorder (Ridley, 1994).

Dizocilpine administration in rats induced behavioral syndrome with characteristics such as stereotypies, hyperlocomotion and ataxia (Zavitsanou *et al.*, 2014). In our current research, positive symptoms were analyzed by stereotyped behavior and results showed that blue-green algae treated rats exhibited a significant amelioration of stereotypic behavior induced by dizocilpine. This shows that preventive and therapeutic effect of blue-green alga has the potential to ameliorate the hyperactive motor deficits observed in dizocilpine-induced SZ model rats. Spirulina contains a number of amino acids of both categories (essential and non-essential) in moderately high amounts as reported in a former study by Liestianty *et al.*, (2019). The essential amino acid contents of spirulina comprises of tryptophan (10mg/gm), phenylalanine (28 mg/gm), lysine (30mg/gm), thionine (33mg/gm), isoleucine (36mg/gm), valine (45mg/gm) and leucine (55mg/gm). Valine, one of higher content present in spirulina is of noteworthy here as it is involved in stimulation of mental capacity and muscle related motor coordination (Liestianty *et al.*, 2019). Therefore, the amelioration of motor deficits induced by dizocilpine may be due to valine content present in spirulina.

In line with positive symptoms, the negative and cognitive symptoms are also the core deficits of SZ and there treatment is basically a vital and unmet clinical need as these symptoms have an impact on patient recovery and re-integration into the society (Jones *et al.*, 2011). Anhedonia is regarded as an important component of depressive symptoms which is represented by an absence of preference to sweetened water in comparison to regular tap water (Mazarati *et al.*, 2007). In SZ, state of anhedonia is particularly a component of the negative and mood symptoms (Yan *et al.*, 2019). In current study, we analyzed the negative symptoms via SPT which revealed significant effects of spirulina on dizocilpine induced anhedonia-like state as evident from increased sucrose consumption in SPT. Blue-green alga also has the richest source of various vitamins in addition to other beneficial nutrients. Vitamin B12 is the largest and most complex group as it represents all of the biologically active cobalmines and it is considered as the most difficult of all groups of vitamins to obtain from vegetable sources. One more interesting fact about this alga is that it has an exceptionally high content of vitamin B12 than other sea weeds (Khan *et al.*, 2005). This vitamin is of vital importance as its deficiency leads to nerve degeneration, pernicious anemia, pronounced fatigue, premature senility and mainly mental illness which resemble SZ (Wolffenbuttel *et al.*, 2019). Previously it has been suggested that negative symptoms of SZ can be improved by supplementation of folate and vitamin B12 (Brown *et al.*, 2014). Therefore, in accordance with the previous findings, we can also justify our present results that vitamin B-12 content of spirulina might be essential for treating the negative symptoms of SZ.

Cognitive deficits also represent an important domain of SZ. It mainly includes deficits in memory (episodic and working), executive functions, and social cognitions (Fan *et al.*, 2019). Indeed, as cognitive deficits are described as the failure to achieve the expected levels of cognitive function then it has been predicted that almost all individuals with SZ are cognitively impaired (Sheffield *et al.*, 2016). In our current study, we analyzed cognitive function by NORT. Results assessed by this test showed that pre-treatment of blue-green alga not only attenuated the cognitive impairment induced by dizocilpine but also exhibited nootropic effects as evident from greater preference index in spirulina treated rats. The present results can be further justified by the presence of amino acid tryptophan in spirulina as it has variety of neuroprotective effects such as it increases utilization of vitamin B complex, improvement in nerve health and also stability of emotions (Demelash *et al.*, 2018). Moreover, it is the precursor of serotonin, which is helpful in preventing mental illnesses such as depression, bipolar disorder, eating and anxiety disorders, schizophrenia, attention deficit disorder, autism and substance use disorder (Jenkins *et al.*, 2016). Therefore, the presence of tryptophan in this blue-green alga may also enhance the serotonergic biosynthesis which ultimately not only attenuate cognitive dysfunction caused by dizocilpine but it also ameliorates the depression-like symptoms as evident from results of anhedonia in SPT in the present findings.

A clear mechanism behind the pathophysiology of SZ is still contentious. However, there is a growing body of evidence that oxidative damage which is defined as a state that arise from an imbalance between toxic reactive oxygen species (ROS) and with antioxidants has become an attractive and effective hypothesis for explaining the pathophysiology of SZ (Maas *et al.* 2017). Moreover, oxidative stress has role in antipsychotic-associated adverse events (Flatow *et al.*, 2013). Enhanced oxidative stress and increased MDA levels in PFC of rats have reported earlier in dizocilpine administration (Ozyurt *et al.*, 2007). GSH is regarded as one of the important antioxidant along with redox regulator that aids in protection of cells against oxidative damage (Lu, 2008). Several lines of evidence also suggested that any impairment in synthesis of GSH may be the leading factor in pathophysiology observed in SZ (Tosic *et al.* 2006; Gysin *et al.* 2007). Report from various functional imaging studies also suggested that after systemic administration of NMDA antagonist, the most affected region of brain is the PFC (Lahti *et al.*, 1995 and Breier *et al.*, 1997). Therefore, PFC was isolated for biochemical estimations in this study. Results clearly revealed that not only preventive but also therapeutic treatment with spirulina combat the oxidative damage induced by dizocilpine, as evident from significant decreased MDA levels and increased GSH levels in PFC as well as in rest

of the brain. Antioxidant effects of spirulina can also be related to former studies, having an evidence that blue-green algae contains ω -6 PUFA, vitamin B12, tocopherols, phytopigments such as carotene and xanthophyll along with phycocyanin, which make it a potent antioxidant (Li *et al.*, 2012). Due to higher content of beta-carotene in spirulina, it has greater neuroprotective as well as potent antioxidant activity, which could be expected to improve the cognitive functions by combating the oxidative stress (Kim *et al.*, 2016). The findings of the current study are summarized in fig. 7.

CONCLUSION

Therefore, from present findings it may be suggested that blue-green alga aids in combating the oxidative stress induced by dizocilpine in SZ animal model. Moreover, due to the potent antioxidant effects, this alga attenuates the psychosis-like symptoms regarding full spectrum of SZ. Accordingly, we have attempted to identify a new supplement which can be used as an adjuvant for the preventive as well as therapeutic treatment of SZ with negligible adverse effects. Limitation of our study is that current finding does not provide neurochemical and histopathological profile in schizophrenic rat brain supplemented with spirulina to determine the core underlying mechanism for the neuroprotective effects of spirulina against SZ. However, this study provides an initial clue for the preventive or therapeutic effects of blue-green alga against the pathogenesis of SZ by ameliorating oxidative stress. Further research can be conducted on neurochemical and histopathological studies to explore mechanism of action of spirulina in animal model of SZ.

ACKNOWLEDGEMENTS

Current study was supported by a grant received from University of Karachi, Karachi, Pakistan.

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