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A randomized controlled trial of 6-week *Chlorella vulgaris* supplementation in patients with major depressive disorder

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ABSTRACT

Background: Major depressive disorder (MDD) is a widespread psychiatric disorder with incapacitating symptoms. Oxidative stress has been identified to play a role in the pathophysiology of MDD.
Objective: To evaluate the therapeutic effectiveness of a chemically defined and antioxidant-rich *Chlorella vulgaris* extract (CVE) as adjunct to standard treatment in patients suffering from MDD.
Methods: Subjects with MDD diagnosis according to DSM-IV criteria who were receiving standard antidepressant therapy were assigned to add-on therapy with CVE (1800 mg/day; $n = 42$), or continued standard antidepressant therapy alone ($n = 50$) for a period of 6 weeks. Changes in the frequency of depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory II (BDI-II) scale.
Results: There were significant reductions in total and subscale BDI-II and HADS scores in both CVE and control groups by the end of trial. The magnitude of reductions in total BDI-II score [−4.14 (−5.30 to −2.97)] as well as physical [−2.34 (−2.84 to −1.84)] and cognitive [−1.12 (−1.62 to −0.61)] subscales were significantly greater in the CVE versus control group, however, reduction of the affective symptoms was greater in the control compared with the CVE group [0.95 (0.18–0.72)]. Total HADS [−3.71 (−4.44 to −2.98)] as well as individual subscales of depression [−1.46 (−2.02 to −0.90)] and anxiety [−2.25 (−2.74 to −1.76)] were reduced to a greater degree in the CVE group. CVE was well tolerated and no serious adverse event was reported.
Conclusion: This pilot exploratory trial provides the first clinical evidence on the efficacy and safety of adjunctive therapy with CVE in improving physical and cognitive symptoms of depression as well as anxiety symptoms in patients who are receiving standard antidepressant therapy.

1. Introduction

Depression is a debilitating mental disorder with a severe impairment to quality of life, and has been predicted to be the second leading cause of global disability by 2020.[1] The prevalence of depression in the global population is 4.3%,[2] and around 8–12% of people experience at least one episode of depression during their life.[3] Although different types of antidepressant agents are available for the treatment of depression and related disorders, still a considerable proportion of patients are not treatment-responsive and require additional options to control their symptoms.[4] Moreover, common antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) have different side effects and drug–drug/drug–food interactions.[5] For these reasons, searching for alternative antidepressant agents with proper efficacy and safety is necessary.[6–8]

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Oxidative stress is an important pathophysiological mechanism for several psychological disorders including major depressive disorder (MDD). Brain tissue is particularly vulnerable to the damaging effects of free radicals owing to its high oxygen utilization, modest content of antioxidants, rich content of lipids, and presence of oxidation-driving metals and neurotoxic excitatory mediators e.g., glutamate.[9,10] Several lines of evidence have shown depleted levels of antioxidants in plasma and brain tissue of patients suffering from MDD.[11–13] Notably, evidence from animal and human studies implies that such redox imbalances in MDD are effectively reversed following antioxidant therapy.[14]

Chlorella vulgaris is a unicellular green microalgae with many pharmacological activities including antioxidant, anti-inflammatory, anti-hypertensive, detoxifying, anti-atherosclerotic, anti-hyperglycemic, and anti-microbial effects.[15–20] This algae has been used as a dietary supplement and alternative medicine in Far East countries for hundreds of years. It has antioxidant and anti-inflammatory capacities and contains several micro- and macro-nutrients, such as carbohydrates, proteins, nucleic acid, essential amino acids, fatty acid (omega 3 and 6), vitamins, dietary fiber, and growth factors, which have all been shown to reduce depressive symptoms through multiple mechanisms.[21,22] In particular, *C. vulgaris* is a rich and diverse source of several antioxidants which have been shown to be protective against depression individually. The antioxidant and anti-inflammatory capacities of has also been shown in previous studies.[16–18,21,22] In spite of numerous health benefits of *C. vulgaris* in experimental models, and the unique antioxidant content of this algae, there has been no randomized controlled trial investigating its efficacy in psychological disorders.

The present study aimed to investigate the impact of short-term supplementation with chemically-defined *C. vulgaris* extract (CVE) as adjunctive to standard antidepressant therapy in patients suffering from MDD.

2. Methods

2.1. Subjects

Included subjects were male and females aged 18–65 years for whom a diagnosis of MDD was made according to the DSM-IV criteria, and were receiving standard antidepressant medications. Exclusion criteria were presence of epilepsy, mental retardation, bipolar disorder, obsessive-compulsive disorder, uncontrolled thyroid disease, or hypersensitivity to algal preparations. Patients who received any psychological intervention or psychotherapy were also excluded from the study. Study participants were recruited from the psychiatry clinics of the Baqiyatallah and Rofeideh Hospitals, both in Tehran, Iran.

2.2. Design

This study was designed as a randomized open-label controlled trial conducted between October 2012 and August 2013. One hundred and twenty-five subjects fulfilled the inclusion criteria and were randomly assigned to receive CVE as adjunct to their standard antidepressant therapy (CVE group; $n = 60$) or continue their standard antidepressant therapy alone (control group; $n = 65$) for a period of 6 weeks. CVE was administered at a daily dose of 1800 mg/day for 6 weeks. CVE was administered in the form of 300 mg tablets. Subjects were asked to take two CVE capsules, three times a day, after each meal with sufficient water. The study was approved by the institutional Ethics Committee, and written informed consent was obtained from participants.

Table 1
Ingredients of *C. vulgaris* extract tablets and their respective quantity according to the manufacturer's* leaflet.

Ingredient	Quantity
Fat (g/100 g)	8.65
Protein (g/100 g)	52.0
Carbohydrates (g/100 g)	13.6
Ash (g/100 g)	6.56
Water (g/100 g)	3.63
Dietary fiber (g/100 g)	15.6
Energy (Kcal/100 g)	340
Fatty acids	
Saturated fatty acid (g/100 g)	2.16
Monounsaturated fatty acid (g/100 g)	1.69
Poly unsaturated fatty acid (g/100 g)	3.34
Trans fatty acid (g/100 g)	0.06
n-3 Fatty acids	
Linoleic acid (g/100 g)	1.282
α-Linolenic acid (g/100 g)	1.964
n-6 Fatty acids	
Octodecatetaenoic acid (g/100 g)	0.003
Eicosadienoic acid (g/100 g)	0.011
Arachidonc acid (g/100 g)	0.009
Docosatetraenoic acid (g/100 g)	0.020
Vitamins	
β-Carotene (mg/100 g)	180.8
Vitamin B1 (mg/100 g)	1.5
Vitamin B2 (mg/100 g)	4.8
Vitamin B3 (mg/100 g)	23.8
Vitamin B5 (mg/100 g)	1.3
Vitamin B6 (mg/100 g)	1.7
Vitamin B12 (μg/100 g)	125.9
Vitamin C (mg/100 g)	15.6
Folic acid (μg/100 g)	26.9
Biotin (μg/100 g)	191.6
Para-amino-benzoic acid (mg/100 g)	0.6
Minerals	
Phosphorus (mg/100 g)	959
Potassium (mg/kg)	21450
Magnesium (mg/kg)	4425
Calcium (mg/kg)	2710
Iron (mg/kg)	680
Copper (mg/kg)	19.0
Zinc (mg/kg)	54.5
Manganese (mg/kg)	39.5
Iodine (mg/kg)	12.9
Chromium (mg/kg)	0.575
Miscellaneous	
Lutein (mg/100 g)	84.3
Lycopin (mg/100 g)	0.307
Zeaxanthin (mg/100 g)	0.679
Chlorophyll (g/kg)	15.21

* Administered *C. vulgais* extract tablets were from Bioprodukte Prof. Steinberg (Produktions- und Vertriebs GmbH & Co., KG, Klötze, Germany).

Administered CVE tablets were from a commercial source (ALGOMED®; Bioprodukte Prof. Steinberg Produktions- und Vertriebs GmbH & Co., KG, Klötze, Germany). The tablets contained 98% *C. vulgaris* powder, 1% separating agent (silicic acid), and 1% plant-based magnesium stearate. The tablets were ~9 mm in diameter and ~300 mg in weight. Chemical composition of CVE is summarized in Table 1.

2.3. Efficacy measures

Efficacy measures in the present study were changes in the psychological status based on the Beck Depression Inventory II (BDI-II) and Hospital Anxiety and Depression Scale (HADS). The HADS is a self-administered rating tool that consists of two subscales addressing anxiety (HADS-A) and depression (HADS-D).[23] Each subscale of HADS consists of seven questions on a four-point