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Chemical and behavioral effects of synthetic agents and natural agents of gamma-oryzanol and Chlorella vulgaris microalgae on depression in rats

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Depression is a psychological disorder that annually involves a significant population all over the world. Natural agents could be used for the treatment of depression. This study was conducted to compare synthetic agent of imipramine (IMP) and natural agents of gamma-oryzanol (GO) and *Chlorella vulgaris* microalgae (CV) on depression in rats. The depression was induced by using stress for 21 days and 6h/day. Fifty rats were divided into 5 groups, including 1) The rats exposed to depression without the treatment (DEP) and 2-4) the rats exposed to depression and treated with 100 mg/kg body weight of GO (GO), *C. vulgaris* (CV) and 30 mg/kg body weight of imipramine (IMP). A group without depression was considered as control (CON). Forced swimming test (FST) and open field test (OFT) were conducted to investigate the behavioral responses. The serum samples were analyzed for interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interferon-gamma (IFN-γ). The gene expression of BDNF and TrkB was also investigated. The results showed that the rats in DEP group spent more time in immobility test and had lower crossing number (P<0.05). The results showed that induction of depression increased the serum concentrations of IL-1β, TNF-α and IFN-γ (P<0.05) and decreased the expressions of BDNF and TrkB (P<0.05). The treatment with IMP, GO and CV decreased the effects of depression on behavioral responses, inflammatory responses and the expressions of BDNF and TrkB. Overall, GO and CV can be used for the treatment of depression following clinical tests.

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KEYWORDS

Animal model; BDNF; gamma-oryzanol; imipramine; inflammatory factors.

Introduction

Depression is a chronic psychiatric disorder that can cause mortality and morbidity in patients [1]. It is a mental illness and a major concern for public health all over the world [2]. The depression not only changes mood, but it also causes cognitive, emotional, homeostatic and psychomotor symptoms [3]. Some patients (20-35%) show symptoms after the treatment of depression [4]. Inflammation is a link between depression and other diseases associated with depression. Depressed patients show patterns for activated inflammatory response [5]. The increase in inflammatory factors is related with the decreased mood [6,7].

Several antidepressant drugs are used for the treatment of the depression such as tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors [8, 9]. The agents are synthetic and may have side effects for patients. Therefore, natural compounds with antidepressant properties and minimum toxicity are required for the treatment of depression.

Medicinal plants and their derivations and their active compounds could be utilized for the treatment of depression owing to their effects on neurotransmitters and expression of neurotrophic factors in the brain [10]. Gamma-oryzanol (GO) is a bioactive compound of brown rice that has a mixture of ferulic acid esters and phytosterols [11]. It is known to have some physiological and pharmaceutical properties such as antioxidant, anti-inflammatory, antidiabetic, and antiallergic properties [12, 13]. It also alleviated depression symptoms anxiety by modulation in serotonergic pathways [14]. *Chlorella vulgaris* is a green microalgae with several pharmacological properties such as antioxidant, and anti-inflammatory [15, 16]. Both GO and *C. vulgaris* have anti-inflammatory properties that might have profitable effects for alleviation of depression symptoms by the modulation in inflammatory system. The preparation of agents with minimum side effects can help to treatment of diseases. Therefore, in this study we aimed to compare synthetic agents and natural agents of GO and *C. vulgaris* microalgae for the treatment of depression in a rat model.

Materials and methods

The induction of depression

The depression was induced by using stress as reported by previous studies. Different stresses were given for 21 days and 6h/day [2, 17].

Experimental groups

In this study, 50 adult male rats with weight of 180±15 g were prepared and studied. The rats were divided into 5 groups (n=10), as follows:

1. The rats exposed to depression without the treatment (DEP);
2. The rats exposed to depression and treated with 100 mg/kg body weight of GO (GO);
3. The rats exposed to depression and treated with 100 mg/kg body weight of *C. vulgaris* (CV);
4. The rats exposed to depression and treated with 30 mg/kg body weight of imipramine (IMP); and,
5. Non-stressed rats and without the treatment (CON).

Both microalgae and GO were orally administrated, while imipramine was intraperitoneally administrated. The treatment was started from first day stress and continued to end of stress period.

Behavioral responses

Forced swimming test (FST) and open field test (OFT) were conducted to investigate the behavioral responses as reported by previous studies [2].

Inflammatory responses

In the end of study, blood samples were collected from 4 rats per group and investigated by RayBiotech Company commercial kits. The serum samples were analyzed for interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interferon-gamma (IFN-γ).

The gene expression of BDNF and TrkB

In the end of study, the gene expression of BDNF and TrkB were investigated in hippocampus of three rats per group as reported by Ge *et al* [18] and based on their primers.

Data analysis

The data were reported as mean ±SD and analyzed by SPSS software 23.0 (Chicago, IL, USA) by using analysis of variance (ANOVA) and Duncan post hoc tests. Significance at p value<0.05 was considered as significant.

Results

Confirmation of depression

The results for immobility are shown in Figure 1. The results showed that immobility time was significantly higher in control rats compared to healthy rats (*P*=0.001). The results approved the depression in groups.

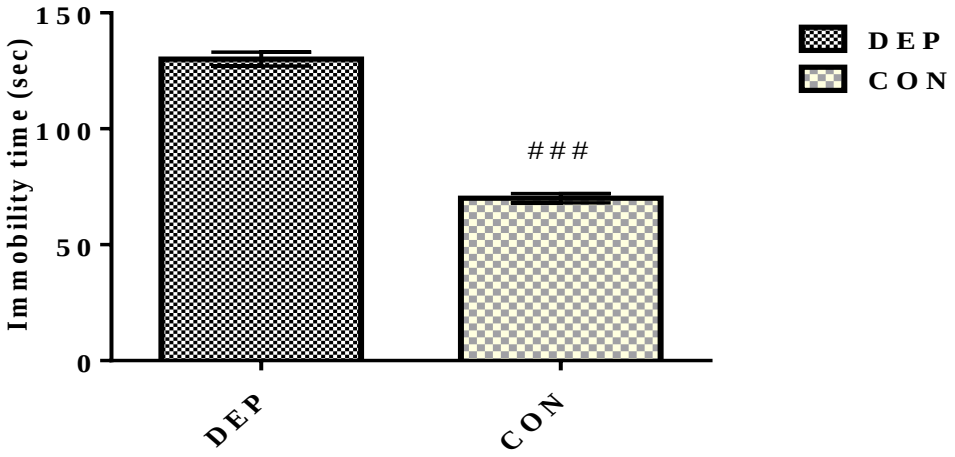

FIGURE 1 Confirmation of depression in the FST on day 24. Superscript # shows significant difference between groups

Behavioral tests

The results for behavioral responses are illustrated in Figure 2A. The results showed that immobility time was significantly higher in depressed rats compared to control rats (*P*=0.001). The rats treated with imipramine showed lower immobility time compared with rats in DEP, GO and CV groups (*P*=0.003). The rats in GO and CV groups showed lower immobility time compared with rats in DEP group (*P*=0.021). The rats in GO and CV did not show significant differences for immobility time (*P*=0.653).

The number of crossing (Figure 2B) was significantly higher in the rats in CON group compared with the rats in DEP groups (*P*=0.0001). The rats in IMP, GO and CV showed higher compared to those in DEP group (*P*=0.0001). The rats in IMP group showed higher crossing number compared with rats in GO group (*P*=0.001) and CV group (*P*=0.001)

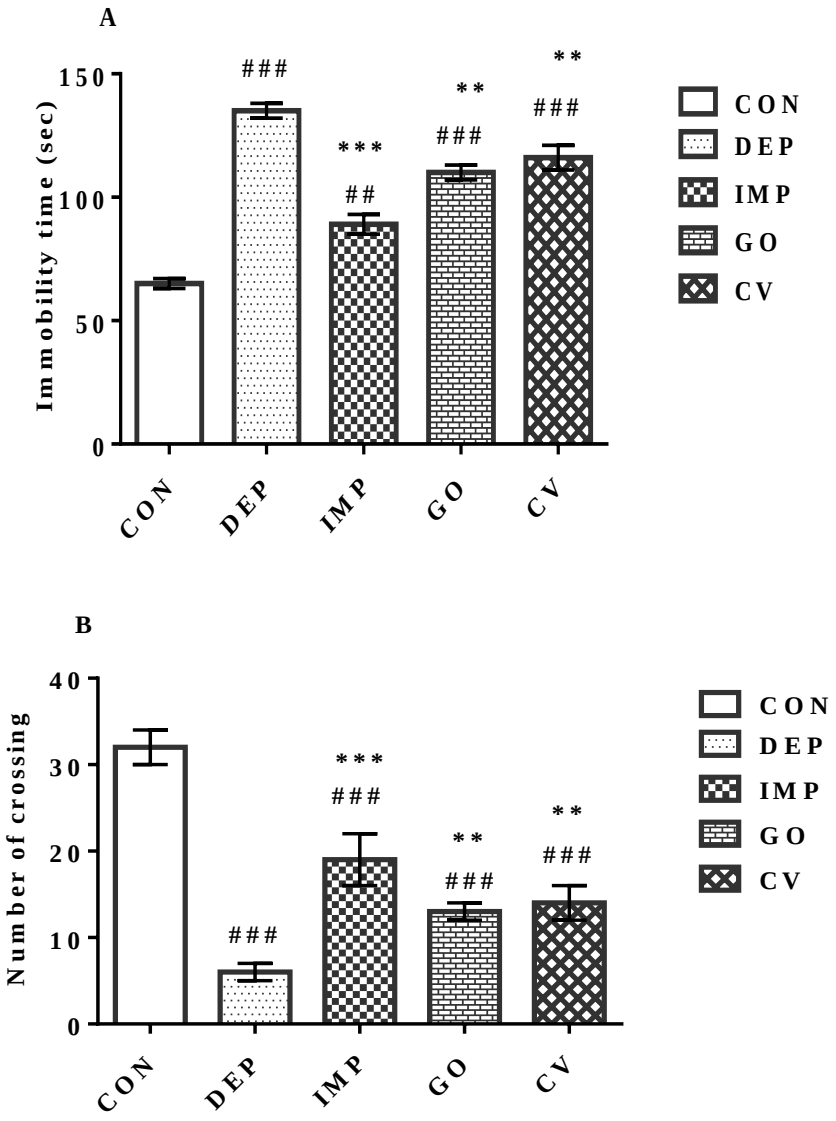

FIGURE 2 Behavioral responses in the rats. Superscript # shows significant difference between other groups with control group, and superscript * shows significant differences between other groups with DEP group.

Inflammatory responses

The results for inflammatory responses are shown in Figure 3. The results showed that the serum concentrations of IL-1β, TNF-α, and IFN-γ were significantly higher in the depressed rats compared with non-depressed rats (P<0.01). The results also showed that the treatment with IMP, GO and CV similarly decreased the serum concentrations of IL-1β, TNF-α, and IFN-γ compared with DEP group (P<0.01)

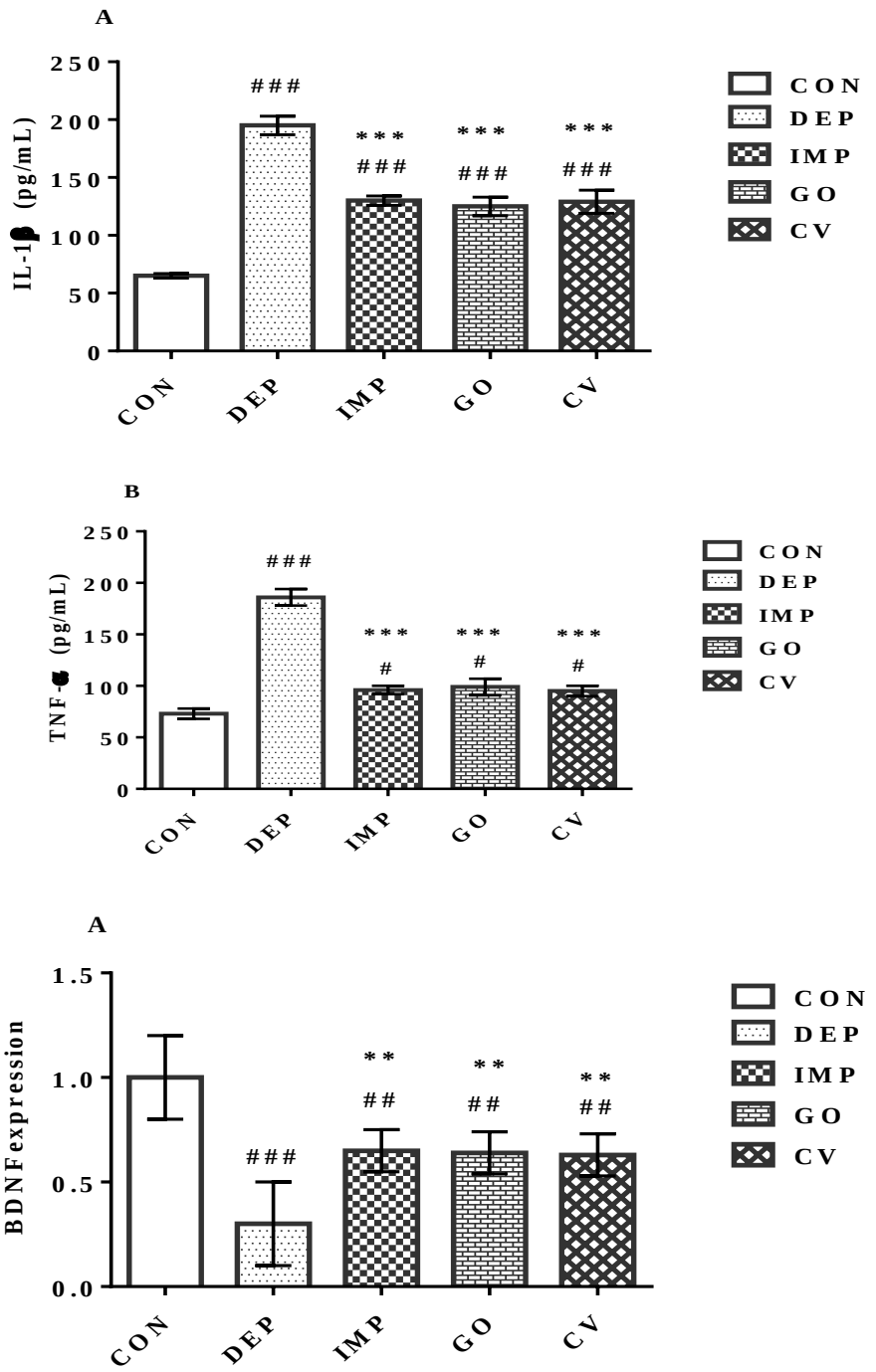

FIGURE 3 The results for inflammatory responses in the rats. Superscript # shows significant difference between other groups with control group, and superscript * shows significant differences between other groups with DEP group

The results for gene expression of BDNF and TrkB

The results for gene expression of BDNF and TrkB are shown in Figure 4. The results showed that the expressions of BDNF and TrkB were significantly lower in the rats in DEP group compared with other groups (P<0.05). The treatment with imipramine, GO and CV increased the expressions of BDNF and TrkB compared with DEP group BDNF and TrkB.

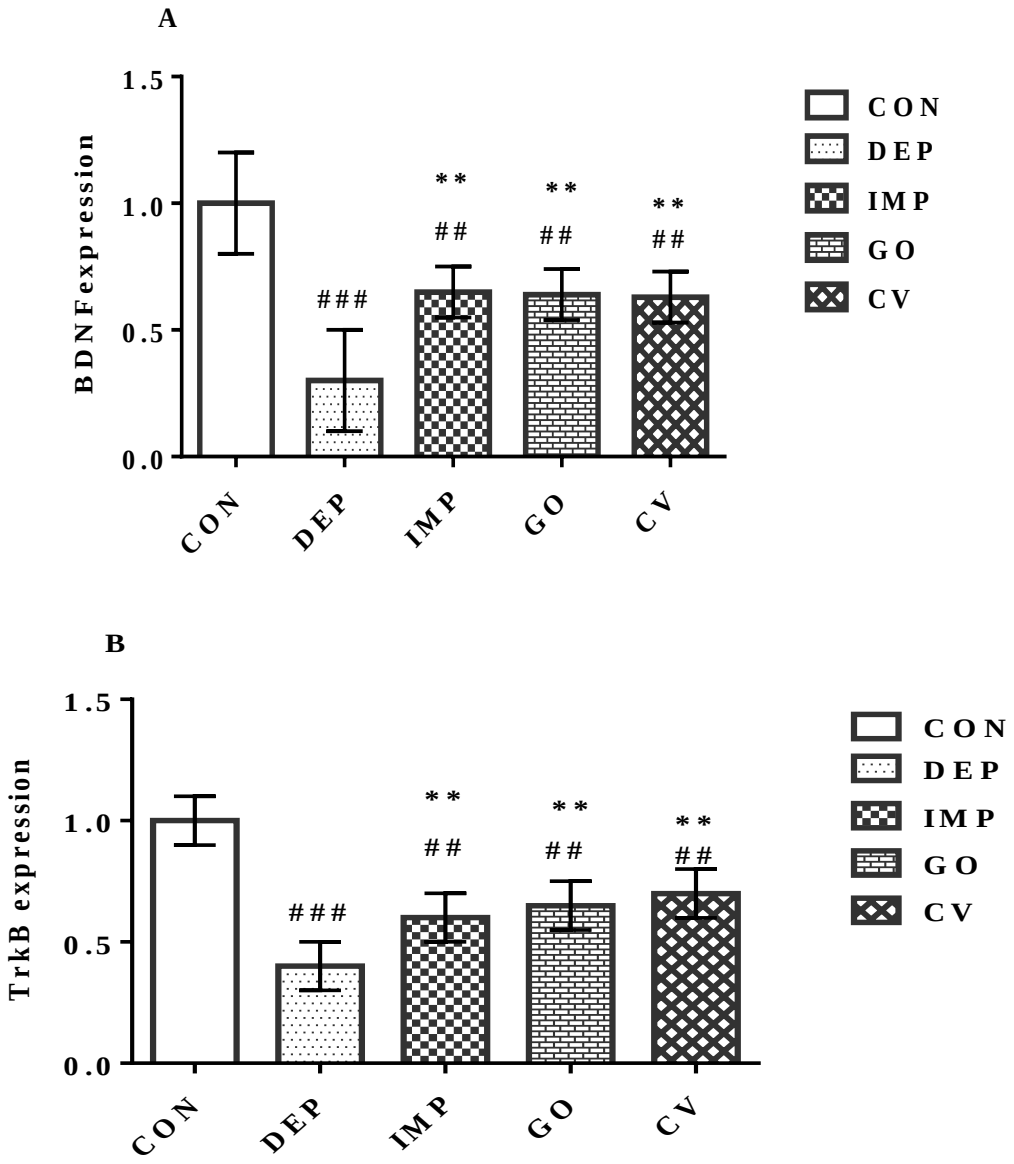

FIGURE 4 The results for the gene expression of BDNF and TrkB in the rats. Superscript # shows significant difference between other groups with control group, and superscript * shows significant differences between other groups with DEP group.

Discussion

The depression is a major disorder across the world and it annually involves a large number of people. The results showed that induction of stress increased depression signs. The obtained results for behavioral responses in the FST are parallel to the results reported by previous studies [19,20]. The results showed that the treatment with imipramine improved behavioral responses compared with DEP group. The results confirmed clinical uses of imipramine for the treatment of the depression. The treatment with imipramine showed better response compared with GO and CV for behavioral responses. The improvement in responses by the administration of CV might be attributed to its compounds. It contains methyl cobalamine that is the more absorbable form of vitamin B12 [21] and efficiency of vitamin B12 in antidepressant regimen for improving

depression was previously reported (22). The results for the effects of GO on the depression are consistent with the results reported by other researchers for the effects of GO on anxiety [14]. The mechanism for action of GO is unknown. It might function by the involvement in the inflammation and the expression of BDNF and TrkB that will be discussed. The results showed that the depression increased the serum concentrations of inflammatory factors. Inflammation is a link between depression and other diseases associated with depression. Depressed patients show patterns for activated inflammatory response (5). Previous studies have reported anti-inflammatory responses of CV [15, 16] and GO [12, 13]. The inflammation is a type of response to disease. Seemingly, natural agents (CV and GO) decrease the inflammation and help to decrease signs for disease. In sum, treatment with GO and CV decreased the inflammation and might help to decrease the depression by decreasing the inflammation. The results showed that the depression decreased the expression of BDNF and TrkB. BDNF is a survival factor for neurons and is a member for the neurotrophic family [23, 24]. It is a signaling molecule in the microglia-neuron signaling pathway, and might be a therapeutic strategy for the treatment of neuropathic pain treatment [25, 26]. TrkB is the high affinity receptor for BDNF. Therefore, BDNF and TrkB have important roles in the nervous system. The mechanism of action for the effects of agents on the expression is unknown and requires more studies.

Conclusion

Treatment with GO and CV decreased depression by the modulation in the inflammation and the expression of genes. This is a preliminary study and opens way for future studies.

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