Original Article

The Brown Alga *Padina australis* Total Extract and Depressive-like Behavior Following BCG Inoculation in Mice

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ABSTRACT

Background: Depression is an important psychological disorder because it is a common mental illness that leads to morbidity and suicide. Although appropriate antidepressant drugs exist, they usually have unpleasant side effects and delayed onset.

Objectives: Introducing new compounds such as medicinal plants and oceanic living organisms such as alga is appropriate. Here the depressive-like effects of *Padina australis* Hauck total extract (PAE) were evaluated following depression induced by Bacillus Calmette–Guérin (BCG) in mice.

Methods: Male NMRI mice (average weight: 27±2 g) were used. A single BCG 0.2 mL/mouse was inoculated. PAE effective dose (40 mg/kg) and imipramine (10 mg/kg) were administered as the reference drug for 14 days. The control animals received normal saline. All treatments were administered intraperitoneally. After evaluating the locomotor activity, different depression criteria were assessed by forced swimming test (FST), sucrose preference (SP) test, and novelty-suppressed feeding test (NSFT).

Results: Depression was induced by BCG. The selected PAE dose did not cause a significant change in the locomotor activity compared with the control (139±16.9 count), while the immobility time in FST reduced (45.1±11.4 s vs BCG, P<0.001). During the NSFT, the latency decreased (94.7±18.5 s vs BCG, P=0.0365), food intake increased (17.4±2.11 mg/g body weight vs BCG, P=0.023), and SP up to 79.3±4.7%. These changes were similar to imipramine.

Conclusion: PAE showed antidepressant-like effects as despair behavior reduced during FST. Based on NSFT, the stress declined, and animal appetite increased, while SP revealed remission of anhedonia. Further studies are suggested regarding the antidepressant effects of PAE different partitions.

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Introduction

Depression impacts performance and quality of life and is a worldwide cause of suicide and death [1]. Depression, with a 7% incidence in a lifetime, has affected the lives of 350 million people globally and is expected to be a major cause of disability by 2030 [2]. The pathophysiology of depression involves irregular monoamine neurotransmitters, hypothalamic-pituitary-adrenal axis dysfunction, inflammation, and cytokine disorders [3-5]. In addition, decreased neurogenesis, mitochondrial disorders, a fall in antioxidant levels, and a rise in the oxidative stress level also have a role in depression [6-9]; meanwhile, anti-inflammatory drugs have provided antidepressant effects [10, 11]. Although many medications have been used to treat and control depression, side effects such as headache, insomnia, drowsiness, ejaculation disorders, dry mouth, and loss of appetite make these difficult for patients to tolerate these drugs [12]. In addition, the therapeutic effects start with a delay, and these problems have increased the interest in introducing alternative therapies for depression, such as vitamins and natural products [13, 14]. The oceans are among the new resources for medicinal plants [15].

The hexane partition of *Sargassum plagyophylum* had antidepressant-like effects during the single and multiple administrations in mice [16]. In addition, this extract could also prevent depressive behavior caused by stress or following dexamethasone injection [17]. *Padina australis* Hauck is a brown alga belonging to the Phaeophyceae class found in the warm waters of most of the world, namely the Persian Gulf [18]. *P. australis* is rich in chemical compounds, including phenolic compounds, carotenoids, steroids, terpenoids, polyphenols, pigments, saponins, β-carotene, chlorophyll A and B and C, and fucoxanthin [19-21]. *P. australis* is a good source of eicosapentaenoic acid, linoleic acid, arachidonic acid, α-linolenic acid, and palmitic acid saturated fatty acids [21]. The chemicals in this alga, including its phenolic extract, have shown antioxidant effects [22]. It also has protective effects by inhibiting free radicals and increasing glutathione levels and cell survival [22]. Seaweeds are invaluable sources of omega-3 and omega-6, long-chain unsaturated fatty acids that have a vital role in the formation of cell membrane parts also structural lipids [23].

Like another alga, such as *S. plagyophylum*, has shown antidepressant-like effects [16, 17], and *P. australis* richness in long-chain unsaturated fatty acids, omega-3 and omega-6 fatty acids, and antioxidant activity [21, 24], it may have positive effects on depression. In this study, depression was induced by Bacillus-Calmette-Guerin (BCG) inoculation in mice. BCG is a weakened living form of *Mycobacterium bovis* that is usually administered in infants for immunization against tuberculosis and against other Mycobacterium infections, leprosy, and Buruli ulcer [25]. After inoculating mice with BCG, in the beginning, an acute sickness behavior continues for 5 days. In the following days, a duration of chronic depressive-like behavior (symptoms such as weight loss, despair behavior, and anhedonia) appears that would continue for several weeks [26]. After BCG initiated depressive-liked behaviors in mice, the preventive effects of *P. australis* alga total extract on depressive behavior were evaluated.

Material and Methods

Study animals

Experiments were conducted on male NMRI mice that weighed around 27 ±2 g and were aged 6-8 weeks. Mice were kept at optimal temperature (21ºC ± 2ºC), humidity, and light (12 h light, starting at 6 AM, and 12 h dark cycle). The animals had free access to water and food during the experimental period, except otherwise mentioned. The treatments were for 2 weeks, and after the experiments, the animals were euthanized in a CO_2-containing chamber. Ten groups of at least 6 animals each were used in the study.

Groups 1-4 received a single injection of three doses of *P. australis* extract, and the control group (normal saline). Groups 5-6 were the BCG inoculation and control groups (a single normal saline injection). Groups 7-8 were *P. australis* (40 mg/kg) and the control group (normal saline) administered for two weeks. Group 9 received BCG inoculation plus *P. australis* (40 mg/kg) for two weeks. Group 10 received BCG inoculation plus imipramine (20 mg/kg) for two weeks.

Animal management was performed according to the guidelines for the care and usage of laboratory animals for conducting animal research in Iran (Ethical No: IR.MUI.REC.1400.176). In addition to considering animal welfare, attempts were made to reduce the number of animals for the experiments.

P. australis extract preparation

P. australis was collected from the Southwest coastline of the Persian Gulf in 2019. The alga was confirmed as *P. australis* by the Agricultural and Natural Resources Research Center of Bushehr and coded: 2669. The alga was

washed several times to ensure salt and contamination removal. It was then dried at room temperature in the shade and ground to powder, then extracted by maceration with methanol-ethyl acetate (1:1) at room temperature. The extraction method was repeated four times, and the solvent evaporated under a vacuum.

Phytochemical standardization

Total phenolic compounds in the crude extract were analyzed using the Folin-Ciocalteu reagent test [27].

Drug administration

BCG (2 mg freeze-dried *Mycobacterium bovis* BCG/vial with 2 mL diluent [Sauton], viable particle count: 1.5-6×10^6/mL, Pasteur institute of Iran) 0.2 mL once per mouse inoculated intraperitoneally [28]. The volume for all the other injections was 10 mL/kg. The tricyclic antidepressant imipramine HCl (Sigma-Aldrich, India) 10 mg/kg was administered as a control positive drug. *P. australis* extract (PAE) at doses of 40, 80, and 160 mg/kg was also administered intraperitoneally (doses were chosen according to pilot studies).

Study design

Behavioral tests were performed one hour after a single dose injection of PAE to choose the best dose. After that, following inoculation of BCG, PAE was administered daily for 14 days. Locomotor activity test, forced swimming test (FST), and sucrose solution preference (SP) test were performed on day 15. At the end of the experiments, 80% food deprivation was considered for the next 18 h, and a novelty-suppressed feeding test (NSFT) was performed on day 16 [29].

Locomotor activity test

This test was evaluated in an open apparatus (Borj Sanat, Iran). Each mouse was placed in the corner and allowed to explore the area for 3 min. The number of zone entries was counted automatically by the device when animals crossed the red beams that divided the ground into 15 zones (horizontal activity), and the number of rears on hindlegs was recorded manually (vertical activity). Finally, the locomotor activity was presented as the total activity count [16, 30].

Forced swimming test

The immobility time during FST reveals animal despair behavior. Mice were placed in a 2-L Pyrex beaker filled with water (25ºC) for 6 min, 2 min was considered for habituation, and immobility was measured during the last 4 min. The immobility time was considered when animals became motionless or only had slight activity needed to keep their head above the water. After the test, mice were dried to avoid hypothermia and returned to their home cage [17, 31].

Sucrose preference test

Lower SP reveals anhedonia, another depression condition in rodents. The test started on day 11 and was performed in three days. The first two days were for habituation to the bottle of sucrose solution (2.5% w/v) added to their cage. On the third day, one sucrose solution bottle and one water bottle were measured and placed in animal cages. The amount consumed from each bottle was measured after 24 h (on day 14), and the SP percentage was calculated [11].

Novelty-suppressed feeding test

The test was done in a novel environment, a Plexiglas box (45×45×20 cm) with 0.5 cm of sawdust bedding. Three chow pieces were weighed and put in a Petri dish in the middle of the box. Each animal was placed in the corner of the apparatus for 20 min, and the latency to feeding and food intake was measured by weighing the residual chow. After the test, the mice were returned to their home cage with normal access to food and water [28].

Data processing and statistical analysis

All statistical evaluation and data processing were done using Excel 2016 and the GraphPad Prism 8 software (La Jolla, CA, USA). Results are presented as mean ± SEM for the study groups, BCG results were compared with the control group by the Student t-test, the treated groups with PAE or imipramine were compared with the control or the BCG alone group using 1-way analysis of variance (ANOVA), followed by Tukey's multiple comparison tests. $P<0.05$ was marked statistically significant.

Results

Phytochemical analysis

The yield of dried extract was calculated as 23.5% (W/W). The total phenolic compounds determined by the Folin-Ciocalteu reagent test was 20.31±0.1 mg GAE/g extract.

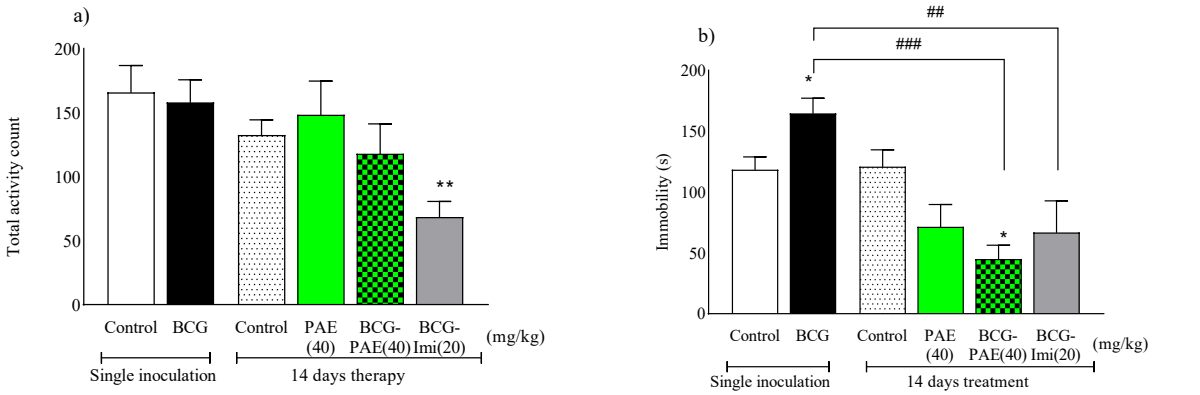

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Figure 1. The effect of BCG *P. australis* extract on locomotor activity test (a) and immobility time during forced swimming test (b) following BCG inoculation total activity presents, horizontal activity plus vertical activity

BCG (0.2 mL/mouse) was inoculated intraperitoneally. Control animals received a normal saline solution. The results are presented as Mean ± SEM and analyzed by ANOVA followed by Tukey's multiple comparison tests (n=6).

* P<0.05, **P<0.01 compared with the control group, ##P<0.01, ###P<0.001 compared with the BCG alone group.

Abbreviations: PAE, *P. australis* extract; Imi, imipramine

Effect of BCG inoculation and PAE on locomotor activity and FST

Following a single injection of each dose of PAE (40, 80, and 160 mg/kg), the locomotor activity counted reduced significantly with PAE 80 and 160 mg/kg (87.9±4.8; P=0.029, 77.3±12.4; P=0.0077 vs control 139±16.9; respectively) (data not shown). On the other hand, during FST, only PAE 40 mg/kg significantly reduced the immobility time (32.3±4.12 s vs control 141±10.0, P<0.001) (data not shown). Therefore, PAE 40 mg/kg was chosen for the rest of the experiments.

As depicted in Figure 1a, after 14 days of BCG inoculation, locomotor activity was not different from the control group (166±21.1). Following PAE administration, there was no significant change in the locomotor activity compared to the control group. Imipramine administration reduced the locomotor activity (68.5±12.2 vs control, $F_{5,33}$=2.35, P=0.0066), although the 1-sample t-test results showed a significant difference (P=0.0025 vs the theoretical mean=0).

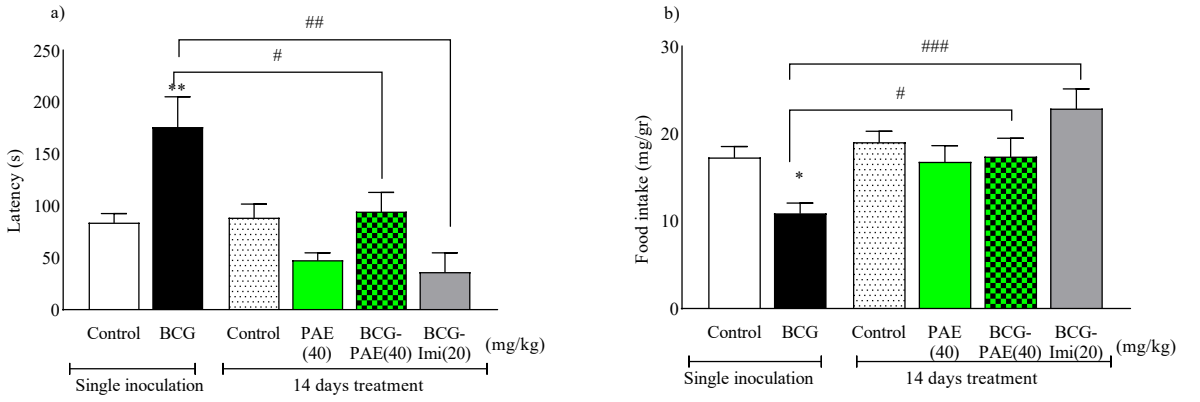

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Figure 2. The effect of BCG *P. australis* extract on the latency time (a) and food intake after 20 min (b) during novelty-suppressed feeding test following BCG inoculation

BCG (0.2 mL/mouse) was inoculated intraperitoneally. The control animals received a normal saline solution. The results are presented as Mean ± SEM and analyzed by ANOVA followed by Tukey's multiple comparison tests (n=6).

* P<0.05, **P<0.01 compared with the control group, # P<0.05, ## P<0.01, ###P<0.001 compared with the BCG alone group.

Abbreviations: PAE, *P. australis* extract; Imi, imipramine.

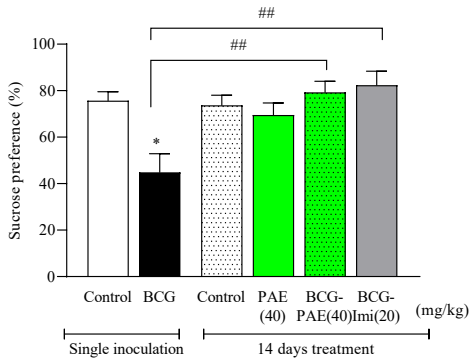

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Figure 3. The effect of BCG *P. australis* extract on the sucrose preference following BCG inoculation, sucrose preference= (sucrose intake/water plus sucrose intake ×100).

BCG (0.2 mL/mouse) was inoculated intraperitoneally. The control animals received a normal saline solution. The results are presented by Mean ± SEM and analyzed by ANOVA followed by Tukey's multiple comparison tests (n=6).

* P<0.05 compared with the control group, ##P<0.01 compared with the BCG alone group. Abbreviations: PAE, P australis extract; Imi: imipramine.

The FST results are presented in Figure 1b. BCG significantly increased the immobility time during FST (165±12.5 s vs control 119±10.6 s, P=0.018). The treatment with PAE in a similar manner as imipramine reduced the immobility time compared to BCG alone group (45.1±11.4 seconds, $F_{5,37}$=0.7494, P<0.001).

Effect of BCG inoculation and PAE on NSFT

Figure 2 (a, b) represents the NSFT results. BCG inoculation significantly increased the latency (176±29.1 s vs control 84.0±8.8 s) (Figure 1a). Meanwhile, food consumption decreased (10.9±1.18 mg/g body weight vs control 17.3±1.24 mg/g body weight) (Figure 1b). Following treatment with PAE the latency significantly decreased compared with BCG alone group (94.7±18.5 s, $F_{5,35}$=7.712, P=0.0365), the food intake during NSFT increased significantly (17.4±2.11 mg/g body weight vs BCG alone group, $F_{5,35}$ = 4.863, P=0.023). These changes were similar to imipramine treatment.

Effect of BCG inoculation and PAE on SP test

As seen in Figure 3, BCG inoculation significantly reduced SP compared to the control group (44.9±7.9% vs 75.7±3.8%, P=0.027). Treatment with PAE significantly increased SP compared with BCG alone group (79.3±4.7%, $F_{5,15}$= 5.82, P=0.0069) similar change was observed following imipramine treatment.

Discussion

The results of the present study showed the antidepressant-like effects of PAE in mice by evaluating different criteria related to depression. The alga reduced the immobility time in FST, inferred as less despair behavior. The time from first food intake reduced, and food intake increased during the NSFT, indicating less stress and a rise in appetite, and increased SP showed remission of anhedonia. FST is commonly used as a helpful tool for antidepressant discovery by evaluating the despair behavior [32]. NSFT is an invaluable animal model revealing sensitivity to chronic antidepressant treatment with more face validity [33]. Although acute models are reasonable for screening, several weeks of treatment is preferable to understand therapeutic antidepressant effects [33]. A novel environment initiates feeding inhibition in animals, or 'hyponeophagia,' an anxiety-related value that is subtle for evaluating chronic antidepressant treatment efficacy [29, 33]. On the other hand, anhedonia is a common symptom in patients with depression [34]; thus, assessing anhedonia in behavioral tests for evaluating depression in animal models is essential [32].

In agreement with previous studies [28], BCG inoculation induces depressive behavior in mice, increases immobility time during FST, increases latency to food intake, decreases appetite during NSFT, and declines SP. BCG initiates chronic depressive-like behavior related to neuroinflammation, which continues for 1 month after inoculation in mice [35]. BCG initiates inflammation and changes in mice's appetite and body weight, despair behavior, and anhedonia [26].

Depressive behavior was prevented following PAE administration in mice; the changes observed in behavior tests were similar to imipramine, the reference drug. Ample fatty acids have been identified in seaweed prod-

ucts, including eicosapentaenoic acid, linoleic acid, arachidonic acid, α-linolenic acid, and saturated fatty palmitic acid. The long-chain unsaturated fatty acids (e.g. omega-3 and omega-6) are key in forming important cell membrane components [23]. *P. australis* is a good source of omega-3 (14.62%) and omega-6 fatty acids (19.28%) [21]. These components could be related to PAE antidepressant-like effects. It has been known for a long time that omega-3 fatty acids, such as docosahexaenoic acid, α-linolenic acid, and eicosapentaenoic acid, are important nutritional values with possible antidepressant effects [13, 36]. Evidently, the human brain has large amounts of long-chain unsaturated fatty acids, and in the nervous system, one-third of fatty acids are long-chain unsaturated fatty acids [37]. Thus, unsaturated fatty acids have a vital role in neurological diseases, and it has been observed that in individuals with depression, there is a decrease in omega-3 fatty acids blood level [37]. Two essential enzymes responsible for the metabolism of polyunsaturated fatty acids phospholipase A2 and cyclooxygenase-2, lead to the production of prostaglandins and inflammation and are responsible for cytokine-induced depression behavior [38]. By antagonizing membrane arachidonic acid, the polyunsaturated fatty acids reduce prostaglandin E2 synthesis, thus impeding inflammation and providing antidepressant activity and neuroprotection [39]. Preclinical and clinical studies have introduced hopeful results regarding the efficacy of anti-inflammatory drugs on depression [11, 40].

In addition, depression may be related to increased cytokine production, while omega-3 fatty acids inhibit cytokine synthesis. Thus, the negative correlation between adipose docosahexaenoic acid and depression may arise from the inhibiting effect of docosahexaenoic acid on cytokine production [41].

On the other hand, the alga *P. australis* has shown the highest antioxidant activity of 53.3% amongst the other 19 seaweed extracts [22]. In mental illnesses such as depression, the balance between reactive oxygen species and antioxidant levels may change; that is, large amounts of reactive oxygen species are produced, or the antioxidant defense in the body declines [42, 43]. It has been seen that antioxidants in a small ratio of one in a hundred are effective against free radicals [6]. Therefore, the antioxidant property of PAE may have played a role in tackling BCG-induced depression.

Conclusion

In conclusion, PAE proved antidepressant-like effects in mice. This effect could be related to its long chain of unsaturated fatty acids or antioxidant content that could prevent inflammation and related depressive behavior induced by BCG inoculation. Further studies are suggested regarding the effect of different partitions of PAE on depressive behavior and the possible mechanism of action.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by Ethics committee of Isfahan University of Medical Sciences (Code:IR.MUI.REC.1400.176)

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Authors' contributions

Conceptualization and Supervision: Azadeh Mesripour and Afsaneh Yegdaneh; Methodology: Azadeh Mesripour; Investigation, Writing-original draft, and Writing -review & editing: All authors; Data collection: Mehrnaz Iravani; Data analysis: Azadeh Mesripour; Funding acquisition and Resources: Azadeh Mesripour.

Conflict of interest

The authors declared no conflict of interest.

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