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Isfahan University of Medical Sciences

Original Article

The brown alga *Padina pavonica* methanol and hexane partitions prevented depressive behavior induced by dexamethasone in mice

Azadeh Mesripour[1,*], Negar Asgari [1], and Afsaneh Yegdaneh[2]

[1]*Department of Pharmacology and Toxicology and Pharmaceutical Science Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.*
[2]*Department of Pharmacognosy, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.*

Abstract

Background and purpose: *Padina pavonica*, a brown alga, displays protection against oxidative stress, neuroinflammation, and neurodegenerative disorders. Considering the beneficial effects of *P. pavonica* and since its antidepressant effects have not yet been studied, we investigated its methanol and hexane partitions (PMP and PHP) in mice model.

Experimental approach: In male mice (25 ± 2 g), depression was initiated by administrating dexamethasone (15 µg/kg) subcutaneously. PMP or PHP (80-160 mg/kg) was administered intraperitoneally. All the injections continued for two weeks. After the locomotor test, different depression criteria were evaluated by forced swim test (FST), marble burying test (MBT), sucrose preference (SP) test, and novelty-suppressed feeding test (NSFT).

Findings/Results: PMP (160 mg/kg) showed antidepressant effects, immobility time decreased significantly during FST (84.6 ± 10.4 s) compared to the control, food intake increased significantly during NSFT (21.1 ± 2.5 mg/g) versus the control, and SP was 81%. PHP (80 mg/kg) reduced immobility time to 124.5 ± 6.7 s compared to the vehicle and increased the SP to 85%. Dexamethasone-induced depression. While co-treatment with PMP or PHP prevented depression initiated by dexamethasone. Only PHP reduced the number of buried marbles after 30 min against the control. The applied doses did not cause significant changes in the locomotor activity.

Conclusion and implications: PMP and PHP exhibited antidepressant-like effects in mice. PHP also reduced the number of buried marbles, implying a reduction in obsessive-like behavior. These observations underscore the constituents inherent in PMP and PHP, which merit further exploration to elucidate their potential therapeutic applications.

Key words: Animal research; Brown algae; Depression; *Padina pavonica.*

INTRODUCTION

Depression is a leading cause of global disability and can tragically result in suicide if it remains untreated. It is also the most ubiquitous psychiatric disorder, affecting an estimated 5.0 to 17.0% of the global population (1). Major depressive disorder is associated with an imbalance in neurotransmitters, including dopamine, norepinephrine, and serotonin (2). Depression's pathophysiology also comprises inflammatory processes, immune dysfunction in individuals, mitochondrial dysfunction, and the appearance of oxidative stress (3). The main treatment for depression involves antidepressants and psychotherapy, which are usually merged for better results. However, due to the extensive occurrence of depression and the dissatisfaction of many patients with existing antidepressants and their adverse effects, there is an urgent necessity for new pharmaceutical interventions. Medicinal plants have long been distinguished as alternative options for treating chronic ailments like hypertension and depression (4,5).

*Corresponding author: A. Mesripour
Tel: +98-3137927089, Fax: +98-3136680011
Email: a_mesripour@pharm.mui.ac.ir

Access this article online

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Brown algae, including seaweed, are known for their diverse bioactive compounds. Seaweed species have pharmacological effects and offer medicinal properties such as antioxidant, anti-inflammatory, cholesterol-regulating effects, and neuroprotective functions (6,7). Compounds found in algae, such as fucoxanthin, fucoidan, and fucosterol, have the potential to target multiple pathological conditions (8).

Within the brown algae group, the *Padina* genus, belonging to the family Dictyotaceae and order Dictyotales, is explicitly noteworthy. *Padina* algae are multicellular seaweeds found in warm seas globally, consisting of the Persian Gulf, Oman Sea, and tidal areas (9,10). Fucosterol is the chief sterol found in brown algae during hexane partition and has antioxidant and butyrylcholinesterase inhibitory activities (11). α-Bisabolol derived from *P. gymnospora* also illustrates cholinesterase inhibitory activity (12). The methanolic partition of the algal species contains phenolics, flavonoids, and tannins, which exhibit health-promoting activities by neutralizing oxidants (13). *P. pavonica*, is an appropriate candidate for research due to its abundance. Also, it is rich in secondary metabolites such as phenolics, flavonoids, saponins, tannins, and alkaloids (14). Additionally, *in-vitro* studies have declared the safety and non-toxicity of *P. pavonica* extract on the WI-38 cell line (14). Limited research has been performed on the biological activities, decidedly the neurological screening of these intriguing organisms. Hence, the purpose of this study was to appraise the impact of *P. pavonica* hexane and methanol partitions (PHP and PMP) sourced from the Persian Gulf on depressive behavior and the obsessive-compulsive disorder (OCD) model in mice. In addition, the impact of PHP and PMP on dexamethasone (Dex) induced depression was also assessed.

MATERIALS AND METHODS

Chemicals

Dexamethasone (8 mg/2 mL ampule; Zahravi Industry, Iran), imipramine (Sigma, Germany), and *P. pavonica* (Persian Gulf coasts of Iran) were used in this study.

Preparation of the extracts

P. pavonica samples sourced from the Persian Gulf were approved by the Agricultural and Natural Resources Research Center of Bushehr (Voucher No. 2662). It was subjected to an ordering processing procedure. First, they were carefully gathered, cleaned to remove impurities and salt residues, and air-dried under shaded conditions at abated temperatures. After this, a maceration technique was employed, using a 1:1 mixture of methanol and ethyl acetate to facilitate the extraction of all secondary metabolites. Then, the obtained extract was subjected to a concentration process, which led to the creation of methanol and hexane partitions through the solvent partitioning. These partitions were further concentrated, and their potential antidepressant properties were subsequently appraised.

The antidepressant doses of PMP and PHP were chosen based on previous studies (9) and pilot studies.

Animals

Male Swiss mice in the adult stage, between 6 to 8 weeks old and weighing 23 to 27 g, were carefully protected in managed surroundings. These conditions included regulated humidity, temperature, and a 12/12-h dark/light cycle. The mice were provided with free access to pellet chow and water. In each cage, a group of seven mice coexisted. All animal experiments strictly adhered to the moral standards established by the National Ethical Committee, with the ethics code IR.MUI.AEC.1401.026 serves as the reference. Every conceivable effort was made during the experiments to minimize any potential discomfort and the total number of animals used.

Experimental design

Animals were randomly divided into 10 groups comprising seven animals each: two groups injected with PMP (80 or 160 mg/kg), and the normal control group receiving normal saline (NS). The PHP group received PHP (80 mg/kg) diluted in 0.1% tween 80 in NS, and the normal control group received the vehicle. Depression was induced by injecting Dex (15 µg/kg) subcutaneously (SC); the control Dex group only received NS subcutaneously (15).

The combination treatment groups were: the Dex-PMP (160 mg/kg) group, the Dex-PHP (80 mg/kg) group, and the Dex-imipramine (10 mg/kg) group that received the standard antidepressant drug. The extracts and imipramine were injected intraperitoneally (IP), and the volume for all injections was 1 mL/100 g. All treatments were administered each day within 8-10 AM, Dex was administered 20 min later in the combination treatment groups for 14 days.

Behavioral tests began on day 15, starting with the locomotor activity test, the marble burying test (MBT), the forced swim test (FST), and finally, the sucrose preference (SP) test. At the end of these experiments, an 80% food deprivation period was introduced for the next 18 h, after which the novelty-suppressed feeding test (NSFT) was carried out on day 16 (16). All experiments were conducted between 8 AM and 1 PM.

Locomotor test

This preliminary test is conducted before behavioral experiments to ascertain the baseline locomotor activity of the subjects. The locomotor appraisal was carried out in an open arena manufactured by Borj Sanat, Iran (40 × 40 × 40 cm), which was divided into fifteen identical divisions using infrared beams. The mice were gently placed in one corner of the device and given the liberty to explore for 3 min. Automated sensors calculated the number of times the mice crossed the beams, while instances of mice standing on their hind legs were manually recorded. The zone entries and hind-leg rearing events were summed to calculate the overall activity level for each animal (17).

Forced swim test

The duration of motionlessness observed throughout the FST serves as a reflection of the animal's despair behavior. Throughout this test, mice were situated in a Pyrex beaker with a 2-L capacity, containing water at a temperature of 25℃ for 6 min. The initial 2 min were allotted for habituation, while the computation of motionlessness was carried out during the final 4 min. Periods of inactivity were recorded when the animals became thoroughly still or exhibited only minimal movements requisite for keeping their heads above the water's surface. After the examination, the mice were attentively dried to counteract hypothermia and returned to their respective home cages (18).

Sucrose preference test

Anhedonia, which is an endophenotype affiliated with depression, was appraised through the SP test. The test spanned three days, with the initial two days as a habituation period. On the first day, the animals were given access to two bottles of sucrose solution (2% w/v) in their cage. On the second day, one bottle contained a sucrose solution and another was filled with water. Finally, on the third day, two bottles were supplied, each holding a precise quantity of sucrose solution and regular tap water. After 24 h, the amount of sucrose solution and water ingested was quantified and the SP level measured; more than 65% was considered sucrose preference over water (19).

Novelty-suppressed feeding test

After adaptation to the experimental circumstance, the animals participated in the NSFT. Each mouse was situated exclusively within an open plastic clear box (40 × 25 cm, depth 20 cm). A pre-weighed portion of standard chow was positioned in the center of this enclosure. The period it took for the mice to approach the food, referred to as the food disposal latency, was delicately noted. Following the NSFT, the remaining food was weighed and the food consumed was documented (19).

Marble burying test

This test measures obsessive-compulsive-like behavior in rodents. The test was conducted in an open plastic clear box (40 × 25 cm, depth 20 cm) covered with 5 cm of fine sawdust. Twelve blue marbles (15 mm diameter) were uniformly placed on sawdust. During the MBT, the number of marbles buried was recorded every 15 min for 30 min (20).

Statistical analysis

The data, presented as mean ± SEM, were analyzed using a one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Statistical significance was established with

P-values less than 0.05. Data analysis and graph plotting were performed using Microsoft Excel 2020 and GraphPad Prism 8.

RESULTS

Phytochemical analysis

The yields of methanolic and hexane partitions were 1.6% and 0.86%, respectively. According to the Folin-Ciocalteu reagent test (21). The total phenolic content of *P. pavonica* was calculated as 12.87 ± 1.04 mg/g gallic acid in extract. The total phenolic compounds determined in the methanolic partition of the dried extract was 10.6 mg GAE/g extract, and in the hexane partition of the dried extract was 8.67 mg GAE/g extract.

The effect of PMP alone and following Dex administration on depressive behavior

As indicated in Table 1, there was no significant difference in the locomotor activity between different groups compared to the normal control groups. The concurrent administration of Dex-PMP significantly decreased the total activity count versus the Dex alone group, but this did not influence the FST results. The FST results are presented in Fig. 1A, after 14 days of administration of PMP (160 mg/kg) alone, immobility time reduced significantly in FST (84.6 ± 10.4 s compared to normal control 152.5 ± 11.5 s, $P < 0.001$). Conversely, PMP at 80 mg/kg did not yield eminent effectiveness. Dex led to an augmentation in immobility time during the FST (196.0 ± 12.3 s versus Dex control 153.6 ± 2.9 s, $P < 0.05$), announcing behavior resembling depression. In the case of the combination treatment involving Dex-PMP, there was a significant subtraction in immobility time (104.0 ± 8.3 s compared to Dex alone and Dex control $P < 0.001$). Pretreatment with the reference drug imipramine also caused a decrease in immobility time during the FST versus Dex alone and Dex control groups.

Based on Fig. 1B, PMP at 160 mg/kg significantly boosted the food intake during NSFT (21.1 ± 2.5 mg/g compared to the normal control 12.0 ± 1.1 mg/g body weight, $P < 0.001$). Food intake after Dex administration was (10.2 ± 0.5 mg/g body weight), PMP co-administration with Dex considerably increased food intake (16.6 ± 0.8 mg/g body weight compared to Dex alone and Dex control groups, $P < 0.01$), changes were parallel to Dex-imipramine group. As shown in Table 1, PMP at 160 mg/kg reduced the latency time to eat compared to the control group. After Dex administration, latency increased; however, this change was not statistically significant compared to the Dex control group. The latency in the Dex-PMP group was lower than in the Dex-alone group, although these changes were nonsignificant. However, Dex-imipramine eminently abated latency time compared to Dex alone ($P < 0.05$) (Table 1).

Table 1. The effect of the PMP on locomotor test, latency during NSFT, sucrose preference, and MBT. Total activity during locomotor test = (horizontal + vertical) exploration; sucrose preference % = (sucrose utilization/sucrose + water utilization) ×100. Control groups received normal saline (1 mL/100 g). Dex and control Dex were injected subcutaneously, and other treatments were intraperitoneally injected for 14 days. Average number of buried marbles after 30 min. Results are expressed as mean ± SEM, n = 7. $^{**}P < 0.01$ indicates significant differences compared to the control group and $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared to Dex.

Groups	Total activity number	Latency (s)	Sucrose preference (%)	Number of marbles buried
Normal control	105.3 ± 13.6	82.0 ± 13.6	62.9 ± 5.8	5.8 ± 1.0
PMP (80 mg/kg)	122.2 ± 7.7	80.7 ± 21.7	61.8 ± 1.5	4.3 ± 1.5
PMP (160 mg/kg)	121.4 ± 18.6	45.8 ± 9.1	81.0 ± 4.9	2.2 ± 1.0
Dex control	146.7 ± 19.1	100.3 ± 13.2	66.5 ± 2.9	6.5 ± 0.7
Dex (15 µg /kg)	193.7 ± 6.4	141.6 ± 29.3	42.2 ± 0.3	5.1 ± 0.5
Dex-PMP (160 mg/kg)	110.5 ± 15.4##	84.5 ± 13.3	84.6 ± 2.8	6.3 ± 1.5
Dex-imipramine (10 mg/kg)	153.6 ± 13.9	64.3 ± 9.9#	85.0 ± 2.3	1.9 ± 0.7**

PMP, *Padina pavonica* methanolic partition; Dex, dexamethasone; PMP, *P. pavonica* methanol partition; PHP, *P. pavonica* hexane partition; NSFT, novelty-suppressed feeding test; MBT, marble burying test.

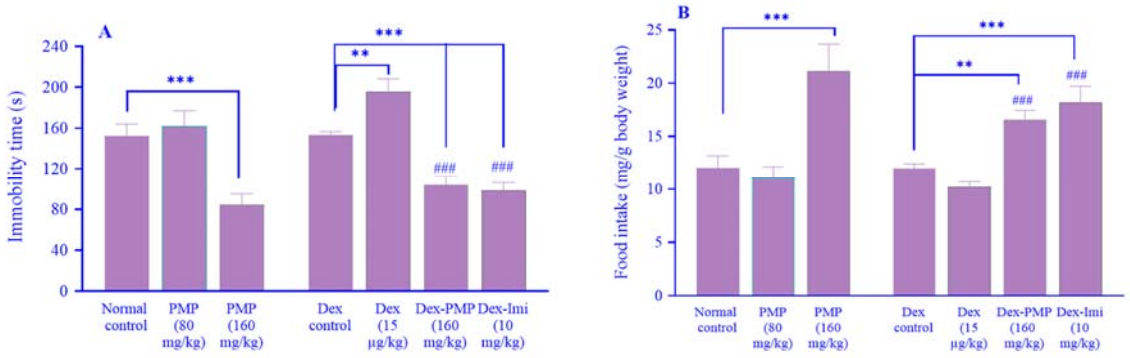

Fig. 1. The effect of the PMP on (A) immobility time during forced swim test, and (B) food intake during novelty suppressed feeding test. Control groups received NS 1 mL/100 g. Dex and Dex control (NS) were injected subcutaneously, and other treatments were intraperitoneally injected for 14 days. Results are expressed as mean ± SEM, n = 7. $^{**}P < 0.01$ and $^{***}P < 0.001$ indicate significant differences compared to the respective control group and $^{###}P < 0.001$ compared to Dex alone. PMP, *Padina pavonica* methanolic partition; NS, normal saline; Dex, dexamethasone; Imi, imipramine.

The SP test results in Table 1 further substantiate the findings from the FST; a deduction in SP below 65% was indicative of anhedonia. PMP at 160 mg/kg increased SP to 81%. The combination of PMP with Dex improved SP similar to Dex-imipramine.

The number of buried marbles after 30 min following PMP administration at a dose of 160 mg/kg decreased insignificantly (Table 1). Additionally, when PMP was co-administered with Dex, the number of marbles buried did not reduce, while Dex-imipramine results presented a significant decline in the number of marbles buried. Therefore, PMP did not show anti-compulsive effects.

The effect of PHP alone and following Dex administration on depressive behavior

Remarkably, modifications occurred without notable alterations in locomotor activity compared to the normal control group throughout the test (Table 2). The potential mood-improving impact of the PHP after administration was examined in the FST. Figure 2A displays the duration of immobility observed during the FST; administering PHP (80 mg/kg) alone resulted in a meaningful diminution in immobility time during the FST (124.5 ± 6.7 s compared to the normal control 157.8 ± 3.3 s, $P < 0.01$). When PHP was co-administered with Dex, the immobility time was significantly abated (136.5 ± 3.4 s) compared to Dex alone ($P < 0.001$), and the changes were similar to the Dex-imipramine group.

Moreover, PHP alone increased food consumption during NSFT based on Fig. 2B (14.9 ± 1.3 mg/g versus normal control 11.3 ± 0.4 mg/g body weight, $P < 0.05$), PHP eminently enhanced food intake when co-administered with Dex (16.7 ± 1.6 mg/g body weight compared with Dex alone, $P < 0.01$ and vs control, $P < 0.05$). The latency time is shown in Table 2, PHP alone abated latency compared to the control group, and Dex-PHP reduced latency compared to Dex alone, although these alterations were insignificant.

The results of SP confirmed FST results as presented in Table 2, where PHP notably increased SP, up to 85%, and the combination of PHP with Dex eminently improved SP up to 86%.

As displayed in Table 2, following PHP the number of buried marbles after 30 min decreased significantly compared to the normal control group ($P < 0.01$). Co-administration of PHP with Dex also eminently reduced the number of buried marbles compared with Dex alone and the control group (at least $P < 0.05$). These results indicated that PHP, unlike PMP, prevented compulsive behavior in mice.

Table 2. The effect of the PHP on locomotor test, latency during NSFT, sucrose preference, and MBT. Total activity during locomotor test = (horizontal + vertical) exploration, sucrose preference % = (sucrose utilization/sucrose + water utilization) ×100. Dex and control Dex (NS) were injected subcutaneously, and other treatments were intraperitoneally injected for 14 days. The normal control group received vehicle (0.1% tween 80 in NS) 1 mL/100 g. Average number of buried marbles after 30 min. Results are expressed as mean ± SEM, n = 7. $^{**}P < 0.01$ and $^{***}P < 0.001$ indicate significant differences compared to control group, $^{\#}P < 0.05$ versus Dex.

Groups	Total activity number	Latency (s)	Sucrose preference (%)	Number of marbles buried
Normal control	159.3 ± 15.2	136.5 ± 18.3	66.6 ± 2.6	7.8 ± 0.5
PHP (80 mg/kg)	113.8 ± 13.3	95.0 ± 8.5	85.2 ± 3.2	3.5 ± 1.2**
Dex control	146.7 ± 19.1	100.3 ± 13.2	66.5 ± 2.9	6.5 ± 0.7
Dex (15 µg/kg)	193.7 ± 6.4	141.6 ± 29.3	42.2 ± 0.3	5.1 ± 0.5
Dex-PHP (80 mg/kg)	122.8 ± 16.4#	92.8 ± 10.9	86.2 ± 1.4	1.8 ± 0.5***,#

PHP, *Padina* pavonica hexanic partition; NS, normal saline; NSFT, novelty-suppressed feeding test; MBT, marble burying test; Dex, dexamethasone

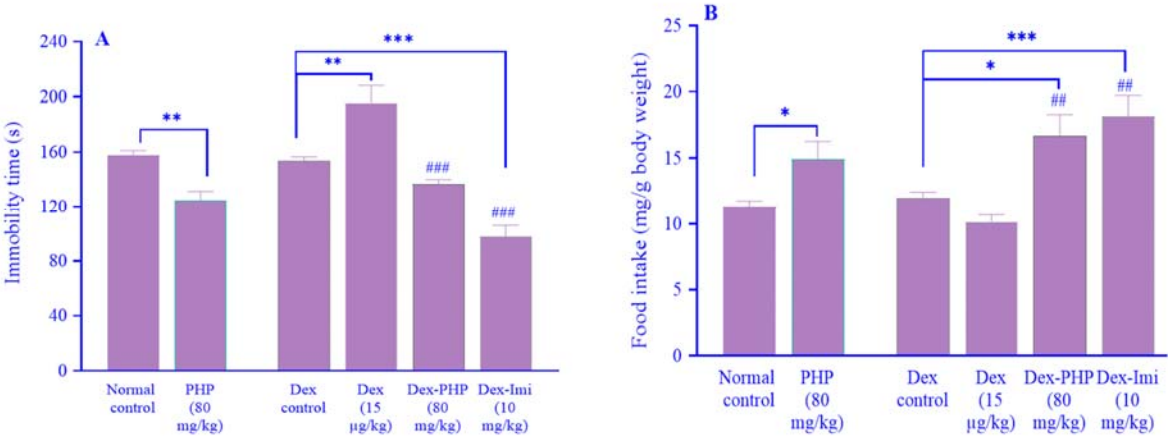

Fig. 2. The effect of the PHP on (A) immobility time during the forced swim test and (B) food intake during the novelty-suppressed feeding test. Dex and Dex control (NS) were injected subcutaneously and other treatments were intraperitoneally injected for 14 days. The normal control group received vehicle (0.1% tween 80 in NS) 1 mL/100 g. Results are expressed as mean ± SEM, n =7. ## $P < 0.01$, ### $P < 0.001$ compared to Dex alone, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared to the respective control group. PHP, *P.pavonica* hexanic partition; NS, normal saline; Dex, dexamethasone; Imi, imipramine.

DISCUSSION

By appraising diverse depression-related criteria, the antidepressant effects of PMP and PHP were confirmed after exposure to Dex in mice. The changes observed by administering PMP (160 mg/kg) and PHP (80 mg/kg) were: a decline in immobility duration in the FST, suggesting improvement in despair behavior; a shorter time to initiate food consumption and the rise of food intake during NSFT, showed the progress in stress and appetite; and an elevation in SP, signifying a potential remission of anhedonia.

Only the PHP decreased the number of buried marbles during MBT, demonstrating a reduction in obsessive-like behavior**.**

The FST is a frequently employed and valuable tool in the search for potential antidepressants, as it appraises behaviors associated with despair (22). In the FST, mice gradually resign hope of escaping from the stressful situation, thus, the length of immobility serves as an indicator of behavioral despair (22). The NSFT is a highly valuable animal model that exposes sensitivity to chronic antidepressant treatment, with enhanced relevance to human responses (23). Usually, by offering mice food in an unfamiliar cage, hypophagia following anxiety occurs. The anxiety level is assessed by measuring the latency and total food consumption. It should be noted that in the animal model, regarding the latency time, chronic treatment with tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) reduces latency, while acute treatment with anxiolytic drugs is effective (24).

The injection of Dex induced depressive behavior in mice in line with previous research (15), as evidenced by an augmentation in immobility time during the FST, an extended latency to food intake, and diminished appetite during the NSFT, along with a decline in SP. Stress and an amplified glucocorticoid response may adversely affect hippocampal neurogenesis (25). Furthermore, evidence points to a potential connection between dysregulation in the hypothalamic-pituitary-adrenal axis and changes in the serotonergic system linked to depression (26). Remarkably, this depressive behavior initiated by Dex was mitigated through the administration of PMP at a dosage of 160 mg/kg and PHP at 80 mg/kg in mice. The observed changes in behavioral tests closely resembled those induced by imipramine, the reference drug for these effects.

Metabolites in algae with unique structures and diverse functions, such as phenolics, alkaloids, carotenoids, polysaccharides, phytosterols, and terpenoids, have made them attractive for medicinal chemistry (6). Algal metabolites, mainly fucoxanthin, fucosterol, and fucoidan, have the potential to advance therapy against mental illnesses (27). The appraised partitions, PMP and PHP, in our study prove to have antidepressant effects.

Fucosterol, the primary sterol found in brown algae, displays numerous advantageous characteristics, incorporating antioxidant and liver-protective qualities, antidiabetic properties, and inhibiting butyrylcholinesterase activity. Fucosterol has demonstrated anti-inflammatory properties (11). Thus, PHP may possess anti-inflammatory capacities because of fucosterol content in the partition. Non-steroidal anti-inflammatory drugs (NSAIDs) have proven beneficial in the treatment of depressive disorders (28). PHP showed an antidepressant-like effect at a lower dose (80 mg/kg) than PMP (160 mg/kg), which could be related to better blood-brain barrier distribution.

Compounds derived from marine algae, such as *P. pavonica*, have been reported to possess strong antioxidant properties (14,29). Detecting natural antioxidants such as bioactive phytochemicals is imperative not only for their protective role in improving diseases but also for their safety compared to synthetic analogs (30). Researchers have previously stated that the methanol extract of *P. Pavonica* recorded the highest total tannin content among other examined seaweeds (14). The examined algal species are notably abundant in phenolics that provide essential support for promoting good health benefits by counteracting the effects of oxidative agents (6).

Additionally, in mental disorders like depression, there exists an inequality between reactive oxygen species and antioxidant levels. This imbalance may manifest as an excessive production of reactive oxygen species or a reduction in the body's antioxidant defenses (30). Antioxidant supplements, when taken alongside conventional antidepressant treatment, have been associated with improved mental well-being, suggesting additional therapeutic benefits (31).

Oligosaccharide furthermore abates inflammatory factors, increase brain-derived neurotrophic factor (BDNF) and choline acetyltransferase levels, and enhance the survival of hippocampal neurons (32). Additionally, these oligosaccharides have been shown to alleviate inflammatory factors, elevate BDNF levels, and promote the survival of hippocampal neurons (33). Laminarin, found in the methanolic partition, has proven neuroprotective effects because of its antioxidant and anti-inflammatory properties (33). Hence, the antioxidant and anti-inflammatory properties found in the methanolic and hexane partitions of this algae hold promise in preventing depression induced by Dex administration.

Additionally, the beneficial effects of seaweed on depressive behavior could be related to vitamins, peptides, and fatty acids that provide valuable health benefits (34). The beneficial effects of vitamins and minerals on depression have been emphasized previously (35,36).

The MBT was measured as an animal model for OCD, burying environment harmless objects by rodents reflects obsessive-compulsive behavior (20,37). Treatment with SSRIs and anxiolytic drugs diminished the behavior of digging and burying harmless objects (38). In the following experiments, only PHP resulted in reducing the marble-burying behavior, this might be related to PHP's

anxiolytic effect or better distribution through the brain. The effects of PMP and PHP on neurotransmitters (epinephrine, dopamine, and serotonin) are also an important question that needs to be addressed in future research.

Neuroprotective effects do not depend on a single property but appear from multiple medicinal properties. This alga, because of its numerous properties, including antioxidant, anti-cholinesterase, and anti-inflammatory, is promising as a dietary or therapeutic agent for conditions related to the nervous system (14).

CONCLUSION

This research was the first to show that the partitions originating from the alga *P. pavonica* were effective in improving depression and obsessive-compulsive behavior in mice.
Therefore, since algae are an invaluable source of phytochemicals such as phenolics, flavonoids, and alkaloids, they could be candidates for future antidepressant drug development.

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Conflict of interest statement

The authors confirmed no conflict of interest in this study.

Authors' contributions

A. Mesripour and A. Yegdaneh contributed to the concept and design of the study; A. Mesripour and N. Asgari acquired, analyzed, and interpreted the data; A. Mesripour and N. Asgari drafted the article and revised it critically for important intellectual content. All authors read and approved the finalized article.

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