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# Analgesic potential of methanolic extract of *fucus vesiculosus*

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ABSTRACT

*Fucus vesiculosus* is a seaweed rich in various phytochemicals. Although it has documented systemic effects such as anti-inflammatory, anti-viral and anti-oxidant, the effects on pain have not been evaluated. This study is aimed at evaluating the analgesic potential of this plant. Methanolic extract of the whole dried plant was prepared by maceration technique and was subjected to phytochemical screening. Phytochemical screening yielded positive results for flavonoids, saponins, tanins and steroids. Mice were divided into five groups (n=5). Normal saline 0.9%, 2ml (negative control), Indomethacin 10 mg/kg (positive control) and extracts at 100 mg/kg, 250 mg/kg and 500 mg/kg were administered orally to mice in their respective groups. The latency to pain was assessed at 0, 30, 60 and 90 minutes for each animal using the hotplate protocol. The latency to pain was increased in groups who received Indomethacin (10 mg/kg) and extracted at all doses (100,250,500 mg/kg) when compared to the negative control (0.9% N/S). However, the results were statistically significant (p-value < 0.05, < 0.001) for Indomethacin and extract-treated groups at 250 mg/kg and 500 mg/kg dose. Acetic induced writhing demonstrated analgesic activity at 100, 250 and 500 mg/kg treated doses, which were statistically significant (p-value < 0.05) when compared with the negative control. Our study has demonstrated the central and peripheral analgesic potential of *fucus vesiculosus* methanolic extract. The specific active constituent and effects at cellular level need to be evaluated.

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## INTRODUCTION

Pain is defined as highly unpleasant physical sensation caused by illness or injury. It is a significant problem in the health care system. Many patients come with this complaint and suffer around the world. It has many burdens on the patient, including financial strain (Duenas *et al.*, 2016). It has terrible effects on social life and work of individual and has many emotional outcomes as well (Duenas *et al.*, 2016). Chronic pain has many impacts on the psychosocial health of the patient, leading to anxiety and depression. The quality of life is also disrupted due to many reasons, such as lack of interest in daily activities and lack of sleep (Henschke *et al.*, 2015). Pain can lead to depressive illness, and depressive illness can further augment pain, which becomes a vicious cycle.

Many analgesics are present nowadays. Commonly used analgesics are acetaminophen and NSAIDs. Acetaminophen is the most widely used pain killer. It is mostly used for mild to moderate pain. It has weak anti-inflammatory activity and is not useful in specific pain management. This drug is much safer when compared to other pain killers (Ather-

such *et al.*, 2018). However, it has a risk of liver damage in high doses (Alempijevic *et al.*, 2017).

NSAIDs are also widely used. They act by inhibiting the enzyme cyclooxygenase and decrease the production of prostaglandins (Grosser and Burton, 2006). NSAIDs are further divided into selective and nonselective blockers of the cyclooxygenase enzyme. The nonselective group block both COX 1 and COX 2 and therefore have many adverse effects such as gastrointestinal bleeding, renal injury and platelet effects (Grosser and Burton, 2006). The selective cox 2 inhibitors (celecoxib) have lesser GIT and renal adverse effects but are expensive (Marcum and Hanlon, 2010). Also, the nonselective group is associated with high cardiovascular problems

(Mamdani *et al.*, 2004). Opioids are another group of analgesics. They have a powerful analgesic effect but have high addictive potential. They act on mu receptors in the CNS. They have adverse effects such as constipation, addiction, cardiovascular problems, miosis, cough suppression, pruritus and respiratory depression (Schug *et al.*, 1992).

*Fucus vesiculosus* is also known as bladderwrack. It is a seaweed which is commonly found around the North Sea, Baltic Sea, Pacific and the Atlantic Ocean. In the 18th century, it was initially used for treating goiter due to iodine deficiency. This plant can grow to 90 cm with a width of 2.5 cm. The adult plant has air paired sacs in it. Fucoidin in this plant has anticoagulant and anti-tumour potential. The anticoagulant effect has been found to be similar to heparin (Drozd *et al.*, 2011). It also has documented immune-enhancing effects. Phlorotannins constituent has shown high antioxidant effects, including radical scavenging activity. This component also has anti-inflammatory activity by inhibiting inflammatory mediators (Airanthi *et al.*, 2011; Kellogg *et al.*, 2015). Alginic acid present in this plant can lead to protection of intestines and gut. It has enhancing the effect on gut flora and prevents colon cancer (Brown *et al.*, 2014). This plant is also used for relief of acidity and heartburn (Leiman *et al.*, 2017). Dietary fiber in this plant is suitable for gastrointestinal health. It also regulates bad cholesterol and sugar levels (Kuznetsova, 2009). It has shown to be helpful in obesity and cholesterol derangements (Patarra *et al.*, 2011). Aminoacids such as aspartic acid and glycine in this plant are essential for many health systems in the body, including the nervous system, immune system and thyroid function. Fucoidin also has proven antiviral potential, against the poliovirus, herpes virus and adenovirus (Ahmadi *et al.*, 2015). Studies are still required to analyze various systemic effects of this plant. *Fucus vesiculosus* is rich in many active constituents. Therefore, our research is aimed at observing any analgesic potential of this plant by using novel animal models.

## MATERIALS AND METHODS

### Extract Preparation

The whole dried plant of Fucus vesiculosus was ordered through GNC herbal company. It was taxonomically identified at Department of Pharmacognosy, King Khalid University, Abha. The shade dried plant was grinded into a fine powder. 50 grams of this powder was placed in 500 ml of methanol (100%) (Hong *et al.*, 2011). It was placed in a dry, dark place for three days with frequent agitation and mixing. After three days, it was filtered, and the filtrate was dried in under vacuum in a rotary evaporator (Buchi Rotavap). The rotations were fixed at 80 per minute and the temperature was adjusted at 60 C.

### Animal selection and maintenance

Adult Swiss albino mice weighing between 25-50 gm of either sex were used in this study. The animals will be housed in standard polypropylene cages at room temperature and provided with standard diet and water *ad libitum.* All experimental process of animals was permitted by the Ethics Committee for Animal Experimentation of the University and carried out in accordance with the Regulations of Experimental Animal Administration. The grouping was as follows:

1. Group 1: Negative control (Normal saline 0.9%, 1 ml)
2. Group 2: Positive control (Indomethacin 10 mg/kg)
3. Group 3: 100 mg/kg extract of Fucus vesiculosus
4. Group 4: 250 mg/kg extract of Fucus vesiculosus
5. Group 5: 500 mg/kg extract of Fucus vesiculosus

### Phytochemical Screening

Qualitative tests were performed to confirm the presence of various phytoconstituents (Steroids, Saponins, Alkaloids, Triterpenoids, Flavonoids and Tannins) (Trease and Evans, 1989).

### Experimental Protocol

### Hot plate method

For central analgesic activity, the hot-plate method of Eddy and Leimbach was used. Twenty-five adult Swiss albino mice of either sex were used in this study. The test extract at 100mg/kg, 250 mg/kg and 500 mg/kg by body weight were used (Zaragozá *et al.*, 2008). The standard positive control was Indomethacin 10 mg/kg and negative (vehicle) control was normal saline, 1 ml. All drugs were administered orally. Extracts and Indomethacin were diluted in 1ml of normal saline before administration. After baseline recording at 0 minutes, the animals were placed on a hot plate maintained at 56 ± 0.5°C for a maximum time of 30 seconds (Hong *et al.*, 2011). Latency to exhibit the nociceptive response such as licking fore and hind paws or jumping was determined before and after at 30, 60 and 90 minutes after oral administration of the extract and controls (Hong *et al.*, 2011). A cut-off time of 30 seconds was selected to avoid tissue damage.

### Acetic acid-induced writhing

The method described by Koster et al. was used for the evaluation of analgesic activity in mice. The experimental animals were divided into five groups consisting of 5 mice in each. All treatments were administered orally. After 45 minutes of administration of standard drug and test samples, each mouse was injected with 0.7% acetic acid at the dose of 10 mL/kg body weight intraperitoneally (Koster *et al.*, 1959). The number of writhing responses produced by each mouse was recorded for 15 minutes commencing just 5 minutes after acetic acid injection.

### Statistical Analysis

All data were expressed as Mean ± SEM and analyzed by one-way analysis of variance (ANOVA). P values less than 0.05 and 0.001 were considered statistically significant.

## RESULTS AND DISCUSSION

### Phytochemical Screening

Phytochemical screening yielded positive results for flavonoids, tannins, steroids and saponins. The test was negative for alkaloids and triterpenoidsTable 1.

### Analgesic activity

### Hot plate method

The results indicated an increase in pain threshold at all doses of extract 100mg/kg, 250mg/kg and 500 mg/kg and Indomethacin 10 mg/kg Figure 1. The reaction to pain increased at 30 minutes for all doses of extracts. Analgesic effect was apparent at 30, 60 and 90 minutes. Extract at 500mg/kg yielded the highest analgesic potential when compared with all other groups. However, the peak analgesic effect was evident for this dose at 60 minutes. Extract at 250mg/kg and 500 mg/kg demonstrated higher analgesic potential when compared with Indomethacin 10mg/kg.

### Acetic acid-induced writhing

Acetic acid-induced writhing was decreased in groups treated with Indomethacin and extract at all doses (100, 250 and 500 mg/kg) Figure 2. This was statistically significant when compared with negative control at p values of <0.05 and 0.001Figure 2. Extract at 250 mg/kg yielded the highest analgesic potential when compared with all other groupsFigure 2.

Pain can be mediated by central and peripheral modes. Centrally acting analgesics act by increasing the threshold for pain and altering the physiological response to pain. However, peripherally acting drugs act by inhibiting the generation of pain impulses at the chemoreceptor level (Shreedhara *et al.*, 2009). The analgesic activity of *fucus vesiculosus* extract was studied by hot plate method and acetic acid-induced writhing, which is a standard pharmacological model for the assessment of analgesia by natural products (Carlsson and Jurna, 1987). The hot plate method is used generally for centrally acting analgesic and acetic acid-induced writhing for peripheral analgesic activity (Bars *et al.*, 2001). *Fucus vesiculosus* extract exhibited significant anti-nociceptive centrally and peripherally. Indomethacin and extracts at 100mg/kg. 250 mg/kg and 500 mg/kg produced an analgesic effect. Data from the hot plate test emphasized the analgesic activity of *fucus vesiculosus* extract and showed a dose and time-dependent strong analgesic activity as compared to the control group.

The slow onset and long duration of analgesic activity of the extract suggested an active metabolite. The centrally mediated analgesia integrated response is affected mostly by opioids receptors (Anjaneyulu and Chopra, 2003). *Fucus vesiculosus* may have exhibited a significant and potential analgesic activity via activation of opioid receptors in the central nervous system, which needs to be investigated. The acetic induced writhing protocol is used for the assessment of peripheral analgesic effects. The results indicated a decrease in writhing at all extract doses. It is well known that acetic acid in some way is responsible for the secretion of endogenous mediators of pain, thereby stimulating the neurons responsible for pain sensation (Arslan *et al.*, 2010).

The chemical compounds responsible for the analgesic effect of the extract were not identified in the present study and needed to be studied further. Our plant yielded positive results for flavonoids,

**Table 1: Phytochemical analysis of a methanolic extract of Fucus vesiculosus**

| | |
|---|---|
| Saponins | Positive |
| Alkaloids | Negative |
| Steroids | Positive |
| Tannins | Positive |
| Flavonoids | Positive |
| Triterpenoids | Negative |

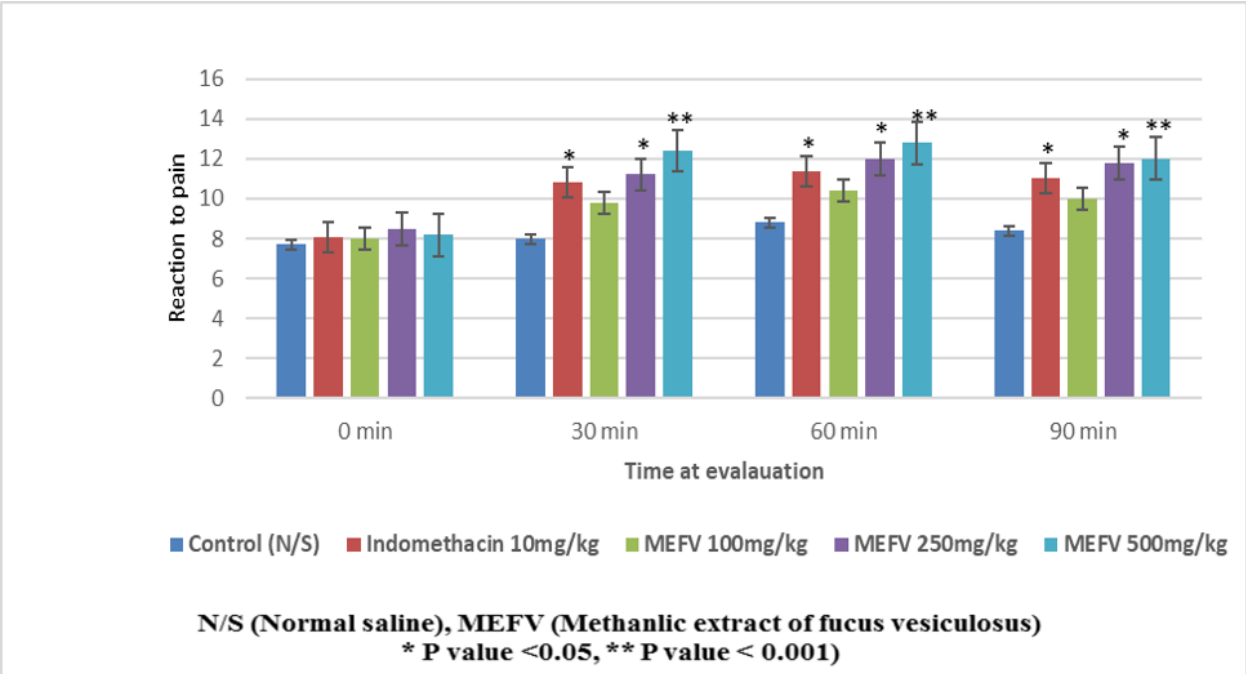


**Figure 1: Evaluation of analgesic potential (Hotplate Method)**

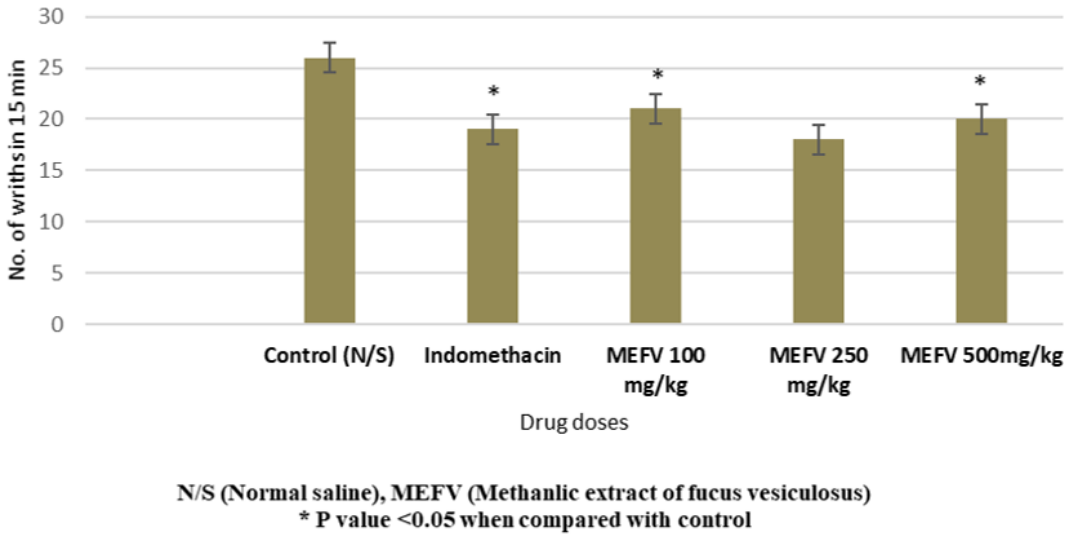


**Figure 2: Evaluation ofanalgesic potential (Acetic acidinduced writhing)**

steroids, tannins and saponins. Flavonoids and alkaloids have been linked with anti-nociceptive effects. Studies have shown that flavonoids have analgesic effects. Flavonoids have shown to inhibit both inflammatory and neuropathic pain through mechanisms involving the inhibition of cytokine production (e.g., IL-1b) and prostaglandin and inducing nitric oxide (NO) production and endogenous opioid-dependent mechanisms (Filho *et al.*, 2008; Valério *et al.*, 2009). Flavonoids have also shown to inhibit the production of intermediate and directly acting nociceptive mediators related to pain as well as directly inhibiting nociceptor sensitization by activating neuronal mechanisms which include the release of endogenous opioids (Xiao *et al.*, 2016; Hiruma-Lima *et al.*, 2000). This plant has demonstrated central and peripheral analgesic potential. The active constituents responsible for this effect need to be evaluated. The tests need to be validated by further pain model experiments. Also, the mechanism at the cellular level needs to be investigated. If proven further, *fucus vesiculosus* could be an additional alternative, safer medication for the treatment of acute and chronic pain.

## CONCLUSION

Our study has concluded significant analgesic potential of methanolic extract of *fucus vesiculosus.* After further evaluation and identification of potential analgesic constituents, this plant could be a new addition in the management of pain disorders.

### Ethical Issue

All experimental process of animals was approved by the Ethics Committee for Animal Experimentation of the King Khalid University and carried out in accordance with the Regulations of Experimental Animal Administration issued by the University.

### Conflict of Interest

The authors declare that there are no conflicts of interest.

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