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Anti-Inflammatory Effects of Celery Seed Hydroalcoholic Extract on Carrageenan-Induced Paw Edema in Rats.

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ABSTRACT

The present study investigated the antioxidant effect of wild celery seeds following reports in this regard. Wild celery seeds were provided by Isfahan Gol Daroo Co. and approved by the Department of Pharmacology. In order to prepare the extract, 70% ethanol was applied using the soaking method. Rats received 25, 50 and 100 mg/kg hydroxy extract of wild celery seed, respectively, and positive and negative control groups received 300 mg of aspirin and 5 ml/kg physiologic serum intraperitoneally, respectively. After half an hour, 100 ml of 1% carrageenan was subcutaneously injected to the paws of the rats in all groups and paw size changes were assessed using a plethysmometer every hour for 5 hours after the injection of carrageenan. All doses had an anti-inflammatory effect, and the 100 mg/kg dose of the extract had an anti-inflammatory effect similar to aspirin in all of the measured times. Because there was no significant difference between the anti-inflammatory effect of the 100 mg/kg dose and aspirin, the 100 mg/kg dose was recognized as the optimal dose. The hydroalcoholic extract of the seeds of wild celery has a dose-dependent anti-inflammatory effect.

Keywords: Celery, aspirin, carrageenan, inflammation, rat

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INTRODUCTION

The immune system protects the human body against pathogenic factors by white blood cells and substances released by them. The process of the accumulation of white blood cells and the release of chemicals secreted by them is manifested in the form of inflammation. In the case of some diseases, the immune system induces inflammatory reactions while there is no substance to deal with and suppress them. This is a case of autoimmune disease, due to which the body might harm some of its healthy organs [1-2].

One of the most common methods for the treatment of inflammations induced by different diseases is the application of corticosteroids and nonsteroidal anti-inflammatory drugs. Since most of the drugs in this group cause several side effects including gastrointestinal and hematological side effects, the application of anti-inflammatory medicinal herbs without such side effects can have a special place in treatment.

Celery (Apium graveolens) is a plant variety in the family Apiaceae. This plant was two years old and its maximum length was 100 cm. The seed of this plant is used for medicinal purposes. This wild plant grows in salty soil, along marshes, salty waters, the coast of seas and salty springs [3]. It tastes slightly pungent and its leaves are similar to parsley. Furthermore, its color is greenish white [4]. It originated from southern Europe but it can be discovered all over the world. Celery is found in different areas of Iran including the provinces of Semnan, Khuzestan and Sistan and Baluchistan [5].

As it was mentioned before, it is a plant with antioxidant properties and prevents the formation of free radicals [6]. Various physiological effects such as anti-inflammatory [7] and anti-cancer [8] effects have recently been attributed to it. Celery seeds contain antioxidant compounds [1] and their anti-cancer effects are mainly due to falcarinol, which is the most active cytotoxic compound and a polyacetylene [10]. It has recently been proven to be allergen [11].

The essential oil in the plant's seeds is more than its root, and is equivalent to 2.5-3%. Wild celery seeds contain limonene (70-80%) and up to 10% selenine. It also contains a flavonoid called apiin [12,13]. Other celery essential oils include paracymene, β -pinene, β -triptol, α-santalol, n-butyl phthalaldehyde, sedanolide, ostenol, apigravin and apiumetin [14]. In addition to limonene and selenine, wild celery contains vitamins A and C, and has very high antioxidant properties. Additionally, the vitamin C found in it strengthens the immune system, and via the oxidation of cholesterol, free radicals can reduce the chance of myocardial infarction and cerebrovascular accident. Moreover, it contains coumarins such as bergapten and furanocoumarin which lower the level of serotonin [13].

In some traditional herb resources, celery is claimed to aggravate epilepsy seizures, whiles others consider it diuretic and carminative [15]. Recent research on celery suggest effects such as reduced blood lipid [16,17], liver protection against oxidant [18], anticancer effect [19,20] and allergen [21] and antimicrobial properties [23, 32].

A study by Ahmadi, *et al* suggested that the methanolic extract of celery has more antioxidant effect compared to of synthetic α-tocopherol and less effect compared to ascorbic acid [24].

Another research by Nasri *et al* indicated that the hydroalcoholic extract of celery has analgesic effects [25].

Considering what was said, the present study investigated the effect of hydroalcoholic extract of wild celery seed on the inflammation caused by injecting carrageenan into the claw of male rats.

MATERIALS AND METHOD

This study used wild celery seed, carrageenan, powdered aspirin (made by Daroupakhsh Co.), 96% ethanol (Manufactured Khorramshahr Alcohol Co.) and physiology serum. The seed was provided by Isfahan Gol Daroo Co. and identified by the Department of Pharmacology of Ahvaz Faculty of Pharmacy.

In order to prepare the hydroalcoholic extract, 70% ethanol was applied using the soaking method in a way that 300 g seed was soaked in 790 cc 70% ethanol and filtered after 72 hours. Afterwards, 400 cc of 70%

ethanol was added to have better extraction and filtered again after 72 hours. The resulting extract was concentrated by a vacuum distillation device for 24 hours and the resulting product was dried in an over at the temperature of 35 ° C. After weighing (51 g), the dried extract was refrigerated in a suitable container. Grouping animals and assessment of inflammation: In this study, 30 young male rats of Wistar strain with the weight range of 150-180 g were received from the of Animal Breeding and Maintenance Center of Ahvaz Jondishapour University of Medical Sciences. Rats were maintained in the animal room of Ahvaz School of Pharmacology in the temperature of 23±2°C, humidity of 50% and light cycle of 12 hours light and 12 hours darkness.

Experiments were conducted in a quiet environment. The animals were brought to the laboratory an hour before the experiment to adapt to the conditions. Furthermore, each rat was used only once. After being selected and weighed, rats were randomly categorized in 5 groups (with 6 rats in each). After being numbered, they were injected with the following method.

Groups received 25, 50 and 100 mg/kg hydroxy extract of wild celery seed, respectively, and positive and negative control groups intraperitoneally received 300 mg of aspirin and 5 ml/kg physiologic serum, respectively. Half an hour later, 100 µl 1% carrageenan solution was subcutaneously injected to the paw of rats in different groups, and paw size changes were assessed using a plethysmometer every hour for 5 hours using a plethysmometer device. Due to rapid changes in the size of rats' paw during the first hour after the injection of carrageenan, inflammation was assessed 3 times in the first hour, and their resultant was recorded as size in the first hour. Before the injection of carrageenan, the paw sizes of rats in different groups were measured and recorded as paw size at the time of 0 [26,27]. The anti-inflammatory effect of different doses of the extract was compared with the negative control group (5 ml/kg of physiologic serum) and positive control group (300 mg/kg of aspirin). According to the results, the hydroalcoholic extract of wild celery seeds had a dose-dependent anti-inflammatory effect.

The following formula was used to calculate rat paw edema in percentage:

$$\text{Relative pawedema}\% = \frac{V_2 - V_1}{V_1} \times 10($$

V_1: Rat paw size before the injection of carrageenan

V_2: Rat paw size after the injection of carrageenan

Linear model test, ANOVA statistical method and Tukey's auxiliary test were used to compare the anti-inflammatory effect of the extract

RESULTS

Comparison of the anti-inflammatory effect of hydroalcoholic extract of wild celery seeds with the doses of 25, 50 and 100 mg/kg with the group receiving physiology serum showed that this effect is significantly higher than physiology serum ($p<0.05$) (diagram 1). Comparison of the anti-inflammatory effect of hydroalcoholic extract of wild celery seeds with the doses of 25 and 50 mg/kg with the group receiving aspirin (300 mg/kg) showed that this effect is significantly lower than aspirin ($p<0.05$) (diagram 2). However, there was no significant difference between the anti-inflammatory effect of the hydroalcoholic extract of wild celery seeds with the dose of 100 mg/kg and aspirin. (diagram 2)

Comparison of the anti-inflammatory effects of hydroalcoholic extract of wild celery seeds with the doses of 25, 50 and 100 mg/kg indicated that this effect is significant and dose-dependent.

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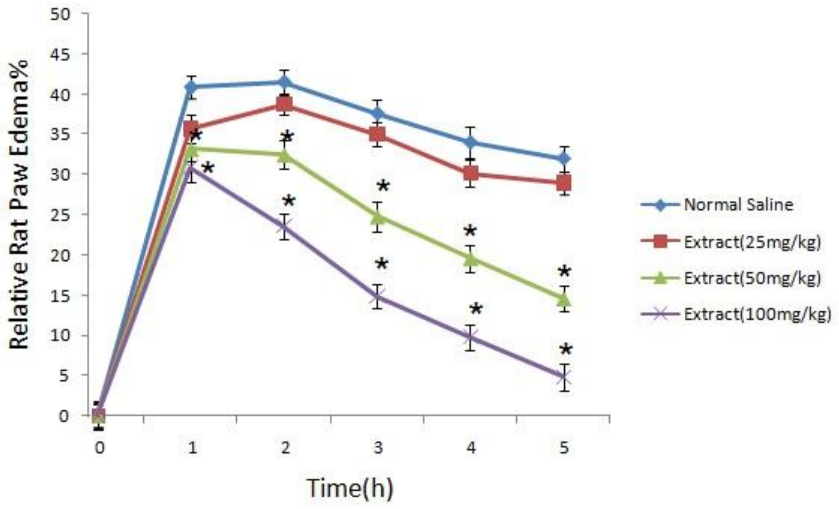

Diagram 1: comparing the anti-inflammatory effect of doses 25, 50, & 100 mg/kg of hydroalcoholic extract of celery's seed with normal saline 5 mg/kg on the created edema resulted from carrageenan hypodermic injection in the rats paw

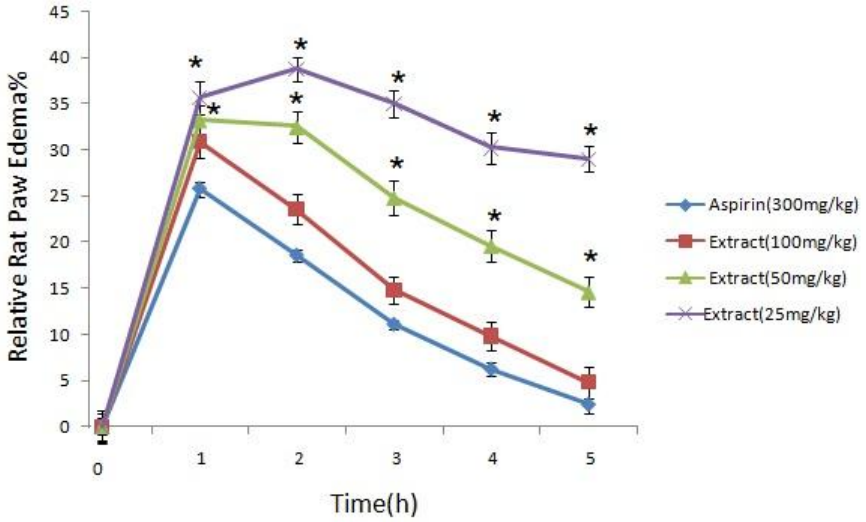

Diagram 2: comparing the anti-inflammatory effect of doses 25, 50, & 100 mg/kg of celery's seed hydroalcoholic extract with aspirin 300mg/kg on the created edema resulted from hypodermic carrageenan injection in the rats paw
*** The difference with the aspirin receiver group is significant (p<0.05)**

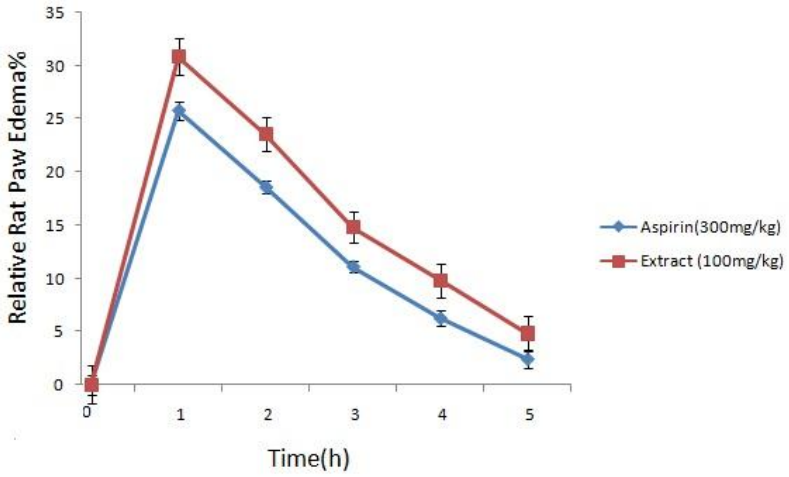

Diagram3: comparing the anti-inflammatory effect of hydroalcoholic extract of wild celery seed (100mg/kg) with the aspirin receiver group (300mg/kg) on the created edema resulted from hypodermic injection of carrageenan in the rats paw

DISCUSSION

In this study, 1% carrageenan-induced edema model was used in order to investigate the anti-inflammatory effect of celery seed extract. This method is widely used in order to investigate inflammation [26, 28]. Carrageenan test has 2 separate phases; the first phase includes the burning effect, while in the second phase, the inflammatory effects of carrageenan manifest themselves to show that nonsteroidal anti-inflammatory drugs and corticosteroids can inhibit the second phase [29], while opioids including morphine can inhibit both phases 1 and 2 [30].

Celery contains flavonoid apiins which controls edama [12,13]. As a result, the anti-inflammatory effect of this extract can be attributed to flavonoid apiins. The inhibitory effect of flavonoids on acute and chronic inflammation is due to their effect on pain signal pathways including the activity of NF kappa B factor and kinase phosphorylation of MAP. In addition, flavonoids reduce the accumulation of floating lipids which are essential for signaling pain. Flavonoid apiin inhibits prostaglandin E2 and leukotriene C4 in rats and also thromboxane B_2 synthesis in human platelets [31,32]. According to reports, the effects of flavonoids include reduction in the activity of acetyl cholesterol acyltransferase enzyme in hepatic cells and also hydroxymethyl glutathione coenzyme reductase (HMG-GA) enzyme [33, 34].

Most existing analgesic and anti-inflammatory drugs decrease inflammation and pain by inhibiting cyclooxygenase-2 enzymes which convert arachidonic acid to prostaglandin.

A study carried out by Cheraghi *et al* determined that the limonene found in herbal extracts has anti-inflammatory and analgesic effects and interrupts the synthesis of prostaglandin through the inhibition of oxygenase. Another by Hamza *et al* indicated that fennel has anti-inflammatory properties. Since fennel and celery are both of the Apiaceae family, the anti-inflammatory properties of celery is justifiable.

The present study showed that the anti-inflammatory effect of hydroalcoholic extract of celery seed has dose-dependent anti-inflammatory effects, and the best dose of the extract is 100 mg/kg. It should be noted that the 100 mg/kg dose has an anti-inflammatory effect equal to a 300 mg/kg dose of aspirin. Therefore, one of the mechanisms of celery extracts could be the inhibition of prostaglandin synthesis, which requires subsequent studies to be proved. No side effect was observed in animals receiving various doses of celery extract. .

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