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Anti-Inflammatory and Analgesics Activities of Watercress (Eruca Sativa) Extract in Rats

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Abstract

The increased use of traditional anti-inflammatory drugs, which have many side effects, scientists and researchers have turned towards natural products to avoid the side effects of traditional chemical drugs. Plants are used in ancient times due to their association with humans as food and medicine. Different parts of plant have been common among people and pharmaceutical industry used in food and medical industries for production of drugs used in treatment of most diseases a variety of active constituents with wide range of pharmacological actions have been approval in recent years. The analgesic and anti- inflammatory effect of some of these plants has also been found. Among these plants, watercress (Eruca sativa) was used as food in different area of the world. The present study aimed to investigate the analgesic and antiinflammatory properties of watercress (Eruca sativa) leaves extract (WE) using rats. Evaluated of analgesic activities were done through hot plate, tail immersion, and writhing assay tests at different WE doses (100,200 and 300 mg/kg) using male albino rats. Antiinflammatory assay was performed by carrageenan induced paw edema of WE at different doses (100,200 and 300 mg/kg). Morphine and aspirin were employed as a standard for analgesic tests while Indomethacin was used for anti-inflammatory studies, The present study demonstrated that watercress (Eruca sativa) leaves extract (WE) have analgesic and anti-inflammatory properties through inhibition the release mediators. In the current study, the higher dose of WE (300mg/kg) exhibited greater analgesic and antiinflammatory activities compared to the control and standard drugs. WE also showed good effects on pain and inflammation and therefore it can be said that WE can be used as a good alternative to relieve the effects of pain and inflammation without side effects of NSAIDs.

Keywords: Watercress (Eruca sativa); Analgesic; Anti-inflammatory; Conventional; Plants

Introduction

Pain and inflammation remain among the most common global health problems that humans face socially and economically throughout the world, regardless of the availability of medicines or their high prices [1,2]. Inflammation and pain are common manifestations for many diseases of various endogenous and or exogenous mediators and considered as nature defense mechanism aimed to remove the injury and the tissue healing [3]. Pain brought on by tissue injury or probable occur is considered a source of anxiety and discomfort for humans due to the constant unpleasant sensory impact on a location in the human body and may affect the movement and activity of the entire human body in many cases [4], Pains consider mechanism forces these injured to quickly seek treatment for these injuries and recover from them [5]. Many people is influenced by pain and inflammation, which are difficult health problems over the world particularly developing countries [6]. Many Opioids and non-opioids materials were found as anti-inflammatory drugs to treat both acute and chronic pains [7,8] reported the acute and chronic pains leads to the development and increase of the disease condition in people infected with these infections. Inflammation is considered a natural response to movement and vital processes taking place within the body's cells, and it is a signal of the biological line of defense to confront the dangers of movement, infection, damage to cells and tissues, such as redness, swelling, high body temperature, and pain[8-10]. Moreover, inflammation produced from endogenous metabolic

processes are consider the most important sources of free radicals react with lipids, proteins, carbohydrates and damage all types of biomolecules [11-13]. Therefore, it is necessary to rapid combat pain and inflammation and also in need to search using new sources produce analgesics and anti-inflammatory drugs [14,15]. Recent experimental studies of pain and inflammation has been shown that many types of medications used as antidepressants, such as amitriptyline and nortriptyline, Imipramine, fluoxetine, clomipramine, maprotiline, desipramine and doxepin widely used to treat various types of pain and inflammation [8,10,16,17]. Long-term use of conventional anti-inflammatories causes stunted growth, high blood sugar, high blood pressure, and osteoporosis. [18,19]. Other studies reported that the long-term use of anti-inflammatory drugs causes toxicity to the heart, digestive system, kidneys, and liver, in addition to addiction and imbalanced hormonal disorders [20,21]. Antiinflammatory drugs, especially opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are used as analgesics to reduce and eliminate pain completely [15,22]. NSAIDs are among the most clinically widely used in medicine due to their efficacy for a wide range of pain and inflammatory conditions and used for treatment of inflammation-related diseases like arthritis, asthma, and cardiovascular disease [10,23]. However, the long-term administration of NSAID may induce gastro-intestinal ulcers, bleeding, and renal disorders. Different pharmacological approaches were used for treated pain and inflammation as opioids analgesics corticosteroids and some combination therapy to enhance efficacy [16,17], indicated these drugs having side effects,\ including bronchospasm, gastric ulcer, cardiac abnormalities and renal damage. Therefore, researchers are now focusing on plants and their products/compounds [7,15]. such as polyphenols, polysaccharides, alkaloids, flavonoids, steroids, and terpenes as they have different pharmacological activities including analgesic, antipyretic and anti-inflammatory effects [24,25,26].These medications are used with extreme caution because they are narcotic substances and their effectiveness in treating pain and inflammation is questionable [16]. Therefore, new anti-inflammatory and analgesic drugs lacking those effects are being searched all over the world as alternatives to NSAIDs and opiates [23,27,28].Some studies showed the use of biosynthetic drug as treatment of analgesic and inflammation produces disturbances in human body organs and other side effects [18,29]and hence different substances of plant origin are gaining importance for the treatment of analgesic and inflammation. Plants are used in ancient times due to their association with humans as food and medicine for many diseases for many years [30,31]. Different parts of plant have been common among people and pharmaceutical industry were found extensively utilized in food and medical industries to synthesize and produce drugs of biological activity in the treatment of most diseases [32,33]. Other investigators [34,35], showed that the most population in the developing countries depends on traditional medicines for treatment of diseases due to inexpensive of herbal medicines availability and the lack of medical facilities [35,36]. Various plant products as alkaloids, saponins, triterpenes, glycosides, polysaccharides, polyphenols and flavonoids have shown anticancer properties [26,37]. Other phytoconstituents such as tannins and anthraquinone were heals wounds and inflammations [34,38]. Plants are an important main source for the production of new chemicals [39,40,41] that have therapeutic effects for various diseases and necessary research strategy to search for new analgesic and anti-inflammatory drugs [42,43,44]. Plants and their components were also used to prevent epidemics and various diseases, as it was found most of them have antioxidant, anti-inflammatory and anti-parasitic properties [36,45,46]. According to the increases required for treatment for analgesic and anti-inflammatory this leads to scientists have intensified their efforts to search for other sources to produce plant derived materials and compounds that can be used to treat pain and inflammation [10,47,48]. Recently, many natural compounds such as terpenoids, phenolic, flavonoids, lignans and others were discovered from plant sources [34,49,50], they manifested that these compounds have anti-inflammatory, antitumor and anticarcinogenic activities. Natural products have been regarded as important sources of potential chemotherapeutic agents and drugs have shown antiinflammatory activity [46,51,52]. Among natural products, plant extract, have antimicrobial, antifungal, anti-diarrhoea, anti-viral, antitumor, antifertility and anti-inflammatory activities [49-56]. Different studies reported different biological activities of substances or compounds were isolated from plants origin used as antidiabetic [13,57], antihypertensive [58], cancer chemopreventive effects [59] anticancer activities, [60], and antiepileptic properties [46,61] due to their phytochemical constituents. Other investigators reported some plants have been use, in treatment of disorders and other biological activities including antifungal and antibacterial effects due to its antioxidant properties [62]. Polysaccharides were isolated from Portulaca oleracea prevents vascular inflammation, and dysfunction in mice [13,63]. Plant extract are non-toxic and biodegradable that consequently suitable for different pharmaceutical and biomedical uses [64]. Recent study has shown that some plant extract intake cause improve in some biochemical parameters [60]. Different plants extract have been shown the potential health impacts in preventing some diseases and have antiinflammatory activities [64,65]. Current researchers concentrate to examine new kinds of natural products shown maintenance health and analgesic and anti-inflammatory [66,67]. Phytochemicals such as polyphenols, flavonoids and fatty acids have considerable interest in the field of food chemistry, pharmacy and medicine due to their biological effects including analgesic and inflammation properties [46,60]. Plant-based substances may act as a physiological modulator for

the treatment of pain and inflammation. Plant contains different compounds which exert different kinds of pharmacological activity [59,64,68] more than those of synthetic compounds. Many plant extracts and their constituents were found to be used for treatment of many kinds of human diseases [60,69]. Different studies were done for extraction of pure bioactive compounds from plant [70]. Most studies have been shown the beneficial effects of diets rich in plant in reducing the inflammation [71] correlate increased phenolic compounds levels in foods with reduced disease mortality. Flavonoids consider a major group of polyphenolic compounds that considered are essential constituents of plant cells possess [62,72,73]. Therefore, watercress (Eruca sativa) extract can be used as strong sources of novel analgesic and ant-inflammatory agents [74,75,76]. The present research was done to investigate the effects of watercress (Eruca sativa) extract (WE) against pain, analgesic and anti-inflammatory activities using male albino rats.

Materials and Methods

Materials

- A fresh watercress (Eruca sativa) as whole plants were obtained from local vegetable market in Egypt. The plants were cleaned carefully and damaged plants were removed, washed with tap-water followed by distilled water and cut into small pieces and stored at 4 º C till used.
- Chemicals used in the present study, Morphine, aspirin, Indomethacin, carrageenan, and acetic acid solution were obtained from Sigma Chemicals Co., St Louis, USA.
- Thirty five male albino rats (Rattus norvgicus), weighing 160±1.02 g/kg were purchased from Biological Products of National Research Center, Cairo, Egypt. Rats were kept under controlled temperature with 12±1h light/dark cycle at the Institute of Biological Products of National Research Center. Rats were fed with standard commercial pellet diet and given water ad libitum. Further, the animals were under investigation up to a period of 2 weeks for mortality and behaviors. After two week of acclimatization, the rats were then divided into seven groups, 5 rats each, on the basis of their body weight, housed in wire screen cages. Rat group administered saline (10 mg / kg) only was used as control group. Three rat groups orally administered the standard drugs for analgesic and anti-inflammatory assays (morphine,10 mg/kg for the hot plate, aspirin 150 mg/kg for the acetic acid-induced writhing, and indomethacin, 25 mg/kg for the carrageenan-induced paw edema).The remaining three rat groups were administered WE at different doses of 100, 200 and 300 mg per kg body weight respectively, Following a period of one hour after oral administration of saline, standard drugs or extracts, rats were intraperitoneally injected. Study was carried out in agreement with NRC and approval was done by ethical review committee of NRC, Dokki, and Cairo, Egypt.

Methods

Preparation of Extract

A known weight of fresh watercress (Eruca sativa), was ground in a food grinder (mincer) and mixed well with hot water (1:1 V/V) twice using a homogenizer for 5 min. The homogenate was filtered through cheesecloth and Whatman No.1 filter paper. The obtained watercress (Eruca sativa) extract (WE) was used for chemical analysis and oral administration to the rats [40].

Analytical methods

Protein concentration was measured using bovine serum albumin as a standard [77]. Lipids were extracted with chloroform-methanol mixture (2:1 V/V), according to the method previous described [78]. Total carbohydrate value was also estimated [79]. Ashes were quantified gravimetrically after incineration in a muffle oven at 550 °C. Phenolic and flavonoid were estimation [80].Total phenolic content (TPC) was determined [81,82]. Total flavonoid contents (TFC) was estimated spectrophotometrically [83]. Flavonoids was identified using apigenine, quercetin and catechin as standard [84,85]. Fatty acids composition of WE were also estimated [86,87] using gas liquid chromatography (GLC).

Cytotoxicity

Cytotoxicity test of the present extract (WE) was measurement according to the method described previous [88,89], Watercress extract (Eruca sativa) extract (WE) were administered orally to overnight fasted rat at the doses of 100, 200 and 300 mg/kg body weight (b. w.). After administration WE, the rats were observed continuously for 72 hours. Rats were under investigation for a period of two weeks for following their general behavior, toxicity, physiologically reaction and mortality [90,91]. The doses were selected based on cytotoxicity study.

Anti-inflammatory and analgesic assay

For the analgesic and anti-inflammatory activity tests, rats were divided into seven groups, each consisting of 5 animals [40,88]. One group was orally administered distilled water and used as control group, three group were designated as the standard (morphine 20 mg/kg for the hot plate method, aspirin 150 mg/kg for the acetic acid-induced writhing, and indomethacin 10 mg/kg for the carrageenan-induced paw edema). The remaining three treated groups were given orally three different doses of WE (100, 200, and 300 mg/kg b.w. respectively).

Analgesic activities

Hot plate method

Hot plate test was done to evaluate the analgesic activities of extract used in the present study. Pain was induced by placing the rat on a hot plate at 55 ±1 °C and the response time was recorded as an index of analgesic activity. Rats were reacted to the thermal pain by licking of their hind paw and jumping where the reaction time was measured in a regular time interval and the reaction strength of each rat was determined in a regular intervals of at 0 min, 30, 60, 90 and 120 min and the time increase was taken as an index of analgesic activity. Analgesia was compared the groups ertr administered WE doses with control and standard drug groups [26,90].

Tail immersion test

The method described previous [92] was used in this test. Rats were divided into seven groups of 5 rats each. The lower end portion of rats tail 5 cm were immersed in hot water maintained at 55 ± 0.5∘ C [93,94]. Within a few minutes, the rats reacted by withdrawing the tail from hot water. The time for tail withdrawal from the hot water was taken as the reaction time and recorded using stopwatch. The time reaction was measured in seconds for the rat withdrawal their tail from the water and was taken as the reaction time. The reaction time was measured [23]. Oral administration of WE doses (100, 200 and 300 mg/kg, b. w.), saline and standard drug, 30min before the immersion of the tail. The time reaction is taken at 0, 30, 60, 90 and 120 minutes.

Acetic Acid-Induced Writhing Assay

Analgesic activity of extract was determined by acetic acid-induced writhing test [95,96], Rat of either five were given WE doses, One hour later, rats in their respective groups received intraperitoneal injections of 1 % acetic acid (10 mL/kg b.w.). The analgesic activities of the WE doses were measured five minutes after the acetic acid injection by counting the numbers of writhing, which is characterized by contraction of the abdominal muscle together with stretching of the hind limbs for 30 minutes. The numbers of abdominal writhing were counted for 20 min observation beginning at 5 min after the injection. The rats were treated with WE (100, 200 and 300 mg/kg b. w.), 30 min before administration of acetic acid. The percent reduction in the number of writhes relative to the control group was used as an index of analgesia [95,97,98].The significant reduction in number of writhes of treated groups was compared to that of the control and standard groups. The percentage inhibition of abdominal constrictions was calculated [90].

Anti-Inflammatory Activity

Carrageenan induction test

Anti-inflammatory activity was investigated using paw edema method [98,99] using carrageenan and plethysmometer for anti-inflammatory assay. Rats were in fasting condition before start the experiment, For induction of edema, an hour after oral administration of control, standard drug and WE tests and the paw edema volumes were recorded after 30 min, 60 min, 90 min. and 120 min s of carrageenan injected using plethysmometer [99,100]. Acute inflammation was induced half an hour after treatment by injection of carrageenan (0.1 mL freshly prepared) in left hind paw of rats [99,101]. The rat paw volume was measured at 1, 2, 3, 4 and 5hrs after the carrageenan injection [102].The difference between the rats paw volumes indicated to the degree of inflammation [103]. Edema was expressed as percent increase in rat paw volume due to administration carrageenan compared to rat paw given the control and standard drugs. The average increase in paw volume of each group was calculated and compared with the control and the standard groups [8].

Statistical Analysis

Data were analyzed using ANOVA statistical and the results were presented as mean value
± Standard error (SE).

Results and Discussion

Chemical composition of watercress (E. sativa) extract (WE)

Natural products have been widely used in treat of pain and inflammation. Watercress (E. sativa) is among natural products widely used between ancient people societies for treating some diseases [104,105]. Little scientific reports were found in the literature about activities of watercress (E. sativa) in analgesic and anti-inflammatory using experimental animal. Phytochemicals an evidence for the pharmacological potential of the plant secondary metabolites having different activities in fighting cytotoxicity and diseases [106]. Watercress (Eruca sativa) extract sample (WE) was obtained and used for chemical composition. Results in (table 1) revealed the chemical composition of watercress (E. sativa) extract (WE). Chemical analysis of WE revealed the presence of different contents of protein, lipid, carbohydrate, phenolic and flavonoid as shown in (Table 1). WE contain different percentages of protein, lipid and carbohydrates (24.40, 22.60 and 48.20% respectively) Similar results were obtained by other investigators [31,76], they found higher protein content in watercress (Eruca sativa) seeds than the other plant seeds. Other investigators found the protein content of plant extracts was 21.7% [32,107]. Results also showed the lipid contents in WE (22.60%) which are in the range with those reported by other investigators [37,108] using different plant extracts. Higher level of carbohydrates was observed in WE (48.20%) as shown in Table (1). Similar results were obtained by several investigators [32,107,109]. Data in (Table 1) showed the WE contain suitable content of phenol (28.20 mg/g) and flavonoid

(22.80 mg/g).These results are higher than those reported by other studies [76,109,110], they reported the total phenolic content was ranged from 12.7 to 25.6mg/100g in plant extract. Other investigators [111,112,113] reported the phenolic content was varied from 15.9mg/g to 22.7mg/g in different plant extracts These results are in agreement with the finding of other investigators [107.114,115] found the phenolic contents ranged from 0.98 to 3.35mg gallic acid equivalents per gram. Moreover, several studies [13,116,117] determined the content of phenolic compounds at a level of 0.44mg/g as gallic acid equivalents. Results in Table (1) showed higher flavonoid content in WE (22.80 mg/g). The present results are in a good agreement with those reported by other investigators [110,113]. Other investigators [46,60,76] found the flavonoid contents in three samples of Eurca sativa was ranged from 23 to 25%. Other studies [111,118] found lower flavonoid contents in radish, and Lettuce extracts. Lower flavonoid contents in safflower and coriander extracts was also obtained [32,119]. The present results showed significant and correlation with flavonoids and phenolic, suggest their involvement in various important characteristics such as analgesic and anti- inflammatory activities [46,117,120] reported phenolics and flavonoids have potential activities in biological systems, However, the highest flavonoid and phenolic contents were found in WE, have potentially analgesic, anti-inflammatory and antioxidant [23,62,121]. Therefore, WE used in the present study are recognized as dietary elements may be effects on human health and could be used as pharmaceutical and drug for treatment of different diseases. Results also showed the presence of lipids (22.60%) in WE sample as shown in (Table 1). The present results are in agreement with those reported by other investigators [65,122,123] using extract for production of safflower oils. Lower level (8.50%) was obtained from coriander [32]. The lipid content explains potential used of US as natural sources for higher lipid production recognized as dietary elements play an important role in human health. WE lipid in present study was used for analyses and determination of fatty acids (FAs) composition using Gas Liquid Chromatographic (GC). Generally, lipids have saturated fatty acids (SFAs) and unsaturated fatty acids (USFAs) as major contents. Different values of USFAs and SFAs were found in different plant lipids [31,124]. The percentages of SFAs, monounsaturated fatty acids (MUSFA) and polyunsaturated fatty acids (PUSFAs) were 14.40%, 26.80% and 58.80% respectively in the obtained WE sample as shown in (Table 1). Results also showed the PUSFAs were predominant than that of SFAs. These results are in agreement with those obtained by other investigators [86,125] found the USFAs were predominant than that of SFAs in different types of plant extracts. The analyses of WE sample using GC revealed the presence of of 7 main fatty acids linolinic acid C18:3 ω-3), linoleic acid (C18:2 ω-6) and oleic acid (C18:1 ω-9), palmitic acid (C16:0), stearic acid (C18::0), arachidic acid (C20:0) and behenic acid (C22::0) as shown in Figure (1).These variations induced differences in SFAs, MUSFA and PUSFAs as shown in Table (1). Five main fatty acids were detected in purslane extract [126]. Results showed higher percentage of PUSFAs, linolenic acid C18:3 (22.60 %) in WE, These results were quite close to the finding of other investigators [115,127], they detected the content of C18:3 was ranged from 23.65% to 37.5%while other study found the C18:3content was 10.56 [118]. Other workers found the C18:3 contents in rapeseed and coriander extracts was ranged from 5.2%to15.0% [32,107,128]. The WE analyses showed higher C18:2 content (36.20%), these results are higher than those reported by other investigators using coriander and watercress extracts [32,108,129] found C18:2 content was ranged from 12.3% to 16.60%. The level of C18:2 content was ranged from 5.9% to 14.5% in rapeseed extract [52,123]. The higher level of C18:1(26.80%) was found in WE as shown in Figure(1). These results are quite close in agreement to the previous finding [128,130]. Other studies [13,31] found the content of C18:1 was 22.2% in chickpeas extract while. 20.9% of C18:1 was obtained from radish extract [127,128]. Lower levels (9-15%) were obtained of C18:1 in dill and safflower extracts [107,119]. Lower level (9.90%) of C18:1 was found in watercress extracts [132] but lowest level (7.5%) obtained from coriander extract [32,62] while. Results showed percentages of SFAs (14.40%) in WE as shown in Figure (1). SFAs contents in rapeseed extract was 9.20% [128]. Many investigators [52,108,118] found the percentages of SFAs was ranged from 9.0 to 9.6 % in in different plant extract samples Similar results were obtained by other investigators [31,133] they found SFA content was ranged from 6.9% to 12.40% when they were used different plant extracts. These results are lower than those reported by other investigators [32,107,132] found 22.4% SFAs content in safflower extract. Results showed C16:0 and C18::0, C20:0 and C22::0 were identified in WE (Figure 1). Results also showed the percentages of C16:0 (6.80%)) and C18:0 (3.20%) were predominant in SFAs followed by C20:0 and C22:0(2.40 and 1.60% respectively). These results are in agreement with those obtained by other investigators [37,131] used different plant extracts. These results are in accordance with those finding by previous studies [31,128,130] obtained similar results of C16:0 and C18:0 percentages. C16:0 content was 5.7% while the C18:0 content was 5.0% in safflower extract [115]. Other investigators [31,32,132] reported the C16:0 content was 3.8% and 4.08% in watercress and coriander respectively. The C20:0 content was higher in US (2.4%). Many investigators obtained similar results of SFAs with coriander, lettuce and dill seed extracts [32,107,108]. These results are higher than those obtained by other investigators [107,118,132] found different ranges in the content of C16:0 (20–22%), C18:0 (1.5%) and C20:0(1.4%) using radish and watercress extracts [76,127]. Different variations (0.2-1.4% and 1.4-2.6%) were observed in the conent of C20:0 on using chickpeas [109,118,133] and purslane

samples [118,131]. C22:0 level was 1.60 % as shown in (Figure1). Zambiazi et al. [134] found C22:0 in the samples of sunflower extract was 0.8%. However, it was excellent for the extraction of bioactive compounds involved in the prevention and treatment of different diseases. In this work, the effect of WE containing bioactive compounds possessing analgesic and anti-inflammatory activities was investigated by well-known pharmacological methods [13,19,135].

Table 1: *Chemical composition of watercress (Eruca sativa) extract (WE). (Mean values of three samples).*

Watercress extract (WE)	**Protein (%)**
Protein (%)	24.40
Lipids (%)	22.60
Carbohydrate (%)	48.20
Ash (%)	4.80
Phenolic (mg GAE/g DW)	28.20
Flavonoid (mg CE /gDW)	22.80

Table 2: *Reaction time of different treatments after doses administration. (Mean values ± SE).*

Reaction time **Rat groups**	**0 min**	**30 min**	**60 min**	**90 min**	**120 min**
Control	3.10±0.56	3.40±0.50	3.62±0.60	4.40±0.66	4.52±0.62
Standard	3.40±0.44	8.60±0.28	8.80±0.40	10.08±0.60	11.30±2.80
WE (100 mg/kg)	3.04±0.52	3.82±0.82	4.14±0.66	4.96±0.68	5.30±1.02
WE (200 mg/kg)	3.08±0.40	6.10±0.90	6.36±0.82	7.52±0.54	9.90±0.32
WE (300 mg/kg)	3.10±0.64	7.84±0.60	8.12±0.84	8.92±0.86	9.98±0.30

Table 3: *Analgesic activity (Reaction time minutes) of WE by tail immersion.*

Reaction time **Rat groups**	**0 min**	**30 min**	**60 min**	**90 min**	**120 min**
Control	0.80 ±0.02	1.04 ±0.10	1.48 ±0.20	1.60 ±0.26	2.40±0.28
Standard	2.80±0.02	5.60 ±0.20	6.88±0.40	6.40±0.40	8.64±0.60
WE (100 mg/kg)	0.80±0.01	1.60±0.20	2.40±0.20	3.90±0.20	4.20±0.40
WE (200 mg/kg)	0.86 ±0.20	2.02 ±0.26	4.10 ±0.26	4.80 ±0.40	7.40 ±0.80
WE (300 mg/kg)	0.94 ±0.08	3.10 ±0.40	6.40± 0.38	6.90 ±0.40	8.20±0.90

Table 4: *Analgesic effects of WE on rats-induced acetic acid. (Mean value of 5 rats ± SE).*

Rat groups	**Mean of Writhing ± SE**	**Inhibition (%)**
Control	60.16±1.24	0
Standard	20.92±0.88	65.22
WE (100 mg/kg)	38.34±1.05	36.27
WE (200 mg/kg)	28.16±1.01	53.20
WE (300 mg/kg)	22.02±1.04	63.34

It seems that in WE, more phenolic, flavonoids and fatty acids with analgesic and anti-inflammatory activities [101,136,137] may account for more pronounced pharmacological properties with analgesic and anti-inflammatory activities [22,23,98]. In addition, polyphenols with analgesic and anti-inflammatory activities in WE is the reason for its pharmacological effects, which can reconfirm more effective role of fatty acids compared to polyphenols for decreasing pain and inflammation [19,135].

Analgesic Activities

Hot plate test

Hot plate method is the most significant method suitable to evaluate and determine the central analgesic activity including spinal reflexes of WE in rats. The paws of rats are very sensitive to heat at temperatures which are not damaging the skin. The responses are jumping, withdrawal and licking of the paws. The time until these responses occur is prolonged after administration of centrally acting analgesics [138,139] indicated the Jumping and paw licking are considered supraspinally integrated behavioral responses, and the time of the latency to the onset of this reaction following injection is a measure of the analgesic activity [121]. In this study, we used morphine (10 mg/kg body weight) as a standard and three doses of WE (100,200 and 300 mg/kg body weight) compared to control. The effect of WE doses in hot plate method was shown in (Table 2). Results showed significant analgesic effect by delaying the reaction time intervals (0 -120 minutes). The reaction time (paw licking / jumping response) in rat groups with different doses of WE (100, 200 and 300 mg/kg) were found to be increase started from 30 min. and remains significant increases till 120 min. as compared to control rat group (Table 2). The duration of analgesic effect was more in WE dose, 300 mg/kg compared to other two doses (100 and 200 mg/kg). Hot-plate test was also used to distinguish between peripheral and central effects [46,135,139]. The maximum analgesic activities of all doses of the WE (100, 200 and 300 mg/kg) were observed at 60 and 120 minutes of observation as compared with the s tandard drug as shown in table (2). These results are in accordance with previous study [121,140], reported the hot plate test is an easy and suitable method for determination of central analgesic activity. These results of analgesic activity of WE are attributed due to the presence of high levels of phenolic, flavonoids and FAs in WE (Table 1 and Figure 1 respectively). Thus, we containing phenolic, flavonoids and FAs have analgesic effect. WE exhibited significant increase in reaction time compared to control in rats showing central analgesic effect. Other findings [19,140,141] showed reduced of prostaglandins due to the presence of flavonoids might be responsible for analgesic activity as prostaglandins are involved in the process of pain perception [31,142] previously reported the presence of phenolic and flavonoids in some plant seeds are considered to have a role in biological system due to their capability of quenching free-radicals [60,120]. Other investigators [143,144] reported the presence of these flavonoids halt key enzyme prostaglandin synthetase involved in the process of pain perception. The reduced availability of prostaglandins is due to the presence of flavonoids might be responsible for analgesic activity [137,141]. The inhibition was significant at the dose of 200 and 300mg/kg body weight as compared to that of the standard drug, (Morphine 10 mg/kg b.w.) at 30 minutes after treatment. These results indicate that, WE at the dose of 200 and 300 mg/kg showed the significant increase in time as compared to control, produce significant analgesic activity. The WE showed a rapid onset of analgesic action at all WE doses than standard. The highest analgesic activity was observed at 60 and 120 minutes. WE showed highest significant analgesic activity at the dose of 300 mg/kg as compared to other two doses [19,40,145]. Based on the increased rat response times in the hot-plate test, it can be concluded that the WE has a central analgesic activity [139].

Tail immersion test

Tail immersion test was considered to determine the analgesics activities of WE in rats. Results showed significant elongation of reaction time of the WE doses after 60 and 120 minutes (Table 3). Maximum elongation in the reaction time percentage was observed at WE dose of 300mg/kg body weight after 60 and 120 minutes (76.86 % and 70.74% respectively) as compared to control rat group. Results also showed the reaction time percentage was observed at standard drug after 60 and 120 minutes (78.48 % and 72.22 % respectively) as compared to control rat group. WE at a dose of 200 mg/kg body weight showed elongation in the reaction time percentage (63.90 % and 67.56 % respectively) after 60 and 120 minutes. Lower elongation reaction time percentage (38.33 and 42.86 %) was observed at WE dose of 100 mg/kg body weight after 60 and 120 minutes respectively. The present WE with various compounds may act through a central and peripheral analgesic mechanism while NSAIDs block only peripheral pain [146]. Nonsteroidal anti-inflammatory drugs inhibit only peripheral pain while extract inhibit both peripheral and central mechanism of pain, suggesting that the plant extract may act as a narcotic analgesic [138,147]. Flavonoids may increase the amount of endogenous serotonin which may be involved in the mechanism of central analgesic activity [146,147]. Moreover, WE showed highest analgesic activity in all the experimental rats which may be due to the presence of high level of flavonoid which are responsible for free radical scavenging activity, as these free radicals are involved during pain stimulation, and antioxidants showed reduction in such pain [148]. The results of the present study have shown that the WE exhibited very high analgesic activities. These activities may be due to the presence of polyphenol and flavonoids compounds WE. Flavonoids and saponins are well known for their ability to inhibit pain perception as well as anti-inflammatory properties due to their inhibitory effects on enzymes involved in the production of the chemical mediator of inflammation [149]. Thus, the presence of phenolic and flavonoids in WE might be responsible for the analgesic activity in rats [19.22,23].

Acetic acid induced writhing Assay

Acetic acid induced writhing test is commonly used for peripherally acting agents [150] that simulates visceral pain, and the writhing accompanied by abdominal muscular contraction [19,23].The acetic acid induced writhing response is a sensitive procedure to evaluate peripherally acting analgesics [15,146,147]. In the present study, significant analgesic activity was observed by

using WE at different doses. In this test pain occurs by the liberation of endogenous substances like arachidonic acid and prostaglandin causes activation of peritoneal receptors leads to abdominal constriction [44,152]. Intra-peritoneal injection of acetic acid causes intense pain and acute inflammation in that area. The endogenous substances stimulate nerve endings and causes the indirect stimulation of peritoneal nociceptors [114,128].Writhing is manifested by the abdominal muscles constriction, extension of the forelimbs and elongation of the body. WE significantly decrease the abdominal constriction, indicated that the WE had dose-dependent effect but has lower effectiveness than standard drug [142,116].Therefore, it can be suggested that WE contain some pharmacologically active compounds which block the endogenous substances and arachidonic acid metabolites which cause excitation of the pain nerve endings [153]. The effect of WE at different doses (100, 200 and 300 mg/kg) on writhing rats by induction of acetic acid solution (1%) as shown in Table 4. Results showed the administration of WE doses (100, 200, and 300 mg/kg) has significantly lowered the number of acetic acid-induced writhing (abdominal constrictions of rats), compared to the standard and control rat group. The effect of these doses reached a maximum inhibition of 63.34% at the dose of 300 mg/kg. However, the WE extract dose (300 mg/kg) response was lower as compared to the standard drug (65.22 %) rat group. These results indicate protective effect of WE due to the presence of different levels of FAs (Figure 1).Similar results were obtained by other investigators [19,23,142]. Thus the higher dose of the WE extract had greater protection of writhing in rats group [19,22] than other rat groups given other doses of the same extract (Table 4). Thus, WE possessed antinociceptive effect against acetic acid-induced abdominal writhing response in rats.

Anti-Inflammatory Activity

Carrageenan-induced hind paw edema test (inflammation test) was performed to estimate the anti-inflammatory effect of WE doses (100, 200 and 300 mg/kg body weight) in rats [135]. Carrageenan-induced paw edema is being an in-vivo investigational model for acute inflammation which have been extensively used to determine the anti-inflammatory effect of new investigational agents [19,136]. The development of edema in paw of rat after the injection of carrageenan is due to release of some inflammatory mediators elevated level of prostaglan-dins, proteases and other mediators cause pain [135,154]. Result of anti- inflammatory effects of WE doses (100,200 and 300 mg/kg) were illustrated (Figure 2). In the present study carrageenan administration in rats causes inflammation that induce edema [106], Endomethacine used as anti-inflammatory standard drug were compared with control [138].

Results showed the paw volume of carrageenan induced rat was increased till 5 hour due to the inflammation development and then paw volume was decreased (Figure 2). The paw volumes and inhibition by the WE doses and standard drugs are shown in Figure (2). Carrageenan injection was administered one hour after treatment of extracts at three doses (100,200 and 300 mg/kg) and indomethacin. Measurement of paw size was taken before carrageenan injection and then 1,2,3,4 and 5 hours after carrageenan injection. Results showed the inhibition inflammation induced by carrageenan is much pronounced one hour after injection of carrageenan with maximum values observed at 5 hours after administration (Figure 2). The WE tested doses (100, 200 and 300 mg/kg) showed a significant reduction in paw edema with various degrees [134,136,148] that starts from 1 to 5 hr. after induction as compared to the control in carrageenan-induced paw edema rat groups. These results suggest that it interferes with the effects which inhibit the release of mediators involved inflammation [19,135,155] Since prostaglandins involved in pain perception are inhibited by flavonoids, it could be suggested that reduced availability of prostaglandins by flavonoids, phenol and FAs were present in WE might be responsible for its analgesic and anti-inflammatory effect [19,46,135]. However, the inhibition was the highest at 3h at 200mg/kg WE dose which was slightly lower than indomethacin effect. Indomethacin significantly reduced the paw volume at 2, 3, 4 and 5 hours as compared to the control and with the lower dose of WE (100 mg/kg). The medium dose (200 mg/kg) and higher (300mg/kg) doses of WE had comparable anti-inflammatory activity to control at all observations. The maximum edema inhibition of WE doses (100, 200, and 300 mg/kg) was accomplished 5 hours %. (Figure 2) after induction, with the values of 23.8%, 31.9%, and 32.5. [154]. There are considerable value of percent inhibition of inflammation was found by determining the percentage of change in paw volume after treatment.

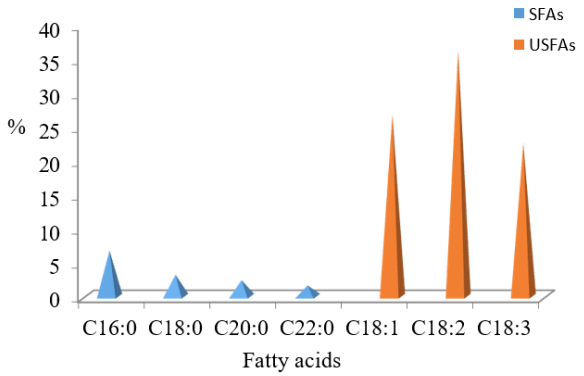

Figure 1: *SFAs and USFAs contents in we.*

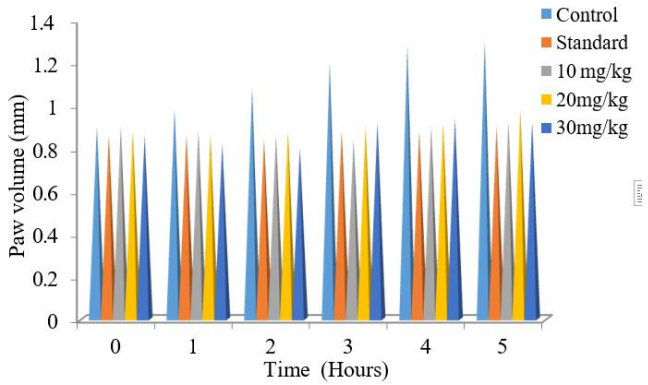

Figure 2: *Effect of WE on Carrageenan - induced rat paw edema.*

The largest value of percentage inhibition of inflammation from control was found at 5hour after treatment (Figure 2). The inhibition was significant at the dose of 300 mg/kg (52.625%) to that of the standard drug (Figure 2), These results are in the range (58.985%) reported previous [19,135].The significant anti-inflammatory activity exhibited by WE at a dose used (300 mg/kg body weight) against edema induced by carrageenan in rats compared to the control group is an indication that, WE have pharmacological activity. Anti-inflammatory activity of standard and WE were observed in the present study may be due to the inhibition of release of inflammatory mediators. The present study demonstrated that oral dose of WE repressed the edema throughout all stages of inflammation (1 -5 hrs.) due to inactivation of inflammation mediator substances [144], reported L. sativa as an analgesic and anti- inflammatory agents. Phytochemical constituents of WE were illustrated in Tables (1) and (Figure1) revealed the presence of phenols, flavonoids and fatty acids (FAs) in different concentrations [31,46,138] stated the anti-inflammatory properties of these phytochemicals Therefore, it seems that analgesic and anti-inflammatory potential of WE. Similar with the effects of non-steroidal anti-inflammatory medications, such as indomethacin, the observed edema inhibition was higher implying that the anti-inflammatory activity is mediated by inhibition of mediators. WE displayed significant antiinflammatory activity against carrageenan-induced paw edema [19,22].The presence of phenolic, flavonoids, and FAs levels present in WE (Table 1 and Figure 1) indicated to analgesic and anti-inflammatory effects of WE [19,138,156]. Moreover, the present results revealed a significant increase reaction time to heat stimuli, strongly suggests that the mechanism of the WE may be mediators inhibition [19,135], reported the phenolic and flavonoids are known to inhibit prostaglandin synthetase and possess antiinflammatory analgesic activity [135,156]. Thus, the results of the present study indicates that WE were found to be effective as anti- inflammatory and analgesc agents and can be effective as therapeutic agent to treat inflammatory and analgesc conditions [156].

Conclusion

The present study concluded that the aqueous extract of watercress (Eureka sativa) at certain doses (100, 200 and 300 mg/kg) possesses analgesic and anti-inflammatory activities in rats due to their effect in inhibition the release of inflammatory mediators. Moreover, this is a preliminary study and further study is needed to find out the potential mechanism of action and isolate the active compounds responsible for analgesic and anti- inflammatory activities in rats. Thus, plant extracts particularly watercress (Eureka sativa) extract, consider better way than conventional, biosynthetic and chemical treatment of pain and inflammation.

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