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The therapeutic effect of aqueous extract of *Prosopis farcta* fruit on the inflammatory response induced by carrageenan in male albino rats

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Abstract

Traditional medicine used *Prosopis farcta* as a dried fruit before scientists discovered the active biological components that give this fruit its pain-relieving properties. This research looked at how well a dried fruit extract of P. farcta (AEP) worked by checking for signs of inflammation in albino rats that given carrageenan (CRG) induced tissue damage in rats. There were 32 male Rattus norvegicus animals split into four equal groups. The control group got 1 ml of physiologic solution, and the CRG group got 100 µl of a carrageenan solution dissolved in 1 ml to induce inflammation. The CRG & AEP 300 group was given AEP 300 mg/kg bw an hour after being given 100 µl of the CRG solution dissolved in 1 ml. After one hour of giving 100 ml of the dissolved CRG solution in 1 ml, the CRG & AEP 400 group received AEP 400 mg/kg bw. administered all groups orally for 30 consecutive days. They found that serum levels of C-reactive protein (CRP), MDA, the ratio of CRP to albumin (CAR), and white blood cells count (WBC) increased significantly. Concurrently, glutathione peroxidase (GPx) and albumin exhibited significant reduction. CRG caused to lower plasma CRP, MDA, and CAR levels. Carrageenan also caused a drop in GPx activity and increased ESR levels. The conclusion shows that the water-based extract of *Prosopis farcta* fruits can help reduce the inflammatory response linked to CRG. This is supported by the fact that certain blood and plasma parameters went down in this study.

Keywords: CRP; Albumin; CAR; GPx; MDA; *Prosopis farcta*; Carrageenan

1. Introduction

Prosopis farcta, also known as Syrian mesquite, is a flowering herb indigenous to Asia and is a member of the Fabaceae family. Traditional medicine across various Asian nations utilizes the fruits of *P. farcta* because they possess numerous bioactive components [1], [2]. The fruit extract is mostly made up of bioactive compounds and essential substances, like gallic and vanillic acids, alkaloids, quinones, phenolic compounds, glycosides, tannins, triterpenoids, and phytochemicals that naturally fight free radicals and can be used in medicine and the food industry [2], [3].

Researchers are increasingly linking the biological effects to the phytochemical makeup, specifically the C-glycosyl flavone content. Researchers in the field of epidemiology have found that eating certain phytochemicals may make you less likely to get certain diseases or long-term conditions. People have used two dried fruits to treat a variety of illnesses, including nephrolithiasis. These conditions include asthma, calluses, diabetes, diarrhea, scabies, otitis, rheumatism, abdominal discomfort (ulcer), fever, influenza, lactation, hepatic infection, malaria, conjunctivitis, pancreatic calculi, and cardiovascular disorders [2], [4]. The conditions include gestation, neonatal ailments, dermal lacerations, and thermal injuries. Furthermore, studies have established the therapeutic advantages of treating diabetic foot ulcers, laryngitis, and dyspnea. It possesses antispasmodic, anti-inflammatory, and analgesic effects [5], [6].

Exhibit intriguing antispasmodic, antipyretic, anticancer, antidiabetic, and wound-healing attributes [7]. Numerous investigations, both in vivo and in vitro, revealed antioxidant, antibacterial, and anticancer properties in an experiment

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[8]. The results indicated that the elevated levels of phenols and flavonoids are directly accountable for their antioxidant effects [9]. The n-butanol, ethyl acetate, and 5-fluorouracil extracts from the upper parts of *P. farcta* were shown to be effective at killing different types of human carcinoma cells [10].

Red algae (Chondrus crispus) produces the polysaccharide carrageenan (E407), which causes inflammation in rats [11], [12], Acute inflammation results in the emergence of biphasic inflammatory responses within the paw tissue [13]. The main objective of the current research is to ascertain the therapeutic properties of Eucalyptus leaves and their role in mitigating the inflammatory activity of carrageenan. The current study might offer a quick and safe way to alleviate the inflammation brought on by large doses of carrageenan in rats using three different concentrations of the aqueous extract from the fruits of *P. farcta*.

2. Materials and Methods

2.1. Extract preparation

We obtained the dried fruits of *Prosopis farcta* from the Ibn Sina herbarium, situated on Al Nasr District Street in Kerbela, Iraq. We derived the aqueous extract of *P. farcta* fruit (AEP), a standardized water extract, from the fruits of *P. farcta*. We cleaned the fruits, removed the cores, and used a mechanical grinder to reduce them to a fine powder. A 500-gram sample of powdered fruit dissolved in 500 mL of purified water and allowed to stand for 24 hours at room temperature (25 ± 2 °C) before filtration. We then placed the filtrate in a stainless-steel plate and dried it for 12 hours at 30 °C in an oven.[14] We stored the concentrated extract in refrigerators in clearly labeled containers until we needed it for the study. We diluted the crude extract with distilled water and administered it to the rats as the final product. Carrageenan acquired from Reflecta Laboratory Supplies in South Africa. All other reagents employed in the practical application were of analytical grade

2.2. Animals and experimental protocol

Thirty-two male *Rattus norvegicus*, averaging 180–200 g in weight, were utilized for the study. The present study sourced animals from the animal house at the College of Pharmacy, University of Karbala. The procedure adheres to the requirements set forth by the National Institutes of Health (NIH), and the research design received approval from the local committee. The animals housed in groups of four within cages, with unrestricted access to food and water. After a two-week acclimation period, the animals divided into four equal groups: group I (control) received distilled water; group II (carrageenan) was administered 100 µl of a carrageenan solution dissolved in 1 milliliter to induce inflammation [15]. Group III were orally treated with AEP (300 mg/kg bw) [16]. after one hour of dosing with 100 µl of the CRG solution dissolved in 1 milliliter. Group IV was orally treated with AEP (400 mg/kg bw) [17], after one hour of dosing with 100 µl of the CRG solution dissolved in 1 milliliter. All groups orally administered for 30 consecutive days.

2.3. Experimental parameters

The C-reactive protein (CRP) and albumin were measured using Rat CRP and Albumin Detection Kits from Chondrex (USA), and the CRP/albumin ratio This ratio is called "APRs." It is calculated by dividing the level of CRP by the albumin level [18], erythrocyte sedimentation rate (ESR), white blood cell (WBC) leucocyte count measured by using BC-3000Plus hematology machines Mindray (India), malondialdehyde (MDA) measured by using Dojindo's MDA Assay Kit (Japan), and glutathione peroxidase (GPx) measured by using the rat glutathione peroxidase (GPX) ELISA Kit Siga-Aldrich (Germany).

2.4. Statistical analysis

The statistical significance among the groups was evaluated using IBM SPSS Statistics (22.0) and a one-way ANOVA table. A P-value of less than 0.05 ($P < 0.05$) was considered significant. The least significant difference was taken to verify the validity of the observed effects.

3. Results

Table 1 Parameters assessment in various experimental groupings**.**

groups	CRP (mg/dl)	Albumin (mg/dl)	CRP/ALB ratio	ESR mm/hr

Control group	0.11 ± 0.30	4.50 ± 0.30	0.20 ± 0.01	2.10 ± 0.10
CRG group	1.04 ± 0.27[a]	2.50 ± 0.30[a]	0.40 ± 0.18[a]	3.20 ± 0.15[a]
CRG & AEP 300	0.61 ± 0.31[b]	2.60 ± 0.20[a]	0.20 ± 0.15[ab]	2.50 ± 0.30[ab]
CRG & AEP 400	0.19 ± 0.35[b]	3.90 ± 0.30[b]	0.05 ± 0.02[b]	2.50 ± 0.40[ab]

The values are clearly mean ± SD value, n = 6 in each group, [a] show the difference in statistics. With a control group, [b] statistical disparity according to CRG group, (P < 0.05).

Table 2 Parameters assessment in various experimental groupings.

groups	MDA (µmol/l)	GPx (IU/l)	WBC (x103/µL)
Control group	1.15 ±0.12	45.15 ± 3.50	04.50 ± 1.00
CRG group	2.90 ± 0.5[a]	30.75 ± 4.50[a]	14.50 ± 2.00[a]
CRG & AEP 300	2.06 ± 0.45[ab]	40.50 ± 3.10[b]	09.50 ± 1.00[ab]
CRG & AEP 400	1.80 ± 0.18[ab]	41.50 ± 3.20[b]	07.50 ± 2.00[ab]

The values are clearly mean ± SD value, n = 6 in each group, [a] show the difference in statistics. With a control group, [b] statistical disparity according to CRG group, (P < 0.05).

3.1. C-reactive protein

Table 1 and 2 showed significant differences in blood parameter levels, i.e., CRG group . The experiment's blood parameters (CRP, CAR, MDA, GPx, ESR, WBC, and albumin) may be altered by CRG. While there was a significant increase (P < 0.05) between the CRG and CRG & PFFAE, 300, 400 groups compared to the control group, there were no discernible differences in the levels of CRP between the treatment groups (CRG & AEP 400 & 300) and the control (P = 0.05), which could be explained by CRG group high level of CRG -induced inflammation. [19].

3.2. Albumin and albumin/CRP ratio (CRP)

All study groups had significantly lower albumin levels than the control group (P > 0.05), the CRG and CRG & AEP 300 groups had lower albumin levels than the CRG & AEP 400 and control groups. Table 1 indicated no significant differences in the albumin/CRP ratio between CRG & AEP 300,400 and control groups (P = 0.05), in contrast to the CRG group.

3.3. ESR

The ESR levels showed a significant increase (P < 0.05) in CRG & AEP 300,400 compared to control group; however, there were no significant differences (P = 0.05) between CRG & AEP 300,400 and CRG groups and the control group on the other hand.

3.4. MDA and GPx

The findings of table 1, showed that, in comparison to the control group, all research groups had significantly higher MDA rates (P < 0.05); however, the CRG & AEP 300,400 groups show a significantly lower MDA rate (P > 0.05) compare to the CRG group. All experimental groups, including CRG group, had higher MDA values than the control group. Also CRG group had considerably lower levels (P > 0.05) of GPx compare to the CRG & AEP 300,400 and control groups, whereas no significant differences (P = 0.05) between CRG & AEP 300,400 groups and control group.

3.5. WBC count

Regarding the WBC count showed in table 2, it was found that all research groups show a substantial increase (P > 0.05), especially in CRG group compare to the control group. In contrast, the CRG & AEP 300,400 groups experienced a significant reduction (P > 0.05) compared to the CRG group.

4. Discussion

4.1. The effect of carrageenan on the Blood parameters levels

According to experimental data in Table 1 and 2, in this investigation, CRG increased inflammatory markers, while GPx and albumin levels decreased in the CRG group. The results may be because CRG caused an inflammatory response in

the rats' internal tissues, such as the liver, stomach, and kidneys. This led to higher levels of MDA, C-reactive protein, ESR, and WBC count. CRG stimulates the release of pro-inflammatory cytokines, activates innate immunity pathways, and initiates or intensifies the inflammatory response [19]. rise in the level of CRP in CRG group as opposed to other experimental groups, which confirms the role of CRG in stimulating inflammatory factors, by stimulated the production of cytokines/chemokines by neutrophils or macrophages [20], which in turn increase CRP levels [21].This is also the case for substances. The levels of MDA and the count of WBC increased in this group as opposed to the experimental and control groups. CRG stimulates oxidative stress through the production of ROS [22], and plays a crucial role in many diseases, such as liver injury [23].

4.2. The effect of *P. farcta* extract on the CRP level

The CRP levels gradually decreased in the treatment groups (CRG & AEP 300, 400 groups); after dosed with CRG, this indicates that the AEP lessened the effects of CRG in these groups relative to CRG group, and the lower concentration of the AEP 300 mg/kg, had less effect on the CRP level.

CRP is extensively employed as a marker for diagnosing and managing inflammation and tissue injury associated with sepsis, trauma, and malignancies [24]. The secondary actions of CRP following binding exhibit several key properties of antibodies, functioning as an inflammatory mediator and enhancing the host's defense against infection [25]. Rats' myocardial infarction provides direct evidence of its role in exacerbating tissue damage due to its inflammatory effects [26]. Moreover, elevated levels of CRP serve as a sign of inflammation [27], [28]. So, the fact that the groups that got 0.30 and 0.45 mg/kg of the AEP showed less swelling supports the idea that it works as an anti-inflammatory [5], caused by CRG, which increases the liver's synthesis of CRP [29]. The plasma half-life percentage of CRP is around 19 hours old in the bloodstream and rises within 6 hours following inflammation or tissue injury. It reaches its zenith after 2–3 days of initiating inflammation but diminishes swiftly as the inflammatory condition resolves [30]. This elucidates its diminished presence in the CRG & AEP 300, 400 groups compared to its equivalent in the CRG group.

4.3. The effect of *P. farcta* extract on the Albumin level

Albumin levels significantly decreased CRG group while remaining unaffected in-AEP 400 group, in addition, compared to the control group, the rats in the AEP 300 group could not raise their albumin levels after being given CRG and then AEP at a dose of 300 mg/kg. This shows how important the water-based extract of *P. farcta* is; it works well to reduce the damage caused by CRG, especially when there are high concentrations of the extract.

Albumin plays an important role in physiology because it keeps osmotic pressure steady, controls acid-base balance, stops platelets from working and blood vessels from leaking, and distributes body fluids [31], and binding critical components in the circulatory system [32]. Additionally, its designation as an antioxidant results from its ability to trap free radicals [33], when inflammation starts, the concentration slowly drops, especially in hepatocytes, where levels can show several conditions and diseases, including kidney disease, liver disease, poor nutrition, inflammation, and cancer. Consequently, physicians may utilize this measure to assess patient nutrition and monitor infections, which leads to a notable reduction in its concentration [34], [35]. Unlike CRP, which rises during inflammation [36], a decrease in serum albumin (< 3.5 g/dL) Chronic liver disease and impaired synthesis frequently cause the death of hepatocellular cells, leading to a decrease in albumin levels. Albumin levels drop during inflammatory conditions, and it has been suggested that this substance is very important for controlling production during inflammation [37], [38], the reduced albumin level in the CRG group suggests hepatocyte damage. The initial increase observed in the therapeutic groups receiving 300 and 400 mg/kg concentrations of aqueous extract of *P. farcta* suggests an enhancement in the physiological condition of these groups attributable to the extract's effects.

4.4. The effect of *P. farcta* extract on the CAR level

The present study assessed the albumin/CRP ratio to confirm the inverse correlation between albumin and CRP levels. Recent studies have examined the interactions between albumin and C-reactive protein (CRP). Clinical conditions recognize the albumin-to-CRP ratio, or CAR, as a novel biomarker [39]. Recent studies have investigated CAR in patients with various malignant tumors [40], within the framework of cardiovascular disease [41], by correlating the modified early warning score (MEWS) with the cardiac arrest ratio, we can expedite the diagnosis of these critically unwell patients [42]. The CAR is often used as a way to measure inflammatory activity and figure out how bad and how quickly inflammatory diseases are getting worse using a standard recording system. It is a better way to show inflammation than just measuring CRP or albumin on its own [43]. The increase was seen in people who had acute pancreatitis. The CAR was calculated in this study to support the results about the levels of CRP and albumin, which are related in a way that is opposite to what was found. It is still clear that the *P. farcta* extract has an effect on the CAR because of how it changes CRP and albumin.

4.5. The effect of *P. farcta* extract on the ESR level

Due to ESR's low sensitivity to basic inflammation, it takes 24–28 hours for the initial spike to begin and then decreases once the inflammation goes away. Its delayed reaction to inflammation precludes its use in disease diagnosis [44]. The ESR is influenced by a wide range of physiological and pathological factors, including variations in plasma fibrinogen concentration, alterations in the size, shape, and quantity of aqueous chloride, and the presence of acute-phase reactants such as immunoglobulins [45]. Likely, the rates of ESR will vary for each experimental group. This means that it is not a specific indicator of diseases—the rate at which disease-related factors such as inflammation change. This study didn't try to cause a specific disease. Instead, it examined how repeated exposure to high concentrations of CRG causes inflammation. Therefore, we took into account several considerations during the experimental design. The main goal was to find male laboratory animals to test how sensitive ESR was to physiological factors. We compared males to females, including pregnant women, menstruating women, and natural females [46]. The efficacy of treating several diseases is contingent upon prompt identification of the patient's condition. The ESR is an essential test for this objective [47]. Moreover, the induction of a pathological state in healthy and middle-aged laboratory rats using CRG may be inadequate to provoke significant inflammatory responses that elevate ESR levels, particularly as this biomarker is frequently employed to evaluate and monitor specific conditions such as rheumatoid arthritis [48]. Ultimately, the availability of more sensitive and precise inflammatory indicators renders ESR frequently inadvisable as a diagnostic test [49]. Consequently, there was a distinct impact of *P. farcta* on the ESR level in the current investigation; ESR was influenced by the elevated doses of CRG.

4.6. The effect of *P. farcta* extract on the GPx and MDA levels

The present study compared oxidants and antioxidants, which significantly influenced by many physiological factors resulting from the effects of CRG and P. farcta. The groups that received the least amount of CRG and treatment AEP 300 had the highest MDA levels of all the groups that were tested. Notably, giving 400 mg/kg of an aqueous extract of *P. farcta* along with CRG greatly lowered MDA levels, bringing them to the lowest levels seen in the control and AEP 400 groups [50]. The diminished proportion of MDA in the AEP 400 post-CRG administration attributed to the inverse relationship between oxidants and GPx levels.

Oxidants and antioxidants are pivotal parameters analyzed in this study due to their modulation by several physiological factors stemming from the influence of CRG and the impact of *P. farcta*; as a by-product of oxidative reactions, MDA serves as a crucial indicator of oxidative stress [51]. This occurs owing to the formation of free radicals that elevate lipid oxidation, resulting from an imbalance between oxidizing agents and antioxidants, leading to cellular damage, including that of liver cells [52], [53]. Thereby, its accumulation in the bloodstream results in an excess of free fatty acids, leading to hyperlipidemia, which can induce the overproduction of ROS, thereby damaging mitochondrial DNA [54]. MDA from lipid peroxide is linked to a significant contribution due to the presence of two carbonyl groups inside the molecule, influencing its activity [55]. The diminished levels of antioxidants, including SOD, GPx, and glucose, or the excessive production of ROS, such as hydroxyl radicals (OH^-), superoxide anions (O_2^-), and hydrogen peroxide (H_2O_2), may elevate oxidative stress, thereby raising the levels of MDA [56]**.** The primary inflammatory variables include elevated oxidative chemicals, oxidative stress, and ROS levels [57]. Elevated levels of ROS result in the oxidation of polyunsaturated fatty acids (PUFAs) prevalent in cell membranes, producing MDA. As a result, the synthesis of SOD, GPx, and Catlaz diminished. In conditions of oxidative stress, this MDA may function as a biomarker for cellular damage caused by free radicals [58]. It can be asserted that the cellular mechanisms for mitigating oxidative stress involve the enhancement of antioxidants that engage with oxidants (free radicals and their variants) [59]. This system operates within the minimal thresholds of fat oxidation by-products and is insufficient to address the substantial accumulation that contributes to cellular aging and many pathological diseases [60], [61].

The inverse relationship between oxidants and GPx levels elucidates the reduced MDA % in groups treated with the aqueous extract of *P. farcta*, attributing the impact of GPx to the presence of flavonoids [9], Polyphenols stop oxidation reactions by giving free radicals one electron in exchange for a non-double electron. This lowers the number of free radicals [62]. Consequently, GPX is a vital antioxidant for sustaining normal metabolic functions in the body. Recent studies link variations in GPx to the onset, progression, and management of several tumor types [63]**,** and prevention. In addition to being an antioxidant, GPx is very important for human health because it stops the production of free radicals through a unique chemical interaction [64], and eliminating free radicals from their initial state [52]. Consequently, there are contrasting outcomes between MDA and GPx levels [65].

4.7. The effect of P. farcta extract on the WBC count

The increased WBC count in the CRG group progressively reduced following the administration of AEP at doses of 300 and 400 mg/kg, leading to a substantial decrease compared to the CRG group. These results are consistent with the study by Shakeri and Boskabady, 2017 [66].

Inflammation significantly influences leukocytes (WBC), which are immunologically significant and present in greater quantities in pathogenic conditions [67]. The WBC count in the CRG group went down gradually after treatment with AEP 300 and 400. This suggests two main things: factors that led to more inflammation in the blood of the experimental rats (CRG), which seen in all the groups. Some other things have helped lower the number of cases of CRG-induced inflammation in AEP 300 and 400, which involved an aqueous extract of *P. farcta* [68]. This indicates that the WBC count in this group is more comparable to that of the control group.

5. Conclusion

The aqueous extract of P. farcta fruits demonstrated a significant effect on reducing inflammatory markers in laboratory albino rats, including CRP, albumin, GPx, MDA, and WBC. Antioxidants like gallic and vanillic acids, along with anti-inflammatory compounds like apigenin, quercetin, and luteolin, are responsible for this effect [13], [69]. Various flavonoids function as anti-inflammatory agents, effectively lowering CRP levels [70]. The treatment groups receiving high concentrations of the aqueous extract of P. farcta exhibited a significant effect on ESR and MDA levels, resulting in a reduction in the percentage of MDA. The conclusion shows that the water-based extract of *Prosopis farcta* fruits can help reduce the inflammatory response linked to CRG. This is supported by the fact that certain blood and plasma parameters went down in this study.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Statement of ethical approval

The Branch of Basic Sciences Ethical Review Committee, Kerbala University, Iraq, approved the study design and assigned an approval number.

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