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Research Article

EVALUATING THE ANTI-INFLAMMATORY ACTIVITY OF ETHYL ACETATE AND METHANOL EXTRACTS OF *LORANTHUS EUROPAEUS* SEEDS IN RAT MODELS OF EXPERIMENTALLY INDUCED CHRONIC INFLAMMATION: A COMPARATIVE STUDY WITH DEXAMETHASONE

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ABSTRACT

Objective: *Loranthus europaeus* is a parasitic plant that lives on the branches of trees. The present study aimed to evaluate the anti-inflammatory effects of two different extracts on chronic inflammation induced by cotton pellets in rats.

Methods: *Loranthus* seed was extracted by maceration with absolute methanol, in which dry *Loranthus* seeds were triturated in a mortar and macerated with 500 mL of methanol. After 24 h, the mixture was filtered, and the residue was re-extracted. The filtrates were combined and dried under vacuum. The mixture was mixed with 100 mL of distilled water and fractionated by petroleum ether and ethyl acetate using 70 mL × 3 times each. The organic fractions were dried, filtered, and evaporated to dryness. Ethyl acetate and methanol fractions at a dose of 100 mg/kg were tested for suppressive effect for chronic inflammation using the cotton pellet-induced granuloma technique compared with dexamethasone.

Results: Both fractions of *L. europaeus* seeds showed a significant decrease in the weight of exudate and weight of granuloma when compared with the negative control. Furthermore, both fractions showed a significant increase in these two parameters when compared to the standard group (dexamethasone group).

Conclusion: The present study showed that the ethyl acetate fraction has a significant suppressive effect on chronic inflammatory processes in rats when compared with the methanol fraction.

Keywords: Alkaloids, Dexamethasone, Ethyl acetate, Flavonoid, *Loranthus europaeus*, Methanol.

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INTRODUCTION

Before the advent of contemporary medicine and its array of synthetic pharmaceuticals, ancient civilizations adeptly utilized plants to address prevalent disorders and even critical illnesses [1]. On woody trees, different parasitic plants used in medicine have been grown; one of them is *Loranthus europaeus*. It is a member of the showy mistletoe family, Loranthaceae [2].

L. europaeus contains different active constituents, mainly polyphenols such as kaempferol, quercetin, and alkaloids. There are other compounds belonging to glycosides, carbohydrates, aldehydes, ketones, proteins, polysaccharides, terpenes, and phenolic acid (caffeic and gallic acid). Several fatty acids are present in *Loranthus* seeds, such as palmitic acid, paraffin, and wax alcohol [2].

Mistletoe has historically been used to treat a variety of conditions, including swellings, tumors, epilepsy, hysteria, delirium, vertigo, antispasmodic, tonic, and narcotic, as well as liver and spleen illnesses, labor pains, heart weakness, edema, eczema, foot ulcers, burns, and granulating wounds [3].

According to earlier research, *L. europaeus* possesses a variety of pharmacological properties, including antioxidant activity brought on by the presence of gallic and caffeic acids and a wound and burn healing effect due to the presence of glycosides, carbohydrates, aldehydes, ketones, triterpenoids, proteins, and polysaccharides. Antimicrobial effect [4] and anti-inflammatory effect due to the presence of flavonoids (quercetin, kaempferol, and rutin) [2]. The antitumor effect of the extract's phytochemical analysis reveals that, in addition to alkaloids, flavonoids are crucial in regulating cell growth. The production of various adducts with proteins and DNA was demonstrated by the anticancer effect. According to recent scientific studies, mistletoe extracts (a) cause apoptosis, (b) activate immunocompetent cells that limit the development of cancer cells, and (c) shield mononuclear cell DNA [5].

One of the several pharmacological effects of *L. europaeus* that has been investigated is its anti-inflammatory properties. Due to the presence of distinct bioactive components in each extract, it has been discovered that two distinct organic solvent extracts (ethyl acetate and methanol extracts) of *L. europaeus* seeds significantly reduced acute inflammation when it was produced in rats [6]. When compared to other conventional therapies, the application of *L. europaeus* in the form of 40% ointment to treat acute cutaneous leishmaniasis yields highly favorable results, according to another study on the plant. The aim of the present study is to evaluate the anti-inflammatory effects of two different extracts on chronic inflammation induced by cotton pellets in rats.

METHODS

Materials and instruments

Rat Tumor Necrosis Factor Alpha enzyme-linked immunosorbent assay (ELISA) Kit, MyBioSource, USA; Rat Interleukin (IL) 6 ELISA Kit, MyBioSource, USA; Rat IL-8/CXCL15 ELISA Kit, MyBioSource, USA; Rat C-reactive protein ELISA Kit, MyBioSource, USA; Rat MCP-1 ELISA Kit, MyBioSource, USA; Dexamethasone Sodium Phosphate 4 mg/mL (Hikma, USA). Microplate *ELISA reader (LABEX, India).*

Plants collection

The seeds were purchased from the Iraqi market. The authentication was achieved in the Department of Pharmacognosy and Medicinal

Plants/College of Pharmacy/University of Baghdad. A voucher sample was kept at the Department of Pharmacognosy and Medicinal Plants, College of Pharmacy/University of Baghdad. The plant seeds are crushed by a mortar and pestle to be extracted by maceration.

Plant extraction
After crushing 100 g of *Loranthus* seed, the crushed seed was reweighed again and macerated with 500 mL of 90% methanol. After 24 h, the crushed seed was filtered, and the marc was macerated again for another 24 h with 500 mL of 90% methanol.

The filtrates were collected and mixed together, then under reduced pressure by a rotary evaporator, methanol was removed. The methanolic fraction was mixed with 100 mL of distilled water and fractionated by petroleum ether and ethyl acetate, respectively, using 70 mL 3 times each. The organic fractions were dried using anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The remaining methanol fraction was mixed with an equal volume of methanol and evaporated [7].

Preliminary chemical tests
For both fractions, phytochemical analysis was done. To detect the presence of alkaloids, Mayer's reagent was performed. For the detection of polyphenols, 5% ethanolic potassium hydroxide was performed. For tannins, the $FeCl_3$ test was done. The foam test was used to detect saponins. Meanwhile, for reduced sugar, Benedict's test was done. Ninhydrin test for proteins [8].

Experimental design
Adult male Wistar albino rats were used in this study. Their weight ranged from 200 to 215 g. The animals were obtained from the animal house in the College of Pharmacy/University of Baghdad. The animals were acclimatized for 7 days by standing in plastic cages at 25±2°C and a light: dark cycle of 12:12 h. Animals were fed with a standard rodent food. At the beginning of the study, the cotton pellet was added on day 1 on next day (day 2) the animal receive their treatments for7 successive days. the water is allowed ad *libitum* during study). Ethical approval had been submitted for the present study, and the committee approve it.

In the present study, the rats have been divided into four groups with six rats.
- First group (control group): Receive dimethyl sulfoxide intraperitoneally
- Second group (test group): Receive ethyl acetate fraction at a dose of 100 mg/kg intraperitoneally
- Third group (test group): Receive a methanol fraction at a dose of 100 mg/kg intraperitoneally
- Fourth group (standard group): Receive dexamethasone at a dose of 1 mg/kg intraperitoneally.

All fraction doses and vehicles were administered for 7 consecutive days after 1 day of cotton pellet implantation.

Induction of chronic inflammation induced by cotton pellet
The evaluation of anti-inflammatory activity of two organic fractions of *L. europaeus* (ethyl acetate and methanol extracts) was accomplished by induction of chronic inflammation using the cotton pellet technique [9].

The cotton pellets that were used in this study were sterilized by autoclave for 30 min (at 120°C under 15 lb pressure) and weighed 10±1 mg. On the ventral region of the animal, each animal was implanted with four pellets subcutaneously, two on either side.

All groups started to administer their medications or extracts as mentioned above after cotton was implanted for 7 consecutive days. On day 8, the animals were lightly anesthetized, and the pellets were collected with the granuloma tissues by removing extraneous tissues. The cotton pellets were weighed when wet to determine the wet weight. To dry the wet cotton pellet, it was placed in an incubator for 18 h at 60°C until all the exudates dried (constant weight). After completing the drying process, the cotton pellet was weighed again. To get the quantity of exudate (in mg), the wet weight of the pellet was subtracted from the dry pellet weight, whereas the granuloma tissue (dry weight of granuloma) was calculated by subtracting the weight of the dry cotton pellet from 10 mg. The percent inhibition of exudate and granuloma tissue formation was determined.

Sample collection
On day 9, the animals were anesthetized by ethyl diether, and blood was collected from the jugular vein. Then, the animals were euthanized by cervical dislocation, and the cotton pellets were removed and weighed for subsequent analysis [10].

After standing for 30 min, samples were centrifuged at 3500 rpm for 10 min in an EBA20® centrifuge (Andreas Hettich GmbH & Co. KG, Germany). The supernatant was collected and stored at −20°C to be analyzed for determination of C-reactive protein [11], monocyte chemoattractant protein-1 [12], tumor necrosis factor-α [13], IL-1β, IL-6, IL-8, and IL-10 levels [13] by the ELISA technique.

Measurement of different pro-inflammatory parameters by ELISA technique
For the measurement of different pro-inflammatory cytokines, the ELISA technique was used, utilizing rat ELISA kits. The ELISA technique used in this study was based on sandwich techniques, which are used for quantitative analysis. The protocol of this technique is based on the fact that the antibody specific for each parameter was pre-coated onto a microplate, and then the standard and samples are pipetted into the pre-coated wells. After removing any unbound or excess substances, a biotin-conjugated antibody specific for each parameter was added to the wells. After removing the excess solvents by washing, streptavidin-conjugated horseradish peroxidase is added to the wells. The unbound avidin-enzyme reagent was removed by washing. The intensity of color was measured by a spectrophotometer at a wavelength of 450 nm±10 nm; the intensity of color is directly proportional to the quantity of each parameter [14].

Statistical analysis
Data are expressed as mean±STD; unless otherwise indicated, statistical analyses were performed using one-way analysis of variance followed by *post hoc* Tukey's test. If $p<0.05$, it is considered significant. SPSS GraphPad InStat 7 (GraphPad Software Inc., La Jolla, CA, USA) software was used to perform statistical analysis.

$$\text{Inhibition percent} = [(b-a)/b]*100$$

Where,
a = mean of the test group and the standard group animals after the cotton pellet is removed
b = mean of the control group after the cotton pellet is removed.

RESULTS

In Table 1, the phytochemical analysis of the methanol fraction and ethyl acetate fractions of *L. europaeus* revealed the existence of flavonoids, tannins, reduce sugar, proteins, and saponins, whereas the alkaloids are absent in the methanolic fraction.

In Table 2 and Fig. 1, a dose of 100 mg/kg of ethyl acetate fraction showed significantly higher weight of exudate as compared to the standard group (dexamethasone group) ($p<0.05$), but the weight of exudate for the same fraction showed a significant decrease as compared to the negative control group ($p<0.05$). The methanol fraction of *Loranthus* seeds at a dose of 100 mg/kg shows a significantly higher weight of exudate as compared to the standard group (dexamethasone group) ($p<0.05$), but the same fraction shows a significant decrease in weight of exudate when compared to the control group (dimethylsulfoxide group) ($p<0.05$). The methanol fraction shows a significantly higher mean weight of exudate formation when compared with the ethyl

Table 1: The phytochemical analysis of the methanol fraction and ethyl acetate fractions of *Loranthus europaeus*

Fractions	Flavonoids	tannins	Saponin	Alkaloids	Reduce sugar	Protein
Methanol fraction	+	++	++	-	+	+
Ethyl acetate fraction	++	+	tr	++	tr	+

++: Abundant, +: Present, tr: Trace, -: Absent

Table 2: Effects of ethyl acetate extract and methanol extract of *Loranthus europaeus* with dexamethasone on exudate weight and inhibition of exudates (%) in chronic inflammation induced by cotton pellets in rats

Groups	Exudates weight (mg)	% of Inhibition
Dimethylsulfoxide (control group)	116±4.3	------
Dexamethasone 1 mg/kg (standard group)	55.29±1.27*	52.33
Methanol fraction 100 mg/kg	103.15±4.07*#a	11.07
Ethyl acetate fraction 100 mg/kg	71.29±7.19*#b	38.5

Data are expressed as mean±SD (n=6). *p<0.05 versus control (dimethylsulfoxide) group; #p<0.05 versus dexamethasone group; Values with different superscript letters (a, b) are significantly different (p<0.05) between the two extract groups

Table 3: Effects of ethyl acetate extract and methanol extract of *Loranthus europaeus* with dexamethasone on the mean weight of granuloma and inhibition of granuloma formation (%) in chronic inflammation induced by cotton pellet in rats

Groups	Granuloma weight (mg)	% of Inhibition
Dimethylsulfoxide (control group)	31.5±1.33	------
Dexamethasone 1 mg/kg (standard group)	9±1.21*	71.42
Methanol fraction 100 mg/kg	21.93±1.2*#a	30.35
Ethyl acetate fraction 100 mg/kg	12.5±3.1*#b	60.31

Data are expressed as mean±S.D (n=6). *p<0.05 versus control (dimethylsulfoxide) group; #p<0.05 versus dexamethasone group; values with different superscript letters (a, b) are significantly different (p<0.05) between the two extract groups

acetate fraction of *L. europaeus* (p0.05).

In Table 3 and Fig. 2, at dose 100 mg/kg for each fractions (ethyl acetate fraction – methanol fraction) the weight of granuloma shows a significantly higher as compared to the standard group (dexamethasone group) (p<0.05), whereas both fractions shows a significant decrease in weight of granuloma as compared to the control group (dimethylsulfoxide group) (p<0.05). The methanol fraction shows a significantly higher mean weight of granuloma formation when compared with the ethyl acetate fraction of *L. europaeus* (p<0.05).

In Table 4 and Fig. 3, biochemical analysis of different proinflammatory mediators that were measured in the dexamethasone group and the ethyl acetate fraction of *L. europaeus* showed a significant decrease as compared to the negative control group (p<0.05). In the same table, the same biochemical parameters that were measured in the methanolic fraction showed a significantly higher value as compared with the dexamethasone group (p<0.05). Besides, the ethyl acetate fraction showed a significant decrease in all measured proinflammatory cytokines as compared to the methanol group of *L. europaeus* (p<0.05).

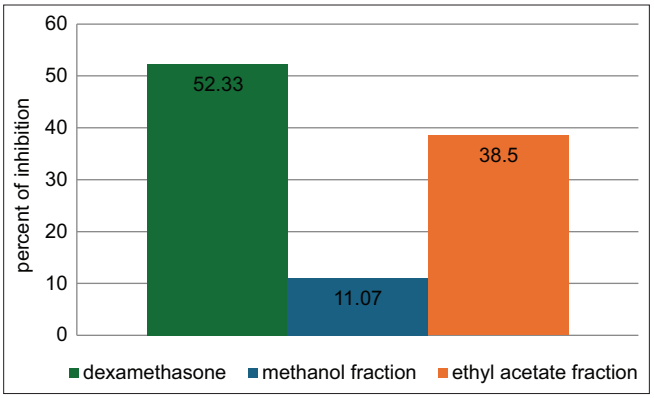

Fig. 1: Percent inhibition of exudate formation in cotton pellet-induced granuloma in rats treated with vehicle (control), dexamethasone (1 mg/kg), methanol extract (100 mg/kg), or ethyl acetate extract (100 mg/kg) of *Loranthus europaeus*

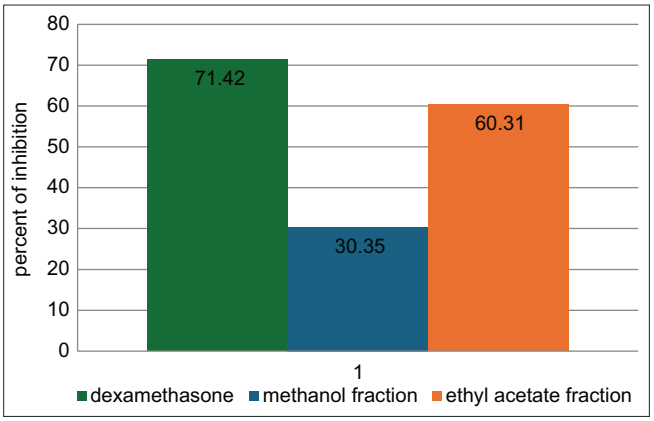

Fig. 2: Percent inhibition of granuloma formation in cotton pellet-induced granuloma in rats treated with vehicle (control), dexamethasone (1 mg/kg), methanol extract (100 mg/kg), or ethyl acetate extract (100 mg/kg) of *Loranthus europaeus*

DISCUSSION

One aspect of the body's immunological reaction is inflammation. At first, inflammation is beneficial, but it can occasionally become self-reinforcing by causing more inflammation. In reaction to the pre-existing inflammation, more inflammation is produced [15]. Chronic inflammation is a kind of inflammation that persists over a period of months or even years. Either an autoimmune reaction to a self-antigen – the immune system assaults healthy tissue, mistaking it (them) for dangerous pathogens – or a failure to eradicate whatever was causing the acute inflammation might cause it. A persistent low-intensity chronic irritant [16].

Based on phytochemical findings in the present study, flavonoids were present in both fractions (methanol-ethyl acetate fraction), whereas alkaloids were present in the ethyl acetate fraction only.

It has long been known that natural goods are a significant source of medicinally effective medications. It is well known that natural product structures are advantageous lead structures due to their high chemical diversity, biochemical specificity, and other molecular characteristics [17].

Flavonoids are low molecular weight bioactive polyphenols [18]. Numerous biological actions of flavonoids have been documented; from this action, they work as antioxidants and anti-inflammatories. A previous study had shown that the presence of flavonoids causes

Table 4: Effects of ethyl acetate extract and methanol extract of *Loranthus europaeus* with dexamethasone on different inflammatory mediators in chronic inflammation induced by cotton pellet in rats

Inflammatory parameters	Dimethyl sulfoxide (control group)	Dexamethasone 1 mg/kg (standard group) (%)	Methanol fraction 100 mg/kg (%)	Ethyl acetate fraction 100 mg/kg (%)
Tumor necrosis factor-α (pg/mL)	67.34±11.4	33.62±9.3 (50.07)	45.66±11.5[a] (32.19)	39.23±14.3[b] (41.74)
Interleukin-1B (pg/mL)	68.23±9.6	26.43±6.4 (61.26)	40.44±14.9[a] (40.73)	31.45±10.3[b] (53.91)
Interleukin-6 (pg/mL)	82.47±9.4	41.87±12.9 (49.23)	55.65±15.3[a] (32.52)	47.56±14.3[b] (42.33)
Interleukin-8 (pg/mL)	99.41±8.5	68.89±15.5 (30.7)	81.58±18.4[a] (17.94)	74.54±10.5[b] (25.02)
C-reactive protein (ng/mL)	596.3±17.4	383.4±23.5 (35.7)	480.4±22.5[a] (19.44)	401.3±25.9[b] (32.7)
Monocyte Chemoattractant Protein-1 (pg/mL)	63.45±9.4	28.34±7.4 (55.33)	41.75±11.3[a] (34.2)	33.57±11.7[b] (47.1)

Data are expressed as mean±SD (n=6). For each cytokine, means with different superscript letters (a, b) differ significantly ($p<0.05$) between the methanol and ethyl acetate extract groups. All treatment groups (dexamethasone, methanol, and ethyl acetate) were significantly different ($p<0.05$) from the control group. The dexamethasone group was significantly different ($p<0.05$) from both extract groups for all parameters

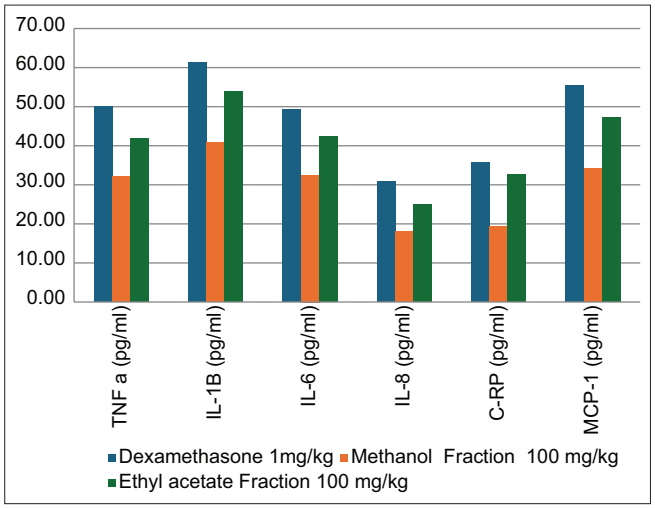

Fig. 3: Effects of ethyl acetate extract and methanol extract of *Loranthus europaeus* with dexamethasone on the percent inhibition of different inflammatory parameters in chronic inflammation induced by cotton pellet in rats

inhibition of lipid peroxidation, cyclooxygenase, and lipoxygenase enzyme activities by working as an antioxidant [19]. Other studies have shown that flavonoids have been shown to suppress the synthesis of proteinoids, leukotrienes, and other inflammatory mediators such as adhesion molecules, cytokines, and chemokines [20-22]. These findings are synonymous with the findings of the present study results. According to phytochemical investigation, both fractions contain flavonoids, and these flavonoids significantly decrease the mean weight of exudate, as shown in Table 2, the mean weight of granuloma, as shown in Table 3, and the significant decrease in the production of different pro-inflammatory cytokines, as shown in Table 4, as compared with the negative control for both fractions.

According to the phytochemical investigation in Table 1, alkaloids are present in the ethyl acetate fraction but not in the methanol fraction. Alkaloids are a group of naturally occurring chemical compounds that contain basic nitrogen atoms. Alkaloids had different pharmacological effects [23]. A previous study had shown that alkaloids act as anti-inflammatory agents by inhibiting the growth of lymphocytes triggered by mitogens and antigens, the cytotoxicity of natural killer cells, the release of histamine by mast cells, and the production of IL-1 by human monocytes, besides alkaloids potentially inhibiting a key pro-inflammatory transcription factor such as NF-κB [24]. The presence of alkaloids in the ethyl acetate but not the methanol fraction synergizes the anti-inflammatory activity, as shown in Tables 2-4.

In the present study, different pro-inflammatory cytokines were measured. Some of these cytokines are directly linked to acute-phase inflammation, but a previous study had found that some of the acute-phase pro-inflammatory cytokines play a crucial role in pathogenesis and granuloma formation during chronic inflammatory processes. Besides, they found that the blockage of such types of cytokines decreases the pathogenesis of inflammation. This illustrates the elevation of such types of cytokines in Table 4 as compared to the negative control [25].

CONCLUSION

According to the present study, the pharmacological properties of flavonoids and alkaloids play a cornerstone in the suppression of chronic inflammation. These properties make the ethyl acetate fraction, which has two types of anti-inflammatory bioactive compounds (flavonoids and alkaloids), more suppressive to the induction of chronic inflammation than what is seen in the methanol fraction, which contains only flavonoids. Stepwise fractionation that is used in the present study provides an acceptable degree of separation of these active constituents according to their polarities; it could be realized that the synergistic effect between flavonoids and alkaloids has higher efficacy in the suppression of chronic inflammation than flavonoids alone. The anti-inflammatory effect of these fractions was not as potent as compared with dexamethasone.

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AUTHOR CONTRIBUTIONS

All authors equally contributed.

STATEMENT OF ETHICS

The study protocol was reviewed and approved by the local Ethics Research Committee for animal study in the College of Pharmacy/ University of Baghdad. (approval number REC022025103A).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

FUNDING SOURCES

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