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Anti-inflammatory activity of some medicinal plants extracts commonly used in traditional medicine in healthy and diabetic rats.

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Abstract: Inflammation is a protective immune system reaction that guards the individual against infection. It is a big global issue. many anti-inflammation drugs have side effects. As a result, a different therapy module may be required. Due to their great efficacy and lack of side effects. This study examined the anti-inflammation activity of *Rhus coriaria*, *Globularai arabica*, and *Malva slyvesitris* in diabetic rats with paw edema caused by carrageenan. Rats were separated into two groups: non diabetic and diabetic rats. Each group have five sub groups seven rats/ group. Group 1, treated with saline for non-diabetic and diabetic rats. Groups 2, treated with aspirin as a positive control for non-diabetic and diabetic rats. Groups 3, 4 and 5, were treated orally with pants extract with concentration 50, 100 and 200 mg/kg for non-diabetic and diabetic rats. Il-6 levels were measured in all treated groups after 7 hr of treatment. The results showed that methanolic extracts of R. coriaria and *G. arabica* at 200 mg/kg significantly (P< 0.01) decreases paw edema in diabetic rats compared with non-diabetic rats (P< 0.01). This resuts may imply that *R. coriaria and G. arabica* have potent anti-inflammatory properties in response to paw edema. The level of Il-6 was decreased in groups treated with 200 mg/kg *R. coriraia* and *G. arabica* indicating high efficacy on anti-inflammatory activity. in addition, *M. slyversries* has low activity. conclusion, extracts of *R. coriaria* and *G. arabica* exhibit anti-inflammatory effect in diabetic rats with paw edema.

Keywords: *Rhus coriaria*, *Globulara arabica*, *Malva slyverstris*, Anti-inflammation, *Rat Paw*

1. Introduction

Since the beginning of time, herbal remedies have been utilized as the foundation of health care worldwide. They are still widely used and play a vital part in international trade. Their therapeutic, pharmacological, and economic value is still recognized, but the extent to which this is recognized varies significantly between countries (Alsarayreh, *et al.*, 2022). Plant components are increasingly being used in pharmacological research and drug development because they can be used as starting materials for drug production or as models for biologically active molecules (Al Qaisi *et al.*, 2022; Laaroussi, *et al.*, 2022). According to the United Nations Convention on Biological

Diversity, conservation and sustainable use of biological diversity are vital for addressing the world's rising population's food, health, and other demands. This requires obtaining access to and transferring genetic resources as well as technology (Alsarayreh *et al*., 2022) .

Inflammation is a critical physiological reaction to a range of potentially damaging events, including physical trauma, microbial infection, and chemicals. It helps prevent tissue injury. encourages healing and protects from infection by foreign bodies. Inflammation and carcinogenesis are well known in cancer (Cutone *et al*., 2020). The research of medicinal plants' use in the treatment of inflammation requires additional investigation and detail (haddou *et al*., 2023). The majority of Jordan's endemic plants are Middle Eastern (Mediterranean) in origin, and several are medicinal in nature. Sumac is a vital herb in Jordanian traditional medicine(Alsarayreh *et al*., 2021)·*R. coriaria* figure (1A) is a member of the Anacardiaceae family, which is widely referred to as Sumac in Mediterranean nations. Due to its sour flavor, it is a classic spice. It is also employed as an astringent and anti-inflammatory substance in folk medicine in Jordan(Kali *et al*., 2022). It possesses a variety of pharmacological properties, including antibacterial, anti-diabetic, hepatoprotective, hypoglycemia, and DNA protective properties .Numerous studies have proven that *Rhus* spp is rich in phenols. (Al Assi *et al*., 2023) Additionally, the mineral content of *R. coriaria* contains flavonoid and gallotannins found in its fruits, in order to determine its dietary value (Kumar *et al*., 2018). Furthermore, Other investigations have demonstrated that *R. coriaria* extracts have a great capacity for healing of different types of wound in rats and a strong effect in type 2 diabetic rats against dyslipidemia, lipid peroxidation, and hyperglycemia (Alsamri *et al*., 2021).

Globularia arabica (figure 1 B) belongs to the family Plantaginaceae which is the only species of *Globularia* in Jordan. In Jordan *G. arabica* is being used in traditional medicine. Likewise, The antibacterial and anti-tumor properties of *G. arabica* and *G. alypum* are well-known (Oran and Raies, 1999). According to Ghlissia *Methanolic extract of Globularia alypum* promotes healing of wound and have anti-inflammatory activates in rats and have antioxidant and antibacterial properties. The greeneries of *Globularia* were crushed to a gunpowder or squashed and spotted on the site of injures in the wound area. a wound to heal it. Some activites potential of *G. arabica* were reported as a hypoglycemic. Antioxidant, anti-tuberculosis and anti-inflammatory agent (Es-Safi *et al*., 2007).

Malva sylvestris (figure 1C), belong to the family Malvaceae commonly known as mallow (Khleifat *et al*., 2022). Its anti-inflammatory and anticancer effects have been characterized as beneficial for gingivitis, abscesses, tooth discomfort, urological disease, insect bites, and ulcerous wounds, as well as particular problems in numerous systems of the body (Fernández-Rojas and Gutiérrez-Venegas, 2018).

Figure 1: Selected plants for the present study representative images of the selected plant species A: *Rhus coriaria* B: *Globularia arabica* C: *Malva sylvestris*. (Alsarayreh, et al., 2022)

Leaves takes in salads, its boiled and added to soups, *M. sylvestris* possesses anti-inflammatory characteristics as a result of the mucilage, phenols, and tannins. *M. sylvestris* is referred to in folklore as "Panirak.". This plant contains a high concentration of mucilage and polysaccharides, which are used for a variety of reasons (Amiri *et al.,* 2021). The study evaluated the efficacy of *R. coriaria, Globularia arabica and Malva sylvestris* methanol extracts against paw oedema in diabetic rats model.

2.Methodology

2.1 plant samples collection

The leaves of *G. arabica* and *M. sylvestris*, as well as seed of *R. coriaria*, its collected in Jun 2021 from various locations throughout Jordan and recognized and authentic by Prof. Sawsan Oran of Jordan University's Biology Department. A voucher specimen with the number (MU2021-22- 23-24). has deposited in mutah university.

2.1.2 Preparation of methanolic plants extracts.

G. arabica and *M. sylvestris* leaves, as well as *R. coriaria* fruits, were washed, dried, blended, and 100% methanolic. The extract (100 g) steeped in 1000 mL methanol for four days at a temperature of 25oC with constant shaking. Using a rotary evaporator, the extract was stored at -20°C in an airtight container.

2.1.3 Liquid chromatography mass spectroscopy (LCMS)

LCMS analysis was performed using a gradient of solvents A and B as a mobile phase, where 0.1% (v/v) formic acid dissolved in water represents solvent A and 0.1% (v/v) formic acid dissolved in acetonitrile represents solvent B. The analysis was conducted using the following parameters for the experiment: Agilent Zorbax Eclipse XDB-C18 column (2.1x150 mm x 3.5 μm), 25 °C, 1 μl injection volume and 18 mg sample/ml methanol. SIL-30AC autosampler with cooler, Shimadzu CBM-20A system controller, LC-30AD pump and CTO-30 column oven were used to inject the plant extract into the mass detector. Shimadzu LC-MS 8030, electrospray ion-mass spectrometer (ESI-MS), skimmer 65 V and a fragmentor voltage of 125 V. Nitrogen gas with 99.99% purity and 10 L/min flow rate was used as a drying gas under positive ion mode. In addition, 45 pounds per square inch (psi) nebulizer and 350 °C capillary temperature were used in this part of the experiments. After that, the eluent was scanned primary from 100 to 1000 mass/number of ions (m/z) and secondary scan from 50 to 100 m/z MRM mode. The results were validated by authentic standard compounds.

2.2 Animals used in this study

Male rats weighing between 150 and 250 g used to assess the activity of methanolic extracts of *G. arabica*, *M. sylvestris*, and *R. coriaria*. The rat was housed in ordinary plastic cages at Mutah University's. With constant temp at 24°C using 12-hour light/12-hour darkness cycle. The animals were provided with pelleted food and drink on a free-choice basis. The study received approval under reference number 49-2021. The rats were separated into two groups: non-diabetic rats and diabetic rats. Each section was divided into five groups, each of which had seven rats Table (1).

2.2.1 Toxicity Study of plant extract

The study employed male Wistar rats (150–200 g) that had been fasted overnight. Five groups of two animals each were formed. As indicated in the table (2), groups 1 to 4 got 2ml/group plant extract orally. The control group (group 5) received normal saline via the same way (2 mL/group).

Table 1: Treatment groups in assessing the anti-inflammatory effect of the plants extracts.

Non-diabetic rats		Diabetic rats	
Group	Received	Group	Received
1.	Normal saline	7	Normal saline
2.	Normal saline + 1% carra	8	Normal saline + 1% carra
3.	150mg/ aspirin + 1% carra	9	150mg/kg aspirin + 1% carra
4.	50 mg/kg plant extract + 1% carra	10	50 mg/kg plant extract + 1% carra
5.	100 mg/kg plant extract +1% carra	11	100 mg/kg plant extract +1% carra
6.	200 mg/kg plant extract + 1% carra	12	200 mg/kg plant extract + 1% carra

This method divided into three stages, with each stage's outcomes suggesting if it should be discontinued or carried to the next. Within 36 hr, general toxicity signs and death were found in each group. If no death is observed during these stages, the test substance's LD50 is reported to be larger than 5000 mg/kg, indicating its safety. However, if thre is a death a confirmatory test should be undertaken to prove the material was truly the cause of death. This test entails simply administering the dose of the test drug that resulted in death (or the lowest dose that resulted in death in a circumstance with multiple deaths) to four animals. Then, over the next 24 hr, surveillance should begin one hour after administration and continue every two hours. two animals from the four animals die, it should serve as a confirmation and validation of the test result. This method has many advantages, including the use of a small number of animals, the exploration of a large range of doses, and it is easy and low-cost (Al Qaisi *et al.*, 2024)

Table (2) Recommended doses for toxicity study of the plant extract

Stage	**doses (mg/kg /body weight)**				
	g1	g 2	g 3	g 4	g 5
1	100	200	400	800	Saline
2	1000	1500	2000		
3	3000	4000	5000		

And using the following formula to calculate

LD_{50}: $LD_{50} = (M_0 + M_1) / _2$

Where M_0 = large dose that gave no death and M_1 = Smal dose that gave death

2.2.3 Diabetes induction

Streptozotocin (65 mg/kg body weight) injected intraperitoneally to induce diabetes. In order to determine whether diabetes had developed, the fasting blood glucose level was checked after three days (Abu Hajleh *et al.*, 2023)· Diabetic animals had blood sugar levels more than or equal to 200 milligrams per deciliter (Alhabashneh *et al.*, 2022).

2.2.4 Induction of hind paw edema:

Rats used to assess the anti-oedematous action of the methanolic extract of of *G. arabica* and *M. sylvestris* and *R. coriaria* was examined in the rats using sub plantar injection of 0.1 mL of 1% carrageenan in all groups. Oral administration of the aspirin the extract of the plants dissolved in 1 mL of normal saline using oral gavage needles, control groups of non-diabetic and diabetic rats received orally with 1 ml of saline. The rat paw injected with 0.1 mL of 1 percent carrageenan one hour later. At 0 hr, 3 hr , and 7 hr after injection of the carrageenan, paw thickness was assessed (Watanabe *et al.*, 2008). The paw edema was estimated as the percentage size of the paw width as related reference groups.

2.2.5 Determination of the levels of IL-6 in serum samples

Seven hours after the carrageenan injection, blood obtained from all groups. The serum was separated for the enzyme-linked immune sorbent test to assess the levels IL-6 (ELISA).

3. Statistical analysis

There was a mean and a standard deviation for the data. ANOVA with Tukey's HSD post-hoc test was used to determine the statistical significance of differences between groups using Graph Pad Prism version 7. P 0.05 was considered significant.

4. Results and Discussion

4.1 Toxicology Investigation

Toxicity study have reported that the groups received orally of the *R. coriaria* and *M. sylvestris* methanolic extract were safe and non-toxic up to (4500 mg/kg). The methanolic extract of *G. arabica* leaf was safe up to (3500 mg/kg) as shown in table (3). The doses of the extract of *R. coriaria* administered were chosen based on a previously reported LD_{50} in rats more than (1975 mg/kg body wt.) (Mohammadi *et al.*, 2016; Al-Saraireh *et al.*, 2021) in *G. arabica* was (up to 1000 mg/kg wt.) (Merghache *et al.*, 2013). However, *M. slyvesries* LD_{50} was (up to 2000 mg/kg wt.) (Yeole *et al.*, 2010).

Table 3: lethal doses of *R. coriaria*, *G. arabica* and *M. sylvestris* methanolic extract.

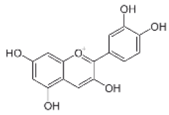
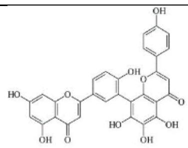
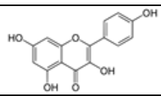
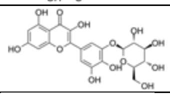
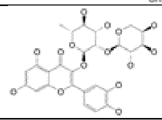
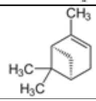
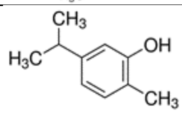
	Plant extract	LD50 doses (mg/kg /bdw)
1	*R. coriaria*	4500
2	*G. arabica*	3500
3	*M. slyvestries*	4500

4.2 Phytochemical analysis of the plants extracts

The yielded extracts obtained by methanol extraction of fruit *R. coriaria,* and leaves of *G. arabica* and *M. sylvestris* were about 13.4%, 12.5% and 18.6 % w/w on dry weight basis, respectively. The active constituents available in *G. arabica, M. sylvestris* leaves *and* fruits of *R. coriaria* methanolic extract were identified using LCMS (table 4, 5, and 6). Myricetin 3-glucoside and Cyanidin are the major constituents in *R. coriaria* (representing 13% and 12%) respectively. Also, the second abundant ingredient in *R. coriaria* fruits methanolic extract is Quercetin 3-O-alpha-L-rhamnopyranoside (representing 9.5%). Other constituents were also available at different percentages, the active constituents available in *G. arabica* and *M. sylvestris* leaf extract. L-linalool (10.5%) and heptadecane (9%) were the major constituents of *G. arabica* methanolic extract. However, the Hexanoic acid (11.2%), Phytol (10.2%) and Stigmasterol (10.2%) were the major constituents of *M. sylvestris* leaf extract.

Phytochemical screening of the medical plants *G. arabica, M. sylvestris* leaves and fruits of *R. coriaria* methanolic extract showed the presence of flavonoids, alkaloids, proteins, amino acids, tannins, phenols, glycosides and carbohydrates (table 4, 5 and 6). The main attraction of the phytochemicals was the presence of phenols and flavonoids (Yu *et al.*, 2002). Flavonoids are polyphenols with its main action is anti-inflammatory during wound. They are widely distributed plant metabolites, which also have anti-oxidant activity as free radical scavenging properties. Moreover, the polyphenols have also redox characteristics, which act as reducing agents, hydrogen donors, and singlet and triplet oxygen scavengers. This makes polyphenols the most important herbal chemicals with antioxidant activity (Mohankumar *et al.*, 2018).The results of the present study agreement with previous studies reported that Cyanidin , Sumaflavone and Kaempferol exhibits pronounced anti-inflammatory effects by suppressing pro-inflammatory cytokines and inhibiting the NF-κB signaling pathway (Lee *et al.*, 2020, Menezes *et al.*, 2021, Ren *et al.*, 2019) , moreover, Myricetin 3-glucoside, quercetin 3-O-alpha-L-rhamnopyranoside and carvacrol has been shown to inhibit the activation of the NF-κB signaling pathway, which is crucial in the regulation of inflammatory responses. And it could be a valuable natural compound for the treatment of inflammatory diseases. (Guo *et al.*, 2019, Shabir *et al.*, 2022, Somensi *et al.*, 2022).

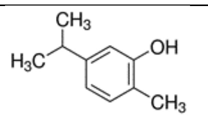
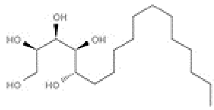
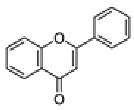
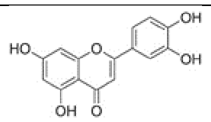
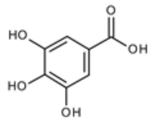
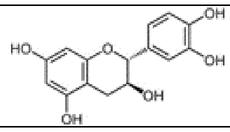
Table 4: Chemical constituents of *R. coriaria* fruit extract identified by LCMS.

NO	Chemical Compound	Molecular formula	Molecular structure	Molecular weight	Percent %
1	Cyanidin	$C_{15}H_{11}O_6$		287.24	12
2	Sumaflavone	$C_{30}H_{18}O_{11}$		554.46	8.4
3	Kaempferol	$C_{15}H_{10}O_6$		286.24	8.4
4	Myricetin 3-glucoside	$C_{21}H_{20}O_{13}$		480.37	13
5	Quercetin 3-O-alpha-Lrhamnopyranoside	$C_{21}H_{20}O_{11}$		448.38	9.5
6	α-pinene	$C_{10}H_{16}$		136.23	8.4
7	Carvacrol	$C_{10}H_{14}O$		150.22	7.4

Results obtained in the present study revealed that the levels of these phyto constituents were considerable using liquid chromatography mass spectroscopy, and this study agreement with (Abdallah *et al.*, 2019). reported that the *R. coriaria* fruits methanolic extract contain more than 80 phytochemicals (tannins, (iso) flavonoids, terpenoids. This makes it as important ingredients in the food and pharmaceutical industries. Sumac contains a variety of phytochemicals, including polyphenols, tannins, flavonoids, organic acids, and essential oils. In addition, it is usually used in herbel for research field for its phytochemical contents and bioactive properties (Elsherif *et al.*, 2022). Also, *R. coriaria* has been found to be rich source of flavonoids, tannins, polyphenolic compounds, organic acids, and other varieties of phytochemicals which have strong antioxidant activeties against a variety of ailments

The results of the present study shows that the major constituent in *R. coriaria* is cyanidin, our finding are in support of the study of (Acquaviva *et al.*, 2003). who reported that cyaniding has protective effect on DNA damage, free radical scavenging activity and inhibition of xanthine oxidoreductase activity. It has been shown that anthocyanins have strong antioxidant characteristics, which makes them viable class of substance for treatment of diseases where the free radical generation is the major factor. Moreover, cyaniding has several protective activities, such as anti-inflammatory, anti-thrombotic, insulinotropic, gastro-protectiveanti-microbial, chemopreventive, and epigenetic. These activities have strong therapeutic effects against *H. pylori* infection, periodontal and age-related disorders, type 2 diabetes, cardiovascular disease, metabolic syndrome, and oral cancer (Olivas-Aguirre *et al.*, 2016).

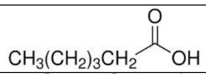
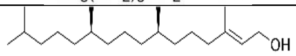
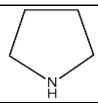
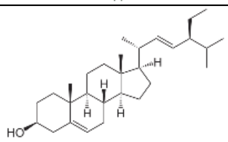
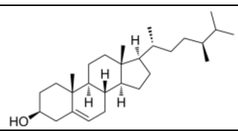
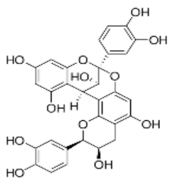
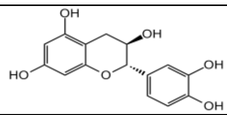
Table 5: Chemical constituents of *G. arabica* leaf extract identified by LCMS.

NO	Chemical Compound	Molecular formula	Molecular structure	Molecular weight	Percent %
1	L-linalool	$C_{10}H_{18}O$		154.25	10.5
2	Heptadecane	$C_{17}H_{36}$		240.47	9
3	Flavone	$C_{15}H_{10}O_2$		222.24	6.7
4	Luteolin	$C_{15}H_{10}O_6$		286.24	7.5
5	Gallic acid	$C_7H_6O_5$		170.12	8.7
6	Catechin	$C_{15}H_{14}O_6$		290.27	7.2

Also, myricetin is another consistent that has been found in *R. coriaria* and the result of the present study are coincided with other study that reported that it has antibacterial and antioxidant activeties. In addation, myricetin posseses neuroprotective properties and other diseases such as Alzheimer's, Parkinson's, and Huntington's. Moreover, myricetin has antidiabetic, anticancer, immunomodulatory, cardiovascular, analgesic, and antihypertensive activities (Taheri *et al.*, 2020). Several studies have been demonstrated that myricetin treatment enhanced wound re-epithelialization accompanied by increase fibroblasts density, blood capillaries, cell proliferation and powerful wound healing properties. Also, it has shown that myricetin decreased the inflammatory parameters in LPS stimulated fibroblasts and keratinocytes which might activates wound-healing process after treatment with higher dose (Sklenářová *et al.*, 2021)

Moreover, the leaves of *G. alypum* has been described to contain a high level of phenol and flavonoids, syringing and iridoids which have strong antioxidant activity that can be used, in food processing and medical technology (Chograni *et al.*, 2013). The *G. alypum* contain about 73 chemicals in the volatile profile with n-hexadecanoic acid forms 13.5 % which has being the most prevalent an antioxidant activity. Also, the *G. arabica* methanolic extract contain linalool in accordance with the study reported that it has antioxidant activity as well as cardiovascular modulator, analgesic, antianxiety and anti-cancer properties (Jabir *et al.*, 2013).Previous study showed that L-linalool, Heptadecane , Flavone, Gallic acid and Catechin a naturally occurring terpene alcohol found in many flowers and spice plants it has been demonstrated significant anti-inflammatory properties in scientific studies its effects by inhibiting the production of pro-inflammatory cytokines and chemokines, and reducing the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in LPS-stimulated macrophages (Peana et al., 2002, Kim et al., 2013, Verma et al., 2013).

Table 6: Chemical constituents of *M. sylvestris* leaf extract identified by LCMS.

NO	Chemical Compound	Molecular formula	Molecular structure	Molecular weight	Percent %
1	Hexanoic acid	$C_6H_{12}O_2$		116.16	11.2
2	Phytol	$C_{20}H_{4}0O$		296.5	10.2
3	Pyrrolidine	C_4H_9N		71.12	9.4
4	Stigmasterol	$C_{29}H_{48}O$		412.7	10.2
5	Campesterol	$C_{28}H_{48}O$		400.68	8.3
6	procyanidin	$C_{30}H_{26}O_{13}$		594.52	8.4
7	Catechin	$C_{15}H_{14}O_6$		290.27	7.2

The present study showed that phytochemicals analysis of the *M. sylvestris* methanolic extract contains polyphenols, flavonoids, and tannins which have therapeutic activity of wound healing which is in agreement with previous studies. Moreover, the volatile profile of *M. sylvestris* such as phytol have described as an antioxidant and analgesic effects (Dowek *et al.*, 2020). Also, saponins, alkaloids, and flavonoids has been confirmed to treat a variety of diseases and have antioxidant activities (Mousavi *et al.*, 2021). In addition, the present finding showed that other bioactive compounds such as Hexanoic acid, Phytol and Stigmasterol are the major constituent of *M. sylvestris* leaf extract which showed less effect on wound healing and anti-inflammatory activity. However, other studies reported that the phytol (PHY) is an acyclic natural diterpene alcohol have antibacterial, antioxidant, anticancer properties, anti-inflammatory and anti-arthritic activity (Carvalho *et al.*, 2020). In addition, it has been recommended that it can be used as a precursor material for the production of synthetic vitamin E and vitamin K1. However, the topical application of stigmasterol was observed to decrease carrageenan-induced paw oedema and to inhibit 12-Otetradecanoylphorbol acetate (TPA)-induced ear oedema. Also, it was found to minimize neurological impairments and infarct damage caused by ischemic reperfusion injures. (Subedi *et al.*, 2019). Pyrrolidine and stigmasterol's diverse biological activities on a range of metabolic disorders have been investigated through molecular docking and in vitro and in vivo assays. Strong pharmacological effects, including anti-inflammatory, anti-diabetic, anti-cancer, anti-osteoarthritis, immunomodulatory, antiparasitic, antifungal, antibacterial, antioxidant, and neuroprotective qualities, are indicated by the findings (Bakrim *et al.*, 2022). Epicatechins, catechins, and flavan-3-ol units make up the naturally occurring polyphenol procyanidin (Dasiman *et al.*, 2022). A diterpene belonging to the long-chain unsaturated acyclic alcohol family is phytol (PYT). Numerous biological effects are exhibited by PYT and some of its derivatives, such as phytanic acid (PA) (Islam *et al.*, 2018). Hexanoic acid (Hx) Hx-IR results also strongly imply that it is a desirable tool for the molecular characterization of the plant alarmed state. (Aranega-Bou *et al.*, 2014).

4.3 Paw oedema treated by plants extracts

The maximum thickness of the paw oedema was obtained in rats 7 hr after carrageenan. Results of the study showed that all the plants extracts used in the treatment (50 to 200 mg/kg) of *R. coriaria* caused significant (P <0.05) decrease of oedema thickness in normal rats. As compared to aspirin used as a control. The (200 mg/kg) extract caused a 1.5-fold increase more than aspirin (table 7). Moreover, the methanolic extract of *R. coriaria* was significantly (P <0.05) higher than aspirin (150 mg/kg) as a control table (8) Furthermore, *G. arabica* methanolic extract decreased the paw oedema in nondiabetic and diabetic rats (table 9 and 10). However, *M. sylvestris* methanolic extract showed mild effect on paw edema in nondiabetic and diabetic rats (table 11 and 12) as compared to *R. coriaria* and *G. arabica* methanolic extract.

Table 7: Activity of *R. coriaria* extracts and aspirin on paw oedema in non-healthy rats

NO	Groups	Paw diameter (mm) 0 hr	3hr	7hr
1	Normal saline	4.75 ±0.27	4.26 ± 0.36	4 ±0.54
2	Normal saline +1% Carra	5.79 ± 0.49	7.22 ± 0.3	9.48 ± 0.11
3	Acetylsalicylic acid (150 mg/kg) +1% Carra	5.48 ±0.12	6.62 ± 0.48 *	6.05 ±0.16 *
4	*R. coriaria* (50 mg/kg) +1% Carra	5.33 ±0.34	6.15 ± 0.6 *	5.95 ± 0.18 *
5	*R. coriaria* (100 mg/kg)+1% Carra	5.25 ± 0.53	5.98 ± 0.16 *	5.65 ± 0.17 *
6	*R. coriaria* (200 mg/kg)+1% Carra	5.36 ± 0.2	5.96 ± 0.17*	4.21 ± 0.40 *

* Significant at P < 0.05 over control; M ± S.D of 7 rats

Table 8: Activity of *R. coriaria* extracts and aspirin on paw oedema in diabetic rats

NO	Groups	Paw diameter (mm) 0 hr	3 hr	7 hr
7	Normal saline	4.67 ±0.57	4.8 ±0.52	5.21 ±0.36
8	Normal saline +1% Carra	5.47 ± 0.42	8.49 ± 1	10.10 ± 0.21
9	aspirin (150 mg/kg) +1% Carra	5.10 ±0.27	7.33 ± 0.55*	6.44 ±0.17 *
10	*R. coriaria* (50 mg/kg) +1% Carra	5.14 ±0.14	7.85 ± 0.21*	8.35 ± 0.32 *
11	*R. coriaria* (100 mg/kg)+1% Carra	5.08 ± 0. 3	7.46 ± 0.45	7.84 ± 0.61 *
12	*R. coriaria* (200 mg/kg)+1% Carra	5.00 ± 0.41	7.23 ± 0.47*	6.02 ± 0.16 *

* Significant at P < 0.05 over control; M ± S.D of 7 rats

Table 9: Effect of *G. arabica* methanolic extracts and aspirin on paw oedema in healthy rats

NO	Group	Paw diameter (mm)		
		0 hr	3 hr	7 hr
1	Normal saline	4.98 ±0.38	4.52 ±0.39	4.18 ±0.31
2	Normal saline +1% Carra	5.25 ± 0.5	7.27 ±0.51	8.78 ±0.30
3	aspirin (150 mg/kg) +1% Carra	4.37 ±0.89	5.73 ±0.66 *	5 ±0.55 *
4	*G. arabica* (50 mg/kg) +1% Carra	4.87 ±0.12	6.35 ± 0.23 *	6.5 ± 0.38 *
5	*G. arabica* (100 mg/kg)+1% Carra	4.8 ±0.10	6.25 ±0.17 *	6.2 ± 0.51 *
6	*G. arabica* (200 mg/kg)+1% Carra	4.83 ±0.51	6.12 ±0.10 *	5.34 ±0.31 *

* Significant at P < 0.05 over control; M ± S.D of 7 rats

Table 10: Effect of *G. arabica* methanolic extracts and aspirin on paw oedema in diabetic rats

NO	Groups	Paw diameter (mm)		
		0 hr	3 hr	7 hr
7	Normal saline	4.95 ±0.62	4.65 ±0.54	4.88 ±0.50
8	Normal saline +1% Carra	5.47 ± 0.42	8.49 ±0.10*	10.1 ± 0.21*
9	aspirin (150 mg/kg) +1% Carra	5.1 ±0.27	7.33 ± 0.55	6.44 ± 0.17
10	*G. arabica* (50 mg/kg) +1% Carra	5.1 4 ± 0.14	7.8 ± 0.21 *	8.35 ± 0.32 *
11	*G. arabica* (100 mg/kg)+1% Carra	5.08 ±0.30	7.46 ± 0.45*	7.84 ± 0.61 *
12	*G. arabica* (200 mg/kg)+1% Carra	5 ±0.41	7.23 ± 0.47 *	6.2 ± 0.16*

* Significant at P < 0.05 over control; M ± S.D of 7 rats

Table 11: Effect of *M. sylvestris* methanolic extracts and aspirin on paw oedema in non-diabetic rats

No	Groups	Paw diameter (mm)		
		0 hr	3 hr	7 hr
1	Normal saline	4.91 ±0.39	5.12 ±0.20	4.8 ±0.34
2	Normal saline +1% Carr	5.66 ±0.20	7.59 ±0.66	9.39 ±0.59
3	aspirin (150 mg/kg) +1% Carra	4.89 ±0.49	6.63 ±0.98 *	4.1 ±0.60*
4	*M. sylvestris* (50 mg/kg) +1% Carra	5.1 ±0.21	7.08 ±0.24	7.39 ±0.22 *
5	*M. sylvestris* (100 mg/kg)+1% Carra	5 ±0.12	7.02 ±0.40	7.2 ±0.90 *
6	*M. sylvestris* (200 mg/kg)+1% Carra	4.9 ±0.06	6.98 ±0.25*	6.78 ±0.6*

* Significant at P < 0.05 over control; M ± S.D of 7 rats

Table 12: Effect of *M. sylvestris* methanolic extracts and aspirin on paw oedema in diabetic rats

No	Groups	Paw diameter (mm)		
		0 hr	3 hr	7 hr
7	Normal saline	4.83 ±0.53	5.09 ±0.47	5.35 ±0.49
8	Normal saline +1% Carra	5.14 ±0.52	7.36 ±0.47	9.55 ±0.79
9	aspirin (150 mg/kg) +1% Carra	4.67 ±0.48	6.49 ±0.53*	5.93 ±0.46 *
10	*M. sylvestris* (50 mg/kg) +1% Carra	4.7 ±0.39	6.9 ±0.39	8.3 ± 0.49 *
11	*M. sylvestris* (100 mg/kg)+ 1% Carra	4.65 ±0.45	6.83 ±0.21	8.2 ±0.53 *
12	*M. sylvestris* (200 mg/kg)+ 1% Carra	4.6 ±.52	6.54 ±0.28 *	7.55 ±0.44 *

4.4 Determination the levels of IL-6 in the serum

ELISA was employed to determine of the IL-6 in blood samples collected from different groups of animals. The Intra planter injection of carrageenan significantly (P <0.05) increased the levels of IL-6 compared to control group. The methanolic extracts of *G. arabica*, *M. sylvestris* leaf extract and *R. coriaria* fruit extract (at 100 and 200mg/kg body wt) decreased IL-6 (pg/ml) level compared to the noticeable increase of IL-6 in carrageenan-treated group (figure 2, 3 and 4).

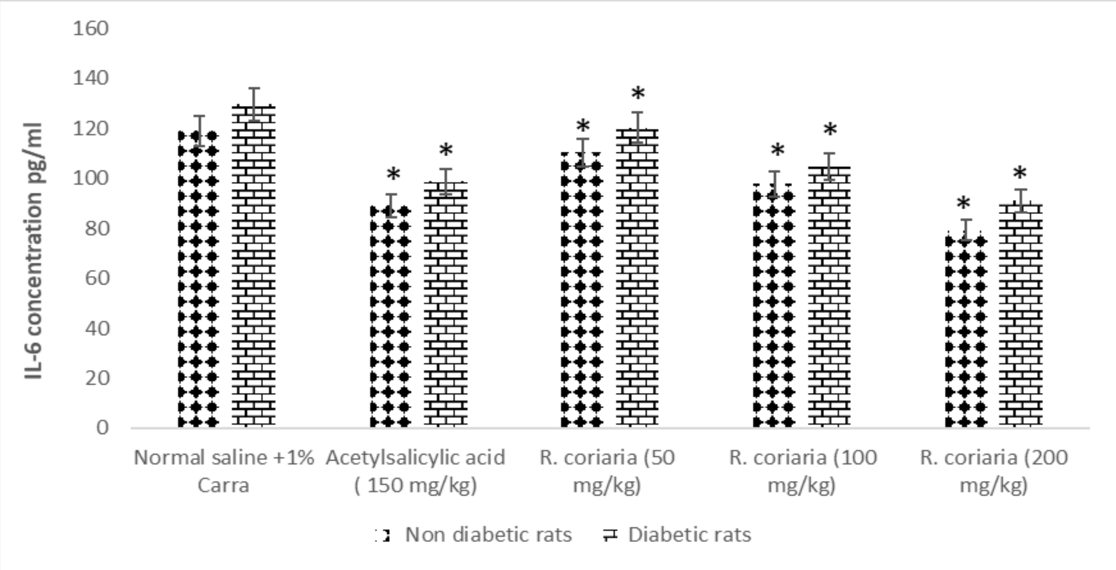


Figure (2) Activity of *R. coriaria* extracts on IL6 level in paw edema in non-diabetic and diabetic rats after 7 hrs. * Significant at P < 0.05 over control; M ± S.D of 7 rats

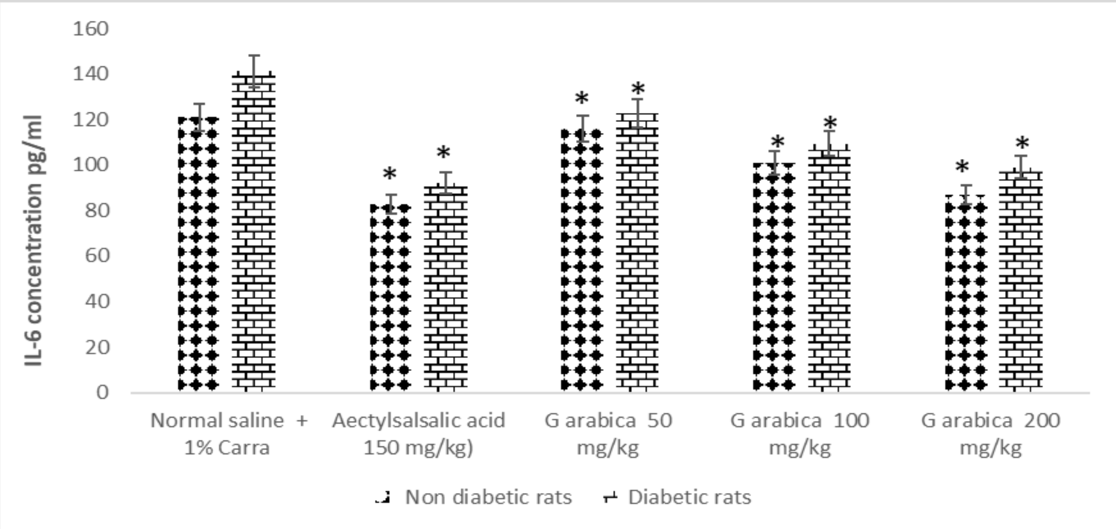


Figure (3): Activity of *G. arabica* extracts on IL6 level in paw edema in non-diabetic and diabetic rats after 7hrs. * Significant at P < 0.05 over control; M ± S.D of 7 rats

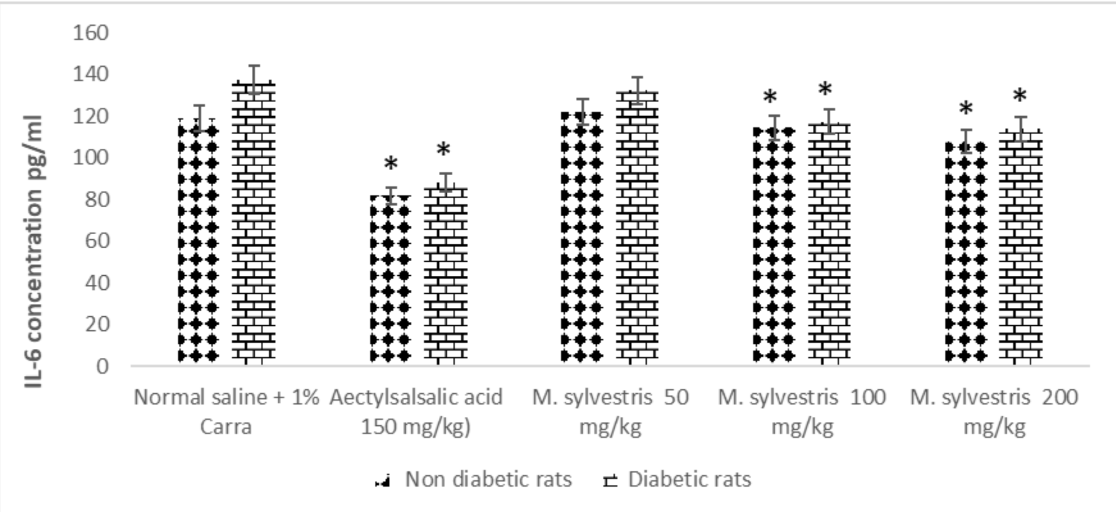


Figure (4): Activity of *M. sylvestris* extracts on IL6 level in paw edema in non-diabetic and non-diabetic rats after 7 hrs. * Significant at P < 0.05 over control; M ± S.D of 7 rats

4.5 Evaluating the anti-inflammatory activities of G. arabica, M. sylvestris, leaves and R. coriaria fruits methanolic extracts

Inflammation its mechanism against harmful stimuli such as damaged cells, irritants and pathogens, and its sub sides upon healing is complete. However, inflammation may be inappropriately occurring which required anti-inflammatory drugs to modulate inflammation. (Maroon *et al*., 2010). The non-steroidal anti-inflammatory drugs have many side effects and therefore the need to search for other powerful alternative with minimal adverse effects. The present study investigates the effect *G. arabica*, *M. sylvestris* leaves and of *R. coriaria* fruits methanolic extracts on carrageenan-induced paw edema. All these plant extracts significantly ($P < 0.05$) decreased paw edema in the footpad of the rat indicating that they have the ability to regulate inflammation.

R. coriaria seed extract had anti-inflammatory potential by decreasing hind paw carrageenan-induced inflammation. *R. coriaria* decreased the formation of pro-inflammatory mediators like histamine and serotonin, as well as mRNA for inflammation-inducing molecules such as interleukin-18 and interleukin-1, according to earlier research (Momeni *et al.*, 2019). In addition, our results are coincided with previous studies which showed *R. toxicodendron* and *R. tripartite* and *R. retinorhaea* extracts exhibited considerable decrease of inflammation of carrageenan-induced paw oedema. Also, a similar study has shown that *R. coriaria* extract has protective in the management of skin inflammation. Moreover, the present study showed that seed methanolic extract of *R. coriaria* have a strong anti-inflammation action against oedema in diabetes animals (Alsarayreh *et al*., 2021).

Myricetin is the main consistent of the *R. coriaria* methanolic extract which has an important role in anti-inflammation. This is supported by the study of (Semwal *et al.*, 2016). who showed myricetin showed anti-inflammation activities in several inflammatory types such as carrageenan-induced hind paw inflammation rheumatoid arthritis. Also, myricetin inhibited the inflammatory response induced by *Porphyromonas gingivalis* and inhibited PGs produced by LPS in rat peritoneal macrophages. Likewise, present study in agreement with that of (Kroes *et al.*, 1992). which reported that gallic acid showed anti-inflammation action against zymosan-induced footpad swelling in rats.

Moreover, the present finding indicating that the methanolic extract of *G. arabica* decreased the paw-oedema in both healthy and diabetic rats. the results in comparable with that of (Hennia *et al*., 2018). which reported that the butanol extract of *G. alypum* deceased the paw-oedema in mice as compared to aspirin at a dose of 2 mg/ml. Also, another finding of the present study showed that the methanolic leaf extract of *M. sylvestris* significantly inhibits paw-oedema in both non-dabetic and diabetic rats. Likewise, these results in agreement with that of the (Saputra, 2022). which reported that the *malva* flower extract can be used in bronchial allergic asthma and reduce inflammatory cells by preventing cellular infiltration.

4.6 Determining levels of IL-6 in the serum samples

Interlukine-6 is a cytokine which has several function that evoke the production of many proteins involved in inflammatory reactions (Yu *et al.*, 2002). this study reporeted that the levels of IL-6 in the serum of animals, which orally treated, with 200 mg/kg methanolic extract of *G. arabica*, *M. sylvestris* leaves and the fruits of *R. coriaria* were significantly ($P < 0.05$) decreased as compared to carrageenan-treated group. This effect can be attributed to the active compounds such as cyaniding which decreases IL-6. These results are coincided with other studies which reported that the recived of cyanidin significantly decreased serum levels of TNF-α, IL-1β and IL-6. Also, and inhibites LPS-induced inflammation and deceases the activation of (NF-κB) and (MAPK) pathways (Sun and Li, 2018). Moreover, it has been found that Cyanidin had anti-inflammatory activity by inhibition of

LPS-stimulated TNFalpha and IL-6 mRNA expression and secretion of these proteins by human monocyte/macrophage cell line (THP-1 cells). These finding are in agreement with previously reported that gallic acid and myricetin decreased the levels of IL-6 in CFA-induced arthritis model and synovial cells in the rats (Jiang *et al.*, 2016).

Furthemore, linoleic acid was the majar constituent of *G. arabica* methanolic leaf extract and these results might be supported by the study of (Marion-Letellier *et al.*, 2008) who found that linoleic acid reduced the secretion of pro-inflammatory cytokines such as IL-6. Similarly, the present finding showed that phytol makes up 10.2% of *M. sylvestris* methanolic leaf extract and these results in agreement with the previously reported that the phytol has a potential anti-inflammatory effect in joints and the spinal cord (Ruchawapol *et al.*, 2021).

Conclusion

The current study had focused on the remarkable potential phototherapy of commonly available plants *G. arabica* , *R. coriaria* and *M. sylvestri* for their pharmacological benefits, these plants exhibited high activity as anti-inflammatory efficacy against diabetic and non-diabetic rats' generated hind paw oedema. In addition, the methanolic extracts of these plants is rather safe and showed no signs of systemic toxicity in the rat. Also, the preliminary phytochemical analysis and LCMS analysis of the current study may open the door for future research in identification and standardization of bioactive compounds of the plant materials. These findings are encouraging, a potential choice for developing novel anti-inflammatory medicines with less side effects.

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Conflict of Interest*:* The authors declare that there are no conflicts of interest.
Compliance with Ethical Standards*:* Experiment protocols were authorized by the FIOCRUZ Committee of Ethics for the Use of Animals (CEUA LW16/14), and all experiments were conducted in ctableompliance with these criteria.

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