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Evaluation of Anti-Inflammatory and Antidiabetic Activity of Ethanolic Extract of *Alhagi maurorum* on Animal Model

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ABSTRACT

The current study was conducted to determine the anti-inflammatory and anti-diabetic effects of ethanolic extract of plant *Alhagi maurorum*. Plant was collected from Baluchistan province district Quetta, Pakistan. Anti-inflammatory activity was carried out in albino rat by the method of carragenaan induced paw edema and histamine induced paw edema. In carragenaan induced paw edema plant extract at a dose of 250 mg/kg has decreased thickness of paw (12.5%) and exhibited a significant effect ($P<0.05$) and at a dose of 500mg/kg has decreased thickness of paw (46.87%) and has produced a significant effect ($P<0.05$). In histamine induced paw edema the plant extract at a dose of 250 mg/kg has decreased diameter of paw (22.41%) and has produced a significant effect ($P<0.05$) and at a dose of 500mg/kg had showed a higher percentage inhibition (44.82%) and exhibited a significant effect ($P<0.05$). Anti-diabetic activity was conducted in albino rabbits by evaluating anti-diabetic effect of plant extract in normo-glycemic rabbits and alloxan induced diabetic rabbits. In normoglycemic rabbits 250mg/kg of plant extract produce non-significant reduction in blood glucose level ($P>0.05$) while 500mg/kg decrease blood glucose level significantly ($P<0.05$). In alloxan induced diabetic rabbits non-significant reduction in blood glucose level was observed by administration of plant extract at a dose of 250mg/kg ($P>0.05$) and in a dose of 500mg/kg has decreased blood glucose level significantly ($P<0.05$). It was concluded that ethanolic extract of plant *Alhagi maurorum* has antidiabetic and anti-inflammatory effects in animals.

INTRODUCTION

Plants used for the treatment of various diseases since the time of Egyptians. They had a great knowledge about medicinal herbs and its uses in various pathological conditions (Shanab *et al.*, 2005). Medicinal plants are being used by Asian Indians, South American, Native Americans and Chinese used many medicinal plants (Abu-Shanab *et al.*, 2005; Foster, 1992; García-Alvarado *et al.*, 2001; Grover *et al.*, 2002; Vuksan *et al.*, 2000). Worldwide many drugs are derived from medicinal plants. In Europe, out over 1300 medicinal plants are used out of which 90% are obtained from remote areas. Top 150 drugs used in USA out of which 118 drugs are from plant source (Balunas & Kinghorn, 2005). For the primary healthcare in developing countries, 80% of the people used herbal products and in developed countries 25% medicines are obtained from plants (Hamilton, 2004).

Nowadays many synthetic medicines are produced from several plants**.** In the field of both herbal and allopathic therapy many researchers have done a great work to investigate the phytochemicals in last decades. In view of recent studies in under-developed countries, many people depend on conventional physicians. The plant oriented medicines are used more commonly due to unavailability of modern medicines. Plant contains many chemical compounds, and these chemicals has different role in the field of medicine, but plant extracts may cause toxic effects to both human and animals due to over-dosage. About one fourth of modern medicines are extracted from plants. Examples of some common medicine related to plant origin are vinblastine & vincristine, quinidine & quinine, digoxin, atropine, morphine & codeine. To obtain extracts from medicinal plant is a complicated procedure as bioassays are required and experiment should be producible, rapid, and inexpensive.

One of the major endocrine disorder in many developing countries is Type 2 diabetes (Yaseen *et al.*, 2015). It is expected that in the year 2035 the number of diabetic patients will increase to 592 million worldwide(Giovannini *et al.*, 2016). Diabetes effects on metabolism and there is decrease amount of insulin or change the action of insulin on various cells of the body(Yagi & Yagi, 2018). Person suffer from diabetes express a number of symptoms like blurred vision, hypotension, pruritus, polyphagia, weight loss, tachycardia, polyuria, and polydipsia (Surya *et al.*, 2014). Diabetes develop due to changes in normal life style and diet (Rahati *et al.*, 2014). Diabetes mellitus is treated using oral hypoglycemic drugs, insulin, and modification in diet. Plant based medicines give an alternative way of treatment for the treatment of diabetes because chemical drugs produce many side effects (Singh *et al.*, 2008;

Yanardağ *et al.*, 2003).Inflammation starts when mammalian tissue injured due to any type of agent this will generate pathophysiological response that will lead to accumulation of blood cell and plasmatic fluid in tissue spaces. Inflammation is the protective and defensive mechanism and it will stop the spread of infectious agent (Sosa *et al.*, 2002).

The most common drugs used worldwide for the treatment of various inflammatory conditions are NSAIDS. These drugs are used for various conditions such as soft tissue injuries, osteoarthritis and fractures (Boursinos *et al.*, 2009). Various types of NSAIDS like Naproxen and Ibuprofen are use in inflammation. Glucocorticoids like prednisone and cortisone are also use as anti-inflammatory agents. However, due to high cost, toxicity and side effects such as renal damage, hypertension, ulceration and bleeding, there is need of development of newly formed plant based drugs therefore, the developments of potent anti-inflammatory drugs from the natural products are now under considerations (Srinivasan *et al.*, 2001).

Within this context, *Alhagi maurorum* is associated with family Leguminosae. For many topical infections *Alhagi maurorum* is used in the different area of Khyber Pakhtunkhwa Pakistan. Mainly this plant is originated from region including area from the Mediterranean to Russia but now it is found in many other areas of the world including Southern Africa, Western United States and Australia. *Alhagi maurorum* is the single species of genus Alhagi (Leguminosae) and have the deepest root system and can grow in drought. In a country like Iran, this plant is used for treatment and management of rheumatism, gastric ulcer, gastrointestinal disorders, appetite suppressant, as diuretic, and jaundice. As traditional medicine in southwest of Iran *Alhagi maurorum* is used to treat heartburn resulted due to Gastro Esophageal Reflux Disease (Sulaiman, 2013). Based on the evidence, the current study was conducted to determine the anti-inflammatory and anti-diabetic effects of ethanolic extract of plant *Alhagi maurorum*.

METHODOLOGY

Chemicals and drugs

The chemical used in the study were Histamine, Carrageenan and Alloxan monohydrate. Drugs used in this research were Glibenclamide and Diclofenac Sodium. All these chemical were purchased from local market in Quetta city (Singh *et al.*, 2008).

Collection and extraction of *Alhagi maurorum*

The aerial parts of plant were collected from Hanna valley of Quetta city. The plant was washed three times with tap water and then dried in a shade. The whole plant was cut down into small parts. The chopped material was macerated for two weeks at 25^{o}C. The ethanolic extract of plant was filtered and the filtrate was evaporated by rotary evaporator.

Determination of Anti-Inflammatory Activity

Carrageenan induced paw edema

Albino rats were selected for this study. Twenty-four animals were divided into four groups and six animals were placed in each group. Group I was considered as control group and distilled water at dose of 2 ml/kg orally has given to this group. The plant extract having dose of 250 and 500 mg /kg were given orally to groups II and III and standard drug diclofenac was administered orally having dose of 50mg/kg to group IV. One hour of the treatment, a sign of inflammation and edema was produced when carrageenan administered by injection in right hind paw at dose of (0.1 ml, 1%, w/v in saline). The paw volume was then measured at 0 min, 1 hour, 2 hour, 3 hour, 4 hour and 5 hour after the administration of phlogistic agent by using the digital vernier caliper (Parra *et al.*, 2019).

The percentage inhibition was calculated by the following formula:

$$\% \text{ inhibition} = \frac{(Ct\text{-}Co)\ \text{control} - (Ct\text{-}Co)\ \text{treated}}{(Ct\text{-}Co)\ \text{control}}$$

Where $(C_t - C_0)_{control}$ is the difference in the size of paw at 5 hours in control rats, and $(C_t - C_0)_{treated}$ is the difference in the size of paw at 5 hours in rat treated either with the standard drug or plant extract (Banerjee *et al.*, 2012).

Histamine induced paw edema

Albino rats weighing between 150 - 250 g used for the study and were remained in fasting condition one night before test and during the experiment. Anti-inflammatory activity of ethanolic extracts of *Alhagi maurorum* was determined against Histamine induced paw edema and the dose of plant extract was 250 and 500 mg/kg. The rats were divided into 4 groups and 6 animals were placed in each group. Group I was considered as a control group and distilled water was given to this group at a dose of 2 ml/kg (p.o). Plant extract was

administered at dose of 250 and 500 mg/kg through oral route to groups II and III, standard drug Indomethacin was given orally to group IV. The dose of Diclofenac was 50 mg/kg for group IV. One hour after the treatment, a sign of inflammation and edema was produced when Histamine administered by injection in right hind paw at dose of (0.1 ml, 1%, w/v in saline). The paw volume was measured at 0min, 1 hour, 2 hours, 3 hours, 4 hours and 5 hours of the administration of phlogistic agent, using the vernier caliper. The percentage inhibition was calculated by the following formula:

$$\% \text{ inhibition} = \frac{(Ct\text{-}Co)\ \text{control} - (Ct\text{-}Co)\ \text{treated}}{(Ct\text{-}Co)\ \text{control}}$$

Where $(C_t - C_0)_{control}$ is the difference in the size of paw at 5 hours in control rat, and $(C_t - C_0)_{treated}$ is the difference in the size of paw at 5 hours in rat treated either with the standard drug or plant extract.(Banerjee *et al*., 2012).

Determination of Antidiabetic activity

Animals used

48 albino rabbits weighing about 1.2-1.5 kg were used in this study. Animal were place in standard temperature (23 ± 12ºC). Grass and green leaves were provided to animals.

Induction of experimental diabetes

Diabetes was induced in animals by injecting alloxan monohydrate at a dose of 150mg/kg of body weight (Akhtar *et al.*, 2002). Blood glucose level was measured after three days in each rabbit. The rabbits having blood glucose level increased from 250mg/dl to 300mg/dl were considered diabetic and were selected for further study (Olajide *et al.*, 1999).

Antidiabetic activity of plant extract in normoglycemic rabbits

In this experiment, antidiabetic activity was determined in rabbits having normal glucose concentration. Animals were divided into four groups and each group contains six rabbits. 20 ml of 2% gum tragacanth was given to group I, which was considered as untreated normal control. Plant extract of *Alhagi maurorum* at a dose of 250mg/kg and 500mg/kg were administered orally to group II and III. Group IV received standard drug Glibenclamide orally (3mg/kg). After the administration of gum tragacanth, plant extract and Glibenclamide blood glucose level were measured in time interval of 0, 1, 2, 4 and 6 hours.

Antidiabetic activity of plant extract in alloxan induced diabetic rabbits

In this experiment, antidiabetic activity was determined in alloxan induced diabetic rabbits. Animals were divided into four groups and each group contains 6 rabbits. 20 ml of 2% gum tragacanth was given to group I which was considered as untreated normal control. Plant extract of *Alhagi maurorum* at a dose of 250mg/kg and 500mg/kg orally was administered to group II and III. Group IV received standard drug Glibenclamide orally (3mg/kg). after the administration of gum tragacanth, plant extract and Glibenclamide blood glucose level were measured in time interval of 0,1, 2, 4 and 6 hours(Rashid *et al*., 2013).

RESULTS

Carrageenan induced paw edema

In carrageenan induced paw edema the methanolic extract of plant *Alhagi maurorum* showed significant anti-inflammatory effects. In 250 mg/kg of plant extract showed significant reduction of paw edema (12.5%) showing a significant effect ($p < 0.05$) and at a dose of 500mg/kg showed a higher percentage inhibition (46.87%) showing a significant effect ($p < 0.05$). The standard drug diclofenac sodium at a dose of 10mg/kg reduce paw edema (90.62%).

Histamine induced paw edema

In histamine induced paw edema the ethanolic extract of plant *Alhagi maurorum* showed significant anti-inflammatory effects. In 250 mg/kg of plant extract showed significant reduction of paw edema (22.41%) showing a significant effect ($p < 0.05$) and at a dose of 500mg/kg showed a higher percentage inhibition (44.82%) showing a significant effect ($p < 0.05$). The standard drug diclofenac sodium at a dose of 10mg/kg reduce paw edema (89.65%).

Effect of plant extract in normoglycemic rabbits

The plant extract of *Alhagi maurorum*in a dose of 250mg/kg produce non-significant reduction in blood glucose level in normoglycemic rabbit ($p > 0.05$). Ethanolic extract of *Alhagi maurorum* at a dose of 500mg/kg decreased blood glucose level significantly ($p < 0.05$). The results have shown that the reduction in blood glucose level of normoglycemic rabbits was dose dependent. When dose was increased to 500mg/kg then glucose level decrease from 105±1.84 to 69±2.25 after 6 hours.

Effect of plant extract in alloxan induced diabetic rabbits

The plant extract of *Alhagi maurorum* in a dose of 250mg/kg produce non-significant reduction in blood glucose level in alloxan induced diabetic rabbits (p >0.05). Ethanolic extract of *Alhagi maurorum* in a dose of 500mg/kg decrease blood glucose level significantly (p <0.05). The result showed that the reduction in blood glucose level of alloxan induced diabetic rabbit's rabbits was dose dependent. When dose was increased to 500mg/kg then glucose level decreases from 273±5.86 to 194.16±9.84 after 6 hour.

Table No. 1: Effect of ethanolic extract of *Alhagi maurorum* against carrageenan induced paw edema in rats

Group	Dose	0hr	1hr	2hr	3hr	4hr	5hr	% age inhibition
Control/normal saline	0.5ml	2.27±0.20	2.57±0.23	3.06±0.28	2.99±0.19	3.06±0.26	3.23±0.23	N/A
Crude plant extract of *Alhagi maurorum*	250mg/kg	2.29±0.22	2.77±0.14	2.95±0.10	3.19±0.14	3.11±0.19	3.13±0.21	12.5%
Crude plant extract of *Alhagi maurorum*	500mg/kg	2.55±0.07	3.36±0.10	3.65±0.14	3.46±0.10	3.16±0.11	3.06±0.15	46.87%
Diclofenac sodium	10mg/kg	2.29±0.01	3.22±0.00	3.33±0.01	3.36±0.01	2.54±0.02	2.38±0.012	90.62%

All values are mean ± SEM; n=5; * = Significant results (P<0.05), ** = highly significant results (P<0.01).

Table No. 2: Effect of ethanolic extract of *Alhagi maurorum* against histamine induced paw edema in rat

Group	Dose	0hr	1hr	2hr	3hr	4hr	5hr	%age inhibition
Control/normal saline	0.5ml	2.46±0.18	2.84±0.22	3.31±0.27	3.29±0.23	3.46±0.25	3.62±0.22	N/A
Crude plant extract of *Alhagi maurorum*	250mg/kg	2.29±0.22	2.84±0.12	3.03±0.09	3.25±0.12	3.18±0.17	3.19±0.20	22.41%
Crude plant extract of *Alhagi maurorum*	500mg/kg	2.54±0.07	3.08±0.18	3.51±0.16	3.68±0.10	3.06±0.14	3.18±0.20	44.82%
Diclofenac sodium	10mg/kg	2.50±0.01	3.27±0.15	3.59±0.13	3.79±0.09	2.76±0.04	2.62±0.03	89.65%

All values are mean ± SEM; n=5; * = Significant results (P<0.05), ** = highly significant results (P<0.01).

Table No. 3: Effect of ethanolic extract of *Alhagi maurorum* in normoglycemic rabbits

Group	**Dose**	**0hr**	**1hr**	**2hr**	4hr	6hr
Control/ 2% gum tragacanth solution	2 ml	98.5.16±3.00	99.5±3.36	91.66±3.90	95.66±3.24	96±2.35
Crude plant extract of *Alhagi maurorum*	250mg/kg	105.66±2.62	1.3.83±3.57	96.16±2.05	93±1.71	90.33±1.02
Crude plant extract of *Alhagi maurorum*	500mg/kg	105±1.84	100.5±2.61	93±2.51	76.5±2.06	69±2.25
Glibenclamide	3mg/kg	103.83±3.45	89.66±2.84	83±1.80	70.83±1.22	60.66±1.05

All values are mean ± SEM; n=5; * = Significant results (P<0.05), ** = highly significant results(P<0.01).

Table No. 4: Effect of ethanolic extract of *Alhagi maurorum* in Alloxan induce diabetic rabbits

Group	**Dose**	**0hr**	**1hr**	**2hr**	**4hr**	**6hr**
Control/ 2% gum tragacanth solution	2 ml	270.16±4.02	271.83±5.10	267.83±4.70	273.16±3.80	276.16±2.10
Crude plant extract of *Alhagi maurorum*	250mg/kg	274.33±4.58	268.66±4.17	260.66±5.43	246±6.36	236.83±6.74
Crude plant extract of *Alhagi maurorum*	500mg/kg	273.66±5.86	243±5.37	226±7.84	206±7.78	194.16±9.84
Glibenclamide	3mg/kg	270.83±5.81	221.83±5.66	157±9.00	123.33±8.80	99±5.96

All values are mean ± SEM; n=5; * = Significant results (P<0.05), ** = highly significant results(P<0.01).

DISCUSSIONS

Anti-inflammatory

The most accurate and authentic method to evaluate the anti-inflammatory activity of anti-inflammatory agents is carrageenan induce paw edema. The inflammation produces by inducing carrageenan is due to release of many inflammatory chemical mediators like histamine, prostaglandin and bradykinin and beside these events the permeability of blood vessel also increased due to release of hydroxytryptamine (Vinegar *et al.*, 1969). Leakage of plasma protein and fluid and migration of white blood cells mostly neutrophils and macrophage produce edema into injured area (Iwalewa *et al.*, 2007). acute inflammation produce by the Carrageenan at the site of injury is due to synthesis of inflammatory chemicals that are responsible for fever and pain and the ethanolic extract of plant *Alhagi maurorum* may inhibit the release of these inflammatory chemicals (Bhalke & Pal, 2012). Carrageenan induces inflammation in two phases. First hour of inflammation is initial phase and during this phase histamine and serotonin is released from damage tissues. Leukotriene, bradykinin, protease prostaglandin and lysozyme release in second phase and many steroidal and non-steroidal drugs anti-inflammatory drugs are useful in second phase of inflammation (Silva *et al.*, 2005). Arachidonic acid produce prostaglandins by the action of cyclooxygenase and there are two type of cyclooxygenase COX-1 and COX-2. Prostaglandin produce by COX-1 is responsible for homeostasis of gastrointestinal track and COX-2 produce prostaglandins that involve in inflammation (Hinz *et al.*, 2000).

When free radical and ROS interacts with lipid bilayer of cell cause lipid peroxidation that finally responsible for oxidative degradation of lipids, resulting in cell damage. Plant extract of *Alhagi maurorum* possess antioxidant and free radical scavenging activity (Neamah, 2012). The oxidative stress due to ROS may produce damages in subcellular level and may cause different types of diseases in human for example cancer, diabetes mellitus, Parkinson disease, neurodegenerative disorders, and atherosclerosis.

It is found after phytochemical test that *Alhagi maurorum* contain many chemical compounds like glycosides, flavonoids, anthraquinone, saponins, alkaloids, steroids and tannins as major constituents (Rahman *et al.*, 2011). Other chemical constituents present in plant extract of *A. maurorum* are hydroxybenzoic acid, coumaric acid, β-sitosterol and cinnamic acid (Ahmad *et al.*, 2009). Flavonoids and Plant polyphenols contain anti-inflammatory properties and these anti-inflammatory properties is due to changing the function of inflammatory enzymes such

as NOS, COX and phospholipase A2, inhibiting free radicals and also interfere in release of pro inflammatory cytokines such as TNF-α and IL-1β (El-Zahar *et al*., 2022).

The result of this study shown that the ethanolic extract of plant Alhagi maurorum has anti-inflammatory activity in carrageenan induced paw edema and histamine induced paw edema. Plant extract deceases edema in both test and anti-inflammatory activity does not depend on dose. When we compare 250mg/kg dose of plant extract with control group in carrageenan induce paw edema the percentage inhibition in a dose of 250mg/kg is 12% and produce significant reduction in paw volume ($P<0.05$). The percentage inhibition in a dose of 500mg/kg is 46% and show significant reduction in paw volume ($P<0.05$). In histamine induce paw edema the percentage inhibition in a dose of 250mg/kg is 22.41% and decrease paw edema significantly ($P<0.05$). However, plant extract reduce inflammation significantly ($P<0.05$) at dose 500mg/kg and decrease paw edema to 44.82%. The anti-inflammatory effect of Ethanolic extract of plant *Alhagi maurorum* may be due to blocking a release of 5HT which are produced by the action of histamine. The vascular permeability increased by the action of histamine as an important inflammatory chemical mediator (Vasudevan *et al.*, 2007).

Antidiabetic activity

Diabetes mellitus is a metabolic disorder in which glucose level increases due to decrease ability of β-cells of pancreas to produce adequate amount of insulin (Rashid *et al.*, 2013). Antidiabetic activity in normal rabbits and alloxan induced diabetes in rabbits have been established in previous studies (Akhtar *et al.*, 2008). In this study we have evaluated the antidiabetic effects of ethanolic extract of plant *Alhagi maurorum.* Diabetes mellitus type 1 is due to inhibition of insulin release from the pancreas (Ke *et al.*, 2009). Ethanolic extract of plant *Alhagi maurorum* has no effect on insulin secretion and nor considered to be effective in regeneration of beta cell of pancreas. The antidiabetic effect of *Alhagi maurorum* may be due to presence of rutin and gallic acid that are essential constituents of this plant. In this regard, Translocation of GLUT4 receptor from the vesicle in cytoplasm into cell membrane and increase absorption of glucose from blood plasma is due to gallic acid. Hypoglycemic effect of *Alhagi maurorum* may be due to phenolic compounds that are essential constituents of this plant (Sheweita *et al.*, 2016). Quercetin is a flavonoid present in *Alhagi maurorum* is responsible for the translocation of GLUT4 and increase absorption of glucose (Dhanya *et al*., 2014). Another important chemical rutin is considered to be effective hypoglycemic agent

that increase insulin dependent kinase activity in which insulin act on its receptor start a signaling pathway and as a result of this event translocation of GLUT4 and uptake of glucose increased (Hsu *et al*., 2014). Concentration of calcium has also increased in skeletal muscle by the action of rutin and calcium may effect in translocation of GLUT 4 that subsequently increase glucose absorption (Kappel *et al*., 2013).

CONCLUSION

Current study was carried out to evaluate the antidiabetic and anti-inflammatory effects of ethanolic extract of plant *Alhagi maurorum.* This study reveals that the ethanolic extract of plant ***Alhagi maurorum*** produced significant anti-inflammatory and anti-diabetic effects and this property may be due to many biochemical substance as an essential active constituent present in the plant however there is a need of further research on active constituent that are responsible to produce antidiabetic and anti-inflammatory effects.

REFERENCES

1. Abu-Shanab, B., ADWAN, G. M., Abu-Safiya, D., Jarrar, N., & Adwan, K. (2005). Antibacterial activities of some plant extracts utilized in popular medicine in Palestine. *Turkish Journal of Biology*, *28*(2-4), 99-102.
2. Ahmad, S., Ahmad, I., Saleem, M., Jabbar, A., Nisar-Ur-Rehman, Saeed-Ul-Hassan, S., Akhtar, K. S., & Choudhary, M. I. (2009). Secondary metabolites from *Alhagi maurorum*. *Journal of The Chemical Society of Pakistan*, *31*(6), 960-963.
3. Akhtar, M., Khan, M., & Malik, M. (2002). Hypoglycaemic activity of *Alpinia galanga* rhizome and its extracts in rabbits. *Fitoterapia*, *73*(7-8), 623-628.
4. Akhtar, M. S., Sajid, S. M., Akhtar, M. S., & Ahmad, M. (2008). Hypoglycaemic effect of *Berberis aristata* roots, aqueous and methanolic extracts in normal and alloxan-diabetic rabbits. *Pharmacologyonline*, *2*, 845-856.
5. Balunas, M. J., & Kinghorn, A. D. (2005). Drug discovery from medicinal plants. *Life sciences*, *78*(5), 431-441.
6. Banerjee, S., Mukherjee, A., & Chatterjee, T. K. (2012). Evaluation of analgesic activities of methanolic extract of medicinal plant *Juniperus communis* Linn. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(5), 547-550.
7. Bhalke, R. D., & Pal, S. C. (2012). Anti-inflammatory and antinociceptive activity of *Pterospermum acerifolium* leaves. *Asian J Pharm Clin Res*, *5*(2), 23-26.
8. Boursinos, L., Karachalios, T., Poultsides, L., & Malizos, K. (2009). Do steroids, conventional non-steroidal anti-inflammatory drugs and selective Cox-2 inhibitors adversely affect fracture healing. *J Musculoskelet Neuronal Interact*, *9*(1), 44-52.
9. Dhanya, R., Arun, K., Syama, H., Nisha, P., Sundaresan, A., Kumar, T. S., & Jayamurthy, P. (2014). Rutin and quercetin enhance glucose uptake in L6 myotubes under oxidative stress induced by tertiary butyl hydrogen peroxide. *Food chemistry*, *158*, 546-554.
10. El-Zahar, H., Menze, E. T., Handoussa, H., Osman, A. K., El-Shazly, M., Mostafa, N. M., & Swilam, N. (2022). UPLC-PDA-MS/MS Profiling and Healing Activity of Polyphenol-Rich Fraction of *Alhagi maurorum* against Oral Ulcer in Rats. *Plants*, *11*(3), 455. https://www.mdpi.com/2223-7747/11/3/455
11. Foster, S. (1992). Medicinal plant conservation and genetic resources: Examples from the temperate Northern hemisphere. WOCMAP I-Medicinal and Aromatic Plants Conference: part 4 of 4 330,

12. García-Alvarado, J. S., Verde-Star, M. J., & Heredia, N. L. (2001). Traditional uses and scientific knowledge of medicinal plants from Mexico and Central America. *Journal of herbs, spices & medicinal plants*, *8*(2-3), 37-89.
13. Giovannini, P., Howes, M.-J. R., & Edwards, S. E. (2016). Medicinal plants used in the traditional management of diabetes and its sequelae in Central America: A review. *Journal of ethnopharmacology*, *184*, 58-71.
14. Grover, J., Yadav, S., & Vats, V. (2002). Medicinal plants of India with anti-diabetic potential. *Journal of ethnopharmacology*, *81*(1), 81-100.
15. Hamilton, A. C. (2004). Medicinal plants, conservation and livelihoods. *Biodiversity & Conservation*, *13*(8), 1477-1517.
16. Hinz, B., Brune, K., & Pahl, A. (2000). Cyclooxygenase-2 expression in lipopolysaccharide-stimulated human monocytes is modulated by cyclic AMP, prostaglandin E2, and nonsteroidal anti-inflammatory drugs. *Biochemical and biophysical research communications*, *278*(3), 790-796.
17. Hsu, C. Y., Shih, H. Y., Chia, Y. C., Lee, C. H., Ashida, H., Lai, Y. K., & Weng, C. F. (2014). Rutin potentiates insulin receptor kinase to enhance insulin-dependent glucose transporter 4 translocation. *Molecular Nutrition & Food Research*, *58*(6), 1168-1176.
18. Iwalewa, E., McGaw, L., Naidoo, V., & Eloff, J. (2007). Inflammation: the foundation of diseases and disorders. A review of phytomedicines of South African origin used to treat pain and inflammatory conditions. *African Journal of Biotechnology*, *6*(25).
19. Kappel, V. D., Zanatta, L., Postal, B. G., & Silva, F. R. M. B. (2013). Rutin potentiates calcium uptake via voltage-dependent calcium channel associated with stimulation of glucose uptake in skeletal muscle. *Archives of biochemistry and biophysics*, *532*(2), 55-60.
20. Ke, Y. D., Delerue, F., Gladbach, A., Götz, J., & Ittner, L. M. (2009). Experimental diabetes mellitus exacerbates tau pathology in a transgenic mouse model of Alzheimer's disease. *PloS one*, *4*(11), e7917.
21. Neamah, N. F. (2012). A pharmacological evaluation of aqueous extract of *Alhagi maurorum*. *Global Journal of Pharmacology*, *6*(1), 41-46.
22. Olajide, O., Awe, S., & Makinde, J. (1999). Purgative effect of the methanol extract of *Morinda lucida*. *Fitoterapia*, *70*(1), 1-4.
23. Parra, S. A., Kalpesh, G., Ashok, D., & Mohammad, I. (2019). Evaluation of anti-inflammatory and analgesic activity of methanolic extract of *Berberis lycium* Royle. *J Med Plants*, *7*, 39-45.
24. Rahati, S., Shahraki, M., Arjomand, G., & Shahraki, T. (2014). Food pattern, lifestyle and diabetes mellitus. *International journal of high risk behaviors & addiction*, *3*(1).
25. Rahman, S. M. A., Abd-Ellatif, S. A., Deraz, S. F., & Khalil, A. A. (2011). Antibacterial activity of some wild medicinal plants collected from western Mediterranean coast, Egypt: Natural alternatives for infectious disease treatment. *African Journal of Biotechnology*, *10*(52), 10733-10743.
26. Rashid, M., Bashir, S., Mushtaq, M. N., Khan, H. U., Malik, M. N. H., Qayyum, A., & ur Rahaman, M. S. (2013). Comparative hypoglycemic activity of different extracts of *Teucrium stocksianum* in diabetic rabbits. ||| *Bangladesh Journal of Pharmacology*, *8*(2), 186-193.
27. Shanab, B., Adwan, G., Abu-Safiya, D., Jarrar, N., & Adwan, K. (2005). Antibacterial activities of some plant extracts utilized in popular medicine in Palestine. *Turkish Journal of Biology*, *28*(2-4), 99-102.
28. Sheweita, S., Mashaly, S., Newairy, A., Abdou, H., & Eweda, S. (2016). Changes in oxidative stress and antioxidant enzyme activities in streptozotocin-induced diabetes mellitus in rats: role of *Alhagi maurorum* extracts. *Oxidative medicine and cellular longevity*, *2016*.
29. Silva, G. N., Martins, F. R., Matheus, M. E., Leitão, S. G., & Fernandes, P. D. (2005). Investigation of anti-inflammatory and antinociceptive activities of *Lantana trifolia*. *Journal of ethnopharmacology*, *100*(3), 254-259.
30. Singh, A. B., Chaturvedi, J., Narender, T., & Srivastava, A. K. (2008). Preliminary studies on the hypoglycemic effect of *Peganum harmala* L. seeds ethanol extract on normal and streptozotocin induced diabetic rats. *Indian Journal of clinical biochemistry*, *23*(4), 391-393.
31. Sosa, S., Balick, M., Arvigo, R., Esposito, R., Pizza, C., Altinier, G., & Tubaro, A. (2002). Screening of the topical anti-inflammatory activity of some Central American plants. *Journal of ethnopharmacology*, *81*(2), 211-215.

32. Srinivasan, K., Muruganandan, S., Lal, J., Chandra, S., Tandan, S., & Prakash, V. R. (2001). Evaluation of anti-inflammatory activity of *Pongamia pinnata* leaves in rats. *Journal of ethnopharmacology*, *78*(2-3), 151-157.

33. Sulaiman, G. M. (2013). Antimicrobial and cytotoxic activities of methanol extract of *Alhagi maurorum*. *African journal of microbiology research*, *7*(16), 1548-1557.

34. Surya, S., Salam, A. D., Tomy, D. V., Carla, B., Kumar, R. A., & Sunil, C. (2014). Diabetes mellitus and medicinal plants-a review. *Asian Pacific Journal of Tropical Disease*, *4*(5), 337-347.

35. Vasudevan, M., Gunnam, K. K., & Parle, M. (2007). Antinociceptive and anti-inflammatory effects of *Thespesia populnea* bark extract. *Journal of ethnopharmacology*, *109*(2), 264-270.

36. Vinegar, R., Schreiber, W., & Hugo, R. (1969). Biphasic development of carrageenin edema in rats. *Journal of pharmacology and experimental therapeutics*, *166*(1), 96-103.

37. Vuksan, V., Stavro, M. P., Sievenpiper, J. L., Beljan-Zdravkovic, U., Leiter, L. A., Josse, R. G., & Xu, Z. (2000). Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. *Diabetes care*, *23*(9), 1221-1226.

38. Yagi, S. M., & Yagi, A. I. (2018). Traditional medicinal plants used for the treatment of diabetes in the Sudan: a review. *African Journal of Pharmacy and Pharmacology*, *12*(3), 27-40.

39. Yanardağ, R., Bolkent, Ş., Tabakoğlu-Oğuz, A., & Özsoy-Saçan, Ö. (2003). Effects of P*etroselinum crispum* extract on pancreatic B cells and blood glucose of streptozotocin-induced diabetic rats. *Biological and Pharmaceutical Bulletin*, *26*(8), 1206-1210.

40. Yaseen, G., Ahmad, M., Zafar, M., Sultana, S., Kayani, S., Cetto, A. A., & Shaheen, S. (2015). Traditional management of diabetes in Pakistan: ethnobotanical investigation from traditional health practitioners. *Journal of ethnopharmacology*, *174*, 91-117.