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Research Article
Interaction Between Myrrh and Glibenclamide on Organ Damage in Diabetic Rats, a Morphological Study

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Abstract

Myrrh (*Commiphora molmol* Engl.) is a medicinal herb widely used in different herbal preparations and is reported to possess several pharmacological effects including antidiabetic action. The present study determines the effect of myrrh, glibenclamide and the effect of co-administration of myrrh with glibenclamide on organ damage due to diabetes in rats. Myrrh was administered at two different doses of 500 and 1000 mg kg^{-1} orally, while glibenclamide was given at a dose of 0.6 mg kg^{-1} orally. Diabetes was induced using alloxan using method for induction of type 2 diabetes in rats. The blood glucose levels were determined to confirm the induction of diabetes and just before sacrificing the animals. All the treatments were given for a period of two weeks after diabetes induction. The animals were sacrificed and the weight of kidney, liver and pancreas were determined. The organs were subjected to histopathological examination. Myrrh at both doses prevented organ damage to varying degrees and augmented the effect of glibenclamide in preventing organ damage. It was concluded that myrrh prevents organ damage in diabetic rats and potentiates the effect of glibenclamide probably due to its antidiabetic and antioxidant effects.

Key words: Myrrh, glibenclamide, alloxan, diabetes, interaction, organ damage, drug-herb, hyperglycemia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Commiphora molmol Engl. (Burseraceae), known commonly as ''myrrh'' or murr (in Arabic) is one of the most common herbs. It is reported to possess several pharmacological activities that include antihypertensive (Al-Howiriny *et al*., 2005), hypolipidemic (Ramesh *et al*., 2012), antiinfective (Shen *et al*., 2012), antiulcer (Al-Harbi *et al*., 1997) and anticancer effects (Gao *et al*., 2015).

Earlier report on the antidiabetic effect of myrrh indicates that it reduces hyperglycemia, hyperinsulinemia and lipid peroxidation and protein oxidation in high-fructose-induced diabetic rats (Ramesh *et al*., 2012). Though several biochemical parameters were determined in the above study, the effect of actual organ damage due to reduction in hyperglycemia and oxidative stress were not determined in the above study. Furthermore, herbal preparations are usually not used alone in chronic diabetic conditions and many patients prefer to consume herbal products with modern medicine to achieve extra effects for reducing diabetic complications.

Herbal preparations are usually not used alone in chronic diabetic conditions and many patients prefer to consume herbal products with modern medicine to achieve extra effects for reducing diabetic complications. There are several reports on the pharmacodynamic interactions between antidiabetic herbs and modern hypoglycemic agents. Some of these reports indicate that combined administration of antidiabetic herbs with oral hypoglycemic agents may produce additive/synergistic effects, while there are few reports that caution the simultaneous use of herbs with oral hypoglycemic drugs. Kamble *et al*. (2016) reported that co-administration of *Gymnema sylvestre* extract with glimepiride produced enhanced antidiabetic effect without significantly altering the pharmacokinetics of glimepiride. Similar observation were made when *Radix astragali* was coadministered with pioglitazone (Yuan *et al*., 2012) and *Memordica charantia* was administered along rosiglitazone (Nivitabishekam *et al*., 2009). Garlic (*Allium sativum*) extract was also reported to enhance the antidiabetic effect of glibenclamide (Poonam *et al*., 2013). However, Koren *et al.* (2015) reported that coadministration of antidiabetic herbs with oral hypoglycemic agents should be avoided or at most precautions should be taken while choosing these combinations due to pharmaceutical complexities.

The present study was carried out to determine the effect of myrrh on organ damage in alloxan induced diabetes in rats and its interaction with glibenclamide, a known oral hypoglycemic agent.

MATERIALS AND METHODS

Materials: *Commiphora molmol* oleo-gum-resin was purchased from local market in Riyadh (Saudi Arabia). It was identified and authenticated by Prof. A. M. Sadabi, College of Applied Medical Sciences, Shaqra University (Saudi Arabia). A suspension of the myrrh was prepared in water by mixing finely powdered myrrh with water without addition of any suspending agent. This suspension was stored in refrigerator at 2-4°C until use.

Preliminary phytochemical analysis: The myrrh suspension was subjected to preliminary phytochemical screening commonly used methods (Finar, 1993; Mukherjee, 2002).

Animals: Male Wistar albino rats weighing between 180-210 g were used. The animals were maintained under standard conditions of 12:12 h light dark cycle at a temperature of 25±2°C. The experimental protocol was approved by the research committee of the institute for its ethical and scientific content.

Alloxan induced diabetes in rats: The method reported by Devaki *et al.* (2011) was followed. Briefly, diabetes was induced single intra peritoneal injection of alloxan monohydrate (150 mg kg^{-1}) in saline. Successful induction of diabetes was confirmed by measurement of blood glucose levels after 72 h and by observation of excess thirst and frequent urination. Animals with fasting blood glucose level of more than 200 mg dL^{-1} were considered as diabetic. One group of animals served as normal and were not given alloxan. The diabetic animals were then divided into six different groups and received the following treatments for two weeks; one group (group 2) served as control and received vehicle while group 3 received glibenclamide (0.6 mg kg^{-1}, p.o.) (Hamzeh *et al*., 2014). The fourth and fifth group rats were treated with myrrh suspension at doses of 500 or 1000 mg kg^{-1} b.wt. The doses were selected from pilot studies. The last two groups received combination of myrrh (500 mg kg^{-1}) with glibenclamide (0.6 mg kg^{-1}, p.o.) and myrrh (1000 mg kg^{-1}) with glibenclamide (0.6 mg kg^{-1}, p.o.), respectively. Blood glucose levels were determined 6 h after the last dose of drugs. The change in blood glucose levels was calculated by subtracting the final serum glucose levels with initial diabetic serum glucose levels. The animals were sacrificed and organs were removed. The weight of kidney, liver, heart and pancreas were determined. The organs were subjected to histopathological studies to determine the damage.

Statistical analysis: Values are expressed as Mean±Standard Error of Mean (SEM). Statistical significance was determined by one-way analysis of variance (ANOVA) followed by Tukey's test for comparison of all parameters. The statistical analysis was done using computer software (Graphpad Instat DATASET 1, ISD, software version 3.0 for Windows). Values of $p<0.05$ were considered to indicate statistical significance.

RESULTS

The phytochemical analysis of the myrrh suspension revealed presence of sesquiterpines (isoprenoids), sterols, steroids, furanose squiterpenes, oxidase enzymes, ethanol soluble resins, tannins, acidic polysaccharides, alcohol-soluble resin, volatile oils, lindestrene and curzerenone.

Administration of alloxan produced diabeties in all the animals to varying degrees. The percentage of diabetic induction was around 57% (animals showing fasting blood glucose of more than 200 mg dL^{-1}). The diabetic animals showed hyperdipsia, hyperphagia and polyuria. Around 33% of diabetic control animals died before the end of two week treatment period. However, diabetic animals treated with myrrh and/or glibenclamide survived till they were sacrificed after two weeks of diabetic induction.

The difference in fasting serum glucose levels (final serum glucose levels at two weeks of treatment-initial diabetic serum glucose levels) in various treatment groups is shown in Table 1. Glibenclamide, as expected produced good antidiabetic effects while both the doses of myrrh showed moderate hypoglycemic effect in diabetic rats. Co-administration of myrrh with glibenclamide was more effective in reducing serum glucose levels. There was no significant difference in the body weight, of animals before induction of diabetes or two weeks after induction of diabetes in any of the treatment groups. However, the normal group of animals and diabetic control animals showed significant increase and decrease in body weight, respectively two weeks after start of the experiment when compared to initial values. The weight of organs; kidney, liver, pancreas and heart in diabetic control animals were significantly more than normal animals. Glibenclamide alone or with either dose of myrrh significantly reduced the liver weight compared to diabetic control animals. Administration of glibenclamide with either dose of myrrh significantly reduced the weight of the kidney compared to diabetic control animals.

All the treatments were effective in preventing nephropathy. Sections of the kidney from diabetic animals revealed hydropic changes in renal tubules and mild glomerulopnephritis, while treatment with either dose of myrrh alone or in combination with glibenclamide prevented this reversible kidney damage (Fig. 1). There was severe damage to islet cells of pancreas in control diabetic animals. The islet cells were restored to varying degrees after treatment with either dose of myrrh alone or in combination with glibenclamide (Fig. 2). Sections of the liver showed that there was no distinct difference between the control diabetic animals and the treatment group on the cytoarchitecture of the liver.

DISCUSSION

In the present study, administration of myrrh attenuated the increased blood glucose levels observed after induction of diabetes with alloxan in rats. The effect was dose dependent and it was augmented by simultaneous co-administration of glibenclamide. The effect of organ damage, a serious complication associated with diabetes was also studied wherein myrrh alone or in combination with prevented kidney damage and also reduced the damage to the islet cells of pancreas.

Table 1: Effect of myrrh and glibenclamide on blood glucose levels and different organ weights

Treatments	Difference in serum glucose level (final-initial diabetic glucose levels)	Body weight (just before induction of diabetes)	Body weight (final, two weeks after diabetes)	Kidney weight (final b.wt. %)	Liver weight (final b.wt. %)	Pancreas (final b.wt. %)
Normal	3.166±4.809	143.21±18.02	193.25±13.59*	0.41±0.032	2.23±0.201	0.096±0.013
Control	41.16±8.159***	156.23±6.78	105.26±13.65*	0.51±0.017*	2.99±0.170*	0.134±0.0062
Glibenclamide (0.6 mg kg^{-1})	8.65±4.58^{+++}	152.56±9.58	140.23±7.89	0.43±0.018	2.10±0.215^{++}	0.101±0.0093
Myrrh (500 mg kg^{-1}, p.o.)	18.50±4.580^{+++}	136.21±12.56	123.06±6.21	0.49±0.024	2.74±0.110	0.110±0.0260
Myrrh (1000 mg kg^{-1}, p.o.)	14.00±2.608^{+++}	162.56±17.54	142.10±12.21	0.49±0.017	2.97±0.098	0.127±0.0630
Myrrh (500 mg kg^{-1}, p.o)+ Glibenclamide (0.6 mg kg^{-1})	6.66±1.757^{+++}	159.41±20.21	147.98±9.87	0.43±0.013^{+}	2.03±0.178^{++}	0.151±0.0780
Myrrh (1000 mg kg^{-1}, p.o.)+ Glibenclamide (0.6 mg kg^{-1})	4.166±3.656$^{+++@@@}$	142.89±12.64	162.62±13.50	0.42±0.012^{+}	1.95±0.135^{++}	0.081±0.0082

All values are Mean±SEM, n = 6, *$p<0.05$, ***$p<0.001$ when compared to normal control. $^{+}p<0.05$, $^{++}p<0.01$, $^{+++}p<0.001$ when compared to control, $^{@@@}p<0.001$ when compared to glibenclamide of same dose alone

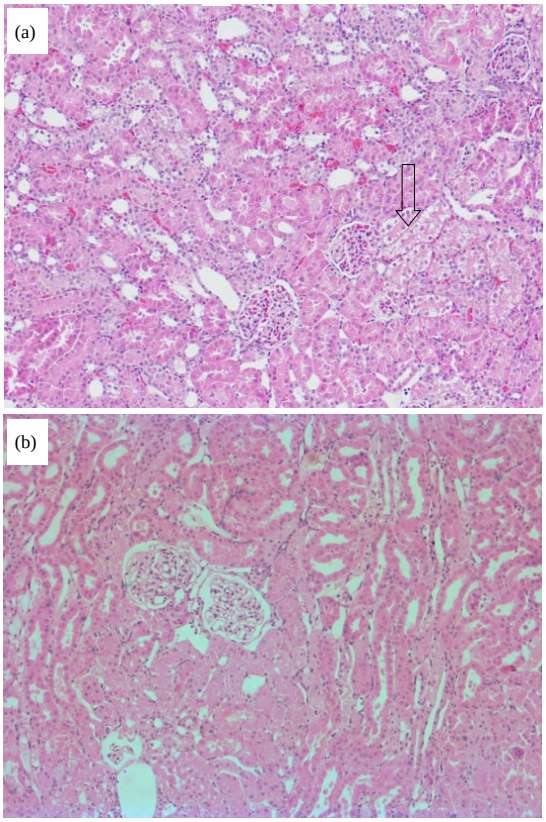

Fig. 1(a-b): Histology of kidney from untreated rat showing (a) Hydropic change in proximnal convoluted tubule and (b) Normal kidney in animals treated with myrrh (500 mg kg^{-1}, p.o.)+glibenclamide (0.6 mg kg^{-1}) (100X)

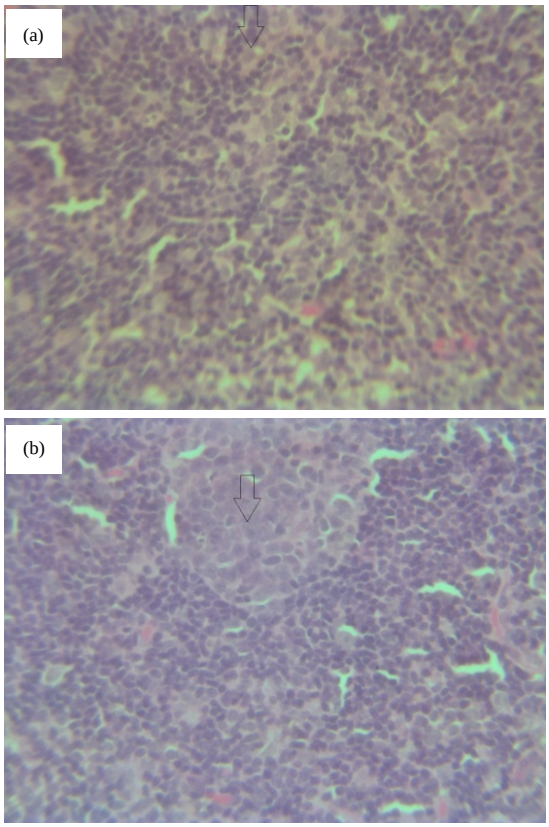

Fig. 2(a-b): Histology of pancreas from untreated rat showing (a) Complete loss of islet cells and (b) Partial loss of pancreas in animals treated with myrrh (500 mg kg^{-1}, p.o.)+glibenclamide (0.6 mg kg^{-1}) (400X)

The use of herbs is progressively growing across the world. Certain herbal supplements can cause potentially dangerous side effects when taken with prescription drugs and the number of cases reported for the emerging herb-drug interactions are already on the rise (Rahal *et al*., 2013). Consumption of myrrh by diabetic patients is a common practice in different parts of world, with the belief that it has a useful hypoglycaemic potential. Perhaps the best-researched use of myrrh is to lower blood sugar levels in diabetic patients.

Glibenclamide belong to sulfonylurea group of oral hypoglycemic agents. It is known to increase insulin secretion from the beta-cells of islet of langerhans (Rendell, 2004). Alloxan is a valuable agent for experimental induction of diabetes in both adult and neonatal rats (Dorner and Plagemann, 1994).

Myrrh is one of the most widely used herbs in the Arabian countries and is commonly known as 'Balsam of Mecca' to show its importance in the Arabian society. As mentioned earlier, myrrh is reported to possess several pharmacological effects such as anti-inflammatory, antipyretic and antihistaminic effects (Shen *et al*., 2012) and hypolipidemic potential (Siddiqui and Mazumder, 2012). Apart from that, the phytochemistry of myrrh has been extensively studied. It is reported to have volatile oils (up to 17%), resins (up to 40%) and gum (up to 60%). The different volatile oils present include terpenes, sesquiterpenes, esters, cinnamaldehyde, cuminaldehyde, cumic alcohol, eugenol, heerabolene, limonene, dipentene, pinene, m-cresol and cadinene were identified. The resins present include commiphoric acids, commiphorinic acid, herrabomyrrhols, heeraboresene, commiferin, ketosteroids, compesterol, fl-sitosterol, cholesterol etc. (Evans *et al*., 2009).

The mechanism of action for antidiabetic effect cannot be explained with the present data. However, earlier reports suggest that myrrh produces its antidiabetic effect through its

antihyperglycemic, hypolipidemic and antioxidant activities (Ramesh and Saralakumari, 2012). Further, the antihyperglycemic effect is reported to be due to presence of furanoses quiterpenes (Ubillas *et al*., 1999). It is known that antioxidants prevent organ damage under several types of stress. Hence, it is assumed that the prevention of nephritic damage by myrrh and attenuation of pancreatic damage could be due to its antioxidant effect. However, the antihyperglycemic have also contributed to less organ damage by reducing blood glucose levels.

Co-administration of high dose of myrrh with glibeclamide augmented the antidiabetic effect. This synergistic effect could be due to mixture of augmented hypoglycemic and antioxidant action of myrrh. The present study reveals that myrrh supplementation with antidiabetic drugs will benefit diabetic patients through augmentation of glibenclamide effect and by reducing organ damage.

The use of herbs is progressively growing across the world. Certain herbal supplements can cause potentially dangerous side effects when taken with prescription drugs and the number of cases reported for the emerging herb–drug interactions are already on the rise. Consumption of myrrh by diabetic patients is a common practice in different parts of world, with the belief that it has a useful hypoglycaemic potential. Perhaps the best-researched use of myrrh is to lower blood sugar levels in diabetic patients.

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As mentioned earlier, administration of an antidiabetic herb with a hypoglycaemic drug for the treatment of diabetes may pose for potential drug-herb interaction that may have beneficial or adverse effects. It is generally believed that the use of herbs wit medicine enhance good effects and reduce the adverse effects of drugs. The results of the present study indicate that combining myrrh with glibenclamide could provide an opportunity to reduce the dose of glibenclamide, which may help in minimizing the adverse effects of glibenclamide as well as achieve enhanced therapeutic effect. At the same time, proper precaution and care should be taken to avoid severe hypoglycaemia that may occur due to combination of these agents. Although, myrrh is considered to be very safe, study on long-term effects of myrrh should be studied before using this combination.

Hence, it is recommend that combine administration of myrrh with oral hypoglycemic agents in clinical practice should be done only after thorough investigation on the pharmacokinetic interactions. It is believed that antidiabetic herbs may interfere with pharmacokinetics of oral hypoglycemic agents (Koren *et al*., 2015). The co administration of herbal antidiabetic drugs with oral hypoglycemic agents is also known severe hypoglycemia that could be fatal (Sobieraj and Freyer, 2010).

CONCLUSION

To conclude, myrrh prevents organ damage in alloxan induced diabetes in rats and co-administration of glibenclamide augments this effect. Further studies on interaction of myrrh with other antidiabetic agents will provide more insight into the mechanism of interaction. Moreover, isolation of constituents of myrrh and evaluation of their antidiabetic potential and interactions may lead to discovery of newer drugs.

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SIGNIFICANT STATEMENT

- Myrrh (*Commiphora molmol* Engl.) is a widely used medicinal herb and possesses several pharmacological effects
- It is known to have hypoglycemic and antidiabetic effects, but its effect on organ damage in diabetes is unknown
- Prevention of organ damage in diabetic patients is known to reduce mortality and it is widely believed that herbal medicines and herbal supplements can help in reducing organ damage
- The results of the present study reveals that myrrh supplementation with antidiabetic drugs will benefit diabetic patients through augmentation of glibenclamide effect and by reducing organ damage

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