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Antidiabetic Effect of Essential Oil from *Artemisia sieberi* Growing in Jordan in Normal and Alloxan Induced Diabetic Rats

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Abstract: The aim of this study was to evaluate the effects of essential oil extracted from aerial parts of *Artemisia sieberi* in normal and alloxan induced diabetic rats. Fifty rats were divided into five groups of 10 each. Group I normal rats received 1 mL day⁻¹ of dimethyl sulfoxide (control); group II normal rats received a single dose (80 mg kg⁻¹ b.wt.) of essential oil extract of *Artemisia sieberi*; group III diabetic rats received 1 mL day⁻¹ of dimethyl sulfoxide; group IV diabetic rats received the oil extract (80 mg kg⁻¹ b.wt.); group V diabetic rats received metformin (14.2 mg kg⁻¹ b.wt.). All treatments were orally administered once a day for six weeks. Changes in blood glucose concentration, body weight and food and water intake were measured and the data obtained were compared with that of metformin. The essential oil extract significantly ($p < 0.05$) lowered blood glucose level as well as food and water intake in diabetic rats accompanied by an increase in body weight gain with no apparent side effect when compared with untreated diabetic rats. These effects were found to be closely similar to that of metformin, a common antidiabetic drug. On other hand, no apparent improvement on body weight gain in diabetic rats treated with metformin. In addition, for all parameters measured, the oil extract showed no effect in normal rats. In conclusion, the essential oil of *Artemisia sieberi* exhibited antidiabetic activity in alloxan-induced diabetic rats. Present findings support the possible use of the essential oil of *Artemisia sieberi* as a remedy for diabetes mellitus in humans.

Key words: Alloxan, antidiabetic, *Artemisia sieberi*, metformin, essential oil

INTRODUCTION

Diabetes Mellitus (DM) is the most common chronic metabolic disorder that is characterized by hyperglycaemia. It may be due to relative or absolute deficiency of insulin action on blood sugar (Atkinson and Maclaren, 1994; King *et al.*, 1998; Hamon *et al.*, 2005). The DM is also considered a major health problem that affects millions of people worldwide. According to the American Diabetes Association, about 15.7 million people in USA (5.9% of the US population) have DM in 2002 and with approximately 5.4 million of these people do not know if they have it (King *et al.*, 1998; Narayan *et al.*, 2003). DM is also considered the third leading cause of disability and death in United State. In Jordan, it is anticipated that the prevalence of type II DM in adults aged 25 years or older will be around 23% in next few years.

Patients with DM need life long treatment with drugs in addition of diet control and exercise (Luna and Feinglos, 2001; Shah *et al.*, 2006). Insulin, metformin, tolbutamide, sulfonylureas and glibenclamide are the most

commonly drugs of choice for treatment of DM in Jordan. Unwanted side effects, such as hypoglycemic episodes nausea, diarrhea, skin rash, respiratory infections, liver damage and headaches and others might occur during consumption of these antidiabetic synthetic drugs (Luna and Feinglos, 2001; Abbasi *et al.*, 2004; Digman *et al.*, 2005; Shah *et al.*, 2006). On other hand, medicinal plant products are considered to be quite safe and usually cause very few side effects when compared with synthetic drugs. In addition, medicinal plants are available and cheaper than synthetic drugs. In this regards, the uses of medicinal plants are recommended by the World Health Organization, particularly for patients in rural regions of poor countries who are unable to purchase the synthetic medications (WHO, 1998). Therefore, extensive research has been directed toward the use of medicinal plants to control DM and its complications.

Data generated from different numbers of aromatic medicinal plant extracts demonstrated multiple beneficial therapeutic values for several metabolic disorders, including DM (Vermis *et al.*, 1995; Sabu and Kuttan, 2002;

Burt, 2004; Bakkali *et al.*, 2008). These studies also revealed the presence of several numbers of bioactive compounds with a wide range of activities, including antioxidants, particularly from essential oils obtained from those aromatic plant species. Antioxidant activity of essential oils was found to be due to the presence of polyphenol and flavonoids compounds and among others. Therefore, essential oils derived from plant extracts have recently attracted considerable attention for being as sources of antioxidant compounds. Moreover, previous and recent evidences strongly support the role of antioxidant compounds derived from plant extracts in the treatment of DM and other diseases in various experimental animal models (Giugliano *et al.*, 1996; Ceriello *et al.*, 1996; Penkofer *et al.*, 2002; Ceriello, 2003; Rahimi *et al.*, 2005; Irshaid and Mansi, 2009a, b). Thus, the efficacy and medicinal properties of essential oil derived from aromatic plants have been recently studied by many investigators.

Essential oils are commonly used in traditional medicine as antiseptic, antimicrobial, virucidal, fungicidal, analgesic, sedative, anti-inflammatory, spasmolytic and anesthesia as well as in food industry as preservative (Zareba *et al.*, 2005; Burt, 2004; Bakkali *et al.*, 2008; Sabu and Kuttan, 2002). Essential oils were first extracted from aromatic plants by steam or hydro-distillation by Arabs. Biochemical analyses showed that essential oils are mixture of a variety of lipid soluble and volatile compounds such as terpenes and terpenoids, phenol-derived aromatic and aliphatic components that are characterized by their strong odor (Zareba *et al.*, 2005; Burt, 2004; Bakkali *et al.*, 2008; Sabu and Kuttan, 2002). These analyses also characterize most of them as antioxidants. Essential oil extracts have also been known to contain at least 100 alkaloid compounds as well as other pharmacologically active compounds. Moreover, their quality and quantity were shown to vary according to method of extraction, climate, soil composition, plant organ, age and vegetative cycle stage.

Furthermore, ethnobotanical studies reported that at least 1,200 species of plants with antihyperglycemic or hypoglycemic activity have been identified as remedies for DM around the world (Marrif *et al.*, 1995; Khalil, 1995; Afif and Irmaileh, 2000; Irshaid and Mansi, 2009a, b). *Artemisia sieberi* (*A. sieberi*) is one of them which grows wild in Jordan and it is commonly known as Sheeh (Khalil *et al.*, 1995; Afif and Irmaileh, 2000; Mansi and Lahham, 2008). This strong aromatic dwarf shrub is becoming very popular in Jordan for the treatment of DM and other ailments (Afif and Irmaileh, 2000; Hudaib and Aburjai, 2006). An antioxidant activity of extract from this plant was previously reported

(Amr, 1995). According to a recent study by Hudaib and Aburjai (2006), forty different compounds have been identified in the essential oils of this plant by GC/MS analyses. These include phenol, alcohol, ketone and monotepenes compounds. Recently, its hypoglycemic activity in aqueous extract has been reported in diabetic animals (Mansi and Lahham, 2008). However, prior to our current study, the effects of essential oil extract obtained from *A. sieberi* have not yet been evaluated in Jordan. Furthermore, there is no report on the antidiabetic activity of essential oil derived from *A. sieberi* in the available literature. Therefore, the present research work was conducted to study the comparative efficacy of essential oil extract from *A. sieberi* and metformin on blood glucose concentration, water intake, food intake and body weight in alloxan induced diabetic rats.

MATERIALS AND METHODS

Plant material: *A. sieberi* was collected in spring 2009 just before flowering from Al-Mafraq district, approximately 68 Km North-East of Amman. The climate in the area of Al-Mafraq is semi-arid with an annual average rainfall of approximately 170 mm with almost no rainfall in the summer. The plant was identified by Professor J. Lahham, taxonomist, at the herbarium of the Department of Biological Sciences, Faculty of Sciences, Yarmouk University, Irbid, Jordan. The voucher specimen (No. AHE-1-007) was deposited in the Department of Biological Sciences, Faculty of Sciences, Al al-Bayt University, Al-Mafraq, Jordan.

Preparation of oil extraction: *A. sieberi* aerial parts (leaves and stems) were cut into small pieces and washed with tap water. The aerial parts were air-dried in the dark room for 7 days. Air-dried parts were then powdered mechanically. The resulting powdered part was subjected to hydrodistillation using a Clevenger-type apparatus for 3 h (Hudaib and Aburjai, 2006). The oil yield was 1.1% (v/w) from aerial parts. After the separation of essential oil, the oil was diluted by dimethyl sulfoxide (DMSO).

Determination of LD50: An acute toxicity study was conducted to estimate the LD50 using different doses of the oil extract of *A. sieberi*. A total of 50 mice weighting between 25-27 g were used in this study. The mice were obtained from the animal house of the Department of Biological Sciences, Faculty of Science, Jordan University, Amman. Mice were left one week to acclimatize to laboratory conditions (25°C temperature, 40% humidity and daily 12 h day-night cycle). Mice were

fed with normal dried feed (Hamoodah Dairy Company, Amman) and water *ad libitum*. Experimental mice were given orally of each required dose (100, 200, 400, 600 and 800 mg/kg/day). Deaths were observed and recorded daily for 30 days. After the LD50 was determined (800 mg kg⁻¹ b.wt.), one dose at 80 mg kg⁻¹ b.wt. (1/10 of LD50) was selected and used in this study. The dose was prepared by dissolving an appropriate amount of this essential oil extract in DMSO to obtain the desired concentration.

Induction of diabetes in rats: Male Wister rats weighing 135 to 150 g were used for this study. All rats were obtained from the animal house of the Jordan University of Science and Technology, Irbid, Jordan. The rats were harbored in stainless steel cages under standard laboratory condition of 12 h light/dark cycle throughout the experimental periods. They had access to normal food (Top Fed, Sapele) and water *ad libitum*. The animals were carefully checked and monitored every day for any sign of toxicity or changes during entire period of experiment. Alloxan monohydrate was purchased from BOH Chemical, LTD (Poole, England) and was dissolved in sterile normal saline (8.5% NaCl). To induce diabetes, the rats were injected intraperitoneally with freshly prepared aqueous solution of alloxan following a 24 h fast in a dose of 150 mg kg⁻¹ b.wt. After measuring fasting blood sugar, diabetic status was determined. Rats with blood glucose of 250 mg dL⁻¹ or more were classified as diabetic rats and were used for the subsequent experiments. Non-diabetic control rats were injected with normal saline (0.5 mL kg⁻¹ b.wt.) instead of alloxan.

Experimental design: Fifty rats were divided into five experimental groups of 10 rats each. Group I consisted of normal rats that received only DMSO (0.5 mL kg⁻¹ b.wt.) and served as control group. Group II consisted of normal rats that received 80 mg kg⁻¹ body weight of *A. sieberi* oil extract. Group III consisted of alloxan-induced diabetic rats that received only DMSO (0.5 mL kg⁻¹ b.wt.). Groups IV consisted of alloxan-induced diabetic rats that received *A. sieberi* oil extract (80 mg kg⁻¹ b.wt.). Group V consisted of alloxan-induced diabetic rats that received metformin (14.2 mg kg⁻¹ b.wt.). Rats were maintained in these treatment regimens for six weeks with free access to food and water *ad libitum*. These experiments complied with the guidelines of our animal ethics committee which was established in accordance with the internationally accepted principles for laboratory animal use and care. Daily measurements of body weight and food and water intake were recorded.

Blood collection and glucose determination: For blood glucose level determination, blood samples were collected from the fasted rats of the five groups prior to the treatment with above schedule and three times per week after oral administration of treatments up to 6 weeks. Blood samples were collected by snipping tail with sharp razor and blood glucose level was then measured immediately by Haemo-Glukotest (20-800R) glucose strips supplied by M/S Boehringer Mannheim India Ltd.

Statistical analysis: The results were expressed as mean±standard deviation. Differences between groups were analyzed with student's t-test analysis. Differences between groups were considered significant at the conventional level of significance (95% confidence limit and probability level of 0.05). The results were taken as significant if p<0.05.

RESULTS

The toxicity effects of essential oil extract derived from *A. sieberi* on experimental animals was tested *in vivo* against mice and thirty days survival was used. *A. sieberi* oil extract was giving orally. Toxicity study in these mice revealed that the half of mice died at concentration of 800 mg kg⁻¹ b.wt. within thirty days after dosing. Thus, the LD50 value for oil extract of *A. sieberi* was 800 mg kg⁻¹ b.wt. The safe dose in mice was established to be 80 mg kg⁻¹ b.wt., 1/10 of the LD50. Moreover, our data also revealed that the normal rats treated with *A. sieberi* essential oil extract (Group II, 80 mg kg⁻¹ b.wt.) experienced no change in behavior and also no signs of toxicities were noticed.

To examine the effect of treatment of *A. sieberi* oil extract on body weight in the alloxan-treated rats, all animals were monitored for gain in body weight. It can be seen that the average body weight gain in treated normal rats (Group II) with *A. sieberi* oil extract was closely similar to the normal group (Control I) over the 6 weeks of experimental period (Table 1). Present study also showed

Table 1: Effect of oral administration of *Artemisia sieberi* essential oil extract (80 mg kg⁻¹ b.wt.) and Metformin (14.2 mg kg⁻¹ b.wt.) for six weeks on body weight gain (g) in alloxan diabetic rats

Group	Treatment	Body weight (g)		Gain in body weight (g)
		Initial	sixth week	
I (normal rats)	DMSO	140±7.2	206±8.8	66
II (normal rats)	Oil extract	141±9.3	203±9.1	64
III (diabetic rats)	DMSO	145±8.6	122±7.5*	-23
IV (diabetic rats)	Oil extract	139±6.5	161±10.6**	22
V (diabetic rats)	Metformin	145±7.7	132±5.2**	-13

Values are the mean values±SD of 10 rats; *Statistically significant when compared to control group (I) at p<0.05; **Statistically significant when compared to untreated diabetic group (III) at p<0.05

Table 2: Effect of oral administration of *Artemisia sieberi* essential oil extract (80 mg kg⁻¹ b.wt.) and metformin (14.2 mg kg⁻¹ b.wt.) for six weeks on water intake (mL day⁻¹) in alloxan diabetic rats

Water intake (mL day ⁻¹)				
Group	First week	Second week	Fourth week	Sixth week
I	24.3±3.1	26.8±7.7	27.5±2.32	31.4±8.3
II	32.4±2.5	29.3±8.4	28.6±3.4	32.2±11.3
III	91.8±15.5*	84.6±11.7*	93.8±12.4*	81.5±9.5*
IV	65.4±14.9**	67.6±12.7**	66.1±8.3**	61.6±12.6**
V	54.8±12.3**	57.5±9.4**	53.4±13.4**	51.5±11.3**

Values are the mean values±SD of 10 rats; *Statistically significant when compared to control group (I) at p<0.05; **Statistically significant when compared to untreated diabetic group (III) at p<0.05

Table 3: Effect of oral administration of *Artemisia sieberi* essential oil extract (80 mg kg⁻¹ b.wt.) and metformin (14.2 mg kg⁻¹ b.wt.) for six weeks on food intake (g day⁻¹) in alloxan diabetic rats

Food intake (g day ⁻¹)				
Group	First week	Second week	Fourth week	Sixth week
I	19.7±4.2	20.3±3.5	22.8±6.3	20.8±6.6
II	24.5±3.4	21.6±4.8	19.9±3.8	21.3±8.7
III	32.5±7.1*	36.3±6.3*	34.6±4.9*	39.2±5.9*
IV	21.1±5.6**	26.2±3.3**	23.7±6.8**	28.9±4.9**
V	24.4±4.3**	22.9±5.2**	27.4±3.7**	26.2±5.2**

Values are the mean values±SD of 10 rats; *Statistically significant when compared to control group (I) at p<0.05; **Statistically significant when compared to untreated diabetic group (III) at p<0.05

that the control rats (Group I) gained weight over the six weeks of experimental period, with the mean body weight increasing by 66 g. Moreover, the untreated diabetic rats (Group II) lost an average of 23 g after six weeks (p<0.05). Treatment with *A. sieberi* oil extract resulted in significant weight gain (Group IV) when compared with that of the untreated diabetic rats (Group III). On other hand, diabetic rats treated with metformin (Group V) showed significant weight loss (p<0.05) when compared with diabetic rats treated with *A. sieberi* (Group IV) or with normal rats treated with *A. sieberi* (Group II).

Present results in Table 2 revealed that water intake in untreated diabetic group (Group III) were significantly higher (p<0.05) than that of the normal rats (Groups I and II). On other hand, there were significant decreases in water intake in diabetic rats treated with *A. sieberi* oil extract (Groups IV) or metformin treated diabetic rats (Group V), as compared to untreated diabetic rats (Group III) during the entire interval of the experiment (p<0.05). By contrast, the average values of water intake of normal rats treated with *A. sieberi* oil extract (Group II) were closely similar to that of control rats (Group I) during the entire period of the study. Similarly, our results in Table 3 revealed that food intake was significantly increased (p<0.05) in untreated diabetic group (III) when compared with other groups (I and II). On other hand, food intake was significant decreased in diabetic rats

Table 4: Effect of oral administration of *Artemisia sieberi* essential oil extract (80 mg kg⁻¹ b.wt.) and metformin (14.2 mg kg⁻¹ b.wt.) for six weeks on blood glucose concentration (mg dL⁻¹) in alloxan diabetic rats

Serum glucose concentration (mg dL ⁻¹)				
Group	First week	Second week	Fourth week	Sixth week
I	95.4±4.81	88.9±3.6	88.7±7.5	94.5±9.6
II	91.3±6.3	86.2±9.6	89.9±8.7	101.7±11.5
III	354.4±21.3*	376.9±27.8*	361.7±30.3*	349.1±28.3*
IV	228.8±24.5**	202.8±24.5**	198.6±24.4**	209.6±29.3**
V	201.6±19.4**	182.7±23.7**	185.1±18.5**	188.1±19.5**

Values are the mean values ± standard deviation of 10 rats; *: Statistically significant when compared to control group (I) at p<0.05; **: Statistically significant when compared to untreated diabetic group (III) at p<0.05

treated with *A. sieberi* oil extract (Groups IV) or metformin treated diabetic rats (Group V), when compared with untreated diabetic rats (Group III) during the entire interval of the experiment (p<0.05). Further, there was little or no effect on the average values of food intake between normal rats treated with *A. sieberi* oil extract (Group II) and control rats (Group I).

The results for the effect of essential oil extract of *A. sieberi* in the mean values of blood glucose levels on normal and diabetic rats are summarized in Table 4. At the beginning of the experiment or at zero time, there were no statistically significant differences in the mean values of blood glucose levels (values range from 88 to 95 mg dL⁻¹) between all experimental groups. After injection of alloxan, the mean values of blood glucose levels in untreated diabetic rats (Group III) were remained above 349 mg dL⁻¹ during the entire period of the study, which were significantly higher than those of the control rats (Group I; about 90 mg dL; p<0.05). Importantly, during the entire period of the study, the rats receiving the essential oil extract (Group IV) had significantly (p<0.05) lower blood glucose level values (mean value: 209 mg dL⁻¹) than those of the untreated diabetic rats (Group III; 349 mg dL⁻¹). Nonetheless, these reductions in blood glucose level values in group III were remained to be significantly (p<0.05) higher than those of the control rats (Group I, mean value: 91 mg dL⁻¹). Further, our results indicated that no notable differences were observed between the two mean values of blood glucose levels for normal rats treated with oil extract (Group II) and control rats (Group I) during the entire period of the experiment. Similarly, our results also showed that the mean values of blood glucose levels (209 mg dL⁻¹) in diabetic rats treated with *A. sieberi* oil extract (Group II) were closely similar to those achieved in diabetic rats treated with metformin (Group V, 189 mg dL⁻¹), a synthetic oral hypoglycemic agent.

DISCUSSION

A. sieberi is a well known traditional medicinal plant that can be used for treatment of DM and other ailments

in Jordan (Afif and Irmaileh, 2000; Mansi and Lahham, 2008). In this study, we attempted to examine the potential antidiabetic effect of essential oil obtained from *A. sieberi* in experimentally induced diabetic rats, since there are limited studies on this issue. According to our results, the LD50 was estimated to be about 800 mg kg⁻¹ b.wt. A dose of 1/10 of the LD50 (80 mg kg⁻¹ b.wt.) was used to investigate the potential antidiabetic effect of this extract in alloxan diabetic rats. Present results revealed that no sign of toxicity or death were seen either immediately or during interval of the treatment period in both normal and diabetic rats after repeated oral administration of dose of 80 mg kg⁻¹ b.wt. of oil extract of *A. sieberi* for 6 weeks.

Injection of alloxan in rats cause significantly increased in blood glucose level. This finding is in consistent with and further supported by previous studies which reported that the diabetogenic action of alloxan is mediated by the formation of reactive oxygen species (Szkudelski, 2001). The action of these free radicals can induce rapid death of beta-cells of pancreas, resulting in partial or complete loss of insulin synthesis and leading to the development of hyperglycemia and its complications. This is also in consistent with the fact that blood glucose level might have increased due to gluconeogenesis in the absence of insulin (Sherwin and Sacca, 1984; Yao *et al.*, 2006). On other hand, our current study revealed for the first time that chronic oral administration of *A. sieberi* oil extract at 80 mg kg⁻¹ b.wt. exhibited a significant reduction in blood glucose level in alloxan-induced diabetic rats in comparable to metformin, a common hypoglycemia drug. In addition, no effects were observed in mean values of blood glucose levels in normal rats treated with this plant oil extract. Thus, our results support the traditional belief that *A. sieberi* extract could improve diabetic conditions by lowering blood glucose level. In addition, we can conclude that essential oil extract of *A. sieberi* is safe and as effective as metformin.

Furthermore, our current study also showed that injection of rats with alloxan compound lead to reduction of mean value of body weight accompanied by an increase in the mean values of food and water intake. These results further support the fact that the most classic symptoms for people with diabetes are thirst, frequent urination, fatigue, weight loss (Atkinson and Maclaren, 1994; Hannon *et al.*, 2005). Poor or defect of glucose utilization can also lead to weight loss and sense of fatigue despite of normal or even increased of food intake. In addition, body weight loss and fatigue can also result due to loss of fluid. To compensate for loss of body weight and fluid, the animals should increase food and

water intake as a consequence to such changes. On other hand, our data also revealed that treatment of diabetic rats with the oil extract of *A. sieberi* appears to have positive effects on body weight gain as well as in reduction of both food and water intake. These improvements might be explained by the partial reduction in blood glucose levels in alloxan induced diabetic rats. By contrast, our results showed that rats treated with metformin exhibited low body weight gain compared to rats treated with *A. sieberi* oil extract. This finding is also in complete accordance with previous studies which reported that metformin exerts its effects in diabetic patients by decreased glucose production, increased fatty acid oxidation in hepatocytes and increased glucose uptake in skeletal muscle (Mithieux *et al.*, 2002; Cheng *et al.*, 2006). Taken together, these findings allow us to suggest that the essential oil extract of *A. sieberi* reduce blood glucose level through mechanisms that might be completely different from that described for metformin.

Moreover, the active principles in the *A. sieberi* oil extract, which may be responsible for or contribute to the observed antidiabetic effect, are unknown in our study. Therefore, the precise mechanism of action of essential oil extract of *A. sieberi* in normalization of glucose level among diabetic rats is not yet understood. Nonetheless, these studies allow us to speculate that the oil extract of *A. sieberi* might contains bioactive compounds with antioxidant activities which might reverse the toxic action of alloxan and thus stimulate the regeneration of new beta pancreatic cells or enhancing the repairing process of partially damaged beta pancreatic cells which are responsible for synthesis of insulin. However, there is no support in data for these claims. It is important to mention that antioxidant compounds, either naturally or synthetic, could provide protective effects against various disease including DM (Giugliano *et al.*, 1996; Ceriello *et al.*, 1996; Penckofer *et al.*, 2002; Ceriello, 2003; Rahimi *et al.*, 2005; Batubara *et al.*, 2010). Antioxidant compounds are also known to exhibit their biological activity through scavenging of free radicals. Moreover, many phytochemical studies done by different group of investigators indicated that flavonoids, polyphenols and monoterpenoids are the major constituents of the *Artemisia* essential oil; these compounds have been shown to exert a potent antioxidant activity (Marrif *et al.*, 1995; Sabu and Kuttan, 2002; Zareba *et al.*, 2005, Vermin *et al.*, 1995; Hudaib and Aburjai, 2006; Bakkali *et al.*, 2008; Mohamed *et al.*, 2010). These studies revealed that there are a wide range of variations in antioxidant compositions in term of quantity or quality among these species. These studies also suggest a beneficial role of *Artemisia* species in treating

obesity, hyperglycemia, hypertriglyceridemia, hypercholesterolemia and particularly oxidative stress. It has also been reported that plant extracts produce significant antihyperglycemic effects in diabetic rats via various mechanisms, including but not limited to increasing glucose uptake by the peripheral tissues, or by improving secretion of insulin and among others (Marrif *et al.*, 1995; Sabu and Kuttan, 2002; Zareba *et al.*, 2005; Irshaid and Mansi, 2009a, b). Therefore, additional study will be required to characterize the details of the mechanism(s) by which essential oil extract of *A. sieberi* might normalize the glucose level in alloxan induced diabetic rats.

Interestingly, our results demonstrated for the first time that oil extract of *A. sieberi* at dose of 80 mg kg⁻¹ b.wt. is important as metformin because this extract showed a significant reduction of the blood glucose level in alloxan induced diabetes. Further, we also found that at the doses used, the oil extract was less potent than metformin in decreasing blood glucose level. However, it may be recognized that the oil extract of *A. sieberi* is a crude mixture of some active compounds of unknown concentrations and it is possible that some of the active compounds in the pure form would be more potent than metformin. It is also worth mentioning that the usefulness of metformin drug in the treatment of diabetic patients may be affected by its some side effects (Mithieux *et al.*, 2002; Abbasi *et al.*, 2004; Cheng *et al.*, 2006; Yao *et al.*, 2006). The first sign of toxicity of metformin in diabetic patients may be a cardiovascular system depression. In contrast, our study reported that normal or diabetic rats treated with *A. sieberi* did not develop any sign of toxicity or change in behavior either immediately or during the post-treatment period at the therapeutic dose. Taken together, our results lead us to suggest that this dose also seems to be safe as compared to metformin.

Furthermore, it is too early to establish a pharmacological and toxicological profile for the oil extract of *A. sieberi* for both mice and humans. This is because there is no enough information regarding the repeated dose toxicity of oil extract of *A. sieberi* or its constituents in mice or related species. In addition, it is worth to mention that natural products are not always necessarily safe and dosages can be important. Also the doses of *A. sieberi* oil extract used in the present work were relatively quite low compared to doses used by other investigators for closely related species (Marrif *et al.*, 1995; Sabu and Kuttan, 2002; Zareba *et al.*, 2005; Bakkali *et al.*, 2008). At this time, there is not enough scientific information to determine an appropriate range of doses for *A. sieberi* in diabetic human or to know if this oil extract of *A. sieberi* is safe, particularly for human. It is

also important to mention that antidiabetic drugs might interact with *A. sieberi* and thus, taking this plant extract along with antidiabetic drugs might cause severe reduction in your blood glucose level. Moreover, it has also been reported that some people who take *A. sieberi* experience decreased in both blood pressure and heart rate.

CONCLUSIONS

In conclusion, current data indicated for the first time that oral administration of *A. sieberi* oil extract at 80 mg kg⁻¹ b.wt. exhibited a significant reduction in blood glucose levels as well as in food and water intake accompanied by significant improvement in body weight gain in alloxan-induced diabetic rats in comparable to metformin, a common hypoglycemia drug. We suggest that these positive effects are probably due to the presence of bioactive agents with antidiabetic activity causing in an increase in glucose utilization and metabolism by unknown mechanism(s). Therefore, additional studies are underway to investigate the mechanism(s) by which essential oil of *A. sieberi* might normalize the blood glucose levels and the potential effects of this oil extract of *A. sieberi* on functions of some rat organs of normal and diabetic rats.

Moreover, our data revealed that efficacy of essential oil extract of *A. sieberi* is a closely similar to that of metformin. No visible sign of toxicity or death were also seen either immediately or during interval of the treatment period in both normal and diabetic rats after repeated oral administration of dose of 80 mg kg⁻¹ b.wt. of this extract, indicating that this extract is safe. In addition, our data support the traditional belief that *A. sieberi* aerial parts possessed antidiabetic effects and the plant might be used to improve diabetic conditions in both animals and humans.

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