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Evaluation of *Kelussia odoratissima* Mozaff. extract on serum biochemical parameters and hepatica enzymes in the Persian Shepherd dogs

Ardalan Moieni[1], SaamTorkan[*2], Fatemeh Malekpoor[3]

[1]*Graduated From the Veterinary Medicine, Faculty of veterinary medicine, Islamic Azad university of Shahrekord, Shahrekord, Iran;*

[2]*Department of Clinical Science, Faculty of veterinary medicine, Islamic Azad university of Shahrekord, Shahrekord, Iran;*

***Email:** saamtorkan@gmail.com

[3]*Department of Medical Plants,Research Center of Medicinal Plants & Ethno-veterinary, Islamic Azad university of Shahrekord, Shahrekord, Iran;*

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ABSTRACT

Background & Aim: Nowadays**,** attention has increasingly been directed toward the treatment of animal's disease using medicinal herbs. This research was conducted to evaluate the impact of *Kelussia odoratissima* Mozaff extract on dog serum biochemical parameters and hepatica enzymes over time.

Experimental: 32 adult dogs were randomly assigned to four groups. The first (control) group did not receive any pharmaceutical compound. The second group received 150 mg/kg of hydro-alcoholic extract of *k.odoratissima*. The third and the forth groups received 300 and 450 mg/kg of the extract, respectively. Finally, the blood samples were collected on days 0, 5, 10, and 15 for serum biochemical parameters analysis including the level of blood sugar, cholesterol, triglyceride, LDL and HDL, alanine aminotransferase, aspartate aminotransferases, and alkaline phosphatase.

Results: Comparing to the control group, the levels of fast blood sugar, low density lipoprotein, high density lipoprotein, trigliceride, cholesterol, Alanin aminotransferase and aspartate aminotransferase in treated groups were significantly different over time and at various doses of the extract ($P<0.05$). However, the level of Alkaline-phosphatase (ALP) factor did not change throughout this study ($P>0.05$).

Recommended applications/industries: Considering the results of this study, anti-diabetic, anti-atherosclerotic and antioxidant effects of *Kelussia odoratissima* can be concluded. Then, the possibility of employing *K. odoratissima* extract in drugs for the treatment of mentioned diseases can be suggested.

1. Introduction

Recently, natural compounds have received much attention in the treatment of chronic metabolic disorders like dyslipidemia and diabetes mellitus. Experimental and epidemiological investigations comprehensively indicated that herbal medicines have chemoprotective effects on chronic illnesses. Vegetables and fruits as sources of bioactive components have antidiabetic, antioxidant, anti-inflammatory, and anticancer features so that they have beneficial effects onbody health (Shahreza, 2017).

It was demonstrated that high amounts of fat in the blood can harden the arteries, or quicken the atherosclerosis process which is being one of the five firsts causes of death in the world. Some remarkable evidences including the manner of the metabolism, the role of amount and kind of plasma fats, particularly lipoproteins in provoking and exacerbating the cardiovascular disease indicate that a decrease in LDL level through controlling the diet or using lipid-lowering agents, such as stains, can reduce the probability of encountering to cardiovascular disease (Kooti *et al.*, 2014).

Since the medicines available for the treatment of dyslipidemia, as well as chemical synthetic lipid-lowering medicines, are not completely safe and without side effects (Kafeshani *et al.*, 2017), scientists are always trying to find traditional herbal substitutions with lower toxicity (Palsamy and Subramanian, 2009; Tashakori-Sabzevar *et al.*, 2016).

For a very long period, medicinal herbs were traditionally and particularly used in Eastern countries toheal numerous health problems such as diabetes, cardiovascular problems, liver diseases, hypertension, and cancer.

According to the study of Kim *et al*., (2007), almost 50% of people in USA and about 33%in Australia prefer to use herbal medicines duo to fewer side effects and anti-diabetic properties. In traditional medicine, diabetics were provided with numerous plants such as *Garlic, Cayenne Pepper*,*Crataegus*and*Kelussia* (Jurikova *et al*., 2012; Soleymanifard *et al*., 2014; Moghadam *et al*., 2013; Renault *et al*., 2003). Among them *Kelussia* species (*Apium graveolens*) showed some positive synergistic effects on diabetes and hypertension treatment and the plant seeds had no toxicologically significant effects (Broadhurst *et al*., 2000). *Kelussia odoratissima* Mozaff. is a type of well-known indigenous Iranian herb and a medicinal fodder plant commonly found in grazing lands of Iran. This plant is perennial and very aromatic with cylindrical stalks and 120 to 200 cm height. Its leaves are large and have base, its inflorescence is big, and its terminal umbel is completely fertile. It is from Apiaceae family and called *Keluss* in Persian. This plant grows in the highlands and snowfall areas of the central Zagros having at least 2500 meters height above sea level and an annual precipitation of about 400 mm, which is often in the form of snow. Mountainous elevations of the three areas of Kouhrang, Bazoft and Doab Smsami in Chaharmahal and Bakhtiari province are of main natural habitats of this plant. Traditional medicine enumerates the anti-inflammatory, analgesic, rheumatism healing, and blood refining properties for its aboveground organs. The seeds and roots can be boiled and used to treat common cold and severe coughs (Pirbalouti, 2009). The anti-inflammatory, analgesic, anxiolytic, and anti-soporific effects of its essence and extract has been proved by many studies and investigations. Also, anti-allergic, blood vessel protection, antithrombotic, gastrointestinal preservation, anti-diabetic, anti-lipid-peroxidase, and anti-cancer effects have been reported in some other studies (Shakerian *et al*., 2009). Analysis of the plant essential oil revealed differences in the content of active compounds depending on region of sample collection. The main constituents of the essential oils were 3-n butyl phtalide (34.1 to 45.6%), Neophyadiene (42.2 to 68.2%), 3-tetradeceneylacetate (1.1-5.2%), butylidenephthalide (1.1 to 9.2%), hexadecanoic (1.1 to 5.3%), and 6-butyl-1.4-cycloheptadin (1.1 to 6.1%) (Pirbalouti, 2009; Rabbani *et al*., 2011; Shakerian *et al*., 2009).

With regard to the lack of relevant studies on the hypoglycemic-hypolipidemic effects of *K.odoratissima* and general changes in serum biochemical factors resulting from the use of its extract in the animal sort of samples like dogs; the present study conducted to investigate the effects of *K.odoratissima* on the parameters related to serum lipids profile and hepatical enzymes in dogs.

2. Materials and Methods

2.1. Plant collection

Plant organs including leaves and stalks of *Kelussia odoratissima* were collected from the Koohrang mountainous area in Chaharmahal va Bakhtiari province, Iran. The accessions of plants were transferred from natural habitats at the early growing stage on 15 April to 5 May 2017. The identification and authentication of the plant were carried out at the Research Center of Medicinal Plants of Islamic Azad University, Shahrekord branch, and the Voucher Specimen Number was SHK 2611. The samples were dried for a week under shaded and ventilated conditions and then powdered by a grinder.

2.2. Extract preparation

The aerial parts of the plant were shade dried and ground into a powder (100 g), macerated in 200 ml of ethanol 70% and filtered and then were dried at 35°C under rotary vacuum evaporator (Model Zirbus 302w, Italy). The extract samples were stored in universal bottles and refrigerated at 4°C prior to use.

2.3. Animals

In the present study, 32 adult male dogs from the Persian Shepherd breed with a weight range of 25-30 kg were used. During the experiment, the dogs were kept in separate cages under standard conditions at 25-30°C and in the 12-hour light-darkness cycle, so that they could easily access to water and food. The dogs were fed with fixed diet (cooked chicken, i.e. chicken heads and paws) for 1 month. Also, they were given anti-parasitic medications of Mebendazole and Praziquantel (based on recommended dosage) since two weeks before starting the experiment to remove any digestive parasitic disease. They have also been cleansed of skin parasites through injection of Ivermectin hypodermic and anti-parasitic shampoo. Then, their health was carefully examined before start of the study. All of their vital signs, such as heart rate, respiratory rate, body temperature, and blood pressure, were checked and recorded. All of the dogs were examined at least twice a day and were kept in separate cages; the place was rinsed every day; its floor and the cages were disinfected once every 4 days and all of the reports were recorded. Finally, once every 24 h, and for 15 days, the animals were fed with a specified dose of the obtained extract (Vahid Dastjerdi *et al.*, 2017). This study was carried out in Veterinary Hospital of Islamic Azad university, Shahrekord branch, located in Kian city, Iran (Mosallanejad *et al.*, 2018). Animals were fed every day at 9 A.M and after one hour they were given the specified dosage of the extract. Dogs were randomly divided into four groups of eight members as follow:

- The first group was a control group that did not receive anything other than water and food.
- The second group received 150 mg/kg of hydro-alcoholic extract of *k.odoratissima*.
- The third group received 300 mg/kg of hydro-alcoholic extract of *k.odoratissim.*
- The fourth group received 450 mg/kg of hydro-alcoholic extract of *k.odoratissima*.

2.4. Sampling and tests

Blood vessels of hand (Cephalic veins) were used to draw blood in this manner: the dogs were restrained; hairs covering the target place were shaved; then it was disinfected with alcohol; and bloodletting was performed gently. Collecting blood specimens was carried out for each dog individually four times on 1^{st}, 5^{th}, 10^{th}, 15^{th} days during the research by syringes. Afterwards, the specimens were transferred to the separate and marked test tubes and immediately transferred to the Specialty Laboratory of Clinical Pathology inside Ayatollah Kashani Hospital in Shahrekord, Iran.

Later, the intended factors of FBS, Cholesterol (CHOL), Triglyceride (TGL), Low density lipoprotein (LDL), High density lipoprotein (HDL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Alkaline-phosphatase (ALP) were measured by enzymatic and photometric methods in the laboratory equipped with Spectrophotometric kits of Pars Azmoon Co. and Eco-Plast Auto Analyzer machine (2006GD100139, Italy).

2.5. Statistical analysis

The collected data were analyzed using SPSS (version 22; SPSS Inc., Chicago, Ill., USA). Data were shown as Mean ± SD. Two way of ANOVA was used to assess the main role of time, group, and time × group interactions. In addition, the LSD post hoc test was used to compare all pairs of groups. The results were considered significant at p-values<0.05.

3. Results and discussion

The effects of *Kelussia* extract on reducing the level of blood sugar, lipid and liver enzymes have been approved by several previous studies (Momtazi*et al.*, 2017). Therefore, in present study, the effects of *k.*odoratissima on the biochemical factors of fast blood sugar (FBS), cholesterol (CHOL), triglyceride (TGL), low density lipoprotein (LDL), high density lipoprotein (HDL), alanine aminotransferase (ALT), alkaline-phosphatase (ALP), and aspartate aminotransferase (AST) in the blood serum of the animals were evaluated.

3.1. Fast blood sugar (FBS)

Comparing the FBS levels of the four groups indicated that there was no significant difference among the groups before intervention and at 5th day after intervention (P>0.05). However, on the 15th day, the average levels of FBS in the dogs receiving the *Kelussia* extract were significantly lower than the control group (P<0.01), but there was no significant difference (P>0.05) between groups 3 and 4 (receiving 300 mg and 450 mg extract, respectively).

On the other hand, data analysis showed that time, group, and interaction of time × group had a significant effect on FBS changes (P_{time}<0.001, P_{group}= 0.014, $P_{time \times group}$=0.044). Over a 15 day trial period, significant decreases were observed in the levels of dogs' blood sugar. Furthermore, the extract had a significant effect on the blood sugar reduction, with a noticeable decreases on the 15th day in the groups 3 and 4 which receiving 300 mg and 450 mg of *Kelussia* extract (Table 1).

Yusni *et al.*, (2018) investigated the effects of *Kelussia* leaf extract (*Apium graveolens* L.) in treatment of blood glucose and insulin levels in elderly pre-diabetics. They pointed out that *Apium graveolens* extract significantly decreased FBS level comparing to control group. They attributed the FBS reduction effects of *Kelussia* to the compounds like the flavonoids apigenin, luteolin, phenolics, and apigenin which inhibits the aldose reductase enzyme. It is the main enzyme in the polyol pathway (sorbitol-aldose-reductase pathway), a process that converts blood glucose to sorbitol. Increased levels of sorbitol in diabetic patients will cause complications such as cataracts, neuropathy, and retinopathy.

Table 1: Comparison of the average levels of FBS of the four studied groups at three times

Variables	Time	Control	*Kelussia odoratissima* extract			P1	P2	P3
			150mg	300mg	450mg			
FBS mg/dl	Baseline	87.75±4.43[a]	92.25±6.24[a]	87.00±2.16[a]	89.50±4.79[a]	<0.001	0.014	0.044
	5 days	86.25±4.79[a]	89.25±5.92[a]	85.00±1.82[a]	83.75±4.64[a]			
	10 days	84.75±2.36[a]	85.75±4.03[a]	80.75±6.50[ab]	79.00±6.48[b]			
	15 days	84.25±4.34[a]	80.50±1.00[b]	73.00±8.04[c]	71.75±3.86[c]			

The similar letters in each row indicate lack of difference and non-similar letters indicate a significant difference.
P1: time, P2: group, P3: time × group interaction.

3.2. Lipid profiles

Hyperlipidemic is defined as the increasing of lipid concentration (triglyceride or cholesterol) in blood. Hypertriglyseridmi (i.e. increased blood triglyceride concentration over 200 mg/dsl) is cause of lipemi. Hyperlipidemi in dogs is divided into rudimentary and secondary; the latter is more general in dogs (Xenoulis and Steiner, 2010).

In the present study, the evaluation of lipid profiles i.e. LDL, HDL, TG, and TCH among the four groups showed that, in general, all of the lipid parameters were not significantly different (P>0.05) at the beginning of the study. Besides, the average levels of LDL and HDL did not show any significant difference (P>0.05) among the four groups until the fifth and tenth day, respectively. But at day15, treated groups with 450, 300 mg of extract showed the lowest LDL values of 37.75 and 36.50, respectively, and the highest HDL values of 200.50 and 208, respectively (P<0.05). On the other hand, the results of two way of ANOVA showed that time, group, and interaction of time × group had a significant effect on changes in LDL and HDL levels (P<0.05, Table 2). Also, Triglyceride (TG) and total cholesterol (TCH) level of the three groups under intervention had a significant difference with the control group since 5th day (P<0.05). On the 15thday, even though the average levels of these two factors were not significantly different among third and fourth groups, they were notably different from the first (150 mg/kg extract) and the control groups (P<0.05). The results indicated that time, group and interaction of time × group had a significant effect on TCH and TG levels (P <0.05, Table 2).

In a similar study by Rafieian *et al.*, (2011), the effect of *k.odoratissima* powder on blood lipids of patients was compared with the Lovastatin. Patients were randomly divided into two groups: control group received Lovastatin (40 mg per day) and the second group received Lovastatin (40 mg per day) plus 2 grams of *k.odoratissima* powder. Blood specimens were taken from both groups on first, 14th and 30th days, and the blood lipid parameters were measured.

The results represented a significant decrease of cholesterol, triglyceride, LDL and VLDL levels in both groups (P <0.05). On the other hand, the amount of HDL increased in the treated group; LDL / HDL ratio decreased in both groups (P <0.001) and no changes in blood sugar (FBS) were observed among them. Eventually, they mentioned the positive effects of consuming this herb beside Lovastatin (Rafieian-Kopaei *et al.*, 2009).

Table 2: Comparison of the average level of lipid profile of the studied groups at three times

Variables	Time	Control	*Kelussia odoratissima* extract			P1	P2	P3
			150mg	300mg	450mg			
LDL (mg/dl)	Baseline	53.50±2.52[a]	52.50±5.92[a]	55.00±4.16[a]	53.25±2.99[a]	<0.001	0.138	<0.001
	5 days	51.75±3.50[a]	51.75±4.72[a]	53.25±4.27[a]	50.25±1.89[a]			
	10 days	51.50±3.11[a]	44.75±4.50[b]	44.75±3.69[b]	44.00±4.55[b]			
	15 days	48.75±2.63[a]	44.00±4.08[b]	37.75±1.71[c]	36.50±1.73[c]			
HDL mg/dl	Baseline	175.00±7.87[a]	171.25±11.95[a]	173.00±8.45[a]	170.25±6.95[a]	<0.001	0.377	0.002
	5 days	175.50±7.42[a]	177.00±8.12[a]	174.50±7.94[a]	179.25±9.78[a]			
	10 days	174.25±9.95[a]	182.00±5.59[a]	188.25±10.91[a]	187.50±14.01[a]			
	15 days	177.25±11.87[c]	189.25±6.50[b]	200.50±13.8[ab]	208.00±13.74[a]			
TG mg/dl	Baseline	121.50±2.89[a]	107.50±17.08[a]	126.00±1.83[a]	107.25±26.27[a]	<0.001	<0.001	<0.001
	5 days	124.50±4.20[a]	94.75±7.09[b]	91.50±6.76[b]	89.00±12.46[b]			
	10 days	121.00±2.94[a]	93.50±9.26[b]	71.25±8.54[c]	69.00±15.81[c]			
	15 days	124.25±2.22[a]	90.75±8.85[b]	63.00±8.12[c]	59.75±12.58[c]			
Total Cholesterol mg/dl	Baseline	220.50±14.98[a]	229.75±4.11[a]	217.25±2.50[a]	223.25±2.50[a]	<0.001	<0.001	<0.001
	5 days	211.25±8.54[b]	221.00±6.98[a]	218.00±4.69[a]	220.50±2.38[a]			
	10 days	203.00±8.52[b]	218.25±6.29[a]	216.50±5.00[a]	214.25±3.30[a]			
	15 days	210.50±4.20[a]	212.75±4.57[a]	206.75±7.93[b]	200.00±2.16[b]			

(a, b, c) The similar letters in each row indicate lack of difference and non-similar letters indicate a significant difference.
P1: time main effect, P2: group main effect, P3: interaction time × group

Shahrani *et al.*, (2009) investigated the effects of *k.odoratissima* extract and olive oil on blood lipid profile (triglyceride, LDL, HDL, VLDL) and FBS factors of 70 mice. The results indicated that, after 2 weeks, the extract of *k.odoratissima* effectively reduced plasma lipoprotein and blood sugar levels in the group that received 10% of *k.odoratissima* extract (P <0.05). In the group receiving 20% of the extract, a significant decrease was observed only in cholesterol, LDL, and HDL levels (Shahrani et al., 2009).

The hypolipidemic effect of the extract of celery seed on 40 adult male albino mice was studied by Mansi *et al.*, (2009). They reported that using the extract of the plant seed significantly reduced the serum total cholesterol, TGL, and LDL levels while significantly increasing HDL in the treated groups. Therefore, the results of this study showed that oral consumption of celery would probably improve the blood lipid parameters (Mansi *et al.*, 2009).

A number of previous studies have also noted the effect of celery in controlling hyperglycemia and hyperlipidemia in rats (Tashakori-Sabzevar *et al.*, 2016; Kooti *et al.*, 2014).

Different studies have shown that *k.odoratissima* flavonoids mainly contain 3, 4, 7-trihydroxyflavone, caffeic acid, and phthalide. Since mentioned flavonoids are all in form of aglycone, they have fast intestinal absorption due to the specific structure. Therefore, decrease in the blood lipid was expected after *k.odoratissima* consumption. Also, caffeic acid with antioxidant properties can decrease harmful lipids through inhibition of cholesterol biosynthesis. The cholesterol synthesis regulation is normally done by HMG-CoA. The conversion reaction of HMG-CoA to mevalonate takes place by the mediation of HMG-CoA reductase and NADPH (Nicotine amide adenine dinucleotide phosphate) that is the main affecting point of statins anti-hypercholesterolemic agents (Kafeshani, *et al.*, 2017).

3.3. liver enzymes

Liver, as a major organs in the body, is responsible for regulating many metabolic and physiological processes such as producing bile, detoxification, excreting waste materials and synthesizing and adjusting some essential hormones in the body. AST, ALT, ALP, and ALT are the most important and functional liver diagnostic enzymes, whose rise in the blood are symptoms of damages to liver. These enzymes are considered as specific criteria for the diagnosis of hepatocellular necrosis because they are released into the blood stream in the event of damage to the hepatocytes cell membrane. Therefore, measuring the levels of ALP and AST enzymes is clinically and toxicologically important so that the increase in AST and ALT levels are regarded as hepatocellular damage and increase in ALP level is considered as an indicator of the defect in flow and excretion of bile (Yahooi *et al.*, 2017).

In the present study, the evaluation of liver enzymes showed that the AST, ALT and ALPH were not significantly different at the beginning of the study (P>0.05). However, from 5th to 15th day, the ALT enzyme in the control group was significantly higher than the treated groups receiving different amount of *Kelussia* extract (P<0.05). On the 10th and 15th day, although the level of this enzyme in all of the treated groups was lower than the control group, but there was no significant difference between groups receiving 300 and 450 mg/kg of the extract (P>0.05) and also they showed lower levels of ALT enzyme compared to group receiving 150 mg/kg of the extract (P<0.05).

Table 3: Comparison of the average levels of liver enzymes of the four studied groups at three time

Variables	Time	Control	*Kelussia* extract 150mg	*Kelussia* extract 300mg	*Kelussia* extract 450mg	P1	P2	P3
ALT IU/L	**Baseline**	55.00±2.94^a	59.00±3.56^a	61.00±7.53^a	56.75±5.91^a	<0.001	0.003	<0.001
	5 days	53.00±2.45^a	41.25±6.60^b	40.75±10.34^b	39.00±7.16^b			
	10 days	52.00±2.45^a	38.50±6.35^b	29.50±8.43^c	29.50±1.91^c			
	15 days	51.00±2.58^a	34.75±3.69^b	26.50±4.51^c	25.75±6.13^c			
AST IU/L	**Baseline**	27.00±4.76^a	28.25±3.30^a	25.00±4.76^a	24.00±2.16^a	<0.001	0.318	0.019
	5 days	27.25±5.56^a	26.00±3.65^a	25.00±4.97^a	22.50±2.08^a			
	10 days	27.75±6.39^a	22.75±1.26^a	24.25±3.95^a	22.00±1.15^a			
	15 days	26.50±5.07^a	22.25±1.71^a	21.50±2.65^b	20.50±1.29^b			
ALPH IU/L	**Baseline**	64.25±23.77^a	76.25±32.46^a	77.75±15.11^a	68.50±20.62^a	0.002	0.908	0.294
	5 days	63.25±25.79^a	75.00±34.09^a	72.00±16.14^a	63.50±7.05^a			
	10 days	61.00±21.74^a	69.75±30.44^a	66.25±12.50^a	60.50±5.74^a			
	15 days	64.75±23.57^a	67.50±30.86^a	61.75±7.85^a	59.50±9.04^a			

(a, b, c) The similar letters in each row indicate lack of difference and non-similar letters indicate a significant difference.
P1: time, P2: group, P3: interaction of time × group

Data analysis showed that time, group and interaction of time × group had a significant effect on ALT level (P_{time}<0.001, P_{group} = 0.003, $P_{time \times group}$<0.001). In other words, after 5 days, a significant decrease of ALT level was observed in groups and the highest reduction was on the 10th day in the groups receiving 450 and 300 mg/kg of *Kelussia* extract (Table 3). The AST enzyme level was significantly different between the 4 groups only on the 15th day (P<0.05) with the highest level of 26.50 and 22.25 in the control group and the group receiving 150 mg/kg of essence, respectively, and the lowest levels of 21.50 and 20.50 in groups receiving 300 and 450 mg/kg extract, respectively (P<0.05).

ALPH enzyme level did not show any significant changes in the group receiving 450 mg/kg of the extract during 15 days of study (P>0.05, Table 3).

The effects of hepatical protection of the celery against toxicity induced by carbon tetrachloride in adult male was studied by Taleban Pour *et al.*, (2015). They reported significant increase of liver enzymes in the CCL_4 group and a significant decrease of the AST enzyme in groups treated by 400 mg/kg and 600 mg/kg of extract. There was a decrease in ALT level in the treated group with 600 mg/kg of celery extract, too. They attributed these effects to the antioxidant activity of flavonoids and possibly some compounds such as Apigenin and luteolin (Taleban pour *et al*, 2015).

Similar observations have been reported in some other previous studies (Tashakori-Sabzevar *et al.*, 2016; Hosseini *et al.*, 2017).

4. Conclusion

Based on the present results, consumption of *k.odoratissima* extract for 15 days with different doses, led to a decrease in the levels of FBS, LDL, TG, CHOL, AST, ALT and increase in the level of HDL. No hepatotoxic effects (increased levels of liver enzymes such as AST, ALT and ALP) were observed due to the extract consumption. Therefore, more attentions can be directed toward anti-diabetic, anti-atherosclerotic and antioxidant effects of *k.odoratissima* especially for treatment of animals suffering from diabetes, high cholesterol and hepatical diseases. In addition, more studies are suggested to be done on toxication caused by different species that use this plant.

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