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The effects of hyssop hydroalcoholic extract on the serum biochemical factors of rats

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ABSTRACT

Background & Aim: Investigating the effects of medicinal plants on the basal physiology of the body is one of the main topics in the application of medicinal plants. Hyssop (*Hyssopus officinalis*) or Zofa is one of most important medicinal plants in Iran with numerous therapeutic properties such as antibacterial, antifungal, anti-inflammatory, and analgesic effects. However, there is limited information on its effects on the basal physiology of the body. The aim of this study was to investigate the effects of hydroalcoholic extract of hyssop on liver and kidney activities in rats under normal physiological conditions.

Experimental: For this purpose, 32 male rats of the Wistar breed were used. The rats were allocated to one control group and three experimental groups. The experimental groups received the hydroalcoholic extract of Zufa at 150, 100 and 50 mg/kg concentration levels for 21 days. After the trial, blood samples were collected to measure liver and kidney health indices.

Results: The results showed that hyssop extract did not significantly affect cholesterol and ALT levels (P>0.05); while, significantly reduction in AST levels was observed. Consumption of hyssop extract at the concentration of 150 mg/kg b.w significantly increased GGT level (P<0.05); however, a significant decrease (P<0.05) was observed in creatinine and BUN parameters at the concentration level of 100 mg/kg. Consumption of hyssop extract did not affect HDL levels, whereas, at the concentration level of 150 mg/kg, LDL levels were significantly decreased (P<0.05). Moreover, a decreasing trend in glucose and triglyceride levels was observed with the consumption of hyssop extract.

Recommended applications/industries: Generally, Zufa extract at 100 mg/kg concentration level can effectively lower blood sugar without any negative effects on the liver and kidney health.

1. Introduction

The demand for herbal medicines is growing given their fewer side effects and higher diversity of the affecting compounds. The variety of the composition of medicinal plants in many cases leads to the synergic impacts so that despite gradual effects, the effects are more stable compared to other medicines (Chang *et al.*, 2017; Bugayong *et al.*, 2019; Maroyi and Semenya, 2019; Raissy *et al.*, 2020; Raissy *et al.*, 2022). More than 80% of pharmaceutical research works in the world are focused on these plants (Rashidi *et al.*, 2013). Over the recent years, the application of medicinal plants to achieve preventive and therapeutic effects

have been reported on a wide range of neural, digestive, and brain diseases (Bahmani *et al.*, 2014; Jivad and Rabiei, 2014; Tangjitman *et al.*, 2015; Lundstrom *et al.*, 2017; Sahoo, 2018). Hyssop (*Hyssopus officinalis*) of Lamiaceae family (Nasirpour *et al.*, 2014) is recommended for viral infections like the flu, sore throat, bronchitis, and asthma (Jivad and Rabiei, 2014).In addition, hyssop essence and extract are used in the food industry in products like sauce, liquor, and hot spices (Dehghanzadeh *et al.*, 2012). The compounds found in hyssop vary depending on the region and growth condition so that different compounds like flavonoids, tannin, thymol, carvacrol, mirtonic acid, pinik acid, and so on can be found in it. Each of these compounds is a source of a specific therapeutic effect such as antibacterial, antifungal, antiinflammation, and analgesic effects (Hatipoğlu *et al.*, 2013; Said-Al Ahl *et al.*, 2015). Ghasemi et al. (2009) studied the antifungal effects of alcoholic extract of hyssop on Saprolegnia fungus and compared the results with Nystatin, an antifungal chemical drug in fish. They showed that hyssop inhibited the fungus growth and had a better antifungal effect compared to chemical drugs (GhasemiPirbalouti *et al.*, 2009). Another study showed that hyssop has antimicrobial effects on bacteria and yeasts due to the compounds like thymol, gamaterpinen, carvacrol, and parasmin (Dehghanzadeh *et al.*, 2012). In addition, there are reports about the antibacterial effects of hyssop on E. coli, staphylococcus aureus, and Listeria monocytogenes. There are evidence of the positive effects of hyssop on preventing bacterial growth (Nasirpour *et al.*, 2014). Salehi and Setorki (2018) examined analgesic and anti-inflammatory effects of ethanolic extract of hyssop in mice and showed that the hyssop ethanolic extract had analgesic and anti-inflammatory effects on small mice (Salehi and Setorki, 2018). Moreover, the antiplatelet activity of hyssop has been reported by some studies on mice and pigs (Tognolini *et al.*, 2006). Hyssop contains a wide range of phenolic compounds with antioxidant effects (Alizadeh *et al.*, 2010). In this regard, Dorman et al. (2012) showed that acetonic extract of hyssop has a considerable effect on surpassing free radicals (Dorman and Deans, 2000). The majority of studies on hyssop have been limited to specific cases, while there is no fundamental study in vivo on physiological effects. Taking into account the key role of the kidney and liver in maintaining body's physiological balance, the present study is an attempt to examine the effects of hyssop on these two organs using the blood parameters mesurement.

2. Materials and Methods

2.1. Preparation of extract

To prepare a hydroalcoholic extract, hyssop was purchased from local medicinal herb market and the plant was identified in Herbal Research Center, Islamic Azad University, Shahrekord through comparing the samples with available herbarium samples. In order to extract preparetion, the procedure of Alinejad et al. (2013) were followed so that first the plant was wetted in water/alcohol solution (30/70), and then the solvent was removed using a rotary evaporator. Afterwards, the extract was dried and prepared at different concentration levels (50, 100, 150 mg/kg).

2.2. Laboratory animals

Totally, 32 Wistar rats were procured from the laboratory animal breeding house, Islamic Azad University, Shahrekord Branch. During the experiment, the rats were kept in the department for keeping lab animals with 12/12 day/night cycle at 22.2°C and standard diet until the animals reached the proper weight (170-240 g) and physiological conditions. The rats' condition remained unchanged throughout the study.

2.3. Grouping and implementation of lab treatments

To conduct the experiments, 32 male rats were randomly allocated to four groups of eight. The groups were control group (no extract and only distilled water was given to the subjects); treatment 1 (50 mg/kg of the extract was given using nasogastric (NG) tube; T1); treatment 2: (100 mg/kg was given using NG tube; T2); treatment 3 (150 mg/kg was given using NG tube; T3). The experiment took 21 days, and the interventions were done every day at the same hour.

2.4. Sampling and blood parameters

At the end of the treatment, 4 mL blood samples were taken from the rats' hearts after anesthesia using Ketamine Xylazine and in observance of ethical codes. After extracting the serum, cholesterol, triglyceride,

creatinine, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferases (AST), gamma-glutamine transferase (GGT), fast blood sugar (FBS), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured using a spectrophotometer and Pars Azmoon kits.

2.5. Statistical analysis

The collected data were analyzed in SPSS24 using ANOVA, general linear model (GLM), and nonparametric tools. The mean scores were compared using Duncan multi-range test with a probability level of 5% ($P< 0.05$).

3. Results and discussion

Medicinal plants are characterized by various compounds with pharmaceutical, antimicrobe, antiinflammation, and growth stimulation effects. These compounds are far less expensive and more accessible than synthetic medicines. These advantages have attracted the attention of research centers, and currently, more than one-third of the medicines used for human cases are from plant sources (Mulabagal and Tsay, 2004; Bakkali *et al.*, 2008). Hyssop is one of the plants that has attracted a great deal of attention from researchers. Due to the key role of the liver and kidney in base metabolism and preservation of the physiological balance of the body, assessing these two organs gives us a reliable index of the effect of herbal plants on the body. Considering the many studies on hyssop therapeutic effects, the effect of this plant on liver and kidney function was studied using blood parameters. The results are listed in Tables 1– 3.

3.1. Changes in liver factors

Table 1 lists the changes in the liver factors; clearly, there is no significant difference in the concentration of cholesterol level between the groups ($P>0.05$). In addition, the values decreased by using hyssop extract. Given the role of the liver in cholesterol synthesis, blood cholesterol is an indicator of liver health, as with liver failure, the blood cholesterol decreases (Hall and Cash, 2012). No change in cholesterol concentration after using hyssop extract showed that it had no negative effect on the cholesterol metabolism function of the liver. Akbarizade *et al.* (2020) studied the effects of hyssop on the performance and immunity of broiler chickens under cold stress. They reported that hyssop extract did not significantly affect cholesterol, so their results are almost consistent with the present study (Akbarizadeh *et al.*, 2020). The liver secretes the ALT and AST enzymes and they are an indicative of the liver health (Hall and Cash, 2012). In this study, ALT levels were not significantly different between the groups after receiving hyssop ($P>0.05$). However, with higher concentrations of hyssop extract (100 and 150 mg/kg), the level of ALT increased compared to the control group, which indicates that the effect of hyssop extract on ALT level is dose dependent. Unlike ALT level, the results showed that hyssop significantly lowered AST level ($P<0.05$). The significant decrease in AST depends on the concentration of hyssop extract; still, there was no linear relationship between hyssop concentration and decrease in AST index. The highest and lowest decreases of AST, were observed at concentration of 50 and 100 mg/kg of hyssop extract, respectively, while increasing hyssop concentration to 150 mg/kg did not cause any notable changes. A probable explanation for the decrease in AST level can be the presence of antioxidant compounds in hyssop (phenol trimibat, flavonoids, mircen compounds, and homolene). So that, an increase in hyssop concentration might increase its supportive effect on deactivating free radicals, which in turn decreases the production of AST by the liver cells (Lu *et al.*, 2002). Eidi *et al.* (2009) studied the effect of hydroalcoholic extract of olive leaves on AST and ALT levels in rats serum after carbon tetrachloride poisoning. The results indicated a decrease in the enzymes after feeding the subjects with the extract, which is consistent with our results (Eidi *et al.*, 2009). A comparison of GGT levels between groups showed a significant effect by Hyssop extract on GGT concentration ($P<0.05$). That is, an increase in the extract concentration from 50 and 100 to 150 mg/kg significantly increased GGT levels. However, there was no significant difference between groups receiving 50 and 100 mg/kg of the extract. A significant increase in GGT levels with 150 mg/kg of hyssop extract is indicative of the negative effects of the higher doses of Hyssop on liver health.

Table 1. Effect of hydroalcoholic extract of hyssop on cholesterol, ALT, AST and GGT levels in serum of the rats.

Groups (mg/kg)	Cholesterol (mg/dl)	ALT (U/L)	AST (U/L)	GGT (lU/L)
Control	64.88 ±10.37	36.88 ± 7.16	175.88 ± 4.12	4.20 ± 1.89
T1	60.38 ± 4.00	35.13 ± 6.10	138.13 ± 7.41	6.71 ± 4.00
T2	60.63 ± 7.67	37.75 ± 5.12	79.13 ± 8.42	5.72 ± 1.12
T3	61.38 ± 8.72	37.13 ± 2.85	107.13 ± 14.69	8.75 ± 1.80
Significance level	0.66	0.80	0.001**	0.001**

Control: received no extract (zero/Control), T1: received 50 mg/kg b.w hyssop extract, T2: received 100 mg/kg b.w hyssop extract, T3: received 150 mg/kg b.w hyssop extract. ALT: Alanine aminotransferease, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase.

3.2. Changes in renal factors

Table 2 lists the changes in the renal factors. The kidney functional disorder can be determined based on urea nitrogen and Creatinine levels (Hall and Cash, 2012). Clearly, concentration of BUN in the blood serum was significantly different only between T1 and T2 groups (P<0.05). Despite this significant difference, no definite trend in reducing BUN concentration was observed between the groups. The limited decrease can be attributed to flavonoid, mircene, and homonene compounds that improve the kidney function (Mazzanti *et al.*, 1998). Creatinine levels in different groups indicated that depending on the concentration, hyssop extract significantly decreased concentration of creatinine (P<0.05). Among the groups, the highest decrease was observed in group receiving 100mg/kg of extract. However, there was no linear relationship between the extract consumption and the decrease in creatinine concentration. Hyssop with concentration of 50 and 100 mg/kg b.w significantly reduced creatinine level compared to the control group; while at concentration of 150 mg/kg, no significant decrease (P>0.05) was observed compared to the control group.

Modaresi et al. (2006) studied the effects of the ginger hydroalcoholic extract on BUN and creatinine in small lab mice and they showed a decrease in BUN and BUN/creatinine ratio in the treated mice, while creatinine concentration remained unchanged (Modaresi *et al.*, 2006).

Table 2. Effect of hydroalcoholic extract of hyssop on creatinine and BUN in serum of the rats

Groups (mg/kg)	Creatinine (mg/dL)	BUN (mg/dL)
Control	1.02 ± 0.13 ^{c}	22.88 ± 1.36^{ab}
T1	0.83 ± 0.13^{ab}	23.88 ± 2.64 ^{b}
T2	0.80 ± 0.12 ^{a}	21.00 ± 1.31 ^{a}
T3	0.96 ± 0.07^{bc}	22.38 ± 1.92^{ab}
Significance level	0.002**	0.038*

Control: received no extract (zero/Control), T1: received 50 mg/kg b.w hyssop extract, T2: received 100 mg/kg b.w hyssop extract, T3: received 150 mg/kg b.w hyssop extract. BNU: Blood urea nitrogen.

3.3. Changes in other parameters

Table 3 lists changes in other parameters, and as can be seen, hyssop extract (100 and 150 mg/kg) decreased FBS compared to the control group (P<0.05). Hyssop extract at concentration of 50 mg/kg did not create a significant change compared to the control group; although, there was an increase in FBS (P>0.05). The observed decrease in blood glucose might be due to phenolic acids and flavonoids found in hyssop extract. Other studies have supported the effects of flavonoids on reducing plasma sugar (Lu *et al.*, 2002). Anandh et al. (2006) reported that the hypoglycemic effect of quercetin, as a flavonoid compound, was evident in diabetic rats induced with alloxan (AnandhBabu *et al.*, 2006). In another study, Solar et al. (2006) highlighted the positive effects of hyssop on lowering blood sugar (Solar *et al.*, 2006). Pouraboli and Ranjbar (2014) studied the effect of carrot seed extract on glucose serum level in male rats with diabetes type 1 and reported a decrease of glucose level in the serum (Pouraboli and Ranjbar, 2014). A comparison of triglyceride concentration between different groups showed a significant reduction (P<0.05) only between control and T1 groups (68.75 and 48.5 U/L), respectively. No significant difference was observed in higher concentrations of hyssop despite numerical reduction (P>0.05).

These findings showed that the effects of hyssop depend on its concentration. The decrease in triglyceride concentration in the treatment groups compared to the control group can be explained by the fact that with glycemic control and a decrease in blood glucose caused by the extract, the share of glucose increases in supplying energy. Through this, a decrease in blood serum glyceride happens. Hyssop reduces blood glucose, and to supply energy demand, more fat sources will be used, which in turn reduces serum triglycerides level in the blood.

A study by Heydarian *et al.* (2008) on the effect of wild pistachio on the liver phosphatidate phosphohydrolase, serum lipids, and lipoproteins of rats showed that the pistachio decreased activity of this enzyme and liver triglyceride synthesis (Heydarian *et al.*, 2008). Despite the fact that there was no significant difference between the groups in terms of HDL parameter (P>0.05), there was a significant difference in LDL parameter (P<0.05). So that LDL decreased with a higher concentration of hyssop extract (150 mg/kg), while 50 and 100 mg/kg of hyssop did not significantly decrease LDL level. A study by Saeb et al. (2004) on the effects of wild pistachio powder on lipids and lipoproteins in female rabbit blood serum indicated that the powder had a significant effect on lowering cholesterol concentration and LDL level (Saeb *et al.*, 2004).

Table 3. Effect of hydroalcoholic extract of hyssop on FBS, Triglyceride, HDL, and LDL levels in serum of the rats.

Group (mg/kg)	FBS (mg/dL)	Triglyceride (U/L)	HDL (U/L)	LDL (mg/dL)
Control	206.75 ±36.09	68.75 ± 13.02	35.75 ± 2.60	19.71 ± 2.08
T1	229.13 ± 24.51	48.50 ± 14.32	36.00 ± 2.27	16.21 ± 3.13
T2	168.63 ± 31.70	58.63 ± 13.34	38.25 ± 5.52	18.57 ± 5.06
T3	178.38 ± 50.05	56.88 ± 13.90	37.88 ± 2.42	11.48 ± 1.76
Significance level	0.011*	0.049*	0.37	0.001**

Control: received no extract (zero/Control), T1: received 50 mg/kg b.w hyssop extract, T2: received 100 mg/kg b.w hyssop extract, T3: received 150 mg/kg b.w hyssop extract. FBS: Fast blood sugar, HDL: High-density lipoprotein, LDL: Low-density lipoprotein.

4. Conclusion

In general, hyssop extract does not negatively affect the measured parameters of the liver and kidney function. Moreover, the positive effects of hyssop extract depend on its concentration were observed. The highest positive effects on liver, kidney, and FBS parameters were achieved with hyssop extract concentration of 100 mg/kg.

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