Original Article

Effect Of Aqueous Alcoholic Extract Of Devil's Claw On The Serum Levels Of Adiponectin, Agouti, Omentin, Amylin, Orexin A, Resistin, Chemerin, Ghrelin, Leptin, NPY, And Epinephrine In Weight Changes In Rats

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Abstract

Background: Nowadays, obesity and its complications are considered a serious human society's problem, due to which it seems necessary to find the best ways to lose weight. Nowadays, herbal compounds, due to fewer side effects, more availability, and less toxicity get more attention. The present study aims to investigate the effect of Aqueous alcoholic extract of devil's claw on the serum levels of obesity-related-peptides such as adiponectin, agouti, omentin, amylin, orexin A, resistin, chemerin, ghrelin, leptin, NPY, and epinephrine in weight changes in rats.

Method and materials: Forty adult male Wistar rats (180- 200 grams) were used. Then the rats were divided into five groups: control (no treatment), sham (1 ml of distilled water), and devil's claw groups with concentrations of 150, 300, and 600 mg/kg (by gavage/ n=8/ 28 day). On the 29th day, animals were weighted and blood samples were taken. ELISA kit was used to measure the serum concentrations of obesity-related-peptides.

Results: Devil's claw extract reduces food intake by lowering orexin, resistin, and chemerin, which increase in obesity, and raising adipokines that cause weight adjustment and reduction of food intakes such as adiponectin, ghrelin, norepinephrine, omentin, and amylin in a dose-dependent manner.

Conclusion: This study revealed that devil's claw extract has anti-obesity effects, especially at higher doses. These findings suggest that devil's claw reduces NPY and rises leptin, thereby preventing appetite. This herb has anti-inflammatory and antioxidant effects, alters adiponectins secretion, causes weight loss, and reduce the lipid profile; examining the details of these signaling is recommended.

Keywords: Devil's claw, Body weight, Rat

Introduction:

Nowadays, obesity is one of the important problems in human societies and can cause chronic diseases such as cardiovascular disease, diabetes, hyperlipidemia, and hormonal disorders (1). In addition to these physiological problems, obesity disrupts the psychosocial dimension and reduces their quality of life (2). Owing to the physical and psychological effects of obesity, experts are trying to reduce the prevalence of obesity in various ways. Several mechanisms are involved in the physiology of obesity; regulation of energy homeostasis, the balance between energy intake, energy consumption, and energy storage play major roles in obesity (1, 2).

Some critical hormones in energy homeostasis are adiponectin, omentin, amylin, ghrelin, epinephrine, Agouti-Related Protein (AgRP), orexin A, resistin, and chemerin. Adiponectin and omentin secreted from adipose tissues, affect fat and glucose metabolism. It has been shown that increasing the expression of the adiponectin gene can cause weight loss (3). On the other hand, inflammatory conditions such as obesity can reduce the expression of the omentin gene (4). Amylin is secreted from the pancreatic Beta cells along with insulin, inhibits food intake, and slows gastric emptying. Also, it has been shown that a lack of amylin gene causes weight gain and obesity(5).

Agouti and neuropeptide-expressing neurons Y (NPY), neurons in the arcuate nucleus (ARC) of the hypothalamus, are important mediators of food intake. Agouti increases food intake with a delay, but the intake is maintained longer than NPY. Agouti neurons in the arcuate nucleus are key mediators of food intake, and their activity increases due to fasting and decreases after satiety. The researchers hypothesize that the activity of AGRP neurons increases under physiological conditions due to the endocrine ghrelin and ppAR$_\gamma$ messages (6). Ghrelin, a 28-amino acid peptide hormone, was found in the stomach and arcuate nucleus of the hypothalamus; its receptor is located in Agouti-associated neurons and NPY. Previous studies have indicated that ghrelin and growth hormone secretagogue receptors (GHS-R) play a role in regulating energy homeostasis and increasing food intake and weight (7). Orexin is a neuropeptide that increases food intake and food search in conditions of food deprivation (8). Resistin, an adipokine, is secreted from adipose tissue and increases inflammation and insulin resistance in obesity (9). Chemerin is also an adipokine that increases again in obesity and increases in inflammation and glucose intolerance (10).

Due to the prevalence of obesity in today's society and its complications, it seems necessary to find a way with the least side effects to reduce appetite and, subsequently weight loss. Obesity disrupts various systems through β2 receptors and the immune system; therefore, non-inflammatory strategies are important in treating obesity (11). Various studies have demonstrated the capability of food bioactive compounds to prevent obesity and adipose tissue inflammation (12, 13).

Herbal compounds, due to fewer side effects, more availability, and less toxicity in higher doses, are now more considered by researchers for replacement with chemical drugs (14-16). Despite different herbs' benefits studies, interesting systematic reviews have been discussed about them. For example, in a survey of 77 studies, a significant decrease in body weight was proven. No significant adverse effects or mortality were observed; this review showed that most of the introduced herbals had been shown to have antioxidant effects, and with regard to the role of oxidative stress in the pathophysiology of obesity was confirmed (14).

Devil's claw is a common name for two plant species related to the genus of Harpagophytum de Candolle ex Meissner (Pedaliaceae) (17, 18). The main ingredient of Devil's claw is Harpagoside, which belongs to the iridoid glycoside family and is the main and effective compound of this plant (18, 19).

For a long time, the natives of China used this plant in the form of tea and infusion to treat gastrointestinal problems and rheumatism symptoms (20-22). It has also been used as a fever-reducing drug, a stimulant for the liver, gallbladder, and urinary tract, and in the allergy treatment (17, 22). Previous studies have shown the devil's claw plant benefits for weight reduction by increasing obestatin and cholecystokinin levels and subsequently reducing appetite (23-25). Thus, the present study aims to investigate the effect of aqueous alcoholic extract of this plant on the serum levels of adiponectin, agouti, omentin, amylin, orexin A, resistin, chemerin, ghrelin, and epinephrine in weight changes in rats following the administration of this extract.

Materials:

Animals

This experiment was performed based on the Jahrom University of Medical Science's animal protection guideline with the ethics code IR.JUMS.REC.1398.125. In this study, forty adult male Wistar rats weighing 180 to 200 grams were used. The rats were kept in a room with standard conditions of 12:12 hours dark and light, and a controlled temperature of 22-23°C with easy access to water and food. The rats were divided into five groups: Control (no treatment), sham (animals received one ml distilled water by gavage), and experimental groups, which received devil's claw with concentrations of 150, 300, and 600 mg/kg (by gavage); each group consisted of 8 rats (23). Distilled water and aqueous-alcoholic extract of the devil's claw were fed to the animals by gavage for 28 days.

Extraction method: To prepare the aqueous alcoholic extract of the devil's claw plant, 300 grams of devil's claw with 70% ethanol (4 liters) were placed in a rotary apparatus for 4 hours at a temperature of 80 °C. This process was repeated two times and then the extract was filtered through a filter (Millipore, Billerica, MA, USA 0.45 μm). The extracted samples were then dried by freezing and turned into a yellow powder (23, 26).

Plant and herbarium collection method:

Test protocol

On the 29th day, animals were weighted; blood samples were taken from their hearts by a five-cc syringe under anesthesia with Ketamine and Xylazine. Their serum was separated by a centrifuge at 3000 rpm for 15 minutes and froze at -20 °C for evaluation. ELISA kits used to measure serum concentrations of obestatin, adiponectin, agouti, omentin, amylin, orexin A, resistin, chemerin, ghrelin, and epinephrine.

Statistical analysis:

Statistical analysis was performed using SPSS-21. The results were analyzed by ANOVA and Duncan test at a significant level of $p \leq 0.05$. Data were reported as Mean ± SD.

Results:

The aqueous alcoholic extract of devil's claw at concentrations of 300 and 600 mg/kg significantly reduced animals' body weight and the concentration of NPY, orexin A, resistin, and chemerin compared to the control groups. In contrast, the dose of 150 mg/kg could not make significant difference. The results of the present study show the beneficial effect of aqueous alcoholic extract of devil's claw on increasing serum levels of amylin, adiponectin, omentin, ghrelin, epinephrine, and leptin, and decreasing the serum levels of orexin-A, resistin, and chemerin. Based on the results, it was found that the doses of 300 and 600 mg/kg were the effective doses and 600 mg/kg had the greatest effect on weight loss and appetite reduction in rats (Fig1 and Table 1).

Fig.1. weight loss, AgRP, NPY, and Glucose changes in different doses of Devil claws' extract in comparison

with control group.

According to Duncan test, averages available in each row have at least a common letter; they have no significant difference in the level of 5% Duncan test. Averages were presented as mean±SD. P≤0.05 was considered statistically significant.

The results indicated that 300 and 600 mg/kg of devil's claw extract could significantly increase the serum concentrations of adiponectin, ghrelin, and epinephrine compared to the control groups. Assessing the serum level of omentin showed that two doses of 300 and 600 mg/kg could cause a significant increase in its serum level compared to the control group and the 150 mg/kg extract group; the effect of the 600 mg/kg dose was more significant. In the group in which the serum level of amylin was measured, the aqueous-alcoholic extract of devil's claw in doses of 150 and 600 mg/kg significantly increased amylin concentration compared to the control groups. No significant difference was observed. In the group in which the agouti level was measured, no significant differences were observed between the groups in any extract concentrations (Table 1).

Table 1. Adiponectin, Epinephrine, Omentin-1, Amylin, Orexin-A, Resistin, and Chemerin changes in various doses of Devil claws' extract in comparison with the control group

Groups Parameters	Control	Sham	Devil's claw extract 150 (mg/kg)	Devil's claw extract 300 (mg/kg)	Devil's claw extract 600 (mg/kg)
Adiponectin (Mean ± SD)	10.18 ± 1.3[a]	10.22±0.8 [a]	10.93±1.4 [a]	12.1±0.7 [b]	13.92±0.7 [c]
Epinephrine (Mean ± SD)	49.02±3.7 [a]	49.63±3.2 [a]	55.57±1.9 [a]	64.6±8.7 [b]	71.63±8.4 [b]
Omentin (Mean ± SD)	4.22±0.4 [a]	4.25±0.3 [a]	4.61±0.3 [a]	5.71±0.3 [b]	6.72±0.6 [c]
Amylin (Mean ± SEM)	25.59±1.2 [a]	25.54±1.2 [a]	26.84±1.9 [a]	29.26±2.5 [b]	41.02±3.7[c]
Orexin A (Mean ± SD)	222.25±7.5 [c]	223.57±8.0 [c]	217.72±10.5 [c]	199.07±11.9 [b]	178.35±7.8 [a]
Resistin (Mean ± SD)	149.39±2.5 [c]	150.01±3.7 [c]	144.63±3.1[c]	129.17±4.2 [b]	109.64±9.8 [a]
Chemerin (Mean ± SD)	28.36±0.9 [c]	27.7±1.1 [c]	27.35±1.1 [c]	23.66±0.9 [b]	21.62±1.3 [a]

According to Duncan test, averages available in each row have at least a common letter; they have no significant difference in the level of 5% Duncan test. Averages were presented as mean±SD. P≤0.05 was considered statistically significant.

Discussion

The results of the present study showed that administration of 300 and 600 mg/kg aqueous alcoholic extract of Devil's claw increases the serum levels of adiponectin, ghrelin, epinephrine, leptin, and omentin and decreases serum levels of orexin-A, resistin, NPY, and chemerin, which followed by losing weight. A study conducted by

Torres-Fuentes et al. (2014) showed the inhibitory effect of devil's claw extract on appetite (25). This study revealed that devil's claw extract has an anti-obesity effects on male C57BL/6 mice due to affecting ghrelin receptor activation. The result of our study was consistent with that of Torres-Fuentes (25). This effect is probably applied to be modulated by the growth hormone receptor GHS-R1 and reducing the availability of this receptor for the appetizing effects of ghrelin.

To confirm these effects, there are other studies that have shown the devil's claw appetite inhibition through growth hormone receptors (27). In addition, several studies have shown that intake of a high-fiber diet reduces obesity, hunger, food intake, and weight, and increases feelings of satiety(28). Dried devil's claw root is also high in fiber (29). Thus, through various fiber mechanisms such as gastric distention and delayed emptying, interference in digestion and absorption of food, increased insulin and glycemic responses, fiber affects the secretion of glucagon-like peptide (GLP-1) and neurotensin and reduces fat absorption and increases energy excretion (27, 30-32). This may also have anti-obesity effects of this extract. Another study showed that the hydroalcoholic extract of the devil's claw increased obestatin secretion. This peptide causes weight loss by limiting appetite, increasing leptin secretion, and decreasing NPY (24). Our study also confirmed this theory regarding the role of high devil's claw on the reduction of NPY and the rise of leptin.

Our previous studies have shown that the hydroalcoholic extract of the devil's claw causes weight loss by increasing the secretion of cholecystokinin (CCK) and leptin through the block of orexigenic neurons, especially NPY (33). Devil's claw extract has strong antioxidant effects (34). In confirming these results, another study showed that devil's claw extract could improve brain degenerative changes through its anti-inflammatory and antioxidant effects. Devil's claw increases cell survival by reducing lipid peroxidation and increasing the catalase activity, superoxide dismutase, and glutathione (35).

Studies have shown that fasting increases adiponectin secretion to maintain energy homeostasis (36). In our study, consumption of devil's claw extract appeared to have a similar effect, thereby helping to curb energy expenditure. This effect may have been applied through a central effect on NPY since a study showed that NPY neurons in the hypothalamus express adiponectin receptors (37). By binding to the receptor (AdipoR1) adiponectin inhibits NPY neurons and reduces food intake (36).

Amylin causes weight loss by reducing energy intake. Devil's claw extract may centrally affect the secretion of this peptide (38). Stimulation of AgRP neurons increases food intake. This increase is delayed relative to NPY but takes longer. This increase occurs through ghrelin and GHS-R (6) since ghrelin is an endogenous GHS-R ligand, and by inhibiting this receptor, ghrelin cannot apply its anorexigenic effects (39).

One research revealed that Devil's claw root extract increased calcium flow inside the cell by binding to GHS-R but did not induce internalization in the receptor. Therefore, it does not work exactly like its main agonist (7). This step is necessary for the orexigenic effects of ghrelin. Thus, the anti-anorectic effects of Devil's claw may be applied by reducing the availability of the receptor for the orexigenic effect of ghrelin (23, 37).

Adipose tissue is an endocrine organ that secretes several adiponectin, one of which is resistin. These adiponectin modulate insulin sensitivity and inflammation. In obese people, inflammatory conditions invade macrophages and increase the production of TNFα, IL-6, and resistin, which interfere with the action of insulin on the liver (9). Therefore, reducing resistin in rats treated with devil's claw extract can prevent metabolic complications in obesity (9). In obese people, the level of chemerin in the bloodstream is higher than in healthy, and in adipose tissue, the receptor expression shows an upregulation; Inflammation can increase chemerin signaling. Previous studies have shown that TNFα causes upregulation in chemerin expression in human, rat and bovine preadipocytes (10), which can prove the mechanism by which Devil's claw affects these obesity-related peptides.

Conclusion

Devil's claw extract reduces food intake by reducing orexin, resistin, and chemerin, which increase in obesity and increasing adipokines that cause weight adjustment and reduction of food intakes, such as adiponectin, ghrelin, norepinephrine, omentin, and amylin in a dose-dependent manner. However, it does not affect Agouti secretion. Although it is recommended to investigate the possible signaling details of devil's claw extract on the secretion of

adipokines and their interactions, these results can be useful in designing non-pharmacological methods for the treatment and prevention of obesity.

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Conflict of interest

The authors have declared no conflicts of interest.

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Author’s contribution

H.H and H.K.J conceived of the presented idea. H.H, N.S, F.M, H.K.J, N.S.J, R.M, S.R, and S.D performed the experiments. H.K.J, B.E, N.S, F.M, M.D, H.K.J, and N.S.J wrote the manuscript with support from other authors. Manuscript has been read and approved by authors.

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