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Original article

Antioxidant Potential, Hypoglycemic Effect and Safety of *Ajuga chamaecistus* Ging. ssp. *tomentella* (Boiss.) Rech. f. Aerial Parts

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Abstract

Background and objective: *Ajuga* species (Lamiaceae) are traditionally used in the treatment of jaundice, joint pain, sciatic nerve, and diabetes in different countries. The aim of this study was to investigate the antioxidant and hypoglycemic activities and safety of *Ajuga chamaecistus* ssp. *tomentella*. **Methods:** Antioxidant activity, radical scavenging effect, and total phenolics content of the aqueous and methanol extracts were assessed using ferric reducing antioxidant power (FRAP), 2, 2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging and Folin-Ciocalteu methods. Streptozotocin (STZ) induced diabetic mice were studied in separate groups comprising aqueous and methanol extracts (200, 400, 800 mg/kg), metformin (500 mg/kg) and a negative control group. **Results:** The n-butanol fraction showed the most phenolics content (26.5 mg GAE/g of extract) and the highest antioxidant power (346.7 mmol FeII/g of extract) as well as the most considerable radical scavenging activity (IC_{50}=15.34 µg/mL). In STZ-diabetic mice, repeated oral administration of all doses of extracts showed a significant decrease in plasma glucose levels after 3, 14 and 28 days. The results of acute toxicity study showed that the ethanol extract was non-toxic up to the dose of 6000 mg/kg. Based on the sub-chronic toxicity results, a significant decrease in cholesterol and triglyceride was observed after using the extract (1000 mg/kg) for 23rd and 45th days. Histopathology of animal tissues revealed no significant differences in animal tissues between treated and control groups after 23 and 45 days. **Conclusion:** our study indicated the antioxidant potential, safety and hypoglycemic effect of *A. chamaecistus* ssp. *tomentella* extracts.

Keywords: *Ajuga chamaecistus* ssp. *tomentella*; antioxidant activity; hypoglycemic effect; safety

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Introduction

Diabetes mellitus is one of the major debilitating chronic disorders in the world and the number of people with diabetes mellitus is increasing. Currently, there are more than 220 million people with diagnosed diabetes [1]. Diabetes mellitus is caused by inefficiency of the pancreatic β-cells to

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secret insulin (type 1 diabetes) and/or the insulin function (type 2 diabetes) leading to progressive impairment of glucose tolerance and hyperglycemia [2,3]. Both types of diabetes can lead to chronic elevation of glucose levels that cause oxidative stress [4].

Clinical studies have shown the efficacy of plants in the modulation of oxidative stress associated with diabetes mellitus [5]; therefore, the use of antioxidants can protect beta cells and endothelial cells against diabetes-induced stress oxidative injury [6]. Plants with antioxidant properties would be useful in the treatment of patients with diabetes [6]. According to previous studies, more than 800 plants have been reported to have anti-diabetic activity [7]. Furthermore, recent studies demonstrated that more than 1200 plants are used in traditional medicine for their allied hypoglycemic activity [8].

The genus *Ajuga* [Kamaphytus] has been used for the treatment of jaundice, joint pain, gout, amenorrhea, sciatica and wound healing in traditional Persian medicine [9]. It has been also used as anthelmintic, against intestinal disorders [10], and as anti-diabetic in traditional medicines of different countries [11,12]. *Ajuga chamaecistus* comprises five exclusive subspecies, while *Ajuga chamaecistus* ssp. *tomentella* is endemic to Iran [13].

Several pharmacological studies on many species of this genus have been asserted in different ethnobotanical reports such as hypoglycemic [14], anti-inflammatory [15], analgesic, anabolic, antioxidant, anti-arthritis, antipyretic, hepatoprotective, cardiotonic, antibacterial and antifungal [16] properties. Some active compounds from *Ajuga* species such as flavonoids, iridoids [17], withanolides [18], phenylethyl glycosides [19] and phytoecdysteroids [20] have been identified.

The chemical composition of the essential oil from *A. chamaecistus* ssp. *tomentella* has indicated the main compounds as thymol, exo-fenchol, β-pinene, 1-octen-3-ol, α-terpineol, 2-hexanol, α-thujene, α-pinene, while the thymol has shown the highest level [21]. In 2012, Sadati et al., identified 10 natural compound in a phytochemical study of the plant including 20-hydroxyecdysone, cyasterone, ajugalactone, makisterone A, and 24-dehydroprecyasterone (phytoecdysteroids), 8-acetylharpagide (iridoid), *cis*- and *trans*-melilotoside , lavandulifolioside, leonoside B, and martynoside (phenylethanoid glycosides). They also showed that the extracts of the herb and the isolated compounds had no cytotoxic effects on cancerous or normal cells [22,23].

Examining the analgesic effects of this plant, it was found that the aqueous extract and hexane and diethyl ether fractions obtained from the methanol extract showed analgesic and inflammatory effects that suggested the use of this plant in the treatment of arthritis and sciatic nerve pain [24]. In a recent study, a chemical compound called ajugalide-E has been isolated and identified from the hexane fraction of this plant which showed larvicidal effects against *Anopheles stephensi* larvae [25].

The purpose of this study was to determine the antioxidant activity, hypoglycemic effect, acute and sub chronic toxicity of some extracts from aerial parts of *A. chamaecistus* ssp. *tomentella*, an attempt to confirm the traditional use of the plant.

Material and Methods

Ethical considerations

This study was approved by the ethics committee of Tehran University of Medical Sciences (TUMS), Tehran, Iran (IR.TUMS.PSRC.REC.1395.1166, 12/06/2016).

Plant material

Aerial parts of *A. chamaecistus Ging* ssp. *tomentella* (Boiss) Rech. f. were collected from "Sorkhe Hesar", east of Tehran, Iran, in June 2014 and verified by Prof. G Amin. A voucher specimen (THE-6697) was deposited at the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

Methanol extract and fractions

The air-dried and ground aerial parts of *A. chamaecistus* ssp. *tomentella* (250 g) were extracted with methanol 80% (3×1 L) at room temperature, in three days. The solvent was evaporated in a rotary evaporator and a vacuum oven to give a dark brown extract (45 g). The extract (30 g) was suspended in water and partitioned between hexane, diethyl ether (DEE), and n-butanol (NB) (Merck, Germany). After removal of solvents, DEE and NB fraction were studied for antioxidant activity.

Aqueous extract

Two hundred and fifty grams of the powdered