Mini Review article

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Mountain tea (*Sideritis* plants): A potential anti-atherogenic agent?

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ABSTRACT

Atherosclerosis consists the leading cause of cardiovascular diseases. Over the last years, medicinal plants are considered as efficient agents in the prevention and adjuvant therapy of atherosclerosis. Mountain tea (*Sideritis* plants) is used as traditional remedy against common cold and gastrointestinal disorders. Its beneficial properties are attributed to its rich bioactive constituents. Polyphenols exhibit a broad range of pharmacological activities such as antioxidant, anti-inflammatory and anti-atherosclerotic effects. The present review summarizes and discusses the potential of mountain tea as an anti-atherogenic agent based on its bioactive chemical compounds and their reported pharmacological activities.

KEY WORDS: *Mountain tea, genus Sideritis, antioxidant, anti-inflammatory, potential anti-atherogenic activity, polyphenols*

INTRODUCTION

Cardiovascular diseases (CVD) consist the number one cause of death worldwide, representing the 31% of all the deaths in the world[1]. Major role in the development of these diseases holds atherosclerosis[2], a multifactional chronic disease associated with inflammation, oxidative stress, endothelial dysfunction, and aging[3,4]. Furthermore, external risk factors such as smoking, obesity and unhealthy diet could contribute to the development of atherosclerosis[2]. To prevent its progression in any stage, the adoption of healthy lifestyle interventions from early age seems to be great essential. Healthy diet, physical activity and abstinence from tobacco are basic recommendations of clinical strategies for its prevention[2].

Medicinal plants are predominant ingredients of healthy diets and especially of Mediterranean diet. A current review carried out by Kirichenko et al. (2020) thoroughly described the medicinal plants which have exerted anti-atherosclerotic activity in experimental and clinical studies[5]. This activity is mainly attributed to their content of bioactive compounds with pleiotropic effects such as antioxidant and anti-inflammatory properties, acting with different mechanisms of actions[5,6]. Medicinal plants with potential anti-atherosclerotic activity are especially interesting, since generally natural products

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are considered as safer agents compared to conventional drugs due to their fewer side effects and are suitable for long-term use. Therefore, plant-based medications could be used as suitable candidates for a long-term application for prevention and adjuvant treatment of atherosclerosis.

Plants of Lamiaceae family are well-known medicinal plants with a broad range of pharmacological activities. Many of them are extensively used in traditional medicine for various applications since antiquity. In recent years, a genus of this family which has attracted great scientific interest is genus *Sideritis* L. Its traditional beverages, widely well-known as mountain tea, have been the subject of various phytochemical and pharmacological studies due to their significant health benefits. Of great importance are its antioxidant and anti-inflammatory activities, which have been thoroughly investigated by *in vitro* and *in vivo* studies. However, so far, there is no report on its anti-atherogenic effects. Thus, the aim of the present review was to summarize and discuss the potential of this important genus as an anti-atherogenic agent based on its bioactive chemical compounds and their reported pharmacological activities.

Methods

A comprehensive research of previously published literature data about genus *Sideritis* was performed. Electronic databases including Scopus, PubMed, and Google Scholar were searched with keywords related to the anti-atherosclerotic activity of genus *Sideritis*, its bioactive compounds (e.g. flavonoids, phenylethanoid glycosides) and their pharmacological activity.

Bioactive compounds of Mountain Tea

Phytochemical studies in genus *Sideritis* have revealed the presence of many phytochemicals, mainly polyphenols including flavonoids, phenylethanoid glycosides and phenolic acids[7-9]. Regarding the flavonoid load, *Sideritis* spp. are characterized by 8-hydroxyflavone 7-allosylglucosides (isoscutellarein and hypolaetin derivatives). In addition, these plants contain 5,7-dihydroxyflavones (apigenin derivatives) and their glucosides. Another common chemical category of genus *Sideritis* is the phenylethanoid glycosides. Acteoside and martynoside were identified from several *Sideritis* plants. Although plants of Lamiaceae family are rich in diverse phenolic acids, chlorogenic acid is the major representative in *Sideritis* species. It is noteworthy to point out that the variations of the phytochemical content among *Sideritis* plants depend on various factors such as environmental conditions and geographical origin of plant materials.

Flavonoids

Previous studies have showed that the consumption of flavonoid-rich diets can reduce the risk of cardiovascular diseases and atherosclerosis[10,11]. Particularly, flavonoids can act with various mechanisms of action in atherosclerotic progression, including antioxidant, anti-inflammatory, antiplatelet, vasodilatory, antihypertensive and lipid regulation[10,12]. Concerning the antioxidant activity, they mainly act through direct scavenging of free radicals, metal chelation, inhibition of ROS producing enzymes (e.g. lipoxygenases, NADPH oxidases), up-regulating of cellular antioxidants, inhibition of LDL oxidation, induction of antioxidant enzymes and inhibition of NF-κB pathway. Furthermore, flavonoids exhibit anti-inflammatory activity since they decrease enzymes which participate on inflammation pathways such as cyclooxygenases (COX-1 and mainly COX-2) and lipoxygenases, as well as they reduce NO production. In addition, these constituents are capable of diminishing the expression of pro-inflammatory cytokines (e.g. IL-1b, IL-6, IL-8, TNFα) and regulate NF-κB activation. Some flavonoids also possess anti-platelet effects, acting as reverse antagonisms on the thromboxane A2 receptor and inhibiting serotonin, collagen, ADP induced platelet coagulation, PAF, P-selectin and calcium mobilization. Though, they induce PECAM-1 activation. Additionally, flavonoids increase validation and enhance the endothelial function through improving eNOS activity and expression, the prostacyclin production, and the increase of EDHF-mediated relaxation, whereas they inhibit iNOS and ET-1 action and synthesis. Lipid accumulation which is observed in atherosclerosis is also regulated by flavonoids through decreasing cholesterol synthesis, hepatic secretion of ApoB-100 and foam cell formation, as well as, they upregulate LDL, HDL, fatty acid metabolizing enzymes and PPARγ.

Flavonoids are main constituents of *Sideritis* species. Among them, kaempferol (3-hydroxyflavone) and apigenin (flavone) have been extensively investigated for their great bioactivities, including antioxidant, anti-inflammatory and cardioprotective effects[10,11,13,14], revealing them as potential preventative anti-atherogenic agents. Characteristic flavonoids of *Sideritis* species are glycosides, acetylated or not, of isoscutellarein and hypolaetin, as well as their methylated derivatives. The antioxidant and anti-inflammatory effects of these constituents have been reported previously[7,15]. Consequently, it is expected that mountain tea could also exert anti-atherogenic activity due to its bioactive flavonoids.

Phenylethanoid glycosides

Phenylethanoid glycosides are phenolic derivatives which characterize genus *Sideritis*. Numerous pharmacolog-

ical activities have been reported such as antioxidant, anti-inflammatory, and anti-hypertensive effects[16]. Regarding their antioxidant properties, major mechanisms of action are through the direct scavenging of free radicals, metal chelation, and inhibition of ROS producing enzymes[17]. Moreover, these compounds have shown anti-inflammatory activity, resulting in the reduction of cyclooxygenases, lipoxygenases, NO production, pro-inflammatory cytokines and regulation of NF-κB activation[17]. Acteoside is one of the most occurrent phenylethanoid glycoside in *Sideritis* species with a broad range of pharmacological activities, mainly antioxidant and anti-inflammatory[18]. Martin-Nizard et al., (2003) exhibited that four phenylethanoid glycosides, including acteoside, inhibited LDL oxidation *in vitro*[19]. Furthermore, these compounds were able to completely abolish the capacity of copper-oxidized LDL (Cu-LDL)-induced BAEC ET-1 liberation[20], and revealed anti-atherosclerotic effects, since ET-1 secretion is increased in atheroma and promote atherosclerosis. Another study carried out by Chiou et al. (2003) mentioned that acteoside reduced the risk of atherosclerosis, not only by protecting LDL from oxidative modification, but also by its free radical-scavenging properties[21]. In addition, acteoside demonstrated inhibition of cell adhesion molecules (CAMs) which are involved in the pathogenesis of atherosclerosis and inflammation by decreasing phosphorylation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK)[22]. Currently, acteoside showed to reduce the expression of inflammatory mediators (NO, COX-2 and prostaglandin E2) and to suppress the phosphorylation of NF-κB in primary rat chondrocytes treated with IL-1b[23]. Notably, acteoside at high dosage through oral administration does not cause genotoxicity[23]. The above findings indicate that acteoside could be considered as a promising natural agent to attenuate or prevent the development of atherosclerosis. This bioactive compound which is a major constituent in mountain tea could contribute to its potential anti-atherogenic effects.

Phenolic acids

Phenolic acids are widely well-known for their important biological activities[24]. Chlorogenic acid is one of the most abundant phenolic acids in human diet and in species of genus *Sideritis*. In recent years, chlorogenic acid has gained considerable attention due to its great antioxidant, anti-inflammatory, anti-diabetic, anti-obesity, and antihypertension properties[25]. It is considered as a potential natural anti-atherosclerotic agent because of its hypolipidemic, anti-inflammatory, antioxidative, antiplatelet and vascular endothelial properties[26]. Wu et al. (2014) evaluated the effect of chlorogenic acid on atherosclerosis development *in vivo* in ApoE knock-out mice, as well as its mechanism of action[27]. They mentioned that this phenolic compound decreased the atherosclerotic lesion area and vascular dilatation in aortic root compared to the control compound, atorvastatin. Furthermore, chlorogenic acid reduced cholesterol, triglycerides, LDL and inflammatory markers in plasma. The oxLDL-induced lipid accumulation was suppressed by chlorogenic derivatives in RAW264.7 cells, as well as cholesterol efflux was stimulated. In addition, chlorogenic acid improved the mRNA levels of PPARγ, LXRα, ABCA1, ABCG1 and the transcriptional activity of PPARγ.

CONCLUSION

The data presented here demonstrate that mountain tea potentially reduces atherosclerosis development due to its rich content in polyphenols. Polyphenols have been thoroughly studied for their significant pharmacological effects. Of great importance are their antioxidant and anti-inflammatory activities. Thus, mountain tea could exert potent anti-atherogenic effects, in parallel to its strong antioxidant and anti-inflammatory capacity. It can be suggested that it could be used as a natural agent in terms of prevention and treatment of atherosclerosis. However, further *in vivo* studies are necessary in order to specify its anti-atherogenic effects and its exact mechanisms of action.

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ΠΕΡΙΛΗΨΗ

Τσάι του βουνού: Πιθανός αντι-αθηρογόνος παράγοντας;

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Η αθηροσκλήρωση αποτελεί την κύρια αιτία καρδιαγγειακών παθήσεων. Τα τελευταία χρόνια, τα φαρμακευτικά φυτά θεωρούνται αποτελεσματικοί παράγοντες στην πρόληψη και στη συμπληρωματική θεραπεία της αθηροσκλήρωσης. Το τσάι του βουνού (Σιδηρίτις) χρησιμοποιείται στη παραδοσιακή θεραπευτική έναντι του κοινού κρυολογήματος και των γαστρεντερικών διαταραχών. Οι ευεργετικές του ιδιότητες αποδίδονται στα βιοδραστικά συστατικά του. Οι πολυφαινόλες εμφανίζουν ένα ευρύ φάσμα φαρμακολογικών δράσεων όπως αντιοξειδωτική, αντιφλεγμονώδη και αντι-αθηροσκληρωτική δράση. Η παρούσα ανασκόπηση συνοψίζει και συζητά τη πιθανότητα το τσάι του βουνού να αποτελεί συμπληρωματικό αντι-αθηρογόνο παράγοντα βάσει των βιοδραστικών δευτερογενών μεταβολιτών του και τις αναφερόμενες φαρμακολογικές τους δράσεις.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Τσάι του βουνού, γένος Sideritis, αντιοξειδωτική, αντιφλεγμονώδη, πιθανή αντι-αθηρογενετική δράση, πολυφαινόλες*

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