Review Article

Potential Antithrombotic Effect of *Crataegus* Species

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ABSTRACT

Hawthorn (*Crataegus*), a highly important medicinal and aromatic plant, has been used for many years in the treatment of various diseases. In folk medicine, hawthorn has been used to treat asthma, hyperlipidemia, heart failure, and pain. Today, one of the predominant uses of hawthorn extract is to combat *Cardiovascular* diseases (CVDs), such as angina, hypertension, arrhythmias, and congestive heart failure. *Crataegus* species contain flavonoids, proanthocyanidins, organic acids and certain amines. Since thrombus is one of the most common causes of many CVDs, the purpose of this review is to evaluate the antithrombotic effect of various hawthorn species and some of their constituents. In the previously conducted research, we have investigated the antithrombotic effects of the ethanol extracts of *Crataegus orientalis*, *C. monogyna*, *C. davisii*, and also, apigenin, vitexin, quercetin, hyperoside, flavonoids which are found in the *Crataegus* species, in the carrageenan-induced tail thrombosis model. Our results have shown that the extracts and the flavonoids of the *Crataegus* species are potentially effective against thrombosis and therefore it can be considered as candidates for the development of new antithrombotic agents and for use in complementary medicine as well.

INTRODUCTION

Medicinal and aromatic plants (MAPs) play an important role in primary health care around the world. A member of the Rosacea family, hawthorn (*Crataegus* spp.) is one of the most important medicinal plants and has been used for the treatment of various diseases. *Crataegus* spp. is comprised of approximately 300 species. It has been reported that many different species of hawthorn are used as herbal drugs in China, Germany, France, and England.[1-2] The extracts or tinctures derived from the leaves, flowers, and/or fruits of *Crataegus* spp have been used for the treatment of cardiovascular diseases, including angina, hypertension, arrhythmias, and congestive heart failure.[1-3] The main constituents of hawthorn are flavonoids, proanthocyanidins, organic acids, sugars, and certain amines. It has been well-documented that certain flavonoids, such as apigenin, vitexin, rutin, quercetin and hyperoside, are largely found in the *Crataegus* species.[4-5] The leaf, flower and fruit constituents which responsible for free radical scavenging activity are epicatechin, vitexin, hyperoside, and chlorogenic acid. They are among the best anti-lipoperoxidants, which are believed to be effective in the treatment of CVD. In addition, the *Crataegus* species have anti-inflammatory, analgesic effects and hypolipidemic.[3,6-8]

The thrombosis formation is a complex process involving blood vessel injury, platelet adhesion, and aggregation. It also plays a major role in the formation of atherosclerotic plaques and CVD. Thrombus formation leads to the occlusion of vessels. As CVDs are one of the chief causes of morbidity and mortality throughout the world, effective treatment and prevention of thrombosis are key in mitigating these diseases.[9-11] In this review, we aimed to compile our studies which have conducted on various hawthorn

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species and some of their constituents to evaluate their antithrombotic effect.

MATERIALS AND METHODS

We used the carrageenan-induced tail thrombosis model in our studies. This model is particularly useful for studying antithrombotic and thrombolytic agents on small laboratory animals without causing them severe stress. In this model, once carrageenan is administrated, a red wine-colored part appears in the tail tip of the rodent, the extent of thrombosis increases over time, and typical dry necrosis is observed in the pathogen region.[12-13] All extracts and flavonoids were administered in amounts of 50, 100, 200 and 300mg/kg. After test material administration of test materials, 40 microliters of Type-I carrageenan was administered intraplantarly. Carrageenans are polysaccharide polymers which are extracted from red seaweeds. Kappa-carrageenan is the most potent thrombogenic of the carrageenan types. Type I carrageenan contains high amounts of kappa carrageenan. In mice, the length of tail thrombosis was measured and photographed between the 24h and 72h period at predetermined time intervals.[14-16]

RESULTS AND DISCUSSION

Crataegus species and their flavonoids have significant antithrombotic effects. High doses of the ethanol extract of *C. orientalis* and *C. monagyna* leaves had a significant antithrombotic effect at all time intervals, whereas low doses of *C. davisii* extract were more significant than the high doses of extract between hour 24 and hour 72. Vitexin and apigenin showed antithrombotic activity at all doses, while hyperoside and quercetin showed a significant effect only at high doses for all time intervals.[14-16] Flavonoids are important biologically active compounds that are found in many medicinal plants. The pharmacological effects that hawtorn has are thought to originate from the flavonoids that it contains. Flavonoids are potentially effective in the treatment of inflammation, pain, cancer, rheumatic disease, depression, allergies, CVDs, and diabetes mellitus.[17] In our studies, the flavonoids have been shown to play a significant role in the antithrombotic effect of the *Crataegus* species.

In our studies, we used carrageenan, which is commonly employed in different pharmacological studies (e.g. anti-inflammatory and antithrombotic), to generate the formation of thrombus. It has been reported that the thrombotic activity of carrageenan results from the activation of the Hageman factor, also known as factor XII, which is followed by intravascular coagulation.[18] Inhibiting TXA_2 release, decreasing the level of Ca^{+2} in platelets or blocking glycoprotein IIb/IIIa receptors may be the mechanism of the antithrombotic effects of flavonoids. It has been reported that thrombosis mechanisms of carrageenan originate from interleukin-1 (IL-1) and the tumor necrosis factor (TNF) which are released from local blood vessel inflammation. These factors impair the function of normal endothelial cells, leading to impaired balance between hemagglutination and fibrinolysis.[19-20] As stated above, flavonoids have anti-inflammatory and antioxidant effects, and thrombosis formation is significantly related with inflammation. Therefore we think that these effects are associated with the antithrombotic effects of *Crataegus* extract and their flavonoids. It has been reported that some of the antithrombotic action mechanisms of flavonoids include the elevation of cAMP levels in platelets, reduction in phospholipase C formation and intracellular Ca^{+2} levels, and inhibition of TxA_2 formation.[17]

CONCLUSION

Crataegus species and their flavonoids can be used against thrombosis as therapeutic agents in complementary medicine. They can also contribute to the development of new antithrombotic agents. Hawthorn should be used with caution, in terms of side effects, when combined with other antithrombotic drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

MAPs: Medicinal and aromatic plants; **CVDs:** Cardiovascular diseases; **IL:** Interleukin; **TNF:** Tumor necrosis factor; **TXA2:** Thromboxane A2.

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PICTORIAL ABSTRACT

24h after carrageenan injection the antithrombotic effect of ethanol extract of *Crataegus orientalis* (a: SF, b: 200mg/kg *Crataegus orientalis* extract, c: 300mg/kg *Crataegus orientalis* extract

SUMMARY

- The ethanol extracts of *Crataegus orientalis, C. monogyna, C. davisii* have antithrombotic effect at different doses.
- Apigenin, vitexin, quercetin, hyperoside, flavonoids which are found in the Crataegus species and they showed antithrombotic effect at carrageenan-induced tail thrombosis model.
- Crataegus species and their flavonoids can be used against thrombosis as therapeutic agents in complementary medicine.

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