

## Mechanisms of Action that Contribute to Efficacy of *Aesculus hippocastanum* (Aescin, Horse Chestnut) in Hemorrhoidal Disease: Pharmacokinetics and Therapeutic Profile

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### Abstract

The use of medical remedies including flavonoids, diosmin, calcium besilate and horse chestnut etc. is very common and found very useful in the relief of symptoms and pain related to hemorrhoidal disease, even in pre and postoperative period. The active constituent found in horse chestnut seed extract (HCSE), aescin (*Aesculus hippocastanum*, *hippocastanaceae*), is a mixture of triterpene saponins present in two forms (alpha and beta) with other constituents including bioflavonoids (quercetin and kaempferol), proanthocyanidin A2 (an antioxidant), and the coumarins fraxin and aesculin. Aescin molecule, itself, has all antiedematous, anti-inflammatory and venotonic properties. Venotonic effect is mediated by its sensitizing activity on Calcium channels in the vessel wall, which results in a powerful contractility. Increased prostaglandin F2 release also antagonizes the effects of vasodilatory amines, and aescin preserves connective tissue structure by antagonizing the proteoglycan degradation. When given two times daily (per oral, 50 mg aescin in tablet form), adequate therapeutic steady-state levels and excellent bioavailability are achieved. In the present study, we interrogated the commonly used HCSE, aescin, which is responsible for its anti-exudative, venotonic, venoprotective and anti-inflammatory properties and recently investigated apoptotic and antioxidative effects, by help of experimental and clinical studies published in the English-written literature.

**Keywords:** Hemorrhoid; Horse Chestnut; Aescin; *Aesculus hippocastanum*; Medical Treatment

### *Aesculus hippocastanum*

Horse chestnut is a rapidly growing tree which is native to Balkan peninsula, West and Middle Asia and Northern America. The tree has four to seven leaflets and the fruit contains a bright brown-colored seed. The most important active constituent of horse chestnut seed extract (HCSE) is aescin (*Aesculus hippocastanum*, *hippocastanaceae*). It is a mixture of triterpene saponins present in alpha and beta forms, distinguished by their different levels of water solubility and melting points. The other main constituents of HCSE are flavonoids (quercetin and kaempferol), proanthocyanidin A2 (an antioxidant), aesculin and fraxine [1,2].

### Mechanism of action

Aescin, the primary component of HCSE, has antiedematous, anti-inflammatory and venotonic properties [3]. The primary action can be attributable to decreased vascular permeability, allowing a higher sensitivity of calcium channels, resulting in increased venous and arterial tone [4]. This sensitizing effect to ions and other molecules like serotonin (5-hydroxytryptamine, 5-HT) enhances venous contractile activity and explains its anti-edematous property. It has also been suggested that aescin-stimulated release of prostaglandin F2

antagonizes the effects of vasodilatory enzymes, serotonin and histamine, and vessel wall tonus is preserved. Aescin has also been shown to preserve connective tissue structure by antagonizing elastase and hyaluronidase, which are responsible for proteoglycan degradation [1,4]. The anti-inflammatory effect of aescin has been attributed to its interference with neutrophil activation and adherence. The associated release of inflammatory mediators are inhibited, as well. Proanthocyanidin A2, an antioxidant, found in triterpene saponin constitute of aesculin may explain its role in the battle against oxidative stress and free oxygen radicals which are proven to be important factors in the etiopathogenesis of many diseases including hemorrhoids [1]. In a recent study, it has been shown that HCSE inhibits lysosomal enzymes, free radicals and lipid peroxidation products [5]. In another study published in 2013, aescin has an apoptotic effect, which is vital in the clearance of damaged cells in the inflammatory environment [6].

### Pharmacokinetics and toxicity

Aescin is generally well tolerated. The reported rate of adverse reactions ranges from 0.9 to 3% [7]. Nausea, diarrhea, dizziness, headache and itching are among the most commonly seen side effects. Lesser skin sensitivities characterized by redness and itching and a case of acute anaphylactic reaction have been reported in case of its topical application [8]. The most commonly employed oral dosage of aescin is 100 - 150 mg/day. However, in acute hemorrhoidal crises, the dosage can be doubled safely. In a recent randomized study done with 50 mg aescin in tablet form given to 18 Caucasian volunteers of both sexes, kinetic evaluations covering a 24h cycle of two successive dose intervals has been evaluated [9]. This study confirmed the data from the previous trials done with a  $T_{max}$  around 2h after first dose and a  $t_{1/2}$  around 6 - 8h. All these findings confirm the excellent bioavailability of beta aescin and the potential to sustain steady-state level necessary for therapeutic effect when given two times/day (per oral). Clinically, a double-blinded placebo-controlled study evaluating efficacy and safety of aescin in patients with acute hemorrhoidal crises has shown that 40 mg aescin, used three times/day per oral, for a two-month period was safe [10]. In this study, 38 patients using aescin tablets and 34 patients in the placebo group were compared. Rectoscopic exam at the beginning of treatment revealed bleeding and swelling in 28 and 34 patients using aescin tablets, respectively; versus 18 and 33 patients in the placebo group. 81% of treatment group showed a considerable improvement in symptoms versus 32.4% in the placebo. Rectoscopic exam showed an important improvement in bleeding in aescin group (94.8%) versus 61.8% in the placebo group; swelling also improved in 86.9% and 38.3% in treatment and placebo groups, respectively. In this study, improvement in symptoms was reported on average after 6 days of treatment while endoscopic signs of healing were recorded after 2 weeks. Several other pharmacokinetic studies have shown that the drugs' plasma half-life is 1h and blood concentration is measured as above 5 ng/mL even after 24h after administration [1]. The retard tablet forms are also available making the release of active ingredient slower and extending the efficacy period. In this form, the drug will be effective in lower doses, and can be recommended even in postoperative period to overcome the discomforting edema [1,4].

### Conclusion

In conclusion, studies with aescin (HCSE) have provided an important amount of evidence for a clinically significant activity in hemorrhoidal disease. Antiedematous, anti-inflammatory, antioxidant, apoptotic and venotonic effects of aescin are important in the relief of symptoms. The excellent tolerability of the active agent in the drug indicates this treatment is of definite benefit in these patients.

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