



Aesculus Hippocastanum (Aescin, Horse Chestnut) in the Management of Hemorrhoidal Disease: Review

Hemoroidal Hastalığın Tedavisinde Aesculus Hippocastanum (Aescin, At Kestanesi) Kullanımı: Derleme

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ABSTRACT

Medical treatment is very important in the relief of symptoms and pain related to hemorrhoidal disease, even in advanced cases with absolute surgical indication. Medical remedies containing components such as flavonoids, diosmin, calcium dobesilate, oxerutin, and horse chestnut (*Aesculus hippocastanum*, Hippocastanaceae family) are commonly used in the medical management of hemorrhoidal disease. The primary active constituent found in horse chestnut seed extract, aescin, is a mixture of triterpene saponins present in two forms, alpha and beta, which are distinguished by their water solubility and melting points; other constituents include bioflavonoids (quercetin and kaempferol), proanthocyanidin A2 (an antioxidant), and the coumarins fraxin and aesculin. The anti-inflammatory, antiinflammatory and venotonic properties observed are due exclusively to aescin. Its venotonic effect was shown to be mediated by its sensitizing activity on ion channels in the vessel wall, especially to calcium, which results in an increase in contractility. It has also been proposed that enhanced release of prostaglandin F2 antagonizes the vasodilatory effects of histamine and serotonin, and venous wall damage is reduced by antagonizing proteoglycan degradation, which aids in the preservation of connective tissue integrity. Horse chestnut extract, which owes its antiseptic, venotonic, vasoprotective, and antiinflammatory properties to its aescin content, has emerged as an important agent that can facilitate the treatment of every stage of hemorrhoidal disease. In this review, we investigated these effects as well as its more recently studied apoptotic and antioxidant effects in light of experimental and clinical studies published in the literature.

Keywords: Hemorrhoid, horse chestnut, aescin, aesculus hippocastanum, medical treatment

ÖZ

Cerrahi tedavi indikasyonu olan ileri derecede hemoroidler de dahil olmak üzere tüm hemoroid çeşitlerinin semptomatik tedavisi ve ağrı sağaltımında medikal tedavi büyük önem taşımaktadır. Hemoroidin medikal tedavisinde, flavonoid, diosmin, kalsiyum besilat, okserutin, at kestanesi, vb. maddeleri içeren ilaçlar yaygın olarak kullanılmaktadır. At kestanesi, içeriğinde yer alan aescin'in (*Aesculus hippocastanum*, hippocastanaceae ailesi) suda çözünürlük ve erime noktasına göre birbirinden ayırılan alfa ve beta triterpene saponin karışımından oluştuğu; bunun dışındaki bileşenlerin ise bioflavonoidler (quercetin ve kaempferol), proanthocyanidin A2 (bir antioksidan) ve coumarinler (fraxin ve aesculin) olduğu gösterilmiştir. Antiödematöz, antiinflamatuvar ve venotonik etkileri triterpene saponin içeriğine bağlanmaktadır. Venöz damar duvarındaki iyon kanallarında, özellikle kalsiyuma, duyarlılığı artırarak kontraksiyonu artırdığı ve tonik etkisini gösterdiği ispatlanmıştır. Ayrıca, ven duvarında artan prostaglandin F2 salınımı ile histamin ve serotonin'in vazodilatör etkisinin antagonize edildiği; üstelik doku mukopolisakkarid katabolizmasında azalmaya yol açarak bağ doku integritesini korumaya da yardım ettiği ileri sürülmektedir. Bu çalışmada, hemoroidal hastalığın her evresinde tedaviye yardım edebilecek önemli bir ajan olarak ortaya çıkan at kestanesinin aescin içeriğine bağlı antioksidatif, venotonik, venoprotektif ve antiinflamatuvar özellikleri ile, son zamanlarda üzerinde çalışılmakta olan, apoptotik ve antioksidatif özellikleri, literatürde yer alan deneysel ve klinik çalışmalar eşliğinde irdelenmiştir.

Anahtar Kelimeler: Hemoroid, at kestanesi, aescin, aesculus hippocastanum, medikal tedavi



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Introduction

Hemorrhoidal disease is an anorectal condition involving symptomatic enlargement and distal displacement of the normal anal cushions. The term hemorrhoid is derived from a combination of the Greek words haima (blood) and rhoos (flow), and awareness of the condition and efforts to manage it date back centuries. Hemorrhoidal disease can affect over 30% of the population at any stage of life and affects both sexes.¹ The main theories regarding its development include abnormal dilation of the hemorrhoidal plexuses originating from branches of superior and middle hemorrhoidal veins, excessive distension of arteriovenous anastomoses adjacent to the anal cushions, distal displacement and prolapse of the anal pads, and destruction of the surrounding connective tissue over time. Genetic factors, anatomical structure, diet, constipation, and factors that increase intra-abdominal pressure (excessive straining, multiple pregnancy, chronic cough) have been implicated in its etiology. Age-related deformation of the supporting connective tissue becomes more evident starting in the third decade. Symptoms may include venous distension, erosion, bleeding, and thrombosis.² Hemorrhoids are classified according to location (internal/external/mixed) and degree of prolapse (grade 1-4).² External hemorrhoids originate from the inferior hemorrhoidal plexus, are covered by modified squamous epithelium, and form below the dentate line; they may become thrombotic or ulcerated. Internal hemorrhoids originate from the superior or middle hemorrhoidal plexus and are covered by mucosa. In grade 1 hemorrhoids, the vessels in the anal canal increase in number and size, and may cause anal bleeding during defecation. Grade 2 and 3 hemorrhoids prolapse from the anal canal upon defecation, but grade 3 hemorrhoids require manual reduction. Grade 4 hemorrhoids are prolapsed and irreducible.³ Hemorrhoids may also arise both above and below the dentate line, which are called mixed (interno-external) hemorrhoids. Following history-taking and clinical, digital rectal, and rectosigmoidoscopic examinations, a definitive diagnosis is made and the treatment phase begins. Medical treatment is critical in relieving the symptoms and pain caused by hemorrhoidal disease at all stages, including advanced cases with absolute surgical indication. Constipation relief medications, dietary restriction with a fiber-rich diet, and sitz baths are often suggested to alleviate symptoms. Increasing fiber and water intake, reducing consumption of oily and spicy foods, practicing anal hygiene, avoiding straining while defecating, and avoiding medications that cause constipation and diarrhea are also important.⁴ The efficacy of topical creams, ointments, and suppositories used to reduce edema and pain is debated.⁵ However, medications containing

substances such as flavonoids, diosmin, calcium dobesilate, oxerutin, and horse chestnut are widely used in the medical treatment of hemorrhoids.⁶ A meta-analysis by Alonso-Coello et al.⁷ comparing patients who did and did not take flavonoids showed that the use of flavonoids reduced the incidence of anal bleeding and pain by 65% and recurrence by 47%. The venotonic effect of flavonoids was first exploited in venous insufficiency and edema. Micronized purified flavonoid fraction (MPFF) consisting of 90% diosmin and 10% hesperidin has been used in the treatment of hemorrhoids. Micronization of the particles was shown to accelerate their effect, and some randomized trials suggested that it decreased bleeding by 67%, pain by 65%, and itching by 35%, with a 47% reduction in recurrence.² In other studies it was claimed that MPFF also reduced bleeding and pain after hemorrhoidectomy.⁸ Following these studies, horse chestnut extract (aescin), which has been used as an herbal product for centuries, gained attention as a part of an increasingly widespread treatment approach using vasoactive drugs, due to its anti-hemorrhagic and anti-inflammatory effects. In fact, the utility of horse chestnut in hemorrhoid treatment was demonstrated clinically in other studies conducted long before the Alonso-Coello et al.⁷ study highlighting the effects of flavonoid drugs. In a placebo-controlled study including 80 patients, those treated with 40 mg aescin (horse chestnut extract) 3 times a day showed improvement in hemorrhoid symptoms and endoscopic findings; bleeding was reduced by 94% after two weeks of treatment, while 81% of patients had a marked decrease in symptoms within 6 days.⁹ In that study, the patients showed fairly high drug tolerance, and the effect of aescin against hemorrhoidal bleeding and edema was determined to be highly significant. The anti-edema and anti-inflammatory properties of aescin and its relationship with the hypothalamic-pituitary-adrenal axis were discovered and published long before the abovementioned studies.¹⁰ Horse chestnut (*Aesculus hippocastanum*, Hippocastanaceae family) possesses antiseptic and venotonic effects due to its aescin content.^{9,10} Its vasoprotective and anti-inflammatory properties have also been the subject of research. The molecular effect of aescin in chronic venous insufficiency, hemorrhoids, and postoperative edema has been associated both *in vitro* and *in vivo* with the restoration of venous tension via facilitation of ion transport through channels in the vessel walls.¹¹ In order to understand the mechanisms of these actions, one must first focus on the molecular structure of aescin. Aescin, the primary active compound in horse chestnut extract, is a mixture of two forms of triterpene saponin, alpha and beta, which are distinguished by their solubility in water and melting point. Other

components of horse chestnut include bioflavonoids (quercetin and kaempferol), proanthocyanidin A2 (an antioxidant) and coumarins (fraxin and aesculin).¹² Lorenz and Marek¹³ first recognized the anti-edematous and vasoprotective properties of horse chestnut extract in 1960 and attributed them to another active agent, aesculin. Similarly, in a study conducted in 2001, Sirtori¹⁴ attributed the anti-edematous, anti-inflammatory, and venotonic effects of aescin to the triterpene saponin component. It has been demonstrated in animal studies that it exerts its tonic effect by increasing the sensitivity of ion channels in the venous vessel wall, particularly to calcium.^{15,16} These studies also showed that increased release of prostaglandin F2 in the venous wall antagonized the vasodilator activity of histamine and serotonin 5-hydroxytryptamine and suggested that it also contributes to the preservation of connective tissue integrity by reducing catabolism of tissue mucopolysaccharides.¹⁷ The triterpene saponin content of aescin contains the antioxidant proanthocyanidin A2. As we understand more about the role of oxidative stress and free radical mechanisms in the etiopathogenesis of various diseases, recent studies in this area have started to focus on the antioxidant properties of horse chestnut. Kucukkurt et al.¹⁸ determined that horse chestnut has antioxidant properties that inhibit free radicals, lipid peroxidation, and lysosomal enzymes. Based on the hemorrhoidal symptomatic relief provided by aescin-containing horse chestnut tea used in the Turkish community, they investigated its effects on the blood and tissue antioxidant defense system of male rats *in vivo*. The authors measured oxidative stress markers malonyl dialdehyde, reduced glutathione, and superoxide dismutase as well as catalase levels in blood and tissue samples of male rats who received aescin extract (100 mg/kg) mixed with either standard feed or high-fat feed for 5 weeks. Aescin was shown to have protective effects against oxidative stress even in rats eating high-fat feed and under high oxidative stress. In a 2013 study by Güney et al.¹⁹, aescin significantly increased apoptosis, which has a vital role in clearing damaged cells, in an H-ras transformed 5RP7 cell line. Considering the role of oxidative stress and apoptosis in inflammation, the antioxidant and apoptotic effects of aescin are gaining value. In addition to these effects, a recent study also suggested that aescin extract chemosensitized human pancreatic cancer cells by inhibiting the nuclear factor kappa B signaling pathway.²⁰ That study emphasized the role of aescin's aforementioned apoptotic activity. In pharmacokinetic studies on aescin, the active component had a half-life of approximately 17 hours when taken orally, and blood levels remained above 5 ng/mL even 24 hours after intake. Because it is formulated as a retard

tablet, the active agent is released slowly and maintained at therapeutic blood concentrations for a longer time. In a comparative bioavailability study including solutions containing horse chestnut seed extract, the retard tablet formulation provided a maximum blood concentration only 5% lower but maintained efficacy in the blood for longer. This pharmacokinetic profile enables extended activity at low doses. The prolonged action of the drug and its anti-edematous and anti-inflammatory properties suggested that it may be beneficial during recovery following hemorrhoid surgery, and its use for this indication is rapidly increasing.^{14,21} Side effects have been reported at rates of 0.6-3% in clinical trials, and mostly consist of dizziness, headache, pruritus, and gastrointestinal symptoms.^{22,23} In summary, horse chestnut extract, which possesses antiseptic, venotonic, vasoprotective, and anti-inflammatory properties due to its aescin content, is emerging as an important agent that can facilitate the treatment of hemorrhoidal disease at every stage. Moreover, its apoptotic and antioxidant properties, which have received more attention recently, also make this herbal medicine worth further investigation.

Ethics

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ü., Concept: F.E., Design: F.E., Data Collection or Processing: E.Ü., Analysis or Interpretation: E.Ü., F.E., Literature Search: E.Ü., Writing: E.Ü., F.E.

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