

A REVIEW ON β -ESCIN

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Abstract

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β - escin is a mixture of triterpene saponins and other components including alpha aescin, progestoescigenin, barringtonol, cryptoescin and benzyopyrones. Baescin or β -escin isolated from the horse chestnut seeds (*Aesculus hippocastanum* L.) β -escin has been traditionally used to treat conditions such as chronic venous insufficiency, inflammation, hemorrhoids, edema, elevated glucose, obesity, and cerebral ischemic damage. The drug shows its property in clinical trial's patient with HIV-1 used as a traditional medicines.

Introduction

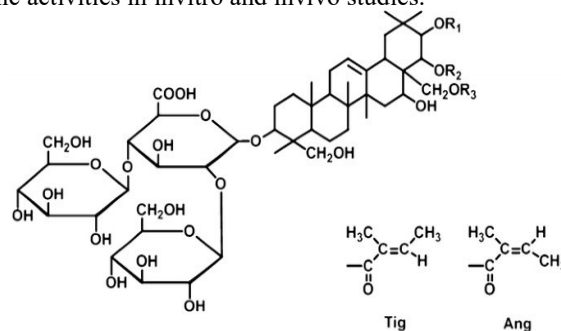
Escin is the active component of *Aesculus hippocastanum*, the horse chestnut, which was itself for centuries,[1] and is still used to treat certain conditions, including hemorrhoids,[2] varicose veins, hematoma, and venous congestion.[3] Escin was first isolated in 1953, and has demonstrated antiedematous, anti-inflammatory, and venotonic properties in various preparations.[4] It has also shown effectiveness as an adjunct or alternative to compression therapy, and is known to act directly on endothelial hypoxia [5]. chronic venous insufficiency (CVI) used as a traditional medicine [15,16].

The clinical reports on vascular efficacy of β -escin draw particular attention to improved microcirculation, reduced vascular permeability, increased venous tone and venous return, all which lead to edema reduction (reviewed in [17,18]). It has been suggested that the observed effects result from protection of endothelial cells from hypoxia and inflammatory stimuli provided by the drug [19]. In fact, as shown in preclinical studies, β -escin conserves ATP during oxygen shortage [20], decreases histamine response [21] and cytokine release [22], attenuates serotonin-induced capillary hyperpermeability [23], suppresses extravasation and leukocyte migration [24] and preserves endothelial cell morphology [25]. Worth mentioning are also data indicating antioxidant potential of β -escin [26,27] and its inhibitory effect on hyaluronidase, an enzyme implicated in the pathogenesis of CVI [28]. In more recent studies inflammation attenuating properties of β -escin has been linked to its modulatory effect on the TNF- α -mediated inflammatory pathways [29].

Despite the therapeutic significance of β -escin and the popularity of the drug which in the United States and Europe remains one of the bestselling herbal extracts accounting for 226 million U.S. dollar-market in 2014 (IMS Kilochem), its exact mechanism of action remains unknown [18]. In the present study we applied a broad experimental approach, including global discovery type and targeted proteomic methods in conjunction with cellular biology tools to identify novel pathways underlying the protective effects of β -escin in human endothelial cells under inflammatory conditions. The obtained results indicate that the vascular antiinflammatory mechanism of β -escin involves disturbances in cholesterol homeostasis leading to cytoskeletal perturbations followed by decreased NF κ B activation.

Chemistry of β - ESCIN

Aescin or escin, is a pentacyclic triterpene that exists in two series of α and β isomer [30] defined by position of an acetyl group at C22 and C28, respectively (Fig.1). β -escin, the major active component in extracts of horse chestnut seeds (HCSE), is primarily composed of escin Ia and escin Ib [31], while α -escin is mainly composed of isoescin Ia and isoescin Ib. In the late nineties, Yoshikawa et al. isolated the bioactive triterpene oligoglycoside escin Ia, Ib, and IIIa, and isoescins Ia, Ib, and V from the seeds of the horse chestnut tree, and explained the structure based on the chemical and physicochemical evidence [32,33]. Haralampidis et al. reviewed the biosynthesis of triterpenoid saponins and cyclisation of 2,3-oxidosqualene. Here, we review reports from various investigators over the last two decades describing β -escin major, the active principle of *Aesculus hippocastanum* L. (Hippocastanaceae), focusing on its anti-carcinogenic activities in invitro and invivo studies.



Saponins	R ₁	R ₂	R ₃
Escin Ia (β)	Tig	-COCH ₃	-H
Escin Ib (β)	Ang	-COCH ₃	-H
Isoescin Ia (α)	Tig	-H	-COCH ₃
Isoescin Ib (α)	Ang	-H	-COCH ₃

Fig.1 Escin

Mechanism of β -escin

β escin has many pharmacological and biochemical activity, including venous insufficiency (CVI), haemorrhoids and post-operative oedema. In one controlled trial aescin was shown to be as effective as compression therapy as an alternative to medical treatment for CVI. The therapeutic benefit is well supported by a number of experimental investigations in different animal models, indicative of clearcut anti-oedematous, antiinflammatory and venotonic properties, mainly related to the molecular mechanism of the agent, allowing improved entry of ions into channels, thus raising venous tension in both in vitro and in vivo conditions. Other mechanisms, i.e. release of PGF₂ from veins, antagonism to 5-HT and histamine, reduced catabolism of tissue mucopolysaccharides, further underline the wide ranging mechanisms of the therapeutic activity of aescin. Aescin exists in two forms, α and β . β -aescin (b-escin) appears to be the active component of the mixture and is the molecular form present in major available pharmaceutical products. Beta-aescin has cytotoxic activity toward human colon adenocarcinoma cell lines.[34]

Anti Edematous

HCSE administration increases sensitization to calcium ions, decrease permeability of small vessels, and enhance venous contractile activity, thereby improving venous tone and having a 'sealing effect' at the sight of injury. The end result is decreased edema and swelling [35,36,37]. β -escin's anti-edematous property is also attributed in part to its inhibition of hypoxia and the resultant reduction of ATP content in endothelial cells, reduced endothelial ATP levels initiate the release of prostaglandins, platelet activating factor and neutrophil chemotaxis, leading to venous stasis and edema [38,39]. β -escin also reduced the adherence and activation of white blood cells, thereby inhibiting edema and protecting the vessels [40].

Anti inflammatory

The anti-inflammatory property of βescin have been demonstrated in animal model and suggest it interferes with the release of inflammatory mediators by decreasing leukocyte activation n adhesiveness. In a rat model of pleurisy, βescin administration decreases leukocyte migration into pleural cavity and inhibited the release of inflammatory mediators[42]. A human study of patients with chronic insufficiency showed 5gm βescin given intravenously twice daily for a week resulted in a 33-percent reduction of leukocyte density, a 50-percent decrease in macrophage number, and a 46-percent increase in neutrophils in inflammatory exudates.

In vivo Anti-cancer Effects of β-escin

Therapeutic plants have a long history of utilization in customary medication. Ethno-herbal data on therapeutic plants and their utilization by indigenous societies is valuable in the preservation of conventional societies, biodiversity, network medicinal services and medication advancement[44]. The anti-carcinogenic activities of βescin have been established in animal models of some cancers. We have shown a dose dependent chemo preventive effect of β-escin (250 and 500 ppm) on the formation of azoxymethane (AOM) induced colonic aberrant crypt foci (ACF) containing four or more aberrant crypts in F344 rats [44]. The potential antitumor activity of β-escin was evaluated by Zhou et al. [18] in hepatocellular carcinoma in vivo. At a dose of 2.8 mg/kg, escin caused a 43.5 % inhibition of H22 tumor growth in mice. Wang et al. [45] observed that escin augmented the therapeutic effect of gemcitabine in xenografts of the BxPC-3 cell line in nude mice. Tumors were established by subcutaneous injection of 5×10^6 BxPC-3 cells into the flanks of six-week-old nude mice. When tumors reached a volume of 120 mm³, the mice were injected IP with 2 mg/kg of β-escin once daily and/or 100 mg/kg gemcitabine twice weekly. A significant reduction of tumor volume (251.9 ± 43.8 mm³) was observed in the group receiving the combination therapy, compared with the control group (536.1 ± 59.3 mm³) or the groups given either agent alone. Recently, we found that administration of 500 ppm of βescin significantly suppressed formation of (methyl nitrosamino)-1-(3-pyridyl)-1butanone NNK induced lung adenoma and adenocarcinoma formation in female A/J mice by >40 % at 20 weeks, and by 53.3 % ($p < 0.0001$) at 36 weeks of age [46]. The above studies clearly support the potential chemopreventive properties of naturally occurring βescin. Thus, it will be important to carry out further studies to establish the optimal dose range and the efficacy of β-escin in various animal models of adenocarcinoma.

Pharmacokinetics

Very high concentration of β-escin were measured in skin and muscle tissues underlying the site of topical application of radiolabelled sodium escinate. Low values were measured in internal organs, blood, urine, skin and musculature from other parts of the body. A range of 0.5-1% of the applied dose was excreted in urine within 24 hours of administration. The total elimination (bile and urine) was calculated at 1-2.5% of the dose. Less than one half is excreted as β-escin, the remainder as metabolites [47].

However, the availability of β-escin to skin and muscle tissue may not be as high as reported in the study, since the radioactivity detected may have been carried by the metabolites of βescin as well as by β-escin itself. Studies indicate that β-escin is eliminated quickly following intravenous injection, with two-thirds excreted via bile and one-third by renal elimination [48].

Clinical Uses of β-Escin

β-Escin has been traditionally used to treat conditions such as chronic venous insufficiency [49], inflammation, hemorrhoids, edema, elevated glucose [50], obesity, and cerebral ischemic damage [51-52], and in clinical trials in patients with HIV-1 [53]. HCSE is widely used in Europe for chronic venous insufficiency (CVI), a syndrome characterized by lower extremity edema and varicosities [56-58]. The anti-inflammatory effects of β-escin are mainly attributable to its antihistaminic and anti-serotonergic activities [54]. β-Escin dose dependently enhanced hypoxia induced activation of human endothelial cells and caused inhibition of phospholipase A2, an enzyme responsible for the release of precursors of inflammatory mediators. Recently, Liu et al. observed the in vitro effects of escin on the inflammatory reaction of human periodontal ligament cells, finding a significant blockade of the expression of Toll-like receptor (TLR)2 and decreased pro-inflammatory cytokines interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-6 induced by lipopolysaccharide (LPS; 62). A recent study showed that escin has a potent protective effect on LPS-induced acute lung injury by inhibiting the inflammatory response [55]. Escin also exerts synergistic

anti-inflammatory effects with glucocorticoids [56]. In addition, escin significantly inhibited NF- κ B activation and down regulated the expression of TNF- α , alleviating brain domains rats with traumatic brain injuries[57]. A recent study demonstrated that β -escin has strong anti-allergic properties [58-59]. Although most of these experiments have shown the anti-inflammatory effects of β -escin, there are no studies of the effects of β -escin on inflammation in animal models of carcinogen-induced cancers.

Conclusion

Several studies have examined the benefits of β -escin. The initial evidence supporting the anticancer effects of β -escin come from a number of in vitro studies, which report a significant downregulation of cyclin D, NF- κ B, STAT3, AP-1, and several anti-apoptotic proteins, including Bcl2, Bcl-xL, and survivin. The few preclinical trials conducted in animal models of cancer showed that β -escin has protective and antitumor properties. The ability of β -escin to affect gene transcription and to induce apoptosis in malignant cells supports its potential for cancer chemoprevention and justifies further investigation in drug development programs. It is essential to understand the mechanisms by which β -escin acts on the molecular level to inhibit the carcinogenic process. Given the potential of β -escin as an anti-cancer agent, future studies should focus on detailed preclinical toxicity, bioavailability, pharmacodynamics, tissue distribution, and extensive evaluation of tumor inhibition using adenoma and adenocarcinoma as efficacy end points, before undertaking extensive clinical trials. Later research should examine the synthesis and development of analogs that might prove useful for human clinical studies.

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