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Anti-inflammatory and Anti-cancer Properties of β-Escin, a Triterpene Saponin

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Abstract Horse chestnut seed extract is well known for its anti-edematous and anti-inflammatory medicinal properties. More recently, potential anti-carcinogenic properties have been described. β-Escin, a pentacyclic triterpene saponin with aglycone moieties, is the main active compound in horse chestnut seed extract. Here, we summarize the anti-cancer properties of β-escin in preclinical models, and its potential pharmacological use as an anti-inflammatory agent for the treatment of edema and chronic venous insufficiency. The major mechanisms for the anti-inflammatory activities are through modulation of eicosanoids and nuclear factor-kappa B (NF-kB). Anti-proliferation activities occur via induction of p21 and decreased expression of cyclin D1 and anti-apoptotic members of the Bcl-2 family of proteins. In addition, we discuss the clinical pharmacokinetics of β-escin and review the factors that determine its absorption, bioavailability, and distribution in animals. Despite the many beneficial effects of β-escin, it has been studied less extensively in models of cancer. Further studies are warranted to assess the usefulness of β-escin for cancer prevention and therapy.

Keywords β-Escin · Cancer prevention · Pharmacokinetics · Horse chestnut seed extract · Bioavailability

Abbreviations

iNOS	Inducible nitric oxide synthase
COX-2	Cyclooxygenase
NO	Nitric oxide
NF-kB	Nuclear factor-kB (NF-κB)
VEGF	Vascular endothelial growth factor
HCSE	Horse chestnut seed extract
IL-6	Interleukin-6
CVI	Chronic venous insufficiency
RIA	Radioimmunosorbent assay
IKK	IkappaB kinase complex
Stat3	Signal transducer and activator of transcription 3
JAK	Janus kinase 2
TLR	Toll-like receptor
IL-1β	Interleukin-1β
TNF	Tumor necrosis factor
LPS	Lipopolysaccharide
ALDH	Aldehyde dehydrogenase
CL	Clearance
MRT	Mean residence time
LC	Liquid chromatography
MS	Mass spectrometry
Cdks	Cyclin dependent kinases
Rb	Retinoblastoma
CXC	Chemokine receptor kinase
CRPC	Castration-resistant prostate cancer

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Introduction

Millions of people die each year from chronic diseases, which are a global epidemic [1]. The elimination of risk factors to prevent any given chronic disease has had limited success in reducing the burden of diseases such as cancer, cardiovascular disease, and diabetes [2]. There has been considerable recent public and scientific interest in the use of phytochemicals derived from dietary components or traditional medicines to combat or

prevent human diseases. Among the phytochemicals, triterpenoids are major components of medicinally used herbs and plant extracts [3]. Triterpenoids are metabolites of isopentenyl pyrophosphate oligomers and are ubiquitously distributed throughout the plant kingdom in the form of free triterpenoids, triterpenic glycosides (saponins), phytosterols, and/or their precursors.

Saponins The saponins are a vast group of glycoside compounds found abundantly in plant families like *Sapindaceae*, *Aceraceae*, *Hippocastanaceae*, *Cucurbitaceae*, and *Araliaceae* [4••]. Structurally, saponins are a class of secondary plant metabolites consisting of a sugar moiety glycosidically linked to a hydrophobic aglycone (sapogenin), which may be triterpene or steroidal [4••, 5]. Based on the nature of their aglycone skeleton, the saponins are classified into two groups. The first group consists of the steroidal saponins, which are almost exclusively present in monocotyledonous angiosperms [5]. The second group consists of the triterpenoid saponins, which occur in dicotyledonous angiosperms [6]. Some authors distinguish a third group, called steroidal amines or steroidal alkaloids. The aglycone (glycoside-free) portions of the saponins are termed sapogenins. The number of saccharide chains attached to the sapogenin/aglycone core can vary. The lipophilic aglycone can be any one of a wide variety of polycyclic organic structures originating from the serial addition of 10-carbon (C10) terpene units to compose a C30 triterpene skeleton [7], often with subsequent alteration to produce a C27 steroidal skeleton. Triterpenoid saponins have an aglycone triterpenoid C30 skeleton comprising a pentacyclic structure.

These triterpenoid saponins occur in a number of plant species, both wild and cultivated, that possess divergent biological activities [8–10]. They appear in different plant families and have been isolated from many species by numerous investigators (reviewed in Sprag et al.; 8). The genus Aesculus, commonly called the "buckeye", includes some of the most widely distributed plants in the Northern Hemisphere; this genus consists of 13–19 species that are currently found in eastern Asia, North America, and Europe [11]. Raven et al. [12] and Qiu et al. [13] have documented the North American origin of Aesculus and its family Hippocastanaceae, and their subsequent migration to other continents.

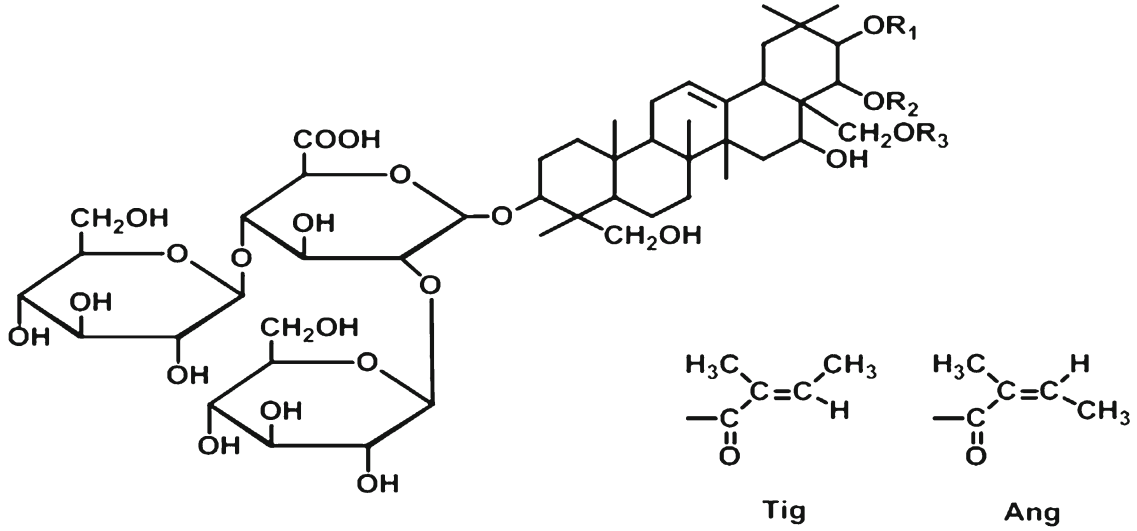
β-Escin Aescin, or escin, is a pentacyclic triterpene that exists in two series of α and β isomers [14, 15•] defined by the position of an acetyl group at C22 and C28, respectively (Fig. 1 and Table 1). β-Escin, the major active component in extracts of horse chestnut seeds (HCSE), is primarily composed of escin Ia and escin Ib [27], while α-escin is mainly composed of isoescin Ia and isoescin Ib. In the late nineties, Yoshikawa et al. isolated the bioactive triterpene oligoglycoside escins Ia, Ib, and IIIa, and isoescins Ia, Ib, and V from the seeds of the horse chestnut tree, and explained the structures based on the chemical and physicochemical evidence [28, 29]. Haralampidis et al. [30] reviewed the biosynthesis of triterpenoid saponins and addressed advances in the areas of the glycosylation of sapogenins and the 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 in vitro and in vivo studies.

Medicinal Uses of β-Escin

The use of β-escin as a folk medicine has been well documented. In China, β-escin has been used traditionally to prevent formation of gas in the gastrointestinal tract, promote the appetite and digestion of food, and as an antiseptic, antioxidant, analgesic, antipyretic, and anti-hemorrhoidal agent [31]. It has been reported previously to exhibit anti-edematous, anti-inflammatory, and anti-carcinogenic properties in various disease models [27]. Perhaps one of the most often prescribed uses is for the treatment of varicose veins and wound healing. It is now recognized that β-escin has some anti-cancer properties.

In vitro Anti-cancer Properties of β-Escin

The mode of action of β-escin varies considerably with the cell type, the concentration, and the time of treatment. Guo et al. [16] reported that β-escin can inhibit the growth of various tumor cell lines, including a human oral mucosal cell line (KB cells), and mouse liver cancer (H22) and sarcoma (S180) cell lines. We demonstrated that β-escin exhibits anti-cancer activity via the induction of p21 in human colon cancer cell lines HT-29 and HCT-116 [17••]. Studies have shown that induction of p21waf1/cip1 leads to reduced cell proliferation of mammalian cells and leads to binding of cyclin-dependent kinase (Cdk2) at amino acids residues 139–164, which are required by the cyclin A and E complex. β-Escin decreases phospho-Rb and cyclin A levels, leading to growth arrest of human colon cancer cells in the G1-S phase and inhibition of further progression and proliferation [17••]. The Rb (retinoblastoma) protein family contains important substrates of the Cdks, and is phosphorylated and dephosphorylated during the cell cycle. The hyperphosphorylated (inactive) form predominates in proliferating cells, whereas the



Saponins	R_1	R_2	R_3
Escin Ia (β)	Tig	-COCH3	-H
Escin Ib (β)	Ang	-COCH3	-H
Isoescin Ia (α)	Tig	-H	-COCH3
Isoescin Ib (α)	Ang	-H	- COCH3

Fig. 1 Structure of β-escin (Figure is adapted from Wei F. et al., publication, Journal of Liquid Chromatography and Related Technologies, 2005; 28: 763–773)

hypophosphorylated (active) form is generally more abundant in quiescent or differentiating cells.

Later studies from other investigators revealed the anti-cancer properties of β-escin in different human cancer cell lines. Zhou et al. [18] demonstrated that β-escin regulates cell cycle progression through the induction of G1/S phase arrest accompanied by significant induction of apoptosis in HepG2 hepatocarcinoma cells. Harikumar et al. [19] reported that escin exhibits antitumor potential against KBM-5 human chronic myeloid leukemia, A293 human embryonic kidney carcinoma leukemia, H1299 human lung adenocarcinoma, Jurkat human T-cell leukemia, and U266 human multiple myeloma cell lines. They reported that Escin suppressed nuclear activation of nuclear factor-kappa B (NF-κB) through inhibition of IkappaB kinase complex (IKK) alpha phosphorylation and degradation, and inhibition of IKK activation, leading to downregulation of NF-kB-regulated cell survival and abrogation of NF-kB-dependent reporter activity [19]. Piao et al. found that treatment of castration-resistant prostate cancer (CRPC) cells, PC-3, and DU-145 cells with β-escin induced G2/M cell cycle arrest with induction of p21, pro-apoptotic proteins like cleaved caspase-3, and poly adenosine diphosphate ribose polymerase (PARP). Tan et al. [21] found that treatment of human hepatocarcinoma HepG2 and PLC/PRF5 cells with β-escin suppressed constitutive and interleukin-6 (IL-6)-inducible signal transducer and activator of transcription 3 (STAT3) activation, and caused downregulation of STAT3-regulated genes, with associated inhibition of c-SRC, Janus kinase 2 (JAK2) activation, cyclin D1, Bcl-2, Bcl-xL, survivin, and vascular endothelial growth factor (VEGF).

A recent study by Ming et al. [22] also demonstrated the anti-cancer effects of β-escin in human hepatocellular carcinoma cells. They showed that β-escin could inhibit proliferation and substantially enhance cytotoxicity of paclitaxel and doxorubicin by downregulating cyclin D1, Bcl-2, Bcl-xL, survivin, and VEGF. Shen et al. [23] reported that treatment of human cholangiocarcinoma cell lines QBC939, Sk-ChA-1, and MZ-ChA-1 with β-escin induces growth arrest and increases apoptosis with collapse of the mitochondrial membrane potential and the activation of the caspase-3 pathway. Ji et al. [24] showed that β-escin inhibits nitric oxide (NO) production and growth of A549 human lung cancer cells by suppressing the JAK/STAT/inducible nitric oxide (iNOS) signaling pathway. Wang et al. [25•] revealed that β-escin can potentiate the anti-cancer effect of gemcitabine in pancreatic cancer cell lines.

Numerous proteins, including c-myc, cyclin D1, Bcl-2, COX-2, Bcl-xL, and survivin, are regulated by NF-kB at the

Table 1 Anticancer effects of β-Escin in vitro and in vivo studies

S.No.	Type of cancer	Organ site/cell lines or animal model	Molecular markers ↓inhibition ↑induction	Reference (#)
In vitro studies				
1)	Human oral, mice liver cancer and sarcoma cell line	KB cells(human Oral) H22 and S180 (Mice)	Growth	Guo et al. [16]
2)	Human colon cancer	HT-29, HCT-116	↑pRB, cyclins A and E ↑p21, apoptosis	Patlolla et al. [17••]
3)	Hepatocarcinoma	HepG2	↓G1/S phase ↑apoptosis	Zhou et al. [18]
4)	Human tumor cells	KBM-5 , A293, H1299 Jurkat, U266	↓COX-2, IAP-2, ICAM-1, MMP-9 VEGF, Bcl-2, Cyclin-D1, Nf-KB, IKK-γ	Harikumar et al. [19]
5)	Human prostate cancer cells	CRPC, PC-3 and DU-145	↓Bcl-2, Bcl-xL, xIAP, cIAP1 ↑Apoptosis, G2/M arrest	Piao et al. [20]
6)	Human hepatocarcinoma	HepG2, PLC/PRF5	↓STAT-3, c-SRC, JAK2, Cyclin D1, Bcl-2, Bcl-xL, Survivin and VEGF	Tan et al. [21]
7)	Human hepatocarcinoma	SMMC-7721	↑Caspase-3,9 and 8 activity Bcl-2	Ming et al. [22]
8)	Human cholangiocarcinoma	QBC939, Sk-ChA-1, and MZ-ChA-1	↓G1/S and G2M phases ↓caspase-3 activity	Shen et al. [23]
9)	Lung carcinoma	A549	iNOS, JAK, STAT 1 & 3 p38 MAPK	Ji DB et al. [24]
10)	Human pancreatic cancer	BxPC-3 & Panc-1	↓c-Myc, COX-2, cyclin D1, survivin, Bcl-2 and Bcl-xL ↑caspase-3 activity	Wang YW et al. [25•]
11)	Human lung cancer	H460	↑Aldh1A1, RhoA, Rock ↓p21	Patlolla et al. [26•]
In vivo studies				
1)	Colon cancer	AOM induced ACF, Formation in F344 rats	↓Preneoplastic lesions, ACF formation	Patlolla et al. [17••]
2)	Hepatocarcinoma	H22 tumors on nude mice	↓43.5 % tumor inhibition	Zhou et al. [18]
3)	Human pancreatic cancer	BxPC-3 nude mice	↓Reduced tumor volume	Wang YW et al. [25•]
4)	Human lung cancer	NNK induced lung cancer in A/J mice	↓40–53 % lung tumor inhibition	Patlolla et al. [26•]

transcriptional level and are linked to chemo-resistance [32–35]. Wang et al. [25•] examined the effect of escin alone or in combination with gemcitabine on the expression of the NF-kB-regulated gene products implicated in cell proliferation, c-myc, cyclin D1, and cyclooxygenase-2 (COX-2), and antiapoptosis, Bcl-2, Bcl-xL, and survivin. They found that the combination downregulated the constitutive expression of c-myc, cyclin D1, Bcl-2, COX-2, Bcl-xL, and survivin in BxPC-3 and PANC-1 human pancreatic cancer cells. Recently, Rammon et al. [36] showed that a combination of Escin with gemcitabine or cisplastin resulted in a significant cytotoxic effect in PANC-1 human pancreatic cells, inducing apoptosis and downregulating the NF-kB signaling pathway [36].

Recently, Guney et al. [37] found that β-escin had potent antiproliferative effects on H-Ras 5RP7 cells, and increased vacuolization and chromatin condensation compared with control, as assessed with transmission electron microscopy [37]. We recently found that treatment of the H460 human lung cancer cell line with different concentrations of β-escin (0–40 μM) induced p21 levels, suppressed Rho A and Rock protein expression, and caused a significant reduction (~60–85 %) in the subpopulation of cells with elevated aldehyde dehydrogenase (ALDH) activity [26•].

From these reports, it is clear that β-escin has a number of anti-cancer activities, including induction of cell cycle arrest and apoptosis, against several human cancer cell lines [16, 17••, 18, 23]. β-Escin has been shown to exhibit significant anti-proliferative activity by inhibiting transcription factors that are involved in various signaling pathways, like JAK, STAT, NFkB, and activator protein-1 (AP-1), in different cell lines [19, 21, 24, 25•]. Studies have shown that β-escin prompts apoptosis [17••] by inducing the cleavage of caspase-3 and caspase-8 [23] and modulating the expression levels of Bcl-2 and Bcl-xL family members [25•]. These events are preceded by the generation of reactive oxygen species (ROS; 29). Recently, Lee et al. [38] showed the potential impact of β-escin in inhibiting AGS human gastric cancer cells' migration and invasion by modulating the CXC motif chemokine receptor CXCL16/CXCR axis [38].

In vivo Anti-cancer Effects of β-Escin

The anti-carcinogenic activities of β-escin have been established in animal models of some cancers. We have shown a dose-dependent chemopreventive 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 [17••]. 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. [25•] 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 mean volume of 120 mm^3, 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 mm^3) was observed in the group receiving the combination therapy, compared with the control group (536.1±59.3 mm^3) or the groups given either agent alone. Recently, we found that administration of 500 ppm of β-escin significantly suppressed formation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone 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 [26•]. The above studies clearly support the potential chemopreventive properties of naturally occurring β-escin. 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 and Pharmacodynamics of β-Escin in Animals

Some studies on the absorption, distribution, metabolism, and excretion of β-escin in rodents have been conducted. Among these, some findings support the notion that β-Escin undergoes a rapid and efficient metabolism that severely curtails the availability of the parent compound. Previously, it was shown that escin 1a undergoes extensive metabolism into isoescin Ia, desacylescin I, 21β-O-tigloylprotoaescigenin, and protoaescigenin by enzymes of human intestinal bacteria, including *Lactobacillus brevis* [39]. Desacylescin I showed potential inhibitory effects on the growth of mouse sarcoma-180, hepatic carcinoma H22, and lung carcinoma *in vitro*. Wu et al. [40••] investigated the pharmacokinetics of escin Ia and isoescin Ia in the rat, with a particular focus on their interconversion. Rats were injected with 1.7 mg/kg of a sodium escinate solution containing 0.5 mg/kg escin Ia and 0.5 mg/kg isoescin Ia via the tail vein and an IV (0.5 mg/kg via the tail vein) or oral (4 mg/kg by gavage) dose of pure escin Ia or isoescin Ia solution. The clearance (CL; drug amount eliminated per unit of time/drug concentration in plasma) values for escin Ia and isoescin Ia were 726 and 207 ml/min, respectively. This exceeds the hepatic blood flow, due to significant first-pass metabolism in the gut [40••], further supporting the previous studies of Yang et al. [39] that showed extensive metabolism in the gut and low bioavailability of escin isomers. The $t_{1/2}$ and mean residence time MRT values for sodium escinate were significantly higher than those for the individual escin Ia and isoescin Ia isomers ($P<0.05$). Thus, the combination found in herbal preparations may be superior to individual isomers in prolonging the duration of action of escin in vivo [40••]. Bidirectional interconversion of the isomers was found to occur, with the conversion of escin Ia to isoescin Ia being much faster than the reverse reaction. The mechanism of this trans-esterification reaction in vivo, that is, whether it is chemically or enzymatically mediated, requires further study. Whether such a superior benefit will actually translate to humans must also be determined. Further studies using radiolabeled tracers are needed to fully evaluate the tissue distribution, metabolism, absorption, and excretion of β-escin.

Clinical Pharmacokinetics of β-Escin

In China, escin has been widely used in clinical settings to prevent inflammatory edema after trauma, such as fracture and surgery [41–43]. A few studies on the pharmacokinetics of β-escin and escin-containing extracts in humans have been conducted. Pabst et al. [44] reported that topical application of 1 % or 2 % escin to individuals with sports injuries was well tolerated and resolved spontaneous pain better than placebo. Montenegro et al. [45] carried out an in vitro skin permeation study on the feasibility of using escin in aqueous solutions and gels. Using a solid phase extraction method vs. conventional HPLC procedures, they determined the maximum amount of escin that diffused through the skin. Schrader et al. [46] used a radioimmunosorbent assay (RIA) to compare the relative oral bioavailability of β-escin from a sugar-coated tablet formulation (CAS 11072-93-8) to that from a reference preparation in 18 healthy male volunteers over a 48-h period. They found that the test preparation exceeded the maximum bioavailability of the reference preparation without adverse side effects.

Although it is well established that escin is the active principle in HCSE, Lowe D et al. [47] used an RIA method and observed heterogeneity in the bioavailability and pharmacokinetic data with β-escin from different extracts, and between different preparations from the same extract. When considering commercial preparations of HCSE available around the world, knowing the ratio of α- to β-escin is essential. Clinical trials were used to estimate the total β-escin in biosamples in

the past, since the available analytical methods were limited and hampered resolution of the individual α- and β-escins. In order to assay the individual escins and to better characterize the clinical pharmacokinetics and other properties in biosamples, a specific and sensitive liquid chromatography (LC)-mass spectrometry (MS)/MS method has been developed and validated for the simultaneous quantification of escin Ia and escin Ib in human plasma [48, 49]. The assay is characterized by simple sample preparation and greater sensitivity than the RIA method. It has a lower limit of quantitation of 33 pg/ml for each saponin, compared with 0.5 ng/mL for total escin.

Li et al. [48] assessed the plasma concentrations of escin Ia and escin Ib in a clinical trial in which 10 healthy male volunteers received a single intravenous infusion of sodium escinate containing 10 mg of escin saponins, including 3.0 mg escin Ia and 2.0 mg escin Ib. They found that the pharmacokinetics of escin Ia and escin Ib were significantly different from those of the total β-escin reported previously [46, 50]. Later, Wu et al. [49] carried out a study with 10 healthy male volunteers aged 20–30 years with body mass index indexes (BMI) of 20–24. Participants were given a single oral dose of two sodium escinate tablets, each tablet containing 30 mg of escin saponins of different escins with 9.3, 5.7, 8.4, and 3.6 mg of escin Ia, escin Ib, isoescin Ia, and isoescin Ib, with 250-mL water. They detected the four saponins in human plasma for 36 h after a single oral dose of sodium escinate, with the peak concentrations of the four saponins in the range of 0.38–1.8 ng/mL at approximately 2 h after dosing. They also found that β-escins cleared from human plasma more rapidly than α-escins. The maximal plasma concentrations (Cmax) for each of the isomers observed in this study (in ng/mL) were 0.77 ±0.64 for escin Ia, 0.38±0.26 for escin Ib, 1.82±1.60 for isoescin Ia, and 0.74±0.73 for isoescin Ib. In order to develop β-escin for use as a pure drug, detailed studies of its absorption, distribution, metabolism, excretion, and pharmacokinetics are needed.

Clinical Uses of β-Escin

β-Escin has been traditionally used to treat conditions such as chronic venous insufficiency [51–54], inflammation [31], hemorrhoids [55], edema, elevated glucose [28, 56], obesity [57], and cerebral ischemic damage [58], and in clinical trials in patients with HIV-1 [59]. HCSE is widely used in Europe for chronic venous insufficiency (CVI), a syndrome characterized by lower extremity edema and varicosities [51–54]. The anti-inflammatory effects of β-escin are mainly attributable to its anti-histaminic and anti-serotoninergic activities [31]. 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 [60]. Recently, Liu et al. [61] 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 [62]. Escin also exerts synergistic anti-inflammatory effects with glucocorticoids [63]. In addition, escin significantly inhibited NF-κB activation and downregulated the expression of TNF-α, alleviating brain edema in rats with traumatic brain injuries [64]. A recent study demonstrated that β-escin has strong anti-allergic properties [65•]. 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.

Concluding Remarks and Future Prospects

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-kB, 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. Moreover, β-escin has been shown to be nontoxic in large doses, even at 500 mg/kg body weight. 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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Compliance with Ethics Guidelines

Conflict of Interest Jagan M. R. Patlolla and Chinthalapally V. Rao declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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