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REVIEW

Glucocorticoid-Like Activity of Escin: A New Mechanism for an Old Drug

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Abstract: Saponins are a group of compounds used in clinical practice in the management of several diseases. Escin is a natural mixture of triterpene saponins which mainly consist of several isoforms, in which the α- and β-escin are predominant. β-escin is the major active compound that exerts a therapeutic effect by relieving tissue edema, promoting venous drainage, and reducing inflammation. In this review, we describe the features of its glucocorticoid-like activity that could explain its clinical effects. Using PubMed, Embase Cochrane library and reference lists for articles published until October 01, 2020, we documented that escin is likely able to exert its anti-inflammatory and anti-edematous effects through a glucocorticoid-like activity, but without the development of glucocorticoid-like adverse drug reactions.

Keywords: escin, mechanism of action, glucocorticoid-like activity, clinical efficacy

Introduction

Within the bioactive components presented in the plant kingdom, saponins have been extensively applied in clinical practice owing to their broad range of biochemical and pharmacological activities.[1] Several saponins have been characterized according to the nature of the functional groups present on their aglycone skeleton as well as the number of sugar chains.[1] As natural compounds composed of a steroidal or triterpenoid aglycone attached with oligosaccharide chains, saponins can be subdivided further into i) steroidal and ii) triterpenoid glycosides, mostly found in monocotyledons and dicotyledons, respectively.[2] Escin is a natural mixture of triterpene saponins extracted from both seeds and seed shell of Aesculus hippocastanum (dicotyledons) which mainly consist of several isoforms, in which the α- and β-escin are predominant.[3] β-escin is the major active compound that exerts a therapeutic effect by relieving tissue edema, promoting venous drainage, and reducing inflammation.[4–6] Even if the pharmacological activity of escin has been well reported,[5,7] in the present review we describe the features of its glucocorticoid-like activity that could explain its clinical effects.

Methods

PubMed, Embase, Cochrane library and reference lists were searched for articles published until October 01, 2020 using the keywords: "escin", "mechanism action", "cytokines" "edema", "inflammation", "glucocorticoids". Secondary searches included articles cited in sources identified by the previous search. We enclosed randomized control trials (RCTs), open trials, case series, and case reports.

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Glucocorticoids and Glucocorticoid-Like Activity of Escin

Glucocorticoids are a heterogeneous group of steroidal drugs which are capable to exert anti-inflammatory, anti-edematous, and immuno-modulator effects through binding to their receptors.[8] The glucocorticoid receptor (GR) is a superfamily protein of conserved nuclear receptor and is able to mediate physiologically different actions of the glucocorticoid hormones by acting as a ligand-dependent transcription factor. This class of receptor is a protein shuttling between the cytoplasm and the nucleus, with nuclear translocation occurring upon its binding to glucocorticoid ligand. In fact, unbound GR is localized in the cytoplasm of almost all cells and is stabilized by chaperone proteins such as heat-shock proteins (Hsp) 70, Hsp90, and immunophilin.[9] Upon binding with glucocorticoids, the GR dissociates from chaperone proteins and translocates together with its ligand into the nucleus within 10 to 30 min.[10] In the nucleus, homodimers of the glucocorticoid–GR complex interact within 5 to 120 min with specific DNA sequences (glucocorticoid responsive elements),[11] inducing genomic action with two mechanisms: transrepression and transactivation.[10]

The mechanism of transrepression suppresses the synthesis of proinflammatory proteins such as interleukin (IL)-1, IL-2, IL-6, IL-8, vascular endothelial growth factor, cyclooxygenase-2 (COX-2), prostaglandins (PGs), tumor necrosis factor -α (TNF-α) and interferon-γ, involved in inflammation, pain and edema.[12,13]

The mechanism of transactivation results in increases of IκB (inhibitor of nuclear factor κB) and lipocortin 1, involved in anti-inflammatory and anti-edema effects, and in regulator proteins (involved in metabolism) which are responsible for metabolic-endocrine side effects.[13]

In particular, anti-inflammatory effects are related to the inhibition of NF-κB pathway,[14] and decrease of both pro-inflammatory genes (such as intercellular adhesion molecule 1 (ICAM-1), TNF-α, and IL-1β) and its transcription factors.[15–18] The mechanism of action of glucocorticoid also includes the increased expression of proteins with anti-inflammatory activities, such as glucocorticoid-induced leucine zipper (GILZ),[19,20] which mediates many of the glucocorticoid activities,[21,22] including inhibition of RAS/RAF/MAPK pathways,[23,24] and of nuclear factor-κB (NF-κB) activity.[25] At the same time, however, through both mechanisms of transrepression and transactivation, glucocorticoids can also induce the development of several adverse drug reactions (eg, immunodepression, infections, bone disease) that limit their clinical use, particularly for a high dose and for a long time.[26,27] It is worth for us to here mention that the glucocorticoid cortisol (also known as hydrocortisone) is the endogenous ligand for GR and that the polycyclic moiety of the triterpene skeleton in β-escin displays a similarity with it. Similarities between the pharmacological effects of glucocorticoids and escin have been reported in several publications: oral administration of escin has been shown to inhibit carrageenan-induced paw edema and decrease the production of prostaglandin E2 (PGE2);[28] in the same model, the systemic administration of dexamethasone or escin were both shown to reduce paw edema, with authors suggesting that the anti-inflammatory effect of escin is correlated with the glucocorticoid receptor/NF-κB signaling pathway, but not the COX/PGF2α signaling pathway.[29] On the other hand, corticosterone has been shown to suppress IL-1β-induced PGE2 expression.[30] The possibility that escin and corticosteroid might – at least partially – share similar pharmacologic pathways was also suggested by a publication reporting that escin exerts synergistic anti-inflammatory effects with low doses of glucocorticoids in vivo and in vitro (31).

Therefore, it is possible that both the anti-inflammatory and the anti-edema effects of escin could be related to a modulatory binding with GR, suggesting a glucocorticoid-like activity. Many of the pharmacological and clinical effects reported for escin are focused on the capillary endothelium, and recent literature highlights that the endothelial response to glucocorticoids involves inhibition of pro-inflammatory pathways which determine increased capillary permeability and consequent tissue edema.[32]

It is worth noting that the glucocorticoid-like activity of escin could also be non-genomic. In particular, non-genomic effects of glucocorticoid exist and include direct interaction of GR's ligand with intracellular mediators and modulation of several signaling pathways, eg, protein kinase C, phosphatidylinositol-specific phospholipase C, and src kinase pathways, resulting in rapid glucocorticoid effects.[10,33] Non genomic glucocorticoid-like effects of escin have been described. In particular, in an animal model of indomethacin-induced gastric ulcer, Wang et al documented that intragastric escin (at doses of 0.45, 0.9 or 1.8 mg/kg) has a protective effect on gastric mucosa,[34] through the decrease of the contents of malondialdehyde, TNF-α, P-selectin, vascular cell

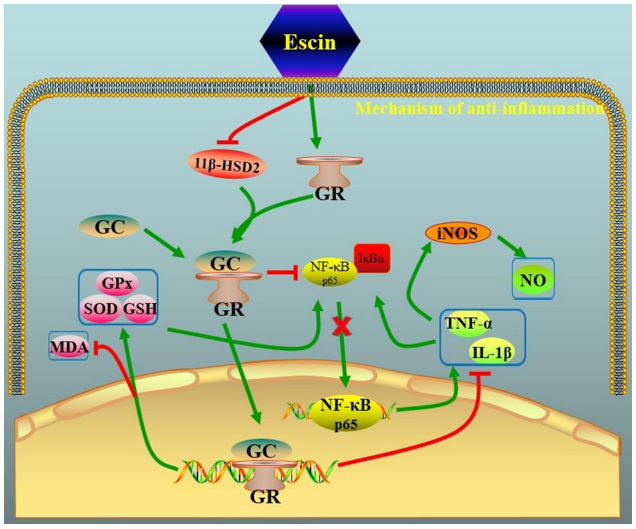

Figure 1 Schematic representation of glucocorticoid-like mechanism of action of escin. The administration of escin is able to both block 11-beta-HSD2 (11-β-hydroxysteroid dehydrogenase type 2) and induce the expression of GR (glucocorticoid receptor) that binding to GC (glucocorticoid) blocks the activation of NF-KB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway as well as the transcription of proinflammatory mediators (eg, Interleukin-1beta and tumor necrosis factor (TNF)-alfa) that normally activates IkB (inhibitor of kB) pathway and iNOS (inducible nitric oxide synthase). Moreover, the GC-GR complex blocks the activation of MDA (methylenedioxyamphetamine) and induces the transcription of antioxidant mediators (ie, super oxide dismutase, SOD; glutathione, GSH).

adhesion molecule 1 (VCAM-1) and myeloperoxidase activity. These data suggest that the protective effects of escin on gastric mucosa were related to its anti-inflammatory and antioxidant effects,[34] as it was also documented for other phytochemical compounds.[35–38] Moreover, recently, Zhao and colleagues evaluated the anti-inflammatory and the anti-edematous effects of external use of escin gel (at doses of 0.02 and 0.04 g/kg) in animal models of pain, paw edema and capillary permeability.[39] In this study, the authors documented that the anti-inflammatory effects of escin were related to down-regulation of pro-inflammatory mediators (ie, PGE2, TNF-α, and IL-1β), through the increased expression of GR. This is in agreement with the study of Xin et al and Jiang et al that reported an increase of the GR's expression in the lungs and livers after escin injection,[40,41] which leads to a potent protective effect on acute lung and liver injury induced by endotoxin (Figure 1). In particular, as above mentioned, Xin et al evaluated the anti-inflammatory effects of escin (low dose) alone and low dose of escin combined with glucocorticoid (corticosterone low dose; Cort), in both animal model of paw edema, pleuritis and in cell culture of murine macrophagic cells.[31] In animal model, the administration of escin plus Cort was able to reduce the paw edema, the volume of exudates, and the number of white blood cells in pleuritis. Moreover, in cell culture exposed to lipopolysaccharide revealed that escin plus Cort markedly reduced the content of TNF-α and IL-1β, suggesting that escin and glucocorticoid have a synergistic anti-inflammatory effect related to the down-regulation of pro-inflammatory mediators. Salvador et al reported that glucocorticoids are able to reduce edema formation by altering endothelial cell barrier function.[42] The anti-edema effect was also reported for escin.[5] In particular, Annoni et al reported that escin was able to consistently induce an increase in venous tone upon stimulation of human saphenous vein segments with norepinephrine.[43] This may explain why escin prevents pathological increases in blood vessel permeability in which reorganization of cytoskeleton is emerging.[44,45] Moreover, in primary isolated umbilical veins, Bougelet et al showed that escin (100–750 μg/mL), was able to reduce the hypoxia-induced endothelial damage as well as the formation of superoxide anions and leukotriene B4.[46] Therefore, in hypoxic condition causing disruption and reorganization of endothelial cytoskeleton,

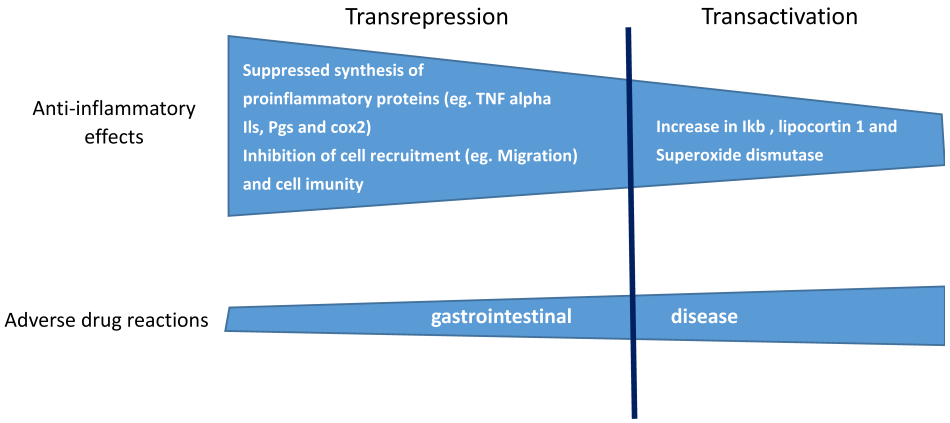

Figure 2 Schematic representation of genomic mechanisms of glucocorticoid-like effects of escin. Escin is able to induce antiinflammatory effects through transrepression and transactivation mechanisms. These mechanisms are also involved in the development of gastrointestinal adverse drug reactions.

Table 1 Effects of Escin in Several Experimental Models

Experimental Model	Effect of Escin
In vitro pancreatic lipase	Effectively suppressed the pancreatic lipase activity
Male obese mice	Normalized diabetic hyperglycemia
Female obese mice	Reduced weight gain, adipose tissue mass, lipid levels in plasma.

escin may have the capability to limit the vascular damage, thereby limiting vascular extravasation and resulting edema formation.

Taken together, all these studies suggested that both the anti-inflammatory and the anti-edematous effects of escin seem to be related with the involvement of GRs. Even if glucocorticoid use is related to the development of adverse drug reactions, related to genomic mechanisms transactivation and transrepression,[10] escin use probably for a difference in the effects of transactivation and transrepression (Figure 2) does not induce the development of adverse drug reactions.[5,7]

In agreement with previous experimental studies, other results documented that escin does not increase the endogenous corticosterone secretion, and does not lead to immune cell apoptosis in the spleen and thymus of mice compared with glucocorticoids.[47,48] Moreover, in an animal model assessing the effect of chronic treatment with escin on post-surgical bone fracture healing and wound healing, Zhang et al have documented that escin does not inhibit bone healing and the wound healing process.[49] In line with the above-mentioned results, Jeepipalli et al reported that escin is able to improve several metabolic outcomes in obese animals (Table 1).[50] These data suggest that even if escin and glucocorticoids share similar chemical structures (both belonging to tetracyclic triterpenoids), and several pharmacological and clinical effects, they have different safety, with escin expected not to inhibit the physiological tissue repair processes or immunological function.

Conclusion

Taken together, these data indicate that escin is able to exert the anti-inflammatory and the anti-edematous effects through a glucocorticoid-like activity (ie, partial agonist of GR, increased expression/transcription of GR), but without the development of glucocorticoid-like adverse drug reactions, probably related to its selective agonist with antagonist activity, which attenuate the side effects of glucocorticoid at high level, secreted by body itself or administered.

Ethics Statements

The authors confirm the table and figures are original.

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Disclosure

The authors report no conflicts of interest in this work.

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