Anti-Inflammatory and Gastroprotective Effects of Escin

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Abstract

Escan is a triterpenoid saponin extracted from the fruit of Aesculus wilsonii Rehd. and Aesculus hippocastanum (Hippocastanaceae). Clinically, it is widely used in the treatment of edema induced by either trauma or surgery, as well as treating chronic venous insufficiency. The anti-inflammatory and antiedema effects of escin have been extensively investigated. This article systematically reviews the effects of escin on inflammation and gastrointestinal diseases, including its role in inflammation, as an antioxidant, and in inhibiting gastric acid secretion and promoting gastrointestinal movement, especially, the molecular mechanism. The advantages and potential uses of escin have also been discussed.

Keywords
escin, triterpenoid, anti-inflammatory, gastrointestinal protection, mechanisms, Aesculus hippocastanum

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Escan is a naturally occurring triterpenoid extracted from the fruit of Aesculus hippocastanum (Hippocastanaceae), which is found worldwide, especially in Iran, China, Japan, USA, northern India, Asia Minor, and Europe. Escin is also extracted from the seeds of Aesculus chinensis Bunge var. chekiangensis (Hu et Fang) Fang and Aesculus wilsonii Rehd. in China, Aesculus turbinata Bl. in Japan, and A. hippocastanum Linn. in Europe. It is the primary active component of hippocastanus extracts (HCE). Escin is a triterpene saponin mixture consisting of 2 forms, α-escin and β-escin. When an aqueous solution of β-escin is heated at 100 °C, it changes into α-escin. Escin was first used in clinical practice in Germany as a natural medicine, Reparil, in which the active component is β-escin.

In China, escin consists of the total saponin extracted from the traditional Chinese medicine, A. wilsonii Rehd., which is listed in the Chinese Pharmacopoeia to relieve bloating and gastric pain. The main active ingredient of escin includes 4 forms, namely, escin A, B, C, and D (Figure 1). Escin A (escin Ia) and B (escin Ib) are called β-escin, whereas escin C (isosescin Ia) and D (isosescin Ib) are called α-escin. Escin sodium (C₅₅H₇₅O₂₄Na) injection, comprising the sodium salt of escin, is approved in China and is generally used to treat inflammation and edema caused by trauma or surgery. Escin has no serious side effects. The most common ones are phlebitis and allergic reactions when administered intravenously.

Besides being traditionally used to treat edema and chronic venous insufficiency, a number of studies show that escin has pharmacological effects, such as anti-inflammatory, gastrointestinal tract protective, and antitumor. This article systematically reviews the anti-inflammatory and gastroprotective effects of escin.

Anti-Inflammatory Effects of Escin

The antiedema and anti-inflammatory effects of escin have been studied extensively. In the past decades, the anti-inflammatory effects of escin and its pharmacological mechanism of action have been actively explored. Table 1 lists the anti-inflammatory properties of escin.

Inflammation is the protective response of the body to stimuli, which refers to a defensive response of a living factor with a vascular system to a damaging factor and is the central link of the inflammatory process. The local reactions of inflammation include edema, pain, and dysfunction. Fever and an increase in peripheral blood neutrophils are systemic reactions of inflammation. In fact, inflammation is a complex biological response of body tissues to both pathogens and physiological damage, which involves immune cells, blood vessel alterations, and molecular mediators. Cell stimulation triggers the expression of proinflammatory genes and downstream
signaling, which, in turn, results in the release of proinflammatory cytokines and chemokines, such as tumor necrosis factor (TNF) and interleukin (IL)-1β, which have autocrine and paracrine effects leading to the local activation of macrophages and neutrophils. The activation of endothelial cells by proinflammatory cytokines leads to an increase in vascular permeability in the injured tissues, resulting in capillary leakage and vasodilation.

Inflammation can be categorized as acute and chronic. Accumulating evidence shows that escin can attenuate both acute and chronic inflammation. To study acute inflammation, the carrageenan-induced paw edema, xylene-induced ear edema, acute lung injury induced by endotoxins, and acetic acid-induced increase in vascular permeability and spinal cord injury mouse models have been used. On the other hand, animal models, including cotton pellet-induced granuloma in rats, rheumatoid arthritis (RA), osteoarthritis, and periodontitis, have been routinely used to study chronic inflammation.\textsuperscript{19}

**Effect of Escin on Acute Inflammation**

Escin is effective in alleviating certain severe inflammation. Anti-inflammatory effects correspond with antiedema effects, as inflammation and edema are interrelated. Inflammatory edema occurs when protein-rich fluid leaks out of the blood vessels and collects in the interstitium.

Escin can reduce cerebral edema and the permeability of the blood-brain barrier, relieving brain edema caused by acute omethoate exposure.\textsuperscript{12} Inflammation is an important manifestation representing a dysfunction in the blood-brain barrier. Microvascular endothelial cells exposed to TNF-α, IL-1β, and IL-6 increase paracellular permeability.\textsuperscript{20} The changes in the TNF-α, IL-1β, and IL-6 levels in omethoate-poisoned rats are associated with the dysfunction of the blood-brain barrier. An increase in the levels of matrix metalloproteinase-9, cyclooxygenase-2, prostaglandin E\textsubscript{2}, and TNF-α causes dysfunction of the blood-brain barrier. Treatment with escin decreases the TNF-α and brain water levels and alleviates histopathological changes associated with the permeability of the blood-brain barrier.\textsuperscript{12} Cerebral ischemia is a cause of disability or even death in adults, and considerable evidence shows that inflammation significantly contributes to cerebral damage after ischemia.\textsuperscript{30} Studies demonstrate that escin exerts neuroprotective effects in the middle cerebral artery occlusion rat model by reducing the migration of neutrophils and decreasing the protein expression of adhesion molecules (intercellular adhesion molecule-1 and E-selection).\textsuperscript{31} Later research showed that escin can also attenuate ischemic brain injury by increasing the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) and reducing malondialdehyde (MDA) levels. Escin has a neuroprotective effect on transient cerebral ischemia in mice. It not only protects hippocampal neurons but also promotes learning and memory recovery in the mouse model of cerebral ischemia.\textsuperscript{12} A study shows that escin can significantly downregulate the gene expression of complement factor 3, TNF-α, and CD40 and upregulate the expression of granulocyte-macrophage colony-stimulating factor, indicating that escin can protect hippocampal neurons in mice with cerebral ischemia, which may be related to the regulation of certain inflammatory genes.\textsuperscript{30} Spinal cord injury can be attenuated by escin treatment.\textsuperscript{32} Studies reveal that escin has significant neuroprotective effects and leads to better locomotor recovery.\textsuperscript{33}

Acute lung injury is induced by many factors and eventually leads to acute respiratory distress syndrome, which is associated with inflammation, which involves the recruitment and release of proinflammatory mediators. Eventually, these processes can cause acute respiratory distress syndrome. In methyl-parathion-induced lung injury, escin can downregulate the levels of inflammatory mediators such as NO, TNF-α, and IL-1β.\textsuperscript{34} Escin also can enhance endogenous antioxidant capacity, upregulate glucocorticoid receptor (GR) expression, and increase the activities of SOD and glutathione peroxidase in the lung.\textsuperscript{35} Escin exerts protective effects in severe acute lung inflammation, which can be demonstrated by the fact that escin reduces mortality in rats due to pulmonary edema caused by exposure to phosgene.\textsuperscript{21} Escin has a therapeutic effect on acute pulmonary edema caused by the epinephrine in rats, and its effect may be better than that of dexamethasone (4 mg/kg).\textsuperscript{21,22} Escin (1.8 or 3.6 mg/kg) has a therapeutic effect on lung injury caused by endotoxins in rats, and the effect is equivalent to that of methylprednisolone (600 mg/kg).\textsuperscript{23} Escin can enhance endogenous antioxidant capacity, increase
venous tension, upregulate GR expression, attenuate the inflammatory reaction, and thus, inhibit acute inflammation and reduce tissue damage.35 The typical symptoms of coronavirus disease 2019 (COVID-19) include pneumonia and inflammatory exudates.37 Escin has immense potential in the therapy of severe pneumonia;23,38 it can reduce the levels of exudates on acute inflammation, which results in an effect similar to that of glucocorticoids (GCs). However, escin has no obvious inhibitory effect on the immune system, which is an advantage over GCs.11 Accumulating evidence suggests that sodium escin may be a potential compound to treat COVID-19 owing to its efficacy in alleviating acute lung injury and inflammation.

Further studies show that the combination of escin and GCs has synergistic anti-inflammatory effects in carrageenan-induced paw edema and pleuritis in bilaterally adrenalectomized rats.39 Escin and prednisone have a synergistic effect in inhibiting paw swelling induced by adjuvant-induced arthritis.27 The combination of escin and GCs can reduce the adverse effect of GC administration alone, such as drug resistance after long-term use and osteoporosis. The anti-inflammatory effect of escin is similar to that of di洛fenac and dexamethasone (4 mg/kg).40 Dexamethasone, a steroidal anti-inflammatory drug, is commonly used clinically to treat inflammatory diseases, and undesirable effects may occur after long-term treatment. Escin shows a better anti-inflammation ability than

Table 1. Anti-inflammatory Effect of Escin in Different Models.

| Compounds          | Doses/routes of administration | Model                                                                 | Effects                                                                 | Authors |
|--------------------|--------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------|---------|
| Escin              | i.v.:                           | Cerebral edema induced by acute omeothate poisoning in Sprague-Dawley rats | Attenuates cerebral edema                                              | Wang et al12 |
| Sodium salt of escin | i.v.:                           | Transient cerebral ischemia in mice                                   | Attenuates ischemic brain injury                                        | Zhang et al20 |
| Sodium salt of escin | i.v.:                           | Lipopolysaccharide-induced lung injury in mice; lung injury is induced by methylparathion; pulmonary edema caused by phosgene; pulmonary edema caused by epinephrine in rats | Protects from severe acute lung inflammation; reduces mortality in rats after pulmonary edema | Fu et al, Pan et al, Gallelli et al21-23 |
| Sodium salt of escin | i.v.:                           | Liver injury induced by carbon tetrachloride and endotoxin; liver damage induced by organophosphate; liver damage caused by p-methylthiophosphate | Protects from LPS-induced liver injury                                  | Jiang et al24 |
| Sodium salt of escin | p.o.:                           | Rheumatoid arthritis and pleuritis in bilaterally adrenalectomized rats | Reduces arthritic index                                                 | Zhang et al25 |
| Sodium salt of escin | i.v.:                           | Acetic acid-induced increase in capillary permeability in mice; cotton pellet granuloma in rats | Alleviates capillary permeability; decreases granuloma weight           | Fu et al17 |
| Sodium salt of escin | i.v.:                           | Carrageenan-induced paw edema; acetic acid-induced capillary permeability | Alleviates paw edema; alleviates capillary; permeability                | Wang et al16 |
| Sodium salt of escin | i.v.:                           | Otitis media induced by peptidoglycan polysaccharide in Tlr 2/fl mice | Mitigates the severity of otitis media                                 | Zhang et al26 |
| Sodium salt of escin | i.g.:                           | Adjuvant-induced arthritis in rats                                     | Inhibits paw swelling; brings about a reduction in the arthritis index | Du et al27 |

Abbreviations: i.g., intragastric; i.v., intravenous; p.o., orally.
Sodium salt of escin: consisting of A, B, C, and D and containing at least 65% of A and B.
dexamethasone. It inhibits inflammation from 4 to 24 hours after treatment in carrageenan-induced paw edema and acetic acid-induced vascular permeability in rats. A study shows that escin has no adverse effect on the immune system, suggesting its superiority to GC. Escin is a potent anti-inflammatory drug with a long duration of effect without causing immunosuppression. The anti-inflammatory effect of escin depends on GCs, which can be observed in adrenalecetomized mice.

The liver is the primary organ for drug metabolism, and damage to the liver can severely affect health. Escin (1.8 or 3.6 mg/kg) can ameliorate liver injury induced by carbon tetra-chloride and endotoxin. Escin can also reverse organophosphate-induced liver damage. Liver damage caused by either β-methyltiophosphate or methyl parathion is reduced after escin administration, which is related to its antioxidant and anti-inflammatory effects. Treatment with escin after liver injury can inhibit the migration of inflammatory cells, reduce the degree of necrosis, and decrease the activities of serum alanine aminotransferase and aspartate aminotransferase. It can downregulate the inflammatory mediators, such as TNF-α, IL-1β, NO, and the expression of 11 beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in the liver. It also upregulates GR expression and increases endogenous antioxidant capacity. However, escin has no effect on the expression of 11 beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in the liver. Alleviation of lung injury or liver damage caused by lipopolysaccharide (LPS) is associated with the upregulation of GR and the enhancement of endogenous antioxidant capacity after treatment with escin.

A study has explored the effects of otitis media induced by peptidoglycan polysaccharide (PGPS) in TLR2-deficient (Tlr2−/−) mice and reports that escin can alleviate the severity of adrenalecetomized mice.

**Mechanism of the Anti-Inflammatory Effect of Escin**

Previous studies show that escin can affect the pituitary-adrenaline system and upregulate the release of adrenocorticotrophic hormone and GCs in rats, thereby exhibiting potential anti-inflammatory effects. The effects of escin can be attributed to an increase in the secretion of prostaglandin F2α (PGF2α) and GCs.

Recent studies have shown that the mechanism of escin in alleviating inflammation is related to the upregulation of GR expression, a decrease in 11β-HSD2 expression, and a reduction of GC inactivation in tissues, thus promoting the binding of GCs to the GR (Figure 2). The activated GR transfers into the nucleus and combines with the reaction elements on DNA, thereby inhibiting the release of the inflammatory mediators (TNF-α, IL-1β, and IL-6), decreasing MDA, and promoting the release of antioxidation factors (SOD, glutathione, GPx). On the other hand, escin can inhibit the activation of nuclear factor-kappa B (NF-κB) and further downregulate the expression of TNF-α, IL-1β, and certain other inflammatory mediators. A decrease in TNF-α inhibits the expression of inducible nitric oxide synthase (iNOS) and decreases the production of NO. Changes in the levels of the inflammation and antioxidation factor, in turn, inhibit the activation of NF-κB.

GR is a ligand-dependent transcription factor, which is a member of the nuclear hormone receptor superfamily. GR is a major regulator of the immune system owing to its anti-inflammatory and immunosuppressive activity. Activated GR interacts with co-suppressor molecules to attenuate NF-κB-associated coactivator activity, thereby reducing histone acetylation, chromatin remodeling, and RNA polymerase II action. The upregulation of GR retains the physiological and therapeutic effects of endogenous and exogenous GCs and promotes the treatment of endotoxemia. Pretreatment with escin significantly increases the expression of GR, and this may be one of the mechanisms of alleviating inflammation. It has an advantage over non-steroidal anti-inflammatory drugs (NSAIDs) and GCs in the treatment of acute inflammation for gastrointestinal protection owing to fewer adverse effects.

The expression of iNOS in vivo is related to TNF-α and IL-1β. TNF-dependent iNOS expression requires NF-κB activation. Escin inhibits NF-κB activation and, therefore, decreases TNF-dependent iNOS expression.

Escin inhibits the expression of p65 in the livers of LPS-treated mice, and it has also been demonstrated that escin significantly inhibits NF-κB expression. The mechanism may be related to the GR/NF-κB rather than the COX/PGF2α.
signaling pathway. The anti-inflammatory effect of escin in periodontitis is associated with the downregulation of inflammatory factors (TNF-α, IL-1β, IL-6) and is related to the TLR2 signaling pathway. Escin does not affect wound healing and bone cell activity at the same time, which suggests that escin treatment does not delay the healing of wound tissues, as observed in the case of GC.

Protective Effects of Escin on the Digestive System

Gastric emptying time and gastrointestinal transit time are vital aspects related to the digestive system, which play an important role in determining the quality of life. Gastric emptying time is an essential factor in maintaining the normal function of the gastrointestinal tract. Increased peristalsis promotes gastric emptying. When the gastrointestinal mucosa is damaged, it interferes with digestion, absorption, barrier function, and causes secretion dysfunction and affects gastrointestinal motility.

Ileus is a common complication caused by intestinal adhesion and is usually accompanied by pain, nausea, vomiting, abdominal distension, and gastrointestinal spasms. Prokinetic drugs are widely used for the treatment of ileus clinically although they have undesirable side effects. NSAIDs and GCs are used in the treatment of gastroenteritis to reduce inflammation and pain. In some patients, adhesion causes intestinal obstruction and pain. 

The Chinese medicine, Aesculus wilsonii Rehd. has been shown to accelerate gastrointestinal motility and to have gastroprotective effects.

**Physiological and Pathological Significance of Gastrointestinal Motility and Mucous Membrane Injury**

Gastrointestinal motility is an essential factor in maintaining the normal function of the gastrointestinal tract. Increased peristalsis promotes gastric emptying. When the gastrointestinal mucosa is damaged, it interferes with digestion, absorption, barrier function, and causes secretion dysfunction and affects gastrointestinal motility.

Postoperative peritoneal adhesions are a common complication of abdominal surgery. Drugs, for example, acetylcholinesterase inhibitors, can cause gastrointestinal side effects. These drugs can cause gastric emptying. When the gastrointestinal mucosa is damaged, it interferes with digestion, absorption, and barrier function, and causes secretion dysfunction and affects gastrointestinal motility.
Effects of Escin on Gastrointestinal Motility

Escin can promote gastrointestinal transit, which reduces the incidence of ileus,\(^{60}\) constipation,\(^{61}\) and postoperative adhesions.\(^{17,62}\) A randomized, double-blind, controlled clinical trial investigated the effects of intravenous injection of escin on the bowels of patients undergoing abdominal surgery, which showed that escin can improve gastrointestinal transit in patients after surgery.\(^{17}\) Another clinical trial showed that escin can shorten the recovery time of gastrointestinal motility in patients undergoing colorectal surgery,\(^{63}\) while there are also reports of escin being able to inhibit intestinal injury in cecal ligation and puncture (CLP).\(^{48}\)

Mastuda et al have shown that the acceleration in gastrointestinal transit is mediated by endogenous prostaglandin (PGs) and constitutive NO, especially at the dose of 25 mg/kg.\(^{61,64}\) It is reported that 5-hydroxytryptamine 2 (5-HT2) receptors are widely distributed in the central and peripheral tissues.\(^{65}\) The 5-HT2 receptor is directly stimulated causing contraction of the gastrointestinal smooth muscle and intestinal vascular smooth muscle.\(^{61}\) These receptor-mediated effects include the partial contraction of the ileum of Guinea pigs.\(^{66}\) In 2000, Mastuda et al showed that pretreatment with reserpine, which depletes 5-HT, reduced the effect of escin on gastrointestinal transit in mice.\(^{61}\) Therefore, these results suggest that escin stimulates gastrointestinal transit by the binding of 5-HT to the 5-HT2A receptor, which in turn leads to the release of NO and PGs. In addition, studies have confirmed that pretreatment with L-NAME (an inhibitor of constitutive and inducible NO synthase), but not with dexamethasone (an inhibitor of inducible NO synthase), damages the acceleration of gastrointestinal transit.\(^{64}\) Consequently, it has been proven that constitutive NO, rather than inducible NO, mediates the acceleration of gastrointestinal transit after treatment using escin.\(^{64}\) A pilot postoperative ileus study showed that escin promoted the recovery of gastrointestinal motility in patients after colorectal surgery.\(^{63}\) This study showed that patients taking escin (5, 15, and 25 mg) have a shorter recovery time of gastrointestinal motility, especially those receiving a dose of 25 mg. Interestingly, some researchers believe that the sympathetic nerves are also involved in the acceleration of gastrointestinal transit by escin; however, the mechanism of action is unclear.\(^{53}\)
Escan Suppress Gastric Emptying

Studies show that escin can suppress gastric emptying in rats, especially at the dose of 25 mg/kg.61,68 These findings suggest that escin inhibiting gastric emptying in patients with diabetes or obesity, which can lead to the control of postprandial blood glucose levels.61,68 The higher the gastric emptying rate, the faster the absorption of food and the higher the postprandial blood glucose levels in patients with diabetes. Thus, a reduction in gastric emptying can extend the absorption of food after meals, thereby improving blood glucose control.67

Similar to gastrointestinal transport, endogenous PGs are also involved in the inhibition of gastric emptying by escin. The effect of escin in inhibiting gastric emptying was reduced in mice pretreated with 6,7-dimethyl-5-tyrosine methyl ester hydrochloride (a tyrosine hydroxylase inhibitor), reserpine (a catecholamine depletor), and 6-hydroxydopamine hydrochloride (a dopamine depletor). These indications suggest that catecholamines, possibly dopamine (DA), are involved in the inhibition of gastric emptying by escin.67 Capsaicin is widely used to cut off capsaicin-sensitive afferent nerves following which the neurotoxic capsaicin inhibits the arterial function of the central nervous system and its ability to release neuropeptides.69 PGs are the major metabolites of arachidonic acid, and dopamine 2 (D2) receptor agonists may affect the release of arachidonic acid.65 In conclusion, to a certain extent, capsaicin-sensitive sensory nerves (CPSNs) mediate the synthesis and release of dopamine that act through the central D2 receptor, leading to the release of PGs.67 Additionally, studies show that the central nervous system is also involved in the inhibition of gastric emptying by escin and that the inhibition of gastric emptying induced by escin is attenuated in streptozotocin-pretreated mice.65

The mechanism of escin on gastric emptying may be associated with dopamine. Dopamine is found in the central nervous system and stomach. Previous studies show that the inhibition of gastric emptying by escin is associated with CPSNs. Further studies show that the effect is mediated by CPSNs to promote dopamine production to activate the central D2 receptor, which promotes the release of PGs.61

Protective Effects of Escin on the Gastrointestinal Mucosa

Studies show that escin can reduce gastric lesions induced by ethanol in rats. Gastric lesions include gastric mucosal lesions and gastric ulcers. Indomethacin can cause gastric ulcers in mice, while ethanol can cause gastric mucosal injury, mucosal edema, epithelial bleeding, cell shedding, and inflammatory cell infiltration. Endogenous mediators, such as lipid peroxidation products, vasoactive amines, or peptides and oxygen-free radicals, are believed to be involved in the pathogenesis of gastric mucosal lesions. Nevertheless, these conditions can be prevented by the use of escin.

It has been shown that TNF-α levels are significantly increased after indomethacin exposure in mice, which in turn stimulate the expression of P-selectin and vascular cell adhesion molecule (VCAM)-1. However, escin reduces the levels of TNF-α, P-selectin, and VCAM-1 in gastric tissues.71 In addition, escin decreases gastric inflammation and neutrophil infiltration caused by indomethacin. These results demonstrate that escin inhibits neutrophil infiltration and subsequent inflammatory responses, thereby preventing gastric ulcers caused by indomethacin in mice.72 Furthermore, the levels of SOD, chloramphenicol acetyltransferase,73 and GPx were significantly reduced by indomethacin in the gastric tissue of mice. SOD, CAT, and GPx activities were significantly increased when mice were treated with escin.74 These findings suggest that escin has protective effects on the oxidative damage of gastric tissue induced by indomethacin. In addition, it has been reported that the CPSN has a protective effect on ethanol-induced gastric mucosal injury in rats; as discussed previously, stimulation of the capsaicin-sensitive afferent nerves by capsaicin can indirectly induce the release of PGs. Moreover, studies show that escin can inhibit H+ /K+ ATPase, reduce gastric acid secretion, increase the activity of SOD, CAT, and GPx, and decrease the levels of TNF-α and VCAM-1, thus protecting the ulcerous mucosa.75 These findings confirm the protective effect of escin on the gastrointestinal tract (Figure 3).

Conclusion and Outlooks

Escan exhibits potent anti-inflammatory effects in acute and chronic inflammations. Based on existing evidence, escin can be described as having a long duration of action like GC, but without the adverse reactions associated with it. Escin exerts its effects on alleviating inflammation, mainly by regulating the GR, which is different from the mechanisms of action of GCs and NSAIDs. The effects of escin on the gastrointestinal tract are associated with both neuroendocrine regulation and anti-inflammation, which also help in explaining the therapeutic effects of traditional Chinese medicine, A. wilsoni. In future studies, the molecular mechanisms of escin regulating GR and its role in treating acute viral pneumonia need to be investigated.

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