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REVIEW ARTICLE

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Therapeutic potential of *Asiaticoside* in wound healing after endoscopic submucosal dissection (ESD)

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ABSTRACT

Context: Endoscopic submucosal dissection (ESD) is the standard treatment for early gastrointestinal cancers but is often complicated by delayed healing and stenosis. Current therapies like proton pump inhibitors primarily suppress acid without actively promoting mucosal regeneration. *Asiaticoside* (AS), a triterpenoid from *Centella asiatica*, shows promise in tissue repair.

Objective: This review evaluates the therapeutic potential of AS for ESD-induced wound healing, focusing on its pharmacological mechanisms and emerging delivery strategies.

Methods: A comprehensive literature search was conducted using databases such as PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI). Relevant *in vitro*, preclinical, and clinical studies regarding AS, wound healing, fibrosis, and drug delivery systems were selected and synthesized to analyze efficacy and safety.

Results: AS accelerates healing through multifaceted mechanisms: it exerts anti-inflammatory effects *via* NF-κB and MAPK pathways, reduces oxidative stress through Nrf2/HO-1 signaling, and inhibits fibrosis by modulating TGF-β/Smad axes. Additionally, AS promotes angiogenesis and collagen synthesis. While clinical data supports its use in skin wounds, its gastrointestinal application is hindered by poor bioavailability. Novel delivery systems, including hydrogels and microneedles, are identified as solutions for localized, sustained release.

Conclusion: AS offers a promising therapeutic evolution, moving from reliance on passive acid suppression toward a synergistic model that integrates acid control with active mucosal regeneration for ESD management. Future research should focus on optimizing endoscope-compatible delivery platforms to facilitate clinical translation and reduce postoperative complications.

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Introduction

The global burden of gastrointestinal (GI) cancers continues to rise, underscoring the importance of early detection and minimally invasive therapeutic strategies in improving patient survival and quality of life. Among the available therapeutic options, endoscopic submucosal dissection (ESD) is widely regarded as the gold standard for treating early GI cancers, offering significant advantages including preservation of GI structural integrity, high en bloc resection rates, reduced recurrence, and improved quality of life compared to conventional surgical approaches (Draganov et al. 2019; Ge and Aihara 2022). Despite its clinical efficacy, ESD is frequently accompanied by postoperative complications, including delayed ulcer healing, bleeding, perforation and stenosis, which significantly impair recovery and increase healthcare costs (Gweon and Yang 2023; Okubo and Ishihara 2023; Zhu et al. 2024). Current postoperative management primarily relies on proton pump inhibitors (PPIs), mucosal protective agents, and hemostatic clips. While these measures provide symptomatic relief and acid suppression, they do not actively enhance mucosal regeneration or modulate fibrosis, which are crucial for complete and durable wound healing. Moreover, recent clinical findings have raised questions about the efficacy of PPIs, particularly in esophageal ESD, where their impact on healing rates appears

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limited. This presents a critical unmet clinical need for novel, biologically active therapies that can promote tissue regeneration, prevent fibrosis, and reduce the risk of adverse events following ESD.

In recent years, increasing attention has been directed toward natural compounds with pro-healing properties. *Centella asiatica* (L.) Urban, a traditional medicinal herb from the Apiaceae family, has long been used in skin wound management due to its anti-inflammatory, antioxidant, and pro-healing effects (Witkowska et al. 2024). *Asiaticoside* (AS), one of its primary bioactive constituents, has demonstrated therapeutic benefits in various dermatological conditions, including burns, ischemic wounds, ulcers, and atopic dermatitis (Bandopadhyay et al. 2023). However, the application of AS in GI wound healing, specifically following ESD, remains largely underexplored. While direct clinical trials on ESD wounds are currently nascent, the physiological similarities between mucosal and cutaneous wound healing – particularly in the phases of inflammation, proliferation, and remodeling – suggest a strong translational potential.

Therefore, this review aims to bridge the gap between the established dermatological efficacy of AS and the specific challenges of ESD-induced wounds. We comprehensively evaluate the therapeutic potential of AS by integrating current evidence from pharmacological studies, preclinical models, and clinical trials. We systematically summarize the multifaceted biological activities of AS including its anti-inflammatory, antioxidant, antifibrotic, and pro-healing effects, and elucidate the underlying molecular mechanisms involving key signaling pathways such as NF-κB, MAPK, NLRP3, TGF-β/Smad, JAK2/STAT3, and Nrf2/HO-1. In addition, we explore the GI protective properties of AS and highlight its demonstrated efficacy in cutaneous wound healing as a rationale for its potential application in GI mucosal repair. Recognizing the challenges posed by AS's poor oral bioavailability and the complex GI environment, we further discuss emerging drug delivery strategies, including hydrogels, microneedles, and stimuli-responsive biomaterials, that may facilitate targeted, localized, and sustained AS delivery to ESD-induced wound sites. By shifting the therapeutic paradigm from effective acid suppression alone to a comprehensive strategy combining acid control with active mucosal regeneration, AS-based strategies may offer a novel and synergistic approach to minimizing ESD-related complications and improving long-term outcomes.

Methodology

To ensure a comprehensive evaluation of the therapeutic potential of AS in ESD-induced wound healing, a systematic literature search was performed. We searched electronic databases including PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) for articles published from inception to October 2025. The search strategy employed combinations of keywords such as 'asiaticoside', 'endoscopic submucosal dissection', 'wound healing', 'pharmacological activity', 'inflammation', 'oxidative stress', 'fibrosis', 'angiogenesis', 'hydrogels', 'microneedles', 'nanoparticles', and 'drug delivery'. This review included original experimental research investigating the multifaceted pharmacological activities of AS, covering preclinical and clinical studies that evaluated AS or *Centella asiatica* extracts in both cutaneous and gastrointestinal wound repair. We also examined research on innovative drug delivery systems, such as hydrogels and microneedles, alongside studies elucidating the specific molecular signaling pathways modulated by AS. Conversely, studies were excluded if they lacked accessible full texts, contained unpublished data, or were non-English language publications. We further excluded research that did not use AS as a primary intervention or bioactive component, as well as studies irrelevant to wound healing. The detailed selection workflow is presented in Figure 1.

Challenges and therapeutic rationale in ESD-induced wound healing

Challenges in current ESD postoperative management

ESD is a well-established endoscopic resection technique that is widely adopted for the treatment of early GI cancers. However, ESD entails submucosal dissection and electrocautery, leading to significant mucosal injury. The healing process comprises a complex interplay of inflammation, oxidative stress, angiogenesis, and extracellular matrix (ECM) remodeling (He et al. 2021; Tian et al. 2021). Disruption

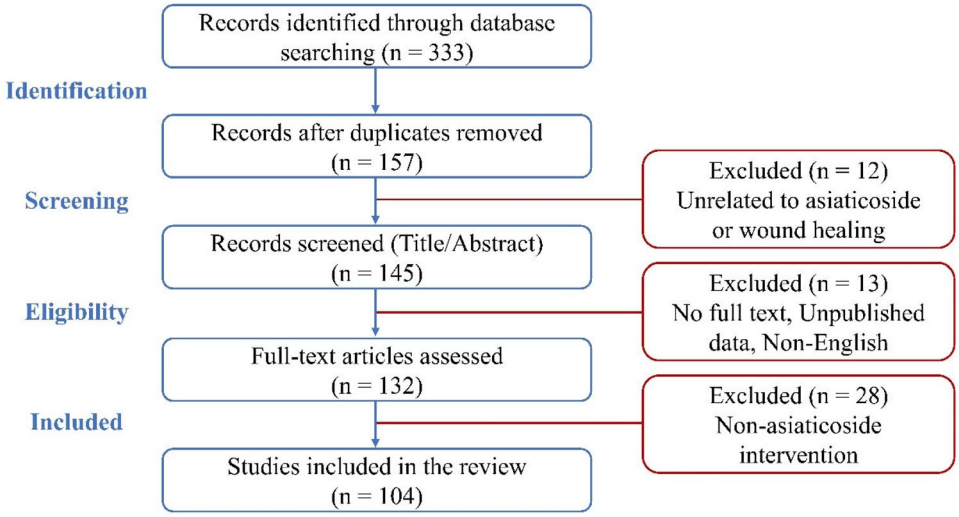

Figure 1. Flowchart of the literature search and study selection process.

of any of these processes can lead to delayed or aberrant healing. Suboptimal healing and the incidence of postoperative adverse events (AEs) remain major barriers to the wider clinical adoption of ESD. Common complications including bleeding, perforation, stenosis and electrocoagulation syndrome significantly impair patients' quality of life and impose substantial economic burdens (Ishihara et al. 2020; Tanaka et al. 2020; Tsutsumi et al. 2021; Chen et al. 2025a, 2025b). These concerns are supported by data from large-scale multicenter studies.

A Japanese multicenter prospective study of approximately 10,000 patients undergoing gastric ESD reported the following complication rates: postoperative bleeding (4.4%), intraoperative perforation (2.3%), delayed perforation (0.4%), transfusion requirement (0.7%), and emergency surgery (0.2%) (Suzuki et al. 2019). A Western multicenter cohort study reported early bleeding, delayed bleeding, and perforation rates following gastric ESD as 4.3%, 3.4%, and 2.4%, respectively (Bhandari et al. 2023). The European Society of Gastrointestinal Endoscopy (ESGE) has reported that the most common AEs associated with ESD include postoperative bleeding (1–2% in the esophagus, 5–10% in the stomach, 5–17% in the duodenum, and 2.7% in the colorectum) and perforation (< 3% of cases) (Libânio et al. 2023). Notably, 5–20% of ESD-induced ulcers remain unhealed at 8 weeks post-procedure, and prolonged healing duration is directly correlated with increased risk of complications (Chen et al. 2024a). Therefore, optimizing postoperative management strategies to enhance ulcer healing is essential for maximizing the clinical benefits of ESD.

PPIs are the mainstay of post-ESD therapy, reducing acid-mediated injury and creating a favorable environment for re-epithelialization. However, their therapeutic efficacy has been increasingly questioned by recent evidence. The Japan Gastroenterological Endoscopy Society (Ishihara et al. 2020) evaluated the effectiveness of PPIs following esophageal endoscopic resection for esophageal cancer and found no significant effect on ulcer healing rates (84% without PPIs vs. 85% with PPIs). Additionally, no differences in AEs were observed between the groups. Consequently, they strongly advised against the routine use of PPIs after esophageal ESD, except in patients with reflux esophagitis. Furthermore, the optimal duration of PPI therapy remains undefined (Kim et al. 2024; Chen et al. 2024a). Emerging agents, such as potassium-competitive acid blockers (P-CABs), may provide stronger acid suppression and potentially greater efficacy in treating ESD-induced ulcers. However, a meta-analysis revealed no significant differences between vonoprazan (VPZ) and PPIs in terms of ulcer healing, shrinkage rates, or perforation rates (Chen et al. 2024b). A multicenter randomized controlled trial demonstrated that a 3-week course of VPZ was not inferior to an 8-week course in treating ESD-induced ulcers (Kato et al. 2023). Therefore, Eikichi Ihara proposed that excessive gastric acid suppression may not be necessary for the healing of ESD-induced ulcers (Ihara et al. 2025). In addition, long-term use of PPIs or VPZ is associated with adverse outcomes, including pneumonia, *Clostridium difficile* infection, acute kidney injury, fractures, osteoporosis, vitamin B12 deficiency,

hypomagnesemia, fundic gland polyps, and malignancies (Abramowitz et al. 2016; Perry et al. 2020; Savarino et al. 2020; Rameau et al. 2021; Watanabe et al. 2021). PPI exposure has also been correlated with increased infection risk in cirrhotic patients (Mahmud et al. 2022) and accelerated renal dysfunction in patients with chronic kidney disease (Liabeuf et al. 2021). Other approaches, including mucosal protectants, hemostatic sprays, and endoscopic clips, help create a favorable environment for healing but remain largely passive, lacking the ability to actively stimulate tissue regeneration or regulate key biological processes such as inflammation and fibrosis.

Parallels between cutaneous and gastrointestinal mucosal wound healing

Since direct clinical evidence of AS in ESD-induced wounds is currently limited, the rationale for its application is grounded in the biological homology between cutaneous and GI mucosal repair. Although the local environments differ significantly – with the skin exposed to the external atmosphere and the GI tract subjected to acidic or enzymatic stress – the fundamental cellular and molecular mechanisms of repair are remarkably conserved. Both cutaneous and mucosal healing progress through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling.

Immediately following injury, the hemostatic phase is triggered in both tissues, where platelet aggregation and fibrin clot formation create a provisional matrix that will serve as the foundational scaffold for all subsequent healing (Rodrigues et al. 2019; Jung et al. 2023).

During the inflammatory phase, the recruitment of neutrophils and macrophages is critical for clearing necrotic debris and preventing infection (Lu et al. 2019; Rodrigues et al. 2019; Tian et al. 2021; Peña and Martin 2024). In both cutaneous and mucosal environments, this process is driven by the NF-κB pathway and pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Crucially, chronic or excessive inflammation in either tissue delays healing and triggers fibrotic signaling, a key target for AS's anti-inflammatory properties.

The proliferative phase is characterized by synchronous re-epithelialization and granulation tissue formation (Wilkinson and Hardman 2020; Tarnawski and Ahluwalia 2021). Similar to keratinocyte migration in cutaneous wounds, mucosal healing relies on rapid epithelial restitution and proliferation from crypt cells. Simultaneously, fibroblasts (or myofibroblasts) are activated to deposit ECM, while VEGF-driven angiogenesis restores the vascular supply essential for tissue regeneration (Tarnawski and Ahluwalia 2012).

Finally, the remodeling phase determines the quality of the healed tissue. This phase involves the reorganization of collagen fibers and the maturation of the ECM, predominantly regulated by the TGF-β/Smad signaling pathway (Xiaojie et al. 2022; Zhou et al. 2025c). It is vital to note that the pathological outcome of aberrant remodeling is identical in mechanism despite the anatomical difference: uncontrolled fibroblast activity leads to hypertrophic scarring in the skin and esophageal/gastric strictures in the GI tract. This shared pathophysiology provides the fundamental basis for repurposing anti-scarring agents like AS from dermatology to gastroenterology.

Given that AS has been proven to effectively modulate these specific shared pathways – inhibiting dysregulated inflammation, promoting revascularization, and regulating collagen maturation to prevent cutaneous fibrosis – it possesses a robust scientific rationale for application in GI mucosal regeneration. This parallel is particularly relevant for ESD-induced wounds, which, unlike peptic ulcers, are extensive, artificial defects extending into the submucosa, bearing a closer pathophysiological resemblance to deep cutaneous excisional wounds than to superficial mucosal erosions. Therefore, integrating AS as a complementary therapy to standard acid suppression represents a targeted strategy specifically addressing the complex healing requirements of post-ESD defects. This approach advances the therapeutic paradigm from sole reliance on passive acid suppression to a synergistic model that combines acid control with active mucosal regeneration.

Physicochemical properties and gastrointestinal fate of *Centella asiatica* triterpenoids

Understanding the physicochemical characteristics of *Centella asiatica* triterpenoids is a prerequisite for developing effective endoscopic delivery systems. The primary bioactive constituents are pentacyclic

triterpenoids, which exist in two forms: the aglycones (*Asiatic Acid* [AA] and *Madecassic Acid* [MA]) and their corresponding glycosides (*Asiaticoside* [AS] and *Madecassoside* [MS]) (Razif et al. 2025). These compounds share a similar triterpenoid skeleton but differ significantly in their glycosylation status, which dictates their solubility, permeability, and stability within the GI tract.

Solubility and lipophilicity

The therapeutic application of these triterpenoids in the GI tract is heavily influenced by their solubility-permeability interplay. The aglycones (AA and MA) are highly lipophilic molecules with low molecular weights (AA: ~488 Da; MA: ~504 Da) and high partition coefficients (AA LogP: 4.81; MA LogP: 3.52), according to DrugBank data. These properties facilitate passive membrane diffusion but suffering from extremely poor water solubility (AA: 0.0114 mg/mL; MA: 0.0356 mg/mL; DrugBank) (Nagoor Meeran et al. 2018; Win et al. 2021). This poor solubility is the rate-limiting step for their dissolution and subsequent absorption in the aqueous GI fluids. Conversely, the glycosides (AS and MS) possess bulky sugar chains (trisaccharides) attached to the C-28 carboxylate group. While this glycosylation significantly increases their molecular weight (AS: ~959 Da; MS: ~975 Da; DrugBank) and hydrophilicity (AS LogP: 0.73; MS LogP: −0.03; DrugBank), thereby enhancing water solubility, it simultaneously reduces their membrane permeability due to increased polarity and molecular size (Boonyarattanasoonthorn et al. 2022).

Impact of gastrointestinal pH variations

The human GI tract presents a dynamic pH environment, ranging from the highly acidic stomach (pH 1.0–2.5) to the neutral or slightly alkaline small intestine (pH 6.0–8.0), a gradient that critically affects the ionization, solubility, and stability of Centella triterpenoids.

In the gastric environment (pH 1.0–2.5), the aglycones AA and MA, which contain a carboxylic acid group with a pKa of approximately 4.5–5.0 (DrugBank), exist predominantly in their unionized, protonated form. While this unionized state is theoretically more permeable to lipid membranes, the extremely low pH causes these hydrophobic molecules to precipitate, thereby severely limiting their bioavailability (Yuan et al. 2015). In contrast, AS acts as a glycoside prodrug that exhibits relative chemical stability compared to other saponins (Chysirichote et al. 2025); although glycosidic bonds can be susceptible to acid hydrolysis, a significant portion of AS transits the stomach intact. This stability renders AS a superior candidate for intragastric delivery compared to the acid-sensitive precipitation observed with aglycones.

As the chyme enters the small intestine (pH 6.0–8.0), the pH rises above the pKa of the aglycones, causing AA and MA to become deprotonated (ionized) and form carboxylate anions. This ionization enhances their solubility in intestinal fluids but simultaneously reduces their affinity for the lipophilic enterocyte membrane, potentially hindering passive diffusion. For AS, the intestinal environment presents a distinct challenge where its large molecular size prevents direct absorption; instead, AS relies on sequential hydrolysis by intestinal brush border enzymes and, more importantly, colonic microbiota to cleave the sugar moiety, releasing the lipophilic active metabolite AA for absorption (Songvut et al. 2021).

Rationale for selecting Asiaticoside for ESD formulations

Despite AA being the ultimate bioactive metabolite, AS is prioritized for developing standardized clinical-grade formulations for ESD-induced wounds for several physicochemical reasons. First, AS serves as the primary marker compound for quality control in major pharmacopoeias (Bandopadhyay et al. 2023), ensuring the standardization required for clinical drug development. Second, structurally, AS acts as a glycoside prodrug that is converted into the active metabolite AA by intestinal flora (Gray et al. 2018; Sun et al. 2020); this conversion mechanism offers a sustained therapeutic window crucial for the prolonged healing process (4–8 weeks) of ESD ulcers, avoiding the rapid clearance

often seen with direct acid administration. Finally, AS has demonstrated specific efficacy in modulating the collagen I/III ratio to prevent hypertrophic scarring (Hashim et al. 2011; Ghiulai et al. 2020), directly addressing the risk of post-ESD stricture (see below).

Pharmacological activities of AS

AS, a predominant triterpenoid saponin derived from *Centella asiatica*, has demonstrated multiple biological activities, including anti-inflammatory, antioxidant, antifibrotic, and pro-healing effects. This section aims to detail the pharmacological activities of AS to elucidate its therapeutic potential in enhancing ESD-induced wound healing, drawing upon evidence from both dermatological and gastrointestinal models.

Anti-inflammatory effect

The inflammatory process involves a cascade of events, including immune cell recruitment, secretion of pro-inflammatory cytokines/chemokines, and expression of cell adhesion molecules. While controlled inflammation protects tissues from injury, excessive or dysregulated inflammation can impair healing and lead to adverse outcomes, thereby necessitating pharmacological intervention. Figure 2 shows that AS exerts anti-inflammatory effects by modulating key inflammatory signaling pathways, as demonstrated across various disease models.

Macrophages act as key regulators of the inflammatory response. Seon et al. demonstrated that AS reduces the expression of pro-inflammatory cytokines, including TNF-α and IL-6, while upregulating the anti-inflammatory cytokine IL-10 in LPS-induced RAW 264.7 macrophages (Seon et al. 2021b). Subsequent studies revealed that AS promotes M2 macrophage polarization both *in vitro* and *in vivo*. For instance, Huang et al. encapsulated AS into polylactic-co-glycolic acid (PLGA) nanofibers and co-cultured them with murine macrophages, demonstrating that AS enhanced M2 polarization

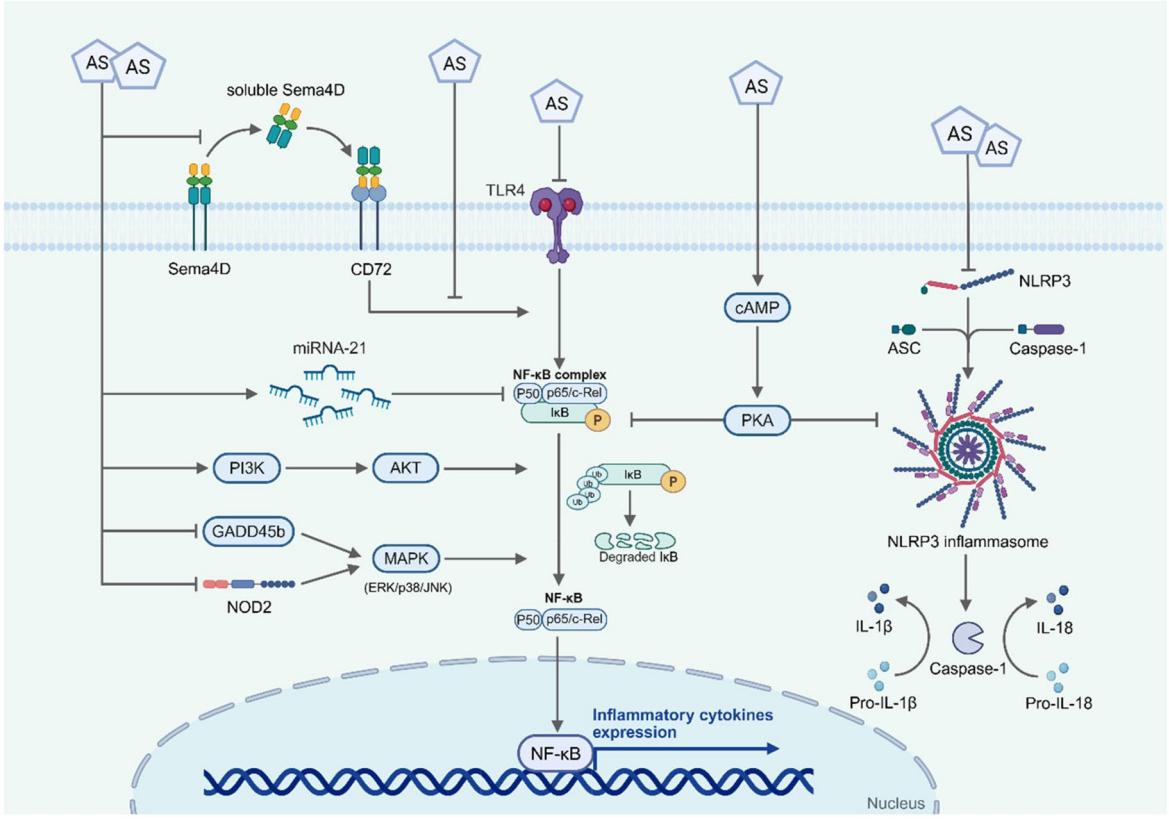

Figure 2. The anti-inflammatory effects of Asiaticoside (AS). Created in https://BioRender.com.

and downregulated cytokines such as IL-1β, IL-6, IL-12, IL-18, inducible nitric oxide synthase (iNOS), and TNF-α (Huang et al. 2020). Similarly, Liu et al. confirmed *in vivo* that AS increases the M2/M1 macrophage ratio in rat full-thickness wound models (Liu et al. 2021). Paradoxically, Li et al. reported that AS suppressed IL-4/IL-13-induced M2 macrophage polarization in THP-1-derived macrophages, suggesting context-dependent regulatory mechanisms that warrant further investigation (Li and Wang 2022).

AS suppresses the nuclear factor κB (NF-κB) signaling pathway, a critical regulator of inflammation, immune responses, apoptosis, and cellular differentiation. MicroRNA (miRNA) −21 inhibits NF-κB, negatively regulates the inflammatory response, and promotes the production of anti-inflammatory cytokines (Săsăran et al. 2021). Zhang et al. demonstrated that AS upregulates miRNA-21 and inhibits the Semaphorin 4D (Sema4D)/CD72/NF-κB pathway. This mechanism significantly reduced pro-inflammatory cytokine secretion and enhanced anti-inflammatory mediator production, ultimately restoring cytokine homeostasis (Zhang et al. 2024). Consistently, AS reduced pro-inflammatory mediators nitric oxide (NO) and prostaglandin E_2 (PGE_2) production in macrophages, though the effect was not as strong as that of AA (Yun et al. 2008). *In vivo*, AS administration attenuated cyclooxygenase-2 (COX-2) expression and PGE_2 production in rats (Wan et al. 2013).

The anti-inflammatory properties of AS have demonstrated neuroprotective effects in various neurological disorders. In Alzheimer's disease (AD) models, oral AS inhibited microglial activation and pro-inflammatory cytokine expression, improving cognitive deficits through p38 mitogen-activated protein kinase (MAPK) pathway inhibition (Liu et al. 2023a). The NOD-like receptor protein 3 (NLRP3) inflammasome is a protein complex that regulates innate immune responses by activating caspase-1 and inflammatory cytokines IL-1β and IL-18, and plays an important role in inflammation-related diseases (Chen et al. 2023). He et al. discovered that AS directly interacts with the NLRP3 protein, thereby inhibiting inflammasome assembly/activation and alleviating Parkinson's disease (PD) symptoms in both *in vivo* and *in vitro* experiments (He et al. 2024). Wang et al. elucidated an additional mechanism whereby AS may activate cyclic AMP (cAMP)/protein kinase A (PKA) signaling to suppress NF-κB and NLRP3-driven neuroinflammation, conferring antidepressant effects (Wang et al. 2020). Previous studies (Chen et al. 2014; Zhang et al. 2020a) have demonstrated that AS has a protective effect on cerebral ischemia-reperfusion injury (CIRI). In the CIRI model, elevated protein expression levels within the NOD2/MAPK/NF-κB signaling pathway were observed. AS reduced the expression of these pathway-related proteins in a dose-dependent manner, with effects reversible by NOD2 agonist administration. These results proved that AS exerted anti-inflammatory and neuroprotective effects through the NOD2/MAPK/NF-κB signaling pathway (Zhang et al. 2020a). The research by Chen et al. also found that AS could attenuate microglial activation, inhibit p38 MAPK signaling pathway, and suppress abnormally elevated iNOS activity and NO production in a model of transient cerebral hypoperfusion followed by reperfusion (Chen et al. 2014). Spinal cord injury (SCI) is a severe traumatic lesion, primarily caused by external impact events such as motor vehicle accidents and falls from elevated heights. In the SCI rat models, AS significantly suppressed the expression of p38-MAPK, and reduced the levels of iNOS, caspase-3, NF-κB p65 unit, TNF-α, IL-1β and IL-6 (Luo et al. 2015; Fan et al. 2020). These data confirm that AS attenuates SCI through both anti-inflammatory and anti-apoptotic mechanisms. Multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system (CNS), is characterized by microglial and astrocytic activation. AS inhibited the activation of these glial cells, reduced NO and TNF-α production, and exhibited therapeutic potential in slowing MS progression (Madhu and Prakash 2018). Diabetic Encephalopathy (DE) refers to a spectrum of neurodegenerative complications in individuals with diabetes mellitus, characterized by cognitive impairment, neurophysiological dysfunction, and structural brain alterations. These pathological changes are primarily attributed to chronic hyperglycemic exposure-induced neuronal damage, with neuroinflammation emerging as a pivotal pathological mechanism (Luo et al. 2024). AS regulates the inflammatory pathway mediated by phosphoinositide 3-kinase (PI3K)/protein kinase B(AKT)/NF-κB and upregulates synaptic protein expression, thereby exerting a beneficial effect on the prevention and treatment of hyperglycemia-induced cognitive deficits (Yin et al. 2015).

The anti-inflammatory effect of AS is closely related to its therapeutic effects on various diseases such as anti-tumor, promoting healing, and promoting pulp regeneration. AS has shown an impact on mast cell-mediated allergic inflammation. It inhibits FcεRI-mediated signaling activation and suppresses the nuclear translocation of NF-κB p65, thereby reducing the secretion of inflammatory cytokines such as TNF-α, IL-8, IL-1β and IL-4. In addition, AS inhibited calcium uptake, thereby reducing IgE-mediated mast cell degranulation and histamine release (Jiang et al. 2017). A study confirmed that AS significantly decreased IL-6 and TNF-α in MCF-7 cells and xenografts *via* the caspase-9/NF-κB pathway (Al-Saeedi 2023). This supports AS inhibitory abilities in breast cancer survival and progression. A recent study has shown that encapsulating AS in nanosponges and incorporating them into hydrogels can reduce the expression of inflammatory cytokines in an inflammatory pulp model *in vitro* and promote human dental pulp regeneration (Soe et al. 2025). In a study on diabetic retinopathy (DR), AS improved high glucose-induced inflammation and apoptosis of retinal pigment epithelial (RPE) cells by activating the cAMP/PKA signaling pathway and inhibiting the levels of inflammatory factors (Zhang et al. 2022). Lj et al. (2020) reported that AS attenuates the inflammatory response induced by hyperoxic conditions by downregulating the expression of microRNA-155 (miR-155) and upregulating the expression of suppressor of cytokine signaling 1 (SOCS1). Wu et al. (2021) employed a *caerulein*-induced mild acute pancreatitis model in mice to investigate the anti-inflammatory effects of AS. The results demonstrated that AS exerts anti-inflammatory effects by suppressing the toll-like receptor 4 (TLR4) pathway, thereby reducing the expression levels of receptor-interacting protein 3 (RIP3) and phosphorylated mixed lineage kinase domain-like pseudokinase (p-MLKL) in pancreatic tissue.

In conclusion, AS exhibits broad anti-inflammatory potential across diverse pathological conditions by modulating key signaling pathways, including NF-κB, MAPK, NLRP3, and cAMP/PKA. These anti-inflammatory actions are essential for mitigating excessive inflammatory responses during the early phase (inflammatory stage) of ESD-induced wound healing. By dampening neutrophil infiltration and pro-inflammatory cytokine storms, AS may facilitate the transition to the proliferative phase and reduce the risk of delayed healing.

Antioxidant effect

The balance between oxidant production and antioxidant defenses is essential for maintaining physiological homeostasis in humans. Disruption of this equilibrium leads to tissue damage, a condition known as oxidative stress (Forman and Zhang 2021). Enhancing antioxidant defenses and reducing the accumulation of reactive oxygen species (ROS) are critical strategies for mitigating oxidative stress. Enzymatic antioxidants, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), constitute essential components of the antioxidant defense system. Nuclear factor-erythroid 2-related factor-2 (Nrf2) is a transcription factor that regulates redox homeostasis. It binds to antioxidant response elements (ARE) in promoter regions and induces antioxidant enzyme expression in response to oxidative stress (Wang et al. 2022a). Heme oxygenase-1 (HO-1), a phase II antioxidant enzyme regulated by Nrf2, modulates the expression of SOD, GSH-Px, and CAT, thereby contributing to cytoprotection (Zhang et al. 2021). When ROS accumulation overwhelms endogenous defenses, they attack cellular macromolecules (lipids, proteins, nucleic acids), impairing cellular function. Malondialdehyde (MDA), an end-product of lipid peroxidation, serves as a biomarker for oxidative stress severity. As shown in Figure 3, AS, a well-characterized antioxidant compound, represents a promising therapeutic or adjunctive strategy for oxidative stress-related disorders.

AS mitigates oxidative stress by activating the Nrf2/HO-1 pathway, upregulating the expression of SOD and NAD(P)H dehydrogenase (Quinone) 1 (NQO-1), and reducing levels of ROS and MDA. In HepG2 cells stimulated with free fatty acids (FFAs), AS treatment increases both nuclear and total Nrf2 expression, reduces ROS levels, and attenuates lipid accumulation. This effect has also been validated in high-fat diet (HFD)-induced nonalcoholic fatty liver disease (NAFLD) mouse models (Wei et al. 2025). Similarly, in a diabetic nephropathy model, AS activates the Nrf2/HO-1 pathway, increases HO-1 and NQO1 expression, enhances SOD activity, and reduces ROS and MDA levels

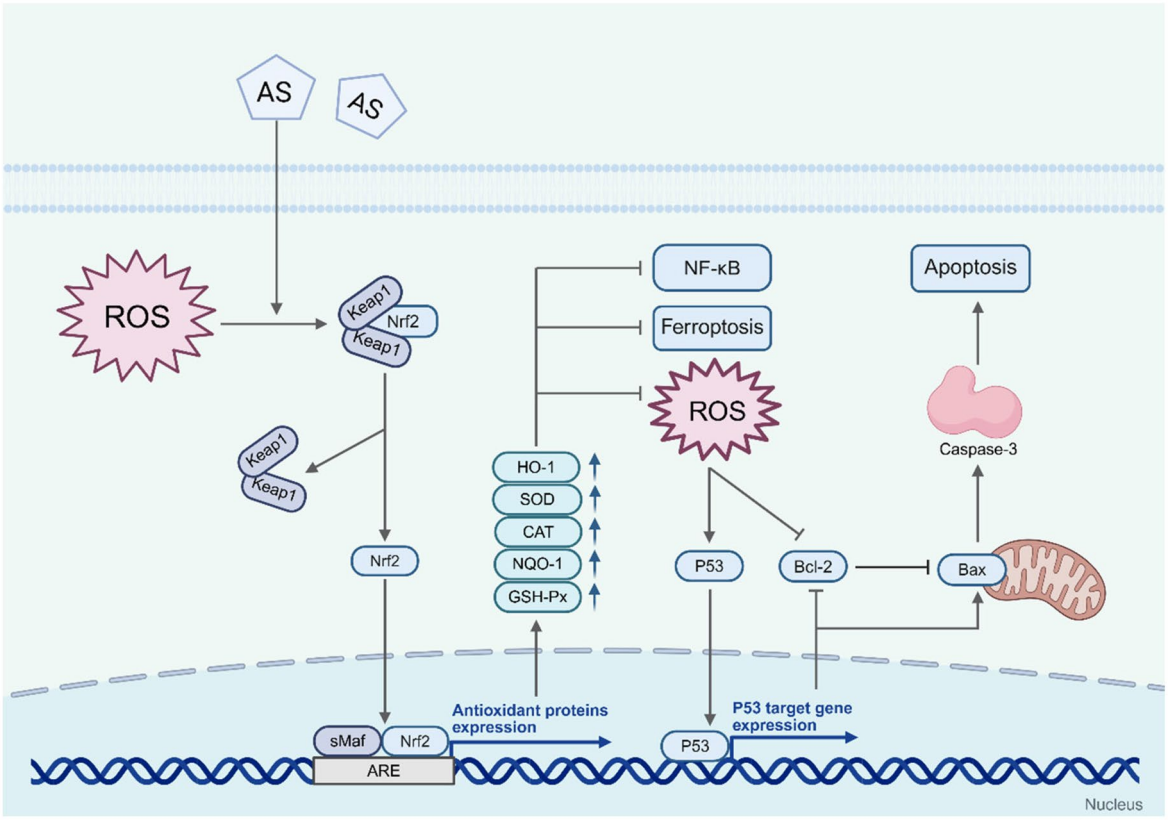

Figure 3. The antioxidant effects of *Asiaticoside* (AS). Created in https://BioRender.com.

(Zhuang et al. 2024). Gao et al. demonstrated that AS-mediated Nrf2 activation is essential for its protective effects, as these are abolished in Nrf2 knockout ($Nrf2^{-/-}$) mice (Gao et al. 2024). Liang et al. further elucidated that AS attenuates tert-butyl hydroperoxide (t-BHP)-induced oxidative injury and apoptosis in human umbilical vein endothelial cells (HUVECs) *via* the ROS-dependent p53/B-cell lymphoma-2 (Bcl-2)/caspase-3 signaling pathway (Liang et al. 2023). This conclusion was confirmed in a study on age-related macular degeneration (AMD), where the anti-apoptotic efficacy of AS was attributed to the activation of the Nrf2/HO-1 antioxidant pathway (Park et al. 2021). Interestingly, Liu et al. demonstrated that the antioxidant activity of AS also plays an anti-fatigue role in mice (Liu et al. 2023b). Ferroptosis is an iron-dependent programmed cell death modality characterized by lipid peroxidation. A recent study has shown that AS alleviates ferroptosis through Nrf2 activation and ARE-mediated antioxidant responses, thereby exerting antidepressant properties (Zhou et al. 2025a). In chondrocytes, AS protects against oxidative stress by inhibiting p65 nuclear translocation while activating Nrf2/HO-1 signaling, suggesting therapeutic potential for osteoarthritis (Luo et al. 2022). Notably, among triterpenoids, AA exhibits superior antioxidant efficacy compared to other derivatives (Lim et al. 2024).

However, conflicting evidence exists. Buranasudja et al. reported that the major triterpenoids in *Centella asiatica* (AS, MS, etc.) did not account for its antioxidant activity (Buranasudja et al. 2021). Arora et al. observed that triterpene-free *Centella asiatica* extracts reduced MDA levels in scopolamine-treated rats, while triterpene-enriched fractions failed to exhibit these protective effects (Arora et al. 2018). Additionally, the *Centella asiatica* extracts were reported to increase SOD activity, whereas CAT activity remained unaffected (Hong et al. 2021). These conflicting findings underscore the necessity for further mechanistic investigations into the antioxidant activity of AS. AS-mediated antioxidant defense plays a vital role in protecting proliferating mucosal cells and nascent vasculature from oxidative damage during the proliferative phase. By reducing ROS generated by ischemia-reperfusion injury and inflammatory cells, AS may help preserve epithelial cell viability and promote re-epithelialization in ESD-induced wounds.

Antifibrotic effect

AS exerts significant antifibrotic effects by targeting multiple key signaling pathways, as shown in Figure 4. The transforming growth factor-β (TGF-β)/Small mothers against decapentaplegic (Smad) signaling pathway, particularly TGF-β1, is widely recognized as a central profibrotic mediator. Studies have demonstrated that AS inhibits the TGF-β/Smad pathway *via* activation of Nrf2, thereby downregulating profibrotic gene expression and preventing mesothelial-mesenchymal transition (MMT) and peritoneal fibrosis (PF) (Zhao et al. 2020). In addition, AS also suppresses MMT and alleviates PF by modulating the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway. In TGF-β1-stimulated HMrSV5 cells, AS treatment reduces the phosphorylation of JAK2 and STAT3, decreases nuclear STAT3 translocation, upregulates E-cadherin expression, and downregulates the expression of various fibrotic markers, including vimentin, α-smooth muscle actin (α-SMA), fibronectin, and collagen type I alpha 1 (Col1A1) (Sun et al. 2023). In pulmonary fibrosis models, the antifibrotic effects of AS are closely associated with the upregulation of the adenosine 2 A receptor (A2AR), which is known to exert protective roles in fibrosis across multiple organs, including the lungs, heart, and kidneys. AS enhances A2AR expression in lung tissue, and through activation of downstream cAMP/Ras-related protein 1 (Rap1) signaling (Luo et al. 2020) and the bone morphogenetic protein 7 (BMP7)/Smad1/5 axis (Zhang et al. 2020c), effectively attenuates bleomycin (BLM)-induced pulmonary fibrosis. Notably, AS has also been shown to prevent pulmonary arterial hypertension and to reduce elastin and collagen fiber deposition in pulmonary arteries by modulating the TGF-β/Smad2/3 pathway (Wang et al. 2015). In hepatic fibrosis models, AS inhibits the activation of hepatic stellate cells by suppressing the Jagged-1/Notch-1 signaling pathway. This leads to reduced collagen deposition, decreased α-SMA expression, and improved key biochemical indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hydroxyproline levels (Xiao and Zhang 2023). Collectively, these findings strongly suggest that AS effectively prevents and treats various fibrotic diseases by simultaneously targeting multiple signaling pathways and molecular mediators.

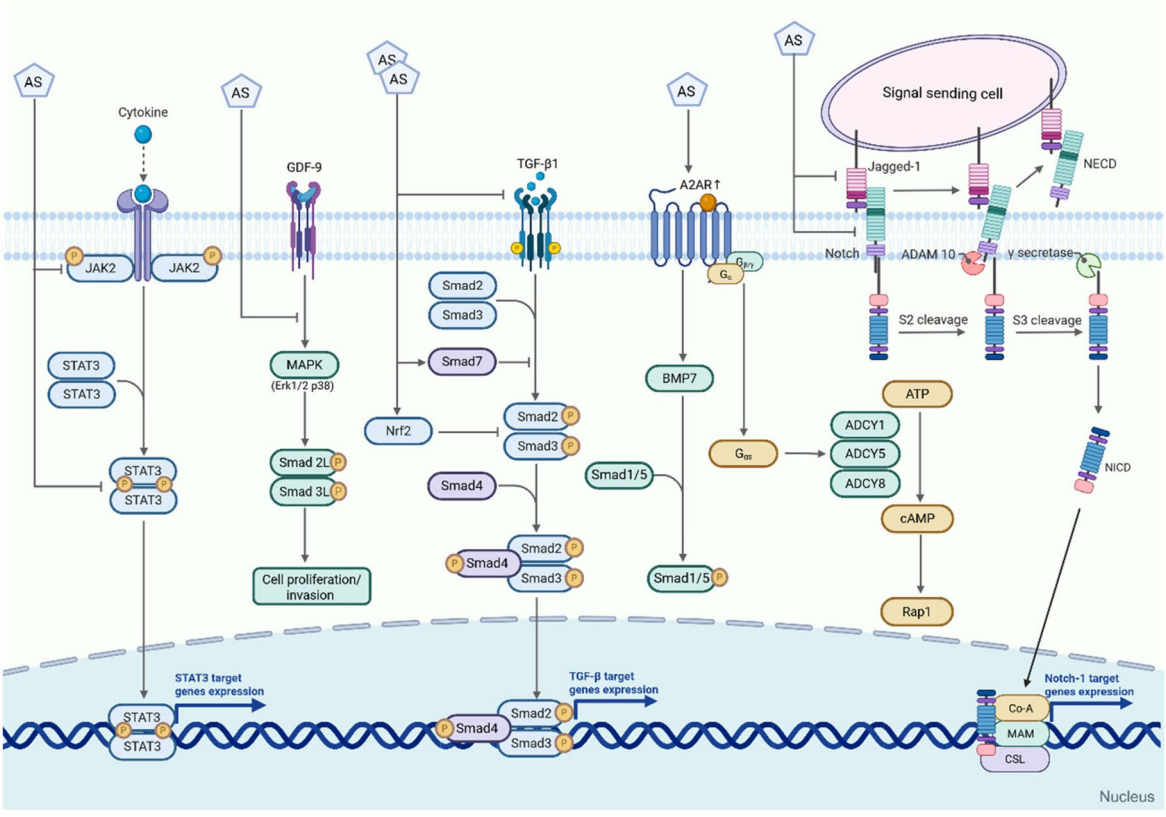

Figure 4. The antifibrotic effects of *Asiaticoside* (AS). Created in https://BioRender.com.

In addition, the antifibrotic effects of AS have been shown to contribute to the prevention of pathological scar formation during cutaneous wound healing. These scars are characterized by excessive fibroblast proliferation, overproduction of collagen, and abnormal ECM deposition, with TGF-β1 serving as a central driving factor. In keloid fibroblasts (KFs), AS effectively inhibits cell proliferation and the expression of type I and III collagen (Col I/III) by downregulating profibrotic TGF-β receptors I and II (TGF-βRI/II) and upregulating the inhibitory Smad7, without significantly affecting the expression or phosphorylation of Smad2/3/4. This results in the blockade of TGF-β signaling (Tang et al. 2011). This effect has been further validated in a rabbit ear hypertrophic scar model, in which oral administration of AS significantly decreased the expression of TGF-β1 and Col I/III genes, while upregulating Smad7 and peroxisome proliferator-activated receptor-γ (PPAR-γ). Histological analysis revealed reduced collagen density and improved fiber organization in AS-treated scars, suggesting a role in ECM remodeling (Huang et al. 2021). Moreover, AS targets other profibrotic signaling pathways. Growth differentiation factor-9 (GDF-9) has been shown to promote the proliferation, migration, and invasion of KFs. AS inhibits these pathological behaviors by suppressing activation of the GDF-9/MAPK/Smad signaling axis (Wu et al. 2017). In hypertrophic scar fibroblasts (HSFs), AS attenuates cellular activity and migration through inhibition of STAT3 phosphorylation, along with simultaneous downregulation of the TGF-β pathway. This leads to decreased expression of Col I, fibronectin 1 (FN1), α-SMA, and TGF-β1 (Tan et al. 2023).

This antifibrotic activity is particularly relevant to the remodeling phase of ESD-induced wound healing, during which uncontrolled TGF-β signaling promotes collagen overproduction and stricture formation. AS may help prevent stenosis by normalizing ECM deposition and promoting regenerative rather than fibrotic healing. Notably, AS exhibits dual regulatory properties. While AS has been shown to strongly inhibit fibrotic processes involved in pathological scar formation, previous studies have also demonstrated that it can accelerate normal cutaneous wound healing by promoting fibroblast proliferation and collagen synthesis (as detailed below) (Lu et al. 2004; Yuliati et al. 2015). This dual function-enhancing normal tissue repair while suppressing excessive scar formation-suggests that precise control of the timing and dosage of AS administration is crucial for its clinical application and warrants further investigation.

Pro-healing effect

The mechanism of skin wound healing comprises multiple complex and overlapping stages, including inflammation activation, cell proliferation, re-epithelialization, and ECM remodeling, all of which require the collaborative efforts of various cell types (Sorg et al. 2017; Abazari et al. 2022). Substantial evidence has demonstrated that during wound healing, AS not only exerts anti-inflammatory and antioxidant effects but also promotes cell migration, proliferation, angiogenesis, and matrix remodeling (Ruksiriwanich et al. 2020). Specifically, AS treatment significantly enhances the migration rate and adhesion capacity of both human dermal fibroblasts (HDFs) and human epidermal keratinocytes (HEKs), while promoting the proliferation of HDFs in a dose-dependent manner (Lee et al. 2012). Furthermore, AS potently induces angiogenesis by upregulating the expression of vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), endothelial nitric oxide synthase (eNOS), and cluster of differentiation 34 (CD34) (Nie et al. 2020; Mu et al. 2025). Concurrently, AS facilitates ECM remodeling by enhancing collagen biosynthesis and maintaining a balanced collagen I/III ratio, thereby suppressing pathological scarring. Table 1 presents the pro-healing mechanisms of AS in wound repair.

In diabetic ulcer wounds, AS has been shown to promote wound healing through multiple pathways. A recent study developed a novel *asiaticoside*-nitric oxide (ASNO) hydrogel by combining AS with NO for diabetic wound treatment. The study demonstrated that ASNO attenuated SRC/STAT3 pathway activation while simultaneously upregulating the expression of EGFR and VEGFA. These effects enhanced angiogenesis, stimulated cell proliferation and hair follicle regeneration, and accelerated wound closure in diabetic ulcers (Mu et al. 2025). Furthermore, ASNO treatment alleviated metabolic dysregulation in diabetic wounds. Another study found that ASNO modulated the Wnt/β-catenin signaling pathway, increased the expression of VEGF, iNOS, eNOS, and CD34, enhanced

Table 1. Pro-healing mechanisms of *Asiaticoside* (AS) in wound repair.

Wound type	Biological effects	Molecular mechanisms	*In vitro* models	*In vivo* models	Delivery system	Ref.
Diabetic ulcers	Enhances angiogenesis, cell proliferation, and hair follicle regeneration; increases collagen deposition; improves metabolic disorders	Inhibits SRC/STAT3 signaling pathway; increases EGFR and VEGFA expression	HaCaT cells	Rat diabetic wound model	ASNO hydrogels	(Mu et al. 2025)
	Promotes cell proliferation and migration; inhibits bacterial growth; enhances angiogenesis; attenuates inflammation	Regulates Wnt/β-catenin signaling pathway; increases expression of VEGF, iNOS, eNOS, and CD34	HFF-1 cells	Rat diabetic wound model	ASNO hydrogels	(Nie et al. 2020)
	Promotes cell proliferation and migration; promotes diabetic wound healing	Regulates miRNA-21-5p/TGF-β1/Smad7/TIMP3 signaling pathway	HaCaT cells	Rat diabetic wound model	ASNO hydrogels	(Liu et al. 2024b)
	Promotes cell proliferation and migration; enhances angiogenesis and re-epithelialization; inhibits abnormal apoptosis	Regulates Bcl-2/Bax/Caspase-3/PARP signaling pathway	HFF-1 cells	Rat diabetic wound model	ASNO hydrogels	(Ye et al. 2025)
	Enhances cell migration and re-epithelialization; increases collagen synthesis	Increases collagen type I and α-SMA expression	Mouse dermal fibroblasts (L929)	Rat diabetic wound model	AS polymeric nanoparticles	(Narisepalli et al. 2023)
	Facilitates cell proliferation and migration; regulates angiogenesis; accelerates the wound healing	Increases CD31 and Ki67 expression	HUVECs, Mouse fibroblasts	Rat diabetic wound model	MN-MXenes-AS microneedle patch	(Wang et al. 2022b)
Burn wounds	Accelerates re-epithelialization; reduces inflammation; promotes collagen deposition; stimulates neovascularization	Increases VEGF, CD31, PCNA expression; decreases TNF-α and IL-6 expression	–	Rat deep partial-thickness burn injury model	AS-loaded coaxial electrospun nanofibers	(Zhu et al. 2016)
	Promotes cell proliferation and migration, angiogenesis, and macrophage polarization; inhibits bacterial growth; reduces inflammation; improve collagen deposition	Increases VEGF, PDGF-BB expression; activates CDH5, PECAM1, VEGFA signaling pathway; increases TGF-β1, IL-4 expression; decreases IFN-γ and TNF-α expression; activates Wnt/Ca^{2+} signaling pathway	L929 cells, HUVECs, RAW264.7 cells	Rat burn-wound infection model	RQLAg hydrogels	(Feng et al. 2023)
	Stimulates angiogenesis and cell proliferation	Increases VEGF, MCP-1, IL-1β expression	HaCaT cells, THP-1 differentiated macrophages	Rat full-thickness burn injury model	Ointment (10^{-8}% AS)	(Kimura et al. 2008)
Excisional wounds	Anti-inflammatory; promotes macrophage polarization, angiogenesis, and collagen deposition; inhibits scar formation	Decreases IL-6 and TNF-α expression; increases VEGF expression; reduces collagen I/III ratio	HDF-α cells, HUVECs, RAW264.7 cells	Rat full-thickness wound model	SNF-AS hydrogels	(Liu et al. 2021)

(*Continued*)

Table 1. Continued.

Wound type	Biological effects	Molecular mechanisms	*In vitro* models	*In vivo* models	Delivery system	Ref.
	Inhibits inflammation; promotes macrophage polarization, angiogenesis, and ECM remodeling; inhibits scar formation	Increases VEGF and PDGF-BB expression; decreases IL-6 and TNF-α expression; reduces collagen I/III ratio	HDF-α cells, HUVECs, RAW264.7 cells	Rat full-thickness model	SNF-AS-Mg hydrogels	(Yang et al. 2024)
	Promotes cell proliferation, migration, and wound closure; enhances re-epithelialization, collagen synthesis and angiogenesis	Increases CD31 expression; reduces collagen I/III ratio	HaCaT cells, HSF cells	Rat full-thickness excision wound model	AS-loaded porous microspheres	(Peng et al. 2013; Zhang et al. 2016)
	Anti-inflammatory, pro-angiogenic, anti-scar	Decreases TNF-α expression; increases VEGF expression	Mouse fibroblast cells	Rat circular full-thickness skin wound model	AS@PDA-OQG hydrogels	(Deng et al. 2024)
	Reduces inflammation; promotes fibroblast proliferation and migration; promotes ECM synthesis; inhibits scarring	Modulates TLR4/MAPK/NF-κB signaling pathway, decreases IL-6, TNF-α, iNOS, MMP-9, COX-2 expression, increases IL-10, CD31, vimentin expression	RAW264.7 cells, *Ex vivo* wound infection model	LPS inflamed rat full-thickness wound model	Collagen-AS/εPLL artificial skin substitute	(Seon et al. 2021a)
	Anti-inflammatory; promotes angiogenesis and healing; improves collagen deposition	Decreases IL-6 expression; increases VEGF expression; reduces collagen I/III ratio	HSF cells	Rat full-thickness excisional wound model	AS&PNS hydrogels	(Huang et al. 2025)
Other wounds	Improves skin flap survival	Increases VEGF and SOD expression; reduces MDA expression and inflammatory infiltration	–	Rat skin flap model	Oral administration	(Feng et al. 2021)
	Promotes oral wound healing	Increases Col1A1 mRNA expression	Human gingival fibroblasts	–	–	(Suriyah et al. 2021)
	Induces periodontal tissue regeneration	Activates Wnt/β-catenin signaling pathway; increases OSX and DMP1 expression	Human periodontal ligament cells	–	–	(Fitri et al. 2018)

SRC, sarcoma; STAT3, signal transducer and activator of transcription 3; EGFR, epidermal growth factor receptor; VEGFA, vascular endothelial growth factor A; HaCaT, human immortalized keratinocytes; ASNO, *asiaticoside*-nitric oxide; Wnt, wingless-related integration site; VEGF, vascular endothelial growth factor; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; CD34, differentiation 34; HFF-1, human foreskin fibroblasts; miRNA-21-5p, microRNA-21-5p; TGF-β1, transforming growth factor-β1; Smad7, small mothers against decapentaplegic 7; TIMP3, tissue inhibitor of metalloproteinase-3; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2-associated X protein; PARP, poly [ADP-ribose] polymerase; α-SMA, α-smooth muscle actin; L929, mouse dermal fibroblasts; CD31, differentiation 31; HUVECs, human umbilical vein endothelial cells; PCNA, proliferating cell nuclear antigen; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; PDGF-BB, platelet-derived growth factor-BB; CDH5, endothelial cadherin; PECAM1, platelet-endothelial cell adhesion molecule-1; IL-4, interleukin-4; IFN-γ, interferon-γ; RQLAg, rColMA/QCSG/LIP@AS/Ag@MOF; MCP-1, monocyte chemoattractant protein-1; IL-1β, interleukin-1β; HDF-α, human dermal fibroblasts; SNF, silk nanofiber; ECM, extracellular matrix; HSF, human skin fibroblast; AS@PDA, polydopamine-encapsulated *asiaticoside*; TLR4, toll-like receptor 4; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; MMP-9, matrix metalloproteinase-9; COX-2, cyclooxygenase-2; IL-10, interleukin-10; LPS, lipopolysaccharide; PNS, panax notoginseng saponins; SOD, superoxide dismutase; MDA, malondialdehyde; Col1A1, collagen type I alpha 1; OSX, osterix; DMP1, dentin matrix protein1. -, not mentioned.

fibroblast proliferation and migration, and ultimately accelerated the healing of diabetic ulcer wounds (Nie et al. 2020). Liu et al. demonstrated that ASNO promoted diabetic wound healing *via* the miRNA-21-5p/TGF-β1/Smad7/tissue inhibitor of metalloproteinase-3 (TIMP3) signaling pathway (Liu et al. 2024b). Ye et al. found that ASNO enhanced fibroblast proliferation, migration, and angiogenesis through the Bcl-2/Bcl-2-associated X protein (Bax)/Caspase-3/Poly [ADP-ribose] polymerase (PARP)

pathway. By improving abnormal apoptosis, ASNO promoted the healing of chronic wounds in diabetic patients (Ye et al. 2025). Moreover, both *in vitro* and *in vivo* experiments demonstrated that encapsulating AS in polymeric nanoparticles and incorporating it into a gelatin based hydrogel enhanced fibroblast migration, accelerated re-epithelialization, and increased Col I synthesis, thereby promoting effective diabetic wound healing (Narisepalli et al. 2023). Wang et al. developed MXene-integrated microneedles for the sustained release of AS, which accelerated the healing of diabetic foot ulcers (DFUs) (Wang et al. 2022b).

AS also demonstrates potent pro-healing effects in burn wounds. Zhu et al. established a deep partial-thickness burn model in rats to evaluate the healing efficacy of AS-loaded coaxially electrospinning nanofibers. Histological analysis showed that, compared to the model control, the AS-loaded coaxial nanofibers accelerated re-epithelialization in desquamated areas, reduced inflammatory cell infiltration, and increased collagen deposition and neovascularization. Immunohistochemical analysis confirmed increased expression of VEGF, CD31, and proliferating cell nuclear antigen (PCNA), further supporting the enhanced wound healing effect (Zhu et al. 2016). In a Sprague Dawley (SD) rat burn-wound infection model, an injectable antibacterial hydrogel containing AS-loaded liposomes and ultrafine silver nanoparticles achieved the highest healing rate (Feng et al. 2023). After 14 days, the experimental group exhibited complete wound closure with newly formed skin, achieving a wound healing rate of up to 100%. Kimura et al. (2008) investigated the effect and mechanism of low-dose AS in promoting burn wound repair. They concluded that AS-enhanced healing might be attributed to angiogenesis promotion mediated by elevated VEGF expression, which was induced by increased IL-1β from recruited macrophages and/or enhanced monocyte chemoattractant protein-1 (MCP-1) expression in keratinocytes and/or macrophages.

Excisional wounds represent another widely used wound model, and AS has demonstrated pro-healing properties in this context. Yang et al. (2024) incorporated AS and magnesium ions into silk nanofibers (SNFs) to fabricate SNF-AS-Mg hydrogels. *In vitro* and *in vivo* experiments confirmed that the SNF-AS-Mg hydrogels exhibit excellent biocompatibility. The synergistic effects of AS and Mg promote enhanced M2 polarization of macrophages and angiogenesis during the inflammatory phase, while effectively inhibiting excessive collagen deposition and scar formation during the remodeling phase. Using rat full-thickness wound model, Liu et al. (2021) demonstrated that the SNF-AS hydrogels significantly promoted wound healing and exhibited enhanced scar suppression compared to the free AS solution. The wounds treated with the AS-loaded hydrogel exhibited a significantly greater amount of deposited collagen, demonstrated a uniform network structure, and showed a lower type I to type III collagen ratio, indicating high-quality wound healing. In the study by Zhang et al. a 10 mm × 10 mm full-thickness skin excision was created, extending down to the subcutaneous panniculus carnosus layer (Peng et al. 2013). The authors developed porous microspheres for the sustained release of AS to improve its bioavailability and enhance therapeutic efficacy. In regenerated skin samples from the AS microsphere group, the presence of skin appendages, normalized collagen composition, and increased neovascular density closely resembled that of normal skin, demonstrating significant acceleration of re-epithelialization, collagen synthesis, and angiogenesis during excisional wound healing in rats (Zhang et al. 2016). Similarly, in a full-thickness rat wound model, Deng et al. demonstrated that incorporating polydopamine-encapsulated AS nanoparticles into an OQG hydrogel accelerated wound healing, reduced inflammation, promoted angiogenesis, and minimized scar formation (Deng et al. 2024). Seon et al. reported that AS release *via* a scaffold significantly attenuated the initial inflammatory response. By enhancing fibroblast migration, proliferation, and ECM synthesis, the progression through wound healing phases was markedly accelerated (Seon et al. 2021a). A recent study showed that a co-assembled AS and panax notoginseng saponins (PNS) hydrogel significantly enhanced wound healing by reducing IL-6 levels and increasing VEGF expression. Treatment with the AS-PNS hydrogel also normalized epidermal thickness and improved collagen fiber organization at the wound site. This novel hydrogel material offers a simple and effective strategy for clinical skin wound management (Huang et al. 2025).

AS also exerts therapeutic effects in other types of wound healing. Feng et al. demonstrated that oral administration of AS in a rat random skin flap model increased VEGF and SOD levels, reduced

MDA and inflammatory infiltration, and ultimately improved flap survival rate (Feng et al. 2021). Col1A1 is known to play a crucial role in wound healing. In human gingival fibroblasts, AS upregulated Col1A1 mRNA expression, thereby facilitating oral wound repair (Suriyah et al. 2021). AS also induced osteogenic differentiation in human periodontal ligament (hPDL) cells by activating the Wnt/β-catenin signaling pathway, suggesting its therapeutic potential in periodontal tissue regeneration (Fitri et al. 2018).

Collectively, these pro-healing effects synergistically accelerate all phases of ESD-induced wound healing. During the transition from inflammation to proliferation, enhanced angiogenesis alleviates tissue hypoxia, thereby creating a favorable microenvironment for cellular activities. In the proliferative phase, fibroblast-driven granulation tissue formation effectively fills the submucosal defect, thereby restoring tissue structure and integrity. During the remodeling phase, the maintenance of a balanced collagen I/III ratio minimizes excessive scar formation, thereby reducing the risk of ESD-induced stenosis. This multifactorial action underscores AS's potential to optimize the entire wound-healing cascade in ESD-induced mucosal injuries.

Gastrointestinal protective effect

While direct studies on ESD wounds are limited, the efficacy of AS in other GI injury models provides a strong rationale for its potential application. In a rat model of acetic acid-induced gastric ulcer, which closely mimics the submucosal damage caused by ESD, Cheng et al. reported that AS promoted angiogenesis, accelerated epithelial proliferation, and inhibited myeloperoxidase (MPO) activity during the ulcer healing phase (Cheng et al. 2004). In the same year, Guo et al. reported that AS suppressed iNOS expression, thereby facilitating gastric ulcer healing in rats (Guo et al. 2004). These findings confirm that the pro-healing mechanisms observed in skin (angiogenesis and inflammation modulation) are active and effective within the gastric environment. Recently, Wannasarit et al. utilized the anti-ulcer properties of AS to develop a raft-forming gastro-retentive formulation based on *Centella asiatica* extract-solid dispersions. This system was designed to achieve sustained delivery of AS in the stomach. *In vivo* experiments confirmed that this formulation exhibited superior therapeutic efficacy compared to the standard anti-ulcer agent, lansoprazole (Wannasarit et al. 2020). AS also exerts protective effects against colitis. In a dextran sulfate sodium (DSS)-induced rat colitis model, AS treatment significantly alleviated colitis symptoms (Liu et al. 2024a). Furthermore, AS attenuated inflammation by inhibiting the activation of TLR4/NF-κB and MAPK signaling pathways, thereby reducing pro-inflammatory cytokine release. AS administration restored intestinal barrier integrity by upregulating tight junction proteins, including claudin-3, occludin, and ZO-1. Additionally, AS rebalanced gut microbiota composition in DSS-treated mice by enhancing microbial diversity.

Clinical trials on skin wound healing

Clinical evidence for AS primarily derives from *Centella asiatica* extracts rather than from pure AS monotherapy, as detailed in Table 2. In a split-face, double-blind, randomized, placebo-controlled trial (Damkerngsuntorn et al. 2020), 30 patients with facial acne scars underwent 2940 nm erbium-doped yttrium aluminum garnet (Er: YAG) laser treatment. One side of the face was randomly treated with 0.05% w/w ECa 233 gel (containing 51% MS and 38% AS), while the other received a placebo gel. Follow-up revealed significant improvements in erythema, crusting/scabbing, and overall wound appearance in the ECa 233-treated group, suggesting its potential as a post-laser treatment to enhance wound esthetics. Namviriyachote et al. (2020) developed a polyurethane-biomacromolecule composite foam dressing containing AS for clinical evaluation. Among 28 wounds across 14 subjects, wounds were randomly assigned to receive one of two treatments: either the selected polyurethane-combined foam dressing impregnated with AS and silver nanoparticles (study group), or a gauze dressing containing 0.5% chlorhexidine acetate, the standard treatment widely used in clinical practice (comparative group). The study found that the selected foam dressing resulted in faster wound closure, greater

re-epithelialization, and lower pain scores compared to the standard gauze dressing soaked with chlorhexidine. Changsan et al. (2023) formulated a polymeric spray film containing *Centella asiatica* leaf extract, which included AA, MA, AS, and MS at concentrations of 0.20 ± 0.02 mg/mL, 0.16 ± 0.01 mg/mL, 0.32 ± 0.03 mg/mL, and 0.10 ± 0.00 mg/mL, respectively. They conducted a multicenter, randomized, controlled trial. The cohort consisted of 60 volunteers with clean-contaminated wounds (class 1), who were randomly assigned to the control group ($n = 30$) and the test group ($n = 30$). The study revealed significantly lower Pressure Ulcer Scale for Healing (PUSH Tool) and exudate scores in the test group, with mean healing times of 4.6 ± 1.1 days versus 4.87 ± 1.0 days in the control group. These findings suggested that the polymeric spray film containing *Centella asiatica* extract promoted wound repair and demonstrated clinical utility in acute wound management.

Surakunprapha et al. (2020) incorporated herbal extracts of *Allium cepa*, *Centella asiatica*, *Aloe vera*, and paper mulberry into a silicone gel. They conducted a prospective, randomized, double-blind study to evaluate the efficacy of topical silicone gel combined with herbal extracts in promoting sternotomy scar healing. Their results demonstrated that post-sternotomy scars tended to exhibit improved vascularity and pigmentation when treated with silicone gel combined with herbal extracts. Jenwitheesuk et al. (2018) evaluated the efficacy of a *Centella asiatica* extract-based cream in preventing scar formation at split-thickness skin graft donor sites. Thirty patients aged over 20 years were randomly assigned to two groups, with different creams applied to each side of the donor site. Cream A contained 7% *Centella asiatica* extract, while Cream B served as a placebo. This study demonstrated that the *Centella asiatica*-based cream improved scar appearance and skin pigmentation. Based on objective measurements and extended follow-up, the *Centella asiatica* cream may serve as a promising alternative for improving hypertrophic scars. A single-center, randomized, controlled, open-label study demonstrated that a cream containing *Centella asiatica* extract is a safe and effective alternative to hydrocolloid fiber dressings for treating diabetic foot ulcers, with comparable efficacy and safety (Kuo et al. 2012). Overall, these trials confirmed that AS-rich formulations consistently provide therapeutic benefits for various types of wounds.

Safety and pharmacokinetics of AS

Preclinical evaluations have confirmed that AS possesses a favorable safety profile. In acute toxicity studies, AS exhibited a lethal dose (LD_{50}) > 2000 mg/kg, and sub-chronic toxicity trials revealed no significant toxicity at doses ≤ 500 mg/kg, indicating a high safety margin (Sampath et al. 2012; Songvut et al. 2021).

Extensive genotoxicity assessments indicate that AS does not pose a mutagenic risk. Standardized genotoxicity batteries, including the bacterial reverse mutation assay (Ames test) using *Salmonella typhimurium* and *Escherichia coli* strains (Kwon et al. 2003; Florinsiah et al. 2014), have consistently yielded negative results for *Centella asiatica* extracts and its triterpenoid components, with or without metabolic activation. Furthermore, *in vivo* mammalian erythrocyte micronucleus tests and *in vitro* chromosomal aberration assays have demonstrated no evidence of clastogenic or aneugenic potential at therapeutic doses (Kwon et al. 2003). Far from promoting tumorigenesis, emerging evidence suggests that AS may exert anti-tumor effects; for instance, it has been shown to inhibit the proliferation of cancer cell lines *via* the regulation of apoptosis and cell cycle arrest pathways (Zhou et al. 2020). This lack of genotoxicity, combined with potential anti-neoplastic properties, supports the safety of AS for application in the post-resection bed of gastrointestinal tumors.

Wright assessed the drug interaction potential of a *Centella asiatica* water extract (containing 64.13 ± 0.78 mg/g dry extract of AS) by evaluating its inhibition or induction of cytochrome P450 (CYP450) enzymes. The aqueous extract of *Centella asiatica* (CAW-R61J) acted as a relatively weak reversible inhibitor of most tested CYP450 isoforms, with the strongest inhibition observed for CYP2C9 (half-maximal inhibitory concentration: 330 µg/mL). Notably, it was not a time-dependent inhibitor of any CYP450 isoform, thereby minimizing the risk of drug interactions (Wright et al. 2020). These results are consistent with previous research (Savai et al. 2015a). Pan et al. found that *Centella asiatica* ethanol and dichloromethane extracts selectively inhibited CYP2C9 activity, while AS itself exhibited

Table 2. Clinical trials on *Asiaticoside* (AS)-containing formulations for wound healing.

Ref	Study design	Population & wound type	Intervention	Control group	Key outcomes	Conclusion
(Damkerngsuntorn et al. 2020)	Split-face, double-blind randomized, controlled trial	30 patients with facial acne scars (post-laser)	0.05% w/w ECa 233 gel (38% AS + 51% MS)	Placebo gel	↑ Improvement in erythema, crusting/scabbing, overall wound appearance	Potential as post-laser treatment to enhance wound esthetics.
(Namviriyachote et al. 2020)	Prospective, randomized, clinical trial	14 subjects with 28 acute traumatic abrasion wounds or dermal burn wounds	Polyurethane foam + AS + silver nanoparticles	Gauze + 0.5% chlorhexidine acetate	↓ Wound closure time, ↑ re-epithelialization, ↓ pain score	Superior efficacy in acute wound management.
(Changsan et al. 2023)	Multicenter, randomized, controlled trial	60 volunteers with clean-contaminated wounds	Polymeric spray film solution (AS 0.32 ± 0.03 mg/mL)	Purified water	↓PUSH Tool scores, ↓exudate scores; ↓mean healing time	Promotes acute wound repair with no adverse effects.
(Surakunprapha et al. 2020)	Prospective, randomized, double-blind study	46 patients with post-sternotomy scars	Silicone gel + herbal extracts (incl. *Centella asiatica*)	Silicone gel	↑ Better scar vascularity and pigmentation.	Improves scar quality post-surgery.
(Jenwitheesuk et al. 2018)	Prospective randomized, double-blind control study	30 patients with split-thickness skin graft donor sites	Cream A: 7% *Centella asiatica* extract	Cream B: Placebo	↑ Scar outcomes, ↑ skin pigmentation improvement	Effective alternative for preventing hypertrophic scars.
(Kuo et al. 2012)	Single-center, randomized, controlled, open-label study	24 patients with diabetic foot ulcers	Cream containing *Centella asiatica* extract	Hydrocolloid fiber dressings	Comparable efficacy and safety	Safe and effective alternative for DFU treatment.

↑, increase significantly; ↓, decrease significantly. ECa 233 gel, a standardized extract of *Centella asiatica*; AS, *asiaticoside*; MS, madecassoside; DFU, diabetic foot ulcer.

no inhibition against CYP2C9, CYP2D6, or CYP3A4 (Pan et al. 2010). However, Savai et al. suggested that alcoholic extracts of *Centella asiatica* might cause adverse herb-drug interactions when co-administered with CYP3A4/CYP2D6 substrate drugs in humans (Savai et al. 2015b). As these studies were primarily *in vitro*, further *in vivo* and clinical investigations are needed to confirm the safety of AS.

Pharmacokinetic studies can provide insights into appropriate clinical administration routes. Liu et al. reported that following a single caudal vein injection of AS (40 mg/kg) in rats, the values of the peak concentration (C_{max}), half-life ($T_{1/2}$), area under the concentration/time curve (AUC_{0-t}), and time to peak concentration (T_{max}) were 3347.9 ± 786.9 ng/mL, 23.4 ± 9.6 min, 81,443.67 ± 57,156.81 ng/(mL·min), and 5 min, respectively (Liu et al. 2010). Hengjumrut et al. (2018) reported that when AS (38 mg/kg) was administered orally to rats, the C_{max}, $T_{1/2}$, AUC_{0-t}, and T_{max} were 658.17 ± 597.56 μg/L, 4.20 ± 0.91 h, 1937.19 ± 464.40 μg·h/L, and 0.62 ± 0.79 h, respectively. However, the absolute bioavailability of AS was low (1.86%), which is consistent with a previous study by Liu et al. conducted in 2010 (Liu et al. 2010). This may be attributed to poor solubility, delayed absorption, variability in GI transit time, or fecal excretion. Boonyarattanasoonthorn et al. (2022) enhanced the oral bioavailability of AS by increasing its water solubility. An alternative explanation involves the conversion of AS to AA in the GI tract, mediated by digestive enzymes or microbial activity (Grimaldi et al. 1990). Rush et al. (1993) found that equimolar oral doses of AS (24 mg) and AA (12 mg), when administered separately, resulted in similar total 12-hour plasma concentrations (area under the curve, AUC) of AA in humans. This suggests that the therapeutic effects of AS may be mediated through its conversion to AA.

Following intravenous administration, AS shows extensive tissue distribution – including liver, kidney, spleen, lung, heart, skin, stomach, and brain – where it undergoes primary metabolism to MA and AA, with 80–90% of the administered dose excreted *via* feces as these metabolites. Songvut et al. (2021) demonstrated in humans that, after oral administration of ECa 233, the unchanged form of AS in plasma was primarily excreted in urine, while the metabolite AA was mainly excreted *via* feces. This conclusion was further supported by Wright et al. (2022). In addition, studies have shown that AS and MS can interconvert *in vivo*, with the conversion rate of AS to MS being higher than that in the reverse direction (Hengjumrut et al. 2018; Boonyarattanasoonthorn et al. 2022).

Feasibility and challenges in ESD-induced wound treatment

The regenerative process of ESD-induced wound healing involves cellular proliferation, migration, re-epithelialization, granulation tissue formation, angiogenesis, and dynamic cell-ECM interactions (Tarnawski and Ahluwalia 2021). The remodeling phase, characterized by ECM maturation, may progress into pathological fibrosis if dysregulated. AS strategically modulates these multistage repair cascades by concurrently attenuating inflammation, mitigating oxidative stress, stimulating proliferation, and suppressing fibrosis. By targeting the conserved pathways of tissue repair shared by skin and mucosa, AS complements the limitations of existing PPIs and P-CABs. While acid suppressants create a neutral pH environment essential for preventing further damage, they do not actively accelerate the cellular phases of repair. AS fills this therapeutic void by stimulating the underlying healing pathology, suggesting that a combination of PPIs (environment optimization) and AS (tissue regeneration) could offer superior clinical outcomes, as summarized in Table 3.

However, the clinical translation of AS for ESD-induced wound treatment faces several significant challenges. First, there is currently no effective method for delivering AS locally to the wound site *via* endoscopy. The extremely low oral bioavailability of AS hinders the maintenance of effective systemic or local concentrations. Therefore, targeted delivery systems are required to precisely deliver AS to ESD-induced wound sites. Second, the GI environment is highly complex and markedly different from that of external wounds. The strongly acidic gastric environment, digestive enzymes, and microbial metabolism can lead to structural degradation and reduced pharmacological activity of AS. Preserving the pharmacological activity of AS under these biochemical conditions requires further investigation. Finally, dynamic clearance mechanisms pose a major challenge: GI peristalsis generates shear forces that dislodge unbound AS from the wound site. Complete healing of ESD-induced

Table 3. Therapeutic comparison and potential synergy: *Asiaticoside* (AS) and acid-suppressive agents in ESD-induced ulcer management.

	PPIs/P-CABs	AS
Primary mechanism	Gastric acid suppression	Multi-target: anti-inflammatory, antioxidant, antifibrotic, pro-cell migration/proliferation, pro-angiogenesis and matrix remodeling.
Ulcer healing rate impact	Limited benefit (Ishihara et al. 2020; Kato et al. 2023; Chen et al. 2024b; Ihara et al. 2025)	Reduces the severity of the ulcer and promotes ulcer healing (Wannasarit et al. 2020)
Fibrosis/stenosis prevention	No effect	Regulates TGF-β/Smad, JAK2/STAT3, cAMP/Rap1, BMP7/Smad, GDF-9/MAPK/Smad, Jagged-1/Notch-1 signaling pathway; promotes COL I/III balance.
Long-term safety concerns	Pneumonia, *Clostridium difficile* infection, acute kidney injury, osteoporosis, and malignancies (Abramowitz et al. 2016; Perry et al. 2020; Savarino et al. 2020; Liabeuf et al. 2021; Rameau et al. 2021; Watanabe et al. 2021; Mahmud et al. 2022)	Low toxicity (LD_{50} >2000 mg/kg) (Sampath et al. 2012; Songvut et al. 2021)
Delivery feasibility	Oral administration	Requires localized endoscopic delivery

ESD, endoscopic submucosal dissection; PPIs, proton pump inhibitors; P-CABs, potassium-competitive acid blockers; TGF-β/Smad, transforming growth factor-β/small mothers against decapentaplegic; JAK2/STAT3, the janus kinase 2/signal transducer and activator of transcription 3; cAMP/Rap1, cyclic AMP/ras-related protein 1; BMP7/Smad, bone morphogenetic protein 7/small mothers against decapentaplegic; GDF-9/MAPK/Smad, growth differentiation factor-9/mitogen-activated protein kinase/small mothers against decapentaplegic; COL I/III, type I and III collagen.

artificial ulcers typically requires 4–8 weeks, necessitating the long-term retention of AS at the wound site. This necessitates the development of AS formulations with prolonged adhesion, controlled release kinetics aligned with healing phases, and mechanical resilience against peristaltic deformation.

Future research should first validate the therapeutic efficacy of AS in ESD-induced wound healing through both *in vitro* and *in vivo* experiments. Subsequently, efforts should be directed toward the development of novel delivery systems for AS. Precise application to irregular and bleeding wounds *via* endoscopic channels requires the use of innovative formulations (e.g., sprayable hydrogels, adhesive patches) that exhibit rapid mucoadhesion and sustained drug release. Microneedle arrays, a novel drug delivery system composed of microscale needle arrays, have attracted increasing attention in recent years and offer several advantages: (1) Microneedles can effectively penetrate physical barriers at the wound site (e.g., mucus, exudate) and anchor directly to the wound bed for localized drug release (Lyu et al. 2023). (2) Microneedles can be loaded with a wide range of therapeutics, including small molecules (Tekko et al. 2020; Zhang et al. 2020b), macromolecules (Korkmaz et al. 2016), and nanoparticles (Guillot et al. 2023; Ding et al. 2024). (3) Diverse microneedle fabrication materials enable precise control over drug release kinetics. Polymers such as polylactic-co-glycolic acid (PLGA) and polycaprolactone (PCL) possess specific mechanical properties and degradation profiles, facilitating sustained drug release over periods ranging from weeks to years *in vivo* (Fredenberg et al. 2011). (4) Specialized structural designs (e.g., suction-cup-like structures) enhance the adhesive properties of microneedles under both dry and wet conditions (Zhang et al. 2020d). (5) Stimuli-responsive materials incorporated into microneedles can monitor wound conditions through various biochemical and physical cues (e.g., pH, ROS), thereby enabling on-demand drug delivery tailored to specific wound healing stages (Aghabegi Moghanjoughi et al. 2016). Microneedles are currently being extensively investigated for wound healing and tissue regeneration across various tissues, including skin, cardiac, bone, tendon, ocular, vascular, oral, hair, and spinal applications. Although microneedles hold significant promise for ESD-induced wound healing, their rigidity poses a risk of perforation in the thin-walled GI tract. Flexible or dissolvable variants may offer a better balance between efficacy and safety. Concurrently, the development of alternative biomaterials warrants further exploration. Several novel biomaterials (Bao et al. 2021) are also being investigated for ESD-induced wound treatment, including pH-responsive bioadhesives (Xie et al. 2024), polyurethane/small intestinal submucosa (PU/SIS) hydrogels (Zhao et al. 2021), two-component in-situ hydrogels prepared from maleimide-based oxidized sodium alginate and sulfhydryl carboxymethyl-chitosan (Lei et al. 2023), and konjac glucomannan/sodium alginate/ε-poly-l-lysine hydrogels (Zhou et al. 2025b). AS, when delivered *via* these emerging biomaterials and drug delivery systems, holds strong potential as a clinically viable option for treating ESD-induced wounds.

In conclusion, AS-based therapy represents a paradigm shift from passive acid suppression to active mucosal regeneration in the management of ESD-induced wounds. Despite substantial challenges, recent advancements in biomaterials and endoscopic drug delivery systems provide a feasible pathway for realizing the clinical potential of AS. This therapeutic transformation has the potential to significantly reduce postoperative complications (notably bleeding and stricture formation), lower healthcare costs, and improve the quality of life for patients undergoing ESD procedures.

Author contributions

CRediT: **Qinghua Li**: Conceptualization, Visualization, Writing – original draft, Writing – review & editing; **Wangqi Chen**: Writing – original draft; **Yuxia Xie**: Writing – review & editing; **Hong Zhu**: Supervision.

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The datasets during and/or analyzed during the current study is available from the corresponding author on request.

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