Article

Salvianolic acids: Molecular mechanisms, pharmacological properties, pharmacokinetics, clinical applications, and future perspectives

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Abstract

Salvianolic acids, particularly salvianolic acid A (SAA) and salvianolic acid B (SAB), are the principal water-soluble polyphenolic constituents derived from the traditional Chinese medicinal herb *Salvia miltiorrhiza* Bunge (Danshen). With a history of over two millennia in treating cardiovascular disorders, these compounds have garnered substantial scientific interest due to their pleiotropic pharmacological activities. This comprehensive review synthesizes current knowledge regarding the discovery, physicochemical properties, extraction methodologies, pharmacokinetic profiles, and multifaceted therapeutic mechanisms of salvianolic acids. Preclinical evidence robustly demonstrates that salvianolic acids confer significant cardioprotective, neuroprotective, anti-inflammatory, antioxidant, anticancer, antiplatelet, hepatoprotective, and nephroprotective effects through the modulation of key signaling pathways, including NF-κB, Nrf2, MAPK, and NLRP3 inflammasome cascades. Clinical investigations, primarily utilizing injectable formulations, indicate favorable safety and tolerability in human subjects, with preliminary efficacy observed in mitigating major adverse cardiovascular events and angina as adjuvant therapy. However, the clinical translation of salvianolic acids is hindered by considerable challenges, most notably poor oral bioavailability attributable to low membrane permeability and extensive first-pass metabolism, as well as inherent chemical instability under physiological conditions. Ongoing research into advanced drug delivery systems, such as nanoparticle encapsulation and sustained-release formulations, presents promising avenues to overcome these pharmacokinetic limitations. While substantial progress has been made in elucidating the molecular pharmacology of salvianolic acids, further large-scale, multicenter clinical trials and in-depth mechanistic studies are imperative to fully establish their therapeutic utility and facilitate their integration into evidence-based global medical practice.

Keywords salvianolic acid A; salvianolic acid B; *Salvia miltiorrhiza*; cardiovascular protection; anti-inflammatory; pharmacokinetics; bioavailability; oxidative stress.

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1 Introduction

Salvianolic acids (SAs) represent a family of water-soluble phenolic acid compounds derived predominantly from the dried root and rhizome of *Salvia miltiorrhiza* Bunge (Danshen), a botanical drug that has been used for over 2000 years in traditional Chinese medicine for the treatment of cardiovascular and inflammatory disorders (Zhang, 2017a-b; Jiang et al., 2024; Zhao et al., 2024; Yang et al., 2025). The major bioactive constituents of *S. miltiorrhiza* are broadly classified into two categories: lipophilic diterpenoid tanshinones (e.g., tanshinone IIA, cryptotanshinone) and hydrophilic phenolic acids (e.g., salvianolic acids A and B) (Yang et al., 2025). Among the hydrophilic fraction, salvianolic acid A (SAA) and salvianolic acid B (SAB, also referred to as SalB) constitute the most abundant and pharmacologically significant polyphenolic compounds (Jiang et al., 2024; Zhao et al., 2024).

In recent decades, salvianolic acids have emerged as molecules of considerable scientific interest due to their pleiotropic pharmacological activities, including cardioprotective, neuroprotective, anti-inflammatory, antioxidant, anticancer, antiplatelet, hepatoprotective, and nephroprotective effects (Jiang et al., 2024; Qin et al., 2019; Yang et al., 2024; Zhao et al., 2023; Zeng et al., 2025). The increasing global burden of cardiovascular diseases, neurodegenerative disorders, metabolic syndromes, and malignancies has driven intensive research into natural product-derived therapeutics with multitarget mechanisms and favorable safety profiles (Yang et al., 2025; Qin et al., 2019). Salvianolic acids, with their evolutionarily optimized polyphenolic structures, exemplify such promising candidates (Qin et al., 2019).

Despite the substantial body of preclinical evidence supporting the therapeutic potential of salvianolic acids, their clinical translation faces several challenges, most notably poor oral bioavailability due to extensive first-pass metabolism and low membrane permeability (Yang et al., 2025; Chen et al., 2022; Lai et al., 2011). Furthermore, the chemical instability of certain salvianolic acid species under physiological conditions complicates pharmaceutical formulation and storage (Wang et al., 2021). Nevertheless, advancements in drug delivery technologies, including nanoparticle-based carriers, sustained-release microcapsules, and osmotic pump systems, offer promising strategies to overcome these pharmacokinetic limitations (Wang et al., 2021; Yang et al., 2025).

This comprehensive review synthesizes current knowledge regarding the discovery, physicochemical properties, extraction and purification methodologies, pharmacokinetic behavior, and diverse pharmacological mechanisms of salvianolic acids, with particular emphasis on salvianolic acids A and B. Additionally, this review critically examines clinical trial data, safety profiles, quality control standards, and the principal challenges and future directions that will shape the continued development of salvianolic acids as therapeutic agents.

2 Discovery and History

2.1 Traditional Medicinal Use and Modern Scientific Identification

The medicinal use of *Salvia miltiorrhiza* Bunge (Danshen；丹参; Fig. 1) can be traced back more than two millennia in ancient Chinese medical practice, where it was primarily employed for activating blood circulation, resolving stasis, and treating cardiovascular and cerebrovascular ailments (Yang et al., 2025; Yang et al., 2024). Traditional Chinese medicine formulations containing Danshen (丹参) were historically prescribed for conditions that, in modern terminology, correspond to angina pectoris, myocardial infarction, and various circulatory disturbances (Yang et al., 2025).

The systematic phytochemical investigation of *S. miltiorrhiza* began in earnest during the mid-20th century. Initial studies focused predominantly on the lipophilic diterpenoid tanshinones, which were among the first bioactive constituents to be isolated and structurally characterized from this botanical source (Yang et al.,

2025). However, the recognition that Danshen also contained substantial quantities of water-soluble phenolic acids marked a pivotal turning point in understanding its pharmacological complexity (Yang et al., 2025; Yang et al., 2024).

Fig. 1 *Salvia miltiorrhiza* Bunge (Source: https://middletonnurseries.co.uk/wp-content/uploads/2025/11/Salvia-miltiorrhiza-%E2%80%98Weilarhiza.webp）

Salvianolic acids were identified as the principal water-soluble constituents responsible for many of the antioxidant and cardiovascular protective effects historically attributed to Danshen preparations (Jiang et al., 2024; Yang et al., 2024). Structural elucidation studies revealed that salvianolic acids are polyphenolic compounds derived biosynthetically from the condensation of caffeic acid units and danshensu (3-(3,4-dihydroxyphenyl)-2-hydroxypropanoic acid) (Qin et al., 2019). Salvianolic acid B, a tetrameric caffeic acid compound, was recognized as the most abundant salvianolic acid species in *S. miltiorrhiza* root material (Zhao et al., 2024; Wang et al., 2021).

2.2 Molecular Characterization and Nomenclature

The salvianolic acid family encompasses a diverse array of structurally related polyphenolic compounds, including salvianolic acid A, salvianolic acid B (also termed lithospermic acid B), salvianolic acid C, salvianolic acid D, and several minor constituents (Ho and Hong, 2011; Jiang et al., 2024; Qin et al., 2019). Salvianolic acid A is formed through the condensation of one molecule of danshensu with two molecules of caffeic acid (Yang et al., 2024). Salvianolic acid B, in contrast, comprises two molecules of danshensu and one molecule of prolithospermic acid, forming a tetrameric structure (Wang et al., 2021; Jiang et al., 2024).

The isolation of pure salvianolic acid components from complex botanical matrices represented a significant analytical achievement. Advanced chromatographic techniques, including high-performance liquid chromatography (HPLC) coupled with mass spectrometry (LC-MS/MS) and nuclear magnetic resonance (NMR) spectroscopy, have been instrumental in the definitive structural characterization of individual salvianolic acid species (Qi et al., 2013; Zeng et al., 2017; Zeng et al., 2025).

3 Physicochemical Properties and Extraction

3.1 Botanical Sources and Distribution

Salvianolic acids are primarily obtained from *Salvia miltiorrhiza* Bunge (Family: Lamiaceae), a perennial herb native to China and widely cultivated in several East Asian countries (Zhang, 2017a-b; Yang et al., 2025; Zhao et al., 2024; Fig. 1). The root and rhizome (Salviae miltiorrhizae Radix et Rhizoma, SMR) serve as the primary

medicinal parts and contain the highest concentrations of bioactive salvianolic acids (Zeng et al., 2025; Yang et al., 2025).

Quantitative analyses have demonstrated that the content of salvianolic acids in SMR varies considerably depending on geographical origin, cultivation conditions, harvest time, and post-harvest processing (Zeng et al., 2025; Zeng et al., 2017). Representative studies employing ultra-performance liquid chromatography (UPLC) have reported danshensu concentrations ranging from approximately 1508.37 to 3418.88 μg/g and salvianolic acid B concentrations from 3157.77 to 5116.33 μg/g in different batches of herbal material (Zeng et al., 2025; Qi et al., 2013). Salvianolic acid B consistently represents the most abundant individual salvianolic acid component, accounting for a substantial proportion of the total phenolic acid content (Zhao et al., 2024; Zeng et al., 2025).

3.2 Chemical Structure

Salvianolic acids are polyphenolic compounds characterized by the presence of multiple catechol moieties, carboxyl groups, and conjugated double-bond systems that collectively confer potent antioxidant properties (Jiang et al., 2024; Qin et al., 2019). The chemical structures of the major salvianolic acids are as follows:

Salvianolic acid A (SAA) is a trimeric compound formed through the condensation of danshensu with two caffeic acid units. Its molecular formula is $C_{26}H_{22}O_{10}$, and it possesses multiple phenolic hydroxyl groups that enable effective scavenging of reactive oxygen species (ROS) (Yang et al., 2024; Jiang et al., 2024; Fig. 2).

Salvianolic acid B (SAB, SalB) is a tetrameric caffeic acid derivative with the molecular formula $C_{36}H_{30}O_{16}$. It is structurally composed of two danshensu molecules and one prolithospermic acid moiety linked via ester bonds (Wang et al., 2021; Jiang et al., 2024). The ester linkages in SAB render the molecule susceptible to hydrolysis under physiological conditions, contributing to its chemical instability (Wang et al., 2021; Qi et al., 2013; Fig. 2).

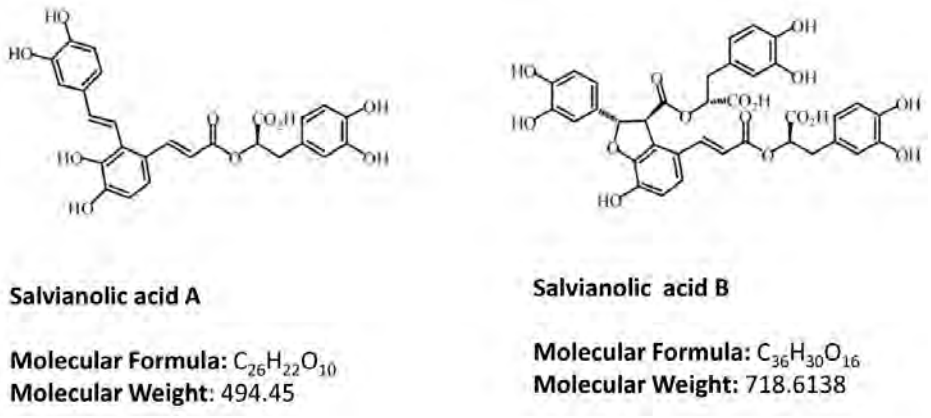

Fig. 2 Chemical structure of salvianolic acid A and salvianolic acid B (Source: Ho and Hong, 2011).

The polyphenolic architecture of salvianolic acids, particularly the presence of ortho-dihydroxyl (catechol) groups, underlies their capacity to donate hydrogen atoms and electrons, thereby neutralizing free radicals and terminating radical chain reactions (Jiang et al., 2024; Yang et al., 2024).

3.3 Physicochemical Properties

Salvianolic acids are highly hydrophilic compounds that exhibit excellent water solubility, a property that distinguishes them from the lipophilic tanshinone constituents of Danshen (Jiang et al., 2024; Chen et al.,

2022). Salvianolic acid has been described as possessing the greatest hydrophilic property among Danshen constituents (Jiang et al., 2024).

The high aqueous solubility of salvianolic acids facilitates their formulation as injectable preparations and their dispersion in biological fluids. However, this hydrophilicity simultaneously presents challenges for oral bioavailability, as the compounds exhibit low permeability across biological membranes, including the intestinal epithelium (Lai et al., 2011; Chen et al., 2022). Salvianolic acids are classified as extremely hydrophilic compounds with low permeabilities, resulting in poor oral bioavailabilities (Wang et al., 2021).

Chemical stability represents another critical physicochemical consideration. Salvianolic acid B is particularly susceptible to degradation, with ester bond hydrolysis occurring readily under physiological pH and temperature conditions (Wang et al., 2021; Qi et al., 2013). This instability has important implications for pharmaceutical formulation, storage, and pharmacokinetic evaluation (Wang et al., 2021).

3.4 Extraction and Purification Technologies

The efficient extraction and purification of salvianolic acids from *S. miltiorrhiza* plant material have been the subject of extensive technological development. Traditional extraction methods, including heating reflux extraction (HRE), have been widely employed but suffer from relatively low efficiency and prolonged processing times (Zeng et al., 2025).

Recent innovations have focused on enhancing extraction yields while preserving the structural integrity of the labile salvianolic acid compounds. A sequential smashing tissue-microwave assisted extraction (ST-MAE) method was developed to extract salvianolic acids from SMR with significantly improved efficiency compared to conventional approaches (Zeng et al., 2025). This method combines mechanical tissue disruption with microwave-assisted heating to accelerate mass transfer and increase extraction yields. Optimization studies using response surface methodology (RSM) and an artificial neural network embedded in a genetic algorithm (ANN-GA) demonstrated that the ST-MAE method increased salvianolic acid yields by approximately 2.03-fold, 1.95-fold, and 1.90-fold compared to smashing tissue extraction, microwave extraction, and heating reflux extraction, respectively (Zeng et al., 2025). The Weibull model was found to accurately describe the time-dependent extraction behavior of ten major salvianolic acid species, reflecting efficient diffusion and compound stability under optimized conditions (Zeng et al., 2025).

Green extraction approaches employing bio-derived solvents have also been investigated. Systematic evaluation of solvents including glycerol carbonate, ethylene glycol, levulinic acid, glycerolformal, ethyl lactate, and γ-valerolactone has been conducted for the simultaneous extraction of salvianolic acid B and tanshinones from *S. miltiorrhiza* root (Wang et al., 2025).

Following extraction, macroporous resin adsorption has been established as an effective purification strategy. In optimized protocols, the purified extract was found to contain 65.87% salvianolic acids, representing a 3.6-fold enrichment relative to the crude extract (Zeng et al., 2025). The antioxidant activity of the purified extract, as measured by DPPH, ABTS, FRAP, and ORAC assays, was significantly enhanced compared to the crude material (Zeng et al., 2025).

3.5 Pharmacokinetics

The pharmacokinetic behavior of salvianolic acids is characterized by rapid absorption following intravenous administration, extensive metabolism, and limited oral bioavailability (Qi et al., 2013; Lai et al., 2011; Chen et al., 2022).

Metabolism. Following intravenous administration of salvianolic acid B in rats, LC-IT/TOF-MS analysis identified nine metabolites in bile, plasma, and urine, including methylated metabolites of SAB, lithospermic acid (LSA), decarboxylation and methylation metabolites of LSA, salvianolic acid S (SAS), and dehydrated-SAS (Qi et al., 2013). The study established that methylation constitutes the dominant metabolic

pathway for SAB in rats (Qi et al., 2013). The half-life ($t_{1/2}$) of both monomethyl-SAB and LSA was found to be very short, with monomethyl-SAB exhibiting a larger area under the plasma concentration-time curve (AUC) than LSA (Qi et al., 2013).

Bioavailability and Absorption Enhancement. Comparative pharmacokinetic studies of rosmarinic acid, salvianolic acid A, and salvianolic acid B in rats revealed that co-administration with borneol significantly altered the pharmacokinetic parameters of all three salvianolic acids, with their bioavailability increasing by different degrees (Lai et al., 2011). These findings indicated that borneol could enhance the intestinal absorption, decrease the distribution, and inhibit the metabolism of salvianolic acids (Lai et al., 2011).

First-in-Human Studies. A first-in-human (FIH), randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, and pharmacokinetics of single and multiple ascending doses of salvianolic acid A in 116 healthy Chinese subjects across dose ranges of 10–300 mg (single dose) and 60–200 mg (multiple doses) (Chen et al., 2022). SAA was well tolerated at all dose levels, with a low overall incidence of treatment-emergent adverse events that appeared to be no dose-related (Chen et al., 2022). Pharmacokinetic analysis revealed a lack of dose proportionality, with the 90% confidence intervals of the slope β for Cmax (1.214 [1.150–1.278]) and AUC0–t (1.222 [1.156–1.288]) falling outside the predefined acceptance range, indicating higher than expected exposure (Chen et al., 2022). Physiologically based pharmacokinetic (PBPK) modeling suggested that the transfer ability saturation of hepatic organic anion-transporting polypeptide 1B1 (OATP1B1) and P-glycoprotein (P-gp) might result in a relatively low distribution rate at higher doses (Chen et al., 2022).

A separate phase 1, randomized, double-blind, placebo-controlled study evaluated the safety, tolerance, and pharmacokinetics of salvianolic acid B injection in healthy Chinese volunteers (Cheng et al., 2023). In the single-ascending-dose study, peak plasma concentration and AUC of salvianolic acid B progressively increased in a dose-dependent manner across 75, 150, and 300 mg dose levels (Cheng et al., 2023). No accumulation was observed after five consecutive days of administration of 150 mg salvianolic acid B (Cheng et al., 2023).

Challenges and Limitations. The clinical application of salvianolic acids is constrained by low oral bioavailability, which is attributed to poor stability and low permeability (Yang et al., 2025; Qi et al., 2013). These pharmacokinetic limitations have motivated the development of advanced drug delivery systems, including self-emulsifying drug delivery systems (SEDDS), sustained-release microcapsules, and controlled-porosity osmotic pump tablets (Wang et al., 2021; Tong et al., 2013; Kan et al., 2014).

4 Pharmacological Actions and Mechanisms

Salvianolic acids are regulatory and controlling factors in the human body's biological network (Zhang, 2016, 2018, 2026, 2027a-d, 2028a-b).

4.1 Cardiovascular and Cerebrovascular Protection

Cardiovascular protection constitutes the most extensively documented pharmacological activity of salvianolic acids. Salvianolic acid A and salvianolic acid B have been shown to exert protective effects against myocardial ischemia-reperfusion injury, atherosclerosis, cardiac hypertrophy, and cardiac fibrosis (Jiang et al., 2024; Yang et al., 2025; Yang et al., 2024).

Myocardial Ischemia - Reperfusion Injury. Diabetes mellitus significantly increases myocardial vulnerability to ischemia-reperfusion injury, a phenomenon attributed to elevated reactive oxygen species (ROS) production, ferroptosis, and disruption of protective signaling pathways (Jiang et al., 2024). Salvianolic acid shows great potential in myocardial protection in diabetes mellitus (Jiang et al., 2024). Mechanistically, salvianolic acid A inhibits apoptosis by targeting the JNK/Akt pathway (Huang and Zhang, 2012; Li and

Zhang, 2013), whereas salvianolic acid B exerts anti-apoptotic effects through modulation of the NF-κB pathway (Jiang et al., 2024). A thorough understanding of the protective mechanism of salvianolic acid could expand its potential uses in developing medicines for treating diabetes mellitus related myocardial ischemia-reperfusion (Jiang et al., 2024).

Salvianolic acid B has been shown to reduce infarct size and improve cardiac function following ischemia-reperfusion injury through multiple mechanisms, including attenuation of oxidative stress, suppression of inflammation, promotion of neovascularization, regulation of vascular function, and inhibition of myocardial apoptosis (Jiang et al., 2024; Zhao et al., 2023; Yang et al., 2024).

Atherosclerosis. Salvianolic acid B has demonstrated significant anti-atherosclerotic effects in both in vivo and in vitro models. In LDLR−/− mice fed a high-fat diet to establish an atherosclerosis model, SalB treatment significantly reduced serum total cholesterol, triglycerides, and low-density lipoprotein cholesterol levels, decreased foam cell deposition and inflammatory cell infiltration, and attenuated atherosclerotic plaque formation (Zhao et al., 2023). Under TNF-α stimulation, SalB reduced reactive oxygen species release and reversed the nuclear translocation of NF-κB p65 (Zhao et al., 2023). These protective effects were mediated through modulation of the NF-κB/NLRP3 inflammasome signaling pathway (Zhao et al., 2023). In parallel studies, SalB attenuated the inflammatory response in atherosclerosis via regulation of MAPKs/NF-κB signaling pathways in LDLR−/− mice and RAW264.7 cells (Zhang et al., 2022).

Neuroprotection and Ischemic Stroke. Salvianolic acids exhibit pronounced neuroprotective effects in preclinical models of cerebral ischemia. Salvianolic acid A has garnered considerable interest for its potential in ameliorating post-stroke neuroinflammation (Yang et al., 2024). Preclinical studies have demonstrated that SalA modulates pro-inflammatory cytokines, inflammatory signaling pathways, peripheral immune cell infiltration through blood-brain barrier disruption, and endothelial cell function (Yang et al., 2024). Notably, the pharmacokinetic profile of SalA in the context of stroke is characterized by enhanced cerebral penetration post-ischemia, which makes it particularly suitable as a therapeutic agent (Yang et al., 2024).

Preliminary clinical findings have demonstrated that salvianolic acids have a positive impact on cerebral perfusion and neurological deficits in stroke patients, warranting further investigation (Yang et al., 2024). Acute treatment with salvianolic acid A produces neuroprotection in stroke models by inducing excitatory long-term synaptic depression, with evidence suggesting that acute treatment of SAA is neuroprotective by improving long-term functional outcomes through a synaptic LTD-like process, providing a promising adjunct to current therapies to enable better recovery for acute ischemic stroke (Li et al., 2025).

Salvianolic acid B has demonstrated multifaceted neuroprotective mechanisms. In animal models of cerebral ischemia-reperfusion injury, SalB reduces infarct size and enhances neurological recovery via anti-inflammatory, anti-oxidative stress, and angiogenic pathways (Wang and Li, 2025). It protects the blood-brain barrier and inhibits neuronal apoptosis in stroke models (Wang and Li, 2025). In experimental subarachnoid hemorrhage, SalB provides protection against oxidative damage by upregulating the Nrf2 antioxidant signaling pathway, which may be modulated by SIRT1 activation (Zhang et al., 2018). The reduction in oxidative damage was associated with suppressed reactive oxygen species generation, decreased lipid peroxidation, and increased glutathione peroxidase, glutathione, and superoxide dismutase activities (Zhang et al., 2018). In traumatic brain injury models, SalB mitigates oxidative stress through the Nrf2/Peroxiredoxin 2 pathway and reduces inflammatory response via the Nrf2/Toll-like receptor 4/Myeloid differentiation primary response protein 88 pathway in a dose-dependent manner (Wang et al., 2025).

In Alzheimer‘s disease models, SalB suppresses amyloid-beta formation and neuroinflammation, and in spinal cord injury models, SalB alleviates edema and promotes motor function recovery (Wang and Li, 2025). Additionally, SalB exhibits antidepressant and analgesic effects in pain-depression comorbidity models (Wang

and Li, 2025).

Salvianolic acids for injection (SAFI) serve as a safe and effective treatment option for cardiovascular and cerebrovascular conditions by influencing various signaling pathways and molecular targets associated with these diseases (Yang et al., 2024; Wang and Li, 2025).

4.2 Anti-inflammatory and Antioxidant Activities

The anti-inflammatory and antioxidant properties of salvianolic acids are intimately linked and constitute fundamental mechanisms underlying their diverse therapeutic effects (Jiang et al., 2024; Yang et al., 2024).

NF-κB *Pathway Modulation*. Salvianolic acids exert potent anti-inflammatory effects primarily through inhibition of the nuclear factor kappa-B (NF-κB) signaling pathway. Salvianolic acid A reduces protein expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) and reduces translocation of NF-κB to nuclei in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages (Huang et al., 2013). Salvianolic acid A modulates NF-κB-dependent inflammatory pathways through IKKβ inhibition, and these anti-inflammatory effects aid in understanding the pharmacology and mode of action of salvianolic acid A (Huang et al., 2013).

Salvianolic acid B inhibits TNF-α/NF-κB and TLR4/NF-κB signaling pathways to repress the expression of proinflammatory factors IL-1β and TNF-α (Zhang et al., 2022). Furthermore, SalB inhibits TNF-α-activated NF-κB and AP-1 DNA binding activities in a dose-dependent manner in human umbilical vein endothelial cells (HUVECs) (Zhou et al., 2005). The NF-κB and ERK-AP-1 pathways are possible targets of SalB in the regulation of TNF-α-stimulated PAI-1 production in HUVECs (Zhou et al., 2005).

Nrf2 *Antioxidant Pathway Activation*. Salvianolic acids activate the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant response pathway, which orchestrates the expression of numerous cytoprotective enzymes. Salvianolic acid A protects retinal pigment epithelial cells against oxidative stress through activation of Nrf2/HO-1 signaling (Zhang et al., 2014). Salvianolic acid A protects the kidney against oxidative stress by activating the Akt/GSK-3β/Nrf2 signaling pathway and inhibiting the NF-κB signaling pathway in 5/6 nephrectomized rats (Zhang et al., 2019).

Salvianolic acid B exerts cerebroprotective effects after subarachnoid hemorrhage and traumatic brain injury via Nrf2-dependent antioxidant and anti-inflammatory cascades (Zhang et al., 2018; Wang et al., 2025). The cardioprotective and neuroprotective effects of salvianolic acids are not solely attributable to their function as reactive oxygen species scavengers but also involve the reduction of inflammation and metalloproteinase expression from aortic smooth muscle cells and indirect regulation of immune function (Jiang et al., 2024).

4.3 Anticancer Activity

Salvianolic acids have emerged as potent anti-cancer molecules with activity against multiple malignancies through targeting of diverse deregulated signaling networks (Ma et al., 2019; Qin et al., 2019).

Mechanisms of Action. Salvianolic acid A and B fight cancer progression by prompting apoptosis, halting cell cycle progression, and adjourning metastasis by targeting multiple deregulated signaling networks of cancer (Qin et al., 2019). These compounds target and cause activity modulation of various protein kinases, transcriptional factors, apoptosis-related factors, cytokines, cell cycle regulators, enzymes, and hormones that are associated with proliferation, metastasis, invasion, and angiogenesis (Qin et al., 2019). Moreover, salvianolic acid A and B display potency toward sensitizing cancer cells to chemotherapeutic drugs (Qin et al., 2019).

Breast Cancer. *Salvia miltiorrhiza* has been investigated for breast cancer treatment, with studies examining its phytochemistry, derivatives, nanoparticles, and potential mechanisms (Zhao et al., 2022). Salvianolic acid B, a natural compound, shows anti-cancer activity by inhibiting breast cancer cell proliferation and inducing cell apoptosis (Qin et al., 2019; Zhao et al., 2022).

Fibrosis and Cancer. Salvianolic acids have been recognized as potential sources of natural drugs for the treatment of fibrosis disease and cancer, with studies highlighting the importance of these compounds as novel and attractive drugs for fibrosis disease and cancer (Wang and Zhang, 2019).

Translational Potential. The anticancer mechanisms of salvianolic acid B have been comprehensively reviewed, with focus on route of administration, pharmacokinetic parameters, cancer type, study model, drug concentrations, involved signaling pathways, safety and toxicity, efficacy, and mechanisms of action (Chanda et al., 2025). The review purposes that salvianolic acid A and B supply a novel opportunity for drug discovery, but further experimentation is mandatory to embellish the knowledge of their pharmacological usage and to access their toxicological limits in order to establish these compounds as potential multitarget future drugs (Qin et al., 2019).

4.4 Antiplatelet Aggregation

Salvianolic acids possess significant antiplatelet and antithrombotic activities that contribute to their cardiovascular protective effects (Bi et al., 2025; Fan et al., 2010).

Salvianolic Acid A. Intravenously administered salvianolic acid A (2.5–10 mg/kg) inhibits platelet aggregation induced by adenosine diphosphate (ADP) in a dose-dependent manner (Fan et al., 2010). Notably, SAA does not affect coagulation parameters in rats after intravenous administration for five successive days (Fan et al., 2010). In a model of arterio-venous shunt, SAA significantly reduced thrombus weight and increased plasma cAMP levels determined by radioimmunoassay (Fan et al., 2010).

In a clinical study involving 40 acute coronary syndrome (ACS) patients, ex vivo treatment of platelets with salvianolic acid A (0.1 mg/ml) significantly reduced platelet aggregation and activation (Bi et al., 2025). Intriguingly, no significant difference was found between the three types of ACS patients in the antiplatelet effect of SAA (Bi et al., 2025).

Comparison with Other Antiplatelet Agents. Salvianolic acids were found to be much better than aspirin in preventing the incidence of cardio-cerebral ischemic disease and may avoid hemorrhage risk in clinical application (Zhang et al., 2018). Both aspirin and salvianolic acids have the same antiplatelet aggregation effect, but their mechanisms differ; aspirin inhibits both thromboxane (TXA_2) and prostacyclin (PGI_2) (Zhang et al., 2018).

Synergistic Combinations. A combination of salvianolic acid A and C synergistically inhibited platelet aggregation in vitro, whereas salvianolic acid B antagonized this effect (Chanda et al., 2025). This finding revealed the anti-thrombotic activity of Danhong injection, a Danshen-based formulation (Chanda et al., 2025).

4.5 Hepatoprotective Effects

Salvianolic acids exhibit significant protective effects against various forms of hepatic injury, including chemical-induced hepatotoxicity and metabolic liver disease (Zhang et al., 2024; Ding et al., 2016).

Acute Liver Injury. Salvianolic acid demonstrates protective effects against carbon tetrachloride (CCl_4)-induced acute liver injury in rats, with the mechanism relevant to improvement of anti-oxidative activity. Salvianolic acid extract prevents Tripterygium wilfordii polyglycosides-induced acute liver injury by modulating bile acid metabolism (Zhang et al., 2024). Salvianolic acid extract, as a hydrophilic component of *Salvia miltiorrhiza*, has significant antioxidant and hepatoprotective effects (Zhang et al., 2024).

Non-alcoholic Fatty Liver Disease (NAFLD). Salvianolic acid A has been shown to have hepatoprotective effects against high-fat diet (HFD)-induced NAFLD (Ding et al., 2016). SalA treatment significantly attenuated HFD-induced obesity and liver injury and markedly decreased lipid accumulation in HFD-fed rat livers (Ding et al., 2016). Moreover, SalA treatment ameliorated HFD-induced hepatic inflammation and oxidative stress by decreasing hepatotoxic levels of cytokines, suppressing the overproduction of reactive oxygen species (ROS) and malondialdehyde (MDA), and preventing the decreased expression of superoxide

dismutase (SOD) (Ding et al., 2016). Importantly, SalA reversed the HFD- or palmitic acid-induced activation of the NLRP3 inflammasome, the nuclear translocation of ChREBP, and the up-regulation of FAS, effects that were accompanied by TXNIP down-regulation (Ding et al., 2016). This study demonstrated for the first time that SalA protects against HFD-induced NAFLD by ameliorating hepatic lipid accumulation and inflammation, and these protective effects may be partially due to regulation of the TXNIP/NLRP3 and TXNIP/ChREBP pathways (Ding et al., 2016).

Liver Fibrosis. Salvianolic acid B exerts protective effects against liver fibrosis through multiple signaling pathways (Zhao et al., 2024; Yang et al., 2025).

4.6 Nephroprotective Effects

Salvianolic acids have demonstrated considerable promise in the prevention and treatment of kidney diseases through their anti-inflammatory, anti-oxidant, anti-apoptotic, and anti-fibrotic actions (Chen et al., 2026).

Acute Kidney Injury and Chronic Kidney Disease. Kidney disease affects millions of people worldwide, and conventional treatments often produce suboptimal outcomes and are associated with various adverse effects (Chen et al., 2026). Salvianolic acids, the principal bioactive constituents of *Salvia miltiorrhiza*, are widely used in the management of renal disorders (Chen et al., 2026). Their renoprotective actions arise from the modulation of multiple pathological processes, including inflammation, oxidative stress, apoptosis, mitochondrial dysfunction, endoplasmic reticulum stress, and autophagy dysregulation (Chen et al., 2026).

Salvianolic Acid A in Nephroprotection. Salvianolic acid A effectively attenuates kidney injury and inflammation in an established animal model of 5/6 nephrectomized (5/6Nx) rats (Zhang et al., 2019). The protective mechanism involves activation of the Akt/GSK-3β/Nrf2 signaling pathway and inhibition of the NF-κB signaling pathway (Zhang et al., 2019). SAA attenuates kidney injury and inflammation by inhibiting NF-κB and p38 MAPK signaling pathways in 5/6 nephrectomized rats (Zhang et al., 2018). SAA improves kidney injury in rats by regulating MAPKs and TGF-β1/Smads signaling pathways (Chanda et al., 2025). In Zucker diabetic fatty rats, SAA demonstrates protective effects against diabetic nephropathy and inhibits lipoprotein-associated phospholipase A2 (Lp-PLA2) expression (Chen et al., 2019).

Salvianolic Acid B in Renal Fibrosis. The nephroprotective effects of salvianolic acid A and B in renal interstitial fibrosis are mediated via the PDGF-C/PDGFR-α signaling pathway (Yao et al., 2022). The protective effects of salvianolic acid B are mainly related to its anti-inflammatory, antioxidant, anti- or pro-apoptotic, anti- or pro-autophagy, anti-fibrotic, and metabolism-regulating functions (Chen et al., 2026).

Clinical Implications. Salvianolic acids hold promise as potential therapeutic agents for kidney diseases, including acute kidney injury, diabetic kidney disease, and nephrotic syndrome (Chen et al., 2026). Further studies are needed to confirm these molecular mechanisms and identify specific targets. Additionally, large-scale, long-term, multicenter clinical trials are crucial to evaluate the efficacy and safety of salvianolic acids in treating kidney diseases (Chen et al., 2026).

5 Clinical Applications and Formulations

5.1 Approved Formulations and Clinical Use

Salvianolic acid preparations have been developed as pharmaceutical products and are widely used in clinical practice, particularly in China (Zhang et al., 2024; Yang et al., 2025).

Salvianolic Acids for Injection (SAFI). As a successful case, Salvianolic Acid for Injection (SAFI) is widely used clinically in the treatment of cardiovascular diseases since 2012 (Tong et al., 2016). Phenolic acids in SAFI possess different pharmacological effects, including antioxidant activity, free radical scavenging, inhibition of platelet function, and improvement of microcirculation (Tong et al., 2016). SAFI serves as a safe and effective treatment option for cardiovascular and cerebrovascular conditions by influencing various

signaling pathways and molecular targets associated with these diseases (Yang et al., 2024).

Salvianolic Acid Salts for Injection. Salvianolic acid salts for injection represent another clinically utilized formulation (Zhang et al., 2024).

5.2 Clinical Trial Evidence

Systematic Reviews and Meta-Analyses. A systematic review and meta-analysis evaluated the efficacy and safety of salvianolic acid preparations for adjuvant therapy in coronary heart disease, angina, and cerebral infarction (Zhang et al., 2024). The analysis included 16 randomized controlled trials involving 2018 patients (Zhang et al., 2024). The results showed that salvianolic acid preparations for adjuvant therapy on coronary heart disease and angina significantly reduced the risk of the composite outcomes of major adverse cardiovascular events (MACEs) [RR = 0.46, 95% CI (0.31, 0.67), P < 0.001; NNT = 12.19] and angina [RR = 0.49, 95% CI (0.33, 0.73), P < 0.001; NNT = 14.44] in the 180-day follow-up subgroup (Zhang et al., 2024). There were no significant differences in the risk of cardiovascular death, myocardial infarction, stroke, or revascularization between the intervention group and the control group (Zhang et al., 2024). No statistical difference was found in the risk of adverse drug reactions between the intervention group and the control group (P = 0.10), and the major adverse drug reactions included elevated ALT/AST, abdominal distension, nausea, dizziness/headache, and fatigue (Zhang et al., 2024). The conclusion was that in the 180-day follow-up subgroup, salvianolic acid preparations for adjuvant therapy on coronary heart disease and angina could reduce the risk of angina and were safe, though the conclusions require further confirmation (Zhang et al., 2024).

Phase 1 Safety and Tolerability Studies. The first-in-human study of salvianolic acid A demonstrated that SAA was well tolerated at all dose levels, following both single and multiple doses, with a low overall incidence of treatment-emergent adverse events that appeared to be no dose-related (Chen et al., 2022). SAA showed well-characterized pharmacokinetics and was generally well tolerated in the dose range investigated (Chen et al., 2022).

A randomized, double-blind, placebo-controlled phase 1 clinical trial of salvianolic acid B injection evaluated safety, tolerance, and pharmacokinetics in healthy Chinese volunteers (Cheng et al., 2023). In the single-ascending-dose study groups, there were 41 adverse events in 24 cases (51.1%, 24/47) (Cheng et al., 2023). In the multiple-ascending-dose study groups, there were 13 adverse events in eight cases (50.0%, 8/16) (Cheng et al., 2023). Adverse events related to the treatment included increased alanine aminotransferase (4.0%), increased bilirubin (2.0%), increased creatinine kinase-MB (2.0%), increased brain natriuretic peptide (8.0%), increased urine N-acetyl-β-D-glucosidase (4.0%), dizziness (2.0%), and chest discomfort (2.0%) (Cheng et al., 2023). No serious adverse events occurred, and no volunteers withdrew from the trial (Cheng et al., 2023). Salvianolic acid B injections administered up to 300 mg in a single dose and 250 mg for five consecutive days showed excellent safety and tolerability in healthy Chinese volunteers (Cheng et al., 2023).

Ongoing and Planned Trials. Additional clinical studies are evaluating the effects and adverse effects of salvianolic acid on acute ischemic stroke onset within 72 hours, assessing improvement of ischemic area perfusion and clinical function scores (Wang et al., 2023). A phase 1 study of continuous administration of salvianolic acid A tablet has been conducted to evaluate safety and pharmacokinetics (Cui, 2018).

5.3 Quality Control and Standardization

Quality control of salvianolic acid-containing products is essential for ensuring batch-to-batch consistency, therapeutic efficacy, and safety (Chen et al., 2020; Zeng et al., 2017).

Chromatographic Fingerprinting. UPLC fingerprint analysis of water extracts of Radix et Rhizoma Salviae Miltiorrhizae and stems and leaves of *Salvia miltiorrhiza* has been developed, with salvianolic acids identified as common components (Zeng et al., 2017). The results showed that salvianolic acids in different batches varied considerably in content but kept consistent in composition (Zeng et al., 2017). HPLC

fingerprinting combined with simultaneous determination of multiple bioactive compounds has been established as a helpful method for the quality control of *S. przewalskii* (Wang et al., 2017). Fingerprint and multi-component quantification analysis of *Salvia miltiorrhiza* extract intermediate from Xutong injection has been reported, with HPLC-UV fingerprint combined with quantitative determination of indicators providing reference for quality evaluation (Chen et al., 2020).

Reference Standards. Salvianolic acids A and B are commonly used as reference standards in analytical and quality control applications for herbal products and traditional Chinese medicines (Wang and Zhang, 2020).

Pharmacopoeial Standards. The Pharmacopoeia of the People‘s Republic of China includes standards for *Salvia miltiorrhiza* and its preparations, providing official guidelines for quality assessment (Zhang et al., 2024).

5.4 Safety Profile and Adverse Effects

The safety profile of salvianolic acids has been evaluated in multiple clinical studies and preclinical toxicological assessments (Yang et al., 2025; Chen et al., 2022; Cheng et al., 2023).

Clinical Safety Data. In the systematic review of salvianolic acid preparations, no statistical difference was found in the risk of adverse drug reactions between the intervention group and the control group ($P = 0.10$), and there was no statistical difference in the risk of various adverse drug reactions ($P = 0.25$) (Zhang et al., 2024). The phase 1 study of salvianolic acid B demonstrated that injections administered up to 300 mg in a single dose and 250 mg for five consecutive days showed excellent safety and tolerability (Cheng et al., 2023). The first-in-human study of salvianolic acid A showed that SAA was well tolerated at all dose levels (Chen et al., 2022).

Adverse Reactions. Reported adverse reactions have included elevated liver enzymes (ALT/AST), increased bilirubin, increased creatinine kinase-MB, increased brain natriuretic peptide, increased urine N-acetyl-β-D-glucosidase, dizziness, chest discomfort, abdominal distension, nausea, and fatigue (Cheng et al., 2023; Zhang et al., 2024). Importantly, no serious adverse events have been reported in the clinical trials to date (Cheng et al., 2023).

Skin Test Considerations. In the phase 1 study of salvianolic acid B, 66 volunteers received a skin test, and three were excluded because of a positive result, suggesting that hypersensitivity reactions may occur in a small subset of individuals (Cheng et al., 2023).

Toxicological Considerations. The clinical application of salvianolic acids is limited not only by low oral bioavailability but also by possible adverse reactions such as liver and kidney damage (Yang et al., 2025). Fortunately, methods such as nanotechnology and drug delivery systems may significantly improve bioavailability and reduce adverse reactions (Yang et al., 2025).

6 Challenges and Limitations

Despite the substantial preclinical and clinical evidence supporting the therapeutic potential of salvianolic acids, several significant challenges and limitations constrain their broader clinical application and pharmaceutical development.

6.1 Poor Oral Bioavailability

The most prominent limitation of salvianolic acids is their poor oral bioavailability, which is attributable to multiple factors (Yang et al., 2025; Chen et al., 2022; Lai et al., 2011). Salvianolic acids are extremely hydrophilic compounds with low permeabilities, resulting in poor oral bioavailabilities (Wang et al., 2021). The pharmacokinetics study of salvianolic acid B indicated that SAB has poor stability and low permeability (Qi et al., 2013). Additionally, salvianolic acids undergo extensive first-pass metabolism, including

methylation and hydrolysis, which further reduces systemic exposure (Qi et al., 2013; Yang et al., 2025).

6.2 Chemical Instability

Salvianolic acid B is chemically unstable and easily degraded under physiological conditions (Wang et al., 2021). The ester bonds in salvianolic acid B are susceptible to hydrolysis, leading to degradation products with altered or diminished pharmacological activity (Qi et al., 2013; Wang et al., 2021). This chemical instability complicates pharmaceutical formulation, storage, and shelf-life considerations (Wang et al., 2021).

6.3 Limited Clinical Trial Data

Although clinical studies have demonstrated the safety and preliminary efficacy of salvianolic acid preparations, the overall body of clinical evidence remains limited in scope and scale (Zhang et al., 2024; Chen et al., 2022). Most clinical trials have been conducted in Chinese populations, and data on efficacy and safety in diverse ethnic populations are lacking (Zhang et al., 2024). Long-term safety data beyond 180-day follow-up are insufficient (Zhang et al., 2024). Large-scale, multicenter, randomized controlled trials with extended follow-up periods are needed to confirm the therapeutic benefits and establish optimal dosing regimens (Chen et al., 2026; Zhang et al., 2024).

6.4 Mechanism of Action Incompletely Elucidated

While multiple signaling pathways have been implicated in the pharmacological actions of salvianolic acids, the precise molecular targets and downstream effectors remain incompletely characterized (Yang et al., 2025; Qin et al., 2019). The multitarget nature of salvianolic acids, while therapeutically advantageous, complicates the identification of primary mechanisms and the prediction of drug interactions (Qin et al., 2019).

6.5 Standardization and Quality Control

The content of salvianolic acids in *S. miltiorrhiza* varies considerably depending on geographical origin, cultivation conditions, and processing methods (Zeng et al., 2025; Zeng et al., 2017). Although chromatographic fingerprinting and multi-component quantification have been developed for quality control, the lack of universally accepted reference standards and validated analytical methods across different regulatory jurisdictions remains a challenge (Chen et al., 2020; Zeng et al., 2017).

6.6 Potential Adverse Reactions

Although clinical studies have reported a favorable safety profile, possible adverse reactions such as liver and kidney damage have been noted (Yang et al., 2025). The incidence of treatment-emergent adverse events in the phase 1 study of salvianolic acid B was approximately 50%, though most events were mild and transient (Cheng et al., 2023). The small number of individuals exhibiting positive skin test reactions suggests the need for continued vigilance regarding hypersensitivity (Cheng et al., 2023).

7 Future Perspectives and Research Directions

7.1 Advanced Drug Delivery Systems

Addressing the poor oral bioavailability of salvianolic acids is a research priority. Nanotechnology-based approaches, including nanoparticle encapsulation, liposomal formulations, and polymeric micelles, offer promising strategies to enhance absorption and protect compounds from degradation (Yang et al., 2025). Sustained-release microcapsules of salvianolic acid have been successfully prepared using marine polysaccharides as carriers, with the microcapsules exhibiting certain sustained release characteristics in vitro (Wang et al., 2021). Controlled-porosity osmotic pump tablets for salvianolic acid have been prepared and optimized using artificial neural network methods, with the release rate of salvianolic acid B and total salvianolic acids found to be consistent in the optimized formulation (Kan et al., 2014). Self-emulsifying drug delivery systems (SEDDS) for salvianolic acid B have been developed, and this formulation can slow down the release of SalB in artificial intestinal fluid (Tong et al., 2013). Hydrogel particles have been investigated

for salvianolic acid encapsulation and delivery (Wang et al., 2021).

7.2 Elucidation of Molecular Mechanisms

Further research is needed to fully elucidate the molecular mechanisms underlying the diverse pharmacological effects of salvianolic acids (Yang et al., 2025; Qin et al., 2019). The identification of specific protein targets, the characterization of binding affinities and kinetics, and the mapping of downstream signaling cascades will provide a more comprehensive understanding of how salvianolic acids exert their therapeutic effects (Yang et al., 2025). The utilization of SalB in combination with other drugs and the validation of molecular mechanisms and targets represent important research directions (Zhao et al., 2024).

7.3 Large-Scale Clinical Trials

Large-scale, long-term, multicenter clinical trials are crucial to evaluate the efficacy and safety of salvianolic acids across various disease indications (Chen et al., 2026; Zhang et al., 2024). Future trials should include diverse patient populations, incorporate extended follow-up periods, and employ standardized outcome measures to generate robust evidence for regulatory approval and clinical adoption (Chen et al., 2026).

7.4 Interdisciplinary Approaches

An interdisciplinary approach that integrates pharmacology, medicinal chemistry, pharmacokinetics, toxicology, and clinical medicine will be essential to unlock the full therapeutic potential of salvianolic acids (Yang et al., 2025). Bridging the gap between traditional Chinese medicine and contemporary biomedical innovation will promote the global application of *Salvia miltiorrhiza* and its bioactive constituents (Yang et al., 2025).

7.5 Combination Therapy Strategies

The potential for salvianolic acids to be used in combination with other therapeutic agents warrants further investigation. Salvianolic acid A and B display potency toward sensitizing cancer cells to chemotherapeutic drugs (Qin et al., 2019). The synergistic antiplatelet effects observed with combinations of salvianolic acid A and C suggest that rational combination strategies may enhance therapeutic efficacy while minimizing adverse effects (Chanda et al., 2025).

7.6 Structural Modification and Derivative Development

Structure-activity relationship studies and the synthesis of salvianolic acid derivatives may yield compounds with improved pharmacokinetic properties, enhanced stability, and greater target selectivity (Yang et al., 2025). Medicinal chemistry approaches could optimize the polyphenolic scaffold to overcome the limitations of the natural compounds while preserving their pleiotropic pharmacological activities.

8 Conclusion

Salvianolic acids, particularly salvianolic acid A and salvianolic acid B, represent a remarkable class of polyphenolic natural products with broad-spectrum pharmacological activities and significant therapeutic potential. Derived from the traditional Chinese medicinal herb *Salvia miltiorrhiza*, these compounds have been shown to exert cardioprotective, neuroprotective, anti-inflammatory, antioxidant, anticancer, antiplatelet, hepatoprotective, and nephroprotective effects through modulation of multiple signaling pathways, including NF-κB, Nrf2, JNK/Akt, MAPK, NLRP3 inflammasome, and TXNIP/ChREBP pathways.

Clinical studies have demonstrated that salvianolic acid preparations, particularly injectable formulations, are generally safe and well tolerated in human subjects, with preliminary evidence supporting their efficacy as adjuvant therapy for coronary heart disease, angina, and ischemic stroke. The systematic review evidence indicates that salvianolic acid preparations can significantly reduce the risk of major adverse cardiovascular events and angina in patients with cardiovascular disease.

However, several challenges remain to be addressed before salvianolic acids can achieve broader clinical

application. Poor oral bioavailability, chemical instability, limited clinical trial data, incomplete mechanistic understanding, and standardization issues constitute the principal barriers to pharmaceutical development. Ongoing research into advanced drug delivery systems, including nanoparticle-based formulations, sustained-release microcapsules, and osmotic pump technologies, offers promising solutions to overcome the pharmacokinetic limitations of these compounds.

Future research should prioritize large-scale, multicenter clinical trials to confirm efficacy and safety across diverse patient populations and disease indications. Elucidation of specific molecular targets and downstream signaling mechanisms will deepen our understanding of salvianolic acid pharmacology and may identify novel therapeutic applications. Interdisciplinary approaches that bridge traditional knowledge with contemporary biomedical science will be essential to unlock the full therapeutic potential of salvianolic acids and to establish these compounds as evidence-based therapeutic agents for cardiovascular, cerebrovascular, inflammatory, and malignant diseases.

In conclusion, salvianolic acids exemplify the tremendous potential of natural product-derived therapeutics. With continued research investment and technological innovation, these evolutionarily optimized polyphenolic compounds may emerge as valuable additions to the modern pharmacopoeia, offering safe and effective treatment options for diseases that impose substantial global health burdens.

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