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Review Article

Phytochemical small molecules from *Stauntonia chinensis* DC as multi-target modulators: molecular mechanisms and therapeutic potential

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Abstract: *Stauntonia chinensis* is a medicinal vine used in East Asian traditional medicine and is rich in saponins and triterpenoids with putative multi-target activities. Pre-clinical studies have reported that these compounds exert anti-inflammatory, antioxidant, neuroprotective, and anticancer effects. Evidence supporting these effects are mostly originated from heterogeneous *in vitro*, *in vivo*, and computational studies, which have reported modulation of signaling pathways, such as nuclear factor-κB (NF-κB), nuclear factor erythroid 2-related factor 2 (Nrf2), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathways. Despite these encouraging findings, clinical translation remains limited. Major barriers include poor oral bioavailability, rapid pharmacokinetics, hemolytic effects, and variability in extract standardization. This review evaluates whether phytochemical small molecules derived from *Stauntonia chinensis* DC exhibit mechanistically coherent and experimentally substantiated multi-target molecular actions. To this end, phytochemical characterization, mechanistic evidence, pharmacokinetics, toxicity, formulation, and translational considerations are systematically integrated to provide a translational roadmap for *S. chinensis*-derived compound, bridging traditional use with potential clinical applications in complex diseases. Furthermore, sophisticated delivery systems such as liposomes, nanoparticles, and phytosomes, and the rational structural optimization to enhance safety and pharmacokinetics are discussed.

Keywords: *Stauntonia chinensis*, triterpenoids, multi-target pharmacology, drug delivery systems, translational medicine

Introduction

Stauntonia chinensis (*S. chinensis*) is a perennial climbing vine of the family of Lardizabalaceae, and is widely used in traditional Chinese medicine (TCM) with numerous therapeutic properties [1]. Its stems, leaves, fruits, and even roots are prepared as decoctions or extracts for medical use. *S. chinensis* has historically been valued as an analgesic, anti-inflammatory, and neuroprotective agent and has been traditionally applied in the treatment of neuropathic disorders, pain and circulatory dysfunction. These ethnopharmacological applications reflect empirical tradition that continues to inform contemporary drug discovery endeavors. Recent studies have identified *S. chinensis* as a source of high triterpenoid saponins and other phytochemicals [1-3]. Their putative therapeutic effects are associated with the broad pharmacological activities, including antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective actions [4, 5]. Notably, these phytochemicals tend to modulate multiple cellular targets and signaling nodes, which is consistent with the holistic, multi-target paradigm underlying traditional herbal medicine [6, 7]. This review evaluates whether phytochemical small molecules from *S. chinensis* DC demonstrate mechanistically coherent, experimentally validated multi-target activities that distinguish them from other triterpenoid-rich plants

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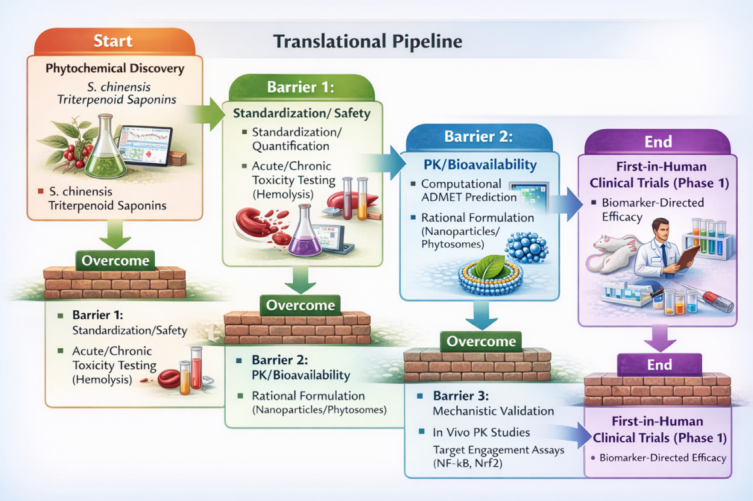

Figure 1. Translational roadmap: integrating multi-target potential with pharmacokinetic and safety barriers. This roadmap illustrates the relationship between the inherent structural features of *S. chinensis* triterpenoid saponins (amphiphilic nature, large molecular weight) and the resulting dual outcomes: significant multi-target potential (NF-κB, Nrf2) and restrictive translational barriers (low bioavailability, rapid clearance, and hemolysis). Successful clinical translation requires the implementation of mandatory formulation strategies (nanoparticles, phytosomes) and rational structural design. Notes: NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2-related factor 2.

and substantiate their proposed translational potential.

Scientific rationale for exploring phytochemical small molecules derived from *S. chinensis*

Rationale for multi-target drug discovery

Triterpenoid saponins are structurally diverse, rendering them prone to interact with multiple molecular targets. Consequently, the bioactive constituents of *S. chinensis* represent promising candidates for multi-target drug development [4, 8].

Advances in high-throughput screening, network pharmacology, and molecular docking technologies have facilitated the systematic discovery of bioactive small molecules derived from *S. chinensis* [6, 8, 9]. These compounds have been shown to regulate key pathways, such as NF-κB, Nrf2, and PI3K/Akt, which are implicated in neurodegenerative diseases, inflammatory disorders, and cancer [4, 10, 11]. Existing mechanistic studies provide a scientific rationale for prioritizing *S. chinensis*-derived phytochemical small molecules as focal candidates in contemporary drug discovery pipelines.

It's critical to bridge the gap between the natural therapeutic potential and translational liabilities of small molecules from *S. chinensis*, thereby preventing attrition during drug development. The distinctive chemical features of triterpenoid saponins, including high molecular weight and amphiphilic properties, confer both multi-target pharmacological activity and inherent pharmacokinetic limitations. The positive multi-target effects, such as modulation of NF-κB and Nrf2 signaling pathways, as shown in the translational roadmap (**Figure 1**), have to be balanced with notable chemical liabilities, including poor oral bioavailability (typically <10%), rapid systemic clearance, and the risk of dose-dependent hemolytic toxicity [12, 13]. Successful clinical translation of these compounds hinges on overcoming these challenges through advanced drug delivery systems, such as liposomal and nanoparticle-based systems, and rational structural optimization guided by computational studies [6, 14].

Translational challenges of natural multi-target compounds

Multifaceted diseases, including cancer, chronic inflammatory diseases, neurodegenerative illnesses, arise from the dysregulation of multiple interconnected molecular pathways rather than a single causative mechanism. Single-target drugs often fail to achieve sustained clinical efficacy due to compensatory redundancy within biological networks. In contrast, multi-target modulators can simultaneously regulate multiple signaling nodes, improving treatment efficacy while mitigating adverse outcomes.

Natural multi-target modulators include the terpene saponins derived from *S. chinensis* [15, 16]. According to preclinical literature, these compounds can attenuate oxidative stress, modulate apoptotic signaling pathways, and inhibit the secretion of pro-inflammatory cyto-

kines across diverse cellular context. Such pleiotropic activity underscores their potential utility in the treatment of multifactorial disease. Moreover, network pharmacology and computational modeling have demonstrated that these compounds can engage multiple molecular targets simultaneously, supporting their potential value in polypharmacology-based drug design.

Botanical and ethnopharmacological background

Botanical overview of Stauntonia chinensis

Stauntonia chinensis is a species of the genus *Stauntonia* within the Lardizabalaceae family, which comprises multiple species distributed across East and Southeast Asia. It is a perennial evergreen climbing plant native to China, Vietnam, and surrounding areas. The stems, leaves, fruit, and roots of *S. chinensis* are all considered medicinal and are prepared as decoctions or extracts for therapeutic use [1].

Traditional and ethnopharmacological uses

The use of *S. chinensis* in TCM has a long history, primarily attributed to its neuroprotective, analgesic, and anti-inflammatory properties. Plant extracts and decoctions have been utilized to alleviate inflammation, pain, and neuropathy. In folk medicine, saponin-containing extracts of stems and fruits have also been employed to promote general health and improve blood circulation [5, 10, 17]. Recent studies have reported promising anti-cancer and immunomodulatory activities, consistent with these traditional medicinal claims. For example, ginsenoside Rg3, a triterpenoid saponin commonly found in Panax ginseng and used in TCM oncology practice (e.g., Shenyi capsule), has demonstrated clinical benefits in combination with conventional therapies for non-small cell lung cancer and other tumors, with evidence of improved immune function and adjunctive anticancer effects in patients [18].

Relevance to modern drug discovery

Multi-target pharmacological profile of triterpenoid saponins positions the bioactive compounds of *S. chinensis* as attractive candidates for modern pharmacological studies, particularly in the context of inflammation, oxidative stress, and signaling pathways involving NF-κB and Nrf2 [6, 9, 11]. These compounds have been increasingly investigated using network pharmacology and molecular docking, which suggest their potential in multi-target drug development. The integration of traditional medicinal knowledge and modern computational and experimental approaches highlights *S. chinensis* as a valuable source of naturally derived compounds for drug discovery.

Phytochemistry and bioactive small molecules

Overview of identified phytochemicals

Phytochemical investigations over recent decades have demonstrated that *S. chinensis* contains a diverse array of small molecules, including triterpenoid saponins, pentacyclic triterpenoids, and other glycosides, which collectively contribute to its broad pharmacological properties [1]. Advances in high-resolution analytical techniques, particularly liquid chromatography coupled with tandem mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR), have substantially expanded the established molecular repertoire of the genus Stauntonia [13]. These structural clarification discoveries have enabled precise characterizations of saponin aglycones, glycosidic moieties, and patterns that are critical for biological activity.

Triterpenoid saponins as the predominant chemical constituents

Recent composition profiling indicates that triterpenoid saponins represent the most bioactive class of phytochemicals in *S. chinensis*. These saponins are mostly anchored on oleanane- or lupane-type pentacyclic triterpenoid saponins conjugated with mono - or oligosaccharide chains [4, 19]. Pentacyclic triterpenoids are known to preferentially interact with lipid membranes, immune receptors, and intracellular signaling components, largely owing to their amphiphilic structure [4, 13]. Moreover, anti-inflammatory and immunomodulatory activities reported for saponin scaffolds from related species, including *Stauntonia hexaphylla*, indicate that structural-functional relationships are conserved across the genus [1, 4, 5].

Several saponins derived from *S. chinensis* have also been reported to exert central nervous system (CNS) - related analgesic effects

through both peripheral and central mechanisms [20]. Variations in glycosylation patterns influence enzyme stability, membrane permeability, and receptor affinity. In addition, shared structural motifs (e.g., hydroxyl-rich ends, carboxylated rings, and branched sugar chains) exhibit similarities to pharmacologically active saponins from other medicinal plants, contributing to their multi-target effect.

Pentacyclic triterpenoids and aglycones

S. chinensis also contains free pentacyclic triterpenoid aglycones in addition to glycosylated saponins. A significant number of these aglycones contain natural product scaffolds that have been extensively documented for their anti-inflammatory, antioxidant, and anti-cancer activities in pharmaceutical research [4, 10, 17, 21]. Reviews focusing on pentacyclic triterpenoid have indicated their regulatory roles in apoptotic signaling, inflammatory cascades, and oxidative stress-related pathways. Such mechanistic properties are relevant to the pharmacological actions of *Stauntonia* species and provide a biochemical rationale for their broad therapeutic applicability.

Additional bioactive small molecules

Evidence at the genus level indicates the presence of phenolic acids, flavonoids, steroidal constituents, and minor terpenoid derivatives. Although present in lower abundance, these metabolites are identified as auxiliary contributors to the therapeutic effects of *S. chinaensis*, especially in antioxidant effects and immunomodulatory regulation. Studies in related species, such as *Stauntonia hexaphylla*, have demonstrated that even low levels of non-saponin terpenoids and triterpene glycosides can modulate anti-inflammatory signaling, thereby expanding the repertoire of small molecules associated with the genus [22].

Innovations in analytical and structural elucidation techniques

Recent advances in high-resolution mass spectrometry, two-dimensional NMR, and computational dereplication have played a key role in resolving the structural of complex saponins and triterpenoids. Network-based compound annotation approaches and *in silico* prediction software has accelerated the identification of a candidate molecule and facilitated the search of multi-target bioactive constituents. Collectively, these strategies are critical for elucidating the chemical basis of *S. chinensis* pharmacology and form an essential foundation for translational research in multi-target drug discovery.

Pharmacological activities of *S. chinensis*' phytochemicals

Overview and evidence limitations

Available experimental evidence suggests that *S. chinensis* contains pentacyclic triterpenoids and triterpenoid saponins with diverse biological activities. However, the strength and specificity of this evidence vary substantially across pharmacological domains. Direct experimental validation specific to *S. chinensis* is currently limited, and many reported activities are inferred from studies on structurally related triterpenoids, or other *Stauntonia* species.

A critical evaluation of current literature reveals substantial heterogeneity between experimental models, which limits cross-study comparability. As summarized in **Table 1**, the most robust evidence for *S. chinensis*-derived compounds is observed in the analgesia field, supported by preclinical studies. In contrast, general anti-inflammatory, antioxidant, and antiproliferative effects are frequently inferred from investigations of general triterpenoid scaffolds rather than plant-specific compounds. In addition, key translational parameters, including poor oral bioavailability (typically <10%) and dose-related hemolytic toxicity, are well recognized in general TCM but remain largely uncharacterized for *S. chinensis*-derived compounds, underscoring the need for plant-specific pharmacokinetic and toxicological evaluation [23, 24].

Analgesic and anti-inflammatory activities

Among the reported pharmacological effects, the analgesic potential of *S. chinensis* is one of the most widely described, with triterpenoid saponins considered major contributors. In a preclinical study, central and peripheral administration of *S. chinensis* preparations reduced microglial proliferation and PSD-95 expression, indicating a potent modulatory effect on neuropathic pain. Additional evidence shows that

Table 1. Critical synthesis of experimental evidence specific to Stauntonia chinensis and its general triterpenoid saponin class

Compound/Extract	Experimental Model/System	Dose/Concentration Range	Specific *S. chinensis* Finding	Mechanistic Insight (Evidence Strength)	Critical Limitation
S. chinensis injection	Rat neuropathic pain model; microglia assays	*In vivo* doses reported in original study	Reduced microglial proliferation; decreased PSD-95 expression; improved pain thresholds	Confirmed Central & Peripheral Analgesic/ Anti-inflammatory action	No pharmacokinetic (PK) data reported; extract not standardized.
Purified triterpenoid saponins (from *S. chinensis*)	Mouse pain model; neuronal assays	Active component doses in mg/kg	Demonstrated analgesic effects; reduced inflammatory mediator release	Modulation of nociceptive receptor activity (Implied/Direct)	Tested only in acute pain models; limited toxicity data.
TCM saponins (General Class)	*In vivo* PK, toxicity	Oral & IV doses	(Analogy: Low oral bioavailability (<10%); dose-dependent hemolysis)	Directly informs safety and PK profile of the chemical class	Not specific to *S. chinensis*; provides baseline liability data only.
Triterpenoid saponins (General Class)	*In vitro* assays (e.g., Macrophages)	Varies, μM levels	(Analogy: Suppression of inflammatory cytokines; Nrf2 activation)	NF-κB inhibition; Nrf2 activation (Mechanistic confirmation for general class)	In vitro data only; not validated for *S. chinensis* components; no ADMET evaluation

This table compiles primary experimental data, distinguishing specific in vivo findings for S. chinensis extracts or compound (highlighted in the text) from critical analogical data derived from the general triterpenoid saponin class, especially concerning toxicity and PK limitations.

Table 2. Integrated mechanistic profile of *S. chinensis* (critical evaluation)

Targeted Pathway	Primary Role in *S. chinensis*	Molecular Target/Effect	Evidence Status (Rigour)
NF-κB Signaling	Anti-inflammatory, Analgesic	Downregulation of pro-inflammatory cytokines (TNF-α, IL-1β); Reduced macrophage activation	Direct (Efficacy): Confirmed in *in vivo* rat pain model via surrogate markers (microglial reduction). Mechanistic Limitation: Direct molecular target interaction is often deduced.
Nrf2/HO-1 Pathway	Antioxidant, Cytoprotective	Upregulation of self-protective enzymes (SOD, catalase, GPx); Reduced ROS	Inferred/Analogical: Primarily supported by studies on the general triterpenoid scaffold. Limitation: Lack of *S. chinensis*-specific Nrf2 modulation assays.
PI3K/Akt/MAPK	Anti-proliferative, Immunomodulatory Potential	Inhibition of Akt phosphorylation; Regulation of ERK/JNK/p38	Inferred/Computational: Potential based on molecular docking and network pharmacology predictions. Limitation: Lacks direct *in vivo* validation and causal links are frequently deduced.
Apoptotic Signaling	Anti-tumor Potential	Modulation of Bax/Bcl-2 axis; Induction of apoptosis	Speculative: Mechanism extrapolated from general triterpenoid activity against cancer cell lines. Limitation: No dedicated *S. chinensis* anti-tumor studies.

This table identifies the major molecular pathways modulated by *S. chinensis* phytochemicals and critically assesses the evidentiary status (direct, inferred, or computational) of the mechanistic claims, acknowledging the reliance on surrogate markers in current literature.

purified triterpenoid saponins can influence nociceptive signaling, inflammatory mediator release, and putative membrane-associated receptors involved in pain pathways [25]. These analgesic effects are broadly consistent with the regulation of essential inflammatory signaling by pentacyclic triterpenoids, including NF-κB, Nrf2, and PI3K/Akt signaling pathways. Reviews of triterpenoid bioactivity have reported inhibition on pro-inflammatory cytokine production, attenuation of oxidative stress, and suppression of macrophage infiltration. Studies in related *Stauntonia* species, including *S. hexaphylla*, also demonstrated reductions in inflammatory markers, supporting a conserved chemical and pharmacological profile of the genus [26, 27]. However, the anti-inflammatory claims are largely inferred rather than conclusively demonstrated.

Immunomodulatory actions

Phytochemicals derived from *S. chinensis* have been proposed to exert immunomodulatory effects, largely attributable to the structural characteristics of their saponins, which interact with immune cell membranes and pattern-recognition receptors. This is justified by the fact that triterpenoid saponins modulate NF-κB and Nrf2 signaling pathways, both of which are fundamental to the regulation of inflammation and immune homeostasis [4, 5]. However, direct evidence demonstrating immunomodulatory activity of isolated *S. chinensis* compounds remains limited. Current reports implicating that NF-κB and Nrf2 signaling pathways are primarily inferred from downstream marker changes or extrapolated from studies of saponins derived from other plants.

Antioxidant and cytoprotective properties

Terpenoids and saponins in *S. chinensis* are inferred to contribute to antioxidant activities through multi-node molecular regulation, based on structural and mechanistic analogies. Evidence suggests that these compounds may activate Nrf2 signaling, upregulating downstream antioxidant enzymes and attenuating cell damage induced by reactive oxygen species (ROS) [4, 5]. Given the established crosstalk between inflammatory and oxidative signaling, such antioxidant effects may indirectly support immunomodulation and analgesia outcomes. This multi-pathway targeting is typical of natural triterpenoids in general, and the structural similarity of *S. chinensis* components to oxidative-stress modulators supports their pharmacological relevance. While these mechanisms are biologically plausible, direct evidence of Nrf2 activation by *S. chinensis* phytochemicals in defined experimental systems remains limited.

Anti-tumor multi-target synergy and potential

Although anti-tumor activity is least experimentally claimed for *S. chinensis*, its key chemical classes share mechanistic features with established polypharmacological triterpenoid anticancer agents. Existing reviews indicate that such triterpenoids can modulate apoptosis, inhibit abnormal proliferation, and modulate key oncogenic signaling pathways, including PI3K/Akt, NF-κB, and mitogen-activated protein kinase (MAPK) pathways [10, 17, 28]. These pathways overlap with those implicated in the inflammatory, oxidative stress, and immune-related effects attributed to *S. chinensis* extracts, which are integral to cancer biology. But these anti-tumor effects should currently be regarded as hypothetical pharmacological potential rather than validated therapeutic activity.

Molecular mechanisms and multi-target pathway modulation

Overview of multi-target signaling

Pentacyclic triterpenoids and triterpenoid saponins derived from *S. chinensis* participate in a complex system of intracellular signaling pathways, reflecting their multi-target pharmacological properties. The multi-pathway regulatory effects attributed to these compounds are summarized in **Table 2**, highlighting key molecular nodes, along with the corresponding mechanistic outcome.

The rigor of the existing evidence supporting the multi-target pharmacology of *S. chinensis* needs to be assessed by a critical appraisal. As illustrated in the Evidence Pyramid (**Figure 2**), mechanistic data are stratified according to levels of experimental validation, thereby distinguishing well-substantiated activities from putative effects. The highest level of rigor is observed in studies reporting *in vivo* pharmacological activity, particularly the confirmed cen-

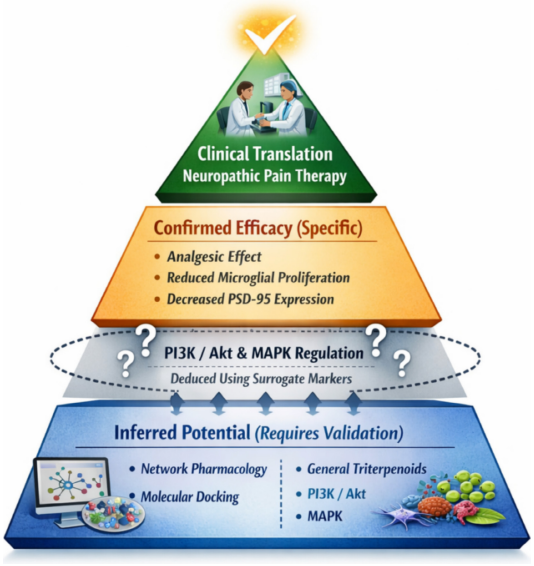

Figure 2. Evidence pyramid illustrating the mechanistic rigor of multi-target claims for *S. chinensis*. This pyramid depicts the strength of evidence supporting the multi-target claims. The apex represents the highest rigor (confirmed *in vivo* efficacy specific to *S. chinensis*), the middle tier represents validated mechanistic markers (NF-κB, Nrf2), and the broad base represents claims largely supported by computational inference or extrapolation from the triterpenoid class (e.g., PI3K/Akt, MAPK). Notes: PI3K/Akt, phosphatidylinositol 3-kinase/protein kinase B; MAPK, mitogen-activated protein kinase.

tral and peripheral analgesic effects of *S. chinensis* extracts, which have been directly associated with reduced microglial cell proliferation and decreased expression of PSD-95 in experimental models of neuropathic pain [3]. Moderate levels of evidence support anti-inflammatory and antioxidant activities, such as the modulation of NF-κB and Nrf2 signaling pathways. These effects are verified by the inhibition of inflammatory cytokines and the activation of protective enzymes, although they are frequently inferred from surrogate biomarkers. In contrast, claims of modulation of more complex signaling pathways such as PI3K/Akt and MAPK are generally confined to the lowest tier of evidence and are primarily derived from computational studies (e.g., network pharmacology and molecular docking) or structural similarity to other triterpenoids [29, 30]. Addressing these evidence gaps is essential for the rational development of therapeutics with clinical efficacy. While network pharmacology and molecular docking analyses provide useful hypothesis-generation tools, they cannot replace experimental verification.

NF-κB-mediated inflammatory regulation

Key anti-inflammatory processes attributed to *S. chinensis* phytochemicals include suppression of NF-κB activity and inhibition of pro-inflammatory cytokine production, such as TNF-α, IL-1β, and IL-6. The immunomodulatory and analgesic effects can be mechanistically explained by downregulation of NF-κB-mediated transcriptional activity of inflammatory mediators. It is noteworthy that the regulation of NF-κB signaling is multifaceted, involving not only direct kinase inhibition but also the modulation of key adapter protein stability. For instance, recent research has identified UFL1 as a crucial regulator that maintains the stability of STING, a central adapter in the DNA-sensing pathway, thereby preventing its TRIM29-mediated K48-linked ubiquitination and proteasomal degradation, which in turn sustains the activation of both NF-κB and IRF3 pathways and potentiates antiviral immune responses [31]. While this illustrates a distinct regulatory node within immune signaling networks, the anti-inflammatory actions of *S. chinensis* constituents have been more closely linked to the direct modulation of canonical kinase pathways. Triterpenoid saponins also suppress PI3K/Akt signaling, which inhibits the release of cytokines and macrophage activation, a pattern consistent with findings in other *Stauntonia* species [32].

Nrf2/HO-1 antioxidant signaling

The activation of nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) axis represents one of the pathways through which *S. chinensis*-derived small molecules may exert antioxidant and cytoprotective effects. Upon Nrf2 activation, the self-protective antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPOx), are upregulated, thereby mitigating cellular damage induced by ROS [33]. In addition, crosstalk between NF-κB and the Nrf2 signaling pathways enables coordinated suppression of inflammation and oxidative stress, resulting in a multi-layered protective effect.

Pharmacokinetics, bioavailability, and toxicity

Pharmacokinetic characteristics

Natural saponins and triterpenoids derived from *Stauntonia* species are characterized by

high molecular weight, low solubility, and interactions with biological membranes. Consequently, the oral absorption and bioavailability of saponins are normally poor, largely due to intestinal enzyme and gut microbiome degradation, as well as the low gastrointestinal permeability. The compounds accumulate in highly perfused organs such as the liver and kidneys, where they are metabolized by hepatic cytochrome P450-mediated oxidation and phase II conjugation reactions. Recent advances in nanotechnology-based delivery systems aim to enhance systemic exposure and achieve therapeutically relevant concentrations at target tissues [13].

Bioavailability constraints

The clinical application of saponins is constrained by unfavorable pharmacokinetic properties. In the gastrointestinal tract, the amphiphilic nature limits efficient gastrointestinal absorption, while glycosidic moieties are prone to hydrolysis, further compromising absorption and metabolic stability [34]. Solubility and membrane permeability can be enhanced through rational structural modifications, including optimization of glycosylation patterns without abolishing intrinsic bioactivity. Computational structure-property models such as quantitative structure-activity relationship (QSAR) and descriptor-based approaches have been shown to predict solubility and membrane permeability from molecular structure alone, providing a rational framework to assess how modifications like glycosylation may impact ADME properties [35].

Hemolytic and hepatotoxic of saponins

Hemolysis represents another major toxicity concern associated with saponins and is primarily attributed to their interaction with cholesterol in erythrocyte membranes, leading to membrane destabilization. Systematic reviews indicate that this hemolytic effect is structure-dependent, with steroidal saponins exhibiting lower hemolytic potential than triterpenoid saponins. In addition to hemolysis, preclinical studies have reported dose-dependent and compound-specific hepatotoxicity [36]. Analyses of hundreds of phytochemicals associated with herb-induced liver injury note that glycosides and saponin-derived compounds occur in multiple medicinal plants with documented hepatotoxic potential, illustrating that some saponins can contribute to liver toxicity [37].

In vivo pharmacokinetic studies

In animal models, experimental research has shown that saponins exhibit low oral bioavailability (typically <10%) and short elimination half-life, resulting limited systemic exposure following oral administration. Although intravenous administration markedly improves bioavailability, it is impractical for long-term or routine therapeutic use. Currently, advanced delivery strategies, including liposomal encapsulation and nanoformulations, are being developed to prolong circulation time [12].

ADMET prediction and computational pharmacology

The drug-likeness of triterpenoids and saponins can be systematically evaluated using computational pharmacokinetics modeling and ADMET (absorption, distribution, metabolism, excretion, and toxicity) approaches [38]. Molecular docking and network pharmacology analyses suggest that specific structural motifs are associated with reduced hepatotoxicity and improved permeability, providing a rational basis for structural optimization. Moreover, *in silico* techniques enable the prediction of interactions with metabolic enzymes and transporters, *facilitating early identification of potential pharmacokinetic liabilities prior to in vivo validation*.

Drug delivery and pharmaceutical formulation

Nanoparticle- and liposome-based delivery

Stauntonia-derived triterpenoids and saponins are characterized by poor solubility, low oral bioavailability, and a high clearance rate, which limit their therapeutic potential. To solve these issues, it has been actively investigated that nanoparticle-based delivery systems such as liposomes, polymeric nanoparticles, and phytosomes can be used to solve these problems [9]. Nanoparticles have easier targeting of the tissues and are more stable to enzyme degradation, whereas liposomes can encapsulate compounds, including hydrophilic ones and lipophilic ones, improving systemic circulation and bioavailability. One application of the oral

range is the use of phytosomes (the complexation of phytoconstituents with phospholipids), which enhance cellular uptake and absorption [8, 15].

Solubility enhancement strategies

Poor solubility represents a major obstacle to the clinical applicability of natural triterpenoids. Various formulation strategies, including particle size reduction, solid dispersion systems, self-emulsifying drug delivery systems, and inclusion complex formation with cyclodextrins, have been shown to significantly enhance dissolution rate and solubility [12, 13, 19, 34]. Computational analyses suggest that additional solubility enhancement through the use of co-solvents, surfactants, or structural modification can be achieved without compromising bioactivity.

Controlled-release formulations

Sustained-release nanoparticles and biodegradable polymeric matrices in the form of controlled-release systems address the issues of rapid clearance and low half-lives of triterpenoids and saponins. Controlled-release delivery systems enable prolonged drug release, maintenance of stable plasma concentrations, and reduced dosing frequency, which may collectively improve therapeutic efficacy while potentially mitigating dose-related toxicity [12, 14].

Translational perspective and future directions

Relevance for future clinical practice

Stauntonia-derived triterpenoids and saponins exhibit multi-target pharmacological properties, conferring promising therapeutic potential. Preclinical evidence suggest significant potential in oncology, neuropathic pain, and neuroinflammation, with observed anti-proliferative, pro-apoptotic, and anti-inflammatory effects linked to modulation of NF-κB, Nrf2, and PI3K/Akt signaling pathways [3, 4, 11, 17]. For example, saponins isolated from plant sources demonstrated cytotoxic activity against human cancer cell lines by enhancing apoptotic markers (caspase-3, BAX), suppressing inflammation via downregulation of pro-inflammatory cytokines, and modulating NF-κB and PI3K/Akt signaling, while also activating Nrf2-mediated antioxidant responses in preclinical cellular models [39].

Challenges in clinical translation

Despite their notable pharmacological potential, challenges remain for their direct clinical translation. Key pharmacokinetic barriers include rapid systemic clearance, low oral bioavailability, and suboptimal tissue distribution. Toxicological concerns, especially hemolytic activity and hepatotoxicity, require careful dose optimization. Batch-to-batch variability and the lack of standardized extraction, purification, and quantification protocols pose challenges to regulatory approval and reproducibility [12, 13, 36].

Preclinical progression requirements

Successful clinical translation requires a comprehensive preclinical evaluation. Drug profiling should systematically assess target engagement, absorption, distribution, metabolism, and elimination (ADME) properties. Potential side effects, including immuno-toxicity, hepatotoxicity, and hemolytic activity must be evaluated through acute, sub-chronic, and chronic toxicological assessment. To ensure regulatory feasibility and reproducibility, both isolated compounds and extracts must be standardized, precisely quantifying triterpenoids and saponins. Furthermore, *in vitro* and *in vivo* validations are required to confirm modulation of relevant molecular pathways and identify pharmacodynamic biomarkers that can be translated into clinical assessment [6, 12, 38].

Preclinical testing should follow a scheduled framework to enable efficient progression toward clinical research, as shown in **Figure 3**.

Phase I: Discovery and Standardization. This initial phase focuses on rigorous chemical characterization and standardization of extracts (e.g., triterpenoid saponin) to assure reproducibility and regulatory acceptability [1, 13].

Phase II: Validation and Optimization. During this phase, experimental pharmacokinetic studies should be integrated with computational ADMET predictions. Rational formulation strategies (e.g., liposomes and phytosomes) should be prioritized to address low oral bioavailability and short elimination half-life. Importantly, formal safety evaluations must encompass acute, sub-chronic, and chronic toxicity studies, with particular attention to hemolysis and hepato-

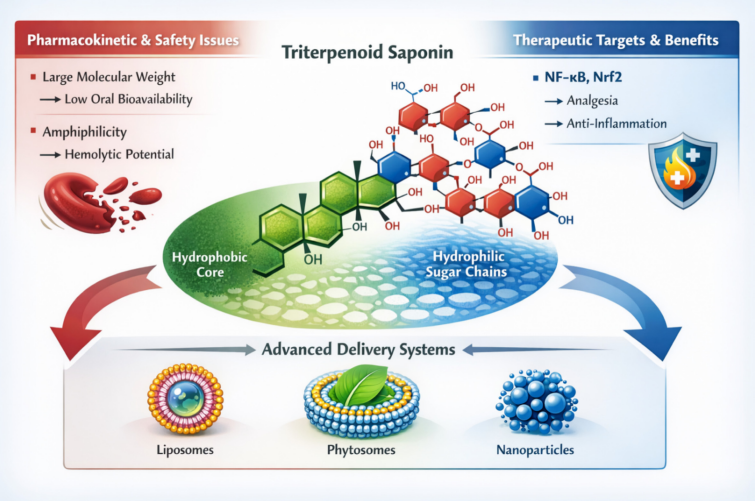

Figure 3. Integrated translational pipeline for *S. chinensis*-derived lead compounds. This sequential pipeline details the mandatory phases for developing *S. chinensis* phytochemicals from prioritized leads to clinical candidates. It emphasizes the integration of crucial safety and pharmacokinetic assessments (e.g., ADMET prediction, hemolysis testing) and required technical steps (standardization, nanoformulation) to ensure regulatory viability and address inherent pharmacokinetic liabilities. Notes: ADMET, absorption, distribution, metabolism, excretion, and toxicity.

toxicity, which are known class-specific risks of saponin. Structural and formulation optimization should be completed at this stage before advancement [12, 14, 34].

Phase III: Clinical Entry. Biomarker-guided efficacy studies, supported by standardized pharmacological and toxicological testing, will provide the translational evidence required to support first-in-human clinical trials [6, 38].

Plans for advancing toward clinical trials

Translational development of Stauntonia-derived compounds requires a combined strategy encompassing formulation optimization, dose testing, and biomarker-based evaluation [6]. Standardized dosing should be based on purified compounds or well-characterized extracts, supported by *in vivo* bioavailability and pharmacokinetic modeling [8]. Early signals of efficacy and safety may be measured using validated biomarkers of oxidative stress, inflammatory cytokines, or pathway-specific readouts [9]. It is plausible to use computational ADMET predictions and network pharmacology to pre-select lead compounds with good efficacy-safety profiles before advancing into formal pre-clinical development and eventual clinical testing [38].

Existing knowledge gaps and future directions

Despite promising pharmacological evidence, substantial gaps remain in the mechanistic understanding of *S. chinensis*-derived triterpenoids and saponins. The precise molecular mediators underlying recognized anti-inflammatory, neuroprotective, and anticancer effects remain incompletely elucidated. In many cases, proposed targets - such as transcription factors or signaling proteins - are inferred from surrogate pathway readouts rather than demonstrated through direct molecular interaction or target engagement assays. Addressing these gaps through rigorous experimental validation is essential to enable rational drug design and successful translation to clinically viable therapeutics [4, 6, 29, 30].

Requirement for structure-function verification

Although *S. chinensis* triterpenoid saponins demonstrate structural diversity consistent with multi-target pharmacology, systematic structure-activity relationship (SAR) data remain largely unavailable. Future Investigations should combine both *in vivo* and *in vitro* experiments with SAR analyses and computational docking to identify specific structural motifs that confer therapeutic efficacy while minimizing toxicity [19, 24, 38].

Priorities of pharmacokinetic improvement

The key obstacles to clinical translation include high systemic clearance, low oral bioavailability, and poor tissue distribution. Nanoparticle-based methods, including liposomal and phytosomal delivery systems, and chemical modification, warrant systematic evaluation to improve pharmacokinetic performance. Computational ADMET predictions should be used to complement experimental pharmacokinetic studies to enhance and accelerate the selection of candidates with favorable ADME profiles [12, 14, 19, 34].

Human safety considerations

Current safety evidence is limited to *in vitro* and animal research. Key safety concerns include dose-dependent toxicity, hepatotoxicity, and hemolytic activity. To date, *S. chinensis*-derived compounds haven't undergone formal human safety tests or clinical trials. Preclinical safety studies using standardized compounds or extracts are necessary to establish tolerable dose ranges, identify possible side effects, and define pharmacodynamic biomarkers [12, 36].

Selection of optimal drug candidates

Priority should be given to *S. chinensis*-derived compounds that demonstrate multi-target anti-inflammatory, anti-oxidant, and anti-proliferative activities along with reduced hemolytic potential. Among the identified phytochemicals, pentacyclic triterpenoids represent the most promising lead candidates due to their favorable ADMET profiles and structural stability. These compounds are well suited for further development using advanced formulation strategies, such as nanoparticle - or liposome-based delivery systems [10, 17, 19, 24].

Conclusion

Stauntonia chinensis represents an important source of triterpenoids and bioactive saponins with various pharmacological characteristics. These compounds exhibit anti-oxidant, anti-inflammatory, neuroprotective, and anti-cancer properties, which are consistent with traditional medicinal claims and support its potential relevance in the treatment of complex diseases. However, direct experimental evidence specific to *S. chinensis* remains limited, with the strongest support confined to selected preclinical analgesic effects [1].

Pharmacological activities other than analgesic effects are inferred from class effects of triterpenoid, studies on related species, or computational analyses rather than plant-specific validation. Proposed multi-target mechanisms involving NF-κB, Nrf2, PI3K/Akt, and MAPK pathways are largely hypothesis-generating, based on surrogate markers or *in silico* approaches, and therefore require rigorous experimental confirmation. In addition, key translational gaps persist, particularly the lack of systematic pharmacokinetic and toxicological data. Overall, *S. chinensis* should currently be regarded as an exploratory pharmacological resource. Future progress will depend on evidence-driven validation rather than extrapolation from related compounds or species [3, 4].

Disclosure of conflict of interest

None.

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References

[1] Miao MS, Tian S, Liu WM, Ma QG, Wei RR and Zhang ZH. The genus Stauntonia DC.: botany, phytochemistry, bioactivity, and application. Comb Chem High Throughput Screen 2025; 28: 1-22.

[2] Hu X, Wang S, Xu J, Wang DB, Chen Y and Yang GZ. Triterpenoid saponins from Stauntonia chinensis ameliorate insulin resistance via the AMP-activated protein kinase and IR/IRS-1/PI3K/Akt pathways in insulin-resistant HepG2 cells. Int J Mol Sci 2014; 15: 10446-10458.

[3] Deng W, Zou H, Qian L, de Souza SC, Chen Q and Cao S. Stauntonia chinensis injection relieves neuropathic pain by increasing the expression of PSD-95 and reducing the proliferation of phagocytic microglia. Ibrain 2023; 10: 3-18.

[4] Mantiniotou M, Athanasiadis V, Kalompatsios D, Bozinou E and Lalas SI. Therapeutic capabilities of triterpenes and triterpenoids in immune and inflammatory processes: a review. Compounds 2025; 5: 2.

[5] Shen L, Luo H, Fan L, Tian X, Tang A, Wu X, Dong K and Su Z. Potential immunoregulatory mechanism of plant saponins: a review. Molecules 2023; 29: 113.

[6] Maddeboina K, Yada B, Kumari S, McHale C, Pal D and Durden DL. Recent advances in multitarget-directed ligands via in silico drug discovery. Drug Discov Today 2024; 29: 103904.

[7] Ryszkiewicz P, Malinowska B and Schlicker E. Polypharmacology: new drugs in 2023-2024. Pharmacol Rep 2025; 77: 543-560.

[8] Li L, Yang L, Yang L, He C, He Y, Chen L, Dong Q, Zhang H, Chen S and Li P. Network pharmacology: a bright guiding light on the way to ex-

plore the personalized precise medication of traditional Chinese medicine. Chin Med 2023; 18: 146.
[9] Zhai Y, Liu L, Zhang F, Chen X, Wang H, Zhou J, Chai K, Liu J, Lei H, Lu P, Guo M, Guo J and Wu J. Network pharmacology: a crucial approach in traditional Chinese medicine research. Chin Med 2025; 20: 8.
[10] Zhao ZX, Zou QY, Ma YH, Morris-Natschke SL, Li XY, Shi LC, Ma GX, Xu XD, Yang MH, Zhao ZJ, Li YX, Xue J, Chen CH and Wu HF. Recent progress on triterpenoid derivatives and their anticancer potential. Phytochemistry 2025; 229: 114257.
[11] Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, Zeng C, Zhou T and Zhang J. NF-κB in biology and targeted therapy: new insights and translational implications. Signal Transduct Target Ther 2024; 9: 53.
[12] Ma Y, Zhao Y, Luo M, Jiang Q, Liu S, Jia Q, Bai Z, Wu F and Xie J. Advancements and challenges in pharmacokinetic and pharmacodynamic research on the traditional Chinese medicine saponins: a comprehensive review. Front Pharmacol 2024; 15: 1393409.
[13] Fordos S, Amin S, Abid N, Pasha I, Khan MKI, Amin A, Gulzar M, Subtain M and Abdi G. Saponins: advances in extraction techniques, functional properties, and industrial applications. Appl Food Res 2025; 5: 101146.
[14] Sharmila A, Bhadra P, Kishore C, Selvaraj CI, Kavalakatt J and Bishayee A. Nanoformulated terpenoids in cancer: a review of therapeutic applications, mechanisms, and challenges. Cancers (Basel) 2025; 17: 3013.
[15] Chen Y, Yang F, Wang S, Wang D, Xu J and Yang G. Triterpenoid saponins from Stauntonia chinensis. Bull Korean Chem Soc 2014; 35: 1-6.
[16] Ouyang M, Wu J, Hu X, Liu C and Zhou D. Decoding the power of saponins in ferroptosis regulation and disease intervention: a review. J Pharm Pharmacol 2025; 77: 593-608.
[17] Aly SH, Elbadry AMM, Doghish AS and El-Nashar HAS. Unveiling the pharmacological potential of plant triterpenoids in breast cancer management: an updated review. Naunyn Schmiedebergs Arch Pharmacol 2024; 397: 5571-5596.
[18] Sun M, Ye Y, Xiao L, Duan X, Zhang Y and Zhang H. Anticancer effects of ginsenoside Rg3. Int J Mol Med 2017; 39: 507-518.
[19] Teng W, Zhou Z, Cao J and Guo Q. Recent advances of natural pentacyclic triterpenoids as bioactive delivery system for synergetic biological applications. Foods 2024; 13: 2226.
[20] Gong JH, Zhang CM, Wu B, Zhang ZX, Zhou ZY, Zhu JH, Liu H, Rong Y, Yin Q, Chen YT, Zheng R, Yang GZ, Yang XF and Chen S. Central and peripheral analgesic active components of triterpenoid saponins from Stauntonia chinensis and their action mechanism. Front Pharmacol 2023; 14: 1275041.
[21] AlMousa LA, Pandey P, Lakhanpal S, Kyada AK, H M, Nayak PP, Hussain A, Hasan TN, Alagal RI and Khan F. An updated review deciphering the anticancer potential of pentacyclic triterpene lupeol and its nanoformulations. Front Pharmacol 2025; 16: 1594901.
[22] Sharipov A, Tursunov K, Fazliev S, Azimova B and Razzokov J. Hypoglycemic and anti-inflammatory effects of triterpene glycoside fractions from Aeculus hippocastanum seeds. Molecules 2021; 26: 3784.
[23] Yang D, Han N, Wang YW, Zhai JX, Liu ZH, Li SK and Yin J. Pentacyclic triterpenoid saponins, poterinasides A-J, from Silverweed Cinquefoil Roots promising hepatoprotective and anti-inflammatory Agents. J Org Chem 2021; 86: 11220-11236.
[24] Wimmer Z. Selected pentacyclic triterpenoids and their derivatives as biologically active compounds. Molecules 2025; 30: 3106.
[25] Chen S, Rong Y, Liu M, Cheng S, Liu X, Li X, Yu Y, Yang G and Yang X. Analgesic effects of triterpenoid saponins from Stauntonia chinensis via selective increase in inhibitory synaptic response in mouse cortical neurons. Front Pharmacol 2018; 9: 1302.
[26] Pant T, Uche N, Juric M, Zielonka J and Bai X. Regulation of immunomodulatory networks by Nrf2-activation in immune cells: redox control and therapeutic potential in inflammatory diseases. Redox Biol 2024; 70: 103077.
[27] Moralev AD, Zenkova MA and Markov AV. Complex inhibitory activity of pentacyclic triterpenoids against cutaneous melanoma in vitro and in vivo: a literature review and reconstruction of their melanoma-related protein interactome. ACS Pharmacol Transl Sci 2024; 7: 3358-3384.
[28] Jiang M, Hong C, Zou W, Ye Z, Lu L, Liu Y, Zhang T and Ding Y. Recent advances in the anti-tumor activities of saponins through cholesterol regulation. Front Pharmacol 2025; 15: 1469392.
[29] Liu Z and Liu J. Integrative network pharmacology and experimental validation of anti-inflammatory triterpenoids from hawthorn leaves. Sci Rep 2025; 15: 21765.
[30] Liu T, Wang J, Tong Y, Wu L, Xie Y, He P, Lin S and Hu X. Integrating network pharmacology and animal experimental validation to investigate the action mechanism of oleanolic acid in obesity. J Transl Med 2024; 22: 86.
[31] Tao Y, Yin S, Liu Y, Li C, Chen Y, Han D, Huang J, Xu S, Zou Z and Yu Y. UFL1 promotes antiviral immune response by maintaining STING stabil-

ity independent of UFMylation. Cell Death Differ 2023; 30: 16-26.
[32] Shu C, Ren C, Chen Q, Wang Y, Li R, Zhang Y, Yang S, Wang C and Li Y. Targeting inhibition of the inflammatory response: advances in the treatment of myocardial fibrosis with natural medicine and active ingredients. Front Cardiovasc Med 2025; 12: 1627255.
[33] Heurtaux T, Bouvier DS, Benani A, Helgueta Romero S, Frauenknecht KBM, Mittelbronn M and Sinkkonen L. Normal and pathological NRF2 signalling in the central nervous system. Antioxidants (Basel) 2022; 11: 1426.
[34] Liao Y, Li Z, Zhou Q, Sheng M, Qu Q, Shi Y, Yang J, Lv L, Dai X and Shi X. Saponin surfactants used in drug delivery systems: a new application for natural medicine components. Int J Pharm 2021; 603: 120709.
[35] Singha S, Agrawal S, Kumar A, Abbas H, Kumar A and Ranjan V. Computational pharmacology and pharmacokinetics of betanin: an integrated ADMET, SwissADME, DFT, and target prediction study. J Pharm Sci 2025; 114: 1-12.
[36] Soltani M, Parivar K, Baharara J, Kerachian MA and Asili J. Hemolytic and cytotoxic properties of saponin purified from Holothuria leucospilota sea cucumber. Rep Biochem Mol Biol 2014; 3: 43-50.
[37] Quan NV, Dang Xuan T and Teschke R. Potential hepatotoxins found in herbal medicinal products: a systematic review. Int J Mol Sci 2020; 21: 5011.
[38] Bi X, Wang Y, Wang J and Liu C. Machine learning for multi-target drug discovery: challenges and opportunities in systems pharmacology. Pharmaceutics 2025; 17: 1186.
[39] Khan MI, Karima G, Khan MZ, Shin JH and Kim JD. Therapeutic effects of saponins for the prevention and treatment of cancer by ameliorating inflammation and angiogenesis and inducing antioxidant and apoptotic effects in human cells. Int J Mol Sci 2022; 23: 10665.