

# Natural Multi-Target Synergistic Antimicrobial: Construction and Performance Research Review of *Sapindus* Extract Disinfection System

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**Abstract:** The prolonged use of conventional disinfectants has intensified microbial resistance, environmental persistence, and human-health concerns. Plant-derived alternatives that act through multi-target mechanisms offer a promising route to mitigate these issues. *Sapindus mukorossi* pericarp is rich in triterpenoid saponins that function as natural surfactants and exhibit broad-spectrum antimicrobial activity via membrane disruption, biofilm inhibition, and metabolic interference. When combined with nanomaterials or other botanical actives, these saponins display pronounced synergistic effects that further suppress resistance development. This review synthesizes recent advances in green extraction, nano-formulation, and synergistic formulation of *Sapindus* extracts, and maps their applications in neonatal and maternal care, clinical hygiene, and post-harvest preservation. Current bottlenecks in mechanistic elucidation, scale-up, and regulatory acceptance are discussed, together with future research directions aimed at commercializing robust, low-resistance natural disinfection technologies.

**Keywords:** *Sapindus* saponins; Multi-target synergistic antimicrobial; Natural disinfectants; Green extraction; Nanotechnology

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## 1. Introduction

With the significant enhancement of global public health awareness, the use of disinfectants in daily life and healthcare is increasingly widespread. However, traditional chemical disinfectants represented by quaternary ammonium salts and chlorine-containing disinfectants, due to their single target of action, easily lead to microbial resistance (such as the emergence of tolerant bacteria and superbugs)<sup>[1]</sup>; simultaneously, their irritation to human mucous membranes, potential sensitization, and persistent pollution to the ecological environment have also attracted widespread attention<sup>[2,3]</sup>. Against this backdrop, developing natural, plant-based disinfectants that are green, safe, efficient, and less prone to inducing microbial resistance has become a key research direction in scientific research and industry.

*Sapindus* (*Sapindus mukorossi* Gaertn.), as a traditional medicinal plant, its medicinal value was recorded early in the *Compendium of Materia Medica*, believed to have effects of “clearing heat and resolving phlegm, eliminating accumulation and killing insects.” Modern pharmacological research further reveals that “*Sapindus* saponins” rich in *Sapindus* pericarp are a class of structurally complex “triterpenoid saponin compounds” and are excellent natural non-ionic surfactants<sup>[4,5]</sup>. They not only have good detergency and foaming capabilities but are also confirmed to have multiple biological activities such as broad-spectrum antimicrobial, antiviral, anti-inflammatory, and antioxidant effects<sup>[6]</sup>.

Particularly crucially, *Sapindus* extracts, as a “multi-component natural complex system,” their antimicrobial activity is not reliant on a single compound or molecular target, but through the synergistic effects of multiple active components such as saponins, oleanolic acid, and flavonoids<sup>[7,15]</sup>, simultaneously disrupting multiple critical processes, including microbial membrane integrity, energy metabolism systems, and biofilm formation<sup>[8,9]</sup>. This “multi-target synergistic antimicrobial” mechanism can greatly increase the difficulty of microbial resistance development and is the core innovation point that subverts the limitations of traditional chemical disinfectants.

Although *Sapindus* demonstrates great potential in the natural disinfection field, its in-depth resource development still faces many challenges: on one hand, traditional extraction and purification processes have problems such as high energy consumption, low saponin purity, and easy destruction of heat-sensitive components; on the other hand, the inherent instability of natural products also restricts product shelf life and application effects<sup>[10]</sup>. Therefore, this paper aims to focus closely on the core advantage of “multi-target synergistic antimicrobial,” systematically reviewing the green preparation technology of *Sapindus* extracts, multiple antimicrobial mechanisms, disinfection system construction strategies, and their application prospects in multiple fields, aiming to provide a complete theoretical support and solution for overcoming technical bottlenecks such as low efficiency and poor stability of natural disinfection products and promoting their industrialization process.

## 2. Green extraction, purification, and stabilization technologies for *Sapindus* extracts

The primary step in constructing efficient and stable *Sapindus* natural disinfection systems is to achieve efficient, environmentally friendly extraction and long-term stability of their active components.

### 2.1. Main active components and their structural basis

The major bioactive constituents of *Sapindus* are triterpenoid saponins (e.g., Sapindoside A and B), composed of hydrophobic aglycones and hydrophilic sugar chains (Figure 1). These structurally diverse saponins, along with oleanolic acid, lupeol, and  $\beta$ -sitosterol, form a complex bioactive matrix that underpins their synergistic antimicrobial effects<sup>[6]</sup>.

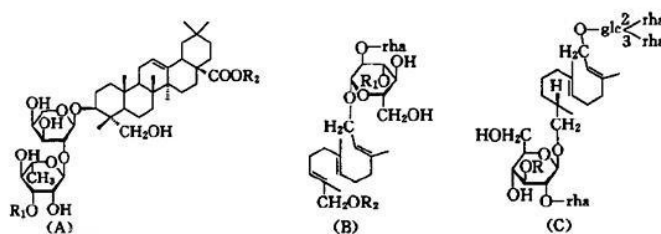


Figure 1. Saponin structure schematic diagram

According to the forestry industry standard (LY/T 3105—2019), *Sapindus* saponin products can be classified into saponin liquid (total saponin content  $\geq 160$  mg/g) and saponin powder (total saponin content  $\geq 38\%$ ). Additionally, *Sapindus* extracts also contain active components such as oleanolic acid, lupeol, and  $\beta$ -sitosterol, which together with saponins form a complex mixture of bioactive compounds that collectively enable multi-target synergistic effects <sup>[11]</sup>.

## 2.2. Application and development of green extraction and purification technologies

To overcome the drawbacks of solvent reflux methods, including excessive time consumption, high energy consumption, large organic solvent usage, and potential degradation of heat-sensitive saponins, a series of green extraction techniques have been developed and optimized for isolating *Sapindus* saponins.

**Ultrasound-assisted extraction:** This technology utilizes the cavitation effect generated by ultrasound to form localized high temperature and pressure in liquids, instantly breaking plant cell walls, thereby significantly improving the dissolution efficiency and rate of saponins, while allowing extraction at lower temperatures, effectively protecting heat-sensitive active components <sup>[12]</sup>.

**Microwave-assisted extraction:** Microwaves can selectively heat polar molecules (such as water and ethanol) internally, causing sudden increases in internal cell pressure leading to rupture, thereby achieving rapid and efficient extraction. This method offers significant advantages including uniform heating, fast speed, and low solvent consumption.

In terms of purification, macroporous adsorption resin methods (such as D101 resin) are commonly used and effective approaches for preparing high-purity *Sapindus* saponins, capable of significantly enriching saponin components and enhancing the activity of final products <sup>[13]</sup>.

## 2.3. Nano-stabilization and functionalization strategies

To address the problem of natural extracts being prone to degradation and inactivation due to light, heat, and oxygen exposure, resulting in short product shelf life, nanotechnology is considered a key solution <sup>[14]</sup>.

By constructing carriers such as nanoemulsions, liposomes, or polymer nanoparticles, *Sapindus* saponins can be encapsulated within protective shells <sup>[16]</sup>. This not only significantly improves their physicochemical stability and extends product shelf life but also enables controlled release of active components, enhancing their contact and interaction efficiency with microbial cell membranes, and even achieving targeted delivery. For example, studies have successfully utilized *Sapindus* extract itself as both reducing agent and stabilizer to prepare silver nanoparticles <sup>[17]</sup> with particle sizes ranging from 10–40 nm. This composite system demonstrates significant synergistic antimicrobial enhancement effects against *Escherichia coli*.

## 3. Systematic analysis of multi-target synergistic antimicrobial mechanisms

The antimicrobial action of *Sapindus* extracts is not a single pathway but rather a complex process involving multiple interconnected and synergistic pathways and links, which can be systematically summarized as follows:

### 3.1. Primary attack: Physical disruption of cell membrane integrity

As natural surfactants, *Sapindus* saponin molecules can insert their hydrophobic ends into microbial cell membranes (phospholipid bilayers) while exposing their hydrophilic ends to the aqueous phase. This insertion

behavior forms transient or permanent pores in the membrane, leading to irreversible leakage of small molecules (such as potassium ions) and macromolecules (such as proteins and nucleic acids) from within cells, causing osmotic imbalance and rapid cell death <sup>[18]</sup>. This physicochemically driven disruption occurs rapidly and, because it does not target specific metabolic enzymes or gene targets, microorganisms find it difficult to develop effective resistance through single gene mutations <sup>[1]</sup>.

### **3.2. Deep intervention: Inhibition of biofilm formation and interference with energy metabolism**

Inhibition and removal of biofilms: Biofilms serve as important barriers to bacterial and fungal resistance. In-depth studies have confirmed that *Sapindus* saponins can significantly reduce the surface hydrophobicity and adhesion of microorganisms such as *Candida albicans*, effectively preventing early biofilm formation. More importantly, even after biofilm maturation, higher concentrations of saponins can disrupt the extracellular polymeric substance (EPS) matrix, disintegrating the formed dense biofilm structure. Research indicates that 0.16 mg/mL of *Sapindus* saponins can inhibit early *Candida albicans* biofilm formation, while 0.64 mg/mL concentration can remove mature biofilms, with effects superior to those of fluconazole at the same concentration <sup>[19]</sup>.

Interference with cellular energy metabolism and enzyme activity: After disrupting membrane structure, saponin components can further enter bacterial cells, reducing pathogen glucose utilization <sup>[21]</sup> and inhibiting the activity of key metabolic enzymes such as ATP synthase and respiratory chain-related enzymes, thereby hindering energy (ATP) production and further affecting the synthesis of proteins, nucleic acids, and other vital substances, ultimately inhibiting microbial growth and reproduction from the root.

### **3.3. Synergistic enhancement: Networked antimicrobial action constructed by multi-components**

Different active components in *Sapindus* extracts, such as saponins and oleanolic acid, can produce significant synergistic effects. For example, saponins first disrupt the cell membrane barrier, increasing the probability and flux of other small molecule active components (such as oleanolic acid) entering cells, which then interfere with intracellular processes such as DNA replication or protein synthesis. This sequential mechanism—initial membrane disruption followed by intracellular interference—produces a synergistic antimicrobial effect greater than the sum of individual actions <sup>[20]</sup>. This multi-component, multi-target synergistic network requires microorganisms to simultaneously undergo multiple difficult or even impossible adaptive mutations to survive, greatly delaying the emergence and development of resistance.

## **4. Collaborative construction and performance optimization of *Sapindus* natural disinfection systems**

### **4.1. Innovative construction of synergistic composite systems**

To maximize antimicrobial efficacy, broaden antimicrobial spectrum <sup>[22]</sup> and reduce usage irritation, scientific compounding of *Sapindus* extracts with other natural active substances represents a key technical pathway.

Compounding with plant extracts: Research shows that *Sapindus* demonstrates strong synergistic effects with plant extracts <sup>[23]</sup> such as *Magnolia grandiflora* and *Schima superba* in inhibiting *Magnaporthe oryzae*. Similar principles can be extended to the disinfection field, for example, by compounding *Sapindus* saponins

with tea tree oil, *Melia azedarach* extracts, etc., to develop specialized disinfection or care products targeting specific pathogens (such as *Cutibacterium acnes*, *Malassezia*).

Composite with nanomaterials: As mentioned earlier, the preparation of nano-silver composite antimicrobial solutions using *Sapindus* extract represents a successful example <sup>[16]</sup>. In this process, *Sapindus* saponins serve as both reducing agents and stabilizers, producing synergy with nano-silver in attacking microbial cell membranes and generating reactive oxygen species (ROS), significantly enhancing the killing effect against Gram-negative bacteria such as *Escherichia coli*.

## 4.2. Broad-spectrum and high-efficiency antimicrobial performance

Numerous *in vitro* studies have confirmed that *Sapindus* extracts possess broad-spectrum and high-efficiency antimicrobial activity (Table 1). They show significant inhibitory effects <sup>[22]</sup> against Gram-positive bacteria (such as *Staphylococcus aureus*, *Bacillus subtilis*), Gram-negative bacteria (such as *Escherichia coli*, *Salmonella paratyphi B*), and fungi (such as *Candida albicans*, *Aspergillus niger*). Through quantitative evaluation using minimum inhibitory concentration (MIC) and bactericidal kinetic experiments, their efficacy is comparable to some chemical disinfectants and even superior to certain traditional antifungal drugs (such as fluconazole) in inhibiting and removing fungal biofilms.

**Table 1.** Examples of antimicrobial activity of *Sapindus* extracts against common microorganisms

Microorganism type	Representative pathogen	<i>Sapindus</i> extract activity performance
Gram-positive bacteria	<i>Staphylococcus aureus</i>	Significant growth inhibition
Gram-negative bacteria	<i>Escherichia coli</i>	Increased inhibition zone diameter (synergistic with nano-silver)
Fungi	<i>Candida albicans</i>	Inhibits biofilm formation, removes mature biofilms
Fungi	<i>Aspergillus niger</i>	Exhibits antimicrobial activity

## 5. Application prospects, core challenges, and future outlook

### 5.1. Multi-dimensional industrial application scenarios

Vertical deepening: Specialized disinfection products: Based on their high efficiency against specific pathogens, medical-grade environmental disinfectants and instrument rinsing solutions targeting multidrug-resistant bacteria (such as MRSA) in hospitals can be developed; or functional skincare products such as anti-acne cleansing foams and toners targeting *Cutibacterium acnes* can be developed.

Horizontal expansion: Series of daily and special products:

- (1) Maternal, infant, and pet care: Utilizing their natural mildness and low irritation characteristics, develop baby clothing disinfectants, toy cleaning sprays, pet shampoos, etc., to meet the needs of sensitive groups and special families.
- (2) Agriculture and food fields: Based on their anti-plant pathogen activity, develop natural soaking solutions or sprays for post-harvest preservation of fruits and vegetables, as well as biopesticides for organic crop cultivation.
- (3) Frontier integration: Intelligent responsive disinfection systems: Explore loading *Sapindus* nano-disinfection systems onto smart hydrogels, electrospun fiber membranes, or device surfaces to develop self-cleaning materials or intelligent disinfection equipment that can release active components in

response to microbial infection microenvironments (such as pH changes, enzyme activation).

## 5.2. Core challenges and future research directions

- (1) A more comprehensive understanding of the underlying mechanisms is still needed: Current understanding of “multi-target synergy” remains largely at the level of phenotypic observation and physiological/biochemical aspects <sup>[24]</sup>. Future research urgently needs to utilize technologies such as proteomics, metabolomics, and molecular dynamics simulation to directly identify specific protein targets of *Sapindus* saponins in pathogen cells <sup>[25]</sup>, accurately mapping the molecular networks and regulatory pathways of their synergistic actions.
- (2) Industrial scaling bottlenecks for green technologies: Ultrasound and microwave-assisted extraction, as well as nanoencapsulation technologies, have matured at the laboratory level [12,26], but when transitioning to large-scale continuous production, numerous engineering and technical challenges remain to be overcome in terms of equipment scaling, energy consumption control, process stability, and production costs.
- (3) Standardization system construction and regulatory support: The chemical composition of natural products is affected by factors such as origin and season, leading to batch variability, which poses challenges for product quality consistency control. It is necessary to establish a full-chain quality control system and standards from GAP cultivation of *Sapindus* raw materials to terminal products, and to promote regulatory agencies to establish and improve review and approval regulations for such novel plant-derived disinfection products.

## 6. Conclusion

*Sapindus* extracts, with their multi-component composition and unique multi-target synergistic antimicrobial mechanism, provide a highly promising green solution that aligns with sustainable development concepts for addressing the three core problems associated with chemical disinfectants: drug resistance, safety, and environmental pollution. By integrating green extraction and purification technologies, scientific compounding and nano-composite strategies, and advanced stabilization processes, it is possible to effectively construct an efficient, stable, safe, and resistance-resistant natural disinfection system. Although challenges remain in deep analysis of molecular mechanisms, industrial scale-up production, and standardization construction, with continuous deepening of interdisciplinary research and continuous progress in engineering technologies, *Sapindus*-based natural disinfection products are expected to achieve large-scale applications in multiple fields such as daily chemicals, medical care, agriculture, and food, ultimately fostering a sustainable balance between public health, environmental protection, and industrial innovation.

## Disclosure statement

The authors declare no conflict of interest.

## Author contributions

Yiqing Chen integrated materials and wrote this paper. Chenxi Wei was responsible for data collection. Jiaqi

Liu performed the translation of the paper. Zhi Li conceived the idea of the study and reviewed this paper.

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