Pharmacy Reports

https://doi.org/10.51511/pr.86

REVIEW

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The pharmacological potential of sappan wood (*Caesalpinia sappan* L.): A review of recent evidence

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Abstract: Sappan wood (*Caesalpinia sappan* L.) has been used in traditional Asian medicine for centuries, but its pharmacological properties have only recently been systematically investigated using modern scientific methods. This review aims to synthesize current research on the pharmacological activities of sappan wood and assess its potential for development into evidence-based therapeutic applications. A systematic literature search following PRISMA 2020 guidelines was conducted in ScienceDirect and PubMed databases using specific keywords. Articles published between 2014-2024 investigating the pharmacological properties of sappan wood were included, yielding nine studies for qualitative analysis. Evidence demonstrates that sappan wood possesses significant anti-inflammatory, antibacterial, antioxidant, wound healing, antidiabetic, and anti-HIV properties. Brazilin emerges as a key bioactive compound, though synergistic effects among multiple constituents enhance certain activities. Multiple mechanisms of action were identified, including inhibition of pro-inflammatory cytokines, antibacterial effects against both Gram-positive and Gram-negative bacteria, and activation of antioxidant pathways. Sappan wood shows promising potential as a source of natural pharmacological agents with diverse therapeutic applications. Future research should focus on clinical validation, standardization of extracts, and elucidation of molecular mechanisms to facilitate its integration into modern healthcare.

Keywords: Caesalpinia sappan, brazilin, anti-inflammatory, antibacterial, natural product pharmacology

Introduction

Sappan wood (*Caesalpinia sappan* L.), also known as Brazilwood or Suou, is a medicinal plant belonging to the Fabaceae family that has been utilized for centuries throughout Southeast and South Asia, particularly in Malaysia, Indonesia, India, and China [1]. Historically valued as a natural red dye source before the advent of synthetic alternatives, sappan wood has maintained cultural and medicinal significance across various Asian traditional medicine systems.

In traditional medicine, sappan wood is typically prepared by decoction, where the heartwood is boiled in water to extract its therapeutic compounds. These preparations have been used to treat a diverse range of conditions including skin diseases, wounds, ulcers, diarrhea, dysentery, diabetes, and inflammatory disorders [2]. The longstanding use of sappan wood in traditional healing practices suggests inherent pharmacological properties worthy of scientific investigation.

Phytochemical analyses have revealed that sappan wood contains numerous bioactive constituents including homoisoflavonoids, flavonoids, phenolic compounds, triterpenoids, steroids, alkaloids, saponins, and tannins. Among these, brazilin and its oxidized derivative brazilein stand out as the principal bioactive compounds belonging to the homoisoflavone group [3,4]. Additional specific compounds identified include sappanchalcone, sappanone B, caesalpin J, and protosappanin A, which contribute to the plant's diverse pharmacological activities.

Contemporary scientific research has begun to validate many of the traditional medicinal uses of sappan wood through systematic investigation of its pharmacological properties. Studies have demonstrated antioxidant [5], anticancer, antimicrobial, anti-inflammatory [3], and antidiabetic [6]. This pharmacological potential provides more significant opportunities for developing effective and safe natural medicines made from sappan wood.

Despite this promising research, several knowledge gaps remain. The mechanisms of action for many of sappan wood's therapeutic effects are not fully elucidated, optimal extraction methods have not been standardized, and clinical studies validating preclinical findings are limited. Furthermore, synergistic interactions between compounds in sappan wood extracts require further investigation, as evidence suggests that whole extracts sometimes exhibit greater efficacy than isolated compounds.

In an era where antimicrobial resistance, chronic inflammatory conditions, and metabolic disorders pose significant public health challenges, natural products with multifaceted pharmacological properties represent valuable resources for drug discovery and development. This review aims to provide a comprehensive analysis of current research (2014-2024) on the pharmacological activities of sappan wood, examining the methodologies and outcomes of key studies, identifying mechanistic insights, and highlighting promising directions for future research. By synthesizing this evidence, we seek to advance understanding of sappan wood's therapeutic potential and facilitate its integration into evidence-based pharmaceutical applications and modern healthcare practices.

Methods

This narrative review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) 2020 framework to minimize bias and ensure methodological rigor. The study followed a structured approach comprising four main phases: identification, screening, eligibility assessment, and inclusion.

Search strategy and information sources

A comprehensive literature search was performed using two reputable scientific databases: ScienceDirect (https://www.sciencedirect.com/) and PubMed (https://pmc.ncbi.nlm.nih.gov/). The search was conducted using the following keyword combination: "*Caesalpinia sappan*" AND "pharmacology" AND ("Stem" OR "bark" OR "wood"). The search was restricted to publications from January 2014 to October 29, 2024.

Study selection process

The identified articles were imported into Zotero software (version 6.0.36) for systematic management and deduplication. Following the PRISMA guidelines, articles were screened based on predetermined inclusion criteria: (i) original research articles published in peer-reviewed journals, (ii) studies investigating pharmacological effects of extracts derived from sappan wood (*Caesalpinia sappan* L.), (iii) articles published in English, (iv) in vivo, in vitro, or in silico studies with clear methodological descriptions.

Exclusion criteria included: (i) review articles, conference abstracts, and book chapters, (ii) studies focusing on plants other than *Caesalpinia sappan* L., (iii) studies investigating only the phytochemical composition without pharmacological evaluation, (iv) articles not accessible in full text

Data extraction and analysis

From each included study, the following data were systematically extracted: (i) pharmacological effects investigated, (ii) study type (in vivo, in vitro, or in silico), (iii) test models and experimental subjects, (iv) test substances and their concentrations, (v) key findings and outcomes, (vi) methodological approaches. The extracted data were organized into a comprehensive table to facilitate comparison across studies and identification of patterns in the pharmacological properties of sappan wood.

Figure 1 presents the PRISMA flow diagram illustrating the literature identification, screening, eligibility assessment, and final inclusion process that resulted in nine articles meeting all criteria for qualitative synthesis.

Results

The analysis results from the nine selected journal articles were used to identify the pharmacological effects of sappan wood (*Caesalpinia sappan* L.) in preclinical and clinical trials conducted between 2014 and 2024. The results are presented in Table 1, which includes the core assays and key findings from each study.

The selected studies demonstrate that sappan wood exhibits diverse pharmacological activities. Sugiaman et al. (2024) [7] found that sappan wood extract cream has significant anti-inflammatory activity in *Porphyromonas gingivalis*-induced gingivitis rat models, evidenced by decreased NF-kB protein expression and reduced expression of pro-inflammatory genes (TNF-α, IL-1β, IL-6, and P38). Their histological examinations showed

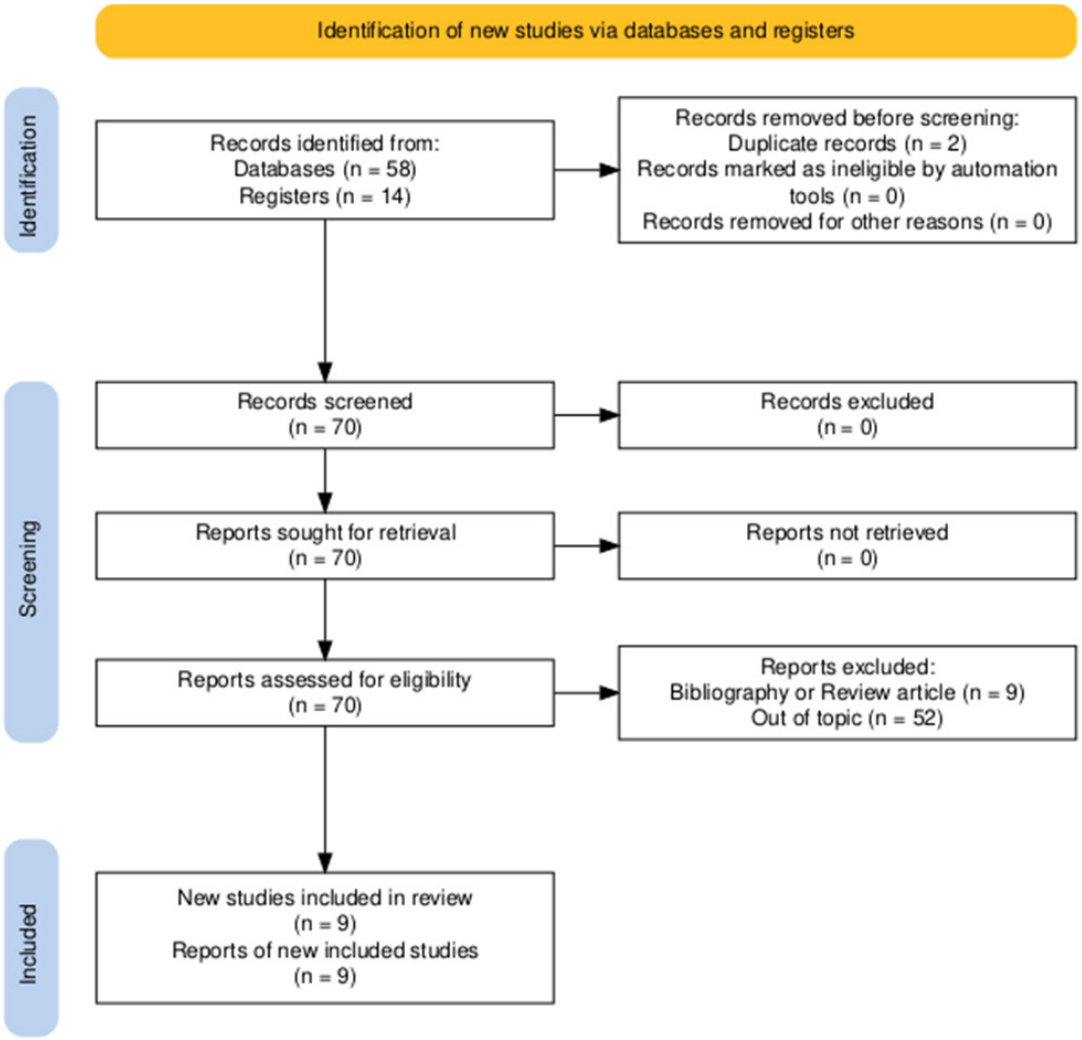

Figure 1. PRISMA diagram of analysis of sappan wood as a pharmacological agent

increased collagen density and angiogenesis, with lower inflammation scores after treatment with sappan wood extract cream.

Nirmal and Panichayupakaranant (2015) [8] demonstrated that brazilin-rich extract (BRE) of sappan wood possesses significant anti-inflammatory activity through protein denaturation inhibition, with as little as 0.1 μg/mL concentration inhibiting protein denaturation by 54.1%. The same study also confirmed antioxidant properties of BRE using three different methods (DPPH radical scavenging, reducing power, and β-carotene bleaching assays), with BRE showing antioxidant activity comparable to pure brazilin.

Bukke et al. (2015) [9] evaluated the antibacterial activity of different parts of sappan wood extracted with various solvents. Their findings revealed that the heart wood extracts exhibited the highest antibacterial activity against tested bacterial strains, with methanol extracts showing maximum inhibition zones against *Klebsiella pneumoniae* (30.3 mm) and *Bacillus subtilis* (27.3 mm).

Puttipan et al. (2018) [10] identified brazilin as the major active compound in sappan wood's ethanolic fractionated extract (F-EtOH), showing significant inhibition against *Streptococcus mutans* biofilm formation. Chukiatsiri et al. (2024) [11] demonstrated that sappan wood extract could effectively treat *Escherichia coli* infection in piglets, with the extract inhibiting *E. coli* growth at a minimal inhibition concentration (MIC) of 16-34 mg/ml, performing similarly to the antibiotic enrofloxacin.

Hwang and Shim (2018) [12] found that both sappan wood extract and its major compound, brazilin, protected human epidermal keratinocytes from UVA-induced oxidative stress via glutathione peroxidase 7 (GPX7) activation, suggesting potential applications

Table 1. Pharmacological effect studies of sappan wood based on publications 2014-2024

Pharmacological effects	Study type	Test model	Test substance	Result	Reference
Anti inflammatory	In vivo	Male mice induced with *Porphyromonas gingivalis* bacteria	Cream with 60 mg ethanol extract of sappan wood; topical; applied once and twice daily for 14 days	Sappan wood ethanol extract, especially the cream given twice a day, can reduce inflammation and improve blood vessel formation.	[7]
	In vitro	Antidenutiration activity using Bovine Serum Albumin 0,2%	Brazilin, BRE (Brazilin-Rich Extract), and CSE (C. sappan ethanol extract) with concentrations of 0.1-5 µg/mL	Brazilin, BRE, and CSE were predicted to have anti-inflammatory activity with 50% inhibition at a 0.1 µg/mL concentration.	[8]
Antibacterial	In vitro	Gram-positive: *Bacillus subtilis* Gram-negative: *Klebsiella pneumonia, Escherichia coli*	Petroleum ether, chloroform, methanol, and water extracts of the heartwood, leaves, bark, and seeds of sappan wood at a concentration of 5 mg/mL; Incubation for 18-24 hours.	All solvents in sappan wood kernel extract had more potent antibacterial activity than other plant parts of sappan wood.	[9]
	In vitro	Gram-positive: *Staphylococcus aureus dan Staphylococcu epidermidis* Gram-negative: *Escherichia coli, Pseudomonas aeruginosa, dan Salmonella typhimurium*	Brazilin, BRE (Brazilin-Rich Extract), dan CSE (*C. sappan* ethanol extract)	Brazilin, BRE, and CSE can inhibit DNA and protein synthesis in cells	[8]
	In vitro	*Streptococcus mutan*	Hexane, ethyl acetate, and ethanol extracts of sappan wood	Sappan wood extract has potential antibacterial activity	[10]
	In vivo	Piglets with diarrhea due to *Escherichia coli* infection	Sappan wood extract at a dose of 500 mg/kg; peroral	Sappan wood extract is thought to have antibacterial activity at a concentration of 1%	[11]
Antioxidant	In vitro	DPPH assay, Reducing power assay, β-carotene bleaching assay	Brazilin, BRE (Brazilin-Rich Extract), dan CSE (*C. sappan* ethanol extract)	Sappan wood extract has potential antioxidant activity	[8]
	In vitro	Normal human epidermal keratinocytes (NHEKs) exposed to UVA radiation	Caesalpinia sappan L. (CSL) extract at 20 µg/mL and brazilin at 1 µg/mL concentration.	Sappan wood extract and brazilin have the potential to reduce oxidative stress.	[12]
Antidiabetes	In silico	Binding analysis with network pharmacology approach	Phytochemicals of sappan wood Type 2 Diabetes Mellitus (T2DM)-related proteins (PPARG, PPARA, PPARD, FABP3, FABP4, MMP1, NR1H3)	The compound fisetin has a strong potential to be an antidiabetic agent. This is indicated by binding solid affinity	[13]
Anti-HIV	In silico	Binding analysis by molecular docking	3-Deoxysappanchalcone; Sappanchalcone; 3R-(3,4-Dihydroxybenzyl)-7-hydroxychroman-4-one; Episappol; 4-O-Methylepisappol; 4-O-Methylsappanol; 4-(7-Hydroxy-2,2-dimethyl-9 β H-1,3,5-trioxa-cyclopenta [α]naphthalen-3 α-ylmethyl)-benzene-1,2-diol; Brazilin; Protosappanin A	Sappanchalcone has potent inhibitory activity against HIV-1 integrase.	[14]
Wound Healing	In vivo	Wound size, histology, and Evaluation of IL-2 cytokine levels in male rats	Sappan wood ethanol extract with concentrations of 6.5%, 15%, 30%	Ethanol extract with a concentration of 6.5% has the highest potential wound healing activity	[15]

for treating oxidative stress-induced photoaging of skin.

Adnan et al. (2022) [13] employed a network pharmacology approach to identify fisetin tetramethyl ether as a key chemical compound in sappan wood methanol extract with potential anti-diabetic properties. Their molecular docking and quantum chemistry analysis revealed this compound's strong binding affinity with type-2 diabetes mellitus (T2DM) associated signaling pathways and target receptors, particularly the peroxisome proliferator-activated receptor gamma (PPARG).

Tewtrakul et al. (2015) [14] isolated nine compounds from sappan wood and tested them for anti-HIV-1 integrase activity, finding that sappanchalcone displayed the strongest inhibitory effect with an IC_{50} value of 2.3 μM, followed by protosappanin A (IC_{50} = 12.6 μM).

Sucita et al. (2024) [15] investigated sappan wood extract's efficacy in wound healing, testing different concentrations (6.5%, 15%, and 30%) on incision wounds in albino rats. Their results showed that all treatment groups exhibited significant improvement in wound healing parameters (collagen deposition, reduced polymorphonuclear neutrophils, increased angiogenesis, and improved fibrosis degree) compared to control groups, with the 6.5% concentration demonstrating the most significant wound healing activity.

Anti-inflammatory activity

Sappan wood demonstrates significant anti-inflammatory properties as evidenced by Sugiaman et al. (2024) [7], whose in vivo study on rats with *P. gingivalis*-induced gingivitis showed that sappan wood extract cream reduced the expression of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) while increasing collagen density and angiogenesis in gingival tissue. This anti-inflammatory effect was observed through multiple assessment methods, including histological examination, immunohistochemistry for NF-kB protein expression, and quantitative real-time PCR for measuring cytokine gene expression.

The in vitro findings of Nirmal and Panichayupakaranant (2015) [8] further support sappan wood's anti-inflammatory potential through a different mechanism. Their study demonstrated that sappan wood extracts (CSE), brazilin-rich extract (BRE), and pure brazilin could inhibit protein denaturation at concentrations as low as 0.1 μg/mL. This is particularly significant because protein denaturation is a well-documented cause of inflammation, and compounds that can prevent this process are considered to have anti-inflammatory properties. Notably, the inhibition percentages at 0.1 μg/mL were 61.9% for CSE, 54.1% for BRE, and 46.8% for brazilin, suggesting that compounds in the extract may work synergistically to provide enhanced anti-inflammatory effects compared to isolated brazilin.

The collective evidence from both in vivo and in vitro studies suggests that sappan wood extracts could be valuable natural anti-inflammatory agents with potential applications in treating various inflammatory conditions. The multiple mechanisms of action—including cytokine suppression, NF-kB pathway inhibition, and protein denaturation prevention—indicate a comprehensive anti-inflammatory profile that merits further investigation in clinical settings.

Antibacterial activity

Sappan wood exhibits potent antibacterial properties against both Gram-positive and Gram-negative bacteria. Bukke et al. (2015) [9] demonstrated that heart wood extracts showed superior antibacterial activity compared to extracts from other plant parts, with methanol extracts particularly effective against *K. pneumoniae* and *B. subtilis*. Their study revealed that different extraction solvents yielded different activity levels, with methanol and chloroform extracts generally showing higher inhibition zones than petroleum ether extracts, suggesting that the choice of solvent significantly influences the extraction of active antibacterial compounds.

Nirmal and Panichayupakaranant (2015) [8] observed that Gram-positive bacteria (*S. aureus* and *S. epidermidis*) were more susceptible to sappan wood extracts than Gram-negative bacteria (*E. coli*, *P. aeruginosa*, and *S. typhimurium*). Their study established minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values, providing quantitative evidence of sappan wood's antibacterial efficacy. The research suggested that brazilin plays a crucial role in the antibacterial activity of sappan wood extracts, likely through inhibition of bacterial DNA and protein synthesis.

Puttipan et al. (2018) [10] specifically investigated sappan wood's activity against oral pathogens, finding that ethanolic fractionated extract (F-EtOH) effectively inhibited *Streptococcus mutans* biofilm formation. This

is particularly relevant for potential dental applications, as *S. mutans* is a primary causative agent of dental caries.

The in vivo study by Chukiatsiri et al. (2024) [11] translated these laboratory findings to a clinical application, demonstrating that sappan wood extract effectively treated *E. coli* infections in piglets with results comparable to conventional antibiotics. This research provides valuable evidence for sappan wood's potential use as an alternative to antibiotics in veterinary medicine, which is increasingly important in the context of rising antimicrobial resistance.

The consistent antibacterial efficacy demonstrated across multiple studies against diverse bacterial species suggests that sappan wood could be a promising source of natural antibacterial agents for both human and veterinary applications.

Antioxidant activity

Sappan wood has demonstrated significant antioxidant properties through multiple testing methodologies. Nirmal and Panichayupakaranant (2015) [8] employed three distinct assays—DPPH radical scavenging, reducing power, and β-carotene bleaching—to comprehensively evaluate the antioxidant capacity of brazilin and sappan wood extracts. In the DPPH assay, while pure brazilin showed activity comparable to quercetin (a known potent antioxidant), the brazilin-rich extract (BRE) exhibited substantial activity despite containing only 39% brazilin, suggesting synergistic effects among compounds in the extract.

The biological relevance of these antioxidant properties was demonstrated by Hwang and Shim (2018) [12], that found that both sappan wood extract and brazilin protected human epidermal keratinocytes against UVA-induced oxidative stress. Their study revealed a specific mechanism—the activation of glutathione peroxidase 7 (GPX7)—through which sappan wood components reduce reactive oxygen species production. This finding is significant as it connects sappan wood's antioxidant activity to a specific cellular pathway involved in protecting against photoaging and oxidative damage.

The established antioxidant properties of sappan wood suggest potential applications in dermatological products, anti-aging formulations, and preventive healthcare. The combination of multiple antioxidant mechanisms indicates a broad-spectrum protective effect that could be valuable in conditions associated with oxidative stress.

Antidiabetes potential

The antidiabetic potential of sappan wood has been investigated through advanced computational approaches by Adnan et al. (2022) [13]. Their network pharmacology study identified fisetin tetramethyl ether as a key bioactive compound with strong binding affinity to type-2 diabetes mellitus (T2DM) associated proteins, particularly peroxisome proliferator-activated receptor gamma (PPARG). The computational analysis suggested that this compound could potentially activate the PPAR signaling pathway, which plays a crucial role in glucose metabolism and insulin sensitivity.

What makes this finding promising is that the binding affinity of fisetin tetramethyl ether exceeded that of metformin, a conventional first-line medication for T2DM treatment. This computational evidence provides a strong rationale for further experimental validation of sappan wood's antidiabetic properties and the development of fisetin tetramethyl ether as a potential therapeutic agent.

While this research remains at the computational stage, it highlights a promising direction for future experimental and clinical studies on sappan wood's antidiabetic activity. The identification of specific compounds and target proteins offers a mechanistic understanding that could facilitate more targeted approaches in developing sappan wood-based antidiabetic formulations.

Anti-HIV activity

Tewtrakul et al. (2015) [14] made contributions to understanding sappan wood's anti-HIV potential by isolating and testing nine compounds for their activity against HIV-1 integrase (IN), an essential enzyme in the HIV lifecycle. Their findings revealed that sappanchalcone exhibited the most potent inhibitory effect with an IC_{50} value of 2.3 μM, followed by protosappanin A (12.6 μM). The structure-activity relationship analysis identified the vicinal hydroxyl moiety as essential for anti-HIV-1 integrase activity, providing valuable insights for potential drug development.

The molecular docking studies further elucidated the binding mechanisms of these compounds with the HIV-1 integrase enzyme. Sappanchalcone was found

to interact with specific amino acid residues in the core domain of the enzyme, explaining its inhibitory potency. The comparable activity of sappanchalcone to suramin, a known HIV-1 integrase inhibitor, underscores the potential of sappan wood compounds as candidates for antiretroviral therapy development.

While further validation through in vivo studies and clinical trials is necessary, these findings establish a scientific basis for exploring sappan wood compounds in the development of novel anti-HIV agents, which remains an important research area given the ongoing challenges in HIV treatment.

Wound healing properties

The wound healing potential of sappan wood was comprehensively investigated by Sucita et al. (2024) through an in vivo study on incision wounds in albino rats [15]. Their research tested three different concentrations of sappan wood ethanol extract (6.5%, 15%, and 30%) applied topically twice daily for 15 days. Multiple parameters were evaluated, including collagen deposition, inflammatory cell infiltration, angiogenesis, fibrosis degree, and IL-2 levels, providing a thorough assessment of the wound healing process.

Interestingly, while all three concentrations showed significant improvement in wound healing parameters compared to control groups, the lowest concentration (6.5%) demonstrated the most significant efficacy. This non-linear dose-response suggests an optimal concentration range for wound healing applications, which is valuable information for potential formulation development.

The observed effects on multiple aspects of wound healing—including anti-inflammatory action, enhancement of collagen deposition, promotion of angiogenesis, and modulation of cytokine responses—indicate a comprehensive wound healing profile. These multifaceted effects align with the other pharmacological properties of sappan wood discussed earlier, particularly its anti-inflammatory and antioxidant activities, which likely contribute to its wound healing efficacy.

The wound healing properties of sappan wood extract offer promising applications in dermatology and wound care, with potential for development into topical formulations for various wound types. Further research could explore specific formulations, stability, and efficacy in different wound models to optimize its therapeutic potential.

Conclusion

This study shows that sappan wood extract has diverse pharmacological potential. This is demonstrated by several preclinical studies that investigated its pharmacological activities, such as anti-inflammatory, antibacterial, antioxidant, antidiabetic, anti-HIV, and wound healing properties. However, further research is needed to test the pharmacological mechanisms of the main active compounds of sappan wood in human clinical trials. Additionally, chronic toxicity studies are necessary to ensure its safety for long-term use.

Acknowledgment

The authors gratefully acknowledge the individuals and institutions who contributed to the completion of this review article. Their thoughtful feedback and constructive criticism substantially enhanced the quality of this work. We extend our sincere appreciation to our peers and colleagues for their support and intellectual exchanges throughout this project.

Declaration of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

Conceptualization: KTW; Methodology: KTW; Investigation: KRDY, LW; Data Curation: KRDY; Formal Analysis: KTW, LW; Visualization: LW; Writing - Original Draft: KTW; Writing - Review & Editing: KTW, GBO; Supervision: GBO; Project Administration: KTW.

Received: November 25, 2024
Revised: December 17, 2024
Accepted: January 1, 2025
Published: February 1, 2025

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