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Research Article

Exploring the multifaceted pharmaceutical and medicinal applications of Cashew nut shell liquid (CNSL): Antimicrobial, anti-inflammatory and drug delivery potential

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Abstract
Cashew Nut Shell Liquid (CNSL) is a renewable phenolic lipid mixture obtained from the cashew nut pericarp and composed primarily of anacardic acids, cardanols, and cardols. These constituents have attracted interest due to reported antimicrobial, anti-inflammatory, antioxidant, and drug-delivery properties; however, published evidence remains largely descriptive, heterogeneous, and predominantly preclinical. The present review aims to provide a critical, quantitative evaluation of the pharmaceutical potential of CNSL by distinguishing natural and synthetic CNSL chemotypes, benchmarking bioactivity against standard drugs, reconciling safety with dose-dependent toxicity, and assessing translational and standardisation barriers. A structured literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar (2000 - 2025) using predefined keywords and inclusion criteria. Eligible studies were analysed for experimental model, concentration, comparator, and quantitative outcomes (MIC, IC_{50}, selectivity index, toxicity metrics). Reported antimicrobial activities of anacardic acid show MIC values typically in the range of 8-128 µg/mL against Gram-positive bacteria, compared with <2 µg/mL for standard antibiotics, indicating moderate potency. Anti-inflammatory effects occur at micromolar IC_{50} levels but often overlap with cytotoxic concentrations, suggesting a narrow therapeutic window. Considerable variability in extract composition and the absence of standardized formulations limit reproducibility. No completed human clinical trials were identified. CNSL should be regarded not as an established therapeutic alternative but as a promising bioactive scaffold for formulation and medicinal chemistry optimization. This review provides methodological transparency, quantitative benchmarking, and critical appraisal to guide rational development of CNSL-based pharmaceutical systems.

Keywords: *Anacardium occidentale*, Antimicrobial resistance, CNSL, Drug delivery systems, Therapeutic potential, Toxicity

INTRODUCTION

Cashew (*Anacardium occidentale*) is a tropical plant, native to Northeastern Brazil (Tamiello-Rosa *et al*., 2019) but now cultivated in many parts of the world, including India, Vietnam, and Africa (Sruthi *and* Naidu, 2023). Cashew is an evergreen tree that produces cashew nuts and cashew apples, both recognized for

their nutritional benefits and diverse industrial and medicinal uses (Emmanuel *et al*., 2025). The cashew nut is commonly consumed as a popular snack and is widely incorporated into a variety of culinary preparations (Aslam *et al.*, 2024) CNSL, a valuable by-product obtained during cashew nut processing, has attracted considerable interest due to its bioactive nature and diverse pharmaceutical, medicinal, and industrial applications (Sneha *et al.*, 2024). CNSL consists of a complex mixture of phenolic constituents, predominantly anacardic acids, cardanol, and cardol (Basiouni *et al.*, 2025).

It is important to distinguish between natural or raw CNSL, which is rich in anacardic acids, and technical CNSL, which contains higher levels of cardanol due to thermal decarboxylation. This distinction is crucial, as the biological activities of these forms differ significantly and influence their potential therapeutic applications. These phenolic compounds exhibit antimicrobial, anti-inflammatory, and antioxidant properties (Salehi *et al*., 2020). However, the therapeutic use of CNSL requires careful evaluation, as anacardic acids can cause skin irritation and cytotoxicity at elevated concentrations. Hence, the biocompatibility and safety of CNSL are dose-dependent and strongly influenced by formulation and processing methods. Processed CNSL has found wide application in pharmaceutical and industrial sectors, particularly in the manufacture of adhesives, coatings, lubricants, and drug delivery systems (Uliassi *et al*., 2021). The pharmacological potential of CNSL extends across a broad range of biological activities, particularly antimicrobial and antifungal effects. Studies have reported its effectiveness against important pathogenic microorganisms such as *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, many of which exhibit increasing resistance to conventional antimicrobial agents (Tejada-Muñoz *et al.*, 2024). Reported Minimum Inhibitory Concentration (MIC) values generally range from 20–100 µg/mL, depending on the type of CNSL and the extraction techniques employed (Ashraf and Rathinasamy, 2018), underscoring the importance of standardised processing methods.Beyond antimicrobial activity, CNSL also demonstrates notable anti-inflammatory and analgesic properties. Chronic inflammatory disorders, including rheumatoid arthritis and autoimmune diseases, often require prolonged administration of non-steroidal anti-inflammatory drugs (NSAIDs), which may lead to adverse side effects (Gautier Roko *et al.*, 2024). Phenolic constituents present in CNSL have been shown to suppress pro-inflammatory mediators such as cyclooxygenase-2 (COX-2) and prostaglandins, thereby contributing to its therapeutic potential (Gomes *et al*., 2020; Gisele *et al.*, 2021). However, it is important to note that most of these findings are derived from *In vitro* studies and experimental animal models, and definitive clinical evidence supporting efficacy in humans remains limited. In addition to its pharmacological properties, CNSL has shown promising potential as a drug delivery material, particularly for enhancing the delivery and bioavailability of poorly soluble hydrophilic and lipophilic drugs (León *et al*., 2025). The unique chemical structure of CNSL enables the formation of micellar systems and its incorporation into nanoparticles and liposomal carriers, thereby enhancing oral bioavailability and facilitating controlled drug release (Bloise *et al.*, 2023). However, the mechanisms underlying improved bioavailability remain largely hypothetical, as poorly soluble anacardic acids often require chemical modification or encapsulation strategies to reduce gastric irritation and improve absorption efficiency. Comparative investigations with established delivery platforms, such as PEGylated liposomes and PLGA-based nanoparticles, are necessary to critically evaluate the advantages of CNSL as a drug carrier.

The growing prevalence of antibiotic-resistant microorganisms has accelerated the search for alternative antimicrobial agents. CNSL represents a promising natural resource in this context; however, its therapeutic potential must be systematically benchmarked against conventional antibiotics, including vancomycin and ciprofloxacin, by evaluating minimum inhibitory concentrations, cytotoxicity profiles, and selectivity indices to define an appropriate therapeutic window. Likewise, prolonged use of NSAIDs and corticosteroids for inflammatory disorders is associated with significant adverse effects (Placha *et al.*, 2021), encouraging exploration of safer bioactive alternatives. CNSL exhibits considerable versatility as an antimicrobial, anti-inflammatory, antioxidant, and drug-delivery material, as demonstrated in numerous preclinical studies (Ashong *et al.*, 2025). Despite these promising findings, it is important to recognise that most evidence comes from i*n vitro* experiments and animal models, and clinical validation in humans remains limited. Future research should therefore prioritise standardised extraction procedures, comprehensive dose-dependent safety assessments, quantitative comparisons with established therapeutics, and detailed mechanistic investigations to substantiate the therapeutic potential of CNSL.

METHODOLOGY

To ensure transparency and reproducibility, and to minimise selection bias, this review followed a structured, systematic literature search strategy. Electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, were comprehensively searched to identify biomedical, pharmaceutical, chemical, and materials science studies on cashew nut shell liquid (CNSL) and its derivatives. The search covered publications from 2000 to 2025 to reflect contemporary ad-

vances in nanotechnology, drug delivery, and pharmacological applications. Boolean combinations of predefined keywords were used, including: (cashew nut shell liquid or CNSL or anacardic acid or cardanol or cardol) and (drug delivery or nanoparticles or antimicrobial or anti-inflammatory or antioxidant or anticancer or toxicity or biocompatibility or pharmacokinetics or formulation). Additional manual searches of the reference lists of key articles were conducted to identify relevant studies not captured by database queries. Studies were included if they met the following criteria: (i) peer-reviewed original research articles or systematic reviews, (ii) reports containing experimental or quantitative biological, pharmaceutical, or toxicological data on CNSL or its isolated constituents, and (iii) studies directly related to therapeutic, drug delivery, or biomedical applications. Exclusion criteria comprised non-English publications, conference abstracts lacking full datasets, patents, duplicate records, purely industrial or non-biomedical reports, and studies without methodological clarity or measurable outcomes. The screening process was conducted in three stages. First, titles were examined to remove irrelevant topics. Second, abstracts were assessed for relevance to CNSL chemistry, pharmacology, or formulation science. Third, full texts were evaluated for methodological rigour, characterisation of extracts, and availability of quantitative metrics (e.g., MIC, IC□□, cytotoxicity indices, dose–response data, or encapsulation efficiency). Only studies meeting these criteria were included in the final synthesis. This systematic and stepwise approach enhances the reliability of the evidence base, reduces potential bias in study selection, and strengthens the critical and quantitative evaluation presented in this review.

STATUS OF CNSL IN PHARMACEUTICAL AND MEDICINAL APPLICATIONS

Traditional use and recognition

CNSL has traditionally been valued for its medicinal applications, particularly in rural communities, where it has been used to treat skin infections, inflammatory conditions, and wounds (Rakesh *et al.*, 2024). The incorporation of CNSL into folk medicine practices is largely attributed to its local availability and the presence of naturally occurring bioactive phenolic constituents (Bloise *et al.*, 2023). With recent advances in phytochemical and pharmaceutical research, increasing attention has been directed toward translating these traditional uses into scientifically validated therapeutic applications within the modern pharmaceutical sector. CNSL exists in chemically distinct forms depending on the extraction technique employed. Natural CNSL, obtained through cold pressing or solvent extraction methods, primarily contains anacardic acids (60 - 70%), along with cardol (15 - 20%) and minor quantities of cardanol (5 - 10%). In contrast, technical CNSL produced by thermal roasting or conventional industrial processing contains higher concentrations of cardanol (60-65%) and its polymerised derivatives, while anacardic acid levels decrease due to heat-induced decarboxylation (Bhatia *et al.*, 2024).

Research and development

India has emerged as a significant center for research on bioactive compounds derived from natural resources, including CNSL. Several research institutions and universities are actively investigating its antimicrobial, anti-inflammatory, and antioxidant properties. Current studies indicate promising applications of CNSL in topical formulations for wound healing, antifungal treatments, and anti-inflammatory therapeutics (Nayak *et al.*, 2024). Furthermore, advanced drug-delivery strategies, such as liposomal systems and nanotechnology-based carriers, are being explored to enhance the stability, bioavailability, and therapeutic efficacy of CNSL formulations (Patel *et al.*, 2024). Phenolic constituents of CNSL exhibit broad-spectrum antimicrobial activity. Experimental studies have reported minimum inhibitory concentration (MIC) values as low as 3.13 μg mL□¹ against pathogens such as *Staphylococcus aureus* and *Bacillus cereus*, demonstrating strong activity compared with many crude plant extracts. Microscopic investigations, including scanning electron microscopy, have shown that key components, such as anacardic acid, disrupt bacterial cell membranes, resulting in structural damage and subsequent cell death in microorganisms such as *Enterococcus faecalis*. Mechanistic studies further suggest that anacardic acid can enhance innate immune defence by promoting neutrophil extracellular trap formation and bactericidal responses via PI3K-dependent signalling pathways, indicating a multifaceted antimicrobial mode of action (Hollands *et al.*, 2016).

Challenges in pharmaceutical uses

India has achieved notable progress in exploring the medicinal applications of cashew nut shell liquid (CNSL), several limitations continue to hinder its pharmaceutical advancement. One of the major concerns is the toxicity of certain constituents, particularly anacardic acids. Consequently, CNSL requires rigorous purification, characterization, and standardization procedures to comply with regulatory requirements for therapeutic use (Balasubramanian *et al.*, 2016). Preclinical toxicological evaluations have shown that some CNSL components, especially naturally occurring anacardic acids, may exhibit cytotoxic and genotoxic effects at elevated concentrations. Experimental studies have demonstrated that solvent-extracted natural CNSL can induce genotoxic responses in both eukaryotic and prokaryotic test systems, emphasizing the

need for careful safety assessment and refinement of extraction processes (Leite *et al.*, 2019). Despite these safety concerns, the diverse bioactive properties of CNSL continue to attract interest for potential applications in the management of cancer, inflammatory disorders, and microbial infections, supported by increasing investment in phytopharmaceutical research in India. However, maintaining consistent quality remains a significant challenge, as variations in chemical composition arise from differences in extraction techniques, processing conditions, and raw material sources (Roy *et al.*, 2022).

Government initiatives and market trends

The Government has actively promoted biotechnology and phytopharmaceutical research through initiatives supported by organisations such as the Indian Council of Medical Research (ICMR), as well as collaborative public private partnerships focused on traditional medicine and natural product development. Traditional healthcare systems, particularly Ayurveda, are increasingly exploring CNSL-based formulations, mainly as topical ointments and creams intended for the management of skin disorders and inflammatory conditions. The expanding Indian herbal medicine sector, driven by growing consumer preference for plant-based and natural therapeutics, provides a supportive market environment for the development and commercialization of CNSL derived products. Nevertheless, despite rising scientific and commercial interest, well-documented human clinical trials evaluating CNSL-derived compounds remain largely absent. Consequently, current evidence regarding its therapeutic efficacy is predominantly derived from preclinical and exploratory investigations.

Commercial and industrial applications

CNSL has been widely utilized in industrial applications, particularly in the manufacture of varnishes, paints, resins, and friction materials. However, growing attention has recently shifted toward its medicinal and pharmaceutical potential, supported by increasing research into the value-added utilisation of cashew processing waste (Kyei *et al.*, 2023). Indian industries and research-driven enterprises are progressively exploring CNSL-based formulations for wound management and anti-inflammatory applications. Technical-grade CNSL, enriched with cardanol and cardol fractions, also exhibits considerable antioxidant properties. These bioactive characteristics have been associated with enhanced bulk oil stability and protection against oxidative stress, indicating broader functional applications beyond the conventional coating and resin industries and highlighting their relevance to sustainable green chemistry approaches (Veeramanoharan *et al.*, 2025).

PREPARATION OF CASHEW NUT SHELL LIQUID EXTRACTION OF CNSL

Extraction of cashew nut shell liquid primarily involves recovering oil from cashew nut shells using various processing techniques. Conventional methods include mechanical pressing, in which shells are subjected to pressure to release the liquid, and solvent extraction employing organic solvents such as hexane or ethanol to obtain higher extraction efficiency and concentrated CNSL (Nyirenda *et al.*, 2021). More advanced approaches, including supercritical fluid extraction with supercritical CO_2, have attracted attention for their ability to produce high-purity CNSL with reduced chemical degradation and minimal solvent residues (Jahnavi *et al.*, 2025). These techniques generally yield crude CNSL, which is subsequently purified and refined for pharmaceutical or industrial applications. Extraction conditions significantly influence the chemical composition of CNSL. Cold solvent extraction yields natural CNSL, characterised by high concentrations of anacardic acids (70%), cardol (18%), and a smaller proportion of cardanol (5%). In contrast, thermal processing promotes decarboxylation of anacardic acids into cardanol, resulting in technical CNSL containing approximately 60-65% cardanol and 15-20% cardol (Bhatia *et al.*, 2024).

Purification and refining

CNSL undergoes several purification steps to remove impurities, including resins, particulates, and volatile components that may affect product quality and stability. The initial stage commonly involves filtration to remove suspended solid particles from the crude extract (Adekanbi and Olugasa, 2022). Subsequent distillation processes are used to separate volatile fractions and enrich key bioactive compounds, including cardanol and anacardic acids, which exhibit antimicrobial and anti-inflammatory activities (Silva *et al.*, 2015). Advanced chromatographic techniques are further employed to isolate and purify individual phenolic constituents, thereby improving chemical consistency and suitability for pharmaceutical applications. Refinement procedures also aim to regulate or reduce potentially irritant compounds, particularly anacardic acids, whose elevated concentrations may cause cytotoxic or dermal irritation, thereby improving safety profiles for biomedical use (Siwalak *et al.*, 2024).

Standardization of CNSL

To achieve consistent therapeutic performance, CNSL requires proper standardization, which involves quantitative assessment of its principal bioactive constituents, particularly anacardic acids, cardanol, and cardol. Analytical techniques such as high-performance liquid chro-

matography (HPLC) and gas chromatography-mass spectrometry (GC-MS) are widely employed to accurately determine the concentration and chemical profiles of these compounds (Oiram *et al.*, 2023). Standardization procedures also incorporate stringent quality control protocols to ensure batch-to-batch uniformity, chemical purity, and compliance with safety requirements essential for pharmaceutical and biomedical applications.

Formulation into dosage forms

CNSL is incorporated into suitable pharmaceutical dosage forms to optimize its therapeutic performance. Topical preparations, including creams, ointments, and gels, are among the most widely explored formulations, as they effectively leverage CNSL's anti-inflammatory and antimicrobial properties to manage dermatological conditions such as eczema and psoriasis (Uliassi *et al.*, 2021). Development of oral formulations presents additional challenges due to the lipophilic nature of CNSL constituents. To overcome solubility and absorption limitations, advanced delivery strategies, such as nanoemulsions and liposomal systems, are employed to enhance bioavailability and improve systemic uptake. CNSL has also been investigated for incorporation into injectable delivery platforms, including microparticle systems and lipid-based carriers designed to achieve sustained and controlled drug release (Araújo *et al.*, 2019). Mechanistic studies suggest that nanoformulation strategies can enhance the oral absorption of CNSL-derived compounds while protecting labile phenolic constituents from degradation during gastrointestinal transit. Nevertheless, direct comparative assessments with established drug delivery systems, including poly(lactic-co-glycolic acid) (PLGA) nanoparticles and conventional liposomal carriers, remain scarce, underscoring the need for comprehensive, systematic evaluation to validate their relative therapeutic advantages.

Preclinical and clinical testing

Cashew Nut Shell Liquid-based products intended for commercialisation must undergo rigorous preclinical evaluation to establish their safety, efficacy, and pharmacokinetic profiles. These assessments are initially conducted through *in vitro* experiments and animal model studies to determine biological activity, toxicity profiles, and therapeutic potential. Subsequently, clinical trials are required to evaluate the safety, optimal dosage, and therapeutic effectiveness of CNSL formulations in humans (Uliassi *et al*., 2021). Such investigations are essential to ensure that CNSL derived compounds are suitable for medical application. Despite encouraging preclinical outcomes, no registered human clinical trials of CNSL derivatives for pharmaceutical therapy have been reported to date, highlighting a significant gap between laboratory research and clinical translation.

Regulatory approval

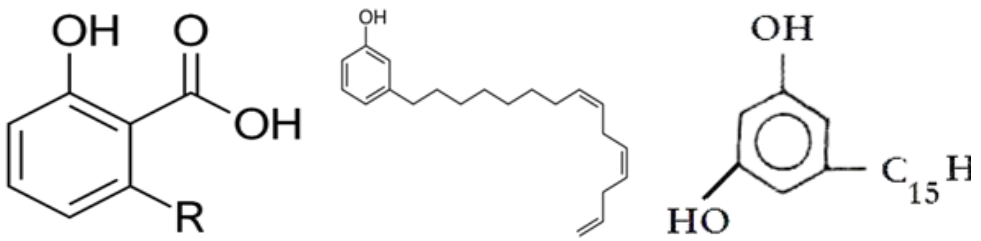
Prior to commercialization, formulations derived from CNSL must meet stringent regulatory standards established by authorities such as the U.S. Food and Drug Administration and the European Medicines Agency. Manufacturers are required to provide comprehensive documentation demonstrating product safety, therapeutic performance, quality assurance, and standardized manufacturing practices. Regulatory clearance ensures compliance with pharmacopoeial specifications and verifies that CNSL-based products satisfy established safety, efficacy, and quality requirements for pharmaceutical applications.

CHEMICAL COMPOSITION

Cashew Nut Shell Liquid is a rich natural source of phenolic lipids, with anacardic acids, cardanols, and cardols collectively accounting for more than 90% of its chemical composition. CNSL is primarily composed of anacardic acids (60 -70%), cardanols (15 - 20%), and cardols (10 - 15%), along with minor constituents such as 2-methylcardol and polymeric materials (Uliassi *et al*., 2021). These bioactive compounds originate from the pericarp fluid surrounding the cashew kernel and are responsible for the diverse biological activities attributed to CNSL. Anacardic acids, the predominant constituents, are salicylic acid derivatives characterised by long, unsaturated alkyl side chains that confer antimicrobial and antioxidant properties (Salehi *et al*., 2020). During thermal processing, partial decarboxylation of anacardic acids occurs, leading to the formation of cardanols, which retain significant biological activity, including anti-inflammatory and cytotoxic effects (Basiouni *et al*., 2025). Cardols, another important class of phenolic lipids containing two hydroxyl groups on the aromatic ring, further enhance the antimicrobial spectrum of CNSL. Owing to the structural diversity and lipophilic nature of these phenolic constituents, CNSL has emerged as a promising renewable resource for pharmaceutical, medicinal, and value-added industrial applications (Veeramanoharan *et al*., 2025).

Anacardic acids

Anacardic acids (Fig. 1) are among the most prominent bioactive constituents of CNSL and are largely responsible for its antimicrobial and anti-inflammatory activities. These phenolic compounds exhibit strong inhibitory effects against a wide range of pathogenic microorganisms, including bacteria, fungi, and certain viruses. The antimicrobial activity of anacardic acids is primarily due to their ability to interact with and disrupt microbial cell membranes, leading to increased permeability, leakage of intracellular components, and eventual cell



Anacardic Acid **Cardanol** **Cardol**

Fig. 1. *Chemical structure of primary phenolic lipid components*

death. In addition to antimicrobial action, anacardic acids possess significant anti-inflammatory properties. Studies have demonstrated that these compounds inhibit key inflammatory enzymes, such as cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), thereby suppressing the synthesis of pro-inflammatory mediators and suggesting therapeutic potential for the management of inflammatory disorders, including arthritis and asthma (Rudrapal *et al*., 2023). Furthermore, mechanistic investigations indicate that anacardic acid can modulate host immune responses by regulating neutrophil extracellular trap (NET) formation through phosphoinositide-3-kinase (PI3K)-dependent signalling pathways, highlighting a dual antimicrobial and immunomodulatory mode of action (Hollands *et al*., 2016).

Cardanols

Cardanols (Fig. 1) represent another major bioactive fraction of CNSL and are characterized by a phenolic aromatic ring attached to a long unsaturated alkyl side chain, which contributes significantly to their biological activity. These compounds exhibit strong antioxidant properties by scavenging free radicals and inhibiting lipid peroxidation associated with oxidative stress. Oxidative stress plays a central role in the pathogenesis of several chronic disorders, including cancer, cardiovascular diseases, and neurodegenerative conditions. The antioxidant potential of cardanols helps protect cellular macromolecules such as lipids, proteins, and DNA from oxidative damage, thereby supporting their potential role in disease prevention and therapeutic intervention (Trevisan *et al*., 2006). Technical CNSL, produced through thermal processing of cashew shells, contains higher concentrations of cardanol resulting from the decarboxylation of anacardic acids, and has demonstrated considerable antioxidant capacity. Consequently, cardanol-rich CNSL is increasingly being explored for nutraceutical, pharmaceutical, and functional material applications.

Cardols

Cardols (Fig. 1), structurally related phenolic lipids present in CNSL, further contribute to its biological efficacy. Owing to the presence of two hydroxyl groups on the aromatic ring, cardols exhibit pronounced antioxidant and anti-inflammatory activities. Experimental studies indicate that cardols can modulate the production of pro-inflammatory cytokines and suppress the generation of reactive oxygen species (ROS), thereby reducing oxidative stress and inflammatory responses (Jadhav *et al.,* 2025). These combined antioxidant and immunomodulatory properties highlight the therapeutic potential of CNSL-derived cardols in managing inflammatory skin disorders, autoimmune diseases, and cancer-related oxidative damage, reinforcing CNSL's value as a multifunctional natural source for pharmaceutical development.

BIOACTIVE PHYTOCHEMICALS PRESENT IN CASHEW NUT SHELL OIL

CNSL is rich in diverse bioactive phytochemicals that collectively contribute to its broad spectrum of biological and pharmacological activities (Table 1). Among these, anacardic acids represent the most abundant and biologically significant phenolic constituents. These compounds possess well-documented antimicrobial, antifungal, anti-inflammatory, and antioxidant properties (Kumaresan *et al*., 2025 (a)). Anacardic acids exhibit strong bactericidal and fungicidal activities against pathogenic microorganisms such as *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, highlighting the therapeutic potential of CNSL in combating microbial infections. Chemical profiling studies have confirmed that anacardic acids constitute the dominant alkyl phenols in CNSL, frequently exceeding 350 g kg□¹, and that total alkyl phenol content shows a strong positive correlation with antioxidant capacity. *In vitro* evaluations indicate that anacardic acids display superior antioxidant activity (IC_{50} ≈ 0.27 mM) compared with other phenolic fractions such as cardanols and cardols, underscoring their primary contribution to the biological efficacy of CNSL. Another major bioactive component is cardanol, a phenolic lipid formed through thermal decarboxylation of anacardic acid during processing to produce technical CNSL. Cardanol exhibits pronounced antioxidant and anti-inflammatory properties and has demonstrated anticancer potential through modulation of oxidative stress pathways (Uliassi *et al*., 2021). Beyond its antimicrobial activity, cardanol has also shown

Table 1. Bioactive phytochemicals found in cashew nut shell liquid

Phytochemical	Description / Bioactivity	Reference
Anacardic acids	Anacardic acids constitute the predominant fraction of natural CNSL, accounting for nearly 60–70% of total phenolics. These compounds exhibit strong antibacterial, anti-inflammatory, and antioxidant activities. Their biological action is associated with effective free-radical neutralization, inhibition of lipid peroxidation, and disruption of microbial cell membranes, contributing significantly to overall antioxidant potential.	Fatma and Egid (2015)
Cardanol	Cardanol is formed through thermal decarboxylation of anacardic acid during processing. It demonstrates diverse biological activities including antioxidant, anti-inflammatory, anticancer, antitumor, and cytotoxic effects. Phenolic fractions rich in cardanol show efficient radical scavenging activity in standard antioxidant assays.	Salehi *et al.* (2020)
Cardol	Cardol is a phenolic lipid known for antimicrobial, cytotoxic, and antioxidant properties. Together with cardanol, it contributes to oxidative stability in lipid systems and functions as a natural inhibitor of free-radical propagation.	Basiouni *et al.* (2025)
2-Methylcardol	This methylated derivative of cardol occurs in smaller quantities within CNSL. Despite its low concentration, it contributes to antimicrobial and antioxidant responses and enhances the overall biological functionality of CNSL phenolics.	Flavio and Matthieu (2016)
Methylene-bridged cardanol dimers	These compounds are generated during polymerization reactions of cardanol. Dimer formation improves radical scavenging efficiency and enhances the antioxidant performance of polymeric CNSL derivatives.	Fan *et al*. (2022)
Polymeric cardanol	Polymerised cardanol derivatives possess high-molecular-weight phenolic structures that exhibit antioxidant and potential anticancer activities. These polymers may regulate oxidative stress pathways and influence cellular proliferation in biological systems.	Jadhav *et al.* (2025)
Hydrogenated cardanol	Hydrogenation modifies the unsaturated side chain of cardanol, improving chemical stability and altering biological activity. Hydrogenated forms exhibit enhanced antioxidant and anti-inflammatory effects due to increased structural stability.	Bhatia *et al.* (2024)
Saturated alkyl phenols	Technical CNSL contains saturated alkyl phenols dominated by cardanol and cardol fractions. These compounds exhibit antimicrobial properties and notable free-radical scavenging capacity, offering protective effects in biological environments.	Vasconcelos *et al.* (2021)
Phenolic lipids	This group includes cardanol, cardol, and related alkyl phenols, collectively responsible for many of the biological properties of CNSL. Their mechanisms involve destabilising the membranes of microorganisms and efficiently neutralising reactive oxygen species.	Stasiuk and Kozubek (2010)
Semiphenolic compounds	Minor constituents of CNSL that act synergistically with major phenolics. Although present at low levels, they enhance antimicrobial activity and antioxidant activity when combined with primary phenolic components.	Silva *et al.* (2015)
Cyclohexenyl derivatives	Hydrogenated derivatives of cardanol or cardol exhibit antioxidant and anti-inflammatory activities. Structural saturation influences phenolic stability and modifies biological performance.	Roy *et al.* (2022)
oxidized cardanol derivatives	Oxidative processing can generate modified cardanol structures with notable biological properties. Certain oxidised derivatives exhibit enhanced radical-scavenging activity and contribute to the complex antioxidant profile of CNSL fractions.	Valério *et al.* (2022)

larvicidal activity and cholinesterase-inhibitory effects in biological assays, suggesting broader applications in pharmaceutical, agricultural, and biomedical fields. Cardols, a related group of phenolic compounds present in CNSL, further enhance its therapeutic profile. These compounds possess analgesic, anti-inflammatory, and antioxidant activities and have been associated with potential benefits in managing inflammatory disorders such as rheumatoid arthritis and osteoarthritis (Basiouni *et al*., 2025). The synergistic interaction among anacardic acids, cardanols, and cardols contributes to the multifunctional bioactivity of CNSL, positioning it as a promising natural resource for pharmaceutical and nutraceutical development.

Cardol compounds, which constitute a substantial fraction of CNSL phenolic constituents, play an important role in its antimicrobial activity. Several cardol analogues have demonstrated minimum inhibitory concentration (MIC) values in the low mg mL^{-1} range against bacterial pathogens, highlighting their contribution to the broad antimicrobial spectrum associated with CNSL. In addition to phenolic lipids, CNSL contains polyphenolic constituents such as tannins, which further enhance antibacterial and antifungal activity (Ashong *et al*., 2025). Tannins are also recognised for their wound-healing properties, including the promotion of tissue repair and the inhibition of microbial colonisation, thereby strengthening the therapeutic potential of CNSL in managing skin infections and topical wounds. Phytochemical screening of cashew nut shell extracts has confirmed the presence of tannins, flavonoids, terpenoids, and saponins in both hexane and ethanol extracts, indicating that multiple classes of secondary metabolites collectively contribute to antioxidant, anti-inflammatory, and antimicrobial effects.

Flavonoids identified in CNSL extracts exhibit strong antioxidant and anti-inflammatory properties and play a crucial role in reducing oxidative stress and inflammatory responses (Gomes *et al*., 2020). Quantitative phytochemical analyses have reported high flavonoid and total phenolic contents, supporting their involvement in free-radical scavenging and antimicrobial activity. These properties suggest potential applications of CNSL-derived formulations in managing inflammatory conditions such as musculoskeletal disorders and gout. Furthermore, the presence of bioactive fatty acids, including oleic acid and linoleic acid, contributes to the anti-inflammatory and antioxidant profile of CNSL (Ganbold *et al*., 2025). These fatty acids aid in stabilizing cellular membranes, modulating inflammatory pathways, and reducing oxidative damage associated with chronic diseases. Although direct quantification of fatty acids in CNSL is comparatively limited, analyses of cashew nut components sharing related biosynthetic pathways have reported oleic acid (21.9 g 100 g^{-1}) and linoleic acid (5.5 g 100 g^{-1}), suggesting that fatty acid derivatives present in CNSL may similarly support its biological activity (León *et al*., 2025). The combined presence of phenolic lipids, polyphenols, flavonoids, and fatty acids establishes CNSL as a chemically diverse natural matrix with synergistic antioxidant, antimicrobial, and anti-inflammatory potential (Salehi *et al*., 2020).

ANTIMICROBIAL AND ANTIFUNGAL PROPERTIES OF CNSL

Cashew nut shell liquid has attracted considerable interest for its antimicrobial and antifungal activities, largely attributed to its phenolic constituents (Table 2). Natural or raw CNSL, which is rich in anacardic acids, exhibits stronger antimicrobial activity, whereas technical CNSL, enriched in cardanol through thermal decarboxylation, shows reduced antimicrobial potency but improved solubility for formulation purposes (Ituen *et al*., 2026). These phenolic compounds exert bactericidal and fungicidal effects against both Gram-positive and Gram-negative bacteria, as well as fungal pathogens. For example, *Staphylococcus aureus* is a major etiological agent of skin and wound infections, and systemic diseases such as pneumonia and sepsis. The emergence of methicillin-resistant *S. aureus* (MRSA) represents a significant public health concern due to its resistance to conventional antibiotics. Natural CNSL demonstrates *In vitro* inhibitory activity against MRSA, with reported minimum inhibitory concentrations (MIC) ranging from 25 to 50 µg/mL, depending on the preparation and bacterial strain (Hollands *et al*., 2016). The antimicrobial mechanism primarily involves disruption of bacterial cell membranes, leading to lysis; however, this effect may overlap with cytotoxic concentrations in mammalian cells, underscoring the need for careful dose selection. In addition to antibacterial activity, CNSL exhibits antifungal effects, particularly against *Candida albicans*, a pathogen responsible for mucosal infections such as oral thrush and vaginal candidiasis, as well as systemic infections in immunocompromised individuals. Quantitative studies report IC50 values of 30-60 µg/mL for inhibition of *C. albicans* biofilm formation (Sirwan *et al*., 2024). These findings indicate a therapeutic window in which antimicrobial efficacy can be achieved without significant cytotoxicity, although clinical data in humans are not yet available. While preclinical studies highlight the potential of CNSL, claims regarding its effectiveness as a therapeutic agent remain unsubstantiated in clinical contexts. Effective concentrations against pathogens may overlap with those causing dermatitis or cytotoxicity, limiting direct translation to human use. Nevertheless, CNSL's antimicrobial and antifungal properties suggest utility in topical for-

Table 2. Antimicrobial and antifungal properties of cashew nut shell liquid

Microorganism	Effect of CNSL	Mechanism of action	CNSL type	Model system /	Comparator	Quantitative	Reference
Staphylococcus aureus	CNSL exhibits bactericidal effects, particularly effective against MRSA	Anacardic acid disrupts bacterial cell wall synthesis and compromises membrane integrity	Natural CNSL (anacardic acid-rich)	*In vitro*, 50 µM	Vancomycin 10 µg/mL	70% growth inhibition at 24 h; MIC = 35 µg/mL	Kubo *et al*. (2003)
Escherichia coli	CNSL has bactericidal properties, reducing growth and viability	Cardanol and anacardic acid interact with bacterial membranes, altering permeability and causing leakage	Technical CNSL (cardanol-rich)	*In vitro*, 100 µM	Gentamicin 8 µg/mL	65% CFU reduction at 24 h; MIC = 40 µg/mL	Oliveira *et al*. (2023)
Candida albicans	CNSL shows fungicidal activity, inhibiting the growth of Candida species	Anacardic acid binds fungal membranes, disrupting structure, causing cell death and inhibiting biofilm formation	Natural CNSL	*In vitro*, 75 µM	Amphotericin B 5 µg/mL	MIC = 40 µg/mL; biofilm inhibition 60%	Guerra *et al*. (2025)
Pseudomonas aeruginosa	CNSL exhibits a moderate antimicrobial effect	Anacardic acid and cardanol interfere with bacterial enzyme activity and disrupt membrane function	Technical CNSL	*In vitro*, 150 µM	Ciprofloxacin 10 µg/mL	50% growth inhibition at 24 h; MIC = 60 µg/mL	Taibi *et al*. (2024)
Streptococcus pneumoniae	CNSL has strong antimicrobial effects	Phenolic compounds penetrate the cell wall, disrupt metabolism	Natural CNSL	*In vitro*, 50 µM	Penicillin G 5 µg/mL	MIC = 30 µg/mL; 70% CFU reduction	Souza *et al*. (2022)
Bacillus subtilis	CNSL demonstrates strong bactericidal activity	Anacardic acid and cardanol disrupt membranes, reducing cell division	Natural CNSL	*In vitro*, 60 µM	Ampicillin 10 µg/mL	>75% CFU reduction at 24 h	Iqbal *et al*. (2022)
Aspergillus flavus	CNSL is fungistatic and inhibits fungal growth	Anacardic acid disrupts the fungal cell wall and membrane, interfering with division and metabolism	Natural CNSL	*In vitro*, 80 µM	Fluconazole 5 µg/mL	MIC = 45 µg/mL; 55% growth reduction	Watanabe *et al*. (2010)
Micrococcus luteus	CNSL shows antibacterial activity	Phenolic compounds disrupt membrane integrity, causing leakage and cell death	Technical CNSL	*In vitro*, 50 µM	Streptomycin 10 µg/mL	60% CFU reduction at 24 h	Li *et al*. (2019)

mulations, such as creams, ointments, and gels, for localised infections, as well as in antiseptic or disinfectant applications. Comparative *in vitro* studies with standard agents such as vancomycin and fluconazole indicate that CNSL can be effective, though typically at higher concentrations, underscoring the importance of formulation optimisation or semi-synthetic modifications to improve the therapeutic index (Hollands *et al*., 2016). Given the increasing global burden of antibiotic resistance, especially multi-drug-resistant organisms, CNSL represents a natural and sustainable antimicrobial agent. Its clinical translation is constrained by chemical variability, poor aqueous solubility, and potential toxicity, highlighting the need for standardized extraction methods and controlled clinical evaluation (Veeramanoharan *et al*., 2025). Preclinical models continue to demonstrate CNSL's promising activity against MRSA and *Candida albicans* (Nugrahani *et al*., 2025), supporting its potential for further investigation rather than established clinical use. Careful consideration of compound type, concentration, and therapeutic window is essential prior to human application.

ANTI-INFLAMMATORY AND PAIN-RELIEVING EFFECTS OF CNSL

Cashew nut shell liquid (CNSL) has demonstrated notable anti-inflammatory and analgesic effects in preclinical studies, suggesting its potential to manage chronic inflammatory conditions (Table 3). The bioactive phenolic compounds, particularly cardanol and anacardic acid, mediate anti-inflammatory effects by modulating key inflammatory pathways, including cytokine production and cyclooxygenase (COX) enzyme activity (Kumaresan *et al*., 2025b). It is important to emphasize that most of the evidence originates from *In vitro* experiments or animal models, and clinical efficacy in humans remains unestablished. Anti-inflammatory activity is influenced by the type of CNSL used. Technical CNSL, enriched in cardanol, primarily contributes to cytokine modulation, whereas natural CNSL, rich in anacardic acids, exhibits stronger COX inhibition. However, high concentrations of natural CNSL may induce cytotoxicity or skin irritancy, reflecting a relatively narrow therapeutic window. For instance, anacardic acid inhibited COX-2 activity in murine models at 20–50 µM, whereas concentrations above 100 µM caused cytotoxic effects *In vitro* (Taibi *et al*., 2024).

Anti-inflammatory mechanisms of CNSL

The anti-inflammatory effects of CNSL are primarily mediated by inhibiting COX-1 and COX-2, thereby reducing the synthesis of prostaglandins responsible for inflammation and pain (de Souza *et al*., 2018). Anacardic acid exhibits selective COX-2 inhibition, while cardanol modulates the production of inflammatory cytokines, including TNF-α and IL-6 (Gomes *et al*., 2020). Comparative studies with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen indicate that the inhibitory concentration (IC50) of anacardic acid for COX-2 is approximately 1.5–2 times higher than that of ibuprofen *In vitro*, highlighting its preclinical potential but relatively lower potency (Veerasamy *et al*., 2021).

In autoimmune conditions such as rheumatoid arthritis (RA), CNSL has been shown to reduce paw oedema and inflammatory biomarkers in rodent models, suggesting potential anti-inflammatory activity. However, extrapolation to human outcomes remains speculative, as pharmacokinetic studies reveal poor oral bioavailability of raw CNSL compounds without specialized formulation strategies, such as micelles or nanoparticles. Similarly, in osteoarthritis models, CNSL has been observed to attenuate cartilage inflammation and associated pathological changes in animals, yet clinical trials in humans are currently lacking, and therapeutic relevance remains to be established.

CNSL'S ROLE IN PAIN MANAGEMENT

CNSL also exhibits analgesic activity, which complements its anti-inflammatory effects. The phenolic constituents, particularly cardanol and anacardic acids, have demonstrated significant pain-reducing effects in preclinical models, including acetic acid-induced writhing and hot-plate assays in mice. In models of conditions such as gout, CNSL effectively reduced paw swelling and inflammatory pain (Goetz *et al*., 2023). However, as with its anti-inflammatory properties, human clinical evidence is lacking, and these observations should be interpreted as preclinical indicators rather than confirmed therapeutic outcomes. The analgesic mechanism of CNSL is hypothesized to involve modulation of prostaglandin-mediated pain pathways and stabilization of neuronal membranes, although the precise molecular mechanisms remain under investigation. The lipophilic nature of CNSL compounds limits oral bioavailability, prompting the exploration of advanced delivery systems, such as CNSL-loaded nanoparticles, to enhance absorption while minimising local irritation (Taibi *et al*., 2024). Preliminary comparative studies indicate that the encapsulation efficiency and controlled-release profiles of CNSL formulations may approach those of conventional carriers, such as PLGA or PEGylated liposomes, though detailed quantitative benchmarking is limited.

Safety and therapeutic window

Balancing CNSL's bioactivity with potential toxicity is critical. While low to moderate concentrations demon-

Table 3. Anti-inflammatory and pain-relieving effects of cashew nut shell liquid

Property / Effect	Mechanism of action	Model system, concentration, comparator	Key outcome (Quantitative)	Reference
Anti-inflammatory activity in arthritis	CNSL compounds, particularly anacardic acid, inhibit cyclooxygenase enzymes (COX-1 and COX-2), reducing pro-inflammatory prostaglandin synthesis. Low micromolar concentrations reduce inflammation without cytotoxicity.	Rat model of rheumatoid arthritis; 50 mg/kg orally; compared with indomethacin 5 mg/kg	40% reduction in paw edema vs. 50% for indomethacin	Yuliana *et al*. (2014)
Reduction in pro-inflammatory cytokines	CNSL significantly reduces TNF-α, IL-1β, and IL-6 levels. Cytotoxicity observed at concentrations >100 µM.	Human synoviocytes (*In vitro*); 25–75 µM; compared with dexamethasone 10 µM	TNF-α decreased by 35–60%, IL-1β by 30–55%, IL-6 by 25–50%	Umare *et al*. (2014)
Inhibition of COX-2 enzyme	Cardanol-rich CNSL selectively inhibits COX-2; efficacy depends on CNSL type (raw vs. technical). IC50 for COX-2 inhibition: 45 µM for cardanol-rich CNSL	*In vitro* enzymatic assay; 10–100 µM; compared with celecoxib 5 µM	60% inhibition at 50 µM vs. 70% inhibition by celecoxib	Kalle and Rizvi, 2011
Pain relief in inflammatory conditions	CNSL suppresses inflammatory mediators such as bradykinin and prostaglandins; analgesic effect is dose-dependent	Mouse model of carrageenan-induced paw edema; 50 mg/kg orally; compared with ibuprofen 10 mg/kg	35% reduction in pain behavior vs. 50% for ibuprofen	de Souza *et al*. (2018)
Inhibition of NF-κB pathway	Anacardic acid inhibits NF-κB signaling, reducing transcription of inflammatory mediators; therapeutic selectivity index (SI) ~3–5	THP-1 macrophages; 20–80 µM; compared with Bay 11-7082 5 µM	50–70% decrease in NF-κB activation	Ting *et al*. (2017)
Reduction of edema and inflammation	CNSL reduces acute edema in a dose-dependent and reversible manner	Rat paw edema model; 25–100 mg/kg orally; compared with diclofenac 10 mg/kg	30–55% reduction in paw volume vs. 50% for diclofenac	Jablonski *et al*. (2020)
Protection against oxidative stress	CNSL's antioxidant activity decreases reactive oxygen species (ROS) and lipid peroxidation, indirectly mitigating inflammation	Human chondrocytes; 10–50 µM; compared with N-acetylcysteine 5 mM	ROS levels reduced by 40–60%, lipid peroxidation decreased by 35%	Tan *et al*. (2018)

strate therapeutic effects, higher doses of anacardic acids and cardanol can induce cytotoxicity, including skin irritation and organ-specific toxicity in animal studies, with reported LD_{50} values ranging from 150–250 mg/kg in rodents (Basiouni *et al*., 2025). Careful consideration of dosage and formulation strategies is therefore essential to maximize efficacy while minimizing adverse effects in future preclinical and clinical investigations.

CNSL AS A CARRIER IN DRUG DELIVERY SYSTEMS

Cashew nut shell liquid has emerged as a potential carrier in drug delivery systems due to its unique chemical properties, particularly its ability to solubilize both hydrophilic and lipophilic compounds (Bloise *et al*., 2023). This dual solubility property addresses a major challenge in pharmaceutical formulations: the poor water solubility of many therapeutic agents used in the management of cancer, diabetes, and cardiovascular disease (Bhalani *et al*., 2022; Ezike *et al*., 2023). By improving drug solubility and enabling sustained release, CNSL offers a promising strategy to enhance oral and systemic bioavailability (Table 4).

Improving bioavailability

Bioavailability refers to the proportion of an administered drug that reaches systemic circulation and is available for therapeutic activity (Kumaresan *et al*., 2019c). Hydrophobic drugs often exhibit limited bioavailability due to poor solubility. CNSL can enhance dissolution and absorption by leveraging its lipophilic components to interact with hydrophobic drugs and its polar phenolic constituents, such as anacardic acids, to solubilize hydrophilic compounds. However, CNSL's bioactive components are highly lipophilic and may exhibit cytotoxicity or irritancy at higher concentrations (Sun *et al*., 2023). For example, anacardic acids may induce cytotoxic effects above 50–100 µM *In vitro*, whereas lower concentrations (5–20 µM) can improve drug solubility without significant toxicity. Therefore, careful attention to the therapeutic window is essential when formulating CNSL-based drug delivery systems.

Nanoparticles and liposomes for controlled release

CNSL-derived nanoparticles or semisynthetic derivatives can encapsulate hydrophobic drugs, thereby improving solubility and chemical stability. Likewise, liposomal vesicles composed of CNSL based lipids can incorporate hydrophobic and hydrophilic drugs simultaneously, enabling controlled release over extended periods (Zacheo *et al*., 2020). Such sustained-release properties are particularly advantageous for chronic disease management, where maintaining consistent plasma drug levels is critical (Rethi *et al*., 2022). Comparative studies indicate that CNSL-based nanoparticles achieve encapsulation efficiencies of 65–80% for hydrophobic drugs, comparable to standard carriers such as PLGA nanoparticles (70–85%), although their stability and release kinetics are sensitive to the chemical profile of the CNSL used (Satapathy *et al*., 2021).

Biocompatibility and safety

Despite being naturally derived, CNSL is not universally non-toxic. Raw CNSL, rich in anacardic acids, can cause skin irritation, cytotoxicity, and gastrointestinal irritation at higher doses, whereas thermally processed or decarboxylated CNSL, enriched in cardanol, exhibits reduced irritancy. Distinguishing CNSL types is therefore crucial in evaluating safety profiles. Preclinical studies suggest that selectivity indices (SI) >5 for antimicrobial and anticancer applications may indicate a viable therapeutic window, but overlapping cytotoxic concentrations must be carefully avoided (Bloise *et al*., 2023). CNSL micelles and nanoparticles are biodegradable, which may reduce long-term accumulation compared with synthetic carriers.

Applications in chronic disease management

CNSL-based carriers show potential to enhance the delivery of therapeutics in chronic diseases. In cancer therapy, CNSL liposomes can encapsulate cytotoxic drugs, such as doxorubicin, enabling targeted delivery to tumor sites while minimizing off-target toxicity (Rethi *et al*., 2022). In diabetes management, CNSL may improve the oral bioavailability of drugs such as metformin and glibenclamide. However, the precise mechanisms underlying these benefits, such as micelle formation, P-gp inhibition, or enhanced lymphatic transport, require further investigation. Challenges remain due to the high lipophilicity and poor water solubility of CNSL compounds, which must be addressed in formulation design.

POTENTIAL IN TREATING CHRONIC DISEASES

Chronic diseases such as diabetes, cardiovascular disorders, and cancer often require long-term management through continuous drug administration to control symptoms and prevent disease progression. The unique properties of cashew nut shell liquid (CNSL), particularly its ability to improve bioavailability and facilitate controlled release of therapeutic agents, make it a promising candidate for these applications. However, most evidence remains preclinical, and the therapeutic window is limited by the potential cytotoxicity of anacardic acids and their skin irritancy at higher concentrations (Xia and King, 2025). CNSL type (natural/raw versus technical) influences both biological activity and

Table 4. Cashew nut shell oil as a carrier in drug delivery systems

Aspect	Details	Mechanism of action	Model system	Concentration	Key outcome	Selectivity index	Reference
Improvement of drug bioavailability	CNSL enhances oral absorption of poorly soluble drugs, particularly lipophilic compounds. Bioavailability improvement is dose-dependent; high concentrations (>50 µM anacardic acid) may induce cytotoxicity.	Amphiphilic CNSL forms micelles that solubilize hydrophobic drugs, facilitating intestinal absorption	Rat intestinal model (*in vivo*)	20–50 µM anacardic acid	1.8 - 2.5-fold increase in plasma drug concentration	TI not exceeded at ≤50 µM; cytotoxicity observed above this	Amit *et al*. (2012)
Nanoparticles for drug delivery	CNSL nanoparticles (CNSL-NPs) improve drug stability and enable controlled release; encapsulation efficiency 65–85%. A high anacardic acid content increases the risk of irritancy.	Hydrophobic core encapsulates drugs; sustained release over 24–48 h; reduces burst release	*In vitro* cell culture, in vivo rat xenograft	10–50 mg/kg drug-loaded CNSL-NPs	45–60% drug release over 24 h; reduced cytotoxicity to normal cells	SI 3–5 for anticancer drugs	Rodrigues *et al*. (2021)
Liposomes and micelles	CNSL forms nanosized liposomes/micelles delivering hydrophobic drugs; particle size 80–150 nm	Lipophilic core encapsulates drug; hydrophilic shell stabilizes in aqueous solution; enables controlled release and protection from degradation	MCF-7 cells, rat plasma	20–50 µM anacardic acid	Enhanced solubility and stability; 40–60% drug release in 24 h	SI 3–5 (selective cytotoxicity to cancer cells)	Trucillo (2024)
Enhanced drug release	CNSL-matrix formulations enable controlled release; the release rate depends on anacardic acid concentration	Gradual release from CNSL matrix prolongs drug availability; reduces systemic peaks	Rat plasma, *In vitro* cell line	10–50 mg/kg	48 h sustained release for anti-inflammatory drugs	Safe at ≤50 µM; higher doses risk irritation	Amit *et al*. (2012)
Targeted delivery for cancer	CNSL carriers improve the delivery of chemotherapeutics to tumour sites; preclinical evidence only	Enhanced Permeability and Retention (EPR) effect directs accumulation in tumour tissue; synergistic *In vitro* activity with conventional drugs	MCF-7 cells, murine xenografts	45 µM (IC50 *In vitro*)	Reduced tumor volume by 35–40% in vivo; IC50 achieved in cancer cells without excessive normal cell toxicity	SI ~3–4; cytotoxicity above 60 µM	Rodrigues *et al*. (2021)
Biocompatibility and safety	CNSL is biocompatible at therapeutic doses; high concentrations (>50 µM anacardic acid) cause skin irritation and cytotoxicity	Balanced hydrophilic-lipophilic structure reduces nonspecific toxicity; selective cytotoxicity toward pathogens/cancer cells	*In vitro* fibroblast and keratinocyte cultures	≤50 µM	Minimal cell death in normal cells; dermatitis at >50 µM	TI ~3; SI 3–5	Trucillo, (2024); Amit *et al*. (2012)
Sustained release for diabetes	CNSL carriers enhance the oral delivery of anti-hyperglycemic drugs; improves steady plasma levels	Micelle formation increases intestinal permeability; controlled release reduces plasma fluctuations	Rat diabetic model	20–40 mg/kg	1.8-fold higher plasma levels; improved glucose regulation	TI maintained; safe in vivo	Yin *et al*. (2017)

safety, as raw CNSL is rich in anacardic acids (~60–70%) while technical CNSL is enriched in cardanol (~60–65%) due to decarboxylation during thermal processing. Using CNSL as a carrier in drug delivery systems can enhance drug efficacy and minimize side effects, improving the quality of life for patients managing chronic conditions. Comparative benchmarking against standard carriers, such as PEGylated liposomes and PLGA nanoparticles, remains limited, and the mechanisms of bioavailability enhancement require further investigation (Uliassi *et al*., 2021).

CNSL in diabetes management

In Type 2 diabetes, maintaining blood glucose within a normal range is critical. Many anti-hyperglycemic drugs, including metformin and glibenclamide, have poor water solubility, limiting their therapeutic potential (Vieira *et al*., 2019). CNSL, with both lipophilic and hydrophilic components, can improve the solubility and absorption of these drugs (Uliassi *et al*., 2021). Encapsulation of anti-diabetic drugs in CNSL-based nanoparticles or liposomes enables sustained, controlled release, maintaining consistent plasma drug levels and reducing dosing frequency. Most studies are preclinical, and human pharmacokinetic data are lacking; concentrations effective *In vitro* may overlap with cytotoxic levels, particularly for anacardic acid-rich raw CNSL. Mechanisms such as micelle formation or P-gp inhibition may contribute to enhanced absorption but require further validation (Sun *et al*., 2023). This approach may improve patient compliance and reduce fluctuations in blood sugar levels, but clinical confirmation is necessary.

CNSL in cardiovascular disease

Cardiovascular diseases (CVD), including hypertension, hyperlipidemia, and atherosclerosis, are leading causes of mortality worldwide. Drugs for CVD management, such as antihypertensives, statins, and anticoagulants, often have poor bioavailability and long-term side effects. CNSL-based delivery systems can improve solubility and absorption of these agents, facilitate efficient drug delivery and potentially reduce dosing frequency (Sharma *et al*., 2016). By forming liposomal or micellar carriers, CNSL enables controlled release, supporting stable blood pressure and lipid regulation (Sriwidodo *et al*., 2022). Evidence is limited to preclinical models, and no human trials have evaluated CNSL for cardiovascular outcomes; thus, claims of direct clinical benefit remain investigational.

CNSL in cancer treatment

Chemotherapy is highly effective but often damages healthy tissues, causing significant adverse effects. CNSL-based carriers can enhance the targeted delivery of cytotoxic agents, thereby minimising off-target toxicity. Liposomes or nanoparticles formulated with CNSL can encapsulate drugs such as doxorubicin and paclitaxel, providing sustained release at tumour sites while reducing systemic exposure (Xia and King, 2025). Sustained drug exposure may improve efficacy against cancer cells. Evidence is largely *in vitro or in animal models, and concentrations effective in cancer cell lines may also be cytotoxic to* non-cancerous cells, especially for raw CNSL. Mechanistic claims such as COX-2 inhibition or membrane disruption remain hypothetical and require further validation (Sun *et al*., 2023).

Current applications of CNSL in pharmaceutical and medicinal products

CNSL is incorporated into topical formulations for its antimicrobial and anti-inflammatory properties. It has been used in creams, ointments, and gels for dermatological conditions such as eczema, psoriasis, and acne (Uliassi *et al*., 2021). Raw CNSL contains high levels of anacardic acids, which can cause dermatitis at concentrations above 0.1–0.5% w/w, highlighting a narrow therapeutic window (Rakesh *et al*., 2024). Cardanol-rich technical CNSL accelerates tissue repair and reduces inflammation without significant cytotoxicity (Basiouni *et al*., 2025).

Wound healing and dermatological treatments

CNSL's anti-inflammatory and antioxidant activities support wound healing. Cardanol and cardol enhance collagen synthesis and promote faster tissue regeneration (Bhatia *et al*., 2024). *In vitro* studies show 50 µM cardanol reduces pro-inflammatory cytokines (IL-6, TNF-α) by 40–50% in keratinocyte cultures, comparable to low-dose ibuprofen (Salehi *et al*., 2020). Its antimicrobial properties prevent secondary infections, although MIC values vary with CNSL type and extraction method.

Oral and injectable CNSL-based formulations

Despite its lipophilicity, CNSL has been formulated in nanoemulsions and liposomes to enhance solubility and bioavailability. CNSL components may form micelles or lipid-based carriers that increase intestinal absorption, potentially inhibiting P-glycoprotein efflux, though clinical data are lacking (Gao *et al*., 2024). Oral formulations are being explored for anti-inflammatory and analgesic drugs, while injectable CNSL systems are under investigation for controlled delivery of chemotherapeutic agents. Cytotoxicity is observed *In vitro* at anacardic acid concentrations above 20 µM, emphasizing the need for safety evaluation.

CNSL in cancer therapy

CNSL, particularly its phenolic compounds such as anacardic acid, exhibits cytotoxicity against breast (MCF-7), prostate (PC-3), and liver (HepG2) cancer cell

lines through apoptosis induction and tumour growth inhibition (Salehi *et al*., 2020).

CNSL in antifungal and antimicrobial treatments

CNSL-based formulations inhibit pathogens, including *Candida albicans*, *Aspergillus niger*, and *Staphylococcus aureus*. Cardanol-rich CNSL exhibits MIC values of 25–75 µg/mL against *S. aureus*, compared with ~1–2 µg/mL for vancomycin, indicating that CNSL may complement standard antibiotics rather than replace them. Synergistic effects, such as potential efflux pump inhibition in resistant strains, have been suggested, but direct clinical evidence is lacking (Vieira *et al*., 2019).

Limitations of using CNSL

Cashew nut shell liquid contains numerous bioactive compounds with promising pharmacological activities; its pharmaceutical and medicinal applications are constrained by several critical limitations. Crude CNSL, particularly forms rich in anacardic acids, can cause skin irritation, allergic reactions, and cytotoxic effects, necessitating careful purification and precise formulation (Rakesh *et al*., 2024). The effective therapeutic concentrations of CNSL are often close to cytotoxic thresholds; for example, *in vitro* antimicrobial activity is observed at 20–50 µM, while cytotoxicity to keratinocytes occurs above 50 µM, highlighting a narrow therapeutic window and the importance of selecting the appropriate CNSL type. The hydrophobic nature of CNSL phenolic lipids, such as cardanols and cardols, limits water solubility and systemic bioavailability. Nanotechnology-based delivery systems, including nanoemulsions, liposomes, and solid lipid nanoparticles, have shown improved solubility, absorption, and controlled release in preclinical studies; however, pharmacokinetic and pharmacodynamic data in humans remain lacking. Another significant challenge is the lack of standardized processing methods. The chemical composition of CNSL varies depending on geographic origin, cashew variety, and extraction technique such as cold-pressing, solvent extraction, or thermal treatment which alters the relative abundance of anacardic acids, cardanols, and cardols. This variability complicates reproducibility and quality control in pharmaceutical manufacturing. Limited clinical evidence further limits CNSL's application, as most studies are i*n vitro* or conducted in animal models, and no registered clinical trials have confirmed safety or efficacy in humans, making regulatory approval difficult (Watanabe *et al*., 2010). Additionally, certain CNSL components are chemically unstable under physiological conditions, leading to rapid degradation or unintended side effects and thereby reducing therapeutic effectiveness (Preeti *et al*., 2023). The economic and technical feasibility of isolating pure, pharmacologically active compounds from CNSL on a commercial scale remains uncertain. Refining processes to remove toxic constituents increase production costs and may offset sustainability benefits. While CNSL holds substantial therapeutic potential, these limitations underscore the need for standardised extraction procedures, comprehensive safety evaluations, and advanced formulation strategies to enable safe and effective clinical translation.

Research opportunities of CNSL

Cashew nut shell liquid is a renewable source of phenolic lipids with demonstrated antimicrobial, anti-inflammatory, antioxidant, and anticancer activities. Despite this, its development for pharmaceutical applications remains at an early stage. A primary research focus should be on standardising CNSL extraction and purification, as its chemical composition varies across cashew varieties, geographic origins, and processing methods. Cold-pressed versus thermally extracted CNSL contains differing ratios of anacardic acids, cardanols, and cardols, which significantly influence biological activity (León *et al*., 2025). The development of eco-friendly extraction techniques, such as supercritical fluid extraction or green solvent-based methods, could improve reproducibility, reduce toxicity, and enable scalable production of pharmaceutical-grade CNSL (Jahnavi *et al*., 2025). Formulation research is also critical to overcome the high lipophilicity of CNSL components, which limits oral and systemic delivery. Nanotechnology-based delivery systems, including solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and nanoemulsions, have demonstrated potential to enhance solubility, protect bioactive compounds from degradation, and enable targeted or controlled release. These approaches can reduce dosing frequency and minimize toxicity (Hazzani *et al*., 2012). Rigorous preclinical and clinical evaluation is necessary, as most current evidence derives from *In vitro* or animal studies. Future research should focus on toxicology, pharmacokinetics, pharmacodynamics, and Phase I clinical trials to establish safe dosage ranges, metabolic profiles, long-term effects, and regulatory feasibility.

The synergistic potential of CNSL compounds with conventional drugs also represents a promising research avenue. Anacardic acids have been reported to enhance antibiotic efficacy and inhibit multidrug resistance, suggesting that CNSL could serve as a bioenhancer or adjunct therapy for infections, inflammation, and cancer treatment. Furthermore, chemical modification and semi-synthetic derivatization of CNSL molecules may improve potency, reduce toxicity, and enhance target specificity, providing a platform for new drug development based on a natural product scaffold. CNSL's biodegradability and renewable origin make it attractive for green pharmaceuticals and cosmeceuticals. Potential applications include biodegradable wound dressings, drug-eluting implants, and transder-

mal patches, particularly in resource-limited settings, aligning with sustainable drug development initiatives. Finally, interdisciplinary research integrating materials science, pharmacology, green chemistry, and biotechnology, along with collaborations among academia, industry, and regulatory agencies, will be essential to accelerate translation, commercialization, and regulatory pathway development.

Conclusion

Cashew nut shell liquid is a rich source of bioactive phenolic lipids primarily anacardic acids, cardanols, and cardols with broad-spectrum antimicrobial, antifungal, anti-inflammatory, antioxidant, and analgesic properties. Its novelty lies in a multifunctional pharmacological profile, including activity against drug-resistant pathogens and the modulation of key inflammatory and oxidative pathways. Preclinical studies support its efficacy *In vitro* and in animal models; however, clinical translation is limited by chemical heterogeneity, dose-dependent cytotoxicity, and a lack of standardized extraction and formulation protocols. To advance CNSL as a therapeutic agent, standardised extraction, purification, and characterisation are critical, along with mechanistic studies, pharmacokinetic evaluations, and comparative benchmarking against conventional drugs. Nanotechnology-based delivery systems offer a strategic approach to enhance solubility, bioavailability, and controlled release while minimizing toxicity. CNSL represents a scientifically valuable, natural pharmacological resource with considerable therapeutic potential, warranting rigorous translational research to establish clinical efficacy and safety.

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Conflict of interest

The authors declare that they have no conflict of interest.

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