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Review Article

Unveiling the Therapeutic Arsenal of *Cassia fistula* L.: Traditional Wisdom to Modern Biomedical Applications

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Abstract

Cassia fistula L., widely known as the golden shower tree, has been deeply rooted in traditional medicine systems for centuries and is now emerging as a potential candidate in modern pharmacotherapy. This review comprehensively explores the phytochemical, pharmacological, and nanotechnological dimensions of *C. fistula*, synthesizing recent preclinical and in vitro evidence. The plant exhibits a broad spectrum of therapeutic properties, including antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, antimicrobial, and anticancer activities—largely attributed to key phytoconstituents such as rhein, emodin, quercetin, and kaempferol. Advances in green nanotechnology have further enhanced its biomedical relevance, with silver and gold nanoparticles synthesized from *C. fistula* extracts demonstrating increased cytotoxicity, bioavailability, and targeted delivery. While traditional usage and animal studies suggest a favorable safety profile, data on reproductive toxicity, nanotoxicity, and human clinical trials remain limited. Regulatory challenges, including phytochemical standardization, dose optimization, and formulation consistency, must be addressed to ensure safe translation from bench to bedside. Future research should prioritize clinical validation, sustainable sourcing, and mechanistic insights into molecular pathways to fully realize the therapeutic potential of *Cassia fistula* in integrated healthcare systems.

Keywords: *Cassia fistula;* Phytochemicals; Nanotechnology; Pharmacological activities; Traditional medicine.

1. Introduction

Medicinal plants have long played a pivotal role in healthcare systems worldwide, serving as both curative agents and cultural cornerstones. Among these, *Cassia fistula* L., commonly known as the golden shower tree or "Amaltas" in traditional Indian medicine, has garnered considerable attention due to its broad spectrum of pharmacological properties and phytochemical richness. Indigenous to the Indian subcontinent and Southeast Asia, *C. fistula* belongs to the Fabaceae family and is widely revered in systems such as Ayurveda, Siddha, and Unani for its purgative, febrifugal, laxative, and antimicrobial benefits.[1–3]

The rising interest in *C. fistula* is not merely due to its traditional utility but is increasingly driven by modern scientific evidence supporting its potential therapeutic applications. Numerous studies have identified potent phytochemicals in various parts of the plant—particularly the pods, bark, leaves, and flowers—including anthraquinones (rhein, chrysophanol), flavonoids, tannins, glycosides, sennosides, and proanthocyanidins, which are known to exhibit antioxidant, anticancer, hepatoprotective, anti-inflammatory, and antimicrobial activities.[4–7]

Furthermore, in the context of emerging health challenges such as drug-resistant infections, metabolic disorders, and inflammatory diseases, *C. fistula* has shown promising bioactivity in both in vitro and in vivo models.[8–10] Global reports also emphasize the urgent need for plant-derived therapeutic agents to address antimicrobial resistance and chronic disease burden.[11,12]

Additionally, nanotechnology has opened new avenues for the application of *C. fistula*-derived compounds in precision medicine. Silver and gold nanoparticles synthesized using *C. fistula* extracts have demonstrated enhanced antimicrobial and cytotoxic effects, establishing the plant as a candidate for biosynthetic nanomedicine.[13–15]

This review aims to comprehensively summarize the ethnobotanical legacy, phytochemical composition, pharmacological activities, nanotechnological applications, pharmacokinetic interactions, and translational opportunities of *Cassia fistula*. In doing so, it bridges traditional knowledge and contemporary scientific validation, offering insights into its development as a multi-targeted therapeutic agent.

2. Botanical and Ethnobotanical Overview

2.1 Botanical Identity and Morphology

Cassia fistula L., belonging to the family Fabaceae (Caesalpinioideae), is a medium-sized, deciduous tree widely distributed throughout the Indian subcontinent, Southeast Asia, and parts of Africa. Commonly known as the golden shower tree or Indian laburnum, it is appreciated for its vibrant yellow racemose inflorescences and traditional medicinal applications. The tree typically reaches 6–12 meters in height, featuring pinnate compound leaves arranged alternately with 4–8 pairs of elliptical to ovate leaflets.[1,2]

The flowers are pendulous, bright yellow, and borne on long racemes, with each flower measuring approximately 4–5 cm in diameter. The fruit is a cylindrical pod, up to 60 cm long, containing multiple dark brown seeds embedded in a sticky, sweet, and musky pulp. The bark is greyish-white in young trees and darkens with age, and the root system is characterized by a reddish-brown hue with lenticels and coarse texture.[2]

This morphological diversity is also linked to the plant's pharmacological versatility, as different plant parts (leaves, bark, flowers, seeds, pods, roots) harbor specific phytoconstituents. The morphological attributes of *C. fistula* serve not only as identification tools but also as markers of chemical maturity and therapeutic potential.[6]

2.2 Taxonomy and Nomenclature

The taxonomic classification of *C. fistula* is as follows: Kingdom: Plantae; Subkingdom: Tracheobionta; Division: Magnoliophyta; Class: Magnoliopsida; Order: Fabales; Family: Fabaceae; Genus: Cassia; Species: *C. fistula* L.

Locally, *C. fistula* is referred to by various vernacular names: "Amaltas" in Hindi, "Aragvadha" in Sanskrit (meaning "disease killer"), "Konna" in Malayalam, and "Sonalu" in Bengali, reflecting its ethnomedical significance in diverse linguistic and cultural regions.[4]

2.3 Geographical Distribution and Ecology

Cassia fistula is native to India and Sri Lanka but has been widely cultivated in tropical and subtropical regions including Thailand, Malaysia, Indonesia, China, and parts of East Africa and South America. In India, it thrives in deciduous forests, along roadsides, and in mixed monsoon zones up to 1300 meters in elevation, particularly in the Western Ghats and Deccan Plateau.[6]

The tree is well-adapted to a variety of soil types—ranging from clayey loam to red sandy—and shows tolerance to drought and saline conditions. Its cultivation is favored by tropical climates with annual rainfall between 500 to 3000 mm and temperature ranges from -5°C to 45°C. Despite being deciduous, it exhibits ornamental evergreen traits in regions with consistent humidity.[4]

2.4 Ethnomedicinal Applications

Historically, *C. fistula* has occupied a prominent place in traditional medicine systems, especially Ayurveda, Siddha, and Unani. Classical Ayurvedic texts describe its utility in treating conditions such as constipation, skin disorders, fever, and arthritis. The plant is considered "Raktaprasadana" (blood purifier) and has been used as a purgative, febrifuge, and anti-periodic agent.[2,3]

The pulp of the fruit pod is a well-known gentle laxative, safe for pediatric and geriatric populations. Leaves are used in poultices to treat inflammation, facial paralysis, and insect bites, while bark and seeds are utilized for treating skin eruptions, ulcers, and diabetes.[3,16,17]

A comparative ethnopharmacological survey in rural Indian and Thai communities has revealed consistent use of *C. fistula* for purgative, hepatic, and dermatologic indications—supporting its traditional usage with cross-cultural consensus.[9,18]

2.5 Phenological Variation and Therapeutic Quality

Recent ecological research indicates that seasonal and geographic variability can influence the concentration of active phytochemicals in *C. fistula*, particularly anthraquinones and flavonoids. For example, trees exposed to higher UV radiation and drier climates tend to produce pods with elevated antioxidant content. These phenological insights are essential for developing standardized cultivation and harvesting strategies aimed at optimizing therapeutic efficacy.[4]

3. Phytochemical Diversity

The therapeutic efficacy of *Cassia fistula* is largely attributed to its diverse secondary metabolites, which include a wide array of anthraquinones, flavonoids, tannins, alkaloids, sterols, saponins, glycosides, terpenoids, and phenolic compounds.[4] These bioactive molecules are differentially distributed across various parts of the plant, and several studies have demonstrated their concentration and potency vary with environmental factors, plant maturity, and extraction methods (Table 1).

Table 1: Organ-Specific Phytochemical Profile.[4,6]

Plant Part	Major Phytochemicals	Pharmacological Implications
Fruit Pulp	Rhein, emodin, sennosides, tannins	Laxative, anticancer, antioxidant
Leaves	Kaempferol, quercetin, apigenin	Anti-inflammatory, antioxidant
Flowers	Flavonoids, anthraquinones	Antioxidant, antibacterial
Bark	Lupeol, β-sitosterol, tannins	Anti-inflammatory, hepatoprotective
Roots	Sterols, alkaloids	Antimicrobial, analgesic
Seeds	Alkaloids, phenolic acids	CNS activity, antimicrobial

3.1 Anthraquinones

Among the hallmark constituents of *C. fistula*, anthraquinones such as rhein, emodin, chrysophanol, and physcion are especially abundant in the fruit pulp and pods. These compounds are known for their purgative, anticancer, and anti-inflammatory properties. Rhein and chrysophanol have also demonstrated anti-arthritic effects by modulating inflammatory cytokines.[9]

3.2 Flavonoids

Flavonoids such as kaempferol, luteolin, quercetin, and apigenin are widely present in the leaves and flowers of *C. fistula*, and are responsible for potent antioxidant and hepatoprotective activities.[6,14,19] These compounds exert radical-scavenging effects through hydrogen-donating ability and inhibition of lipid peroxidation, contributing to the plant's role in oxidative stress mitigation.

3.3 Tannins and Polyphenols

Tannins, especially condensed tannins (proanthocyanidins), have been quantified in both bark and pods of *C. fistula* using Folin–Ciocalteu and vanillin assays. Their astringent properties make them suitable for treating diarrhea and wound healing, while their antioxidant potential supports cardioprotective and anti-aging claims.[4]

3.4 Glycosides and Sennosides

The fruit pulp of *C. fistula* contains sennosides A and B, glycosidic anthraquinones known for their mild laxative effect. These are of particular importance in pediatric and geriatric formulations due to their safety profile and efficacy in constipation management.[2]

3.5 Alkaloids, Sterols, and Terpenoids

Sterols like β-sitosterol and stigmasterol, and triterpenoids such as lupeol, are predominantly found in the bark and roots of *C. fistula*, demonstrating anti-inflammatory, anticancer, and cholesterol-lowering activities. Alkaloids in the seeds have shown antimicrobial effects and potential CNS depressant properties.[4]

4. Influence of Extraction Solvents and Methods

The type of solvent used significantly impacts the yield and bioactivity of extracted phytochemicals. Methanol and ethanol extracts often show the highest antioxidant and antimicrobial potential due to their ability to solubilize both polar and moderately non-polar compounds.[14,20] Aqueous extracts are traditionally used in ethnomedicine but may offer lower concentrations of lipophilic actives. Recent studies have emphasized the use of green extraction techniques, such as ultrasound-assisted and microwave-assisted extraction, which enhance yield while preserving thermolabile constituents.[8,21]

5. Pharmacological Activities

The extensive therapeutic repertoire of *Cassia fistula* L. is underpinned by its rich phytoconstituents—particularly anthraquinones, flavonoids, and polyphenols—which mediate a wide spectrum of bioactivities. Recent preclinical studies have validated its potential in addressing oxidative stress, inflammation, metabolic disorders, microbial infections, and cancer (Figure 1, Table 2 and 3).[22–24]

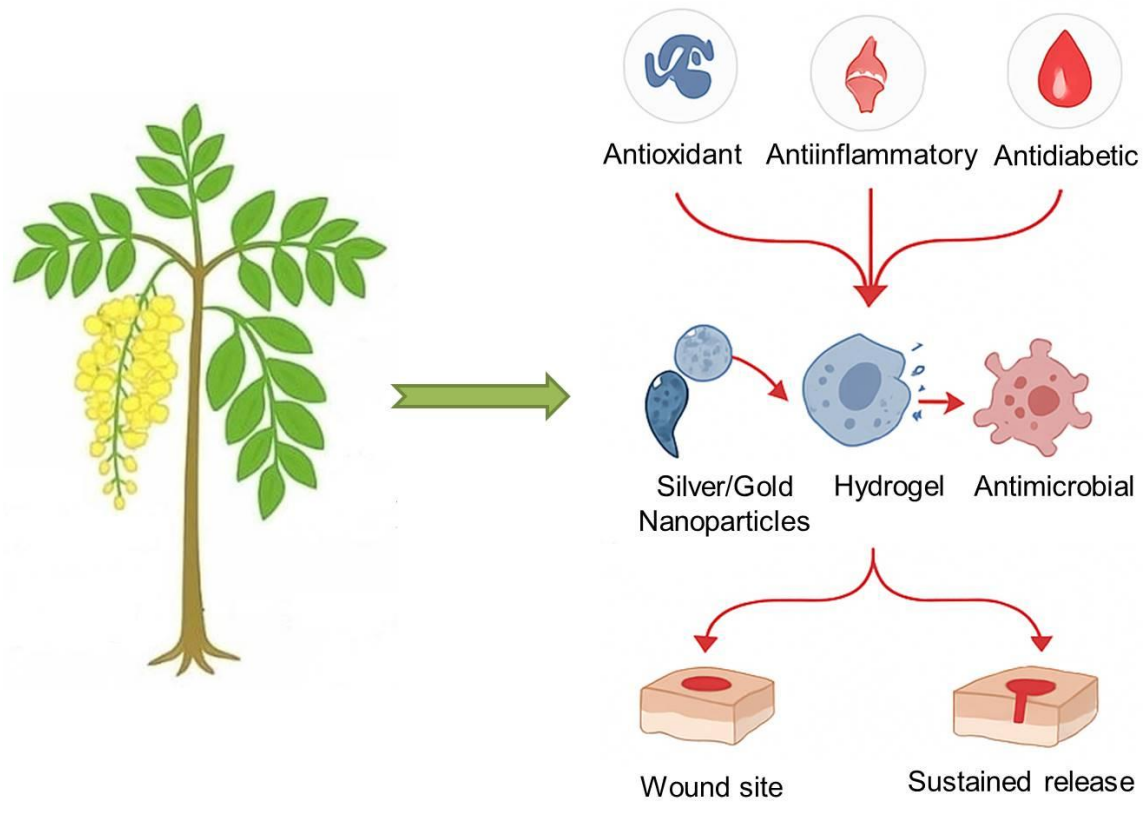

Figure 1: Highlights of Pharmacological Effects of *Cassia fistula.*

Table 2: Phytochemistry of *Cassia fistula* (major plant parts, phytochemicals, and pharmacological implications)

Plant Part	Major Phytochemicals	Pharmacological Implications
Fruit Pulp	Rhein, emodin, sennosides, tannins	Laxative, anticancer, antioxidant[10,26]
Leaves	Kaempferol, quercetin, apigenin	Anti-inflammatory, antioxidant[22,24]
Flowers	Flavonoids, anthraquinones	Antioxidant, antibacterial[5,33]
Bark	Lupeol, β-sitosterol, tannins	Anti-inflammatory, hepatoprotective[30,31]
Roots	Sterols, alkaloids	Antimicrobial, analgesic[34]
Seeds	Alkaloids, phenolic acids	CNS activity, antimicrobial[39]

5.1 Antioxidant Activity

Oxidative stress is a central mechanism in the pathogenesis of chronic diseases such as diabetes, neurodegeneration, and cardiovascular disorders. Extracts of *C. fistula*—particularly from the fruit pulp and flowers—have demonstrated potent antioxidant effects in various in vitro models, including DPPH, ABTS, FRAP, and nitric oxide scavenging assays.[5,6,7] These effects are attributed to polyphenolic compounds such as quercetin, kaempferol, and rhein, which are known to neutralize reactive oxygen species and upregulate endogenous antioxidant enzymes.

A recent study reported that methanolic extracts increased superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in arthritic rats, reducing malondialdehyde (MDA) levels.[25] These findings were supported by solvent-dependent variability in antioxidant activity[20] and neuroprotective effects in *Caenorhabditis elegans*.[26]

5.2 Anti-inflammatory and Anti-arthritic Effects

Ethanolic extracts of *C. fistula* pods and pulp have shown anti-inflammatory activity in acute and chronic models.[25] Collagen-induced arthritic rats treated with fruit extract exhibited reduced paw edema and pro-inflammatory cytokines (TNF-α, IL-6, IL-17).[25] This effect is mediated via inhibition of NF-κB and COX-2, aligning with earlier evidence of anthraquinone immunomodulation.[9,8,27] Rhein further inhibits iNOS and COX-2 in murine models.[22,28] Histological analysis demonstrated reduced synovial hyperplasia, cartilage erosion, and neutrophil infiltration, indicating joint protection. This effect is believed to be mediated via the inhibition of NF-κB and COX-2 pathways, aligning with prior evidence of anthraquinone-based immunomodulation.[8,9]

Rhein, a major anthraquinone isolated from *C. fistula*, exerts potent anti-inflammatory effects by downregulating nuclear factor-κB (NF-κB) signaling, thereby suppressing the expression of pro-inflammatory mediators including TNF-α, IL-6, IL-1β, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). At the same time, rhein enhances antioxidant defense through activation of the Nrf2/HO-1 and PPAR-γ pathways, which collectively reduce oxidative stress and tissue damage[4,24]. These dual actions position *C. fistula* as a promising candidate for inflammatory and autoimmune disorders.

5.3 Antidiabetic and Hypolipidemic Effects

The antidiabetic potential of *C. fistula* has been explored in alloxan- and streptozotocin-induced diabetic rat models. Aqueous and alcoholic extracts of the fruit pulp significantly reduced fasting blood glucose levels, improved glucose tolerance, and restored insulin sensitivity. These effects are linked to the presence of kaempferol, rhein, and lupeol, which modulate key enzymes such as α-glucosidase and glucose-6-phosphatase.[4,29,30] In addition to glycemic control, bark and leaf extracts lowered serum cholesterol, triglycerides, and LDL while raising HDL.[16,31] Recent nutraceutical work also confirmed hypolipidemic effects in hyperlipidemic rats.[32]

In metabolic disease models, *C. fistula* extracts have demonstrated improvements in glucose and lipid regulation. Ultrasonic-assisted extracts from the fruit pulp reduced serum cholesterol, triglycerides, and low-density lipoprotein (LDL), while enhancing high-density lipoprotein (HDL) and improving hepatic enzyme activity in hyperlipidemic rats[5]. Additionally, hematological parameters such as red blood cell count, hemoglobin concentration, and mean corpuscular indices were normalized, highlighting a broader role in maintaining systemic homeostasis[5]. These findings support traditional claims of *C. fistula* as a tonic for metabolic and blood disorders.

5.4 Anticancer and Cytotoxic Properties

Anthraquinones such as rhein and emodin, isolated from *C. fistula*, have shown promising cytotoxic effects against several human cancer cell lines, including MCF-7 (breast), A549 (lung), and HeLa (cervical) cells. Rhein has been reported to induce apoptosis via mitochondrial depolarization and caspase activation, while also exhibiting anti-proliferative effects through downregulation of cyclin D1 and CDK4.[9,22] Moreover, silver nanoparticles synthesized using *C. fistula* extracts have demonstrated enhanced cytotoxicity against MDA-MB-231 breast cancer cells, showing dose-dependent inhibition of cell viability and increased ROS generation. These findings suggest synergistic interactions between phytochemicals and nanocarriers in cancer therapy.[13,33] Molecular docking supports anticancer roles for rhein and kaempferol in ovarian cancer.[34]

5.5 Hepatoprotective Effects

The hepatoprotective efficacy of *C. fistula* has been investigated in models of bromobenzene- and

paracetamol-induced liver toxicity. Methanolic fruit extracts have shown to significantly reduce hepatic enzymes (ALT, AST, ALP), bilirubin, and lipid peroxidation levels, while restoring antioxidant enzymes.[5] Histology confirmed improved hepatic architecture. Early studies demonstrated hepatoprotection in diethylnitrosamine and CCl_4 toxicity models.[35,36]

5.6 Antimicrobial and Antiparasitic Activities

Extracts from various parts of *C. fistula* have displayed broad-spectrum antibacterial and antifungal activity against pathogens such as *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Aspergillus niger*.[3,37] These effects are often attributed to flavonoids, tannins, and saponins that disrupt microbial cell walls and inhibit nucleic acid synthesis. Leaf extracts showed antileishmanial activity with IC_{50} ~43 µg/mL.[8] Antifungal effects against fluconazole-resistant *Candida* strains and antibacterial activity of protease inhibitors have also been documented.[38,39]

5.7 Other Activities

Anthelmintic: Effective against intestinal worms in *Pheretima posthuma* and goat nematodes.[40,41]

Wound healing: Promoted epithelialization and collagen synthesis.[42]

Antitussive/antipyretic: Possibly via prostaglandin modulation.[29]

Analgesic: Demonstrated in hot-plate and tail-flick tests.[30,43]

Neuroprotective/anticonvulsant: Reduced seizure severity in PTZ-induced convulsions.[29,43]

Table 3: Pharmacological activities of *Cassia fistula.*

Pharmacological Activity	Plant Part / Extract Type	Major Active Compounds	Experimental Models	Observed Outcomes	Ref
Antioxidant	Fruit pulp (methanol), flowers (ethanol)	Rhein, quercetin, kaempferol	DPPH, ABTS, FRAP assays; arthritic rat serum	↑ SOD, CAT, GPx; ↓ MDA levels	[5,23]
Anti-inflammatory & Anti-arthritic	Fruit pulp (ethanol)	Rhein, chrysophanol	Collagen-induced arthritis in rats	↓ TNF-α, IL-6, IL-17; ↓ paw edema, joint damage	[23,8]
Antidiabetic & Hypolipidemic	Pulp, bark (aqueous, ethanolic)	Lupeol, kaempferol, sennosides	Alloxan/STZ-induced diabetic rats	↓ FBG, TC, LDL, TG; ↑ HDL, insulin sensitivity	[4,25,26]
Anticancer	Fruit pulp, flowers (ethanol); AgNPs	Rhein, emodin, AgNPs	MCF-7, HeLa, A549 cell lines	↑ Apoptosis, ROS; ↓ proliferation, cyclin D1	[9,28]
Hepatoprotective	Fruit pulp (methanol)	Flavonoids, tannins	Paracetamol/bromobenzene-induced toxicity	↓ ALT, AST, ALP, MDA; ↑ SOD, histological recovery	[30,31]
Antimicrobial	Leaves, bark (methanol/aqueous)	Tannins, flavonoids, alkaloids	*E. coli*, *S. aureus*, *C. albicans*	Inhibition zones; MIC < 100 µg/mL	[20,33,34]
Antiparasitic (Leishmanicidal)	Leaf extract (methanol)	Phenolic acids	*L. donovani* promastigotes	IC_{50} ≈ 43 µg/mL; mitochondrial dysfunction	[8]
Analgesic / Antipyretic	Seeds, leaves (ethanol)	Alkaloids, flavonoids	Tail-flick, hot plate, yeast-induced pyrexia	↑ Pain threshold; ↓ body temp	[39]
Wound Healing	Leaves (paste, ethanol extract)	Flavonoids, saponins	Excision wound model in rats	↑ Collagen deposition; faster re-epithelialization	[37]

6. Advances in formulation and delivery

Beyond direct pharmacological activity, *C. fistula* is also being investigated as a natural excipient in drug delivery systems. Mucilage derived from its seeds has shown promise as a biodegradable polymer in gastroretentive floating tablets of atenolol, where it enhanced gastric residence time and optimized sustained drug release[44]. Nanotechnology-based approaches further highlight its translational potential, with *C. fistula* extracts successfully incorporated into silver and gold nanoparticles for improved antioxidant, antimicrobial, and anticancer activity[6,13]. These advances suggest that *C. fistula* may serve both as an active therapeutic agent and as a novel biomaterial in modern pharmaceutics.

6.1 Nanotechnology and Novel Formulations

The integration of nanotechnology into phytomedicine has opened new dimensions for improving the solubility, bioavailability, stability, and target-specific delivery of plant-derived compounds. *Cassia fistula* L., owing to its rich phytochemical profile, has emerged as a promising candidate in the green synthesis of metallic nanoparticles and the development of novel drug delivery systems (Table 3).[6,13]

6.1.1 Silver and Gold Nanoparticles

The biosynthesis of silver (AgNPs) and gold nanoparticles (AuNPs) using *C. fistula* extracts has gained attention for being eco-friendly, cost-effective, and devoid of toxic reducing agents. Phytochemicals such as flavonoids, phenolic acids, and tannins present in the leaf, bark, and fruit pulp extracts act as both reducing and capping agents, facilitating stable nanoparticle formation. [6,13,33]

In a recent study, silver nanoparticles synthesized from *C. fistula* fruit pulp exhibited an average particle size of 20–40 nm and demonstrated strong antimicrobial activity against *E. coli*, *S. aureus*, and *Candida albicans*. The nanoparticles also showed significant cytotoxicity against MDA-MB-231 breast cancer cells by inducing reactive oxygen species (ROS) generation and mitochondrial damage.[13]

Similarly, gold nanoparticles synthesized using aqueous leaf extract displayed remarkable antioxidant properties and biocompatibility, suggesting their potential utility in drug delivery and diagnostic imaging.[6,14,45]

6.1.2 Green Nanoparticles

Flower tea-derived nanoparticles exhibited antioxidant and antihyperglycemic activities.[14] Iron oxide nanoparticles synthesized using leaf extracts showed drug delivery and imaging potential.[44] Recent computational docking and in silico pharmacokinetic analyses of *C. fistula*-derived rhein and lupeol have further validated their suitability for oral and transdermal nanocarrier-based delivery.[8]

6.2 Novel Formulations

Nanoparticles synthesized from *C. fistula* extracts have demonstrated superior antimicrobial and anticancer efficacy compared to their crude counterparts. This enhanced activity is likely due to: increased surface area-to-volume ratio for better interaction with microbial membranes; enhanced cellular uptake and intracellular ROS generation in cancer cells; sustained release of bioactive components, improving therapeutic duration and potency. This nano-synergism has laid the groundwork for nanoparticle-based therapeutics derived from *C. fistula*, especially in oncology and infectious disease management. [6,13]

C. fistula-based microcapsules, gels, and emulsions were developed for wound healing and dermatology.[42,3] Nanostructured emulsions of seed oil improved antimicrobial activity and skin penetration.[44]

6.2.1 Polymer-Based and Controlled-Release Formulations

In addition to metallic nanoparticles, efforts have been made to formulate *C. fistula* extracts into polymeric matrices for controlled release. For example, polyvinyl alcohol (PVA)-based hydrogel systems incorporating methanolic fruit extracts have shown prolonged release profiles and retained antioxidant activity in vitro, ideal for wound healing and transdermal applications.[15,41]

Encapsulation using biodegradable polymers such as PLGA (poly-lactic-co-glycolic acid) and chitosan has also been proposed to improve oral bioavailability and gastrointestinal stability of anthraquinones and flavonoids—two key therapeutic moieties in *C. fistula*.[8]

6.2.2 Prospects for Smart Delivery Systems

The convergence of *C. fistula* bioactives with smart delivery platforms, including: Liposomes, Solid lipid nanoparticles (SLNs), Nanofibers, Stimuli-responsive hydrogels is currently under exploration to enhance tissue targeting and bypass hepatic first-pass metabolism. These approaches aim to resolve challenges related to poor aqueous solubility, enzymatic degradation, and inconsistent pharmacokinetics that often hinder herbal-based therapeutics.[6]

Table 4: Nanotechnology-based formulations of *Cassia fistula.*

Plant Part / Extract	Formulation / Nanocarrier	Key Phytochemicals	Biological Target / Use	Reported Outcomes	Ref
Fruit pulp (aqueous)	Silver nanoparticles (AgNPs)	Rhein, flavonoids	Antibacterial, anticancer	Enhanced antibacterial activity; ROS-mediated cytotoxicity in MDA-MB-231 cells	13
Leaf extract (aqueous)	Gold nanoparticles (AuNPs)	Tannins, phenolics	Antioxidant, diagnostic	High antioxidant activity, stable particle formation	6
Fruit pulp (methanol)	PVA-based hydrogel matrix	Anthraquinones, polyphenols	Wound healing (topical)	Sustained release, maintained antioxidant activity	26
Pod/leaf extract	PLGA nanoparticles	Rhein, kaempferol	Oral / transdermal delivery	Improved bioavailability, controlled drug release (in vitro)	8
Methanolic extract	Liposome-encapsulated systems (proposed)	Emodin, lupeol	Hepatoprotective, anticancer	Conceptual basis for increased tissue targeting, bypass first-pass metabolism	6

7. Safety, Toxicity, and Clinical Relevance

Despite the promising pharmacological potential of *Cassia fistula* L., a comprehensive understanding of its safety profile is crucial for its rational therapeutic application. Traditionally used in pediatric and geriatric formulations, the plant is considered relatively safe in low to moderate doses. However, emerging experimental evidence suggests that caution must be exercised regarding dose, formulation, and duration of use, especially with concentrated extracts and novel nanocarriers.[45]

7.1 Acute and Sub-chronic Toxicity

Several preclinical studies have assessed the acute and sub-acute toxicity profiles of various *C. fistula* extracts in rodent models. An oral dose of up to 2000 mg/kg of ethanolic and aqueous fruit pulp extract showed no mortality, behavioral changes, or significant alterations in biochemical or hematological parameters, indicating a high safety margin.[48] In a sub-chronic toxicity study, daily oral administration of hydroalcoholic fruit extract (500 mg/kg) for 28 days resulted in no histopathological abnormalities in vital organs, although mild elevation in liver enzymes was observed at higher doses (≥1000 mg/kg), warranting dose optimization in therapeutic applications.[35,44]

7.2 Reproductive and Developmental Toxicity

Limited studies have examined the reproductive toxicity of *C. fistula*. Some reports suggest that methanolic bark extracts may reduce sperm count and motility in male rats at high doses, potentially due to oxidative imbalance or hormonal modulation. However, these findings are not consistent across all studies and require further validation through standardized reproductive toxicity assays.[28,41] No teratogenic effects have been reported in the literature, but data on pregnancy and lactation safety remain insufficient, thus discouraging use in these populations until robust clinical evidence is available.

7.3 Nanotoxicology Considerations

While *C. fistula*-based nanoparticles offer enhanced efficacy, concerns regarding nanoparticle-induced toxicity have also emerged. For instance, biosynthesized silver nanoparticles (AgNPs) from *C. fistula* exhibited dose-dependent cytotoxicity in vitro, raising the importance of thorough dose standardization and biocompatibility testing. Nanoparticle accumulation in organs such as the liver, kidneys, and spleen has been observed in unrelated studies, suggesting that long-term safety assessments are critical before clinical translation of *C. fistula*-based nanoformulations.[44]

7.4 Clinical & Translational Evidence

To date, relatively few controlled human clinical trials have evaluated *Cassia fistula*. Its traditional use as a laxative, particularly the fruit pulp, is well documented in Ayurvedic medicine, and the plant is listed in classical pharmacopeias such as the *Ayurvedic Pharmacopoeia of India* for pediatric constipation and skin disorders. Ayurvedic formulations such as Aragvadharishta, employed for detoxification and gastrointestinal regulation, also contain *C. fistula* as a key ingredient, while standardized pulp preparations such as Rajavriksha Avaleha are formally recognized in traditional practice[11]. Ethnomedical reports continue to suggest applications in hemorrhoids, hepatic dysfunction, and metabolic syndrome, although systematic clinical validation remains limited.

Commercial herbal products containing *C. fistula* are marketed globally as dietary supplements and laxative syrups. However, these are generally unstandardized and lack regulatory oversight, emphasizing the urgent need for pharmacokinetic and pharmacodynamic studies in humans, standardized dose–response trials, and post-marketing surveillance to ensure safety and efficacy[11].

Recent randomized clinical trials have provided stronger evidence for its laxative effects. In children with functional constipation, *C. fistula* emulsion (CFE) was superior to mineral oil, producing a significant increase in defecation frequency (from ~1.7/week to ~10.6/week), softer stool consistency, and reduced pain

over a three-week treatment period, with fewer adverse effects. In geriatric patients, *C. fistula* syrup outperformed lactulose, with greater improvements in stool frequency, consistency, and quality-of-life indices. Similarly, in patients with chronic kidney disease and concurrent constipation, *C. fistula* syrup produced more favorable outcomes than lactulose, including reduced straining, improved stool hardness, and even beneficial effects on biochemical renal parameters.[45]

Taken together, these findings highlight the translational potential of *C. fistula*—extending from traditional formulations to evidence-based clinical use in diverse populations including children, the elderly, and patients with chronic comorbidities.

8. Regulatory and Standardization Challenges

The pharmacological application of *C. fistula* is hindered by the lack of standardization in extract preparation, phytochemical profiling, and clinical dosage guidelines. Regulatory frameworks for herbal medicines in many countries do not enforce stringent quality control or toxicological testing, leading to variability in safety profiles among commercial products.[11]

Advancing *C. fistula* from traditional remedy to evidence-based therapeutic agent will require: comprehensive toxicology protocols; Good Manufacturing Practice (GMP) certification of herbal formulations; establishment of monographs specifying safe dose ranges, and WHO-compliant preclinical-to-clinical translation models.

9. Conclusion and Future Perspectives

Cassia fistula L. exemplifies the convergence of traditional medicine and modern biomedical research. Its ethnopharmacological heritage is strongly supported by preclinical evidence, confirming antioxidant, anti-inflammatory, antidiabetic, anticancer, hepatoprotective, antimicrobial, and wound-healing properties. Despite this promise, translational gaps persist. Most studies remain limited to in vitro or animal models, with scarce clinical trials. Standardization of extracts, molecular target elucidation, and pharmacokinetic profiling are urgently needed.

Omics-based approaches such as metabolomics and proteomics, combined with molecular docking and AI-assisted drug discovery, may help identify novel lead compounds. Nanotechnology also offers new avenues to improve solubility, bioavailability, and targeted delivery, though nanotoxicology studies remain essential.

10. Future directions should include:

1. Rigorous clinical trials for validated indications such as constipation and metabolic disorders.
2. Standardized formulations to ensure reproducible efficacy.
3. Advanced delivery systems (nanoemulsions, gels, capsules) to enhance translational relevance.
4. Safety studies across vulnerable populations such as pregnant women and elderly patients.

By addressing these gaps, *C. fistula* could transition from a traditional remedy to a validated phytopharmaceutical with global impact.

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