REVIEW

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Cassia fistula L.: PHYTOCHEMICAL CONSTITUENTS, PHARMACOLOGICAL ACTIVITIES, DEFENCE MECHANISMS AGAINST HERBIVORES, AND SAFETY PERSPECTIVES—A COMPREHENSIVE REVIEW

Anup Mohan[1], Saumendu Deb Roy[2], Bishal Sarkar[2*]

[1]Chanakya Diagnostic Lab & Polyclinic, Sonari, Charaideo, Assam, 785690, India
[2]Mata Gujri College of Pharmacy, Kishanganj, Bihar, 855107, India

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Abstract

Cassia fistula L. (Fabaceae), also known as golden shower tree or Indian laburnum, is a widely distributed medicinal plant with diverse ethnobotanical applications involving leaves, bark, fruits, flowers, seeds and roots as remedies for constipation, skin diseases, fever, inflammation, diabetes, liver disorders and microbial infections. Therefore, this plant has drawn the attention of researchers and has been studied extensively for its phytochemical compositions and biological properties. This review article systematically summarizes the botanical characteristics, traditional uses, phytochemical and pharmacological properties of its constituents, defense mechanisms against herbivory and safety profile of *C. fistula* L. Various secondary metabolites such as anthraquinones, flavonoids, phenolic compounds, tannins, alkaloids, terpenoids, sterols and glycosides have been reported in different parts of the plant. The major constituents such as rhein, emodin, chrysophanol, physcion, quercetin, kaempferol, catechin and others have been reported to produce diverse pharmacological activities and therapeutic effects against various diseases including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, antitumor, wound healing, neuroprotective, laxative and others. *C. fistula* L. has been reported to produce different defense compounds against herbivory such as tannins, anthraquinones, phenolics and others, which affect palatability, digestion and herbivore feeding behavior. Although animal and clinical trials are still scarce, the available evidence indicates that the plant is safe as per the dose used for medical treatments. The bioactive molecules of *C.fistula* L. have a great potential for phytopharmaceutical development and may induce novel molecular pathways for the treatment of various diseases. However, clinical trials and long-term safety studies need to be carried out to explore the therapeutic potential and understand its ecological interactions in practice.

Keywords

Cassia fistula; Anthraquinones; Pharmacological activities; Phytochemicals; Herbivory defense; Medicinal plants.

Corresponding author: Bishal Sarkar
E-mail: grpbishal@gmail.com ,
Mobile No: +91-8617850175

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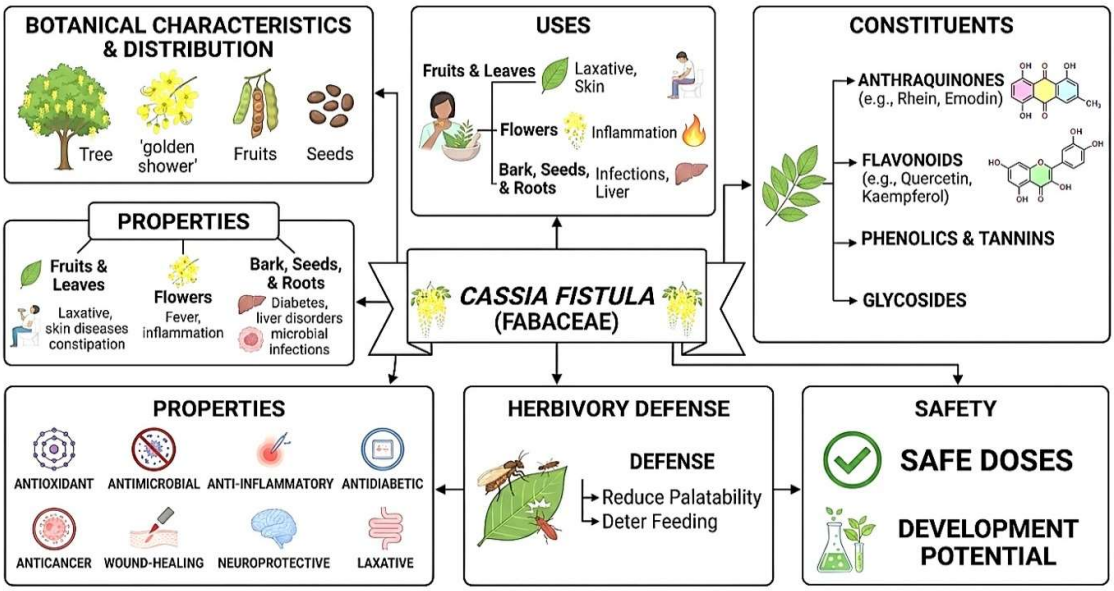
Graphical Abstract



1. Introduction

Medicinal plants have been used as healthcare remedies since ancient times and still hold a vital place in the discovery of modern drugs. According to the World Health Organization, almost 80% of the population of the world has partially or completely depended on traditional herbal medicines for their primary healthcare needs, especially in the developing world where medicinal plants are still easily accessible and culturally accepted [1,2]. Considerable interests have emerged toward plant-based natural resources as promising therapeutic candidates to overcome the increased incidence of chronic diseases, antimicrobial resistance and associated adverse effects of synthetic drugs [3,4]. Among the many species of medicinal plants, *Cassia fistula* L., also known as the golden shower tree and Indian laburnum is one of the most popular and valuable species, both for its widespread use in traditional medicine and for its pharmacological activities [5,9]. The species is a member of the family Fabaceae and is distributed throughout the tropical and subtropical regions of Asia, Africa, and South America [6,16,20]. It is generally cultivated as an ornamental tree due to its attracting yellow inflorescences. Nevertheless, the value of this plant goes far beyond its ornamental uses [7]. Different parts of *C. fistula* including leaves, flowers, fruits, bark, roots and seeds has been used in traditional systems of medicine such as Ayurveda, Siddha, Unani and various indigenous folk healthcare to cure constipation, skin disorder, fever, diabetes, liver diseases, inflammatory disorder and microbial infection [8,9,21]. The plant name "Aragvadha" (disease killer) is mentioned in the ancient Ayurvedic literature indicates the extensive usage of this plant as a medicinal plant in the Indian traditional medicine [18,21]. Plant has been reported as a rich source of biologically active secondary metabolites like anthraquinones, flavonoids, tannins, phenolic acids, glycosides, terpenoids and sterols [9–12]. The major groups of secondary metabolites such as rhein, emodin, chrysophanol, physcion, quercetin and kaempferol have been identified as promising medicinal plants with antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, hepatoprotective, anti-cancer, wound healing properties [5,9,14]. Secondary metabolites of *C. fistula* are biologically active with therapeutic importance. In addition, *C. fistula* plays an important ecological role in plant defense by employing its secondary metabolites in the form of chemical barriers against insect herbivores, herbivorous animals, and infecting pathogens by reducing the palatability, digestibility, or toxic nature [15]. These findings warrant integrative research on *C. fistula* phytochemistry, pharmacology, and its ecological role of protection against herbivory to broaden opportunities for drug discovery and phytopharmaceutical development. Despite various reviews summarizing the pharmacological and phytochemical aspects of the plant, integrative

reviews on the diverse phytochemistry, pharmacological, and protective ecological aspects of *C. fistula* are limited. A critical update on *C. fistula* phytochemistry and their pharmacological activities along with the ecological aspect would serve as an integrated resource for the scientific community.

2. Botanical Description and Taxonomy

Botanical identification and taxonomic classification play an increasingly important role in the utilization, conservation and scientific research of medicinal plants. *Cassia fistula* L. (golden shower tree or Indian laburnum, Fabaceae), considered to be a well-known medicinal plant, has been used by Asia as an ornamental, confectionery, and is also a significant ecological plant, attracting extensive attention. The species has a distinctive morphological property, distributed over a wide geographical region, and can adapt to various environmental conditions. Thus, exploring the taxonomic classification, vernacular names, morphology and habitat of *C. fistula* is essential to distinguish it from missed species and thereby ensure the authenticity of plant material used in phytochemical and pharmacological studies [16-22].

2.1 Taxonomic Classification

Cassia fistula L. (golden shower tree) of the Fabaceae family is one of the most prosperous species and is a well-known medicinal and ornamental tree species in tropical and subtropical areas. Due to its ethnomedicinal importance, phytochemical richness and ecological adaptability, the species is widely investigated (Table 1) [5,16].

The taxonomic classification of *C. fistula* is as follows:

Kingdom: Plantae

Subkingdom: Tracheobionta

Division: Magnoliophyta

Class: Magnoliopsida

Order: Fabales

Family: Fabaceae

Subfamily: Caesalpinioideae

Genus: *Cassia*

Species: *fistula* **[16,17]**

The genus *Cassia* comprises numerous species distributed throughout tropical and subtropical regions of the world, many of which possess important medicinal properties. Among them, *C. fistula* is considered one of the most pharmacologically valuable species owing to its rich content of anthraquinones, flavonoids, tannins, and other bioactive constituents [5,17].

2.2 Vernacular Names

Owing to its wide geographical distribution, *C. fistula* has developed a plethora of common names in several countries. In India, *C. fistula* in vernacular languages is popular as Aragvadha, Amaltas, Indian Laburnum, Golden Shower Tree. This plant is also known by various names in the vernacular languages of Sri Lanka, Bangladesh, Thailand, Myanmar and several African countries where this plant is used for medicinal, ornamental and ecological purposes [16,18].

"Aragvadha" is the Sanskrit name of *C. fistula* and it means "disease killer" because of the long use of this plant in the ancient Ayurveda medicine [18,21].

2.3 Morphological Characteristics

Cassia fistula is a medium-sized deciduous tree which reaches a height of 10-20 m. The canopy is moderately spreading, and the leaves are pinnately compound. Leaves in *Cassia fistula* are bipinnate [17]. The rachis at the base has a few axillary shoots. The leaves are alternate and occur in head [18]. Leaves have four to eight pairs of leaflets and are exstipulate. The leaflets are ovate to elliptic, having basal nerves and wedge-shaped base. Leaflets are borne on the rachis of a pair of leaflets; the leaflets are ovate, ovate-lanceolate or elliptic, and acute. The entire leaf is 20-40 cm long and comprises four to eight pairs of leaflets [16,18]. All leaves are shed before the start of the flowering [17]. The flowers are arranged as long pendulous racemes. The corolla is single, five-lobed [18] and bright yellow [17]. The flowers are arranged as long pendulous racemes and are characterized by five bright yellow petals. Flowering is more common in the dry season. The small, white anthers are distinct [17]. The fruit is a 30-60-cm-long, indehiscent cylindrical pod, thinly coriaceous, pinkish [17,20]. The mature pods are dark brown or black, smooth-edged and compressed at their two ends between the seeds, the seeds being

flattened and arranged parallel in the pod [20]. The pods contain many seeds [20]. The fruit has an external covering in the form of a smooth brownish-black seed coat. The seed is large and flattened. The fruit pulp is sweet and sticky. The seeds are hard with transverse partitions dividing it [20]

2.4 Geographical Distribution and Habitat

Cassia fistula has a native range in the Indian subcontinent but has been extensively naturalized in tropical and subtropical Asia, Africa, Central America, South America and Australia [18,20]. Among several factors, growth of *C. fistula* is heavily influenced by climate as it requires warm climates with minimal adaptation to a wide range of soil conditions, including sandy, loamy and moderately alkaline soils [5,16].

This tree species is widely distributed in deciduous forests, shrublands, roadsides, parks and gardens due to its adaptation to drought and seasonal fluctuations [20]. Besides its medicinal value, the fruits of *C. fistula* generate considerable relative amounts of nectar useful for pollinating insects, which can thereby enhance the short- and long-term biodiversity of tropical ecosystems [19].

Table 1. Taxonomic classification and common vernacular names of *Cassia fistula* L.

Category	Name	References
Kingdom	Plantae	[16,17]
Subkingdom	Tracheobionta	[16,17]
Division	Magnoliophyta	[16,17]
Class	Magnoliopsida	[16,17]
Order	Fabales	[16,17]
Family	Fabaceae	[16,17]
Subfamily	Caesalpinioideae	[16,17]
Genus	*Cassia*	[16,17]
Species	*fistula*	[16,17]
Common English Name	Golden Shower Tree, Indian Laburnum	[16,20]
Sanskrit Name	Aragvadha	[18,21]
Hindi Name	Amaltas	[18,23]
Bengali Name	Sonalu, Bandarlathi	[16,23]
Tamil Name	Kondrai	[18,23]
Telugu Name	Rela Chettu	[18,23]
Malayalam Name	Kanikkonna	[18,23]
Kannada Name	Kakke Mara	[18,23]
Marathi Name	Bahava	[18,23]
Gujarati Name	Garmalo	[18,23]
Punjabi Name	Amaltas	[18,23]
Sinhala Name	Ehela	[19,20]
Thai Name	Ratchaphruek (National Tree of Thailand)	[19,20]

3. Traditional and Ethnomedicinal Uses

Cassia fistula might have been effectively recognized for its medicinal importance in the traditional healthcare systems for centuries and it is used in the treatment of gastrointestinal, skin and liver diseases, fever, inflammation, microbial and other infections. Fruits, leaves, bark, flowers, seeds and roots of this plant are known to be effective against various diseases. *C. fistula* grows in many parts of the world and is widely used in Ayurveda, Siddha, Unani and other traditional indigenous medications. Hence, the plant is one of the top medicinal plants subjected to phytochemical, medicinal, physiological and pharmacological investigations. These investigations have allowed scientists to validate the uses of *C. fistula* reported in various traditional healthcare systems and to identify the biologically active molecules responsible for its

medicinal activities and properties (Table 2) [23,26,27,31,32].

3.1 Ayurvedic Applications

Cassia fistula L., known as Aragvadha in Ayurveda, is an important medicinal plant used in the Indian traditional health care system for centuries. The mythical name "Aragvadha" means "disease killer" and refers to the wide range of therapeutic uses found in the classic Ayurvedic literature [21,23]. According to Ayurvedic philosophy, the plant has mild purgative, cooling, anti-inflammatory and detoxifying actions and is used for a wide range of disorders associated with aggravated Pitta and Kapha doshas [21,22]. The fruit pulp is the most widely used part of the plant and constitutes a safe laxative to relieve constipation or hemorrhoids and gastrointestinal disorders [18,21]. The plant is also used in Ayurvedic formulations for the treatment of fevers, skin diseases, hepatobiliary diseases, as well as inflammatory disorders [17,18]. Fruit, bark, leaves and roots are used as blood purifiers and to aid wound healing [16,21,29,30].

3.2 Folk Medicinal Uses

Exclusively belonging to the world of Ayurveda, *C. fistula* also has a long history of usage as a folk medicine in different parts of Asia, Africa and tropical areas of the world [5,9]. In several local traditions, different parts of the plant have been used for the treatment of diverse diseases and syndromes, including digestive disorders, microbial infections, diabetes, respiratory diseases and dermatological conditions, among others [5,9]. The leaf paste is used to treat skin infections, ringworm, wounds and inflammatory lesions by applying topically in many rural regions of India [22]. Bark decoctions are used to treat fever, diarrhea and dysentery, while the infusions of flowers are applied as a mild laxative and cooling beverage in hot seasons [23]. Extracts of the seed are used in many countries of Southeast Asia to treat intestinal worms and microbial infections [24]. The broad spectrum of ethnomedicinal uses of *C. fistula* in various parts of the world points to interesting chemical constituents that can exert diverse pharmacological activities. These traditional uses of the plant are supported by rather recent scientific studies [9].

3.3 Therapeutic Uses of Different Plant Parts

Leaves

In folk medicine, the leaves of *C. fistula* are used in the management of skin diseases, skin wounds and ulcers, inflammation, and fat. Crushed leaves or leaf paste are applied externally and allowed for acceleration of healing and to prevent infection [10,22]. In some other traditional preparations, leaf decoctions are used for fever and inflammatory disorders.

Flowers

The flowers have a cooling, mild laxative, and antipyretic effect. The flower infusion is used for the treatment of constipation, fever, and urinary disorders, as well as to improve digestion and reduce heat in people [23].

Bark

Traditional medicine uses bark to treat diarrhoea, dysentery, fever, and skin diseases, due to its astringent and antimicrobial properties [17,18].

Fruits

The pulp of the fruit is the most common part of *C. fistula* used in folk medicine. It is a mild natural laxative. Hence, it is used for chronic constipation, hemorrhoids, intestinal disorders, and digestive disturbances. Traditional healers recommend the fruit pulp for the treatment of liver disorders and detoxification [18,21].

Seeds

Seeds have been used as folk remedies to treat skin infections, intestinal parasites, and microbial diseases. Seed preparations are used in traditional systems as antimicrobial and anti-inflammatory agents [24].

Roots

In folk medicine, roots are occasionally used to treat fever, glandular function, rheumatism, and some inflammatory disorders. In comparison with fruits and leaves, roots are usually less used in folk medicine, but the roots have been used as folk remedies for fever, constipation, rheumatism, dermatitis, diuretic, and antipyretic preparations [5,9].

These ethnomedicinal applications of different parts of *Cassia fistula* to treat various diseases (including microbial fever and inflammation) have promoted studies on the phytochemicals and pharmacological

aspects of the plant [9,10]. The in vivo pharmacological assessment of the traditional use of *C. fistula* for the treatment of microbial fever and inflammation is the subject of this review.

Table 2. Traditional and ethnomedicinal uses of different parts of *Cassia fistula* L.

Plant Part	Traditional Uses	System of Medicine	References
Leaves	Wounds, skin diseases, ringworm, inflammation	Folk medicine, Ayurveda	[10,22]
Flowers	Fever, constipation, urinary disorders	Ayurveda, Folk medicine	[23]
Bark	Diarrhea, dysentery, fever, skin diseases	Ayurveda, Folk medicine	[17,18]
Fruit pulp	Laxative, hemorrhoids, digestive disorders	Ayurveda	[18,21]
Seeds	Intestinal worms, microbial infections	Folk medicine	[24]
Roots	Rheumatism, fever, glandular disorders	Traditional medicine	[5,9]

4. Phytochemical Constituents of *Cassia fistula*

Cassia fistula L. is known to contain a variety of secondary metabolites such as anthraquinones, flavonoids, phenolic compounds, tannins, terpenoids, sterols, glycosides and carbohydrates. Various parts of the plant such as leaves, flowers, bark, fruits, seeds and roots contain a source of these numerous bioactive compounds, which play a vital role in studying and exploring its medicinal and ecological properties [9–12]. The composition of such constituents varies qualitatively and quantitatively according to plant part, geographical location, environmental factors and employed extraction method (Table 3) [9,10,31.32]

4.1 Primary Metabolites

Primary metabolites are compounds that play a vital role in plant growth, development and basic metabolic activities. Carbohydrates, proteins, amino acids, lipids and organic acids have been detected in different organs of *C. fistula* [12,22]. Sugars and polysaccharides were found in fruit pulp, and this explains the fruit taste and its traditional use as a natural laxative [18,23]. Proteins and essential amino acids were found in seeds and leaves [17,22].

4.2 Secondary Metabolites

Secondary metabolites comprise the major bioactive compounds of *C. fistula* and are believed to be responsible for the therapeutic properties and ecological defense strategies of the plant.

4.2.1 Anthraquinones

Anthraquinones are a group of compounds that have been extensively studied in *C. fistula*. Fruits, bark, leaves and flowers have yielded rhein, emodin, chrysophanol, physcion, aloe-emodin, and their glycosides [10, 11]. Rhein has anti-inflammatory, antimicrobial, hepatoprotective, and anti-cancer activities. Moreover, this compound exhibits antiproliferative activities and has anti-inflammatory action (antioxidant, etc.) as well [13, 27]. Emodin also has highly anti-oxidative, antidiabetic, and anti-proliferative action. Chrysophanol and physcion possess antimicrobial and anti-inflammatory actions [13, 27]. The high content of anthraquinones in fruit pulp is thought to be responsible for the laxative activity of the plant [18, 21].

4.2.2 Flavonoids

Flavonoids are abundant secondary metabolites in *C. fistula*. Leaf, flower, and fruit contain quercetin, kaempferol, catechin, epicatechin, and their glycosides [10, 12]. Flavonoids are efficient free radical scavengers, metal ion chelators, suppressors of oxidative stress, and they also have strong anti-oxidative action. In addition to the anti-oxidative action, flavonoids have anti-inflammatory, antibacterial, anti-hepatotoxic, anti-cardiotoxic, and antidiabetic effects [14, 26].

4.2.3 Phenolic Compounds

Phenolic compounds are a major group of antioxidant substances in *C. fistula*. Several phenolic acids such as gallic, ellagic, ferulic, caffeic, and chlorogenic acids [25,26] have been identified in various parts of the plant. Phenolic compounds protect plant tissues against oxidative damage and microbial attack. They are also major phytocompounds responsible for the antioxidant, anti-inflammatory and chemopreventive properties of *C. fistula* extracts [4,26].

4.2.4 Tannins

Tannins are polyphenolic compounds, found in the bark, leaves, and fruits of *C. fistula* [10,28] (hydrolysable and condensed). They have strong antioxidant and antimicrobial properties and are also involved in the plant defence mechanisms by reducing the palatability and digestibility of the plant material to herbivorous organisms. For this reason, astringent tannins compounds might be also involved in the traditional use of bark for diarrhoea, dysentery, and wound healing [21,28].

4.2.5 Terpenoids and Sterols

Some terpenoids, lupeol, β-sitosterol, stigmasterol and campesterol in particular, have been reported to have hepatoprotective, anti-inflammatory, antimicrobial properties and anticancer activities, which are exhibited by some natural compounds isolated from *C. fistula* [11,25]. Lupeol, in particular, at least in experimental models, has displayed wound-healing and anti-inflammatory activities.

4.2.6 Glycosides

Glycosides are another major group of compounds found in *C. fistula*, which have already been found in plants, contributing to their biological activities and the bioavailability of the bioactive constituents, i.e. anthraquinone glycosides and flavonoid glycosides [11,25]. In particular, they may act as organic forms of bioactive compounds that usually undergo enzymatic hydrolysis to release their aglycone forms.

4.3 Distribution of Phytoconstituents in Different Plant Parts

Most of the phytochemical compounds found in the fruit pulp, such as anthraquinones, tannins and salicylic acids, are usually found in the leaves, bark and other parts of *C. fistula*, with the difference that leaves contain high amounts of flavonoids and phenolics [9,10]. The seeds contain protein and fatty acids, together with some secondary metabolites and sugars (for example: glucose, xylose, rhamnose, etc.) [9]. Recently, the flowers were found to contain flavonoids, anthraquinones and antioxidant phenolics, which might explain their application in traditional medicine, especially in historical aspects [9].

4.4 Extraction and Characterization Techniques

Phytochemical constituents of *C. fistula*, as well as their ranges of bioactivity, have been the focus of most previous phytochemical studies. Conventional extraction methods such as maceration, Soxhlet extraction, and solvent extraction are commonly used to obtain phytochemical-rich extracts. Solvent systems using methanol, ethanol, ethyl acetate, and water have been employed [12,22]. The use of modern chromatographic and spectroscopic techniques, including high-performance liquid chromatography (HPLC), gas chromatography–mass spectrometry (GC–MS), liquid chromatography–mass spectrometry (LC–MS/MS) and fast Fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR) spectroscopy, has significantly improved the phytochemical profiling of *C. fistula* with respect to its complex phytochemicals and metabolite profiling [25]. HPLC has been successfully used to quantify anthraquinones and flavonoids in the fruit, stem bark, leaves and flower extracts [10,12].

Overall, these phytochemical investigations strongly support the fact that *Cassia fistula* is a rich source of phytochemical constituents having diverse bioactive functions, which could explain its many pharmacological functions as well as its ecological defense mechanism.

5. Pharmacological Activities

Cassia fistula is a species of importance that has long been used in several traditional systems of medicine. Various pharmacological activities such as antioxidant, antimicrobial, anti-inflammatory, antidiabetic, anticancer, laxative, and wound healing have been reported. A rich phytochemical composition of the plant, such as anthraquinones, flavonoids, phenolic compounds, tannins, glycosides, and other compounds, may be responsible for the observed effects of *C. fistula*. In vitro, in vivo, and model organism studies have been performed in order to investigate the pharmacological properties that may improve the health of the people, and some of these activities are reported in the present review. These therapeutic effects of the plant may provide a valuable source of natural therapeutic agents for the treatment and prevention of several diseases. The major pharmacological activities of the plant are presented in detail (Table 4).

Table 3. Major phytochemical constituents identified in *Cassia fistula* and their biological significance

Class	Compounds	Plant Part(s)	Significance	References
Anthraquinones	Rhein, Emodin, Chrysophanol, Physcion, Aloe-emodin	Fruit pulp, Bark, Leaves, Flowers	Laxative, anti-inflammatory, antimicrobial, hepatoprotective, anticancer	[10,11,13,27]
Flavonoids	Quercetin, Kaempferol, Catechin, Epicatechin	Leaves, Flowers, Fruits	Antioxidant, anti-inflammatory, antidiabetic, cardioprotective	[10,12,14,26]
Phenolic Compounds	Gallic acid, Ellagic acid, Ferulic acid, Caffeic acid, Chlorogenic acid	Leaves, Bark, Fruits	Antioxidant, antimicrobial, chemopreventive	[25,26]
Tannins	Hydrolysable tannins, Condensed tannins	Bark, Leaves, Fruits	Astringent, antimicrobial, anti-herbivory defense	[10,21,28]
Terpenoids	Lupeol and related triterpenoids	Bark, Leaves	Anti-inflammatory, wound-healing, hepatoprotective	[11,25]
Sterols	β-Sitosterol, Stigmasterol, Campesterol	Leaves, Bark, Seeds	Anti-inflammatory, cholesterol-lowering, membrane-stabilizing effects	[11,25]
Glycosides	Anthraquinone glycosides, Flavonoid glycosides	Fruits, Flowers, Leaves	Antioxidant, antimicrobial, laxative activity	[11,25]
Carbohydrates and Polysaccharides	Sugars, Mucilage, Polysaccharides	Fruit pulp	Nutritional value, osmotic laxative properties	[18,23]
Proteins and Amino Acids	Essential amino acids and proteins	Seeds, Leaves	Nutritional importance and metabolic functions	[17,22]
Volatile Constituents	Various volatile organic compounds identified by GC–MS	Leaves, Flowers	Defense against herbivores and microbial pathogens	[25]

5.1 Antioxidant Activity

Oxidative stress is involved in the etiology of cardiovascular diseases, diabetes mellitus, neurodegenerative disease and cancer. Thus, natural antioxidants have emerged as efficacious therapeutic agents. A number of studies have demonstrated the potent antioxidant activity of *C. fistula* attributed to its rich phenolic components, flavonoids, anthraquinones and tannins [14,33,35,38].

Siddhuraju et al. [33] determined and reported significant free radical scavenging activity of the methanolic extracts of *C. fistula* stem bark, leaves, flowers and fruit pulp with the stem bark extracts having the maximum antioxidant potential. Bhalodia et al. [38] demonstrated antioxidant activity of *C. fistula* hydroalcoholic fruit pulp extracts and the activity showed strong association with the phenolic and flavonoid content. Thabit et al. [35] evaluated antioxidant and neuroprotective potentials of *C. fistula* in the *Caenorhabditis elegans* model and revealed good protection against oxidative damage. Thus, *C. fistula* has potent antioxidant activity that can be used as a natural source of antioxidant compounds for oxidative diseases.

5.2 Antimicrobial Activity

5.2.1 Antibacterial Activity

The increased occurrence of multidrug-resistant bacterial pathogens has led to a renewed interest in searching for antimicrobial agents from medicinal plants. The plant extracts of *C. fistula* have been found active against both Gram-positive and Gram-negative bacteria [40,41,43,44]. Seyyednejad et al. showed that the various organic extracts of *C. fistula* inhibited the growth of several pathogenic bacterial strains [44]. Similarly, Arulpandi and Sangeetha

isolated a protease inhibitor from the leaves of *C. fistula*, named fistulin, and showed its activity against various bacterial pathogens [43]. These results can be attributed to the presence of anthraquinones, flavonoid, tannins, and other phenolics. These components have been identified to act against gram-positive and gram-negative microorganisms. They affect the microbial metabolism for growth and are inhibited in their activity due to the presence of these compounds

5.2.2 Antifungal Activity

Another biologically active nature of *C. fistula* is its antifungal activity against various fungal species. Bhalodia et al. reported that the flower and fruit extracts of *C. fistula* exhibited good inhibition activity against various fungal pathogens [40,41]. Sony et al. also reported the extracts of *C. fistula* having significant antifungal activity against fluconazole resistant Candida isolates from HIV positive patients [42].

5.3 Anti-inflammatory Activity

Inflammation is a complex biological response that plays an important role in the pathogenesis of various diseases, including some chronic diseases. Many phytochemicals isolated from Cassia fistula such as anthraquinones and flavonoids exhibit significant anti-inflammatory activity. Rhein isolated from the flowers of *C. fistula* by Antonisamy et al. showed anti-inflammatory activity by suppressing inflammatory responses by the inhibition of the production of pro-inflammatory mediators and signaling pathways [13]. The anti-inflammatory activity of *C. fistula* probably plays an important role in the traditional applications of *C. fistula* used to treat rheumatism and inflammatory skin diseases, and other inflammatory diseases. Anthraquinone derivatives may be useful therapeutic agents for the treatment of inflammation-associated diseases [13].

5.4 Antidiabetic Activity

Diabetes mellitus is a metabolic disease characterized by hyperglycemia of a chronic nature due to an imbalance between the physiological control of carbohydrate metabolism and blood glucose regulation, caused by defects in insulin secretion and insulin action or both. *Cassia fistula* has been reported to have antidiabetic effects.

Einstein et al. used several parts of the *C. fistula* plant and found that both the extracts rich in phenolic compounds and flavonoids showed antidiabetic activity [36]. Furthermore, the researchers Jangir and Jain showed that hydroalcoholic pod extracts protect pancreatic tissue in streptozotocin-induced diabetic rats, decreased blood glucose level, and improved many biochemical parameters [37]. The antidiabetic activity of *Cassia fistula* is usually attributed to its antioxidant properties and the ability of the extract to improve insulin action and modulate the activity of enzymes involved in glucose metabolism.

5.5 Anticancer Activity

Natural products continue to be the major source of anticancer agents, and the applications of *C. fistula* against various cancers have been reported in several studies. Methanolic seed extracts of *C. fistula* have shown significant antitumor activity in Ehrlich ascites carcinoma experimental model in mice [45]. Additionally, rhein isolated from *C. fistula* flowers exhibited potent anticancer activity against tumor cells in vitro, which has been reported to be one of the important anthraquinone components of the plant with therapeutic importance [46].

5.6 Wound-Healing Activity

The healing of wounds is a complex biological process undergoing several events such as inflammation, tissue formation, collagen deposition, and remodeling of the tissue. *C. fistula* has been widely used for the treatment of wounds in folk medicine. *In vitro* and *in vivo* wound-healing activity of *C. fistula* extracts has been reported in infected wound models with promising results [47]. *C. fistula* extracts could accelerate wound contraction, enhance collagen synthesis, and proceed the tissue regeneration. This wound-healing activity of *C. fistula* could be due to the antioxidant, antimicrobial, and anti-inflammatory properties of the active flavonoids, tannins and terpenoid components present in the plant.

5.7 Laxative Effect

The laxative effect of *C. fistula* is one of the most studied as it has many pharmacological activities. The fruit pulp contains anthraquinone derivatives and their glycosides that stimulate intestinal motility and hence, facilitates bowel evacuation and removal

of fecal matter. The Laxative activity of *C. fistula* fruit pulp is due to its anthraquinone glycosides, which induce intestinal peristalsis and increase secretion of water to the intestinal lumen [34]. Sakulpanich et al. [34] standardized the pod pulp extracts and found them to be efficacious and safe herbal laxatives. They also concluded that the fruit pulp is a valuable natural laxative as has been traditionally used in Ayurveda for centuries.

5.8 Other Reported Biological Activities

The antioxidant constituents of *C. fistula* were found to offer protection against oxidative stress-induced neuronal damage in *Caenorhabditis elegans*, indicating its potential activity in neurodegenerative disorders Thabit et al. [35] showed that plant extracts protected *C. elegans* against neuronal damage due to oxidative stress. The findings of this review provide a strong rationale for the use of *C. fistula* in the management of diseases and indicate their promising effects. The understanding of the mechanisms involved in the bioactivity of the plant and new perspectives are expected to facilitate future studies.

Table 4. Pharmacological activities of *Cassia fistula* and associated bioactive constituents

Pharmacological Activity	Plant Part/Extract	Bioactive Constituents	Outcomes	References
Antioxidant	Stem bark, leaves, flowers, fruit pulp	Flavonoids, phenolics, tannins	Strong free-radical scavenging and antioxidant activity	[14,33,35,38]
Antibacterial	Leaves, flowers, fruits	Anthraquinones, lectins, tannins	Inhibition of Gram-positive and Gram-negative bacteria	[40,41,43,44]
Antifungal	Flowers, fruits	Phenolics, flavonoids	Activity against fungal pathogens including *Candida* spp.	[40–42]
Anti-inflammatory	Flowers	Rhein, flavonoids	Suppression of inflammatory mediators	[13]
Antidiabetic	Fruits, pods	Flavonoids, phenolics	Improvement of glycemic control and pancreatic protection	[36,37]
Anticancer	Flowers, seeds	Rhein, anthraquinones	Antitumor and antiproliferative activity	[45,46]
Wound-healing	Leaves, extracts	Flavonoids, tannins, terpenoids	Accelerated wound contraction and tissue regeneration	[47]
Laxative	Fruit pulp	Anthraquinone glycosides	Enhanced bowel evacuation and intestinal motility	[34]
Neuroprotective	Whole plant extracts	Antioxidant phytochemicals	Protection against oxidative stress-induced neuronal damage	[35]

6. Defense Mechanisms Against Herbivory

Plants have developed several structural and chemical defense mechanisms against herbivorous insects, grazing animals and pathogens. Chemical defense mechanisms imparted by plant secondary metabolites are the most important defense systems that plant have evolved to lower the damage caused by herbivorous insects and promote the survival of plant life. *Cassia fistula* is a plant with various high value bioactive compounds such as anthraquinones, flavonoids and phenolics and tannins. The plant constituents, other than the medicinal values, also act as natural defense against the herbivorous insects. Secondary metabolites of plants have multiple effects on herbivorous insects, including deterrence, toxicity, low digestibility and feed

quality, anti-nutritional effect, physiological disturbance, etc. [48-50]

6.1 Plant–Herbivore Interactions in *Cassia fistula*

Plant-herbivore interactions are ecologically relevant processes that affect plant fitness, population dynamics and the structure of ecosystems. Selective forces exerted by herbivores stimulate evolutionary arms race between them and host plants, leading to the evolution of various defense mechanisms to overcome herbivore pressure. In *C. fistula*, accumulation of secondary metabolites, especially in leaves, bark, flowers and fruit, limits herbivory, which may be an adaptive strategy in response to attacks by herbivores. Secondary metabolites may act directly by exerting various toxic effects or indirectly by decreasing plant palatability and nutritional value [48,51].

6.2 Role of Tannins as Feeding Deterrents.

The tannins and other polyphenol compounds play an important role in the defense system of *C. fistula.* These compounds are known to bind with dietary proteins and digestive enzymes in the gastrointestinal tract of herbivores. This reduces the nutrient content and digestibility of such plants and may cause herbivores to either avoid them or have a poor growth and reproductive performance [49,52]. In addition, tannins may also contribute to the astringent taste of such plant tissues. In *C. fistula*, the presence of tannins in high concentrations, especially in bark and leaves, may contribute to herbivore resistance [32,49].

6.3 Anthraquinones and Herbivore Avoidance.

The presence of bitter-tasting compounds such as anthraquinones, such as rhein, emodin, chrysophanol and physcion, in *C. fistula* also play an important role in plant defense. Research has been conducted on the ecological functions of various anthraquinones that may explain the lower than usual herbivory on such plants. These compounds may have toxic and growth inhibitory effects on insects and other organisms, and reduce feeding. The high abundance of anthraquinones in fruit pulp and other plant tissues suggest help *C. fistula* to avoid herbivores [53,54].

6.4 Phenolic Compounds as Chemical Defenses

Phenolic compounds are an additional major defence system deployed by *C. fistula*. As noted in the above section, these compounds exhibit antioxidant and antimicrobial activities and can contribute to plant defence against herbivores. Phenolics may reduce digestibility by a variety of mechanisms including inhibition of digestive enzymes, interference with resource absorption, and the induction of oxidative stress in attacking organisms [55]. In addition, phenolics are frequently upregulated by herbivore challenge, as part of a rapidly induced plant defence strategy aimed at minimizing damage during the period of attack [48,55].

6.5 Anti-Feedant and Repellent Properties of Secondary Metabolites

Many secondary metabolites exhibit anti-feedant and repellent properties by influencing herbivore behaviour. Flavonoids, tannins, anthraquinones and terpenoids identified in *C. fistula* may be capable of deterring feeding by causing negative sensations of taste and/or toxicity, or by interrupting the sensory perception mechanisms of herbivorous insects [50,56]. These compounds may also have negative effects on herbivore reproductive mechanisms and growth regulators, as well as digestive enzymes, thereby reducing herbivore fitness. Such chemical defences may have the added benefit of being environmentally friendly, avoiding the use of synthetic pesticides, and thereby anecdotally attracting considerable interest for agricultural applications (Table 5) [56,57].

6.6. Palatability and Digestibility of *Cassia fistula* Leaves

Cassia fistula leaves are rich sources of tannins, phenolics, and flavonoids. The presence of these metabolites is known to reduce the digestibility and palatability of *C. fistula* leaves. It has been observed that herbivorous animals prefer plant tissues which are low in concentration of defensive metabolites, because high concentration of these metabolites can reduce the efficiency of nutrient utilization and digestibility in the gut of these animals [49,52].

The defensive metabolites, therefore, are associated with reducing the nutritional value of the plant, resulting in lower grazing pressure by the herbivores and increasing the chances of plant survival especially in environments where herbivorous animal population is high [58].

Table 5. Major defense-related phytochemicals of *Cassia fistula* and their roles in herbivore deterrence

Class	Compounds	Defense Mechanism	Effect on Herbivores	References
Tannins	Hydrolysable tannins, condensed tannins	Bind dietary proteins and digestive enzymes; reduce nutrient utilization	Reduced feeding efficiency, growth inhibition, decreased palatability	[49,52]
Anthraquinones	Rhein, Emodin, Chrysophanol, Physcion	Bitter taste; physiological toxicity; growth-regulatory interference	Feeding deterrence, impaired larval development, reduced survival	[50,53,54]
Phenolic Compounds	Gallic acid, Ellagic acid, Ferulic acid, Caffeic acid	Antioxidant defense; inhibition of digestive enzymes; oxidative stress induction	Reduced digestibility and nutrient absorption	[55,57]
Flavonoids	Quercetin, Kaempferol, Catechin	Chemical signaling disruption; feeding deterrence; antioxidant protection	Reduced herbivore preference and feeding behavior	[50,57]
Terpenoids	Lupeol and related triterpenoids	Repellent activity; interference with insect physiological processes	Reduced feeding and reproduction	[56,57]
Glycosides	Anthraquinone glycosides, flavonoid glycosides	Release biologically active aglycones after tissue damage	Deterrence and toxicity toward herbivores	[53,54]
Polyphenolic Complexes	Tannin–protein complexes	Lower protein digestibility and nutrient availability	Reduced grazing intensity and growth performance	[49,52]
Volatile Organic Compounds (VOCs)	Plant-derived volatile metabolites	Indirect defense through signaling and repellence	Attraction of natural enemies and herbivore avoidance	[51,57]

6.7. Avoidance of *Cassia Fistula* by Grazing Animals

Traditional observation of the grazing animals in agricultural fields indicate that these animals avoid consuming the leaves of *C. fistula*, even when these are readily available. An important reason for this observed behavior may be associated with the presence of bitter anthraquinones and astringent tannins in the leaves, which reduce the palatability and may also cause digestive upsets when these leaves are eaten in a large quantity [49,53]. The presence of these metabolites works together as an efficient deterrent system against herbivorous animals.

6.8. Ecological Significance of Herbivore Defense

The presence of defensive metabolites in *C. fistula* has bigger ecological roles than those assigned for protecting the plant from herbivores. Defensive metabolites enhance growth and reproduction by reducing herbivory. These metabolites also stabilize the ecosystem dynamics by influencing the trophic interactions among plants, herbivores and microorganisms [48,51]. Thus, the study of defensive metabolites from *C. fistula* may lead to the discovery of novel compounds for pharmaceutical, agricultural and environmental applications. Thus, this information may also help in understanding the evolutionary interactions between plants and their natural enemies (Table 6).

Table 6. Ecological significance of herbivore defense mechanisms in *Cassia fistula*

Defense Mechanism	Phytochemical Groups	Outcome	References
Feeding deterrence	Anthraquinones, tannins, flavonoids	Reduced herbivore attack and tissue consumption	[49,50,53]
Reduced digestibility	Tannins, phenolics	Lower nutrient assimilation by herbivores	[49,52,55]
Direct toxicity	Anthraquinones, terpenoids	Impaired growth and survival of herbivorous insects	[53,56]
Repellent activity	Terpenoids, flavonoids	Avoidance of plant tissues by insects and grazing animals	[50,56,57]
Inducible chemical defense	Phenolics and secondary metabolites	Enhanced resistance following herbivore attack	[51,55,57]
Protection of reproductive structures	Anthraquinones and phenolics in fruits and flowers	Improved seed survival and reproductive fitness	[53,54]
Ecosystem-level adaptation	Multiple secondary metabolites	Increased plant fitness and ecological resilience	[48,51,58]

7. Toxicology and Safety

The therapeutic and toxicological safety of *Cassia fistula* should be clarified. The safety of herbal medicines depends on the plant part used, the method of extraction, the dosage of herb, the duration of administration, and the diversity of the patients who consume the medicine [74]. Assessment of the safety profile depends upon many factors such as the plant part used, the method of extraction, the dose, or the duration of treatment, and the diversity of the patients. Studies have suggested few toxicological effects of the preparations or related substances derived from *C. fistula*. All studies have suggested that there is little toxicological effect at therapeutic doses, and that only excessive consumption of the plant might affect the body, especially bearing in mind that anthraquinones and other secondary metabolites might be biologically active [59,60].

7.1 Acute Toxicity

The results of the acute toxicity study in rodents with different plant extracts of *C. fistula* showed that there were no death or major behavioral changes when there was no evidence of acute toxic effects. Sakulpanich et al reported that the leaves and flowers of *C. fistula* have no acute or chronic toxic effect when they were given orally [34,59]. Sakulpanich et al conducted the preliminary test with a standardized pod pulp extract prepared by using an ethanolic solvent of the pulp of *C. fistula* that was combined with water. They tested as well on mice and rats. In their studies, there was no evidence of the acute toxic effect in the range of tested dose [34]. The above findings are in agreement with the use of the pulp of *Cassia fistula* fruit, as a herbal laxative.

7.2 Subacute and Chronic Toxicity

The long term toxicity of *Cassie fistula* remains unclear. Studies have reported that repeated use of the plant extracts at therapeutic doses does not affect other physiological and pathological processes, thus prompting the need for dose standardization and for long-term toxicity assessment before prescribing its use in treating patients. However, long term consumption of anthraquinone-indicating medications might result in similar consequences as with other medicinal plants [60,61].

7.3. Toxicological Studies of Anthraquinones

It has also been reported that rhein, emodin, chrysophanol, and physcion are a major class of anthraquinones present in *C. fistula*. Previous study has suggested that overexposure to anthraquinones may lead to some adverse effects in the GI tract, such as abdominal cramping, nausea, vomiting, and blood in the stool, due to their stimulant action for the intestinal motility [61]. The acute toxicological studies have suggested that the *C. fistula* fruit pulp is generally safe to use for therapeutic purposes. However, due to the potential abdominal cramps, many people experience abdominal pain, nausea, vomiting, and increased frequency of bowel movement, which could lead to electrolyte and dehydration. Therefore, preparations containing

anthraquinones should be used with caution according to the dosage, as listed in the literature [60,61].

7.4. Safety in Traditional and Clinical Use

The plant *C. fistula* is widely used in Ayurveda, Siddha, and folk medicine over centuries, and the use of *C. fistula* in antiseptic skin care and laxative shades the view of the plant as safe to use. This plant has been used as a mild and well-tolerated laxative as compared to other popular synthetic laxatives, and fruit pulp is considered less likely to cause GI disturbances [25,34]. In fact, the permissible usage (according to dosage) of the plant is justified by in vitro and in vivo studies. However, the safety in humans has not been established due to this unavailability of data from the scientific literature [31]. It is advisable to avoid the use of the plant in pregnant and lactating women, children, elderly patients, and patients suffering from digestive disorders, until the clinical studies validate the safety of the plant.

7.5. Regulatory and Research Considerations

Current literature data and preclinical studies have suggested new promising pharmacology for *Cassia fistula*. However, the development of *C. fistula* based phytopharmaceutical demands a thorough investigation for toxicity analysis. Various studies, including standardization of extract, determination of no-observed-adverse-effect level (NOAEL), chronic toxicity study, reproductive toxicity, genotoxicity, and herb–drug interaction studies are needed for the comprehensive evaluation of the safety of *C. fistula*. This evidence would be absolutely necessary for the development of safe therapeutic alternatives based on *C. fistula* [31,60]. It can be inferred from the well-known application of the plant and the recent literature data that it is a safe medicinal plant. Nevertheless, it needs further toxicological and clinical safety studies for potential application of the plant as a therapeutic agent

9. Conclusion

Cassia fistula L. is a medicinally important plant that has been extensively utilized in traditional healthcare systems for centuries and continues to attract significant scientific interest because of its diverse phytochemical composition and broad spectrum of biological activities. Different parts of this plant, including the fruits, leaves, flowers, bark, seeds, and roots have been shown to contain anthraquinones, flavonoids, phenolic compounds such as chlorogenic acid, tannins and condensed tannins, terpenoids, sterols, and glycosides. The last years also marked variability in the distribution of each phytochemical across geographical regions. Different medicinal uses have been documented for this plant including antifungal, antidiabetic, antitumor, anti-inflammatory, antiulcer, hepatoprotective, wound healing and antimicrobial activities. In this review, the phytochemical profiles and bioactivities of *C. fistula* are summarized, predominately anthraquinones, such as rhein, emodin, chrysophanol, and physcion, flavonoids, and phenolic compounds are most consistently found to contribute significantly to the wide-ranging biological activities of this plant. In addition, from the current literature, antioxidant, antimicrobial, anti-inflammatory, antidiabetic, anticancer, wound-healing, neuroprotective, and laxative properties have been validated in *C. fistula*. Overall, the preclinical evidence supports further investigation of *C. fistula* for both medicinal and therapeutic uses.

It could be concluded from this review that *C. fistula* represents a natural agent for a variety of clinical indications and applications. The plant is also discussed as a potential source of natural chemical defense against herbivory. Herbivores feed less on *C. fistula* plants as compared with other *C. spp*. and fruit consumption is suppressed in animals by *C. fistula* leaves. This is associated with the presence of secondary metabolites, e.g. tannins, anthraquinones, phenolics, flavonoids, in the plant. *C. fistula* has a strong deterrent effect on the feeding of *L. migratoria*, *I. serratus* and *H. variegata*, which may be associated with lower digestibility, inhibition of growth and avoiding the plant. The plant could represent a study model for plant–herbivore relationships. The plant has a lot of herbal applications and promising potential pharmaceutical usages. Most of the toxicological data available has from the fruit pulp is found to be safe at a dose within the traditional therapeutic range. However, efforts for comprehensive toxicological and clinical studies are missing.

In conclusion, *Cassia fistula* is an extensive medicinal plant of great ecological importance with great scope for its future use in drug discovery and phytopharmaceutical advancement. Further interventions via multidisciplinary research studies encompassing phytochemistry, molecular

pharmacology, pharmacology, toxicology, medical phytochemistry, chemical ecology and clinical trials are anticipated to further clarify its therapeutic mechanisms, validate its use in folk medicine, and ensure its safe application in modern medicine.

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