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Review Article

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Pharmacological and Phytochemistry Properties of *Cassia tora* L.

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ABSTRACT

Since the dawn of civilization, plants have been one of the primary sources of medicine. Plant cures have had a revival due to a number of variables, including their efficacy and lower risk of adverse effects when compared to current medications. This review summarises the state of our understanding of Cassia tora Linn's morphology, phytochemistry, and pharmacological properties. Although there have previously been review papers on this plant, this one is offered to gather all the most recent data on its pharmacological and phytochemical activity, which have been intensively studied using a variety of techniques. It has been shown that the plant Cassia tora Linn, also known as Charota in Hindi and Foetid Cassia in English, has a number of pharmacological properties, including antiproliferative, hypolipidemic, immunostimulatory, anticancerous, antimutagenic, and hepatoprotective action. Additionally, research has shown that numerous phytochemical components, namely anthraquinones, chrysophanol, emodin, rhein, euphol, and basseol, are present. These investigations will be valuable in generating interest in Cassia tora Linn, and they may also be helpful in creating novel formulations that are more therapeutic and in providing guidance for further study. This plant has yielded a number of chemical substances, including anthraquinone glycosides, naphthopyrone glycosides, phenolic compounds, flavonoids, etc. The scientific data on many elements of the Cassia tora plant, which is employed in traditional systems of medicine for a range of purposes.

Keywords: *Cassia tora Linn, chrysophanol, Leguminosae, phytochemistry and pharmacology.*

INTRODUCTION

With a 30 to 90 cm height, *Cassia tora* Linn. (Caesalpiniaceae) is a tiny annual plant resembling an upright shrub that thrives in warm, wet soil across tropical Asia and Africa. It mostly grows as a wild shrub in tropical areas and is regarded as a weed everywhere. Although the size of its natural range is unknown, it is mostly found in South Asia (Nadkarni, 1954).

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It is often mistaken with *S. obtusifolia*, or Chinese Senna or Sicklepod. It may be found mostly in the Indian states of Uttar Pradesh and Madhya Pradesh. It mostly grows as a weed in Himachal Pradesh along field borders, roadsides, and other locations (Jain, 1968). It occurs often in hot, humid, and tropical regions (Acharya & Chatterjee, 1975; & Hatano et al., 1991). The Cassia tora Linn. tree has a straight, wooden trunk that is abundantly branched, although hairy stem terminal areas are uncommon. It has around 10 cm long pinnate leaves. Three pairs of opposing, ovate, oblong, and oblique at the base leaflets make up each leaf (Sharma et al., 2005). In the axel of the leaves are bearded yellow blooms. Five petals, each measuring approximately half an inch in diameter, make up the flowers. About 30 to 50 rhombohedral, brown Cassia tora seeds make up each one. The plant produces fruits in the winter and blossoms throughout the rainy season (Bhalerao et al., 2013). Rhomboidal and brown in colour, C. tora seeds are shaped like balls. The C. tora produces flowers and fruits during the wet season. The leaves, seeds, and roots of C. tora have historically been used as culinary components (Ingle et al., 2012). The Aryans eventually created the Ayurveda system from the straightforward home medicines used particularly by the Adivasi and the Adi Janjati or the tribal populations across India. Throughout human history, the straightforward system of and has been employed to treat various ailments, either in the form of plant extracts or as pure chemicals (Dabriyal & Narayana, 1988). Folktales are used to transmit knowledge of these plants from one generation to the next (Ghosh, 1971). Because of the presence of phytochemical elements, medicinal herbal plants, often referred to as saag or potherbs, are advantageous for therapeutic applications as well as for the treatment of human ailments (Kumar & Kumari, 2010). Saag is a corrupted version of the potherb-meaning Sanskrit word Saak. Saag often has a particular position in Indian cuisine due to its flavour and therapeutic qualities. The state is rich in variety, and several species of saag are key aspects of the celebrations and ceremonies; saags are known among the tribal people of many regions of India as leafy laurels (Singh et al., 2001). While some potherbs and snags are grown under cultivation, the majority grow wild and go unused. The leaves, seeds, and roots of medicinal plants naturally contain phytochemicals that act as a defensive mechanism and provide protection against a variety of ailments (Oudhia, 2001). Primary and secondary compounds are phytochemicals. Sags or pot herbs are abundant in a range of metabolites with anti-fungal and antibacterial properties. In photosynthesis, respiration, solute transport, translocation, nutritional absorption, and differentiation, the main metabolites such as Chlorophyll, amino acids, nucleotides (Markwell, 2002), simple carbohydrates, or membrane lipids perform predictable functions (Yen & Chung, 1999). The major metabolite responsible for the leaves' green hue is Chlorophyll. Chlorophyll's spectrum characteristics are crucial for absorbing light energy and converting it into chemical energy for photosynthesis. In most plants, the amount of Chlorophyll determines the variation in leaf colour and the amount of photosynthetic activity. 2013's Shibghatallah Chlorophyll concentration affects nutritional inadequacies, stress, and a plant's ability to photosynthesize per unit of leaf area. (2015) Vimala and Poonghuzhali Plants produce secondary metabolites as a component of their defence mechanism (Indira et al., 2015). Chl-a, Chl-b, accessory pigments, and several other types of Chlorophyll are present in higher plants (Campeanu & Neata, 2012). Among the five primary forms of Chlorophyll, Chl-a and Chl-b are the most well-known and most frequently present in all autotrophic organisms, except bacteria that lack pigment. (Witham & Devlin 1997). Chl-a and Chl-b pigments are linked to light-harvesting mechanisms, accounting for all photosynthesis in higher plants (Butnariu, 2016). The amount of Chlorophyll in leaves is a sign of a healthy plant. The Chlorophyll a to b ratio also reveals how well-developed a plant's photosynthetic

system is. In the growth and development of higher plants, it plays a determining role (Wakefield & Bhattacharjee, 2016). The plant's photosynthesis rate is determined by the chlorophyll concentration, which also reveals the photosynthetic capacity per unit area of the leaf.

Occurrence, Botanical Description and Ethnopharmacology

In Asian nations, the common weed Cassia tora Linn. (Caesalpiniaceae) is a tiny annual plant or undershrub. It grows as a weed all throughout India but is mostly found in its natural condition in Himachal Pradesh, Bihar, and Orissa. It contains "Dadhughnavati," an Ayurvedic remedy that is one of the most effective antifungal compositions. The 1.2 m-tall herbs have complex, paripinnate leaves with three leaf pairs. Bright yellow, axillary flowers that are often in pairs. Pods are 15–25 cm long, long and thin, and obliquely separable. Rhombohedral, green seeds. It is well-known in Ayurveda as a laxative, antiperiodic, and beneficial for conditions such as leprosy, ringworm, bronchitis, cardiac disorders, ophthalmology, skin illnesses, cough, hepatic dysfunction, liver tonic, and haemorrhoids. According to reports, CT seeds have antioxidant activity and include a variety of active compounds, including chrysophenol, emodin, and rhein. This strategy has been linked to several therapeutic qualities, including antibacterial, antihepatotoxic, and antimutagenic actions (Malik et al., 2020).

Botanical classification of *Cassia tora* Linn

	Family Name	Caesalpiniaceae
	Kingdom	Plantae
	Division	Magnoliophyta
	Class	Magnoliopsida
	Subclass	Rosidae
	Order	Fabales
	Family	Fabaceae
	Subfamily	Caesalpinioideae
	Tribe	Cassieae
	Sub-tribe	Cassiinae
	Genus	*Cassia*
	Species	*Tora*
	Botanical Name	*Cassia Tora* Linn.

Description

Leaves:

Researchers estimated the leaf's antioxidant and antiproliferative capabilities after preliminary phytochemical testing revealed the presence of polyphenols (Rejiya et al., 2009). Myricyl alcohol, anthraquinone glycosides, d-mannitol beta-sitosterol, and flavonoids are the main compounds found in leaves. Additionally found in Cassia tora L. were emodin, tricontan-1-ol, stigmasterol, -sistosteral--D-glucoside, freindlen, palmitic, stearic, succinic, and d-tartaric acids, uridine, quercitrin, and isoquercitrin. Kaempferol-3-diglucoside is also present in leaves (Shibata et al., 1969; Raghunathan et al., 1974). Ononitol monohydrate, a potential hepatoprotective component, was found in the leaves of C. tora (Ignacimuthu et al., 2009).

Seeds:

According to Yen et al. (1998), seeds included quercetin and its analogue, as well as emodin, subrofusarin, chrysophanic acid, 1,8-dihydroxy anthraquinone, beta-sitosterol rein similar aglycones, cassia side, rubro-fusarin, and torosachrysone. Various phenolic glycoside including novel compounds were isolated from seeds of Cassia tora (Leguminosae) which are torachrysone tetra glucoside, nor-rubrofusarin gentiobioside, demethyflavasperone gentiobioside, torachrysone gentiobioside, rubrofusarin tri glucoside and torachrysone aminoglycoside, were identified on the basis of spectroscopic

and chemical data (Patil et al., 2004). Two novel naphtha-pyrone glycosides, 9,10-hydroxy-7-methoxy-3-methyl-1H naphtha [2,3-c] and 9,10-hydroxy-7-methoxy-3-mehtyl-1H naphtha [1-6)-O-beta-D-glucopyranosyl] In addition to cassia side and rubrofusarin-6-beta-gentiobioside, pyran-1-one and 6-O-beta-D-glucopyranosyl) oxy]-rubrofusarin were also discovered in the seeds of Cassia tora (Hatani et al., 1999).

Roots:

Anthraquinones, beta-sitosterol, chrysophanic acid, myricyl alcohol, 9-anthrone, naphtha-pyrone, physcion, rubrofusarin, toralactone, leucopelargonidin-3-O-L-rhamnopyranoside, and 6-gentiobioside are all present in some quantity in roots (Chatterjee, 1992).

Other parts:

Sennosides are abundant in pods. Kaemferol and leucopelargonidine are reportedly present in flowers. Leucopelargonidine, 1,3,5-trihydroxy, 6,7-dimethoxy-2-methyle anthraquinone, and beta-sitosterol were all found in the roots of C. tora (Thakur, 1989). Behenic acid, arachidic acid, isostearic acid, palmitic acid, marginic acid, linolineic acid, phenolics including emodine, hexahydroxy flavones, rhein, and a hydroxycoumarin are all present in the stem bark of this plant (Tiwari, 1972).

Ethnobotany

'Pamari Taila' and 'Dadrughani Vati' in Ayurveda both extensively utilize Cassia tora (Thakur et al., 1989). It is often used as a stimulant, tonic, and carminative. (Chatterjee et al., 1992) Its leaves, seeds, and roots are used medicinally. Sennosides, which are known for their therapeutic value, have been found in the plant's leaves (Raghunathan et al., 1974). The seeds and leaves are laxative, acrid, liver tonic, antiperiodic, anthelmintic, cardiotonic, ophthalmic, and expectorant, according to Ayurveda. Traditional medicine claims that the leaves of C. tora contain antirheumatic properties. This herb's compound ayurvedic oil, known as chakramardha tailamu, is effective in treating eczema, ringworm, and other skin conditions (CSIR, 1992). The seeds of C. tora have long been used in Chinese medicine as diuretics and anti-asthmatic aperients. Additionally, it is planned to treat hepatic conditions and enhance visual activity (Nikado et al., 1992). To protect the liver, hot seed extract is taken orally in Korea (Jain, 1991). The seeds are often roasted, then boiled in water to make tea, which is subsequently used as a folk medicine in place of coffee. Heart conditions, dyspepsia, leprosy, ringworm, colic, constipation, flatulence, cough, and bronchitis may all be treated with the leaves and seeds. Pods are used to cure eye conditions as well as diarrhoea. The root is a well-known remedy for snake bites and is bitter, tonic, stomachic, and stomachic (Kapoor, CRC Press, 108–109; & Hemadri et al., 1984). The tribal people of Andhra Pradesh have been treating jaundice using a paste made from the leaves of this plant, peppers, and water (Dastur, 1964). Children with digestive issues are given the leaves because they are alterative, aperient, and antiperiodic (Manojlovic et al., 2006). According to Deore et al. (2009), the plant's leaves, roots, and even the whole plant are used to treat ulcers, helminthiasis, impetigo, and as a purgative. As with tincture-iodine, the pulverized leaves may be used as a poultice to cuts and wounds to speed healing as well as to ulcers to promote suppuration (Wallis, 1967). In 5 to 15 ml dosages, leaf decoction acts as a mild laxative, particularly for young children with fever and teething problems. Leaf poultice is administered locally for gout, sciatica, and joint discomfort. Some traditional natural herb items include Cassia tora splits and powder derived from the plant's seeds. In organic agriculture in India, Cassia tora is used as a natural insecticide. The pet food business is where Cassia tora powder is most often used since the seeds produce yellow, blue, and red coloured dyes that are utilized in dyeing and tanning. It is combined with guar gum for mining and other industrial applications (Soni et al., 2000). Chinese Material Medica claims that it improves blood circulation and that, due to its cool character, it is effective in the treatment of heat syndromes. Ailments brought on by heat, like hyperdactyly, conjunctivitis,

and blindness, affect seed tarts. Chinese doctors traditionally use this plant to cure xerophthalmia, blindness, and conjunctivitis. According to Foster et al. (1992), the seeds are believed to improve eyesight, act as an antiasthenic, aperient, diuretic, and effectively decrease cholesterol and blood pressure. Stems and young, fragile leaves are used as a vegetable and in soups. Cooked and consumed immature fruits are also available. The seeds may be given to cattle as a high-protein feed. According to Jain (1991), Cassia tora Linn. has further uses for irregular childbirth, vermicide, the common cold, epilepsy, night blindness, scabies, scorpion bites, stomachaches, and bone fractures.

PHARMACOLOGICAL PROFILE

Anthelmintic Activity

The anthelmintic activity of the seeds' alcoholic and aqueous extracts against Pheretima posthuma and Ascardia galli was examined. Using piperazine citrate as a standard and pure water as a control, extracts showed considerable anthelmintic action at the maximum dosage of 100 mg/ml. (Deore et al., 2009).

Antiparkinsonian Activity

Cassia tora plant extracts in petroleum ether, methanol, and ethyl acetate were examined for their potential to treat Parkinson's symptoms brought on by oxotremorine. Parkinson's symptoms were lessened by methanolic extract, whereas mild effects were shown with petroleum ether and ethyl acetate extract. (Suryawanshi et al., 2009).

Anticancer Activity

Using human cervical cancer cells (HeLa), methanolic leaf extract was tested for its antiproliferative effects with Cisplatin, an anticancer medication. The plant extracts convincingly showed that C. tora is beneficial against free radical-mediated illnesses by inducing a significant concentration-dependent inhibition of proliferation, decreased DNA content, and apoptosis in HeLa cells. (Rejiya et al., 2009).

Antigenotoxic Activity

The Ames Salmonella/microsome test and the Comet assay were used to analyze water extracts of seeds that had undergone various degrees of roasting. The results showed that aqueous extracts, particularly those that weren't roasted, significantly reduced mutagenicity and that the reduction in anthraquinones in roasted C. tora was responsible for its decreased antigenotoxic potency. (CH Wu et al., 2009)

Antifungal Activity

Using the whole plant approach in vivo, the fungicidal activities of the chloroform fraction of the plant were assessed against Botrytis cinerea, Erysiphe graminis, Phytophthora infestans, Puccinia recondita, Pyricularia grisea, and Rhizoctonia solani. The chloroform fraction showed Strong fungicidal activity against B. cinerea, E. graminis, P. infestans, and R. solani (YM Kim et al., 2004).

Anti-psoriatic Activity

Acute cutaneous toxicity tests on leaf methanol extracts in varying O/W cream concentrations were conducted. Histopathological examination of the mouse tail model's sections showed that there were no Munro microabscesses, elongated rete ridges, or dilated capillary loops. In comparison to the positive control, O/W creams and methanol extract significantly reduced the percentage relative epidermal thickness and the spleen index. (Singhal, et al., 2012).

Antimicrobial Activity

By using a nutrient agar medium and the disc diffusion method, the aqueous and ethanolic extract of Cassia tora leaves were screened against Gramme-positive bacteria, Gramme negative bacteria and also tested against fungi using Ciprofloxacin and Clotrimazole as reference standards for bacteria and fungi, respectively. According to Jayasutha et al. (2011), antifungal activity was shown to be more substantial in the aqueous extract, whereas ethanolic extract was discovered to have considerable action against bacteria.

Antinociception

The acetic acid-induced abdominal constriction and force-induced tail flick procedures were used to examine the antinociceptive impact of the methanolic extract of leaf on mice. When compared to

aspirin, the extract considerably reduced the severity of the abdominal constrictions caused by acetic acid in mice (Chidume et al., 2002).

Nutritionally Unsound Behaviour

Oxalic acid, phytate phosphorus, and tannin concentration of the seeds' antinutritional components were studied as a result of various processing techniques. According to the findings, all processing procedures greatly decreased the amount of oxalic acid (Haritha et al., 2009).

Shigellosis prevention

In comparison to the chloroform, methanol, and petroleum fractions, the ethyl acetate fraction of Cassia tora root exhibited the highest activity, with the zone of inhibition falling between 23 and 25 at concentrations of 200 microgram discs (Awal et al., 2004).

Antiulcer Function

Using an ethanol-induced stomach ulcer model, the antiulcer efficacy of a hydroalcoholic extract of leaves was assessed in albino rats. Using omeprazole as the reference standard, the extract exhibited dose-dependent antiulcer action, reaching its peak at 500 mg/kg body weight (Gulia et al., 2011).

Liver Protective Function

Compared to the reference medicine silymarin ononitol monohydrate, ononitol monohydrate extracted from leaves lowered the levels of serum transaminase and lipid peroxidation. According to histopathological findings, monitor monohydrate has hepatoprotective properties without having any negative side effects (Dhanasekaran et al., 2009). As compared to rats treated with carbon tetrachloride, leaves of cassia Torra also showed a significant drop in the marker enzymes (Rajan et al., 2009).

Negative Behaviour

In Wistar rats, the purgative effects of methanolic extract and isolated aloe-emodin from leaves were assessed. In comparison to the reference substance, sennoside, both the extract and the isolated material demonstrated substantial purgative action (Maity et al., 2003).

Activity in Healing Wounds

With ointment base serving as a control and nitrofurazone ointment serving as a reference standard, the ethanolic extract of the leaves was examined for its impact on wound healing in a rat excision wound model. The capacity of the extract to close wounds was shown to be much higher than that of the control, which was on par with the reference standard. Due to the inclusion of active terpenes, alkaloids, and flavonoids, nitrofurazone ointment (Jayasutha & Josephine, 2011).

Diabetes Prevention

The effects of the butanol fraction of seed on postprandial blood glucose control and insulin secretion from the pancreas of normal and diabetic rats were studied (Nam Choi, 2008). The results showed that the butanol fraction of seed had a beneficial effect on postprandial blood glucose control, which may be partially mediated by stimulated insulin secretion from the pancreas of the diabetic rats. It was also assessed how the fraction derived from the n-butanol soluble component of the ethanolic extract of seeds affected biochemical variables and the regeneration of -cells in rats with alloxan-induced diabetes. When compared to control, oral treatment of the fraction F6 dramatically reduced blood glucose levels in normal and alloxan-induced diabetic rats in both single-dose and multiple-dose experiments. In normal, acute, and sustained therapy compared to control, methanolic extract of seeds exhibits considerable antidiabetic action (Jaina et al., 2011). In the alloxan-induced diabetes model, the n-butanol portion of the methanol extract dramatically lowered blood glucose levels after single doses and sustained therapy, becoming approximately similar to conventional Glibenclamide after the latter (Chaurasia et al., 2011).

Activity of Antioxidants

In tests for nitric oxide, DPPH (1, 1-diphenyl-1,2-picryl hydroxyl) and ABTS (2,2-Azino-bis 3-ethyl benzothiazole-6-sulfonic acid diammonium salt), aqueous leaf extract had more antioxidant and antiradical properties than ethanolic extract. According to Lobo et

al. (2011), the ethyl acetate fraction isolated from the methanolic extract demonstrated antioxidant efficacy. Additionally, it was discovered that the ethyl acetate fraction worked better in protecting LDL from oxidation in a concentration-dependent way. According to the evidence, the ethyl acetate-soluble fraction may protect against atherosclerosis by preventing LDL oxidation (Yen et al., 1998).

Immunosuppressive Activity

Aloeemodin, emodin, chrysophanol, and rhein, four anthraquinones from the Cassia tora plant, were studied for their immunostimulatory effects on lymphocyte proliferation, interferon (IFN) and interleukin 10 (IL-10) secretion by an ELISA assay, and the identification of responding immune cells by flow cytometry. The findings demonstrated that the tested anthraquinones were efficient in promoting the proliferation of dormant human PBMC and/or IFN secretion at non-cytotoxic doses (Chiang et al., 2008; & Meena et al., 2009).

Anti-Inflammatory

Against carrageenan, the leaf's methanolic extract significantly reduced inflammation. Rat hind paw oedema was caused by histamine, serotonin, and dextran in a dose-dependent manner (Maity et al., 1998; & Jain & Patil, 2010).

Activity against Fertility

In female rats, the leaf extract had the strongest antifertility effects. Oestrogenic action has been discovered to be connected to the drug's antifertility effects (Cho et al., 2007; & Pawar et al., 2011).

Hypolipidemic

It was determined if the Cassia tora L. seed ethanolic extract and its fractions had hypolipidemic effects on the hyperlipidemic profile caused by triton. According to Patil et al. (2004), ethanol extract and its ether and water-soluble fractions reduced blood levels of LDL cholesterol, triglycerides, and total cholesterol**.**

CONCLUSION

Cassia tora Linn., a plant utilized in Ayurveda and Traditional Chinese Medicine, has been proven to have a range of medical effects via many tests undertaken on animals like mice, organism strains, and on particular human cells. A number of different researchers has carried out these studies. Because of this, a thorough analysis has shown that it possesses a variety of pharmacological properties, including those that are anti-microbial, anti-cancer, vasodilatory, antioxidant, hypolipidemic, laxative, anti-diabetic, hepatoprotective, anti-inflammatory, immune-stimulatory, pesticidal, anti-estrogenic, kidney protective, cataract protective, skin protective, and neuro-protective properties. The significant bioactive molecules found in Cassia tora leaf and seed extracts like torachrysone, anthraquinones, toralactone, aloe-emodin, rhein, emodin, obtusin, aurantio-obtusin, chrysophanic acid, rubrofurasin, unglycosylated naphthalenes, etc. have shown various medicinal and non-medicinal properties. In addition, Aurantio-Obtusin, a bioactive chemical that is found in Cassia tora and has been demonstrated to be beneficial in suppressing the S protein of SARS-CoV by binding to multiple protein receptors and successfully inhibiting the virus, has been discovered to be present in this plant. It is also known to bind to molecules that have a role in the inflammation of lung tissue that occurs when the lung is sick. Analysis of aurantio-obtusin using bioinformatics led to the discovery of intriguing molecular interactions in silico with viral as well as host components of illness development. In addition, from the point of view of the creation of drugs based on natural pharmacophores, an analysis of the numerous bioactive components of the edible plant Cassia tora is required. This plant is, without a shadow of a question, a veritable treasure mine of potentially beneficial chemical constituents that may be used as therapies, new leads, and hints for the creation of already existing medications. Both the geographical location and the time of year affect the phytochemical changes that occur in C. Tora and its medicinal capabilities. The dangerous characteristics of Cassia tora need to be standardized, and a comprehensive

clinical investigation has to be carried out (Patel et al., 2022).

SUGGESTIONS FOR FUTURE RESEARCH

Here are a few suggestions for directions to take the study on Cassia Tora in the future:

Studies in pharmacology: Carry out research to investigate the possible pharmacological qualities of Cassia tora, including its anti-inflammatory, antioxidant, and anti-diabetic activities. Conduct research on the underlying mechanisms of action of its active chemicals, as well as analyze the safety and effectiveness of these processes using animal and human models, respectively.

Toxicological investigations: Conduct studies to investigate and assess the possible adverse effects of Cassia tora and its active components on humans. Research should be done to identify the safest range of doses for human intake, as well as any possible negative effects that might arise from prolonged usage.

Investigations of the Phytochemistry: Conduct extensive phytochemical investigations of Cassia tora to discover and quantify the active chemicals it contains. Research should be conducted to determine how the composition of its active chemicals is influenced by environmental variables such as soil quality and temperature.

Agricultural research: Carry out research to determine how best to cultivate Cassia tora, taking into account the adoption of environmentally responsible farming methods in order to enhance crop yields and product quality. Investigate how the therapeutic qualities of the plant are affected by a variety of different growth circumstances.

Clinical investigations: Involve human participants in clinical research to determine whether or not Cassia tora and its active components are safe and whether or not they are effective. It is important to investigate the possible therapeutic uses of these compounds in the treatment of a wide range of illnesses and health disorders.

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The author declares no conflict of interest.

Author Contribution

Both authors have participated in critically revising the entire manuscript and approval of the final manuscript.

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