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TINOSOPRA CRISPA: A REVIEW ON PHYTOCHEMISTRY& PHARMACOLOGICAL PROFILE

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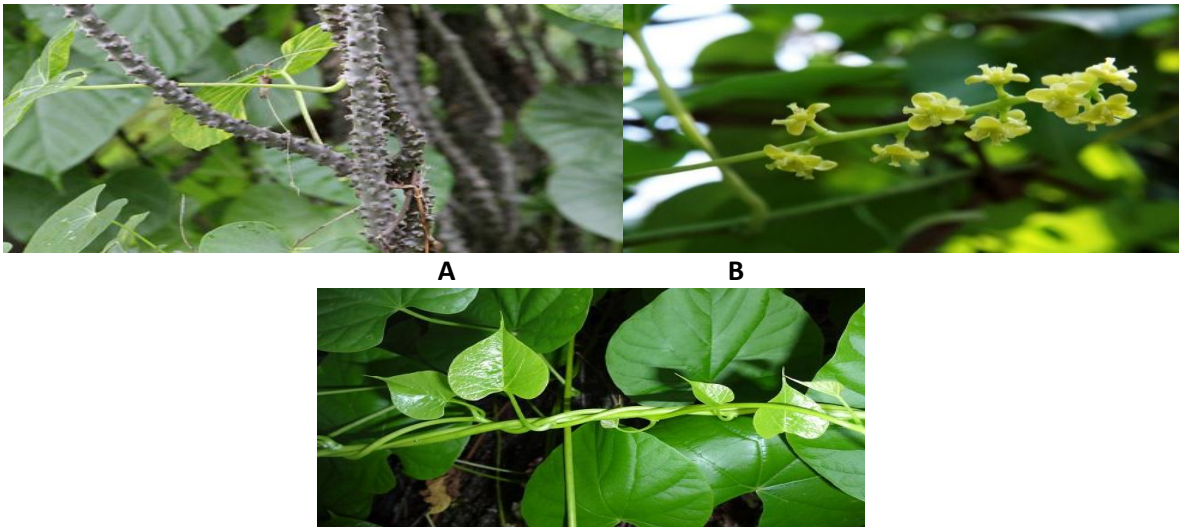
ABSTRACT

Tinospora crispa is utilised in numerous Ayurvedic formulations to treat a wide range of illnesses. The Menispermaceae family includes T. crispa, which is abundantly grown in tropical and subtropical nations like India, Sri Lanka, China, Myanmar, the Philippines, South Africa, Thailand, Bangladesh, and several south-east Asian continents like Indonesia and Malaysia. T. crispa has edible and therapeutic properties in all of its parts, including the roots, stem, bark, and leaves. T. crispa contains a variety of phytochemicals, including polysaccharides, alkaloids, glycosides, aliphatic compounds, diterpenoids, sesquiterpenoids, phenolic compounds, and steroid. This herb contains the beneficial biomarkers tinosporaside, tinosporine, magnosporine, berberine, choline, jatroporrhizine, palmatine, beberine, giloin, giloinsterol, and others. T. crispa has a number of known pharmacological properties, including anti-oxidant, anti-inflammatory, antidiabetic, immunomodulatory activity, anti-toxic, hepatoprotective, anticancer, cardioprotective, radioprotective, antimicrobial, anti-stress, anti-HIV, and many more. It is used to treat a variety of conditions, including colds, fevers, headaches, jaundice, and digestive disorders. The primary focus of this review study is on the phytochemicals and pharmacological properties of T. crispa.

KEYWORDS: *Tinospora crispa*, Phytochemicals, pharmacological activities, immunomodulatory, hepatoprotective, cardioprotective.

INTRODUCTION

Not just in the present, but also in the distant past, trees and plants have been essential to human life. Early man relied on them for both his spiritual requirements, such as magic or ritualistic practises, as well as his physical needs, such as sources for food, housing, clothes, medicine, adornment, and tools. Locally grown medicinal herbs are typically accessible, which When local and traditional treatments have been examined and shown to be non-toxic, secure, affordable, and socially and culturally acceptable, there is every reason to use them[1]. Numerous researchers have extensively studied the genus Tinospora and claim that it contains a number of phytochemicals with notable medicinal efficacy. Tropical lowland areas are home to the about 70 genera and 450 species of plants that make up the Menispermaceae plant family. Rarely shrubs, these are typically climbing or twining plants. Leaves are alternate or lobed, flowers, small chimes, seeds usually hooked or uniform. This family is a rich source of alkaloid and terpenes[2]. Both the traditional medical system and Ayurveda highlight the plant's healing properties. The plant can be found in the tropical region of India from Kumaon to Assam, and further north via West Bengal, Bihar, Deccan, Konkan, Karnataka, and Kerala, up to 1,200 m above sea level. It is a pretty common shrub that grows over hedges and small trees in deciduous and dry woodlands. It enjoys a variety of soil types, from acidic to alkaline, and it requires a moderate amount of soil moisture.[3]



A **B**

C

Fig. 1: A. Flowers of *Tinospora crispa* B. Stem of *Tinospora crispa* C. Leaves of *Tinospora crispa.*

Botanical Description: Large, glabrous, deciduous, climbing shrub *T. crispa*. The stem structure is fibrous, and the transverse slice reveals a yellowish wood with wedge-shaped wood bundles containing big vessels that are radially organised and spaced apart by narrow medullary rays. The stem has rosette-like lenticles, and the bark ranges in colour from creamy white to grey and is deeply spiralled. The leaves are cordate and membranous in texture. Unisexual, small, yellow, and in axillary position, the flowers have a raceme length of 2 to 9 cm and are borne on leaflet branches. Female flowers are often solitary, whereas male blooms are grouped. Curved seeds are present. Fruits have a solitary seed and are meaty. Fruits ripen in the winter and flowers in the summer.[5]

Morphological Description: A big, widely spreading climbing deciduous shrub with many coiling branches is called *Tinospora crispa*. The following types of morphology can be seen in various Tinosporan regions.

- **Stem**

This plant has a long, filiform, fleshy, and climbing stem that is fairly succulent in appearance. The branches give rise to aerial roots. The bark is deeply left spirally and ranges in tint from creamy white to grey.[6]

- **Arial Root:** There are aerial roots, and the fundamental structure of these aerial roots ranges from a tetra to a penta-arch. However, the cortex of the root is split into an inner parenchymatous zone and an exterior thick walled zone.[7]
- **Leaves:** Simple, alternate, exstipulate, round, pulvinate, heart-shaped, partially twisted, and halfway circular leaves of this plant have a length of around 15 petioles. Oval, 10–20 cm long, 7 nerved, profoundly cordate at the base, and membranous are the characteristics of the lamina.[8]
- **Flowers:** Unisexual, receptive, and greenish yellow in hue, flowers only bloom when a plant has no leaves. Female flowers are seen in single inflorescences, while male flowers are grouped. There are two series of three sepals each, totaling six. The inner sepals are smaller than the outer ones. Also, six in number, petals are membranous, free, and smaller than sepals. The flowering season lasts from March to June.[9]
- **Fruit:** They have an orange-red colour, are fleshy, have an aggregate of one to three smooth, ovoid drupelets on a thick stem, and have a sub terminal style scar. Fruits grow in the winter.[10]
- **Seed:** There have been reports of curved seeds in this species. As a result, this family is also known as the moonseed family. The embryo instantly assumed a curved shape, much as seeds do. Additionally, the endocarp has different ornamentations and offers crucial taxonomic characteristics.

Table 1: Traditional uses of *Tinospora crispa.*

Country	Traditional name	Part used	Mode of use	Traditional use
Thailand	Khruea khao ho-Boraphet	Stem Leaves Roots	Infusion Decoction Crushed leaves	Treatment of fever, cholera, diabetes, rheumatism, and snake-bites.[11]
Indonesia	Antawali Brotowali	Stems	Infusion	Treatment of stomach ache and jaundice. To treat fevers caused by smallpox and cholera. Treatment of fever and malaria.[16]
Malaysia	akar patawali or akar seruntum	Whole plant	boiling	Kadazan-dusun community treats hypertension and malaria by drinking boiled plant.[17]
Bangladesh	(Guloncho-ban) Golonchi	Stem	Juice obtained from macerated stems	Garo and Non-Garo traditional medicinal practitioners in Bangladesh use it for the prevention of intestinal disorders.[18]
China	Da ye ruan jin teng	Rattan		Yao communities of China use it for fracture, contusion, bitten by viper, carbuncle, furuncle, septicaemia, fever, scabies, and another tropical ulcer related disorders.[13]
Cambodia	Banndol Pech	stem		Fever Rheumatism[19]
Philippine	Makabuhay	Leaf Stem	Aqueous extract	Treatment of flatulence, Indigestion, diarrhoea, and rheumatism. To treat arthritis when prepared as a poultice with coconut oil.[20]

Phytochemistry

Alkaloids, glycosides, steroids, sesquiterpenoids, aliphatic chemicals, essential oils, a combination of fatty acids, and polysaccharides are the principal chemical components of the plant. Berberine, bitter gilonin, and non-glycoside gelonin gilosterol are some of the alkaloids.[21] Tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodane furano diterpene, diterpenoid furano lactone, tinosporidine, columbin, and b-sitosterol are some of the main phytoconstituents in Tinospora crispa. It has been stated that the plant's stem contains berberine, palmatine, tembertarine, magniflorine, choline, and tinosporin.[22,23] Tinocordiside, a rearranged cadinane sesquiterpene containing a cyclobutane ring and a tricyclic structure, has been discovered in the aqueous fraction of *T. Crispa*.[24] Plant stems have been used to isolate the novel clerodane furano diterpene 2, which has the chemical formula C20H20O8.[25] Tinocordifolin, a novel daucane type sesquiterpene, has been discovered in the stem of *Tinospora crispa*. Tinocordifolin and N-trans-feruloyl tyramine, two novel sesquiterpenes, have been designated combined as tinocordifolioside and tinocordifolin.[26] *Tinospora crispa* aerial parts' methanol extract was subjected to phytochemical analysis, and four new and seven recognised chemicals were found. Tinoscorside A and Tinoscorside B, two new aporphine alkaloids, as well as Tinoscorside C, a new clerodane diterpene, and Tinoscorside D, a new phenylpropanoid, are all described in detail below.[27]

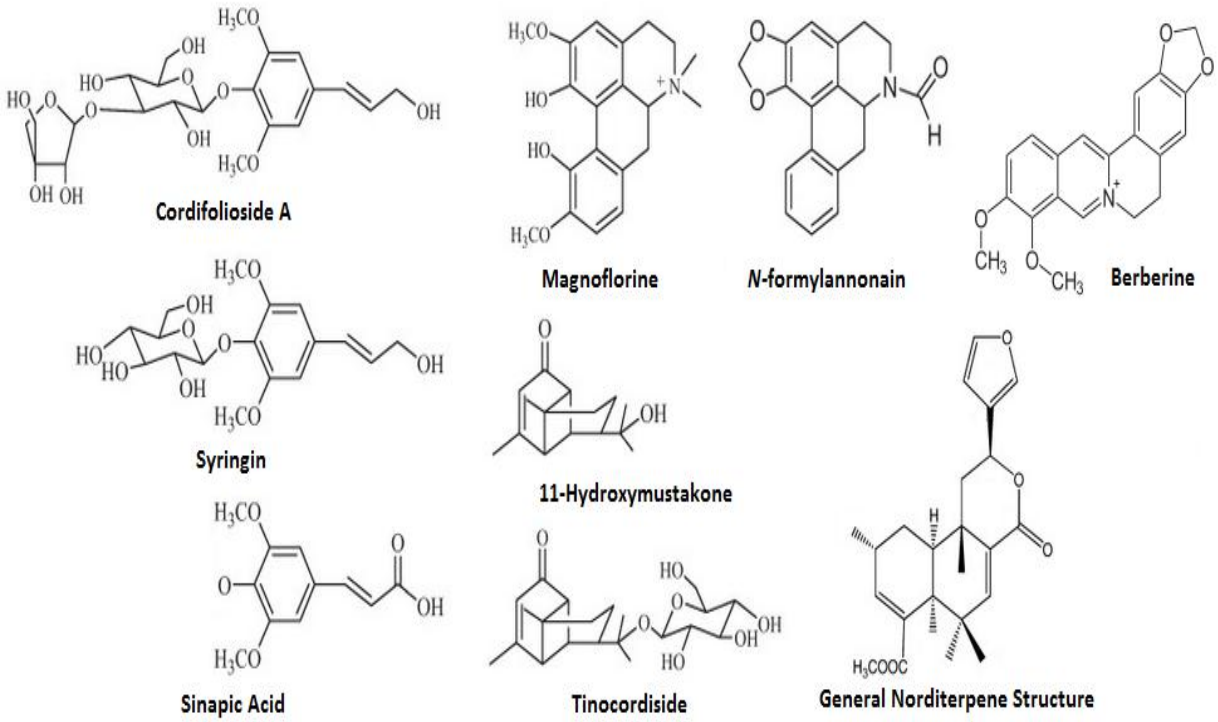


Fig. 2: Chemical constituents of *Tinospora crispa.*

Biological Activities

- **Anti-Diabetic Activity-** Numerous *T. crispa* extracts have been shown to have in vivo antidiabetic activity by pharmacological tests. Numerous biologically active phytoconstituents identified from various plant components, including alkaloids, tannins, cardiac glycosides, flavanoids, saponins, and steroids,[28] have been suggested to mediate its anti-diabetic potential. These substances may be used in both experimental and clinical studies because it has been suggested that they cover a variety of target activities in diabetes situations.
- **Anti-Cancer Activity-** *Tinospora cispa* has anti-cancer properties, which are primarily demonstrated in animal models. Response surface methodology was used to extract the alkaloid palmatine from *Tinospora crispa*, which has been shown to have significant anticancer properties in a mouse skin cancer model caused by 7,12-dimethylbenz (a)anthracene. Eight secondary metabolites from *Tinospora crispa* were tested in a study by Manju Bala et al. against four different human cancer cell lines, including KB (human oral squamous carcinoma), CHOK-1 (hamster ovary), HT[29] (human colon cancer), SiHa (human cervical cancer), and murine primary cells.[30]
- **Immunomodulatory Activity-** Its ability to modulate immune response is well documented for *Tinospora crispa*. There have been reports of potential immunomodulatory and cytotoxic effects of the active substances 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside, and syringing.[31] Aqueous Tinospora extracts have also been shown to have an impact on immune effector cell cytokine production, mitogenicity, stimulation, and activation.[32]
- **Anti-Oxidant Activity-** The *Tinospora crispa* has potential use as an antioxidant in food systems and probably as a nutraceutical in biological systems. *Tinospora crispa* extracts in methanolic, ethanolic, and water revealed notable antioxidant potential in comparison to other solvents, as well as metal chelation and reducing power activity.[33] Aflatoxisis causes the production of free radicals, which *Tinospora crispa* can scavenge. Due to the presence of alkaloids including a choline, tinosporin, isocolumbin, palmatine, tetrahydropalmatine, and magnoflorine, *Tinospora crispa* demonstrated protection against aflatoxin-induced nephrotoxicity.[34]
- **Anti-Microbial Activity-** Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Proteus vulgaris, Shigella flexneri, Salmonella paratyphi, Salmonella typhimurium, Pseudomonas aeruginosa, Enterobacter aerogene, and Serratia marcesenses have all been tested for the anti-bacterial activity of *Tinospora crispa* extracts.[35] The urinary pathogens Klebsiella pneumoniae and Pseudomonas aeruginosa were most effectively inhibited by an aqueous, ethanol, and acetone extract of the leaves and stem of *Tinospora crispa* Hook. F. Thoms.[36] The findings of a study by Francesca Bonvicinia et al. show that components from *Tinospora crispa* had a higher level of inhibitory action against clinical isolates of methicillin-resistant Staphylococcus aureus and Klebsiella pneumoniae that produces carbapenemase.[37]

Tinospora crispa components may serve as a possible source for fresh approaches to treating infectious disorders.

- **Anti-Toxic Activity-** L-DOPA is the gold standard medication for the treatment of Parkinson's disease, but numerous studies have shown that using this medication causes the CNS's remaining dopaminergic neurons to die. When compared to the Sham operated control group, the co-administration of *Tinospora crispa* crude powder preserved the dopaminergic neurons. *Tinospora crispa* crude powder therapy may lessen the side effects of L-DOPA therapy for Parkinson's disease.[38] Alkaloids from *Tinospora crispa*, including choline, tinosporine, isocolumbin, palmetine, tetrahydropalmatine, and magnoflorine, demonstrated protection against nephrotoxicity brought on by aflatoxin. Extracts of the *Tinospora crispa* have been shown to scavenge free radicals produced during aflatoxicosis.[39] In male albino mice, *T. crispa* leaf and stem extract has been shown to have hepatoprotective effects against lead nitrate-induced toxicity. Similar to this, an oral dosage of plant extract prevented liver damage brought on by lead nitrate.[40]
- **Hypoglycaemic activity-** In alloxanized diabetic rats, oral administration of the water extract of *Tinospora crispa* root resulted in a significant increase in body weight, total haemoglobin, and hepatic hexokinase as well as a decrease in blood sugar, brain lipid levels, hepatic glucose-6-phosphatase, serum acid phosphatase, alkaline, and lactate dehydrogenase.[41]
- **Anti-allergic activity-** In clinical research, 83% of the patients receiving treatment with *T. crispa* reported complete alleviation from sneezing. Thus, *Tinospora crispa* was well tolerated and dramatically reduced all allergic rhinitis symptoms.[42]
- **Cardioprotective activity-** Prior *Tinospora crispa* treatment resulted in a dose-dependent decrease in the extent of the infarct as well as in the levels of serum and heart lipid peroxide in rats with an ischemia-reperfusion-induced myocardial infarction.
- **Hepatoprotective-** In one of the tests, goats treated with *Tinospora crispa* shown a considerable improvement in CCl4-induced hepatopathy in terms of both clinical and hemato-biochemical parameters. Hepatitis B and E surface antigens have been shown to be inactivated by *T. crispa* extract de vitro in 48–72 hours.[43]
- **Anti-stress and tonic property-** Clinical trials examining the plant's anti-stress and tonic properties revealed that it had positive effects on kids with mild behavioural problems and cognitive deficits. The I.Q. levels44 have also greatly increased as a result.
- **Anti-inflammatory-** In models of acute and subacute inflammation, the alcoholic extract of *Tinospora crispa* has been shown to have anti-inflammatory effects.[44]
- **Antineoplastic activity-** *Tinospora crispa's* alcoholic extract has been shown to stimulate macrophage functions such as phagocytosis, antigen-presenting capacity, and secretion of interleukin-1 (IL-1), tumour necrosis factor (TNF), and reference nutrient intake (RNI), as well as slow tumour growth and lengthen the lifespan of the tumor-bearing host, in Dalton's lymphoma (DL) bearing mice.[45]
- **Osteoprotective activity-** *Tinospora crispa* treatment had an osteoprotective effect on rats as evidenced by the fact that their tibial bone loss was significantly slower than that of controls. Cross-laps levels and serum osteocalcin were both dramatically decreased. This study shows that *Tinospora crispa* extract has a strong potential for usage as an anti-osteoporotic agent.[46]
- **Antifertility activity-** Male rats were given a 100 mg/d oral dose of a 70–75% methanolic extract of *Tinospora crispa* stem for 60 days, however this did not result in any body weight loss. However, it did significantly reduce the weight of the testes, epididymis, seminal vesicle, and ventral prostate.[41]
- **Anti-ulcer activity-** Treatment with a formulation containing *Tinospora crispa* has been demonstrated to lower ulcer index total acidity, with an increase in the pH of gastric fluid in rats with pylorus ligation and in the injury to the stomach mucosa caused by ethanol in rats.[47]
- **Anti leprotic activity-** In addition to being widely used for Kandu and visarpa (types of skin problems), *Tinospora crispa* is used for its kushtahara (anti-leprotic) characteristics. It has also been demonstrated to exert anti-leprotic action in a combined formulation.[46]
- **Anticholinesterase Activity-** Acetyl cholinesterase is an enzyme that catalyses the breakdown of acetylcholine to choline. Acetylcholine hydrolysis causes the cholinergic synapses to stop transmitting nerve impulses. The Ellman's colorimetric method was used to examine the quaternary alkaloids isolated from *T. crispa* as AChE inhibitors. Different activity characteristics might be seen in the isolated compounds.[48] The AChE inhibitory activity of *T. crispa* alkaloids should be investigated. Parkinson's and Alzheimer's illnesses, senile dementia, ataxia, and myasthenia gravis can all be treated with the AChE inhibition. The findings from the aforementioned study, however, are insufficient to make a significant judgement. Therefore, additional innovative and mechanistic research is required to comprehend the anticholinesterase activity.
- **Atherosclerosis Inhibitory Activity-** By lowering levels of total cholesterol, triglycerides, and low-density lipoproteins, the aqueous extract from *T. crispa* stem given to hypercholesterolemic rabbits postponed the onset of atherosclerosis.[49] High-density lipoprotein levels, on the other hand, were discovered to have dramatically increased. Furthermore, they showed that the *T. crispa* aqueous

and methanol extracts reduced the malondialdehyde level in a dose-dependent manner by boosting the activity of antioxidant enzymes in H2O2-induced HUVECs, such as catalase, superoxide dismutase, and glutathione peroxidase.[50] They also demonstrated that the *T. crispa* aqueous and methanol extracts increased the activity of antioxidant enzymes in H2O2-induced HUVECs, including catalase, superoxide dismutase, and glutathione peroxidase, which in turn decreased the malondialdehyde level in a dose-dependent manner.

- **Antiparasitic Activity-** Plasmodium falciparum development was completely inhibited by the methanol extract of the entire *T. crispa* plant after 72 hours at a dosage of 2.5 mg/Ml[51]. These findings support the traditional use of *T. crispa* as an antimalarial drug even though only crude extracts of *T. crispa* have been investigated for its antimalarial activity and no mechanism of action has been reported. The aforementioned results should spur researchers to better characterise the antiplasmodial action of isolated compounds from *T. crispa* for antimalarial activity.
- **Cytotoxic Activity-** Different *T. crispa* extracts' cytotoxic properties had been investigated. The HeLa, Caov-3 and HepG2 human cancer cell lines were used to test the cytotoxic activities of the aqueous crude extract of *T. crispa* stem. The aqueous extract of *T. crispa* stem had cytotoxic effects equal to those of cisplatin and tamoxifen, with IC50 values for MCF7 of 107 g/mL, HeLa of 165 g/mL, Caov-3 of 100 g/mL, and HepG2 of 165 g/Ml.[52] *Tinospora crispa* extracts had an impact that was on par with or superior to doxorubicin therapy. These experiments, which were only conducted in vitro utilising various cancer cell lines, are of a very preliminary nature. To address the anticancer potential of *T. crispa* with these results would be premature at this time. It is necessary to uncover the active ingredients and underlying mechanisms that underlie the anticancer activities. Future research is also necessary to confirm the therapeutic impact in an in vivo model.
- **Antinociceptive Activity-** At a dose of 666 mL, the dried extract of *T. crispa* stem showed encouraging central analgesic activity.[53] However, there weren't enough doses tested to clearly show a dose-dependent effect. It is challenging to extrapolate any conclusions from this study because there were no negative controls and no evaluated doses. According to one study, *T. crispa's* ethanol extract reduced mice's writhes caused by acetic acid in a dose-dependent way. It was demonstrated that the analgesic response of the ethanol extract at a dose of 300 mg/kg was stronger (92%) than that of acetyl salicylic acid at a dose of 100 mg/kg (81%). To support its historical usage against pain, further research is required.[54]
- **Cytochromes Inhibitory Activities-** The primary enzymes that catalyse the oxidative metabolism of pharmaceuticals and other xenobiotics are called cytochromes P450 (CYPs). It has been observed that CYP isoforms such CYP3A4, CYP2D6, CYP2C9, and CYP2E1 are involved in metabolism. Due to alterations in the metabolic clearance of a co-administered medicine, the inhibition of CYP causes unexpectedly unfavourable drug interactions. The metabolism mediated by CYP3A4 was inhibited by *T. crispa* by about 70%, according to a radiometric assay against CYP3A4.[55] and CYP2D6. N-methyl-14C] erythromycin and [Omethyl- 14C] dextromethorphan was utilised as substrates in human liver microsomes in order to better understand the inhibitory mechanism, and the activity of CYP was assessed by measuring the formation of 14C-formaldehyde. *T. crispa* methanol extract showed a more than 30% increase in CYP3A4 inhibition at a dosage of 0.5 mg/mL[56]. These data show an inhibitory impact of *T. crispa* on CYP3A4 and CYP2D6. To ascertain any potential drug-drug interactions, it is also necessary to explore how *T. crispa* affects the other CYP isomers, including CYP2C9 and CYP2E1.
- **Anti-HIV Activities-** This plant's root extract has been demonstrated to reduce the body's natural resistance against HIV.[57] Reduction in eosinophil count, activation of B lymphocytes, macrophages, haemoglobin level, and polymorphonuclear leucocytes were indicators of this anti-HIV action.[57,58]

CONCLUSION

It is clear from this review that *T. crispa* is an important herbal plant that contributes significantly to the management of health care. Its components or the entire plant are used to cure a variety of human conditions, including colds, fevers, mouth ulcers, digestive problems, etc. It includes a variety of bioactive substances, some of which have been discussed, such as sesquiterpenoids, alkaloids, glycosides, steroids, and aliphatic compounds. Pharmacognosy, analytical work, and numerous pharmacological actions such as antioxidant, anti-inflammatory, anti diabetic, toxic, anti-HIV, antimicrobial, anti-allergic rhinitis, anti-tubercular, anti-angiogenic, and many more were noted in the current revival. Now that *T.crispa* is being used in many ways, people are starting to understand the importance of this remarkable plant during this pandemic catastrophe.

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Conflicts of interests

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

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