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TINOSPORA CORDIFOLIA - FROM A HUMBLE PLANT TO THE MOST BASIC INGREDIENT FOR FOOD. - AN OVERVIEW

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ABSTRACT: Natural products with medicinal value are becoming increasingly important in food preservation. *Tinospora cordifolia,* a plant commonly known as Guduchi, is highly beneficial in the medicinal field and has been used for centuries to treat various diseases. Due to the discovery of active components in *Tinospora* species and their potential for disease control, this plant has gained interest across the globe. Various pharmacological characteristics such as antioxidant, hepatoprotective, neuroprotective, antidiabetic and analgesic antitumor activities support its medicinal properties making it a promising herb with various health benefits. These biological activities of *Tinospora* species can be attributed due to the presence of a wide range of phytoconstituents, including alkaloids, flavonoids, lignans, Furano diterpene glucosides and sterols. The clinical importance of *Tinospora cordifolia* is included in this review to investigate its potential uses as an ingredient for the food industry. The future scope of the review remains in exploiting and isolating antimicrobial compounds to enable new and effective formulations in food preservation.

INTRODUCTION: Herbal preparations have been a vital part of human civilization since infancy. Long ago, it was believed that plants were imbued with a life essence and would naturally cure any ailment when used as medicine for humans. Modern science confirms this ancient belief by showing interest in identifying bioactive compounds found within medicinal plants and using them effectively in medical treatments. Nowadays, with the growing challenges in healthcare systems, researchers are turning their attention toward plants.

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In Indian traditional medicines, there is a record of 25000 plant-derived drug formulations, thereby showing our intense connection to nature's remedies [1]. One such remedy is Tinospora species, traditionally used for jaundice treatment and fever control, among many other beneficial uses. There are 34 species of the Tinospora genus found in Africa, Australia, Asia, Madagascar, and the Pacific regions [2].

This is surprising because naturalized plants aren't native-born to the country they grow in; however, nine plant species were planted for various purposes such as food supplements or medicine but became a part of India's ecosystem. The *T. cordifolia* is a large deciduous climber that grows on the trunks and branches of trees and hedges. The stem consists of succulent bark, and its roots are pendulous fleshy ones that hang from it or branches.

When dryness causes stress to this plant's body parts (stems), they shrink in size with time; their outer surface becomes rough and causes easier separation from other tissues/organs. The leaves of the tree are green and round, with long stems like cords. They have an average diameter between 2.5-7cm. The plant's flowers bloom in the summertime; they can be yellow or light green because they grow on a short stem found at branch joints and small bracts shaped like triangles. Male plants have six petals each, while female ones only hold three different types: outer whorl sepals, which look darker than inner whorls, but both usually appear lighter when touched against sunlight.

The female flowers are solitary, have green sepals that aren't reflexed, and have a short staminode. The ovary comprises 1 to 3 carpels that sit widely separated on the gynophore. It's also dorsally convexed [3]. *T. cordifolia* stems are utilized medicinally due to their active compounds stimulating gastric activity and bile secretions that enrich one's bloodstream. Many other positive effects on health include alleviating spleen enlargement symptoms and effective against chronic diarrhea, asthma, dysentery, urinary, skin diseases and respiratory complaints. The decoction of the plant's stem can be applied topically for washing eye infections or syphilitic sores while also being an antidote in cases of scorpion stings and poison from snakes [4]. Honey and crushed leaves are used together to effectively cure ulcers, gout, skin infections, malaria, women's fertility issues [5]. Honey combined with dried fruit powder is a tonic for jaundice and rheumatic complaints. Children suffering from colds should have honey mixed with ripened juice daily. Whole plant extract is useful in diarrhea, stomach complaints and anemia [4]. The stem is rich in minerals, including calcium, phosphorus, iron, and zinc. This makes it suitable for treating metabolic disorders like anemia or diabetes mellitus [6].

TABLE 1: ETHNOMEDICINAL USES OF INDIAN TINOSPORA FOUND IN DIFFERENT STATES OF INDIA

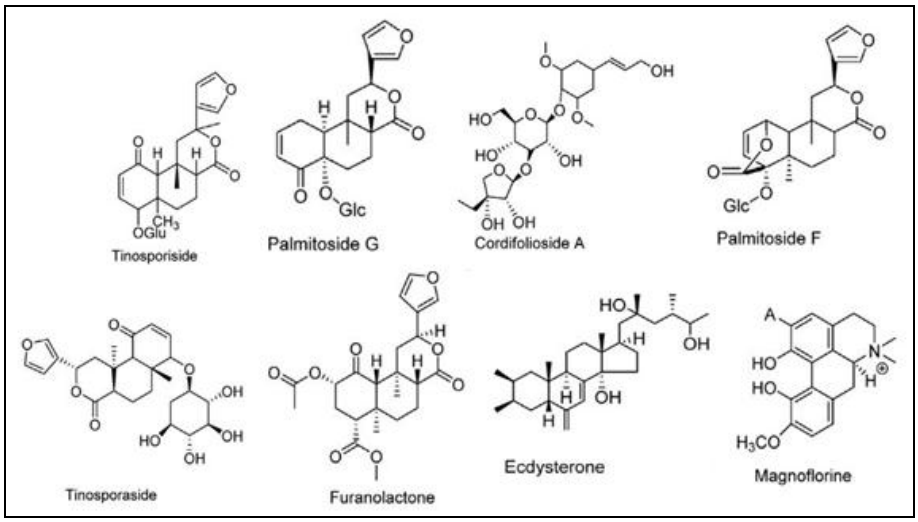
Diseases/ complaints	Mode/parts of application	References
Fever	Pills are prepared from the paste of the stem of the *T. cordifolia* and the roots of Bhatkatiaya (Solanum surattense); Decoction of the stem is administered orally.	6
Cough	Drinking the warm juice of root *T. cordifolia* is used as a treatment for cough and bronchitis.	7
Jaundice, chronic diarrhea, periodic fever	The plant is used in its entirety	8
Cancer, dysentery, diarrhea and periodic fever	Powdered root and stem bark of *T. cordifolia* with milk for cancer; root decoction for dysentery and diarrhea; old stem decoction for periodic fever	4
Balashosha (emaciation in children), daha (burning	Children wear dyed clothes soaked in the juice of Guduchi plant for Balashosha. Paste or juice of *T. cordifolia* leaves and SarsapaBeejachurna is used as a medicine to curedaha	9
Bone fracture	The whole plant paste is used in bone fractures	4
General debility	Decoction the stem with cold and hot water (about 3–4 g) in the morning on an empty stomach, used as a tonic.	10
Kasa (cough)	In equal quantity, powder of *Terminalia chebula*, *T. cordifolia* , and *Trachyspermum Ammi* is taken orally once daily in the morning, with a small amount of salt.	11
Karna Shula (pain in the ear)	Two drops of juice from the leaves are dropped in the infected ear.	5
Asthma	Juice of stem orally given with honey	12

Phytochemistry: The alkaloids, glycosides, diterpenoid lactones, flavonoids, steroids and sesquiterpenoids have been isolated and identified in *Tinospora cordifolia* are summarized below. The amritoside A, amritoside A pentaacetate, amritoside B, amritoside B pentaacetate, amri-

toside C, amritoside C pentaacetate, amritoside D, amritoside Dtetraacetate, tinosponone, tinosporaside, tinosporaside tetraacetate, tinocordioside, Tinocordioside tetraacetate tinoscorside C, borapetoside F, borapetoside B, cordifolide A, tinosporafuranol, tinospora-clerodanol, tinosporafuradiol, tinospora-clerodanoid, cordioside from stemand stem bark [13] syringin, cordifoliside A, cordifoliside A tetraacetate, cordifoliside B, cordifoliside Btetraacetate, cordifoliside C, cordifoliside C tetraacetate, cordifoliside D, cordifoliside D tetraacetate, cordifoliside E, cordi-foliside Etetraacetate [4], 4, 5, 7-trimethoxy-2-naphthol-2-*O*-a-L-arabinofuranosyl-(2)-*O*-a-L-arabinopyranosyl-2-*O*-pentane, b-D-arabinosyl-*O*-geranilan-10-oate, 5, 7-dimethoxy – 2 - naphthol-2-*O*-a-L-arabinopyranosyl-(2′1)-a-L-arabinopyra nosyl-2-*O*-decane [14] have been isolated and characterized from *T. cordifolia* stem.

Tinocordifolin, tinocordifolioside and tinocordifolioside, tetraacetate was isolated and identified from the stem of this plant species. Thetrans-cinnamoyl-2-n-hexany l-7-methoxynaphthyl amide, trans-cinnamoy l-2-n-pentanyl-6,7-dimethoxynaphthyl amide, *trans*-cinnamoyl-2-n-octanyl-7-methoxynaphthyl amide were identified from *T. cordifolia* stem [4]. More than 300 benzoid compounds have been identified from plants which include methyl benzoate, methylsalicylate, phenylacetaldehyde, phenylethyl acetate, benzyl acetate, phenyl ethanol, eugenol, and isoeugenol [15]. Alkaloids are a large group of organic compounds found in nature that contains nitrogen atoms. These nitrogen atoms are usually situated in a cyclic ring system [16]. Based on the cyclic ring system, alkaloids can be classified into several classes such as indoles, acridines, quinolines, isoquinolines, pyrrolidines, pyridines, pyrrolizidines, quinazolines, and tropanes. Alkaloids are usually bitter, colorless, or colored (yellowish liquids) and odorless crystalline solids. They can be yellowish if they have a liquid form, such as nicotine, but most alkaloids in nature tend to take on the solid-state of crystals. Nearly more than 3000 alkaloids have been investigated in different 400 plant species [17]. In addition, several alkaloids (catharanthine, indicine-N-oxide, vincamine, vincristine, ajmalicine, vinblastine, strychnine, quinine, and ajmaline) possess anticancer, antimalarial, anti-inflammatory and antimicrobial activities [18].

The tinoscorside A and B, jatrorrhizine, palmatine, magnoflorine, berberine, isocolumbin, tembetarine have been reported from aerial parts and stem of this plant species. The angelicoidenol 2-O-b-D-apiofuranosyl - (1, 6)- b -D-glucopyranoside secoisolariciresinol - 9′- O – b - D-gluco-pyranoside, cordifoliosides A and B have been identified from *T. cordifolia* aerial parts [19]. Magnoflorine, a quaternary alkaloid isolated from *T. cordifolia*, has been reported to have potent anticancer and antidiabetic properties. In addition, recent studies have shown that magnoflorine has a certain anti-inflammatory effect. Similarly, jatrorrhizine, an isoquinoline alkaloid isolated from *T. cordifolia*, has various bioactivities, such as antioxidant, low host toxicity and highly potent antimicrobial activity [20].



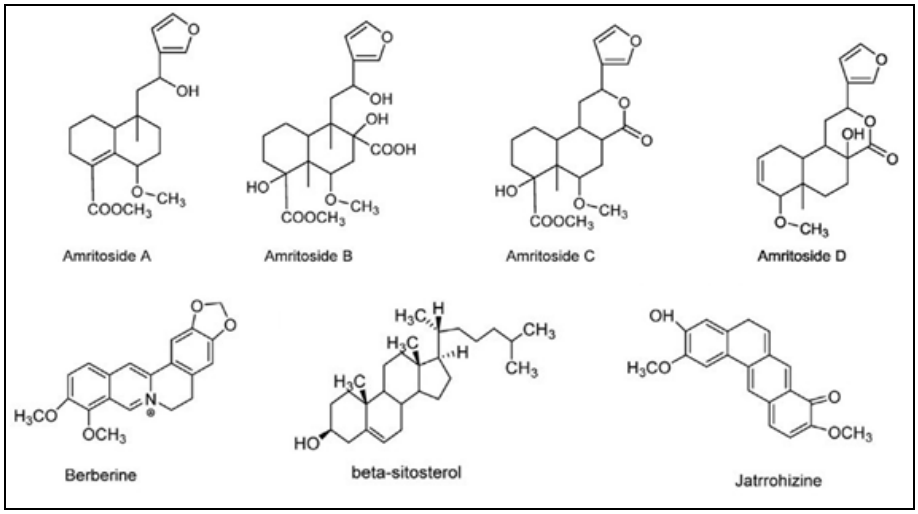


FIG. 1: STRUCTURE OF BIOACTIVE COMPONENTS IN *TINOSPORA CORDIFOLIA*

Flavonoids are considered the largest class of secondary metabolites containing a broad class of polyphenolic compounds with a low molecular weight that share a common skeleton of phenyl-benzo-g-pyran (C6-C3-C6), also known as theflavan nucleus, composed of two phenyl rings (A and B) connected through a pyran ring (C). They are medicinally important metabolites synthesized via the phenylpropanoid pathway, converting phenylalanine into4-coumaroyl CoA. Flavonoids include flavonols, flavones, flavonoids, flavanones, anthocyanidins, and isoflavones and are widely distributed in the leaves was seeds, bark, and flowers of plants [16]. These are hydroxylated phenolic compounds and are known to be produced by the plants in response to microbial infection. The plant-derived flavonoids induce activities of human protective enzymes [21]. The polypodine B 20, 22-acetonide, 20-p-hydroxyecdysone, b-sitosterol, stigmasterol and campesterol were isolated and identified from aerial parts of *T. cordifolia*. Flavonoids play a significant role in foods' sensory and health properties [22]. Plant-derived flavonoids possess anti-viral/bacterial,anti-inflammatory,cardioprotective,antidiabetic,anticancer,anti-aging properties [21]. Various studies have suggested the protective effects of flavonoids against bacterial and viral infections.

TABLE 2: CHEMICAL CONSTITUENTSISOLATEDFROM INDIAN *TINOSPORA* SPECIES FOUND IN RAJASTHAN, UTTAR PRADESH, BIHAR, WEST BENGAL, GUJARAT, PUNJAB, TAMIL NADU, KERALA AND KARNATAKA

Extract type	Plant parts	Isolated compounds	References
Methanolic and ethanolic	Aerial parts and stem	Alkaloids - Tinoscorside A, tinoscorside B, palmatine, tembetarine, jatrorrhizine, magnoflorine, berberine, isocolumbin	18
Ethanolic	Roots	Alkaloids – Tetrahydropalmatin, jatrorrhizine, magnoflorine	11
Methanolic	Cell cultures	Alkaloids – Berberine and jatrorrhizine	23
Methanolic	Aerial parts	Phenylpropene disaccharides - Angelicoidenol 2-O-b-D- apiofuranosyl-b-D-glucopyranoside, secoisolariciresinol-9'-O-b-D-glucopyranoside	24
Methanolic	Stem	Sulfur-containing clerodane diterpene glycoside - Cordifolide A	24
Aqueous-methanolic	Stem	Clerodane furano diterpene glycoside - 2b,3b:15,16-Diepoxy- 4a, 6b-dihydroxy-13,14-clerodadiene-17,12:18,1-diolide	11
Methanolic	Stem and stem bark	Clerodane furano diterpene glucosides - Amritoside A, amritoside A pentaacetate, amritoside B, amritoside B pentaacetate, amritoside C, amritoside C pentaacetate, amritoside D, amritoside D tetraacetate, tinosponone, tinosporaside, tinosporaside tetraacetate, tinocordioside, tinocordioside tetraacetate, tinoscorside C, borapetoside F, borapetoside B, tinosporafuranol ,tinosporaclerodanol, tinosporafuradiol, tinosporaclerodanoid, cordifolide B, cordifolide C	25
Butanoic and methanolic	Stem	Norditerpene furan glycosides – Syringin, cordifoliside A ,cordifoliside A tetraacetate , cordifoliside B , cordifoliside B tetraacetate , cordifoliside C , cordifoliside C tetraacetate , cordifoliside D , cordifoliside D tetraacetate , cordifoliside E , cordifoliside E tetraacetate , 4,5,7-trimethoxy-2-naphthol-	14

		2-O-a-L-arabinofuranosyl-(20-100)-O-a-L-arabinopyranosyl- 200-O-pentane , b-D-arabinosyl-O-geranilan-100-oate, 5,7-dimethoxy-2-naphthol-2-O-a-L-arabinobpyranosyl-(-a-L-arabinopyranosyl-200-O-decane	
Methanolic	Stem	Aromatic amides - Trans-cinnamoyl-2-n-hexanyl-7-methoxynaphthylamide, trans-cinnamoyl-2-n-pentanyl- 6,7-dimethoxynaphthyl amide, trans-cinnamoyl-2-n- octanyl-7-methoxynaphthyl amide	[14]
Methanolic and aqueous-methanolic	Aerial parts	Ecdysteroids and steroids - Polypodine B 20, 22-acetonide, 20-p-hydroxyecdysone, b-sitosterol	[8]

Furanoditerpenoids are a special diterpenoids consisting of one or more furan rings, found in Euphorbiaceae, Fabaceae, Lamiaceae, Asteraceae, Codoniaceae, Dioscoreaceae, Fossombroniaceae, Jamesoniellaceae, Meliaceae, Menispermaceae, Olacaceae, Psathyreaceae, Sapindaceae and Scapaniaceae families. There are seven types of furanodi terpenoids that have been reported from plants: clerodane-, labdane-, cassane-, abietane-, spongian-prenylbisabolane- and miscellaneous types [26]. The columbin-rich ethanol extract of *T. cordifolia* was assessed for its protective effects against acute cold stress in male Sprague-Dawley rats [27].

Pharmacological Attributes of *Tinospora species:* Ethanolic extract of *T. cordifolia* is extensively used to formulate 'Septilin' syrup, recommended to remedy bronchitis and earache. The isolated compounds berberine and jatrorrhizine showed antimicrobial, anti-inflammatory [28].

Antioxidant Activity: Oxidative stress is the main root of a variety of diseases. The food materials promote antioxidative defenses in the human body to combat the non-desirable effects of reactive oxygen species. Plants can biosynthesize a wide range of non-enzymatic antioxidative molecules capable of attenuating the reactive oxygen species-induced oxidative destruction. Ethanolic extract of *T. cordifolia* stem (300 mg/kg b.w.,p.o., for 30 days) significantly ($P < 0.01$) reduced the levels of catalase and superoxide dismutase (57.05 ± 5.67 and 6.69 ± 0.19) in cancer-bearing animals but, it did not show any change in the animals of the control group [13]. The n-butanolic extract of *T. cordifolia* stem (200 mg/mL) showed significant antioxidant activity in DPPH, ABTS, nitric oxide scavenging and iron-chelating assays. The activity could be associated with the presence of phenolic compounds [29].

Antidiabetic Activity: The methanolic extract of *the T. cordifolia* stem was administered (p.o.) for 24 weeks to diabetic rats, and blood glucose levels were monitored in treated and non-treated groups. Methanolic extract lowered the blood glucose levels in treated animals significantly ($P < 0.001$) when compared with normal rats [30]. Ethanolic extract (100 and 200 mg/kg body weight) of *T. cordifolia* stem suppressed 6-phosphatase and fructose 1, 6-diphosphatase activities significantly ($P < 0.001$) but stimulated the formation of glycogen contents in the liver ($P < 0.005$; The formulation of water extract (*T. cordifolia* stem) + honey suspension reduced the levels of blood glucose and glycated hemoglobin in streptozotocin treated Wistar albino rats. Magnoflorine isolated from *T. cordifolia* leaf (100 mg/kg b.w.) significantly reduced serum glucose levels in streptozotocin-induced diabetic Wistar rats [20].

Antistress Activity: Stress stimulates alterations in various physiological responses, even dominating pathological stress. Chronic stress exposure is a causative factor of free radical formation, and reactive oxygen species increase in the body.

Normally stress-induced alterations are self-limiting events that override the 'threshold' limits and become irreversible and pathological. Stress develops various diseases such as hypertension, peptic ulcer, Alzheimer's disease, and depression [17]. Ethanolic extract of *T. cordifolia* fresh leaves (50 mg/kg) showed a significant decrease in the immobility period (force swim and tail immersion tests. In patients with chronic mental stress, serum glucose, triglyceride, cholesterol, anxiety, and depression were higher than in healthy men [31]. The patients were administered with *T. cordifolia* (3 g twice daily) powder and advised to do yoga daily. The experimental study was followed for 60 days, and results revealed that *T. cordifolia* with

continuous yoga practice in patients showed significant antistress activity compared with diazepam [27].

Anticancer/Antitumor Activity: In the present world, cancer is one of the most dreaded diseases and is a leading cause of death worldwide. It comes after cardiovascular disease and infectious diseases in terms of mortality rate. Breast cancer is also categorized as being among those types which are commonest - it accounts for nearly 30% of cases that occur within women. The maximum prevalence of breast cancer is found in South-Central Asian countries [32]. It has been proven that several diseases occur in humans due to the development of oxidative stress. The oxidative stress developed by free radicals seeks stabilization through electron pairing with proteins and DNA in healthy cells of humans, causing DNA and protein damage. These alterations contribute to cancer, cardiovascular problems, and aging disorders [29]. Palmatine isolated from *T. cordifolia* aerial parts reduced the tumour size significantly ($P < 0.05$) and also increased the levels of glutathione, superoxide dismutase, and catalase in the skin of treated animals ($P < 0.05$) [32].

Antimicrobial Activity: Bacterial and fungal infections and multidrug resistance have been immense challenges, threatening human health in the last few decades. Microbial infections are causing the death of millions of people in different countries worldwide. The development of multidrug resistance in microbes has caused the antimicrobial molecules to become less efficacious or even ineffective [33].

However, synthetic antibacterial and antifungal agents have already been used in various countries, yet the usage of plant-derived secondary products attracts the attention of researchers [34]. The plant-derived secondary metabolites have demonstrated promising results in overcoming the multidrug resistance in microbial pathogens [35]. Many people in developing countries use plant-based medicine to treat illnesses. Plants are often used because they're more accessible and cheaper than scientifically developed drugs, which can be prohibitively expensive for many people living in poverty. On the first day, *Escherichia coli* (1x10 viable) cells were injected intraperitoneally to evaluate the antibacterial activity of *T. cordifolia* aqueous extract in the adult Swiss albino mice [36]. The aqueous extract (100 mg/ kg/day by intragastric tube) of the stem was administered to the albino mice. The mice mortality rate in the control group was100%, while the mortality rate was 17.8% in the extract-treated group [37]. In gentamicin-treated animals, mortality was reported as 11.1% ($P < 0.001$). Ethanolic extract of *T. cordifolia* leaf showed maximum inhibitory effects against *Klebsiella pneumoniae* (inhibition zone 12.0 mm) and *Pseudomonas aeruginosa* (inhibition zone 9.0 mm) at 400 mg/mL concentration. Similarly, the ethanol extract of the stem also exhibited potent activity to *K. pneumoniae* (inhibition zone 15.0 mm) but displayed moderate effect against *P. aeruginosa* (inhibition zone 12.0 mm; 400 mg/Ml [35]. Ethanol extract (95%) of *T. cordifolia* showed significant antipyretic activity in Himalayan rabbits (50 mg/mL for 10 days) [31].

Several Tinospora species have been considered for their therapeutic properties due to their strong antidiabetic and antiarthritic activities attributable to high contents of alkaloids, clerodane Furano diterpenes, and glucosides, phenolics, and flavonoids [5]. Many modern medicines are derived from secondary metabolites that have been used for centuries to treat human diseases. Now, various researchers are searching for biologically active natural products and are trying to establish their possible therapeutic roles in disease control mechanisms.

Such new natural products can often serve as chemical templates for designing and synthesizing novel pharmaceutical drugs. Indian Tinospora species possesses immunomodulatory, hypoglycaemic, antiallergic and anti-inflammatory properties [29]. *T. cordifolia* dried fruits are useful in jaundice and rheumatism, while the leaves cure diabetes. Its roots possess antistress, antioxidant, antiulcer, hypoglycemic properties, and the treatment of visceral obstructions.

*T T. cordifolia stem has been used by Indian people to trea*t 1 diabetes. Antidiabetic efficacy and safety of *T. cordifolia* stem capsules (dry powder) in diabetic patients have been proven in clinical trials and in Indian people [38].

T. cordifolia capsules (300 mg/kg/day) showed a significant decrease in mean systolic blood pressure on fixed workload exercise compared to placebo and improved physical performance. In addition, capsules significantly changed the neutrophil and eosinophil counts ($P < 0.05$) and effectively relieved the clinical symptoms in cases of allergic rhinitis, cold and fever [15]. Different parts of Indian *Tinospora* species treat fever, urinary diseases, asthma, gout, diabetes, diarrhoea and skin infections. Various bioactive compounds provide the plant with its antidiabetic, antioxidant, anticancer. Although some studies have been done to reveal the pharmacological activities of *T. cordifolia*, its true potential is yet to be acknowledged. Plant-based medications have always been around. However, different plant species show great disparities in their therapeutic values. The indigenous drug industry has grown more than ever before with this knowledge.

Moreover, many shreds of evidence gathered in earlier studies also confirmed the identified phytochemicals to be bioactive and showed various medicinal properties. It is no surprise that the food industry is always looking for new ways to innovate and break boundaries. In the constantly evolving food industry, ground-breaking products are being appreciated and accepted by different consumers. Global food safety has significant effects on an individual's health. The high-temperature processing techniques to reduce microbial activity may alter foods' nutritional and sensory properties. The use of preservatives reduces the risk of food-borne illnesses but may cause other kinds of illness in the long run, such as diseases related to brain or kidney damage. However, outreach about healthy eating among the educated population has increased, bringing awareness on many vital matters relevant to our overall well-being system, causing positive outcomes over time.

CONCLUSION: The benefits of plant-derived compounds from *Tinospora cordifolia* can be implemented in food to help us prepare and preserve our foods. Moreover, this richly nourished natural product may attract those who want a healthier alternative. This passage discusses a shift towards healthier eating habits among individuals due to their concerns over what they put into their bodies. Studies need to be conducted on how the active compounds interact with the food components and affect the structure-function relationships.

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