ANTI-DIABETIC, ANTI-OXIDANT ACTIVITY AND CHEMICAL CONSTITUENTS OF *Tinospora cordifolia* (Wild) Hook. f. & Thomson TRADITIONALLY USED PLANT OF INDIA-A REVIEW

Rupinder Kaur[1], Simrat Kaur[2], Bhavna Thakur[3], Sugam Gupta[4], Kamla Dhyani[5]*, Sunil Puri[6]

[1]Department of Agriculture, Tula's Institute, Dehradun (Uttarakhand)-248001, India
[2]Department of Chemistry, Mata Gujri College, Fatehgarh Sahib (Punjab)-140406, India
[3]School of Agriculture and Allied Sciences, Doon Business School Group, Dehradun (Uttarakhand)-248001, India
[4]Department of Applied Science Tula's Institute, Dehradun (Uttarakhand)-248001, India
[5]School of Agricultural Sciences, Shri Guru Ram Rai University, Dehradun (Uttarakhand)-248001, India
[6]Department of Biological and Environmental Science, Shoolini University, Solan (HP)-173229, India

***Corresponding author's email: kamladhyanijakhmola@sgrru.ac.in**

Abstract

Tinospora cordifolia, a well-known medicinal herb in Ayurveda, is employed in a number of conventional treatments for a variety of human ailments. Due to its well-known characteristic of having fewer negative effects than medications, natural materials with medical potential are progressively gaining prominence in clinical research and also regarded as a key botanical in the Indian systems of medicine. Common names for this member of the Menispermaceae family include Amrita and Guduchi. The recent discovery of the plant's active ingredients (terpenoids, alkaloids, steroids and lignans) and their biological role in the treatment of disease has sparked widespread interest in the plant. Considering that it has been used to cure a number of diseases, such as skin disorders, diabetes, diarrhea, fever, snake bite, eye disorders, poisonous insects and leprosy. The pharmacological significance of antioxidant activity, antibacterial activity, and anti-diabetic action is highlighted in the current review. Future work on the study will continue to concentrate on understanding the signaling and biochemical pathways which are affected by the compounds from *Tinospora cordifolia*. This study adds fresh information that will aid in the thorough evaluation of the plant as a medicinal agent against developing illnesses.

Keywords: *Tinospora cordifolia*, Giloy, Menispermaceae, Phytochemicals, Antioxidant, Ayurveda, .

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INTRODUCTION:

The Menispermaceae family includes *Tinospora cordifolia* (*T. cordifolia*), also referred to as "Amrita" or "Guduchi" in popular culture. It has long been regarded as one of the key medications in Indian systems of medicine. Guduchi/Amrita and the Latin names for the plant *T. cordifolia* include: Hindi: Giloya; English: Tinospora Gulancha/Indian Tinospora; *Tinospora cordifolia* (Wild) Hook. f. & Thomson. It is a native of India and is primarily found in tropical nations like Sri Lanka and Myanmar (Saha and Ghosh, 2012; Tiwari *et al*., 2018). It has

The plant has been reviewed and researched more thoroughly in contemporary medicine, and most recently the medication has been used to lessen the side effects of chemical treatments. Present work focuses on pharmacological

traits, phytochemical investigations, and prospects for scientific investigation to promote conventional medicine. According to the information provided by Sharma *et al*., 2019 this plant has been recorded as the primary source of cures for numerous disorders in folk medicine in India, including fever, urinary diseases and dyspepsia. Phytomedicine are medical preparations isolated from a combination of one or many herbs in a certain ratio to provide benefits for curing illnesses in humans or animals as well as for aesthetic purposes. Because there were no analgesics or antibiotics in the early 20th century, herbal medicine was the primary type of treatment. Herbal medicine has gradually fallen out of favor with the general public due to the increased use of the allopathic medicine system and their speedy curing outcomes. Due to the lower risk of side effects and greater compatibility system with the human body, around 65-80 percent of individuals continue to utilize phytoremedies for the primary health benefits. Herbal therapy is now more widely used and is more effective than synthetic drugs (Pooja *et al*., 2010).

Tinospora cordifolia is a big, climbing, deciduous shrubby plant which spreads widely and has multiple coiled branches with various morphologies. It is native to tropical parts of India at an altitude of 500 mt. at a temp. of range of 25-45^{0}C. The bark of the plant is whitish to greyish, and the stem is fleshy, filiform and ascending in character. The stem's powder is odorous, bitter, and creamish brown or dark brown in color. It is used to treat high fever, dyspepsia, mild infections and urinary disorders. Starch is extracted from its shoot is referred to as "Guduchi-satva."It is very nutritious and aids with digestion. The root is aerial, squairshin, thread-like, and occasionally constantly continues till it hits the earth. A tetra to penta arch in the basic structure distinguishes aerial roots from other types. Plant lamina is oblong, 10-20 cm long, seven nerved, extensively cordate at its base. Its leaves are simple, heart-shaped, alternate, pulvinate, circular, and somewhat twisted along with long petioles (Fig. 1). Its flowers are axillary, unisexual, yellowish-green in color, and have leaflet branches that range in length from 2-9 cm. While female flowers frequently grow alone, male blooms are typically clustered (Singh *et al*., 2003; Arul *et al*., 2005; Upadhyay *et al*., 2010; Spandana *et al*., 2013; Sinha and Sharma, 2015; Tiwari *et al*., 2018).

Its blooms develop in the summer and its single-seeded fruits ripen in the winter. The form of the seeds and the different ornamentations on the endocarp give essential taxonomic characteristics. In addition to being used as a liniment for erysipelas and as a tonic with honey, fresh leaves along with milk are also used for gout treatment. As per the reports available from Singh *et al*., 2003 one of the ingredients in various ayurvedic medicines used to treat general debility, urinary disorders, fever, and dyspepsia is the stem of *T. cordifolia*. Its chemical constituents are very effective in controlling various human diseases as per the information available from previous studies by Dahiya *et al*., 2011; Mittal *et al*., 2014; Dhama *et al*., 2017; Sharma *et al*., 2019; Modi *et al*., 2021 and Yogeta *et al*., 2021).

PHYTOCHEMISTRY:

Tinospora cordifolia has been shown to contain a variety of substances from different chemical families of secondary metabolites, such as aliphatic substances, alkaloids, phenolic substances, essential oils, terpenoids, glycosides, steroids, different fatty acids, proteins, calcium, phosphorus, and polysaccharides (Table 1 and Fig. 2).

The leaves of this plant contain large amounts of alkaloids, glycosides, flavonoids, and proteins. These chemical compounds have variety of biological effects, including antiseptic, anticancerous, antiinflammatory, antibacterial and antidiabetic activities (Khosa *et al*., 1971; Upadhyay *et al*., 2010; Rajalakshmi *et al*., 2016). Alkaloids, terpenoids (diterpenoids and sesquiterpenoid lactones), steroids, glycosides, phenolics, starch and other miscellaneous compounds enhance these capabilities of pharmacological importance of *Tinospora cordifolia*. Structures of some of the chemical constituents isolated from *Tinospora cordifolia* are given in Fig. 2. With its variety of chemicals that highlight the adaptability of the species in terms of therapeutic applications, a systematic research effort has been launched at several institutions to capitalise on its multifaceted function as a resource for the treatment of illnesses. Since *T. cordifolia* has been suggested as a preventative and prophylactic treatment for COVID 19, demand for it has increased dramatically. It is crucial to collect, characterise, and conserve *T. cordifolia*'s germplasm since it is a significant therapeutic plant (Geetha and Satyabrata, 2023).

Alkaloids are the chief active components extracted from the shoots and roots of Guduchi. Reports are available by Rout *et al*., 2006; Jagetia *et al*., 2006; Patel *et al*., 2009; Upadhyay *et al*., 2010; Patel *et al*., 2011, that 13 alkaloid active components including tetrahydropalmatine, corydine, berberine, isocolumbin, magnoflorine palmetine, choline, aporphine, jatrorrhizine, and tinosporin which have antidiabetics, antiviral, anti-psychiatric, antiinflammatory, anticancerous, and immunomodulatory effects. Mckeown *et al*., 2012; Lv *et al*., 2012 and Sundarraj *et al*., 2012 reported that the steroids isolated from shoot of the plant under study were 20 β-hydroxyecdysone, β-sitosterol, giloinsterol, δ-sitosterol, makisterone A and ecdysterone. Dixit and Khosa, 1971 reported 2, 3, 14, 20, 25-hexahydroxyl-5-cholest-7-ene-6-one steroids from *Tinospora cordifolia*. These steroids were very much effective for curing the glucocorticoid-induced osteoporosis which is brought on by the inflammatory arthritis. They also cause the cell cycle arrest during the G2/M phase and suppress the TNF-, IL-1, COX-2, IL-6, and apoptosis by reducing the c-Myc.

Furanolactone, diterpenoid Lactones, cleodrane derivatives, tinosporin, columbin tinosporides and jateorine are the chemical compounds which are extracted from whole plant of *T. cordifolia*. They demonstrated biological effects like anti-hypertensive, anti-inflammatory, vasodilatation, antiviral, and anti-microbial (Dhanasekaran *et al*., 2009). Evidences of presence of glycosides in the shoot of *T. cordifolia* were reported by Ly *et al*., 2007; Kapil and Sharma, 1997; Chen *et al*., 2000; Baldwin *et al*., 2001; Kim *et al*., 2008 and Yang *et al*., 2010. Their primary active constituents include tinocordifolioside, 18-norcleodrane glucoside, pregnane glycoside, cordifolioside B, C, A, E and D, cordioside, diterpine glucoside, furanoid, syringing, syringing-apiosylglycosides and palmatosides. In the diseases such as dementia, parkinson's disease, ALS, and issues with motor function, they showed immunomodulation. They do this by blocking the NF-k Band, which results in anti-cancer actions.

The *Tinospora cordifolia* plant as a whole contains aliphatic substances such as octacosanol, heptacosanol and nanocosan15-one dichloromethane as active ingredients. They displayed antiinflammatory along with the antinociceptive activities. Additionally, they also prevent TNF- from attaching to the DNA and shields the animals from Parkinsonism caused by 6-hydroxydopamine. Sesquiterpenoids and the antiseptic tinocordifolin are found in

the stem of *T. cordifolia* (Maurya and Handa, 1998). The active ingredients tinosporic acid, N-trans-feruloyltyramine as diacetate, jatrorrhizine, 3-4 tetrahydrofuran and giloin are found in the other portions of *T. cordifolia*. They demonstrated an anti-HIV protective effect (Ghosh *et al*., 2008 and Mukherjee *et al*., 2010).

Dahiya and his co-workers, 2011 reported that tinosporine, clerodane furano diterpine, tinosporaside, and columbin are the main phytoconstituents of *T. cordifolia*, followed by cordifolide, cordifol, heptacosanol, and tinosporide. Alkaloids from the stem of *T. cordifolia*, including tembertarine, berberine, magniflorine, non-glycoside gilonin gilosterol, palmatine, tinosporin and choline have been reported. Akhilraj *et al*., 2023 reported 76 medicinally important compounds out of which major were n-hexadecanoic acid (14.55%), gammasitosterol (11.05%), columbin (4.79%), oleic acid (14.94%), octadecanoic acid (4.77%), stigmasterol (3.94%) were detected using Gas chromatography-mass spectrometry technique from dried powder (stem) of *Tinospora cordifolia*. Structures of some phytochemicals of plant are given in Fig. 3.

Table 1. Chemical constituents isolated from *Tinospora cordifolia*

Phytochemical Compound		**Plant Organ**	**References**
Terpenoids	Furanoid diterpene Furanolactone diterpene Tinosporide Tinosporaside Furanolactone clerodane Diterpene Ecdysterone makisterone, and a number of glucosides were isolated as poly acetate, as well as the phenylpropene disaccharides cordifolioside A, C and B, cordifolioside E and D, Tinocordioside, tinocordifolioside and tinocordifolin are sesquiterpenes Clerodane derivatives Tinosporon Columbin Jateorine	Whole plant	Hanuman *et al*., 1986 Hanuman *et al*., 1988 Gagan *et al*., 1996 Maurya and Handa, 1998 Kohno *et al*., 2002 Zhao *et al*., 2008 Dhanasekaran *et al*., 2009 Yang *et al*., 2010 Sriramaneni *et al*., 2010
Alkaloids	Choline Palmatine Tembeterine Tinosporine Berberine	Stem, Root	Upadhaya *et al*., 2010 Rout, 2006 Patel *et al*., 2009 Patel and Mishra, 2011 Choudhary *et al*., 2013

	1,2-substituted pyrrolidine alkaloids e.g. jatrorrhizine, Magnoflorine Jatrorrhizine		Mittal *et al*., 2014
Steroids	ß-Sitosterol Giloinsterol 20 α- Hydroxy ecdysone	Stem	Lv *et al*., 2012 Sunderraj *et al*., 2012 Mckeown *et al*., 2012
Lignans	3,4- tetrahydofuron	Bark	Hanuman *et al*., 1986
Glycosides	Tinocordiside Cordifolioside A, D, B, C and E Cordioside Tinocordifolioside Syringinapiosyl glycoside 18-norclerodane glucoside Furanoid diterpene glucoside Pregnane glycoside Cordifolioside Palmatosides Syringin	Stem	Kapil and Sharma, 1997 Badwin *et al*., 2001 Karpova *et al*., 1991 Chen *et al*., 2001 Ly *et al*., 2007 Kim *et al*., 2008 Yang *et al*., 2010
Aliphatic compounds	Octacosanol Nonacosan-15-one-dichloromethane Heptacosanol	Whole plant	Khuda *et al*., 1966 Thippeswamy *et al*., 2008 Wang *et al*., 2010 De-oliveria *et al*., 2012
Others	Tinosporidine Cordifol Cordifelone Tinosporic acid N-trans-feruloyltyramine as diacetate 3,4-tetrahydrofuran Giloinin Jatrorrhizine Giloin	Root	Khuda *et al*., 1966 Mukherjee *et al*., 2010 Ghosh *et al*., 2008

Fig. 1: *Tinospora cordifolia* in its natural habitat

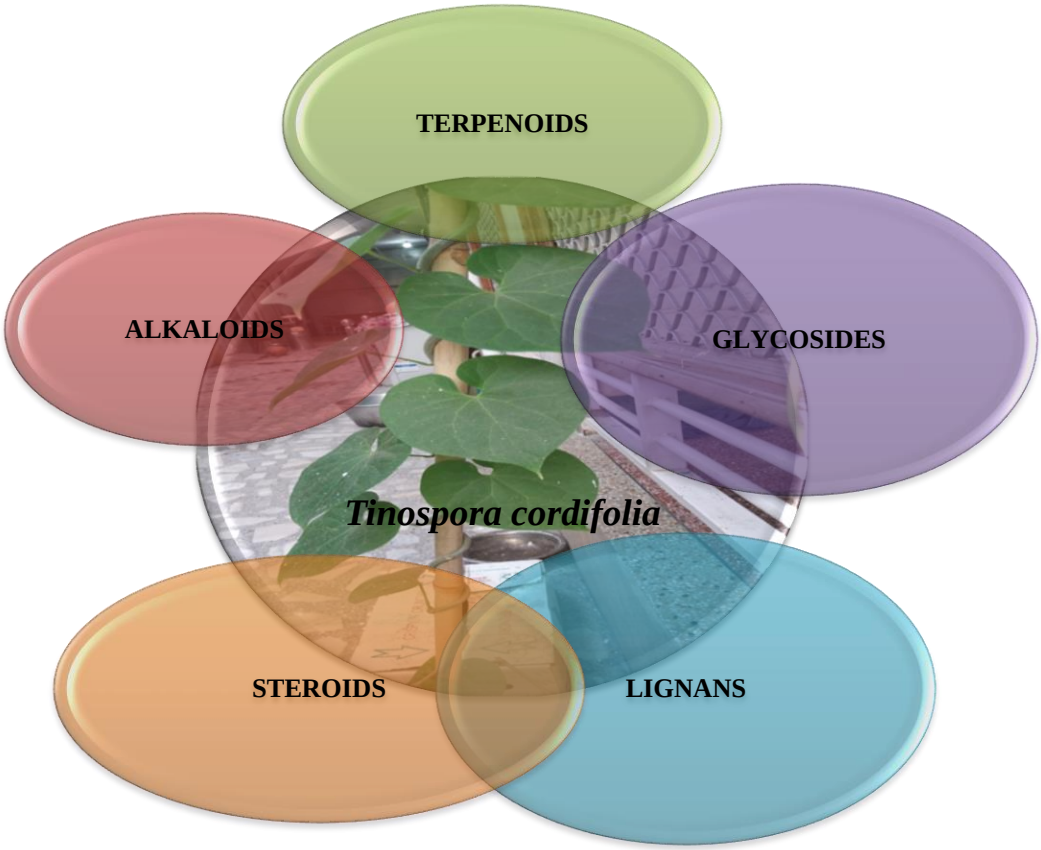
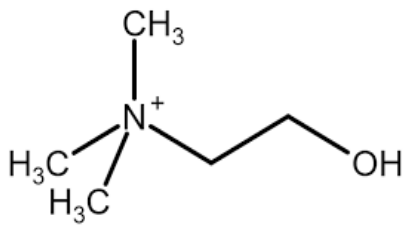
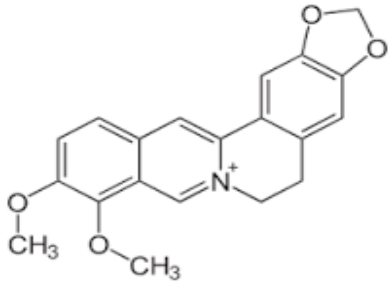
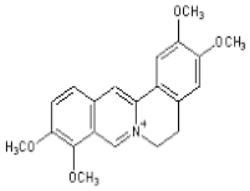
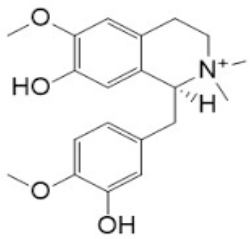
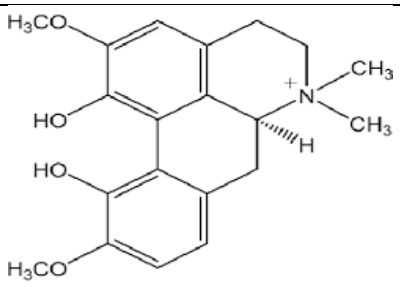
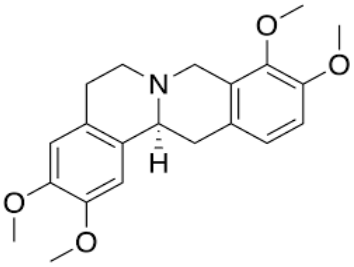
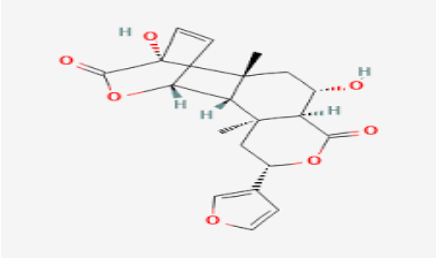
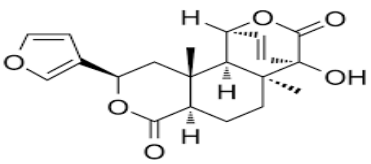
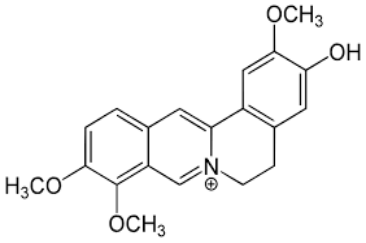
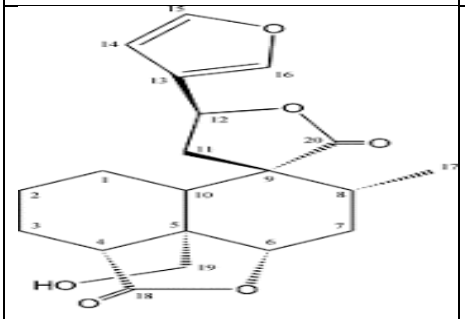
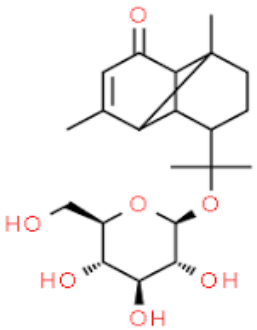
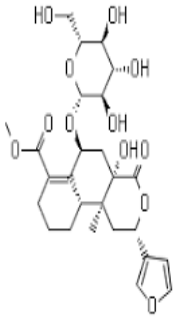


Fig. 2: Important Phytoconstituents classes of *Tinospora cordifolia*

 **Choline**	 **Berberine**	 **Palmatine**
 **Tembetarine**	 **Magnoflorine**	 **Tetrahydropalmatine**
 **Tinosporin**	 **Isocolumbin**	 **Jatrorrhizine**
 **Neo-clerodane**	 **Tinocordiside**	 **Cordioside**

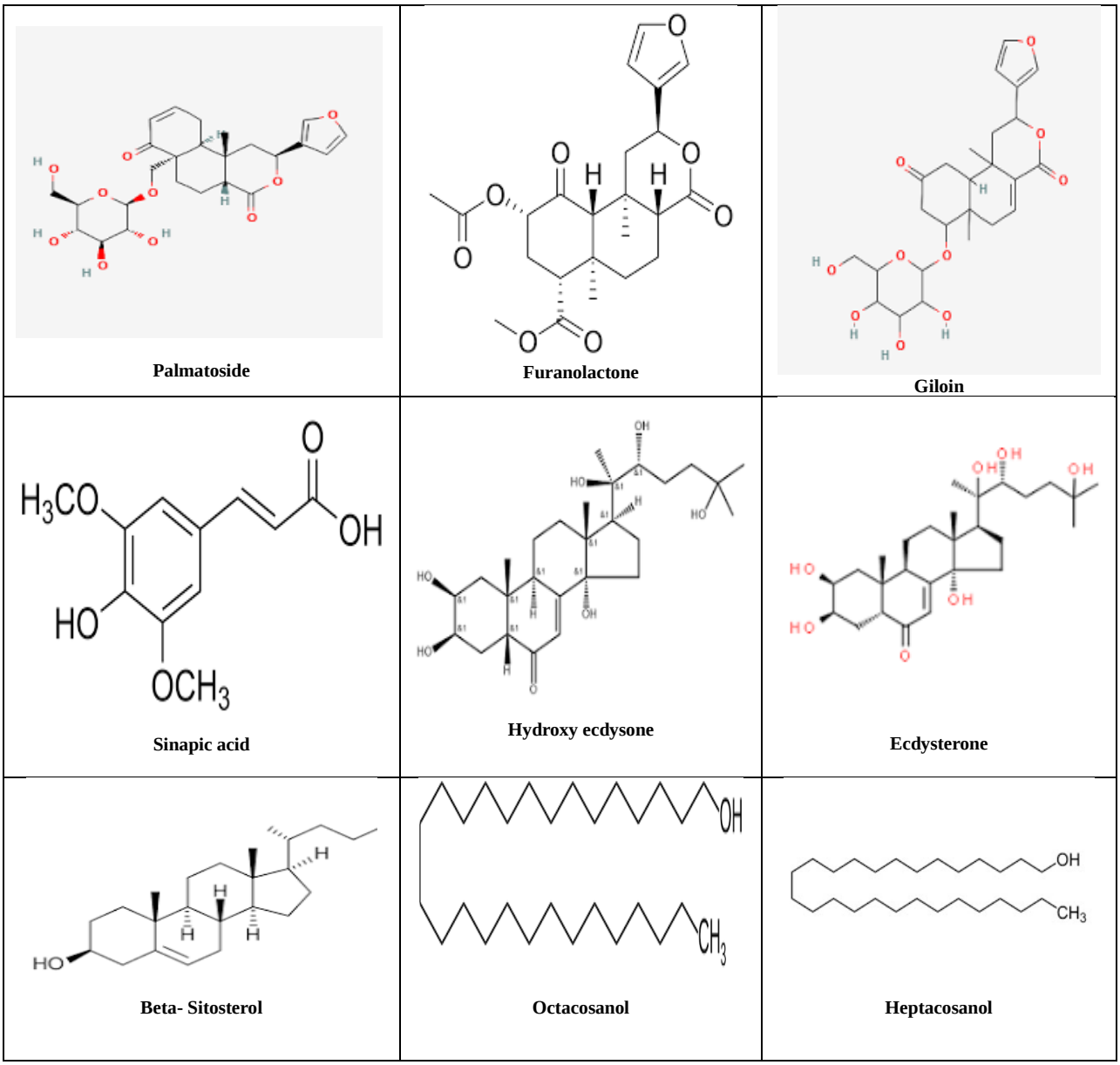


Fig. 3. Structures of different phyto chemicals of *Tinospora cordifolia*.

Due to its allergen-free, spasmolytic, and anti-diabetic properties, *Tinospora cordifolia* has long been acknowledged as the herb that is most frequently employed in traditional systems of medicine. The herb greatly strengthens the immune system. This plant has a lot of beneficial qualities its stem is an effective diuretic and stomachic. Roots of the plant are very important to reduce stress and have anti malarial effects too. It increases blood quality, stimulates biliary secretion, and treats jaundice. The effects of *T. cordifolia* have been the subject of much research, some of which are summarized in this section. The Ayurvedic Pharmacopeia of India lists the stem of *T. cordifolia* as an authentic ayurvedic medication. As reported by different researchers this is a versatile herb which promotes the longevity and so called vayastha or Amrita. In addition, *Tinospora cordifolia* is combined with other plants for

commercial formulations in folk, veterinary, and ayurvedic medicine. It is used as a rasayana to strengthen the body's defenses against illness and the immune system. Although the stem is permitted for use in medicine according to the Ayurvedic Pharmacopoeia of India, the plant is utilized medicinally as a whole.

ANTI-DIABETIC ACTIVITY:

Medications that treat, alleviate, prevent, or stabilize the diabetes in persons are considered anti-diabetic medications. They also include substances that help to maintain the glucose levels in blood. Tannins, alkaloids, flavonoids, cardiac glycosides, steroids and saponins- the main chemical constituents of *Tinospora cordifolia* have been demonstrated to have antidiabetic activities (Zinjarde *et al*., 2011). This makes it possible for it to be broadly applied in both clinical and experimental studies. Alkaloids derived from *T. cordifolia* have been asserted by Patel and Mishra (2011) to have the same effects as insulin and to have actions that are mediated by insulin. The plant's anti-diabetic and lipid-lowering properties are highlighted by Stanely *et al*., (2000) findings which suggest that T. *cordifolia* root extracts reduces the blood sugar and urine glucose levels in diabetic rat models while attenuating brain-mediated cholesterol levels. Gestational hyperglycemia can result in elevated levels of GSH and other reactive species, which can be dangerous for both the mother and the foetus. Stanely and his co-workers (2000) reported that *T. cardifolia* root extract has shown hypoglycemic and hypolipidemic effects on diabetic rats by increasingits body weight, hepatic hexokinase, total hemoglobin, and lowering serum acid phosphatase, alkaline phosphatase, hepatic glucose-6-phosphatase, and lactate dehydrogenase.

Hyponidd, Dihar and Ilogen-Excel are examples of herbal medicinal compounds which contain a variety of herbal plants, including *Tinospora cordifolia* as main constituents. Such compounds were tested in diabetic rat models, and it was discovered that *Tinospora cordifolia* alone is responsible for the anti-diabetic effect in diseased animal. Ilogen Excel's effects were reported to slow down the blood's excess level of glucose and improve insulin effectiveness by boosting the amount of the hormone's systemic circulation. According to reports by Stanely, (2003); Babu and Prince, (2003) and Patel *et al*., (2009), by lowering reactive species and the amount of glucose-mediated hemoglobin, hyponidd lowers the oxidative burden.

When used for 1.5 months in a streptozotocin-induced diabetes mouse, Dihar reduced the blood levels of urea and creatinine while also increasing enzyme activity. Shivananjappa (2012) reported that extracts of *T. cordifolia* was shown to be protective in the presence of greater quantities of enzymes and antioxidant molecules. It has been demonstrated to dramatically reduce the diabetes-associated OS in the maternal liver by reducing malondialdehyde and ROS while increasing GSH and total thiols. According to a clinical investigation by Chougale *et al*., (2009), T. *cordifolia* plant extract inhibits the glucosidase enzyme, lowering post-meal elevated glucose levels. When tested in a diabetic rat model (streptozotocin-induced diabetes), Singh *et al*., (2013) reported that oral administration of T. *cordifolia* leaf extracts also showed anti-diabetic potential through various peripheral pathways including transportation of glucose, glycogen storage, and other mechanisms. As reported by Sangeetha *et al*., (2011), *T. cordifolia*'s the stem extract has antidiabetic potential by improving the efficiency of insulin through the β-

pancreatic cell that secretes it, as well as by supporting other antidiabetic pathways like inhibiting the formation of glucose by promoting the glycogenesis, etc., lowering endogenous glucose, decreasing oxidative stress, and increasing insulin secretion.

ANTI-OXIDANT ACTIVITY:

T. cordifolia's anti-oxidant activity is demonstrated by its ability to scavenge free radicals and other reactive species, respectively (Bhawya *et al*., 2010 and Khan *et al*., 2011). As reported earlier in a diabetic rat model (alloxan induced diabetes), *T. cordifolia* greatly reduces the regulation of the lipid per oxidation process, resulting in decreasing the levels of its reactive free radical species. Sivakumar and Rajan (2010); Stanley and Menon (2001) by their research demonstrated that the plants extract also regulates the antioxidant enzymes like catalase and glutathione, which shows its anti-oxidant activities. By boosting the erythrocytes' membrane lipid peroxide and catalase activity, methanolic extract of *T. cordifolia* stem has been linked to anti-oxidant activity. According to a clinical study by Rawal *et al*., 2004 and Gacche *et al*., 2011 the TC extract has antioxidant properties by increasing GSH levels and decreasing the expression of the gene for inducible nitric oxide synthase. It also has benefits for treating cataracts by blocking the enzyme aldol reductase.

According to a study by Upadhyay *et al*., 2014, ethanol-based TC bark extracts exhibit higher levels of free radical scavenging activity and phenolic content than their methanol-based counterparts. In a rat model, the polysaccharide component 'arabinogalactan' from plants has antioxidant activity via protecting against free radicals (Subramanian *et al*., 2002). According to reports, *T. cordifolia* alters the levels of several enzyme systems, which in turn controls the lipid peroxidation process along with glutathione levels to control the generation of these reactive species and also to maintain the oxidative load (Jayaprakash *et al*., 2015). Due to its antioxidant properties, this plant also shields mice against-radiation by preventing the lipid per oxidation caused by ferrous sulphate (Kapur *et al*., 2010; Patel *et al*., 2013 and Goel *et al*., 2002). Pepticare, a herbal-mineral combination that contains *T. cordifolia*, has also been shown to have powerful antioxidant properties in Ayurvedic medicine.

The formulation was created by Mehra *et al*., 2013 who used the 1-diphenyl-2-picrylhydrazyl a free radical scavenging method to assess its antioxidant efficacy. They calculated the total phenolic and flavonoid content. When compared to the ascorbic acid standard medication, the formulation's results demonstrated an inhibitory concentration (IC50) of 5 g/ml and strong antioxidant activity. In alloxan-induced rats which were diabetic, the ethanol extracts (shoot extract) boosted the erythrocyte membrane lipid peroxide along with catalase activity. But other activities like superoxide dismutase and glutathione peroxidase were found to be decreased. According to George and co-workers (2016) reported antioxidant activity of the ethanolic, methanolic, and water extracts of plant. Methanol extracts from the leaves had a high level of phospho molybdenum and metal chelating activity

Additionally, it reduced the amount of free radical species present in the diabetic rats but increased the activity of an antioxidant enzyme. Methanol extract had a higher capacity to scavenge free radicals than phenol extract (Prince *et al*., 2001; Prince *et al*., 2003; Babu and Prince, 2004; Patel *et al*., 2009; Sivakumar *et al*., 2010; Upadhyay *et al*., 2014 and Jayaprakash *et al*., 2015). This plant influences the numerous enzymatic systems that control the generation of these reactive species and maintain the oxidative load by regulating the glutathione levels and lipid per oxidation process (Bafna *et al*., 2005 and Jayaprakash *et al*., 2015). As per the findings of Premnath *et al*., 2010, the leaves of plant were first dried, made into powder, and then extracted with water, ethanol, methanol, and chloroform. Using a number of in-vitro models, the antioxidant assays DPPH radical scavenging activity, superoxide radical scavenging activity, and lipid per-oxidation inhibitory activity was carried out. The antioxidant activity was best in ethanol extract in comparison to that of other solvent extracts such as chloroform, methanol and water. The results show that ethanol extract has more potent antioxidant components, and there is a direct correlation between the total amount of polyphenols extracted and its anti-oxidant activity.

As per research available by Stanely *et al*., (2001 and 2003) in the rats with diabetes produced by alloxan, it also lowers SOD and GPx activity. Free radical scavenging abilities of *T. cordifolia* extract have been reported (Rawal *et al*., 2004). Extracts from the Leaves of plant also known as saponarin, was discovered to exhibit considerable antioxidant and hydroxyl radical scavenging action in addition to being an alpha-glucosidase inhibitor (Diwanay *et al*., 2004). Alkaloids are present, and they provide protection against nephrotoxicity brought on by aflatoxin (Gupta and Sharma, 2011). The aqueous extract of this plant exhibits radio protective properties that let mice survive exposure to low doses of gamma radiation (Sharma and Pandey, 2010; Kapur *et al*., 2010).

CONCLUSION

T. cordifolia is a medicinal plant that has a wide range of substances. Sesquiterpenoids, alkaloids,, glycosides, steroids, and other bioactive substances have all been discussed. The anti-diabetic, antioxidant properties and chemical constituents of *T. cordifolia* are highlighted in the current review. Since the beginning of Ayurvedic medicine, it has been successfully used, and products made from this plant are used for their better financial along with its therapeutic utilization. In this sense, more research must be done to examine its potential in the prevention and treatment of illnesses. This review can be applied clinically and for additional research purposes in the development of various useful drugs. Authors have made an effort to examine various features of *T. cordifolia* in the hope that it will encourage the academics to focus more on the value addition, which will ultimately boost the economy and jobs. The likelihood of novel medications being created from this plant to treat various human illnesses is higher. The plant may have both therapeutic and commercial benefits.

Conflicts of interests

This work has no conflicts of interest.

RK: Study conception, drafted the manuscript and literature collection, **KD:** collected literatures from different databases and manuscript preparation, **JM:** collected literatures from different databases, **SK:** analyzed and interpreted the findings; and **SP:** conceived and designed the review. All authors have read and agreed with the final version of manuscript

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