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REVIEW ARTICLE

Ethnopharmacological and phytochemical attributes of Indian *Tinospora* species: A comprehensive review

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Abstract Total 34 species of *Tinospora* genus are found in Africa, Australia, Asia, Madagascar and Pacific regions of the World. Nine species of *Tinospora* are naturalized in the different states of India. In traditional medicine, different parts of *Tinospora* are used in the treatment of syphilis, ulcers, bronchitis, jaundice, urinary disease, piles, skin and liver diseases. The information of traditional uses, phytochemical and pharmacological properties of Indian *Tinospora* species was collected from the published books, MSc/MTech, PhD dissertations, PubMed, Wiley, and Elsevier. Moreover, the reference books, the relevant reviews, and the digital records were critically examined to present a complete overview of Indian *Tinospora* species. Indian *Tinospora* species possess various pharmacological attributes such as antioxidant, hepatopotective, radioprotective, neuroprotective, antidiabetic, anthelmintic, antmicrobial, analgesic, anti-fertility, antiarthritic, antitumor, antistress, anti-inflammatory, immunomodulatory, wound healing, and antiulcer activities. These biological activities of Indian *Tinospora* species can be attributed to the presence of a wide range of phytoconstituents including alkaloids (tinoscorsides A-B, palmatine, tembetarine, jatrorrhizine, magnoflorine, berberine, isocolumbin), clerodane furano diterpene glucosides (amritosides A-D, tinoscorside C, borapetoside B and F, and cordifolide C), flavonoids (diosmetin, genkwanin, genkwanin 7-glucoside, and rutin), lignans (Secoisolariciresinol, syringaresinol, makisterone C), and sterols (campesterol, β-sitosterol, stigmasterol). This review describes the detailed botany, ethnomedicinal uses, phytochemistry, pharmacological attributes of 9 Indian Tinospora species. Moreover, we also included the clinical importance and toxicological effects of Indian *Tinospora* species with the aim to investigating its potential uses as ingredients for pharmaceutical industry.

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Contents

1. Introduction

Since the inception of human civilization, plants have been used as a source of natural medicines. Currently, researchers are showing a great interest in the identification of bioactive compounds from medicinal plants. India with its rich plant biodiversity and enormous knowledge of Ayurvedic, Himeopathic, Siddha, Unani system of medicines, provide a strong base for the utilization of plants in general healthcare and common complaints of the people (Bharathi et al., 2018; Nazar et al., 2020). This curing capacity of plants can be substantiated by many scientific studies (Banerjee et al., 2011; Anwar et al., 2016). In response to growing challenges in health care system, researchers are concentrating their attention on plants to isolate and identify the bioactive principles (Russell and Duthie, 2011; Muhammad et al., 2016). The dependability on phytomedicines for treatment of various diseases is higher in present times than never before. In Indian traditional medicines, more than 25,000 plant-derived drug formulations have been recorded (Ashraf et al., 2016). Indian *Tinospora* species are used in the treatment of jaundice, fever, urinary diseases, asthma, gout, diabetes, diarrhoea, skin disease, and snakebites (Gupta and Kumar, 2002; Jakhar et al., 2004). About 34 species of *Tinospora* genus are found in Africa, Australia, Asia, Madagascar and Pacific regions of the World. Nine species of *Tinospora* are naturalized in the different states of India (Udayan and Pradeep, 2009).

T. baenzigeri Forman is a woody climber and distributed in Telyababa forest range, Burhanpur district, Madhya Pradesh state of India (Mishra et al., 2020). It has been used as a traditional medicine in the treatment of headache, cold, fever, diarrhea, ulcer, digestive disorder, and rheumatoid arthritis (Tuntiwachwuttikul and Taylor, 2001). *T. cordifolia* (Willd.) Miers [syn. *Menispermum cordifolium* Willd., *T. gibbericaulis* Handel-Mazzetti, *T. mastersii* Diels, *T. rumphii* Boerlage, *T. thorelii* Gagnepain] is a medicinally and commercially important plant species, commonly known as "*Guduchi*" or "*Amrita*", and distributed in several states of India (Chadha, 1948; Sinha et al., 2004; Sharma et al., 2010; Singh and Chaudhuri, 2017). The leaf decoction is used to enhance body resistance as well as in boosting of immune system of humans (Saha and Ghosh, 2012; Bhattacharyya, 2013; Biswas et al., 2015). The whole plant extracts are widely used in the treatment of jaundice, and rheumatism (Sharma and Pandey, 2010a; Gupta and Sharma, 2011; Sharma et al., 2019), intermittent fever, eye and liver ailments (Choudhary et al., 2013). The alkaloids [jatrorrhizine, palmatine, magnoflorine (Chintalwar et al., 2003; Sarma et al., 2009; Kiem et al., 2010)], clerodane furano diterpene glucosides [cordifoliside D, cordifoliside D tetraacetate, cordifoliside E, cordifoliside E tetraacetate (Gangan et al., 1994, 1995; Sharma et al., 2019)], daucane-type sesquiterpenes [tinocordifolin, tinocordifolioside and tinocordifolioside tetraacetate (Maurya et al., 1997] and sesquiterpenoids (Maurya and Handa, 1998) have

been isolated and identified from *T. cordifolia*. *T. cordifolia* possesses antioxidant (Polu et al., 2017), antiarthritic (Ramya and Maheswari, 2016), antidiabetic (Khedekar et al., 2015), anti-inflammatory (Sannegowda et al., 2015), antiulcer (Antonisamy et al., 2014), and anticancer properties (Bhadane et al., 2018). Whole plant is useful in the treatment of debility, dyspepsia, fever, inflammation, bronchitis, jaundice, urinary, skin and liver related diseases (Anonymous, 1976).

T. crispa (L.) Hook f. and Thomson is an herbaceous climber, found in tropical and subtropical areas of northeast region of India (Pathak et al., 1995; Patel et al., 2013a). In traditional medicines, it has been used in the treatment of jaundice, rheumatism, urinary disorders, fever, malaria, diabetes, fracture, scabies, hypertension, reducing thirst, increasing appetite (Najib Nik a Rahman et al., 1999; Dweck and Cavin, 2006). *T. crispa* showed the presence of alkaloids (Fukuda et al., 1983; Choudhary et al., 2010a), flavonoids (Umi Kalsom and Noor, 1995; Lin, 2009), diterpenes and diterpene glycosides, cis clerodane-type furanoditerpenoids, lignans (Fukuda et al., 1985, 1986; Chung, 2011). Different parts *T. crispa* possesses anti-inflammatory (Abood et al., 2014), antimicrobial (Zakaria et al., 2006), antioxidant (Amom et al., 2008; Zulkhairi et al., 2009), antimalarial (Najib Nik a Rahman et al., 1999) activities.

T. formanii Udayan & Pradeep is a woody dioecious vine and naturalized in the Western Ghats of Thrissur district, Kerala, India (Sheema Dharmapal et al., 2017). *T. glabra* (F. Burm.) Merr. (syn. *M. glabrum* Burm.f..) is a deciduous woody climber, and naturalized in the tropics of Asia, Africa and Australia. *T. glabra* widely occurs in the northeast parts and the Andaman and Nicobar Islands of India (Merrill, 1938; Nayampalli et al., 1982). The water extract is used in the treatment of jaundice, rheumatism, urinary problems, intermittent fever, eye and liver complaints. As per Ayurvedic medicine, plant species possesses adaptogenic and immuno-modulatory properties (Gupta et al., 1967; Rishikesan et al., 2016). *T. maqsoodiana* Mujaffar, Moinuddin and Mustakim is a wood climber and naturalized in Madhya Pradesh state of India (Mujaffar et al., 2014).

T. sinensis (Lour.) Merr. [syn. *Menispermum malabaricum* Lam., syn. *T. malabarica* Miers. (Miers.), *M. tomentosum* (Colebr.) Roxb.] is found in different states of India. Its stem is used in Ayurvedic formulations for the treatment of jaundice and diarrhea (Udayan et al., 2004; Ahmed et al., 2006). Its stem paste is used to heal ankylosis, fracture, lumbar disc herniation, rheumatic complaints and in the treatment of knee joint osteoarthritis (Sahu, 2002; Srinivasan et al., 2008; Chi et al., 2016; Jiang et al., 2017). The Chinese preparation "Qutan Tongluo Tang" (from *T. sinensis*) is useful in the treatment of irregular heartbeat, high fever and diabetes (Liu, 2004; Wang et al., 2005; Chen et al., 2007; Zhang et al., 2010). Phytochemical analysis of different parts of *T. sinensis* revealed the presence of lignans (Maurya et al., 2009; Lam et al., 2018), phenylpropanoid glycosides (Xu et al., 2017a; Jiang et al., 2018), and alkaloids (Srinivasan et al., 2008; Maurya et al., 2009). *T. sinensis* also demonstrated antidiabetic (Sandhyarani and Kumar, 2014a), antistress (Sharma et al., 2007), anticancer (Punitha et al., 2012) activities. *T. smilacina* Benth is a semi deciduous, woody, creeping climber and distributed on Maruthamalai hills, Western Ghats of Tamil Nadu state of India and northern New South Wales and Central Northern Australia (Barr et al., 1988; Parthipan et al., 2016). *T. subcordata* (Miq.) Diels is a small woody vine and found in Khandwa district, Madhya Pradesh state of India (Mishra and Mishra, 2020). As per clinical studies, *T. cordifolia* stem powder (capsules) demonstrated antidiabetic (Mishra et al., 2015b), anti-HIV (Kalikar et al., 2008), wound healing properties in post-operative patients (Shrestha et al., 2017). Similarly, *T. crispa* stem dry extract also exhibited anti-diabetic activity in patients (Sangsuwan et al., 2004). The toxicological effects of *T. cordifolia* stem powder (Sharma and Dabur, 2016; Ghatpande et al., 2019), *T. crispa* stem powder (Langrand et al., 2014) and *T. sinensis* stem powder (Khayum et al., 2009; Nagarkar et al., 2013) have been documented.

So far, no comprehensive review has been systematized to provide botany, traditional uses, phytochemistry, pharmacological attributes of 9 Indian *Tinospora* species in recent years in order to bridge the knowledge gap among scientists. The review will engage and help ethnobotanists, phytochemists, and pharmacologists to know about bioactive potential and pharmaceutical applications of Indian *Tinospora* species.

2. Botany and ethnomedicinal uses of Indian *Tinospora* species

T. baenzigeri is a woody climber, grows up to 15 m high, and stem with scattered pustular-lenticels. Leaves are broadly ovate to orbicular, apex usually long-acuminate, base shallowly to deeply cordate. Male inflorescence appears from the older, leafless stems, pseudoracemose, long (7–20 cm), flowers in 1–3 flowered clusters; sepals pale green, outer 3 ovate and inner 3 obovate; stamens 6, long (2 mm). Fruits are drupes, yellow and orange, radiating from subglobose carpophore, pericarp very thin and endocarp thinly bony (Mishra et al., 2020). In traditional medicine, it is useful in curing of headache, cold, fever, diarrhoea, ulcer, indigestion, and rheumatoid arthritis (Tuntiwachwuttikul and Taylor, 2001; Table 1; Fig. 1).

T. cordifolia is a large deciduous climber, grows on wide range of hedges and trees (Kirtikar and Basu, 1918; Anonymous, 1976). Its stem is green, and contains succulent bark. The pendulous fleshy roots hang from branches, and its roots have pale shining or glabrous bark. On dryness, stem shrinks and bark separates from the wood. Leaves are membranous, round, cordate or heart shaped; contain 2.5–7.0 cm long petiole. The flowers bloom in the summer season. Inflorescence is of raceme type. Male flowers are small, yellow or green in colour, and occur in clusters in the axils of small subulate bracts. Sepals are 6 (3 + 3, outer and inner whorl), membranous, broadly elliptical, concave, yellow. The petals are 6, equal and spathulate, stamen pistillode. Female flowers are solitary, sepals green, margins not reflexed, staminode short; ovary has 1–3 carpels, widely separated on the short fleshy gynophores, and dorsally convexed (Hooker, 1875; Kirtikar and Basu, 2005). *T. cordifolia* stem is used in the stimulation of gastric activity, bile secretions, enrichment of blood composition and to treat skin diseases, spleen enlargement, vaginal and urethral discharges (Sahu, 2002). Stem decoction is used for washing of eyes and syphilitic sores, acts as an antidote to treat snakebites and scorpion stings (Trivedi, 2006; Spandana et al., 2013), and in the treatment of pyorrhoea, malaria, chronic diarrhea, asthma, dysentery, urinary, skin diseases and respiratory complaints (Trivedi, 2009; Pandey et al.,

Table 1 Ethnomedicinal uses of Indian Tinospora found in different states of India.

Species	Diseases/ complaints	Mode/parts of application	References	
T. baenzigeri	Diarrhoea, cold, fever and ulcers	It is used in the treatment of headache, cold, fever, diarrhoea, ulcer, digestive disorder, and rheumatoid arthritis	Tuntiwachwuttikul and Taylor (2001)	
T. cordifolia	Fever	Pills are prepared from the paste of stem of the *T. cordifolia* and the roots of Bhatkatiaya (*Solanum surattense*); Decoction of stem is administered orally also	Chopra (1994), Sharma and Kumar (2013), Upadhyay et al. (2010)	
	Cough	The warm juice of root of *T. cordifolia* is taken orally	Chopra (1994), Sharma and Kumar (2013)	
	Jaundice, chronic diarrhoea, periodic fever	The whole plant is used	Tripathi (2006b), Upadhyay et al. (2010)	
	Cancer, dysentery, diarrhoea and periodic fever	Powdered root and steam bark of T. cordifolia with milk for cancer; root decoction for dysentery and diarrhoea; old stem decoction for periodic fever	Chopra (1994), Tripathi (2006a, b)	
	Balashosha (emaciation in children), daha (burning)	Dyed shirt soaked in juice of Guduchi worn by children for Balashosha; paste or juice of Amrita (*T. cordifolia*) leaves and Sarsapa beeja churna (seed powder of *Brassica campestris*) are used for daha	Sahu (2002), Tripathi (2006a)	
	Bone fracture	The whole plant paste is used in bone fractures	Sharma et al. (2018)	
	General debility	Decoction of stem with cold and hot water (about 3–4 g) in morning in an empty stomach, used as a tonic	Sharma and Kumar (2013), Tripathi (2006b)	
	Kasa (cough)	Powder of Terminalia chebula (Haritiki), Tinospora cordifolia (Amrita) and Trachyspermum ammi (Ajwain) in equal quantity is administered orally once daily early morning with a little salt	Rathore (2002), Saini (2009)	
	Karna Shula (pain in the ear)	Two drops of juice of leaves of allied species or guduchi (*T. sinensis*) are dropped in the affected ear	Chopra (1994), Tripathi (2006a, b)	
	Asthma	Juice of stem orally given with honey	Sharma and Kumar (2013), Upadhyay et al. (2010)	
	Twak-roga (skin disease).	A decoction of the stem is administered orally	Sahu (2002)	
	T. crispa	Pyorrhoea, diabetes, hypertension, injury	In Thai medicine, stem water decoction is used in the treatment of internal inflammations, pyorrhoea, appetite, and in thirst and body temperature management	Kongsaktrakoon et al. (1984), Dweck and Cavin (2006)
Bruises, septicemia, fever, bone fracture, and scabies		In Chinese medicine, it is used to treat bruises, septicemia, fever, bone fracture, scabies, and tropical ulcer-related disorders	Li et al. (2006)	
Parasitic worm's disease; aching eyes and syphilitic sores; wounds		Stem infusion taken as vermifuge; stem decoction use to wash eyes and sores; the crushed leaves applied in wound healing	Dweck and Cavin (2006)	
T. formanii	–	No report is available in literature on traditional uses	–	
T. glabra	–	No traditional values reported in literature	–	
T. maqsoodiana	–	No report is available in literature	–	
T. sinensis	Knee joint osteoarthritis	Decoction is of stem is used	Qin et al. (2006), Hegde and Jayaraj (2016)	

Table 1 (*continued*)

Species	Diseases/ complaints	Mode/parts of application	References
	Lumbar disc herniation	Paste of stem extract of *T. sinensis*	Singh (1998), Tripathi (2006a)
	Ankylosis (acute and chronic arthritis, rheumatic arthritis)	Whole plant paste applied topically to reduce swelling and relieve pain in the joints and muscles	Zhang et al. (2010), Bhardwaj (2011)
	Bone fractures	Decoction of aerial parts used in healing of fractures	Wang et al. (2005), Srivastava (2003)
	Visceral leishmaniasis	Decoction of stem is used	Yadav (2007), Singh et al. (2008)
T. smilacina	Wound injury, rheumatism	In Australian medicine, the leaf, stem and root are used in the treatment pain, wounds, swelling, rheumatism, severe colds, infections and snakebite	Cribb and Cribb (1981), Hungerford et al. (1998)
T. subcordata	–	No report is available in literature on its uses in traditional medicine	–

2012; Ramadevi et al., 2018; Sharmila et al., 2018). The aqueous extract of roots is used as an emetic and analgesic agent, and also useful in the treatment visceral pain (Stanely et al., 2000). The crushed leaves are mixed with honey and used to cure ulcers, gout and bacterial skin infections. Decoction of leaves is useful in malaria and enhancement of women's fertility (Agarwal et al., 2002; Singh et al., 2003a, b, Singh and Chaudhuri, 2017). Dried fruit powder is mixed with ghee or honey and used as a tonic as well as in the treatment of jaundice and rheumatic complaints. The combination of ripened fruit juice and honey is recommended daily (for 3–5 days) for treatment of cold in children (Sahu, 2002). Whole plant extract is useful in diarrhoea, stomach complaints, and anemia (Sujatha and Mariya, 2015; Alsuhaibani and Khan, 2017). The stem is a rich source of copper, calcium, phosphorus, iron, zinc, manganese hence, used in the treatment of metabolic disorders of humans (Upadhyay et al., 2010; Dhama et al., 2017; Table 1; Fig. 1).

T. crispa is an herbaceous vine, with brownish and fleshy stem. The leaves are large (6–12 cm long and 7–12 cm wide), both surfaces glabrous and heart shaped. Flowers are 2–3, small, and yellowish or green in colour. Male inflorescence is slender, longer (5–10 cm), flowers six green, sepals in two whorls (outer three ovate and inner three obovate); female inflorescence long (2–6 cm), one flower per node. Fruits are drupe and long (7–8 mm). As per Vietnamese and Indian traditional medicine system, it is useful in malaria, cough, poor digestion, colitis, and diabetes [Ahmad et al., 2016; Guo et al., 1999) and also used in the treatment of jaundice, rheumatism, bone fractures, scabies, and hypertension (Cowan, 1999; Ahmad et al., 2016). It is taken in the management of thirst (Guo et al., 1999), hunger resistance and heat clearing (Pham and Nguyen, 2020), and used in curing of diabetes (Thomas et al. 2016; Table 1; Fig. 1).

T. formanii is a woody dioecious vine, with thick stem (4 cm), clear concentric rings, brown, smooth papery bark, peeling off into scales. Leaves are alternate, large (6–14 × 4–8 cm), ovate to elliptic-lanceolate, coriaceous, glabrous, acuminate at apex, cordate at base; lateral nerves 3–4 pairs, reticulate venation on lower surface; petioles slender, and long (5–12 cm). Male inflorescences and flowers unknown but, female inflorescence a compound elongated pseudoraceme, long (5–18 cm); sepals 6, triangular ovate, long (2 mm), greenish-yellow. Fruits are drupes, globose, across (2–3 cm), red on maturity; pericarp thin; endocarp broadly elliptic to subrotund in outline. Seeds are oblong, subellipsoid and dorsally convex (Udayan and Pradeep, 2009; Sheema Dharmapal et al., 2017; Table 1; Fig. 1).

T. glabra is a climber, seriate stem, with thin papery bark; leaves oblong-ovate or narrowly to broadly ovate, base cordate to truncate, apex acuminate; male inflorescence axillary, pseudo-racemose, 10–20 cm, flower solitary, bract 1 mm long, female inflorescence similar to male; fruit drupe red, radiating from unbranched short to columnar carpophore, endocarp thinly bony, keeled at apex (Merrill, 1938; Table 1; Fig. 1). *T. maqsoodiana* is similar to *C. cordifolia* but different in its young stems, papillose-glandular, leaf shape triangular-ovate, broad and long, ovate deltoid, elliptic, basal lobes slightly lobed, lamina base cordate to cuneate, endocarp with papillose surface (Mujaffar et al., 2014; Table 1; Fig. 1).

T. sinensis is a large fleshy deciduous climber with shiny stem and papery bark. Its young parts are covered with densely matted woolly hairs. The leaves are broadly ovate to suborbicular, membranous, sparingly pubescent above, pilose beneath with glandular patches at basal nerve axils, abruptly truncate or cuneate or subcordate at base; petioles 5–12 cm long, puberulous, and thickened at base. Flowers are greenish-yellow. Inflorescence is of raceme type, panicles 3–12 cm long, and slender. Pedicels of male flowers are 2–5 mm long, sepals yellowish-green, and glabrous, 6 (3 + 3, outer three ovate, 1–1.5 mm long and inner three broadly elliptic, 3–5 × 2–5 mm); petals six, obliquely rhomboid-ovate (size 3–4 × 1–3 mm); stamens 1.5–2 mm long, anthers dehisce longitudinally. Female flowers are tricarpellary, 2-lobed stigma, gynophore 1 mm long. Fruit is drupe, globose (1–3, 10–13 mm across), red, scarlet or orange red; carpophores 2–3 mm long on 8–10 mm long peduncles, dorsally keeled and ventrally concave, 7–9 × 5–6 mm, tuberculate, flowering occurs in December–February (Matthew, 1981–1984, 1991; Udayan et al., 2004). Leaf and stem juice are used in the treatment of chronic rheumatism,

T. cordifolia

T. sinensis

T. glabra

T. crispa

T. formanii

T. smilacina

Fig. 1 Indian *Tinospora* species reported from different states of India.

ulcerated wounds and piles (Rajgopal et al., 2013). Aqueous extract of whole plant is useful in debility, dyspepsia, fever, inflammation, syphilis, ulcers, bronchitis, jaundice, urinary disease, skin disease and liver disease (Anonymous, 1976). The juice or powder of *T. sinensis* stem is useful in the treatment of diabetes and gastritis (Balami, 2004). *T. sinensis* possesses adaptogenic and immunomodulatory (Kirtikar and Basu, 1993; Rege et al., 1999; Manjrekar et al., 2000), anti-inflammatory (Li et al., 2004a), and anti-diabetic activities (Yonemitsu et al., 1993; Table 1; Fig. 1).

T. smilacina Benth is a semi-deciduous herb, with woody climber stem (7 cm diameter). Leaves are alternate, size 4–5-12 × 4–11 cm, long petioles (2.5–9 cm), five veins, including the midrib, radiate from the base of the leaf blade. Inflorescence slender, male flower sepals arrange in two whorls of three; female flowers also arrange in two whorls of three, outer sepals about 2 mm long, inner sepals petaloid. Fruit is drupe, globular to ellipsoid (6–10 × 6–9 mm) in shape. Seed surface is coarsely rugose (6–7 × 4–5 mm; Barr et al., 1988). As per Australian traditional medicine, whole plant is used in the treatment of pain, wounds, swelling, rheumatism, severe colds, infections and snakebites (Cribb and Cribb, 1981). *T. subcordata* is a small woody climber, glabrous, stem with lenticels; leaves with petioles, long (2.5–8 cm), lamina triangular to broadly triangular, base broadly cordate to truncate with rounded; male inflorescence axillary, long (5–14 cm), pseudo-racemose, long, flowers arrange on slender pedicels, sepals white, outer 3 ovate, inner 3 elliptic, petals 6, obovate-

T. subcordata

T. baenzigeri

T. maqsoodiana

Fig. 1 (*continued*)

cuneate; female inflorescence peudoracemose, flowers arrange on pedicels, sepals and petals similar to male but slightly smaller and petals thin; fruit drupe, red, endocarp bony, elliptic in outline (Mishra and Mishra, 2020; Table 1; Fig. 1).

3. Phytochemistry

The alkaloids, glycosides, diterpenoid lactones, flavonoids, steroids and sesquiterpenoids have been isolated and identified from 4 species of Indian *Tinospora* while other 5 species have not been investigated for the presence of phytochemicals. The state-wise distribution, extract types, parts used, identified compounds and their structures have been mentioned in Table 2 and Fig. 2. No compound is reported from 5 Indian *Tinospora* species (*T. formanii, T. glabra, T. maqsoodiana, T. smilacina* and *T. subcordata*). The isolated and identified compounds from 4 Indian *Tinospora* species (*T. baenzigeri, T. cordifolia, T. crispa* and *T. sinensis*) are summarized below –

Clerodane diterpenes are a large group of plant-derived secondary products found in thousands of plant species from many plant families. During the last few decades, more than 1300 diterpenoids and *nor*-diterpenoids with the clerodane carbon skeleton have been identified from different plant species (Li et al., 2016). Some clerodane diterpenes possess anti-inflammatory, antiparasitic, antifungal, antibacterial, antitumor, opioid receptor agonist, nerve growth factor-potentiating, anti-ulcer, cytotoxic, and antimicrobial activities (Hagiwara, 2019). The Baenzigeride A, and baenzigeroside A (Tuntiwachwuttikul et al., 1999), baenzigeride B and baenzigeroside B (Tuntiwachwuttikul and Taylor, 2001), tinobaenzigeride and tinobaenzigeroside A have been identified from *T. baenzigeri* stem. The isolated compounds (baenzigeride B and baenzigeroside B) showed cytotoxicity against Hep-G2 and MCF-7 cancer cells (IC_{50} 25 Mm; Pudhom et al., 2019; Hanthanong et al., 2019, 2021). The amritoside A, amritoside A pentaacetate, amritoside B, amritoside B pentaacetate, amritoside C, amritoside C pentaacetate, amritoside D, amritoside D tetraacetate (Maurya et al., 1995, 2004), tinosponone, tinosporaside, tinosporaside tetraacetate, tinocordioside, tinocordioside tetraacetate (Iqbal et al., 2005; Puratchimani and Jha, 2007), tinoscorside C, borapetoside F, borapetoside B, cordifolide A (Kiem et al., 2010; Pan et al., 2012), tinosporafuranol, tinosporaclerodanol, tinosporafuradiol, tinosporaclerodanoid (Ahmad et al., 2010; Phan et al., 2010), cordioside (Wazir et al., 1995) from stem and stem bark (Kumar et al., 2019), syringin (Kiem et al., 2010), 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; (Gangan et al., 1994, 1995; Sharma et al., 2018, 2019), 4,5,7-trimethoxy-2-naphthol-2-*O*-α-L-arabinofuranosyl-(2′→1″)-*O*-α-L-arabinopyranosyl-2″-*O*-pentane, β-D-arabinosyl-*O*-geranilan-10′-oate, 5,7-dimethoxy-2-naphthol-2-*O*-α-L-arabinopyranosyl-(2′→1″)-α-L-arabinopyra

Table 2 Chemical constituents isolated from various parts of Indian *Tinospora* species.

Plant species	Distribution (states of India)	Extract type	Plant parts	Isolated Compounds	References
T. baenzigeri	Telyababa forest range, Burhanpur district, Madhya Pradesh, India	Ethanolic	Stem and leaves	Clerodane diterpenoids - Baenzigeride A (**1**), baenzigeroside A (**2**), Baenzigeride B (**3**), , baenzigeroside B (**4**), tinobaenzigeride (**5**), tinobaenzigeroside (**6**), 4-*epi*-baenzigeride A (**7**), 4-*epi*-baenzigeride A glucoside (**8**), tinobaenzin A (**9**), tinobaenzin B (**10**), 4,12-di-*epi*-baenzigeride A (**11**), caruilignan D (**12**)	Tuntiwachwuttikul et al. (1999), Tuntiwachwuttikul and Taylor (2001), Pudhom et al. (2019) Hanthanong et al. (2019, 2021)
T. cordifolia	Rajasthan, Uttar Pradesh, Bihar, West Bengal, Gujarat, Punjab, Tamil Nadu, Kerala and Karnataka	Methanolic and ethanolic	Aerial parts and stem	*Alkaloids* - Tinoscorside A (**13**), tinoscorside B (**14**), palmatine (**15**), tembetarine (**16**), jatrorrhizine (**17**), magnoflorine (**18**), berberine (**19**), isocolumbin (**20**)	Srinivasan et al. (2008), Kiem et al. (2010), Gupta and Sharma (2011), Patel and Mishra (2012), Bala et al. (2015a)
		Ethanolic	Roots	*Alkaloids* – Tetrahydropalmatin (**21**), jatrorrhizine (**17**), magnoflorine (**18**)	Sarma et al. (2009)
		Methanolic	Cell cultures	*Alkaloids* – Berberine (**7**) and jatrorrhizine (**5**)	Chintalwar et al. (2003)
		Methanolic	Aerial parts	*Phenylpropene disaccharides* - Angelicoidenol 2-*O*-β-D-apiofuranosyl-(1→6)- β-D-glucopyranoside (**22**), secoisolariciresinol-9'-*O*-β-D-glucopyranoside (**23**)	Kiem et al. (2010)
		Methanolic	Stem	*Sulfur-containing clerodane diterpene glycoside* - Cordifolide A (**24**)	Pan et al. (2012)
		Aqueous-methanolic	Stem	*Clerodane furano diterpene glycoside* - 2β,3β:15,16-Diepoxy- 4α, 6β-dihydroxy-13 (16),14-clerodadiene-17,12:18,1-diolide (**25**)	Sharma et al. (2018)
		Methanolic	Stem and stem bark	*Clerodane furano diterpene glucosides* - Amritoside A (**26**), amritoside A pentaacetate (**27**), amritoside B (**28**), amritoside B pentaacetate (**29**), amritoside C (**30**), amritoside C pentaacetate (**31**), amritoside D (**32**), amritoside D tetraacetate (**33**), tinosponone (**34**), tinosporaside (**35**), tinosporaside tetraacetate (**36**), tinocordioside (**37**), tinocordioside tetraacetate (**38**), tinoscorside C (**39**), borapetoside F (**40**), borapetoside B (**41**), tinosporafuranol (**42**), tinosporaclerodanol (**43**), tinosporafuradiol (**44**), tinosporaclerodanoid (**45**), cordifolide B (**46**), cordifolide C (**47**)	Maurya et al. (1995, 2004), Ahmad et al. (2010), Kiem et al. (2010), Pan et al. (2012)
		Methanolic	Stem	*Daucane-type sesquiterpene* – Tinocordifolin (**48**), tinocordifolioside (**49**), tinocordifolioside tetraacetate (**50**)	Maurya et al. (1997), Maurya and Handa (1998)
		Butanolic and methanolic	Stem	*Norditerpene furan glycosides* – Syringin (**51**), cordifoliside A (**52**), cordifoliside A tetraacetate (**53**), cordifoliside B (**54**), cordifoliside B tetraacetate (**55**), cordifoliside C (**56**), cordifoliside C tetraacetate (**57**), cordifoliside D (**58**), cordifoliside D tetraacetate (**59**), cordifoliside E (**60**), cordifoliside E tetraacetate (**61**), 4,5,7-trimethoxy-2-naphthol-2-*O*-α-L-arabinofuranosyl-(2′→1′′)-*O*-α-L-arabinopyranosyl-2′′-*O*-pentane (**62**), β-D-arabinosyl-*O*-geranilan-10′-oate (**63**), 5,7-dimethoxy-2-naphthol-2-*O*-α-L-arabino pyranosyl-(2′→1′′)-α-L-arabinopyranosyl-2′′-*O*-decane (**64**)	Gangan et al. (1994, 1995), Kiem et al. (2010) Sultana et al. (2017)
		Methanolic	Stem	*Diterpenic flavanone and phenylpropanoid* - 5-hydroxy-4'-methoxy-7-flavanoxy-(7→7'')-β-*O*-labdan-1-en-3''α,19''-olide-18''-oic acid (**65**), tinoscorside D (**66**)	Kiem et al. 2010; Sultana et al. (2017)
		Methanolic	Stem	*Aromatic amides* - *Trans*-cinnamoyl-2-n-hexanyl-7-methoxynaphthyl amide (**67**), *trans*-cinnamoyl-2-n-pentanyl-6,7-dimethoxynaphthyl amide (**68**), *trans*-	Sultana et al. (2017)

Table 2 (*continued*)

Plant species	Distribution (states of India)	Extract type	Plant parts	Isolated Compounds	References
				cinnamoyl-2-n-octanyl-7-methoxynaphthyl amide (**69**)	
		Methanolic and aqueous-methanolic	Aerial parts	*Ecdysteroids and steroids* - Polypodine B 20, 22-acetonide (**70**), 20-*p*-hydroxyecdysone (**71**), β-sitosterol (**72**)	Pathak et al. (1995), Kiem et al. (2010), Sharma et al. (2018)
		Chloroform	Whole plant	*Diterpenoid furanolactone* – Columbin (**73**)	Swaminathan et al. (1989)
T. crispa	Tropical and sub-tropical regions of India	Methanolic	Stem	*Flavonoids* – apigenin (**74**), diosmetin (**75**), genkwanin (**76**), luteolin 4′-methyl ether 7- glucoside (**77**), genkwanin 7-glucoside (**78**), rutin (**79**), and luteolin 4′-methyl ether 3′ -glucoside (**80**)	Umi Kalsom and Noor (1995), Harwoko and Warsinah (2020).
		Methanolic	Whole plant	*Diterpene and diterpene glucosides* - borapetol A (**81**) and borapetol B (**82**)	Chung (2011)
		Ethanolic	Stem	*Diterpene and diterpene glucosides* - Tinocrispol A (**83**), 6′-*O*-lactoylborapetoside B (**84**), 2-*O*-lactoylborapetoside B (**85**), columbin (**73**), borapetoside B (**41**), borapetoside D (**86**), borapetoside E (**87**), rumphioside B (**88**), syringin (**51**), crispene A (**89**), crispene B (**90**), crispene C (**91**), crispene D (**92**), crispene F (**93**) and crispene G (**94**)	Cavin et al. (1998), Choudhary et al. (2010b), Chung (2011) Lam et al. (2012) Hossen et al. (2016), Al Noman et al. (2018)
		Ethanolic	Aerial parts and stem	*cis-Clerodane-type furanoditerpenoids* - (3*R*,4*R*,5*R*,6*S*,8*R*,9*S*,10*S*,12*S*)-15,16-Epoxy-3,4-epoxy-6-*O*-(β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester (**95**), (1*R*,4*S*,5*R*,8*S*,9*R*,10*S*,12*S*)-15,16-epoxy-4-*O*-(β-D-glucopyranosyl)-cleroda-2,13(16),14-triene-17(12),18(1)-diolide (**96**), (2*R*,5*R*,6*R*,8*R*,9*S*,10*S*,12*S*)-15,16-epoxy-2-hydroxy-6-*O*-(β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester (**97**), (5*R*,6*R*,8*S*,9*R*,10*R*,12*S*)-15,16-epoxy-2-oxo-6-*O*-(β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester (**98**), (2*R*,5*R*,6*R*,8*S*,9*S*,10*S*,12*S*)-15,16-epoxy-2-hydroxy-6-*O*-{β-D-glucopyranosyl-(1-6)α-D-xylopyranosyl}-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester (**99**), (5*R*,6*R*,8*S*,9*R*,10*S*,12*S*)-15,16-epoxy-2-oxo-6-*O*-(β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester (**100**), (5*R*,6*S*,9*S*,10*S*,12*S*)-15,16-epoxy-2-oxo-6-*O*-(β-D-glucopyranosyl)-cleroda-3,7,13(16),14-tetraen-17,12- olid-18-oic acid methyl ester (**101**), (2*R*,5*R*,6*S*,9*S*,10*S*,12*S*)-15,16-epoxy-2-hydroxy-6-*O*-(β-D-glucopyranosyl)-cleroda-3,7,13(16),14-tetraen-17,12-olid-18-oic acid methyl ester (**102**), tinocrispide (**103**), baenzigeride A (**1**), (6*S,* 9 *R*)-vomifoliol (**104**), rumphiol E (**105**)	Choudhary et al. (2010b), Parveen et al. (2021)
		Ethanolic/ chloroform	Stem	*Alkaloids* - *N*-formylasimilobine 2-*O*-β-D-glucopyranoside (**106**), *N-cis*-feruloyltyramine (**107**), *N-trans*-feruloyltyramine (**108**), paprazine (**109**), *N-trans*-caffeoyltyramine (**110**), *N*-demethyl-*N*-formyldehydronornuciferine (**111**), *N*-formylasimilobine 2-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside (**112**), 4,13-dihydroxy-2,8,9-trimethoxydibenzo[a,g]quinolizinium (**113**), columbamine (**114**), dihydrodiscretamin (**115**), magnoflorine (**18**), *N*-formylnornuciferine (**116**), *N*-acetylnornuciferine (**117**), *N*-formylanonaine (**118**), *N*-acetylanonaine (**119**),	Pachaly et al. (1992), Lin (2009), Choudhary et al. (2010a), Chung (2011), Praman et al. (2012), Yusoff et al. (2014),Parveen et al.

(*continued on next page*)

Table 2 (*continued*)

Plant species	Distribution (states of India)	Extract type	Plant parts	Isolated Compounds	References
				tyramine (**120**), higenamine (**121**), salsolinol (**122**). (−)-litcubinine (**123**), and steponine (**124**)	(2021)
		Ethanolic	Stem	*Lignans, and sterols* – Secoisolariciresinol (**125**), syringaresinol (**126**), campesterol (**127**), β-sitosterol (**72**), stigmasterol (**128**), makisterone C (**129**), gorgost-5-en-3-ol, (3β)- (**130**), lathosterol (**131**), ergost-7-en-3-ol (**132**), cholest-5-en-3-ol (3β)- (**133**), cholesta-5,22-dien-3-ol, (3β)-(**134**), ergosta-5,24(28)-dien-3-ol, (3β)- (**135**), desmosterol (**136**), 5,6-dihydroergosterol (**137**), lupeol (**138**), lup-20(29)-en-3-ol, acetate, (3β)-(**139**), 25-hydroxycholesterol, 3-methyl ether (**140**), and betulin (**141**)	Lin (2009), Chung (2011), Praman et al. (2012), Rakib et al. (2020c).
T. formanii	Western Ghats of Thrissur district, Kerala, India	-	-	-	-
T. glabra	Northeast region, Andaman and Nicobar Islands of India	-	-	-	-
T. maqsoodiana	Madhya Pradesh state of India	-	-	-	-
T. sinensis	Assam, Bihar, Orissa, Maharashtra, Andhra Pradesh, Karnataka, Kerala, and Tamil Nadu	Ethanolic	Stem	*Lignans and its glucosides* - Lirioresino-β-dimethyl ether (**142**), tinosposide A (**143**), tinosposide B (**144**), tanegoside (**145**), (+)-pinoresinol *O*-β-D-glucopyranoside (**146**), (+)-pinoresinol monomethyl ether *O*-β-D-glucopyranoside (**147**), (+)-syringaresinol *O*-β-D-glucopyranoside (**148**), (-)-isolariciresinol 3α-*O*-β-D-glucopyranoside (**149**), icariside D1 (**150**), 4-allyl-2-methoxyphenyl 6-*O*-β-D-apiofuranosyl (1→6)-β-D-glucopyranoside (**151**), tinosporide A (**152**), sesamin (**153**), sesamolin (**154**), medioresinol (**155**), syringaresinol (**126**), (+)-epi-syringaresinol **(156),** (+)-glaberide I (**157**)	Li et al., (2004a, 2004b), Maurya et al. (2009), Lam et al. (2018)
		Methanolic	Stem	*Sesquiterpene glucosides* - Tinosinenoside G (**158**), tinosinenoside H (**159**), tinosinenside (**160**)	Li et al. (2007), Jiang et al. (2018)
		Ethanolic	Stem	*Clerodane diterpene glycosides* - Tinosposinenside A (**161**), tinosposinenside B (**162**), tinosposinenside C (**163**), 1-deacetyltinosposide A (**164**)	Li et al. (2007), Dong et al. (2010)
		Methanolic	Stem	*Phenolic glycoside* – Tinosinen (**165**)	Yonemitsu et al. (1993)
		Ethanolic	Stem	*Phenylpropanoid glycosides* - Tinosinenoside I (**166**), tinosinenoside J (**167**) *Diterpenoid glucosides* - Tinosinenoside K (**168**), 4-epi-2-deacetoxytinosinenoside D (**169**), tinosinenoside A (**170**), tinosinenoside B (**171**), borapetoside A (**172**), borapetoside B (**41**), borapetoside C (**173**), borapetoside H (**174**), borapetoside G (**175**), rumphioside A (**176**), rumphioside D (**177**), rumphioside F (**178**), rumphioside I (**179**), cordifolide A (**24**), tinocrisposide (**180**), 6'-*O*-lactoylborapetoside B (**181**), sagittatayunnanoside A (**182**), sagittatayunnanoside B (**183**), sagittatayunnanoside C (**184**), tinosponone (**34**), tinotufolin C (**185**), tinotufolin D (**186**)	Xu et al. (2017a, 2017b), Jiang et al. (2017) Xu et al. (2017a, 2017b), Jiang et al. (2018)
		Methanolic	Stem	*Alkaloids* – Berberine (**19**), 3-hydroxy-2,9,11-trimethoxy-5,6-dihydro isoquino [3,2-a]isoquinolinylium (**187**), palmatine (**15**), jatrorrhizine (**17**), palmatrubin (**188**), tinosporin A (**189**), methyl 4-[formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl] butanoate (**190**), methyl 4-[formyl5-(methoxymethyl)-1H-pyrrol-1-yl] butanoate (**191**), 4-[formyl-5-(methoxymethyl)-1H-pyrrol-1-yl] butanoic acid (**192**), 4-[formyl-5-(hydroxymethyl)-1*H*-pyrrol-1-yl]butanoic acid (**193**)	Srinivasan et al. (2008), Maurya et al. (2009), Lam et al. (2018)
		Methanolic	Stem	*Benzoids* – Rhodiolate (**194**), tinosporin B (**195**), methyl ferulate (**196**), β-	Lam et al. (2018)

Table 2 (*continued*)

Plant species	Distribution (states of India)	Extract type	Plant parts	Isolated Compounds	References
				hydroxypropiovanillone (**197**), tachioside (**198**), icariside D2 (**199**), salidroside (**200**), vanillic acid (**201**), syringic acid (**202**), *p*-hydroxybenzoic acid (**203**), 4-(2-hydroxyethyl) benzoic acid (**204**), isovanillic acid (**205**), cordifolioside A (**206**)	
		Ethanolic	Stem	*Unsaturated carboxylic acid ester* - 4-methyl-heptadec-6-enoic acid ethyl ester (**207**)	Maurya et al. (2009)
		Ethanolic and methanolic	Stem	*Steroids* - β-sitosterol (**72**), daucosterol (**208**), 7α-hydroxysitosterol (**209**), 7α-hydroxystigmasterol (**210**), 6β-hydroxystigmast-4-en-3-one (**211**), 6β-hydroxystigmasta-4,22-dien-3-one (**212**)	Maurya et al. (2009), Dong et al. (2010), Lam et al. (2018)
		Methanolic	Stem	*Terpenes* – Loliolide (**213**), abscisic acid (**214**), 3-*O*-acetyloleanolic acid (**215**), lupeol (**138**), cycloeucalenol (**216**), cycloartane-3β,25-diol (**217**), cycloart-22-ene-3β,25-diol (**218**), malabarolide (**219**)	Lam et al. (2018)
		Methanolic	Stem	*Amides* - N-*cis*-feruloyltyramine (**107**), N-*trans*-feruloyltyramine (**108**), N-*trans*-feruloyldopamine (**220**)	Lam et al. (2018)
		Methanolic	Stem	*Coumarin* – Scopoletin (**221**)	Lam et al. (2018)
		Methanolic	Stem	*Xanthone* – Lichexanthone (**222**)	Lam et al. (2018)
T. smilacina	Western Ghats of Tamil Nadu, India	-	-	-	-
T. subcordata	Khandwa district, Madhya Pradesh state of India	-	-	-	-

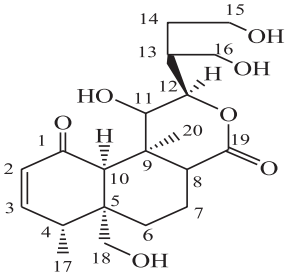
nosyl-2″-*O*-decane (Sultana et al., 2017) have been isolated and characterized from *T. cordifolia* stem (Kattupalli et al., 2019). The tinocrispol A, 6′-*O*-lactoylborapetoside B, columbin, 2-*O*-lactoylborapetoside B (Lam et al., 2012) and borapetosides A-E (Chung, 2011) and borapetoside G and H (Choudhary et al., 2010b; Lam et al., 2012), rumphiosides A and B (Chung, 2011), syringin (Cavin et al., 1998; Chung, 2011), crispene A, B, C, and D (Hossen et al., 2016), crispenes F and G from stem (Al Noman et al., 2018), borapetol A and B were reported from *T. crispa* whole plant (Chung, 2011). Several clerodane-type furanoditerpenoids {(3*R*,4*R*,5*R*,6*S*,8*R*,9*S*,10*S*,12*S*)-15,16-Epoxy-3,4-epoxy-6-*O*-(β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester, rumphiol E, (5*R*,6*R*,8*S*,9*R*,10*S*,12*S*)-15,16-epoxy-2-oxo-6-*O*-(β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester, (5*R*,6*S*,9*S*,10*S*,12*S*)-15,16-epoxy-2-oxo-6-*O*-(β-D-glucopyranosyl)-cleroda-3,7,13(16),14-tetraen-17,12- olid-18-oic acid methyl ester, (2*R*,5*R*,6*S*,9*S*,10*S*,12*S*)-15,16-epoxy-2-hydroxy-6-*O*-(β-D-glucopyranosyl)-cleroda-3,7,13(16),14-tetraen-17,12-olid-18-oic acid methyl ester} from aerial parts (Choudhary et al., 2010b), baenzigeride A, (6*S,* 9 *R*)-vomifoliol and steponine were reported from stem of *T. crispa* (Parveen et al., 2021).

Diterpenoids are secondary products containing 20 atoms of carbon derived from the condensation of four isoprenyl units, widely found in the plant kingdom, and biosynthetically derived from geranylgeranyl diphosphate. They are found in several forms (Sandjo and Kuete, 2013) such as acyclic (phytanes), bicyclic (labdanes, halimanes, clerodanes), tricyclic (pimaranes, abietanes, cassanes, rosanes, vouacapanes, podocarpanes), tetracyclic (trachylobanes, kauranes, aphidicolanes, stemodanes, stemaranes, atisanes, gibberellanes), and macrocyclic diterpenes (taxanes, cembranes, daphnanes, tiglianes, ingenanes). Clerodane diterpenoids have been found in several families of plants (Verbenaceae and Lamiaceae) and possess potent anti-inflammatory and analgesic activities (Gonzalez-Coloma, 2010; Marrero et al., 2010). The tinosinenoside K, 4-*epi*-2-deacetoxytinosinenoside D, tinosinenoside A, tinosinenoside B, borapetoside A, borapetoside B, borapetoside C, borapetoside G, borapetoside H, rumphioside A, rumphioside D, rumphioside F, rumphioside I, cordifolide A, tinocrisposide, 6′-*O*-lactoylborapetoside B, sagittatayunnanoside A, sagittatayunnanoside B, sagittatayunnanoside C, tinosponone were isolated and characterized from *T. sinensis* stem (Jiang et al., 2017, 2018; Xu et al., 2017a, 2017b).

Sesquiterpenes consist of three isoprene units ($C_{15}H_{24}$) with acyclic rings. Biochemical modifications such as oxidation or rearrangement produce the related sesquiterpenoids (Davis and Croteau, 2000). Cyclic sesquiterpenes are more common than cyclic monoterpenes because of the increased chain length and additional double bond in the sesquiterpene precursors (Chizzola, 2013). The plant-derived sesquiterpenoids possess antitumor, antiinflammatory, antibacterial and antiviral activities (Salazar-Gómez et al., 2020; Jiang et al., 2021). The tinocordifolin, tinocordifolioside, and tinocordifolioside tetraacetate were isolated and identified from the stem of this plant species (Maurya et al., 1997; Maurya and Handa, 1998). The *trans*-cinnamoyl-2-n-hexanyl-7-methoxynaphthyl amide, *trans*-cinnamoyl-2-n-pentanyl-6,7-dimethoxynaphthyl amide, *trans*-cinnamoyl-2-n-octanyl-7-methoxynaphthyl amide were identified from *T. cordifolia* stem (Sultana et al., 2017). More than 300 benzoid compounds have been identified from plants which include methylbenzoate, methylsalicylate, phenylacetaldehyde, phenylethyl acetate, benzyl acetate, phenylethanol, eugenol, and isoeugenol (Knudsen and Gershenzon, 2006). The rhodiolate, methyl ferulate, β-hydroxypropiovanillone, 2-methyl-4,5-dimethoxybenzoic acid, vanillic acid, p-hydroxyl phenethanol, tachioside, icariside D2, salidroside, syringin, cordifolioside A, *p*-hydroxybenzoic acid, 4-(2-hydroxyethyl) benzoic acid, syringic acid-4-*O*-α-L-rhamnoside, isovanillic acid, syringic acid have been characterized from *T. sinensis* (Lam et al., 2018). The loliolide, abscisic acid, 3(17)-phytene 1,2-diol, malabarolide, lupeol, 3-*O*-acetyloleanolic acid, cycloeucalenol, cycloabyssinone, cycloartane-3β,25-diol, cycloart-22-ene-3β,25-diol, β-sitosterol, stigmasterol, 7α-hydroxysitosterol, 7α-hydroxystigmasterol, 6β-hydroxystigmast-4-en-3-one, 6β-hydroxystigmasta-4,22-dien-3-one, and 7-ketosterol have been isolated from the aerial parts of *T. sinensis* (Lam et al., 2018).

Alkaloids are a large group of naturally occurring secondary products which contain nitrogen atom(s) in their structures. These nitrogen atoms are usually situated in cyclic ring system (Kurek, 2019). Based on the cyclic ring system, alkaloids can be grouped into several classes such as indoles, acridines, quinolines, isoquinolines, pyrrolidines, pyridines, pyrrolizidines, quinazolines and tropanes. Alkaloids are usually bitter, colorless, coloured (sanguinarine, berberine), odorless crystalline solids, but sometimes they can be yellowish liquids (nicotine). Nearly more than 3000 alkaloids have been investigated in different 4000 plant species (Frédérich et al., 2002; Ge et al., 2015; Gaziano et al., 2016). Several alkaloids (catharanthine, indicine-N-oxide, vincamine, vincristine, ajmalicine, vinblastine, strychnine, quinine, and ajmaline) possess anticancer, antimalarial, anti-inflammatory, and antimicrobial activities (Thawabteh et al., 2019). The tinoscorside A and B (Kiem et al. 2010), jatrorrhizine, palmatine, magnoflorine (Chintalwar et al., 2003; Sarma et al., 2009; Bala et al., 2015b), berberine, isocolumbin, tembetarine (Srinivasan et al., 2008; Reddy and Reddy, 2015) have been reported from aerial parts and stem of this plant species. The angelicoidenol 2-*O*-*β*-D-apiofuranosyl-(1 → 6)-*β*-D-glucopyranoside, secoisolariciresinol-9′-*O*-*β*-D-glucopyranoside, cordifoliosides A and B have been identified from *T. cordifolia* aerial parts (Maurya et al., 1996; Kiem et al., 2010). The *N*-formylasimilobine 2-*O*-β-D-glucopyranoside, *N*-*trans*-feruloyltyramine, paprazine, *N*-demethyl-*N*-formyldehydronornuciferine, *N*-formylasimilobine 2-*O*-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranoside, 4,13-dihydroxy-2,8,9-trimethoxydibenzo[a,g]quinolizinium, columbamine, magnoflorine, dihydrodiscretamin (Choudhary et al., 2010a; Yusoff et al., 2014), *N*-formylnornuciferine, *N*-acetylnornuciferine, *N*-*cis*-feruloyltyramine (Pachaly et al., 1992; Chung, 2011), *N*-*trans*-caffeoyltyramine, *N*-formylanonaine, *N*-acetylanonaine (Lin 2009), tyramine, higenamine, salsolinol and (−)-litcubinine from have been isolated and characterized from *T. crispa* stem (Praman et al., 2012).

Pyrrole alkaloids are heterocyclic organic compounds synthesized by plants and found in Asteraceae, Boraginaceae, Heliotropiaceae, Apocynaceae, Orchidaceae and the Fabaceae families. Approximately 100 pyrrole alkaloids have been recognized and possess toxic hepatotoxic effects (Schramm et al., 2019). The 5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde, methyl 4-[formyl-5-(hydroxymethyl)-1*H*-pyrrol-1-yl] butanoate, methyl 4-[formyl 5-(methoxymethyl)-1*H*-pyrrol-



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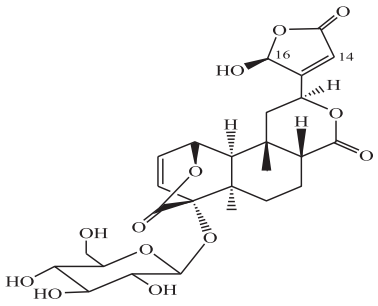

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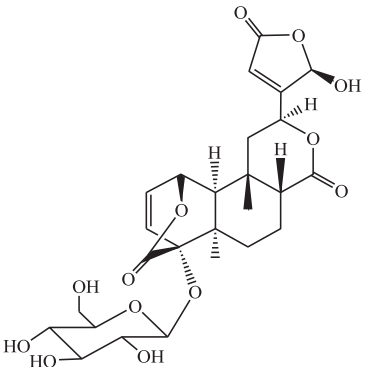

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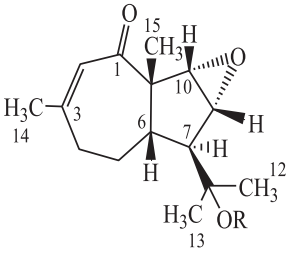
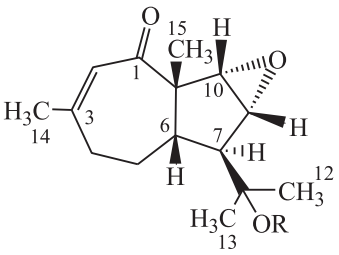
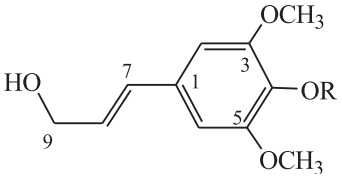


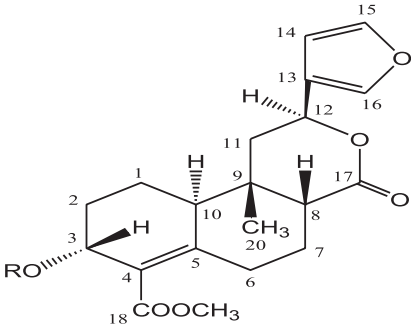
48 R = H



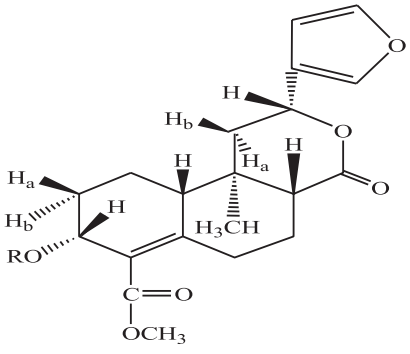
49 R=β-D-glucopyranosyl, **50** R = Tetra-*O*-acetyl-β-D-glucopyranosyl



51 R = *β*-D-glucopyranoside

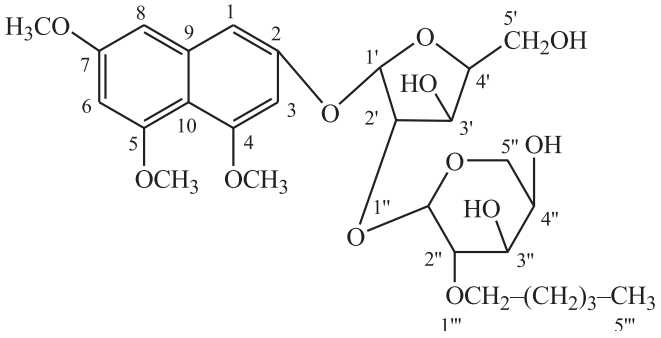


52 R=β-D-glucopyranosyl, **53** R=Tetra-*O*-acetyl-β-D-glucopyranosyl



54 R = β-D-glucopyranosyl, **55** R= Tetra-*O*-acetyl-β-D-glucopyranosyl

Fig. 2 Structures of isolated compounds from Indian *Tinospora* species.



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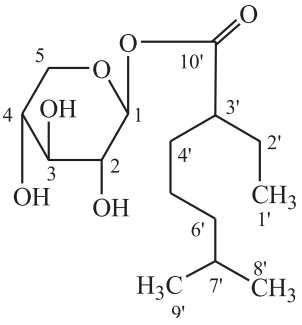

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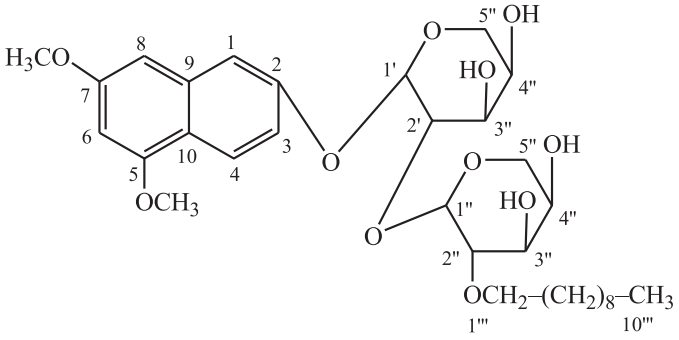

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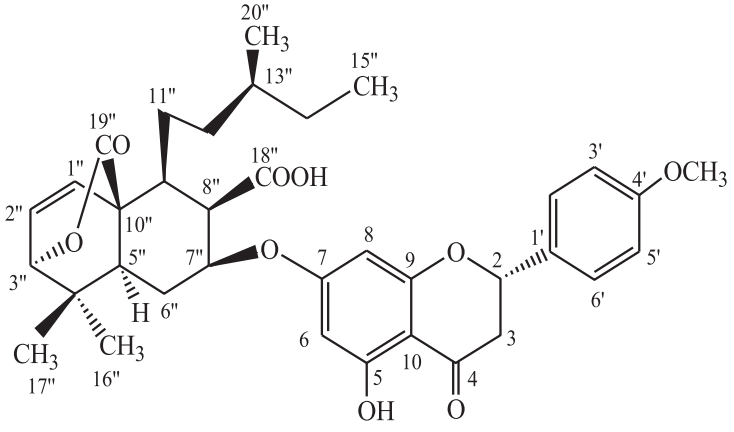

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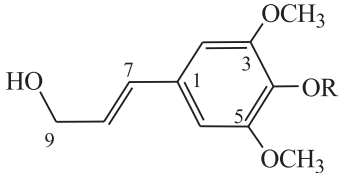

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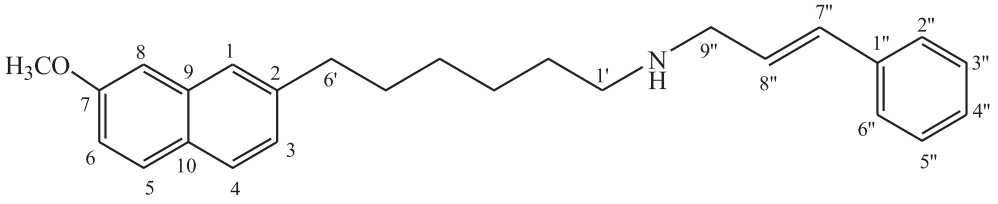

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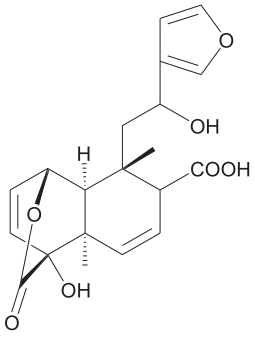
Fig. 2 (*continued*)



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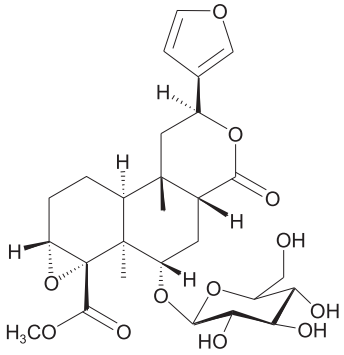

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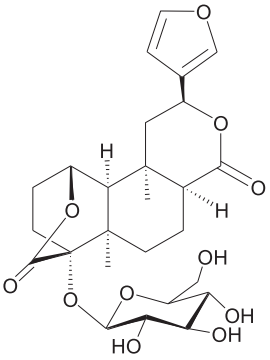

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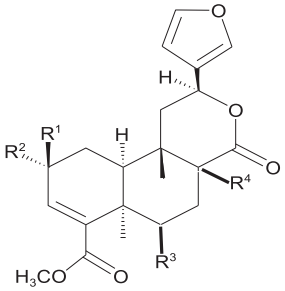
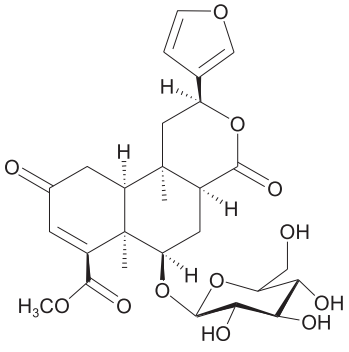


97 R^1 = H, R^2 = OH, R^3 = β-D-Glucopyranosyl, R^4 = β-H, **98** R^1 = 0, R^2 = O, R^3 = β-D-Glucopyranosyl, R^4 = α-H, **99**



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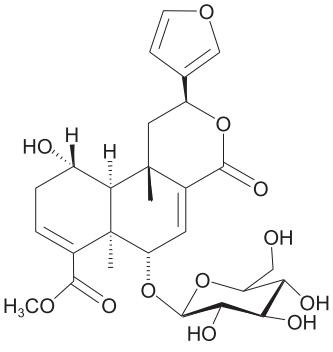

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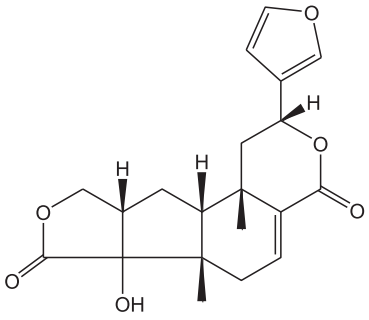

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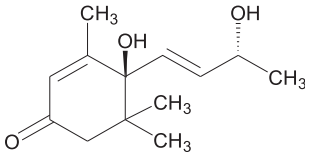

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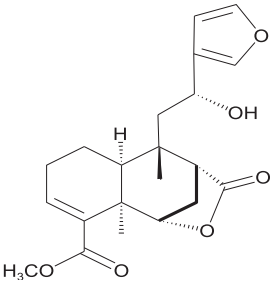

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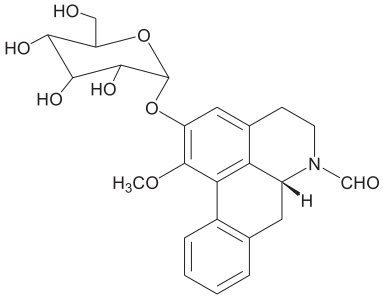

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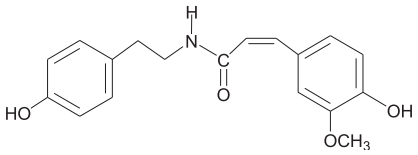

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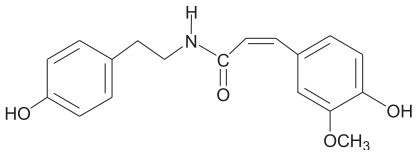

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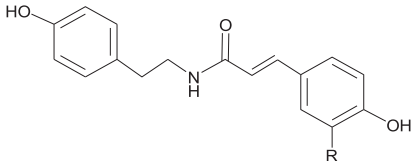
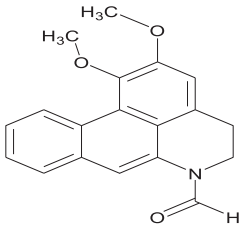


109 R = H, **110** R = OH



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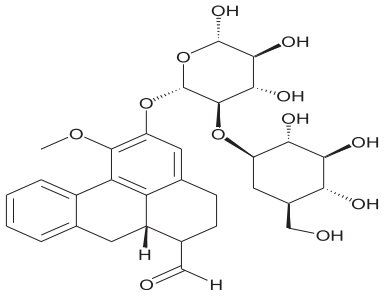

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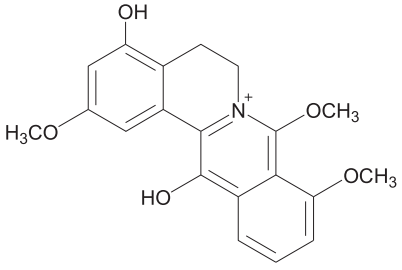

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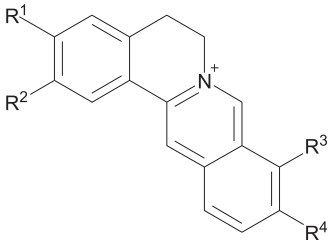
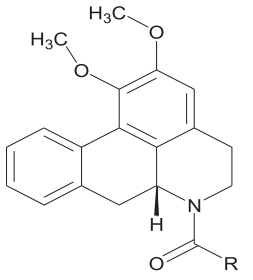
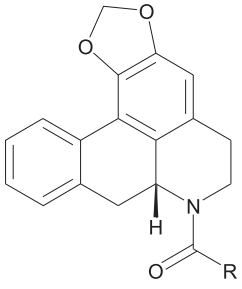


114 $R^1 = OCH_3$, $R^2 = OH$, $R^3 = OCH_3$, $R^4 = OCH_3$, **115** $R^1 = OH$, $R^2 = OH$, $R^3 = OCH_3$, $R^4 = OH$



116 R = H, **117** R = CH_3



118 R = H, **119** R = CH_3

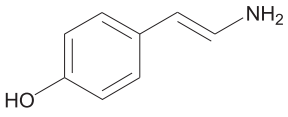


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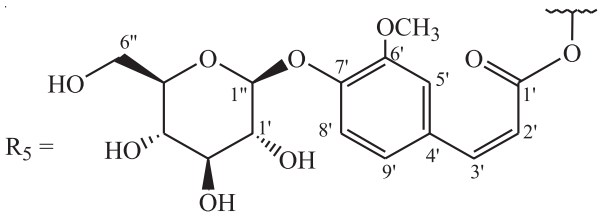
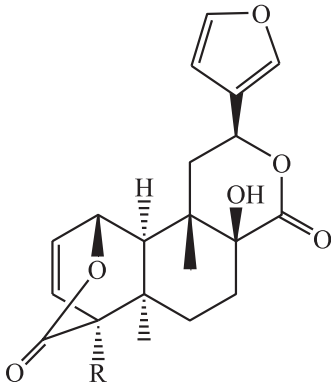
Fig. 2 (*continued*)



168 R_1 = OAc, R_2 = OH, R_3 = α-R_5, **169** R_1 = OH, R_2 = H, R_3 = β-R_4



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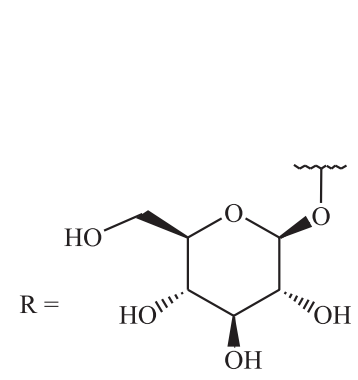

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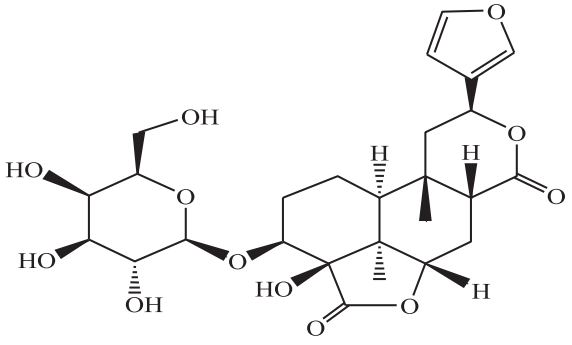

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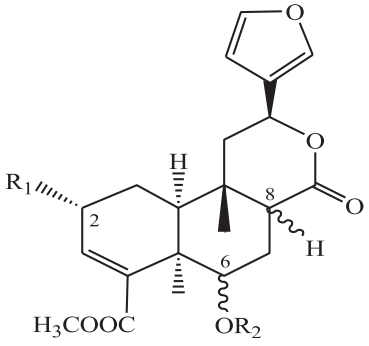
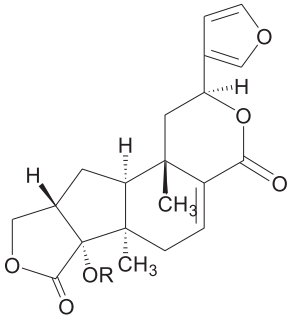
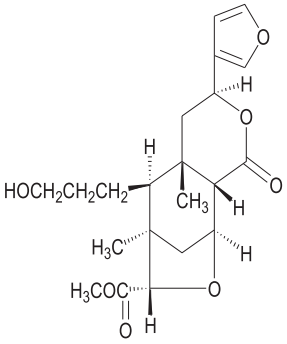


173 R_1 = H, R_2 = β-D-glc, (6α,8β), **174** R_1 = β-D-glc-*O*, R_2 = β-D-glc, (6α,8β)

Fig. 2 (*continued*)



1 R = H, **2** R = GLC



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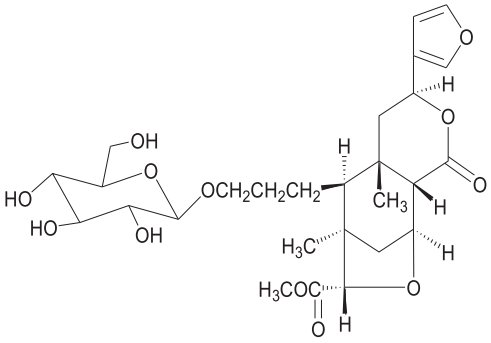

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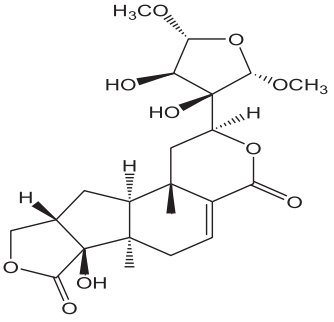

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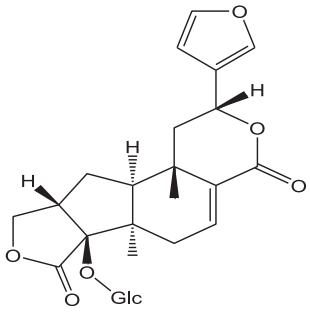

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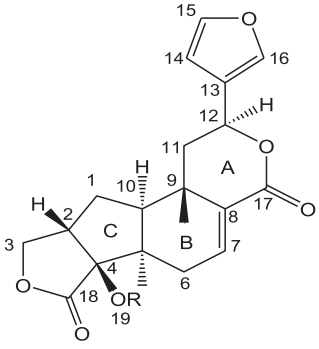
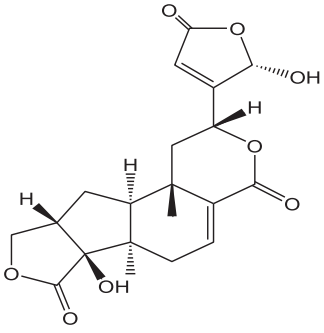


7 R = H, **8** R = Glc



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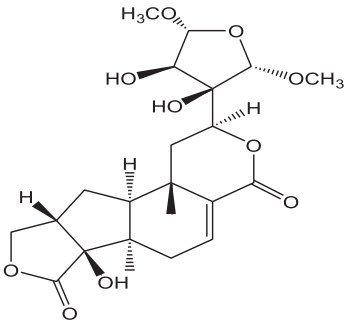

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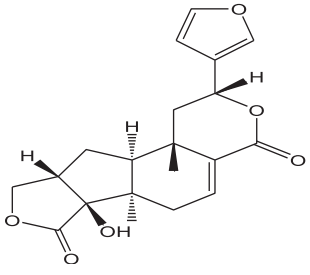

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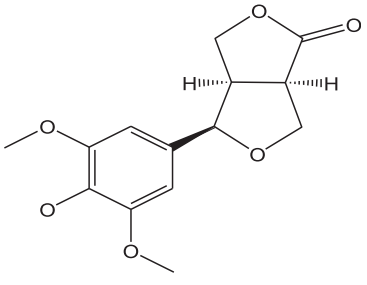
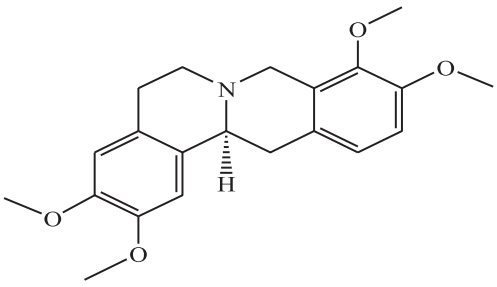


12

Fig. 2 (*continued*)

1yl]butanoate, 4-[formyl-5-(methoxymethyl)-1H-pyrrol-1-yl] butanoic acid, and 4-[formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl] butanoic acid have been obtained from *T. sinensis* (Lam et al., 2018).



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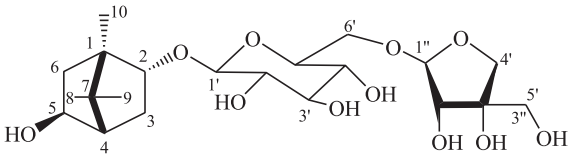

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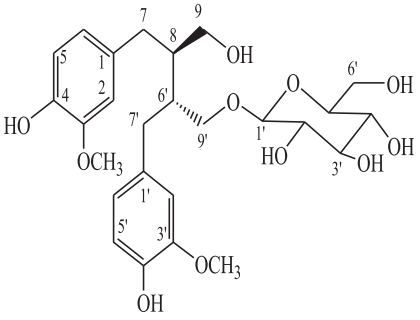

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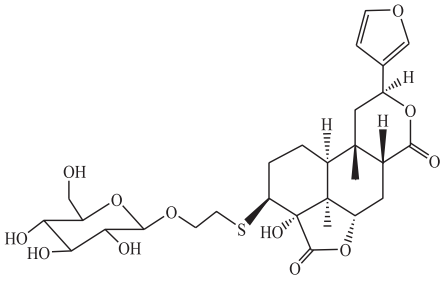

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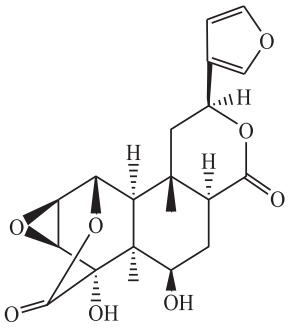

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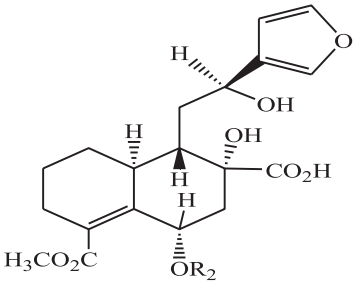
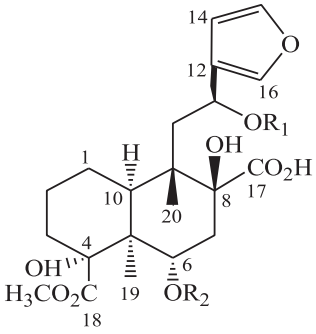


26 R_1 = H, R_2 = *β*-D-glucopyranosyl, **27** R_1 = Ac, R_2 = Tetra-*O*-acetyl-β-D-glucopyranosyl



28 R_1 = H, R_2 = β-D-glucopyranosyl, **29** R_1 = Ac, R_2 = Tetra-*O*-acetyl-β-D-glucopyranosyl

Fig. 2 (*continued*)

Flavonoids are medicinally important secondary metabolites and are synthesized via the phenylpropanoid pathway, converting phenylalanine into 4-coumaroylCoA, which gets in the flavonoid biosynthesis pathway (Falcone Ferreyra et al., 2012). These are hydroxylated phenolic compounds and are known to be produced by the plants in response to microbial infection (Kumar et al., 2013a, 2013b). Activities of human protective enzymes are induced by the plant-derived flavonoids. Various studies have suggested the protective effects of flavonoids against bacterial and viral infections

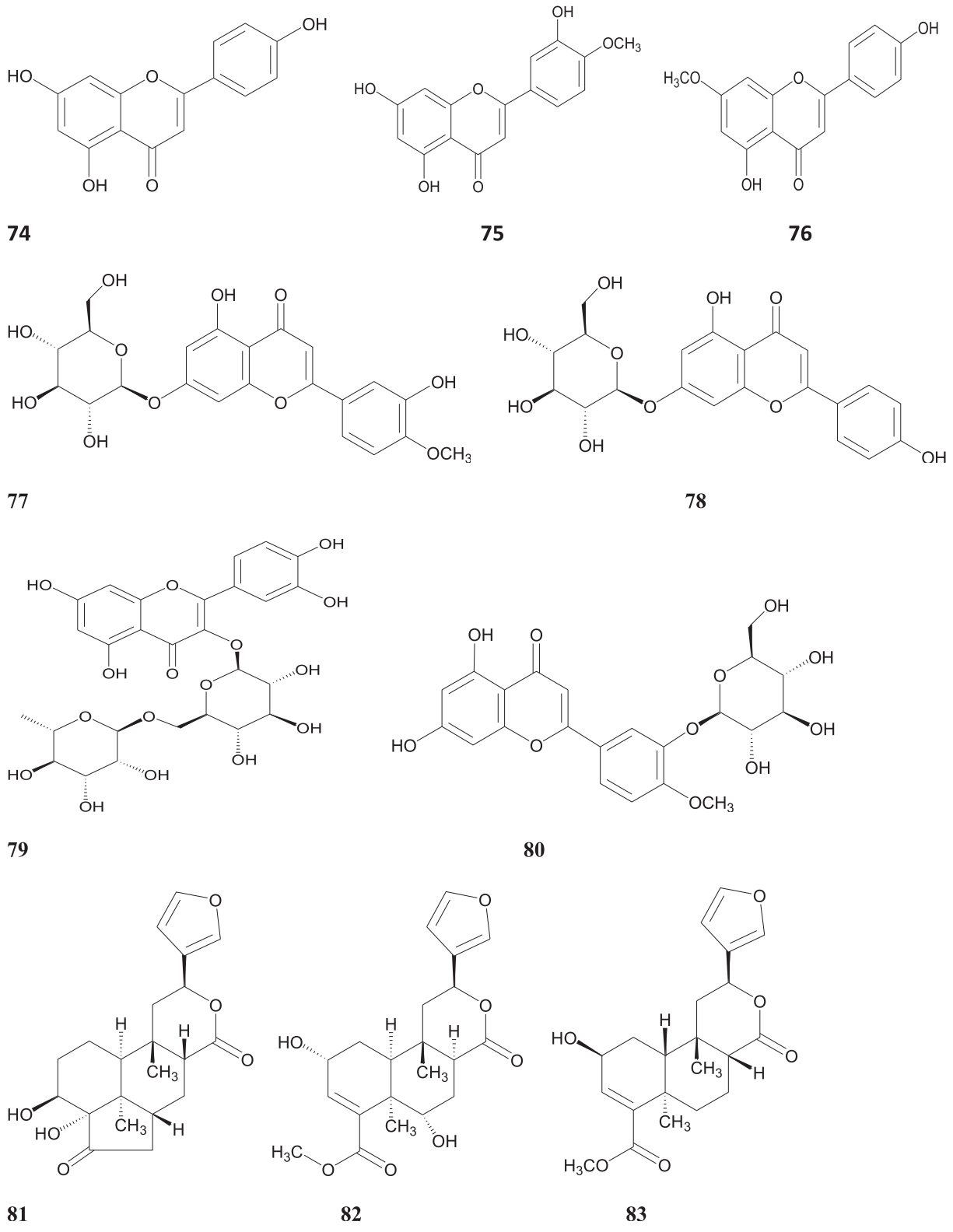
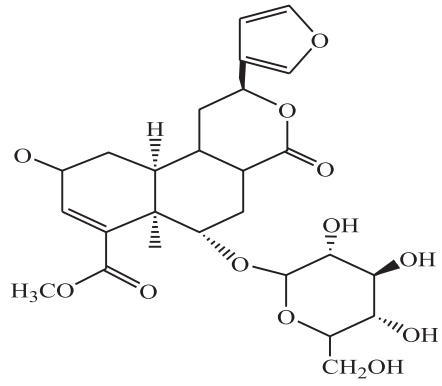


Fig. 2 (*continued*)

and also against cardiovascular diseases, cancers, and other age-related disorders (Rice-Evans et al. 1995; Cook and Samman, 1996; Kumar et al., 2013). Total six compounds (apigenin, diosmetin, genkwanin, luteolin 4′-methyl ether 7- glucoside, genkwanin 7-lucoside, and luteolin 4′-methyl ether 3′ -glucoside (Umi Kalsom and Noor, 1995), and rutin have been identified from *T. crsipa* stem (Harwoko and Warsinah, 2020).

Phytoecdysteroids are natural polyhydroxylated constituents that contain a four-ringed skeleton, usually made up of either 27 carbon atoms or 28–29 carbon atoms (Dini,



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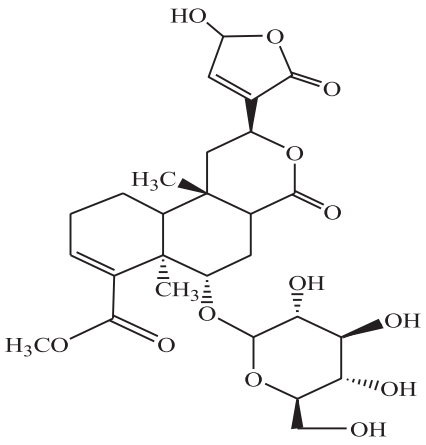

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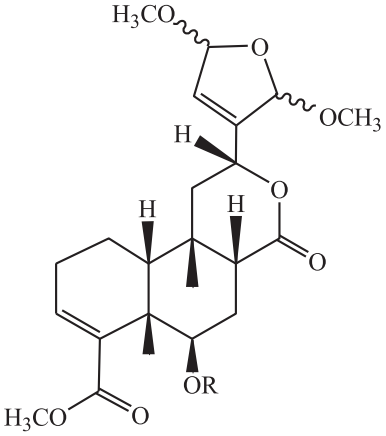
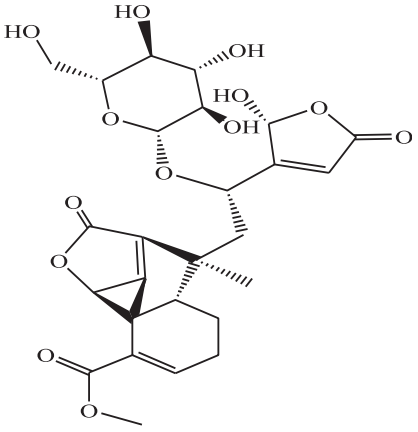


177 R = R =β-D-Glc(Ac)$_4$



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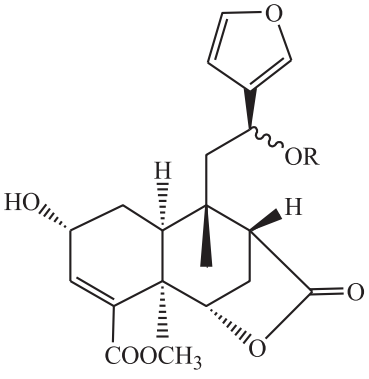
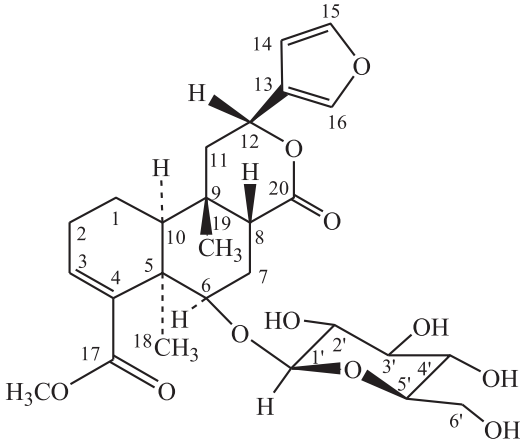


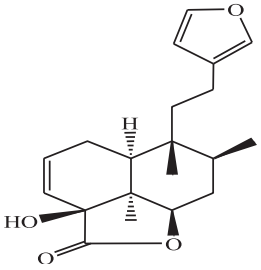
179 R = β-D-glc



180

Fig. 2 (*continued*)

2020). These compounds are derived from S-squalene-2,3-epoxide via acetate-mevalonate pathway and possess hypocholesterolemic activity (Tarkowská, 2019). Phytoecdysteroid-like compounds are found in various families of angiosperms. These compounds accumulate in various plant organs, viz, fruits, seeds, flowers, anthers, leaves, and roots. Phytoecdysteroids (*Ajuga decumbens*) demonstrated significant inhibitory effects on early induction and potent antitumor-promoting activities of Epstein–Barr virus on a mouse skin. Besides anticancer properties, phytoecdysteroids are also used as



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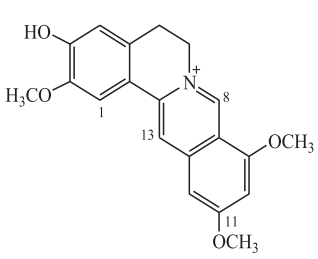

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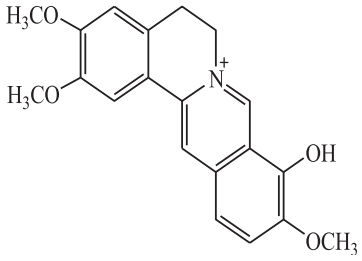

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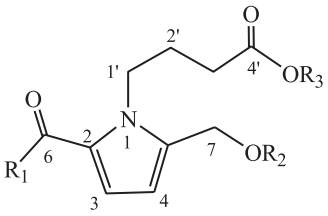
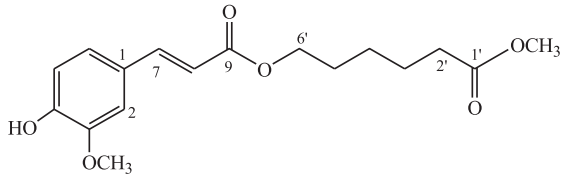


189 R_1 = OH, R_2 = CH_3, R = CH_3, **190** R_1 = H, R_2 = H, R = CH_3, **191** R_1 = H, R_2 = CH_3, R = CH_3, **192** R_1 = H, R_2 = CH_3, R = H, **193** R_1 = H, R_2 = H, R = H



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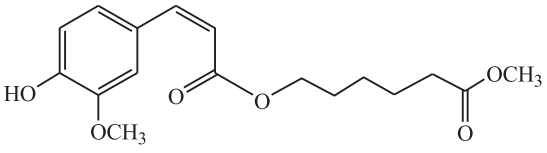

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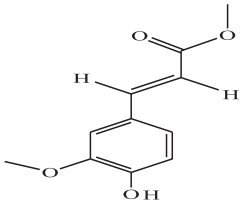

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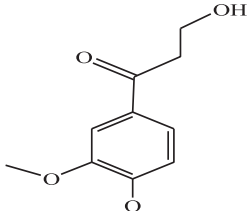

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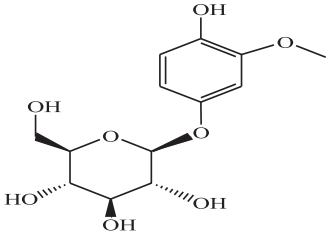
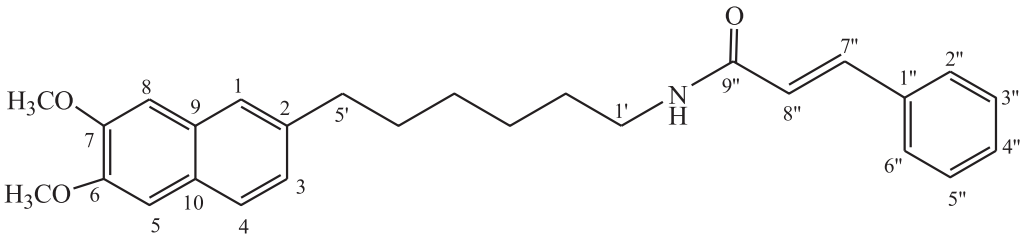


198

Fig. 2 (*continued*)

nutraceutical additives in food products (Bajguz et al., 2015; Saleem and Nazir, 2015). Phytoecdysteroid-like compounds possess antidiabetic, growth-promoting, hepatoprotective, immunoprotective, antioxidant, hypoglycemic, performance-enhancing, anti-osteoporotic, wound healing properties (Adki et al., 2020; Laddha et al., 2020). The polypodine B 20, 22-acetonide, 20-*p*-hydroxyecdysone, *β*-sitosterol, stigmasterol and campesterol were isolated and identified from aerial parts of *T. cordifolia* (Pathak et al., 1995; Kiem et al., 2010).

Lignans are a class of diphenolic constituents found in the bran layer of grain of cereals. Wheat bran contains a secoisolariciresinol diglucoside (a major compound); it is converted



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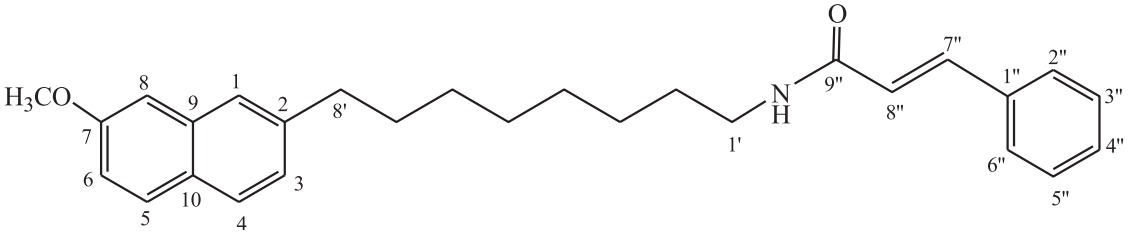

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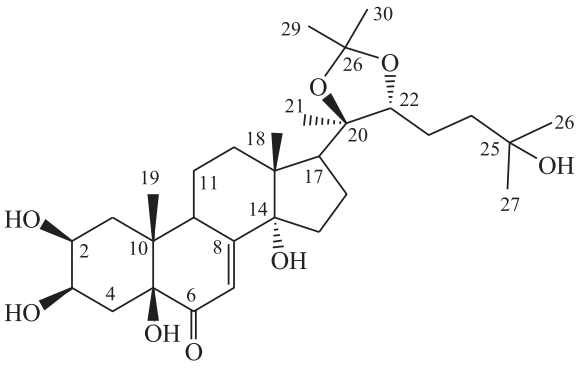

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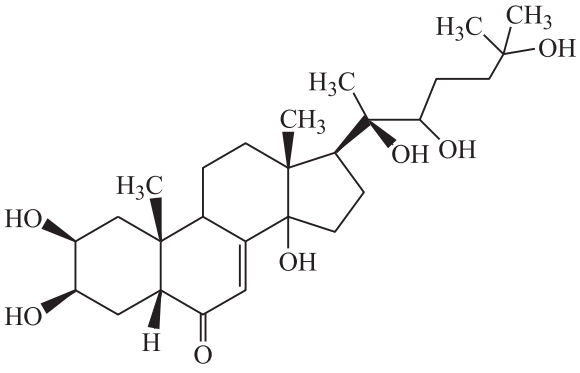

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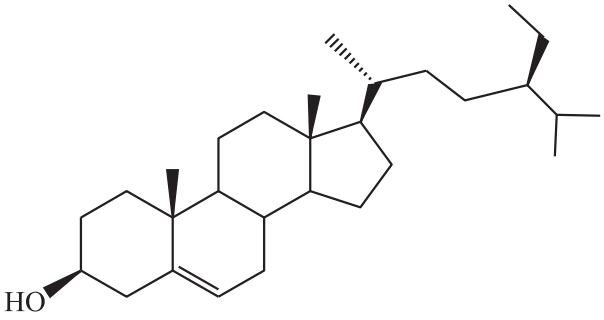

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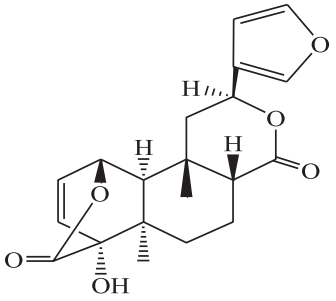
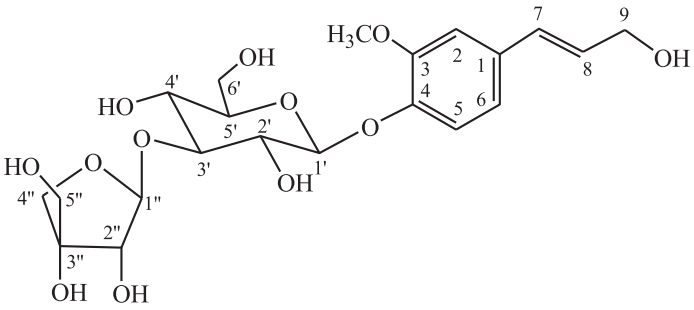


73

Fig. 2 (*continued*)

by intestinal microflora to enterodiol and enterolactone. Lignan are considered as a potent antioxidants and free radical scavengers, leading to decrease in risk of cancer development (Higuchi, 2014). On the basis of cyclization patterns and the way in which oxygen is incorporated into the skeleton, the lignans are divided into eight sub-groups - furofuran, furan, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphthalene, dibenzocyclooctadiene, and dibenzylbutyrolactol (Tsopmo et al., 2013). Secoisolariciresinol, syringaresinol from stem (Chung, 2011), adenosine, uridine and adenine from stem (Praman et al., 2012), benzeneethanamine, camphenol, strophanthidin, retinal, *trans*-geranylgeraniol, 3,4-dihydroxymandelic acid, imidazolidin-4-one, 2-imino-1-(4-methoxy-6-dimethylamino-1,3,5-triazin-2-yl), cholest-22-ene-21-



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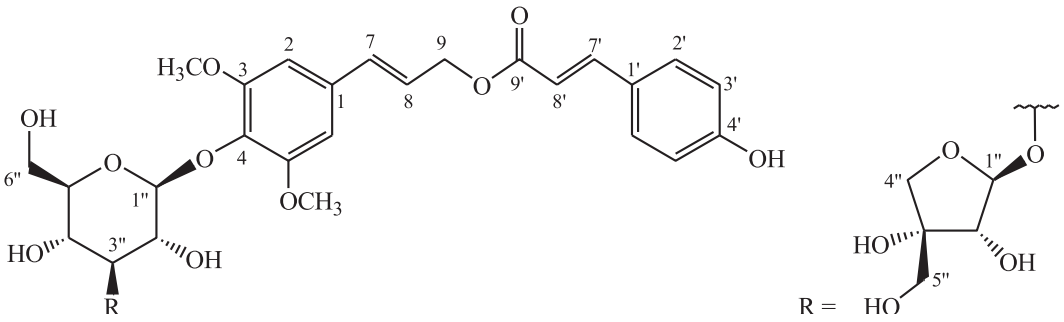

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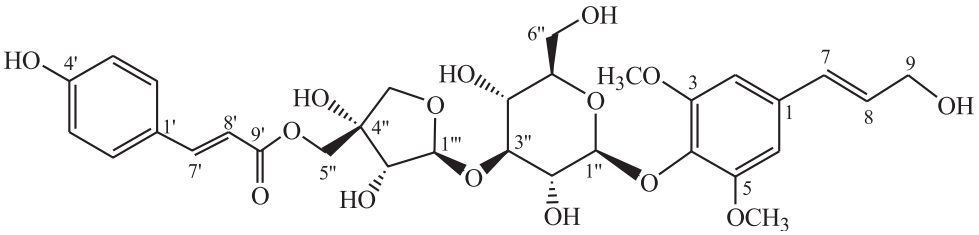

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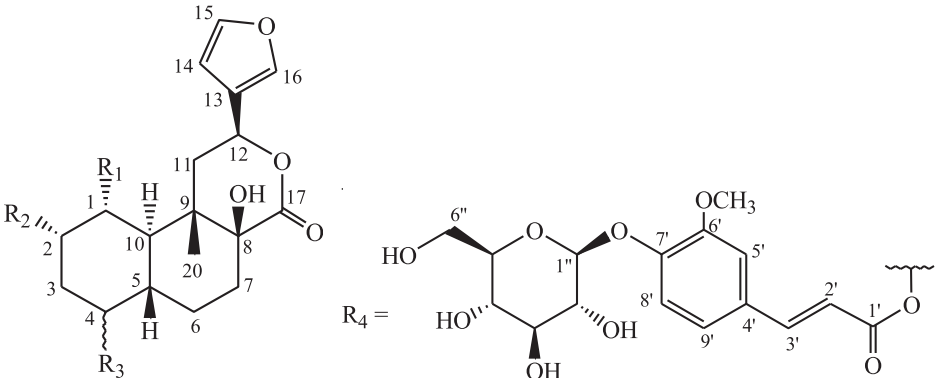
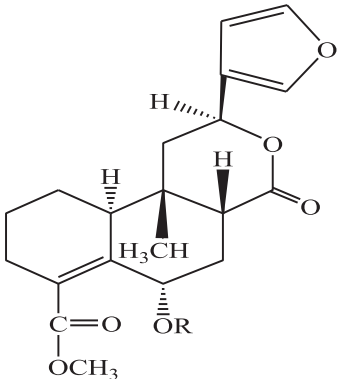
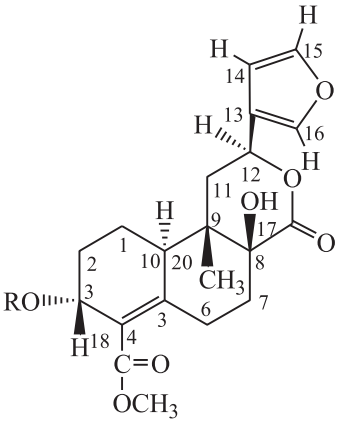


Fig. 2 (*continued*)

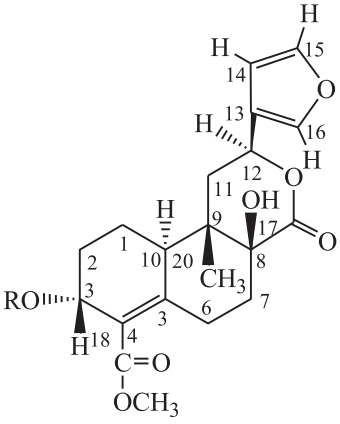
ol, 3,5-dehydro-6-methoxy, δ-mannitol, 1-*O*-(16-hydroxyhexadecyl)-, heneicosanoic acid, methyl ester, gorgost-5-en-3-ol, (3β)-, TMS derivative, retinol, octacosanol, α-santalol, santalol, E-*cis,epi*-β, spiro[4,5]dec-6-en-1-ol, 2,6,10,10-tetramethyl were separated and identified from *T. crispa* whole plant (Lin, 2009; Rakib et al., 2020c). The lirioresino-β-dimethyl ether, tinosposide A, tinosposide B, tanegoside, (+)-pinoresinol *O*-β-D-glucopyranoside (Maurya et al., 2009), (+)-pinoresinol, syringaresinol, medioresinol, (+)-epi-syringaresinol, (+)-pinoresinol monomethyl ether, (+)-glaberide I, sesamin, and sesamolin have been identified from the *T. sinensis* (Li et al., 2004a; Lam et al., 2018). The tinosposinensides A, tinosposinensides B, tinosposinensides C, 1-deacetyltinosposide A (Li et al., 2007), 1-deacetyltinosposide have been reported from ethanolic extract of *T. sinensis* stem (Dong et al., 2010).



56 R=β-D-glucopyranosyl, **57** R= Tetra-*O*-acetyl-β-D-glucopyranosyl



58 R = β-D-glucopyranosyl, **59** R= Tetra-*O*-acetyl-β-D-glucopyranosyl



60 R = β-D-Glucopyranosyl, **61** R= Tetra-*O*-acetyl-β-D-glucopyranosyl

Fig. 2 (*continued*)

4. Pharmacological attributes of *Tinospora* species

Ethanolic extract of *T. cordifolia* is extensively used in the formulation of 'Septilin' syrup, recommended as remedy in the treatment of bronchitis and earache (Spelman, 2001; Singh et al., 2003a, b). The isolated compounds berberine and jatrorrhizine showed antimicrobial, anti-inflammatory (Patgiri et al., 2014), anthelminthic (Pawar et al., 2014), antineoplastic (Jagetia and Rao, 2006b), antidiarrheal, antiulcer (Kumar et al., 2014) and anti-diabetic activities (Agarwal et al., 2002; Sinha et al., 2004; Sangeetha et al., 2013). The pharmacological activities of 9 Indian *Tinospora* species are presented in Table 3.

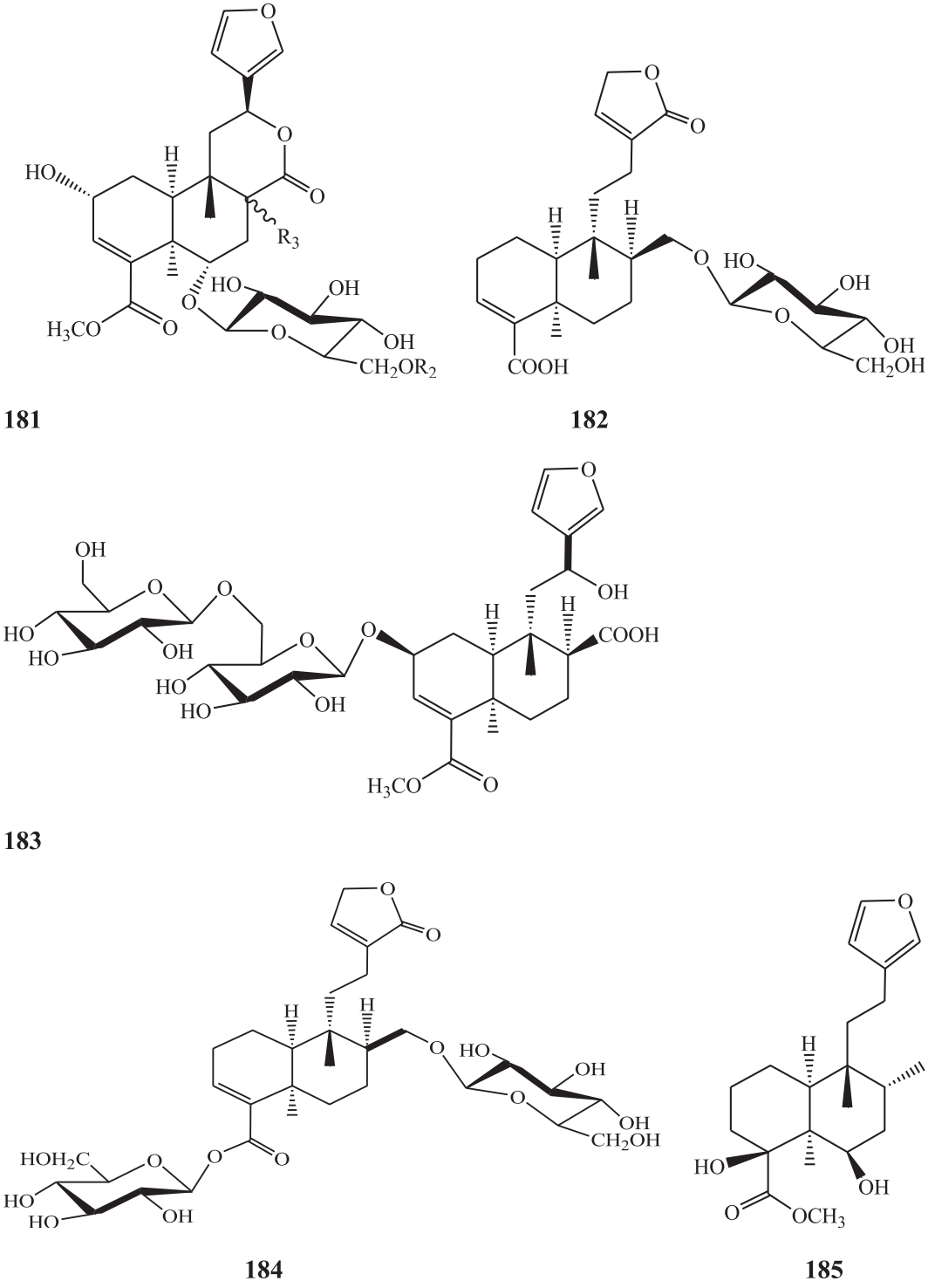


Fig. 2 (*continued*)

4.1. Antioxidant activity

The oxidative stress is considered as a main cause for the development of various diseases. The food materials promote antioxidative defences in human body to combat non-desirable effects of reactive oxygen species. Plants are able to biosynthesize a wide range of non-enzymatic antioxidative molecules capable of attenuating the reactive oxygen species-induced oxidative destruction (Kasote et al., 2015). 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 control group (Jayaprakash et al., 2015; Polu et al., 2017). The n-butanolic extract of *T. cordifolia* stem (200 µg/mL) showed significant antioxidant activity in DPPH, ABTS, nitric

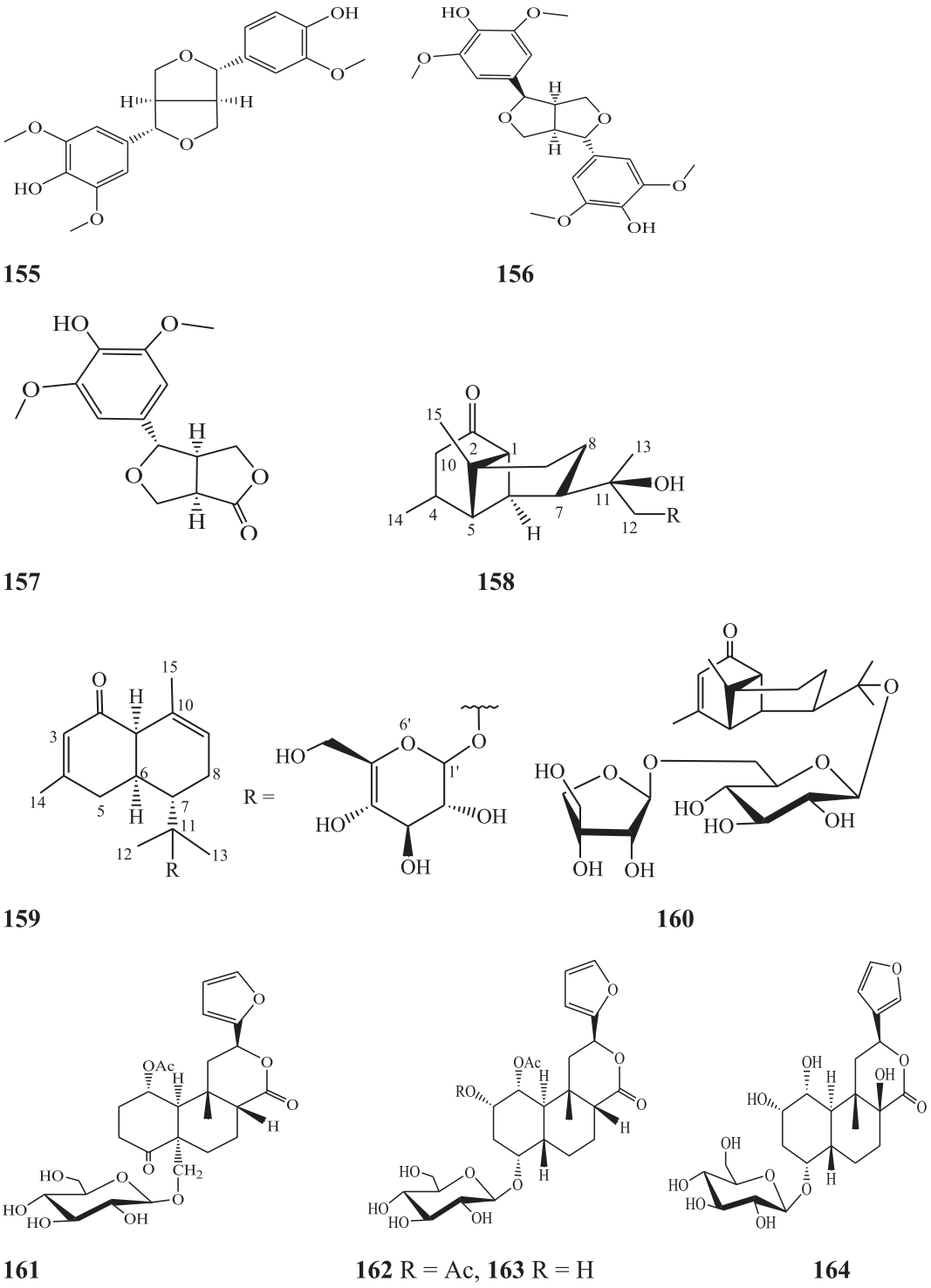
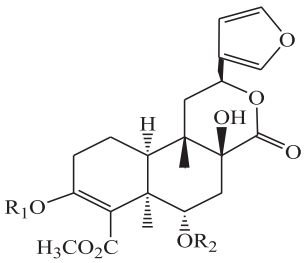


Fig. 2 (*continued*)

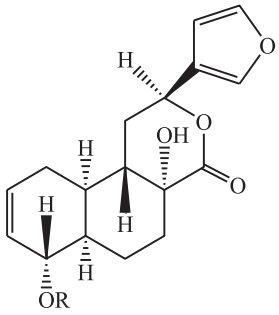
oxide scavenging and iron chelating assays (Polu et al., 2017). The methanol extract of *T. crispa* displayed maximum antioxidant activity which was evaluated by measuring total flavonoid content (9.53 ± 0.50 mg quercetin equivalent/ g sample), total phenolic content (255.33 ± 10.79 mg gallic acid equivalent/g sample), and DPPH free radical scavenging activity (IC_{50} 12 μg/mL). The activity could be associated with the presence of phenolic compounds (Ibahim et al., 2011).

4.2. Anti-diabetic activity

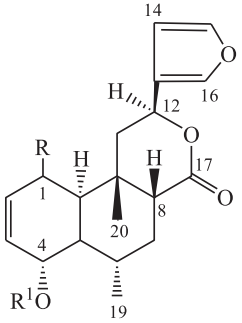
Diabetes mellitus type 2 (an endocrine metabolic disorder) is the main cause (microvascular and macrovascular complications) of morbidity and mortality in human population (Patel et al., 2011a, b). There are about 69.2 million people affected by diabetes and are anticipated to cross 123.5 million



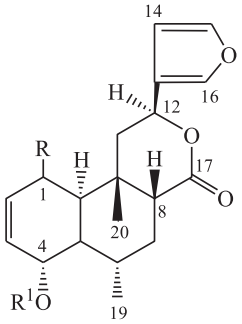
30 R_1 = H, R_2 = β-D-glucopyranosyl, **31** R_1=Ac, R_2= Tetra-*O*-acetyl-β-D-glucopyranosyl



32 R = β-D-glucopyranosyl, **33** R = Tetra-*O*-acetyl-β-D-glucopyranosyl



34 R = O, R^1 = H



35 R = O, R^1 = β-D-glycopyranosyl

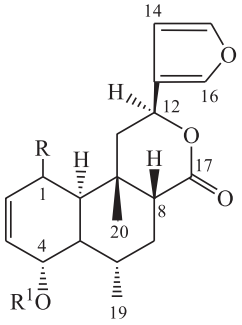
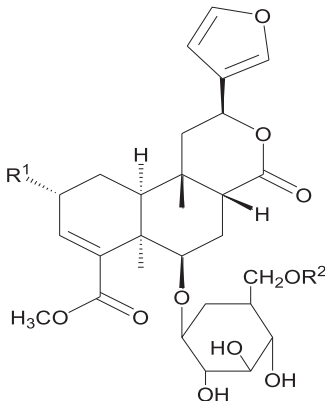
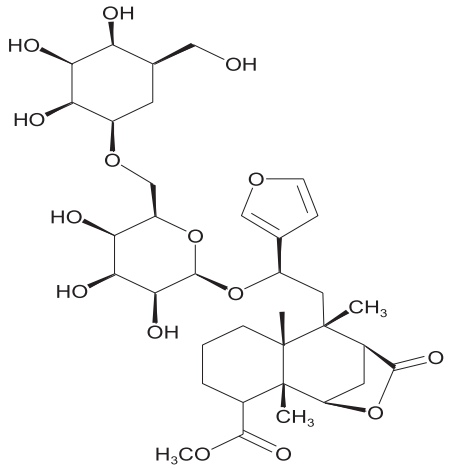


Fig. 2 (*continued*)

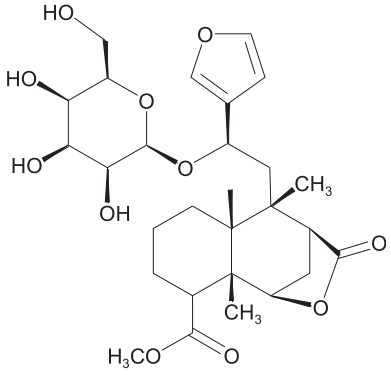
by 2040 in India. Furthermore, about 193 million diabetics remain unfamiliar leading them to the occurrence of several long-term health problems of untreated chronic diabetes (Chawla et al., 2016). The methanolic extract of *T. cordifolia* stem was administered (p.o.) for 24 weeks to diabetic rats and levels of blood glucose 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 (Agrawal et al., 2012). 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 liver ($P < 0.005$; Sangeetha et al., 2011). Ethanol extract increased the body weight, total haemoglobin and hepatic hexokinase activity but, decreased the levels of hepatic glucose-6-phosphatase, serum acid phos-

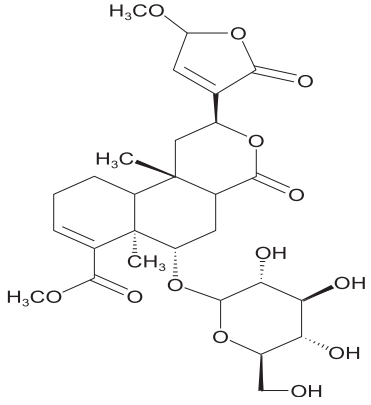


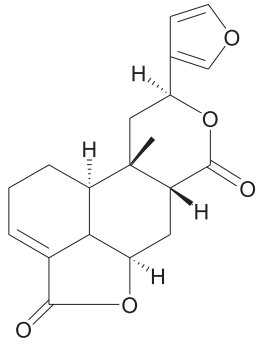


84 R^1 = OH, R^2 = O, **85** R^1 = O-Lactoyl, R^2 = H

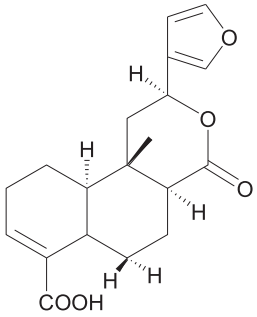
86

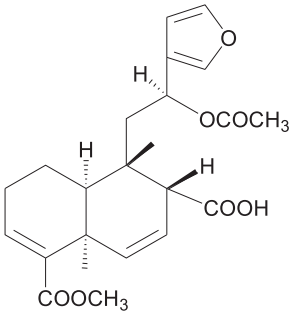


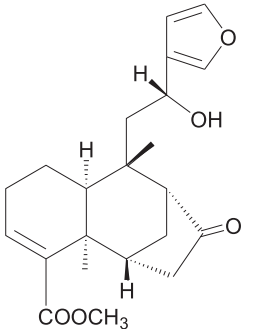


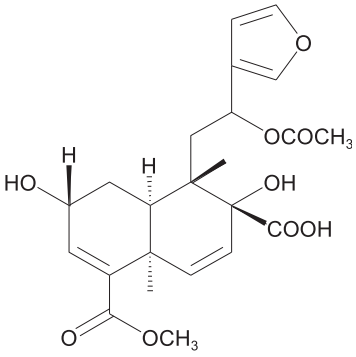


87 **88** **89**









90 **91** **92** **93**

Fig. 2 (*continued*)

phatase, alkaline phosphatase, and lactate dehydrogenase activities in diabetic rats significantly ($P < 0.001$; Stanely et al., 2000). The formulation of water extract (*T. cordifolia* stem) + honey suspension reduced the levels of blood glucose and glycated haemoglobin in streptozotocin treated Wistar albino rats (Khedekar et al., 2015). Magnoflorine isolated from *T. cordifolia* leaf (100 mg/kg b.w.) significantly reduced the levels of serum glucose in streptozotocin-induced diabetic Wistar rats (Cherku et al., 2019). Dry powder of *T. crispa* stem (given 250 mg, twice a daily) showed significant hypoglycemic effect on patients with metabolic syndrome. The dry powder significantly reduced fasting blood glucose levels from the baseline (Sriyapai et al., 2009). Borapetol B isolated from *T. crispa* stem (100 µg/ 100 g b.w.) reduced the levels of blood glucose significantly ($P < 0.001$) but enhanced the levels of insulin in treated normoglycemic Wistar and type 2 diabetic Goto-

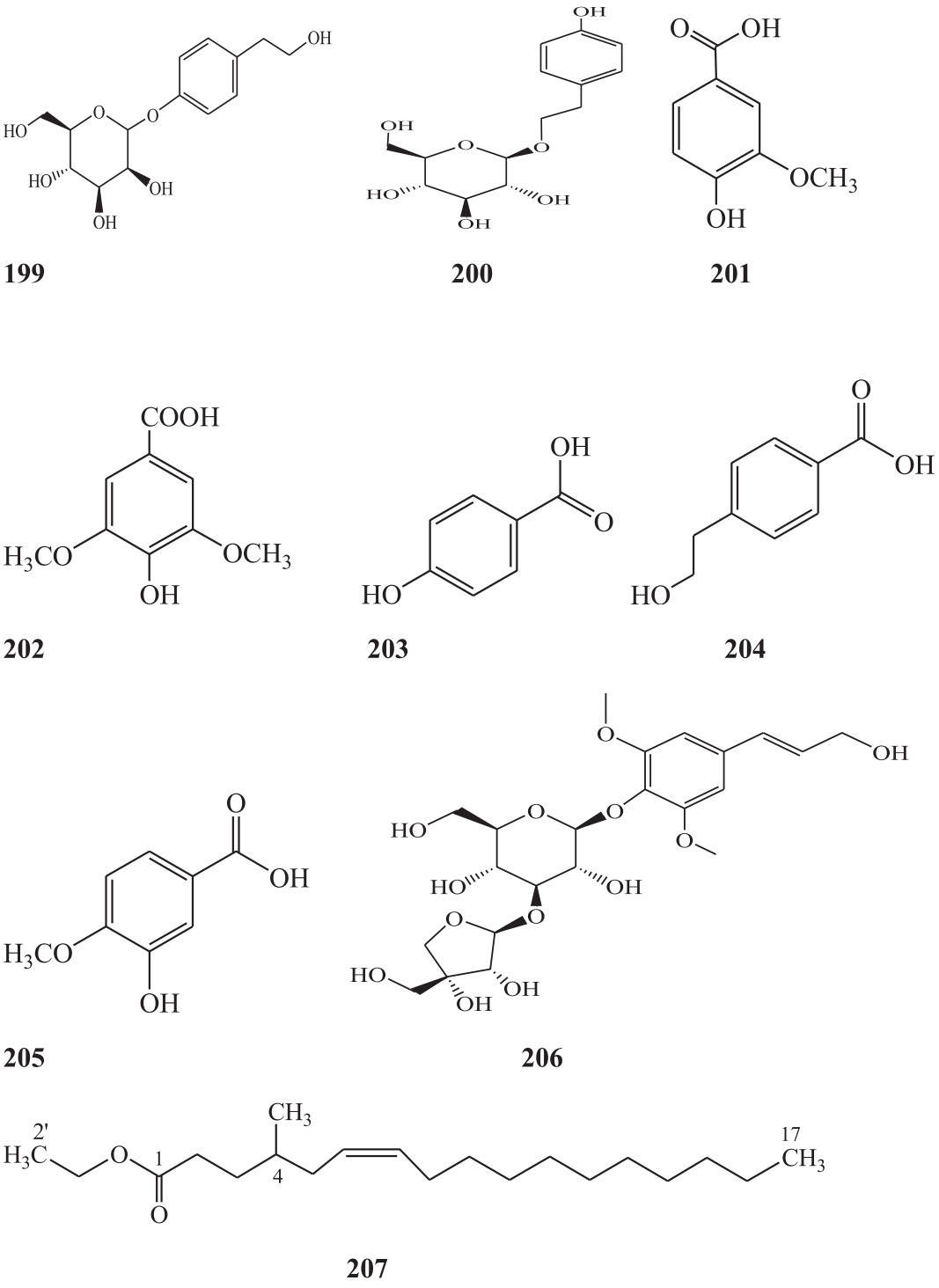


Fig. 2 (*continued*)

Kakizaki rats (Lokman et al., 2013). *T. crispa* extract increased glucose uptake in L6 myotubes which was linked to the enhanced levels of GLUT1 transporter, AMPKα, and PPARγ transcript (Noipha and Ninla-Aesong, 2011). Ethanolic extract of *T. sinensis* flowers (200 mg/kg b. w./day) altered the improper metabolic profile and it was led to hypolipidemia significantly ($P < 0.05$; Sandhyarani and Kumar, 2014a). Similarly, the ethyl acetate extract of leaves demonstrated significant ($P < 0.001$) antidiabetic activity (149 ± 0.66) at 200 mg/kg dose (Pimpriker et al., 2009).

4.3. Anti-arthritic activity

Rheumatoid arthritis is a chronic systemic inflammatory disease that causes joint inflammation, synovial proliferation, and destruction of articular cartilage. The condition gets worse

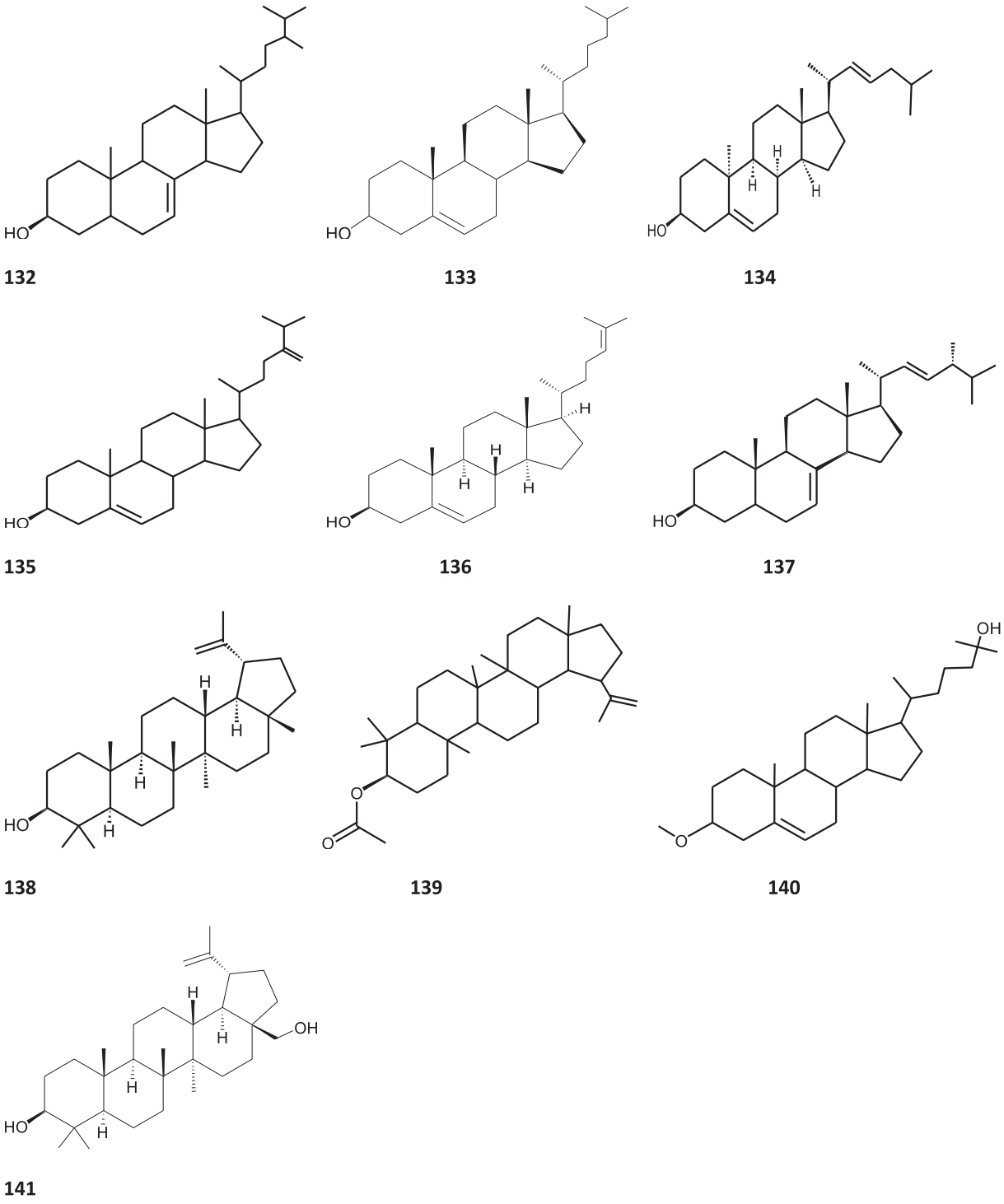
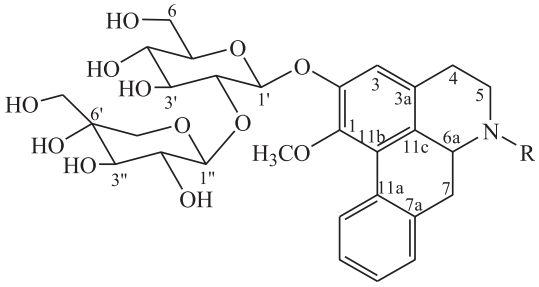


Fig. 2 (*continued*)

over the time unless the inflammation is stopped or slowed. It is the most common cause of physical disability in developed countries, and its prevalence is found between 0.3% – 1.50% in human population (Lin et al., 2006). The *in vitro* results were not found optimistic but, *T. cordifolia* stem extract (p.o.) showed significant results (50 mg/kg b. w./day; given for 21 days followed by treatment for 12 weeks) in ovariectomy-induced bone loss (Abiramasundari et al., 2017). The minimum protein denaturation (23%, 36%, and 43%) was reported in animals treated with methanolic extract of *T. cordifolia* stem bark (100 µg, 250 µg and 500 µg/mL). Methanolic extract of *T. cordifolia* stem significantly inhibited the denaturation of proteins when compared with diclofenac sodium in treated animals (Ramya and Maheswari, 2016).



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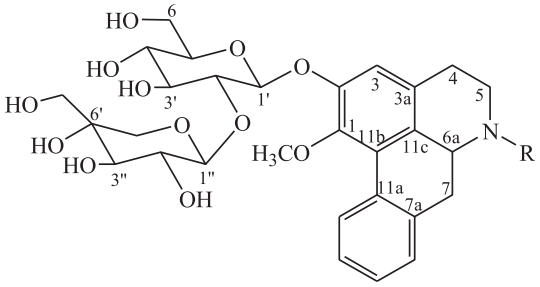
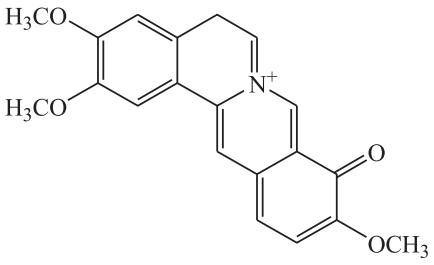


14 R = Acetyl



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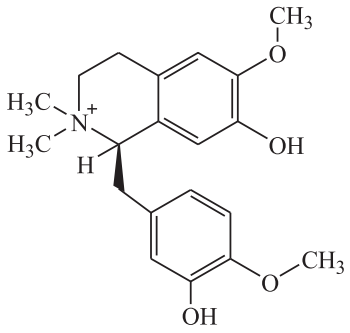

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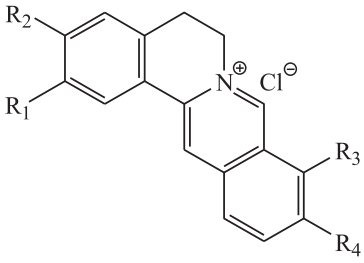
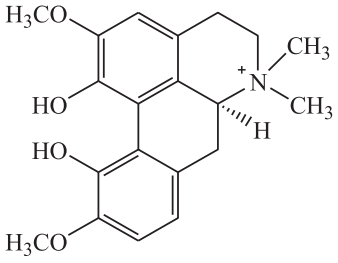


17 R_1=OCH_3, R_2=OH, R_3=OCH_3, R_4=OCH_3



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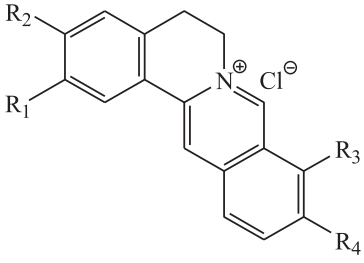

19 R_1= O-CH_2-O, R_3= OCH_3, R_4= OCH_3

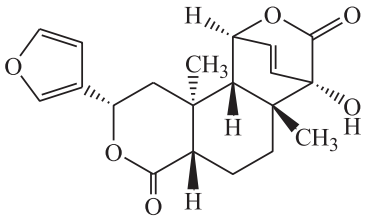

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Fig. 2 (*continued*)

4.4. Anti-stress activity

Stress is known to stimulate alterations in various physiological responses even dominating to pathological stress (Chrousos, 1998). The chronic stress exposure is known as causative factor of free radical formation and reactive oxygen species increase in the body (Wang et al., 2007). Normally stress-induced alterations are self limiting events that override the 'threshold' limits become irreversible and pathological (Seyle, 1973). Stress is involved in the development of various diseases such as hypertension, peptic ulcer, Alzheimer's disease, and depression (Piato et al., 2008). Ethanolic extract of *T. cordifolia* fresh leaves (50 mg/kg) showed significant decrease in the immobility period (force swim and tail immersion tests (Kalabharath et al., 2014). In patients of chronic mental stress, the levels of serum glucose, triglyceride, cholesterol, anxiety, and depression were reported higher than healthy men. The patients were administered with *T. cordifolia* (3 g twice daily)

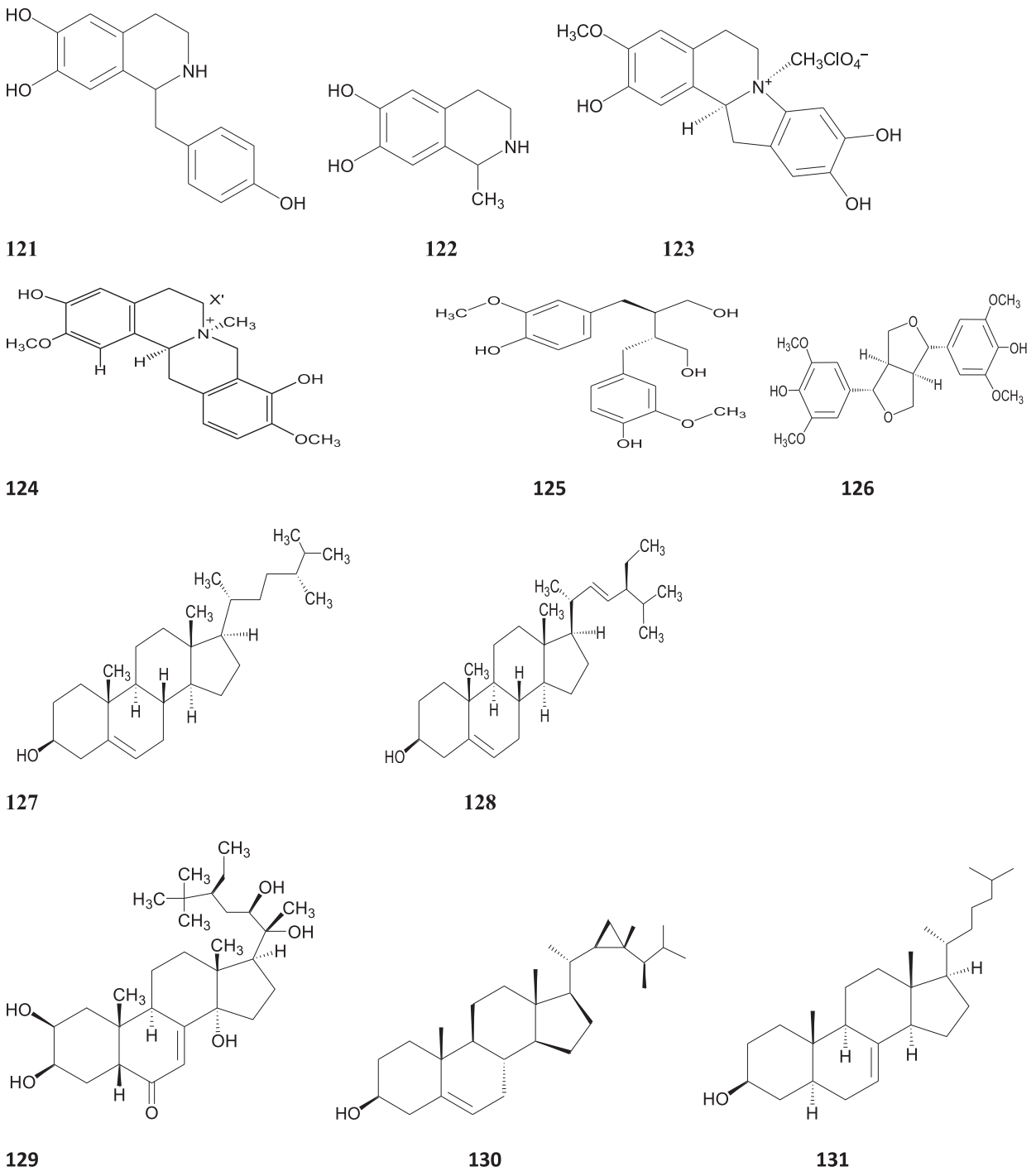
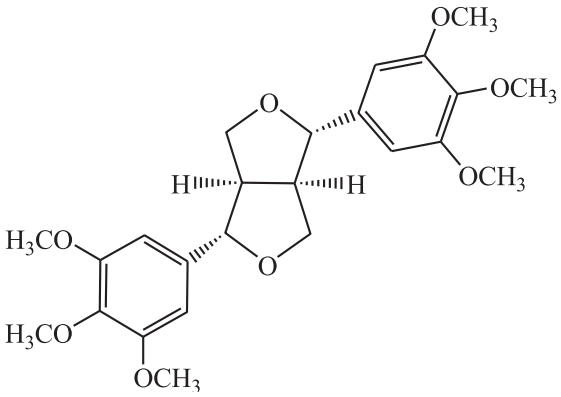


Fig. 2 (*continued*)

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 when compared with diazepam ($P < 0.001$; Biswas et al., 2015). Pretreatment with aqueous and alcoholic extracts of *T. sinensis* had increased the anoxia stress tolerance at the end of 1st, 2nd and 3rd weeks of treatment with both doses i.e., 500 mg/kg ($P < 0.05$) and 1000 mg/kg ($P < 0.01$). Aqueous and alcoholic extracts of *T. sinensis* stem reduced the elevated levels of serum biochemical parameters, and blood cell count. Aqueous extract prevented alterations in the weight of the liver, adrenal gland but increased the weight of spleen in treated animals (Sharma et al., 2007).

4.5. Anticancer/antitumor activity

Cancer is one of the most dreaded disease and is a leading cause of death worldwide. It is the third leading cause of death worldwide following cardiovascular and infectious diseases



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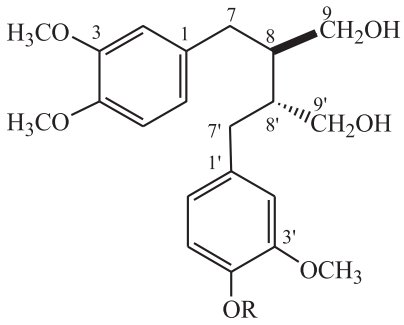
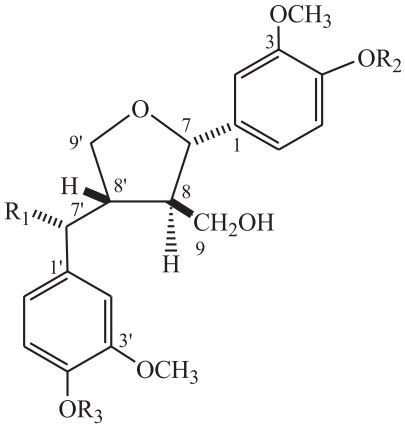
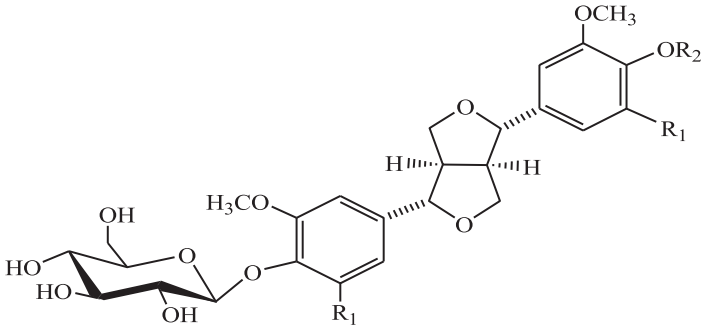


143 β-D-glucopyranose



144 R_1 = H, R_2 = β-D-glucopyranose, R_3 = CH_3,**145** R_1 = β-D-glucopyranose, R_2 = R_3 = H

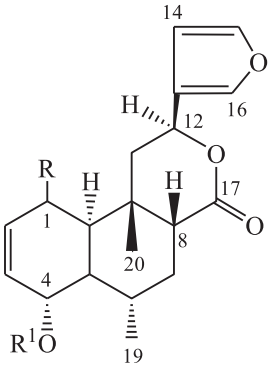


146 R_1 = R_2 =H, **147** R_1 = H, R_2 = CH_3, **148** R_1 = OCH_3, R_2 = H

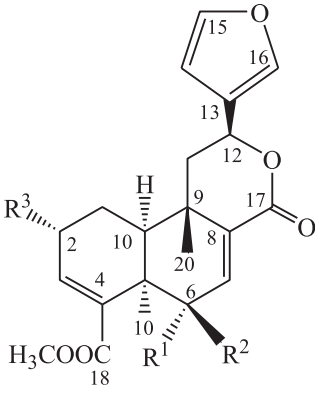
Fig. 2 (*continued*)

(Kelloff, 2008). Breast cancer is the most common type of cancer in women. The maximum prevalence of breast cancer is found in South-Central Asian countries (Soliman et al., 2006). It has been proven that several diseases occur in humans due to development of oxidative stress. The oxidative stress developed by free radicals, seek stabilization through electron pairing with proteins and DNA in healthy cells of human, cause DNA and protein damage. These alterations contribute to the development of cancer, cardiovascular problems, and ageing disorders (Maxwell, 1995; Braca et al., 2002). Due to lack of preventive measures, high cost of chemo- and radiotherapies, and the adverse effects of anticancer agents, attempts are being made to search for novel and effective plant-derived molecules that could suppress cancer development (Babior, 2000; Bhadane et al., 2018). Methanolic extract (20 mg/kg) of *T. cordifolia* stem significantly suppressed tumour directed capillary formation (B16F10 melanoma cell-induced capillary) in rats. Extract inhibited the levels of IL-1β, IL-6, TNF-α, and granulocyte monocyte-colony stimulating factor in treated animals (Leyon and Kuttan, 2004a, b;

36 R = O, R^1 = Tetra-*O*-acetyl-β-D-glucopyranosyl

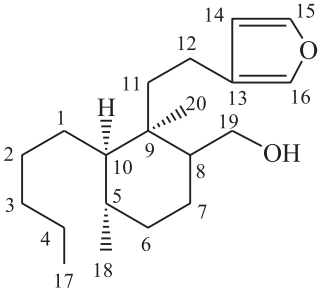


37 R = H_2, R^1 = β-D-glycopyranosyl, **38** R = H_2, R^1 = Tetra-*O*-acetyl-β-D-glucopyranosyl



S = *O*-β-D-glucopyranoside

39 R^1 = H, R^2 = S, R^3 = OH, **40** R^1 = S, R^2 = R^3 = H, **41** R^1 = H, R^2 = S, R^3 = OH, 7, 8-dihydro



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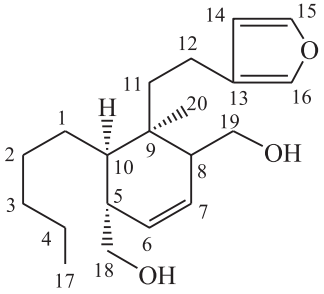

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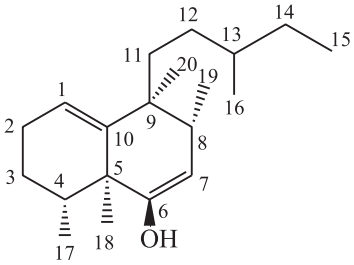


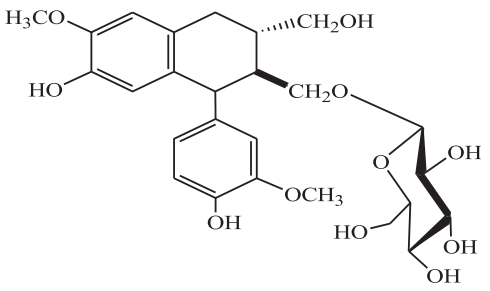
44

Fig. 2 (*continued*)

Jagetia et al., 1998). Hexane fraction of ethanolic extract of *T. cordifolia* stem induced the formation of apoptotic bodies, nuclear condensation, and activation of caspase-3 activity, but suppressed the growth of Ehrlich ascites tumor in mice (Thippeswamy and Salimath, 2007). Palmatine isolated from *T. cordifolia* aerial parts reduced the tumor size significantly ($P < 0.05$) and also increased the levels of glutathione, superoxide dismutase and catalase in the skin of treated animals ($P < 0.05$; Ali and Dixit, 2013). Methanol extract of *T. crispa* stem inhibited the growth of HL-60 (human promyelocytic leukemia cells), HepG2 and virus infected Hep3B human cancer cell lines in dose-dependent manner (Sinchaikul et al., 2007). Ethanolic extract of *T. sinensis* aerial parts showed significant cytotoxicity (IC_{50} 49.87 μg/mL and 112.54 μg/mL) against A375 and A 431 cancer cells, respectively (Punitha et al., 2012).

4.6. Radioprotective activity

The radiation exposure has been increased during last 100 years with the development and use of X-rays and radio-isotopes for therapeutic purposes, and also by testing of nuclear weapons (Donya et al., 2014). The radiation exposure can develop



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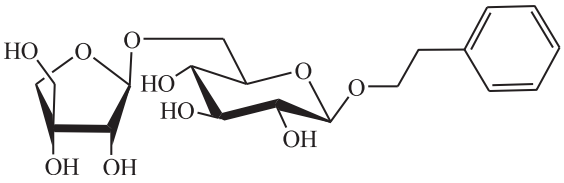

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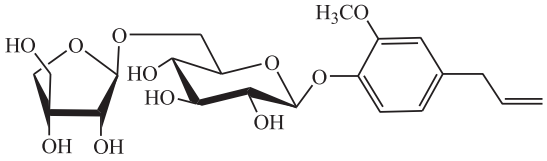

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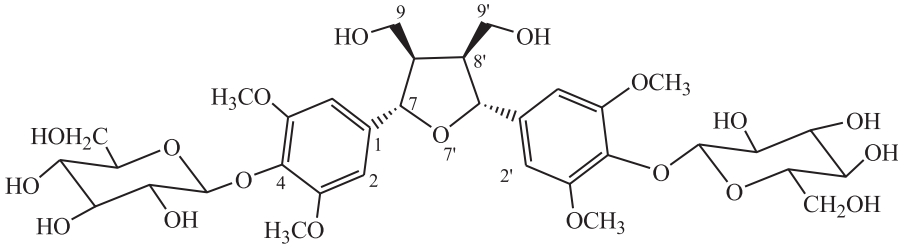

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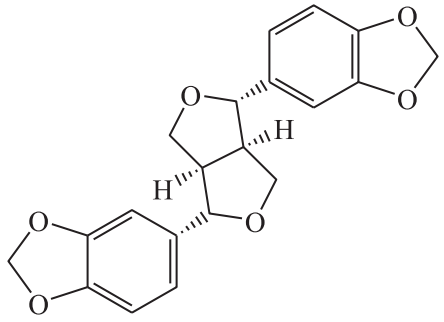

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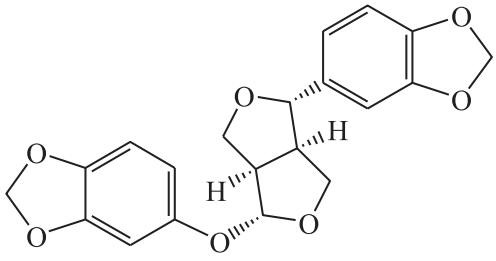

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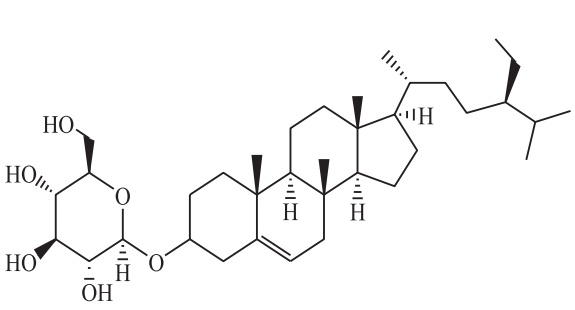
Fig. 2 (*continued*)

mutational changes, immune system alterations, and cancer development in humans (Mamedov et al., 2011). Amifostine (aminothiols) significantly reduced the mortality rate of radio-exposed patients but showed adverse effects. Unfortunately, no safe synthetic radioprotective compounds are available to date; therefore, the investigation of plants has been ongoing for several decades to treat radio exposed patients (Bhandari, 2013). Aqueous-ethanolic extract (1:1, 200 mg/kg) of *T. cordifolia* stem improved the several parameters in treated animals e.g., the spleen weight (49% in irradiated control while 93% in treated), apoptosis (from 19% to 2.8%), DNA fragmentation (from 43% to 20.4%), macrophage adherence (75% in irradiated control while 120% in treated) and macrophage spread size (from 8 μm to 15 μm). Extract also increased the levels of IL-1β, GM-CSF [from 56 pg/mL and 53 pg/mL in irradiated group (control) to 59 pg/mL and 63 pg/mL (treated)] in experimental animals (Singh et al., 2007). Ethanol extract (200 mg/kg b.w.) displayed significant recovery of spleen weight (from 49% to 93%), apoptosis (from 19% to 2.8%) and DNA fragmentation (from 43% to 20.4%). Aqueous extract of *T. cordifolia* showed radioprotective effects in Co-60 gamma irradiated Swiss albino mice. The control group of mice showed sickness, ruffled hair, and diarrhoea hence, died on 14th day. The oral administration of aqueous extract



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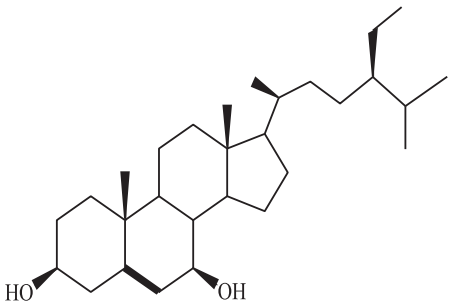

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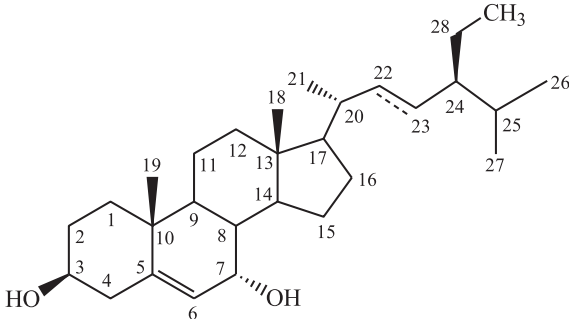

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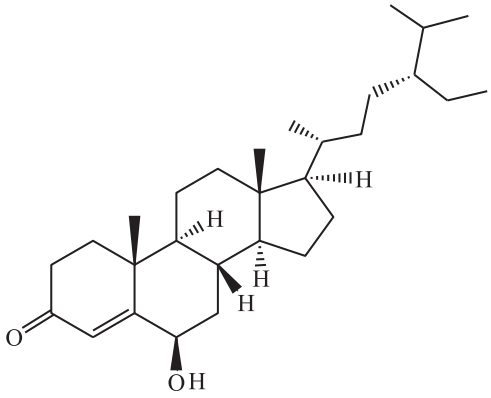

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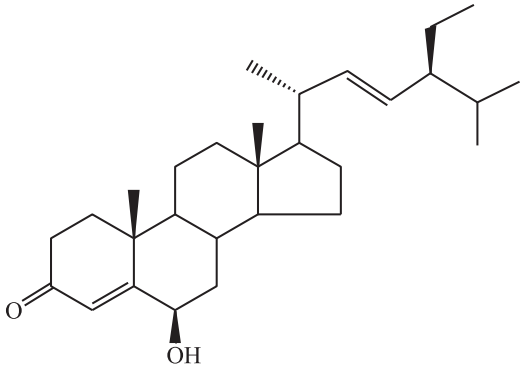

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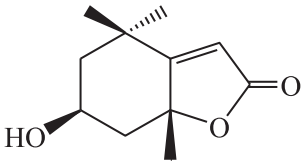


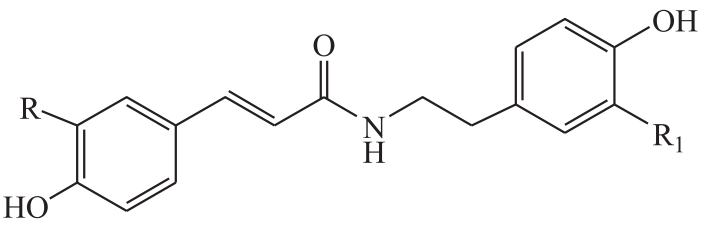
213

Fig. 2 (*continued*)

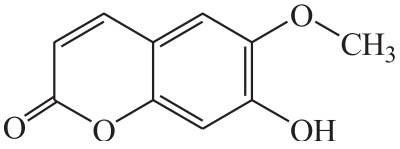
induced more survivability rate in irradiated rats (Pahadiya and Sharma, 2003).

4.7. Hepatoprotective activity

Liver is known as an important organ of human body and has roles in the maintenance, functioning and regulation of homeostasis in all the biochemical pathways of growth, defense mechanisms, digestion, energy supply and reproduction. Hence, it is needed to maintain healthy liver for healthy lifestyles. But sometimes healthy liver is exposed to various exogenous compounds like environmental pollutants, toxic drugs and alcohol which can eventually led to various liver diseases such as hepatocellular, cholestatic, or mixed type of liver disorders (Dange, 2010). The hepatoprotective effect of petroleum ether, ethanolic and aqueous extracts of the leaf, stem and root of *T. cordifolia* were evaluated in carbon tetrachloride-induced liver damage in Wistar albino rats. Out of these tested extracts, the ethanolic extract exhibited significant ($P < 0.01$) hepatoprotective activity in treated animals. Ethanol extract showed significant decrease in the levels of serum bilirubin in treated animals (Kavitha et al., 2011). *T. cordifolia* ethanol extract (100 mg/kg/b. w. for 15 days) showed significant liver hepatoprotective effect in CCl_4 intoxicated rats. A significant decrease in the levels of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transminase, alkaline phosphatase, bilirubin was reported in treated animals (Bishayi et al., 2002). Ethanolic extract of *T. sinensis* roots



220 R = OCH_3, R_1 = OH – *N-trans*-feruloyldopamine



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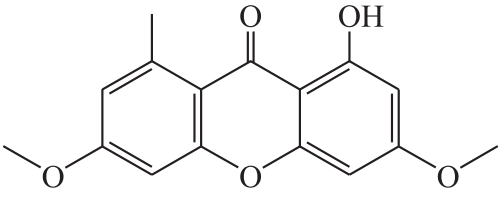

222

Fig. 2 (*continued*)

reduced the sinusoidal dilation along with mild inflammagens in treated animals. This was evident from significant reduction ($P < 0.01$) in serum enzyme levels (Naik et al., 2013).

4.8. Neuroprotective and neuroregenerative activity

Neurodegenerative diseases are caused due to disruptions in functions of the neurons of central nervous system and often resulted in the deterioration of cognitive functions in humans. The deterioration in cognitive functions includes gradual loss in memory, and motor coordination (Adewusi et al., 2010; Nieoullon, 2011). Various plants and plant-derived products have been used in traditional medicine for neuroprotective, memory enhancement, and antiageing purposes (Iriti et al., 2010; Elufioye et al., 2017). Excitotoxicity is connected with the pathological processes of several neurodegenerative diseases viz, trauma, brain injury and memory loss. Butanol extract (20 μg/mL) of *T. cordifolia* stem showed significant ($P < 0.01$) neuroprotective activity against catastrophic glutamate-induced excitotoxicity (Sharma and Kaur, 2018). Ethanolic extract (400 mg/kg) of *T. cordifolia* aerial parts exhibited significant neuroprotective effects by enhancing the levels of dopamine against 6-hydroxy dopamine lesion rat model of Parkinson's disease (Kosaraju et al., 2014).

4.9. Anti-inflammatory activity

Inflammation is the immune system's response to pathogens, damaged cells, toxic constituents, or irradiation, and acts by eliminating harmful stimuli and inducing the healing process (Chen et al., 2018). Non-steroidal drugs are normally used for the treatment of inflammations; however, their prolonged use has adverse side effects (Bhadane et al., 2018). The anti-inflammatory effects of Guduchi Ghana (market product) and aqueous extract of *T. cordifolia* (50 mg/kg, p.o.) were compared in carrageenan-induced paw edema in albino rats. The Guduchi Ghana showed 3-fold higher reduction in paw volume (33.06%) than aqueous extract (11.71%; Patgiri et al., 2014). Similarly, in other study, ethanolic extract (500 mg/kg b. w.) exhibited maximum inhibition of edema (83.21%) in treated male wistar rats. *T. cordifolia* stem extract demonstrated anti-inflammatory effects in both acute (Wesley et al., 2008) and sub-acute inflammations (Ghatpande et al. 2019). Methanolic extract (1 g/kg in a 2 mL volume) of the aerial parts of *T. cordifolia* displayed anti-inflammatory activity against adjuvant arthritis model and bone damage in experimental animals. The antiarthritic activity difference was found significant ($P < 0.05$) in between extract-treated and control groups from day 17 to day 29. Methanolic extract also reduced the activity of IL-1β, TNF-α, IL-6, and IL-17 producing T cells as well as production of chemokines significantly ($P < 0.05$). No major change was reported in IFN-γ levels in animals of control group (Li et al., 2003; Sannegowda et al., 2015). Aqueous extract of *T. cordifolia* protects dopaminergic neurons by inhibiting neuroinflammation in 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine-induced Parkinsonian mouse model. Expression of tumor necrosis factor-α, interleukin-12, pro-inflammatory cytokine genes, and interleukin-1β were reported to be upregulated in 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine-intoxicated mice, while aqueous extract recovered their levels. Moreover, interleukin-10 gene was reported to be downregulated in 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine-intoxicated mice which were significantly recovered by the aqueous extract. The expression of tyrosine hydroxylase was decreased in 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine-intoxicated mice but, its expression was significantly enhanced in aqueous extract treated animals (Birla et al., 2019). Ethanol extract and ethyl acetate fraction of *T. crispa* stem increased the intracellular expressions of cytokine, INF-γ, IL-6, and IL-8 significantly ($P \leq 0.05$) in RAW264.7 macrophages (Abood et al., 2014). Tinocrisposide isolated from *T. crispa* stem (1000 μg/

Table 3 Summary of the pharmacological activities of Indian *Tinospora* species.

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
Antioxidant activity	*T. cordifolia*	Stem	Methanolic	500 mg/kg body weight (b.w.)/ given for 40 days	Lipid peroxidase/catalase/ alloxan-induced diabetic rats/p.o.	Extract increased lipid peroxidase and catalase activities but decreased the superoxide dismutase, glutathione peroxidase activities significantly ($P < 0.01$)	Sivakumar and Rajan (2010)
			Ethanolic	300 mg/kg b. w./ given for 30 days	Catalase and superoxide dismutase/cancer bearing rats/p.o.	Extract significantly reduced catalase and superoxide dismutase (57.05 ± 5.67 and 6.69 ± 0.19) activities in treated animals ($P < 0.01$)	Jayaprakash et al. (2015)
			n-Butanolic	200 µg/mL	DPPH, ABTS, nitric oxide scavenging activity, iron chelating activity/ *in vitro* assays	IC_{50} 14.81 ± 0.53, 29.48 ± 2.23, 58.20 ± 0.70 and 21.17 ± 1.19 µg/mL values reported in DPPH, ABTS, nitric oxide and iron chelating assays	Polu et al. (2017)
	T. sinensis	Stem	Ethanolic	50-150 µg/mL	DPPH, ABTS, DMSO, NO radical scavenging activity, SOD scavenging and lipid peroxidation *in vitro* assays	Extract showed significant antioxidant activity against selected *in vitro* assays (DPPH – IC_{50} = 94.66 ± 0.049 µg/mL; ABST – IC_{50} = 90.44 ± 0.36 µg/mL; DMSO – IC_{50} = 97.99 ± 0.15 µg/mL; NO – IC_{50} = 87.25 ± 2.72 µg/mL; SOD – IC_{50} = 93.72 ± 0.91 µg/mL; lipid peroxidation – IC_{50} = 92.14 ± 0.91 µg/mL)	Jain et al. (2010a)
	T. crispa	Stem	aqueous, methanol and chloroform	10–100 µg/mL	DPPH free radical scavenging assay	Methanol extract significantly increased radical scavenging activity (IC_{50} 12 µg/mL) and radical activity (100%) similar to vitamin	Ibahim et al. (2011)
				0.1–0.5 mg/kg	DPPH free radical scavenging assay	Methanolic extract displayed significant inhibition in DPPH (IC_{50} 0.118 mg/mL) assay	Zulkefli et al. (2013)
				0.0625–1 mg/mL	Metal chelating assay	Methanol extract displayed significant inhibition to metal chelating assays (81.97%)	
				0.0625–1 mg/mL	Reducing power assay	Methanol extract demonstrated antioxidant effect by reducing ferric ion (Fe^{3+}) to ferrous ion (Fe^{2+})	
			Ethanolic	80 µg/mL	DPPH free radical scavenging assay	Extract showed maximum activity (IC_{50} 44.92 ppm)	Warsinah et al. (2020)
Anti-diabetic activity	*T. cordifolia*	Aerial parts	Ethanolic	20 mL/kg b. w./given for 30 days (twice a day) before half an hour of feeding	Antidiabetic effects/alloxan-induced diabetic rats/p.o.	The significant reduction ($P < 0.001$) in levels of blood sugar was observed in treated animals	Kinkar and Patil (2015)

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Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
		Leaf	Magnoflorine, jatrorrhizine, palmatine, and berberine	100 mg/kg b. w.	Wistar rats/ streptozotocin-induced diabetic rats and blood glucose levels/ aldose reductase inhibition assay/ p.o.	Treatment with magnoflorine decreased the serum glucose to normal level similar to that of the standard drug metformin; significant inhibition of aldose reductase activity was also displayed by magnoflorine	Cherku et al. (2019)
		Bark	Methanolic	250 mg/kg b. w./given daily for 100 days	Streptozotocin- induced diabetic rats/male albino Wistar rats/p.o.	Extract significantly decreased the glycosylated hemoglobin level as compared with diabetic control ($P < 0.001$); it also reduced the glucokinase levels but it increased the glucose-6-phoaphatase activity	Rajalakshmi et al. (2009)
		Stem	Aqueous	200 and 400 mg/kg b. w./ given for 30 days	Streptozotocin-induced diabetic albino rats/p.o.	Extract showed significant ($P < 0.05$) anti-diabetic activity in diabetic animals but, did not cause any increase in serum insulin levels or regeneration of pancreatic β cells; it increased hepatic glycogen synthase but decreased glycogen phosphorylase activity	Puranik et al. (2008)
		Root	Aqueous	5.0 g/kg b. w./ given for 6 weeks	Alloxan-induced diabetic albino rats/p.o.	Extract showed maximum hypolipidaemic effect; better than glibenclamide (standard drug)	Prince et al. (1999)
			Ethanolic	5.0 g/kg b. w./ given for 6 weeks	Alloxan-induced diabetic rats/ Swiss albino rats/p.o.	Extract resulted in a significant reduction in blood and urine glucose levels of serum and tissues; extract also prevented a decrease in body weight	Prince and Menon (2003)
		Root, shoot and leaf	Palmatine, jatrorrhizine and magnoflorine	40 mg/kg b. w.	Insulin-mimicking and insulin-releasing effect *in vitro* (rat pancreatic β-cell line, RINm5F) and *in vivo*/p.o.	Palmatine, jatrorrhizine and magnoflorine significantly reduced serum glucose levels and contained the increase in blood glucose levels	Patel and Mishra (2011)
	T. sinensis	Flowers	Ethanolic	200 mg/kg b. w./given per day	Male wistar rats/ hydrogenated groundnut oil induced hypercholesterolemia/p.o.	Extract altered the improper metabolic profile and it was leads to hypolipidemia significantly ($P < 0.05$)	Sandhyarani and Kumar (2014a)
			Aqueous	100 mg/kg b. w./given per day	Male Wistar rats/ hydrogenated groundnut oil induced hyper cholesterolemia/ p.o.	Treatment with extract altered the rearranged metabolic profile and was effective in producing hypolipidemia ($P < 0.05$)	Kumar and Gandhimathi (2014)
		Leaf	Ethyl acetate	200 mg/kg b. w.	Wistar rats of either sex/alloxan induced diabetic rats/p.o.	Extract showed significant ($P < 0.001$) antidiabetic activity (149 ± 0.66)	Pimpriker et al. (2009)

Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
	T. crispa	Stem	Aqueous extract	4 g/L extract dissolved in drinking water	Alloxan-diabetic male Wistar albino rats model	The extract reduced the levels of fasting blood glucose and higher serum insulin	Noor et al. (1989)
				4 g/L extract dissolved in drinking water	Alloxan-diabetic rats; acute intravenous treatment with the extract (50 mg/kg)	Showed improvement in glucose tolerance; acute treatment caused an enhancement in plasma insulin levels	Noor and Ashcroft (1989)
				1 g/kg suspended in 10% Tween 80	Diabetic rats; p.o.	Significantly reduced the levels of glucose in diabetic rats	Hassani et al. (2016)
			9.5% ethanolic extract	250, and 500 mg/kg bw	Normoglycemic and alloxan-diabetic male Sprague-dawley rats model; p.o.	The blood sugar level of diabetic rats decreased after receiving the extract (15.42%)	Anulukanapakorn et al. (2012)
			borapetosides A and C from ethanolic extract	5 mg/kg, ip	Type 1 and Type 2 diabetic induced ICR mice. Type 1 induced by streptozotocin and type 2 induced by fat-rich chow and 20% fructose-sweetened water	Borapetosides A and C reduced the levels of plasma glucose in normal and streptozotocin-induced type 1 diabetic mice. Borapetoside C increased glucose utilization in peripheral tissues but, reduced hepatic gluconeogenesis	Lam et al. (2012)
			Borapetoside A	10 mg/kg	Streptozotocin-induced type 1 diabetes mellitus, diet-induced type 2 diabetes mellitus	Increased the levels of insulin but decreased the levels of blood glucose significantly ($P < 0.05$).	Ruan et al. (2013)
			Borapetoside C	5 mg/kg	Type 2 diabetes mellitus; twice daily a for 7 days	Attenuated the increased plasma glucose induced by oral glucose in normal and type 2 diabetes mellitus mice	Ruan et al. (2012)
			Borapetoside E	10 mg/kg	High fat diet-induced obese mice	Compound significantly improved hyperglycemia, insulin resistance, hepatic steatosis, hyperlipidemia, and oxygen consumption in obese mice	Xu et al. (2017b)
			Borapetol B	10 µg/100 g b. w.	Blood glucose and plasma insulin in normoglycemic Wistar and type 2 diabetic Goto-Kakizaki rats were determined/ glucose tolerance test; p.o.	Compound reduced the levels of blood glucose significantly ($P < 0.001$) but enhanced the levels of insulin in treated normoglycemic Wistar and type 2 diabetic Goto-Kakizaki rats	Lokman et al. (2013)
Anti-arthritic activity	*T. cordifolia*	Aerial parts	Methanolic	1 g/kg/2 mL volume	Male Lewis rats/ adjuvant arthritis/p.o.	Extract suppressed arthritic inflammation and damage in bone and cartilage significantly ($P < 0.05$); extract also altered the levels of mediators of bone remodeling which favors of anti-osteoclastic activity ($P < 0.05$)	Sannegowda et al. (2015)

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Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
		Stem bark	Methanol extract	500 µg/mL	*In vitro*, BSA denaturation essay	Extract showed significant minimum protein denaturation (43%); similarly, the diclofenac sodium showed significant inhibition (88.8 ± 3.4%) at 500 µg/mL concentration	Ramya and Maheswari (2016)
Anti-stress activity	*T. cordifolia*	Aerial parts	Aqueous	200 mg/kg b. w.	male Sprague Dawley rats/ cold water swim stress method/p.o.	Extract decreased the stress levels by inducing the levels of lipid peroxide, serum glucose, and triglycerides significantly ($P < 0.005$)	Biswas and Saha (2015)
		Stem	Ethanolic	100 mg/kg b. w.	Sprague Dawley male rats/cold water swim stress method/p.o.	Extract of both species (*T. cordifolia* and *Centella asiatica*) in combination demonstrated antistress activity	Sarma et al. (1996)
		Fresh leaves	-	50 mg/kg b.w. and 10 mg/kg	Swiss albino mice/ forced swim test/ tail suspension test/	Fresh leaves and imipramine showed significant decrease in the immobility period (forced swim and tail suspension tests)	Kalabharathi et al. (2014)
	T. sinensis	Stem	Aqueous	1000 mg/kg b. w.	Adult swiss albino mice; anoxia stress tolerance, swimming endurance test, cold resistant stress/p.o.	Extract increased the anoxia stress tolerance at the end of 1st, 2nd and 3rd weeks of treatment significantly ($P < 0.01$); it also reduced the elevated levels of serum biochemical parameters, blood cell count, and prevented alterations in the weight of the liver, adrenal gland	Sharma et al. (2007)
Anticancer/ antitumor activity	*T. cordifolia*	Aerial parts	Palmatine	200 mg/kg b. w./given daily for 16 weeks	Swiss albino mice; 7,12-dimethylbenz(a)anthracene-induced skin cancer model in mice/p.o.	Palmatine reduced the tumor size significantly ($P < 0.05$); compound also increased the levels of glutathione, superoxide dismutase, and catalase in the skin of treated animals ($P < 0.05$)	Ali and Dixit (2013)
		Stem	Methanolic	200 mg/kg b. w./given daily for 5 days	BALB/c mice/antitumor assay/i.p.	Extract increased total white blood cell count, bone marrow cells (18.16×106/femur) and α-esterase positive cells (1423/4000 cells) significantly ($P < 0.001$)	Mathew and Kuttan (1999)
			Tinocordiside and yangambin	100 µg concentration	KB and CHOK-1 cells/*in vitro* assay	Tinocordiside demonstrated moderate activity against KB and CHOK-1 cells while yangambin found active against KB cells only	Bala et al. (2015a)
			Methanolic	100 µg/mL	MB-231 human breast cancer cell line/trypan blue dye exclusion assay/methyl tetrazolium *in vitro* assay	Extract showed significant anticancer activity against MDA-MB-231 human breast cancer cell line (IC_{50} 59 ± 4.05 µg/mL in 0.25% DMSO)	Ahmad et al. (2015)

Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
			Dichloromethane	100 mg/kg b. w./given once a daily for 9 days	Female Swiss albino mice/ Ehrlich ascites carcinoma implant assay/p. o.	Maximum anticancer activity was reported at III phase (long-term survivors were 17%)	Jagetia and Rao (2006a)
			Clerodane furano diterpene glycoside (TC-2)	1, 10, 30 and 50 µM for 24 h	HCT116 cells (colon cancer)/ *in vitro* assay	Compound showed significant anticancer activity against cancer cells [IC_{50} 8 µM (HCT116)]	Sharma et al. (2018)
	T. sinensis	Aerial parts	Ethanolic	1000 µg/mL	Human melanoma cancer cell line (A 375) and skin cancer cell line (A 431)/microculture tetrazolium assay/*in vitro*	Extract showed significant cytotoxicity (IC_{50} 49.87 µg/mL and 112.54 µg/mL) against A375 and A 431 cancer cells, respectively	Punitha et al. (2012)
	T. crispa	Stem	Aqueous	100 µg/mL	MCF-7 breast cancer cell lines; MTT assay	Cell viability significantly decreased (IC_{50} 42.75 µg/mL)	Ibahim et al. (2010)
				200 µg/mL	Human cancer cell lines: MCF-7; HeLa; Caov-3; HepG2	IC_{50} values - MCF-7: 107 µg/mL; HeLa: 165 µg/mL; Caov-3: 100 µg/mL; HepG2: 165 µg/mL	Amom et al. (2008)
			Tinocrisposide	100 µg/mL	H1299 and MCF-7 cell lines; MTT assay	H1299 cell line viability decreased significantly (IC_{50} 70.9 µg/mL); MCF-7 cell line (IC_{50} > 100 µg/mL)	Adnan et al. (2016).
			Methanolic	0.03- 1 mg/mL	HL-60 leukemic cells, HepG2 hepatoma cells and Hep3B hepatoma cells	Inhibition with IC_{50} as follows: HL-60: 0.12 mg/mL; HepG2: 1.03 mg/mL; Hep3B: 0.16 mg/mL	Sinchaikul et al. (2007)
		Whole plant	Ethanolic	50.0 mg/mL	Head and neck squamous cell carcinoma cell lines (HN22 and HSC-3 cells); MTT assay	Extract significantly reduced the cell viability (50%) in HN22 cells and (60%) in HSC-3 cells	Phienwej et al. (2015)
			Aqueous, methanol and chloroform	10–100 µg/mL (each extract)	MCF-7, MDA-MB-231, HeLa, and 3T3 fibroblast cells	All extracts showed dose-dependent antiproliferative activity	Ibahim et al. (2011)
Radioprotective activity	*T. cordifolia*	Stem	n-butanol fraction	120 mg/kg b. w./given up to 15th day	Wistar albino mice/endogenous spleen CFU assay /MN assay/i.p.	Extract (120 mg/kg) produced significant protection against radiation in terms of increased survival rate, body weight retention, hematological parameters ($P < 0.01$) but, decreased MN expression ($P < 0.01$)	Patel et al. (2013b)
			Aqueous	10 mg/kg b. w./given per day	Swiss albino mice/ radiation (8 Gy) exposure/p.o.	Extract did not show mortality until day 13 and 50% of the animals survived until day 30	Pahadiya and Sharma (2003)
			Hydroalcoholic	200 mg/kg b. w.	Swiss albino strain 'A' male mice/ endogenous spleen CFU assay/ micronucleus assay/i.p.	Extract rendered significantly higher ($P < 0.05$) CFU counts in comparison to the corresponding irradiated groups	Goel et al. (2004)
			Polysaccharide preparation	4.5 mg/mL	*Saccharomyces cerevisiae* X2180 strain as the *in vivo* test model/ catalase and superoxide dismutase	The preparation did not enhance the expression of the protective enzymes, catalase and superoxide dismutase in	Subramanian et al. (2003)

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Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
					assay	the yeast cells	
		Aerial root	Hydroalcoholic	2000 mg/kgb. w./given once a day for 5 consecutive days	Swiss albino mice (BALB "c" strain)/ lipid peroxidation and glutathione assays/p.o.	The levels of lipid peroxidase were higher in irradiated controls as compared to experimental group (21.42% higher than normal); steady decreasing pattern was followed by ovarian glutathione level up to day 7 in both irradiated control and experimental group	Sharma (2015)
		Root	Aqueous	75 mg/kg b. w./given once a daily for 5 consecutive days	7.5 Gy gamma radiation exposure/ Swiss albino mice/p.o.	Extract administration before irradiation significantly ameliorated radiation induced elevation in lipid peroxidation and decline in glutathione concentration in testes	Sharma et al. (2011)
Hepatoprotective activity	*T. cordifolia*	Stem	Aqueous	2 mL/100 g/ given twice daily for 10, 20 and 30 days	Swiss albino Wistar rats/CCl_4 induced hepatotoxicity/p.o.	Extract administration for 20 days showed significant ($P < 0.05$) limitation of serum bilirubin rise	Kumar et al. (2013)
		Stem bark	Aqueous	250 mg/kg b. w.	Wistar albino male rats/CCl_4 (2:5, v/v in paraffin oil) induced acute liver damage/i.p.	Extract increased superoxide dismutase, catalase, peroxidase levels but decreased lipid peroxidation levels	Singh et al. (2010)
		Stem and leaves	Aqueous	400 mg/kg b. w./given once a daily for 30 days	Male Swiss albino mice/ lead-treated / red blood corpuscles, packed cell volume and hemoglobin value/p.o.	The effects of lead were prevented by concurrent daily administration extract; protected against lead intoxication	Sharma and Pandey (2010a)
			Ethanolic	400 mg/kg b. w./given once a daily for 30 days	Male Swiss albino mice/SOD and CAT assays/lead nitrate induced damage/p.o.	Aqueous extract of stem and leaves along with the lead nitrate increased the activities of catalase but decreased the levels of aspartate aminotransferase, and alanine aminotransferase enzymes	Sharma and Pandey (2010b)
		Root	Aqueous	100 mg/kg b. w./given once a daily for 45 days	Wistar rats/streptozotocin induced liver injury in diabetic rats /p.o.	Significant elevations ($P < 0.001$) in serum alanine aminotransferase and aspartate aminotransferase were reported in the diabetic control rats and after treatment with extract, their serum levels were close to those in the normal control rats	Dhanush et al. (2013)
	T. sinensis	Root	Ethanol	300 mg/kg b. w./ given for 8 days	Wistar albino rats/ CCl_4 induced Hepatotoxicity/p.o.	Extract reduced sinusoidal dilation along with mild inflammagens. Significant reduction in ($P < 0.001$) in serum enzyme levels was reported in treated animals	Naik et al. (2013)

Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
Neuroprotective and neuroregenerative activity	*T. cordifolia*	Stem	Butanol extract	20 µg/mL concentration	Neuronal markers (MAP-2, GAP-43, NF200) and anti-apoptotic marker (Bcl-xL); *in vitro* assay/wound scratch and gelatin zymogram assay	Extract showed neuroprotective and neuroregenerative potential against catastrophic consequences of glutamate-mediated excitotoxicity	Sharma and Kaur (2018)
		Aerial parts	Ethanolic	400 mg/kg b. w./ given once a daily for 30 days	Adult male Wistar rats/6-hydroxy dopamine lesion rat model of Parkinson's disease/p.o.	Extract exhibited significant neuroprotection by increasing the dopamine levels (1.96 ± 0.20 and 2.45 ± 0.40 ng/mg of protein) and complex I activity (77.14 ± 0.89 and 78.50 ± 0.96 nmol/min/mg of protein); iron asymmetry ratio was also significantly attenuated by extract (1.11 ± 0.15)	Kosaraju et al. (2014)
		Flower	Ethanolic	400 mg/kg b.w./ given once a daily (in the morning) for 14 days	Adult male Wistar rat/ lipopolysaccharide-induced neuroinflammation/p.o.	Extract significantly ($P < 0.001$) reduced the body weight, locomotor activity, latency period in passive avoidance test; also decreased the anti-oxidant levels of glutathione, SOD and CAT	Prakash et al. (2017)
Anti-inflammatory activity	*T. cordifolia*	Stem	Chloroform	2000 mg/kg b. w.	RAW264.7 macrophages/*in vitro*/ Swiss albino rats/carrageenan-induced paw model/p.o.	Extract suppressed the lipopolysaccharide-induced upregulation of pro-inflammatory biomarkers activity without hampering of cyclooxygenase 1 activity; the extract showed significant decrease in volume of paw oedema ($P < 0.05$)	Philip et al. (2018)
			Aqueous	120 mg/kg b. w.	Male Swiss albino rats/carrageenan-induced paw edema model/p.o.	Extract showed significant reduction in paw volume ($P < 0.05$)	Deepika et al. (2016)
		Leaf	Methanolic	400 µg/mL	*In vitro* study - lipoxygenase inhibition and protein denaturation assay	Extract inhibited the lipoxygenase activity (IC_{50} 389.3 µg/ml); maximum inhibition of heat induced protein denaturation (75%; IC_{50} 237.6 µg/ml)	Shwetha et al. (2016)
	T. sinensis	Whole plant	Diosgenin	400 µg/kg b. w.	Adult albino rats/ carrageenan-induced paw oedema/p.o.	Diosgenin showed maximum anti-inflammatory activity (82.25%) as compared to the indomethacin (82.01%); significantly ($P < 0.01$) reduced the mean paw edema volume at 3 h of carrageenan injection	Punitha et al. (2013)
	T. crispa	Stem	Aqueous and	600 µg/mL	TNF-α stimulated inflammation	Both extracts displayed significant	Kamarazaman

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Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
			methanolic		in human umbilical vein endothelial cells	suppression of signaling molecules ICAM-1, VCAM-1, MCP-1, M-CSF	et al. (2012a)
			Aqueous and methanolic	600 µg/mL	H_2O_2 and tumor necrosis factor–α-induced inflammation in human umbilical vein endothelial cells; MTT assay	Aqueous extract showed an inhibition on TNF-α induced release of ICAM-1, VCAM-1 signaling molecule whereas nitric oxide secretion was enhanced	Kamarazaman et al. (2012b)
			Methanolic	300 mg/kg	Carrageenan induced inflammation in Sprague-dawley rats; i.p.	Extract significantly suppressed the development of edema	Hipol et al. (2012)
			Tinocrisposide and freeze-dried aqueous extract	1000 µg/mL	*In vitro* hemolytic and anti-inflammatory test; membrane stabilization assay	Tinocrisposide and freeze-dried aqueous extract increased the membrane stability of lysosome cell that was equal to physiological property with erythrocytes and it did not show hemolytic activity	Adnan et al. (2019)
			Ethanolic	300 mg/kg bw	Carrageenan-induced inflammation in Sprague-Dawley rats	Extract significantly ($P < 0.05$) inhibited the development of paw edema	Sulaiman et al. (2008)
Immunomodulatory activity	*T. cordifolia*	Stem	Methanolic and aqueous extract	100 mg/kg b. w.	BALB/c mice/ murine macrophage cell line J774/p.o.	Aqueous extract produced 86.67 ± 13.48 pg/mL of IFN-γ, respectively, whereas methanol extract produced 144.0 ± 11.02 pg/mL of IFN-γ	Alsuhaibani and Khan (2017)
			Aqueous	100 mg/kg b. w./given for 10 days	Swiss albino mice/ agar colony assay/ p.o.	Extract increased the higher number of total white cell count in treated mice (14237 ± 1236); 82% increase in number was statistically found significant ($P < 0.01$)	Thatte et al. (1994)
				80 µg/mL	Macrophage J774A.1 cell line/ viability, phagocytosis and pinocytosis and red blood cell lysis assays	Extract increased phagocytosis and pinocytosis *in vitro*; macrophages demonstrated an increase in phagocytosis to non-infective microbes and live *Escherichia coli*	More and Pai (2017)
				50 mg/kg	Charles Foster strain albino rats/ haemagglutination antibody titre method for humoral immunity and footpad swelling method for cell mediated immunity/p.o.	Increase in antibody titre (22.34%), weight of body (31.79%), spleen (21.86%) and thymus (16.06%) observed in treated animals; significant ($P < 0.05$) decrease in paw edema observed in treated group	Umretia et al. (2013)
			Syringin and cordiol	500 mg/kg b. w.	Guinea pig/*in vitro*/ immunohaemolysis/p.o.	Both compounds significantly ($P < 0.01$) increased the number of IgG antibodies in serum of treated	Kapil and Sharma (1997)

Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
						pigs	
			Cordifolioside A	0.1–2.5 µg/mL	Human neutrophil cells/NBT, NO and chemiluminescence assays/ *in vitro*	The compound showed significant enhancement in phagocytic activity and increase in nitric oxide and reactive oxygen species generation	Sharma et al. (2012)
			Guduchi ImP (25 kDa protein)	60 µg/mL	Female BALB/c mice/intranasal administration on days 1 till day 42/ mitogenic activity	Guduchi ImP administration displayed a significant increase in anti-guduchi ImP IgG (5-7-fold) on day 50	Aranha and Venkatesh (2020)
			Guduchi Satwa (Neem –Guduchi; *Azadirachta indica-T. cordifolia*) extract	300 mg/kg b. w.	Male Wistar rats/ neutrophil adhesion test/p.o.	Guduchi Satwa showed potent immunomodulatory effects in treated animals ($P < 0.01$) than control	Narkhede et al. (2014)
			Aqueous extract	100 mg/kg b.w.	Mice/ cyclophosphamide-induced leukopenia/p.o.	Extract exhibited 60% survival rate; extract also rejuvenate the weakened immune system and eliminate systemic candidiasis	Alrumaihi et al. (2019)
			Ethanolic extract	100 mg/kg b.w.	Male Wister rats/ cyclophosphamide-induced thiobabituric acid assay/p.o.	Extract increased the level of liver mitochondrial enzymes like GSH, CAT and SOD but decreased the level of LPO in liver in treated animals; also enhanced the concentration of melatonin in pineal gland and the level of cytokines (IL-2, IL-10 and TNF-α)	Aher and Wahi (2012)
	T. sinensis	Stem	Aqueous	100 mg/kg (in 0.1% w/v CMC)	Male Wistar rats/ cyclophosphamide-induced anemia/p.o.	Extract showed significant effectivity	Manjrekar et al. (2000), Haque et al. (2017)
	T. crispa		Ethanolic and fractions	1000 µg/mL	Intracellular cytokine determination in LPS-stimulated murine macrophage cell line RAW264.7; MTT proliferation assay	Extract and fractions induced RAW264.7 cell viability and intracellular expressions of cytokine, INF-γ, IL-6, and IL-8	Abood et al. (2014)
			Ethanolic extract and magnoflorine and syringin	12.5 µg/mL	Chemotaxis, phagocytosis, production of inflammatory mediators ROS, NO, PGE2 and pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and MCP-1) on RAW 264.7 macrophages	Ethanolic extract and magnoflorine showed significant stimulatory effects on the chemotaxis, phagocytic activity, ROS and NO productions and the secretions of IL-1β, TNF-α, IL6, PGE2 and MCP-1	Ahmad et al. (2018)
			Ethanolic (80%) and syringin and magnoflorine	4.68 to 75 µg/mL	Immunomodulatory effect in lipopolysaccharide (LPS)-induced U937 human macrophages	Extract stimulated the MyD88-dependent signaling pathways by upregulating the various immune inflammatory related parameters	Haque et al. (2020)

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Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
Wound healing activity	*T. cordifolia*	Root	Ointment (10% ointment -10 g methanolic extract incorporated with 100 g petroleum jelly B.P.)	Extract ointment applied once a daily	Albino mice/ excision and incision wound/ topical administration	Ointment showed significant ($P < 0.01$) wound healing activity in albino mice	Nema et al. (2012)
		Leaf	Ethanolic	300 mg/kg b. w.	Wistar strain albino rats/ excision and incision wound study/granuloma study/p.o.	Extract showed significant increase (8.917 ±0.13 µg) in levels of hydroxyproline in treated animals (6.2 ± 0.10 µg)	Ramachandra et al. (2011)
	T. crispa	Stem	Ethanolic and topical ointment	-	Alloxan monohydrate-induced diabetic albino mice; wound incision model; i.p.	Extract significantly reduced the blood glucose level by almost fifty percent after fourteen days; epithelialization time was increased	Arcueno et al. (2015)
			Methanolic extract and chloroform fraction ointment	100 mg/kg per day	Albino rats; wound excision model;	Treated animals showed high percentage of wound closure area which was similar to the values of standard drug treated group	Vijendren et al. (2017)
Antimicrobial activity	*T. cordifolia*	Stem	Aqueous	50 mg/mL per hole	*Enterococcus faecalis, Salmonella typhi, S. pneumoniae, E. coli*/agar well diffusion assay/*in vitro*	Extract exhibited maximum zone of inhibition against *E. faecalis* (23 mm) and *S. pneumoniae* (24 mm)	Nageswari et al. (2016)
			Ethanolic	0.2 mL/disc	*E. coli, Proteus vulgaris, E. faecalis, S. typhi, S. aureus* and *Serratia marcescens*/ agar disc diffusion assay	Extract exhibited significant antibacterial activity against *P. vulgaris, E. coli* and moderate activity against *E. faecalis*	Jeyachandran et al. (2003)
			Methanolic	1 mg/10 mL	*S. aureus, E. coli, P. aeruginosa, S. typhimurium* and *C. Albicans*/agar well diffusion assay	Extract found active as follows: *S. aureus* (20 mm) *E. coli* (19 mm), *S. typhimurium* (19 mm), *P. aeruginosa* (17 mm) and *C. albicans* (19 mm)	Singh and Saxena (2016)
			Chloroform	400 µg/mL	*E. coli, K. pneumoniae, P. vulgaris, P. aeruginosa*/ agar well diffusion assay	Extract showed maximum zone of inhibition against *P. aeruginosa* and moderate inhibition exhibited against *K. pneumoniae* and *E. coli*	Shanthi and Nelson (2013)
		Leaf	Methanolic	30µL/disc	*E. coli*/agar disc diffusion assay	Extract showed significant inhibition to *E. coli* (0.8 mm)	Prajwala et al. (2018)
		Aerial parts	Ethanolic	40 µL at 2% concentration	*S. mutans*/agar diffusion assay	Maximum inhibition zone (19 mm) recorded against bacteria	Agarwal et al. (2019)
	T. crispa	Roots	Ethanolic, methanolic, aqueous and chloroform	50 µg/disc	*S. pneumoniae*, *E. coli*, and *C. albicans*; disc diffusion assay	Ethanolic extract showed maximum inhibition (3.6 ± 0.2 mm) against *E. coli*	Mohammed et al. (2012)
		Stem	Chloroform, methanol and aqueous	1 mg/disc; 50 µL for MIC	Bacteria - *Bacillus cereus, B. subtilis, S. aureus, E. coli, P. aeruginosa* and *S. typhimurium*;	Methanol extract showed maximum inhibition (4.0 ± 0.5 mm for *B. cereus* and 8.3 ± 0.6 mm for *S. aureus*) to	Awang et al. (2020)

Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
					fungi – *A. niger*, *C. albicans* and *S. cerevisiae*; disc diffusion method; MIC and MBC assays	bacterial species; also displayed significant MIC and MBC	
Antileishmanial activity	*T. sinensis*	Stem	Ethanolic	500 mg/kg b. w./day x 5 oral dose	Hamsters/IC_{50} values analysis assay; p.o.	Extract exhibited an appreciable activity against promastigotes (IC_{50} 37.6 ± 6.2 μg/mL) and intracellular amastigotes (IC_{50} 29.8 ± 3.4 μg/mL); in hamsters, it showed 76.2 ± 9.2% inhibition	Singh et al. (2008)
			3-hydroxy-2,9,11-trimethoxy-5,6-dihydro isoquino [3,2-a] isoquinolinylium	100 mg/mL	Visceral leishmaniasis/*in vitro* antileishmanial activity	Compound resulted in 96.6% inhibition of promastigotes and amastigotes (86.6%)	Maurya et al. (2009)
Analgesic activity	*T. cordifolia*	Stem	"Guduchi" capsules (from the Himalaya Drug Co., Bangalore, India)	300 mg/kg b. w.	Swiss albino rats (male and female)/ hot plate and abdominal writhing methods/p.o.	Extract produced significant analgesia ($P < 0.001$ after 120 minutes	Goel et al. (2014)
			Water and methanol (30/70).	300 mg/kg b. w.	Male and female Swiss mice/acetic acid-induced writhing and thermal tests (hot plate and tail-flick tests)/ p.o.	Extract significantly inhibited the number of writhes in dose-dependent manner; aqueous -methanolic extract showed better results in hot plate-induced analgesia test	Hussain et al. (2015)
			Aqueous	600 mg/kg b. w.	Adult Wistar rats/ hot plate and tail immersion method, acetic acid-induced writhing/p.o.	Extract showed significant ($P < 0.05$) analgesic effects when compared with control group	Gupta et al. (2013)
		Leaf	Aqueous	200 mg/kg b. w.	Swiss albino mice and Wistar rats/ Eddy's hot plate method/p.o.	Extract showed significant increase in the reaction time (pain threshold; $P < 0.001$)	Siddalinga et al. (2011)
	T. sinensis	Leaf	Ethanolic	500 mg/kg b. w.	Adult male Wister rats/tail flick and acetic acid induced writhing tests/p.o.	Extract showed significant ($P < 0.001$) increase in latency time	Sandhyarani, and Kumar (2014b)
	T. crispa	Stem	Methanolic extract, petroleum ether and chloroform fraction	400 mg/kg b. w.	Swiss-albino mice; acetic acid induce writing method; p.o.	Petroleum ether fraction displayed significant analgesic effect (51.94%) when compared with standard (65.12%)	Islam et al. (2014)
		Whole plant	Methanolic, n-hexane and chloroform	400 mg/kg b. w.	Swiss albino mice; acetic acid-induced writhing and formalin-induced paw licking tests; p.o.	Hexane fraction showed significant antinociceptive effect (56.28%; $P < 0.01$) in acetic acid-induced writhing test; chloroform fraction displayed significant inhibition in the late phase (64.36%) of formalin-induced paw licking test	Rakib et al. (2020b)

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Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
Anti-psychotic/ antiepileptic activity	*T. cordifolia*	Stem	Aqueous ethanol (50:50)	500 mg/kg b. w.	Female Wistar albino mice/ amphetamine induced hyperactivity /p.o.	Extract did not show significant antipsychotic activity	Jain et al. (2010b)
		Stem	Methanolic	2000 mg/kg b. w.	Wistar albino rats/ haloperidol induced hyperprolactinemia/sulpiride induced hyperprolactinemia/p.o.	Significant ($P < 0.05$) increase in serum prolactin level and decrease in dopamine level reported in the extract treated animals	Tiwari et al. (2019)
Antiulcer activity	*T. cordifolia*	Stem	Aqueous	400 mg/kg b. w.	Albino Wistar rats/ aspirin induced and ethanol induced gastric ulcer/p.o.	In pylorus ligated rats, the extract demonstrated significant ($P < 0.01$) reduction in gastric volume, total acidity and ulcer index as compared to control	Chandan et al. (2013)
			Ethanolic	600 mg/kg b. w.	Albino Wistar rats/ aspirin and ethanol-induced ulcer/p.o.	Extract showed significant ($P < 0.05$) protection in ethanol-induced gastric lesions	Khan et al. (2015)
			Epoxy clerodane diterpene	50 mg/kg b. w.	Albino Wistar rats/ indomethacin-induced gastric ulcer/p.o.	Compound exerted its antiulcer activity by reinforcement of defensive elements and diminishing the offensive elements	Antonisamy et al. (2014)
		Stem bark	Ethanolic	500 mg/kg b. w.	Albino Wistar rats/ pylorus ligation-induced ulcer and ethanol-induced ulcer/p.o.	Extracts showed reduction in ulcer index, gastric volume, total acidity but, displayed an increase in pH of gastric content in both the models significantly ($P < 0.01$)	Kaur et al. (2014)
		Whole plant	Ethanolic	400 mg/kg b. w.	Male Wistar rats/ pylorus-, stress-, ibuprofen-induced ulcers/p.o.	Extract significantly ($P < 0.05$) reduced the ulcer index; its effect was significantly ($P < 0.05$) lesser than that of famotidine	Bairy et al. (2001)
	T. sinensis	Stem	Aqueous and ethanolic	500 mg/kg b. w. (each)	Adult Swiss albino mice and Wistar rats/pylorus ligation induced gastric ulcers and water immersion stress induced ulcer/p.o.	Extract reduced ulcer index ($P < 0.001$) significantly in all the models	Khayum et al. (2009)
		Leaf	Ethanolic	300 mg/kg b. w.	Adult Swiss albino rats/pylorus ligation induced ulcer and ethanol induced gastric ulcer/p.o.	Extract showed significant ($P < 0.05$) reduction in gastric volume, free acidity and ulcer index as compared to control	Avanapu et al. (2014)
Antifertility activity	*T. cordifolia*	Stem	Ethanolic	100 mg/rat/day given for 60 days	Male albino Wistar rats/sperm motility and density/hormonal assay/p.o.	Extract reduced the formation of round spermatids (73.12%); Leydig cell nuclear area and mature Leydig cell numbers in treated rats significantly ($P < 0.001$)	Gupta and Sharma (2003)
			Aqueous	100 mg/kg b.	Adult Wistar albino rats/	Extract caused a significant	Ittiavirah and

Table 3 (*continued*)

Pharmacological activity	Plant species	Plant parts used	Extract/compounds tested	Concentration/dose tested	Model tested/mode of administration	Study outcomes	References
				w./given for 60 days	antifertility and antiandrogenic activity, sperm motility/p.o.	reduction in average litter size, sperm count, and number of viable and motile sperm	Habeeb Rahman (2013)
		Roots	Methanolic	100 mg/kg b. w./given for 5 days	Fertile female albino rats/fertility test/p.o.	Results revealed that extract exhibit antifertility activity	Fatima Rose et al. (2010)
Antimalarial activity	*T. crispa*	Stem	Methanolic	200 mg/kg b. w.	Female ICR mice; chloroquine-sensitive *Plasmodium berghei* ANKA (PbANKA) strain; p.o.	Extract showed significant inhibitory effect on the parasite (50%; $P < 0.01$)	Niljan et al. (2014)
			Methanolic extract and fractions (F1 – F8)	100 mg/kg b. w.	Male ICR mice; chloroquine-sensitive *P. berghei* ANKA (PbANKA) strain; p.o.	Methanol extract and fraction F5 showed the maximum parasitemia inhibitory effects	Lee et al. (2020)
			Methanolic	2.0 mg/mL	*P. falciparum* 3D7 strain	Extract showed antiplasmodium activity (IC_{50} 0.29 mg/mL) with reducing parasitemia degree (56.83%) after 72 h of incubation	Ihwan et al. (2014)
			Aqueous	500 mg/kg	Female ICR mice; chloroquine-sensitive *P. berghei* strain ANKA (PbANKA)	Extract decreased parasitemia significantly ($P < 0.01$) in infected mice	Somsak et al. (2015)
			Ethanolic	80 mg/kg	Female ICR mice; *P. yoeli* 17X (lethal) strain - infected erythrocytes	Extract decreased parasitemia significantly in infected mice on day 20; extract showed dose-dependent antimalarial activity	Rungruang and Boonmars, (2009)
	T. baenzigeri		Aqueous	500 mg/kg b. w.	Female ICR mice; chloroquine-sensitive *P. berghei* ANKA strain (PbANKA); p.o.	Extract significantly ($P < 0.01$) suppressed parasitemia (74.95% inhibition); extract did not show any toxicity at 2,000 mg/kg; extract showed markedly prolonged mean survival time similar to the chloroquine-treated group	Ounjaijean et al. (2019)

mL) increased the membrane stability of lysosome cell that was equal to physiological property with erythrocytes and it did not show hemolytic activity (Adnan et al., 2019). Diosgenin isolated from *T. sinenesis* whole plant (400 μg/kg) showed maximum anti-inflammatory activity (82.25%-diosgenin; 82.01%-indomethacin; $P < 0.01$) against carrageenan-induced paw edema in animals (Punitha et al., 2013). The ethanol extract of *T. smilacina* stem and root displayed significant inhibitory effect on COX-1, COX-2, 5-LO and PA2 (IC_{50} 63.5, 81.2, 92.1 and 30.5 μg/mL). Extracts did not show cytotoxicity on cell lines of skin fibroblasts, human Caucasian hepatocyte carcinoma and human Caucasian promyelocytic leukaemia cells (HL-60; Li et al., 2004b).

4.10. Immunomodulatory activity

Immune system is the most complex defense system of body and it helps in protection of human body from various types of infections. Modulation in immune system of body by stimulation or suppression mechanisms helps in maintaining the disease-free lifestyles (Nfambi et al., 2015). Guduchi (formulation of *T. cordifolia*; Himalaya Drug Company, India) showed maximum viability (94 ± 0.89%) in J774A.1 macrophage cells at dose of 80 μg/ml (More and Pai, 2011). Similarly, the aqueous extract of *T. cordifolia* stem (80 μg/mL) increased phagocytosis and pinocytosis (*in vitro*) property of macrophage J774A.1 cell line. Moreover, macrophages demonstrated an increase in phagocytosis to non-infective microbes and live Escherichia coli (More and Pai, 2017). The cordifolioside A isolated from *T. cordifolia* stem (0.1–2.5 μg/mL) showed significant enhancement in phagocytic activity and an increase in formation of nitric oxide and reactive oxygen species (Sharma et al., 2012). Guduchi ImP protein (10 μg/mL) demonstrated significant mitogenic activity (~3-fold higher than control) against murine splenocytes. Due to the presence of immunomodulatory protein (Guduchi ImP protein) in *T. cordifolia* stem, the guduchi may be used in Ayurvedic preparations for immunomodilatory actions (Aranha et al., 2012). The aqueous extract of *T. cordifolia* stem (1.56 μg/ml) induced the higher production of IL-6 in splenocytes when compared with un-stimulated cells (Upadhyay et al., 2011; Kumar et al., 2011). Ethanolic extract (8 mg/kg) significantly ($P < 0.001$) increased the neutrophil activity in *Oreochromis mossambicus* (Sudhakaran et al., 2006). Magnoflorine, syringin, N-formylannonain, N-formylnornuciferine, lysicamine, and 1-octacosanol were isolated from the ethanolic extract of *T. crispa* stem. The isolated compound magnoflorine showed significant stimulatory effects on the chemotaxis, phagocytic activity, reactive oxygen species and nitric oxide productions as well as on secretions of IL-1β, TNF-α, IL-6, PGE2 and MCP-1 from RAW 264.7 macrophages (Ahmad et al., 2018). Aqueous extract of *T. sinensis* stem showed greater immunomodulatory effects than *T. cordifolia* in cyclophosphamide-induced anemia in male Wistar rats (Haque et al., 2017).

4.11. Wound healing activity

The healing of wounds is a complex process of repairing of injury of the skin and soft tissues. During the process of healing, an inflammation occurs and the below layers of the skin induce the formation of collagen layer. In the later stage of development, the epithelial tissue is regenerated in skin. Wound healing can be classified into four stages - inflammation, coagulation, proliferation, and remodelling at vicinity of the injury (Mutsaers et al., 1997; Garg and Paliwal, 2011). It is often considered as a major problem in clinical practices (Kokane et al., 2009). The plant-derived extracts and pure compounds are gaining importance in wound healing (Ambika and Nair, 2019). *T. cordifolia* cream (1 g dried powder mixed with 99 g of cold cream) was applied topically over the surface of wound of treated animals and healing was compared with untreated group (control). In treated animals, the process of epithelialisation of wound (20.333 ± 1.633%, percentage of original area in mm^2) was rapid than the animals of control group (24.500 ± 2.167, percentage of original area in mm^2). The results were found significant ($P < 0.05$) in treated animals than control group (Girish and Kamdod, 2012). Methanolic extract of *T. cordifolia* stem (250 mg/kg b. w.) enhanced wound healing in resutured incision, dead space, and excision wound methods significantly ($P < 0.05$) in male Wistar rats. The closure of wound excision in treated animals was not significantly different from that of control group on days 4, 8 but, on 16th (94.60 ± 0.40) and 18th day (99.40 ± 0.40), the significant ($P < 0.0001$) results were obtained. The breaking strength of 10 day old resutured incision in treated animals was significantly ($P < 0.0001$) higher (543.0 ± 34.6 3 g) than that of control (Hashilkar et al., 2016). Ethanolic extract significantly ($P < 0.05$) induced the healing process in resutured incision and dead space wound models (Girish and Priyadarshini, 2012; Singh et al., 2017). Methanolic extract and chloroform fraction ointment of *T. crispa* stem (100 mg/kg/day) showed high percentage of wound closure area and which was similar to that of standard drug (Vijendren et al., 2017).

4.12. Antimicrobial activity

Since last few decades, bacterial and fungal infections, multidrug resistance, have been the immense challenges, which threaten the health of human population. The microbial infections are causing the death of millions of people in different countries of the world. The development of multidrug resistance in microbes has caused the antimicrobial molecules to become less efficacious or even ineffective (Gupta et al., 2019; Khameneh et al., 2019). However, synthetic antibacterial and antifungal agents have been already used in various countries yet, usage of plant-derived secondary products attracts the attention of researchers (Gyawali and Ibrahim, 2014; Moloney, 2016). The plant-derived secondary metabolites have demonstrated promising results in overcoming the multidrug resistance in microbial pathogens (Rossiter et al., 2017). Plants and their products have been used as antimicrobial agents in traditional system of medicine. In developing countries, 70% population are treated with the plant-derived drugs (Mittal and Sharma, 2014; Ojiako, 2015). On first day, *Escherichia coli* (1x10 viable) cells were injected intraperitoneally for the evaluation of antibacterial activity of *T. cordifolia* aqueous extract in the adult Swiss albino mice. The aqueous extract (100 mg/kg/day by intragastric tube) of stem was administered to the albino mice. The mice mortality rate in control group was 100% while in the extract treated group, mortality rate was

reported as 17.8%. In gentamicin treated animals, mortality was reported as 11.1% ($P < 0.001$; Thatte et al., 1992). 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 μg/mL concentration. Similarly, the ethanol extract of 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 μg/mL; Jeyachandran et al., 2003; Shanthi and Nelson, 2013; Agarwal et al., 2019). Ethanol extract (95%) of *T. cordifolia* showed significant antipyretic activity in Himalayan rabbits (50 mg/mL for 10 days; Vedavathy and Rao, 1991; Prasad and Chauhan, 2019). Ethanolic extract of *T. crispa* roots (50 μg/disc) demonstrated maximum antibacterial activity against E. coli (inhibition zone 3.6 ± 0.2 mm; Mahammed et al. 2012).

4.13. Antileishmanial activity

Leishmania donovani is a protozoan animal, infects hyraxes, canidae, rodents, and humans and currently affecting more than 12 million people in different countries of the world. Leishmaniasis (caused by *Leishmania* species) is a parasitic disease found in 98 countries of the world (Alvar et al., 2012). It is considered as a serious health issue worldwide so, researchers are searching novel plant-derived agents that could be used for the treatment of leishmaniasis (Chiheb et al., 1999; El-Aasri et al., 2016). Ethanolic extract of *T. sinensis* stem showed significant antileishmanial activity against promastigotes (IC_{50} 37.6 ± 6.2 μg/mL) and intracellular amastigotes (IC_{50} 29.8 ± 3.4 μg /mL). Therefore, *T. sinensis* may be used in the development of alternative medicine against visceral leishmaniasis (Singh et al., 2008). The 3-hydroxy-2,9,11-trimethoxy-5,6-dihy dro isoquino[3,2-a] isoquinolinylium isolated from *T. sinensis* demonstrated significant *in vitro* antileishmanial activity against *Leishmania donovani* (96.6% inhibition of promastigotes and 86.6% inhibition of amastigotes; Maurya et al., 2009).

4.14. Analgesic activity

Pain is an unpleasant and sensory feeling associated with potential tissue damage and its control is the most important therapeutic priority for human beings (Rang et al., 2003; Hassan et al., 2015). The prostaglandins, and bradykinins (biochemical mediators) act on the nociceptors causing the sensation discharged by tissue damage and are known as the immediate cause of pain. Rapid start and short duration of pain that last for hours are known as acute pain whereas chronic pain is distinguished by continuous pain over a long period of time (Millan, 1999; Banerjee et al., 2012). Many pharmaceutical drugs have been developed by pharmaceutical industries but they are associated with serious adverse effects such as ulceration, gastrointestinal bleeding, addictive potential, respiratory distress, drowsiness, nausea (Laurence et al., 1997; Mate et al., 2008; Raquibul et al., 2010) hence, opportunities are available for researchers in searching of plant-derived molecules for the treatment of pain. Guduchi capsules (300 mg/kg; p.o.) showed statistically significant analgesia (60 min $P < 0.01$; 90 min $P < 0.01$; 120 min $P < 0.05$) in treated animals (Goel et al., 2014). Aqueous-methanol (30:70) extract of *T. cordifolia* stem (300 mg/kg) inhibited the number of writhes in dose-dependent manner (Hussain et al., 2015). Aqueous extract of *T. cordifolia* leaves (200 mg/kg) showed significant ($P < 0.001$) increase in the reaction time (pain threshold) in treated Swiss albino mice and Wistar rats (Siddalingappa et al. 2011). Ethanol extract of *T. sinensis* leaves (500 mg/kg) displayed maximum ($P < 0.001$) increase in latency time in treated rats (Sandhyarani and Kumar, 2014b). The aqueous extract of *T. crispa* stem (666 mL) exhibited promising central analgesic activity (Almeida et al., 2001).

4.15. Anti-psychotic/antiepileptic activity

Due to the ambitious lifestyle, urbanization, and stressful environment, people are suffering by mental disorders. Psychosis is a one of the severe mental condition in which a sufferer experiences a distortion or loss of contact with reality and clouding of consciousness (Yadav et al., 2015). It is characterised by depression, delusion, hallucination, anxiety, sleep disturbance, thought disorder, social isolation and impaired role functioning (McNamara, 1996). Methanol extract of *T. cordifolia* stem showed significant increase ($P < 0.05$) in serum prolactin while decrease in dopamine, superoxide dismutase and catalase levels in haloperidol and sulpiride treated animals ($P < 0.05$; Tiwari et al., 2019). Aqueous-ethanolic extract *T. cordifolia* stem (500 mg/kg b.w.) did not show any antipsychotic activity in amphetamine-induced hyperactivity in mice when compared with standard compound (amphetamine). Extract (500 mg/kg b.w.) displayed a decrease in locomotor activity when compared to the control (Jain et al., 2010b).

4.16. Antiulcer activity

Ulcers are characterized by an open sore of skin or inflamed break in dead tissue of mucous membrane (Chan and Graham, 2004). There are several types of ulcers found in human beings viz, mouth ulcer, esophagus ulcer, peptic ulcer, and genital ulcer (Paguigan et al., 2014). Out of these, peptic ulcer is commonly seen among many people, and characterized by erosion of lining of stomach or the duodenum (Debjit et al., 2010; Vimala and Shoba, 2014). Aqueous extract of *T. cordifolia* stem (400 mg/kg) showed significant ($P < 0.01$) decrease in gastric volume, total acidity and ulcer index in treated animals (Chandan et al., 2013). Ethanol extract of stem (600 mg/kg) demonstrated statistically significant ($P < 0.05$) better protection in aspirin and ethanol-induced ulcers in animals (Khan et al., 2015). Etahnol extract also showed significant protective activity against an 8 h restraint stress induced ulcerization (Sarma et al., 1995). Aqueous extract of *T. sinensis* stem decreased ulcer index ($P < 0.001$) and ulcerogenic effects higher (85.65%) than standard drug (71.52%; Khayum et al., 2009).

4.17. Antifertility activity

Increasing human population throughout the world has detrimental effects on health care, food security, employment, education, housing, and environment hence, it suggests that fertility control is a problem but, in my opinion, it is an issue that needs to be tackled by public health (Gupta and Sharma, 2006; Mamatha et al., 2012; Devi et al., 2015). Ethanolic

extract of *T. cordifolia* stem interrupted the process of spermatogenesis and formation of round spermatids (73.12%) in treated animals. It also reduced the serum testosterone levels and surface area of Sertoli cells when compared to controls ($P < 0.001$). Methanolic (70%) extract (100 mg/kg, given for 5 days) of its roots decreased the fertility index in fertile female albino rats (Fatima Rose et al., 2010).

4.18. Antimalarial activity

Malaria is considered as an important global health issue affecting large human population of the world. As per World Health Organization report, there are about 216 million people suffered in developing countries by malaria in year 2016 (WHO, 2017). Effective drug discovery is still our one of the main efforts to control malaria. During the last few decades, various antimalarial compounds have been reported from plants, and many of these compounds demonstrate potent activity against *Plasmodium falciparum in vitro* (Pan et al., 2018). As plant-derived secondary products are still considered as an important source for discovery and development of therapeutic agents. The aqueous extract of *T. cordifolia* stem in combination with chloroquine showed regression of spleen by 37–50% after six weeks and 45–69% after six months from the start of treatment (Singh, 2005). Methanol extract of *T. crispa* whole plant (2.5 mg/mL) showed significant antimalarial activity against *P. falciparum* after 72 h (Najib Nik a Rahman et al., 1999; Ihwan and Fitri, 2014). The aqueous extract of *T. baenzigeri* stem (500 mg/kg b. w.) significantly ($P < 0.01$) suppressed parasitemia in a dose-dependent manner (74.95% inhibition). Aqueous extract did not show any sign of toxicity up to the dose of 2000 mg/kg in treated rats (Ounjaijean et al., 2019).

5. Discussion

Several *Tinospora* species have been considered for their therapeutic properies owing to their strong antidiabetic and antiarthritic activities attributable to the presence of high contents of alkaloids, clerodane furano diterpenes and glucosides, phenolics and flavonoids (Sarma et al., 2009; Ahmad et al., 2021). Secondary metabolites have been used since long time for the treatment of human diseases and as a result, a large number of current drugs in modern medicine have been formulated from secondary metabolites. Now, various researchers are searching biologically active natural products and are trying to establish their possible therapeutic roles in disease control mechanisms (Newman et al., 2015). Such new natural products can often serve as chemical templates for the design and the synthesis of novel pharmaceutical drugs (Newman and Cragg, 2016). Indian *Tinospora* species possesses immunomodulatory, hypoglycaemic, antiallergic and anti-inflammatory properties (Bhalerao et al., 2016; Lade et al., 2018). *T. cordifolia* dried fruits are useful in jaundice and rheumatism, while the leaves are used in curing diabetes. Its roots possess antistress, antioxidant, antiulcer, and hypoglycemic properties, as well as for the treatment of visceral obstructions (Noreen et al., 1992; Prince et al., 1999).

Alkaloids are nitrogenous and basic compounds present in plant tissues as water soluble salts of organic acids (oxalic, citric, malic, and lactic acids), esters (atropine, scopolamine, cocaine, aconitine), combined with tannins (*Cinchona* bark), or sugars (glycoalkaloids of *Solanum* species) rather than as free bases. Majority of alkaloids are colourless and bitter but orange-yellow (berberine and colchicines), red (betaine), brick red (sanguinarine), or the orange-colored (canadine) alkaloids are also found in plants (Wiart, 2014; Kukula-Koch and Widelski, 2017). Magnoflorine, a quaternary alkaloid isolated from *T. cordifolia* has been reported to have potent anticancer and antidiabetic properties (Guo et al. 2018; Cherku et al., 2019). Recent studies have shown that magnoflorine has a certain anti-inflammatory effect (Li and Wang, 2014). Similarly, jatrorrhizine an isoquinoline alkaloid isolated from *T. cordifolia* has various bioactivities, such as antioxidant, low host toxicity and highly potent antimicrobial activity (Slobodnikova et al., 2004; Rackova et al., 2004).

Furanoditerpenoids are a special group of diterpenoids consisting of one or more furan rings, which are found in members of Euphorbiaceae, Fabaceae, Lamiaceae, Asteraceae, Codoniaceae, Dioscoreaceae, Fossombroniaceae, Jamesoniellaceae, Meliaceae, Menispermaceae, Olacaceae, Psathyrellaceae, Sapindaceae and Scapaniaceae families. There are seven types of furanoditerpenoids have been reported from plants: clerodane-, labdane-, cassane-, abietane-, spongian-, prenylbisabolane- and miscellaneous types (Afiyatullov et al., 2007; Bao et al., 2017; Parveen et al., 2021). The columbin-rich ethanol extract of *T. cordifolia* was assessed for its protective effects against acute cold stress in male Sprague-Dawley rats. The study showed significant biochemical alterations in urinary metabolites. The tricarboxylic acid cycle, renal function, gut microbiota, catecholamines and muscle metabolism were altered by cold stress and the columbin-rich extract restored them to normal level. This study forms the basis of future studies to develop potential biomarkers for cold stress in humans and lay down the optimum dosage of *T. cordifolia* to be given for providing immunity to the body as prophylactic and mitigating agent against cold stress (Gandhi et al., 2012).

Lignans are commonly characterized as phytoestrogens, or fiber-associated compounds found in plants of several families (Pedaliaceae, Asteraceae, Graminae) and used as common foods including grains, nuts, seeds, vegetables, and drinks such as tea, coffee. The dietary (secoisolariciresinol diglucoside) and non-dietary lignans (sesamin, matairesinol, pinoresinol and lariciresinol) possess anti-inflammatory and antioxidative properties (Yoder et al., 2015). Lignans (entroldiol and enterolactone) are involved in cytostatic activity against colon cancer cell lines (Wcislo and Szarlej-Wcislo, 2014). Sesamin and sesamolin found in *T. cordifolia* and *T. sinensis* have been demonstrated to contain several biological properties useful for human health. Excess formation of nitric oxide in lipopolysaccharide-stimulated rat primary microglia cells was significantly reduced when they were administered with sesamin or sesamolin. The neuroprotective effect of sesamin and sesamolin were also reported (*in vivo*) in focal cerebral ischemia stimulated by occlusion of the right common carotid artery and the right middle cerebral artery of animals (Cheng et al., 2006).

Triterpenes are composed of three terpene ($C_{30}H_{48}$) units or consist of six isoprene units, found in various plant families (Solanaceae, Araliaceae, Ranunculaceae, Leguminosae, Caryophyllaceae, Cucurbitaceae, and Umbelliferae). Triterpenes exist in a large variety of structures with nearly 200 different skeletons identified from plant kingdom (Xu et al., 2004;

Rakib et al., 2020a). Based on their chemical structures, triterpenes can be divided into linear, monocyclic, dicyclic, tricyclic or up to pentacyclic compounds (Laszczyk, 2009; Connolly and Hill, 2010). Triterpenoids containing fruits (apple, grape berry, olive, tomato, and mango) possess cardio-protective and antioxidant activities. Several clinical studies have been conducted on humans assessing the potential role of triterpenoid usage in the prevention of chronic diseases, and the possible mechanisms responsible for the observed therapeutic roles (Battineni et al., 2018). Ativiral activity of betulin was widely examined for various types of viruses including human immunodeficiency virus: HIV-1NL4-3 and HIV1JRCSF (X4-HIV-1 and R5-HIV-1, respectively; IC_{50} 0.04 μg/ml; Theo et al. 2009). Betulin also demonstrated anti-herpes symplex virus-1 activity (EC_{50} 84.37 μg/mL; Shamsabadipour et al. 2013). Diosgenin (identified from *T. sinensis*) significantly ($P < 0.01$) reduced the mean paw edema volume at 3 h of carrageenan injection (Punitha et al., 2013).

Flavonoids are considered as the largest class of secondary metabolites containing of a broad class of polyphenolic compounds with low molecular weight that share a common skeleton of phenyl-benzo-g-pyran (C6-C3-C6), also known as the flavan nucleus, composed of two phenyl rings (A and B) connected through a pyran ring (C). Flavonoids include flavonols, flavones, flavonoids, flavanones, anthocyanidins, and isoflavones and are widely distributed the leaves, seeds, bark and flowers of plants (Queiroz Ferreira et al., 2015). Flavonoids also play a significant role on the stability, sensory, and health properties of foods (Santos-Buelga and Feliciano, 2017). Plant-derived flavonoids possess anti-viral/bacterial, anti-inflammatory, cardioprotective, anti-diabetic, anti-cancer, anti-aging, properties (Ragab et al., 2014; Tian et al., 2014; Zhang et al., 2015). Apigenin is a normal dietary flavonoid that is widely present in many fruits, vegetables and flowers and possesses anti-inflammatory, antioxidant, antibacterial and antiviral activities and antidiabetic activities (Papay et al., 2017; Wang and Huang, 2013; Zhu et al., 2016). Diosmetin demonstrated anti-inflammatory and hepatoprotective activities by inhibiting malonaldehyde, inducible nitric oxide synthase, prostaglandin E2, and cyclooxygenase-2 expression, NF-κB signaling pathway activity, hepatocyte apoptosis, and the activities of alanine aminotransferase and aspartate aminotransferase in different models (Yang et al., 2017; Chung et al., 2020).

Diabetes mellitus is an insulin-dependent metabolic disease characterized by prolonged hyperglycemia. This disease has been primarily treated by several synthetic drugs that improve the changed glycemic status in diabetic patients. However, synthetic drugs are capable, they have remarkable adverse effects together with their beneficial effects. Medicinal plants have been used to treat diabetes and related complaints in various healthcare systems around the world. The medicinal plants have been used since long time as primary health care demand, they have not been fully employed as acceptable drugs in the treatment of diabetes because of unavailability of knowledge of their chemical characterization, preparation procedure, possible adverse effects and administration doses. The large number of medicinal plants have been attributed to possess antidiabetic activity in preliminary examinations, but most of them do not reach the clinical trial level due to lack of proper information on the above-mentioned parameters (Ahmed et al., 2021; Naveen et al., 2021). *T. cordifolia* one tablet (500 mg) was given three times a day for 6 months to diabetic patients as add-on therapy. After 6 months of treatment, the fasting blood glucose levels reduced significantly in treated patients (Mishr et al., 2015a).

6. Clinical studies

The use of medicinal plants and their products has been increased tremendously over the past few decades but incidents of adverse effects from usage of herbal medicines are being reported recently (WHO, 2004, 2005). The adverse effects are attributable to several factors including wrong idenfication of plant species, adulteration of herbal products, and contamination with toxic compounds, improper use of herbal medicines by healthcare providers and use of herbal medicines concomitantly with other medicines therefore, rigorous clinical trials of medicinal plants and their products are to be conducted (Singh and Sharma, 2020). One tablet of *T. cordifolia* (500 mg) given to healthy volunteers with morning breakfast. As per clinical studies, no healthy volunteer complained of any negative effects on clinical chemistry and hematological measurements, blood pressure, heart rate, or body weight during and after the period of drug intake at the given dose and duration (Karkal and Bairy, 2007; Table 4). *T. cordifolia* extract (one tablet; 500 mg) reduced the fasting blood glucose levels in the type-2 diabetic patients and also restored the altered functions of liver of patients (Mishr et al., 2015a, b). *T. cordifolia* pills demonstrated positive effects on surgical outcome (92% survival in treated patients and 40% in non-treated patients) of patients of obstructive jaundice (Rege et al., 1993). Capsules (formed from stem extract) improved the physical performance as well as suppressed the activation of sympathetic nervous system (Salve et al., 2015). Aqueous extract of *T. cordifolia* was found effective in relieving the clinical symptoms in patients of allergic rhinitis, cold and fever (Geeta et al., 2017). The aqueous extract showed statistically significant increase in total leucocyte count ($P < 0.001$), absolute lymphocyte count ($P < 0.001$) and lymphocyte percentage ($P < 0.001$) when compared with placebo (Sharma and Sharma, 2015). A randomized double-blind placebo-controlled trial was conducted to validate the efficacy and safety of *T. crispa* in the treatment of type 2 diabetes mellitus patients which of those refused insulin injection and did not respond to oral hypoglycemic drugs (Sangsuwan et al., 2004). Similarly, *T. crsipa* capsules (250 mg stem powder) were also used in clinical study of diabetic patients. Total twenty participants (10 diabetic and 10 healthy) were recruited for this study. Total 10 participants with diabetes mellitus type 2 (7 women and 3 men; age 32 to 64 years) were given 250 mg stem powder daily. The participants with diabetes mellitus 2 responded to oral hypoglycemic drugs and discontinued oral hypoglycemic drugs at least for 1 month during this study. Serum samples from 10 healthy and 10 diabetic participants, who had fasted overnight, were collected every 30–60 min during the 3 h of regular fasting and during the 3 h after consumption of 75 g of glucose with or without consumption of *T. crispa* dry powder capsule (250 mg). The mean serum glucose (areas under the curve) in both healthy and diabetic participants was not significantly different between with and without *T. crispa*. In diabetic patients, the mean serum glucose (areas under the curve) was slightly lower when *T. crispa* (250 mg

Table 4 Clinical studies of Indian *Tinospora* species.

Study	Age (years)	Treatment	Doses	Recommended time (in days)	Useful outcomes	References
T. cordifolia						
A double-blind randomized placebo-controlled study	30 healthy volunteers (22 males and 8 females), age 18–30 years	One tablet of *T. cordifolia*	500 mg taken orally once a daily in the morning with breakfast	21	No volunteer complained of any adverse effects on clinical chemistry and hematological measurements, urinalysis, electrocardiogram, blood pressure, heart rate, or body weight during study	Karkal and Bairy (2007)
Add-on therapy in patients with type-2 diabetes	30 (both male and female); diabetic patients type-2; age 30–60 years	One tablet of *T. cordifolia* (group A was given anti-diabetic medications, *T. cordifolia* was given to group B patients)	500 mg was given three times daily before meals		After 6 months, the fasting blood glucose values were 121.76 ± 29.57 mg/dl in group A and 119.99 ± 34.36 mg/dl in B group; Decrease in the post prandial blood glucose levels was recorded both groups	Mishra et al. (2015a)
Add-on therapy on the blood glucose levels	100 patients (type 2 diabetic); age 30–60 years	One tablet (*T. cordifolia*)	500 mg was given three times daily along with meals	180	Decrease in the fasting, postprandial, and glycosylated hemoglobin levels of the patients was found statistically significant ($P < 0.005$) in treated patients	Mishra et al. (2015b)
Randomized controlled trial	30 (16 men and 14 women) patients of obstructive jaundice; age 17–70 years	*T. cordifolia* pills	65 mg/kg/day dried aqueous extract	21	Post drainage bactobilia observed in 8 patients in group I and 7 in group II but clinical evidence of septicemia was observed in 50% patients in group I as against none in group II; Pills demonstrated positive effects on surgical outcome (92% survival in treated patients and 40% in non-treated patients)	Rege et al. (1993)
Open-label, randomized, placebo-controlled trial	30 participants; blood pressure patients; age 18–45 years	*T. cordifolia* capsule (TC)	Maize starch capsule (placebo), 300 mg/kg/day	28	Capsule (on day 28) showed a significant decrease in mean systolic blood pressure on fixed workload exercise compared to	Salve et al. (2015)

Table 4 (*continued*)

Study	Age (years)	Treatment	Doses	Recommended time (in days)	Useful outcomes	References
					placebo; improved physical performance and suppressed over activation of the sympathetic nervous system	
Open label-controlled trial	30 (15 male and 15 female) healthy persons as control, 60 (male-30, female-30) type- 2 diabetic patients; age 47–57 years	Stem powder	50 mg/kg b. w./day/ stem powder macerated with water; p.o.	15	Stem powder increased the levels of fasting blood sugar (57%), glycosylated hemoglobin (40%); also caused reversal in the levels (fasting blood sugar 9%, glycosylated hemoglobin 14%) in treated patients	Kumar et al. (2016)
Open label-controlled trial	30 clinically diagnosed patients of Sthaulya Roga (obesity); age 16–60 years	Guduchi Sattva Kalpana (group I) and Guduchi Kwatha. Kalpana (group II)	250–500 mg (Guduchi Sattva) 50–100 mL (Guduchi Kwatha) administered 1 h after meal	30	Group A— Patients were treated with Guduchi Sattva Kalpana; group B— Patients were treated with Guduchi Kwatha Kalpana; Guduchi Kwatha is more effective than Guduchi Sattva; Kwatha gets absorbed more easily and quickly than the Sattva which has large amount of starch in it	Kapoor et al. (2013)
Diabetic patients from out patients department (OPD) and inpatient departments (IPD) Group A- treated with Guduchi sattava along with diet and exercise Group B- treated with diet and exercise only; age 30–70 years	50 patients (diabetes mellitus type II) Guduchi sattava	1 g (twice daily) was given orally	90	Guduchi sattava was found very effective in the treatment of diabetes; initial mean value of serum cholesterol level of group A patients was 150 and group B patients was 148	Kundu et al. (2016)	

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Table 4 (*continued*)

Study	Age (years)	Treatment	Doses	Recommended time (in days)	Useful outcomes	References
–	25 patients (acute conditions like fever, cold, allergy and rhinitis)	*T. cordifolia* extract in capsule form (from the Himalaya Drug Company)	250 mg/thrice a day	15	Capsule significantly changed the neutrophil, and eosinophil counts ($P < 0.05$); capsules were found effective in relieving the clinical symptoms in cases of allergic rhinitis, cold and fever	Geeta et al. (2017)
Double blind, randomized and placebo controlled	Thirty healthy volunteers (male-22 and female-8), visual, logical and verbal memories; age 18–30 years	Stem aqueous extract	One tablet (500 mg) placebo was taken once daily (p.o.) in the morning	21	Extract enhanced verbal, logical and learning memories (of immediate and short-term type) in compare to placebo in healthy volunteers	Bairy et al. (2004)
Open labelled randomized controlled trial	Thirty patients (type-2 diabetic); age 50–60 years Encapsulated mature stem	250 mg pre-meal twice a day along with prescribed oral hypoglycemic agents and statin and control group (n = 30) only on OHAs and statin	60	Intervention led to significant reductions in total cholesterol, low density lipoprotein, triglycerides and very low-density lipoprotein; no toxicity was observed in patients		Roy et al. (2015)
Comparative open clinical trial	30 patients (14 men, 16 women) with premature aging due to stress (without any other acute or serious systemic disorders); age 25–60 years	Capsules prepared from the drugs Guduchi (*T. cordifolia*)	Group A – 500 mg soft gelatin capsules of Guduchi were given for 3 months; group B –500 mg soft gelatin capsules of Amalaki were given for 3 months; group C- 500 mg/day capsule of Guduchi and 500 mg/day capsule Amalaki were given for 3 months, once daily in the form of soft gelatin capsule	90	Guduchi and Amalaki were found effective in delaying premature ageing due to stress, but considering the small size of the trial population, the trial should further be extended to larger sample size and for longer trial duration to draw more conclusive evidence	Pal et al. (2017)
An open-labelled, placebo-controlled, randomized controlled trial	400 children (status of immunity in children); children with genetic disorders, severe or chronic illnesses, congenital diseases, mentally challenged; age 1–15 years	Stem and leaf powder	100 mg/kg b. w. twice a daily after food with honey	60	Stem and leaf powder showed significant increase in total leucocyte count ($P < 0.001$), absolute lymphocyte count ($P < 0.001$) and lymphocyte percentage ($P < 0.001$) as compared to placebo; powder significantly improved immunity in children and can	Sharma and Sharma (2015)

Table 4 (*continued*)

Study	Age (years)	Treatment	Doses	Recommended time (in days)	Useful outcomes	References
					be used as an adjuvant to vaccination	
A randomized, double-blind, placebo-controlled	250 patients (dengue); age 18–75 years	Leaf extract, 5 mL twice daily or placebo for five consecutive days	5 mL dosage	5	Extract showed significant increase ($P < 0.05$) in platelet count; can be used to treat thrombocytopenia	Babu et al. (2017)
A randomized double-blind placebo controlled	Seventy-five patients of allergic rhinitis	Stem aqueous extract	–	56	Extract showed 100% relief from sneezing in 83% patients, in 69% from nasal discharge, in 61% from nasal obstruction and in 71% from nasal pruritus	Badar et al. (2005)
A single blind, randomized controlled trial	66 pediatric patients diagnosed with scabies; age 2–22 years	*T. cordifolia* lotion (*T. cordifolia* extract was mixed with 0.15 g methyl paraben and 39.70 g water to form the water paste)	This was done daily for three consecutive days per week for two weeks	14	Lotion exhibited anti-scabies activity comparable with permethrin; its incorporation as therapeutic reagent in *Sarcoptes scabiei* infections is highly recommended	Castillo et al. (2013)
Double-blind, split-mouth study	Forty-eight patients (diagnosed suffering from periodontitis with or without dental fluorosis); age 18–50 years	Guduchi gel [Guduchi stem powder (1500 g); the guduchi gel was prepared in Bapuji Pharmacy College]	6.25%	21	Guduchi gel was delivered into each periodontal pocket using sterile Dispo Van™ single-use bent needle till the gel overflow the site; guduchi gel (6.25%) showed clinically significant anti-inflammatory and antimicrobial effects along with scaling and root planning	Ghosh et al. (2017)
Controlled clinical trial	60 patients (post-operative and traumatic fresh wounds were selected from outpatient department and inpatient department of Shalya Tantra)	Guduchi (stem fiber) as suturing material for skin suturing in post-operative and traumatic wounds	–	7	Guduchi (stem fibers) sutures can be used as a safe alternative for cotton thread in skin closure	Shrestha et al. (2017)
An open label, non-comparative, interventional, and exploratory clinical trial	30 children (19 male and 11 female); growth of children; age 6–8 years	Stem juice	20 mL/day (empty stomach morning)	90	Mean score of skin luster was 0.43 ± 0.5 and it was significantly increased to 1.17 ± 0.37; diet intake was increased significantly; can be used in herbal	Patil (2012)

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Table 4 (*continued*)

Study	Age (years)	Treatment	Doses	Recommended time (in days)	Useful outcomes	References
					formulation for the growth of children	
A prospective double-blind randomized controlled study	Forty-five patients [23 study group (17 males and 6 females) + 22 control group (19 males and 3 females)]; chronic diabetic patients with wounds; age 56.9 years	Stem extract	–	537	Stem extract showed significant improvement in wound healing; also reduced debridements and improved phagocytosis, indicating beneficial effects of immunomodulation for ulcer healing	Purandare, and Supe (2007)
Randomized double-blind placebo-controlled trial	68 patients HIV positive; age 18 – 50 years	Stem aqueous extract (Tinofend, Pharmanza India Ltd, Gujarat)	300 mg	–	Extract caused significant reduction in eosinophil count and hemoglobin percentage; some of common complaints reported in patients (anorexia, nausea, vomiting, and weakness)	Kalikar et al. (2008)
T. crispa						
Randomized double-blind placebo-controlled trial	20 patients with type 2 diabetes mellitus	Stem powder	1 g in capsule given thrice a day	180	Changes in fasting plasma glucose, glycosylated hemoglobin and insulin levels were observed in treated patients; the patients receiving stem powder may have an increased risk of hepatic dysfunction	Sangsuwan et al. (2004)

dry extract) was consumed, but did not reach on levels of statistical significance (478 and 444 mg min/mL, respectively, $P = 0.57$). The results suggest that *T. crispa* consumption cannot affect the levels of serum glucose and insulin in healthy or diabetic patients (Klangjareonchai and Roongpisuthipong, 2012). *T. crispa* dry powder capsule (250 mg twice a day) was given for 2 months to the patients of metabolic syndrome and showed reduced levels of fasting blood glucose significantly when compared with baseline (6.29 ± 10.47 mg/dL, $P < 0.01$; Sriyapai et al., 2009).

7. Toxicological effects

Most of the medicinal plants are non-toxic but, some are poisonous to humans causing damage to certain organs in the body (Okoye et al., 2014). Global use of medicinal plants is growing rapidly and many more new plant-derived products are introduced into the market so, proper attention is needed in safe use of medicinal plants in the treatment of diseases (Ekor, 2014). In alcoholics patients, the higher levels of γ-glutamyl transferase, aspartate transaminase, alanine transaminase, triglycerides, cholesterol, high density lipoproteins and low-density lipoproteins ($P < 0.05$) were reported but aqueous extract of *T. cordifolia* stem decreased their levels in treated patients (Sharma and Dabur, 2016). Acute toxicity result showed that drug (*T. cordifolia* aqueous extract) did not show any signs and symptoms of toxicity or mortality up to an oral dose of 2000 mg/kg in rats. Although the drug (aqueous extract) demonstrated mild to moderate adverse changes in kidney, liver, intestine, and stomach of patients at therapeutic equivalent dose (×10 dose level) in a clinical trial study (Gokarn et al., 2017). No acute toxicity was reported in male albino mice treated (p.o.) with aqueous extract (Sengupta et al., 2011). Embryo-toxic effect of aqueous extracts of *T. cordifolia* leaf and bark was dependent on dose and time of exposure. Leaf extract (10%) showed maximum mortality (100%) while bark extract (10%) exhibited 33.33% mortality in treated animals (Zebrafish embryos; Romagosa et al., 2016). *T. cordifolia* stem is used in the management of depression, treatment of Alzheimer's disease and attention deficit hyperactivity problems. No evidence is available in the literature of serious toxicity of *T. cordifolia* in depression management, Alzheimer's disease and attention deficit hyperactivity disorder (Mutalik, 2011). The high doses of *T. crispa* extract (the patients who received 10 pellets of *T. crispa* per day)

Table 5 Toxicological effects of Indian *Tinospora* species.

Plant species	Plant part	Extract/compound	Dose	Type of toxicity	Model/ symptoms	Reference
T. cordifolia	Fresh stem	Aqueous extract	100 mL extract (3.0 g solid extract) given early in the morning with an empty stomach for 14 days	Chronic liver disease in humans	Extract showed significant decrease in the levels of γ-glutamyl transferase, aspartate transaminase, alanine transaminase, triglyceride, cholesterol, high density lipoproteins and low-density lipoprotein while displayed increase in intestinal absorption and retaining power of liver (that regulated by alcohol-induced multivitamin deficiency) in treated patients	Sharma and Dabur (2016)
		Solidified aqueous extract	2000 mg/kg given for 90 days	Oral acute toxicity in humans	In clinical trials, the acute toxicity result showed that drug did not produce any signs and symptoms of toxicity or mortality up to an oral dose of 2000 mg/kg in rats; although the extract demonstrated mild to moderate adverse changes (in kidney, liver, intestine and stomach) at therapeutic equivalent dose × 10 dose level	Gokarn et al. (2017)
		Aqueous extract (from Chaitanya Pharmaceuticals Ltd, India)	100, 200 or 400 mg/kg b. w.	Acute oral toxicity in rats	Reported results indicate that the extract therapy was able to maintain circulating iron through reduction of inflammatory cytokines and expression of hepcidin in rats	Ghatpande et al. (2019)
	Stem parts	Aqueous extract	150 mg/kg b. w.	Acute toxicity in albino mice; p.o.	No acute toxicity was reported in treated male albino mice	Sengupta et al. (2011)
	Stem	Aqueous extract	300 mg/patient	Patients of HIV positive	Some of common complaints viz. anorexia, nausea, vomiting, and weakness reported in treated patients	Kalikar et al. (2008)
	Leaf and stem bark	Aqueous extract of leaf and stem bark	Embryos were exposed to the different concentrations (10%, 5%, 1%, 0.5%, 0.1%, 0.05%, 0.01%) of each extract	Embryo-toxic and teratogenic effects in Zebrafish (*Danio rerio*) embryos	Maximum mortality (100%) displayed by leaf extract while bark extract showed mortality of 11.11% and 33.33% at 5% and 10% concentrations	Romagosa et al. (2016)
T. crispa	Stem	Aqueous extract	Chronic use of high doses (10 pellets per day) was taken	49-Year-old male with chronic low back pain	*T. crispa* induced toxic hepatitis; problem of dark urine and pale stools, linked with asthenia and right hypochondrial pain which led to jaundice; recovery completed after discontinuation	Langrand et al. (2014)
		Ethanolic	100 and 200 mg/kg b. w. for 8 weeks	Thioacetamide-induced hepatotoxicity in Sprague Dawley rats	Ethanol extract contained certain hepatotoxins which may be responsible for this effect	Kadir et al. (2011)
			4.0 g/kg b. w. per day for 6 months	Bile duct proliferation and focal liver cell hyperplasia	Extract did not cause any signs of toxicity or animal death at a dose of 4.0 g/kg of body weight (g/kg b. w.) but at a dose of 9.26 g/kg/b. w./day to rats caused hepatic and renal toxicities	Chavalittumrong et al. (1997)

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Table 5 (*continued*)

Plant species	Plant part	Extract/compound	Dose	Type of toxicity	Model/ symptoms	Reference
		Herbal preparation	400 mg daily	37 malaria patients	A human hepatotoxicity case was reported due to chronic over use of herbal preparation as a prophylactic agent against malaria	Denis et al. (2007)
T. sinensis	Fresh stem	Aqueous extract	200 and 400 mg/kg b. w. (p.o.; male Wistar rats)	Paracetamol induced hepatic toxicity	Extract significantly reduced the paracetamol induced elevated levels of serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and total bilirubin in experimental animals	Nagarkar et al. (2013)
	Stem	Aqueous, ethanolic and petroleum ether extracts	5000 mg/kg b. w. (adult Swiss albino mice and Wistar rats)	Pylorus ligation induced gastric ulcers and water immersion stress induced ulcer	Aqueous and alcoholic extracts up to a dose of 5000 mg/kg and petroleum ether extract up to a dose of 2000 mg/kg were found safe in treated animals	Khayum et al. (2009)

showed a complaint of dark urine and pale stools, linked with asthenia and right hypochondrial pain which led to jaundice. The histopathological observations also confirmed a toxic reaction in treated patients (Langrand et al., 2014). Acute toxicity results of aqueous extract of *T. crispa* stem displayed LD_{50} values of about 20–24 g/kg and found safe during study (Kongkathip et al., 2006). Satwa (*T. sinensis* formulation) reduced the elevated levels of serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and total bilirubin in paracetamol-induced hepatic toxicity of experimental animals (Nagarkar et al., 2013). Aqueous, alcoholic (up to a dose of 5000 mg/kg b. w.) and petroleum ether extracts (2000 mg/kg) of *T. sinensis* stem did not show any adverse effects in treated Swiss albino mice (pylorus ligation induced gastric ulcers; Khayum et al., 2009). Short-term uses of *T. cordifolia* aqueous extract confirm its safety but long-term use may cause constipation, decrease in blood sugar levels, overstimulation of immune system, complications in pregnant women (Bhardwaj, 2003; Table 5).

8. Tinospora formulations

Some *Tinospora* formulations are used in preclinical and clinical preparations with hepatoprotective, antioxidant, pancreatic islet superoxide dismutase, antiatherogenic, antiarthritis, immunomodulatory, antihyperglycemic, antihyperlipidemic, antidepressant, antiamoebic, and antistress properties (Tasaduq et al., 2003; Deole et al., 2011; Sohni et al., 1995; Nasreen, 2011; Bhattacharya et al. 1997; Mary et al., 2003; Chavali and Forse, 1997). *T. cordifolia* capsules are used in the treatment of diabetes. The capsule is filled with 500 mg of *T. cordifolia* ethanol extract, 2% (w/w) tannins, bitters 10 mg per capsule, as well as 75 mg polysaccharides. Similalrly, tinosporine capsule is filled with water soluble extractive 81.40% (w/w), alcohol soluble extractive 3.85% (w/w), tannins 14.37 (mg/capsule), bitters 12.08 (mg/capsule), and polysaccharides 122.40 (mg/capsule; Rane et al., 2017). *T. cordifolia* displays protective effect by immunomodulation of polymorpho nuclear cells, phagocytes and on macrophage function. The capsule contains a polysaccharide which is responsible for immune-stimulatory effects. It acts by inducing the phagocytic activity of macrophages, formation of reactive oxygen species and nitric oxide in human neutrophil cells (Khare and Katiyar, 2012; Salkar et al. 2014). Rasna Saptak Kwatha is an Ayurvedic polyherbal decoction prescribed as medicine for the treatment of arthritis. Rasna Saptak Kwatha has been traditionally used by Ayurvedic practitioners, to treat various painful afflictions and body joints swelling (Sharma, 2011). Its formulation contains medicinal plants 4 viz. *Pluchea lanceolata, Tribulus terrestris, Tinospora cardifolia, Boerhavia diffusa, Ricinus communis, Cedrus deodara, Cassia fistula* and *Zingiber officinale* (Pandey and Chaudhary, 2017). Crude ethanolic extract of *T. cordifolia* stem incorporated in gel base (10%) showed significant enhancement in tensile strength ($P < 0.05$) of the wound when compared with Curiosin gel and reduction in mean paw size ($P < 0.001$) of the Sprague-Dawley rats when compared with Voltaren as standard drug, respectively. The gel demonstrated negligible irritant activity therefore, *T. cordifolia* gel can be used safely as topical formulations to treat wounds and inflammation (Bagon et al., 2016).

The Hemoliv and HP-1 formulations displayed protective effects against carbon tetrachloride-induced hepatic injury in rats (Panchabhai et al., 2008). The Caps HT2, a polyherbal formulation, containing *T. cordifolia* methanol extract presented anticoagulant, platelet antiaggregatory, lipoprotein lipase releasing, and hypolipidemic properties (Mary et al., 2003). The Diasulin and Dihar (two polyherbal formulations) containing ethanolic extract of *T. cordifolia* roots displayed antihyperlipidemic, antiperoxidative and antioxidant properties (Patel et al., 2009; Saravanan and Pari, 2005). The therapeutic uses of *T. cordifolia* in Ayurvedic formulations with different doses have been validated by practitioners (Panchabhai et al., 2008).

9. Conclusions and future prospects

Different parts of Indian *Tinospora* species are used in the treatment of fever, urinary diseases, asthma, gout, diabetes, diarrhoea, and skin infections. The presence of various bioactive compounds provides the plant for its antidiabetic, antiox-

idant, anticancer, antimicrobial, antifertility, hepatoprotective, radioprotective, antiarthritic antioxidant, hypolipidemic, and anti-inflammatory activities. The clerodane furano diterpene glycosides showed promising anticancer and isoquinoline alkaloids exhibited antidiabetic activities in different models. *T. cordifolia* stem has been used by Indian people in the treatment of diabetes. Antidiabetic efficacy and safety of *T. cordifolia* stem capsules (dry powder) in diabetic patients has proven in clinical trial as well as in Indian people. This attribute of *T. cordifolia* may be exploited by commercialization of these plants for the identification of potential compounds for the treatment of diabetes. *T. cordifolia* capsules (300 mg/kg/day) showed a significant decrease in mean systolic blood pressure on fixed workload exercise when compared to placebo and also improved the physical performance. Capsules significantly changed the neutrophil, and eosinophil counts ($P < 0.05$) and were found effective in relieving the clinical symptoms in cases of allergic rhinitis, cold and fever. Although some studies have done to reveal the antidiabetic activities of *T. cordifolia*, its true potential is yet to be acknowledged. But there is still a need to conduct further scientific-based study to explore the chemical characterizations and pharmacological evaluations of 5 Indian *Tinospora* species (*T. formanii, T. glabra, T. maqsoodiana, T. smilacina,* and *T. subcordata*). More scientific studies are to be conducted on therapeutic and toxicological properties of *Tinospora* that will help in the development of new therapeutic products in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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