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Review Article

Phytochemistry and biological activities of *Tetracera* species

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ABSTRACT

The species of the genus *Tetracera* are utilized as remedies for various illnesses and infections including backache, haemorrhoids, diabetes, jaundice, scurvy, cough, and tooth pain. The root, stem bark, and leaves of these medicinal plants display several physiological activities. The phytochemicals reportedly present in the species include tannins, flavonoids, cardiac glycosides, saponins, phlobatannins, terpenoids, and flavonoids. Ethanol extract or fraction of plants in this genus mostly yielded flavonoids with significant antioxidant, anti-inflammatory, and antidiabetic activities. However, few compounds have been isolated so far from the species, which include pentacyclic lupane-type triterpene derivatives and flavonoids, of which betulinic acid remains the mostly investigated compound. This review documented up-to-date information on folkloric uses, isolated compounds, and pharmacological activities of medicinal plants in *Tetracera* species.

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1. Introduction

From many years ago, medicinal and herbal plants have gained a unique compartment in a broad range of scientific and industrial disciplines. In fact, food industries, food science, fragrance and cosmetics as well as a wide spectrum of medicinal and pharmaceutical approaches are greatly influenced by the high potential of these materials. In the literature and scientific databases, many reviews have argued and implied the remarkable impacts of medicinal plants referring to their valuable bioactive compounds, ethnobotany, traditional and folk medicine, promising biological and pharmaceutical properties and other related characteristics found in herbal plants (Nahar et al., 2021; Mohammadhosseini et al., 2022; Olaoluwa et al., 2022; Thagriki et al., 2022).

The use of traditional medication is trending in Africa due to the culture and availability of these medicinal plants (Cates et al., 2013; Birhan et al., 2017). The documentation of these active medicinal plants, used in different continents was stressed by the World Health Organization (WHO) (WHO, 2008). The accessibility of medicinal plants in many communities cannot be over-emphasized, making them the favoured choice for patients in most continents (Stangeland et al., 2011; Opara and Osayi, 2016). Therefore, there is a need to document the activities and bioactive constituents of these medicinal plants, which will be a guide in their extraction and use in the field of drug discovery (Pejin et al., 2011; Pejin et al., 2012; Koparde et al., 2019; Ogunlakin and Sonibare, 2019; Süntar, 2020; Nahar et al., 2021).

One of the families of interest in herbal medicine and formulation is the Dilleniaceae family. It consists of fourteen genera and about 500 species. This family is uncommon in Africa, however pantropical *Tetracera* species only exist. Horn (Horn, 2007) provided detailed characteristics of the four subfamilies of the

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Dilleniaceae family: Delimoideae, which is the sister of other subfamilies contains the *Tetracera species* (ca. 20 species) only; and a sister to a clade containing the Old World genera and form a monophyletic group sister of the subfamilies paleotropica called Doliocarpoideae, comprising *Davilla* (30), *Curatella* (1 species), *Doliocarpus* (48), *Pinzona* (1) and *Neodillenia* (3), which are mostly referred to as the Neotropical prevalent genera (Horn, 2009; Bruniera and Groppo, 2010); Hibbertioideae (*Hibbertia*, *Adrastaea* and *Pachynema* and was treated as an Old World clade) and Dillenioideae (*Acrotrema*, *Didesmandra*, *Dillenia*, and *Schumacheria*). The genus *Pachynema*, was reclassified in 2007 as a subgroup of *Hibbertia* (Horn, 2009). Recently, *Doliocarpus* (34 species), *Davilla* (30 species), *Tetracera* (15 species), *Neodillenia* (1 species), *Curatella* (1 species), and *Pinzona* (1 species) were discovered in Brazil (Lima et al., 2014). Recent studies on *Tetracera* species have confirmed their therapeutic value, making them medicinal plants of interest in drug development.

This review documents current data on folkloric applications, isolated bioactive compounds, and pharmacological activities of *Tetracera* species. The information on this family was gotten from the electronic copies of studies on the phytochemistry, ethnomedicinal applications, and pharmacological effects of *Tetracera* species and their bioactive compounds. These key terms such as ''*Tetracera* sp.'' or ''Medicinal importance of *Tetracera*" or ''Compounds isolated from *Tetracera*'' were searched on databases such as Google Scholar, PubMed, and SCOPUS focussing on literature from 1960 up to April 2022.

2. Geographical distribution of *Tetracera* species

Except for the Pacific Islands, east of New Britain and New Caledonia, *Tetracera* species are pantropical. All species are found in the lowlands, rarely above 600 m in elevation; the highest collection is from around 1500 m. The genus has no general habitat, with some species found in forests, others in the scrub, and others in more open areas (Hoogland, 1953; Horn, 2009; Wadhwa, 2017). *Tetracera scandens* (L.) Merr. is found in the following countries: Southern China (Yunnan), Burma (Arracan, Tenasserim), Peninsular Siam, Indo-China (Cambodia, Cochinchina), Nicobar Islands, Sumatra, Malay Peninsula, Banka, Java, Borneo (only Kuching and British North Borneo), Philippines, Celebes, Kangean Islands, and Lesser Sunda Islands (Bali, Sumbawa, Flores). It grows in thickets, scrub, hedges, secondary forests, open primary forests, and teak forests (Central and East Java), on moist to rather dry soil, and frequently on banks of rivers (Hoogland, 1953; Nokhala et al., 2020; Mustaqim, 2020; Sari et al., 2020). *Tetracera asiatica* (Lour.) Hoogland is often found along roadsides, in the scrub, hedges, thickets, open forests, as well as, rarely, in woods; it grows at low altitudes, up to 1500 m (Cambodia); it blooms from March to November and fruits from May to February. *Tetracera asiatica* (Lour.) Hoogland is therefore native to South China (Kwangsi, Kwangtung, and Hainan), Indo-China, and Siam (Hoogland, 1953; Li et al., 2003; Xie et al., 2021).

Tetracera indica (Houtt. Ex Christm. & Panz.) Merr. is a small shrub found in open areas, such as abandoned fields; low liana, climbing over low shrubs, in brushwood as well as open forests, common in the Malay Peninsula and Java, less common in South IndoChina as well as Sumatra, and rarely collected in the rest of its range; at low altitudes, up to 600 m (Hoogland, 1953; Hasan et al., 2017; Ozturk et al., 2018). Tetracera akara (Burm. Fil.) Merr. is found throughout the Deccan Peninsula (Malabar and Travancore), Ceylon, Indo-China (Cambodia), Sumatra, Malay Peninsula, West Java, Borneo, and Celebes. It is a climber in lowland forests, reaching altitudes of up to 750 m. (Hoogland, 1953; Rustiami, 2016; Nair et al., 2019; Nursanti and Adriadi, 2019). *Tetracera loueeiri* (Finet & Gagnep.) Pierre ex W.G. Craib, a climber in open forests, scrubs, and hedges, can be found around the Gulf of Siam, on the Malay Peninsula's west coast from Kedah to Setul, on the east coast from Singora northward, and in Indo-China on the east coast north to Bleu Hoa Province (Hoogland, 1953). Sumatra, Malay Peninsula, Banka, and Borneo are all home to *Tetracera macrophylla* Hook.f. & Thomson. It can climb up to 300 meters in altitude in both dry and swampy forests, and thickets (Hoogland, 1953; Putz and Chai, 1987; Addo-Fordjour et al., 2012; Mazlun et al., 2021). *Tetracera arborescens Jack* are found in Sumatra (Tapanuli, East Coast), Malay Peninsula, Banka, Billiton, Borneo, and Java. This is due to its preference for swampy forests, riverside shrubs, open jungles, and wooded borders at low elevations (Hoogland, 1953).

3. Folkloric uses

Tetracera species have found application in folk medicine as medicine for numerous ailments and contagions (Table 1) (Tona et al., 2004; Nguyen et al., 2004; Fenner et al., 2006; Oluwole et al., 2008; Umar et al., 2010; Lawal et al., 2011; Ahmed et al., 2012). This includes hepatitis, dysentery, and blennorrhagia (Subramanyam et al., 2009). *Tetracera* species are used for back pain, haemorrhoids, diabetes mellitus, jaundice, and scurvy. It is used for the treatment of backache, diabetes and as an anti-scorbutic, toothache, and cough, TB (tuberculosis), as a traditional treatment of inflammation, skin infection, and ulcer (Adesanwo et al., 2003; Betti, 2004; Adesanwo et al., 20l3; Fomogne-Fodjo et al., 20l4), treatment of gastrointestinal sores (Burkill, l985) and as purgative, vermifugal, powerful diuretic and as a cure for gastrointestinal discomfort (Burkill, l985).

Tetracera potatoria Afzel. Ex G. Don was also mentioned in the ethnobotanical survey for the treatment of gynaecological disorders, especially menstrual disorders and associated stomach discomfort among premenopausal women in Nigeria (Ogunlakin and Sonibare, 2019). In Cameroon as well, the leaf of *T. potatoria* Afzel. Ex G. Don has been mentioned for the treatment of toothache and gonorrhoea (Johnny et al., 2022). The stem bark and root of *T. alnifonia* Wild. have been used for the treatment of arthritis (Aworinde et al., 2020). The leaves of *T. indica* (Houtt. Ex Christm. & Panz.) Merr. are used to treat diabetes (Taher et al.,

Table 1
Folkloric uses of some species of genus *Tetracera*.

Botanical name	Parts used	Usage form	Uses	References
T. potatoria Afzel. Ex G. Don	Leaves	Juice	To treat female infertility	(Burkill, 1985; Adesanwo et al., 2003; Betti, 2004; Adesanwo et al., 2013; Ogunlakin and Sonibare, 2021; Johnny et al., 2022)
	Leaves and stem	Boiled in the sap	Use as powerful diuretic, vermifugal and purgative, for the treatment of gastrointestinal and other stomach complaints	
	Sap	-	To treat cough and toothache	
	Root	Decoction	To treat intestinal disorders	
	Leaves	Juice	To treat infammation, skin infection and ulcer	
	Leaves	Infusion	To treat toothache and gonorrhoea	
T. alnifonia Wild.	Stem bark	Infusion	To treat arthritis	(Burkill, 1985; Bouquet, 1974; Arkinstall, 1979; Fowler, 2003; Kembelo, 2003; Gbadamosi and Oleyede, 2014; Aworinde et al., 2020; Boumba et al., 2020)
	Root	Infusion	To treat arthritis	
	Leaves	Ground and mix into paste with palm oil	To treat headache, abdominal pain, and rheumatism	
	Leaves	Alcoholic maceration with palm wine	To treat asthma and pyrexia	
	Leaves	Crushed with salt and pimento	Use as aphrodisiac	
	Leaves or stems	Decoction	To treat toothache, stomachache, headache and also wounds	
T. indica (Houtt. Ex Christm. & Panz.) Merr.	Roots	Root powder mix with Rhynchosia albissima root	To induce child labour during delivery	(Hedberg et al., 1983)
T. scandens (Linn.) Merr.	Leaves	Juice	Applied to boils to ripen them	(Tawan, 2001: Nguyen et al., 2004: Purkayastha et al., 2007; Myung et al., 2009; Lee et al., 2009; Umar et al., 2010)
	Leaves	Decoction	Administered after childbirth	
	Roots		Use as astringent in diarrhoea	
	Roots	Juice	To threat mouth ulcers	
	Stem	Sap	To treat eye irritation	
	Stem	Infusion	To treat haemoptysis in tuberculosis	
	Stem	Infusion	To treat oral candidiasis	
	Stem	Infusion	To treat sore throat	
	Stem	Juice	To reduce body heat	
	Stem	Sap	To treat cough	
	Shoots	Poultice	As antidote for bites of poisonous snakes	
	Aerial portion	Juice	To treat burning sensation during urination	

Table 1 Continued

Botanical name	Parts used	Usage form	Uses	References
T. macrophylla Hook.f. & Thomson	Stem	Infusion	To treat sore throat and haemoptysis	(Indonesia and Hoogland, 1958; Mann et al., 2003) (Pardo De, 2008; Ong et al., 2011; Quattrocchi, 2012; Quattrocchi, 2012; Sabran et al., 2016; Roheem et al., 2020; Mazlun et al., 2021)
	Stem bark	Decoction	To alleviate general body weakness	
	Roots and leaves	Poultice	Applied on the body to control itching	
	Roots	Decoction	To control diarrhoea and dysentery	
	Leaves	Infu(sion	To treat chronic diabetes	
	Stembark	Decoction	To treat TB symptoms	
	Root	Decoction	To treat diarrhoea and dysentery	
	Stems sap	Drinking	As treatment for TB and its related symptoms	
T. loureiri	Roots	Juice	As lymphoma treatment by drinking or rubbing on the skin	(Chuakul, 2010; Sritubtim et al., 2014)
	Roots	Decoction	As relieve for muscle pain	
T. sarmentosa (L.) Vahl.	Root	Decoction	To treat rheumatism	(Uddin et al., 2017)
	Root	Decoction	Treatment for bone fracture	
T. akara (Burm. Fil.) Merr.	Roots	Decoction	To cure liver diseases and inflammatory conditions	(Saradamma et al., 1987; Udayan et al., 2009)
	Leaf	Decoction	To treat pulmonary haemorrhages	
	Leaf	Decoction	To treat aphthae	

2012). Decoction of *T. boiviana* Baill. roots are believed to protect against the impact of witchcraft and when mixed with *Rhynchosia albissima* Gand. root act to induce child labour during delivery (Hedberg et al., 1983). Almost all the parts of *T. indica* (Houtt. Ex Christm. & Panz.) Merr. are effective in the treatment of different ailments such as fever, sinus symptoms, flue, skin rashes, piles, skin itching, mouth ulcer, diarrhoea, insect bites, and diabetes (Ahmed et al., 2012). The stems and roots of *T. indica* (Houtt. Ex Christm. & Panz.) Merr. are effective in the management of high blood pressure and the leaves are used in the treatment of fever (Ong et al., 1999) The root of the same plant is used in treating high blood pressure and high fever, while leaves and roots pounded together are used to treat skin itching (Faridah and Nurulhuda, 1999). In folk remedies, the leaves of *T. indica* (Houtt. Ex Christm. & Panz.) Merr. are used to treat diabetes in Malaysia (Ahmed et al., 2012). *Tetracera akara* (Burm. Fil.) Merr. is used by Kani tribe of Kerala to treat chronic liver disorders and inflammatory conditions (Nair et al., 2020). A decoction comprising *T. loureiri* stem and other herbs is a traditional Thai remedy for fatigue and jaundice, as well as to promote overall health (Lee et al., 2022). Furthermore, the pulverized leaves are dispersed in water and administered for treatment of diarrhoea, or boiled with water (i.e., decoction) and applied externally to boils. The root of *Tetracera scandens* (L.) Merr. has also been used for the management of diarrhoea. The stem sap has been administered orally as an antitussive, whereas stem infusion has been used as a gargle for the treatment of oral candidiasis. The roots are ground and their juice is applied to mouth ulcer (Useful Tropical Plants, 2019; Nokhala and Siddiqui, 2020). *Tetracera alnifolia Willd.* Willd. is used to treat pains associated with rheumatoid disorders, as well as abdominal pain, swelling, and gout (Nsonde et al., 2017; Obonga et al., 2018). *Tetracera scandens* (L.) Merr. leaves is used traditionally for the treatment of diabetes mellitus in Malaysia (Nokhala et al., 2019).

4. Phytochemistry

The phytochemicals reportedly present in the root of *T. potatoria* Afzel. Ex G. Don are tannins, flavonoids, phlobatannins, and cardiac glycosides (Oyebanji and Saba, 2011; Adesanwo et al., 20l3), the leaf contains alkaloids, tannins, saponins, phlobatannins, terpenoids,

and flavonoids (Omotayo and Borokini, 2012), while tannins and saponins are present in the stem back (Gbadamosi et al., 2012) as shown in Table 2. *Tetracera alnifolia Willd.* Willd. leaf possesses a high amount of cardiotonic heterosids, flavonoids, and saponosides as well as steroids, alkaloids, terpenoides, and tannins (Nsonde et al., 2017). Phytochemical analysis of *T. alnifolia Willd. Willd.* Willd. leaf and stem extracts showed like composition; nevertheless, alkaloids and saponins were identified only in the stem (Obonga et al., 2018). *Tetracera scandens* (L.) Merr. stem is rich in terpenoids, alkaloids, and phenols (Muliyah et al., 2018). The level of alkaloids in *Tetracera scandens* (L.) Merr. leaves was found to be higher in the unshaded area when compared with the shaded area (Setiawati et al., 2018), however, no alkaloids have been isolated so far.

4.1. Terpenes and their derivatives

Terpene derivatives, 3-*cis*-*p*-coumaroyl maslinic acid (**1**) and 3-*trans*-*p*-coumaroyl maslinic acid (**2**) (Fig. 1) were isolated from *T. boiviniana* Baill. (Starck et al., 1999). Furthermore, β-sitosterol (**3**) and betulonic acid (**4**) were isolated from *Tetracera breyniana* Schltdl. (Starck et al., 1999; Cinthia et al., 2013). The leaves and stems of *T. breyniana* Schltdl. afforded β-sitosterol (**3**) and betulinic acid (**5**) (Lima et al., 2013). Also, betulinic acid (**5**) was isolated from the methanolic extract of *Tetracera potatoria* Afzel. Ex G. Don root (Adesanwo et al., 20l3) and the stem of *T. indica* (Houtt. Ex Christm. & Panz.) Merr. (Abdullah et al., 2013). *Tetracera*noate (**6**), N-hydroxy imidate-*Tetracera*ne (**7**), β-Stigmasterol (**8**), and Stigmast-5-en-3β-yl acetate (**9**) were isolated from the stem bark methanol extract of *T. potatoria* Afzel. Ex G. Don via column chromatography. Betulinic acid (**5**), botulin (**10**), and lupeol (**11**) have also been isolated from the stem bark methanol extract of *T. potatoria* Afzel. Ex G. Don (Fomogne-Fodjo et al., 20l7). Likewise, β-sitosterol (**3**) and betulonic acid (**4**) were isolated from *n*-hexane extract of the stem bark of *Tetracera indica* (Houtt. Ex Christm. & Panz.) Merr. (Muharni et al., 2019). This affirms that *Tetracera species* are rich in pentacyclic lupane-type triterpene derivatives (Table 3).

4.2. Flavonoids

Flavonoids isolated from *Tetracera* spp. are presented in Table 4. Rhamnocitrin 3-sulphate (**12**), a yellow amorphous powder, has been isolated from *T. alnifolia Willd. Willd.* Willd. leaves and stem (N'Goka et al., 2020). 7-O-methylquercetin (**13**) and 7-O-methylkaempferol (**14**) have also been isolated from the *T. breyniana* Schltdl. (De Lima et al., 2013). The leaves and stems of *Tetracera breyniana* Schltdl. yielded quercetin (**20**), 7-O-methylquercetin (**13**), and 7-O-methylkaempferol (rhamnocitrin) (**14**) (De Lima et al., 2013). The bioactivity-guided fractionation of *T. indica* (Houtt. Ex Christm. & Panz.) Merr. leaves crude ethanolic extract afforded 5,7-dihydroxyflavone-O-8-sulphate (**15**), techtochrysin (**16**), wogonin (5,7 di-hydroxy-8-methoxy flavone) (**17**), norwogonin (5,7,8-trihydroxy flavone) (**18**), keamferol (**19**), and quercetin (**20**) (De Lima et al., 2013; Alhasan et al., 2019). Techtochrysin (5-hydroxy-7-methoxyflavone) (**16**), quercetin (**20**), norwogonin (5,7,8-trihydroxy flavone) (**18**), wogonin (5,7 di-hydroxy-8-methoxy flavone) (**17**), and 5,7-dihydroxyl-8-methoxyflavone (**18**) were isolated from *T. indica* (Houtt. Ex Christm. & Panz.) Merr. stems (Abdullah et al., 2014; Hasan et al., 2017), while *T. macrophylla* Hook.f. & Thomson yielded wogonin (5,7 di-hydroxy-8-methoxy flavone) (**17**), betulinic acid (**5**), kaempferol (**19**), quercetin (**20**), and norwogonin (5,7,8-trihydroxy flavone) (**18**) (Roheem, 2018). Apigenin (**21**) (Fig. 1) is the only flavonoid that has been isolated from *T. potatoria* Afzel. Ex G. Don so far (Ogunlakin et al., 2021).

5. Biological and pharmacological activities

5.1. Antioxidant activity

Tetracera potatoria Afzel. Ex G. Don root displayed a strong effect in mopping free radicals. The methanol extract of *T. potatoria* Afzel. Ex G. Don root exhibited a strong antioxidant activity via DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay with IC_{50} of 0.018 mg/mL against ascorbic acid (0.037 mg/mL) (Adesanwo et al., 2013). Ogunlakin et al. (2021) investigated the antioxidant effect of methanol extract and solvent fractions of *T. potatoria* Afzel. Ex G. Don via DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay. It was discovered that dichloromethane and ethyl acetate fractions of *T. potatoria* Afzel. Ex G. Don had an antioxidant activity with IC_{50} values of 89.15 ± 0.50 and 9.52 ± 0.35 µg/mL, respectively compared to ascorbic acid (IC_{50} of 2.76 ± 0.01µg/mL) and rutin (IC_{50} of 20.6 ± 9.26µg/mL). Comparing these results with the total phenolic content (TPC) showed that the ethyl acetate fraction of *T. potatoria* Afzel. Ex G. Don had the highest TPC (7150.18 ± 110.00 µg GAE/g), while the highest total flavonoid content (190.28 ± 12.30 mg QE/g) was reported in methanol extract (Ogunlakin et al., 2021). The effect of *T. potatoria* Afzel. Ex G. Don root extract on the level of cellular antioxidant enzymes such as superoxide dismutase (SOD) in albino rats was investigated by Oluwole et al. (2008). Methanolic extract of *T. potatoria* Afzel. Ex G. Don root improved SOD activity in a dose-dependent trend among all the treated groups. *Tetracera potatoria* Afzel. Ex G. Don expressively upsurges the amount of superoxide dismutase (an antioxidant enzyme) in high-dose treated animals. Increasing doses of *T. potatoria* Afzel. Ex G. Don considerably reduced the level of malondialdehyde (MDA), an indicator of lipid peroxidation (Oluwole et al., 2008). The highest percentage inhibition of DPPH by *T. potatoria* Afzel. Ex G. Don root methanol extract, as reported by Oyebanji et al. (2011), was 82%. Lipid peroxidation assay revealed that *T. potatoria* Afzel. Ex G. Don attenuated lipid peroxides action by 54%. It was concluded that the high antioxidant activity of this plant is due to its abundance of flavonoids, tannins, and phlobatannins, which likely explains its ethnomedical applications against inflammatory conditions (Oyebanji et al., 2011).

Furthermore, betulinic acid (**5**), which was isolated from the root extracts, had a good antioxidant effect (with

Table 2
Reported phytochemical constituents of *Tetracera* spp.

Plant	Part used	Solvent/ mode of extraction	Alkaloids	Tannin	Flavonoids	Cardiac glycosides	Saponin	Reference
T. potatoria Afzel. Ex G. Don	Root	powder	+	+	+	+	+	(Adesanwo et al., 20l3)
	Stem bark	powder	-	+	-	-	+	(Gbadamosi et al., 2012)
		Ethanol Extract	+	+	+	-	-	(Adekunle et al., 2003)
		Cold water	+	+	+	-	-	
		Hot wtaer	+	+	+	-	-	
	Leaf	Powder	+	+	+	-	-	(Omotayo and Borokini, 2012)
T. alnifolia Willd.	Leaf	Powder	+	+	+			(Nsonde et al., 2017)
T. scandens (Linn.) Merr.	stem	powder	+	-	+	-	-	(Muliyah et al., 2018)
	Leaf	powder	+	-	+	-	-	(Setiawati et al., 2018)

Table 3
Terpenes and its derivatives isolated from Tetracera spp. and their yields expressed in percentage.

Plants	Part/extract	Terpene and derivatives isolated	Percentage yield (%)	Number	Reference
T. boiviniana Baill.	Stem/ methyl ethyl ketone	3-cis-p-coumaroyl maslinic acid	2.25	**1**	(Starck et al., 1999; De Lima et al., 2013)
		3-*trans*-p-coumaroyl maslinic acid	6.5	**2**	
		Betulinic acid	7	**5**	
T. breyniana Schltdl.	Leaves/Ethanol	β-Sitosterol	2.174	**3**	(De Lima et al., 2013)
	Stem/Ethanol	Betulinic acid	9.09	**5**	
T. indica (Houtt. Ex Christm. & Panz.) Merr.	Stem/Methanol	Betulinic acid	0.025	**5**	(Abdullah et al., 2013)
	Stem/*n*-hexane	β-Sitosterol	3.6	**3**	(Muharni et al., 2019)
		Betulonic acid	8.8	**4**	
T. potatoria Afzel. Ex G. Don	Stem bark/ methanol	Tetraceranoate	0.028	**6**	(Fomogne-Fodjo et al., 20l7)
		N-Hydroxy imidate-Tetracerane	0.028	**7**	
		β-Stigmasterol	0.38	**8**	
		Stigmast-5-en-3β-yl acetate	0.17	**9**	
		Betulinic acid	3.39	**5**	
		Botulin	0.056	**10**	
		Lupeol	0.34	**11**	
	Root/methanol	Betulinic acid	2.067	**5**	(Adesanwo et al., 20l3)

an IC_{50} of 0.141 mg/mL), but the synergy of ascorbic acid and betulinic acid (**5**) produced a more significant antioxidant effect. This justifies that betulinic acid (**5**), in synergy with other antioxidants could produce a novel and significant antioxidant activity. This supports the idea that *T. potatoria* Afzel. Ex G. Don, which is high in flavonoids, has potent antioxidant properties (Adesanwo et al., 2013). The antioxidant potential of diverse solvent extracts of *T. akara* (Burm. Fil.) Merr. roots was examined. The aqueous extracts displayed the highest phenolic and flavonoid contents. A higher total phenolic content was discovered in the ethanol fraction of the root, which is found to be responsible for its high antioxidant activity, having 86% inhibition against DPPH radicals at 320 µg/mL concentration. Likewise, this solvent extract displayed high superoxide radical

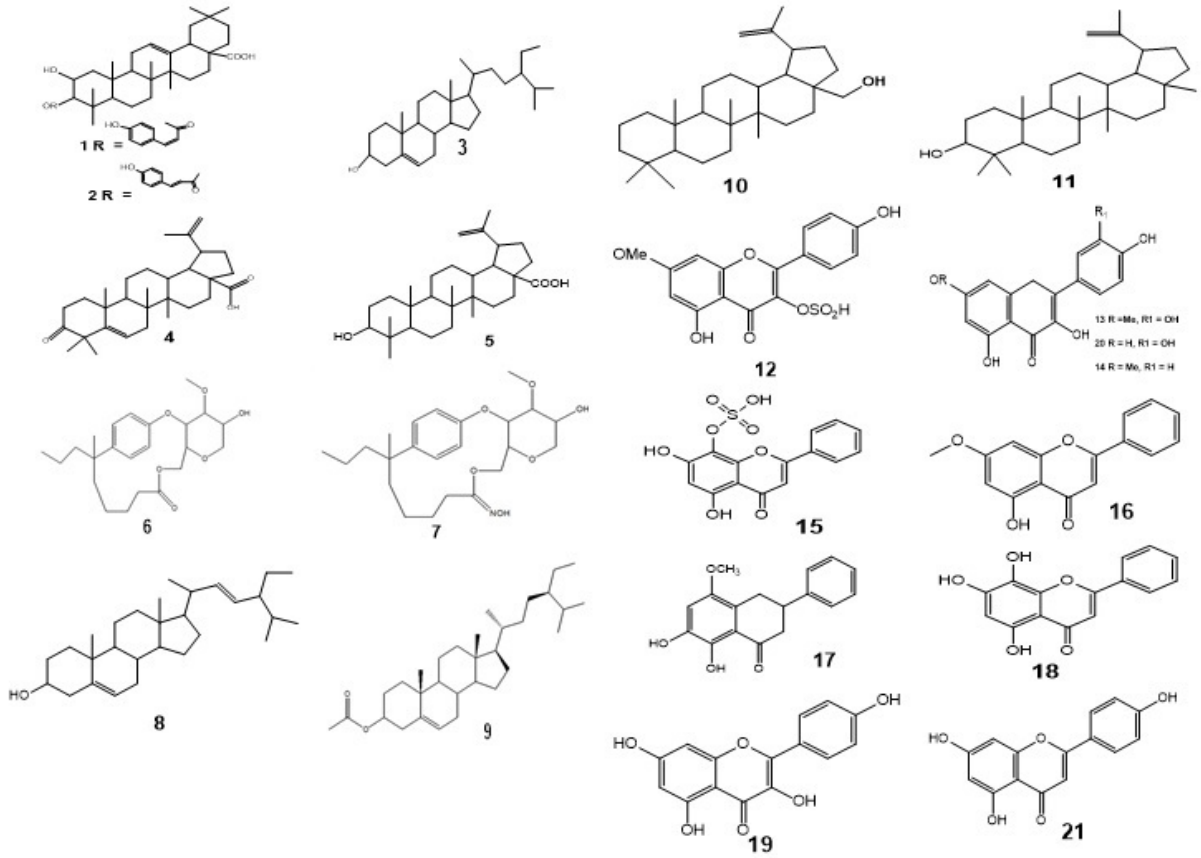

Fig. 1. Molecular structures of the compounds isolated from *Tetracera* spp.

scavenging activity whereas, all solvent fractions except hexane fraction displayed significant nitric oxide radical scavenging effects (Naira et al., 2017). Furthermore, the ethanol extract of *T. macrophylla* Hook.f. & Thomson leaves was found to contain high flavonoids and phenolics, thus exhibiting significant antioxidant activity (Roheem, 2018). Generally, ethanol fraction of *Tetracera species* displayed significant antioxidant activity due to the presence of high flavonoid and phenolic contents in this solvent fraction.

5.2. Anti-inflammatory activity

The evaluation of analgesic and anti-inflammatory influences of methanol extract of *T. potatoria* Afzel. Ex G. Don root, assayed using formalin paw lick test and egg-albumen-induced paw edema in albino rats, revealed a significantly lower writhing response in acetic acid-induced writhing movement. This activity could be via central and peripheral mechanisms (Oyebanji et al., 2013). Furthermore, Betulinic acid (**5**), isolated from ethyl acetate fraction of *T. potatoria* Afzel. Ex G. Don root methanol extracts, was investigated for its anti-inflammatory and anti-nociceptive activity. The study predicted that the mechanism of anti-inflammation is facilitated more via attenuation of prostaglandin release and/or its synthesis. Betulinic acid (**5**) also displayed convincing analgesic activity as revealed through reticence of pain responsiveness in the mice (Oyebanji et al., 2014). The occurrence of several phytochemicals, which include flavonoids and alkaloids contributed to the antinociceptive effect of *T. alnifolia Willd.* (Nsonde et al., 2017). Ethyl acetate (EtOAc) fractions of the stem and leaf of *T. alnifolia* Willd. had potent anti-inflammatory and analgesic activities in albino rats and mice, while the stem fraction (100 mg/kg) showed 55.6 % attenuation of paw edema in rats and 72.9 % nociceptive reaction in mice. The EtOAc fraction (100 mg/kg) of *T. alnifolia* Willd. leaves also reduced the writhing movement in mice (Obonga et al., 2018). Recently, anti-inflammatory effects of ethanol extract of *T. loureiri* on lipopolysaccharide (LPS)-induced inflammatory reaction in RAW264.7 macrophages via reverse transcription-polymerase chain reaction (RT-PCR), Western blotting, and enzyme-linked immunosorbent assay (ELISA) revealed that this plant subdued the appearance of pro-inflammatory intermediaries and cytokines, thereby reducing NF-κB and MAPK signaling pathways in LPS-stimulated macrophages (Lee et al., 2022).

5.3. Hepatoprotective activity

Tetracera akara (Burm. Fil.) Merr. root ethanol extract

Table 4
Flavonoids isolated from *Tetracera* spp. and their yields expressed in percentage.

Plants	Part/extract	Flavonoids isolated	Percentage yield (%)	Number	Reference
T. alnifolia Willd.	leaves and stem	Rhamnocitrin 3-sulphate	1	12	(N'Goka et al., 2020)
T. breyniana Schltdl.	Leaves/ Ethanol	Quercetin	2.391	20	(De Lima et al., 2013)
	Stem/Ethanol	7-*O*-methylquercetin	2.174	13	
		Rhamnocitrin (7-*O*-methylkaempferol)	2.174	14	
T. indica (Houtt. Ex Christm. & Panz.) Merr.	Leaves/ ethanol	5,7-dihydroxyflavone-*O*-8-sulphate	0.063	15	(De Lima et al., 2013; Alhasan et al., 2019)
		Techtochrysin	0.093	16	
		Wogonin (5,7 di-hydroxy-8-methoxy flavone)	14.95	17	
		Norwogonin	1.015	18	
		Keamferol	0.8	19	
		Quercetin	0.755	20	
	Stem/ethanol	Techtochrysin (5-hydroxy-7-methoxyflavone)	-	16	(Abdullah et al., 2014;
		Quercetin	-	20	Hassan et al., 2017)
		Norwogonin (5,7,8-trihydroxy flavone)	-	18	
		Wogonin (5,7 di-hydroxy-8-methoxy flavone)	-	17	
T. macrophylla Hook.f. & Thomson	Stem/successive extraction	Wogonin (5,7 di-hydroxy-8-methoxy flavone)	-	17	(Roheem, 2018)
		Betulinic acid	-	5	
		Kaempferol	-	19	
		Quercetin	-	20	
		Norwogonin (5,7,8-trihydroxy flavone)	-	18	
T. potatoria Afzel. Ex G. Don	Leaf/methanol	Apigenin	0.24	21	(Ogunlakin et al., 2021)

exerted a hepatoprotective effect against acute hepatotoxicity induced by carbon tetrachloride in Wistar rats, which could be due to the bioactive phytoconstituents present in the extract, providing the impetus for the development of a novel hepatoprotective herbal drug (Nair et al., 2019). Ethanolic extract of the root of *T. akara* (Burm. Fil.) Merr. possesses significant hepatoprotective activity mainly by scavenging reactive free radicals, boosting the endogenous antioxidant system in the liver, inhibiting pro-inflammatory mediators (like TNF α, COX-2, iNOS), and promoting the anti-inflammatory IL 10 (Nair et al., 2020).

5.4. Antidiabetic activity

The antidiabetic potential of aqueous and methanol extracts of *T. indica* (Houtt. Ex Christm. & Panz.) Merr. leaves was investigated in normal and alloxan-induced diabetic male albino rats (Sprague Dawley strain). Both extracts exhibited antihyperglycaemic activity in alloxan-induced diabetic rats, without causing hypoglycaemia in normal rats. Furthermore, the aqueous extract also reduced triglyceride accumulation on 3T3-L1 cells in a dose-dependent manner, which is the opposite of what was observed with cells treated with methanol extract (Ahmed et al., 2012). The ethanol extract of *T. macrophylla* Hook.f. & Thomson leaves was found to exhibit good digestive enzyme activity due to the presence of flavonoids and phenolics, proving its effectiveness in the management of diabetes (Roheem, 2018). The α-glucosidase inhibitory activity of 36 hydromethanolic extracts of *Tetracera scandens* (L.) Merr. leaves (0%, 20%, 40%, 60%, 80%, and 100% methanol in water) and establishment of a predictive multivariate model that could be used for the quality evaluation of *Tetracera scandens* (L.) Merr. leaf based on the Fourier transform infrared (FT-IR) spectra of its extracts was investigated by Nokhala et al. (2020a). The AGI potential and the FT-IR fingerprint spectrum were obtained for each extract. The carbon-halide, carbon-oxygen single bonds, and the hydroxyl and carbonyl groups were seen to correlate positively with the α-glucosidase inhibitory activity (Nokhala et al., 2020b). Flavonoids isolated from the leaf of *T. indica*

(Houtt. Ex Christm. & Panz.) Merr. , wogonin (**17**), and norwogonin (**18**) showed weak inhibitory activity while 5,7-dihydroxyflavone-*O*-8-sulphate (**15**), kaempferol (**19**) and quercetin (**20**) displayed strong inhibitory activity against α-glucosidase (Dewi and Maryani 2015; Ma et al. 2015). The significant α-glucosidase inhibitory activity of flavonoids has been ascribed to the presence of hydroxyl substituents on C-3′ and C-4′ of the B ring (Dewi and Maryani 2015), however, 5,7-dihydroxyflavone-O-8-sulphate (**15**) displayed strong α-glucosidase inhibitory activity despite the absence of hydroxyl substituent in the B ring. This suggested different binding orientations of this compound on the active site of the enzyme as compared to other non-sulfated flavonoids (Alhassan et al., 2017). Isolated compounds from effective subfraction (ethyl acetate) of ethanol extract of *T. indica* (Houtt. Ex Christm. & Panz.) Merr., wogonin (**17**), norwogonin (**18**), and techtochrysin (**16**) induced significant adipogenesis like insulin and enhanced adipogenesis like rosiglitazone. Wogonin (**17**) and norwogonin (**18**) also exhibited significant glucose uptake activity (Hasan et al., 2017).

5.5. Xanthine Oxidase Inhibitory activity

Xanthine oxidase is an important enzyme that catalyzes the latter step in the transformation of purines to uric acid and plays a vital role in the production of hyperuricemia and gout. The ethyl acetate fraction (IC_{50} = 21.14 µg/mL) of methanol extract of *T. indica* (Houtt. Ex Christm. & Panz.) Merr. stem significantly inhibited xanthine oxidase, compared to hexane (IC_{50} > 100 µg/mL), DCM (IC_{50} > 100 µg/mL), aqueous (IC_{50} = 35.36 µg/mL) fractions, and methanol extract (IC_{50} = 42.02 µg/mL) (Nguyen et al., 2004).

5.6. Antiproliferative activity

The hexane and DCM fractions of *T. potatoria* Afzel. Ex G. Don methanol extract inhibited the proliferation of Chinese Hamster Ovarian cells, tumorigenic cells, while the crude and ethyl acetate fraction had an insignificant effect on CHO cell proliferation. Crude extract and solvent fractions of *T. potatoria* Afzel. Ex G. Don exerted no inhibitory effect on HeLa cell proliferation. Interestingly, apigenin (**21**), a flavonoid isolated from the DCM fraction of the same plant displayed significant inhibition on the proliferation of HeLa and CHO cell lines (Ogunlakin et al., 2021). The inhibitory influence displayed by apigenin (**21**) on the proliferation of HeLa and CHO cells has been previously reported (Lepley et al., 1996; Souza et al., 2017).

5.7. Effect on polycystic ovarian Syndrome (PCOS)

The effect of *T. potatoria* Afzel. Ex G. Don leaves methanol extract on letrozole-induced PCOS in female albino rats was investigated. Treatment with *T. potatoria* leaf had a curative effect on the irregular menstrual cycle and hormonal imbalance associated with PCOS. Restoration of estrous irregularity and follicular generation to normal following administration of *T. potatoria* could be the physiological effect exerted by phytochemical constituents in the extracts, which uphold the steroidal prestige, allowing fertility to be recuperated (Ogunlakin et al., 2021).

5.8. Antiulcerogenic activity

The effect of methanol extract of *T. potatoria* root on ulcer in albino rats was investigated. Acute pre-treatment of rats with *T. potatoria* and Misoprostol (15 days) caused a significant increase in gastric mucus secretion and mucus cell counts in albino rats. This stimulatory effect of *T. potatoria* on gastric mucus cells and gastric mucus secretion may be comparable to sucralfate and misoprostol, a known drug for treating ulcers (Mertz and Walsh, 1991, Okabe and Amagase, 2005; Oluwole et al., 2008). *Tetracera potatoria* significantly increased the concentration of superoxide dismutase (an antioxidant enzyme) and significantly decreased malondialdehyde (MDA), a marker of lipid peroxidation. The mechanism of action of *T. potatoria Afzel. Ex G. Don* in improving the condition of ulcers victims might be due to the up-secretion of gastric mucus, which led to an increase in the number of gastric mucus cells through cell-proliferation, a mucogenic effect (Oluwole et al., 2008). Adesanwo et al. (2003) also confirmed the anti-ulcerogenic and gastric protective effects of betulinic acid (**5**), one of the bioactive compounds isolated from *T. potatoria* root.

5.9. Antisickling activity

The powdered formulation containing *T. potatoria* Afzel. Ex G. Don bark and other medicinal plants such as *Detarium microcarpum* bark, *Harungana madagascariensis* bark, *Sorghum bicolor* leaves, and *Theobroma cacao* bark exerted beneficial effect in the management of sickle cell anemia. This activity could be linked to the presence of phytochemicals such as tannins, anthraquinones, cardiac glycosides, and alkaloids in this powdered formulation (Gbadamosi et al., 2012).

5.10. Antimicrobial activity

From the study, which investigated the antifungal properties of ethanol, cold water, and boiled water extracts of the root of *T. potatoria* Afzel. Ex G. Don using the disc diffusion agar method, the ethanol extract displayed distinguishable inhibitory effect while cold water extract was the least active against *Aspergillus flavus*, *A. fumigatus*, *A. niger*, *Candida albicans*, *Microsporum audonii*, *Trichoderma viride*, and *Trichophyton mentagrophytes*. Preliminary phytochemical screening revealed the presence of anthocyanins, flavonoids, steroids, and tannins (Adekunle et al., 2003). The stem of *Tetracera scandens (L.) Merr.* also inhibited the growth of *Staphyllococcus aureus* and *Escherichia coli* (Muliyah et al., 2017).
Furthermore, chloroform and methanol extracts of *T. alnifolia* Willd. leaf and root bark inhibited 3 Gram-positive and 4 Gram-negative bacteria viz: *Staphylococcus aureus* UCH 2057, *Streptococcus pneumoniae* UCH 2034, *Bacillus subtillis* UCH 2033, *Pseudomonas*

aeruginosa UCH 2058, *Klebsiella* species UCH 2046, Proteus mirabilis UCH 2055, and Escherichia coli UCH 2052 and also some fungi, *Candida albicans* UCH STC 2036, *Aspergillus niger* PHM 1506, *Trichophyton mentagrophyte* ATCC 4808, *Trichophyton rubrum* ATCC 2894, *Epidermophyton floccosum* ATCC 110227 and *Microsporum canis* ATCC 11622. This confirmed its use in the treatment of respiratory tract infections and superficial mycoses (Lawal et al., 2014). One of the seven compounds isolated from the medium polar extract of *T. potatoria* stem bark, *Tetracera*noate (**6**), demonstrated the supreme inhibitory effect against *M. smegmatis*, while β-stigmasterol (**8**), betulinic acid (**5**), and botulin (**10**) showed considerable anti-mycobacterial activity against both strains (Fomogne-Fodjo et al., 2014; Fomogne-Fodjo et al., 2017).

Ethanol extract *Tetracera scandens* (L.) Merr. extract, via an MT-4 cell-based assay, inhibited effectively HIV replication with an IC_{50} value in the range of 2.0-2.5 µg/ml while the cellular toxicity value (CC_{50}) was more than 40-50 µg/mL concentration, thus yielding a minimum specificity index of 20-fold. This plant extract exhibited this activity by acting as a potent inhibitory agent against HIV-1 RTase activity *in vitro* (Kwon et al., 2011). A patented composition containing ethanol extract of *Tetracera scandens* (L.) Merr. is effective against viral infection by effectively inhibiting reverse transcriptase activities to suppress the synthesis of DNA, thus, effective against most RNA viruses (You et al., 2015).

5.11. Larvicidal activity

In the larvicidal assays, when compared to the synthetic insecticide Temephos, only the hexane fraction from the stem of *T. breyniana* Schltdl. was effective against *Aedes aegypti* larvae. Subsequently, an evaluation of all isolated compounds from *T. breyniana* will be needed to confirm their larvicidal activity (De Lima et al., 2013).

5.12. Toxicity studies

Tetracera indica (Houtt. Ex Christm. & Panz.) Merr. leaves methanol and aqueous extracts displayed no toxicity at a dosage above 5000 mg/kg body weight in albino rats (Taher et al., 2012). *Tetracera alnifolia* Willd. extract displayed no visible signs of delayed toxicity or mortality in albino rats and mice when administered orally at a dosage of 5000 mg/kg body weight (Obonga et al., 2018). However, *T. alnifolia* leaves aqueous extract is considered to be of low toxicity with an LD_{50} greater than 2000 mg/kg. At this dose, the extract exhibited signs of toxicity including dyspnoea and motor impairment (Nsonde et al., 2017). Furthermore, *T. potatoria* Afzel. Ex G. Don extract induced significant decreases in packed cell volume (PCV) and haemoglobin concentration (Hb) but increased white blood cell counts (WBC) after 28 days of its administration in Wistar rats. This indicates that *T. potatoria* root tends to cause anaemia. A compound isolated from this plant - betulinic acid (**5**), also drops the level of PCV while significantly increasing the serum biochemistry (increases in ALT) without any significant effect on the AST. Triglyceride levels were non-significantly reduced in *T. potatoria*-treated rats but were increased in rats administered with betulinic acid. The anaemia observed was regenerative as shown by the increased mean corpuscular volume (MCV) and decrease in the mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) (Oyebanji et al., 2013).

6. Concluding remarks

This review presented the use, phytochemicals isolated, and physiological activities of some plants of *Tetracera* species. In Africa and Asia, these plants are widely used in traditional medicine. Diabetes, tuberculosis, rheumatism, hypertension, eye irritation, ulcer, urinary disorders, body itching, stomachache, snake bites, and diarrhoea have all been reported to be managed by various parts of these medicinal plants. Only a few activities, such as oxidative stress management, anti-inflammatory, hepatoprotective, antidiabetic, XO inhibitory antiproliferative, anti-PCOS, anti-HIV, antiulcerogenic, antisickling, antimicrobial, larvicidal activities, as well as toxicity, have been scientifically established. Ethanol extracts and fractions of these medicinal plants mostly yielded flavonoids with significant antioxidant, anti-inflammatory, and antidiabetic activities. Furthermore, few compounds have been isolated so far, which include terpene derivatives and flavonoids, of which betulinic acid (**5**) remains the mostly investigated compound. The pharmacological effects of the compounds isolated from these species prove that they could be a candidate for the drug discovery. In addition, the mechanisms of action of many of the compounds isolated from these plants are still unclear, necessitating the need for better validation of the efficacy and safety of these medicinal plants.

Conflict of interest

The authors declare that there is no conflict of interest.

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