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REVIEW ARTICLE

# Genus *Tabebuia*: A comprehensive review journey from past achievements to future perspectives



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**Abstract** *Tabebuia* is the largest genus of Bignoniaceae. It is commonly recognized as a therapeutic alternative by rural or remote populations. The results of ethnopharmacological studies indicate the potential use of these plants to treat a large variety of diseases. *Tabebuia* species have been used empirically as anti-inflammatory, anticancer and antimicrobial agents in rural areas of Colombia, Bolivia, Brazil and other Latin-American countries. Due to its great importance in traditional and modern medicine, several *Tabebuia* species have been phytochemically investigated and the potential toxicity of these plants has also been discussed. Variable phytoconstituents are isolated from genus *Tabebuia*, among which; naphthoquinones and phenolic compounds are the most prevalent. The present review aims to provide a critical and comprehensive details about the traditional uses, phytochemical, pharmacological and toxicological properties of twenty *Tabebuia* species. In addition, the reported pharmaceutical documents that support the importance of *Tabebuia* species in traditional systems, are provided. On the other hand, the review also clarify the remaining gaps and thus supply a basis for further investigations. Although recent experimental evidence confirms the pharmacological interest of this genus, further bioguided isolation studies are required to understand the role of a particular compound in the observed biological activities.

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## 1. Introduction

Traditional medicine represents the knowledge, skills and also the practices that depend on beliefs or even experiences belong to specific cultures, for maintenance of health and for prevention, diagnosis or treatment of different illness (Benzie and Wachtel-Galor, 2011). According to World Health Organization, medicinal plants still represent the best source of different drugs (Krishnan, 2018). Plants belonging to family Bignonaceae are commonly employed in traditional medicinal systems (Raju et al., 2011).

Bignonaceae comprises around 116–120 genera and 650–750 species, among them 12 genera and 35 species exist in China, where 21 species are endemic (Zhang and Santisuk, 1998). Mabberley, divided this family into seven tribes mainly distributed in the tropical and sub-tropical parts of the world (Mabberley, 2008; Madhukar et al., 2012). Bignonaceae gets its name from genus *Bignonia* and is also commonly known as trumpet vine or trumpet creeper family (Choudhury et al., 2011), and (Deka et al., 2013). *Tecoma*, *Catalpa*, *Tabebuia*

and *Jacaranda* are some of the well-known members of the family. This family is extensively used in traditional medicine in a number of countries, including Bangladesh (Rahmatullah et al., 2010).

*Tabebuia* is the largest and most important genus of Bignonaceae (Grose and Olmstead, 2007; Ferraz-Filha et al., 2017). Antonio Gomes was the first taxonomist used the word “*Tabebuia*” in the literature in 1803 and then the word used as a generic name by de Candolle in 1838 (Gentry, 1969). The word “*Tabebuia*” comes from the contraction of “tacyba bebuya” meaning “ant wood” referring to ants living in the hollow twigs of some *Tabebuia* species (Gentry, 1970). *Tabebuia*, is a large flowering trees genus that include about 100 species in tropical and subtropical areas (Jimenez-Gonzalez et al., 2013; Gentry, 1970; Bussmann, 2018). *Tabebuia* species are widely used in traditional medicine in treatment of syphilis, malaria, cutaneous infections, stomach disorders, cancer, inflammation, pain, bacterial and fungal infections, anxiety, poor memory, irritability, depression, and for treating diabetes, prostatitis, constipation and allergies (Corrêa and de

**Table 1** The traditional uses of different *Tabebuia* species.

Species name	Common name	Region	Traditional uses	Ref.
<i>T. avellaneda</i> Lorentz ex Griseb	“divine tree”	Tropical rain forests of northeastern Brazil, Central and Latin American	Folk treatment of cancer  For treating eczema, psoriasis, fungal infections, and even skin cancers.  For treatment of ulcers, bacterial and fungal infections	(Rao and Kingston, 1982; Lubeck, 1998; Alonso, 2004; Zhang et al., 2015) (Hashimoto, 1996; Lee et al., 2012) (Suo and Yan, 2016).
			For treating malaria, leishmaniasis, fevers, fungal, bacterial infections and syphilis  For gastrointestinal disturbances, inflammation and tropical diseases  To treat colds, coughs and flu  To treat uterine cancer and liver cirrhosis  Anticancer  Astringent and as a treatment of cutaneous ulcers	(Goel et al., 1987; Guiraud et al., 1994; Schultes and Raffauf, 1990; de Miranda et al., 2001; Twardowschy et al., 2008) (Schultes and Raffauf, 1990; Duke, 1985; Duke and Vasquez, 1994)
			To treat diabetes, malignant tumors, leukemia, other cancers, anemia, and Parkinson’s disease  Anti-inflammatory and for treatment of fungal infections	(Rodrigues, 2006)
			Anti-inflammatory	(Grenand et al., 2004)
			Anti-inflammation and for treatment of influenza  Anticancer	(Schunke, 1993)
			For treating snake bites	(Plowman, 1967)
				(Jones, 1995; Bussmann, 2018)
<i>T. impetiginosa</i> (Mart. ex DC) ( <i>T. avellaneda</i> Lorentz ex Griseb, synome)	Pau d’arco, ipê roxo, taheebo, red (or purple) lapacho (Luebeck, 1999; Mowrey, 2001; Taylor, 2005).	Amazon rain forest, Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guinea, Paraguay, Perú, Surinam, Trinidad, Tobago, and Venezuela.	To treat diabetes, malignant tumors, leukemia, other cancers, anemia, and Parkinson’s disease  Anti-inflammatory and for treatment of fungal infections	(Lewis et al., 2005)
<i>T. aurea</i> (Manso) S. Moore	“craibeira”, “paratudo” and “ipê-amarelo”	South America (from Venezuela to Argentina)	Anti-inflammatory	(Nunes et al., 2003; Reis et al., 2014; Malange et al., 2019)
			Anti-inflammatory and for treatment of influenza  Anticancer	(Agra, 1996)
			For treating snake bites	(Bandoni et al., 1972; Barbosa-Filho et al., 2004)
				(Pott and Pott, 1994; Agra et al., 2007; Hajdu and Hohmann, 2012)
				(Daulatabad and Hosamani, 1991; Agra, 1996; De Abreu et al., 2014)
<i>T. argentea</i> Britt ( <i>T. aurea</i> (Manso) S. Moore synome) <i>T. chrysotricha</i> (Mart. ex DC.) Standley	Silver-trumpet tree, “craibeira”, “paratudo”, and “ipê-amarelo” “ipe”-amarelo or “ipe”	South America (from Venezuela to Argentina) and India	Anti-inflammatory and for treating influenza	(Oga and Sekino, 1969; Graziotin et al., 1992).
<i>T. incana</i> A.H. Gentry	Amazonian tree, “ipê amarelo” and “pau d’arco”	Brazil	Analgesic, antitumor agent, Antidiabetic and for treatment of peptic ulcer	(da Silva et al., 1977; de Oliveira et al., 1993).
			Anti-inflammatory, antimarial, anticancer and for the treatment of kidney and liver disorders	
<i>T. heptaphylla</i> (Vell. Conc.)	“tayí pytá” or “lapacho”	Eastern Paraguay	Anti-inflammatory, anticancer and for treating wounds	(Gupta, 1995; Bernal and Correa, 1989; Ortega Torres et al., 1989; Schmeda-Hirschmann and Papastergiou., 2003).
<i>T. ochracea</i> ssp. <i>neochrysantha</i>	“To hua ri”, “Vero”, and “Cañahuate”	Tropical America, from El Salvador to northwest Venezuela	Antimalarial and for healing ulcers	(Gentry, 1982; Bernal and Correa, 1989; Pérez et al.,

(continued on next page)

**Table 1** (continued)

Species name	Common name	Region	Traditional uses	Ref.
(A. Gentry) <i>T. rosea</i> (Bertol.) DC.,	“Pink Trumpet Tree”	and Colombia Guatemala, Costa Rica, Colombia	Antipyretic and for treating eyes infections Antimalaria and for treatment of rabies, fever, colds, headache, and snake bites For treating throat ailments, fever, and as an astringent Antimicrobial activity	1997) (Gentry, 1992).
			Astringent, anti-inflammatory, antimicrobial, diuretic, and laxative Antimalaria and anticancer (uterine cancer) and for treatment of anaemia, constipation, fever, pain and tonsillitis	(Morton, 1981; lewis et al., 2005) (Binutu and Lajubutu, 1994) (García Barriga, 1975; lewis et al., 2005) (de Almeida et al., 1990; Arenas, 1987; Ramalakshmi and Muthuchelian, 2011; Sichaem et al., 2012) (Madhumitha et al., 2015)
<i>T. billbergii</i>	guayacán	Amazon	Antimicrobial, for treatment of fever, syphilis, malaria, trypanosomiasis, stomach and bladder disorders, and for tumors	(Gómez-Estrada et al., 2012)

Azeredo, 1984; Park et al., 2006; Sichaem et al., 2012; Cragg et al., 2014; Ferreira-Júnior et al., 2015; Regaldo et al., 2017; Ferraz-Filha et al., 2017). Several studies stated the biological efficacy of secondary metabolites isolated from some members of this genus, e.g. lapachol, used in clinical studies as adjuvant in cancer therapy (Rao et al., 1968; Santana and Silva, 1980; Barbosa-Filho et al., 2004).

Bark extract of *Tabebuia* species is known as “taheebo”, “lapacho”, “pau d’arco” or “ipê” and their active components include naphthoquinones, quinines, furanonaphthoquinones, benzoic acid, cyclopentenes dialdehydes and flavonoids (Sharma et al., 1988; Koyama et al., 2000a).

Figures are the simplest way to translate the huge recorded data into informative points. In addition, the aim of the present study is not only to represent the recorded data, but also to explore all the defects and gaps that needed further future investigation. So, we used these statistical figures and information to explore what could the researchers work about in future investigation regarding this genus.

## 2. Traditional uses of some *Tabebuia* species

Portuguese and Spanish population used the names of Pau d’arco and lapacho to identify about 26 species of shrubs and trees belong to *Tabebuia*. These species are indigenous to the American tropics from Mexico to southern South America, the majority of species are found in Brazil and neighboring countries. For curative purposes, native people preferred the inner bark, although the heartwood is more potent. Leaves and flowers are less commonly used (Lewis et al., 2005). In the early 1980s, d’arco became known in North America and Europe. The infusion and decoction of the bark or wood was ingested regularly by at least one million people (Jones,

1995; Lewis et al., 2005). In 1995, d’arco is listed among the top 25 selling herbs in the United States, representing 1.7% of herb sales in United States in 1996 (Arenas, 1977; Lewis et al., 2005). Old native populations used *Tabebuia* extracts as an antidote for snake bites (Rizzini et al., 1988; Ruppelt et al., 1991; Martz, 1992). Table 1 lists the reported traditional uses of different *Tabebuia* species and the region where they are employed.

## 3. Phytochemical studies

To date, about 292 chemical constituents have been isolated from *Tabebuia*, among which, naphthoquinones are considered the main constituents. Other reported classes of secondary metabolites are tannins, flavonoids, alkaloids, and iridoids (Ferreira-Júnior et al., 2015). Several studies provide the preliminary phytochemical screening as a first step for chemical classes’ identification (Jimenez-Gonzalez et al., 2018; Hemamalini et al., 2012a; Sathiya and Muthuchelian, 2008; Madhumitha et al., 2015; da Silva et al., 2017; Mota and Duarte, 2015).

For best knowledge it’s valuable to know that some reported studies consider *T. avellanedae* Lorentz ex Griseb and *T. impetiginosa* Mart. ex DC are synonymous to each other (Fujimoto et al., 1991; Castellanos et al., 2009; Bussmann, 2018).

Table 2 summarizes up all reported data about the phytochemical composition of *Tabebuia* species. The reported phytoconstituents comprise 66 naphthoquinones, 73 flavonoids and phenolic compounds, 26 lignans, 8 coumarins, 31 aldehydes, acids and esters, 30 hydrocarbons, triterpenoids and sterols, 54 iridoids and 4 carotenoids. Each phytochemical is numbered from (1–292) and cited in the text. The structures

**Table 2** Major secondary metabolites reported in *Tabebuia* species.

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
1. Naphthoquinones	<b>(Naphthofuranidine derivatives)</b>	<b>1</b>	<i>T. serratifolia</i>	Trunk wood	(Vidal-Tessier et al., 1988)
	1) 2-ethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>1, 2</b>	<i>T. avallandae</i>	Inner bark	(Steinert et al., 1996)
	2) 2-isopropyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>3</b>	<i>T. incana</i>	Trunk wood	(de Oliveira et al., 1993)
	3) 2-ethyl-5-hydroxynaphtho[2,3- <i>b</i> ]furan-4,9-dione.				
	<b>(Acetyl derivatives of naphthofuranidine)</b>	<b>4</b>	<i>T. avellanedae</i>	Inner bark	(Zhang et al., 2015)
	4) 2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.		<i>T. impetiginosa</i> ( <i>T. avellanedae</i> synome)	Heart wood	(Steinert et al., 1996)
	5) 5-hydroxy-2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.			Bark	(Koyama et al., 2000a; Girard et al., 1988)
	6) 8-hydroxy-2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.				
	7) 6-methoxy-2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.		<i>T. chrysanthra</i>	Bark	(Girard et al., 1988)
	8) 7-methoxy-2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.		<i>T. cassimoides</i>	Stem bark	(Rao and Kingston, 1982)
	9) 8-methoxy-2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>4, 5, 6</b>	<i>T. palmeri</i>	Stem	(Sakhuja et al., 2014)
	10) 7-hydroxy-8-methoxy-2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.		<i>T. rosea</i>	Bark	(Girard et al., 1988)
	11) 7-methoxy-8-hydroxy-2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>4, 6</b>	<i>T. avellanedae</i>	Stem bark	(Wagner et al., 1989)
	12) 7,8-dimethoxy-2-acetyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>4, 7, 9, 12</b>	<i>T. barbata</i>	Bark	(de Saizarbitoria Colman et al., 1997)
		<b>4, 8, 11</b>			
		<b>4, 9, 10, 12</b>	<i>T. ochracea</i>	Inner bark	(Steinert et al., 1996)
			<i>T. ochracea</i> ssp.	Trunk wood	(Zani et al., 1991)
			<i>neochrysanta</i>	Inner stem bark	(Díaz and Medina, 1996)
			<i>T. Billbergii</i>	Inner bark	(Gómez-Estrada et al., 2012)
				Inner bark and trunk wood	
				Inner stem bark	
		<b>11</b>	<i>T. ochracea</i> ssp. <i>neochrysanta</i>	Inner stem bark	(Pérez et al., 1997)
	<b>(1<math>\alpha</math>-hydroxyethyl derivatives of naphthofuran-dione)</b>	<b>13</b>	<i>T. chrysantha</i>	Bark	(Girard et al., 1988)
	13) 2-(1 $\alpha$ -hydroxyethyl naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>13, 14</b>	<i>T. rosea</i>	Bark	(Girard et al., 1988)
		<b>13, 14, 15</b>	<i>T. avellanedae</i>	Inner bark	(Wagner et al., 1989)
	14) 5-hydroxy-2-(1 $\alpha$ -hydroxyethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.		<i>T. impetiginosa</i>	Bark	(Fujimoto et al., 1991; Girard et al., 1988;
	15) 8-hydroxy-2-(1 $\alpha$ -hydroxyethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.		( <i>T. avellanedae</i> , synome)	Koyama et al., 2000a)	
	16) 5,8-dihydroxy-2-(1 $\alpha$ -hydroxyethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>13, 15</b>	<i>T. cassimoides</i>	Stem bark	(Rao and Kingston, 1982)
	17) 6-methoxy-2-(1 $\alpha$ -hydroxyethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>13, 18, 19, 21</b>	<i>T. avallandae</i>	Inner bark	(Steinert et al., 1995; Steinert et al., 1996)
		<b>14</b>	<i>T. ochracea</i>	Trunk wood	(Zani et al., 1991)
	18) 7-methoxy-2-(1 $\alpha$ -hydroxyethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>14, 15</b>	<i>T. rosea</i>	Roots	(Sichaem et al., 2012)
	19) 8-methoxy-2-(1 $\alpha$ -hydroxyethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>14, 15, 16</b>	<i>T. chrysotricha</i>	Wood	(Grazziotin et al., 1992)
	20) 7-methoxy-8-hydroxy-2-(1 $\alpha$ -hydroxyethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>14, 20</b>	<i>T. avellanedae</i>	Inner bark	(Yamashita et al., 2009)
	21) 7,8-dimethoxynaphtho-2-(1 $\alpha$ -hydroxyethyl-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>15</b>	<i>T. incana</i>	Stem bark	(Pérez et al., 1997)
			<i>T. barbata</i>	Bark	(de Saizarbitoria Colman et al., 1997)
		<b>16, 18, 20</b>	<i>T. ochracea</i> ssp. <i>neochrysanta</i>	Bark	(Díaz and Medina, 1996)

(continued on next page)

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
22) 2-(1,2-dihydroxy-1-methyl-ethyl)-5-hydroxy-naphtho[2,3- <i>b</i> ]furan-4,9-dione.	<b>22</b>		<i>T. avellanedae</i>	Inner bark	(Zhang et al., 2015)
23) 2-(1'-methylidenyl)-5-hydroxy-naphtho[2,3- <i>b</i> ]furan-4,9-dione	<b>23</b>		<i>T. rosea</i>	Root	(Sichaem et al., 2012)
24) Lapachol	<b>24</b>		<i>T. avellanedae</i>	Inner bark and Heart wood	(Yamashita et al., 2009; Steinert et al., 1995; wagner et al., 1989; Steinert et al., 1996; Jeon et al., 2011)
			<i>T. impetiginosa</i>	Inner bark	(Park et al., 2006)
			<i>T. aurea</i>	Stem bark	(Barbosa-Filho et al., 2004)
			<i>T. barbata</i>	Bark	(de Saizarbitoria Colman et al., 1997)
			<i>T. billbergii</i>	Trunk wood	(Gomez Estrada et al., 2012)
			<i>T. chrysantha</i>	Heart wood	(Burnett and Thomson, 1968)
			<i>T. chrysotricha</i>	Wood	(Graziotin et al., 1992)
			<i>T. guayacan</i>	Bark	(Manner et al., 1974)
			<i>T. heptaphylla</i>	Trunk wood	(Schmeda-Hirschmann and Papastergiou, 2003)
			<i>T. incana</i>	Trunk wood	(Oliveira et al., 1990)
			<i>T. ochracea</i>	Trunk wood	(Zani et al., 1991)
			<i>T. rosea</i>	Roots	(Joshi et al., 1977; Sichaem et al., 2012)
				Heart wood	(Joshi et al., 1973; Girard et al., 1988)
			<i>T. palmeri</i>	Stem	(Sakhuja et al., 2014)
				Wood	(Villegas et al., 1995)
			<i>T. pentaphylla</i>	Stem bark	(Prakash and Singh, 1980)
				Heart wood	(Rohatgi et al., 1983)
				Leaves and heart wood	(Prakash and Singh, 1981)
			<i>T. serratifolia</i>	Trunk wood	(Oliveira et al., 1999 and Vidal-Tessier et al., 1988)
25) Lapachol methylether.	<b>25, 26, 27</b>		<i>T. avellanedae</i>	Heart wood	(Steinert et al., 1995; Steinert et al., 1996)
26) Desoxy-lapachol					
27) Menaquinone-1					
28) $\alpha$ -Lapachone	<b>28</b>		<i>T. avellanedae</i>	Heart wood	(Steinert et al., 1996)
29) Rhinacantin A			<i>T. chrysantha</i>	Heartwood	(Burnett and Thomson, 1968)
			<i>T. guayacan</i>	Bark	(Manner et al., 1974)
			<i>T. pentaphylla</i>	Heart wood	(Rohatgi et al., 1983)
			<i>T. serratifolia</i>	Trunk wood	(Vidal-Tessier et al., 1988)
			<i>T. heptaphylla</i>	Trunk wood	(Schmeda-Hirschmann and Papastergiou, 2003)
30) Dehydro- $\alpha$ -Lapachone	<b>30</b>		<i>T. avellanedae</i>	Stem bark	(Wagner et al., 1989)

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
			<i>T. chrysanthra</i>	Heartwood	(Burnett and Thomson, 1968)
			<i>T. chrysotricha</i>	Wood and heart	(Steinert et al., 1995)
			<i>T. guayacan</i>	Wood	(Manner et al., 1974)
			<i>T. heptaphylla</i>	Trunk wood	(Schmeda-Hirschmann and Papastergiou, 2003)
			<i>T. palmeri</i>	Wood	(Villegas et al., 1995)
			<i>T. pentaphylla</i>	Heart wood	(Rohatgi et al., 1983)
			<i>T. rosea</i>	Heartwood	(Joshi et al., 1973; Girard et al., 1988)
			<i>T. serratifolia</i>	Roots	(Joshi et al., 1977)
			<i>T. avellaneda</i>	Trunk wood	(Oliveira et al., 1999; Vidal-Tessier et al., 1988)
	31) Dehydro <i>iso-α-lapachone</i>	31	<i>T. heptaphylla</i>	Inner bark	(Steinert et al., 1995)
	32) 5-hydroxydehydro- <i>iso-α-lapachone</i> .		<i>T. incana</i>	Trunk wood	(Schmeda-Hirschmann and Papastergiou, 2003)
			<i>T. pentaphylla</i>	Heart wood	(de Oliveira et al., 1993)
			<i>T. rosea</i>	Heart wood	(Rohatgi et al., 1983)
		32	<i>T. rosea</i>	Root	(Joshi et al., 1973)
		31, 32	<i>T. avellaneda</i>	Root	(Joshi et al., 1977)
	33) 2,3-dihydro-2-(2'-methylethenyl) naphtho[2,3- <i>b</i> ]furan-4,9-dione).	33	<i>T. avallandae</i>	Stem bark	(Sichaem et al., 2012)
	34) Stenocarpone B	34, 35	<i>T. heptaphylla</i>	Inner bark	(Wagner et al., 1989)
	35) Avicequinone A			Trunk wood	(Steinert et al., 1996)
	36) β-Lapachone	36	<i>T. avellaneda</i>	Heartwood	(Schmeda-Hirschmann and Papastergiou, 2003)
	37) Stenocarpoquinone A		<i>T. chrysanthra</i>	Inner bark	(Steinert et al., 1995; Steinert et al., 1996)
			<i>T. guayacan</i>	Heartwood	(Yamashita et al., 2009)
			<i>T. pentaphylla</i>	Inner bark	(Panda et al., 2019)
			<i>T. heptaphylla</i>	Trunk wood	(Manner et al., 1974)
		37	<i>T. heptaphylla</i>	Heart wood	(Rohatgi et al., 1983)
			<i>T. chrysanthra</i>	Trunk wood	(Schmeda-Hirschmann and Papastergiou, 2003)
		36, 37	<i>T. chrysanthra</i>	Heart and sapwood	(Burnett and Thomson, 1968)
	38) Lapachenol	38	<i>T. avallandae</i>	Heart wood	(Steinert et al., 1996)
			<i>T. chrysanthra</i>	Heart wood	(Burnett and Thomson, 1968)
			<i>T. heptaphylla</i>	and sap wood	
			<i>T. heptaphylla</i>	Trunk wood	(Schmeda-Hirschmann and Papastergiou, 2003)
			<i>T. incana</i>	Trunk wood	(de Oliveira et al., 1993)
	(lapachenole derivatives)	39, 40	<i>T. palmeri</i>	Wood	(Villegas et al., 1995)
	39) Dihydro-lapachenole		<i>T. chrysanthra</i>	Heart wood and sap wood	(Burnett and Thomson, 1968)
	40) Nordihydro-lapachenole	41, 42, 43	<i>T. heptaphylla</i>	Trunk wood	(Schmeda-Hirschmann and

(continued on next page)

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
	41) 2,2-dimethyl-3-hydroxy-3,4-dihydro-6-methoxy-4H-naphtho[1,2-b]pyran.				Papastergiou, 2003
	42) 2,2-dimethyl-3 $\alpha$ ,4 $\beta$ -dihydroxy-3,4-dihydro-6-methoxy-4H-naphtho [1,2-b]pyran.				
	43) 2,2-dimethyl-3-hydroxy-3 $\alpha$ ,4 $\beta$ -dihydro-4-oxo-6-methoxy-4H-naphtho[1,2-b]pyran.				
	(Anthraquinone derivatives)				
	44) 1-hydroxyanthraquinone.	44, 45, 46, 47, 48, 51	<i>T. avallandae</i>	Heart wood	Steinert et al., 1996
	45) 1-methoxyanthraquinone.	47, 51	<i>T. impetiginosa</i>	Inner bark	Park et al., 2006
	46) 2-methylanthraquinone.	49, 50	<i>T. chrysanthra</i>	Heart wood	Burnett and Thomson, 1968
	47) 2-hydroxymethylanthraquinone.				
	48) 2-acetoxymethylanthraquinone.				
	49) 2-hydroxy-3-methyl-anthaquinone.				
	50) 1-hydroxy-2-methyl- anthraquinone.				
	51) Anthraquinone-2-carboxylic acid				
	(Naphthalene derivatives)	52, 53	<i>T. heptaphylla</i>	Trunk wood	Schmeda-Hirschmann and Papastergiou, 2003
	52) 2,4-dihydroxy-3-(2,3-dihydroxy-3-methyl-1-oxobutyl)-1-methoxynaphthalene.	53	<i>T. chrysanthra</i>	Sap wood	Burnett and Thomson, 1968
	53) (1-methoxy-naphthalene)				
	54) 3,5-dihydroxy-3-methyl-N-(1-(naphthalen-1-yl)ethyl)pentanamide	54	<i>T. avallandae</i>	Bark	Zhang et al., 2014
	55) 2-hydroxynaphthalene-1,4-dione.	55, 56	<i>T. chrysanthra</i>	Stem	(Panda et al., 2019)
	56) 2-((dimethylamino)methyl)-3 methoxy-naphthalene-1,4-dione.				
	(Naphthofuran derivatives)	57, 58	<i>T. heptaphylla</i>	Trunk wood	Schmeda-Hirschmann, and Papastergiou, 2003
	57) 2,3-dihydro-2-(1-hydroxy-1-methylethyl)-3,4,9-trihydroxynaphtho [2,3-b] furan.				
	58) 4,9-dihydroxynaphtho[2,3-b] furan.				
	59) 9-hydroxy-3-methylnaphto[2,3-b]pyran-2,5,10-trione	59	<i>T. impetiginosa</i>	Stem bark	Koyama et al., 2000a
	60) Dehydrotectol	60	<i>T. pentaphylla</i>	Root bark	Prakash and Garg, 1980
	61) Tetrahydrotectol			Stem bark	Prakash and Singh, 1980
	62) Dimethyl ether tetrahydrotectol			Leaves and heart wood	Prakash and Singh, 1981
			<i>T. rosea</i>	Heart wood	Joshi et al., 1973
		60, 61, 62	<i>T. chrysanthra</i>	Root	Joshi et al., 1977
	63) Tecomaquinone I	63	<i>T. incana</i>	Heart wood	Burnett and Thomson, 1968
	64) Tecomaquinone II	63, 64, 65	<i>T. pentaphylla</i>	Trunk wood	(de Oliveira et al., 1993)
	65) Tecomaquinone III	65, 66	<i>T. rosea</i>	Heart wood	Sharma et al., 1988
	66) Tabebuin			Heartwood	(Khandelwal and Singh, 2008)
2. Flavonoid and phenolics	67) Kaempferol	67, 68	<i>T. pentaphylla</i>	Leaves	Bishay et al., 1987
	68) Quercetin	67, 68, 69	<i>T. argentea</i>	Flowers	Dixit and Srivastava, 1992
	69) Luteolin	70	<i>T. ochracea</i>	Leaves	Blatt et al., 1998

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
	70) Kaempferol 3- <i>O</i> - <i>b</i> -D-glucopyranoside	<b>70, 71</b>	<i>T. nageana</i> Britt.	Flowers	(Santoshnailsetvait 2014; 2016)
	71) Kaempferol 3- <i>O</i> -rutinoside				
	72) kaempferol 3- <i>O</i> -(2'- $\alpha$ -methyl p-coumaryl)- $\beta$ -D-glucoside				
	73) Quercetin 3- <i>O</i> - <i>b</i> -D-glucopyranoside	<b>73 or 76</b>	<i>T. ochracea</i>	Leaves	(Blatt et al., 1998)
	74) Quercetin 3- <i>O</i> -sambubioside	<b>73, 74, 75</b>	<i>T. argentea</i> Britt.	Leaves	(De Abreu et al., 2014)
	75) Quercetin 3- <i>O</i> -robinobioside	<b>73, 76, 77</b>	<i>T. caraiba</i>	Leaves	(Blatt et al., 1996) and (Blatt et al., 1998)
	76) Quercetin-3- <i>O</i> -galactoside				
	77) 3- <i>O</i> -diglycoside of quercetin based on galactose and rhamnose.				
	78) kaempferol-3- <i>O</i> -diglucoside	<b>78, 79</b>	<i>T. pentaphylla</i>	Leaves	(Bishay et al., 1987)
	79) Quercetin-3- <i>O</i> -diglucoside				
	80) Luteolin-7- <i>O</i> -glucoside	<b>80, 81</b>	<i>T. caraiba</i>	Leaves	(Blatt et al., 1996) and (Blatt et al., 1998)
	81) 6-Hydroxyluteolin				
	82) 6-OH-luteolin-7- <i>O</i> -glucoside	<b>80, 82</b>	<i>T. ochracea</i>	Leaves	(Blatt et al., 1998)
		<b>82</b>	<i>T. caraiba</i>	Leaves	(Blatt et al., 1998)
	83) Cyanidin-3-rutinoside	<b>83</b>	<i>T. argentea</i>	Flowers	(Dixit and Srivastava, 1992)
	84) Cyanidin-3-rhamnogluco-5-glucoside	<b>84</b>	<i>T. argentea</i>	Pods	(Swarnalakshmi et al., 1982)
	85) Naringenin	<b>85, 86</b>	<i>T. argentea</i>	Pods	(Swarnalakshmi et al., 1982)
	86) Naringenin-7-glucorhamnoside				
	87) 5,7,4'-Trihydroxyflavone	<b>87</b>	<i>T. palmeri</i>	Flowers	(Sahuja et al., 2014)
	88) 3,4,5-Trihydroxy-7-methoxyflavone	<b>88</b>	<i>T. aurea</i>	Stem bark	(Barbosa-Filho et al., 2004)
	89) Rutin	<b>89</b>	<i>T. argentea</i>	Leaves	(De Abreu et al., 2014)
			<i>T. caraiba</i>	Flowers	(Vinod et al., 2011)
				Flowers	(Swarnalakshmi et al., 1982)
				Leaves	(Blatt et al., 1996; Blatt et al., 1998)
	90) Epigallocatechin gallate	<b>90</b>	<i>T. ochracea</i>	Leaves	(Blatt et al., 1998)
	91) 4a,5,8,8 $\alpha$ -tetrahydro-5-hydroxy-3,7,8-trimethoxy-2-(3,4-dimethoxyphenyl) chromen-4-one (TMF)	<b>91</b>	<i>T. roseo-alba</i>	Leaves	(Ferraz-Filha et al., 2016)
			<i>T. argentea</i>	Flower	(Vinod et al., 2011)
			<i>T. chrysanthia</i>	Stem	(Panda et al., 2020)
	92) Benzyl- <i>b</i> -D-glucopyranoside.	<b>92</b>	<i>T. argentea</i> Britt.	Leaves	(De Abreu et al., 2014)
	93) 1'- <i>O</i> - $\beta$ -(3,4-dihydroxyphenyl)-ethyl-4'- <i>O</i> -caffeooyl- $\alpha$ -L-rhamnopyranosyl-(1'-3')-D-glucopyranoside. ( <b>Acteoside</b> )	<b>93</b>	<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)
		<b>93, 94, 95</b>	<i>T. chrysotricha</i>	Immature legumes	(Ogihara et al., 2015)
	94) 2-(3,4-dihydroxyphenyl)ethyl 1' $\alpha$ -L-rhamnopyranosyl-(1-3)-(6-O-caffeooyl)- $\beta$ -D-glucopyranoside ( <b>Isoacteoside</b> )	<b>93, 94, 96, 97, 98, 99</b>	<i>T. avellaneda</i>	Bark	(Suo et al., 2013)
	95) 2-(3,4-dihydroxyphenyl)ethyl 1' $\alpha$ -Lrhamnopyranosyl-(1-3)-(4-O-caffeooyl)-2-O-acetyl- $\beta$ -D-glucopyranoside ( <b>2'-acetylacteoside</b> )				
	96) 1'- <i>O</i> - $\beta$ -(3,4-dihydroxyphenyl)-ethyl-4'- <i>O</i> -caffeooyl- $\alpha$ -L-fucopyranosyl-(1'-3')-D-				

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**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
	glucopyranoside.				
	100) 4-hydroxymethyl-2-methoxyphenyl 1-O-b-D-[5-O-(3,4-dimethoxybenzoyl)]-apiofuranosyl-(1 → 6)-b-	<b>100, 101, 102, 103</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2005)
	97) 1'-O-β-(3,4-dihydroxyphenyl)-ethyl-D-glucopyranoside.	<b>103, 104, 105</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2006)
	[4'-O-caffeoyl-(α-L-rhamnopyranosyl)]-(l-3')-D-galactopyranoside.				
	101) 4-hydroxymethyl-2-methoxyphenyl 1-O-b-D-[5-O-(4-hydroxybenzoyl)]-apiofuranosyl-(1 → 6)-b-				
	98) 1'-O-β-(3,4-dihydroxyphenyl)-ethyl-[4''-D-glucopyranoside.				
	<i>O</i> -caffeoyl-(α-L-rhamnopyranosyl)]-				
	102) 4-hydroxymethyl-2-methoxyphenyl 1-O-b-D-(l-3')-				
	[5-O-(4-methoxybenzoyl)]-apiofuranosyl-(1 → 6)-b-D-galactopyranoside.				
	D-glucopyranoside.				
	99) 1'-O-β-(3,4-dihydroxyphenyl)-ethyl-[4''-O-caffeoyl-(α-L-fucopyranosyl)]-(l-3')				
	103) 4-(1,2-dihydroxyethyl)-2-methoxyphenyl 1-O-b-D-[5-O-(3,4-dimethoxybenzoyl)]- apiofuranosyl-(1 → 6)-b-D-glucopyranoside.				
	D-galactopyranoside.				
	104) 4-(1,2-dihydroxyethyl)-2-methoxyphenyl 1-O-b-D-[5-O-(4 hydroxy,5-methoxybenzoyl)]-apiofuranosyl-(1 → 6)-b -D-glucopyranoside.				
	105) 4-(1,2-dihydroxyethyl)-2-methoxyphenyl 1-O-b-D-[5-O-(4,5-dimethoxybenzoyl)]-apiofuranosyl-(1 → 6)-b -D-glucopyranoside.				
	106) 3,4-dimethoxyphenyl 1-O-b -D-[5-O-(4-hydroxybenzoyl)]-apiofuranosyl-(1 → 6)-b -D-glucopyranoside.	<b>106</b>	<i>T. chrysotricha</i>	Branches	(Takahashi et al., 2015)
		<b>106, 107, 108, 109</b>	<i>T. avellaneda</i>	Bark	(Awale et al., 2005)
	107) 3,4-dimethoxyphenyl 1-O-b -D-[5-O-(3,4-dimethoxybenzoyl)]-apiofuranosyl-(1 → 6)-b -D-glucopyranoside.	<b>106, 107, 108, 109, 110,</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2004)
		<b>111, 112</b>			
	108) 3,4,5-trimethoxyphenyl 1-O-b -D-[5-O-(4-methoxybenzoyl)]-apiofuranosyl-(1 → 6)-b -D-glucopyranoside.				
	109) 3,4-dimethoxyphenyl 1-O-b -D-[5-O-(4-methoxybenzoyl)]-apiofuranosyl-(1 → 6)-b -D-glucopyranoside.				
	110) 3,4,5-trimethoxyphenyl 1-O-b -D-[5-O-(3,4-methoxybenzoyl)]-apiofuranosyl-(1 → 6)-b -D-glucopyranoside.				

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
	113) 2-(4-hydroxyphenyl)ethyl-1-O- $\beta$ -D-[5-O-113, 114, 115 111) 4-methoxyphenyl 1-O- $\beta$ -D-[5-O-(3, (4-hydroxybenzoyl)]-apiofuranosyl-(1 → 6)- $\beta$ - 4-dimethoxybenzoyl)]-apiofuranosyl-(1 → 6)- $\beta$ - Dglucopyranoside. D-glucopyranoside.	113, 114, 115 113, 114, 116 114, 115, 116	<i>T. avellanedae</i> <i>T. chrysotricha</i> <i>T. impetiginosa</i>	Bark Branches Bark	(Awale et al., 2005) (Takahashi et al., 2015) (Warashina et al., 2004)
	114) 2-(4 hydroxyphenyl)ethyl-1-O- $\beta$ -D-[5-O-(3,4- dimethoxybenzoyl)]-apiofuranosyl-(1 → 6)- $\beta$ - 112) 2,4-dimethoxyphenyl 1-O- $\beta$ -D-[5-O-(3,4- dimethoxybenzoyl)]-apiofuranosyl-(1 → 6)- $\beta$ -D- glucopyranoside D-glucopyranoside.				
	115) 2-(4-hydroxyphenyl)ethyl-1-O- $\beta$ -D-[5-O-(4- methoxybenzoyl)]-apiofuranosyl-(1 → 6)- $\beta$ -D- glucopyranoside.				
	116) 2-(4-hydroxyphenyl)ethyl-1-O- $\beta$ -D-[5-O-(3,4,5- trimethoxybenzoyl)]-apiofuranosyl-(1 → 6)- $\beta$ -D- glucopyranoside.				
	117) 2-methoxy-4-[(1S,2S)-1,2,3-trihydroxypropyl] phenyl 1-O- $\beta$ -D-[6-O-(4-methoxybenzoyl)]- glucopyranoside.	117 117, 118	<i>T. impetiginosa</i> <i>T. impetiginosa</i>	Bark Bark	(Warashina et al., 2005) (Warashina et al., 2006)
	118) 2-methoxy-4-[(1S,2S)-1,2,3trihydroxypropyl] phenyl 1-O- $\beta$ -D-[6-O-(4-hydroxybenzoyl)]- glucopyranoside.				
	119) Osmanthuside H	119	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2004)
	120) 2-(4-hydroxyphenyl)ethyl 5-O- 3'',4''- dimethoxycinnamate- $\beta$ -D-apiosyl-(1 → 6)- $\beta$ -D- glucopyranoside.	120, 121	<i>T. chrysotricha</i>	Branches	(Takahashi et al., 2015)
	121) 2-(4-hydroxyphenyl)ethyl 5-O-trans-feruloyl- $\beta$ - D-apiosyl-(1 → 6)- $\beta$ -D-glucopyranoside (osmanthuside J)				
	122) 3,4 dimethoxyphenyl 1-O- $\beta$ -D-apiofuranosyl- (1 → 6)- $\beta$ -D glucopyranoside.	122, 123	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2006)
	123) 3,4,5-trimethoxyphenyl 1-O- $\beta$ -D- apiofuranosyl-(1 → 6)- $\beta$ -D-glucopyranoside.				
	124) Erythro1,2-bis(4-hydroxy-3-methoxyphenyl)- 1,3-propanediol-4'-O- $\beta$ -Dglucopyranoside.	124, 125	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2006)
	125) Threo-1,2-bis(4-hydroxy-3-methoxyphenyl)-1,3- propanediol-4'-O- $\beta$ -glucopyranoside.				
	126) 2,4-dimethoxyphenyl 1-O- $\beta$ -D-apiofuranosyl- (1 → 6)- $\beta$ -D-glucopyranoside.	126	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2006)
	127) 4-[(3,4-dimethoxybenzoyloxy)methyl]-2- methoxyphenyl 1-O- $\beta$ -D-[5-O-(3,4- dimethoxybenzoyl)]-apiofuranosyl-(1 → 6)- $\beta$ -D-	127, 128, 129, 130 130	<i>T. impetiginosa</i> <i>T. impetiginosa</i>	Bark Bark	(Warashina et al., 2006) (Warashina et al., 2004)

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**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
	glucopyranoside. 128) 4-[(3,4-dimethoxybenzoyl)oxy]methyl]-2-methoxyphenyl 1-O-β-D-January[5-O-(4-hydroxybenzoyl)]-apiofuranosyl-(1 → 6)-β-D-glucopyranoside. 129) 4-[(4-methoxybenzoyl)oxy]methyl]-2-methoxyphenyl 1-O-β-D-[5-O-(4-hydroxybenzoyl)]-apiofuranosyl-(1 → 6)-β-D-glucopyranoside. 130) 4-[(3methoxy-4hydroxybenzoyl)oxy]-methyl]-2-methoxyphenyl 1-O-β-D-[5-O-(3,4-dimethoxybenzoyl)]-apiofuranosyl-(1 → 6)-β-D-glucopyranoside. 131) 5'-O-3,4-dimethoxybenzoyl-β-D-apiofuranoside. 132) 5'-O-4-methoxybenzoyl-β-D-apiofuranoside. 133) 5'-O-4-hydroxybenzoyl-β-D-apiofuranoside. 134) 5'-O-3, 4-dihydroxybenzoyl-β-D-apiofuranoside. 135) Guayin 136) Guayanin 137) ((4S)-3,4-dihydroxy-5-(((2R,3S,4S,5S,6S)-3,4,5-trihydroxy-6-(3,4,5-trimethoxyphenoxy)tetrahydro-2H-pyran-2-yl)methoxy)tetrahydrofuran-3-yl)methyl 4-hydroxybenzoate. 138) ((5R)-5-(((2R,3S,4S,5S,6S)-4,5-dihydroxy-6-(hydroxymethyl)-2-(4-hydroxyphenethoxy)tetrahydro-2H-pyran-3-yl)oxy)-3,4-dihydroxytetrahydrofuran-3-yl)methyl 3,4-dimethoxybenzoate.	<b>131, 132, 133, 134</b> <b>135, 136</b> <b>137, 138</b> <b>139</b> <b>140</b> <b>141</b> <b>142</b> <b>143</b> <b>144, 145</b> <b>146</b>	<i>T. avellanedae</i> <i>T. guayacan</i> <i>T. chrysotricha</i> <i>T. caraiba</i> <i>T. argentea Britt.</i> <i>T. roseo-alba</i> <i>T. avellanedae</i> <i>T. heptaphylla</i> <i>T. palmeri</i> <i>T. impetiginosa</i> <i>T. chrysotricha</i>	Bark Bark Branches Flowers Leaves Bark Bark Trunk wood Flowers Bark Branches	(Suo et al., 2012) (Manners et al., 1975) (Takahashi et al., 2015) (Soares et al., 2020) (De Abreu et al., 2014) (Ferreira-Júnior et al., 2015) (Suo et al., 2012) (Schmeda-Hirschmann, and Papastergiou, 2003) (Sakhuja et al., 2014) (Warashina et al., 2004) (Takahashi et al., 2015)
3. Lignans	140) 5-hydroxyysesamin 5-O-β-D-glucopyranosyl-(1-2)-[β-D-glucopyranosyl-(1-6)]-β-D-glucopyranoside. <b>(Dihydrobenzofuran lignan)</b> 141) Trans-Dihydro-dehydroniconiferylalcohol 4-O-a-Lrhamnopyranoside ( <b>icariside E4</b> ) 142) Avellanedae A 143) Secoisolariciresinol				
	144) Secoisolariciresinol-4-O-β-D-[6-O-(4-methoxybenzoyl)]-glucopyranoside. 145) Secoisolariciresinol-4-O-β-D-[6-O-(3,4-methoxybenzoyl)]-glucopyranoside. 146) (-)-isolariciresinol 3α-O-β-D-glucopyranoside				

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
4. Coumarins	147) Cycloolivil	<b>147</b>	<i>T. heptaphylla</i>	Trunk wood	(Schmeda-Hirschmann, and Papastergiou, 2003)
			<i>T. incana</i>	Trunk wood	(de Oliveira et al., 1993)
			<i>T. ochracea</i>	Trunk wood	(Zani et al., 1991)
			<i>T. palmeri</i>	Flowers	(Sahuja et al., 2014)
			<i>T. serratifolia</i>	Trunk wood	(Oliveira et al., 2001)
	148) Cycloolivil acetonide	<b>148</b>	<i>T. incana</i>	Trunk wood	(de Oliveira et al., 1993)
	149) Olivil	<b>149</b>	<i>T. serratifolia</i>	Trunk wood	(Oliveira et al., 2001)
	150) (+)-lyoniresinol-3 $\alpha$ -O- $\beta$ -D-glucopyranoside.	<b>150</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2005)
	151) (+)-lyoniresinol-3 $\alpha$ -O-(2 $\prime$ -O- $\beta$ -D-apiofuranosyl)- $\beta$ -D-glucopyranoside.	<b>150, 151</b>	<i>T. chrysotricha</i>	Branches	(Takahashi et al., 2015)
	152) [(1S,2R,3R)-7-Hydroxy-1-(4-hydroxy-5-methoxyphenyl)-3-(hydroxymethyl)-8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl]methyl $\beta$ -D-apiofuranosyl- $\beta$ -D-glucopyranoside.	<b>152, 153</b>	<i>T. chrysotricha</i>	Branches	(Takahashi et al., 2015)
	153) [(1S,2R,3R)-7-Hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-3-(hydroxymethyl)-8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl]methyl $\beta$ -D-apiofuranosyl- $\beta$ -D-glucopyranoside.				
	154) Dihydrodehydro-diconiferyl alcohol 9-O- $\beta$ -D-glucopyranoside.	<b>154, 155, 156</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2005)
	155) Dihydrodehydrodiconiferyl alcohol 9'-O- $\beta$ -D-glucopyranoside.				
	156) Dihydrodehydro-diconiferyl alcohol 4-O- $\beta$ -D-glucopyranoside.				
	157) Balanophonin,	<b>157</b>	<i>T. avellanedae</i>	Inner bark	(Zhang et al., 2014)
	158) Balanophonin 4-O- $\beta$ -D-glucopyranoside.	<b>158</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2005)
	159) Isopaulownin	<b>159</b>	<i>T. rosea</i>	Roots	(Sichaem et al., 2012)
	160) Pawlownin	<b>160</b>	<i>T. incana</i>	Trunk wood	(de Oliveira et al., 1993)
	161) Pinoresinol	<b>161, 162, 163, 164</b>	<i>T. avellanedae</i>	Bark	(Zhang et al., 2014)
	162) Epipinoresinol				
	163) 1-(benzo[d][1,3]dioxol-6-yl)-4-(4-hydroxy-3-methoxyphenyl)hexahydrofuro[3,4-c]furan-3a-ol.				
	164) Salicifoliol				
	165) 4-Aryltetralin	<b>165</b>	<i>T. palmeri</i>	Wood	(Villegas et al., 1995)
	166) 3,4-Dihydro-6,8-dihydroxy-3-methylisocoumarin ( <b>6-hydroxymellein</b> )	<b>166</b>	<i>T. avellanedae</i>	Inner bark	(Wagner et al., 1989)
	167) 6 Hydroxymellein-6-O- $\beta$ -D-apiofuranosyl-(1 → 6)- $\beta$ -D-glucopyranosyl.	<b>167</b>	<i>T. impetiginosa</i>	Bark	(Koyama et al., 2000)
	168) 6 Hydroxymellein-6-O- $\beta$ -D-xylopyranosyl-(1 → 6)- $\beta$ -D-glucopyranosyl.	<b>168</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2006)
	169) 6-Hydroxymellein 6-O- $\beta$ -D-[5-O-(4-methoxybenzoyl)]-apiofuranosyl-(1 → 6)- $\beta$ -D-glucopyranoside.	<b>169</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2006)
	170) 6-Hydroxymellein 6-O- $\beta$ -D-[5-O-(3,4-	<b>170, 171</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2004)

(continued on next page)

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
5. Aldehydes, acids and esters	dimethoxybenzoyl]-apiofuranosyl-(1 → 6)-b-D-glucopyranoside.				
	171) 6-hydroxymellein 6-O-b-D-[5-O-(3,4,5-trimethoxybenzoyl)]apiofuranosyl-(1 → 6)-b-D-glucopyranoside.				
	172) 6-Hydroxymellein-6-O-b-D-[6-O-(4-methoxybenzoyl)]-glucopyranoside.	<b>172</b>	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2006)
	173) 1-(5-(hydroxymethyl)furan-2-yl)isochroman-6,7-diol.	<b>173</b>	<i>T. avellanedae</i>	Bark	(Zhang et al., 2014)
	174) 4-methoxybenzaldehyde (anisaldehyde).	<b>174, 175, 176</b>	<i>T. avellanedae</i>	Inner stem bark	(Wagner et al., 1989)
	175) 4-hydroxy-3methoxy benzaldehyde.				
	176) 3,4 dimethoxy benzaldehyde.				
	177) Benzo[b]furan-6-carboxaldehyde.	<b>177</b>	<i>T. avellanedae</i>	Inner bark	(Wagner et al., 1989)
	178) 3,4-dimethoxybenzoic acid (veratric acid).	<b>178</b>	<i>T. rosea</i>	Bark	(Oliveira et al., 1999)
	179) 4-methoxybenzoic acid (p-anisic acid).	<b>178, 179</b>	<i>T. aurea</i>	Stem bark	(Barbosa-Filho et al., 2004)
	180) 4-hydroxybenzoic acid.		<i>T. rosea</i>	Roots	(Sichaem et al., 2012)
	181) 3,4-dihydroxybenzoic acid.	<b>178, 179, 180</b>	<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)
	182) 4-hydroxy-3-methoxybenzoic acid (vanillic acid).	<b>178, 179, 180, 182, 183</b>	<i>T. avellanedae</i>	Inner bark	(Awale et al., 2005)
	183) 3,4,5-trimethoxybenzoic acid.	<b>178, 180, 181</b>	<i>T. palmeri</i>	Stem	(Sakhuja et al., 2014)
	184) 2-methyl Benzoic acid.	<b>180, 181, 185</b>	<i>T. palmeri</i>	Flowers	(Sakhuja et al., 2014)
	185) 4-O-β-glucosylbenzoic acid.	<b>182</b>	<i>T. serratifolia</i>	Bark	(Oliveira et al., 1999)
	186) 4-hydroxycinnamic acid ( <i>E</i> - <i>p</i> -coumaric acid)	<b>186</b>	<i>T. caraiba</i>	Flowers	(Soares et al., 2020)
			<i>T. rosea</i>	Roots	(Sichaem et al., 2012; Oliveira et al., 1999)
(Cyclopentenyl esters)	187) Caffeic acid	<b>187</b>	<i>T. roseo-alba</i>	Leaves	(Ferraz-Filha et al., 2016)
	188) Avellaneine A	<b>188, 189, 190, 191, 192,</b>	<i>T. avellanedae</i>	Inner bark	(Zhang et al., 2016)
	189) Avellaneine B	<b>193, 194, 196</b>			
	190) Avellaneine C	<b>192, 193</b>	<i>T. impetiginosa</i>	Bark	(Koyama et al., 2000b)
	191) Avellaneine D	<b>192, 193, 194</b>	<i>T. rosea</i>	Roots	(Sichaem et al., 2012)
	192) 2-formyl-5-(4'-methoxybenzoyl-oxy)-3-methyl-2-cyclopentene-1-acetaldehyde.	<b>193</b>	<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)
	193) 2-formyl-5-(3',4'-dimethoxybenzoyloxy)-3-methyl-2-cyclopentene-1-acetaldehyde.				
	194) Tabebuialdehyde A				
	195) Avellaneine E				
	196) Avellaneine F				
(Cyclopentyl esters)	197, 198	<i>T. avellanedae</i>	Inner bark	(Zhang et al., 2016)	
	197) Avellaneine G				
	198) Avellaneine H				
	199) Tabebuialdehyde B	<b>199, 200</b>	<i>T. rosea</i>	Roots	(Sichaem et al., 2012)
	200) Tabebuialdehyde C				
	201) Methyl 3,4-dimethoxybenzoate	<b>201</b>	<i>T. palmeri</i>	Stem	(Sakhuja et al., 2014)
	202) 4 -methoxybenzyl-4-methoxybenzoate	<b>202</b>	<i>T. impetiginosa</i>	Stem bark	(Koyama et al., 2000b)

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
6. Hydrocarbons, triterpenoids and sterols	203) Methyl cinnamate.	<b>203, 204</b>	<i>T. aurea</i>	Stem bark	(Barbosa-Filho et al., 2004)
	204) Ethyl <i>p</i> -hydroxycinnamate.				
	205) 1-hexadecanol	<b>205</b>	<i>T. palmeri</i>	Stem and leaves	(Sahuja et al., 2014)
	206) 1-triacontanol	<b>206</b>	<i>T. palmeri</i>	Stem	(Sahuja et al., 2014)
	207) 1-hentriacontanol	<b>207</b>	<i>T. pentaphylla</i>	Leaves	(Prakash and Singh, 1981)
	208) Linoleic acid	<b>208, 209</b>	<i>T. palmeri</i>	Leaves	(Sahuja et al., 2014)
	209) Palmitic acid				
	210) Hexacosane	<b>210, 213</b>	<i>T. pentaphylla</i>	Root bark	(Prakash and Garg, 1980)
	211) Nonacosane	<b>211</b>	<i>T. pentaphylla</i>	Stem bark	(Prakash and Singh, 1980)
	212) Hentriacontane			Heart wood	(Prakash and Singh, 1981)
	213) Hepacosane	<b>212</b>	<i>T. pentaphylla</i>	Leaves	(Prakash and Singh, 1981)
	214) Squalene	<b>214</b>	<i>T. rosea</i>	Flowers	(Madhumitha et al., 2015)
	215) 6-(1-hydroxyundec-3-enyl)-tetrahydropyran-2-one.	<b>215</b>	<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)
	216) Stigmast-5-en-3 $\beta$ -ol.	<b>216</b>	<i>T. palmeri</i>	Stem and flowers	(Sahuja et al., 2014)
	217) $\beta$ sitosteryl- $\beta$ -D-galactoside	<b>217</b>	<i>T. palmeri</i>	Flowers	(Sahuja et al., 2014)
	218) 3 $\beta$ -hydroxy-12-ursen-28-oic acid (ursolic acid	<b>218</b>	<i>T. palmeri</i>	Flowers	(Sahuja et al., 2014)
	219) 3-O- <i>E</i> - <i>p</i> -coumaroylursolic acid	<b>119</b>	<i>T. caraiba</i>	Flowers	(Soares et al., 2020)
	220) 2 $\alpha$ -hydroxyursolic acid (corosolic acid)	<b>119, 120, 121</b>	<i>T. caraiba</i>	Bark	(Soares et al., 2006)
	221) 3 $\beta$ -6 $\beta$ -19 $\alpha$ -trihydroxy-urs-12-en-28-oic acid	<b>221</b>	<i>T. caraiba</i>	Flowers	(Soares et al., 2020)
	222) Stigmasterol		<i>T. rosea</i>	Bark	(Oliveira et al., 1999)
			<i>T. Billbergii</i>	Inner bark	(Gómez-Estrada et al., 2012)
			<i>T. Impetiginosa</i>	Bark	(Koyama et al., 2000b)
			<i>T. roseo-alba</i>	Leaves	(Ferraz-Filha et al., 2016)
	223) $\beta$ -Sitosterol	<b>223</b>	<i>T. aurea</i>	Stem bark	(Barbosa-Filho et al., 2004)
			<i>T. Billbergii</i>	Inner bark	(Gómez-Estrada et al., 2012)
			<i>T. caraiba</i>	Flowers	(Soares et al., 2020)
			<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)
			<i>T. ochracea</i>	Trunk wood	(Zani et al., 1991)
			<i>T. impetiginosa</i>	Bark	(Koyama et al., 2000b)
			<i>T. pentaphylla</i>	Root bark	(Prakash and Garg, 1980)
				Stem bark	(Prakash and Singh, 1980)
				Leaves	(Bishay et al., 1987) (Prakash and Singh, 1981)
			<i>T. rosea</i>	Heart wood	(Joshi et al., 1977)
			<i>T. rosea</i>	Roots	(Joshi et al., 1973; Oliveira et al., 1999)
	224) $\beta$ -sitosterol-3-O- $\beta$ -D-glucopyranoside	<b>224</b>	<i>T. roseo-alba</i>	Leaves	(Ferraz-Filha et al., 2016)
	225) $\beta$ -sitosterol-3-O- $\beta$ -D-(6-O-acyl)-glucopyranoside	<b>224, 225</b>	<i>T. rosea</i>	Bark	(Oliveira et al., 1999)
	226) Sitostenone	<b>226</b>	<i>T. caraiba</i>	Flowers	(Soares et al., 2020)
			<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)

(continued on next page)

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
7. Iridoids	227) $\alpha$ -amyrin	227	<i>T. rosea</i>	Heart wood	(Joshi et al., 1973)
	228) $\beta$ -amyrin	228	<i>T. pentaphylla</i>	Leaves	(Bishay et al., 1987)
			<i>T. caraiba</i>	Bark	(Soares et al., 2006)
				Flowers	(Soares et al., 2020)
	229) Olean-12-en-3-one (beta-Amyrone)	229	<i>T. roseo-alba</i>	Leaves	(Ferraz-Filha et al., 2016)
			<i>T. caraiba</i>	Bark	(Soares et al., 2006)
				Flowers	(Soares et al., 2020)
	230) Betulinic acid	230	<i>T. aurea</i>	Stem bark	(Barbosa-Filho et al., 2004)
	231) Betulin		<i>T. caraiba</i>	Bark	(Soares et al., 2006)
				Flowers	(Soares et al., 2020)
				Leaves	(Bishay et al., 1987)
	232) Oleanolic acid	230, 231 232	<i>T. pentaphylla</i>	Bark	(Soares et al., 2006)
			<i>T. caraiba</i>	Flowers	(Soares et al., 2020)
				Leaves and bark	(Bishay et al., 1987)
				Root	(Prakash and Garg, 1980)
	233) 3- $\beta$ -O-E-p-cumaroyl-ol-12-en-28-oic	233	<i>T. caraiba</i>	Bark	(Soares et al., 2006)
	234) 3 $\beta$ , 6 $\beta$ , 21 $\beta$ -trihydroxyolean-12ene.	234	<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)
	235) 6-epi-aucubin	235	<i>T. chrysanthra</i>	bark	(Bianco et al., 1982a)
	236) 6-O- <i>p</i> -OH-benzoyl-6- <i>epi</i> -aucubin (derwentioside B)	236	<i>T. alba</i>	Bark	(Von Poser et al., 2000)
			<i>T. argentea</i>	leaves	(Piaz et al., 2013)
			<i>T. chrysanthra</i>	Bark	(Bianco et al., 1982c)
			<i>T. chrysotricha</i>	Bark	(Von Poser et al., 2000)
			<i>T. heptaphylla</i>	Branches	(Takahashi et al., 2015)
				Leaves	(Von Poser et al., 2000; Bianco et al., 1982c)
	237) 6- <i>epi</i> -monomelittoside	237	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2005)
	238) 6-O- <i>p</i> -OH-benzoyl- <i>epi</i> -monomelittoside.	238, 239	<i>T. palmeri</i>	flowers	(Sakhuja et al., 2014)
	239) 6-O- <i>p</i> -methoxy-benzoyl- <i>epi</i> -monomelittoside		<i>T. heptaphylla</i>	Leaves	(Bianco et al., 1982b)
	240) 6-O- <i>p</i> -OH-benzoyl-ajugol (6-O-4-OH-benzoyl-ajugol) (6-O-4"-hydroxy benzoyl-leonuride)	240, 241, 242	<i>T. avellaneda</i>	Inner bark and trunk wood	(Nakano et al., 1993; Awale et al., 2005)
	241) 6-O- <i>p</i> -methoxybenzoyl-ajugol or 6-O-4-methoxybenzoyl-ajugol.	240, 241, 242, 243, 244,	<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)
	242) 6-O-3,4-dimethoxybenzoyl-ajugol.	245	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2005)
	243) 6-O-(3,4,5 trimethoxy-benzoyl)-ajugol.	240, 245	<i>T. chrysotricha</i>	Branches	(Takahashi et al., 2015)
	244) 6-O-2,4-dimethoxybenzoyl-ajugol.	241, 242, 243, 244	<i>T. impetiginosa</i>	Bark	(Warashina et al., 2004)
	245) 6-O-(4-hydroxy-3-methoxybenzoyl)ajugol.(6-O-vanillyl-ajugol or 6-O-vanillylleonuride)	245	<i>T. serratifolia</i>	Trunk wood	(Oliveira et al., 2001)
	246) 6- O -(p-coumaroyl)-catalpol (specioside)	246	<i>T. argentea</i>	Leaves	(Piaz et al., 2013)
			<i>T. aurea</i>	Stem bark	(Nocchi et al., 2020)
			<i>T. pentaphylla</i>	Bark	(Bishay et al., 1987)
			<i>T. rosea</i>	Bark	(Compadre et al., 1982)
	247) Catalposide	247	<i>T. argentea</i>	Leaves	(Piaz et al., 2013)
	248) Amphicoside	247, 248, 249	<i>T. chrysotricha</i>	Branches	(Takahashi et al., 2015)

**Table 2** (continued)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
250) Catalpol	<b>250</b>	<i>T. serratifolia</i>	Seeds	(Hegnauer and Kooiman, 1978)	
251) Avellanedaesides A	<b>251, 252, 253, 254, 255</b>	<i>T. avellaneda</i>	Inner bark	(Suo and Yan, 2016)	
249) 6- <i>O</i> -veratrylcatalposide					
252) Avellanedaesides B					
253) Avellanedaesides C					
254) Avellanedaesides D					
255) Avellanedaesides E					
256) Avelladoids A	<b>256, 257, 258, 259, 260,</b>	<i>T. avellaneda</i>	Inner bark	(Zhang et al., 2017)	
257) Avelladoids B	<b>261, 262, 263</b>				
258) Avelladoids C					
259) Avelladoids D					
260) Avelladoids E					
261) Avelladoids F					
262) Avelladoids G					
263) Avelladoids H					
264) 7-hydroxy-1,3-dimethoxy-7-methyl-octa hydro-cyclopenta [c]pyran-5-yl 4-hydroxybenzoate.	<b>264, 265</b>	<i>T. avellaneda</i>	Bark	(Awale et al., 2005)	
265) 7-hydroxy-1,3-dimethoxy-7-methyl-octa hydro-cyclopenta[c]pyran-5-yl 4-hydroxybenzoate.					
266) 6- <i>O</i> -(4-methoxybenzoyl)-5,7-bisdeoxy-cynanchoside.	<b>266, 267, 268, 269, 270</b>	<i>T. impetiginosa</i>	Bark	(warashina et al., 2005; warashina et al., 2006)	
267) 10- <i>O</i> -(4-methoxybenzoyl)-impetiginoside A.					
268) 6- <i>O</i> -(3,4-dimethoxybenzoyl)-crescentin IV 3- <i>O</i> - <i>b</i> -D-glucopyranoside.					
269) 6- <i>O</i> -(4-methoxybenzoyl)-crescentin IV 3- <i>O</i> - <i>b</i> -Dglucopyranoside.					
270) 3- <i>O</i> -(4-hydroxybenzoyl)-10-deoxyeucommiol 6- <i>O</i> - <i>b</i> -Dglucopyranoside.					
271) 4- <i>O</i> -methylcedrusin	<b>271, 272</b>	<i>T. avellaneda</i>	Inner bark	(Iwamoto et al., 2016)	
272) 1-dehydroxy-3,4-dihydroaucubigenin					
273) 3-deoxy-artselaenin	<b>273</b>	<i>T. avellaneda</i>	Bark	(Zhang et al., 2014)	
274) 8 $\alpha$ -methyl-8 $\beta$ -hydroxy-6 $\beta$ -(3',4'-dimethoxy)benzoyloxy-1 $\alpha$ ,3 $\alpha$ -dimethoxy-octahydro-cyclopenta [c]pyran.	<b>274, 275</b>	<i>T. heptaphylla</i>	Trunk bark	(Garcez et al., 2007)	
275) 8 $\alpha$ -methyl-8 $\beta$ -hydroxy-6 $\beta$ -(4'-hydroxy)benzoyloxy-1 $\alpha$ ,3 $\alpha$ -dimethoxy-octahydro-cyclopenta [c]pyran.					
276) 6- <i>O</i> -E-p-cumaroylcatoalpol	<b>276, 277, 278, 279</b>	<i>T. caraiba</i>	Bark	(Soares et al., 2006)	
277) 6- <i>O</i> -E-p-cumaroyljuglutin-A	<b>276, 278, 279</b>	<i>T. caraiba</i>	Trunk bark	(Soares et al., 2020)	
278) Rehmaglutin-D					
279) Juglutin-D					
280) 6- <i>O</i> -E-p-coumaroyljuglutin D	<b>280, 281, 282, 283</b>	<i>T. caraiba</i>	Trunk bark	(Soares et al., 2020)	
281) 6- <i>O</i> -E-p-coumaroyl-3-demethyl-3- <i>O</i> -ethyljuglutin D					
282) 6- <i>O</i> -E-p-coumaroyl-1-demethyl-1- <i>O</i> -					

(continued on next page)

Metabolite classes	Compound name	Cpd. no.	Species name	Part used	References
	ethyljuglутin D. 283) 7-O-E-p-coumaroylijofuranaldehyde.	284, 285, 296, 297, 298	<i>T. argentea</i>	Leaves	(Piaz et al., 2013)
	Argenteoside A 284) Argenteoside B				
	285) Argenteoside B				
	286) Rehnaglutin A				
8. Carotenoids	287) Stereospermoside 288) Pieroside II 289) Lycopene 290) Capsanthin 291) B-carotene 292) Zeaxanthin	299, 290, 291, 292	<i>T. argentea</i>	Flowers	(Dixit and Srivastava, 1992)

of chemical constituents are illustrated in Figs. 1–8 according to the chemical classes.

### 3.1. Naphthoquinones

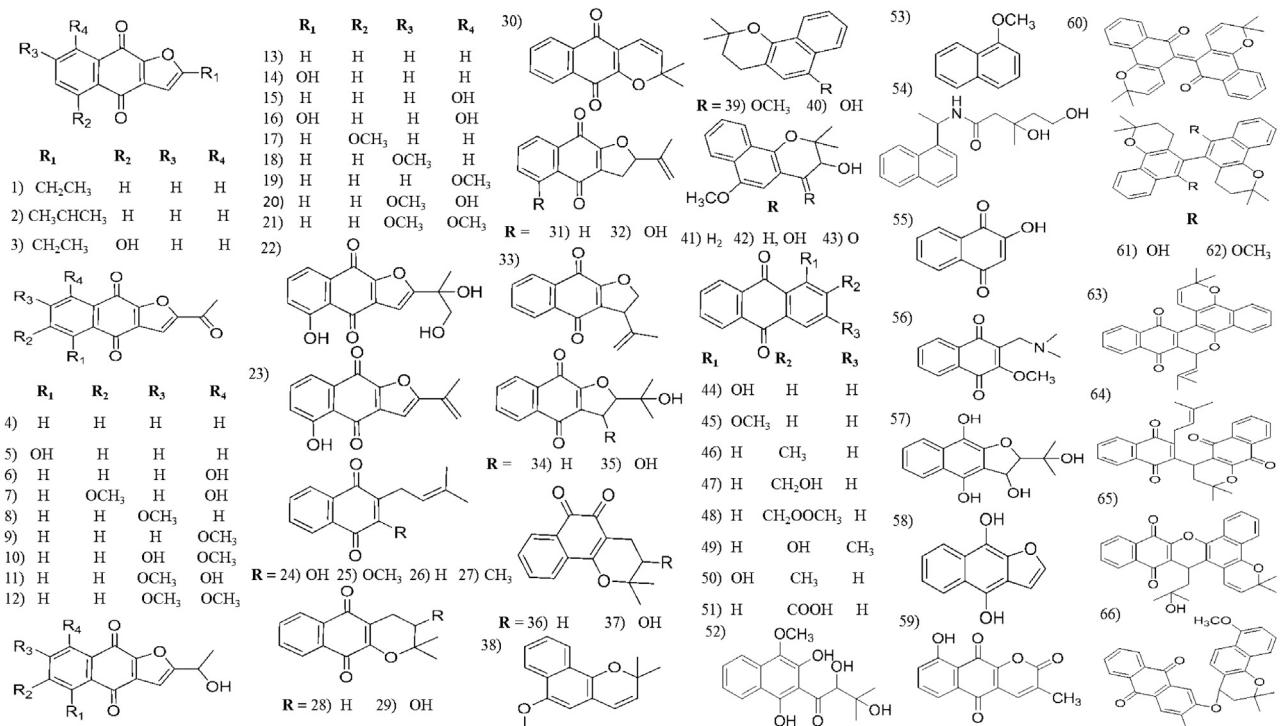
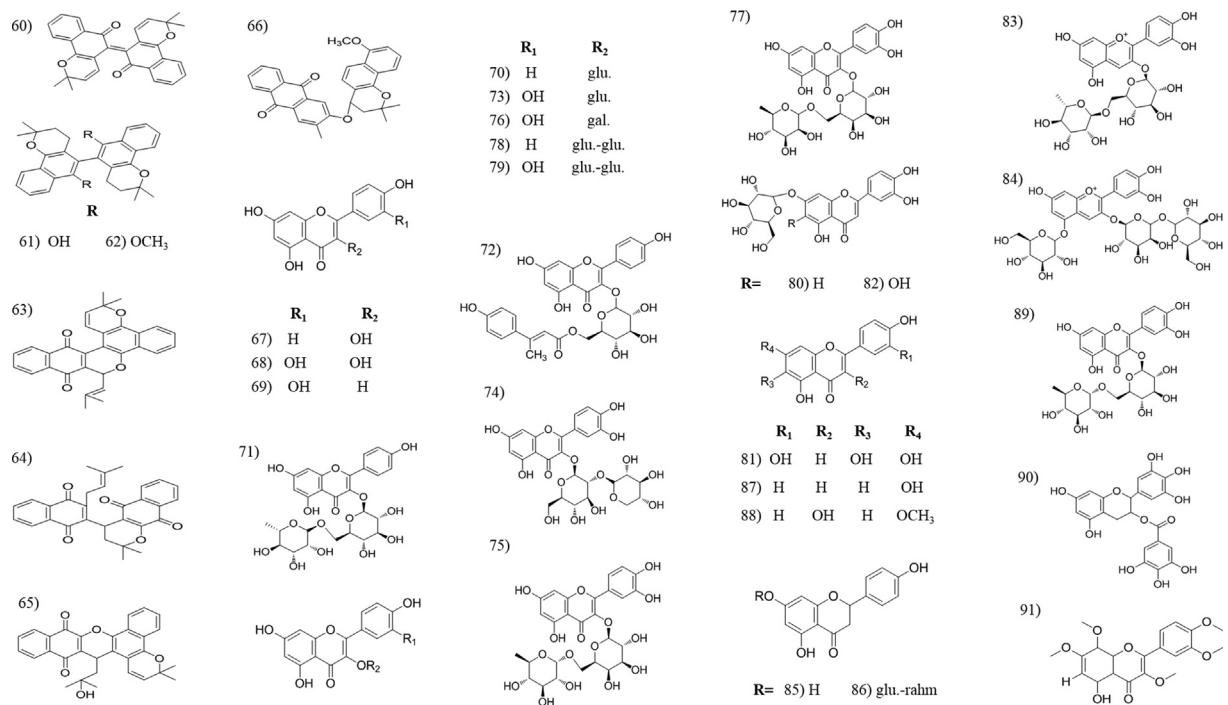
Naphthoquinones are natural aromatic compounds, structurally related to naphthalene, found in several plant families and commercially used for dyeing properties. They are highly reactive organic compounds where their biological activities are attributed to naphthoquinones redox and acid-base properties (Ramos-Peralta et al., 2015). Naphthoquinones are the major constituents of *Tabebuia*. About 66 quinones have been isolated and identified in Table 2. Lapachol is a naturally occurring 1,4-naphthoquinone widely distributed in this genus (Epifano et al., 2014), as well as β-lapachone, the most common naphthoquinone isolated from the genus and is now in clinical trial phase as plant derived anticancer agents (Nirmala et al., 2011). Additionally, β-lapachone, is a potential depigmentation agent for various hyperpigmentation disorders in skin care preparations (Kim et al., 2015b). Naphthoquinones received a special consideration in *Tabebuia* species due to their pharmacological activities (Moura et al., 2001), as anti-inflammatory and wound healing activity (Grazziotin et al., 1992; Kung et al., 2008), antimicrobial activity (Machado et al., 2003; Velasquez et al., 2004; Park et al., 2005; Pereira et al., 2006; Park et al., 2006; Yamashita et al., 2009), antimalarial activity (Pérez et al., 1997), antileishmanial activity (Ali et al., 2010; Gonzalez-Coloma et al., 2012), insecticidal activity (Jeon and Lee, 2011; Jeon et al., 2011; Kim et al., 2013; Borges et al., 2019) and cytotoxic activity (Ueda, et al., 1994; de Saizarbitoria Colman et al., 1997; Yamashita et al., 2009; Morais et al., 2007; Zhang et al., 2015; Sichaem et al., 2012; Woo and Choi, 2005; Woo et al., 2006; Queiroz et al., 2008).

### 3.2. Flavonoids and phenolic compounds

Flavonoids are common plant constituents with a wide range of biological activities, e.g., anti-oxidant, hepatoprotective, antitumour, etc. Most of the *Tabebuia* flavonoids have flavonol structure, whereas the presence of other flavonoid seems to be limited. The majority of the reported flavonoids were isolated from the leaves and flowers of *T. argentea*, *T. pentaphylla*, *T. ochracea* and *T. caraiba*. Phenylethanoids and phenylpropanoid are known for its anti-oxidant, anti-inflammatory and neuroprotective activity (Pan et al., 2003). The majority of these compounds were isolated from *T. avelanadae* and *T. chrysotricha*. To our observation, the anti-oxidant activity of *Tabebuia* extracts is credited to its content of flavonoids and phenolic compounds (Pires et al., 2015; Rahman et al., 2015; Rahman et al., 2019; Suo et al., 2013).

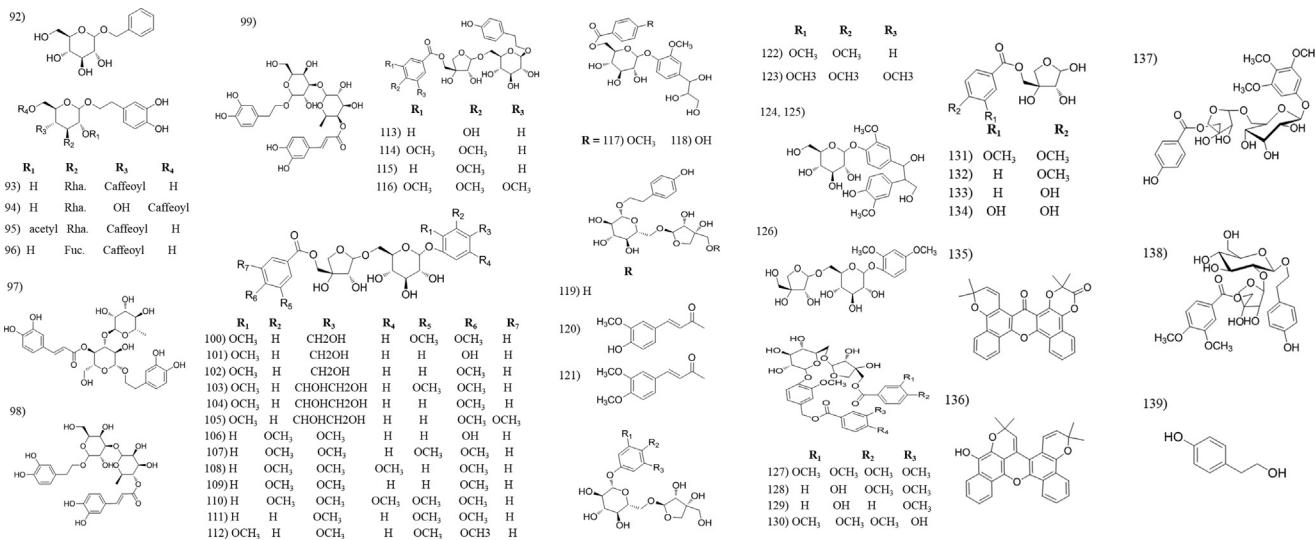
### 3.3. Lignans

Lignans are a large class of secondary metabolites with numerous biological effects, including anticancer, anti-oxidant, anti-hypertensive, antiviral, estrogenic, and insecticidal properties (Simpson and Amos, 2017). Plant lignans, such as sesamin, can converted by intestinal microbiota to mammalian lignans, which have protective effects against hormone-related diseases such as breast cancer (Sato and Matsui, 2012) and fortunately,

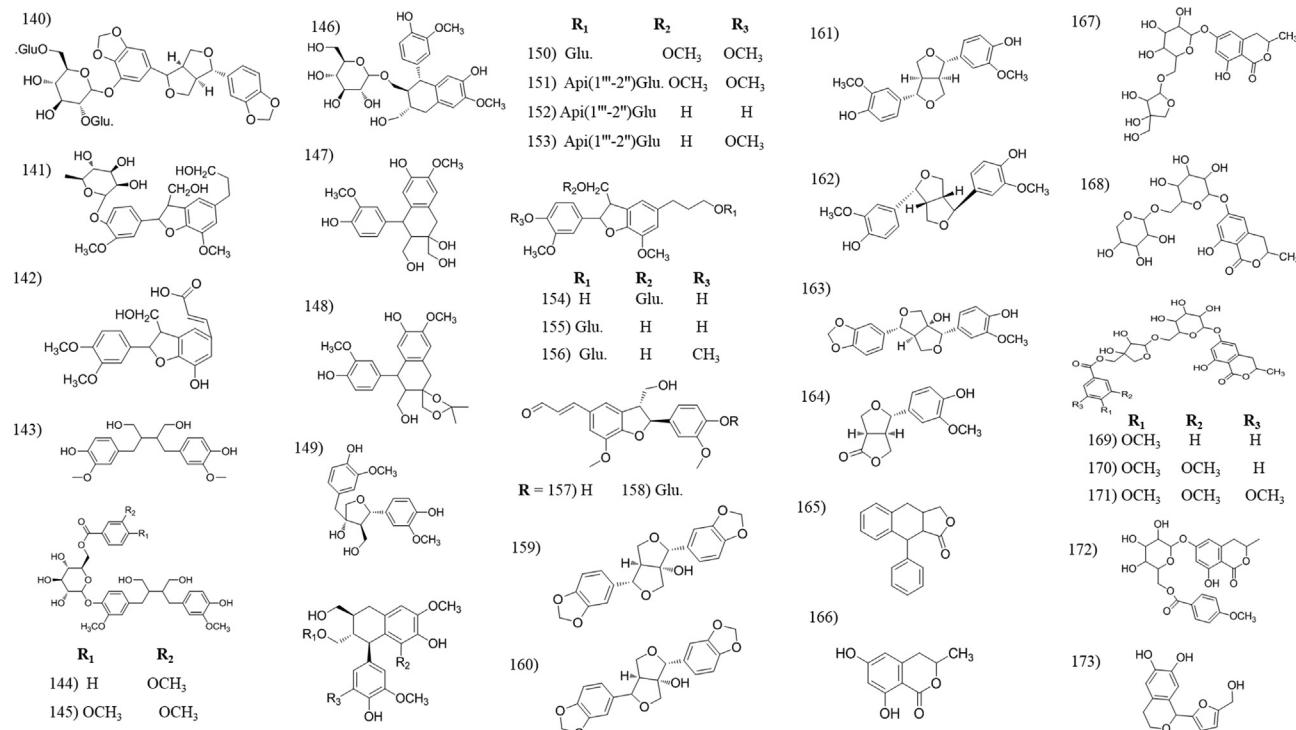
Fig. 1 Chemical structures of naphthoquinones isolated from *Tabebuia* species.Fig. 2 Chemical structures of naphthoquinones and flavonoids isolated from *Tabebuia* species.

5-hydroxyesamin 5-*O*-β-D-glucopyranosyl-(1→2)-[β-D-gluco-pyranosyl-(1→6)]-β-D-glucopyranoside (**140**) was isolated and identified from the leaves of *T. argentea*. Twenty-six lignans were isolated and identified among which, avallandae A (**142**) exhibit anti-inflammatory activity (Suo et al., 2012),

icariside E4 (**141**), had antinociceptive activity (Ferreira-Júnior et al., 2015) and lyoniresinol-3a-*O*-β-D-glucopyranoside (**150**), showed a potent anti-oxidant activity (Takahashi et al., 2015).



**Fig. 3** Chemical structures of phenolic compounds isolated from *Tabebuia* species.



**Fig. 4** Chemical structures of lignans and coumarin compounds isolated from *Tabebuia* species.

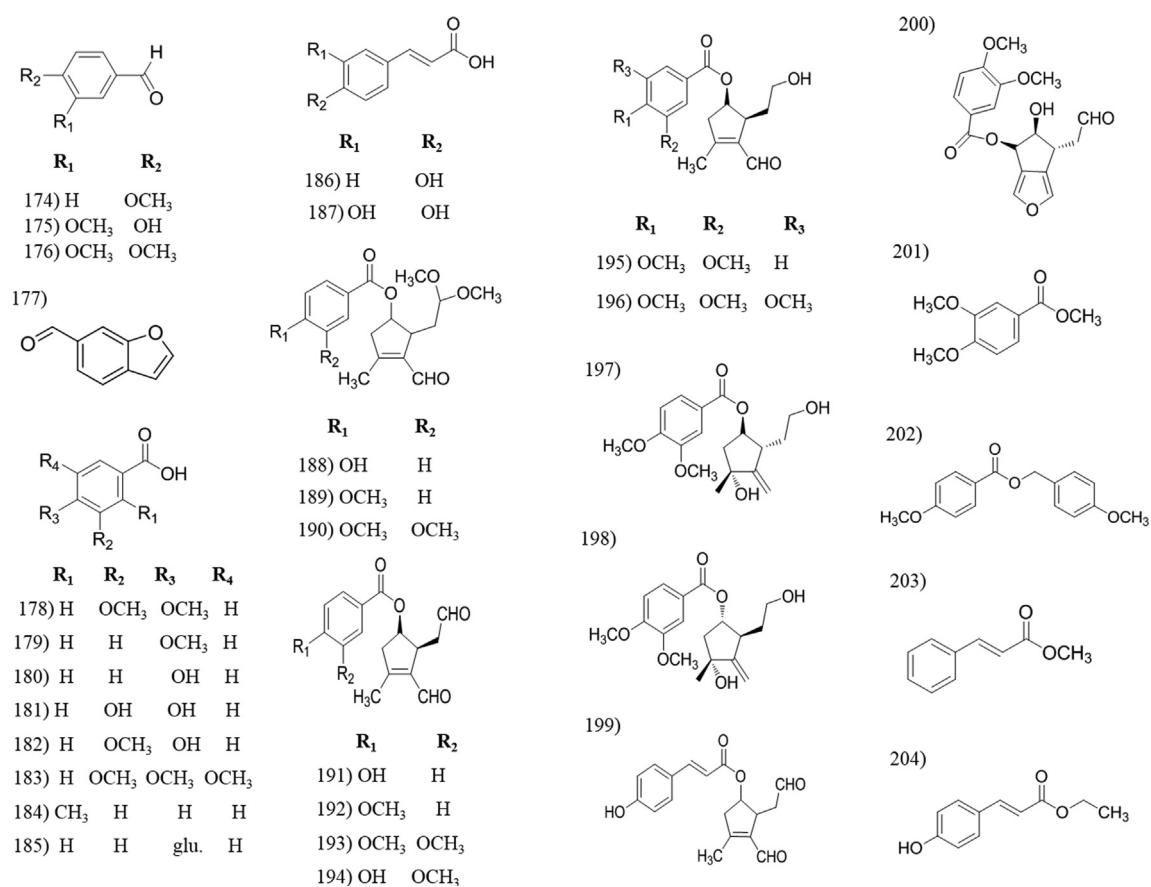
#### 3.4. Coumarins

Coumarins are phenolic substances composed of fused benzene and  $\alpha$ -pyrone rings. They exhibit antithrombotic, anti-inflammatory, vasodilatory and can also antibacterial activities (Bor et al., 2016). Eight coumarin compounds were isolated and identified, from which six of them were isolated and identified by Warashina et al., from the year of 2004–2006 (Warashina et al., 2004; Warashina et al., 2006). The last two, 6-hydroxymellein (166) and the new coumarin 1-(5-(hydroxymethyl)furan-2-yl) isochroman-6,7-diol (173) both

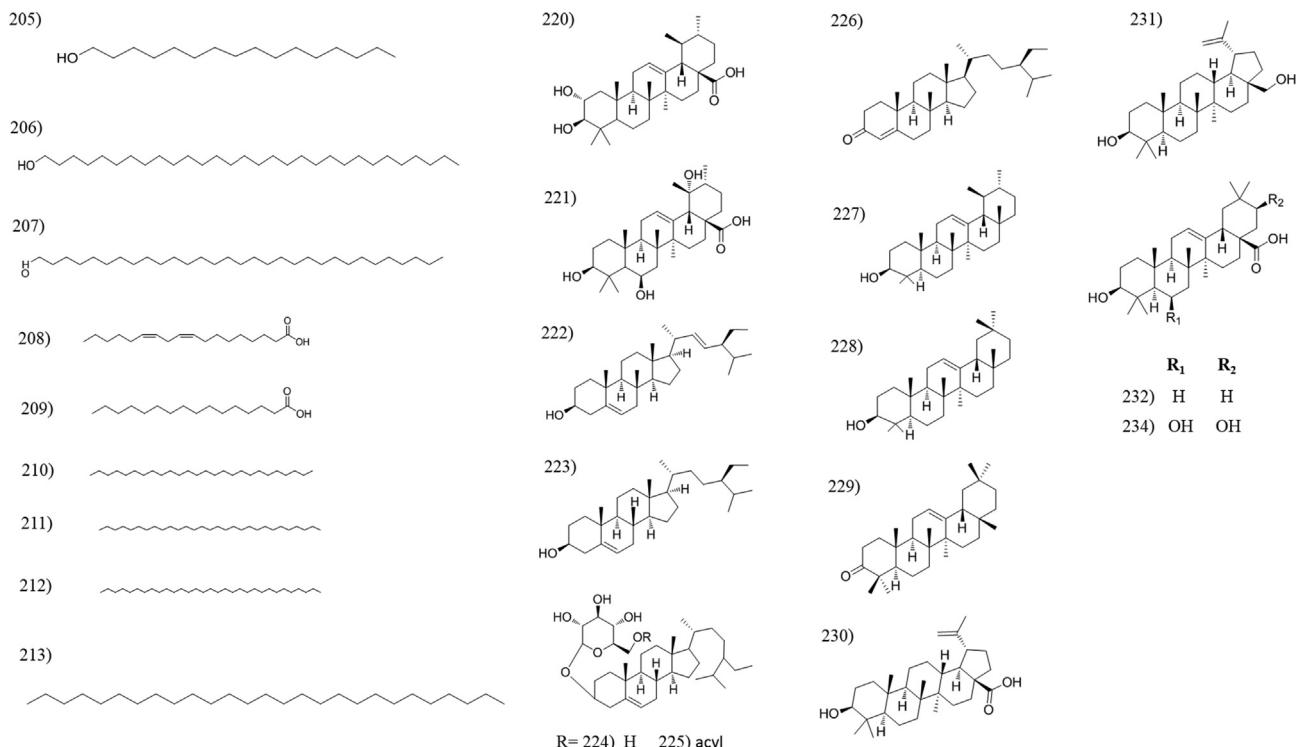
isolated from the bark of *T. avellanedae* (Wagner et al., 1989; Zhang et al., 2014, respectively).

#### 3.5. Aldehyde, acids and esters

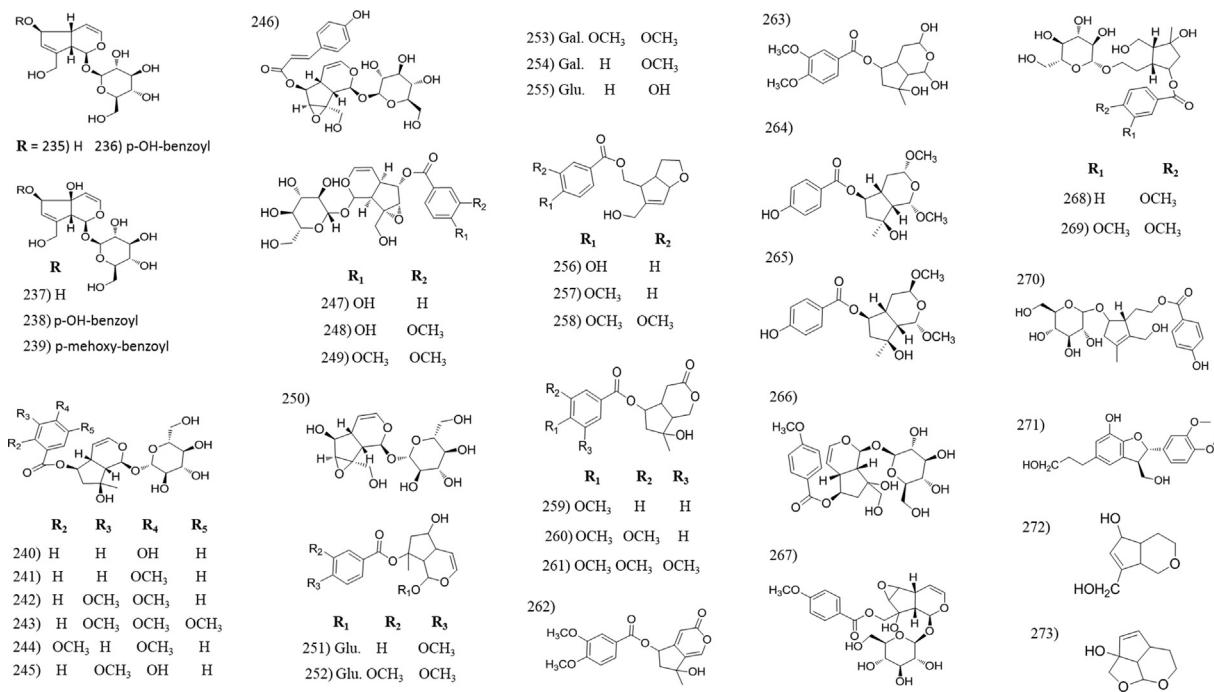
All reported aldehydic compounds, (174–177), were isolated from *T. avellanedae*. The isolated acidic compounds, including eight derivatives of benzoic acid (178–185), 4-hydroxycinnamic acid (186) and caffeic acid (187); were distributed in different *Tabebuia* species including, *T. rosea*, *T. heptaphylla*, *T. aurea*, *T. avellanedae*, *T. palmeri* and *T. roseo-alba*. [Table 2]. Seven-



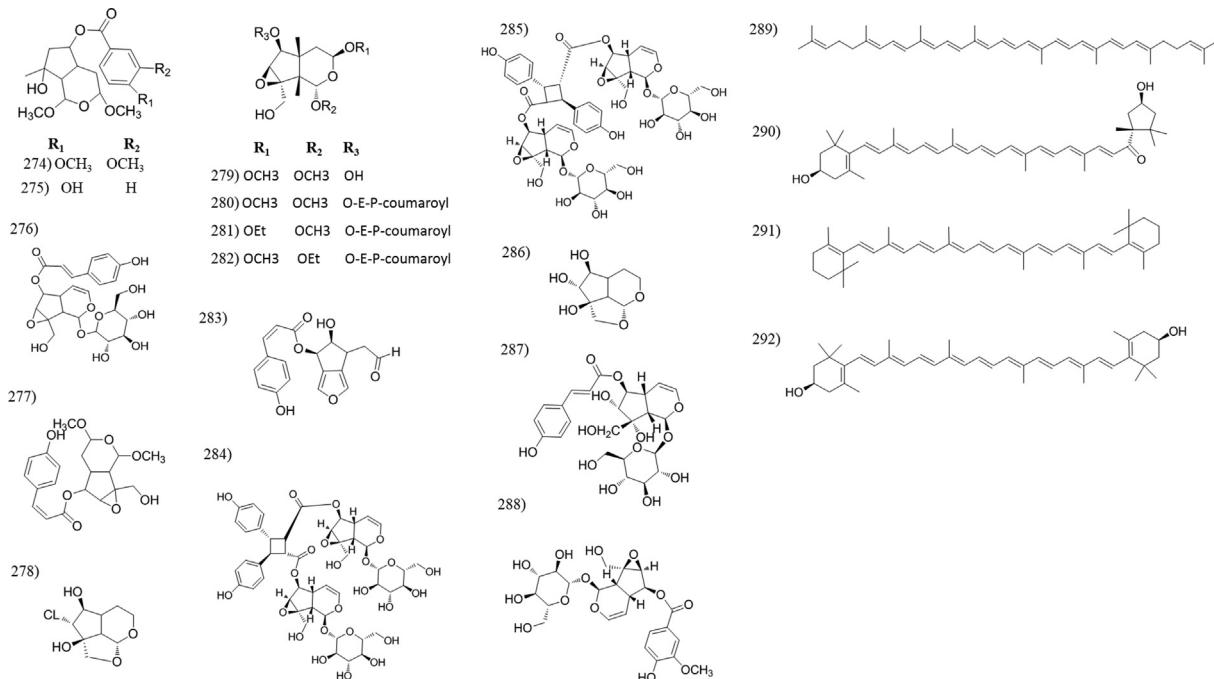
**Fig. 5** Chemical structures of aldehyde, acid and ester compounds isolated from *Tabebuia* species.



**Fig. 6** Chemical structures of hydrocarbons, triterpenes and sterols isolated from *Tabebuia* species.



**Fig. 7** Chemical structures of iridoids isolated from *Tabebuia* species.



**Fig. 8** Chemical structures of iridoids and carotenoid compounds isolated from *Tabebuia* species.

teen ester compounds were isolated from *Tabebuia* species, nine of them identified as cyclopentenyl esters (**188–196**) isolated from *T. avellanedae*, *T. rosea* and *T. heptaphylla*. Two are cyclopentenyl esters (**197–198**) and isolated only from *T. avellanedae*. Tabebui-aldehyde B and C, were isolated from the roots of *T. rosea* while the two benzoate derivatives were isolated from the stem bark of *T. palmeri* and *T. impetiginosa*. The last two are cinnamate derivatives and isolated from the stem bark of *T. aurea*.

### 3.6. Hydrocarbons, triterpenoids and sterols

Three fatty alcohols (**205–207**) and two fatty acids (**208** and **209**) were reported upon investigation of *T. palmeri* and *T. pentaphylla* extracts. Additionally, four hydrocarbons were isolated from *T. pentaphylla* and *T. rosea*. Squalene, a linear triterpene, was isolated from the trunk bark of *T. heptaphylla* (Garcez et al., 2007). Several studies

reported squalene to inhibit the tumor growth in the colon, skin, lung, and breast, and stimulate the immune system against HIV, H1N1, leukemia and herpes (Lozano-Grande et al., 2018). Plant sterols are famous for its ability to reduce cholesterol levels, help in preventing heart disease and heart attacks. Nineteen sterol and triterpene compounds were isolated from different *Tabebuia* species (Table 2, Fig. 6).

### 3.7. Iridoid compounds

Iridoids are reported for its health benefits including anti-inflammatory, anticancer, antimicrobial, antispasmodic, cardioprotective, hepatoprotective, hypoglycemic etc. (Leisner et al., 2017). They are widely distributed in *Tabebuia*. Fifty four iridoid compounds were identified from fifteen *Tabebuia* species [Table 2]. The majority of iridoids were isolated from the bark and wood organs, however twelve iridoids were isolated from other plant organs such as; (296) isolated from leaves of both *T. argentea* and *T. heptaphylla* and flowers of *T. palmeri*, (297–299) from leaves of *T. heptaphylla*, (246, 247 and 284–288) from leaves of *T. argentea* and (250) isolated from the seeds of *T. serratifolia*.

### 3.8. Carotenoids

*Tabebuia* species are rich with carotenoids, this may be the reason for decorative flower colours. Four carotenoid compounds (288–292) were isolated and identified from the yellow flowers of *T. argentea*.

### 3.9. Other constituents identified by GC/MS and other assays from *Tabebuia* species

The GC/MS analysis of *T. impetiginosa* inner bark lead to identification 4-methoxybenzaldehyde, and 4-methoxyphenol as a major volatile constituents (Park et al., 2003). Oleic and linoleic were the most abundant unsaturated fatty acids. In addition, Oxalic, citric, and succinic acids were also identified with  $\alpha$ -tocopherol as the most predominant tocopherols present (Pires et al., 2015). While, the unsaturated fatty acids of *T. argentea* seed oil were expressed in form of linoleic, oleic, vernolic and linolenic acids (Daulatabad and Hosamani, 1991). Moreover, the essential oils analysis of *T. rosea* identified methyl cyclohexane and methyl benzene which representing 65.88% of the total leaf essential oil while the stem bark enclosed n-amyl ketone, methyl cyclohexane and methyl benzene that representing 84.67% (Oloyede et al., 2010).

On the other hand, GC-MS analysis of *T. rosea* leaf extract lead to identification of different classes with aromatic aldehydes (21.81%), representing the main class, in which, 2-furancarboxaldehyde-(5-hydroxy methyl) was the main constituents (Ramalakshmi and Muthuchelian, 2011). In addition, the flower extract showed four major peaks in which Dispiro [1,3-dioxolane 2,2'bicyclo[2.2.1]heptane- 3',2"(1',3'dioxolane)] the main component (Madhumitha et al., 2015).

*T. heptaphylla* wood extract revealed ten compounds from hexane extract in which 2,6-di-*tert*-butylnaphthalene (53.32%) the main and only two compounds were identified in chloroform extract (Borges et al., 2019). For *T. aurea* bark, lapachol with five more compounds were identified (Brito et al., 2020). While, HPLC/DAD/HRESIM of *T. caraiba*

trunk bark, identified nine compounds differ from isolated compounds (Soares et al., 2020).

## 4. Pharmacological and toxicological activity:

### 4.1. Anti-inflammatory activity

Nitric oxide (NO) is an important molecule that regulates a lot of physiological processes. NO is excessively produced when the cell is activated by pro-inflammatory agents such as; tumor necrosis factor (TNF), interferon-gamma (IFN- $\gamma$ ) and interleukin-1 (IL-1), leading to tissue damage or even septic shock (Vincent et al., 2000). The inhibitory activity of NO production, of *T. avellanedae* further supports the traditional utility of this plant as an anti-inflammatory agent. Compounds (113, 240–242 and 264), isolated from *T. avellanedae* water extract, displayed a significant dose-dependent inhibition of NO production in LPS-activated macrophage-like cells with compound 241 being the most potent. The results proved that iridoids are active as inhibitors of NO production, while simple phenolic compounds are inactive (Awale et al., 2005). This was confirmed by Zhang et al., where the new iridoid esters (256, 257 and 258) were shown to exhibit anti-inflammatory activity through inhibition NO and PGE2 production in a dose-dependent manner, without alteration in cell viability (Zhang et al., 2017). Additionally, the aldehydic compounds, (189–191, 193 and 195) reduced the NO production and 193 and 195 decreased the PGE2 production in a dose-dependent manner, without alteration in cell viability. Make the NO production inhibition represented the most pharmacologically target of most *Tabebuia* species (Zhang et al., 2016). The neolignan (142) and benzoyl apiosides (131–134), from the water extract of *T. avellanedae*, inhibited the production of (TNF and IL-1) in cultured human myeloma THP-1 cells stimulated with LPS without any cytotoxicity, the inhibitory activity of both (131 and 132) were more than (133 and 134), suggesting that methoxy groups may play a vital role in activity (Suo et al., 2012). The iridoid glycosides (251–255) also inhibit IL-1 $\beta$  and TNF- $\alpha$  cytokine production and cytochrome CYP3A4 enzyme (Suo and Yan, 2016). In addition,  $\beta$ - lapachone (36) inhibited the neutrophil migration and reduced the concentrations of TNF- $\alpha$ , IL-6 and NO in animals with peritonitis (Sitônia et al., 2013). Not only the active constituents but also water extract of *T. avellanedae* (100 mg/kg for one week, oral administration) completely reduced the mouse ear edema induced by arachidonic acid through inhibition the production of prostaglandin (PG) E<sub>2</sub> and NO in LPS stimulated RAW264.7 cells. This suggests a new strategy for using *T. avellanedae* extract for inflammatory diseases such arthritis and atherosclerosis (Byeon et al., 2008). As discussed by Park et al., upon using taheebo water extract (TWE) with colitis induced by dextran sulfate sodium treatment, TWE reduced body weight loss and colonic tissue inflammation, via up regulating type II T helper immune responses (Park et al., 2017a). In another investigation *T. avellanedae* ethanolic extract (Ta-EE) improved the symptoms associated with osteoarthritis and reduced the serum levels of inflammatory mediators without any toxicity (Park et al., 2017b). These results support park et al., to test Ta-EE on atopic dermatitis (AD) disease. Ta-EE inhibited the mRNA expression of T helper 2 and other proinflammatory cytokines (Park et al., 2018).

*Tabebuia* is traditionally used for its neutralization activity against venom effect. Otero et al investigated the *in vitro* anti-haemorrhagic effect of seventy five plant extracts against *Bothrops atrox* venom where *T. rosea* displayed 100% effectiveness (Otero et al., 2000). Similarly, the hydro-ethanolic extract of *T. aurea* reduced the hemorrhagic and myotoxic activities induced by *B. neuwiedi* venom (Reis et al., 2014), in addition to reducing the hyperalgesia and neuronal injury induced by *B. matogrossensis* venom (VBm)). The study related the activity to the iridoid glycosides content of the plant (Malange et al., 2019).

For uric acid and carrageenan induced inflammatory oedema, the ethanolic extract with (222 and 228) from the leaves of *T. roseo alba*, reduced the serum uric acid levels and decreased the paw edema induced by monosodium urate crystals (Ferraz-Filha et al., 2016). Moreover caffeic and chlorogenic acids, the constituents of the aqueous extract, reduced the serum uric acid and decreased the paw edema (Ferraz-Filha et al., 2017). Both leaves and flowers extracts of *T. aurea* had anti-edematogenic action (Santos et al., 2015). Alcohol and aqueous extracts of the leaves showed dose dependent anti-inflammatory activity in carrageenan induced paw oedema. While 500 mg/kg of alcohol extract showed the highest inhibition (76.92%) after only 24 hrs. (Chandrika et al., 2014). Specioside (246), isolated from *T. aurea*, inhibited leucocyte recruitment into the peritoneal cavity in mice injected with carrageenan (Nocchi et al., 2020).

500 mg/kg of *T. hypoleuca* stem extract showed a significant anti-inflammatory activity against carrageenan-induced paw edema and anti-inflammatory activity at all doses against croton oil induced auricular edema. The activity may be attributed to the presence of tannins, phenols and alkaloids. (Regaldo et al., 2015).

The ethanolic extract with lapachol (24), from *T. crhysotricha* wood, showed a significant difference in the response times to heat stimulus in mice relative to control group (Grazziotin et al., 1992). In contrast,  $\beta$ -lapachone did not showed any protective effect against the lesions induced by azoxymethane in the colon of mice (Higa et al., 2011).

#### 4.2. Anti-ulcer activity

The bark extract of *T. avellanedae*, had a protective effect against gastric lesions in acute and chronic ulceration models, by maintenance the protective factors, such as mucus, prostaglandin and reduction the gastric acidity (Twardowschy et al., 2008). The chronic treatment with *T. avellanedae* ethanolic extract twice a day for 7 days revealed a contraction in the gastric ulcer size and an increase in the mucus layer and cell proliferation (Pereira et al., 2013). Also, the methanolic extract of *T. rosea* (Bertol.) DC exhibited significant anti-ulcerogenic effects using ranitidine as standard drug, these effect might be due the presence of flavonoids (Kiranmai et al., 2013).

#### 4.3. Wound healing activity

The macroscopic analysis showed a complete epithelialization after 14 days treatment with *T. avellanedae* extract on the cutaneous wounds, while the control group still show fibroblasts and lower collagen than treated group (Coelho et al., 2010a). Likewise, bark extract of *T. rosea* reduced the wound diameter

as well as epithelialization time and 100% healing was achieved at the 14th day post excision (Nwonu et al., 2010). On the other hand, ethanolic extract of *T. aurea* leaves showed no scar development better than control groups, and absence of the total re-epithelialization, at the end of fourteen days of treatment (Povoas et al., 2016). Interestingly,  $\beta$ -lapachone (36) was found to increase the cell proliferation, including keratinocytes, and endothelial cells, and thus accelerate wound healing (Kung et al., 2008).

#### 4.4. Antinociceptive activity

Oral administration of *T. avellanedae* aqueous extract (100, 200 and 400 mg/kg), reduced the acetic acid induced nociception by 49.9%, 63.7% and 43.8%, respectively. Also, 200 mg/kg dose reduced the formalin effects at the second phase of experiment by 49.3% and inhibited the edema by 12.9% in rat paw edema model (De Miranda et al., 2001). Moreover, the same dose of the ethanolic extract, induced a significant antinociceptive activity and increased the pain threshold around 30% compared with the control. The extract also inhibited the inflammation by 30–50% (Lee et al., 2012).

The alcoholic and aqueous extracts of *T. aurea* leaves produced an increase in latency time compared to vehicle and a significant inhibition of writhing activity in hot plate and acetic acid induced writhing, where alcohol extract showed the highest activity after 150 min in hot plate method ( $4.63 \pm 0.08$  sec) (Chandrika et al., 2014). Moreover, 100 and 200 mg/kg of the ethanolic extract reduced the nociceptive response in acetic acid and glutamate models (Silva et al., 2018). The methanolic extract of *T. hypoleuca* stems showed significant antinociceptive activity using several nociception models at a doses of 300 and 500 mg/kg. Except, the second phase of formalin test, only the dose of 500 mg/kg give the antinociceptive activity (Regaldo et al., 2017a). In another way, the dihydrobenzofuran lignin (141), from *T. roseo-alba* bark, reduced the number of writhes evoked by acetic acid injection and reduced the nociceptive behavior in the second phase of formalin test by reduction the licking time (Ferreira-Júnior et al., 2015).

#### 4.5. Hepatoprotective and nephroprotective activity

The methanolic extract of *T. rosea* displayed a hepatoprotective effect against the injury induced by paracetamol in rats. The activity was confirmed by the significant reduction in the serum liver enzymes (Hemamalini et al., 2012b). The ethyl acetate and aqueous fractions of *T. aurea* leaves showed remarkable anti-oxidant and nephroprotective activities against carbon tetrachloride (CCl<sub>4</sub>)-induced nephrotoxicity in rats, proved by the improvements of renal serum biomarkers and histopathological features (Mahmoud et al., 2019).

#### 4.6. Anti-obesity activity

Pancreatic lipase inhibitors are used for obesity treatment. Among 24 extracts that showed a lipase inhibitory activity more than 45%, only *T. impetiginosa* ethanolic extract exhibited a significant decrease in the postprandial accumulation of triglyceride levels in rats (Roos et al., 2008). Moreover, this extract can regulate the gene expression related to lipid metabolism in high fat diet-induced obesity in mice (Choi et al.,

2014). Feeding with 0.5% *n*-BuOH fraction of *T. avellanedae* for sixteen weeks showed significant decrease in the body weight of mice compared to control, and significant decrease in the fat mass and triglyceride (TG) levels in ovariectomized (OVX) induced obesity (Iwamoto et al., 2016).  $\beta$ -lapachone decreased the body weight gain by stimulating the browning of white adipose tissue, in addition to increasing the expression of brown adipocyte-specific genes in a high-fat diet mice (Choi et al., 2016).

#### 4.7. Antidepressant activity

The ethanolic extract of *T. avellanedae* (EET) produced antidepressant effect in forced swimming test and tail suspension test (TST) models in mice. The effect depends on the serotonergic, noradrenergic and dopaminergic systems. Furthermore, the extract produced a synergistic effect when combined with conventional antidepressants (Freitas et al., 2010). The Chronic administration of the EET reversed the hyperactivity like behavior and increased the immobility time happened in the TST model, in addition to, reversed biochemical changes (Freitas et al., 2013).

#### 4.8. Antimicrobial activity

Among fourteen plant species used in Paraguay, *T. avellanedae* showed a broad antifungal activity. The dichloromethane (DCM) extract of *T. avellanedae*, displayed a growth inhibition zones against *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Microsporum gypseum*, *Penicillium puruogenum*, *Saccharomyces cerevisiae* and *Trichophyton mentagrophytes*. Methanol (MeOH) and aqueous (Aq.) extracts exhibited activity against only *C. neoformans*, *M. gypseum*, *P. puruogenum* and *T. mentagrophytes* (Portillo et al. 2001). Another study reported that, MeOH extract, of the same species, inhibited the growth of ten *Candida* species, while DCM extract had inhibitory activity only against *Candida krusei* (Hofling et al., 2010). Additionally, the ethanolic extract had moderate inhibitory activity against *Staphylococcus aureus* and no activity against both, *Escherichia coli* and *Pseudomonas aeruginosa* (Lipinski et al., 2013). Hexane extract of the heartwood of *T. avellanedae* displayed antibacterial activity against both methicillin-resistant *S. aureus* and methicillin-sensitive *S. aureus*. The activity was attributed to  $\alpha$ -lapachone and  $\alpha$ -xiloidone, their MIC values were 62.5 mg/L and 125 mg/L, respectively (Machado et al., 2003).

The hydro alcoholic extract of *T. avellanedae* was tested for antimycobacterial activity using a time-to-kill assay. The extract reduced the bacterial growth by 2 orders of magnitude in CFU/mL within half to one hour contact, and no bacterial growth was observed after three hours contact (Oliveira et al. 2009). Another species, *T. rosea*, was tested for antimycobacterial activity where 500 mg/mL methanolic extract exhibited a significant activity against H37RV strain of *Mycobacterium tuberculosis*. Moreover, the antibacterial activity was tested against 5 human pathogens. It was found that *E. coli* was the highly susceptible pathogen (Anupriya et al., 2016).

Binutu and Lajubutu, reported that *T. rosea* (Bertol) D.C. stem bark extract showed better antimicrobial activity than

that of the leaf extract (Binutu and Lajubutu, 1994). However, another study stated that leaf extract showed good inhibitory activity against tested strains with a dose dependent manner. *Klebsiella pneumonia* was more susceptible with inhibition zone ranging from 9.9 to 16.0 mm, while, *S. epidermidis* was the least susceptible with inhibition zone ranging from 8.4 to 13.8 mm (Sathiya and Muthuchelian, 2008). Furthermore, leaf extract was more effective against gram positive bacterial strain and fungal strain with inhibition zone of 19 mm. The gram negative strain *E. coli* was least susceptible with the inhibition zone of 16 mm (Saravanan et al., 2011).

Similarly the antimicrobial activity of *T. roseo-alba* (Ridl.) stem bark extracts was tested. Results indicated activity of the bark methanol extract against *E. coli* and both ethanol and methanol extracts against *S. epidermidis* from (da Silva et al., 2017).

The flower extract of *T. aurea* showed bactericidal action, against *S. epidermidis* (MIC 0.06 mg/ml) and moderate action against *recto S. epidermidis* (MIC: 0.25 mg/mL) while against *S. aureus* (MIC: 0.50 mg/mL) bacteriostatic action was observed. *T. aurea* did not show antiradical activity but the flower extract was cytotoxic in concentrations above >0.5 mg/mL (Santos et al., 2015). The bark extract showed MIC values of 12.5 and 25 mg/mL for both *S. aureus* and *E. coli*, respectively. For *C. albicans*, a MIC of 25 mg/mL was obtained (Brito et al., 2020). Furthermore, all the constituents of *T. aurea* stem bark except 230 showed inhibition activity against *S. aureus* and *Enterococcus faecalis*. Although, 204 showed weak activity against *E. coli*, it showed a marked activity against yeast and filamentous fungi (Barbosa-Filho et al., 2004).

*T. chrysanthia* leaves methanolic extract, showed mild antibacterial activity against *S. aureus*, while chloroform and ether extracts did not show any-bacterial activity (Pérez et al., 2007).

The ethanolic extract of *T. caraiba* is one of four extracts, traditionally used in Cerrado region to inhibit the growth of *C. albicans*. Moreover, hexane and DCM extracts inhibited the growth of *Trichophyton rubrum* (e Silva et al. 2009).

Vinay et al investigated the antimicrobial activity of nano formulation, where silver nanoparticles of *T. argentea* flower extract showed significant effect against gram-positive and gram-negative bacteria (Vinay et al., 2017).

Interestingly, the synergistic effect of *T. impetiginosa* ethanolic extract with ciprofloxacin against *P. aeruginosa* was confirmed (Mehmood et al., 2018). Also, additive potentiation was noted for combinations containing the water extract with erythromycin, chloramphenicol or penicillin-G against *E. coli* and *S. aureus* (Fernandez and Cock, 2020).

The hydro-alcoholic extract of *T. impetiginosa* inhibited 36% of *Helicobacter pylori* growth but had no effect on *Campylobacter jejuni* (Cwikla et al. 2010). Several studies discussed antimicrobial activity of the active constituents from *T. impetiginosa*, where, Lapachol (24), displayed fungicidal activity against *Gloeophyllum trabeum* and *Tinea versicolor* at 60  $\mu$ g/mL and fungistatic activity between 30 and 50  $\mu$ g/mL (Velasquez et al., 2004). Also, 24 and 51, were tested against ten human intestinal bacteria, where, 51 showed a very strong inhibition against *Clostridium paraputrificum*, and 24 showed a moderate activity. Both compounds exhibited weak activity

against both, *C. perfringens* and *E. coli*, and no activity against *Bifidobacterium* strains and *Lactobacillus* stains. It was concluded that the methyl group in the C-2 position of 1, 4-naphthoquinone derivatives might play an important role in the antibacterial activity (Park et al., 2005). Compounds **36**, **37** and **38**, were tested against MRSA, where, all showed antibacterial, but not bactericidal activity. Moreover, **36** and **37**, displayed a considerable inhibitory activity against *S. aureus* (Pereira et al., 2006) and **47** exhibited strong activity against *H. pylori*. In the MIC bioassay, **24**, **47** and **51** were more active than metronidazole but less effective than amoxicillin and tetracycline (Park et al., 2006). **14** and its enantiomer **15** showed the same activity against both fungal and Gram-positive bacteria and were inactive against Gram-negative bacteria (Yamashita et al., 2009).

#### 4.9. Antimalarial activity

The mixture of the naphthoquinones (**14** and **15**), scored the highest antimalarial activity with significant ( $IC_{50}$ )  $1.67 \times 10^{-7}$  against *Plasmodium berghei* and  $6.77 \times 10^{-7}$  against *P. falciparum* (Pérez et al., 1997). All constituents of *T. billbergii* inner bark and trunk wood proved to have anti-malarial activity, with very encouraging  $LC_{50}$ 's ranging from (28–163 µg/ml). The strongest inhibitory activity against *P. berghei* was observed for 2-acetyl-naphtho-[2,3b]-furan-4,9-dione (**4**) with ( $LC_{50}$  28 µg/ml) (Gómez-Estrada et al., 2012).

#### 4.10. Antileishmanial activity

The *n*-hexane and DCM fractions of *T. avellanedae* displayed the highest antileishmanial activity with  $IC_{50}$  of 64 µg/ml and 41 µg/ml, respectively. Compound **24**, isolated from *n*-hexane fraction, exhibited antileishmanial activity with  $IC_{50}$  values of 33 µM and 115 µM, respectively. A mixture of **14** and **15**, from DCM fraction, showed activity with  $IC_{50}$  of 4 µM that is more active than **24**. These results suggested that presence of a furan ring may increase the antileishmanial activity of naphthoquinones (Ali et al., 2010).

The chloroform extract of *T. serratifolia* showed activity against *T. cruzi* and *L. infantum* parasites, with inhibition percentages greater than 96%. Compound (**13**) was the most active constituent against *L. infantum* and *T. cruzi*, with a growth-inhibition concentration of 0.01 µg/mL and this value was lower than Nifurtimox and similar to Amphotericin B (Gonzalez-Coloma et al., 2012).

#### 4.11. Antiviral activity

The ethanolic extracts of both, *T. aurea* stem and *T. cassioides* leaf and stem had no activity against encephalomyocarditis virus, human herpes virus 1 and vaccinia virus Western Reserve strain. The lack of activity may be due to the high cytotoxicity of naphthoquinones present in the extracts (Brandão et al. 2010a). However, another study estimated the antiviral activity of the ethanolic extracts of both, *T. impetiginosa* and *T. serratifolia* against the same viruses and concluded that *T. impetiginosa* extract exerted activity against HHV-1, with a one-half maximal effective concentration ( $EC_{50}$ ) of 166.6 µg/mL (Brandão et al. 2010b).

#### 4.12. Insecticidal activity

6-(1-hydroxyundec-3-enyl)-tetrahydropyran-2-one (**215**), isolated from *T. palmeri*, was previously tested with insecticidal activity against *Bruchus chinensis* using oviposition inhibition assay. Compound **215** showed oviposition inhibition, so helped for the disruption of egg laying in the field and reduced the pest population (Upadhyay et al., 2006). Depending on  $LC_{50}$  values lapachol (**24**) was about 20.8 times more toxic than abamectin against *Tetranychus urticae*. While, benzyl benzoate exhibited higher acaricidal activity than **24** against *T. putrescentiae* (Jeon and Lee, 2011). Both, **24** and its analogues gave similar results against *Laodelphax striatellus*, except for 2, 3-Dichloro-1,4-naphthoquinone and 5,8-Dihydroxy-1,4-naphthoquinone, but naphtho[2,3-*b*]furan-4,9-dione was the most active compound against *Nilaparvata lugens* (0.042 µg/female), followed by its analogue 5,8-Dihydroxy-1,4-naphthoquinone (0.080 µg/female) (Jeon et al., 2011). **24** also scored similar results against *Aedes aegypti* and *Ochlerotatus togoi* larvae with its derivatives (Kim et al., 2013). However, **24** did not exhibit repellent activity against *Reticulitermes* termites, but showed activity to other termites as, *Microcerotermes crassus* and *Kalotermes flavicollis*. On the other hand, **38** and **46**, showed repellence activity against various *Reticulitermes*, as well as *Termitidae* and *Kalotermitidae* species. These study concluded that extracts worked better than isolated compound and small changes in the molecules significantly change the activity (Becker et al., 1972; Castillo and Rossini, 2010). In a recent research, docking analysis was performed to predict the interactions between the major constituents of *T. heptaphylla* wood extracts and the odorant binding receptor of *A. aegypti*. The analysis predicted significant binding of **24** with the internal active pocket of the mosquito odorant binding receptor, that explain why the gel and cream formulations containing *T. heptaphylla* extracts protect up to 3 hr. against the bites of *A. aegypti* (Borges et al., 2019).

A year before, Borges et al., proved that the acetone and ethyl acetate extracts of *T. avellanedae* were more toxic against 3rd instar *A. aegypti* larvae, with  $CL_{50}$  of 100.1 and 151.0 µg/mL, respectively. The mortality values ( $LT_{50}$  and  $LT_{95}$ ) were 38.66 and 66.74 min for ethyl acetate extract, respectively, and 53.47 and 119.96 min for acetone extract, respectively. All extracts presented 100% mortality after 12 hr. The ethanol extract at 333.3 µg/mL strongly deterred oviposition by 89.89% while the ethyl acetate and acetone extracts presented 89.04 and 68.10% deterrence, respectively (Borges et al., 2018).

#### 4.13. Anti-oxidant activity

*T. impetiginosa* volatiles extract was able to inhibit the oxidation of hexanal for 40 days at a level of 5 µg/mL (Park et al., 2003). Moreover, the syrup and methanolic extract of *T. impetiginosa* exhibited the highest anti-oxidant activity, related to their highest amount of phenolics and flavonoids (Pires et al., 2015).

Young and old leaf extracts of *T. heptaphylla* showed a lipid peroxidation inhibition induced by  $H_2O_2$  and  $FeSO_4$  in concentrations of 20 and 200 µg/mL and 2 and 20 mg/mL, respectively (Budni et al., 2007).

In the interested comparative studies, Franco Ospina et al., concluded that the ethanolic extracts of *T. rosea* was more

active as anti-inflammatory, while, *T. ochracea* was more potent as antioxidant. But both species revealed significant antibacterial activity against *S. aureus* (Franco Ospina et al., 2013). In another way, the ethanolic extracts of *T. rosea* and *T. argentea* flower represent a promising natural sources of anti-oxidants suitable for application in nutritional and pharmaceutical fields (Sobiyana et al., 2019). Also, the ethyl acetate fraction of *T. rosea* leaves, scored the highest DPPH radical scavenging activity. Moreover, *n*-hexane, chloroform, and aqueous extracts, in addition to inner bark aqueous extract inhibit the nitric oxide production by over 90%. Furthermore, the inner bark extracts significantly inhibited prostaglandins E2 and tumor necrosis factor alpha (>90%) (Jimenez-Gonzalez et al., 2018).

*T. pallida* leaves (TPL) extract displayed the highest total anti-oxidant capacity in DPPH and hydroxyl radical scavenging activity, and the strongest radical scavenging activity when compared with standards (Rahman et al., 2015). The ethyl acetate fraction (EAF) exhibited the highest phenolic and flavonoids content, and scored the highest total anti-oxidant capacity than other extracts (Rahman et al., 2019). The phenylpropanoid glycosides (93, 94 and 96–99), from *T. avellanedae* water extract, displayed anti-oxidant activity in DPPH assay. Compound 98 exhibited the highest activity with IC<sub>50</sub> of 0.12 μM, however all compounds showed moderate inhibitory activity on CYP3A4 enzyme except, 99 that was the most active with IC<sub>50</sub> value of 15.1 μM. Compounds 97, 98 and 99 were more active than of 93, 94 and 96 in both assays, suggesting that galactose group plays important role in the activity (Suo et al., 2013).

The lignan (150), from *T. chrysotricha*, exhibited the highest DPPH radical-scavenging activity (IC<sub>50</sub>; 17.7 ± 0.2 μM), giving an indication that increasing the number of methoxy groups positively affected the activity (Takahashi et al., 2015).

#### 4.14. Cytotoxic activity

Naphthoquinones are commonly used for treating a number of diseases, including cancer. The antitumor activity of *Tabebuia* was evaluated in several studies. Both compounds 14 and 15 exhibited significant dose-dependent inhibitory effects against Epstein-Barr virus (EBV) expression assay (Ueda, et al., 1994). de Saizarbitoria Colman et al., proved that lapachol (24) is less antiproliferative than other naphthoquinone derivatives, where all the compounds isolated from *T. barbata* except lapachol had a significant cytotoxic activity against A-549 human lung adenocarcinoma, MCF-7 human breast carcinoma and HT-29 human colon carcinoma cells with IC<sub>50</sub> values (15–82.5 μM) (de Saizarbitoria Colman et al., 1997). Also 14 exhibited more potent antiproliferative and higher cancer chemopreventive activity against several human tumor cell lines than its enantiomer 15 with lower effect against normal human cell lines. The study revealed that the presence of hydroxyl group at C-5 is increases antiproliferative activity (Yamashita et al., 2009). The ethanolic extract of *T. incana* and its chloroform fraction showed significant lethality (LC<sub>50</sub> 167 ± 39 and 12 ± 4 mg.ml<sup>-1</sup>, respectively), however, hexane and water-methanol fractions were inactive. The mixture of 14 and 15 was about as active as chloroform fraction (LC<sub>50</sub> 15 ± 10 mg.ml<sup>-1</sup>), from which they were isolated, with the existence of other cytotoxic components (Morais et al.,

2007). Compounds; 15 and 22, from *T. avellanedae* inner bark, were evaluated against A549, SiHa and MCF-7 cell lines and they were able to induce a cell cycle arrest and apoptosis at G2/M phase in A549 cells by strongly decreasing the levels of cyclin protein (A and B) with time dependent manner (Zhang et al., 2015). 14, 23 and 32 showed significant cytotoxic activity against both KB, and HeLa cell lines where 23 was the most active suggesting that the presence of methylethenyl furan-moiety, causes better cytotoxicity against both cell lines (Sichaem et al., 2012). β-lapachone (36) inhibited the growth and induce apoptosis in a time- and dose-dependent manner in the human lung carcinoma cell line A549. The apoptosis was ascribed to down regulation of the levels of both, human telomerase RNA (hTR) and c-myc expression (Woo and Choi, 2005). The activity of 36 on the human hepatoma cell line HepG2 was related to the apoptosis by the formation of apoptotic bodies and DNA fragmentation (Woo et al., 2006). In addition, 36 had anti-proliferative and apoptotic effects on human malignant melanoma by regulation of Sp1-mediated gene products (Bang et al., 2016). Furthermore, 120 mg/kg of *T. avellanedae* extract and 1 mg/kg of 36 prolonged the life span of tumour-bearing mice, and produced the same level of survival. They act synergistically with specific cytokines to enhance the macrophage activation against tumour cells (Queiroz et al., 2008). The activity of *T. avellanedae* inner bark extract against estrogen receptor positive human breast cancer cells was related to the down-regulation of the cell cycle regulatory and estrogen responsive genes, in addition to, up-regulation of both apoptosis and biotic metabolism specific genes (Mukherjee et al., 2009). Furthermore, *T. avellanedae* inner bark under the name of (TNM) was used as an effective nutritional alternative for aromatase positive, post-menopausal breast cancer (Telang et al., 2019).

The *n*-Hexane, chloroform and ethyl acetate fractions of *T. impetiginosa* displayed a significant inhibition of platelet aggregation induced by collagen and arachidonic acid (AA) in a dose-dependent manner. The chloroform fraction, significantly suppressed AA liberation and inhibited the cell proliferation and DNA synthesis (Son et al., 2006). The methanolic extract was evaluated against human tumor and non-tumor cells lines. The extract showed cytotoxic activity, without any toxicity on PLP2 non tumor cell line (Pires et al., 2015).

Total alkaloid extract of *T. rosea* (Bertol.) DC. leaves showed higher toxicity towards human leukemic cells (MOLT-4) than the normal cells in a dose and time dependent manner (Sathiya and Muthuchelian, 2010). The chloroform extract of inner bark displayed the best antiproliferative activity against both HepG2 and B16F10 cell lines (Jimenez-Gonzalez et al., 2018). On the other hand, the cytotoxic activity of *T. roseo-alba* (Ridl.) was observed at the concentration of 500 μg/mL for all samples, while at 100 μg/mL only the proliferation of the macrophages was observed (da Silva et al., 2017).

The hydroethanolic extract of *T. aurea* bark was able to inhibit the growth of cervical carcinoma lineage (HELA) by about 50% at 24–72 h with no significant toxic effects against normal cells such as human fibroblasts (GM0749) (Brito et al., 2020).

For *T. chrysantha* stem, the methanolic extract, showed a direct cytotoxic effect against Ehrlich Ascites Carcinoma (EAC) in a dose-dependent manner with IC<sub>50</sub> value 463.27 μg/mL in MTT assay and 443.58 μg/mL in trypan blue dilution assay (Panda et al., 2019). Panda et al., suggested that

a low dose of *T. chrsantha* extract can be used as a novel product to suppress angiogenesis and cell proliferation associated with angiosarcoma and that the isolated flavonoid (91) functions as specific regulators of target protein-associated angiosarcoma (Panda et al., 2020).

#### 4.15. Cosmetics and skin care activity

*T. avellanedae* extracts inhibited the biosynthesis of prostaglandin E2, thus relieves the skin irritation caused by lactic acid and the erythema caused by UV radiation (Woo et al., 2009). Moreover, the ethanolic extract inhibited both tyrosinase activity as well as melanin biosynthesis (Kim et al., 2015a). β-lapachone (36) was proved to be useful as a potential depigmentation agent for various hyperpigmentation disorders due to its ability to inhibit melanin synthesis and tyrosinase activity at 0.8 μM in melan-a cells, reducing melanogenesis in the human 3D skin tissue culture, as well as inhibition of body pigmentation of zebrafish (Kim et al., 2015b).

*T. impetiginosa* extracts were reported to have a degranulation inhibitory activity which improves skin pigmentation, dermatitis, wrinkles, pruritus, and pain caused by chemicals. Also, *T. impetiginosa* has skin whitening, anti-inflammatory, anti-allergic, and anti-oxidant effects (Osawa et al., 2006). Moreover, the bark extract could stimulate collagen synthesis by human follicle dermal papilla cell (Iwano et al., 2013). In addition, the cosmetic combination of *T. impetiginosa* and *Codium Tomentosum* extracts can selectively proliferate the beneficial microorganism present in the skin, inhibit the pathogenic microorganism and help the skin-beneficial microorganism to maintain the barrier function against the external environment (Lee, 2017).

#### 4.16. Miscellaneous bioactivities

The dimeric iridoid (284), from *T. argentea* efficiently inhibit the chaperone in biochemical and cellular assays. The results revealed C9-type iridoids as a novel class of heat shock protein 90 inhibitors as a therapeutic target for numerous diseases (Piaz et al., 2013).

*T. hypoleuca* stem methanolic extract (500 mg/kg), induced a significant decrease in the fever from the first hour to 4 h. After administration without exerting sedative or hypnotic effects at the tested doses (Regalado et al., 2017b).

*T. impetiginosa* extract could manage the hyper-triglyceridemia and other factors of cardiovascular disease that common in obesity and diabetes (Kiage-Mokua et al., 2018).

*T. avellanedae* is a great candidate for treatment of primary dysmenorrhea as it inhibits the production of PGE2 and reduces COX-2 activity. Quality of life, pain intensity and inflammatory markers were evaluated and the trial approved by the Institutional Review Board at Helfgott Research Institute and the National University of Natural Medicine (McClure et al., 2019).

#### 4.17. Genotoxic activity

The genotoxicity, evaluated via wing somatic mutation and recombination test, revealed that the bark and stem extracts of *T. impetiginosa* were toxic, however not genotoxic by itself,

but it possesses a significant potentiating effect on DXR genotoxicity, considering that *T. impetiginosa* possess anticarcinogenic potential (Sousa et al., 2009). The genotoxic activity of the flower extract was estimated on the blood and liver cells of Wistar rats. Except the dose of 100 mg /kg body weight, a significant increase in DNA damage compared to the control was noted. The genotoxic potential was higher in liver cells but the response in both tissues was related to dose-dependency. While, the DNA damage can be corrected before conversion into mutations (Lemos et al., 2012).

The genotoxic potential of the alkaloid extract of *T. rosea* was tested using micronucleus assay. The number of micronuclei formed even at the highest concentration was insignificant with that of the positive control mitomycin-C, supporting the absence of genotoxicity (Sathiya and Muthuchelian, 2010).

The LD<sub>50</sub> of methanolic and aqueous extracts of *T. aurea* bark was estimated as 4608 μg/mL and 104,656 μg/mL, respectively. The results indicated that both extracts did not induce a significant changes in mitotic index of *Allium cepa* roots or induced the formation of micronuclei. Accordingly, they are cytotoxic, but not mutagenic (Lucas et al., 2019).

## 5. Discussion and future perspectives

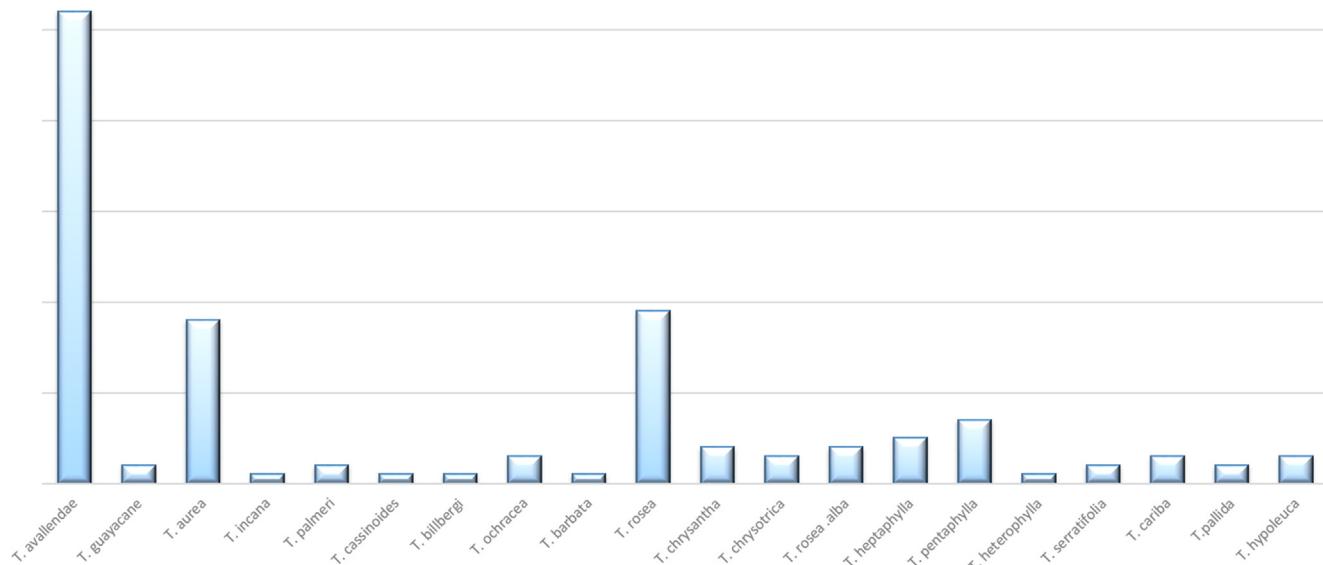
*Tabebuia* has been used for a long time as therapeutic alternative by rural population. The present review summarizes the research progress regarding *Tabebuia* species, with particular consideration to the traditional uses, chemical constituents and biological activities. Pharmacological studies that carried out on crude extracts and pure metabolites provided pragmatic documents for its traditional uses, as *Tabebuia* has been effectively used traditionally for treating syphilis, malaria, skin and stomach disorders, cancer, inflammation, pain, irritability, depression, diabetes, prostatitis, constipation and allergies.

The presented data clearly states that all the reported phytochemical and pharmacological studies, focus extensive attention towards only some species, however, the majority of *Tabebuia* species still require more extensive future investigated as showed in Fig. 9.

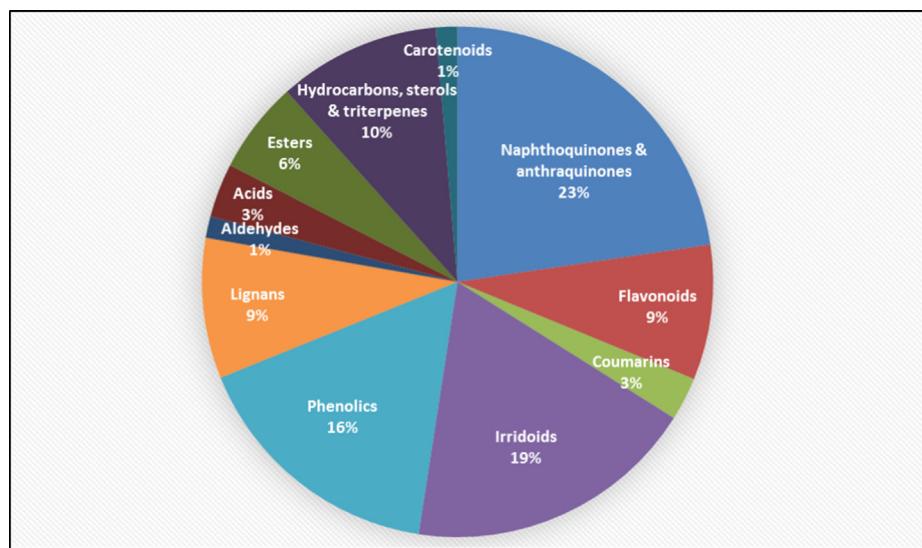
Additionally, the state of the art on *Tabebuia* chemistry gives considerable opportunities for future discoveries. Approximately 292 chemical constituents have been isolated from different *Tabebuia* species (Fig. 10). These metabolites belong to different classes; naphthoquinones, flavonoids, lignans, coumarins, aldehydes, acids, esters, fatty acids, sterols, iridoids and carotenoids. Throughout the chemical achievements, there are still scientific gaps.

First, the total alkaloids extract of *T. rosea* leaves showed cytotoxic activity against human T-cell leukemia (MOLT-4) cells. As this chemical class is unique to *Tabebuia* and the alkaloids are famous for its valuable pharmacological activities. Therefore, future studies are required for precise isolation and identification of each alkaloid structure by an in-depth exploration techniques.

Second, the research of flavonoids, lignans, aldehydes, acids and esters was relatively slow compared with the study of naphthoquinones, anthraquinones and iridoids, while, the study of coumarin compounds is still in its initial stage. Thus, it may be possible that more bio-active components could be identified by using bioactivity guided isolation strategies.



**Fig. 9** The relative percentage of all published chemical and biological reports regarding *Tabebuia* species.



**Fig. 10** The distribution of the secondary metabolites among *Tabebuia* species.

Third, naphthoquinones and anthraquinones in addition to phenyl ethanoid and phenyl propanoid compounds were mainly isolated from the bark and wood organs of *Tabebuia* species. However, screening other organs may provide more chances for discovering a new bioactive principles, likewise flavonoids; that were mainly isolated from the leaves and flowers of *Tabebuia* organs, while the new derivative (**88**) and the new flavonoid (TMF) (**91**) were isolated from the stem of *T. aurea* and *T. chrysanthia*, respectively.

Fourth, Fig. 11 illustrates the relative percentage of the secondary metabolites isolated from each *Tabebuia* species under investigation. These results indicated that *T. pallida* and *T. hypoleuca* are only biologically explored (Rahman et al., 2015; Rahman et al., 2019; Regaldo et al., 2015), while other

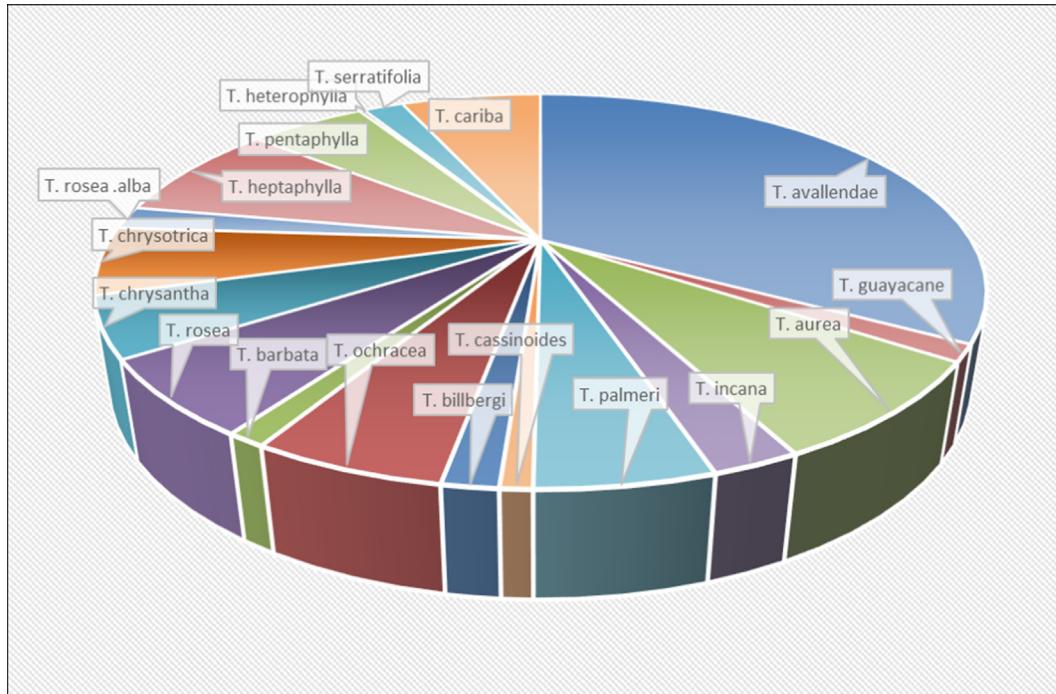
species such as; *T. guayacan*, *T. cassinoidea*, *T. barbata*, *T. heterophylla*, *T. serratifolia* and *T. rosea alba* are insufficiently chemically studied. Taking these in consideration, more studies are needed for better understanding their chemical bases to explain the claimed biological activities.

For further in-depth phytochemical scanning, Fig. 12 is performed to illustrate the type and the relative percentage of each chemical class isolated from *Tabebuia* species. Although there have been marked achievements in the phytochemical studies regarding *Tabebuia* species, there are still some notifications that have not been clarified. These notifications are as the following: (1) Flavonoids are not isolated from *T. avallandae*, although these species take extensive phytochemical attention. (2) Phenyl ethanoid and phenyl propanoid

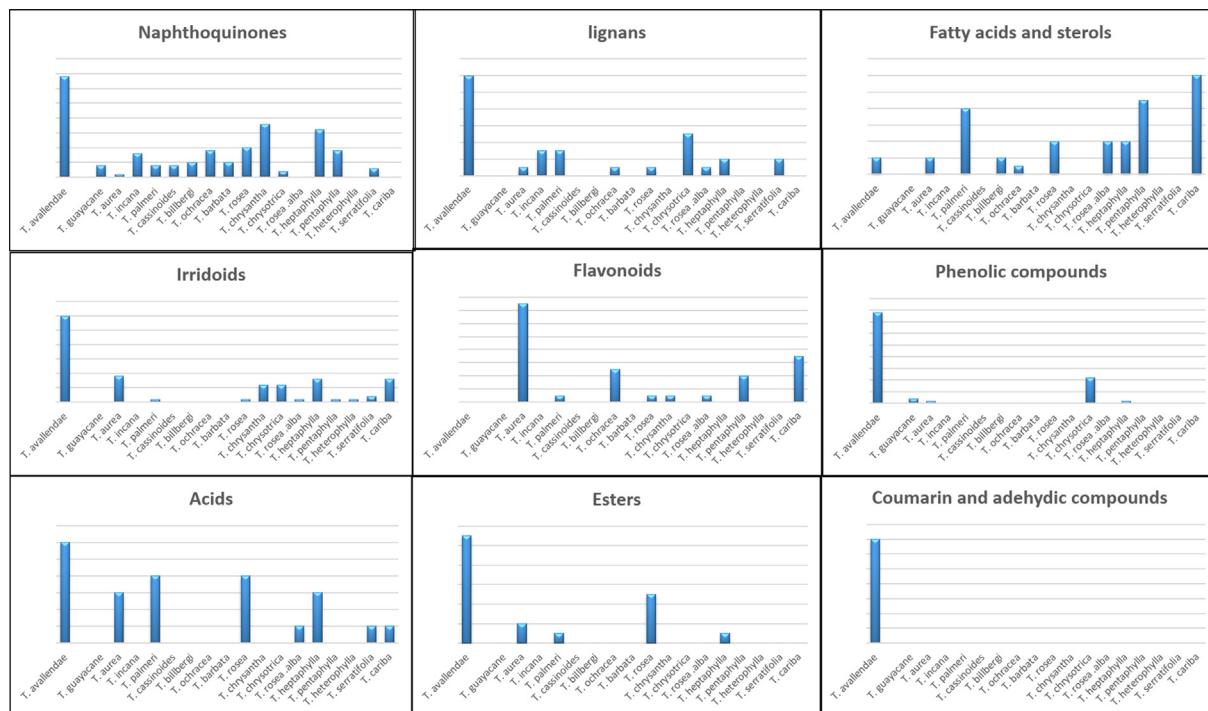
compounds from phenolic chemical class are mainly isolated from *T. avallandae*, although they are recently isolated from other species like; *T. chrysotricha* and *T. caraiba* (Takahashi et al., 2015; Soares et al., 2020), respectively, so further studies are required. (3) Finally, the species and chemical classes that require more phytochemical studies are also obvious. How-

ever, other chemical classes like; naphthoquinones, lignans, iridoids, hydrocarbons, fatty acids and sterols, are widely distributed among different *Tabebuia* species.

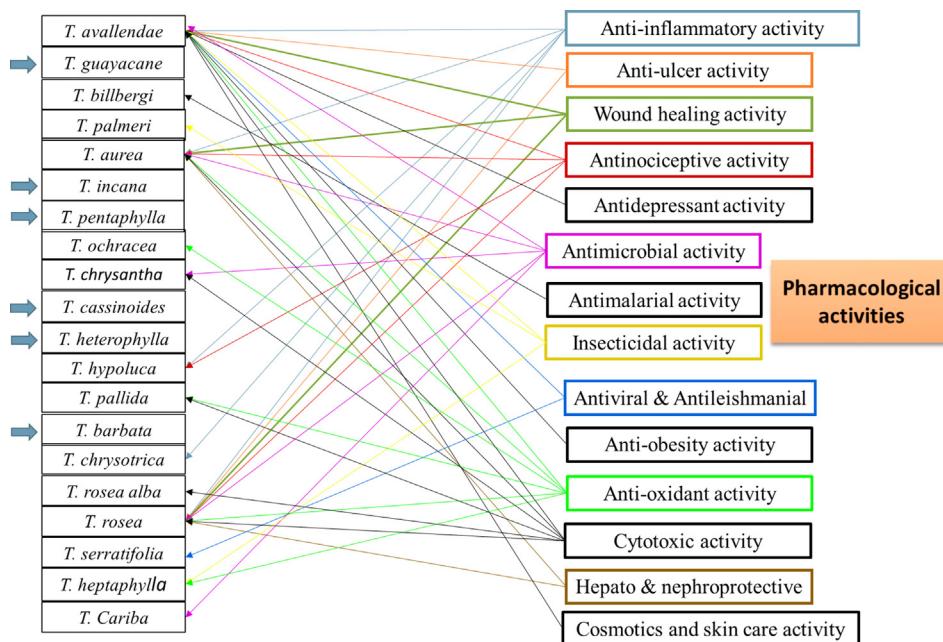
Furthermore, in spite of the large number of pharmacological studies regarding the medicinal importance of *Tabebuia* species, there are still several gaps in our understanding of



**Fig. 11** The relative percentage of secondary metabolites isolated from each *Tabebuia* species.



**Fig. 12** The relative percentage of each chemical classes among different *Tabebuia* species.



**Fig. 13** The pharmacological activities of different *Tabebuia* species.

the applications of these plants. First gap, is that some of the pharmacological activities *in vitro* and *in vivo* studies have been obtained with doses that can be high for clinical study. For example, doses of *Tabebuia* extracts that applied to evaluate anti-inflammatory, antinociceptive and sedative or hypnotic effects (administered 500 mg/kg of extract in mice) are too high for application in clinical studies.

Second, pharmacokinetic data and the penetration capacity of the total extract or the plant's ingredients into the central nervous system is still unstudied. In addition, there are poor reported information focused on the main side effect or the safety of the plant extract or its components.

Third, the promising results confirmed by animal models should be further investigated by clinical studies, like,  $\beta$ -lapachone, the most common naphthoquinone isolated from *T. avallandae* and other *Tabebuia* species is now in clinical trial phase as plant derived anticancer agents (Nirmala et al., 2011).

Fourth, modern studies are now focused on nanosize materials. *T. argentea* silver nanoparticles were successes to possess significant antimicrobial activity against both gram positive and gram negative bacteria (Vinay et al., 2017). So, further studies are needed to illustrate the activity of *Tabebuia* extracts and isolated compound nanoparticles against different pharmacological aspects.

Fifth, analyses of the structure–activity relationships studies are still insufficient.

Sixth, despite, the numerous pharmacological activities of *Tabebuia* species, most of functional mechanisms remain unclear and need further exploration through *in vivo* and *in vitro* experiments.

The different pharmacological activities performed on *Tabebuia* species are illustrated in Fig. 13. The presented data indicated extensive pharmacological studies of some species e.g. *T. avallandae*, *T. aurea* and *T. rosea*, other species like *T. billbergii*, *T. palmeri*, *T. ochracea*, *T. chrysotrica*, *T. rosea alba*,

*T. serratifolia* and *T. cariba*, remain insufficiently studied. Furthermore, some species as *T. guayanac*, *T. cassinoidea*, *T. barbata*, *T. heterophylla*, *T. incana*, *T. pentaphylla* are not pharmacologically reported till now.

Second, *T. avallandae* showed antidepressant, antimalarial and anti-obesity activities. Furthermore, *T. rosea* and *T. aurea* showed significant hepato and nephroprotective activities, respectively. These results suggest similar biological testing for other *Tabebuia* species extracts as well as their isolated pure compounds.

## 6. Conclusion

The current review helps to develop a high resolution picture about genus *Tabebuia*, its most studied species, main active constituents and reported biological activities. It also helps to recognize the importance of different species in traditional systems of medicine. Additionally, it provides suggestion for some *Tabebuia* species that need further phytochemical and/or pharmacological investigations.

## 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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