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Review

Simaroubaceae family: botany, chemical composition and biological activities

Iasmine A.B.S. Alves^a, Henrique M. Miranda^b, Luiz A.L. Soares^{a,b}, Karina P. Randau^{a,b,*}

^aLaboratório de Farmacognosia, Programa de Pós-graduação em Ciências Farmacêuticas, Universidade Federal de Pernambuco, Recife, PE, Brazil

^bLaboratório de Farmacognosia, Departamento de Farmácia, Universidade Federal de Pernambuco, Recife, PE, Brazil

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The Simaroubaceae family includes 32 genera and more than 170 species of trees and brushes of pantropical distribution. The main distribution hot spots are located at tropical areas of America, extending to Africa, Madagascar and regions of Australia bathed by the Pacific. This family is characterized by the presence of quassinoids, secondary metabolites responsible of a wide spectrum of biological activities such as antitumor, antimalarial, antiviral, insecticide, feeding deterrent, amebicide, antiparasitic and herbicidal. Although the chemical and pharmacological potential of Simaroubaceae family as well as its participation in official compendia; such as British, German, French and Brazilian pharmacopoeias, and patent registration, many of its species have not been studied yet. In order to direct further investigation to approach detailed botanical, chemical and pharmacological aspects of the Simaroubaceae, the present work reviews the information regarding the main genera of the family up to 2013.

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Introduction

The Simaroubaceae family includes 32 genera and more than 170 species of trees and brushes of pantropical distribution. It is characterized by its content of bitter substances, mostly responsible for its pharmaceutical properties (Fernando and Quinn, 1992; Muhammad et al., 2004). The principal geographical distribution center is located at tropical America, extending to the west to Africa, Madagascar, Asia (Malaysia) and regions of Australia bathed by the Pacific (Simão et al., 1991; Saraiva et al., 2002;). In Brazil, this family is represented by the genera *Quassia* and *Picrolemma*, in the Amazon, *Castela* and *Picrasma*, to the South; and *Simaba*, *Simarouba* and *Picrolema*, which are present

throughout the country (Arriaga et al., 2002; Almeida et al., 2007) (Fig. 1). Due to the chemical diversity previously described for many species of Simaroubaceae family, it is worth noting that it can be characterized as a promising source of bioactive molecules with remarkable research potential. An example of this is that since 1961, when the first quassinoid structure was elucidated, the growing interest on various species of Simaroubaceae family resulted in the isolation and identification of the more than 200 currently-known quassinoids (Curcino Vieira and Braz-Filho, 2006). Nevertheless, many of its species have not been studied or remain unexplored. In this context, in order to base and direct future studies, the present work is a review of literature from 1846 until 2013, and contemplates botanical, chemical and pharmacological aspects of the family's main species.

* Corresponding author.

E-mail: karina.prandau@ufpe.br (K.P. Randau).

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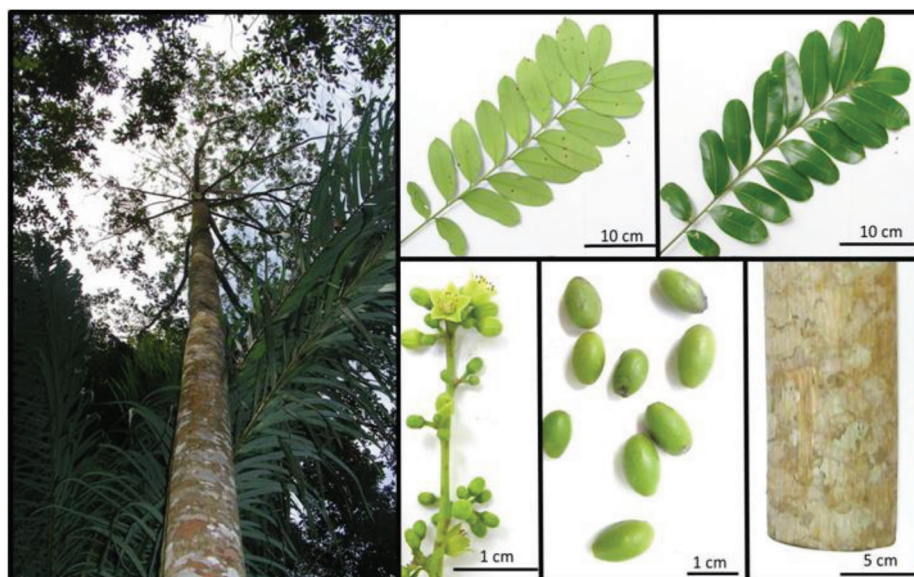


Figure 1 – *Simarouba amara* Aubl. (Simaroubaceae). Source: Tarcisio Leão, 2013.

Materials and methods

Information regarding the botanical descriptions, the isolated and identified chemical constituents, and the pharmacological activities of isolated compounds or crude extracts of the main species of Simaroubaceae family, were retrieved from books and original articles found in several databases (Medline, SciFinder, Periodicos Capes, Science Direct, Scopus and Web of Science) in the period from 1846 to 2013, was performed. The used keywords included Simaroubaceae, *Simarouba*, *Simaba*, *Quassia* and other genera belonging to the family. Once the references were obtained, those considered relevant were selected.

Botany

Extensive bibliography regarding the botanical aspects of the Simarubaceae family composition was found. The subfamilies' affinities have been thoroughly discussed, and five of its six subfamilies; Surianoideae, Kirkioidae, Irvingioideae, Picrammioideae and Alvaradoideae, have been removed from the family. Thus, in this context, only the Simarouboideae subfamily, comprised of 22 genera, would be part of the Simaroubaceae family (Simão et al., 1991; Muhammad et al., 2004).

The Simarubaceae family is botanically related to the Rutaceae, Meliaceae and Burseraceae families, though, in this group, it is more related to the first one in terms of chemical composition, wood anatomy, lack of resin ducts in the bark and in the free stamens. It differs from the others by its absence of secretory cavities containing aromatic oils in leaves and floral parts (Fernando and Quinn, 1992) and by the presence of quassinoids, exclusive of Simaroubaceae (Thomas, 1990).

Planchon (1846) was the first one to propose an intra-family classification, based on the ovary nature (free or connate), number of ovules, type of embryo, length

of filament and number of stamen and petals. In this context, the family was divided in four tribes: Simaroubeae, Harrisonieae, Ailanthae and Spathelieae. Later on, Bentham and Hooker (1862) proposed a classification based on division of the ovary that yielded the tribes Simaroubeae and Picramnieae. Years later, Engler (1874) recognized three tribes: Surianeae, Eusimaroubeae and Picramnieae, taking into account the nature of the carpels and styles, as well as the number of ovules. The last classification of Engler (1931), the most used, was based on the number and nature of the carpels and styles, number and position of ovules, presence or absence of scales at the filaments' base and composition of the leaf. This classification included nine tribes in six subfamilies.

Due to the heterogeneous nature of Simaroubaceae family from the Engler classification (1931), shown in wood anatomy (Webber, 1936; Heimsch, 1942) and pericarp (Fernando and Quinn, 1992), pollen morphology (Erdtman, 1952, 1986; Moncada and Machado, 1987) and phytochemistry (Hilditch and Williams, 1964; Simão et al., 1991); later authors reduced the family even more. Takhtajan (1987), Cronquist (1988) and Thorne (1992) excluded one or more subfamilies. The studies of Fernando and collaborators (1995) on *rbcL* sequence variation clearly showed that Simaroubaceae is polyphyletic, which based the recognition of the families Surianaceae sensu Cronquist, Kirkiaceae and Irvingiaceae, previously segregated to Simaroubaceae.

The genera *Picramnia* and *Alvaradoa*, despite occasionally reported as constituents of the Simaroubaceae family (Balderrama et al., 2001; Rodríguez-Gamboa et al., 2001; Cortadi et al., 2010), were excluded from it and put into the *Picramniaceae* family by Fernando and collaborators (1995). This translocation is supported by the fact that *Picramnia* and *Alvaradoa* are phytochemically characterized by a vast presence of anthraquinones and anthracenic derivatives in comparison

to quassinoids, the taxonomic markers of the Simaroubaceae family (Diaz et al., 2004).

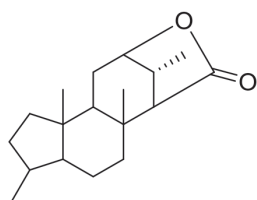
The species from this family have alternate compound or complete leaves, not punctate, with or without thorns. Its flowers are, generally, placed together in axial inflorescences, showing free or fused sepals, free petals, stamens in double of the number of the petals, filaments usually with appendix. The ovary is superior, above a short gynophore or above a four or five carpels disk, generally free at the base and fused by the style with one (in the case of *Quassia*) or two ovules per carpel. Its fruit is a drupe, generally separated in drupelets (Noldin, 2005).

Chemical constituents

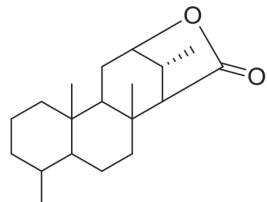
Since 1930, the Simaroubaceae family has been the subject of many studies regarding its chemical constitution, and numerous compounds have been isolated and their structure has been elucidated; among these, quassinoids, alkaloids, triterpenes, steroids, coumarins, anthraquinones, flavonoids and other metabolites (Barbosa et al., 2011) (Chart 1). Quassinoids can be considered a taxonomic marker of the Simaroubaceae family since it is the most abundant group of natural substances and their synthe almost exclusive (Saraiva et al., 2006; Almeida et al., 2007).

Quassinoids

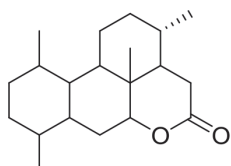
Many genera from the Simaroubaceae family have been reported to express quassinoids (Chart 1). These consist of triterpene degradation products, derived from the euphol/tirucalol series, highly oxygenated and structurally complex. Regarding the basic structure, they can be structurally classified into five groups: C-18 (1), C-19 (2), C-20 (3), C-22 (4) and C-25 (5a,b), though some do not fit any given configuration, such as (+)-polyandrol, eurylactones A and B, ailanquassins A and B, 6-dehydroxylongilactone and others. Most of the isolated quassinoids have a twenty carbon skeleton (Curcino Vieira and Braz-Filho, 2006; Guo et al., 2009).



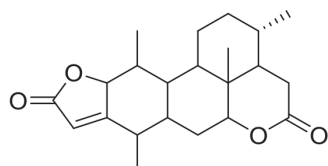
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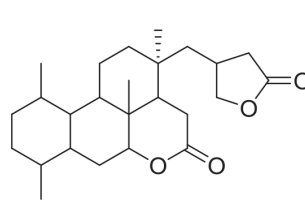
2 C-19



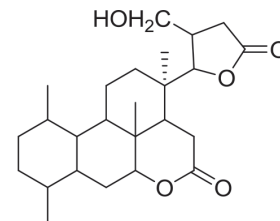
3 C-20



4 C-22

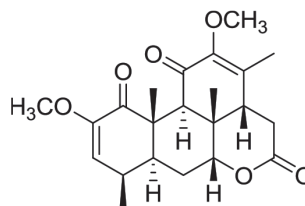


5a C-25

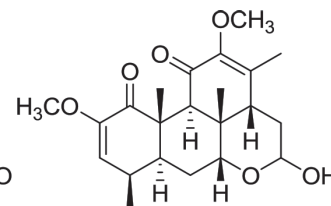


5b C-25

The chemical compounds of this nature were, initially, known as “quassin”, after a physician named Quassi used the bark of Simaroubaceae plants to treat fever. The first isolated and identified quassinoids were quassin (6) and neoquassin (7), from *Quassia amara*; the isolation was done in by Clark (1937) in the 1930's. Furthermore, the structural elucidation was successful until the beginning of the 1960's, when Valenta and collaborators (1961) were able to apply novel techniques, such as Nuclear Magnetic Resonance (NMR). Since then, the interest in diverse species of Simaroubaceae family has increased, which has resulted in the isolation and identification of the more than 200 quassinoids currently known (Curcino Vieira and Braz-Filho, 2006).



6



7

In a recent review, Barbosa and collaborators (2011) described 39 quassinoids isolated from nine species of the genus *Simaba*. Kundu and Laskar (2010) reported 91 terpenoids in eight species of the genus *Ailanthus*, which predominantly included quassinoids.

Alkaloids

Among the alkaloids isolated from the different genera of the Simaroubaceae family (Chart 1), the canthines deserve special attention. They constitute a class of β -carboline alkaloids first described at the end of the 1930's. Canthin-6-ones have been reported to have a large array of activities, such as antiviral, cytotoxic, antiparasitic, antibacterial, high pro-inflammatory cytokines reducer, among others (Showalter, 2013).

Barbosa and collaborators (2011) described eighteen alkaloids isolated from nine species of the genus *Simaba*. Kundu and Laskar (2010) described 25 alkaloids previously isolated from four species of the genus *Ailanthus*: *A. malabarica*, *A. excelsa*, *A. altissima* and *A. giraldii*.

Chart 1

Chemical constituent of the principal genera of the Simaroubaceae family.

Genus	Chemical constituents	Part of the plant	Reference	
Quassinoids				
<i>Ailanthus</i>	ailanthone (8)	Seeds	Okunade et al., 2003	
	shinjulactone	Root	Ishibashi et al., 1983	
	shinjulactones B (9), C, D, E, L, I, J, K	Root, Stem	Ishibashi et al., 1984 Furuno et al., 1984 Ishibashi et al., 1985	
	chaparrinone (10)	Root	Dou et al., 1996a	
	2,12-didemethylquassin	Root	Dou et al., 1996a	
	ailantinone	Root	Ogura et al., 1977	
	glaucarubinone (11)	Root	Ogura et al., 1977	
	glaucarubol (12)	Root	Ogura et al., 1977	
	excelsin	Stem	Joshi et al., 2003	
	glaucarubin (13)	Stem	Joshi et al., 2003	
	glaucarubolone (14)	Stem	Joshi et al., 2003	
	<i>Brucea</i>	bruceins E and D	Seeds	Noorshahida et al., 2009
		2,12-didemethylquassin	Fruit	Dou et al., 1996a
		bruceins A, B, C	Fruit	Bawn et al., 2008
bruceantinol (15)		Fruit	Bawn et al., 2008	
brusatol		Fruit	Bawn et al., 2008	
bruceajavanines A, B		Stem	Kitagawa et al., 1994	
<i>Castela</i>	glaucarubolone (14)	Aerial Parts	Jacobs et al., 2007	
	holacantona	Aerial Parts	Jacobs et al., 2007	
	2,12-didemethylquassin	Root	Dou et al., 1996a	
	chaparrinone (10)	Root	Dou et al., 1996a	
	glaucarubinone (11)	Stem	Dou et al., 1996a	
	amarolide (16)	Leaves	Dou et al., 1996b	
	glaucarubol (12)	Leaves	Dou et al., 1996b	
	chaparrin	Aerial Parts	Geissman and Chandorkar, 1961	
	chapparrolide	Not Described	Mitchell et al., 1971	
	castelanolide	Not Described	Mitchell et al., 1971	
	peninsularinone	Root	Grieco et al., 1994	
	casteloside C	Bark	Kubo and Chaudhuri, 1993	
	chaparramarine	Bark	Kubo et al., 1992	
	castelalin	Bark	Kubo et al., 1993	
	polyandrol	Root	Grieco et al., 1995	
castelanone (17)	Not Described	Polonsky et al., 1979		
<i>Picrasma</i>	picrajavanins A (19) e B	Stem	Yoshikawa et al., 1993	
	javanicins H, I, J, K, L, O, R, S	Leaves	Koike et al., 1991a, b	
	javanicinosides I, J, K, L	Stem	Koike and Ohmoto, 1992	
	javanicins T, U e Z	Stem	Koike et al., 1995	
	nigakilactones B, C, E e F	Leaves, Stem	Chen et al., 2009	
	quassin (6)	Leaves	Shields et al., 2009	
	neoquassin (7)	Stem	Wagner and Nestler, 1978	
	isoquassin	Stem	Wagner and Nestler, 1978	
	picrasins A, B, C, D, E, F, G, H	Stem	Hikino et al., 1975	

Chart 1 cont.

Genus	Chemical constituents	Part of the plant	Reference
<i>Picrolemma</i>	picraqualides A, B, C, D e E	Bark	Yang and Yue, 2004
	kusulactone	Bark	Yang and Yue, 2004
	simalikalactone C	Bark	Yang and Yue, 2004
	picrasinols B, D	Stem	Daido et al., 1995
	picrasinosides B, C, D, E, G, H	Stem	Matsuzaki et al., 1991
	isobrucein B	Stem	Silva et al., 2009b
	neosergeolide	Root, Leaves	Silva et al., 2009b
	sergeolide (20)	Root	Moretti, 1982
	simalikalactone D (21)	Stem	Rodrigues-Filho et al., 1993
	ailatinone	Stem	Rodrigues-Filho et al., 1993
	glaucarubolone (14)	Stem	Rodrigues-Filho et al., 1996
	glaucarubinone (11)	Stem	Rodrigues-Filho et al., 1996
	glaucarubol (12)	Stem	Rodrigues-Filho et al., 1996
	excelsin	Stem	Rodrigues-Filho et al., 1996
<i>Quassia</i>	simalikalactones D (21), E	Leaves	Houël et al., 2009 Cachet et al., 2009
	quassin (6)	Leaves	Bertani et al., 2012
	neoquassin (7)	Leaves	Bertani et al., 2012
	picrasins B, H, I, J, K	Leaves	Cachet et al., 2012
	parain	Stem	Dou et al., 1996a
	quassimarin	Bark	Kupchan and Streelman, 1976
	chaparrinone (10)	Aerial Parts	Latif et al., 2000
	samaderins B, E, X, Y, Z	Stem	Kitagawa et al., 1996
	simarinolide	Stem	Kitagawa et al., 1996
	indaquassins A, B, C, D, E, F	Stem	Koike and Ohmoto, 1993
	brucein D	Stem	Koike and Ohmoto, 1994
<i>Samadera</i>	soulameolide	Stem	Koike and Ohmoto, 1994
	glaucarubin (13)	Not Described	Gibbons et al., 1997
	samaderins B (22), C	Leaves	Merrien and Polonsky, 1971
<i>Simaba</i>	chaparrin	Root, Fruit	Moretti et al., 1986
	chaparrinone (10)	Root	Moretti, 1986
	karinolide	Stem	Moretti, 1986
	simarolide (23)	Root	Moretti, 1986
	simarinolide	Root	Moretti, 1986
	guanepolide	Root	Moretti, 1986
<i>Simarouba</i>	amarolide (16)	Root	Arriaga et al., 2002
	glaucarubinone (11)	Fruit	Gosh et al., 1977
	glaucarubin (13)	Fruit	Mesquita et al., 1997 Ham et al., 1954
	ailanthinone	Fruit	O'Neill et al., 1988
	glaucarubolone (14)	Seeds	Bhatnagar et al., 1984
	glaucarubolol	Seeds	Bhatnagar et al., 1984
	gimarolide (23)	Root	Polonsky, 1964
	chaparrinone (10)	Root	Dou et al., 1996a
	2,12-didemethylquassin	Root	Dou et al., 1996a
	holacantone	Root	Dou et al., 1996a

Chart 1 cont.

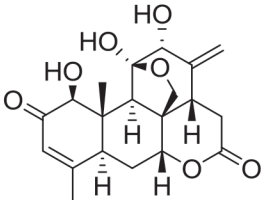
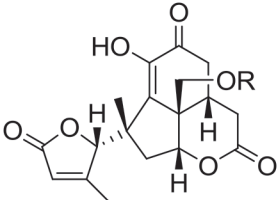
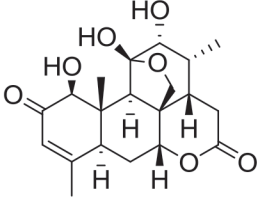
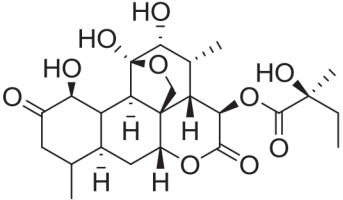
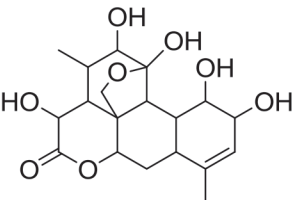
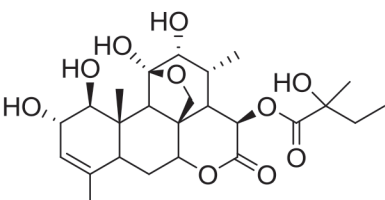
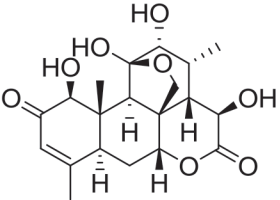
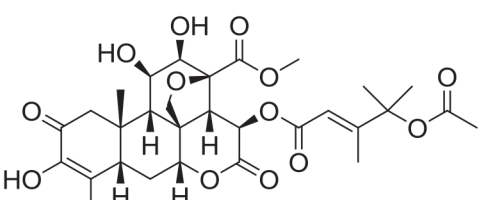
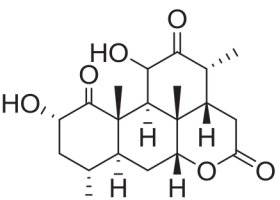
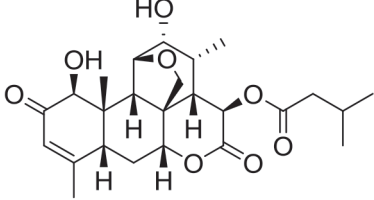
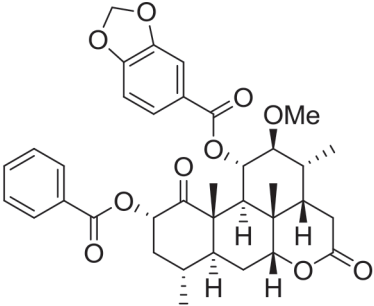
Genus	Chemical constituents	Part of the plant	Reference
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	 <p style="text-align: center;">9</p>		
	 <p style="text-align: center;">10</p>		
	 <p style="text-align: center;">11</p>		
	 <p style="text-align: center;">12</p>		
	 <p style="text-align: center;">13</p>		
	 <p style="text-align: center;">14</p>		
	 <p style="text-align: center;">15</p>		
	 <p style="text-align: center;">16</p>		
	 <p style="text-align: center;">17</p>		
	 <p style="text-align: center;">18</p>		

Chart 1 cont.

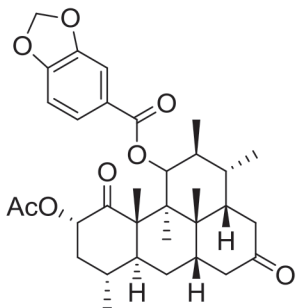
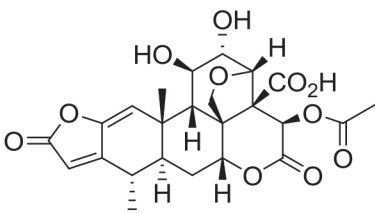
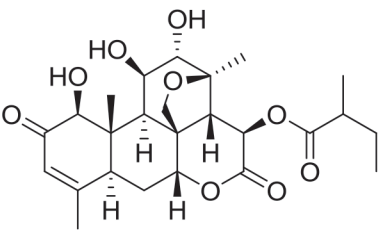
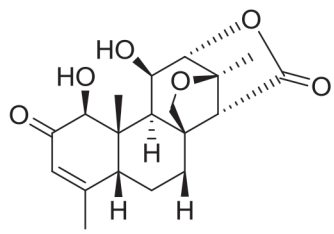
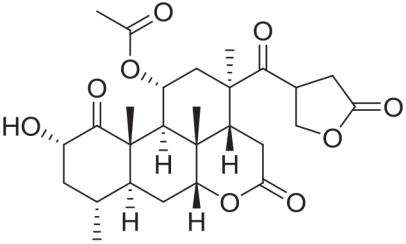
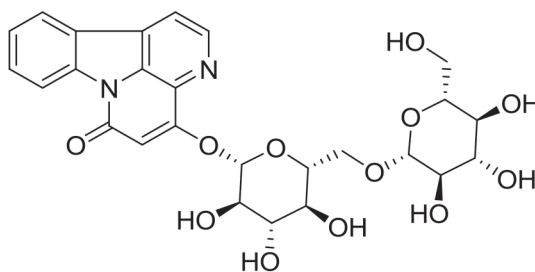
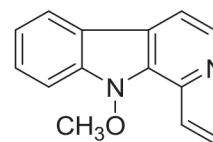
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	 <p style="text-align: center;">21</p>		
	 <p style="text-align: center;">22</p>		
	 <p style="text-align: center;">23</p>		
Alkaloids			
<i>Brucea</i>	bruceacanthinoside (24)	Stem	Kitagawa et al., 1994
<i>Picrasma</i>	4-methoxy-1-ethyl-β-carbolin	Stem	Yoshikawa et al., 1993
	4-methoxy-1-acetyl-β-carbolin	Stem	Yoshikawa et al., 1993
	N-methoxy-1-vinyl-β-carbolin (25)	Stem	Wagner and Nestler, 1978
	β-carbolin-1-yl-4,8-dimethoxy-β-carbolin-1-ylethyl ketone	Stem	Chen et al., 2009
	4,8-dimethoxy-1-vinyl-β-carbolin and other β-carbolins	Stem	Chen et al., 2009
	3-methylcanthin-5,6-dione	Stem	Chen et al., 2009
	dimethoxy-3-(1-hidroxyethyl)-β-carbolin	Stem	Jiao et al., 2010a
	3-etoxy-carbonyl-β-carbolin	Stem	Koike et al., 1990
	picrasidin X (26)	Stem	Jiao et al., 2010a
	quassidins A, B, C, D	Stem	Jiao et al., 2010b
	picrasidin C	Stem	Jiao et al., 2010b
	picrasidin U	Stem	Koike and Ohmoto, 1988
	picrasidin T	Bark	Koike et al., 1987

Chart 1 cont.

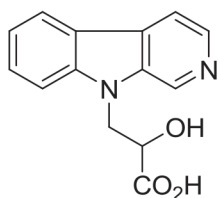
Genus	Chemical constituents	Part of the plant	Reference
<i>Picrolemma</i>	9-methoxycanthin-6-one (27)	Twigs	Rodrigues-Filho et al., 1992
	9-hidroxicanthin-6-one	Twigs	Rodrigues-Filho et al., 1992
	4,5-dimetoxycanthin-6-one	Twigs	Rodrigues-Filho et al., 1992
<i>Quassia</i>	astramelin A (28)	Bark	Tanigushi et al., 2012
	2-methoxycanthin-6-one	Not Described	Raji and Oloyede, 2012
	4-methoxy-5-hidroxicanthin-6-one	Stem	Grandolini et al., 1987
	1-vinyl-4,8-dimetoxi- β -carbolin (29)	Stem	Barbetti et al., 1987
	3-methylcanthin-2,6-dione	Stem	Barbetti et al., 1987
	canthin-2,6-dione	Stem	Koike and Ohmoto, 1994
	2-hidroxi-11-hidroxi-canthin-6-one	Stem	Pettit et al., 1990
	canthin-6-one (30)	Root	Lumonadio and Vanhaelen, 1985
	4-methyltiocanthin-6-one	Root	Ayafor et al., 1993
<i>Samadera</i>	1,8-dihidroxiacridan-9-one	Not described	Gibbons et al., 1997
	2-(10'-acetoxundecanil)-1-acetoximetil-4-quinolone	Not described	Gibbons et al., 1997
<i>Simaba</i>	canthin-2,6-dione (31)	Stem	Saraiva et al., 2006
	9-methoxy-canthin-6-one	Stem	Saraiva et al., 2006
	3-methoxycanthin-2,6-dione	Bark	Giesbrecht et al., 1980
<i>Simarouba</i>	5-hidroxicanthin-6-one (32)	Root	Lassak et al., 1977
	canthin-6-one (30) and other canthinonic alkaloids	Twigs	Rivero-Cruz et al., 2005



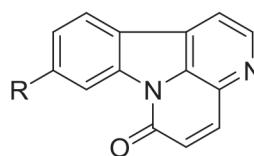
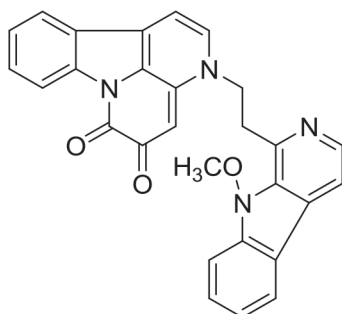
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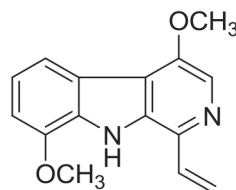
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26

27 R=OCH₃
30 R=H

28



29

Chart 1 cont.

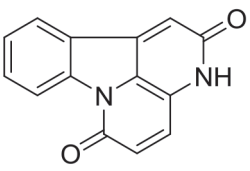
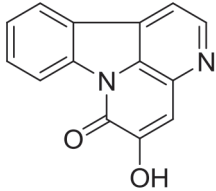
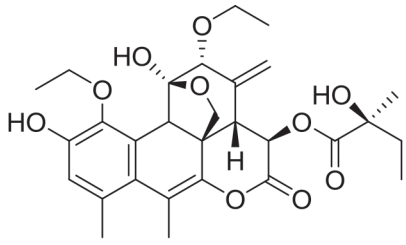
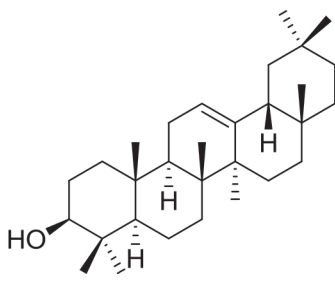
Genus	Chemical constituents	Part of the plant	Reference
	 <p style="text-align: center;">31</p>	 <p style="text-align: center;">32</p>	
Triterpenes			
Ailanthus	AECHL-1 (33)	Root	Lavhale et al., 2009
Castela	α - and β -amirin acetates (34)	Twigs	Jacobs et al., 2007
	nilocitin (35)	Twigs, thorns	Grieco et al., 1999a
Picrolemma	melyanodiol (36)	Stem	Rodrigues-Filho et al., 1993
	dihydroxy-3-oxo-24,25,26,27-tetranorapotirucall-14,20(22)-dien-21,23-olida and others	Stem	Rodrigues-Filho et al., 1993
	21,23-epoxy-7 α ,20,21,24,25-pentahydroxyapotirucall α -14-en-3-one and others	Stem	Rodrigues-Filho et al., 1996
Quassia	quassiols A, B, C, D	Root	Miller and Tinto, 1995a
Tinto et al., 1993	glabretal triterpene (C ₃₅ H ₅₆ O ₇) (37)	Root	Miller and Tinto, 1995b
Simaba	nilocitin (35)	Stem	Saraiva et al., 2006
	taraxerone	Stem	Saraiva et al., 2006
Simarouba	ocotilone (38)	Root	Arriaga et al., 2002
	nilocitina (35)	Twigs	Gosh et al., 1977
	3-episapelin	Fruit	Arriaga et al., 2002
	tirucall-7,24-dien-3-one and others	Fruit	Arriaga et al., 2002
	21,20-anydromelianone	Root	Polonsky et al., 1977
	melianone (39)	Root	Polonsky et al., 1977
	oxo-3-tirucall-7,24-dien	Stem	Polonsky et al., 1976
	Δ^7 -tirucallone (40)	Stem	Polonsky et al., 1977
	simaroubins A, B, C, D	Bark	Grosvenor et al., 2006
	octanorsimaroubin A	Bark	Grosvenor et al., 2006
	24,25-epoxy-3-oxotirucall-8-em-23-ol	Bark	Grosvenor et al., 2006
14-deacetileurilene	Twigs	Rivero-Cruz et al., 2005	
	 <p style="text-align: center;">33</p>	 <p style="text-align: center;">34</p>	

Chart 1 cont.

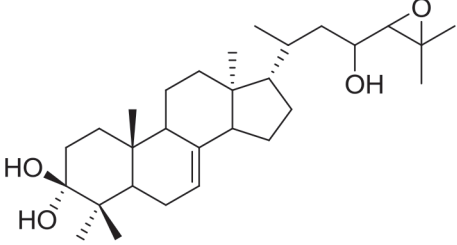
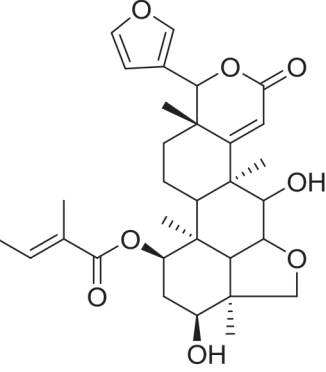
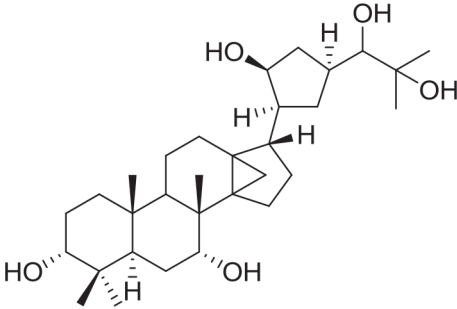
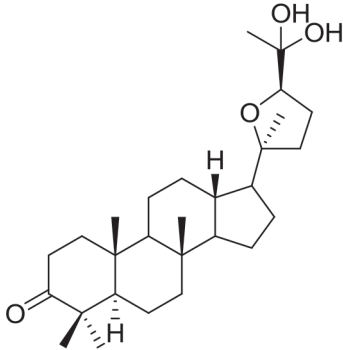
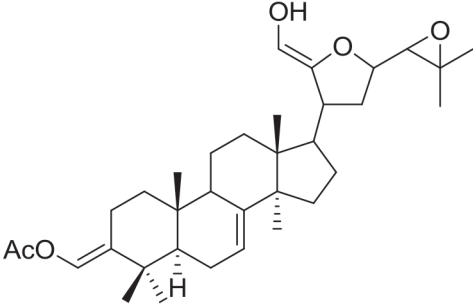
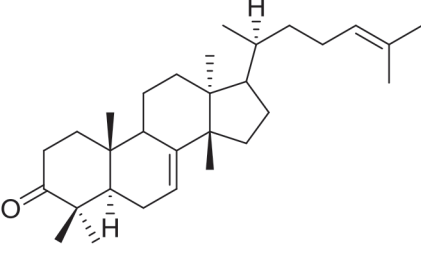
Genus	Chemical constituents	Part of the plant	Reference
	 <p style="text-align: center;">35</p>		
	 <p style="text-align: center;">36</p>		
	 <p style="text-align: center;">37</p>		
	 <p style="text-align: center;">38</p>		
	 <p style="text-align: center;">39</p>		
	 <p style="text-align: center;">40</p>		
Steroids			
<i>Castela</i>	3 α ,17 α ,20(S)-trihidroxypregnane-6,16-dione	Root	Grieco et al., 1994
	(-)-[3 α ,16 β ,17 α ,20(S)]-3,16,17,20-tetrahidroxypregnane-6-one	Twigs, thorns	Grieco et al., 1999b
<i>Picrolemma</i>	β -sitosterol	Stem	Rodrigues-Filho et al., 1993
	stigmasterol	Stem	Rodrigues-Filho et al., 1993
	campesterol (41)	Stem	Rodrigues-Filho et al., 1993
<i>Simarouba</i>	β -sitosterol	Root, Fruit	Arriaga et al., 2002

Chart 1 cont.

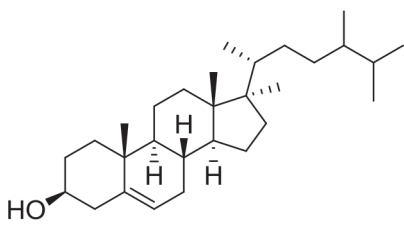
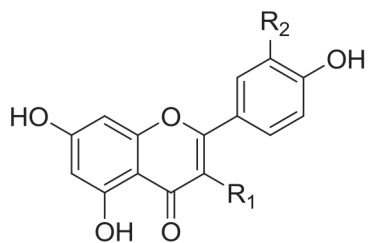
Genus	Chemical constituents	Part of the plant	Reference
	 <p style="text-align: center;">41</p>		
Outros Constituintes			
<i>Ailanthus</i>	apigenin (42)	Leaves	Loizzo et al., 2007
	luteolin	Leaves	Loizzo et al., 2007
	kaempferol (43)	Leaves	Loizzo et al., 2007
	quercetin (44)	Leaves	Loizzo et al., 2007
	escalene	Leaves	Jin et al., 2009
	scopoletin (45)	Leaves	Jin et al., 2009
	astragalin	Leaves	Jin et al., 2009
	scopolin	Leaves	Jin et al., 2009
<i>Castela</i>	scopoletin (45)	Aerial Parts	Jacobs et al., 2007
	methyl vanilate	Aerial Parts	Jacobs et al., 2007
	prosopin	Bark	Kubo et al., 1993
	physetinydol (46)	Bark	Kubo et al., 1993
	methyl gallate	Bark	Kubo et al., 1993
	lucoside 1	Twigs	Grieco et al., 1999b
	(C ₁₉ H ₂₈ O ₈)	Thorns	Grieco et al., 1999b
<i>Picrasma</i>	6-metoxi-7,8-metilenodioxy-coumarin	Stem	Yoshikawa et al., 1993
	nigakialcohol	Leaves	Sugimoto et al., 1978
	vomifoliol (47)	Leaves	Sugimoto et al., 1978
	picrasmalignane A	Stem	Jiao et al., 2011
	buddlenol A, C	Stem	Jiao et al., 2011
	2'-isopicrasine A	Stem	Jiao et al., 2011
	physetin (48)	Stem	Jiao et al., 2011
	arbutin (49)	Fruit	Yoshikawa et al., 1995
	florin	Fruit	Yoshikawa et al., 1995
	coaburaside	Fruit	Yoshikawa et al., 1995
	syringine	Fruit	Yoshikawa et al., 1995
	citrusine B	Fruit	Yoshikawa et al., 1995
	<i>Picrolemma</i>	scopoletin (45)	Twigs
<i>Quassia</i>	gallic acid (50)	Leaves	Fabre et al., 2012
	methyl gallate	Leaves	Fabre et al., 2012
	apiosyl gallate	Leaves	Fabre et al., 2012
	vitexin (51)	Leaves	Fabre et al., 2012
<i>Samadera</i>	(-)-sesamin	Not Described	Gibbons et al., 1997
	fargesin (52)	Not Described	Gibbons et al., 1997
	(-)-eudesmin (53)	Not Described	Gibbons et al., 1997

Chart 1 cont.

Genus	Chemical constituents	Part of the plant	Reference
<i>Simarouba</i>	limonin	Not Described	Gibbons et al., 1997
	melyanodiol	Leaves	Merrien and Polonsky, 1971
	kampferol	Root, Fruit	Arriaga et al., 2002
	epilupeol	Not Described	Gosh et al., 1977
	melyanodiol	Twigs	Rivero-Cruz et al., 2005
	scopoletin	Twigs	Rivero-Cruz et al., 2005
	fraxidin	Twigs	Rivero-Cruz et al., 2005
	palmitic, stearic, oleic, linoleic and linolenic acids	Seeds	Jeyarani and Reddy, 2001 Joshi and Hiremath, 2000
	saponins	Seeds	Govindaraju et al., 2009
	phenolic compounds	Seeds	Govindaraju et al., 2009
	phytic acid (54)	Seeds	Govindaraju et al., 2009
	aminoacids	Seeds	Govindaraju et al., 2009
	saponins	Seeds	Govindaraju et al., 2009
	phenolic compounds	Seeds	Govindaraju et al., 2009
	phytic acid (54)	Seeds	Govindaraju et al., 2009
	aminoacids	Seeds	Govindaraju et al., 2009
	saponins	Seeds	Govindaraju et al., 2009
	phenolic compounds	Seeds	Govindaraju et al., 2009
	phytic acid (54)	Seeds	Govindaraju et al., 2009
	aminoacids	Seeds	Govindaraju et al., 2009



42 $R_1=R_2=H$
43 $R_1=OH; R_2=H$
44 $R_1=R_2=OH$

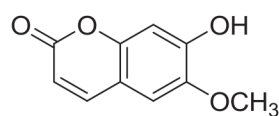
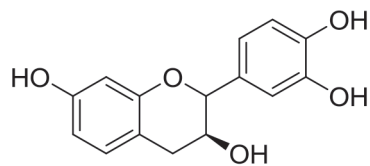
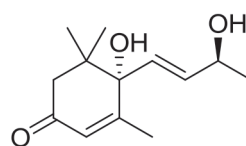
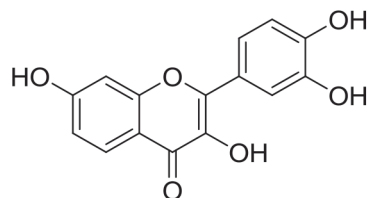
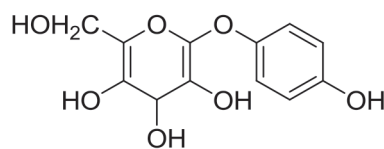
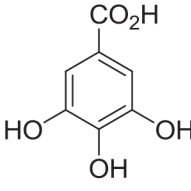
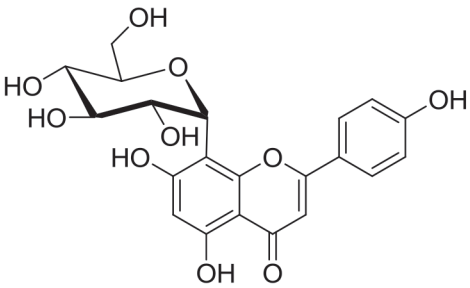
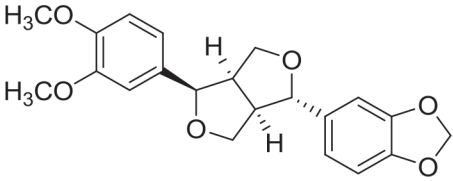
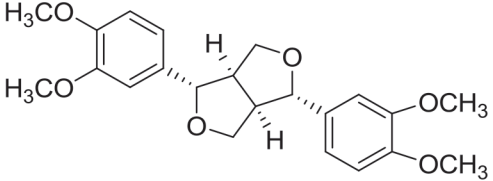
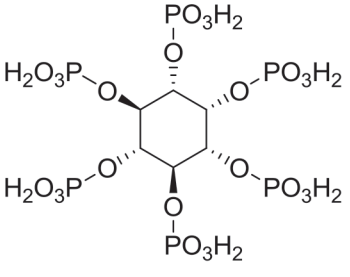
**45****46****47****48****49**

Chart 1 cont.

Genus	Chemical constituents	Part of the plant	Reference
	 <p>50</p>	 <p>51</p>	
	 <p>52</p>	 <p>53</p>	
	 <p>54</p>		

Triterpenes

Twenty triterpenes have been reported in six different species of the genus *Simaba* (Barbosa et al., 2011). Kundu and Laskar (2010) reported 91 terpenoids, quassinoids included. This class of secondary metabolites has been largely reported in the literature for numerous genera of Simaroubaceae, like *Quassia*, *Brucea*, *Picramnia*, *Castela*, *Simarouba* and *Ailanthus* (Chart 1).

Steroids

Eight steroids were isolated from four species of the genus *Simaba* and their structure was elucidated (Barbosa et al., 2011). The isolation of 27 steroids from four species of *Ailanthus* was performed by Kundu and Laskar (2010). These compounds were found in species of the genera *Castela*, *Picrolemma* and *Simarouba* (Chart 1).

Other Constituents

Twenty three metabolites from different classes were isolated from six species of the genus *Simaba* (Barbosa et al., 2011).

Kundu and Laskar (2010) highlighted the presence of nineteen flavonoids in five species of *Ailanthus*, among other metabolites, like chromones, fatty acids, volatile compounds, proteins and others. Polyphenols, anthraquinones, coumarins, flavonoids, lignans, limonoids, quinines, fatty acids, phenylpropanoids and vitamins have been reported for the different species of the Simaroubaceae family (Chart 1), although many species have not been chemically studied yet.

Biological activities

Species from the Simaroubaceae family, known for their medicinal properties, are used traditionally for the treatment of malaria, and also as anthelmintic, antitumor, anti-inflammatory, antiviral, anorectic, tonic, insecticide and amebicide (Simão et al., 1991; Arriaga et al., 2002; Muhammad et al., 2004; Saraiva et al., 2006; Silva et al., 2010). There are reports of the use of *Brucea antidysenterica* in Africa, *Brucea javanica* and *Ailanthus altissima* in China, *Simaba guianensis*, *Quassia amara* and *Simarouba versicolor* in Brazil, *Castela texana* in Mexico (Muhammad et al., 2004; Mendes and Carlini, 2007;

Silva et al., 2010) and *Quassia amara* in French Guyana (Cachet et al., 2009).

The vast range of biological activities of the different species of Simaroubaceae are given, mainly, due to the quassinoids, for which were attributed antitumor, antimalarial, antiviral, anorectic, insecticide, amebicide, antiparasitic and herbicide activities (Bhattacharjee et al., 2008).

Cytotoxic activity

Cytotoxicity, commonly found within the Simaroubaceae family, is primarily attributed to quassinoids. Canthinone alkaloids and terpenoids can also elicit this kind of activity (Rivero-Cruz et al., 2005). In this context, Shields et al. (2009) found that quassin and neoquassin inhibited the CYP1A1 isoenzyme, an isoform of the P450 cytochrome enzyme known for its carcinogenic activity, consequently assuming an important role as a chemoprotector (Shields et al., 2009). Simalikalactone D has also demonstrated a promising cytotoxic activity against mammary human adenocarcinoma cells (Houël et al., 2009).

Rivero-Cruz and collaborators (2005) confirmed the cytotoxic activity of four canthin-6-one derived alkaloids, isolated from *Simarouba glauca*, against human colon cancer, human oral epidermoid cancer, human hormone-dependent prostate cancer and human lung cancer cells. Moreover, against the latter, a squalene-type triterpenoid was also active. Furthermore, Jiang and Zhou (2008) demonstrated the activity of four alkaloids, also derived from canthin-6-one, isolated from *Picrasma quassioides*, against nasopharynx carcinoma cells.

Antitumor activity

Many species of the Simaroubaceae family display prominent antitumor activity, and the main genera are: *Ailanthus*, *Brucea*, *Simarouba*, *Quassia*, *Picrolemma*, *Simaba* and *Picrasma* (Chart 1). The major metabolites related to the antitumoral activity of several species include quassinoids and alkaloids (Rivero-Cruz et al., 2005).

Among the most potent quassinoids with such antitumor activity, *bruceantin*, *bruceantinol*, *glucarubinone* and *simalikalactone D* (Guo et al., 2009) deserve special attention. *Bruceantin* is the main compound studied due to its noted antileukemic activity, which has enabled its use in clinical tests at the United States National Cancer Institute (Polonsky et al., 1978; Bedikian et al., 1979). *Chaparrinone* and *chaparrin* as well as *isobrucein B*, *sergeolide* and *quassimarin*, isolated from species of *Picrolemma*, *Simaba* and *Quassia*, also displayed good antileukemic activity (Kupchan and Streelman, 1976; Moretti et al., 1982; Moretti, 1986).

Ailantinone and *glucarubinone* displayed effects against human pharynx epidermoid carcinoma (Wright et al., 1993). *Glucarubinone* has also been reported to show activity against solid and multiresilient mammary tumors in rats (Valeriotte et al., 1998). *AECHL-1*, a quassinoid isolated from *Ailanthus excelsa*, inhibited the growth of melanoma, prostate cancer, carcinoma and mammary adenocarcinoma cell lines. This last molecule has been proved to be more potent than *paclitaxel* and *cisplatin*, drugs commonly used in therapeutic (Lavhale

et al., 2009). *Quassimarin*, isolated from *Quassia amara*, showed activity against lymphocytic leukemia in rats, and carcinoma nasopharynx cells in human (Kupchan and Streelman, 1976).

Although the antitumor activity of these compounds has been previously determined, most are too toxic for clinical use. However, the search for new natural sources of more potent and less toxic quassinoids, and the structural modification of previously known compounds to lower their toxicity, constitute interesting alternatives for the development of anticancer drugs (Guo et al., 2009).

Antimalarial activity

Many studies with plants from the Simaroubaceae family have shown promising results against chloroquine-resistant *Plasmodium falciparum* cultures, quassinoids being the primary responsible for such activity (Murgu, 1998). Cachet and collaborators (2009) demonstrated the antimalarial activity from *simalikalactone E*. *Simalikalactone D* also showed great *in vivo* and *in vitro* activity (Bertani et al., 2006; Houël et al., 2009) and its synergic effect with *atovaquone*, a classic antimalarial, was later confirmed (Bertani et al., 2012). Other quassinoids that showed significant antimalarial activity include: *ailanthone*, *6 α -tigloyloxichaparrinone* (Okunade et al., 2003), *pasakbumines B* and *C*, *eurycomanone* (Kuo et al., 2004; Chan et al., 2004), *simalikalactone D* (Houël et al., 2009), *orinocinolid* (Muhammad et al., 2004), *isobrucein B* and *neosergeolide* (Andrade-Neto et al., 2007; Silva et al., 2009a). The characteristic structural conformation of quassinoids has a direct relation to their activity, as an α,β -insaturated ketone in the A ring, an epoxymethylene bond in the C ring and esteric functional groups at C-15, essential in the antimalarial activity (Kaur et al., 2009).

The action mechanisms associated include protein synthesis inhibition however it would be different from those observed in tumor cells, given that quassinoids have shown a higher selectivity for *Plasmodium falciparum* in comparison to KB cells (Anderson et al., 1991). Compounds with a higher antimalarial activity include: *simalikalactone D*, *glucarubinone*, *soularubinone* (Polonsky, 1985), *holacanthone*, *2'-acetylglucarubinone* and *ailanthinone* (O'Neill et al., 1988), most of them found in *Simarouba amara*.

Feeding deterrent and insecticide activity

Many quassinoids have been deemed the responsible agents for alterations in feeding behaviour and growth regulation of insects (Govindachari et al., 2001). Previous studies have demonstrated the insecticide activity of these compounds in *Tetranychus urticae*, *Myzus persicae*, *Meloidogyne incognita* (Latif et al., 2000) and *Rhodnius milesi* (Coelho, 2006). *Quassin*, as well as *simalikalactone D*, *bruceantine*, *glucarubinone* and *isobrucein*, has been proven to be an effective aphid antifeedant agent against the Mexican bean beetle (*Epilachna varivestis*), the diamondback moth (*Plutella xylostela*) and the south caterpillar (Daido et al., 1995).

Isobrucein B and *neosergeolide*, quassinoids found in *Picrolemma sprucei*, display larvicidal properties against *Aedes aegypti* larvae (Silva et al., 2009a). *Chaparramarin*, found in

Chart 2

Biological activities of the main genera of Simaroubaceae family.

Genus	Activity	Reference
Ailanthus	Anti asthmatic	Kumar et al., 2011
	Anti allergenic	
	Cytotoxic (carcinoma and mammary adeno-carcinoma, melanoma and prostate cancer)	Lavhale et al., 2009
	Hypotensor: Angiotensin conversion enzyme inhibition	Loizzo et al., 2007
Brucea	Anti plasmodial	Okunade et al., 2003
	Cytotoxic	Ehata et al., 2012
	Antiprotozoa (against <i>Trypanosoma cruzi</i> and <i>T. brucei</i> , <i>Leishmania infantum</i> , <i>Plasmodium falciparum</i>)	
	Hypoglycaemic	Noorshahida et al., 2009
Eurycoma	Antiprotozoa (<i>Trypanosoma evansi</i>)	Bawn et al., 2008
	Increase in spermatogenesis and fertility	Low et al., 2013
Picrolemma	Anthelmintic	Nunomura et al., 2006
	Larvicide (against <i>Aedes aegypti</i>)	Silva et al., 2009a
Quassia	Antimalarial (<i>Plasmodium berghei</i> , <i>Plasmodium falciparum</i> resistant to chloroquine)	Ajaiyeoba et al., 1999
		Bertani et al., 2006, 2012
		Cachet et al., 2009
	Antiulcerogenic	García-Barrantes and Badilla, 2011
		Toma et al., 2002
	Antidiabetic	Hussain et al., 2011
	Antifertilizer	Raji and Bolarinwa, 1997
	Sedating and anticonceptive	Toma et al., 2003
	Cytotoxic (against lymphocytic leukaemia, human nasopharynx carcinoma and human mammary adenocarcinoma)	Kupchan and Streelman, 1976
		Houël et al., 2009
Simarouba	Antifeeding (<i>Bemisia</i> , <i>tabaci</i> and <i>Hypsipyla grandella</i>)	Flores et al., 2008
		Mancebo et al., 2000
	Insecticide (against <i>Tetranychus urticae</i> , <i>Myzus persicae</i> and <i>Meloidogyne incognita</i>)	Latif et al., 2000
	Antimalarial (<i>Plasmodium berghei</i>)	Ajaiyeoba et al., 1999
	Antiulcerogenic	Almeida et al., 2011
Simarouba	Antiplasmodial (<i>Plasmodium falciparum</i> and <i>P. berghei</i>)	O'Neill et al., 1988
	Antiprotozoal (<i>Trypanosoma brucei</i> and <i>T. cruzi</i> , <i>Leishmania infantum</i> and <i>Plasmodium falciparum</i>)	Valdez et al., 2008

Castela tortuosa, has growth inhibitory activity against *Heliopsis virescens* (Kubo et al., 1992). Extracts of *Quassia amara* elicited feeding deterrent activity against *Bemisia tabaci* (Flores et al., 2008) and *Hypsipyla grandella* (Mancebo et al., 2000).

Other biological activities

At high concentrations some quassinoids show *in vitro* antiviral activity. Simalikalactone D is active against Rous sarcoma oncogenic virus (Pierré et al., 1980), Herpes simplex type 1 virus, *Vesicular stomatitis virus*, *Poliomyelitis* and *Semliki forest virus* (Apers et al., 2002), while shinjulactone is active against HIV virus (Okano et al., 1996). Previous reports also found these compounds elicit anti-inflammatory activity (Guo et al., 2009; Hall et al., 1983). In addition, Beyond them brusatol, as

well as samaderins X and B, can be highlighted (Kitagawa et al., 1996). Among the antiviral active alkaloids, those isolated from *Picrasma quassioides* are important, since they were active against tobacco mosaic virus (Chen et al., 2009). Regarding the ameibicide activity of quassinoids (Wright et al., 1988), *bruceantin* was considered the most potent (Gillin et al., 1982).

The herbicidal activity of these compounds was verified in a study that revealed that excelsin was a growth regulator of *Chenopodium album* and *Amaranthus retroflexus* in soy (Guo et al., 2009). Furthermore, Tada and collaborators (1991) reported antiulcerogenic activity for pasakbumins A, B, C and D.

Besides the reported activities of quassinoids and canthinone alkaloids, many pharmacological studies have documented the different activities of many extracts and isolated compounds from Simaroubaceae's species (Chart

1). The anti-inflammatory activity of a seterterpene lactone, two neolignans and a flavonol of *Picrasma quassioides* was proven (Jiao et al., 2011). Species of the genus *Ailanthus* display antiasthmatic and antiallergenic activities (Kumar et al., 2011); hypotensive activity, mediated by Angiotensin Conversion Enzyme (ACE) inhibition by flavonoids (Loizzo et al., 2007); and, in the genus *Castela*, plant growth inhibitory activity (Lin et al., 1995). Species from *Brucea* genus have been shown to have antiprotozoal activity, against two *Trypanosoma* species (*T. cruzi* and *T. brucei*) and *Leishmania infantum* (Ehata et al., 2012), and quassinoids have been attributed to hypoglycemic activity (Noorshahida et al., 2009).

Eurycoma longifolia, stimulated the increase in spermatogenesis and fertility in rats (Low et al., 2013). On the other hand, *Quassia amara* showed antifertilizing properties (Toma et al., 2002; Raji and Bolarinwa, 1997), along with antiulcerogenic activity in acute ulcer-induced models (García-Barrantes and Badilla, 2011); antidiabetic activity, with significant reduction of associated dyslipidemia (Hussain et al., 2011); and analgesic and antiedematogenic activity, probably associated to sedating and muscular relaxing or psychomimetic activities (Toma et al., 2003). *Picrolemma sprucei* exhibits anthelmintic activity against *Haemonchus contortus*, a ruminant's parasite (Nunomura et al., 2006). *Simaba ferruginea* showed antiulcerogenic activity by gastroprotection (Almeida et al., 2011).

The aqueous extract of *Simarouba amara* promoted the differentiation of human skin keratinocytes and increased the production of involucrin, cholesterol and ceramides as well thus it may be used for dry skin as it also improves water retention by the stratum corneum (Bonté et al., 1996; Casetti et al., 2011). Due to these findings, a patent was registered in 1997 for cosmetic or pharmaceutical use for the skin (Bonté et al., 1997).

Discussion and Conclusion

This paper is a review of the botanical, chemical and pharmacological characteristics of the major genera and species of Simaroubaceae family. This family is of great importance and relevance in the ethnopharmacological framework since many of its species are widely used in the folk medicine practice of many countries, and are part of the official compendia. Many genera of this family are employed in the treatment of malaria, cancer, worms, viruses, gastritis, ulcer, inflammation, diarrhea and diabetes, in addition to their insecticide, healing and tonic activities. In addition to the ethnopharmacological uses, plants from the Simaroubaceae family can be highlighted for their chemical diversity, since the presence of quassinoids, alkaloids, terpenes, steroids, flavonoids, anthraquinones, coumarins, saponins, mono- and sesquiterpenes, among others, have been determined. This chemical diversity and the pharmacological activities of the isolated compounds; such as cytotoxicity, antimalarial, insecticidal, antitumor, hypoglycemic, antiulcer activities, among others, characterize the species of this particular family. They are potential sources for the isolation and structural elucidation of new or novel bioactive compounds that could provide information for the development of herbal medicines, phytopharmaceuticals and phyto cosmetics.

Therefore, the compilation of knowledge regarding the triad botany-chemistry-pharmacology of Simaroubaceae family can significantly contribute to the direction, base and development of new and promising research and preventing the knowledge stagnation of recent years.

Authors' contributions

IABSA (M.Sc. student) and HMM contributed in the compilation of databases about the Simaroubaceae family until the year 2013. LALS and KPR, contributed in selecting the main and more relevant information.

Conflicts of interest

The authors declare no conflicts of interest.

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