

## CHEMICAL COMPOSITION, BIOLOGICAL ACTIVITIES AND USES OF ANACARDIACEAE SPECIES: AN UPDATED REVIEW

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The present review, with 169 references, describes a critical updated compilation of studies regarding the Anacardiaceae family. Firstly, it is shown a detailed report of the chemical composition (essential oils, terpenoids, flavonoids, alkyl and alkenyl phenols, and other compounds) of species of all studied genera, followed by the biological properties (*in vitro* and *in vivo* activities) of extracts, enriched fractions, and pure new isolated metabolites. Furthermore, it is reported herein that some deposited processes developed with Anacardiaceae spp. (cosmetic and pharmacological compositions, besides some technological applications) as well as new findings about the biosynthesis of phenolic lipids, the primary chemical marker of the family. Consequently, these outcomes highlight the relevance of this family in developing natural products' chemistry from 2006 to now.

Keywords: Anacardiaceae; specialized metabolites; bioactivity; biosynthesis.

### INTRODUCTION

Anacardiaceae is a family consisting of about 600 species distributed in 76 genera. The genera are subdivided into five tribes (Anacardieae, Dobineae, Rhoeeae, Semecarpeae, and Spondiadeae). The plants of this family are known as sources of edible fruits and condiments such as mango, cashew, pistachios (*Pistacia* spp.), sumac (*Rhus coriaria*) and pink peppercorns (*Schinus terebinthifolia*). Approximately 25% of genera present toxic phenolics, compounds responsible for several contact dermatitis. In general, the poisonous species of this family are restricted to the tribes Anacardieae, Rhoeeae, and Semecarpeae.<sup>1,2</sup>

Phenolic and catecholic lipids are usual compounds present in these plants, which are usually responsible for their toxic properties, whether alone or in mixtures of different saturated or unsaturated aliphatic chains. These compounds are present in different plant parts and frequently occur in *Rhus* species. Thus, species of this family have been frequently studied from a chemical and biological point of view due to their potential as sources of new bioactive compounds. The most studied genera are *Mangifera*, *Spondias*, *Lannea*, *Toxicodendron* (*Rhus*), *Schinus*, *Pistacia*, *Lithraea*, *Tapirira*, *Semecarpus*, *Melanorrhoea* and *Anacardium*. However, most of Anacardiaceae species remain unknown regarding their chemical composition, alongside pharmacological and other biological activities. Although recent reviews about some classes or specific compounds in Anacardiaceae<sup>3,4</sup> and genus *Schinus*<sup>5</sup> were performed, there are just two reviews of all families, the last one dated from 2006.<sup>1,2</sup>

The current review with approximately 170 references is an update of the chemical composition, biological activities in extracts and pure compounds isolated from different Anacardiaceae plant species since 2006. Moreover, some processes, technological applications and new insights about the biosynthesis of phenolic lipids were also reviewed.

### LITERATURE SEARCH STRATEGY

A bibliographic survey of scientific articles published in indexed journals and deposited process patents was performed to

develop this review. For this purpose, the databases SciFinder, Web of Science, Science Direct, PubMed, Scielo and Google Scholar were utilized. All articles published from 2006 to March 2023 were considered, including papers not considered in a previous review. In the quest "Advanced search" feature combined with the keywords "Anacardiaceae", "chemical composition", "bioactivity", "biosynthesis", and all the genera described in specialized literature were used.<sup>6</sup> The titles of articles and patents found were scanned and organized in a file when considered meaningful. Afterward, duplicates were removed and, thus, the abstracts of the articles obtained were checked for relevant information as part of the inclusion strategy. Finally, all articles and patents were carefully read and, after reviewing, 149 papers and 21 patents were selected to compose the present work.

### CHEMICAL COMPOSITION OF ANACARDIACEAE spp.

#### Essential oils (EOs) and volatile other compounds (VOCs)

Studies concerning to essential oils (EOs) and volatile organic compounds (VOCs) of Anacardiaceae family have been frequently developed, especially for edible species such as fruits and seeds. The EOs are usually obtained from plants' leaves, flowers and other aerial parts. The most recent works will be highlighted herein, including the compositions of these metabolites in different species and genera, the identification of new substances and other relevant information.

The investigation of the EOs' chemical composition of *Mangifera indica* (var. "coquinho")<sup>7</sup> indicated that the sesquiterpene hydrocarbons are the leading representative compounds (66.4%) against the oxygenated ones (8.7%), which have presented anticancer, antimicrobial and antioxidant activities. On the other hand, in barks of *M. indica* L. was reported<sup>8</sup> that the sesquiterpene hydrocarbons reached 97.0% in an analog study (Table 1). The other components of these EOs are monoterpenes ( $\leq 2\%$ ).

*Rhus cotinus* L. (syn. *Cotinus coggygia* Scop.) is a European tree commonly grown as an ornamental plant, presenting different cultivars due to the different purple foliage and flowers. The wood of this species presented economic importance, since it was formerly used to make the yellow dye called young fustic (fisetin), now replaced by synthetic dyes. The profile of EOs obtained from the same species

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**Table 1.** Relative composition (%) of the more abundant compounds in the essential oils from some *Mangifera indica*<sup>7,8</sup> varieties

Compounds	Leaves (var. coquinho) (%)	Barks (%)	
Sesquiterpene hydrocarbons	$\alpha$ -gurjunene	24.0	
	$\beta$ -selinene	24.0	
	$\beta$ -caryophyllene	11.2	60.3
	$\alpha$ -humulene	7.2	36.7
Oxygenated sesquiterpenes	caryophyllene oxide	5.5	
	humulene epoxide	2.4	

varies according to the biome, the part of the plant (fresh aerial parts,<sup>9</sup> leaves<sup>10</sup> or flowering aerial parts<sup>11</sup>) and seasonally, even between regions that are close in latitude. Thus, the total composition of monoterpenes was not similar in both cases (Table 2).

*Pistacia* spp. (such as *P. lentiscus* L., *P. vera*, *P. terebinthus* L., and *P. khinjuk* Stocks) are employed in Europe and the Mediterranean region as food, for cooking, and for other purposes (e.g., the oleoresin). Consequently, this is the most probable reason for the expressive number of studies dealing with the EO composition of these species.

The EOs profile of *P. lentiscus* is similar to species from different habitats<sup>12</sup> (Southern Italy and Morocco, Tunisia, Greece or France), but distinct from other EO profiles obtained from specimens from Egypt, Sardinia Island/Italy and Spain, probably due to the different climate and seasonal changes, besides insect presence, physicochemical soil properties, extraction methods and others. Furthermore, mastic gum essential oils (MGEOs) of wild plants of *P. lentiscus*<sup>13</sup> are quantitatively different compared to the cultivated plants, so that the tree age could be another affecting this chemical composition. Other subsequent studies<sup>14,15</sup> present several data that confirm the exact behavior of the EOs profile.

Similarly, the EOs content in *P. terebinthus*<sup>16,17</sup> is also related to the plant organ and population origins. In these studies, the variability of the composition was carefully analyzed by the principal component analysis (PCA), and the conclusion is that abiotic (climatic, edaphic, chemical, among others) and biotic (genotypic diversity and nutritional variations) factors may be related to these variations. At

last, since no previous published data deals with the *P. khinjuk* EO leaf profile, it was impossible to compare the current study with the EO composition of other *P. khinjuk*<sup>18</sup> trees from other regions (particularly from Iran).

Studies employing PCA (Principal Component Analysis) and HCA (Hierarchical Cluster Analysis) permitted to evaluate if EO constituents could reflect the chemotaxonomic relationships in *Pistacia* species. Based on the most abundant compounds present in the EOs (contents  $\geq 3.5\%$ ), the groups were classified as chemotypes (i) Group A ( $\alpha$ -pinene,  $\beta$ -pinene, limonene and terpinen-4-ol, *P. lentiscus*) and (ii) Group B (B1,  $\alpha$ -terpinene, *P. terebinthus*; B2, limonene, *P. vera*).<sup>19</sup> Table 3 summarizes the volatile compounds from *Pistacia* spp., and the examination of the data clearly indicates the monoterpenes are the main compounds – especially  $\alpha$ - and  $\beta$ -pinenes (in *P. lentiscus*),  $\alpha$ -pinene, limonene, and  $\beta$ -ocimene (in *P. terebinthus* and *P. vera*) and myrcene and eudesmol (in *P. khinjuk*).

*Spondias* L. is a genus with about ten species, occurring mainly in Asia, three or four species native to the Neotropics, most of them produce edible fruits. A previous study with *S. pinnata* from east India showed that the major VOCs of whole green fruits were isopropyl myristinate (36.85%), isophorone (6.55%), limonene (4.46%) and linalool (3.57%).<sup>20</sup> However, the EOs from fruits of specimens growing in Egypt was composed mainly of long-chain alkanes (51.1%) besides fatty acid esters (25.7%). The relative most predominant component was *n*-nonacosane (25.0%).<sup>21</sup> Therefore, these results indicate that the profile of the significant constituents of EOs in the green fruits, ripe fruits and fruit peels can change with the plant part studied, even though the extraction methods or geographic locations could also influence such differences, which may partly determine the variation in bioactivity.<sup>22</sup>

Variations in the EO compositions could be related to the investigated species' cultivation, vegetative stage, source or seasonal growing. Furthermore, an increase in the oxygenated monoterpenoid amount, as well as a decrease in the sesquiterpenoid hydrocarbons content, was observed due to the dehydrating of the leaves, while the contents of some minor metabolites (geraniol, eugenol, borneol, terpinen-4-ol, besides others) were stable in the two oils, although were present in small quantities (< 1.0%).<sup>23</sup> Table 4 summarizes the data and presents additional compounds of some *Spondias* spp.

**Table 2.** Relative composition (%) of the most abundant essential oils from *Rhus cotinus*<sup>9-11</sup>

Subgroup	Compounds	Fresh aerial parts <sup>9</sup> (%)	Leaves <sup>10</sup> (%)	Flowering aerial parts <sup>11</sup> (%)
Monoterpene hydrocarbons [66.4-79.6]	$\alpha$ -pinene	5.2	43.1	8.8
	$\beta$ -pinene	30.6	3.4	n.d.
	limonene	12.4	21.3	49.2
	camphene	13.6	n.d.	n.d.
	<i>p</i> -cymene	4.6	n.d.	n.d.
	$\beta$ -myrcene	n.d.	8.5	n.d.
	$\alpha$ -terpinene	n.d.	3.3	n.d.
	( <i>Z</i> )- $\beta$ -ocimene	n.d.	n.d.	13.6
Sesquiterpene hydrocarbons [0-21.4]	( <i>E</i> )- $\beta$ -ocimene	n.d.	n.d.	5.9
	$\beta$ -caryophyllene	4.4	2.4	n.d.
	bicyclogermacrene	12.6	n.d.	n.d.
Oxygenated monoterpenes [0-5.0]	germacrene D	2.0	n.d.	n.d.
	$\alpha$ -terpinolene	n.d.	5.0	n.d.

n.d.: Not detected/quantified.

**Table 3.** Relative composition (%) of the most abundant essential oils from *Pistacia* spp.<sup>12-19</sup>

<i>P. lentiscus</i> L. <sup>12-15</sup>			<i>P. khinjuk</i> Stocks <sup>18</sup>		
		Variation (%)			
Monoterpene hydrocarbons [77.0-85.0]	$\alpha$ -pinene	[2.4-70.8]	myrcene		18.7
	$\beta$ -pinene	[0.3-9.6]	$\alpha$ -eudesmol		12.3
	limonene	[1.0-17.8]	$\beta$ -eudesmol		9.3
	$\beta$ -myrcene/myrcene	[2.5-20.1]	$\delta$ -eudesmol		4.9
	sabinene	[1.0-6.7]	1,7-di- <i>epi</i> - $\beta$ -cedrene		7.3
	$\gamma$ -terpinene	[3.10-6.21]	bicyclogermacrene		5.6
	$\alpha$ -terpinolene	[2.18-2.20]			
Oxygenated monoterpenes [6.0-23.1]	<i>p</i> -cymene	[0.5-7.5]	<i>P. vera</i> <sup>19</sup>		
	terpinen-4-ol	[0.7-21.7]	$\alpha$ -pinene		16.07
	$\alpha$ -terpineol	[2.5-4.0]	$\beta$ -pinene		2.32
Sesquiterpene hydrocarbons [5.0-28.1]	$\beta$ -caryophyllene/ caryophyllene	[2.6-19.9]	$\alpha$ -terpinene		[32.44-41.34]
	$\delta$ -cadinene	11.7	limonene		25.10
	$\alpha$ -muurolene	[0.1-6.9]	$\alpha$ -terpinolene		[1.13-8.02]
			$\beta$ -myrcene		1.29
<i>P. terebinthus</i> L. <sup>16,17</sup>			$\alpha$ -phellandrene		3.85
Monoterpene hydrocarbons [63.90-98.94]	$\alpha$ -pinene	[12.58-66.29]	$\delta$ -terpinene		6.99
	D-limonene//limonene	[13.95-46.29]	$\alpha$ -terpineol		[2.14-4.52]
	( <i>E</i> )- $\beta$ -ocimene// ( <i>Z</i> )- $\beta$ -ocimene	[40.49-44.85]	Oxygenated monoterpenes		
	$\beta$ -pinene	[1.99-20.47]	terpen-4-ol		1.38
	sabinene	[5.61-15.43]	isobornyl acetate		1.74
	$\alpha$ -phellandrene	2.51	germacrene D		8.4
	$\beta$ -phellandrene	3.21	$\beta$ -bourbonene		1.2
	$\beta$ -myrcene	2.79	$\beta$ -elemene		1.3
	$\tau$ -terpinene	2.46	$\beta$ -bisabolene		1.6
	<i>o</i> -cymene	4.72	$\alpha$ -copaene		1.1
Oxygenated monoterpenes	terpinen-4-ol	9.65	$\beta$ -caryophyllene/ ( <i>Z</i> )-caryophyllene		3.67
Sesquiterpene hydrocarbons	$\beta$ -cubebene	2.61	$\delta$ -cadinene		1.41
Oxygenated sesquiterpenes	caryophyllene oxide	1.66	caryophyllene oxide		[1.10-1.51]
			$\alpha$ -cadinol		[1.90-2.12]

Table 5 summarizes the last updates in the VOCs' content of *Schinus* species.<sup>24-38</sup> Different parts of *Schinus terebinthifolia* Raddi (*sin.*: *Schinus terebinthifolia* Raddi) and *S. molle* L. are widely studied, probably due to the employment of these species as folk medicines, and the fruits are used as spicier (pink pepper). The studies with the composition of *S. terebinthifolia* leaves EOs corroborated with seasonal variation previously observed. The oil obtained from specimens harvested in March showed a high concentration of myrcene (15.4%) and (*E*)-caryophyllene (14.7%); in July, these constituents represented only 0.8% and 2.7% (respectively) of the total oil. Germacrene-D content increased from 8.8% in March to 21.0% in July, whereas  $\alpha$ -phellandrene, undetectable in oils collected in March, rose to 18.2% in July. The EOs obtained in July contained 15.5% of oxygenated sesquiterpenes, and these compounds are present in only 5.8% in the oils obtained from March studies.<sup>31</sup>

Other *Schinus* species are frequent sources of essential oils (*S. longifolia*, *S. fasciculata*, *S. lentiscifolius* and *S. weinmannifolius*).<sup>39-41</sup> Likewise, in the former examples, the differences between the found EOs profiles are related to seasonal factors, extraction methodologies and geographical origin.

*Anacardium* genus always presents commercially and economically important species, which have justified extensive studies with its main species, including their flavor-related volatile compounds. Studies with Brazilian *A. occidentale* L. oil, occurring in

different regions, indicate differences in the chemical compositions of major compounds, whose differences are probably associated with genetic variability amongst the populations grown at each location. In the leaf species collected in Minas Gerais state (Brazil), (*E*)-caryophyllene (15.4%), germacrene-D (11.5%) and  $\alpha$ -copaene (10.3%) are the main components. On the other hand, the major compounds from plants cultivated in Pará state (Brazil) were (*E*)- $\beta$ -ocimene (28.8%) and  $\alpha$ -copaene (13.6%). Compared with specimens collected in Nigeria, the composition is also different, and those were composed mainly of  $\beta$ -phellandrene (42.7%).<sup>31</sup> Table 6 also includes the composition of the VOCs of other Anacardiaceae species that were determined for the first time.<sup>42-45</sup>

The literature reports presence of mixtures of essential oils and VOCs in other Anacardiaceae species, such as *Pleyoginium timorense* (Dc.) Leenh,<sup>46</sup> *Pseudospondias microcarpa* (A. Rich) Engl.<sup>47</sup> and *Sclerocarya birrea* subsp. Caffra.<sup>48,49</sup> In these examples, the most predominant metabolites in *P. timorense* fruits<sup>46</sup> were D-limonene (64.51%),  $\gamma$ -terpinene (5.60%),  $\alpha$ -copaene and (*E*)-caryophyllene (4.74%). In *P. microcarpa* fruits,<sup>47</sup>  $\alpha$ -terpinol and borneol (22.9% and 8.2%, for the epicarp), besides vaccenic acid and ascorbic acid 2,6-dihexadecanoate (20.1% and 29.8%, for the hull), caryophyllene oxide and  $\alpha$ -humulene (8.4% and 6.8%, for the seed) and  $\alpha$ -humulene and  $\beta$ -caryophyllene (9.4% and 6.4%, for the kernel) were the main compounds detected. Lastly, in

**Table 4.** Relative composition (%) of the most abundant essential oils from *Spondias* spp.<sup>22,23</sup>

<i>S. pinnata</i> <sup>22</sup> (L. Pinn) Kurz (fruit peels)		Variation (%)			
	ethyl benzoate	9.05			
Aliphatic compounds [39.42%]	methyl salicylate	5.88			
	(Z)-3-hexen-1-ol	4.88			
	2-hexenal	4.17			
Monoterpene hydrocarbons [29.62%]	$\alpha$ -terpineol	13.09			
	$\gamma$ -terpineol	5.55			
	terpinen-4-ol	2.66			
	limonene	2.04			
	isoborneol	1.04			
Aromatics [22.03%]	furfural	17.14			
	ethyl cinnamate	3.55			
<i>S. mombin</i> Linn <sup>23</sup>		fresh leaves (%)		dried leaves (%)	
Sesquiterpene hydrocarbons [67.4-76.66%]	$\beta$ -caryophyllene	27.96	30.90		
	$\gamma$ -cadinene	12.30	9.7		
	$\alpha$ -humulene	8.1	5.4		
	$\beta$ -cadinene	7.8	6.6		
	$\alpha$ -gurjunene	6.4	7.4		
	$\alpha$ -muurolene	5.9	4.2		
Oxygenated monoterpene [9.9-13.2%]	$\beta$ -elemene	4.2	3.2		
	$\gamma$ -muurolene	4.0	-		
	geranial	3.7	3.8		
Oxygenated sesquiterpenes [13.3-15.7%]	neral	6.2	9.4		
	caryophyllene oxide	6.9	6.2		
	5-isocedranol	6.4	9.5		

*Sclerocarya birrea* fruits,<sup>48</sup>  $\beta$ -caryophyllene and  $\alpha$ -humulene (91.3% and 8.3%) were the major compounds of fruit pulp. However, in head-space studies with the whole fruit, heptadecene (16.1%), benzyl 4-methylpentanoate (8.8%), benzyl butyrate (6.7%), (Z)-13-octadecenal (6.2%), cyclopentadecane (5.7%) and (Z)-3-decen-1-ol (8.4%) were the most abundant VOCs. Otherwise, it should be highlighted that the EOs composition of *S. birrea* (A. Rich) Hochst leaves from Benin were different according to the season.<sup>49</sup> Thus, in hot period, the major constituents were 7-*epi*- $\alpha$ -selinene (38  $\pm$  0.03%),  $\alpha$ -muurolene (25  $\pm$  0.03%), valencene (17  $\pm$  0.06%),  $\beta$ -selinene (4.3  $\pm$  0.01%),  $\beta$ -caryophyllene (3.2  $\pm$  0.02%), allo-aromadendrene epoxide (1.5  $\pm$  0.03%) and 14-hydroxy- $\alpha$ -humulene (1.5  $\pm$  0.03%), but in the cold season the EOs was characterized by 7-*epi*- $\alpha$ -selinene (51.7  $\pm$  0.12%),  $\beta$ -selinene (15.1  $\pm$  0.2%), valencene (12.9  $\pm$  0.05%),  $\alpha$ -selinene (8.1  $\pm$  0.03%) and  $\beta$ -caryophyllene (1.8  $\pm$  0.02%). These results constitute the first report of these components in this species.

### Terpenoids and steroids

Terpenoids are the most abundant class of natural products found in plants and have particular importance due to their role in plant physiology, biological properties and some industrial uses. They are present in different Anacardiaceae genera, and some isolates from this family are presented in Figure 1. The isolated compounds of these subclasses are well-known in plants in general as well as in Anacardiaceae spp. Compounds **1-8** were obtained from

**Table 5.** Relative composition (%) of the most abundant essential oils from different parts of *Schinus* spp.<sup>24-38</sup>

<i>S. terebinthifolia</i> <sup>24-30,31</sup>		(% variation)	
	$\alpha$ -pinene	[5.7-44.9]; [1.2 $\pm$ 0.1] <sup>a</sup> and [4.2 $\pm$ 0.1] <sup>b</sup>	
	$\beta$ -pinene	[1.91-15.1]	
	( $\beta$ )-myrcene	[1.56-20.43]; [15.4 $\pm$ 0.9] <sup>a</sup>	
	sylvestrene	3.7	
	$\beta$ -phellandrene	[6.59-7.30]	
Monoterpene hydrocarbons [16.44-77.35] (30.9 <sup>a</sup> and 46.6 <sup>b</sup> )	limonene	[1.40-20.81]; [12.0 $\pm$ 0.6] <sup>a</sup> and [16.7 $\pm$ 1.1] <sup>b</sup>	
	isosylvestrene	13.87	
	$\alpha$ -fenchene	20.75	
	<i>p</i> -cymene	[1.45-2.90]; [3.3 $\pm$ 0.2] <sup>b</sup>	
	$\delta$ -3-carene	[2.69-12.75]	
	sabinene	[2.60-6.20]	
	$\alpha$ -phellandrene	[1.35-14.94]; [18.2 $\pm$ 1.2] <sup>b</sup>	
	$\alpha$ -terpinene	[1.17-2.20]	
	$\gamma$ -terpinene	1.81	
	<i>trans</i> -ocimene/ ( <i>E</i> )- $\beta$ -ocimene	12.32; [2.3 $\pm$ 0.2] <sup>a</sup> and [2.6 $\pm$ 0.1] <sup>b</sup>	
tricyclene	8.3		
Hydrocarbon sesquiterpenes [3.63-72.1] [59.4 <sup>a</sup> and 35.4 <sup>b</sup> ]	$\beta$ -longipinene	[4.35-8.1]	
	$\alpha$ -humulene	[2.5 $\pm$ 0.1] <sup>a</sup>	
	$\beta$ -camigrene	[7.5 $\pm$ 1.0] <sup>a</sup>	
	bicyclogermacrene	[1.01-27.57]	
	germacrene D	[2.65-23.8]; [8.8 $\pm$ 0.3] <sup>a</sup> and [21.0 $\pm$ 1.2] <sup>b</sup>	
	$\delta$ -cadinene	[1.43-9.21]; [3.6 $\pm$ 0.1] <sup>a</sup> and [1.6 $\pm$ 0.1] <sup>b</sup>	
	aromadendrene	1.1 <sup>24</sup>	
	$\beta$ -elemene	1.4; [4.8 $\pm$ 0.3] <sup>a</sup> and [2.1 $\pm$ 0.1] <sup>b</sup>	
	isolongifolene	7.11	
	(Z)- $\beta$ -farnesene	[1.65-6.38]	
	$\alpha$ -copaene	[3.4-7.96]; [1.7 $\pm$ 0.1] <sup>a</sup>	
	$\delta$ -elemene	1.68; [2.4 $\pm$ 0.1] <sup>a</sup> and 2.0 <sup>b</sup>	
	germacrene A	1.66; 2.1 <sup>a</sup> and 1.3 <sup>b</sup>	
	$\alpha$ -cadinene	1.98	
	germacrene B	[1.10-2.01]; [2.1 $\pm$ 0.1] <sup>a</sup> and 1.6 <sup>b</sup>	
$\beta$ -selinene	[4.3 $\pm$ 0.1]		
( <i>E</i> )-( $\beta$ )-caryophyllene	[1.03-35.20]; [14.7 $\pm$ 0.8] <sup>a</sup> and [2.7 $\pm$ 0.2] <sup>b</sup>		
$\gamma$ -cadinene	1.11; [2.3 $\pm$ 0.1] <sup>a</sup>		
$\alpha$ - <i>trans</i> -bergamotene	1.80		
$\alpha$ -amorphene	1.41		
$\alpha$ -muurolene	[2.6 $\pm$ 0.1] <sup>a</sup>		
Oxygenated monoterpene [3.10-17.81]	<i>cis</i> -sabinene hydrate	1.03	
	terpinen-4-ol	[3.42-3.63]	
	$\alpha$ -terpineol	[2.65-14.39]	
	eucalyptol	8.5	
Oxygenated sesquiterpenes [0.31-27.85] [5.8 <sup>a</sup> ; 15.5 <sup>b</sup> ]	spathulenol	[1.02-1.90]; 1.1 <sup>a</sup> and [2.1 $\pm$ 0.1] <sup>b</sup>	
	globulol	2.7	
	viridiflorol	2.2; [2.5 $\pm$ 0.2] <sup>b</sup>	
	cedryl acetate	2.6	
	caryophyllene acetate	2.1	
	caryophyllene alcohol	2.41	
	$\gamma$ -eudesmol	1.49	
$\alpha$ -cadinol	[1.58-11.62]; 1.4 <sup>a</sup> and [3.1 $\pm$ 0.1] <sup>b</sup>		

**Table 5.** Relative composition (%) of the most abundant essential oils from different parts of *Schinus* spp.<sup>24-38</sup> (cont.)

<i>S. terebinthifolia</i> <sup>24-30,31</sup>		(%) variation	<i>c.d.S. molle</i> <sup>28-30,32-36</sup>		Variation (%)
Oxygenated sesquiterpenes [0.31-27.85] [5.8 <sup>a</sup> ; 15.5 <sup>b</sup> ]	τ-cadinol	[1.15-2.67]	Hydrocarbon sesquiterpenes [0.10-31.18]	9- <i>epi</i> ( <i>E</i> )-caryophyllene	1.2
	τ-murolol	5.12		zonarene	1.9
	α-bisabolol	4.37		β-elemene	1.97
	elemol	4.07		germacrene-B	3.87
	<i>cis</i> -cadinen-4-en-7-ol	1.6		α-bisabolene	2.57
	β-caryophyllene oxide	[2.6 ± 0.1] <sup>b</sup>		α-humulene	1.73
	α-murolol	[1.2 ± 0.1] <sup>a</sup> and [2.8 ± 0.1] <sup>b</sup>		α-pinene	[1.21-35.28]
	δ-cadinol	[1.3 ± 0.1] <sup>a</sup> and [2.4 ± 0.1] <sup>b</sup>		β-pinene	[1.32-36.3]
<i>c.d.S. molle</i> <sup>28-30,32-36</sup>		Variation (%)		β-phellandrene	[2.90-38.06]
	globulol	1.2	Hydrocarbon monoterpenes [4.2-98.5]	α-phellandrene	[38.84-55.90]
	ledol	1.5		myrcene	[1.12-6.43]
	ubanol	27.1		α-terpinene	[1.13-1.46]
	<i>epi</i> -α-cadinol	[1.7-27.3]		α-thujene	[1.48-5.72]
	caryophyllene oxide	[1.02-15.3]		terpinolene	[12.23-20.10]
	δ-cadinol	2.11		limonene	[1.80-32.21]
Oxygenated sesquiterpenes [0.29-63.6]	(+)-spathulenol	[1.97-12.4]		sabinene	[2.9-51.74]
	1,10-di- <i>epi</i> -cubanol	[2.5-4.4]		<i>p</i> -cymene	1.46
	<i>epi</i> -α-eudesmol	2.3		γ-terpinene	[1.96-2.39]
	guaial	1.9	<i>S. areira</i> (L.) <sup>37,38</sup>		Variation (%)
	cedrol	1.7		α-phellandrene	[16.2-31.8]
	γ-eudesmol	1.97		3-carene	[20.8-21.3]
longipinanol	6.08	Hydrocarbon monoterpenes [61.0-89.8]	camphene	[1.8-10.9]	
α-bisabolol	1.29		α-pinene	[3.1-7.1]	
murolol	11.8		β-myrcene	[3.4-19.7]	
1,8-cineol	[2.04-7.60]		β-pinene	[2.4-5.5]	
terpin-4-ol	6.1		<i>o</i> -cymene	[3.9-7.5]	
7-formyloxy-sabinen-2-ol	n.d.a.		sabinene	[1.4-4.3]	
terpin-3-en-1,5-diol	n.d.a.	α-terpinolene	5.2		
terpin-2-en-1,4-diol	n.d.a.	<i>p</i> -cymene	[3.0-5.1]		
(-)- <i>trans</i> -pinocarveol	[1.9-4.7]	β-phellandrene	[17.6-19.9]		
nopinone	1.7	(β)-copaene	[1.5-3.1]		
<i>trans</i> -verbenol	4.2	β-cubebene	[1.6-2.9]		
pinocarpone	1.1	(β)-caryophyllene	[1.9-2.3]		
myrtenal	5.3	tricyclene	1.1		
verbenone	6.2	γ-murololene	5.1		
<i>trans</i> -linalool oxide	1.3	β-selinene	1.5		
myrtenol	4.6	α-murololene	1.3		
(-)- <i>trans</i> -carveol	1.1	γ-cadinene	1.4		
eugenol	2.96	δ-cadinene	[2.7-4.6]		
piperitone	1.5	Oxygenated monoterpenes [2.1-3.9]	terpinen-4-ol	[1.2-2.1]	
linalool	[1.60-2.98]		bornyl acetate	[1.4-1.9]	
terpinen-4-ol	[1.74-4.93]		palustrol	1.2	
α-selinene	2.7	Oxygenated sesquiterpenes [2.9-12.9]	globulol	1.1	
<i>allo</i> -aromadendrene	1.7		viridiflorol	1.1	
γ-cadinene	[1.22-9.10]		guaial	6.2	
δ-cadinene	1.14		δ-cadinol	[2.9-3.3]	
bicyclgermacrene	[1.4-18.12]	Esters (2.9)	methyl caprylate	1.6	
ledol	[0.18-6.79]		ethyl hexanoate	1.3	
( <i>E</i> )-caryophyllene/ β-caryophyllene	[1.66-6.08]				

<sup>a</sup>*S. terebinthifolia* collected in March (2008).<sup>31</sup> <sup>b</sup>*S. terebinthifolia* collected in July.<sup>31</sup> The oils were obtained by two methods: <sup>c</sup>using a pilot extractor<sup>28</sup> and a <sup>d</sup>clevenger apparatus.<sup>28</sup> After 6 h extraction by hydrodistillation.<sup>32</sup> n.d.a.: not-determined amount. All the percentages were reported initially with standard deviation.<sup>37</sup>

*Mangifera mekongensis*,<sup>50</sup> so that the esters **1** (mekongsterol A), **2** (mekongsterol B) and **3** (β-sitosteryl-3-*O*-β-D-glucopyranosyl-6-*O*-palmitate) constitute novel derivatives, whereas stigmastane-3,6-dione (**4**), ambonic acid (**5**), ambolic acid (**6**), mangiferonic acid (**7**) and mangiferolic acid (**8**) are common in *Mangifera*. Besides,

compounds **9-10** were obtained from *Mangifera pajang* Kosterm.,<sup>51</sup> metabolites **11-14** from *S. terebinthifolia*<sup>52</sup> and daucosterol (**15**) from *Schinopsis brasiliensis* Engl.<sup>53</sup> It is noteworthy that **14** was named as schinol and possesses a structure different from the previously registered compound named schinol (CAS #6813-07-6).



**Table 6.** Relative composition (%) of the most abundant essential oils from other Anacardiaceae species<sup>42-45</sup>

<i>Anacardium humile</i> (St. Hill fruits) <sup>42</sup>		Variation (%)	
Hydrocarbon monoterpenes [29.9%]	$\alpha$ -pinene	[22.0 $\pm$ 0.9]	
	$\beta$ -pinene	[6.6 $\pm$ 1.3]	
	limonene	[1.3 $\pm$ 0.1]	
Hydrocarbon sesquiterpenes [60.9%]	$\alpha$ -copaene	[2.5 $\pm$ 0.3]	
	$\beta$ -selinene	24.0	
	( <i>E</i> )- $\beta$ -caryophyllene	[31.0 $\pm$ 1.8]	
	$\alpha$ -humulene	[2.9 $\pm$ 0.3]	
	germacrene D	[5.9 $\pm$ 1.7]	
	alloaromadendrene	[1.4 $\pm$ 0.2]	
	bicyclogermacrene	[7.6 $\pm$ 1.2]	
	$\delta$ -cadinene	[9.3 $\pm$ 0.7]; 5.6	
	$\alpha$ -bulnesene	8.0	
	$\gamma$ -cadinene	7.9	
Oxygenated sesquiterpenes [6.3%]	$\alpha$ -neoclovene	7.2	
	cyperene	5.3	
	globulol	[1.4 $\pm$ 0.4]	
<i>Myracrodruon urundeuva</i> (Engl.); <sup>43</sup> (Fr. All.) <sup>44</sup> leaves	<i>epi</i> -globulol	[1.8 $\pm$ 0.2]	
	viridiflorol	[1.4 $\pm$ 0.3]	
	Variation (%)		
Hydrocarbon monoterpenes [80.35-91.00%]	myrcene/ $\alpha$ -myrcene and $\beta$ -myrcene	[4.2 $\pm$ 0.3]; [37.23-42.46]	
	$\delta$ -3-carene	[78.8 $\pm$ 1.7]; 80.41	
	$\beta$ -phellandrene	[3.0 $\pm$ 0.2]	
	$\alpha$ -terpinolene	[4.8 $\pm$ 0.6]	
	$\alpha$ -pinene	1.90	
	$\alpha$ -limonene	1.89	
	<i>o</i> -cymene	1.09	
	Hydrocarbon sesquiterpenes [7.31-8.1%]	viridiflorene	[3.0 $\pm$ 0.2]
$\beta$ -selinene		[2.5 $\pm$ 0.2]	
( <i>E</i> )- $\beta$ -caryophyllene		[1.1 $\pm$ 0.1]; 4.28	
Oxygenated sesquiterpenes	$\alpha$ -bergamotene	1.95	
Carboxylic acids [5.0%]	caryophyllene oxide	1.81	
	hexadecanoic acid	3.13	
<i>Tapirira guianensis</i> Aubl. (leaf and branches) <sup>45</sup>	9-hexadecanoic acid	1.34	
	Variation (%)		
	Hydrocarbon sesquiterpenes [58.49-100.00%]	( <i>E</i> )- $\beta$ -caryophyllene	[19.25-66.87]
		$\alpha$ -selinene	[24.37-31.07]
		$\beta$ -selinene	[42.58-57.56]
		$\alpha$ -zingiberene	[18.61-24.49]
		$\beta$ -sesquiphellandrene	[17.00-20.00]
	Oxygenated sesquiterpenes [1.97-28.86%]	selin-11-en-4 $\alpha$ -ol	[1.02-6.55]
		$\alpha$ -cadinol	[3.89-5.91]
		caryophyllene oxide	[1.86-8.29]
		spathulenol	[1.53-3.41]
		viridiflorol	[1.44-1.99]
humulene epoxide II		[1.19-1.59]	
caryophylla-4(12),8(13)- dien-5 $\alpha$ -ol		[2.00-2.72]	
<i>epi</i> - $\alpha$ -muurolol	[1.24-2.40]		

The structure of compound **14** is previously known as the name of 3-epimasticadienolic acid (CAS #31539-04-5). The substances **11-13**, found in the fruit oil of *S. terebinthifolia*, can be associated with the demonstrated antioxidant activity of the species, to the inhibition of NO synthase production and to antimicrobial properties, as well as **14** is related to antifungal activity<sup>52</sup> against *Paracoccidioides brasiliensis*. From the roots of *Dobinea delavayi* (Baill.) Baill.

were isolated several sesquiterpenes, including new compounds (**16-23**),<sup>54</sup> and ergostane-type compounds (**24-27**) were obtained from the stem bark of *Antrocaryon klaineum* Pierre.<sup>55</sup> The novel compound antrocarine *E* (**24**) was obtained with the known substances (7 $\alpha$ )-7,20-dihydroxyergosta-4,24(28)-dien-3-one (**25**), (6 $\alpha$ ,7 $\alpha$ )-6-methoxyergosta-4,24(28)-dien-7-ol (**26**) and (6 $\alpha$ ,7 $\alpha$ )-ergosta-4,24(28)-diene-6,7-diol (**27**). Lastly, the new steroid-type compound named 3-oxolanosta-1,20(22)-dien-26-oic acid (**28**) was isolated from the galls of *Pistacia integerrima* Stewart.<sup>56</sup>

### Flavonoids and biflavonoids

Flavonoids are common in all plant kingdom, but biflavonoids are restricted in some families, including Anacardiaceae.<sup>1</sup> Figure 2 presents an update of the presence of this class (**29-39**) in species of this family. They were isolated from *Lannea coromandelica* and *L. acida*.<sup>57</sup> From *Semecarpus anacardium* Linn. the biflavonoids nallaflavanone (**40**), anacardufllavanone (**41**), jeedifllavanone (**42**), gallufllavanone (**43**), tetrahydroamentofllavanone (**44**) and semecarpufllavone (**45**) were obtained.<sup>58</sup> This flavonoid subclass is common in Anacardiaceae spp. Robustafllavone (**46**) was obtained for the first time from the leaves of *S. terebinthifolia*<sup>59</sup> and some chalcone derivatives – schinopsonone A (**47**) and schinopsonone B (**48**), besides two known biflavonoid derivatives<sup>53</sup> (**49, 50**) – were isolated from the roots of *Schinopsis brasiliensis* Engl. Moreover, kaempferol-3-*O*- $\beta$ -(2''-sulphategalactopyranoside) (**51**) and quercetin-3-*O*- $\beta$ -(2''-sulphategalactopyranoside) (**52**)<sup>60</sup> were obtained for the first time from aqueous methanol leaf extract of *Harpephyllum caffrum*. In addition, a novel dimer (**53**) C-3/C-3'' of butin (3',4',7-trihydroxyflavanone) was isolated from *C. coggygia* Scop. wood<sup>61</sup> alongside other known compounds (catechin, fisetin, quercetin, butein, sulfuretin, fustin, dihydroquercetagenin, and eriodictyol). From MeOH and EtOH antioxidant extracts of *Pistacia terebinthus* L. fruits<sup>62</sup> it was isolated the new flavone 2-(2,4-dihydroxy-5-methoxyphenyl)-5,7,8-trihydroxy-4*H*-1-benzopyran-4-one (**54**) besides other known flavonoids (apigenin, luteolin, quercetin and luteolin-7-*O*-glucoside). On the other hand, the novel hispolone derivative **55** (methyl 5-(3,4-dihydroxyphenyl)-3-hydroxypenta-2,4-dienoate)<sup>63</sup> was obtained from the mushroom *Inonotus hispidus* growing on *Pistacia atlantica* as well as hispolone, hispidin and other phenolic compounds. The compound **56** (named acuminatanol)<sup>64</sup> was the first 2,2''-bis-dihydrobiflavonol isolated from the aqueous extract of *Trichoscypha acuminata*, being the first example of a bis-dihydroflavonol linked exclusively via the B-rings at C-2' and C-2'' positions. At last, the phytochemical investigation of the leaves of *Sorindeia juglandifolia* A. Rich. led to the obtention of a new C-glucosylflavone (2'',6''-di-*O*-acetyl-7-*O*-methylvitexin),<sup>65</sup> besides other seven known compounds.

### Alkyl and alkenylphenols

Alkyl and alkenylphenols, also known as phenolic lipids, are chemotaxonomic markers of various species of Anacardiaceae. In general, they present a salicylic acid moiety, but some are decarboxylated structures. Figure 3 presents the structures of several alkyl and alkenylphenols isolated from Anacardiaceae spp. Ozorcardic acids A (**57**) and B (**58**), alongside anacardic acid (**59**), were obtained for the first time from *Ozoroa pulcherrima* Schweinf.<sup>66</sup> Furthermore, 3-((7*Z*,10*Z*)-pentadeca-7,10-dien-1-yl)benzene-1,2-diol (**60**) and 3-((8*Z*)-pentadec-8-en-1-yl)benzene-1,2-diol (**61**) are known compounds now obtained from *S. anacardium*<sup>58</sup> and the new alkyl resorcionols (*Z,Z*)-5-(trideca-4,7-dienyl)-benzeno-1,2-diol (**62**), (*Z*)-5-(trideca-4-enyl)-benzeno-1,2-diol (**63**), (*Z,Z*)-5-(pentadeca-6,9-dienyl)-benzeno-1,2-diol (**64**), (*Z,Z*)-5-(trideca-5,8-dienyl)-benzeno-1,2-diol (**65**)

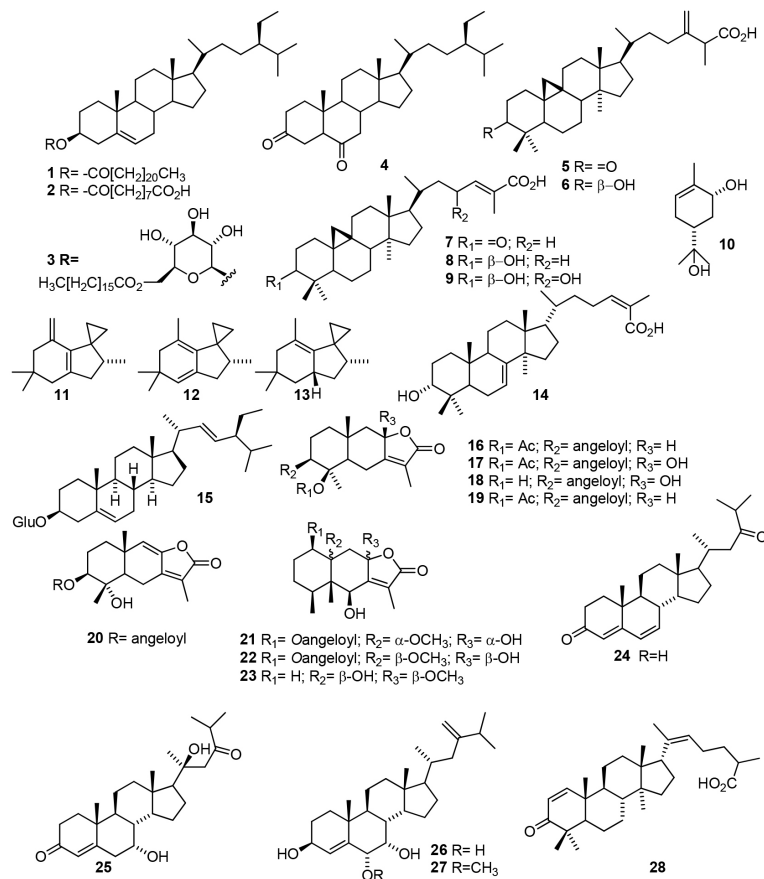


Figure 1. Structures of terpenes and terpenoids obtained from plants of different Anacardiaceae species

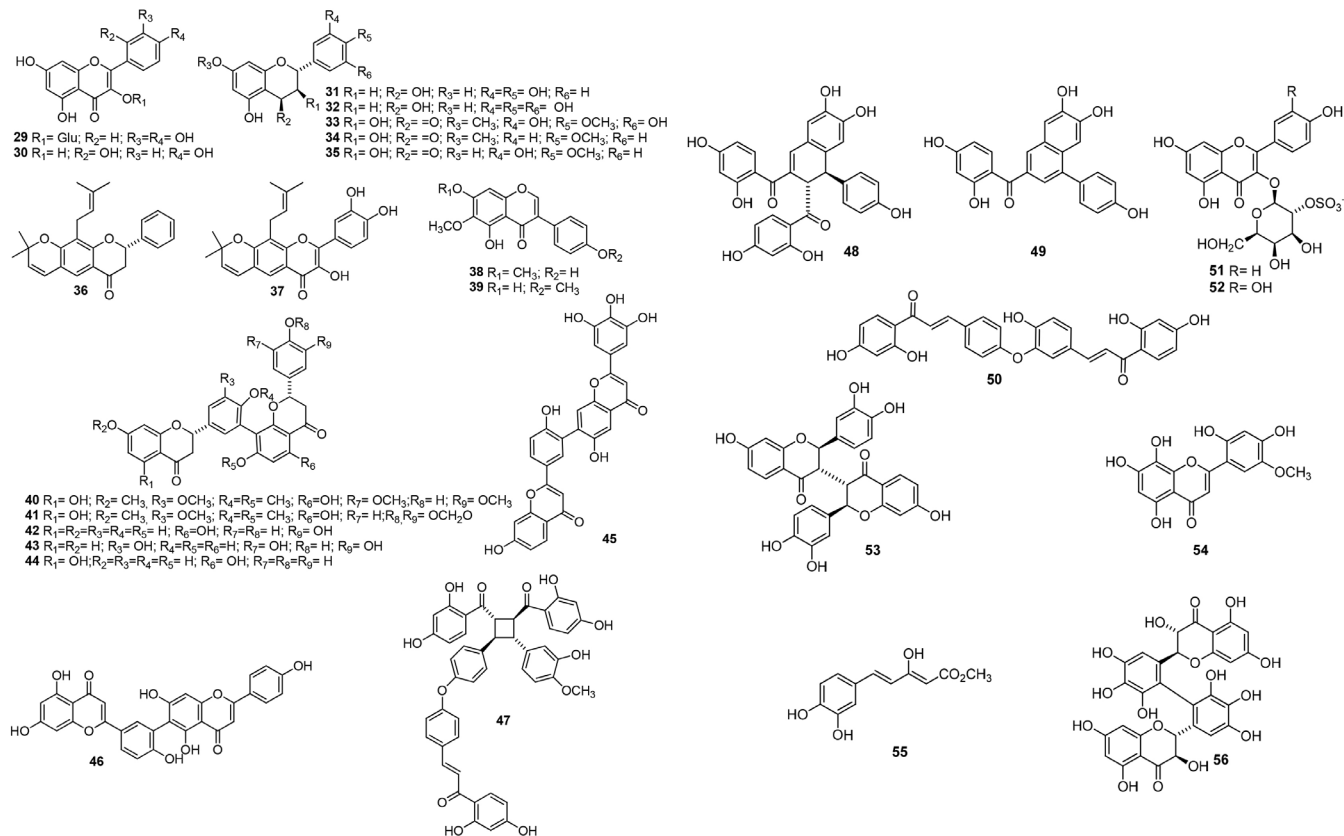


Figure 2. Flavonoids and biflavonoids isolated from plants of different Anacardiaceae species

and (*Z*)-5-(heptadec-6-enyl)-benzeno-1,2-diol (**66**) from *Lithraea molleoides*<sup>67</sup> Vell. Eng. Besides, 3-(2-(heptan-2-yl)-3-methylonyl)phthalic acid (**67**) and 2-hydro-6-[(8'*E*, 11'*E*, 14'*E*)-22'-hydroxydocosa-8',11',14'-trienyl] benzoic acid (**68**) were obtained from sheets of *Spondias mombin*.<sup>68</sup> The presence of (*E*)-double bonds and branched alkyl chains in **67** and **68** are unusual, whose detailed analysis of the NMR and MS data published indicates the need of new experiments to corroborate with the published unusual structures for these compounds. Moreover, three new dihydrobenzofuranols [2-[(10'*Z*)-dodec-10'-enyl]-dihydro-1-benzofuran-5-ol (**69**), 2-[(10'*Z*)-tridec-10'-enyl]-dihydro-1-benzofuran-5-ol (**70**) and 2-[(10'*Z*)-pentadec-10'-enyl]-dihydro-1-benzofuran-5-ol] (**71**) were isolated from *Tapirira guianensis* seeds.<sup>69</sup> On the other hand, unusual dimeric alkylresorcinol named integracin *E* (**72**) was obtained from the stem barks of *Swintonia floribunda*, besides propyl ferulate.<sup>70</sup> At last, gentisic acid derivative **73** (myronic acid) has been isolated for the first time from *Micronychia tsiramiramy* roots<sup>71</sup> with several known compounds previously isolated.

### Miscellaneous compounds isolated from Anacardiaceae

Many other types of metabolites that can occur in Anacardiaceae spp. and were reported in the period of this review update (Figure 4), such as the simple phenolic derivatives butein (**74**) and anacardoside (**75**) from *Semeacarpus anacardium* Linn.<sup>58</sup> Besides, for the first time 1,2,3,4,6-penta-*O*-galloyl-glucoopyranoside (PGG, **76**) was isolated from *Schinus terebinthifolia*<sup>59</sup> and three new metabolites [1,2-benzenedicarboxylic acid-mono(2-ethylhexyl)ester (**77**), (9*E*,12*E*)-tetradeca-9,12-dien-1-yl acetate (**78**) and 3-chloro-*N*-(2-phenylethyl)propanamide (**79**)], the last two atypical compounds, from *Mangifera indica*.<sup>72</sup> (+)-Pinoresinol (**80**), syringaresinol (**81**) and (+)-*epi*-pinoresinol (**82**) were obtained from the stem barks of *Swintonia floribunda*<sup>70</sup> and the antioxidant compounds as the novel biarone disulfuretin (**83**), sulfuretin (**84**) and sulfurein (**85**) were isolated of two separate collections of *Cotinus coggygria* (*R. cotinus*),<sup>73</sup> all of them for the first time in these genera. Moreover, the new lignan (+)-(8*S*,8'*S*)-5'-metoxi-4,4'-di-*O*-methylsecoisolariciresinol (**86**)<sup>74</sup> was obtained from stems of *Buchanania lucida*. Other several studies described the isolation of many novel special metabolites, as the compounds 2,6,3',4'-tetrahydroxy-4-methoxybenzophenone (**87**), 2,6,4'-trihydroxy-4,3'-dimethoxybenzophenone (**88**) and dobiniside A (**89**) from the roots of *Dobinea delavayi*,<sup>75,76</sup> 3-methoxyellagic acid 4-*O*-galactopyranoside<sup>60</sup> (**90**) from the leaves

of *H. caffrum* and the fatty acid ester **91** from *Cyrtocarpa procer*<sup>77</sup> Kunth (besides other known analogues). The new 1,4-benzoquinone derivative (**92**), which can be consider an alkenyl phenol derivative, was isolated from the root of *M. tsiramiramy*,<sup>71</sup> and the novel benzofuran lactone **93** (rhuscolide A)<sup>78</sup> was isolated from the stems of *Rhus chinensis* with other known compounds. At last, the new bischromanone **94** has been obtained from the stems of *Semeacarpus caudata*<sup>79</sup> alongside five known flavonoids (quercetin, naringenin, taxifolin, (+)-eriodictyol and 3,4',7-trihydroxyflavone) and two novel long-chain alkyl compounds 9,11-dihydroxyoctadecan-7-one (**95**) and (-)-3-hydroxydecyl eicosanoate (**96**) from the galls of *Pistacia integerrima* Stewart.<sup>56</sup> The authors signed compound **95** as *rel*-(+)-(9*R*,11*R*) enantiomer; however, they did not present spectrometric data supporting the proposed stereochemistry. Bis(2-ethylhexyl)phthalate is a plasticizer and compound **77** could not be a natural product, as pointed out by the authors. However, once there is no evidence of optical light deviation of **77**, a partial hydrolysate was synthesized from the commercial phthalate. For compounds **78** and **92**, there are also no spectrometric evidence of the stereochemistry and carbon position of the double bonds of the linear carbon chains.

In conclusion, we could highlight the occurrence of  $\beta$ -sitosteryl-3 $\beta$ -glucopyranoside-6'-*O*-fatty acid esters,  $\beta$ -sitosterol, phytol, a mixture of phytol fatty acid esters and  $\beta$ -sitosteryl fatty acid esters, chlorophyll, squalene, the compound **59** and other long-chain constituents in the CH<sub>2</sub>Cl<sub>2</sub> extract of *Dracontomelon dao* (Merr. & Rolfe)<sup>80</sup> leaves, as well as the isolation of **15** together with gallic acid and ethyl gallate from the EtOH extract of *Mauria heterophylla*.<sup>81</sup>

### BIOLOGICAL ACTIVITIES

Anacardiaceae family presents several species that produce compounds with different biological properties. Therefore, in the last decades, numerous studies have employed extracts and some isolated metabolites presenting *in vitro* and *in vivo* activities, mainly as radical quenching, antinociceptive and anti-inflammatory, as well as against microorganisms/strains, cell lines and viruses.

### Biological activities of extracts of Anacardiaceae spp.

#### *In vitro* studies

*Lansea* spp.<sup>82,83</sup> biological studies such as aqueous extracts of *L. barteri* Engl. bark<sup>82</sup> have presented antibacterial activity

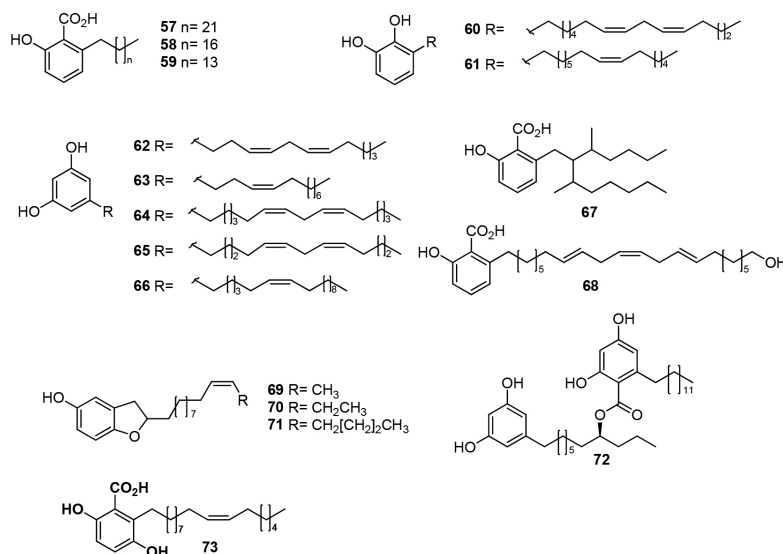
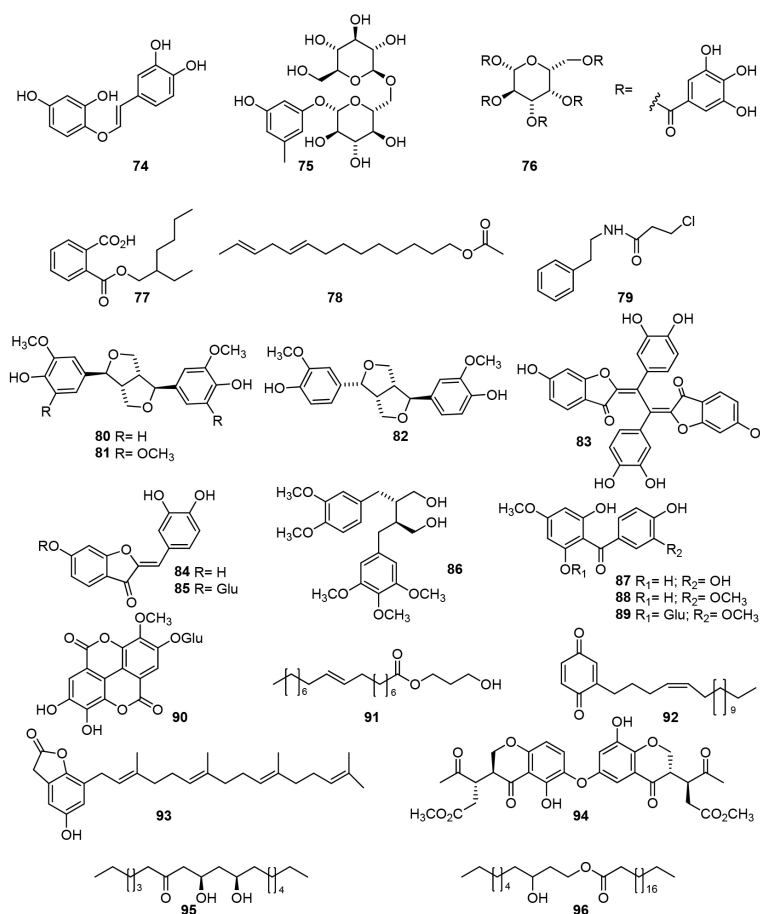


Figure 3. Alkyl, alkenylphenols and acids isolated from several Anacardiaceae species





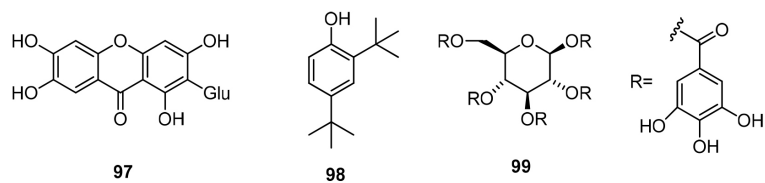
**Figure 4.** Miscellaneous compounds obtained from different *Anacardiaceae* spp

against *Pseudomonas aeruginosa* (MIC = 6.25-25.00 mg mL<sup>-1</sup>, LBE 6.25; 12.5; 25.0; 50.0 and 100.0 mg mL<sup>-1</sup>) and *Acinetobacter baumannii* (MIC = 25.00-43.75 mg mL<sup>-1</sup>, LBE 6.25; 12.5; 25.0; 50.0 and 100.0 mg mL<sup>-1</sup>), including MIC/MBC = 1.0 in all cases. These biological properties are probably due to phenolic/polyphenolic compounds in extracts, whose results may justify the plant's traditional use against urinary infections. Moreover, the ethanolic extract of *L. velutina* A. Rich<sup>83</sup> has presented antioxidant (% DPPH inhibition: 52.81 ± 2.16; % Fe<sup>3+</sup> reducing power/FRAP: 1.74 ± 0.45 mmol EAA 10 g extract<sup>-1</sup>) and antimicrobial activities (against Gram-positive and Gram-negative bacteria strains, with inhibition diameters greater than 8 mm), which is related to the flavonoid (1.770 ± 0.005 mg eq. Quercetin 10 g extract<sup>-1</sup>) and polyphenol (969.67 ± 8.23 mg GAE g extract<sup>-1</sup>) contents.

Concerning the studies dealing with *M. indica*,<sup>84-87</sup> it is known that compounds from this plant present many biological activities, typically related to mangiferin (**97**) and other polyphenolic compounds. The antibacterial activity<sup>84</sup> of (seed) mango kernel extracts were attributed to 2,4-bis(1,1-dimethylethyl)phenol (**98**), and the inhibitory effect<sup>85</sup> over PLA<sub>2</sub> (phospholipase A<sub>2</sub>), hyaluronidase and LAAO (L-amino acid oxidase) is associated with PGG (**99**), which selectively block the PLA<sub>2</sub> and LAAO active sites (Figure 5).

Observed anticancer proprieties<sup>86</sup> are possibly due to mangiferin, and other activities<sup>86,87</sup> (e.g., antidiabetic, antioxidant, and antimicrobial) might be associated with different compounds, such as aglycones, saponins and terpenes.

Crude extract and leaf EtOAc fraction of *Pistacia* spp. and *P. atlantica* Desf. displayed, simultaneously, a stronger antioxidant activity<sup>88</sup> (DPPH assay: IC<sub>50</sub> = 0.0273 ± 0.0001 and 0.0419 ± 0.0010 mg mL<sup>-1</sup>) in comparison on BHA and ascorbic acid (IC<sub>50</sub> = 0.08 ± 0.002 and 0.06 ± 0.002 mg mL<sup>-1</sup>) in DPPH assay due to the presence of flavonoids and tannins. *Pistacia integerrima* Rechinger f. stems EtOAc and CHCl<sub>3</sub> fractions extracts<sup>89</sup> exhibited low to moderate antitumor activity, with dose-dependent cell viability (97.4-100% inhibition of MCF-7 cells lines by at 200 µg mL<sup>-1</sup>) as well as antifungal activities. Moreover, the anti-melanogenic activity<sup>90</sup> of *P. atlantica* subsp. *kurdica* extracts showed significant inhibition of tyrosinase activity and an ensuing reduction of melanin synthesis, what is potentially valuable for treatments for skin hyperpigmentation disorders and new advances in the cosmetic industry. In conclusion, EtOH extracts of *in vitro* samples (under NaCl stress) and *in vivo* (grown naturally) of *P. khinjuc* specimens<sup>91</sup> were compared regarding their antioxidant and antimicrobial properties and, according to the results, samples



**Figure 5.** Some bioactive compounds from *Mangifera indica*

from *in vivo* specimens generally presented higher activities than *in vitro* counterparts.

*Rhus parviflora* aqueous leaf extract was used as a medium (with 0.1 mol L<sup>-1</sup> solution of zinc acetate dehydrate) in ZnO nanoparticles synthesis,<sup>92</sup> which exhibited potential antimicrobial activity against *S. aureus*, *P. aeruginosa*, *A. niger* and *C. albicans*. Likewise, the MeOH:CH<sub>2</sub>Cl<sub>2</sub> (1:1), MeOH and aqueous extracts of *R. vulgaris* Meikle stem bark were bactericidal/bacteriostatic against different microorganisms,<sup>93</sup> in such a way that MeOH extract showed significant activity toward MRSA/methicillin-resistant *Staphylococcus aureus* (MIC 0.391 mg mL<sup>-1</sup> and MBC 1.563 mg mL<sup>-1</sup>). The authors pointed these results supports traditional use of *R. vulgaris* as a toothbrush. On the other hand, extracts' cytotoxicity and mild skin damage warrant further research, so *R. vulgaris* can be recommended to develop effective and safe mouthwashes. Lastly, there are several other *Rhus* spp. who also have shown many mild biological properties<sup>94</sup> (antiviral, antimutagenic, antioxidant, hypoglycemic, antitumour, antimalarial etc.) which depend on their constituents, among which phenolic compounds, flavonoids/biflavonoids and glycosides are the primary bioactive metabolites.

*Schinus* genus is widely present in folk medicine and, in a study with *S. molle* ripe fruits,<sup>95</sup> the hexane and petroleum ether extracts were tested and showed antifungal activity against *Botrytis cinerea*, whose activity was attributed to a composition of oleic and linoleic acids and monoterpenes. The petrol extract was weakly active (at 1000 ppm), although there was a higher suppression for the fungi at this concentration according to the extract. Likewise, different leaf extracts and fractions of *S. lentiscifolius* were tested for the first time against five Gram-positive, three Gram-negative bacteria and four yeasts,<sup>96</sup> which displayed a broad spectrum of weak antibacterial activity with MIC ranging 125 to 250 µg mL<sup>-1</sup>, but a meaningful antifungal activity (MIC = 15.5-25 µg mL<sup>-1</sup>). The EtOAc fraction was the most active, and various compounds were isolated from it, among which the most active metabolite was the moronic acid (**100**) (MIC = 1.52-3.12 µg mL<sup>-1</sup>). Sequentially, **100** was submitted to derivatization (Figure 6) to evaluate the role of carbonyl(C-3) and carboxyl(C-28) groups regarding the activity. The methyl ester derivative of moronic acid (**101**), obtained by treatment with diazomethane, was more active against *Cryptococcus neoformans* (MIC = 50 µg mL<sup>-1</sup>). *Schinus terebinthifolia* is the species more studied, and the last decade studies have shown its antimycobacterial activity against *Mycobacterium bovis* BCG, alongside a significant inhibitory effect on the nitric oxide production (IC<sub>50</sub> 19.23 ± 1.64 µg mL<sup>-1</sup>) and mycobacterial growth (IC<sub>50</sub> 14.53 ± 1.25 µg mL<sup>-1</sup>),<sup>97</sup> what is probably due to the flavonoids therein.

Similarly, some species of *Spondias* have exhibited many applications and useful therapeutic properties. Stem bark aqueous and methanolic extracts of *S. mombin*<sup>98</sup> were evaluated concerning the dose-dependent antioxidant activity, whose outcomes indicated that MeOH extract presented the highest level of active constituents (total phenolic and flavonoids), being more active than the aqueous according to DPPH and FRAP scavenging assays and FTC method. Besides, *S. tuberosa* hexane leaf extracts were studied and presented antioxidant and antifungal activities.<sup>99</sup> Flavonoids, hydrolysable tannins, saponins and terpenes were identified by TLC and HPLC

analysis in the extracts and, likewise, fatty acid methyl esters (saturated and unsaturated) by <sup>1</sup>H NMR data as the main components. The extract showed mild activity in DPPH assay (IC<sub>50</sub> = 234.00 mg mL<sup>-1</sup>) and moderate by ABTS method (IC<sub>50</sub> = 123.33 µg mL<sup>-1</sup>). Moreover, it was also weakly active against *C. albicans* and *glabrata* (MIC<sub>50</sub> 2.0 and 0.078 mg mL<sup>-1</sup>, respectively). Finally, an active fraction from the hydromethanolic extracts of *S. pinnata* stem bark exhibited a high antioxidant effect and radical scavenging potential against ROS and RNS, including the reducing power and inhibiting lipid peroxidation (Fe<sup>2+</sup> *in vitro* chelation and ferritin ion release assays).<sup>100</sup>

In addition, the phytochemical composition of *Searsia chirindensis* leaf<sup>101</sup> organic extracts indicated presence of antibacterial compounds with activity against Gram-negative (*Campylobacter jejuni*, *E. coli* and *Shigella flexneri*) and Gram-positive (*S. aureus*) strains. From the the most active extract (EtOAc) were obtained methyl gallate, myricetin-3-*O*-arabinopyranoside, myricetrin-3-*O*-rhamnoside, kaempferol-3-*O*-rhamnoside and quercetin-3-*O*-arabinofuranoside. All the compounds showed antibacterial activity against all bacterial strains tested (MIC = 30-250 µg mL<sup>-1</sup>), whose activities corroborate to the ethnomedicinal use of *S. chirindensis* against diarrhoea. Furthermore, different phytocompounds from the aqueous-MeOH extract (70%) leaf extract of *Searsia lancea* were evaluated for antibacterial properties (MIC) against four bacterial strains (*Enterococcus faecalis*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae* and *S. aureus*).<sup>102</sup> Thus, an EtOAc chromatographic sub-fraction demonstrated good antibacterial properties (MIC range: 31-61 µg mL<sup>-1</sup> against *E. faecalis* and *S. aureus*) and, based on uncommon GC-MS analysis for medium polar extracts, 81.5% of it consisted of broad-spectrum antibacterial compounds tetracosanol (43.98%) and nonadecanol (37.5%). Therefore, these current findings may support the traditional use of *S. lancea* leaves to manage gastro-intestinal disorders as well as gonorrhoea.

In conclusion, the study of the total extract (a XO inhibitor *in vitro*) of *Terminthia paniculata* (Sanyeqi)<sup>103</sup> and its active fractions yielded six chalcone-flavonone heterodimers (Figure 7). Termipaniculatonones A (**103**) and E (**108**) showed XO inhibitory activity (IC<sub>50</sub> = 55.6 and 89.5 µmol L<sup>-1</sup>, respectively), which took effects via a mix-type mode. Regarding to their action mechanisms, a molecular modeling study revealed that termipaniculatonone A (**103**) was well located into the active site of XO by interacting with Glu802, Arg880, Thr1010 and Val1011 residues. At last, this is the first time wherein the anti-acute gouty arthritis properties of *T. paniculata* and the characteristic biflavonoids as active constituents were related, which provides valuable information for searching new XO inhibitors from natural sources.

Other biological activities of extracts and enriched fractions from different Anacardiaceae spp.<sup>69,104-116</sup> are summarized in Table 7.

#### *In vivo* studies

The *in vivo* antioxidant extracts of *Lannea stuhlmannii* and *L. humilis* were analyzed by HPLC-PDA-ESI-MS/MS and permitted to annotate 22 specialized metabolites, including sulphated flavonoids (Figure 8).<sup>117</sup> The antioxidant behavior of the extracts was observed through the reduction of high levels of AST (serum aspartate aminotransferase) and total bilirubin by the attenuation

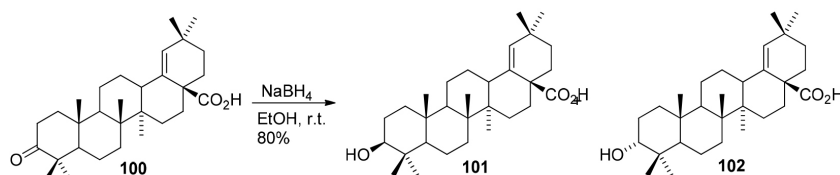


Figure 6. Scheme of reduction of moronic acid (**100**) to morolic (**101**) and acridocarpusic (**102**) acids

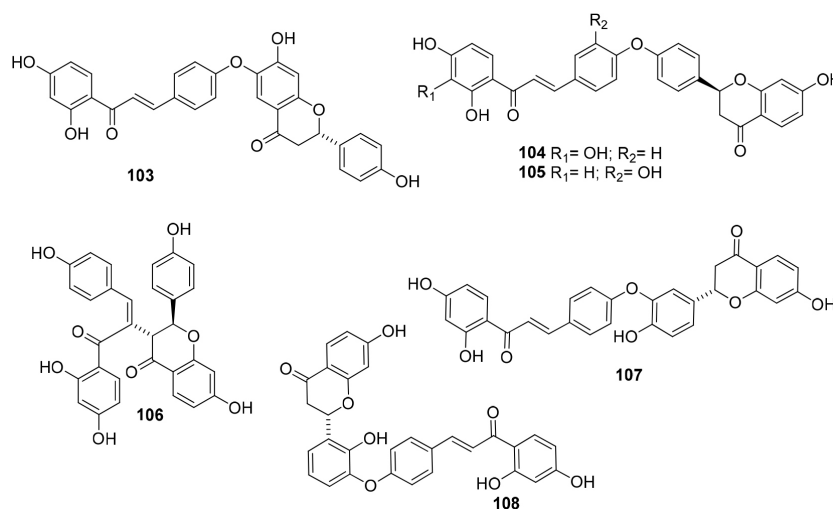


Figure 7. Chalcone-flavones from *Terminthia paniculata*

Table 7. Biological activities *in vitro* of different extracts in other Anacardiaceae spp.

Species	Obtained extracts or isolated substances	Observed activities
<i>Tapirira guianensis</i> <sup>69</sup>	EtOAc and BuOH fractions of MeOH flower ext.; CH <sub>2</sub> Cl <sub>2</sub> soluble fraction from Hex ext. of seeds	Antioxidant according to DPPH assay; Moderate cytotoxicity by Brine Shrimp Test ( <i>A. salina</i> L. lethality)
<i>Anacardium othonianum</i> <sup>104</sup>	EtOH crude ext. of leaves and fractions (Hex, EtOAc, BuOH, and hydro-MeOH)	Antifungal against <i>C. albicans</i> (ATCC 64548) and <i>Trichophyton rubrum</i> (Tr1)
<i>Loxostylis alata</i> <sup>105</sup>	Leaf acetone ext. (and CCl <sub>4</sub> , Hex, CHCl <sub>3</sub> , aqueous MeOH, BuOH and aq. fractions)	Antimicrobial and antibacterial activities against several strains (mediated by lupeol and β-sitosterol); Inhibition of COX-1 (anti-inflammatory activity and antithrombotic effect)
<i>Ozoroa</i> and <i>Searsia</i> spp. <sup>106</sup>	Crude leaf exts. (0,1% HCl:70% acetone:n-Hex) and fractions (DCM, BuOH, EtOAc, Hex, and residue aqueous)	Antibacterial and antifungal activities; Antioxidant according to DPPH, ABTS, hydroxyl radical scavenging, and linolenic acid peroxidation assays; Low cytotoxicity against Vero cell lines
<i>Cyrtocarpa procera</i> <sup>107</sup>	MeOH (1 and 2) fruit extracts; Hex fruit extract	Antibacterial against different Gram-positive and Gram-negative strains; High inhibition of DPPH; Cytotoxic against CasKi cell lines (anticancer activity); Reduction of production of pro-inflammatory cytokines (TNF-α and IL-1β) by macrophages
<i>Schinopsis brasiliensis</i> <sup>108</sup>	CHCl <sub>3</sub> fraction from EtOH:H <sub>2</sub> O crude ext. of stem bark	Moderate toxicity against <i>A. salina</i> ; Larvicidal potential against <i>A. aegypti</i> (for dengue); High molluscicidal activity against <i>Biomphalaria glabrata</i>
<i>Bouea macrophylla</i> <sup>109</sup>	EtOH leaf crude/raw extract	Antibacterial (against several Gram-positive and Gram-negative strains) and antifungal (against <i>C. albicans</i> ); Antioxidant by DPPH and FRAP assays; Inhibition of proliferation of HeLa and HCT116 cells (anticancer activity)
<i>Sorindea warneckeii</i> <sup>110</sup>	EtOH ext. of leaves and fractions (EtOAc, BuOH, Hex, and aqueous)	Antioxidant according to DPPH and Fe <sup>3+</sup> /ferricyanide assays; Inhibition of α-amylase
<i>Anacardium excelsum</i> <sup>111</sup>	EtOH ext. and fractions (petroleum ether, CH <sub>2</sub> Cl <sub>2</sub> , and EtOH/ BuOH)	Antioxidant according to DPPH, ABTS, and DMPD assays
<i>Sclerocarya birrea</i> <sup>112,113</sup>	MeOH extracts of leaves and bark <sup>112</sup> EtOAc and EtOAc/MeOH/water fractions of stem bark (rich in essential oils: 40.5-86.57%) <sup>113</sup>	Antioxidant according to ABTS, O <sub>2</sub> <sup>•-</sup> and NO <sup>•</sup> assays; High anticancer activity against HepG2 and normal human dermal fibroblast cell lines (Calcein AM assay); Inhibition of lipid peroxidation by β-carotene bleaching assay; Antimicrobial against <i>H. pylori</i> (metronidazole- and clarithromycin-resistant strains); MIC <sub>50</sub> = [310-2500 μg mL <sup>-1</sup> ]; terpinen-4-ol and pyrrolidine activities were similar to amoxicillin's (P > 0.05)
<i>S. birrea</i> (subsp. <i>caffra</i> ) <sup>114</sup>	MeOH and acetone stem bark crude extracts; Hex and acetone stem crude bark ext.	Competitive inhibition of α-amylase; Non-competitive inhibition of α-glucosidase
<i>Holigarna longifolia</i> <sup>115</sup>	MeOH extract from bark; Aqueous extract from bark	Antioxidant (DPPH inhibition, against oxidative stress); Moderate clot lysis (compared to streptokinase as standard)
<i>Pleioignium timoriense</i> (DC.) Leenh. <sup>116</sup>	EtOH extract of leaves (rich in known phenolic compounds)	Antioxidant DPPH (IC <sub>50</sub> = 21.9 μg mL <sup>-1</sup> ) and super oxide anion radical scavenging assays (IC <sub>50</sub> = 123.5 μg mL <sup>-1</sup> ) assays Hypoglycemic and anti-inflammatory effects

ext.: Extract.

of deleterious histopathologic changes in the liver (induced by D-GalN) or the protection of hepatocytes from apoptosis, besides an increased expression of Bcl-2 (anti-apoptotic protein). Moreover, molecular docking evaluation showed that some identified compounds from both plants could bind to the Bcl-2:Bim (BH3) interface by hydrophobic interactions (or hydrogen and ionic bonds) with an appreciable binding free energy, whose properties are due to the presence of flavonoids and proanthocyanidins. However, the correct stereochemistry of the catechins were not determined. On the other hand, the diuretic and saluretic effects of an aqueous decoction (LMAq) and EtOAc extract of *L. microcarpa* barks in comparison to amiloride's and furosemide's were reported, in such a way that their mechanism of action seemed more analogous to the furosemides.<sup>118</sup> In this study, it was verified that the diuretic activity (urinary excretion) of LMAq was dose-dependent and that the administration of extracts provided the selective elimination of Na<sup>+</sup> concerning the stabilizing excretion of K<sup>+</sup>, confirming that *L. microcarpa* extracts may be a promising alternative for the therapeutic management of renal and cardiovascular pathologies.

The leaf aqueous extract *in vivo* activities of *Mangifera indica* presented *in vivo* antidiabetic and hypolipidemic activities, which significantly decreased the total serum cholesterol, triglycerides (89.75 ± 0.46%) and very low-density lipoprotein (17.95 ± 0.09%) in rats (200 mg kg<sup>-1</sup> body weight, p.o.) and, simultaneously, increased high-density lipoproteins (30.21 ± 2.59%). The results were almost comparable to those of atorvastatin.<sup>119</sup> Furthermore, studies of the analgesic properties EtOH, and petroleum ether extracts of *M. indica* dried leaves<sup>120</sup> indicated antinociceptive activity (oral dose of 200 mg kg<sup>-1</sup> of body weight, with a writhing inhibition of 44.5-51.7% and 41.6-50.0%, respectively), while CCl<sub>4</sub> presented a mild effect (writhing inhibition of 25-30%). Nevertheless, no investigation was performed to lead to identify the bioactive compounds.

The hypoglycemic effect of MeOH:H<sub>2</sub>O extract of *Pistacia* spp. (e.g., *P. khinjuk*) were evaluated in six groups of Swiss albino mice previously treated with alloxan monohydrate (except the normal group).<sup>121</sup> In normoglycemic mice, the plant extract showed statistically significant hypoglycemic activity at 200 and 500 mg kg<sup>-1</sup> and the blood glucose level decreased. On the other hand, the aqueous ethanolic extracts of leaves of *Sclerocarya birrea* were tested on basal plasma glucose (BPG) and oral tolerance glucose in mice, which significantly reduced peak of hyperglycemia at 100 mg kg<sup>-1</sup> body (p < 0.001), though it did not have a relevant hypoglycemic effect on BPG. Moreover, this study reported that the co-administration of *S. birrea* aqueous EtOH extracts with analogous

extracts of *G. sylvestre* (Asclepiadaceae) enabled a greater cutback on hyperglycemia (47%) compared to the *S. birrea* extract alone (36%).<sup>122</sup> These species are sources of flavonoids, saponosides, tannins and other bioactive metabolites, whose combined use of these plants would be an asset in treating diabetes.

Aqueous extract and enriched flavonoid fraction (FF) of the EtOAc of *Rhus trilobata* were evaluated as a potential alternative against colorectal adenocarcinoma cells and other types of cancer.<sup>123</sup> The toxicological effect of the extracts was determined in female BALB/c mice after 24 h and 14 days of intraperitoneal administration of 200 mg kg<sup>-1</sup> of both extracts. Besides, UPLC-PAD-MS<sup>E</sup> permitted to detect the most abundant compounds in the active extracts. Known compounds such as methyl gallate, epigallocatechin 3-cinnamate, quercetin 3-(2''-alloylglucosyl)-(1→2)-alpha-L-arabinofuranoside, β-PGG (100), 4-O-digalloyl-1,2,3,6-tetra-O-β-D-galloylglucose, myricetin 3-(4''-galloylrhamnoside) and fisetin were annotated, which possibly are responsible for the activity. The evaluation of toxicity did not reveal meaningful anatomical changes nor histological damages.

Similarly, the total flavonoid content of *Rhus cotinus* (e.g. *Cotinus coggygia*)<sup>124</sup> showed a potent *in vivo* antitumor effect in xenograft animal models of ectopic glioblastoma against several lineages of highly malignant cells (IC<sub>50</sub> = 93.57-128.49 μg mL<sup>-1</sup>). This activity (tumor's volume reduction at 25 and 50 mg kg<sup>-1</sup> CCF) was analogous to that temozolomide (positive control). The compounds present in the extract inhibited the growth of tumors in mice in a day-dependent pattern (7-28 days, p < 0.05).

*Spondias pinnata* stands out regarding *in vivo* bioactivity. The investigation of the antioxidant effect of aqueous bark extract<sup>125</sup> (through evaluation of the activity of several enzymes in STZ-diabetic rats) showed that AEs<sub>p</sub> decreased, (i) the LPO (by 17%) and (ii) the alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities by 20, 17 and 36%, respectively. However, the (i) liver reduced liver glutathione (GSH) content and (ii) the activities of glutathione reductase, glutathione peroxidase and glutathione S-transferase were increased by 43, 44, 69 and 52%, respectively (p < 0.05 at a dose of 1.00 g kg<sup>-1</sup>). Furthermore, the EtOAc extract of *S. pinnata*'s stem heartwood exhibited a hepatoprotective effect<sup>126</sup> in rats under CCl<sub>4</sub>-injury induction. The results showed that this extract brought back the altered serum levels of some biochemical markers (SGPT/serum glutamyl pyruvate transaminase, SGOT/serum glutamyl oxalacetic acid transaminase, ALKP/alkaline phosphatase and bilirubin) to near normal range according to a dose-dependent mechanism. Finally, we could highlight in the study of the antipyretic potentials<sup>127</sup> of the

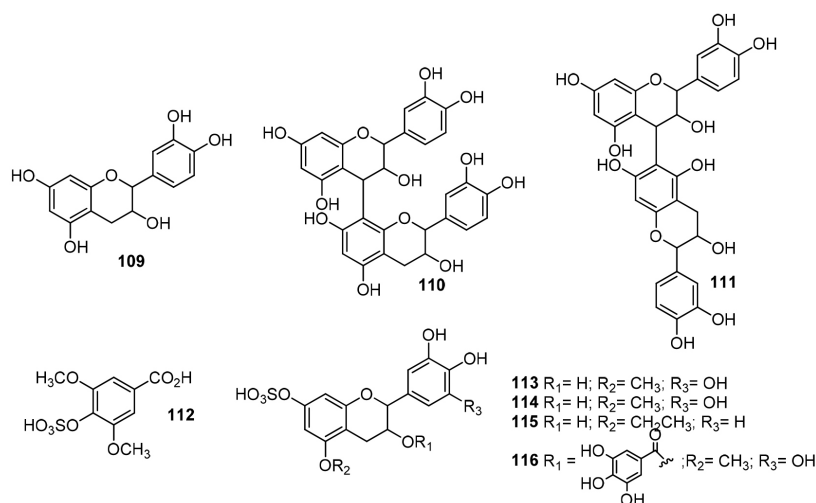


Figure 8. Compounds from active extracts of *Lanea stuhlmannii* and *L. humilis*



acetone and EtOH extracts of *S. pinnata* stem bark were evaluated. The ethanol extract (at 200–400 mg kg<sup>-1</sup> p.o) presented a substantial reduction in yeast-induced elevated temperature in mice (along 1 h up to 5 h) in a dose-dependent manner, being compared to paracetamol. The possible mechanisms of action of *S. pinnata* stem bark extracts and the bioactive compounds still need to be further elucidated.

Moreover, in studies with *Buchnanan lanzan*,<sup>128</sup> the MeOH leaf extract exhibited a significant neuroprotective activity (against AlCl<sub>3</sub> induced Alzheimer's in Albino Wistar rats) in two different doses (200 and 400 mg kg<sup>-1</sup> day<sup>-1</sup>, orally for four weeks). The evaluation of learning and memory outcomes indicated that the leaf part of *B. lanzan* was more active in attenuating memory deficits than other parts. Furthermore, its mechanism of memory retention seems to be similar as compared to standard drugs, which might allow this plant has potential in the treatment of cognitive dysfunctions connected with neurodegenerative disorders.

Lastly, the crude MeOH extract of barks of *Holigarna longifolia* Roxb. and its chromatographic fractions demonstrated neuroprotective activities by increase of phenobarbitone-induced sleeping time of mice, as well as a substantial inflammation inhibitory efficacy compared to positive control. In addition, only MeOH extract provoked a significant antinociceptive activity by inhibiting abdominal writhes produced by AcOH compared to standard analgesic diclofenac sodium, whose outcomes indicate that *H. longifolia* might be a promising neuroprotective plant.<sup>115</sup>

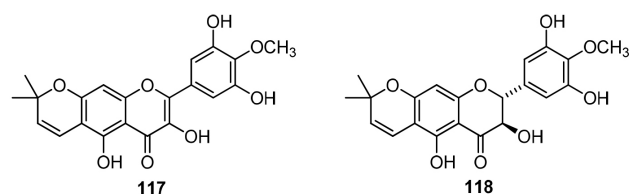
### Biological activities of isolated compounds from Anacardiaceae spp.

#### *In vitro* studies

Firstly, it can stand out that catechin-3-*O*-rhamnoside, a flavonoid isolated from *Lannea kerstingii* Engl. (EtOAc stem bark extract)<sup>129</sup> for the first time, exhibited antimicrobial (diffusion and broth dilution methods) and antioxidant (by DPPH scavenging assay) activities. This compound presented a selective activity against several bacteria and fungi (*Candida* spp.) with MIC ranging from 6.25 µg mL<sup>-1</sup> (for *S. aureus* and MRSA, *B. subtilis*, *E. coli*, *K. pneumonia* and *S. dysenteriae*) to 12.5 µg mL<sup>-1</sup> (for *S. typhi*-*S. enterica*, *C. albicans* and *C. tropicalis*), while the MBC/MFC (minimum bactericidal/fungicidal concentrations) ranged from 12.5 to 50.0 µg mL<sup>-1</sup>. Moreover, these activities are higher than chloramphenicol and positive nystatin controls, probably due to the flavonoid skill to complex with bacterial cell walls and extracellular soluble proteins.

Two new prenylated flavonoids **117** and **118** (Figure 9), alongside four known compounds (myricitrin, betmidin, lupeol and sitosterol) isolated from *L. alata* Engl. roots, might be associated to a good antibacterial and dose-dependent DPPH scavenging activity.<sup>130</sup> Both glycosides presented better antioxidant activity than **117** and **118** and betmidin showed the best antimicrobial activity among all tested metabolites. The presence of 3-*O*-arabinose glucoside might be associated to the activity of betmidin against Gram-positive bacteria. Similarly, the arabinofuranoside's antioxidant effect (followed by the rhamnopyranoside), which was compared to ascorbic acid in high concentrations, corroborates with the ethnomedicinal uses of *L. alata* in the management of Gram-positive bacteria sicknesses. Structural features of **117** and **118** are narrowly related to their properties, such that the lower antioxidant (compared to the glycosides) behavior may be due to the presence of cyclized prenyl moieties thereon. Nevertheless, flavonol **117** is more active than **118** against Gram-negative strains (*Pseudomonas* spp.), what can be related with its planar C2-C3 double bond and suitability to this activity.

Lupeol and a mixture of phenolic lipids (mainly urushiols, with minor amounts of an alkenylphenols) from *Schinopsis lorentzii*



**Figure 9.** Structures of lanneaflavonol (**117**) and dihydroprenylated lanneaflavonol (**118**) isolated from *L. alata* roots

(Griseb.) Engl. and *S. haenkeana* Engl. showed antifungal (against *Fusarium graminearum* and *F. verticillioides*) and antimicotoxigenic effects. In this study, the phenolic lipids were more active than lupeol against *Fusarium* spp. presenting MIC<sub>50</sub> 31 to 28 µg g<sup>-1</sup> for *F. graminearum* and 165 to 150 µg g<sup>-1</sup> for *F. verticillioides*.<sup>131</sup> Besides, the antimicotoxigenic activity was higher than that of ferulic acid, since the fumosinin and deoxynivalenol production was thoroughly inhibited by all bioactive metabolites even at lower concentrations. This activity is relevant to controlling these toxigenic fungi, owing to the stimulation of mycotoxin biosynthesis by several commercial antifungals.

The *in vitro* activities of several EOs of branches, fruits and leaves of *Rhus typhina* L. wood<sup>132</sup> (from Northeast Italy) exhibited high antimicrobial activity *in vitro* against *C. albicans* (inhibition zone 22.6–35.0 mm, MIC 0.02 mg mL<sup>-1</sup>), although only the EOs from leaves and fruits were active against *E. coli* ATCC (inhibition zone 17.6–22.5 mm, MIC 0.064 mg mL<sup>-1</sup>). Furthermore, the antioxidant effect (DPPH assay) of leaf and fruit EOs was superior to that EOs of the branches, as indicated by their respective IC<sub>50</sub> values (2.29 ± 0.10 µg mL<sup>-1</sup>, leaves; 2.54 ± 0.10 µg mL<sup>-1</sup>, fruits; 5.80 ± 0.18 µg mL<sup>-1</sup>, branches).

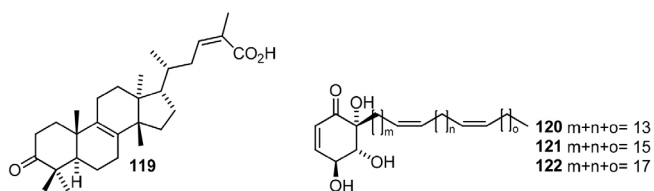
Biological studies with *Mangifera indica*<sup>133</sup> have shown a wide range of applications of active extracts and isolated compounds such as **97**. Mangiferin (1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside) is a pharmacologically active metabolite present in high yields in *M. indica* (bark, roots, fruits, and leaves) and exhibits diverse biological properties, among which are the antibacterial and cytotoxic/anticancer activities. A study reports that the solution of **97** was found to exert promising activity against both Gram-positive and Gram-negative bacteria, which is particularly relevant because known antibiotics resistance. Besides, the cytoprotective potential of **97** for hematopoietic cells from leukemogenesis was verified based on the decreased olive tail moment (OTM) and micronucleus (MN) frequency, so that **97** probably reduces DNA damage in the etoposide-treated mononuclear cells.<sup>133</sup>

Moreover, a study for the characterization of epicuticular leaf DCM extracts and several derivatives of *Lithrea caustica* (Molina) Hook and Arn. showed that litreol ((3-[pentadecyl-10-enyl]-catechol)) and some derivatives behave as inhibitors of 15 soybean and 5 human lipoxygenases (15-sLOX and 5-hLOX).<sup>134</sup> The highest activities were exhibited by litreol (IC<sub>50</sub> = 54.77 µmol L<sup>-1</sup>, against s-LOX; 2.09 µmol L<sup>-1</sup>, against h-LOX) and 3-pentadecylcatechol (IC<sub>50</sub> = 55.28 µmol L<sup>-1</sup>, against s-LOX; 2.74 µmol L<sup>-1</sup>, against h-LOX), in such a way that the respective kinetic studies indicated a mixed and selective inhibition mechanism to 5-hLOX.

Besides, the pistagremic acid (**119**) isolated from the dried galls of *Pistacia integerrima* Stewart exhibited an inhibitory effect against α-glucosidase *in vitro* against yeast (IC<sub>50</sub> = 89.12 ± 0.12 µmol L<sup>-1</sup>),<sup>135</sup> confirming former molecular docking simulations. Thus, a molecular binding mode was explored, and the results indicated hydrogen bonding interactions between this triterpene and significant amino acid residues surrounding the catalytic site of the α-glucosidase, which could be mainly responsible for their role in potent inhibitory activity. Therefore, **119** (Figure 10) showed a promising potential to



be further investigated as a new lead compound for better management of diabetes.



**Figure 10.** Pistagremic acid (**119**) isolated from *Pistacia integreriima* and of pleiogenones A-C (**120-122**) obtained from *Pleiogynium timoriense*

The investigation of a DCM extract of the bark of *Pleiogynium timoriense* against the A2780 ovarian cancer cell line (A2780 OCCL) indicated an  $IC_{50}$  value of  $1.3 \mu\text{g mL}^{-1}$ . Bioassay-directed fractionation of this extract yielded the three new bioactive trihydroxyalkylcyclohexenones (Figure 10) named pleiogenones A (**120**), B (**121**) and C (**122**), which showed a higher antiproliferative activity against the A2780 OCCL presenting  $IC_{50}$  of 0.8, 0.7, and  $0.8 \mu\text{g mL}^{-1}$ , respectively.<sup>136</sup> Compound **72**, named integracin E, obtained from the stem barks of *Swintonia floribunda*,<sup>70</sup> also presented a potent tyrosinase inhibitory activity with an  $IC_{50}$  value of  $48.2 \mu\text{mol L}^{-1}$ .

Likewise, the bioactivity-guided fractionation of EtOAc leaf extract of *Poupartia borbonica* J.F.Gmel. furnished three novel alkyl cyclohexenone derivatives (**123-125**)<sup>137</sup> with absolute configurations assigned (Figure 11). These compounds were active against 3D7 and W2 *Plasmodium falciparum* strains ( $IC_{50} = 0.55\text{-}1.81 \mu\text{mol L}^{-1}$ ) and exhibited *in vitro* cytotoxicity against WI38 human fibroblasts and human cervical cancer (HeLa) cell lines (WST-1 assay), but no hemolytic activity was observed for the extract and pure metabolites. Besides, the MeOH extract was also evaluated, and it displayed moderate antiplasmodial properties *in vitro*, which might be attributed to its flavonoid content, including the unknown compound 3'-*O*-hydroxysulfonylquercetin (**126**). Moreover, studies with *Tapirira guianensis* leaves allowed the obtention of these compounds, which seems to be precursors of alkyl and alkenyl phenols (**127-130**). The cyclohexene derivatives **127** and **128** were in mixture and they also showed against *P. falciparum* strains ( $IC_{50} = 4.7 \pm 0.3$  and  $5.4 \pm 1.7 \mu\text{mol L}^{-1}$ ) against F32 and FcB1 strains. This mixture was also active against *Leshmania amazonensis* ( $IC_{50} = 1.0 \pm 0.1 \mu\text{mol L}^{-1}$ ), *S. aureus* ( $IC_{50} = 75.4 \mu\text{mol L}^{-1}$ ) and *S. epidermidis* ( $IC_{50} = 17.6 \mu\text{mol L}^{-1}$ ).<sup>138</sup>

In sequential studies with *P. borbonica*, the cytotoxicity and pharmacological activities<sup>139</sup> of poupartone B (**123**) were deeply evaluated. A real-time live-cell imaging of different human cancer cell lines and normal fibroblasts treated with **123** was carried out. Thus, this compound showed a potent inhibition of cell proliferation associated with the induction of cell death. Besides,

**123** (at  $1\text{-}2 \mu\text{g mL}^{-1}$ ) induced a rapid retraction of cellular protrusions associated with cell rounding, massive cytoplasmic vacuolization, loss of plasma membrane integrity and plasma membrane bubbling, ultimately leading to paraptosis-like cell death. These results highlight the cytotoxicity of **123** against several *in vitro* cancer cell lineages.

The stem bark  $\text{CHCl}_3$  extract of *Protorus longifolia* (Benrh.) Engl. furnished the known 3-oxo-5 $\alpha$ -lanosta-8,24-dien-21-oic acid (**131**) and 3 $\beta$ -hydroxylanosta-9,24-dien-24-oic acid (**132**), which were screened for several activities (Figure 12).<sup>140</sup> These compounds showed satisfactory anti-platelet aggregation activities dose dependent, so that **131** showed the highest activity ( $IC_{50} = 0.99 \text{ mg mL}^{-1}$ ) on the thrombin-induced platelet aggregation.

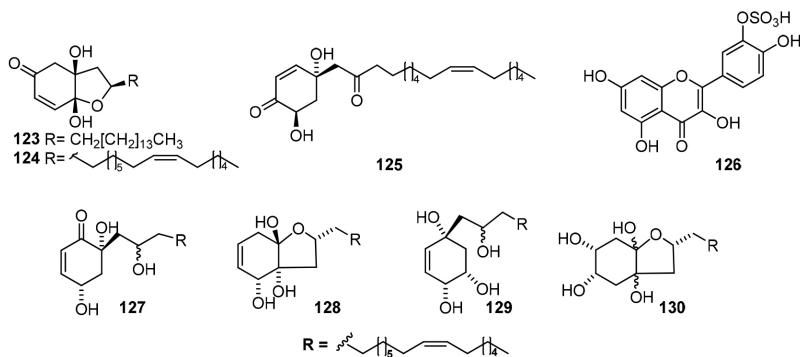
Two different studies with *Semecarpus anacardium* afforded the obtention and 3-(8'(Z),11'(Z)-pentadecadienyl)-catechol (SA-3C) isolated from the plant kernel<sup>141</sup> and tetrahydroamentoflavone<sup>142</sup> from the seeds. The alkylphenol showed cytotoxic activity against tumor cell lines with  $IC_{50}$  values lower than doxorubicin and even multidrug resistant tumor cell lines were equally sensitive to SA-3C. Besides, it induced apoptosis in human leukemia cell lines in a dose-dependent pattern, showed synergistic cytotoxicity with doxorubicin and induced the cell cycle arrest at S- and G<sub>2</sub>/M-phases, what was correlated with inhibition of checkpoint kinases. On the other hand, tetrahydroamentoflavone (THA) exhibited a strong inhibitory effect against xanthine oxidase (XO), what was investigated through a Lineweaver-Burk (LB) plot for the XO inhibition of THA and allopurinol constructed from the kinetic data. In this case,  $IC_{50}$  values of THA and allopurinol for XO inhibition were 92 and  $100 \text{ nmol L}^{-1}$  and their corresponding values for  $K_i$  were 0.982 and  $0.612 \mu\text{mol L}^{-1}$ .

In conclusion, the fruit extract of *Sorindeia juglandifolia* furnished two bioactive simple compounds identified as 2,3,6-trihydroxybenzoic acid and methyl 2,3,6-trihydroxybenzoate.<sup>143</sup> These compounds showed inhibitory effects against *P. falciparum* W2 ( $IC_{50} 16.5 \mu\text{mol L}^{-1}$  and  $13.0 \mu\text{mol L}^{-1}$ ) and falcipain-2 ( $IC_{50} 35.4$  and  $6.1 \mu\text{mol L}^{-1}$ ), respectively.

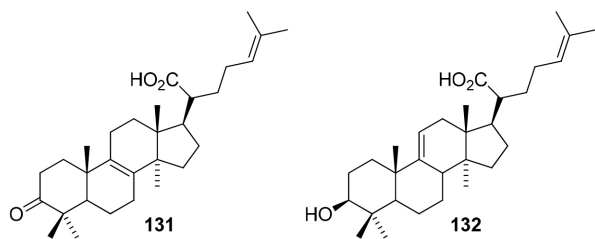
#### *In vivo* studies with pure compounds

To date, there are few examples of *in vivo* studies of isolated metabolites of Anacardiaceae. For instance, compounds isolated from EtOH extracts of leaves of *Schinus polygamus* C. (3-*O*-acetylpupeol,  $\beta$ -sitosterol, lupeol, gallic acid, methyl gallate, kaempferol, quercetin-3- $\alpha$ -*O*-rhamnoside and its aglicone quercetin) were submitted to hepatoprotective, antioxidant and curative *in vivo* studies. Lupeol and gallic acid were evaluated by oral administration in adult male albino rats ( $50\text{-}100 \text{ mg kg}^{-1}$ ) and both compounds showed a significant protection against  $\text{CCl}_4$ -induced liver damage. Besides, a remarkable antioxidant effect (> 90% for both compounds, measured by the activity of enzyme reduced glutathione) was observed.<sup>144</sup>

In addition, the *in vivo* study of antihyperglycemic activity of the



**Figure 11.** New bioactive alkyl and alkenyl cyclohexenone derivatives and sulphorated quercetin from *P. borbonica* and alkenyl derivatives from *T. guianensis*



**Figure 12.** 3-oxo-5 $\alpha$ -lanosta-8,24-dien-21-oic and 3 $\beta$ -hydroxylanosta-9,24-dien-24-oic acids with anti-platelet aggregation activities from *P. longifolia*

methyl ester of 3 $\beta$ -hydroxylanosta-9,24-dien-21-oic acid (**132**) from *P. longifolia* stem bark extract showed antihyperglycemic behavior in an STZ-induced diabetes rat model. This compound showed hypoglycemic effect by reducing blood glucose levels by 37% and improved glucose tolerance in the diabetic rats. Furthermore, a relatively higher hepatic glycogen content, alongside hexokinase and glucokinase activities (with a decrease in glucose-6-phosphatase activity), was observed in the triterpene-treated diabetic group when compared with the diabetic control group. The treatment increased antioxidant status of the diabetic animals, as well as the activity of superoxide dismutase and catalase along with a decrease in malondialdehyde content.<sup>145</sup>

At last, different compounds aforementioned have also exhibited *in vivo* bioactivities; termipaniculatone A<sup>103</sup> (**103**) possesses anti-hyperuricemic and anti-inflammatory activities in mice, 2,3,6-trihydroxy benzoic acid<sup>143</sup> is active against *P. berghei* strain B, with mean parasitaemia suppressive and curative doses of 44.9 mg kg<sup>-1</sup> and 42.2 mg kg<sup>-1</sup>, respectively. The 3 $\beta$ -hydroxylanosta-9,24-dien-24-oic acid<sup>140</sup> (**132**) showed a strong inhibition of the acute inflammation of rat paw but in a higher concentration (500 mg kg<sup>-1</sup>), while pourpatone B (**123**) showed *in vivo* antimalarial (*P. berghei*) growth inhibition at a dose 15 mg kg<sup>-1</sup> day<sup>-1</sup> i.p.<sup>137</sup>

## PROCESSES AND PRODUCT PATENTS BASED ON ANACARDIACEAE spp.

### Employment in cosmetics

During the last two decades three cosmetic formulations were developed based on compounds isolated or present from Anacardiaceae spp. extracts. Ellagic acid or its derivatives, essential oils or foaming agents were employed in formulations with surfactants, thickening agents and other constituents. All evaluate compositions showed a good anti-dandruff effect mainly caused by *Malassezia (Pityrosporum spp. yeasts)*.<sup>146</sup>

Likewise, a hair styling composition in the form of foam relating to a process for shaping keratin fibers was also developed, comprising the application of at least one “mousse” composition, including one or several fresh fruit juices, including species of Anacardiaceae (mango) and/or surfactants. This type of cosmetic formulation was mainly made in an aqueous medium or organic hydrophilic solvent (linear or ramified alcohols), in such a way as to allow to take advantage of some active constituents that are naturally present in fresh fruits (vitamins,  $\alpha$ - and  $\beta$ -hydroxyacids, antioxidants, and anti-inflammatories), which have beneficial properties for the hair and scalp.<sup>147</sup>

At last, a topical cosmetic formulation was elaborated, in which the dedifferentiated plant cells are elicited *in vitro* following a cycle of successive darkness and lighting periods under a CO<sub>2</sub> atmosphere.<sup>148</sup> The compositions with Anacardiaceae spp. and other plants permitted to observe an anti-aging effect, a protective effect for the skin and an antioxidant effect, as well as antifungal and antiradical properties.

### Patents of medical and other biological uses

Several formulations comprising a hydroxylated fatty acid (such as ricinoleic acid) or a triglyceride containing hydroxylated fatty acid (e.g., castor oil) were combined with the liquid from the cashew nut peel (*A. occidentale* and others) and/or alkyl phenols or anardic acids and derivatives, which have presented broad antimicrobial against Gram-positive and Gram-negative bacteria, fungi and protozoans. In this case, for the first time was presented that ricinoleic acid might behave as an oral antibiotic and an antiprotozoal agent, which was followed by extremely low toxicity in comparison with other antibiotics. Therefore, these formulations are developed to the prevention and treatment of pathogenic processes in people and animals (by oral, topical or parenteral administration), as well as to control fermentation (made with yeast – *S. cerevisiae*) and as an antifungal for food and seeds.<sup>149</sup>

An antiviral composition with antiretroviral properties for treating HIV patients, which was made with acetic acid and coconut extracts, a solution of mineral salts (e.g., seawater) and other plant extracts of *Spondias mombin* barks, Liliaceae (*Smilax medica* roots) and Euphorbiaceae (roasted castor beans, *Ricinus* spp.), was developed.<sup>150</sup> The results of these formulations indicated an inhibition of the HIV-1 reverse transcriptase activity (which may exceed 90% compared to the activity measured in the controls) and a decrease in the cytopathogenic effect of HIV-1 in infected cells after the treatment with the antiviral compositions. Besides, the absence of toxicity was observed in mice essays.

On the other hand, a preparation for *in vivo* and *in vitro* applications based on an aqueous *Mangifera indica* fruit extract called sirtuin 1 (SIRT1) is claimed to be an activating agent,<sup>151</sup> which may be used to reduce the risk of obesity, type-II diabetes, high blood lipid levels, arteriosclerosis, and heart illnesses, as well as a cellular and DNA protector. In addition, an aqueous ethanolic dilution of juices or extracts derived from some plants were transformed into a paste/jelly/jam/cake/cream puff/chocolate to be used as functional foods and had anti-stress (e.g., induced by gastric ulcers) and adaptogenic activities. The extracts of *M. indica* (65.0-75.0 wt.%), *Withania somnifera* (3.5-5.0 wt.%, Solanaceae), *Asparagus recemosus* (3.5-5.0 wt.%, Asparagaceae), *Amaranthus hypochondriacus* (10.0-20.0 wt.%, Amaranthaceae) and *Evolvulus alsinoides* (0.2-0.6 wt.%, Convolvulaceae)<sup>152</sup> did not provoke mortality in any of the rats' treated groups, as well as behavior's abnormalities in the animals exposed with herbal preparations. The results of these formulations showed antiulcer proprieties (since they reduce the ulcer index and decrease its severity) and exhibited antioxidant effect by the decrement of lipid peroxidation, the rising of catalase levels and the enhancement of superoxide dismutase activity.

Another invention related to an herbal formulation prepared with several plants (including *M. indica*)<sup>153</sup> developed for the diabetes prevention and treatment, as well as associated damages, was proposed in the period. The formulation developed therein might not only control type-II diabetes, but also offer reversal possibilities in prediabetes and, thereby, possible prevention for diabetes mellitus and its complications. The plant extract composition provides good glycemic management and reduces the glycosylation of hemoglobin, controls the total cholesterol levels, improves cardiovascular health by decreasing hypertension and enhances wound healing of diabetic ulcers. Besides, another minor effect is the reduction systolic and diastolic blood pressure, prevention of oxidative stress and minimization of hypertensive drug dependency.

Compositions and extracts based on *Schinus terebinthifolia* and one or more compounds present in this plant. In certain embodiments, the formula is administered in combination with another antibiotic

agent.<sup>154</sup> These formulations prevent bacterial infections (*e.g.*, caused by *Staphylococci* sp.), besides other skin damages, acne and other corresponding applications. Their main compounds herein were annotated by LC-FTMS (flavonoids, triterpenoids and steroidal saponin, among others), which are known to have many known biological properties.

Anacardic acids were used as an effective formulation for treating anemia and low blood pressure. In these formulations is including at least one anacardic acid of C-15 alkyl/alkenyl chain (**59**) and the  $\Delta^{8,9}$  alkene derivative) isolated from roots and barks aqueous extract of *Ozoroa paniculosa*.<sup>155</sup> The composition was active for oral, rectal, nasal, vaginal or parenteral (subcutaneous, intramuscular, intravenous or intradermal) administration, both to humans and animals. Besides, six active fractions of Anacardiaceae and Asteraceae spp. were employed to elaborate herbal compositions to treat infertility in men presenting no-side effects.<sup>156</sup> The inventors stated that these formulations restored vigor, increased sexual libido, exhibited a healing effect on X and Y chromosome-related diseases and granted other corresponding benefits in synergistic plant compositions.

Some like-urushiol derivatives were synthesized (*e.g.*, 3-*n*-pentadecyl catechol, and/or 3-*n*-heptadecyl catechol), both similar that isolated from poison ivy.<sup>157</sup> They are potential compositions for the prevention and/or prophylactic treatment of contact dermatitis caused by poison ivy and poison oak and other ACD causing plants of the family Anacardiaceae and Ginkgoaceae. The embodiments were effective for tolerizing and desensitizing mammals, including humans. They comprise esters from urushiols and amino acid, or combination of amino acids (*i.e.* di, tri, or poly peptide residue), a carbamate forming compound, a sulphate or phosphate ester or even an ester of a dicarboxylic acid, resulting in a salt forming compounds with water soluble characteristics to facilitate the topic use.

Different insecticidal compositions were prepared in liquid, dehydrated and lyophilized forms, wherein several plants of various families (*e.g.*, *Pistacia vera*, Anacardiaceae) were included, whose constituents (polypeptides alone *vs.* binary systems) expressed as polypeptides/polynucleotides showed pesticidal properties.<sup>158</sup> These combinations showed to be more active than the components individually, whose results are promising for agriculture, ecology, biotechnology and other scientific applications.

The efficacy of the gum of *Odina wodier* Roxb. (*i.e.*, *Rhus odina*), an Asian plant that presents many applications in folk medicine, was evaluated for the first time as a tablet binder.<sup>159</sup> Hitherto, the potential binding capability and an emulsifier have already been studied to stabilize emulsions. Chemical analyzes appointed to the presence of carbohydrates but the absence of tannins and peroxidase enzyme in the “gum odina” compositions, what removed the possibility of oxidative degradation of gum as excipient. The gum shows stable in liquid conditions and no toxicity was observed. These results showed that “gum odina” could be used as pharmaceutical excipients (*e.g.*, tablet binder or emulsifier), being effective in minimal amounts compared to the standard tablet binders.

Furthermore, other studies with Anacardiaceae spp. were developed with new compositions or products that might be applied as (i) antimicrobial coating films for filters and air conditioning equipment (*e.g.*, branch/leaf/rhizome/bark aqueous extracts of different plants, including *Pistacia* spp.),<sup>160</sup> (ii) in procedures for a concentration of xanthenes at high pressure on a semi-industrial scale using extracts of several plants (*e.g.*, *M. indica*)<sup>161</sup> or (iii) to increase the content of desired ingredients in crops (such as fruits and vegetables) by applying succinate dehydrogenase inhibitors (SDIs).<sup>162</sup> Thus, the embodiments of invention (i) were intensely active against harmful microorganisms in the living environment, promoting its cleanliness and preventing microorganisms' degradation. On the

other hand, the use of a hydrophobic stationary phase mixed to a supercritical eluent (pure CO<sub>2</sub> *vs.* a mix of CO<sub>2</sub> with a polar cosolvent in isocratic or gradient mode) in (ii) allowed the obtention of phenolic acids, benzophenones, flavonoids and xanthenes in high amounts (mainly **97**, 5× higher than in original leaf extract), whose process was efficient and avoided losses in the bioactivity of the fractionated substances. At last, the study showed the behavior of several SDIs against various plant species (including mango, sumac, and pistachio), whose results indicated that different types of natural metabolites might have their contents increased thereon, since the SDI is applied to the crop prior to the harvest and at a rate ranging from 1 to 250 g ha<sup>-1</sup>.

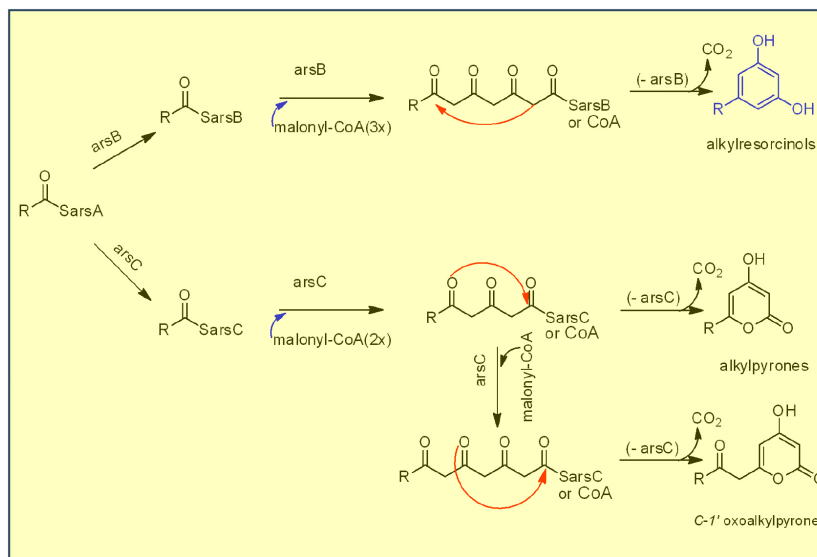
Several formulations, including at least one plant of Asteraceae, Lamiaceae, Anacardiaceae (*P. lentiscus*) and Cistaceae families in treating varroatosis (by *Varroa destructor*, varroa mite) in bees were elaborated.<sup>163</sup> This invention achieves a composition that is harmless for bees and humans and effective in a short time on mites in both phoretic and reproductive phases in opened/operculated cells. Besides, antioxidant formulations from Anacardiaceae spp. (in particular, *Sclerocarya birrea*) were obtained by maceration/extraction of roots, bark, leaves, fruits or their parts (endocarp, mesocarp, epicarp) and using different solvents, whose results suggested that the prepared extracts had outstanding oxidative stability and showed a good antiradical behavior.<sup>164</sup>

Other plant compositions, including Anacardiaceae species prepared with unrefined oils (from natural seedlings) free of phorbolic esters and *trans* fatty acids, were developed for cosmetic, dermatologic, dietetic, insecticide, pharmaceutical, veterinary and eating uses.<sup>165</sup> These compositions exhibited satisfactory outcomes as an antimicrobial/antifungal, germ inhibitor and for the management of cellular functions, including the potential to be employed in external and internal medications. In conclusion, in the same way a formulation comprising sumac (*Rhus* spp.) and oregano can be highlighted<sup>166</sup> once it can be used as a preservative agent to prevent or slow down the deterioration of food products (*e.g.*, for wet and dry baked products). These formulations allowed the storage time of the baked products to be significantly extended, substantially delaying both the appearance of mold (mainly on wet baked goods) and the rancidity, what probably is related to the presence of polyphenols.

## PROGRESS IN BIOSYNTHESIS OF PHENOLIC LIPIDS

Phenolic lipids and derivatives are chemotaxonomic markers of this family, but their biosynthesis is still not completely enlightened.<sup>1</sup> More recent publications have given new contributions, such as the structure and function of polyketide biosynthetic enzymes (PKSs) and the strategies for producing several polyketides.<sup>167</sup> The results indicated that the type III PKSs have involved in the processes of polyphenols and phenolic lipids biosynthesis in plants, bacteria and fungi. Hence, type III PKSs synthesize a broad group of metabolites, since they differ in their preference of starter and extender substrates, the number of condensation steps and the mechanism of intramolecular cyclization of poly- $\beta$ -keto intermediates.

*In vitro* biochemical analysis using *Azotobacter vinelandii* bacterium strains was formerly conducted since alkylresorcinols and alkylpyrones are the major lipids of *A. vinelandii* cyst membranes. Gene disruption analyzes showed that the *ars* gene cluster is essential for biosynthesis, which consists of two types I fatty acid synthase (FAS) genes (*arsA*, *arsD*) and two types III PKSs (*arsB*, *arsC*). Thus, it was observed that the reactions of *arsA*, *arsB*, and *arsD* lead to alkylresorcinols. In contrast, the reactions of *arsA*, *arsC*, and *arsD* lead to alkylpyrones, once *arsB* catalyzes the decarboxylative C2-C7 aldol condensation to produce alkylresorcinols and *arsC* catalyzes the C5 oxygen-C1 lactonization to synthesize alkylpyrones (Figure 13).



**Figure 13.** The biosynthetic pathway of phenolic lipids according to the experiments with *Azotobacter vinelandii* (adapted from Miyanaga)<sup>167</sup>

These features are due to the specific amino acid residues at the type III PKSs active site cavity (Trp281 to alkyresorcinols and Gly284 to alkylpyrones).<sup>167</sup>

Similarly, a study of characterization of an orphan Type III polyketide synthase (PKS/CepA) in uncultivated *Entotheonella* sponge (*Theonella* spp.) provided new information in phenolic lipids' biosynthesis, as well as the metagenomic features related. Three PKS18 amino acid residues (Thr144, Cys205, and Ala209) were crucially involved in its substrate preference (*i.e.*, alkyresorcinols *vs.* alkylpyrones, according to the long-chain alkyl units binding). Nevertheless, for the enzyme BpsA the PKS-like substrate-binding tunnel is composed of Thr, Cys and Phe residues at the corresponding positions. Based on their bioinformatic analyzes, seems CepA was most likely a resorcinol synthase that accepted just long-chain fatty acid starters (**133-138**) directly from several coenzyme-A precursors (Figure 14(a)). In optimized enzymatic assays, two alkyresorcinols, and three alkylpyrones (**139-143**) were obtained (Figure 14(b)). At last, the *in vitro* experiments demonstrate that CepA factor acts as a phenolic lipid synthase, processing long-chain fatty acid acyl-CoA and malonyl-CoA thioesters, wherein the product range includes tetraketide resorcinols as well as tri- and tetraketide  $\alpha$ -pyrones, which were detected for the first time in theonellid sponges of *Entotheonella* species.<sup>168</sup> However, the presence of alkylpyrones might indicate incoherence with the bioinformatic prediction.

In conclusion, the catalytic activity of *O*-methyltransferase *SrsB* in the decarboxylative methylation of alkyresorcinol

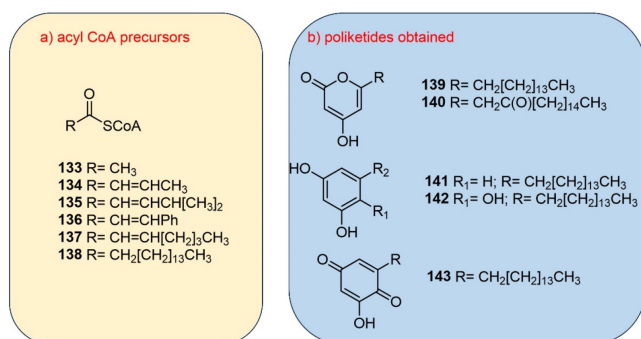
(ARA) along phenolic lipid biosynthesis by *Streptomyces griseus* (or *S. lividans*)<sup>169</sup> was investigated, whose operon (*Srs*) encodes a type III PKS and a flavoprotein hydroxylase. Former studies have reported that *SrsA* enabled the production of an ARA as a direct product rather than a corresponding alkyresorcinol (ARC), while *SrsB* produced alkyresorcinol methyl ester (ARME) in the presence of *S*-adenosyl-L-methionine (SAM). However, *SrsB* has been shown incapable of catalyzing the *O*-methylation of ARC, suggesting that ARA was the substrate of *SrsB*, whose conversion to ARME might take place by (i) the *O*-methylation of the OH-group (C-6) or (ii) the decarboxylation of the neighboring carboxyl group (C-1). These studies proposed that *O*-methylation was coupled with decarboxylation, so that *SrsB* catalyzed the feasible SAM-dependent decarboxylative methylation of ARA, which is the first report of a methyltransferase with this catalytic behavior in an *in vitro* assay (Figure 15).

## CONCLUSIONS

This review presents a detailed report regarding the chemical composition and biological activities of pure compounds and extracts of the Anacardiaceae family. Technological prospectation was also detailed with a variety of patents. Furthermore, new significant information about phenolic lipids biosynthesis was finally pointed out. However, for plants from this family, the biosynthesis of the chemical markers remains unclear, once the biosynthesis update was carried out with microorganisms. This botanical family is significant to pharmacology, the chemistry of natural products and corresponding scientific fields. Therefore, based on the data and the new findings shown hither, further research with the Anacardiaceae family was needed, both to isolate new bioactive compounds and elucidate the compounds responsible for the biological activities, as well as towards alternative contributions to biosynthetic studies of chemotypes/chemotaxonomic markers in this family.

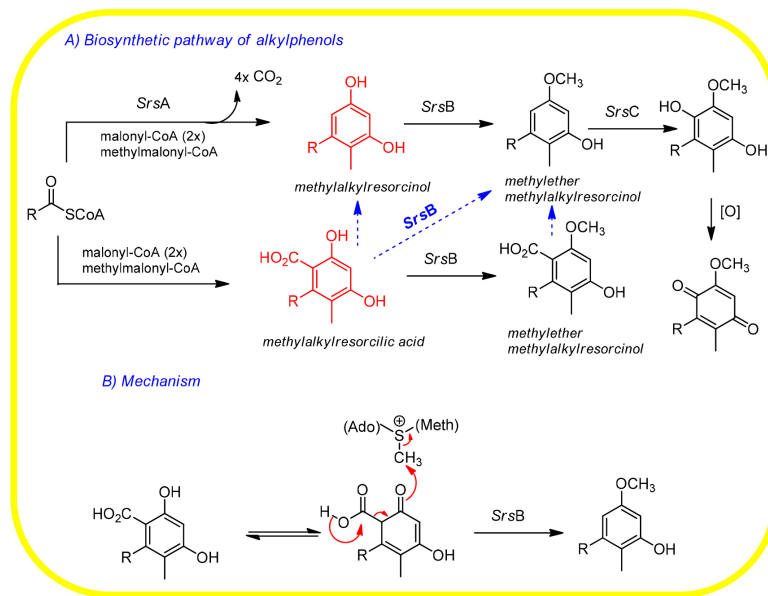
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**Figure 14.** (a) Structures of potential PKS starters used as test substrates. (b) Proposed structures to the tri- or tetraketides obtained by optimized enzymatic assays using theonellid sponges (*CepA* pathway)





**Figure 15.** (A) Scheme of the Srs biosynthetic pathway and (B) proposed mechanism of biosynthesis of alkylresorcinol methyl ester by SrsA and SrsB with the mediation of S-adenosyl-L-methionine (SAM) (adapted from Nakano)<sup>169</sup>

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