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Review Article
Chemical Diversity and Pharmacological Properties of Genus *Acacia*

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Abstract

The genus *Acacia*, an herb distributed worldwide comprises approximately 1200 species of the Fabaceae family belonging to the tribe Acacieae. *Acacia* species are relevance to food and ethnopharmacology and have potential therapeutic uses. This review focuses on natural compounds isolated from plants of genus *Acacia* and their biological activities, based on phytochemical and biological previous studies. This review list 152 chemical constituents from *Acacia's* species as well as their biological activities. The main compounds isolated from *Acacia* species are flavonoids, terpenoids and phenolic acids, accumulated mainly in leaves, pods and stem barks. The compounds isolated from *Acacia* species have been demonstrated to possess multiple pharmacological activities such as; antibacterial and antifungal, antioxidant, anticancer, antiparasitic, cytotoxicity and immunomodulatory properties.

Key words: *Acacia* species, chemical constituents, flavonoids, terpenoids, phenolic acids, biological activities

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

For centuries, humans have relied on nature to meet their primary health needs, precisely for the treatment of a wide spectrum of diseases. The interest in medicinal plant uses has increased in recent decades, because these plants produce a large range of bioactive molecules, making them a rich source of different types of medicines. This approach is attractive, because it constitutes a potential source of bioactive compounds which are safe and often act on multiple and novel target, thereby reducing the potential for resistance.

Many researchers conducted research on medicinal plants for the purpose: (i) To gain knowledge about the pharmacological potential of native plant diversity, (ii) To establish a basis for rational use of medicinal plant species, (iii) To develop inexpensive herbal medicines which exhibit relevant activity, (iv) To discover new prototypes of drugs and (v) To gain information regarding traditional medicines. Medicinal plants constitute a rich source of bioactive molecules which possess new structures and various mechanisms of action with a wide range of biological activities. These innovative features have motivated certain pharmaceutical industry to direct research toward the development of herbal medicines[1]. Fabaceae (also known as Leguminosae) is a cosmopolitan family, represented by 730 genera including *Stylosanthes*, *Tamarindus*, *Caesalpinia*, *Acacia* and over 19400 species[2]. Tribe Acacieae contains just two genera including, the monotypic genus *Faidherbia* that occurs in Africa and the middle East and the cosmopolitan genus *Acacia* which contain about 1200 species, representing the largest genus within sub-family mimosoideae. The *Acacia* species are found all over the world. Almost 1000 of them are found in a wide range in Australian regions followed by 185 species in North and South America, about 144 in the Africa regions (Madagascar included) and 89 species in Asia-pacific[2]. Ethnobotanical data revealed that preparations from different parts of *Acacia* species are used traditionally for diarrhea, diabetes, gastrointestinal disorders, skin diseases and inflammatory diseases[3-6]. *Acacia* is a member of tribe *Acacieae* within sub-family Mimosoideae of the Fabaceae family. The Mimosoideae, which is sometimes treated as a distinct family contains about 50-60 genera that are distributed throughout tropical, subtropical and warm-temperate regions of the world[7].

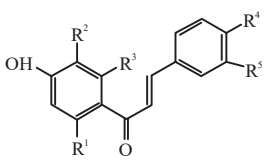
Previous phytochemical investigations of the genus *Acacia* led to the isolation of 152 chemical constituents, including flavonoids, phenolic acids, terpenoids and others compounds. Previous studies demonstrated that extracts and isolated compounds have interesting biological properties such as; antibacterial, antifungal, antioxidant, anticancer, antiparasitic, antidiabetic, cytotoxicity and other activities. To the best of our knowledge, there have been few in depth studies on the chemical diversity of this genus. Based on the study, it compile in this review, the natural compounds isolated from the genus *Acacia* as well as their biological properties.

CHEMICALS CONSTITUENTS

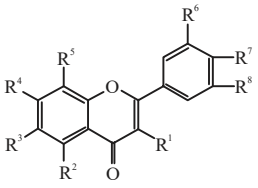
During the seven past decades, about 152 chemical constituents were isolated from the genus *Acacia*, including flavonoids (1-44), terpenoids and phytosterols (45-78), phenolic acids (79-99), fatty acids (100-110), hydrocarbons (111-123) and others compounds (124-152). The class of these compounds, their names, species from which they were isolated and references are compiled in Table 1. Flavonoids, terpenoids and phenolic acids are the predominant compounds isolated from this genus.

Flavonoids: Many flavonol, flavone, chalcone derivatives, flavan-3-ols and flavan-3,4-diols, which constitute the majority of the secondary metabolites from the genus *Acacia* have been reported by Bate-Smith and Swain[8], Adityachaudhury *et al.*[9], Fourie *et al.*[10], Wu *et al.*[11], Clark-Lewis and Dainis[12], Bai *et al.*[13], Malan[14], Muhaisen *et al.*[15], Mutai *et al.*[16], Salem *et al.*[17], Badr *et al.*[18], Maldini *et al.*[19], Brandt *et al.*[20], Biswas and Roymon[21], Nyila *et al.*[22], Van Heerden *et al.*[23], Budzianowski and Skrzypczakowa[24], Ghouila *et al.*[25], Gedara and Galala[26], Yagi *et al.*[27], Ghribia *et al.*[28], Gottlieb and de Sousa[29], Gottlieb and de Sousa[30] and Drewes and Roux[31]. Among them, 6 compounds, 31, 32, 35, 36, 41 and 43 were isolated as glycosides. The most frequently encountered flavonoids are catechin (17) found in 6 species and quercetin (5) in five species. Also, Isoliquiritigenin (1), myricetin-3-O-α-L-rhamnoside (36) and Rutin (43) were relatively common (Fig. 1). Most flavones (6, 4, 10-15, 34 and 44) reported from *Acacia* genus were isolated from *A. confuse*[11].

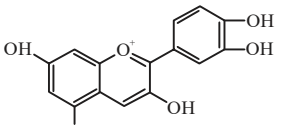
Terpenoids: The triterpenoids are the major class of terpenoids isolated from the genus *Acacia*. Twenty two triterpenoids (53-74) have been reported by Bai *et al.*[13], Joshi *et al.*[32], Perales *et al.*[33], Mutai *et al.*[34], Mutai *et al.*[35], Josm *et al.*[36], Aba *et al.*[37], Mutai *et al.*[38], Anjaneyulu *et al.*[39], Singh and Bhargava[40] and Amoussa *et al.*[41]. Sixteen triterpenoids (53-55, 57-64, 67-68, 70, 73 and 74) have been isolated from *A. mellifera*[16,34,35,38], 4, 56, 68, 69 and 74 from *A. ataxacantha*[36,41], three, 56, 67 and 74 from *A. modesta*[36], 2, 65, 71 from *A. saligna*[26], 2, 67, 72 from *A. raddiana*[40] and



	R^1	R^2	R^3	R^4	R^5
1	H	H	OH	OH	H
2	OH	H	H	H	H
4	H	OH	OH	OH	OH



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
5	OH	H	H	OH	OH	H	OH	H
6	OH	H	H	OH	OH	H	MeO	OH
7	OH	OH	H	MeO	H	MeO	MeO	H
8	H	H	H	OH	OH	H	OH	H



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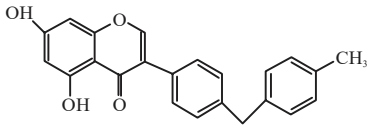

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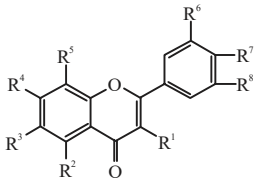
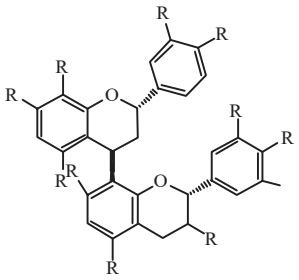
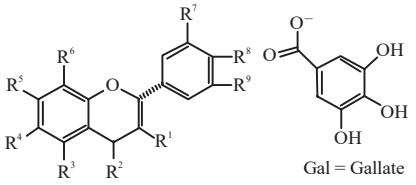


	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
10	MeO	H	H	OH	H	H	OH	OH
11	H	H	H	OH	H	H	OH	OH
13	H	H	H	OH	OH	H	OH	OH
14	H	H	H	OH	OH	H	OH	OH
15	MeO	H	H	OH	OH	H	MeO	OH

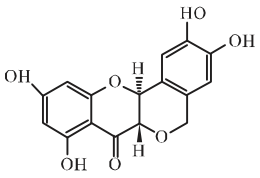


16 R = EtO



Gal = Gallate

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
12	OH	MeO	H	H	OH	OH	H	OH	OH
17	OH	H	OH	H	OH	H	H	OH	OH
18	OH	H	Gal	H	OH	H	H	OH	OH
19	OH	H	OH	H	Gal	H	Gal	OH	H
20	OH	H	OH	H	Gal	H	OH	Gal	H
21	OH	H	OH	H	Gal	H	OH	OH	H
23	Gal	H	OH	H	OH	H	OH	OH	H
24	OH	H	OH	H	OH	H	OH	OH	H
25	OH	H	OH	H	OH	H	OH	OH	OH
27	OH	H	Gal	H	Gal	OH	Gal	H	OH
28	OH	H	OH	H	Gal	H	OH	OH	OH
29	OH	H	OH	H	Gal	H	OH	Gal	OH
30	OH	H	OH	H	Gal	H	OH	OH	OH



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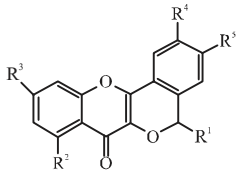
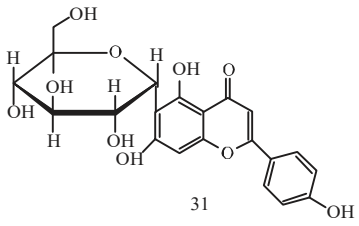


	R^1	R^2	R^3	R^4	R^5
26	OH	H	OH	OH	OH
39	H	H	OH	OH	OH



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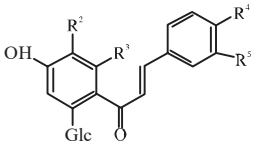
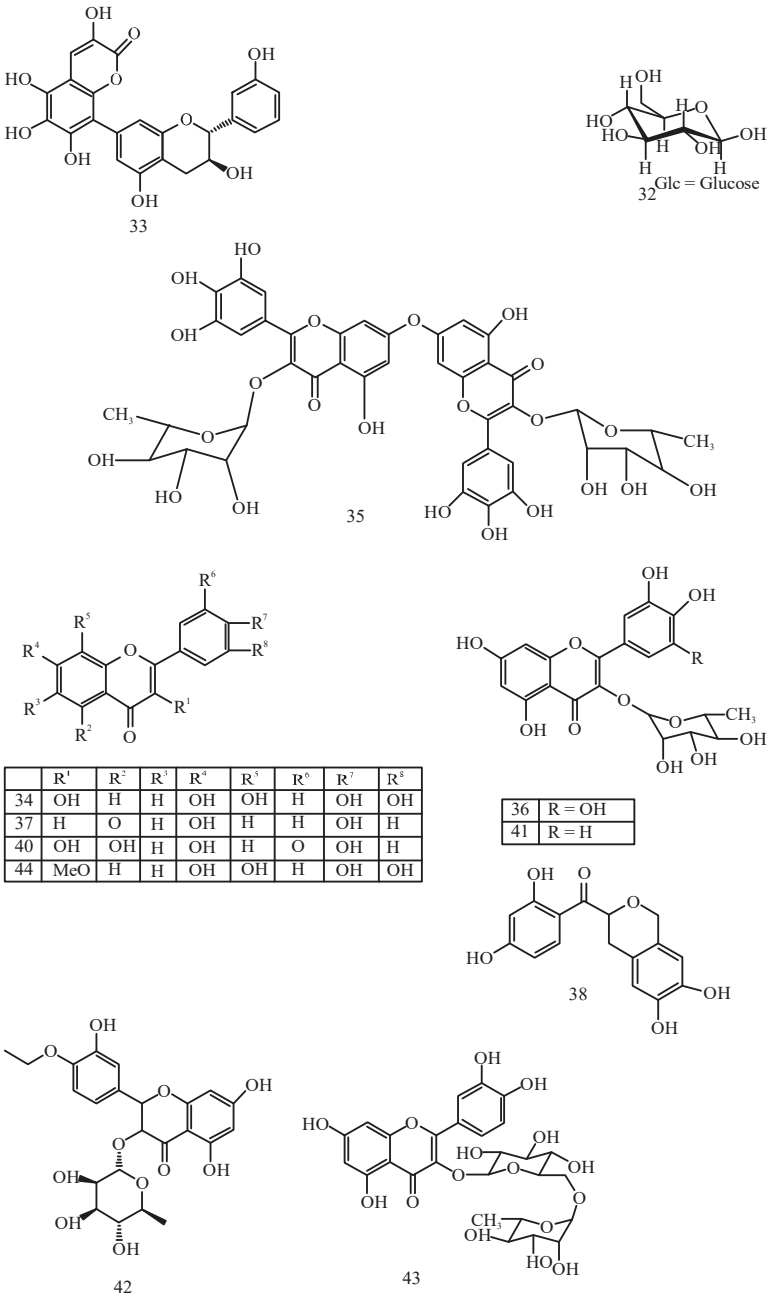


Fig. 1: Continue



	R¹	R²	R³	R⁴	R⁵	R⁶	R⁷	R⁸
34	OH	H	H	OH	OH	H	OH	OH
37	H	O	H	OH	H	H	OH	H
40	OH	OH	H	OH	H	O	OH	H
44	MeO	H	H	OH	OH	H	OH	OH

36	R = OH
41	R = H

Fig. 1: Flavonoids compounds isolated from species of genus *Acacia*

Acacigenin B (66) from *A. concinna*[39]. Additionally, four sesquiterpenoids (49-52), 2 diterpenoids (47 and 48) and 2 monoterpenoids (45 and 46) were also isolated (Fig. 2).

Phytosterols: The 3-acetyl-β-Sitosterol (75), β-Sitosterol (76) and g-Sitosterol (77) were identified from *A. raddiana, A. modesta* and *A. karroo*[22,36,40]. Compound 78 belonging to the sitosterol derivative was also obtained from *Acacia nilotica*[13] (Fig. 2).

Phenolic derivatives: In the recent years, many phenolic derivatives have been reported from the genus *Acacia*. As showed in Table 1, many gallic acid derivatives (79-81, 88, 90-92 and 94) and coumaric acid derivatives (96 and 97) have been isolated since 2008[13,17-19,21,42,43] (Fig. 3). These phenolic acid derivatives were predominantly isolated from *A. nilotica* and *A. arabica*.

Table 1: Chemical constituents isolated from genus *Acacia*

Class and names	Part	Source	References
Flavonoids			
2′, 4, 4′,-Trihydroxychalcone (Isoliquiritigénin)	Whole plant	*A. nigrescens*	Bate-Smith and Swain[8]
2′, 4′-Dihydroxychalcone	Whole plant	*A. neovernicosa*	Adityachaudhury *et al.*[9]
3,3′,4′,7,-Tetrahydroxyflavylium (1+)	-	*A. nigrescens*	Fourie *et al.*[10]
3,4,2, 3, 4-pentahydroxy-trans-chalcone	Heartwood	*A. confusa*	Wu *et al.*[11]
3,4′,7′,8-Tetrahydroxyflavone	-	*A. obtusifolia*	Clark-Lewis and Dainis[12]
3,7,8,3-tetrahydroxy-4-methoxyflavone	Heartwood	*A. confusa*	Wu *et al.*[11]
3′,4′,7-trimethylquercetin	Leaves	*A. nilotica*	Bai *et al.*[13]
4′,7,8-Trihydroxyflavone	Heartwood	*A. nigrescens*	Malan[14]
5, 7-Dihydroxy-4′-(4-methylbenzyl) isoflavone	Leaves	*A. tortilis*	Muhaisen *et al.*[15]
7,3, 4-trihydroxy-3-methoxyflavone	Heartwood	*A. confusa*	Wu *et al.*[11]
7,3, 4-trihydroxyflavone	Heartwood	*A. confusa*	Wu *et al.*[11]
7,8,3, 4-tetrahydroxy-4-methoxyflavan-3-ol	Heartwood	*A. confusa*	Wu *et al.*[11]
7,8,3, 4-tetrahydroxyflavanone	Heartwood	*A. confusa*	Wu *et al.*[11]
7,8,3, 4-tetrahydroxyflavone	Heartwood	*A. confusa*	Wu *et al.*[11]
7,8,3-trihydroxy-3,4-dimethoxyflavone	Heartwood	*A. confusa*	Wu *et al.*[11]
Acetylated epicatechin (4β-8) catechin	Stem bark	*A. mellifera*	Mutai *et al.*[16]
Catechin	Pods	*A. nilotica* and *A. plicosepalus*	Salem *et al.*[17] and Badr *et al.*[18]
Catechin 5-O-gallate	Pods	*A. nilotica*	Salem *et al.*[17]
Catechin-7,3′-digallate	Pods	*A. nilotica*	Maldini *et al.*[19]
Catechin-7,4′-digallate	Pods	*A. nilotica*	Maldini *et al.*[19]
Catechin-7-gallate	Pods	*A. nilotica*	Maldini *et al.*[19]
Crombeone	Heartwood	*A. crombei*	Brandt *et al.*[20]
Epicatecine-3-gallate	Leaves	*A. arabica*	Biswas *et al.*[21]
Epicatechin	Leaves	*A. karroo*	Nyila *et al.*[22]
Epigallocatechin	Leaves	*A. karroo*	Nyila *et al.*[22]
Fasciculiferin	Heartwood	*A. fasciculifera*	Van Heerden *et al.*[23]
Gallocatechin 5-O-gallate	Pods	*A. nilotica*	Salem *et al.*[17]
Gallocatechin-7,3′-digallate	Pods	*A. nilotica*	Maldini *et al.*[19]
Gallocatechin-7,4′-digallate	Pods	*A. nilotica*	Maldini *et al.*[19]
Gallocatechin-7-gallate	Pods	*A. nilotica*	Maldini *et al.*[19]
Hemiphloin (6-C-glucosylnaringenin)	Perianths	*A. retinoide*	Budzianowski and Skrzypczakowa [24]
Isosalipurposide	Yellow flowers	*A. cyanophylla*	Ghouila *et al.*[25]
Loranthin	Whole plant	*A. plicosepalus*	Badr *et al.*[18]
Melanoxetin	Heartwood	*A. confusa*	Wu *et al.*[11]
Myricetin-3-O-rhamnoside (C7-O-C7) myricetin-3-O-rhamnoside	Leaves	*A. saligna*	Gedara and Galala[26]
Myricetin-3-O-α-L-rhamnoside	Leaves and flower	*A. saligna*	Gedara and Galala[26]
Naringenin	Flowers	*A. nilotica* and *A. sptomentos*	Yagi *et al.*[27], Ghribia *et al.*[28]
Peltochalcone	Heartwood	*A. carnei*	Gottlieb[29] and DE-Soussa[30]
Peltogynin	Heartwood	*A. peuce*	Drewes and Roux[31]
Quercetin	Whole plant	*A. plicosepalus*	Badr *et al.*[18]

Table 1: Continue

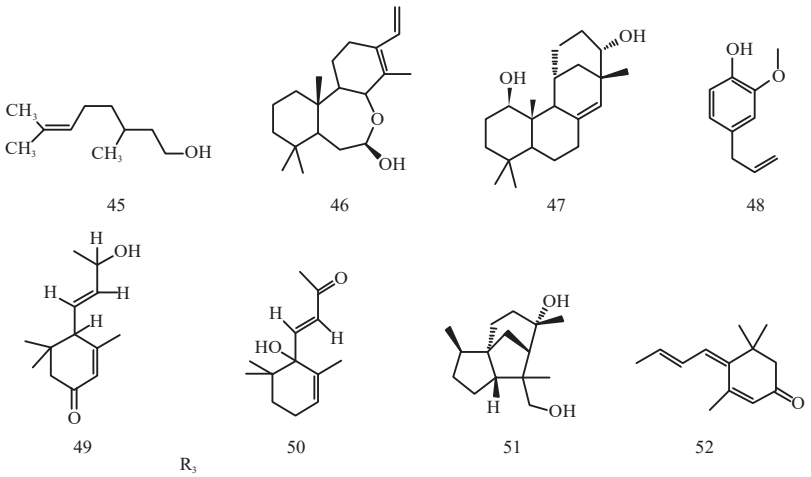
Class and names	Part	Source	References
Quercetin-3-*O*-α-L-rhamnoside	Leaves, flower	*A. saligna*	Gedara and Galala[26]
Quercetin 3-O-(4′-O-acetyl)-rhamnopyranoside	Leaves, bark	*A. arabica*	Biswas *et al.*[21]
Rutin	Whole plant	*A. plicosepalus*	Badr *et al.*[18]
Transilitin	Heartwood	*A. confusa*	Wu *et al.*[11]
Monoterpenoids			
1,3,4-Eugenol	Leaves	*A. nilotica*	Bai *et al.*[13]
Dihydrocitronellol	Leaves	*A. nilotica*	Bai *et al.*[13]
Diterpenoids			
Acaciahemiacetal A	Roots	*A. jacquemontii*	Joshi *et al.*[32]
Leucoxol	Roots bark	*A. leucophloea*	Perales *et al.*[33]
Sesquiterpenoids			
3-Oxo-alpha-ionol	Leaves	*A. nilotica*	Bai *et al.*[13]
4-(1,5-Dihydroxy-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-one	Leaves	*A. nilotica*	Bai *et al.*[13]
Cedrane-8,13-diol	Leaves	*A. nilotica*	Bai *et al.*[13]
Megastigmatrienone	Leaves	*A. nilotica*	Bai *et al.*[13]
Triterpenoids			
(20R)-28-hydroxylupen-30-al-3-one	Stem bark	*A. mellifera*	Mutai *et al.*[34]
(20S)-3β-hydroxylupan-30-al	Stem bark	*A. mellifera*	Mutai *et al.*[34]
(20S)-oxolupane-30-al, (20*R*)-oxolupane-30-al	Stem bark	*A. mellifera*	Mutai *et al.*[34,35]
α-amyrin	Stem bark/root	*A. modesta* and *A. ataxacantha*	Josm *et al.*[36] and Aba *et al.*[37]
28-hydroxy-3-oxo-lup-20-(29)-en-30-al	Stem bark	*A. mellifera*	Mutai *et al.*[38]
28-hydroxy-lup-20-(29)-en-3-one	Stem bark	*A. mellifera*	Mutai *et al.*[38]
3-(E)-cis coumaroylbetulin	Stem bark	*A. mellifera*	Mutai *et al.*[16]
3-(Z)-trans coumaroylbetulin	Stem bark	*A. mellifera*	Mutai *et al.*[16]
30-hydroxylup-20-(29)-en-3-one	Stem bark	*A. mellifera*	Mutai *et al.*[34]
30-hydroxylup-20-(29)-en-3β-ol	Stem bark	*A. mellifera*	Mutai *et al.*[34]
3-hydroxy-lup-20-(29)-en-30-al	Stem bark	*A. mellifera*	Mutai *et al.*[38]
3-oxo-lup-20-(29)-en-30-al	Stem bark	*A. mellifera*	Mutai *et al.*[38]
3-β-O-*trans-p*-coumaroyl-Erythrodiol	Leaves	*A. saligna*	Gedara and Galala[26]
Acacigenin B	Pods	*A. concinna*	Anjaneyulu *et al.*[39]
Betulin	Heartwood/stem bark	*A. raddiana, A. modesta* and *A. mellifera*	Mutai *et al.*[16,38], Josm *et al.*[36] and Singh and Bhargava[40]
Betulinic acid	Stem bark	*A. mellifera, A. ataxacantha*	Mutai *et al.*[38], Anjaneyulu *et al.*[39] and Amoussa *et al.*[41]
Betulinic acid-3-trans-caffeate	Stem bark	*A. ataxacantha*	Amoussa *et al.*[41]
Betulonic acid	Stem bark	*A. mellifera*	Mutai *et al.*[38]
Erythrodiol	Leaves	*A. saligna*	Gedara and Galala[26]
Friedelin	Heartwood	*A. raddiana*	Singh and Bhargava[40]
Lupenone	Stem bark	*A. mellifera*	Mutai *et al.*[38]
Lupeol	Stem bark	*A. mellifera, A. modesta* and *A. ataxacantha*	Mutai *et al.*[16,38] and Amoussa *et al.*[41]

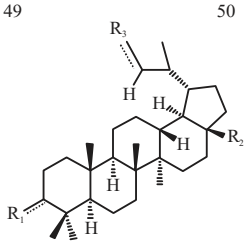
Table 1: Continue

Class and names	Part	Source	References
Phytosterols			
3-Acetyl-β-Sitosterol	Heartwood	*A. raddiana*	Singh and Bhargava[40]
β-Sitosterol	Leaves	*A. karroo*	Nyila *et al.*[22]
γ-Sitosterol	Heartwood, bark	*A. raddiana* and *A. modesta*	Josm *et al.*[36] and Singh and Bhargava[40]
δ-5-Avenasterol	Leaves	*A. nilotica*	Bai *et al.*[13]
Phenolic acids			
1,3-di-O-galloyl-β-D-glucopyranose	Pods	*A. nilotica*	Maldini *et al.*[19]
1,6-di-O-galloyl-β-D-glucopyranose	Pods	*A. nilotica*	Maldini *et al.*[19]
1-O-galloyl-β-D-glucose	Pods	*A. nilotica*	Salem *et al.*[17]
3, 4, 5-trihydroxybenzoate	Bark	*A. arabica*	Biswas *et al.*[21]
3,4-dihydroxybenzoic acid	Heartwood	*A. confusa*	Wu *et al.*[11]
3,4-dihydroxybenzoic acid ethyl ester	Heartwood	*A. confusa*	Wu *et al.*[11]
3,4-dihydroxybenzoic acid methyl ester	Heartwood	*A. confusa*	Wu *et al.*[11]
Caffeic acid phenethyl ester (CAPE)	Leaves	*A. arabica*	Biswas *et al.*[21]
Cinnamic acid	Leaves	*A. nilotica*	Bai *et al.*[13]
Digallic acid	Pods	*A. nilotica*	Salem *et al.*[17]
Ferulic acid	Leaves/bark	*A. arabica*	Biswas *et al.*[21]
Gallic acid	Pods	*A. nilotica* and *A. plicosepalus*	Salem *et al.*[17] and Badr *et al.*[18]
Gallic acid methyl ester	Pods/leaves/bark	*A. farnesiana, A. plicosepalus, A. nilotica* and *A. arabica*	Salem *et al.*[17], Badr *et al.*[18], Biswas *et al.*[21] and Sanchez[42]
Gallic acid methyl ester-4-gallate	Pods	*A. nilotica*	Maldini *et al.*[19]
Homoisocatechin	Heartwood	*A. catechu*	Azad *et al.*[43]
m-Digallic acid	Leaves	*A. confusa*	Arthur and Ko[44]
Methyl 3,4,5-trimethoxybenzoate	Leaves and bark	*A. arabica*	Biswas *et al.*[21]
p-Coumaroyl-glucoside	Leaves and bark	*A. arabica*	Biswas *et al.*[21]
p-Coumaroylquinicacid	Leaves and bark	*A. arabica*	Biswas *et al.*[21]
Phthalic acid	Leaves	*A. nilotica*	Bai *et al.*[13]
Terephthalic acid ester of neopentyl glycol cyclic dimer	Leaves	*A. nilotica*	Bai *et al.*[13]
Fatty acids			
Arachidonic acid	Leaves	*A. nilotica*	Bai *et al.*[13]
Isopropyl palmitate	Leaves	*A. nilotica*	Bai *et al.*[13]
Linolenic acid	Leaves	*A. nilotica*	Bai *et al.*[13]
Linolenic acid, methyl ester	Leaves	*A. nilotica*	Bai *et al.*[13]
Myristic acid	Leaves, bark	*A. nilotica* and *A. arabica*	Bai *et al.*[13] and Biswas *et al.*[21]
Oleic acid	Leaves, bark	*A. arabica*	Biswas *et al.*[21]
Palmitic acid	Leaves, bark	*A. arabica*	Biswas *et al.*[21]
Palmitic acid, ethyl ester	Leaves	*A. nilotica*	Bai *et al.*[13]
Stearic acid	Leaves	*A. nilotica*	Bai *et al.*[13]
Stearic acid ethyl ester	Leaves	*A. nilotica*	Bai *et al.*[13]
γ-Linolenic acid	Leaves	*A. nilotica*	Bai *et al.*[13]

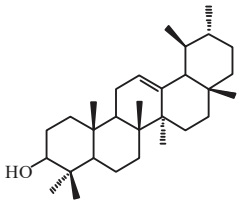
Table 1: Continue

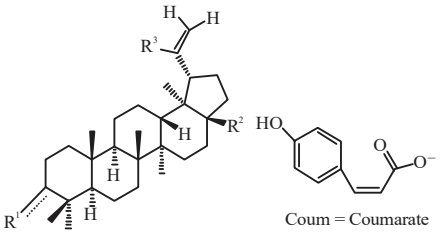
Class and names	Part	Source	References
Hydrocarbons			
1,11-Hexadecadiyne	Leaves	*A. nilotica*	Bai *et al.*[13]
1,54-Dibromotetrapentacontane	Leaves	*A. nilotica*	Bai *et al.*[13]
1-Chlorohexadecane	Leaves	*A. nilotica*	Bai *et al.*[13]
Decane, 3,7-dimethyl	Leaves	*A. nilotica*	Bai *et al.*[13]
Dotriacontane	Leaves	*A. nilotica*	Bai *et al.*[13]
Eicosane	Leaves	*A. nilotica*	Bai *et al.*[13]
Hentriacontane	Stem bark	*A. modesta*	Josm *et al.*[36]
Heptadecane	Leaves	*A. nilotica*	Bai *et al.*[13]
Hexatriacontane	Leaves	*A. nilotica*	Bai *et al.*[13]
Neophytadiene	Leaves	*A. nilotica*	Bai *et al.*[13]
Nonane, 5-(2-methylpropyl)	Leaves	*A. nilotica*	Bai *et al.*[13]
Octacosane	Stem bark	*A. modesta*	Josm *et al.*[36]
Octadecane, 3-ethyl-5-(2-ethylbutyl)	Leaves	*A. nilotica*	Bai *et al.*[13]
Others compounds			
1,3,5-Trisilacyclohexane	Leaves	*A. nilotica*	Bai *et al.*[13]
2-Cyclohexylethylamine	Leaves and stems	*A. rigidula*	Clement *et al.*[45]
2,4 Dimethyl-butylphenol	Leaves	*A. nilotica*	Bai *et al.*[13]
2,6,6-Trimethyl-2-hydroxycyclohexylidene acetolactone	Leaves	*A. nilotica*	Bai *et al.*[13]
2-Methyl-6-methoxy-4,7-benzofurandione	Blackwood	*A. melanoxylon*	Schmalle[46]
2-O-β-L-Arabinofuranosyl-L-Arabinose	Gum	*A. nilotica*	Chalk *et al.*[47]
3',5'-Dimethoxyacetophenone	Leaves	*A. nilotica*	Bai *et al.*[13]
3,7-Dihydroxy-4-methoxy-3-(4′-hydroxybenzyl) chroman	Heartwood	*A. raddiana*	Singh and Bhargava[40]
3-Hydroxy-4-methoxy phenethylamine	Leaves and stems	*A. rigidula*	Clement *et al.*[45]
Acacipetalin	Leaves	*A. stolonifera.*	Rimington[48]
Crombenin	Heartwood	*A. carnie Maiden*	Brandt and Roux[49]
Decyl sulfide	Leaves	*A. nilotica*	Bai *et al.*[13]
Dipalmitin	Leaves	*A. nilotica*	Bai *et al.*[13]
Fasciculiferol	Heartwood	*A. fasciculifera*	Van Heerden *et al.*[23]
Fumaric acid	Leaves	*A. nilotica*	Bai *et al.*[13]
γ-Glutamylalbizziine	Seed	*A. georginae*	Ito and Fowden[50]
γ-Glutamylasparagine	Seed	*A. georginae*	Ito and Fowden[50]
Nilocarbamate : octyl 2-hydroxyph-enylcarbamate	Seed-pod	*A. nilotica*	Mbatchou and Oumar[51]
N-methyltryptamine	Bark	*A. midenii*	Fitzgeral and Sioumis[52]
Octacosanol	Stem bark/heartwood	*A. modesta* and *A. raddiana*	Josm *et al.*[36] and Singh and Bhargava[40]
Oxirane, hexadecyl-(1,2-epoxyoctadecane)	Leaves	*A. nilotica*	Bai *et al.*[13]
Palmitoyl chloride	Leaves	*A. nilotica*	Bai *et al.*[13]
Phenol, 4,4'-methylenebis[2,6-bis(1,1-dimethylethyl)	Leaves	*A. nilotica*	Bai *et al.*[13]
Phosphoric acid, bis(trimethylsilyl)monomethyl ester	Leaves	*A. nilotica*	Bai *et al.*[13]
Phthalic acid, butyloctyl ester	Leaves	*A. nilotica*	Bai *et al.*[13]
Pinitol [(1S,2S,4S,5R)-6-methoxycyclohexane-1,2,3,4,5-pentol]	Stem bark	*A. modesta*	Josm *et al.*[36]
Spirostane saponin: (25S)-5-β-spirostan-3β-yl-3-O-β-D-xylopyranosyl(1-3)-O-β-D-xylopyranosyl(1-4)-β-D-galactopyranoside	Leaves	*A. saligna*	Gedara and Galala[26]
Tryptamine	Bark	*A. simplicifolia*	Shoji *et al.*[53]
Acthaside	Bark	*A. ataxacantha*	Amoussa *et al.*[54]



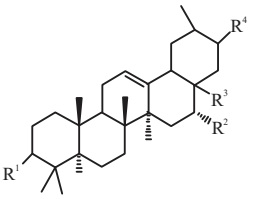


	R^1	R^2	R^3
53	O	MeO	O
54	OH	Me	O
55	O	Me	O

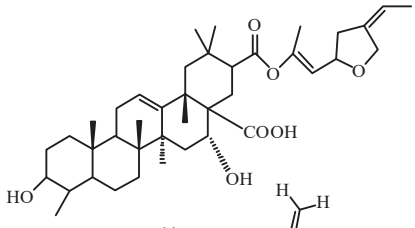


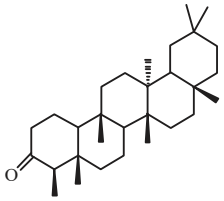


	R^1	R^2	R^3
57	O	MeO	CHO
58	O	MeO	Me
59	Cis-Coum	MeO	H
60	Trans-Coum	MeO	H
61	O	Me	MeO
62	OH	Me	MeO
63	OH	Me	CHO
64	O	Me	CHO
68	OH	MeO	Me
69	OH	COOH	Me
70	O	COOH	Me
73	O	Me	Me
74	OH	Me	Me



	R^1	R^2	R^3	R^4
65	Coum	H	MeO	H
70	OH	H	MeO	H





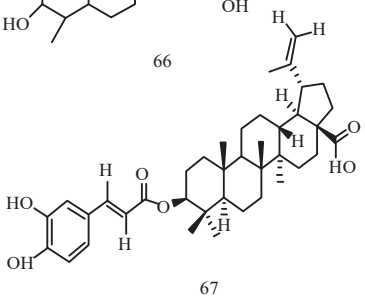
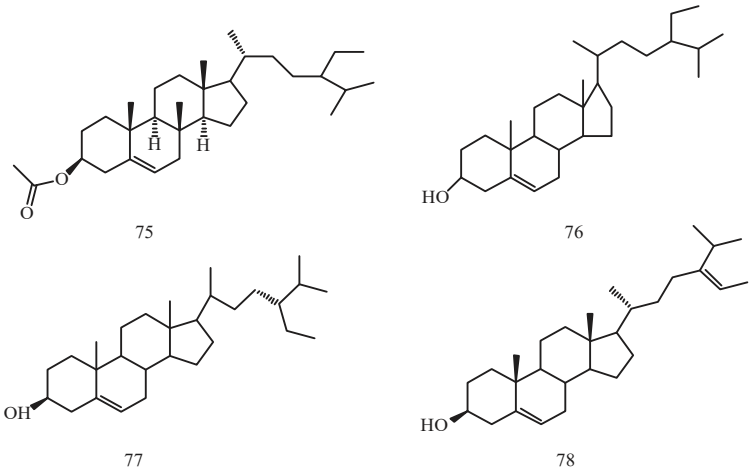


Fig. 2: Continue



75 76 77 78

Fig. 2: Chemical structures of terpenoids and phytosterols isolated from the genus *Acacia*

Fatty acids: The most of fatty acids which were found in the genus *Acacia*, were isolated from *A. nilotica* (100-104, 107-110)[13] and *A. Arabica* (104-106)[21] (Fig. 4).

Hydrocarbons: To date, 13 hydrocarbons, 111-123 have been reported in the genus *Acacia* (Fig. 5), mainly isolated from *A. nilotica* and *A. modesta* species[13,36].

OTHER COMPOUNDS

The others constituents (Fig. 6) found in the genus *Acacia*, contain saponosides such as; Spirostane saponin (150)[26], alkaloids, N-methyltryptamine (142)[52], Tryptamine (151)[53] and peptides, ɣ-Glutamylalbizziine (139), ɣ-Glutamylasparagine (140)[50]. Most of these compounds were isolated from *Acacia nilotica* species. Recently, Acthaside (7-hydroxy-2-methyl-6-[β-galactopyranosyl-propyl]-4H-chromen-4-one), a new chromen derivative (152) was also isolated from *Acacia ataxacantha*[54].

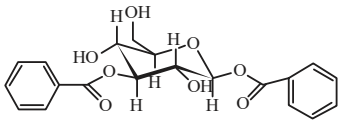
Biological activities: The frequent use of *Acacia* species to treat diseases inspired many search on their pharmacological properties[17-19,22,26]. The secondary metabolites from genus *Acacia* possess multiple biological activities such as; antibacterial, antifungal, antioxidant, anticancer, antiparasitic, antidiabetic, immunomodulatory and cytotoxic (Table 2).

Antimicrobial activity: *Acacia* mellifera is used widely in Africa against various diseases. The stem bark was used in African ethnomedicine for the treatment of diarrhea, eye problems in livestock, pneumonia, malaria, primary infection of syphilis, sterility and stomach ache[55]. Three terpenoids such as (20S)-oxolupane-30-al (55), (20R)-oxolupane-30-al (55′) and betulinic acid (68) were isolated from stem bark of this specie. The antibacterial activity of these compounds was conducted by using disc diffusion method on Mueller-Hinton agar against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and clinical isolates of *Enterococcus feacalis*. At a concentration of 1 mg mL^{-1}, these 3 triterpenoids showed antibacterial activity against *S. aureus* with inhibition zones (IZD) of 10, 10 and 9 mm for compounds 55, 55′ and 68, respectively[35]. In the same study, the authors reported that these compounds had no significant activity against *Escherichia coli* ATCC 25922 and clinical isolates of *Enterococcus feacalis*. Amoussa *et al.*[41] isolated betulinic acid-3-trans-caffeate (69) from *Acacia ataxacantha* and also proven its antimicrobial activity against *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus feacalis*, *Pseudomonas aeruginosa* and *Candida albicans* with MIC values ranging from 12.5-50 μg mL^{-1}.

The gallic acid methyl ester (91) isolated from *Acacia farnesiana* exhibited also an appreciable antibacterial activity against 2 references strains of *Vibrio cholera* (569-B and 1837) with the minimum bactericidal concentration values of 30±1 and 50±1 μg mL^{-1}, respectively[42]. Loranthin (33) isolated from *Acacia plicosepalus* by Badr *et al.*[18] possess significant antibacterial activity against *Staphylococcus aureus* (ATCC 6538) with an inhibition zone of 22 mm. Another pathogenic agent, *Listeria monocytogenes* (LMG 21263) was susceptible to flavonoids (Epicatechin 24, epigallocatechin 25) and phytosterol such as; β-sitosterol (76), which were all isolated from *Acacia karrod*'s leaves by Nyila *et al.*[22]. According the results of these authors[22], compound (76) showed a MIC value of 31.25 μg mL^{-1} against *L. monocytogenes* with a bactericidal effect at 125 μg mL^{-1}. Epigallocatechin (25) was active against *L. monocytogenes* with MIC value of

Table 2: Bioactive compounds of *Acacia* species with relevant biological activity

Numbers	Names	Source	Biological activity	Reference
17	Catechin	*A. nilotica*	Anti-cancer	Salem *et al.*[17]
18	Catechin-5-O-gallate	*A. nilotica*	Anti-cancer	Salem *et al.*[17]
19	Catechin-7,3′-di-O-gallate	*A. nilotica*	Antioxidant	Maldini *et al.*[19]
20	Catechin-7,4'-di-O-gallate	*A. nilotica*	Antioxidant	Maldini *et al.*[19]
24	Epicatechin	*A. karroo*	Antibacterial	Sanchez[42]
25	Epigallocatechin	*A. karroo*	Antibacterial	Sanchez[42]
27	Gallocatechin-5-O-gallate	*A. nilotica*	Anti-cancer	Salem *et al.*[17]
32	Isosalipurposide	*A. cyanophylla*	Antioxidant	Ghribia *et al.*[28]
33	Loranthin	*A. plicosepalus*	Antibacterial, antioxidant	Badr *et al.*[18]
34	Melanoxetin	*A. confusa*	Inflammatory Mediator	Wu *et al.*[11]
35	Myricetin-3-O-rhamnoside (C7-O-C7) myricetin-3-O-rhamnoside	*A. saligna*	Antioxidant, cytotoxicity	Gedara and Galala[26]
36	Myricetin-3-O-α-L-rhamnoside	*A. saligna*	Antioxidant, cytotoxicity	Gedara and Galala[26]
41	Quercetin-3-O-a-L-rhamnoside	*A. mellifera*	Cytotoxicity	Gedara and Galala[26]
55,55′	(20S) and (20R)-oxolupane-30-al	*A. mellifera*	Antibacterial	Mutai *et al.*[35]
57	28-hydroxy-3-oxo-lup-20-(29)-en-30-al	*A. saligna*	Cytotoxicity	Mutai *et al.*[38]
63	3-hydroxy-lup-20-(29)-en-30-al	*A. mellifera*	Cytotoxicity	Mutai *et al.*[38]
65	3b-O-trans-p-coumaroyl- erythrodiol	*A. saligna*	Cytotoxicity	Gedara and Galala[26]
67	Betulin	*A. mellifera*	Antimalarial	Mutai *et al.*[16]
68	Betulinic acid	*A. mellifera*	Antibacterial	Mutai *et al.*[35]
69	Betulinic acid-3-trans-caffeate	*A. ataxacantha*	Antibacterial, antifungal, antioxidant	Amoussa *et al.*[41]
71	Erythrodiol	*A. saligna*	Cytotoxicity	Gedara and Galala[26]
76	β-sitosterol	*A. karroo*	Antibacterial	Nyila *et al.*[22]
90	Gallic acid	*A. nilotica*	Anti-cancer	Salem *et al.*[17]
91	Gallic acid methyl ester	*A. farnesiana*	Antibacterial	Azad *et al.*[43]
141	Nilocarbamate	*A. nilotica* Willd	Antifungal	Shoji *et al.*[53]
150	Spirostane saponin	*A. saligna*	Cytotoxicity	Gedara and Galala[26]
152	Acthaside	*A. ataxacantha*	Antibacterial, antifungal, antioxidant	Amoussa *et al.*[54]



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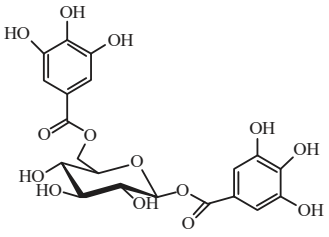

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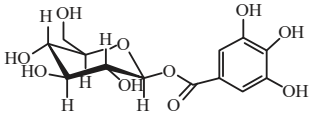

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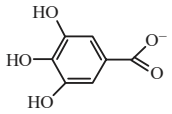

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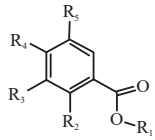
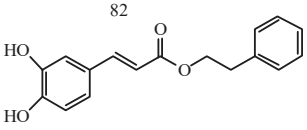
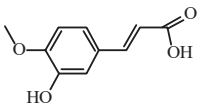




86

	R^1	R^2	R^3	R^4	R^5
83	H	H	OH	OH	H
84	Et	H	OH	OH	H
85	Me	H	OH	OH	H
90	H	H	OH	OH	OH
91	Me	H	OH	OH	OH
98	H	COOH	H	H	H
99	H	H	H	COOH	H



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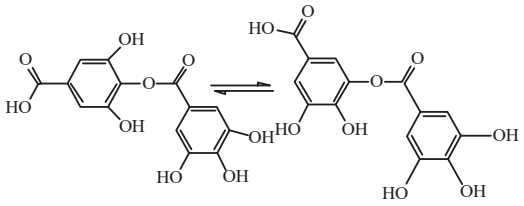

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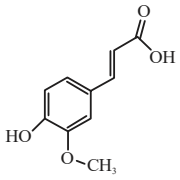

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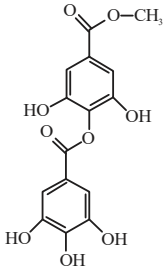

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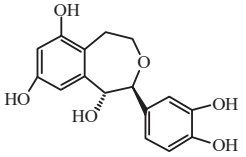

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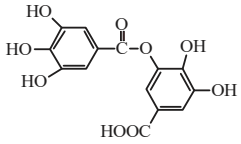

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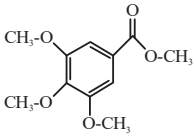

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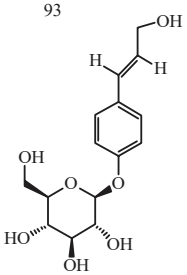

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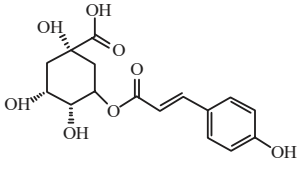

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Fig. 3: Chemical structures of phenolic acids isolated from the genus *Acacia*

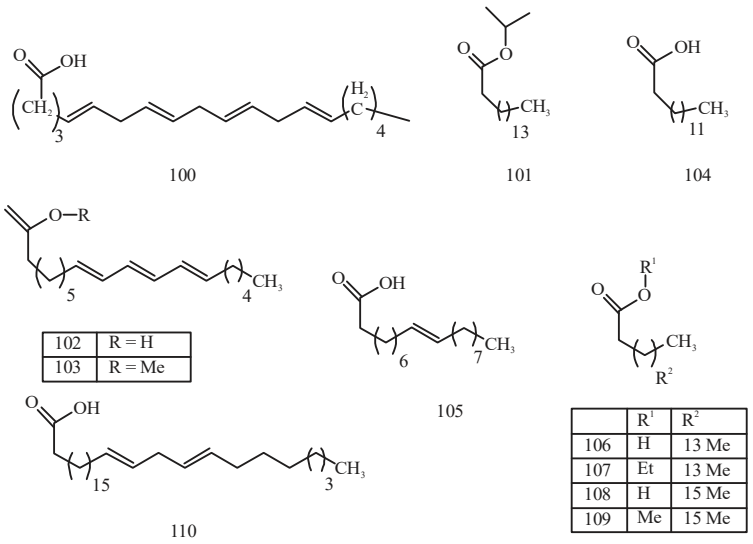

Fig. 4: Chemical structures of fatty acids isolated from the genus *Acacia*

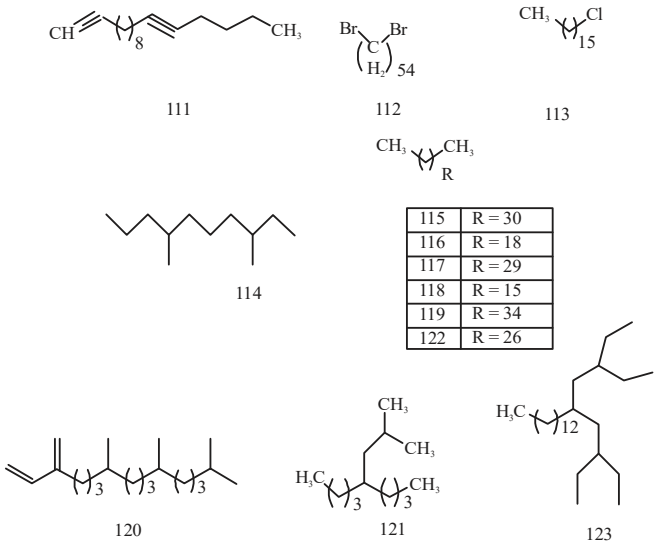

Fig. 5: Chemical structures of hydrocarbons isolated from the genus *Acacia*

0.062 mg mL^{-1} while, Epicatechin (24) was less active (MIC >0.5 mg mL^{-1}). In addition, the selectivity index (SI = IC_{50}/MIC) of compound 76 (2.05) was higher than that of compounds 25 (0.466). *Acacia nilotica* is another species almost ubiquitously found in different parts of the world. This species has been recognized in folk medicine for its traditional use in the treatment of various chronic and non-chronic diseases[55]. Interesting studies concerning antifungal activity of *A. nilotica* was recently reported by Sharma *et al.*[56]. The crude hexane extract from the stem-bark of *A. nilotica* was tested for the antifungal activity against important phytopathogens, *Alternaria brassicae*, *Fusarium oxysporum ciceris* and *Rhizoctonia solani* by food poison method. The results showed that the crude hexane extract presented mycelial inhibition against *Rhizoctonia solani* (58.04%) followed by *Alternaria brassicae* (51.85%) and *Fusarium oxysporum* (46.09%). Mbatchou and Oumar[51] reported that Nilocarbamate (141) from the seed-pod of *A. nilotica* showed significant activity against *Aspergillus fumigatus* (IZD = 9 mm) at 500 µg/disc while *Candida albicans* was resistant to nilocarbamate. On the other hand, Mutai *et al.*[35] reported that the triterpenoïd 55 was active against a frequent pathogen of dermatophytose, *Microsporum gypseum* with IZD = 21 mm. Acthaside (7-hydroxy-2-methyl-6-[β-galactopyranosyl-propyl]-4H-chromen-4-one), a new chromen derivative (152) isolated from *Acacia ataxcantha* by Amoussa *et al.*[54] exhibited also a

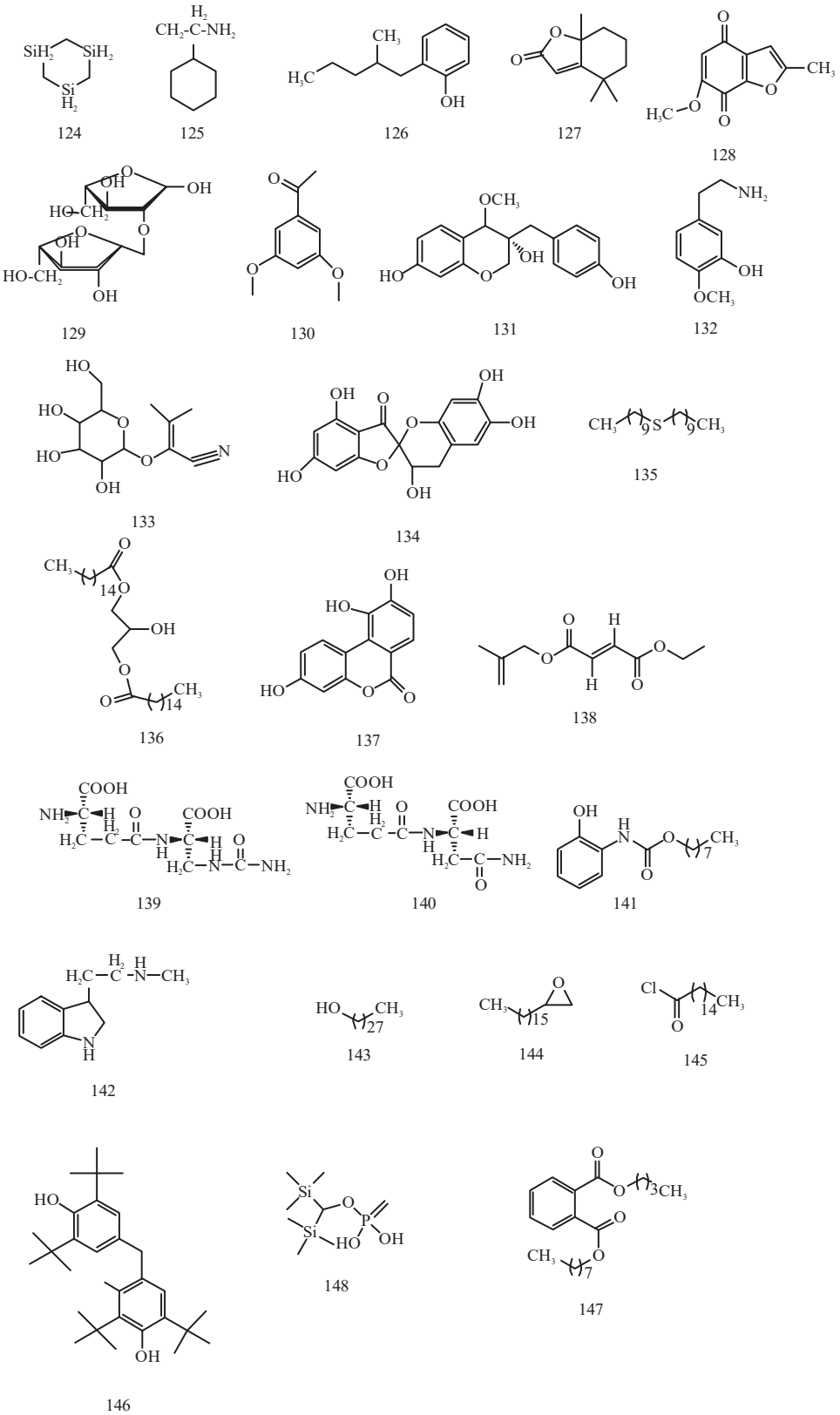

Fig. 6: Continue

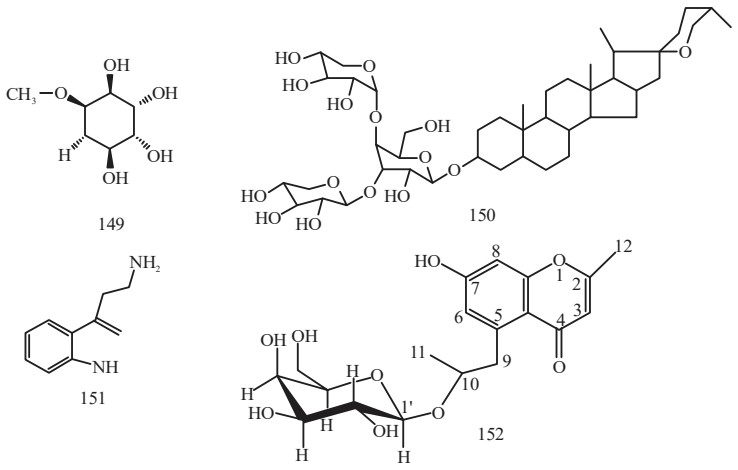

Fig. 6: Chemical structures of others compounds isolated from the genus *Acacia*

significant antibacterial activity against 6 references microorganism strains such as; *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Staphylococcus aureus* Methicillin Resistant, *Pseudomonas aeruginosa* and *Candida albicans* with the minimum bactericidal concentration values ranging from 25-50 μg mL^{-1}.

Antimalarial activity: Many reports on natural products from various species were made in order to fight parasitic diseases. Some authors were interested in the study of antiprotozoal activities of extracts and molecules from the genus *Acacia*. *Plasmodium falciparum* and *Plasmodium berghei* were the most studied. Mutai *et al.*[16] found that dichloromethane extract of aerial parts from *Acacia karroo* showed moderate activity (IC_{50} = 60.0±12.3 μg mL^{-1}) against *Plasmodium falciparum* 3D7 strain. Likewise, betulin (67) isolated from the stem bark of *Acacia mellifera* demonstrated considerable antimalarial activity in mice infected with *Plasmodium berghei* parasites. Parasitemia inhibition percentage of 67 was 33.37% with a chemosuppression percentage of 24.80%.

Antioxidant activity: *Acacia* species are rich source of polyphenolic compounds known for their strong antioxidant properties that help in prevention and therapy of various oxidative stress related diseases including cardiovascular, neurodegenerative and cancer. Antioxidant activity has been intensively evaluated on *Acacia* species by several authors with *in vitro* assays using radicals such as 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis[3-ethylbenzothiazoline-6-sulphonic acid] (ABTS).

Ghribia *et al.*[28] reported that isosalipurposide (32), a secondary metabolite contained in flower extracts of *Acacia cyanophylla* showed antioxidant activity against DPPH at 981.90 μg mL^{-1} and ABTS radical cation at 310.34 μg mL^{-1}. In other hand, 32 exhibited an acetylcholinesterase inhibitory activity with IC_{50} value[28] of 52.04 μg mL^{-1}. Another polyphenolic, Loranthin (33) showed interesting free radical scavenging activity as it displayed 38.5% inhibition when using DPPH reagent[18]. Catechin derivatives such as; Catechin-7,3'-di-O-gallate (19) and Catechin-7,4'-di-O-gallate (20) presented also the strongest scavenging activity towards ABTS radical, with TEAC (Trolox Equivalent Antioxidant Capacity) values of 3.11 mM, 3.05 mM, respectively[19]. Gedara and Galala[26] found that Myricetin-3-O-rhamnoside (C7-O-C7) myricetin-3-O-rhamnoside (35) and myricetin-3-O-α-L-rhamnoside (36) showed potent free radical scavenging capacities. Recently, Amoussa *et al.*[41] found that betulinic acid-3-trans-caffeate (69) isolated from *Acacia ataxacantha* had interesting antioxidant activity with an IC_{50} of 3.57 μg mL^{-1} on DPPH radicals. A new chromen derivative (152) isolated from the same specie has also significant antioxidant activity with an IC_{50} value of 3.61±0.12 μg mL^{-1} in DPPH essay[54].

Anticancer activity: Plants have an almost unlimited capacity to produce substances that attract researchers in the quest for new and novel chemotherapeutics[57]. The antitumor area has the greatest impact of plant derived drugs, where drugs like vinblastine, vincristine, taxol and camptothecin have improved the chemotherapy of some cancers[58]. The continuing search for new anticancer compounds in plant medicines and traditional foods is a realistic and promising strategy for its prevention[59]. Thus, the search for anticancer molecules from plant biodiversity continues and species of the genus *Acacia* have not escaped this wave of investigation on natural anticancer molecules. *Acacia nilotica* is a thorny tree that produces pods with a characteristic beaded necklace

appearance[17]. Anti-uveal melanoma activity-guided fractionation of methanol extract of pods of this species led to the isolation of Catechin (17), Catechin-5-O-gallate (18), Gallocatechin 5-O-gallate (27) and Gallic acid (90) by Salem *et al.*[17]. The authors evaluated activities of these compounds towards the uveal melanoma cell lines 92.1 and OCM3. Gallic acid (90) was the most active with an IC_{50} value of 1.6 and 3.3 μg mL^{-1}, respectively. Gallocatechin 5-O-gallate (27) displayed similar activity as the standard anti-cancer drug, epigallocatechin 3-O-gallate, with IC_{50} values of 4.8 and 5.1 μg mL^{-1} towards cell lines 92.1, 11 and 8.2 μg mL^{-1} towards OCM3. Catechin-5-O-gallate (18) was less active while catechin (17) had weak activity indicating the importance of the presence of galloyl moieties[17]. Additionally, different parts of this plant have been used. Recent literature investigated the biological activities of this species including its antioxidant and chemopreventive[60], antidiabetic and hypolipidemic[61], antileishmanial[62], antiplasmodial[63] and molluscicidal activities[64].

Anti-diabetic activity: Diabete is considered as one of the five leading causes of death in the world. Apart from currently available therapeutic options, many herbal medicines have been recommended for the treatment of diabetes[65,66]. Several biological studies were performed on the effect of extracts on species of genus *Acacia*. Thus, by a process of release of insulin by the pancreatic beta cells, the injection of seeds of *Acacia arabica* (2, 3 and 4 g kg^{-1}, p.o.) exerts an important hypoglycemic effect in rabbits[67]. In streptozotocin-nicotinamide induced diabetic rats, the aqueous extract of *Acacia tortilis* polysaccharide (AEATP) showed significant reduction blood glucose level after 7 days of administration of AEATP at 500 and 1000 mg kg^{-1} compared to untreated diabetic rats[68]. On the other hand, the administration of the ethanolic extract of the bark of *Acacia ataxacantha* (125 mg kg^{-1}, b.wt.) leads to a significant reduction in fasting blood sugar level in streptozotocin-induced diabetic rats model[69]. These results were correlated with the fact that there was a significant difference in the hepatic glucose and glycogen levels in all the treatment groups compared to the normal control[69].

Immunomodulatory activity: Many herbal medicines extracts or combinations of medicinal plants may have activities on one or more cytokines[70]. Herbal medicines can favorably regulate the entire immune system due to their capacities control the immune system in a pleiotropic manner and this, by induction of a regulatory T cell subset and certain macrophages types[71]. No immunomodulatory study has been done on compounds isolated from the genus *Acacia*[72]. The only studies found in the literature concerning the extracts of some species. Indeed, the role of Hot Aqueous Extract (HAE) of the leaves of *Acacia nilotica* in splenocyte stimulation to influence immune response and cytokine induction was reported. Splenocytes treated with HAE *in vitro* revealed 24.78, 6.21, 6.69, 8.15 and 11.86% reduction in the IL-10 secretion at dose rate of 31.25, 62.5, 125, 250 and 500 g mL^{-1} HAE of *A. nilotica* leaves, respectively[55].

Cytotoxicity: Many families of secondary metabolites are found in the leaves, bark and heartwood of *Acacia* species. Cytotoxicity of compounds isolated from these species was reported. Several compounds isolated from *Acacia saligna* and *Acacia mellifera* present a potent cytotoxic effect. Erythrodiol (71), 3b-O-trans-p-coumaroyl-erythrodiol (65), quercetin-3-O-a-L-rhamnoside (41), myricetin-3-O-a-L-rhamnoside (36), spirostane saponin (150) and biflavonoid glycoside myricetin-3-O-rhamnoside (C7-O-C7) myricetin-3-O-rhamnoside (35) were isolated from the leaves of *Acacia saligna*[26]. The cytotoxic activity of these compounds was evaluated by Sulforhodamine B (SRB) screening assay[26]. These authors showed that compound 150 exhibited a potent cytotoxic activity with IC_{50} of 2.8 μg mL^{-1}. Compounds (71) and (65) exhibited a moderate cytotoxicity (IC_{50} = 11.0 and 11.2 μg mL^{-1}), respectively. According to authors, these results indicated that, the factor which increased the cytotoxic potential of erythrodiol (71) is the acetylation. However, the acylation with a coumaroyl moiety at C-3 had no significant role on the cytotoxic activity of erythrodiol. In addition, flavonoids glycosides 36, 41 and 35 exhibited a weak cytotoxicity (IC_{50} =14, 17.2 and 17.8 μg mL^{-1}), respectively. Others compounds isolated from stem bark of *Acacia mellifera* by Mutai *et al.*[38] showed also cytotoxicity activity. It is the case of 28-hydroxy-3-oxo-lup-20-(29)-en-30-al (57) and 3-hydroxy-lup-20-(29)-en-30-al (63). Metabolites (57) and (63) showed significant cytotoxicity against NSCLC-N6 cell line derived from a human non-small-cell broncho-pulmonary carcinoma[38]. Anti-tumoral effect of compounds (18) and (27) were also assessed for their cytotoxicity towards the normal ARPE-19 cells where they showed no significant cytotoxicity, indicating their selectivity for tumor cells[17].

OTHER ACTIVITIES

Acacia confusa has been recognized for its strong capacity to reduce the production of Nitric Oxide (NO)[11]. The 28% of NO production in lipopolysaccharide (LPS)-activated RAW 264.7 macrophages was inhibited in the ethanolic extract-treated cells at 50 μg mL^{-1}. Among all fractions derived from this extract, the ethyl acetate (EtOAc) fraction exhibited

the best inhibitory activity[11]. Compound (34) isolated from EtOAc fraction of this species markedly suppressed (-60%) the PGE2 production in LPS-stimulated RAW 264.7 cells at a dose of 100 μM. As reported by Ghribia *et al.*[28], butanolic extract of *A. cyanophylla* showed anti-acetylcholinesterase activity with the IC_{50} value of 16.03 μg mL^{-1}. Isosalipurposide (32), isolated from *A. cyanophylla* by the same authors was also found to be active against acetylcholinesterase with an IC_{50} value of 52.04 μg mL^{-1}. Recently, preliminary studies carried out on *Acacia hockii*, another *Acacia* species, have shown significant antimicrobial and antioxidant activities[73,74]. This species constitute new avenues for the discovery of new bioactive compounds. Several other species of the genus *Acacia* remain to be investigated[75].

CONCLUSION

Phytochemical investigations on the species of the genus *Acacia* led to the isolation of more than 152 natural compounds during previous years. The predominant constituents isolated from plant extracts of the genus *Acacia* were mainly flavonoids, terpenoids and phenolic derivatives. The most studied species for their chemical constituent were *A. nilotica*, *A. mellifera* and *A. Arabica*. *Acacia ataxacantha*, *A. crombie*, *A. tortilis* and *A. simplicifolia* were the least studied species of the genus *Acacia*. Biological studies on pure chemical constituents and some crude extracts indicated antimicrobial, anti-parasitic, antioxidant, antidiabetic, anti-cancer and cytotoxicity activities. To fully exploit the therapeutic value of the genus *Acacia*, the least studied species of this genus should be subject to further research because they could be a significant source of new molecules with interesting biological properties.

SIGNIFICANCE STATEMENTS

The discovery of new herbal medicines is currently becoming difficult due to several obstacles, namely the lack of knowledge of the most active family, genus and species and necessary for a thorough investigation. The class of compound to search it's also of utmost importance. The chemical diversity of the *Acacia* species as well as their pharmacological properties are discussed in this article in order to provide chemical and/or biological information for a better exploitation of the species of this genus. Thus, this present review constitutes for researchers a real track to exploit for the discovery of new natural compounds with pharmacological potentials.

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