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Ethnobotany, Phytochemistry, and Biological Activities of *Taxodium* Rich.

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Abstract: *Taxodium* Rich. is a genus of the family Cupressaceae. The trees are especially prized for their rot and termite resistant wood. *Taxodium* leaves and cones, which are particularly rich in essential oils were used as folk medicine to treat skin, gastro-intestinal, respiratory, inflammation, and infections**.** Preliminary bioactivity assays reported antimicrobial, antitumor, antitermitic, antispasmodic and bronchodilator activities of the extracts or isolates from *Taxodium* but further pharmacological investigations of bioactive compounds are not available. To data, at least 130 compounds have been identified from extant or fossil *Taxodium*. Fifty-seven compounds have been isolated primarily from the cones, leaves, and branches of extant *Taxodium*, with diterpenoids and flavonoids as the major components. At least three major abietane diterpenoids (sugiol (**1**), ferruginol (**2**), and 6,7-dehydroferruginol (**3**)) are also identified in the fossil *Taxodium* by GC/MS. The diterpenoids may be important marker compounds for understanding the evolution of the genus *Taxodium*. However, the taxonomy and evolutionary pattern of *Taxodium* remains elusive until a full understanding of the chemical constituents of all *Taxodium* taxa is determined.

Keywords: *Taxodium*, baldcypress, pondcypress, montezuma cypress, fossil, essential oils, diterpenoids, flavonoids, biological activities, pharmacological activities.

INTRODUCTION

Taxodium Rich. is a genus of Cupressaceae with three extant taxa ranging from the eastern United States through Mexico to Guatemala [1]. The trees are especially prized for their wood, of which the heartwood is extremely rot and termite resistant [2]. *Taxodium* leaves and cones, which are particularly rich in essential oils were used as folk medicine to treat skin, gastro-intestinal, respiratory, inflammation, and infections [3, 4]. *In vitro* assays support some of the medicinal uses but need to be confirmed by further pharmacological investigations and human clinical trials. It is well known that diterpenoids and flavonoids are the main secondary metabolites of this genus and are responsible for some of the bioactivities. To date, a chemical and pharmacological review of *Taxodium* is not available. Hence, the present review is an endeavor mainly focusing on the research reports of the ethnobotany, phytochemistry, and biological and pharmacological properties of the genus *Taxodium*.

ETHNOBOTANICAL USES

It is generally accepted that there are three taxa in the genus *Taxodium*. These three taxa were treated as three separate species *T. distichum* (L.) Rich., *T. ascendens* Brongn., and *T. mexicanum* Carr. (*T. mucronatum* Ten. or *T. huegelii* C. Lawson) [5] as two species, one having two varieties [6, 7]. But more commonly three varieties are recognized under one polymorphic species *T. distichum* (L.) Rich.: var *distichum*, var. *imbricarium* (Nutt.) Croom., and var. *mexicanum* (Carr.) Gord. [1, 8, 9]. Earlier DNA analysis using cleaved amplified polymorphic sequences [10] and allozyme analysis [11] support the treatment of varietal status of *T. ascendens* (*T. distichum* var. *imbricarium*). Recent DNA sequencing and terpenoid analyses support the recognition of *Taxodium* Rich. as a monotypic genus with three varieties under *T. distichum* [12]. In this review, we adopt this classification.

Taxodium distichum var. *distichum* is known as baldcypress and distributed in the eastern United States from Maryland and Illinois south into Florida and Central Texas [13]. *Taxodium distichum* var. *imbricarium*, pondcypress, is native to the southeastern United States from Florida and the Gulf Coast east of Texas, and up the Atlantic coast to North Carolina [13]. *Taxodium distichum* var. *mexicanum*, Montezuma or Mexican cypress, is distributed in much of Mexico, the southernmost Texas of the United States as well as Huehuetenango Department in Guatemala. Both baldcypress and pondcypress are deciduous while Montezuma cypress is semi-evergreen. *Taxodium* trees can grow on rivers, lake margins, swamps, wet poorly drained habitats and are tolerant to various soil conditions and air pollution [14]. These fast-growing and long-lived conifers have been widely used for landscape in many countries. The heartwood of baldcypress is used for building materials, and has been reported to resist the attacks of the subterranean termite, *Coptotermes formosanus* Shiraki [2, 15] (Fig. **1**). The cones and seeds of *Taxodium* tend to be discovered from ancient stratum, and there are several reports of the fossil conifer and sediments of ancient flora [16, 17]. Montezuma cypress is the national tree of Mexico, and in addition to its historical and cultural

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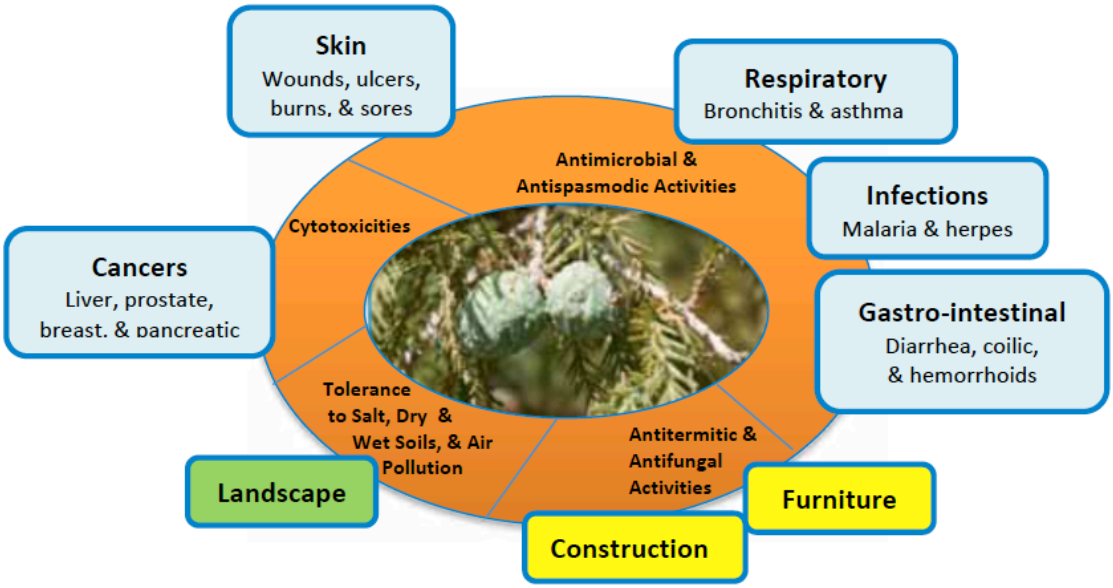

Fig. (1). Bioactivities, ecological features, and uses of *Taxodium*.

importance, it has great ecological value [18]. These trees reach considerable size and age and they are the largest and oldest species of tree in Mexico [19]. *Taxodium* had wide distribution throughout North America, Europe, and East Asia during the Cretaceous until the Pleistocene [10]. Several fossil species have been identified, e.g., *T. wallissii* Aulenback et LePage (late Cretaceous), *T. dubium* (Sternberg) Heer (early Tertiary), and *T. balticum* Sveshn. Et Budants (Eocene) [17, 20].

The leaves and seeds of *Taxodium* have been used for treatment of malaria and liver diseases [21]. The seeds of *Taxodium* have been reported to possess antitumor activities [22, 23]. Several parts of Montezuma cypress were used by the Aztecs; in particular, the gummy resin that can be obtained from a cut tree or its burned wood was used as a medicine. Pieces of the burned bark were placed directly on sores, burns and ulcerations of the skin. In addition, chest pains could be treated and potentially cured by inhaling the smoke from burning wood and branches. Currently, the bark, branches, leaves and cones of this tree are used to create infusions or ointments for the treatment of wounds, gout, cardiac diseases, hemorrhoids, ulcers and varices, to relieve rheumatic pain, or as antispasmodics for the treatment of diarrhea and bronchial problems [3, 4]. Martínez reported that resinous parts of the leaves and cones may effectively treat herpes and leg tumors and reduce inflammation and rapidly resolve articular diseases [24]. Infusions of the leaves have also been reported as hypoglycemic [25]. The only published pharmacological study on this species detailed a vasorelaxant effect of the aqueous extract from the aerial part of the tree [26]. The recorded treatment effects of the medicinal products derived from the *Taxodium* taxa have not been further verified by additional pharmacological or controlled clinical studies.

CHEMICAL CONSTITUENTS

Natural products isolated from plants provide an unparalleled source of chemical diversity for discovery of biologically active molecules. The constituents and functions of *Taxodium* have been investigated by both isolation-to-bioassay and bioassay-guided isolation approaches via various chromatographic techniques including thin layer chromatography (TLC), high performance liquid chromatography (HPLC), ultra performance liquid chromatography (UPLC), gas chromatography (GC), and multidimensional chromatography. Among these techniques, liquid chromatography is used most frequently. This review article covers the reports on 130 compounds isolated or identified from the extant *T. distichum* and the fossil *T. balticum* and *T. dubium*: 23 major compounds from essential oils (Table **1**) and 107 non-essential oil compounds such as diterpenoids, triterpenoids, steroids, lignins, flavonoids, and other compounds (Table **2**). From the cones, seeds, leaves, and branches of the three extant taxa of *Taxodium,* 57 compounds, including 16 diterpenoids (**1**-**14**, **21**, and **22**), two triterpenoids (**26** and **27**), two steroids (**50** and **51**), six lignins (**52**-**57**), 25 flavonoids (**58**-**82**), and six other compounds (**102**-**107**) have been isolated and more than 60 compounds have been identified from the essential oils and four aliphatic lipids (**91**-**94**) by gas chromatography-mass spectroscopy (GC-MS). 50 compounds have been identified from the fossil *T. balticum* and *T. dubium* by GC-MS. Interestingly, four of these compounds including three diterpenoids: sugiol (**1**), feruginol (**2**), and 6,7-dehydroferruginol (**5**) and one steroid *β*-sitosterol (**50**) were also isolated from extant species as major compounds. However, existing data do not provide a complete profile of chemical constituents of *Taxodium* because chemical investigation is limited on extant or fossil taxa. In Tables **1** and **2**, any taxon lacking data of any compound or class of compounds is not an indication that these compounds or class of compounds in the taxon do not exist. Their absence may be due to the incomplete chemical investigation. Thus, it is premature to make chemical comparisons among any extant taxa, fossil species, or between extant and fossil *Taxodium*.

Chemical Composition of Essential Oils

GC is sensitive in detecting volatile chemical compounds or non-volatile compounds readily derivatized. Structural

Table 1. Comparison of the Major Compounds of the Essential oils of *Taxodium distichum* var. *distichum* from Different Regions (by GC/MS Analysis)

Compounds	%						
	Egypt [27]	Nigeria [29]		Italy [28]			China [30]
	Cones	Cones	Leaves	Cones	Leaves	Branches	Cones
α-pinene	87.3	60.5	0.9	71.3	79.7	53.7	
limonene	1.3	1.7		18.7	3.7	6.3	
caryophyllene oxide							41.7
camphene	1.0	0.1		0.7	2.1	2.2	
β-pinene	1.7	2.3		1.3	0.9	0.8	
myrcene	2.0	2.2		2.2	1.7	1.7	
bornyl acetate	0.5	0.9	1.8	1.0	1.5	5.6	6.2
β-caryophyllene		1.6	11.4	1.8	3.5	7.6	
α-humulene			1.7		0.4	0.9	
α-terpineol	0.1		2.6		0.9	1.3	
germacrene D					2.5	1.8	
thujopsene	3.7	17.6	27.7				
β-chamigrene		0.6	1.3				
cuparene	0.3	1.8	6.3				
widdrol		1.9	12.8				
perilla ketone							5.5
3-thujopsanone		0.3	1.2				
α-bisabolol		0.3	2.8				
pimara-8(14),15-diene		0.5	13.1				
abietatriene			2.7				
abietadiene			1.7				
α-asarone							5.5
$C_{15}H_{24}O$		4.0	9.2				

information and selectivity available from mass spectrometry (MS) has made the combination of GC and MS more effective. GC/MS has been used for analysis of volatile organic compounds of the leaves and cones of *T. distichum* var. *distichum* from different locations (Table **1**). The chemical composition of essential oils varies significantly with both plant tissues and geographical location. In Egypt, the cone oil was composed predominately of monoterpenoids with α-pinene as the major compound. 46 compounds were detected from the essential oils obtained by steam distillation (0.8% v/w) from the cone of the baldcypress and the major constituents included α-pinene (87.3%), thujopsene (3.7%), myrcene (2.0%), β-pinene (1.7%), limonene (1.3%), and camphene (1.0%) [27]. The compositions of the essential oil of baldcypress from Nigeria or Italy are similar to that in Egypt. However, the oils in Italy had obviously higher content in limonene and more oxygenated monoterpenoids and sesquiterpenoid hydrocarbons [28]. The oils from Nigeria contained much lower α-pinene level but had higher thujopsene content [29]. Thujopsene was not reported in the sample from Italy. In a Chinese report, α-pinene was not detected in the cones, and the major components are caryophyllene oxide (41.67%), bornyl acetate (6.24%), perilla ketone (5.45%), and α-asarone (5.39%) [30]. These differences in different regions may not represent geographic variations, instead factors such as provenance, local habitat, collection season, and analytical methods may have contributed to the analytical results.

Diterpenoids

Diterpenoids are a class of natural compounds that possess a core skeleton of 20 carbones. Their formation can be rationalized by considering the different types of cyclization of geranylgeranyl diphosphate (GGPP), and they are found

Table 2. Compounds Isolated or Identified from the Extant or Fossil *Taxodium*

No.	Compound	T.D.D.	T.D.M	T.D.I.	T.B*	T.D*	References
	Diterpenoids						
1	sugiol	cones			cones		[15, 16, 28, 31]
2	ferruginol	cones seeds			cones		[15, 16, 28, 31, 32]
3	xanthoperol	cones					[15, 28, 31]
4	5,6-dehydrosugiol	cones					[15, 28, 31]
5	6,7-dehydroferruginol	cones			cones		[15, 16, 28, 31]
6	taxodistine A	cones					[33]
7	taxodistine B	cones					[33]
8	14-deoxycoleon U	cones seeds					[15, 28, 31, 32]
9	salvinolone	cones					[15, 28, 31]
10	taxodione	cones seeds leaves					[15, 31, 32, 34, 35]
11	6,7-dehydro-8-hydrotaxodone	leaves					[34]
12	taxodone	cones seeds					[15, 31, 32, 34, 35]
13	6,7-dehydroroyleanone	cones					[15, 28, 31]
14	taxodal	cones					[15, 28, 31, 36]
15	dehydroabietane				cones		[16]
16	simonellite				cones		[16]
17	retene				cones		[16]
18	dehydroabietol				cones		[16]
19	hinokiol				cones		[16]
20	fichtelite					cones	[28, 31, 33]
21	sandaracopimaric acid	cones					[15, 28, 31]
22	8β-hydroxypimar-15-en-19-oic acid	cones leaves	Cones leaves				[34, 35]
23	α-phyllocabietane				cones		[16]
24	diaromatic totarane				cones		[16]
25	totarol					cones	[16]
	Triterpenoids						
26	cycloneolitsol			leaves			[37]
27	cyclobalanone			leaves			[37]
28	isochamaecydin				cones		[16, 17]
29	chamaecydin				cones		[16, 17]
30	24,25-dinoroleana-1,3,5(10),12-tetraene				cones		[16]
31	24,25-dinorursa-1,3,5(10),12-tetraene				cones		[16]
32	24,25-dinorlupa-1,3,5(10)-triene				cones		[16]

(Table 2) contd….

No.	Compound	T.D.D.	T.D.M	T.D.I.	T.B*	T.D*	References
33	1,2,4a,9-tetramethyl-1,1a,2,3,4,4a,5,6-octahydropicene				cones		[16]
34	2,2,4a,9-tetramethyl-1,1a,2,3,4,4a,5,6-octahydropicene				cones		[16]
35	3,10-dimethyl-3,4-(3'-isopropyl-cyclopenteno)-1,2,3,4-tetrahydrochrysene				cones		[16]
36	homohopane					cones	[16]
37	fernene					cones	[16]
38	friedelin					cones	[16]
39	α-amyrin					cones	[38]
40	β-amyrin					cones	[38]
41	β-amyron					cones	[38]
42	allobetulone					cones	[38]
43	29,30-bisnorneohop-13(18)-ene				cones		[16]
44	22R-17α(H),21β (H)-homohopane				cones		[16]
	Steroids						
45	stigmast-4-ene				cones		[16]
46	stigmast-5-ene				cones		[16]
47	stigmastanol				cones		[16]
48	stigmastanol-3-one				cones	cones	[16, 38]
49	24-ethylcholesta-4,6,22-triene				cones		[16]
50	β-sitosterol		Leaves, branches		cones		[16, 34, 39]
51	campasterol	seeds					[34]
	Lignins						
52	(7'*S*, 8'*S*)-3,3'-dimethoxy-9,4',9'-trihydroxy-4,8'-oxyneolignan-7'-O-β-D-glucopyranoside		leaves branches				[39]
53	(7'*S*, 8'*R*)-4, 7'-epoxy-3, 3'-dimethoxy-4,9,3',4',9'-lignanepentol-4'-O-β-D-glucopyranoside		leaves branches				[39]
54	taxodascendin			leaves branches			[40, 41]
55	cryptoresinol			leaves branches			[40, 41]
56	sequosempervirin B			leaves branches			[41]
57	agatharesinol			leaves branches			[40, 41]
	Flavonoids						
58	3,5,7,3',5'-pentahydroxyflavan			leaves branches			[40]

(Table 2) contd….

No.	Compound	T.D.D.	T.D.M	T.D.I.	T.B*	T.D*	References
59	versulin		leaves				[42]
60	quercetin	leaves	leaves branches				[34, 39, 43]
61	quercetin 3'-methyl ether	leaves					[34]
62	quercetin-3-O-α-L-arabinofuranoside		branches				[42]
63	quercetin-3-O-α-L-arabinofuranoside	leaves branches	leaves branches				[34, 39, 42, 43]
64	avicularin	leaves	leaves branches				[34, 39, 42]
65	flavone,3-hydroxy-3',4',5,7-tetramethoxy-α-L-arabinopyranoside	leaves					[43]
66	isorhamnetin-3-O-α-L-arabinopyranoside	leaves branches	leaves branches				[39, 42, 43]
67	quercetin-3-O-β-glucopyranoside	leaves	leaves				[34, 42]
68	quercetin-3-O-β-D-galactoside	leaves branches	leaves branches				[34, 37, 42]
69	isorhamnetin-3-O-β-galactopyranoside	branches	leaves branches				[34, 42]
70	distichin	leaves					[43]
71	Apigenin-7-O-β-D-glucoside	branches					[42]
72	luteolin-7-O-β-D-glucoside	branches					[42]
73	selgin-7-O- β-D-glucoside	branches					[42]
74	amenthoflavone	leaves	leaves branches				[42, 44]
75	podocarpusflavone A		leaves branches				[44, 45]
76	4''',7''-dimethyl-amentoflavone		leaves branches				[44]
77	bilobetin	leaves					[44, 45]
78	7,4',4'''-trimethyl-amentoflavone	leaves	leaves				[45, 46]
79	hinokiflavone	leaves	leaves				[45, 46]
80	isocryptomerin	leaves	leaves				[45, 46]
81	cryptomerin A		leaves				[45]
82	cryptomerin B		leaves				[45]
	Miscellaneous						
83	*n*-alkanes *n*-C_{14} to *n*-C_{33}				cones	cones	[16, 38]
84	*n*-alkan-2-ones *n*-C_{23} to *n*-C_{33} (odd members)				cones	cones	[16, 38]
85	n-alkanoic acids *n*-C_{24} to *n*-C_{28} (even members)				cones	cones	[16, 38]
86	n-alkanols *n*-C_{22} to *n*-C_{26} (even members)				cones	cones	[16, 38]

(Table 2) contd….

No.	Compound	T.D.D.	T.D.M	T.D.I.	T.B*	T.D*	References
87	*n*-nonacosan-10-ol				cones	cones	[16, 38]
88	*n*-nonacosan-10-one					cones	[38]
89	succinic acid				cones		[16]
90	glutaric acid				cones		[16]
91	palmitic acid	Seeds**					[47]
92	oleic acid	Seeds**					[47]
93	linoleic acid	Seeds**					[47]
94	α-linolenic acid	Seeds**					[47]
95	glycerol				cones		[16]
96	vanillic acid				cones		[16]
97	vanillin				cones		[16]
98	3-hydroxybenzoic acid				cones		[16]
99	4-hydroxybenzoic acid				cones		[16]
100	3,4-dihydroxybenzoic acid				cones		[16]
101	syringic acid				cones		[16]
102	sequoyitol	cones					[43]
103	shilimic acid		branches				[39]
104	shilimic acid methyl ester		leaves branches				[39]
105	koaburside			leaves branches			[41]
106	3,4-dimethoxyphenyl-β-D-glucopyranoside			leaves branches			[41]
107	2-furaldehyde	cones					[48]

T.D.D. = *T. distichum* (L.) Rich. var. *distichum* (synonymy: *T. distichum* var. *nutans* (Aiton) Sweet)
T.D.M. = *T. distichum* (L.) Rich. var. *mexicanum* (Carr.) Gord. (synonymy: *T. mucronatum* Ten. and *T. mexicanum* Carr.)
T.D.I. = *T. distichum* (L.) Rich. var. *imbricarium* (Nutt.) Croom (synonymy: *T. ascendens* Brongn., *Cupressus disticha* L. var. *imbricaria* Nutt.)
T.B. = T. *balticum*
T.D. = T. *dubium*
*identified by GC/MS from the fossil of *T. balticum* or *T. dubium* (Eocene). ** identified by open-tubular GC from the extant *T. distichum* var. *distichum*.

in many different plant families and some animals. Diterpenoids are of interest as many have been found to have biological activity; paclitaxel (taxol), cafestol, and kahweol all display anticancer properties. Diterpenoids isolated from *Taxodium* are a main group. Twenty-five diterpenoids were reported, including 12 compounds from the fossil cones of the *T. balticum* and *T. dubium*. According to their structure, this group is further classified into four types: abietane, pimarane, totarane, and kaurane.

Abietane-type diterpenoids: Abietane-type diterpenoids are widely distributed in the plant kingdom and have antitumor, cytotoxic, antifungal, and antibacterial activities. It is known that the abietane-type diterpenoids are the major compounds in the cones of *Taxodium* species (Table **2**; Fig. **2**). The earlier novel diterpenoid quinone methide tumor inhibitors, taxodione (**10**) and taxodone (**12**) were isolated from *T. distichum* var. *distichum* in 1968 [22]. Other major abietane-type diterpenoids isolated from the cones of *T. distichum* var. *distichum* cones include sugiol (**1**), ferruginol (**2**), 6,7-dehydroferruginol (**5**), taxodistine A (**6**), taxodistine B (**7**), 14-deoxycoleon U (**8**), and salvinolone (**9**) [31, 33, 36]. The irregular abietane-type diterpenoid denominated taxodal (**14**) from the cones of *T. distichum* var. *distichum* [36] is valuable for understanding the biosynthesis of abietane-type diterpenoids in plants. It is interesting to emphasize that sugiol (**1**), ferruginol (**2**), and 6,7-dehydroferruginol (**5**) have been identified in the extract of the fossil *T. balticum* [16, 38].

Pimarane-type diterpenoids: According to the recent report of Porto *et al.* [49], "the pimarane-type diterpenoids can potentially be another important source of secondary plant metabolites for the development of new anti-infective agents against microorganisms responsible for caries disease. In this subgroup, only two pimarane-type diterpenoids

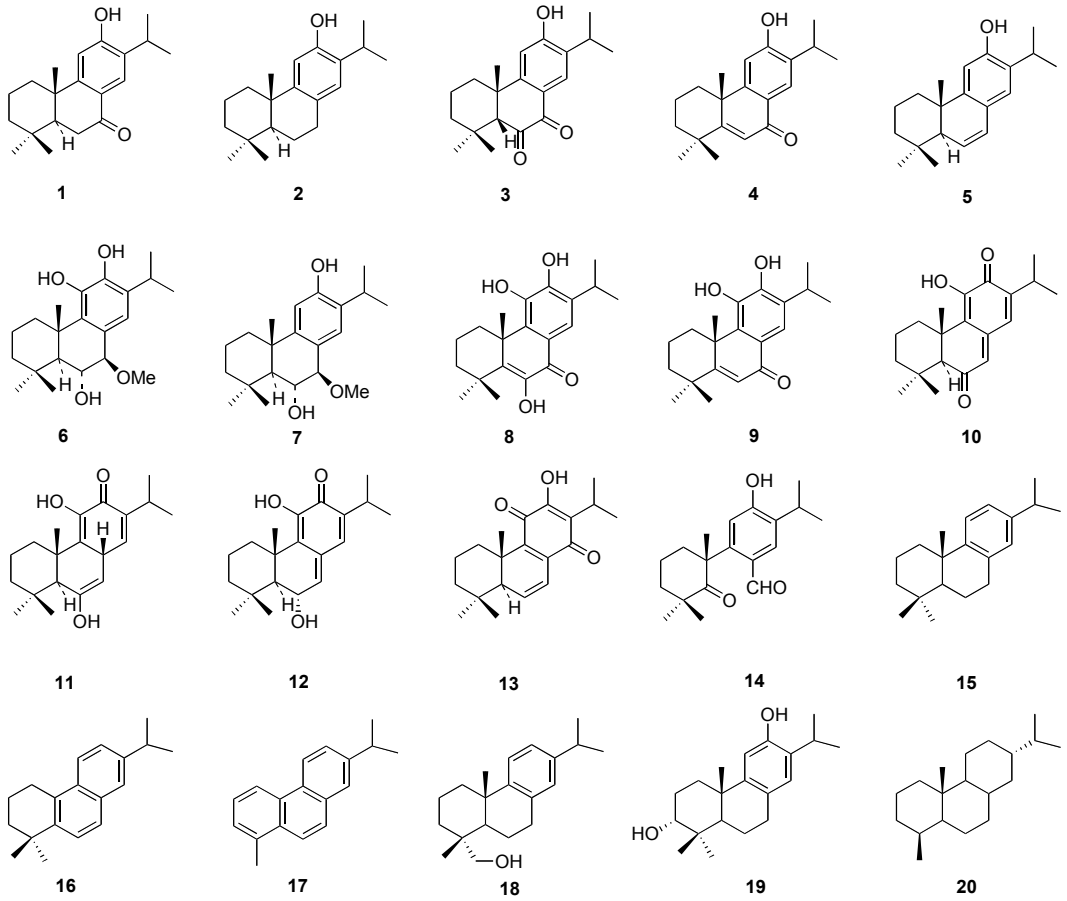

Fig. (2). Abietane-type diterpenoids identified from *Taxodium*.

(Table **2**; Fig. **3**), sandaracopimaric acid (**21**) and 8β-hydroxypimar-15-en-19-oic acid (**22**) were identified from the cones and leaves of *T. distichum* var. *distichum* [28, 37] and the latter was also found in var. *mexicanum* [35].

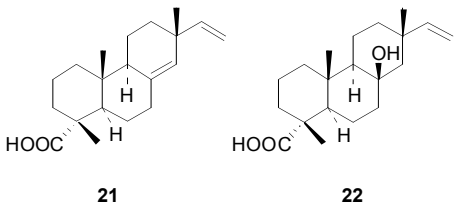

Fig. (3). Pimarane-type diterpenoids isolated from *Taxodium*.

Kaurane- and totarane-type Diterpenoids: These two subgroups are rare in the genus *Taxodium*, only three compounds (Table **2**; Fig. **4**), α-phyllocladane (**23**), diaromatic totarane (**24**), and totarol (**25**), were identified from the fossil *T. balticum* or *T. dubium* by GC-MS analysis [16, 38].

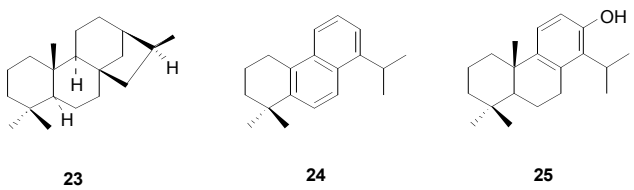

Fig. (4). Kaurane and totarane-type diterpenoids identified from fossil *Taxodium balticum* or *T. dubium*.

Triterpenoids

Most triterpenoids were reported in the fossil *Taxodium* (Table **2**; Fig. **5**). Some aromatic triterpenoids (**28-35**) were detected in the cones of *T. balticum* extracts [16, 17, 38]. Those aromatic triterpenoid hydrocarbons are comprised of monoaromatic derivatives of the oleanane, ursane, and lupine series. Two compounds isochamaecydin (**28**) and chamaecydin (**29**) with a molecular mass of 448 daltons and similar mass spectra are detected as major components in the aromatic fraction from the seed cones of *T. balticum* from clays of the Eocene Zeitz formation in Germany [17]. The fossil cone of *T. balticum* contains two hopanoids, 29,30-bisnorneohop-13(18)-ene (**43**) and 22R-17α(H),21β(H)-homohopane (**44**) [16]. From another fossil species, *T. dubium,* seven triterpenoids (**36-42**) were detected by GC analysis [38].

To date, only two C-32 cycloartane-type triterpenoids, cycloneolitsol (**26**) and cyclobalanone (**27**), were isolated from the leaves of extant *T. distichum* var. *imbricarium* [37]. The presence of cycloartanes in *T. distichum* var. *distichum* may suggest implication for its chemotaxonomic significance in conifers [37].

Steroids

Steroids are also mainly reported in the fossils of *Taxodium* (Table **2**; Fig. **6**). Stigmast-4-ene (**45**), stigmast-5-ene (**46**), stigmastanol (**47**), stigmastanol-3-one (**48**), 24-ethylcholesta-4,6,22-triene (**49**), and β-sitosterol (**50**) were

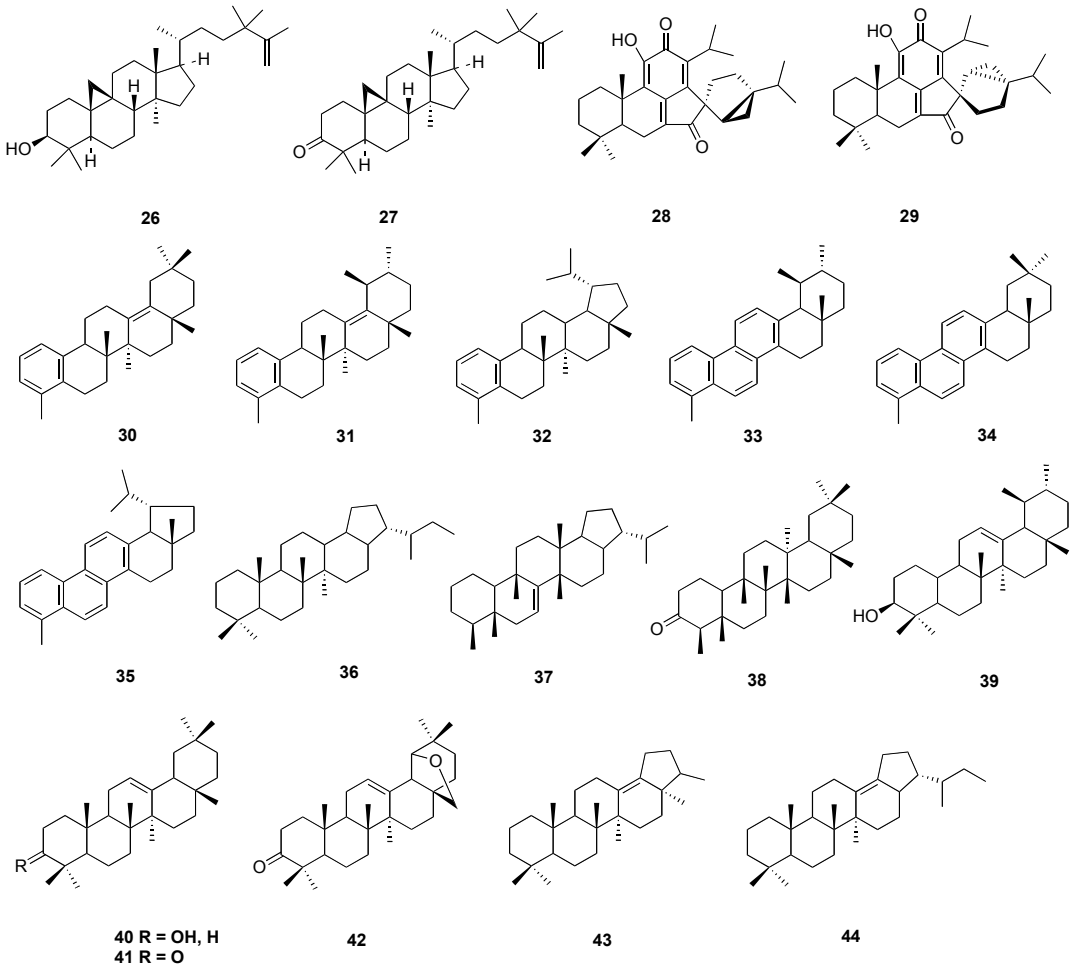

Fig. (5). Triterpenoids identified from *Taxodium*.

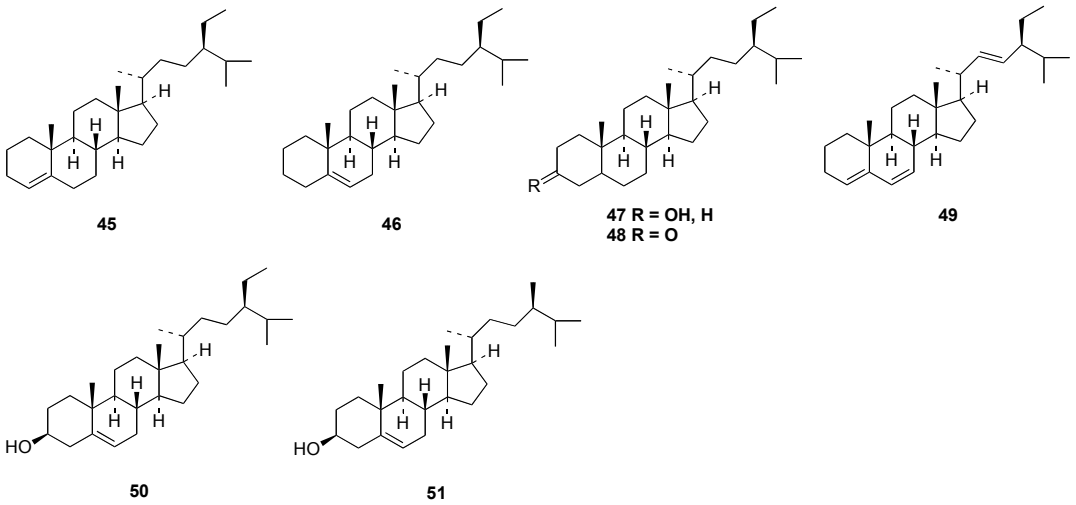

Fig. (6). Steroids isolated from *Taxodium*.

identified from the fossil cones of *T. balticum* with stigmastanol-3-one (**48**) in *T. dubium* [16, 38]. These compounds are nonspecific markers because the biological precursor *β*-sitosterol (**50**) is ubiquitous. *β*-Sitosterol (**50**) and campesterol (**51**) were isolated from the leaves and branches of *T. distichum* var. *mexicanum* and the seeds oil of *T. distichum* var. *distichum*, respectively [34, 39].

Lignins

To data, six lignins have been isolated and identified from the extant *Taxodium* (Table **2**; Fig. **7**). Two lignin derivatives, (7'S, 8'S)-3,3'-dimethoxy-9,4',9'-trihydroxy-4,8'-oxyneolignan-7'-O-*β*-D-glucopyranoside (**52**) and (7'S, 8'R)-4,7'-epoxy-3,3'-dimethoxy-4,9,3',4',9'-lignanepentol-4'-O-*β*-D-glucopyranoside (**53**) have been isolated from the leaves

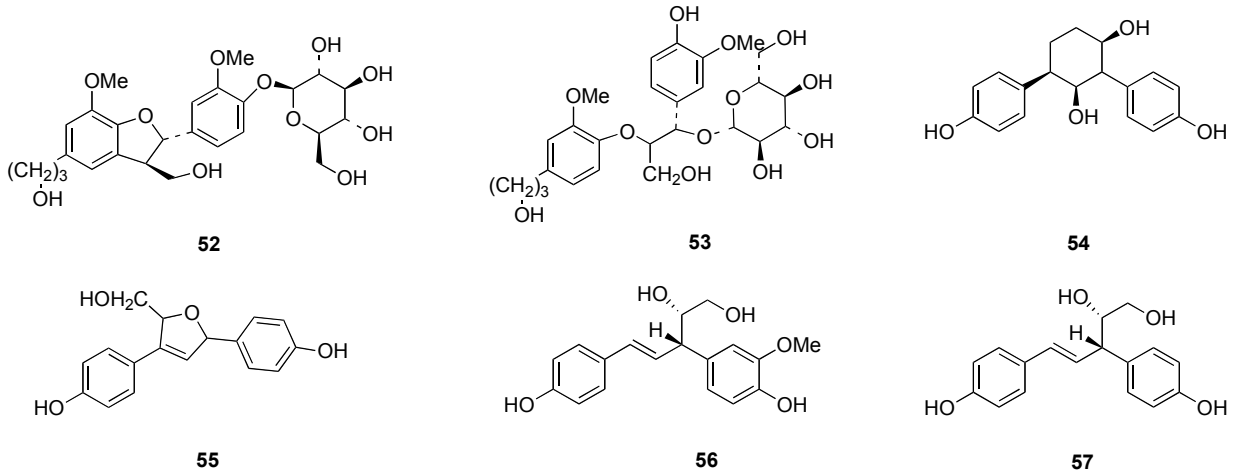

Fig. (7). Lignins isolated from *Taxodium*.

and branches of *T. distichum* var. *mexicanum* [39]. Four norlignans (**54**-**57**) have been isolated from the branches and leaves of *T. distichum* var. *imbricarium* [40, 41]. No report on lignins from *T. distichum* var. *distichum* is available.

Flavonoids

Flavonoids are a group of uniquitous and diverse molecules produced via the phenylpropanoid pathway in higher plants, and about 2% of all the photosynthesized carbon is converted into flavonoids [50]. Flavonoids are one of the main components of the genus *Taxodium*. A total of 25 flavonoids including flavanone, flavone and their glycosides, flavonol and their glycosides, and biflavones have been isolated from extant *Taxodium* (Table **2**; Fig. **8**). The sugars in Table **2** are assumed to be in the furanose form and have the α-linkage for arabinose, and in the pyranose form have the β-linkage for glucoside and galactose. Quercetin (**60**), avicularin (**64**), isorhamnetin-3-arabinoside (**66**), and distichin (**70**), were identified from the leaves of *T. distichum* var. *distichum* [43]. Two flavonoid glycosides, quercetin 3-O-β-D-glucoside (**67**) and quercetin 3-O-β-D-galactoside (**68**) were isolated from extract of leaves of *T. distichum* var. *mexicanum* [35]. Walter *et al.* reported 10 flavone and flavonol glycosides from the branches of *T. distichum* var. *distichum* [42]. Nine biflavones (**74**-**82**) composing of two apigenins or its patial methyl ester via C-C (8-3') or C-O (6-4') linkage were isolated from the leaves and branches of *T. distichum* var. *distichum* and var. *mexicanum* [44-46].

Other Compounds

The aliphatic lipids including *n*-alkanes (*n*-C_{14} to *n*-C_{33}) (**83**), *n*-alkan-2-ones (*n*-C_{23} to *n*-C_{33}) (**84**), *n*-alkanoic acids (*n*-C_{24} to *n*-C_{28}) (**85**), *n*-alkanol (*n*-C_{22} to *n*-C_{26}) (**86**), *n*-nonacosan-10-ol (**87**), and *n*-nonacosan-10-one (**88**), succinic acid (**89**), and glutaric acid (**90**) were identified in the extract of fossil *Taxodium* (Table **2**; Fig. **9**) by GC/MS analysis [16, 38]. Among them, the *n*-nonacosan-10-ol (**87**), and its ketone *n*-nonacosan-10-one (**88**) were abundant in fossils [16, 38]. In addition, polyol (**95**) or polyphenols (**96**-**101**) were detected from the fossil *T. balticum* [16].

Extant *Taxodium* contain chemical components similar to fossils. Open-tubular GC analysis of the seeds of extant *T. distichum* var. *distichum* indicated that palmitic acid (**91**), oleic acid (**92**), linoleic acid (**93**), and α-linolenic acid (**94**) are major lipids with nonmethylene-interrupted polyenoic (NMIP) acids as minor compounds [47]. Sequoyitol (**102**) and shilimic acid (**103**) have been isolated from the leaves of *T. distichum* var. *distichum* [34, 43], and the methyl ester of shilimic acid (**104**) was isolated from the leaves and branches of *T. distichum* var. *mexicanum* (Table **2**) [39]. Two phenylglucosides (**105**-**106**), koaburside and 3,4-dimethoxyphenyl-β-D-glucopyranoside were isolated from the branches and leaves of *T. distichum* var. *imbricarium* [41]. 2-furaldehyde (**107**) was isolated from baldcypress in 1981 [48] (Table **2**; Fig. **9**). It was also reported that *T. distichum* var. *distichum* contains proanthocyanidins in leaves [51], polysaccharides in wood [52], and tannins and polyphenols in wood and bark [53].

BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

Ethnobotanical uses of *Taxodium* have been well documented and there are also interests for further investigation of the *Taxodium* and the isolated compounds in term of modern medicine. The existing biological and pharmacological reports of *Taxodium* are primarily restricted to *in vitro* activities. In fact, the biological and pharmacological properties of *Taxodium* extracts and isolates cannot be fully understood without extensive investigations in the chemical constituents of extant taxa.

Antimicrobial Activities

The essential oil from the cones of baldcypress trees grown exhibited potent antimicrobial activities against bacteria *Bacillus subtilis* (ATCC 6633), *Stapbylococcus aureus* (ATCC 6536), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), *Proteus mirabtlis* (ATCC 4630), *Klebsiella pneumonia* (ATCC 10031), and *Citrbacter diwersus* (CI 98) and the fungus *Candida albicanswas* (ATCC 32354) [27]. However, it is interesting that the oil of the leaves and cones collected from Nigeria exhibited only weak antibacterial activities against *B. cereus* (ATCC 14579), *S. aureus* (ATCC 29213), *P. aeruginosa* (ATCC 27853), and *E. coli* (ATCC 25922) (MIC >150 μg/mL) but potent activity against the fungus *Aspergillus niger* (ATCC

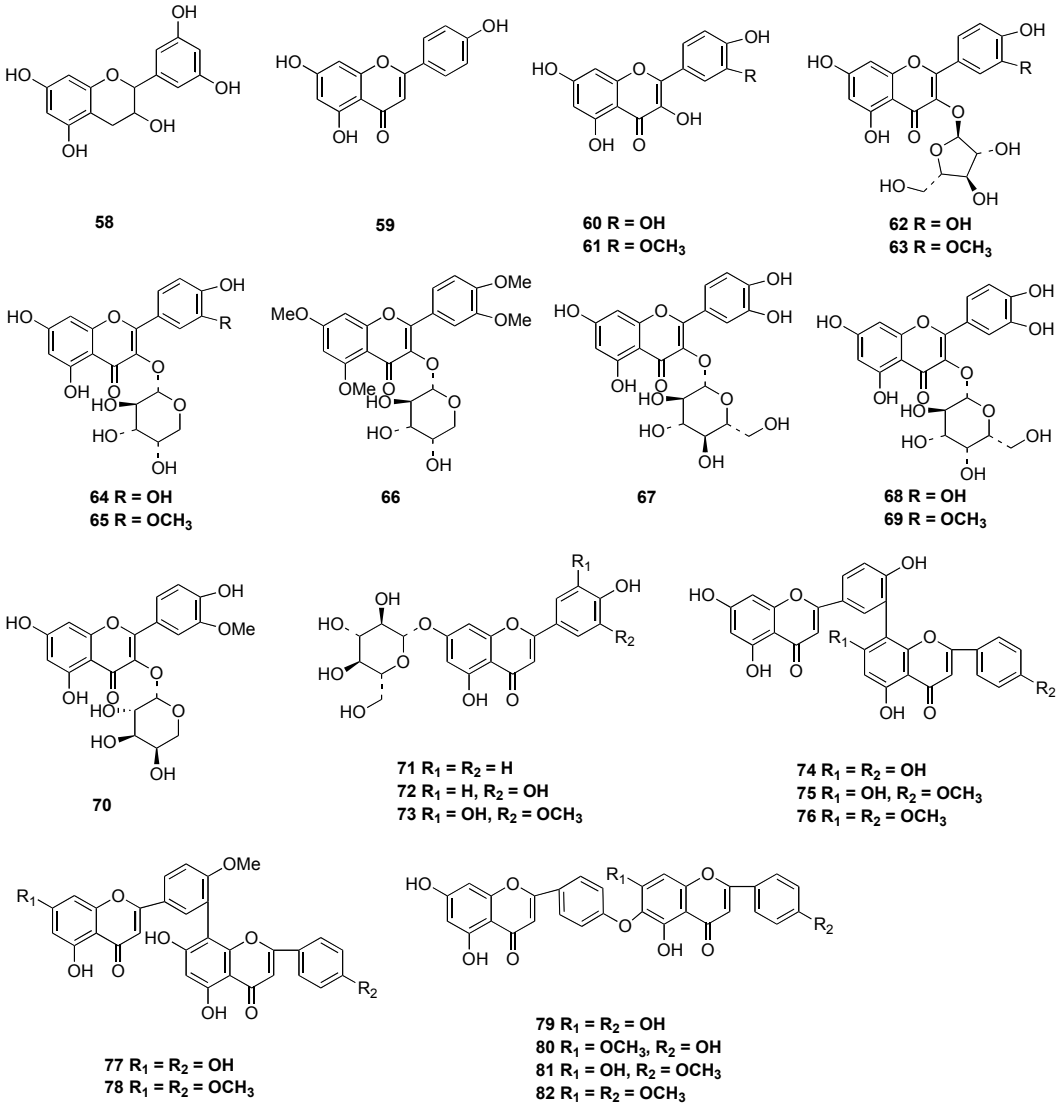

Fig. (8). Flavonoids isolated from *Taxodium*.

16401) (19.5 μg/mL) [29]. The difference in antibacterial activity of the oils between the two reports cannot be simply attributed to the higher content of α-pinene in Egypt samples (Table **1**) because this compound has a weak antibacterial effect [29].

Non-essential oils in *Taxodium* also showed antimicrobial activities. The methanol extract of the Montezuma cypress showed potent antibacterial activity and may have potential in the treatment of gastrointestinal disorders caused by *Helicobacter pylori* [54]. Accumulating evidence indicates that diterpenoids are a group of primary active compounds responsible for antimicrobial activities of *Taxodium*. Two diterpenoids obtained from other sources but commonly occurred in the cones of *Taxodium* showed antibacterial activities. Taxodione (**10**) was reported to exhibit antibacterial activities against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) [31]. Sugiol (**1**) showed antibacterial effect against foodborne pathogens and detrimental effect on morphology of *Listeria monocytogenes* [55]. Taxodione (**10**) and 14-deoxycoleon U (**8**) isolated from the cones of baldcypress were found highly active against both wood-decay fungi *Trametes versicolor* (white-rot) and *Fomitopsis palustris* (brown-rot) [56]. The SAR analysis of the diterpenoids suggests a strong relationship between the positions of hydroxyl group and antifungal activity [28]. Two abietane-type diterpenoids with quinone structures at the C rings, cryptoquinone and 7-hydroxy-11,14-dioxo-8,12-abietadiene, obtained from other sources were also reported to have antifungal activities [22, 23, 31].

Cytotoxicities

There are only few reports on cytotoxicities of extracts or isolates from *Taxodium*. The seeds of baldcypress were reported to possess bioactivities against human tumor cell lines [22, 23, 57]. The cone essential oils of baldcypress can effectively inhibit certain human tumor cells at higher dosage (inhibit 99.77% of prostate tumor PC-3 cells at 100 μg/mL, 100% of liver tumor Hep G2 cells at 250 μg/mL, and 100% of breast (ductal) tumor Hs 578T cells at 250 μg/mL) [29]. Taxodistines A (**6**) and B (**7**) isolated from the cones of baldcypress showed cytotoxicity against murine lymphoma P388 cells at IC_{50} 0.43 and 6.5 μg/mL, respectively [33]. Martínez *et al.* reported that taxodione (**10**) and taxodone (**12**) from resins of the leaves and cones of Montezuma

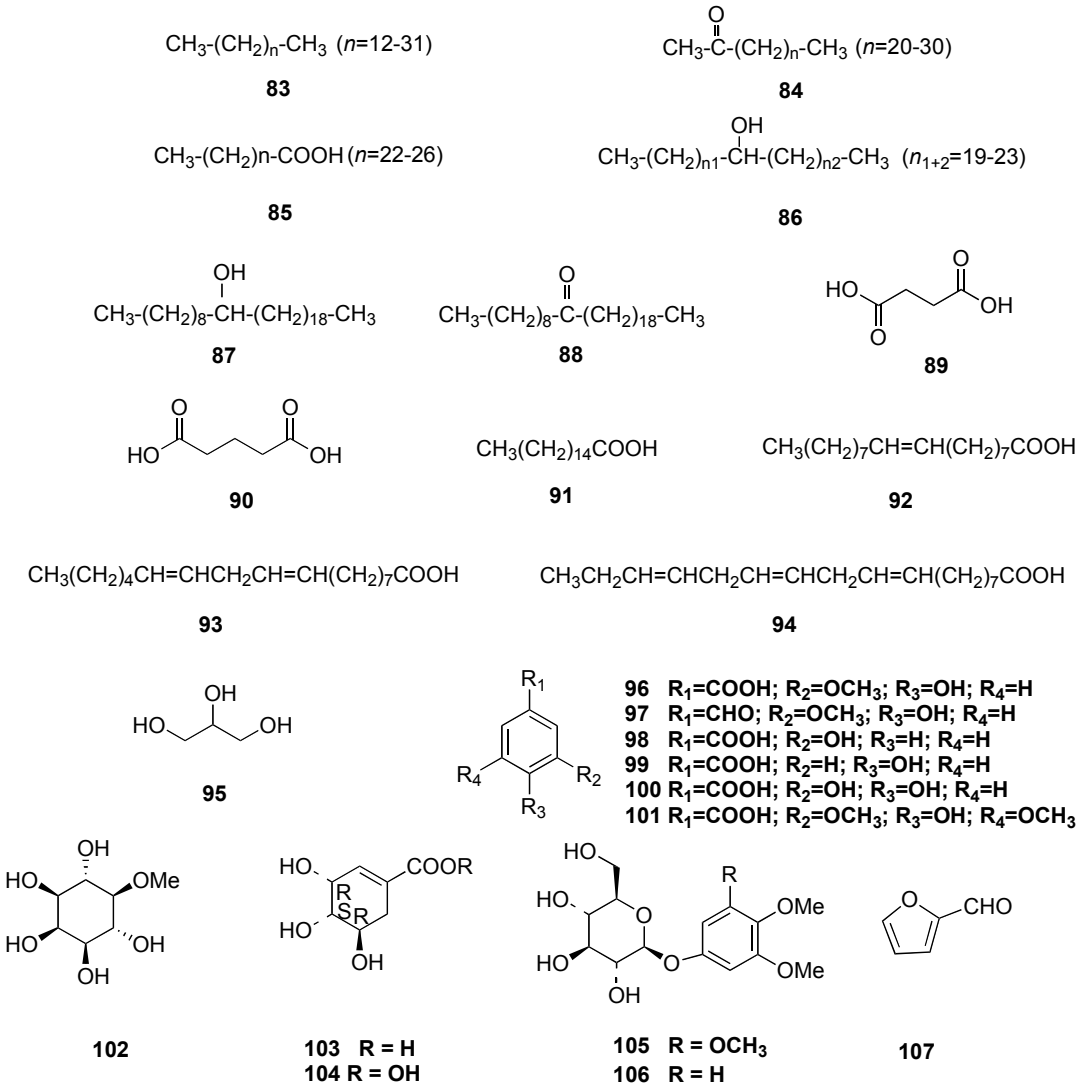

Fig. (9). Other compounds isolated from *Taxodium*.

cypress can cure leg tumors and reduce inflammation and rapidly resolve articular diseases. The treatment results are still yet to be independently verified and the mechanisms of action of essential oils or compounds of *Taxodium* as anti-tumor agents are essentially unknown. It was reported that the polymerization of microtubules of cells was inhibited 90% by taxodistine B (**7**) at the concentration of 100 μM, and 45% by taxodione (**10**) at 100 μM. Taxodistine A (**6**) did not inhibit the polymerization process at higher concentration (200 μM) [31]. Methanol extract of branches and leaves of pondcypress showed inhibitory activity on carbonic anhydrase II with an IC_{50} value of 4.27 μg/mL. The acetone extract and methanol extract inhibited cathepsin B with IC_{50} values of 2.12 and 3.71 μg/mL, respectively [41]. Sugiol (**1**) isolated from the medicinal *Peltodon longipes* was shown to possess cytotoxic activity against the human pancreatic cancer cell line MIA PaCa-2, and also found the relaxation activity of human DNA topoisomerases I and II [58]. Aspects of the biological activity of sugiol (**1**) continues to be explored and shown to possess xanthine oxidase inhibitory activity [58]. Sugiol (**1**) and ferruginol (**2**) have near 100% aldose reductase (AR) inhibition efficacy at concentration of 5 and 25 μM, respectively [59]. Ferruginol (**2**) showed effects on gastric secretion, endogenous prostaglandins and non-protein sulfhydryls, and its mechanism of assessment of action was elevated *in vitro* models in mice and rats [60, 61]. Some of natural biflavones inhibit cathepsin B and cathepsin K, especially HIF with IC_{50} of 0.58 mM against cathepsin B [62, 63]. In addition, taxodione (**10**) also showed HIV-1 PR inhibitory activity in 0.1 mM concentraction [32].

Antitermitic Activities

Several abietane-type diterpenoids isolated from baldcypress cones exhibited potential in termite control. 6,7-Dehydroroyleanone (**13**) and taxodione (**20**) showed potent termicidal activity against the subterranean termite, *Reticulitermes speratus* Kolbe while 14-deoxycoleon U (**8**) and xanthoperol (**3**) showed antifeedant activity [31].

Antispasmodic and Bronchodilator Activities

The leaf hexane extract of Montezuma cypress produced a concentration-dependent relaxant effect on intestinal and tracheal smooth muscle and were evaluated *in vitro* by testing spontaneous contractions of rabbit jejunum and agonist-induced contractions of guinea pig ileum and rat trachea [4].

CONCLUSIONS

None of the three taxa of *Taxodium* have been extensively investigated for chemical constituents although abietane-type diterpenoids and flavonoids are reported as major compounds of the genus. To date, 57 compounds have been isolated from the three taxa of extant *Taxodium* with more than 60 compounds were identified from the essential oils. Interestingly, 50 compounds have been identified from the fossil *Taxodium* while four occur in the extant species as major compounds. The existing *in vitro* reports have demonstrated various biological and pharmacological activities of *Taxodium*. Diterpenoids from *Taxodium* may be further studied for their potential biological and pharmaceutical activities against inflammation and oxidative stresses associated with serious disease, such as diabetes and cardiovascular diseases. The diterpenoids identified in *Taxodium* have provided important and interesting evidence of evolutionary pattern and taxonomy of the genus. In fact, the abundant phenolic abietanes (sugiol (**1**), ferruginol (**2**), and 6,7-dehydroferruginol (**5**)) in both extant and fossil *Taxodium* may be used as chemosystematic markers for the phylogenetic and systematic comparison of the taxa. These compounds are common in many genera of conifers and are also in some flowering plants (e.g., in Lamiaceae). To fully reveal the evolution and taxonomic puzzle as well as medicinal value of *Taxodium*, however, it is necessary to have systematic studies on chemical constituents of *Taxodium* particularly *T. distichum* var. *imbricarium* and var. *mexicanum* as well as their biological and pharmacological properties.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

GC	=	Gas chromatography
GC/MS	=	Gas chromatography-mass spectroscopy
GGPP	=	Geranylgeranyl diphosphate
Hep G2	=	A human liver tumor cell line
HIF	=	Hypoxia-inducible factor
HPLC	=	High performance liquid chromatography
MIA PaCa-2	=	A human pancreatic carcinoma cell line
MRSA	=	Methicillin-resistant *Stapbylococcus aureus*
NMIP	=	Nonmethylene-interrupted polyenoic
P388	=	A murine lymphoma cell line
PC-3	=	A human prostate cancer cell line
SAR	=	Structure activity relationship
TLC	=	Thin layer chromatography
UPLC	=	Ultra performance liquid chromatography
VRE	=	Vancomycin-resistant *Enterococcus*

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