Pharmaceutical Sciences Asia

Pharm Sci Asia 2021; 48(4), 300-319

DOI:10.29090/psa.2021.04.20.174

Review Article

Phytochemical content and biological activity of the genus Cycas, Family Cycadaceae: A review

Naglaa Afifi[1],
Abeer Moawad[1],
Marwa Hassan[1],
Dalia Al Amir[1],
Ahlam Elwekeel[1],
Elham Amin[1,2*]

[1] Department of Pharmacognosy, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
[2] Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Qassim University, Buraidah, Kingdom of Saudi Arabia.

***Corresponding author:**
Elham Amin
Elham_bns@yahoo.com,
Elham.Saleh@pharm.bsu.edu.eg

Keywords:
Cycas, Cycadaceae, Review, Phytochemical, Biological

Pharmaceutical Sciences Asia © 2021 by Faculty of Pharmacy, Mahidol University, Thailand is licensed under CC BY-NC-ND 4.0. To view a copy of this license, visit https:// www.creativecommons.org/ licenses/by-nc-nd/4.0/

ABSTRACT

Genus *Cycas*, Cycadaceae family, contains about 117 species. Nevertheless, few species have been phytochemically and pharmacologically studied. To date Eighty-eight secondary metabolites, including flavonoids, terpenoids, lignans, aromatic acids and sterols were isolated and identified from nineteen *Cycas* species. Among the isolated compounds flavonoids are the most prevalent metabolites. The extracts as well as pure compounds isolated from *Cycas* species were reported to exhibit a wide range of biological activities including; antimicrobial, anti-oxidant, antidiabetic, cytotoxic, anthelmintic, analgesic, anti-arthritic, anti-inflammatory and thrombolytic activities. The present review highlights the reported phytochemical content as well as the pharmacological potential of *Cycas* species. Interestingly, it indicates that; almost all the previous investigation of the biological activity of pure compounds isolated from this genus was directed towards its flavonoid content. Accordingly, more biological studies are needed to figure out the possible role of other isolated compounds in the observed biological activities and/or the reported traditional uses of different *Cycas* species. Moreover, further studies are required to investigate other unexplored species.

1. INTRODUCTION

Order Cycadales plants are commonly called Cycads. Formerly, all living genera of Cycads were classified within a single family; the Cycadaceae,[1] till Johnson in 1959 recognized two additional families, the Stangeriaceae and the Zamiaceae[2]. *Cycas* is the only accepted genus in family Cycadaceae[3]. Currently, about 117 species are classified under this genus[4].

Cycas is native to tropical and subtropical regions. It grows very slowly in woodlands and drier mountain slopes, exposed to the sun. *Cycas* is a short palm-like plant, it is cultivated in parks because of its unique beauty. The individual plants are dioecious, with thick cylindrical trunk and conspicuous crown of pinnate compound leaves. Foliage leaves are unipinnate compound, with many thick and leathery sessile leaflets of spine apex. A single midrib runs along the entire length. The pinna margin is of a taxonomic value, for example, it is revolute in *C. revoluta* or flat in *C. circinalis*. Annually, two crowns of leaves are produced; in spring and in autumn[5].

Herein, an overview about the previously reported phytochemical and biological studies of genus *Cycas* is presented. This information provides a preliminary step for developing more

researches about the possible medicinal and pharmaceutical applications of different *Cycas* species. Moreover, the collected data about previously investigated species could suggest new candidate for phytochemical and biological exploration.

2. CHEMICAL CONSTITUENTS

The species of the *Cycas* genus are a rich source of several compounds belonging to different chemical classes. Eighty-eight compounds have been reported from the nineteen *Cycas* species; (*C. aenigma*, *C. armstrongii*, *C. beddomei*, *C. circinalis*, *C. curanii*, *C. edentata*, *C. flabellata*, *C. lacrimans*, *C. mindanaensis*, *C. nitida*, *C. panzhihuaensis*, *C. pectinata*, *C. revoluta*, *C. riuminiana*, *C. rumphii*, *C. sancti-lasallei*, *C. vespertilio*, *C. wadei*, *C. zambalensis*). These compounds include; flavonoids, terpenoids, norisoprenoid, lignans, monolignols, aromatic acids and sterols, in addition to other miscellaneous compounds. Their names, structures, plant sources, biological activities and references are represented in Figures1-5 and Tables 1-5.

2.1. Flavonoids

Flavonoids are ubiquitous group of naturally occurring polyphenolic compounds characterized by the flavan nucleus[6] and represent the major active components of the genus *Cycas*. Most flavonoids were isolated from *C. circinalis* and *C. revoluta* by using different chromatographic techniques e.g. column chromatography and RP-HPLC. The reviewed structural types of flavonoids belong to flavan-3-ols, flavanones, flavanone, flavone, isoflavones and biflavonoids.

2.1.1. Mono flavonoids and their glycosides

Phytochemical investigations of *C. circinalis* afforded four flavan-3-ols (**1-4**) including catechin (**1**)[7], epicatechin (**2**)[8], epigallocatechin (**3**)[8], and gallocatechin (**4**)[8]. In addition to three flavanones and flavanone glycosides; (2S)-naringenin (**5**), neohesperdine (**6**) and prunin (naringenin-7-*O*-glucoside; **7**) were isolated from *C. revoluta*[8-10]. (2S)-naringenin (**5**), Prunin (Naringenin-7-*O*-glucoside, **7**) and naringin (naringenin 7-*O*-neohesperidoside, **8**) were isolated from *C. armstrongii*[11]. Four flavone-*C*-glycosides; vicenin-2 (violanthin; **9)** and 2″-glucosylvitexin (**10**) were isolated from *C. circinalis*[8]. PanzhihuaCycaside (Apigenin-8-*C*-*β*-D-glucopyranosyl(1→6)-*β*-D-galacopyranosyl(1→2)-[*β*-D-glucopyranosyl(1→4)]-*α*-L-rhamnopyranosyl(1→6)-*β*-D-glucopyranoside (**11**) was reported in *C. panzhihuaensis*[12]. Vitexin-2″-rhamnoside (**12**) was afforded from *C. revoluta*[10]. Phytochemical investigations of *C. revoluta* led to isolation of 5,6,7,8,3′,4′-hexamethoxyflavone (**13**) and 5,6,7,8,4′-pentamethoxyflavone (**14**)[13]. Rutin (**15)** is the sole flavon-3-ol glycoside isolated from *Cycas* species[9]. Two new isoflavonoids with different skeleton were isolated from genus *Cycas*; 7,3′-dihydroxyisoflavones (**16**) was isolated from *C. revoluta*[13] while wadeiol (**17**) was obtained from *C. wadei*[14].

2.1.2. Biflavonoids

Biflavonoids; the most common flavonoid in genus *Cycas*; are oxidative coupling products leading to biflavones, chalcone-flavone, biflavanones and flavanone-flavones, dimers in which the two components are connected either C-C or C-O-C bond[15].

Till now, eighteen biflavonoids (**18-35**) were isolated from *Cycas* species, incuding six biflavones (**18-23);** amentoflavone (**18**) was isolated from *C. armstrongii*[11], *C. beddomei*[16], *C. circinalis*[8], *C. panzhihuaensis*[17], *C. pectinata*[18], *C. revoluta*[8,9] and *C. rumphii*[19]. Amentoflavone-4′- *O*- *α*- D-glucopyranoside **(19)**[9] in addition to hinokiflavone (**20**) were isolated from *C. revoluta* [8,9]. Podocarpusflavone A (**21**) is 4‴-*O*-methyl amentoflavone which was isolated from *C. panzhihuaensis*[17] and *C. revoluta*[8,9]. 4′-*O*-methylamentoflavone (bilobetin) (**22**) was obtained from *C. circinalis*[8]. 4′,4‴-Di-*O*-methylamentoflavone (isoginkgetin; **23**) was isolated from *C. armstrongii*[11] and *C. circinalis*[7,8].

Five biflavanones (**24-28**) were isolated from three *Cycas* species; two new biflavanones: tetrahydrohinokiflavone (**24)** was isolated from *C. beddomei*[16,20] and *C. revoluta*[8]. 7,7″-Di-*O*-methyltetrahydrohinokiflavone **(25**) was isolated from *C. beddomei*[20]. Moawad et al, (2010) isolated (2S,2″S)-2,3,2″,3″-tetrahydroamentoflavone (**26**) from *C. revoluta*[8], (2S,2″S)-2,3,2″,3″-tetrahydro-4′-*O*-methylamentoflavone (tetrahydrobilobetin; **27**) and (2S,2″S)-2,3,2″,3″-tetrahydro-4′,4‴-di-*O*-methylamentoflavone (tetrahydroisoginkgetin; **28**) from *C. circinalis*[8].

Concerning flavanone-flavones biflavonoids phytochemical investigation of leaflets of *C. circinalis and C. revoluta and C. pectina* fruits afforded seven flavanone-flavones biflavonoids

Table1. Flavonoids from the genus *Cycas*.

No.	Compound	Molecules (Mol. Wt)	Plant source	Plant Organ	Biological activity	Ref.
(1)	Catechin	$C_{15}H_{14}O_6$ (290.079)	*C. circinalis*	Leaflets	-	7
(2)	Epicatechin	$C_{15}H_{14}O_6$ (290.079)			-	8
(3)	Epigallocatechin	$C_{15}H_{14}O_7$ (306.270)			-	8
(4)	Gallocatechin	$C_{15}H_{14}O_7$ (306.270)			-	8
(5)	(2S)-naringenin	$C_{15}H_{12}O_5$ (272.256)	*C. armstrongii*		-	11
			C. circinalis & *C. revoluta*		-	8,9
(6)	Neohesperdine	$C_{28}H_{34}O_{15}$ (610.565)	*C. revoluta*		Strong cytotoxic activity against MCF 7 cell line (IC_{50} = 4.73 µg/ml) compared to doxorubicin (IC_{50} = 4.13 µg/ml) Anti-oxidant activity nearly 2-4 folds higher than that of quercetin at a dose of 12.5 µg/ml	9
(7)	Prunin (Naringenin-7-*O*-glucoside)	$C_{21}H_{22}O_{10}$ (434.397)	*C. armstrongii*		-	11
			C. revoluta		Weak antimicrobial activity (IC_{50} >10 mg/mL).	10
(8)	Naringin (Naringenin 7-*O*-neohesperidoside)	$C_{27}H_{32}O_{14}$ (580.539)	*C. armstrongii*		-	11
(9)	Vicenin-2 (violanthin)	$C_{27}H_{30}O_{15}$ (594.522)	*C. circinalis*	Leaflets	-	8
(10)	2″-Glucosylvitexin	$C_{27}H_{30}O_{15}$ (594.522)			-	8
(11)	PanzhihuaCycaside (Apigenin-8-*C*-*β*-D-glucopyranosyl(1→6)-*β*-D-galacopyranosyl(1→2)-[*β*-D-glucopyranosyl(1→4)]-*α*-L-rhamnopyranosyl(1→6)-*β*-D-glucopyranoside	$C_{39}H_{50}O_{24}$ (902.805)	*C. panzhihuaensis*		-	12
(12)	Vitexin-2″-rhamnoside	$C_{27}H_{30}O_{14}$ (578.523)	*C. revoluta*		Significant activity towards *Leishmania donavani* (IC_{50} = 13.8 mM, IC_{90} = 34.6mM). Weak antimicrobial activity (IC_{50} >10mg/mL).	10
(13)	5,6,7,8,3′,4′-Hexamethoxyflavone	$C_{21}H_{22}O_8$ (402.399)	*C. revoluta*		-	13
(14)	5,6,7,8,4′-Pentamethoxyflavone	$C_{20}H_{20}O_7$ (372.373)			-	13
(15)	Rutin	$C_{27}H_{30}O_{16}$ (610.521)			-	9
(16)	7,3′-Dihydroxyisoflavones	$C_{15}H_{10}O_4$ (254.241)			-	13
(17)	Wadeiol	$C_{16}H_{14}O_5$ (286.283)	*C. wadei*		-	14
(18)	Amentoflavone	$C_{30}H_{18}O_{10}$ (538.464)	*C. armstrongii*		-	11
			C. beddomei		-	16
			C. panzhihuaensis		-	17

•reported in Cycas literature
Mol Wt: Molecular weight
- No biological activities; about these compounds; reported while studying these species

Table1. Flavonoids from the genus *Cycas*. (cont.)

No.	Compound	Molecules (Mol. Wt)	Plant source	Plant Organ	Biological activity	Ref.
(18)	Amentoflavone		*C. pectinata*	Leaflets	Significantly high inhibitory potency against α-glucosidase (IC_{50} 8.09±0.023 µM, and α-amylase (IC_{50} 73.6±0.48 µM).	18
			C. revoluta		Strong cytotoxic activity (IC_{50}=18.70 µg/ml) against MCF 7 breast cancer cell compared to doxorubicin (IC_{50} = 4.13 µg/ml) Anti-oxidant activity using DPPH method (nearly 2 to 4 folds higher than that of quercetin at a dose of 12.5 µg/ml	9
			C. revoluta & C. circinalis		-	8
			C. rumphii		-	19
(19)	Amentoflavone- 4′-*O*- α-D-glucopyranoside	$C_{37}H_{30}O_{15}$ (714.632)	*C. revoluta*		Anti-oxidant activity using DPPH method (nearly two to four folds higher than that of quercetin at a dose of 12.5 µg/ml)	9
(20)	Hinokiflavone	$C_{30}H_{18}O_{10}$ (538.464)			-	8,9
(21)	Podocarpus flavone A	$C_{31}H_{20}O_{10}$ (552.491)	*C. revoluta*		Strong cytotoxic activity against MCF 7 breast cancer cell (IC_{50} = 6.12 µg/ml) compared to doxorubicin (IC_{50} = 4.13 µg/ml)	8,9
			C. panzhihuaensis		-	17
(22)	4′-*O*-Methylamentoflavone (Bilobetin)	$C_{31}H_{20}O_{10}$ (552.105)	*C. circinalis*		-	8
(23)	4′,4‴-di-*O*-Methylamentoflavone (Isoginkgetin).	$C_{32}H_{22}O_{10}$ (566.518)	*C. armstrongii*		-	11
			C. circinalis		-	8
(24)	Tetrahydrohinokiflavone	$C_{30}H_{22}O_{10}$ (542.121)	*C. beddomei*	Stems	-	20
				Leaflets	-	16
			C. revoluta		-	8
(25)	7,7″-di-O-Methyltetrahydrohinokiflavone	$C_{32}H_{26}O_{10}$ (570.550)	*C. beddomei*	Stems	-	20
(26)	(2S,2″S)-2,3,2″,3″-Tetrahydroamentoflavone	$C_{30}H_{22}O_{10}$ (542.496)	*C. revoluta*	Leaflets	-	8
(27)	(2S,2″ S)-2,3,2″,3″-Tetrahydro-4′*O* methylamentoflavone (Tetrahydrobilobetin)	$C_{31}H_{24}O_{10}$ (556.523)	*C. circinalis*	Leaflets	Moderate antibacterial activity when tested against *Staphylococcus aureus* (IC_{50} values of 9.6 µM) and methicillin-resistant *S. aureus* (MRSA; IC_{50} values of 12.5 µM).	8
(28)	(2S,2″S)-2,3,2″,3″-Tetrahydro-4′,4‴-di*O* methylamentoflavone (Tetrahydroisoginkgetin)	$C_{32}H_{26}O_{10}$ (570.550)			Moderate antibacterial activity when tested against *Staphylococcus aureus* (IC_{50} values of 3.8 µM) and methicillin-resistant *S. aureus* (MRSA; IC_{50} values of 5.9 µM).	8

•reported in Cycas literature
Mol Wt: Molecular weight
- No biological activities; about these compounds; reported while studying these species

Table1. Flavonoids from the genus *Cycas*. (cont.)

No.	Compound	Molecules (Mol. Wt)	Plant source	Plant Organ	Biological activity	Ref.
(**29**)	2,3-Dihydroamentoflavone	$C_{30}H_{20}O_{10}$ (540.480)	*C. armstrongii*	Leaflets	-	11
			C. pectinata	Fruits	Significantly high inhibitory potency against α-glucosidase 9.77±0.032 µM, and α-amylase (IC_{50} 39.69±0.39 µM. This is the first report of bioactivity guided isolation of anti-diabetic constituents from the traditionally used fruits of *C. pectinata*	18
			C. revoluta & *C. circinalis*	Leaflets	Moderate antibacterial activity against *Staphylococcus aureus* (IC_{50} value 8.2 µM) and methicillin-resistant *S. aureus* (MRSA; IC_{50} value of 11.5 µM).	8
(**30**)	(2S)I-(2,3)-dihydro-I-7-O-β-D-glucopyranosylamentoflavone	$C_{36}H_{30}O_{15}$ (702.621)	*C. revoluta*	Leaflets	Weak antimicrobial activity (IC_{50} >10mg/mL).	10
(**31**)	(2S)-I-(2,3)-dihydro-I-7, II-7-di-O-β-D-glucopyranosylamentoflavone	$C_{42}H_{40}O_{20}$ (864.762)			Weak antimicrobial activity (IC_{50} >10mg/mL).	10
(**32**)	(2S)-2,3dihydroisocryptomerin	$C_{31}H_{22}O_{10}$ (554.507)			-	8
(**33**)	(2S)-2,3-dihydrohinokiflavone	$C_{30}H_{20}O_{10}$ (540.480)	*C. armstrongii*	Leaflets	-	11
			C. revoluta		-	8
			C. panzhihuaensis		-	12
(**34**)	(2S)-2,3-dihydro-4′O – methylamentoflavone (Dihydrobilobetin)	$C_{31}H_{22}O_{10}$ (554.121)	*C. armstrongii*	Leaflets	-	11
			C. circinalis		-	7,8
			C. revoluta	Leaflets &female cones	Strong activityt against MRSA, E. coli, Salmonella abony, Aspergillusniger, Candida albicans, and others	21
(**35**)	(2S,2″S)-2,3 dihydro-4′,4‴-di-*O* – methylamentoflavone (Dihydroisoginkgetin)	$C_{32}H_{24}O_{10}$ (568.534)	*C. circinalis*	Leaflets	-	8

•reported in Cycas literature
Mol Wt: Molecular weight
- No biological activities; about these compounds; reported while studying these species

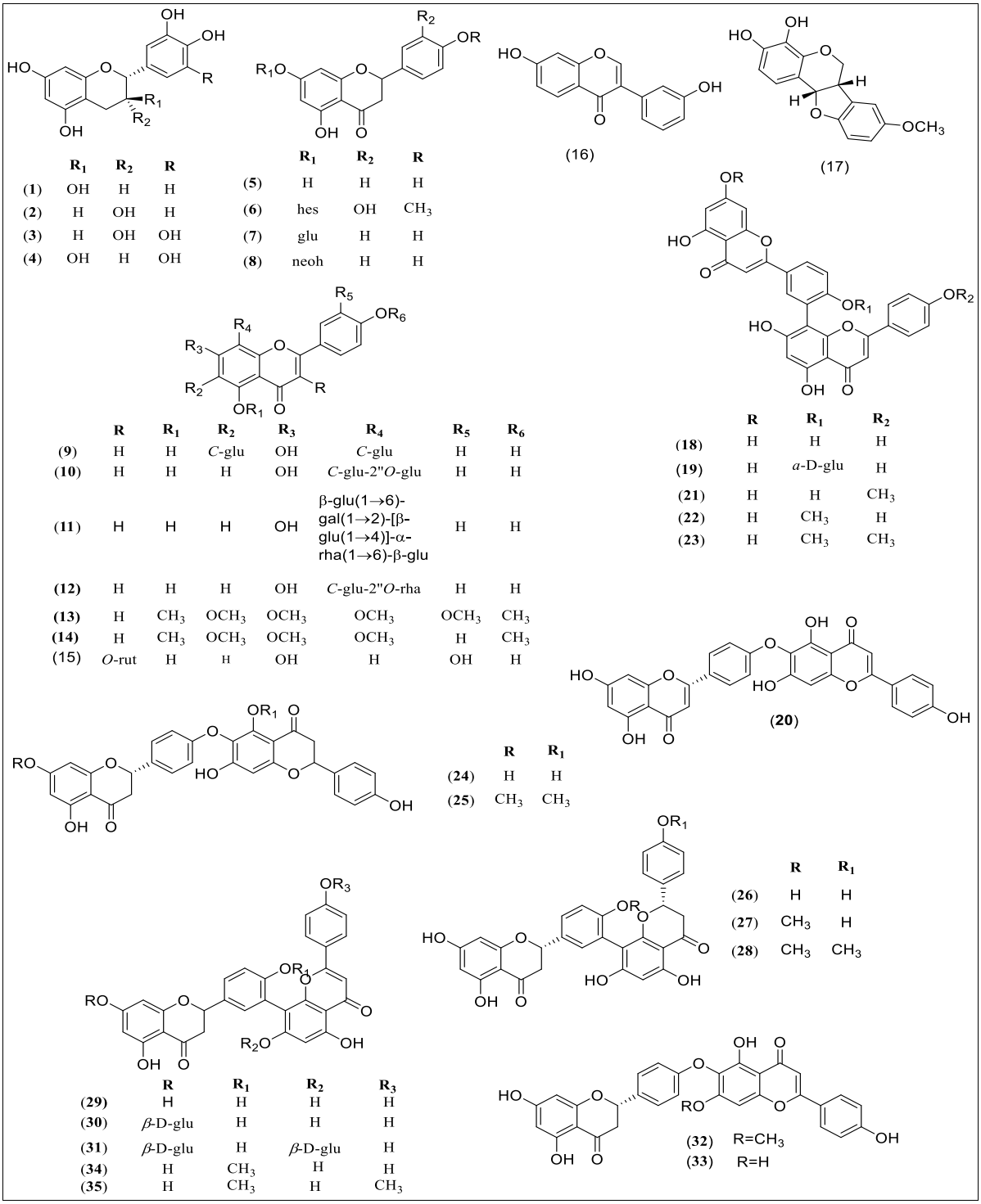


Figure 1. Flavonoids from the genus *Cycas*.
gal= galactoside, glu=glucoside, hes= hesperidoside, neoh=neohesperidose, Rha= rhamnoside, rut = rutinoside

(**29**-**35**). 2,3-Dihydroamentoflavone (**29**) was obtained from *C. armstrongii*[11], *C. pectinata*[18] and *C. revoluta*[8]. (2S)I-(2,3)-dihydro-I-7-O-*β*-D-glucopyranosylamentoflavone (**30**)[10], (2S)-I-(2, 3)-dihydro-I-7, II-7-di-O-*β*-D-glucopyranosylamentoflavone (**31**)[10] and (2S)-2,3dihydroisocryptomerin (**32**)[8] were isolated from *C. revoluta*. (2S)-2,3-dihydrohinokiflavone (**33**) was obtained from *C. armstrongii*[11], *C. panzhihuaensis*[12] and *C. revoluta*[8]. (2S)-2,3-dihydro-4′-*O*-methylamentoflavone (**34**)[8,21] and (2S,2″S)-2,3-dihydro-4′,4‴-di-*O*–methylamentoflavone (Dihydroisoginkgetin) (**35**) were isolated from *C. circinalis*[8].

2.2. Terpenoids

The terpenoids represent a large group of natural products which are derived from C_5

isoprene units. Typical structures of terpenoids contain carbon skeletons of $(C_5)_n$, and are classified according to the number of isoprenoid units incorporated as hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}) and tetraterpenes (C_{40})[22]. All subclasses of terpenoids were reported in Cycas species except hemiterpenes, monoterpenes and sesterterpenes.

2.2.1. Diterpenes

The diterpenoids are among the main components of the genus *Cycas*. The structural types of diterpenoids include isopimarane, labdanes, abietane and acyclic diterpenes. Different diterpenoids were isolated from the nine *Cycas* species; *C. aenigma*, *C. curanii*, *C. edentate*, *C. lacrimans*, *C. nitida*, *C. riuminiana*, *C. sancti-lasallei*, *C. vespertilio*, *C. zambalensis*, by using column chromatography. Chemical investigation of *C. nitida* led to isolation of 2α,18-hydroxy-isopimara-7,15-diene (**36**)[23]. 2α,18- dihydroxy-isopimara-7,15-diene (**37**) was obtained from *C. lacrimans*[24] and *C sancti-lasallei*[25]. Labda-8(17),13 (16),14-trien-18-ol (**38**) and abietatriene (**39**) were isolated from *C. nitida*[23]. 9αH-isopimara-7,15-diene (**40**) was isolated from *C. edentate*[26], *C. lacrimans*[27] and *C. vespertilio*[28]. While isopimaran-19-ol (**41**) was found in *C. lacrimans*[27] and *C. zambalensis*[29]. 3-oxoisopimara-7,15-diene (**42**) was separated from *C. zambalensis*[29], Phytol (**43**) was separated from *C. curanii*[11,30], Phytyl fatty acid ester (**44**) was reported in *C. aenigma*[31] besides, *C. curanii*[30], *C. riuminiana*[32], *C. sancti-lasallei*[33] and *C. vespertilio*[28].

2.2.2. Sesquiterpene

Only one sesquiterpene alcohol**;** Selen-4 (15)-en-1β-11-diol (**45**), was isolated from *C. wadei* by adopting silica gel column chromatography[14].

2.2.3. Triterpenes

Five triterpenes have been identified in the genus *Cycas*. Three pentacyclic triterpenoids were obtained from *C. vespertilio;* α-amyrin acetate, lupeol acetate and adianenone (**46-48**)[9,28, 34]. Another pentacyclic triterpenoid; *β*-amyrin (**49**) was separated from *C. revoluta*[9]. Squalene (**50**) is a linear triterpenes which was isolated from *C. aenigma*[31], *C. curanii*[30], *C. flabellata*[35], *C. mindanaensis*[36], *C. nitida*[23,37], *C. riuminiana*[32], *C. sancti-lasallei*[33], *C. vespertilio*[28], *C. wadei*[38] and *C. zambalensis*[29].

2.2.4. Tetraterpenes

Two carotenoids were reported in *Cycas* species (**51** and **52**); *β*-carotene (**51**) was reported from *C. zambalensis* leaflets[29]. Lutein (**52**) was isolated from leaflets of *C.* curanii[30], *C. flabellate* [35], *C. riuminiana*[32], *C. sancti-lasallei*[39] and *C. zambalensis*[29].

2.3. Norisoprenoid

Norisoprenoids are volatile metabolites (C_9-C_{13}) produced from the degradation of carotenoids. They can be obtained as a result of in vivo enzymatic degradation or postharvest thermal degradation of foods containing carotenoids[40]. Leaflets of *C. circinalis* and *C. revoluta* yielded (−)-loliolide (**53)** and (6 S ,7 E ,9 S)6,9-dihydroxy-4,7-megastigmadien-3-one (vomifoliol ; **54**), respectively[8].

2.4. Lignans

Lignans are polyphenolic secondary metabolites derived from polymerization of phenyl propenes by connection between C(8) and C(8`)[41]. They exhibited different biological activities[41]. Nine lignans; isolated by column chromatography; were reported from certain members of genus *Cycas*. *C. vespertilio*[34,42] and *C. aenigma*[43] have yielded pinoresinol (**55**). Sesamin (**56**) was isolated from *C. vespertilio*[42] and *C. sancti-lasallei*[44]. Both paulownin (**57**)[42] and (+)-lariciresinol (**57**)[34,42] were obtained from *C. vespertilio*. (+)-lariciresinol (**58**) was separated from *C. revoluta*[8]. 8-hydroxypinoresinol (**59**) was obtained from *C. sancti-lasallei*[44]. Two benzofurans lignans; (+)-(7S,8R)-dihydrodehydrodiconiferyl alcohol (3′-methylcedrusin**; 60**) and Balanophonin **(61**) were identified in *C. circinalis*[8] and *C. zambalensi*[29]. (+)-isolaricerisinol (**62**) was separated from *C. revoluta*[8]. 2-[2-hydroxy -5-(3-hydroxypropyl)-3-methoxyphenyl]-1-(4-hydroxy3-methoxyphenyl) propane-1,3-diol (**63**) was obtained from *C. sancti-lasallei*[39] and *C. aenigm*a[43].

2.5. Aromatic acids and their derivatives

Aromatic acids are relatively simple in structure, easily identified and quantified in plants. Most aromatic acids and its derivatives are products of the shikimate and acetate pathways. Aromatic acids are found in plant cell in

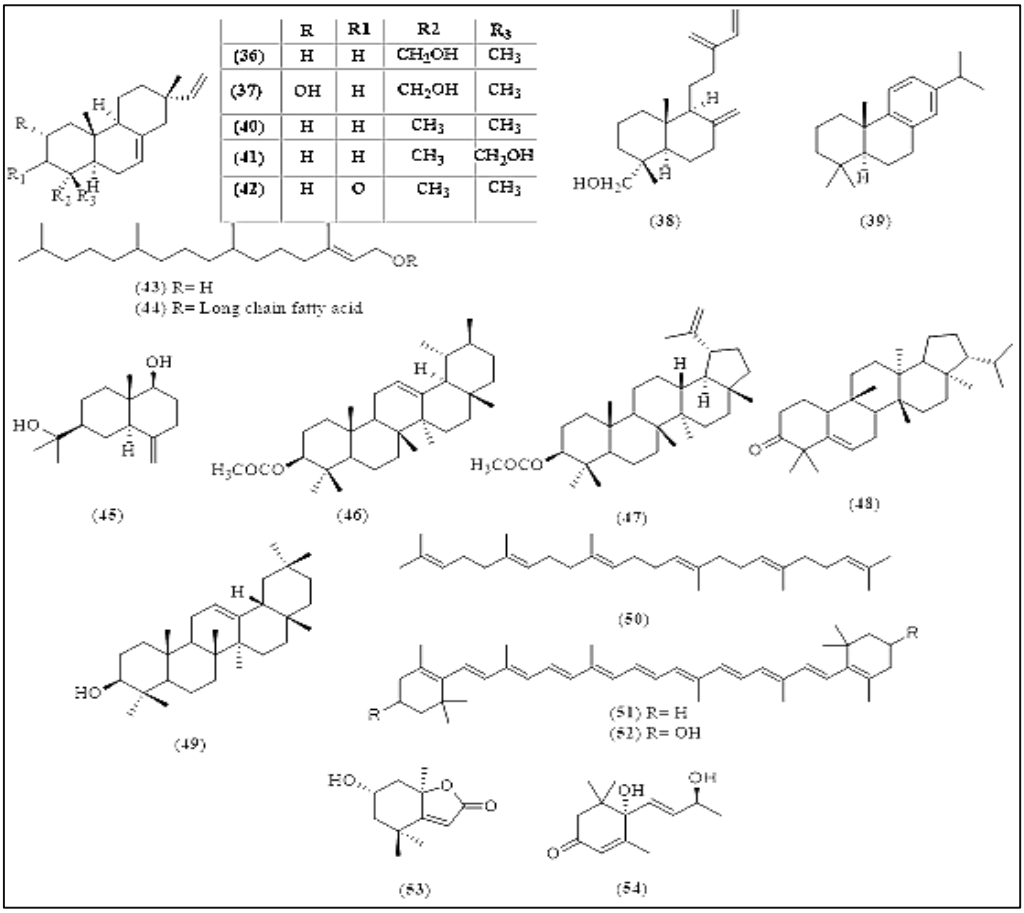
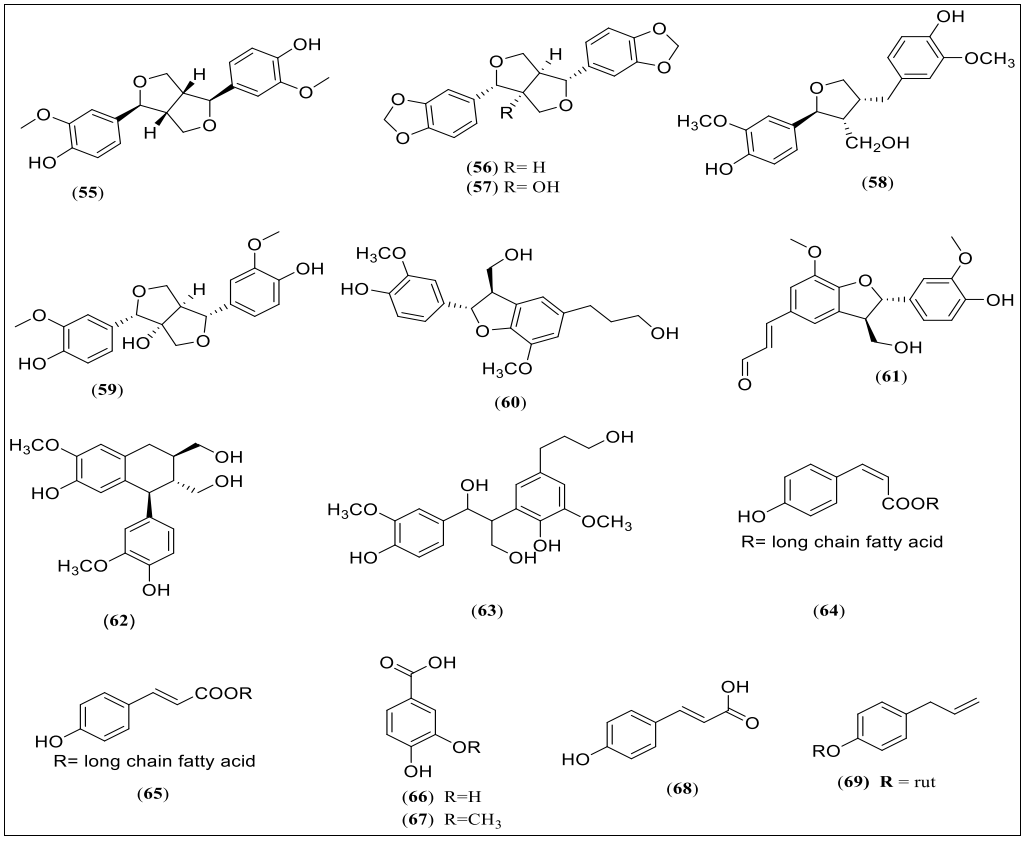


Figure 2. Terpenoids and norisoprenoid from the genus *Cycas*.



rut = rutinoside

Figure 3. Lignans, aromatic acids and simple phenolic derivatives from the genus *Cycas.*

Table 2. Terpenoids and norisoprenoid from the genus *Cycas.*

No.	compound	Molecular formula (Mol.Wt)	Plant source	Organ	Ref.
(36)	2α,18-hydroxy-isopimara-7,15-diene	$C_{20}H_{32}O$ (288.475)	*C. nitida*	Megasporophyll lamina	23
(37)	2α,18-dihydroxy-isopimara-7,15-diene	$C_{20}H_{32}O_2$ (304.474)	*C. lacrimans*	Sarcotesta	24
			C. sancti-lasallei	Leaflets	25
(38)	Labda-8(17),13(16),14-trien-18-ol	$C_{20}H_{31}O$ (287.467)	*C. nitida*	Petiole and rachis	23
(39)	Abietatriene	$C_{20}H_{30}$ (270.460)		Roots	23
(40)	9αH-isopimara-7,15-diene	$C_{20}H_{32}$ (272.476)	*C. edentata*	Bark	26
			C. lacrimans		27
			C. vespertilio		28
				Roots	28
(41)	Isopimaran-19-ol	$C_{20}H_{32}O$ (288.475)	*C. lacrimans*	Megasporophyll lamina	27
			C. zambalensis	Bark	29
(42)	3Oxoisopimara-7,15-diene	$C_{20}H_{30}O$ (286.459)	*C. zambalensis*	Bark	29
(43)	Phytol	$C_{20}H_{40}O$ (296.539)	*C. curanii*	Leaflets	11
					30
(44)	Phytyl fatty acid ester		*C. aenigma*	Roots	31
			C. curanii	Petiole	30
			C. riuminiana	Leaflets	32
			C. sancti-lasallei	Endotesta	33
			C. vespertilio	Petiole and rachis	28
				Endotesta	28
(45)	Selen-4(15)-en-1*β*-11-diol	$C_{15}H_{26}O_2$ (238.371)	*C. wadei*	Roots	14
(46)	*α*-amyrin acetate	$C_{32}H_{52}O_2$ (468.766)	*C. vespertilio*	Male cone	34
(47)	lupeol acetate	$C_{32}H_{52}O_2$ (468.766)			34
(48)	adianenone	$C_{30}H_{48}O$ (424.713)		Roots	28
(49)	*β*-amyrin	$C_{30}H_{50}O$ (426.729)	*C. revoluta*	Leaflets	9
(50)	Squalene	$C_{30}H_{50}$ (410.730)	*C. aenigma*	Microsporophyll lamina	31
			C. curanii	Sarcotesta	30
			C. flabellata	Leaflets	35
			C. mindanaensis	Leaflets	36
			C. nitida	Roots	23
				Bark	37
				Leaflets	37
				Roots	37
			C. riuminiana	Leaflets	32
			C. sancti-lasallei	Sarcotesta	33
			C. vespertilio	Bark	28

Table 2. Terpenoids and norisoprenoid from the genus *Cycas*. (cont.)

No.	compound	Molecular formula (Mol.Wt)	Plant source	Organ	Ref.
(50)	Squalene	$C_{30}H_{50}$ (410.730)	*C. vespertilio*	Petiole and rachis	28
				Endotesta	28
			C. wadei	Petiole and rachis	38
				Roots	38
			C. zambalensis	Petiole and rachis	29
				Leaflets	29
(51)	*β*-carotene	$C_{40}H_{56}$ (536.888)	*C. zambalensis*	Leaflets	29
(52)	Lutein	$C_{40}H_{56}O_2$ (568.886)	*C.* curanii		30
			C. flabellata		35
			C. riuminiana		32
			C. sancti-lasallei		39
			C. zambalensis		29
(53)	(−)-loliolide	$C_{11}H_{16}O_3$ (196.246)	*C. circinalis*		8
(54)	(6 S ,7 E ,9 S)6,9-dihydroxy-4,7-megastigmadien-3-one (vomifoliol)	$C_{13}H_{20}O_3$ (224.30)	*C. revoluta*		8

Table 3. Lignans, aromatic acids and simple phenolic derivatives from the genus *Cycas*.

No.	compound	Molecular formula (Mol.Wt)	Plant source	Organ	Ref.
(55)	Pinoresinol	$C_{20}H_{22}O_6$ (358.1416)	*C. vespertilio*	The cone base	42
				Male cone	34
			C. aenigma	Leaflets	43
(56)	Sesamin	$C_{20}H_{18}O_6$ (354.3580)	*C. vespertilio*	The cone base	42
			C. sancti-lasallei	Petiole, rachis and sclerotesta	44
(57)	paulownin	$C_{20}H_{18}O_7$ (370.3570)	*C. vespertilio*	The cone base	42
(58)	(+)-lariciresinol	$C_{20}H_{24}O_6$ (360.4060)	*C. vespertilio*	Cataphylls	42
				Male cone	34
			C. revoluta	Leaflets	8
(59)	8-hydroxypinoresinol	$C_{20}H_{22}O_7$ (374.3890)	*C. sancti-lasallei*	Petiole, rachis, and sclerotesta	44
(60)	(+)-(7 S ,8 R)-dihydrodehydrodiconiferyl alcohol (3′-methylcedrusin)	$C_{20}H_{24}O_6$ (360.4060)	*C. circinalis*	Leaflets	8
			C. zambalensis	Roots	29
(61)	Balanophonin	$C_{20}H_{20}O_6$ (356.126)	*C. zambalensis*	Leaflets	29
(62)	(+)-isolaricerisinol	$C_{20}H_{24}O_6$ (360.4060)	*C. revoluta*		8
(63)	2-[2-hydroxy-5-(3-hydroxypropyl)-3-methoxyphenyl]-1-(4-hydroxy3-methoxyphenyl)propane-1,3-diol	$C_{20}H_{26}O_7$ (378.4210)	*C. sancti-lasallei*		39
			C. aenigma		43

Table 3. Lignans, aromatic acids and simple phenolic derivatives from the genus *Cycas*. (cont.)

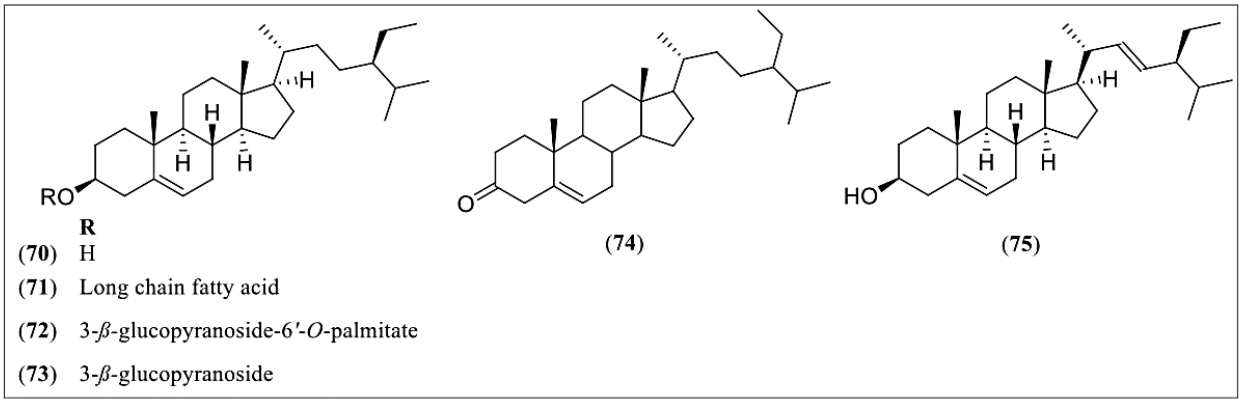
No.	compound	Molecular formula (Mol.Wt)	Plant source	Organ	Ref.
(64)	*cis-4*-hydroxycinnamate fatty acid esters		*C. vespertilio*	Unripe sarcotesta	42
			C. lacrimans	Sarcotesta	46
(65)	*trans-4*-hydroxycinnamate fatty acid esters		*C.vespertilio*	Unripe sarcotesta	42
			C. lacrimans	Sarcotesta	46
(66)	Protocatechuic acid	$C_7H_6O_4$ (154.1210)	*C. revoluta*	Leaflets	10
(67)	vanillic acid	$C_8H_8O_4$ (168.1480)	*C. panzhihuaensis*	Leaflets	12
			C. armstrongii		11
(68)	*p*-coumaric acid	$C_9H_8O_3$ (164.1600)	*C. armstrongii*	Leaflets	11
(69)	chavicol *β* rutinoside	$C_{21}H_{30}O_{10}$ (442.4610)	*C. panzhihuaensis*		17

Table 4. Sterols from the genus *Cycas*.

No.	compound	Mol.Wt	Plant source	Organ	Ref.
(70)	*β*-sitosterol	$C_{29}H_{50}O$ (414.718)	*C. aenigma*	Microsporophyll lamina and roots	31
			C. armstrongi	Leaflets	11
			C. curanii	Endotesta, lamina , leaflets, roots sarcotesta and sclerotesta	30
			C. edentata	Bark and endotesta	26
			C. flabellata	Bark and megasporophyll lamina	35
			C. lacrimans	Endotesta, petiole, rachis, roots, sarcotesta and sclerotesta	46
			C. mindanaensis	Bark, megasporophyll lamina, petiole and rachis	36
			C. nitida	Bark, roots and sarcotesta	37
			C. panzhihuaensis	Leaflets	17,12
			C. revoluta	Leaflets	9
			C. riuminiana	Leaflets and roots	32
			C. sancti-lasallei	Leaflets, sarcotesta and sclerotesta	39,33
			C. vespertilio	Cataphylls, Cone, endotesta, leaflets, Petiole, rachis, roots, sarcotesta and sclelerotesta	
			C. wadei	Endotesta, leaflets, petiole, rachis, roots and sarcotesta	38
			C. zambalensis	Petiole and rachis	29
(71)	*β*-sitosteryl fatty acid ester		*C. aenigma*	Roots	31
			C. curanii	Bark, lamina, petiole and sarcotesta	30
			C. edentata	Bark	26
			C. flabellata	Megasporophyll lamina and sarcotesta	35
			C. mindanaensis	Bark, petiole and rachis	36

Table 4. Sterols from the genus *Cycas*. (cont.)

No.	compound	Mol.Wt	Plant source	Organ	Ref.
(**71**)	*β*-sitosteryl fatty acid ester		*C. nitida*	Roots and sarcotesta	37
			C. riuminiana	Endotesta	32
			C. sancti-lasallei	Bark and megasporophyll lamina	39,33
			C. wadei	Megasporophyll lamina and sclerotesta	38
(**72**)	*β*-sitosteryl-3-*β*-glucopyranoside-6′-*O*-palmitate	$C_{51}H_{90}O_7$ (815.274)	*C. edentata*		47
			C. lacrimans		46
(**73**)	*β*-sitosterol-3-*O*–glucoside	$C_{35}H_{60}O_6$ (576.859)	*C. armstrongi*	Leaflets	11
			C. circinalis		7
			C. panzhihuaensis		17,12
(**74**)	*β*-sitosterone	$C_{29}H_{48}O$ (412.702)	*C. curanii*	Petiole	
(**75**)	Stigmasterol	$C_{29}H_{48}O$ (412.702)	*C. aenigma*	Roots	31
			C. edentata	Bark	47
			C. flabellata	Bark and megasporophyll lamina	35
			C. lacrimans	Petiole and rachis	46
			C. mindanaensis	Megasporophyll lamina, petiole and rachis	36
			C. nitida	Sclerotesta	
			C. riuminiana	Leaflets, roots	32
			C. sancti-lasallei	Endotesta, leaflets, sarcotesta and sclerotesta	39,33
			C. vespertilio	Cataphylls, cone. Endotesta and leaflets	42,34,28
			C. wadei	Petiole, rachis and roots	38



R

(**70**) H

(**71**) Long chain fatty acid

(**72**) 3-*β*-glucopyranoside-6′-*O*-palmitate

(**73**) 3-*β*-glucopyranoside

(**74**)

(**75**)

Figure 4. Sterols from the genus Cycas.

the form of glycosides or ester form. Few aromatic acids were reported about genus *Cycas*[45], Cis and trans-4-hydroxycinnamate fatty acid esters (**64** and **65**) were obtained from *C. lacrimans*[46] and *C. vespertilio*[42]. Three aromatic acids were detected in the genus *Cycas* (**66-68**); Protocatechuic acid (**66**) was separated by RP- HPLC from *C. revoluta*[10] and it showed weak antimicrobial activity (IC_{50} >10 mg/mL)[10]. Vanillic acid (**67**) was obtained from *C. armstrongii*[11] and *C. panzhihuaensis*[12]. *P*-coumaric acid (**68**) was isolated from *C. armstrongii*[11]. Chavicol *β* rutinoside (**69**) is a phenyl propene isolated from *C. panzhihuaensis*[17].

2.6. Sterols

Steroids are diverse group of biologically active secondary metabolites produced by plants. Steroid compounds are modified triterpenoids containing the tetracyclic ring system of lanosterol but lacking the three methyl groups at C-4 and C-14[22]. A total of six sterols (**70-75**) were isolated from genus *Cycas* by using column chromatography. *β*-sitosterol (**70**) was identified in *C. aenigma*[31], *C. armstrongi*[11], *C. curanii*[30], *C. edentata*[26], *C. flabellata*[35], *C. lacrimans*[46], *C. mindanaensis*[36], *C. nitida*[37], *C. panzhihuaensis*[12,17], *C. revoluta*[9], *C. riuminiana*[32], *C. sancti-lasallei*[33,39], *C. vespertilio*[28,34,42], *C. wadei*[38] and *C. zambalensis* [29]. *β*-sitosteryl fatty acid ester (**71**) was obtained from *C. aenigma*[31], *C. curanii*[30], *C. edentata*[26], *flabellata*[35], *C. mindanaensis*[36], *C. nitida*[37], *C. riuminiana*[32], *C. sancti-lasallei*[33,39] and *C. wadei*[38]. *β*-sitosteryl-3-*β*-glucopyranoside-6′-*O*-palmitate (**72**) was isolated from sarcotesta of *C. edentata*[47] and *C. lacrimans*[46]. *β*-sitosterol-3-*O*-glucoside (**73**) was obtained from *C. armstrongi*[11], *C. circinalis*[7] and *C. panzhihuaensis* leaflets[12,17]. Phytochemical investigation of *C. curanii* petiole led to isolation of *β*-sitosterone (**74**)[30]. Stigmasterol (**75**) was obtained from *C. aenigma*[31], *C. edentata*[47], *C. flabellata*[35], *C. lacrimans*[46], *C. mindanaensis*[36], *C. nitida*[37], *C. riuminiana*[32], *C. sancti-lasallei*[33,39] *C. vespertilio*[28,34,42] and *C. wadei*[38].

2.7. Other compounds

Chemical investigation of petiole, rachis and sclerotesta of *C. sancti-lasallei* yielded 4-hydroxymethyl-3,5-dimethyldihydro-2-furanone (**76**)[44]. α-tocopherol (**77**) was reported in *C. mindanaensis*[36], *C. riuminiana*[32] and *C. wadei*[38]. Palmitic acid (**78**) was reported in *C. panzhihuaensis* leaves[17]. Oleic acid (**79**) was reported from *C. lacrimans*[27] and *C. wadei*[38], while linoleic acid (**80**) from *C. riuminiana*[32] and *C. wadei*[38]. Investigation of sarcotesta of *C. lacrimans* led to monoacylmonogalactosylglycerol (**81**) isolation[48]. Investigation of *C. lacrimans* has been yielded to isolation of 1,2-dioleylglycerol (**82**)[27]. Triacylglycerol fatty acid esters (**83**) were isolated from *C. aenigma*[31], *C. curanii*[11], *C. lacrimans*[46], *C. mindanaensis*[36], *C. nitida*[37], *C. riuminiana*[32], *C. sancti-lasallei*[33] , *C. vespertilio*[42] *and C. wadei*[38]. Trilinolein (**84**) was obtained from *C. wadei*[38]. 1-methyl-*β*-D-glucose (**85**) was separated from *C. circinalis*[7]. Chlorophyll a (**86**) was obtained from *C. curanii*[30], *C. edentat*[29] and *C. zambalensis*[47] . Gymnosperms are relatively poor in nitrogen containing compounds. However, in few cases such as non-protein amino acid, N-(3′-one-5′-methyl)hexyl-alanine (**87**) was detected in *C. armstrongi* leaflets[11]. Another nitrogen containing compound; Cycasin (**88**) was isolated from *C. revoluta* seeds[49]. Some fatty alcohols were isolated from *C. aenigma*, *C. nitida and C. wadei*[34,36-38,43]. Fatty acid methyl esters were identified in *C. edentata*, *C. flabellata*, *C. lacrimans*, *C. nitida* and *C. riuminiana*[32,35,37,47]. Long chain 1-alkene has been identified in leaflets of *C. curanii*, *C. flabellata*, *C. mindanaensis* and *C. riuminiana* [30,32,35,36]. Some hydrocarbons were obtained from *C. mindanaensis* and *C. wadei*[36,38].

3. TRADITIONAL AND PHARMACOLOGICAL USES

Cycas species have variable uses that could be classified into three types; edible, medicinal and ornamental uses. They can be used as source of food as in Australia and Asia (India and Japan), where the starch of stem is extracted and prepared in the form of Sago. The megasporophylls can be used for regulating the flow of vital energy and pain resulted from disorders of various organs. Also it is useful for kidneys. Seeds are used in hypertention, rheumatic pains and cold[50]. *C. circinalis* is exported from Japan as an ornamental where it is used for bosai[51].

3.1. Traditional uses

The traditional uses of *Cycas* species revealed a few medicinal properties possessed by these species. For example, *C. rumphi* seeds are used as emetic and for boils and sores treatment. *C. rumphi* pollen is believed to be narcotic. Stem of *C. pectinato* is used as hair wash in diseased hair roots. The peculiar odor of *Cycas* male cones

Table 5. Other compounds from the genus *Cycas*.

No.	Compound	Chemical class	Mol.wt	Plant source	Organ	Ref.
(76)	4-hydroxymethyl-3,5-dimethyldihydro-2-furanone	Furanone	$C_7H_{12}O_3$ (144.17)	*C. sancti-lasallei*	Petiole, rachis and sclerotesta	44
(77)	α-tocopherol	Type of vitamin E	$C_{29}H_{50}O_2$ (430.7071)	*C. mindanaensis*	Leaflets	36
				C. riuminiana		32
				C. wadei	Megasporophyll lamina	38
(78)	Palmitic acid	Saturated fatty acid	$C_{16}H_{32}O_2$ (256.43)	*C. panzhihuaensis*	leaves	17
(79)	Oleic acid	Monounsaturated fatty acid	$C_{18}H_{34}O_2$ (282.4680)	*C. lacrimans*	Leaflets	27
				C. wadei	Sarcotesta	38
(80)	Linoleic acid	Doubly unsaturated fatty acid	$C_{18}H_{32}O_2$ (280452)	*C. riuminiana*	Leaflets	32
				C. wadei	Sarcotesta	38
(81)	Monoacylmonogalactosylglycerol	Glycerol derivatives	$C_{28}H_{48}O_9$ (528.683)	*C. lacrimans*	Sarcotesta	48
(82)	1,2-dioleylglycerol	Glycerol derivatives	$C_{40}H_{73}O_6$ (650.018)	*C. lacrimans*	Leaflets	27
(83)	Triacylglycerol fatty acid esters	Glycerol derivatives		*C. aenigma*	petiole and rachis	31
				C. curanii	Endotesta, sarcotesta, leaflets, petiole and roots	11
				C. lacrimans	Bark, leaflets, endotesta and sclerotesta	46
				C. mindanaensis	Roots, petiole and rachis	36
				C. nitida	Roots, Sarcotesta and sclerotesta	37
				C. riuminiana	Leaflets, endotesta and sarcotesta	32
				C. wadei	Sclerotesta, endotesta and megasporophyll lamina	38
(84)	Trilinolein	Triglyceride	$C_{57}H_{98}O_6$ (879.405)	*C. wadei*	Sarcotesta	38
(85)	1-methyl-*β*-D-glucose	Monosaccharide	$C_6H_{14}O_6$ (194.183)	*C. circinalis*	Leaflets	7
(86)	Chlorophyll a	Green pigments chlorophyll	$C_{36}H_{37}MgN_4O_5$ (630.02)	*C. curanii*		30
				C. edentate		29
				C. zambalensis		47
(87)	N-(3′-one-5′-methyl)hexyl-alanine	Non-protein amino acids	$C_{10}H_{19}NO_3$ (201.266)	*C. armstrongi*	Leaflets	11
(88)	Cycasin	Glucoside	$C_8H_{16}N_2O_7$ (252.223)	*C. revoluta*	seeds	49

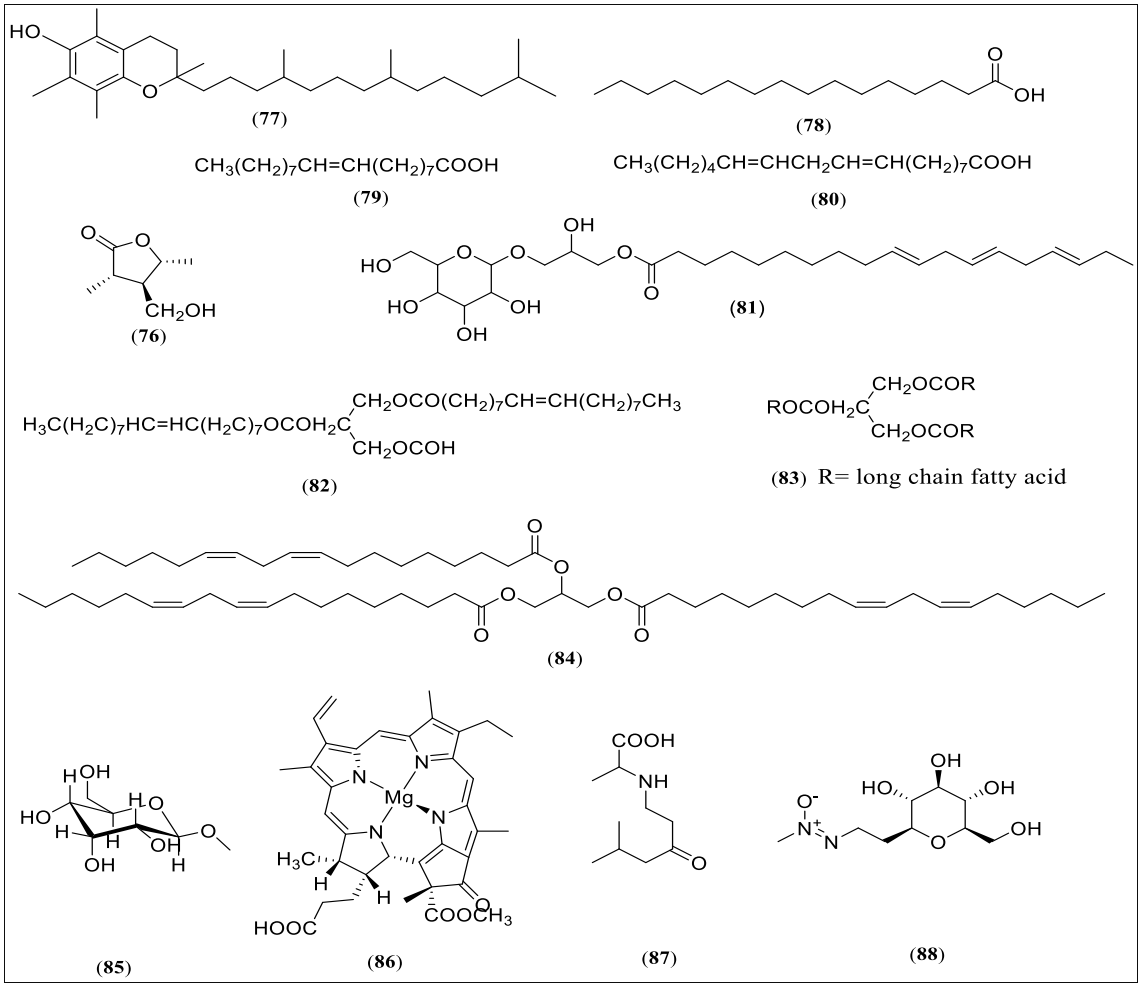


Figure 5. Other compounds from genus *Cycas.*

Table 6. Traditional uses of of the gynus *Cycas.*

Plant	Organ	Country	Traditional Use	Ref.
C. beddomei	Male cones	India	Major ingredient in rejuvenating tonics	50
C. circinalis	Bark and seeds	Southern Asia, Indonesia and Philippines.	Sores and swelling	54, 55
	Pollen		Narcotic	54, 55
	Tender leaves		Flatulence and vomiting	54, 55
	Terminal bud	Colombia	Dressing of ulcerated wounds, of swollen glands, and of boils	54, 55
C. pectinata	Pounded stem	Assam (India)	Hair wash for diseased hair roots	55
C. revoluta	Seeds	Indonesia	An emetic	56
	Seed flour	Ceylon	Bowel complains and hemorrhoids	56
	Tender leaves	Indonesia	Flatulence and vomiting	56
	Male bracts	India	Narcotic, stimulant and aphrodisiac properties	56
	Female cone	India	Relief kidney pain	56
C. rumphii	Pollen	India	Narcotic	56
	Male cone bracts		Anodyne	

expel bugs, sometimes rats[52,53]. Among *Cycas* species, *C. beddomei*, *C. circinalis*, *C. revoluta* and *C. rumphii* have been reported as important folk species. A summary of their used organs, geographical distribution, and traditional uses are presented in Table 6.

3.2. Pharmacological activities

Reviewing the literature, several biological activities have been reported, such as; antimicrobial, anti-oxidant, anti diabetic, cytotoxic, anthelmintic, analgesic, anti-arthritic, anti-inflammatory, thrombolytic and neuropharmacological defects treatments. This part highlights the pharmacological aspects carried out on the extracts and/or the isolated pure compounds, in a

trial for its possible potential as medicinal agents.

3.2.1. Antimicrobial activity

Kalpashree and Raveesha tested the water, petroleum ether, chloroform and methanol extracts of sarcotesta, sclerotesta and endotesta of *C. circinalis* for their activity against *B. cereus* (MTCC 1272), *S. aureus* (MTCC 7443), *E. coli* (MTCC 7410) and *Xanthomonas axonapodis* pv malvacearum (plant pathogenic bacteria; isolated from cotton plant) by agar cup diffusion method. Results revealed that only methanol extract of ovule-endotesta showed activity against all the tested bacteria higher than that of Vancomycin and Penicillin[57]. Moawad et al. studied the antimicrobial activity for thirteen biflavonoids (**18**, **20**, **22-24, 26-29**& **32-35**) isolated from *C. circinalis* and *C. revoluta* leaflets using CLSI methods. They concluded that compounds **27-29** displayed moderate antibacterial activity against *S. aureus* (IC_{50} values of 9.6, 3.8 and 8.2 µM, respectively) and MRSA (IC_{50} values of 12.5, 5.9 and 11.5 µM, respectively). Compounds (**18**, **20**, **22-24, 26-29**& **32-35**) showed no antifungal, antimalarial, or antileishmanial activity[8]. The antimicrobial activity of *C. circinalis* ethanolic extract was studied by Kirby-Bauer disk diffusion method using eight microorganisms; *Aspergillus niger, A. flavus, A. oryzae, Penicillium chrysogenu, B. subtilis, E. coli, Salmonella typhi* and *S. aureus*. It showed 0.7 mm of the zone of inhibition for *Staphylococcus aureus* with no activity with other species[58].

The hydroalcoholic and chloroform extracts of leaves of *C. revoluta* were tested for activity against some microorganisms by well diffusion method. Hydroalcoholic extracts of *C. revoluta* leaves showed a potent activity against *E.coli, Klebsiella pneumoniae* and *Saccharomycesc cerevisae* while chloroform extract showed similar activity against *E.coli* and *Saccharomyces cerevisae*. But it showed no activity against *Lactococcus* sp., *Streptococcus pyogenes*, *Aspergillus niger* and *Candida albicans*[59]. Methanol, ethanol and ethyl acetate extracts of *C. revoluta* leaves were subjected to their activity against six bacterial strains including both Gram-positive and Gram-negative bacteria; *E. coli, S. aureaus, P. aeruginosa, S. typhimurium, K. pneumonia* and *B. subtilis* using Agar well diffusion method. The extracts showed antibacterial activity against all strains producing zone of inhibition ranging from 40.33±0.66 to 25±0.34 mm[60]. Prunin (naringenin-7-*O*-glucoside; **7)**, vitexin-2″-rhamnoside **(11)**, (2S)I-(2,3)-dihydro-I-7-O-*β*-D-glucopyranosylamentoflavone **(28)**, (2S)-I-(2,3)-dihydro-I-7, II-7-di-O-*β*-D-glucopyranosylamentoflavone **(31)** and protocatechuic acid **(66**) showed low activities against *Candida albicans* ATCC90028, *C. glabrata* ATCC 90030, *C. krusei* ATCC 6258, *Cryptococcus neoformans* ATCC 90113 and *Aspergillus fumigatus* ATCC 204305, as well as *Staphylococcus aureus* ATCC 29213, *methicillin-resistant S. aureus* ATCC 33591, *E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853 and *Mycobacterium intracellulare* ATCC 23068 (IC_{50} > 10mg/mL). vitexin-2″-rhamnoside (**11**) from *C. revoluta* showed significant activity towards *Leishmania donavani* (IC_{50} = 13.8 mM, IC_{90} = 34.6 mM) comparing with amphotericin B (IC_{50} = 0.1 mM, IC_{90} = 0.35 mM) as positive control[10]. Hydro-alcoholic and chloroformic extracts of leaves and chloroformic extracts of cones of *C. revoluta* were screened for their antimicrobial activity against certain bacterial and fungal strains along with MRSA. The results showed that the extracts and (2S)-2,3-dihydro-4′*O* -methylamentoflavone (**34**) showed a good activity against MRSA, *E. coli, Salmonella abony, Aspergillus niger* and *Candida albicans*[21]. Novel antimicrobial peptides from *C. revoluta* showed 50% inhibition of the growth of plant pathogenic fungi, Gram-positive and Gram-negative bacteria (IC_{50} = 7.0-8.9 µg/ml)[61]. The chloroformic and hydro-alcoholic extracts of leaves and female cones of *C. revoluta* were tested against MRSA, E. coli, *Salmonella abony*, *Aspergillus niger*, *Candida albicans* and other pathogens. The results showed that both the leaves and female cones of *C. revoluta* are potent antimicrobial agents. Besides that chloroformic extracts of the cones exhibited a potent antimicrobial activity in comparison to the chloroformic extracts of leaves[62].

The antibacterial activity of *C. siamensis* seed extract was studied using filter paper method, agar dilution and fluorescent staining methods. The extract showed a strong antibacterial activity[63].

3.2.2. Anti-oxidant activity

The *in vitro* anti-oxidant activity of *C. pectinata* leaves methanol extract was evaluated by DPPH scavenging assay. It exhibited a moderate radical scavenging activity (IC_{50} = 631.44 µg/mL) in comparing ascorbic acid (IC_{50} = 19.08 µg/mL)[64]. *In vitro* anti-oxidant activities of hydroalcoholic and chloroform extracts *C. revoluta* leaves were

determined by superoxide anion radical scavenging activity. The hydroalcoholic extract showed potent anti-oxidant activity in comparison to chloroform extract[59]. Methanol, ethanol and ethyl acetate extracts of *C. revoluta* leaves were tested for their anti-oxidant potential using DPPH assay.

All extracts gave a potent anti-oxidant activities; while, the strongest activity was observed (110.25 µg/ml) in case of methanolic extract[60]. Neohesperdine (**6**), amentoflavone (**18**) and amentoflavone- 4′-*O*- *α*-D- glucopyranoside (**19**) from *C. revolute* showed anti-oxidant activity nearly two to four folds higher than that of quercetin at a dose of 12.5 µg/mL when tested using DPPH method[9].

3.2.3. Antidiabetic activity

Amentoflavone (**17**) and 2,3-dihydroamentoflavone (**29**) isolated from the fruits of *C. pectinata* and exhibited a significant inhibitory potency against *α*-glucosidase (IC_{50} 8.09±0.023 and 9.77±0.032 µM, respectively) and α-amylase (IC_{50} 73.6±0.48 and 39.69±0.39 µM, respectively)[18].

3.2.4. Cytotoxic activities

The ethyl acetate extract of *C. revoluta* leaflets showed weak cytotoxic effect against human hepatocarcinoma cell line (Hep-G2 cells, IC_{50} = 207.9 mg/mL); however, it showed moderate cytotoxic effect against raw murine macrophage (RAW 264.7, IC_{50} = 160.8 mg/mL)[10]. Negm et al., (2016) studied the activity of *C. revoluta* methanol extract and its fractions (petroleum ether, methylene chloride, ethyl acetate and n-butanol) against MCF7 breast cancer cell and HepG2 liver cancer cell line using SRB assay. Ethyl acetate fraction showed the highest inhibitory activity (69.06%) against MCF7 cell line followed by n-butanol and methylene chloride fractions (66.58% and 65.93%, respectively). n-Butanol fraction was the most active extract against HepG2 cell line (68.4%) followed by petroleum ether and methylene chloride (64.12% and 62.15%, respectively)[9]. Neohesperdine (**6**), Amentoflavone (**18**) and Amentoflavone- 4′- *O-α* D-glucopyranoside (**19**) were isolated from *C. revoluta* and showed strong activity (IC_{50} = 4.73, 18.7 and 6.12 µg/mL) against MCF 7 cell line compared to doxorubicin as a standard (IC_{50} = 4.13 µg/mL)[9]. The methanolic extract of *C. revolute* cone was evaluated for anti-colon cancer property by using Cell Viability Assay, Colony Formation Assay, ROS Determination, Flow cytometry, DAPI staining assay, Tunel assay. The extract showed significant anti-colon cancer activity by reducing proliferation and inducing apoptosis in colon cancer cell (HCT-8) line. The IC_{50} value was found to be 500 ± 1.09 µg/mL against HCT-8 cell[65].

3.2.5. Anthelmintic activity

Evaluation of the anthelmintic potential of aqueous, alcoholic and methanolic extracts of *C. beddomei* against *Pheretima posthuma* was carried out. Results indicated that the leaf and male cone extracts showed higher activity than bark extracts. While, pith and female cones did not show any activity[66].

3.2.6. Analgesic activity

Analgesic activity of methanol and aqueous extracts of male cone of *C. beddomei* (250 to 1000 mg) was tested using acetic acid-induced writhing test. Results showed that extracts exhibited activity compared to that of diazepam at 10 mg concentration[67].

3.2.7. *Anti-arthritic activity*

The methanol extract of *C. beddomei* male cone at 250, 500 and 1000 mg concentrations and aqueous extract at 1000 mg showed more significant activity comparing to the standard drug Diclofenac in minimizing arthritis[67].

3.2.8. Anti-inflammatory activity

The anti-inflammatory activity of methanol extract of *C. pectinata* leaves was evaluated by a protein denaturation assay. The 500 µg/mL of methanol extract showed 38.12% of the maximum protein denaturation inhibition, whereas diclofenac sodium showed 83.50% inhibition[64].

3.2.9. *Thrombolytic activity*

The methanol extract of *C. pectinata* leaves showed a moderate clot lysis ability in different concentrations and the 10 mg/mL concentration showed 35.72% ($P < 0.001$) clot lysis activity. The positive control streptokinase exhibited 74.52% clot lysis activity, while normal saline showed only a minor amount of clot lysis (4.49%)[64].

3.2.10. Treating neuropharmacological defects

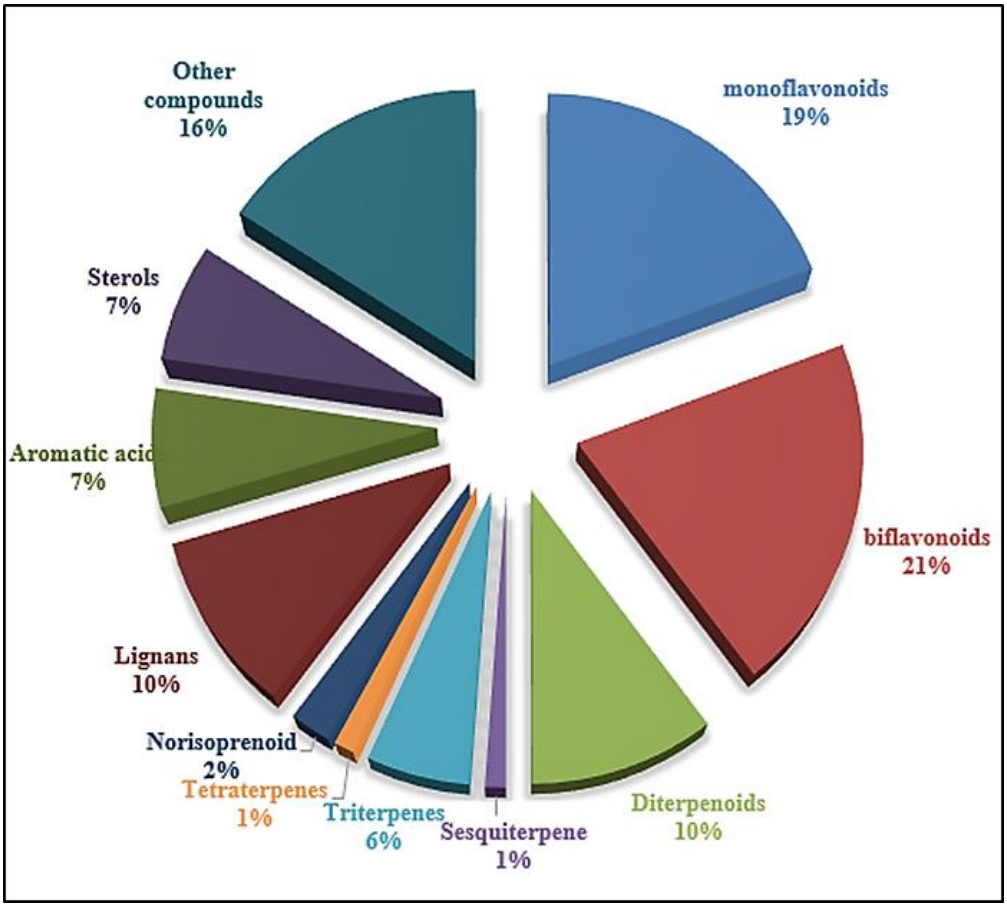


Figure 6. Distribution of different chemical classes in genus *Cycas.*

The methanol extract of *C. pectinata* leaves was evaluated for treating the neuropharmacological defects. It induced a dose-dependent reduction in locomotor activity, with a significant anxiolytic effect[64].

4. CONCLUSIONS

To date, phytochemical investigations on *Cycas* species afforded a total of eighty-eight different chemical constituents from only nineteen species. These phytoconstituents belong to variable classes of secondary metabolites (Figure 6). All flavonoids (**1**-**35**) were identified in the different leaves except four flavonoids; tetrahydrohinokiflavone (**24**) from *C. beddomei* stems and *C. revoluta* leaflets, 7,7″-di-*O*-methyltetrahydrohinokiflavone (**25**) from *C. beddomei* stems, 2,3-dihydroamentoflavone (**29**) from *C. armstrongii*, *C. revoluta* and *C. circinalis* leaflets and *C. pectinata* fruits, (2S)-2,3-dihydro-4′*O* –methy lamentoflavone (**34**) from *C. circinalis* and *C. revoluta* leaflets and female cones. Terpene compounds including; sesquiterpenoides, diterpenoides, triterpenoids as well as tetraterpenoids are isolated from *Cycas* species. Diterpenoids (**36**-**44**) were detected in leaves (five compounds), sarcotesta (one compound), endotesta (one compound), roots (three compounds) and bark (three compounds). One sesquiterpene**;** Selen-4(15)-en-1β-11-diol (**45**) was isolated from *C. wadei* roots. Triterpenes (**46**-**50**) were isolated from male cone (one triterpene), roots (two triterpenes), leaves (two triterpene), microsporophyll lamina (one triterpene), sarcotesta (one triterpene) and bark (one triterpene). Two tetraterpenes; *β*-carotene (**51**) and lutein (**52**); were reported from genus *Cycas*. (−)-loliolide (**53**) and (6S,7E,9S)6,9-dihydroxy-4,7-megastigmadien -3-one (vomifoliol; **54**) are two norisoprenoid separated only from leaflets of *C. circinalis* and *C. revoluta* in genus *Cycas*. Lignans (**55**-**63**) were isolated from leaflets (7 compounds), cones (4 compounds, sclerotesta (1 compound) and root (1 compound). Aromatic acid and simple phenolic derivatives (**64**-**69**) were identified in leaflets (four compounds) and sclerotesta (two compounds). Other classes as furanone derivatives, carotenoids, saturated and unsaturated fatty acids, glycerol derivatives, monosaccharide, non-protein amino acids and glucoside were also rarely detected in this genus.

It is noteworthy that, although more than one hundred species are now included under genus *Cycas*, few species have been investigated. Only nineteen out of 117 species, have been phytochemically and biologically studied. About 15 flavonoid compounds of 88 identified compounds have been studied for their biological activities as; α-glucosidase inhibitory, antileishmanial, anti-oxidant and cytotoxic effects. More studies on the extracts of plants and compounds; especially non-flavonoids compounds; isolated from this genus should be carried out; in order to validate their medicinal values, toxicity and confirming their traditional uses. This article compactly reviews the phytochemistry and biological activities of genus *Cycas.* This is an attempt to document the information on different *Cycas* species and to highlight the needs for more research in the future.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

None to declare.

Ethics approval

None to declare.

Article info:

Received October 6, 2020
Received in revised form January 27, 2021
Accepted January 28, 2021

References:

1. Bhatnagar S, Moitra A. Gymnosperms: New age international; 1996.
2. Johnson LA. The families of Cycads and the Zamiaceae of Australia; 1959.
3. Walters T, Osborne R. Cycad classification: concepts and recommendations: CABI; 2004.
4. Calonje M, Stevenson D, Stanberg L. The world list of Cycads, online edition [Internet]. 2013-2019. 2019.
5. Rashid A. An introduction to archegoniate plants: Vikas Publishing House; 2016.
6. Watson RR. Complementary and aternative therapies and the aging Population: An evidence-based approach: Academic Press; 2011.
7. Moawad A. Comparative phytochemical and biological study of certain plants of family Cycadaceae cultivated in Egypt. Ph.D. [Thesis]. Beni-Suef: Beni-Suef university; 2011.
8. Moawad A, Hetta M, Zjawiony JK, Jacob MR, Hifnawy M, Marais JP, et al. Phytochemical investigation of *Cycas circinalis* and *Cycas revoluta* leaflets: moderately active antibacterial biflavonoids. Planta Med. 2010;76 (08):796-802.
9. Negm WA, Ibrahim AE-RS, El-Seoud KA, Attia GI, Ragab AE. A New cytotoxic and antioxidant amentoflavone monoglucoside from *Cycas revoluta* Thunb growing in Egypt. J Pharm Sci Res. 2016;8(5):343.
10. Moawad A, Hetta M, Zjawiony JK, Ferreira D, Hifnawy M. Two new dihydroamentoflavone glycosides from *Cycas revoluta*. Nat Prod Res. 2014;28(1):41-7.
11. Ismail A, Hassan HM, Moawad AS, Abdel Fattah SM, Sherif NH, Abdelmohsen UR, et al. Chemical composition and therapeutic potential of three *Cycas* species in brain damage and pancreatitis provoked by γ-radiation exposure in rats. J Radiat Res Appl Sci. 2020;13(1):200-14.
12. Yan Z, Shu Lin P, Chao Luan L, Ming Kui W, Li Sheng D. A new C-glycosylflavone from the leaves of *Cycas panzhihuaensis*. J Integr Plant Biol. 2002;44(1):101-3.
13. Xu Y, Dai QC, Luan ZZ, Xiang Z, Wu J, Fan YL, editors. The isolation and identification compounds from *Cycas revoluta*. Medicine and Biopharmaceutical: Proceedings of the 2015 International Conference; 2016: World Scientific.
14. Ragasa CY, Ng VAS, Agoo EMG, Shen CC. An isoflavonoid phtoalexin and a sesquiterpene from *Cycas wadei*. Int J Pharmacogn Phytochem. 2016;8(4):686-9.
15. Rowe JW. Natural products of woody plants: chemicals extraneous to the lignocellulosic cell wall: Springer Science & Business Media; 2012.
16. Rani MS, Rao CV, Gunasekar D, Blond A, Bodo B. A biflavonoid from *Cycas beddomei*. Phytochemistry. 1998;47(2):319-21.
17. Zhou Y, Zhang X, Jiang S, Li C, Peng S. Chemical constituents of *Cycas panzhihuaensis*. Chin J Appl Environ Biol. 1999;5:367-70.
18. Laishram S, Sheikh Y, Moirangthem D, Deb L, Pal B, Talukdar N, et al. Anti-diabetic molecules from *Cycas pectinata* Griff. traditionally used by the Maiba-Maibi. Phytomedicine. 2015;22(1):23-6.
19. Uddin Q, Malik A, Azam S, Hadi N, Azmi A, Parveen N, et al. The biflavonoid, amentoflavone degrades DNA in the presence of copper ions. Toxicol In Vitro. 2004;18(4):435-40.
20. Jayaprakasam B, Damu A, Gunasekar D, Blond A, Bodo B. A biflavanone from *Cycas beddomei*. Phytochemistry. 2000;53(4):515-7.
21. Sharma R, Katiyar A, Mathur A. Screening of solvent extracts of *Cycas revoluta* for isolation of antimicrobial compound. Biolife. 2014;2(4):1218-28.
22. Dewick PM. Medicinal natural products: a biosynthetic approach: John Wiley & Sons; 2002.
23. Ragasa CY, Ng VAS, Agoo EMG, Shen CC. Diterpenes from *Cycas nitida*. Pharm Lett. 2016;8(1):148-52.
24. Ragasa C, Ng VA, Agoo EM, Shen CC. Monoacyl monogalactosyl glycerol from *Cycas lacrimans*. Int J Toxicol Pharmacol Res. 2015;7:259-63.
25. Ragasa CY, Ng VAS, Agoo EMG, Shen CC. An isopimarane diterpene from *Cycas sancti-lasallei*. Scholars Research Library. 2015;7(9):168-71.
26. Ragasa CY, Ng VAS, Agoo EMG, Shen CC. Chemical constituents of *Cycas edentata*. Int J Pharm Sci Rev Res. 2015;33(2):107-9.
27. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Chemical constituents of *Cycas lacrimans*. Int J Pharmacog Phytochem Res. 2015;7(3):616-20.
28. Ragasa CY, Ng VAS, Agoo EMG, Shen CC. Terpenoids and sterols from *Cycas vespertilio*. Chem Nat Compd. 2016;52(3):536-8.

29. Ragasa CY, Ng VAS, Agoo EMG, Shen CC. Chemical constituents of *Cycas Zambalensis*. Chem Nat Compd. 2016;52(1):136-8.
30. Ng VAS, Agoo EM, Shen CC, Ragasa CY. Chemical constituents of *Cycas curanii* (J. Schust.) KD Hill. Int J Pharm Clin Res. 2015;8(1):100-3.
31. Vincent Antonio S. Ng EMGA, Chien-Chang Shen, and Consolacion Y. Ragasa Secondary Metabolites from *Cycas aenigma*. Res J Pharm Biol Chem Sci. 2015;6(6) :267-70.
32. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Chemical constituents of *Cycas riuminiana*. Der Pharma Chem. 2015;7(10):485-9.
33. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Chemical constituents of *Cycas sancti-lasallei*. J Appl Pharm Sci. 2015;5(1):012-7.
34. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Secondary metabolites from the male cone of *Cycas vespertilio*. Int J Pharmacog Phytochem Res. 2015;7(4):727-31.
35. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Secondary metabolites from *Cycas flabellata*. Res J Pharm Biol Chem Sci. 2016;7(2):1653-7.
36. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Chemical constituent of *Cycas mindanaensis*. Der Pharma Chem. 2015;7(12):323-7.
37. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Chemical constituents of *Cycas nitida*. Res J Pharm Biol Chem Sci. 2015;6(6):1305-9.
38. Ragasa CY, Ng VAS, Agoo EMG, Shen CC. Chemical constituents of *Cycas wadei*. Der Pharma Chemica. 2015;7(11):294-8.
39. Ragasa C, Ng V, Agoo E, Shen C. A neolignan from *Cycas sancti-lasallei*. Der Pharma Chem. 2015;7(7):373-6.
40. Mahattanatawee K, Rouseff R, Valim MF, Naim M. Identification and aroma impact of norisoprenoids in orange juice. J Agric Food Chem. 2005;53(2):393-7.
41. Bandichhor R, Basler B, Brandes S, Hiersemann M, Helmboldt H, Nosse B, et al. Natural product synthesis I: targets, methods, oncepts: Springer Science & Business Media; 2005.
42. Ragasa CY, Ng VAS, Agoo EMG, Shen CC. Chemical constituents of *Cycas vespertilio*. Rev Bras Farmacogn. 2015;25(5):526-8.
43. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Chemical constituents of *Cycas aenigma*. J Appl Pharm Sci. 2015;5(09):032-6.
44. Ragasa C, Ng VA, Agoo EM, Shen CC. Lignans and a furanone from *Cycas sancti-lasallei*. Int J Pharmacogn Phytochem Res. 2015;7:884-7.
45. Dakshini K, Foy CL. Principles and practices in plant ecology: allelochemical interactions: CRC press; 1999.
46. Ng VAS, Agoo E, Shen CC, Ragasa CY. Secondary metabolites from *Cycas lacrimans*. Int J Pharm Clin Res. 2015;7(5):356-9.
47. Ng VAS, Agoo EMG, Shen CC, Ragasa CY. Secondary metabolites from *Cycas edentata*. J Pharm Sci Res. 2015;7(9):643.
48. Ragasa CY, Ng VAS, Agoo EMG, CC. S. Monoacyl monogalactosyl glycerol from *Cycas lacrimans*. Int J Toxicol Pharmacol Res. 2015;7(5):259-63.
49. Nishida K, Kobayashi A, Nagahama T. Studies On cycasin, a new toxic glycoside, of *Cycas revoluta* Thunb: part 1. isolation and the structure of cycasin. Journal of the Agricultural Chemical Society of Japan. 1955;19(1):77-84.
50. Bahadur B, Rajam MV, Sahijram L, Krishnamurthy K. Plant biology and biotechnology: Volume I: Plant diversity, organization, function and improvement: Springer; 2015.
51. Duke JA. Handbook of nuts: herbal reference library. 1st Edition ed. Boca Raton: CRC press; 2017. p.135.
52. Alamgir AN. Therapeutic use of medicinal plants and their extracts: volume 1. Springer International Publishing AG; 2017. p.191.
53. Jain SK, DeFilipps RA. Medicinal plants of India: Reference Publications; 1991.
54. Chopra RN, Nayar SL, Chopra IC. Glossary of Indian medicinal plants: Council of Scientific & Industrial Research New Delhi; 1956.
55. Kumar A. Botany for Degree Students: Gymnosperms: S. Chand Publishing; 2006.
56. Williams C. Medicinal plants in Australia Volume 3: Plants, potions and poisons: Rosenberg Publishing; 2012.
57. Kalpashree M, Raveesha K. Antibacterial activity of *Cycas circinalis* ovules-a naked seeded gymnosperm. Int J Herb Med. 2013;1(3):53-5.
58. Ging S. Antimicrobial and antioxidant activity of *Cycas circinalis* L. and *Ionidium suffruticosum* Ging. Innov J Med Sci. 2016;5:12-4.
59. Mourya MK, Prakash A, Swami A, Singh GK, Mathur A. Leaves of *Cycas revoluta*: Potent antimicrobial and antioxidant agent. World J Sci Technol. 2011;1(10):11-20.
60. Zaffar M, Munis MFH, Rasul F, Masood S, Hassan SW, Imran M, et al. Biological assays of plant extracts from *Araucaria columnaris* and *Cycas revoluta*. J Food Agric Environ. 2014;12(1):128-31.
61. Yokoyama S, Kato K, Koba A, Minami Y, Watanabe K, Yagi F. Purification, characterization, and sequencing of antimicrobial peptides, Cy-AMP1, Cy-AMP2, and Cy-AMP3, from the Cycad (*Cycas revoluta*) seeds. Peptides. 2008;29(12):2110-7.
62. Lal K, Ahmed N, Mathur A. Study of the antimicrobial profile and phytochemical composition of solvent extracts of leaves and female cones of *Cycas revoluta*. Int J Curr Microbiol App Sci. 2017;6(4):2514-22.
63. Su Su Y, Wu Sa Q, Yao Z, Xiu Juan Y. Antibacterial activity of water extracts of *Cycas siamensis* seeds. J Anhui Agric Univ. 2017;2017(31):5.
64. Tareq AM, Farhad S, Uddin AN, Hoque M, Nasrin MS, Uddin MMR, et al. Chemical profiles, pharmacological properties, and in silico studies provide new insights on *Cycas pectinata*. Heliyon. 2020;6(6):e04061.
65. Bera S, Das B, De A, Barua A, Das S, De B, et al. Metabolite profiling and in-vitro colon cancer protective activity of *Cycas revoluta* cone extract. Nat Prod Res. 2020;34(4):599-603.
66. Alekhya C, Yasodamma N, Chaithra D. Anthelmintic activity studies on *Pheretima posthuma* with *Cycas beddomei* Dyer. leaf, bark, and male cone extracts. Int Jour Pharm Bio Sci. 2013;4(2):34-8.
67. Alekhya C, Yasodamma N. Analgesic and anti-arthritic activity of *Cycas beddomei* dyer. Male cone extracts. World J Pharm Res. 2016;5:1635-52.