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Review article

A review of phytochemical and biological studies of *Cycas* species growing in Middle East

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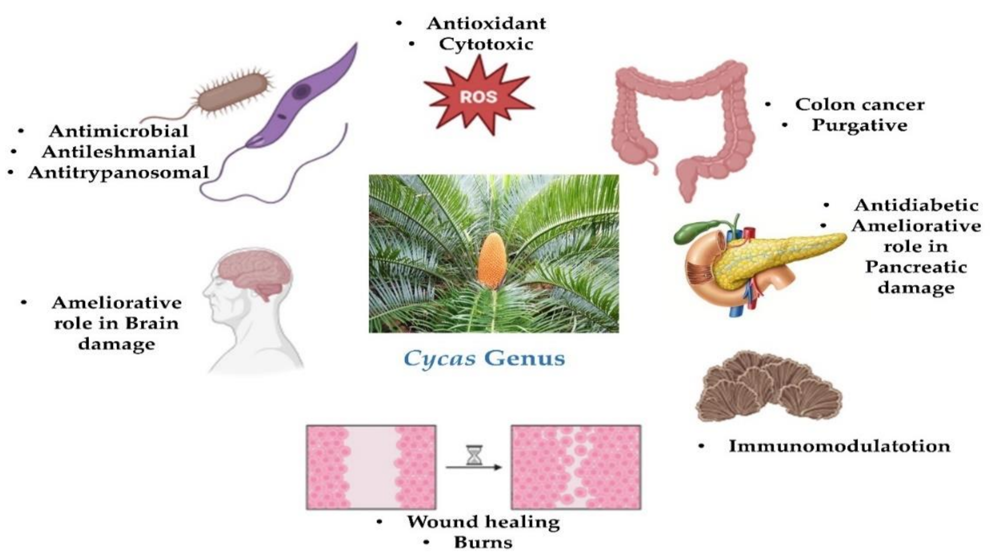
Abstract:

The genus *Cycas*, commonly known as cycads, represents a fascinating group of ancient gymnosperms with a lengthy evolutionary history that dates back to the Mesozoic era. The taxonomy, morphology, ecology, and conservation status of the genus *Cycas* are all covered in detail in this abstract. A review of phytochemical constituents and biological activities of *Cycas* species has been presented. Notably, while there are approximately 580 species of this genus distributed worldwide, only nine species grow in the Middle East, and just three of these have been studied phytochemically. *Cycas* species are of particular interest due to their unique evolutionary position, ecological roles, and potential medicinal properties. This review provides a comprehensive overview of the genus *Cycas*, integrating biological activity, chemical diversity, traditional knowledge, and economic and ecological significance. By synthesizing research across these fields, we seek to create a holistic view of the species, highlighting its historical, current, and potential future significance, relevance in the realms of ecology, ethnobotany, and medicine. Hence, this review highlights the phytochemical studies of *Cycas* species, underscoring their potential as a source of bioactive molecules with applications in medicine and beyond.

Keywords: *Cycas*, species, economic, phytochemical, traditional, pharmacological.



INTRODUCTION

For thousands of years, herbal remedies have played a significant role in the treatment and management of a wide range of diseases and improvement of the quality of human life. A large numbers of drugs, commonly used worldwide, are nowadays derived throughout scientifically based investigation of traditionally used remedies, especially medicinal plants. This trend facilitates medication with natural products rather than synthetic analogues, which could be harmful. The potential of higher plants as a source for new drugs is still largely unexplored. A relatively small number has been phytochemically investigated and the fraction submitted to biological or pharmacological screening is even smaller (1). According to taxonomy, there are more than a hundred species of *Cycas*, which are found in tropical and subtropical climates. They exhibit a great diversity in terms of leaf form, reproductive structures, and preferred habitats. *Cycas* species names are related to palms; the term "palm" in Greek means kykas, is where they got their name. The aerial trunk of *Cycas* plants is columnar, and their leaf crowns are pinnately complex. The stem is usually unbranched. a spiral-shaped crown of leaves at the top of the underground tuberous stems of immature plants. Cones are spirally aggregated reproductive organs made of highly modified leaves called sporophylls, which are produced by cyclops. Numerous sporangia, or pollen capsules, are carried by each male sporophyll and are often found on the underside. Although every female sporophyll is home to ovules, usually two (2). *Cycas* is known to be the only genus of family Cycadaceae and represented in Egypt (3), by nine species; *Cycas armstrongii* Miq., *Cycas revoluta* Thunb., *Cycas circinalis* L., *Cycas litoralis* K.D. Hill, *Cycas thouarsii* R.Br., *Cycas media* R.Br, *Cycas tansachana* K.D. Hill, *Cycas rumphii* Miq. and *Cycas pectinata* Griff. (4). In China and Japan, some available pharmaceuticals used for treatment of cancer and hepatitis contain *Cycas revoluta* Thunb. and *C. circinalis* L. plants (5), They were also directed for anticancer, antimicrobial, antimalarial and antileshmanial activities.

Taxonomy of *Cycas*

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Cycadophyta
Class	Cycadopsida
Order	Cycadales
Family	Cycadaceae
Genus	*Cycas*
Species	*Cycas armstrongii* Miq.
	Cycas circinalis L.
	Cycas revoluta Thunb.
	Cycas litoralis K.D. Hill
	Cycas media R.Br
	Cycas pectinata Griff
	Cycas rumphii Miq.
	Cycas tansachana K.D. Hill
	Cycas thouarsii R.Br.

Morphology

Cycas is the only genus currently recognized in the cycad family Cycadaceae. The most well-known species is *Cycas* revoluta, which is commonly grown under the names "sago palm, Japanese cycad, Sotetsu, king sago palm" despite not actually being a palm. The generic name comes from Greek kykas and means "palm tree". The species of this genus are concentrated around the equatorial regions. The plants are dioecious, and the family Cycadaceae is unique among the cycads in not forming seed cones on female plants, but rather a group of leaf-like structures each with seeds on the lower margins, and pollen cones on male individuals. *Cycas* plants are dioecious palm like trees with aerial or subterranean, cylindrical stems.

The caudex is cylindrical, surrounded by the persistent petiole base. Most species form distinct branched or unbranched trunks but in some species the main trunk can be subterranean with the leaf crown appearing to arise directly from the ground. Spirally arranged, pinnate or very rarely bipinnate, lower leaflets are frequently reduced to spines, and leaves are produced in seasonal growth flushes intermingled with cataphylls. Horizontal ptyxis circinate, longitudinal ptyxis erect or infrequently reflexed. Most species' stomata are restricted to the abaxial surface of the leaflets, which have a single, thick midrib and no lateral veins. Each ptyxis is involute. Pubescent leaves with simple or branching transparent hairs, at least when they are young. Each microsporophyll has a simple, sterile apex that frequently develops into an inverted spine. Microsporophylls are aggregated into determinate male cones. On its abaxial surfaces, every microsporophyll has a large number of microsporangia, or pollen sacs. Microsporangia with slits for opening. Megasporophylls are spirally arranged in an indeterminate terminal rosette, with the central axis continuing vegetative growth, and are loosely or tightly imbricate. Two to many (rarely one) ovules that are obliquely pointed outward (ascending), marginally implanted on the stipe. In the distal zone beyond the ovule-bearing stipe, megasporophyll apically dilated into a pinnatifid, pectinate, toothed, or whole lamina. The seeds are subglobular to ellipsoidal, and beneath the inner woody sclerotesta, there may or may not be spongy tissue. The outer sarcotesta is fleshy and can be yellow, orange, or brown. Endosperm haploid, generated from the female gametophyte. Embryo is straight, features a long, spirally twisted suspensor and two cotyledons that are typically connected at the tips. platyspermic seeds with cryptocotylar germination. Photographs of *Cycas* species growing in middle east are shown in Figure.1.

Ecological Significance of genus *Cycas*:

Cycads have an ancient fossil record, they are considered as living representatives of an ancient plant lineage and their interactions with animals (13). They play an important role in nitrogen fixation in soils and enhancing their fertility by the association with cyanobacteria, its commonly known as endosymbiosis (14).

Economic and Ethnobotanical significances of genus *Cycas*:

Indigenous tribes around the world have used the numerous species of the genus *Cycas* for a wide range of customary uses. Many elements of human life have benefited from the use of these ancient plants, also known as cycads, from food and medicine to cultural and ceremonial rituals. These are a few noteworthy traditional use for various *Cycas* species.

- Nutrition:

Sago palms, or *Cycas revoluta*, are among the most well-known *Cycas* species because of their starchy pith, which is taken out of the center of the trunk. For many indigenous populations in Southeast Asia and the Pacific Islands, processed sago has long been a staple diet. It is a substantial source of carbohydrates that is processed, extracted, and added to a number of traditional meals. (15), Cakes made in Sri Lanka are made from the starch extracted from its seeds (16).

- Traditional Medicine:

Cycas rumphii pollen grains are used to reduce discomfort and ease pain. *Cycas circinalis* seed paste is applied topically to heal wounds, boils, swellings, and skin conditions and is used to heal ulcers. For the purpose of preventing blood vomiting, young *Cycas revoluta* leaves are juiced, while blood vomiting, stomach issues, and many skin problems are treated using extract from its young plants. *Cycas revoluta* tincture made from its seeds is applied to certain conditions like as headache, nausea, and sore throat. A purgative is made by decocting seeds. Ulcerated sores and swollen glands are treated with *Cycas circinalis* terminal buds. Hair roots are treated with the stem of *Cycas pectinata* (16, 17).

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. Photographs of *Cycas* species growing in middle east are shown in Figure.1.

Figure 1. Photograph for *Cycas* species in middle east (1): *Cycas armstrongii* Miq., (2): *Cycas circinalis* L., (3): *Cycas revoluta* Thunb., (4): *Cycas litoralis* K.D. Hill ., (5): *Cycas media* R.Br, (6): *Cycas pectinata* Griff ., (7): *Cycas rumphii* Miq., (8): *Cycas tansachana* K.D. Hill ., (9): *Cycas thouarsii* R.Br. (6-12)

- Cultural and Ritual Importance:

Different *Cycas* Species: For indigenous groups, a variety of *Cycas* species have ceremonial and cultural significance (18) . Certain plants are included into ceremonies, rituals, and customs in some

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societies because they are revered. There can be symbolic significance to the existence of particular *Cycas* species in particular places.

- Constructions and fibers source:

Native American tribes have utilized some *Cycas* species, especially those with dense, sturdy wood, for building projects. These species provide wood that can be used to make tools, create traditional shelters, or even build ceremonial buildings. Traditional textiles have been woven using fibres that taken from the leaves or trunks of some *Cycas* species. These fabrics can be used to make baskets, apparel, and other objects of functional and cultural value. its leaves are utilised to make baskets, hats and mats (16).

- Insects Repellent:

Many *Cycas* species like *Cycas sphaerica* are used, as insect repellent properties have long been associated with the fronds of this plant. Frequently burned, these fronds produce compounds that repel pests and insects, offering a useful defense against annoyances (19).

- Ornamental purposes: Cycads often referred to as cycads, are well-liked options for ornamental landscaping because of their unique look, hardiness, and flexibility. Many species in the genus *Cycas* are grown for their beautiful appearance, which gives gardens, parks, and public areas a hint of ancient charm (20). Cycads are valuable decorative plants in areas with limited water supplies or sporadic water restrictions since they are typically resistant to drought conditions. They can endure in dry conditions because of their ability to hold water in their pithy stems. In addition, they can be found growing in a variety of soil types, such as clay, sandy, and loamy soils. Their versatility in landscaping projects is increased by this adaptability, which qualifies them for a range of garden designs and soil types; they are prized for their lengthy lifespans and for giving landscapes a timeless beauty as ornamental plants. These plants' slow growth guarantees that they keep their visual appeal for a long time, which helps to create sturdy and long-lasting garden elements in Urban areas (21). Sago palm or *Cycas revoluta*, one of the most extensively grown varieties, is the main applications of *Cycas* as an ornamental plant and is valued for its eye-catching and perfectly symmetrical feather-like fronds. Because of its glossy, deep green foliage, which create an exotic, tropical atmosphere, it's a popular choice for landscaping (22).

Chemical composition of genus *Cycas*:

The diverse range of chemicals and metabolic processes found in the chemistry of *Cycas* species, popularly referred to as cycads, have developed over millions of years. Since they are ancient gymnosperms, cycads provide a unique window into the chemical adaptations that have enabled these plants to flourish in a variety of global environments, predating even flowering plants. A fascinating story of natural chemicals, metabolic pathways, and ecological interactions is revealed by the chemistry of *Cycas* species, from their historic uses in indigenous societies to their contemporary applications in pharmacology and ecology. *Cycas* species exhibit a wide range of secondary metabolites and a vast repertory of phytochemical constituents. These comprise phenolic chemicals, alkaloids, flavonoids, and terpenoids, each of which adds to the distinct chemical signature of various *Cycas* species. The investigation of these phytochemicals offers important new information for a number of scientific fields in addition to providing evidence for the evolutionary tactics employed by cycads. Chemical investigation of the constituents of genus *Cycas* resulted in isolation and identification of including different classes as flavonoids, phenolic acids, catechins and sterols. All constituents are listed in Table (1), Figure (2).

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Table 1: List of reported compounds from different *Cycas* species

***C. armstrongii* Miq.**	**Phytochemistry**	N-(3'-one-5'-methyl)-hexyl-alanine, β-sitosterol, Stigmasterol, Naringenin, Kaempferol aglycone, Dihydroamentoflavone, Dihydrobilobetin, 2,3-Dihydrohinokiflavone, Amentoflavone, β-sitosterol glucoside, Isoginkgetin , Pruinin, Naringin, Vanillic acid, P- Coumaric acid, 4-Acetoxybenzoic acid butyl ester, Isopimara-7,15-dien-19-ol, Isopimara-7,15-diene, Phthalic acid dibutyl ester, Pregnane-3,12,14,20-tetrol, Pinoresinol, Glanduloidin C, Neo*Cycas*in A, Neo*Cycas*in J, Lanosterol, Salvileucolide methyl ester, β-carotene.(4). Vitexin, Vitexin-2″-rhamnoside, Caffeine (6). Catechin, Epicatechin, Epigallo-catechin 3-gallate (14)
	Biology	Antimicrobial, antileshmanial, antitrypanosomal, antioxidant and an ameliorative role on γ radiation toxicity in brain and pancreas (4)
***C. circinalis* L.**	**Phytochemistry**	Glucosyloxyazoxymethane (*Cycas*in) (23), Methylazoxymethanol (24), Caffeic acid , p-hydroxybenzoic acid, Vanillic acid, p-coumaric acid, Protocatechuic acid and Ferulic acid (25) N-(3'-one-5'-methyl)-hexylalanine and Leucine betaine (26) Naringenin, Dihydroamentoflavone, Dihydrobilobetin, Dihydroisoginkgetin, Tetrahydrobilobetin, Tetrahydroisoginkgetin, Amentoflavone, Bilobetin, Isoginkgetin, Dihydrohinokiflavone, Vitexin-glucoside, Vicenin-2, Catechin, Epicatechin, Gallocatechin, Epigallocatechin, Methyl glucose, Loliolide, Dihydrodehydrodiconiferyl alcohol, β-Sitosterol glucoside (27), a-amino-b-methylaminopropionic acid (28) Isopimara-7,15-dien-19-ol, Isopimara-7,15-diene, 9,12-Dihydroxy-15-nonadecenoic acid, Pinoresinol, Neo*Cycas*in A, Neo*Cycas*in J, Lanosterol, Salvileucolide methyl ester, β-carotene, Kaempferol-3-O-Rhamnosyl-(1→2)-galactoside (4)
	Biology	Antibacterial (29), immunomodulatory activity (30) Antimicrobial, antileshmanial, antitrypanosomal, antioxidant and an ameliorative role on γ radiation toxicity in brain and pancreas (4)
***C. revoluta* Thunb.**	**Phytochemistry**	Sotetsuflavone (31), Caffeic acid , p-hydroxybenzoic acid, Vanillic acid, p-coumaric acid, Protocatechuic acid and Ferulic acid (25). Sugars; Arabinose, Galactose, Fucose , Rhamnose, Methylrhamnose and Mannose (32). *Cycas*indene, *Cycas*thioamide (33) *Cycas*in and Macrozamin (34). Minerals; Ca, Mg, Fe, Zn (35) Polyphenols; Naringenin, Prunin, Dihydroamentoflavone, Dihydroamentoflavone monoglucoside,

		Dihydroamentoflavone diglucoside, Tetrahydroamentoflavone, Amentoflavone, Podocarpusflavone A, Hinokiflavone, Dihydrohinokiflavone, Dihydroisocryptomerin, Tetrahydrohinokiflavone, Vitexin rhamnoside, Vomifoliol, Lariciresinol, Isolariciresinol, Protocatechuic acid (27). 5,6,7,8,3',4'-hexamethoxyflavone , 5,6,7,8,4-pentamethoxyflavone, 7,3'-dihydroisoflavones (36) 4-Acetoxybenzoic acid butyl ester, Isopimara-7,15-diene, Isopimara-7,15-dien-19-ol, 5,8-Dihydroxy-9,12-octadecadienoic acid, 5-hydroxy-6,7,8-trimethoxy-flavanone, Neo*Cycas*in A, Neo*Cycas*in J, Lanosterol, Salvileucolide methyl ester, β-carotene, kaempferol 3-O-rutinoside (4)
	Biology	Colon cancer protective activity (37), antimicrobial (38), cytotoxic and antioxidant (39). Antileshmanial, antitrypanosomal, antioxidant and an ameliorative role on γ radiation toxicity in brain and pancreas (4)
***C. litoralis* K.D. Hill**	**Phytochemistry**	No reports
	Biology	
***C. media* R.Br**	**Phytochemistry**	a-amino-b-methylaminopropionic acid (40), Sequoyitol (41) and Macrozamin (42)
	Biology	Anti-Biofilm and antibacterial Activities (7)
***C. pectinata* Griff.**	**Phytochemistry**	Amentoflavone and 2,3-dihydroamentoflavone (8)
	Biology	Anti-diabetic (8)
***C. rumphii* Miq.**	**Phytochemistry**	Amentoflavone (43), *Cycas*indene (10) Caffeic acid , p-hydroxybenzoic acid, Vanillic acid, P-coumaric acid, Protocatechuic acid and Ferulic acid (25)
	Biology	Antibacterial (11)
***C. tansachana* K.D. Hill**	**Phytochemistry**	No reports
	Biology	
***C. thouarsii* R.Br.**	**Phytochemistry**	Shikimic acid, Quinic acid, Chlorogenic acid, Trigonelline, Ferulic Acid, Rosmarinic acid, Quercetin 3-O-glucuronide, Homoorientin, Hesperetin-7-O-neohesperidoside, Vitexin-2’’-O-rhamnoside, Delphinidin 3-rutinoside, Vitexin, Luteolin-7-O-glucoside, Kaempferol-7-neohesperidoside, Luteolin, , Isorhamnetin,, Prunin, Apigenin-7-O-glucoside , Peonidin-3-glucoside, Quercetin-3-Glucuronide, Naringenin, Apigenin, Genistein (12).
	Biology	Antibacterial activity and wound healing (12)

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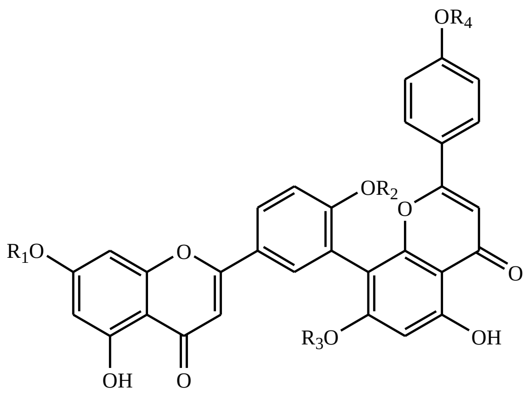
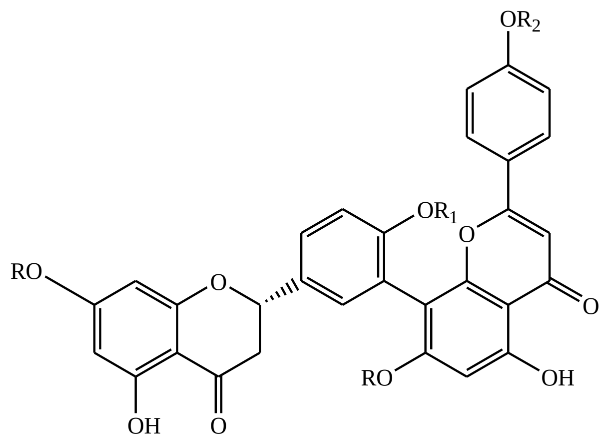
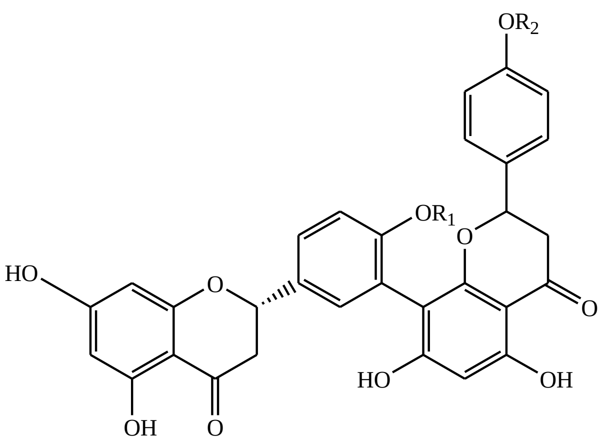


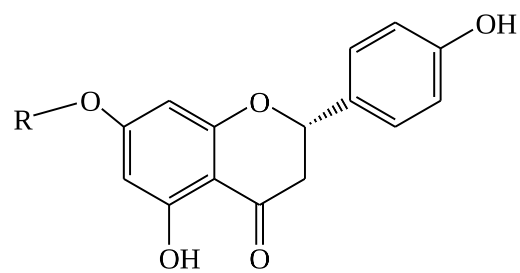
	R_1	R_2	R_3	R_4
Amentoflavone	H	H	H	H
Sotetsuflavone	H	H	CH_3	H
Podocarpusflavone A	H	H	H	CH_3
Bilobetin	H	CH_3	H	H
Isoginkgetin	H	CH_3	H	CH_3



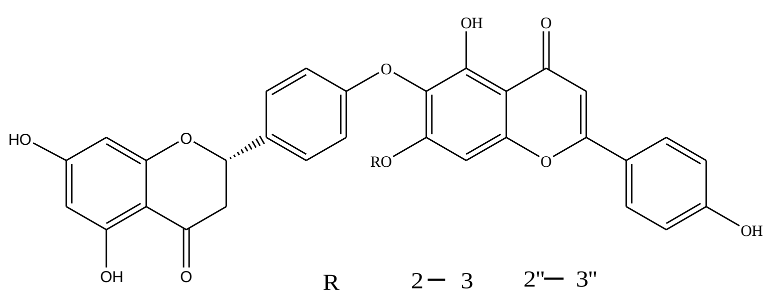
	R_1	R_2
Dihydroamentoflavone	H	H
Dihydrobilobetin	CH_3	H
Dihydroisoginkgetin	CH_3	CH_3



	R_1	R_2
Tetrahydroamentoflavone	H	H
Tetrahydrobilobetin	CH_3	H
Tetrahydroisoginkgetin	CH_3	CH_3

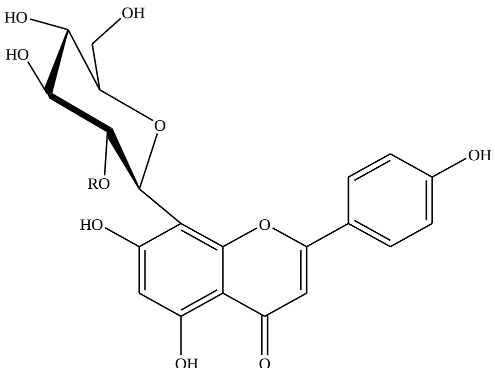


Naringenin	R = H
Prunin	R= β-D-glucose
Naringin	R = rhamnose (1→2) glucosyl

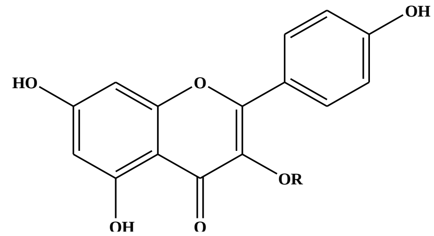


	R	2— 3	2''— 3''
Dihydrohinokiflavone	H		
Dihydroisocryptomerin	CH3		
Hinokiflavone	H	C=C H	
Tetrahydrohinokiflavone	H		CH–CH_2

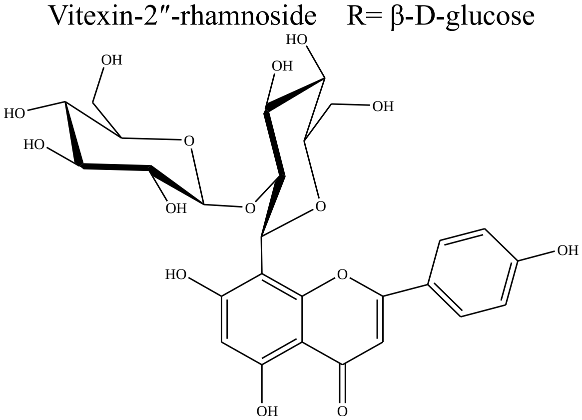
Figure 2: Structures of reported compounds from different *Cycas* species



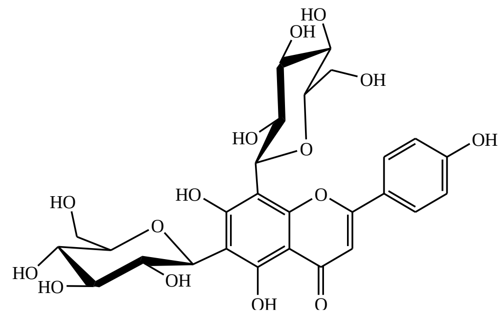
Vitexin R = H
Vitexin-2″-rhamnoside R= β-D-glucose



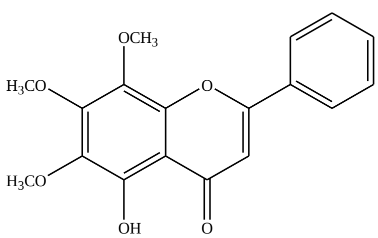
Kaempferol (R= H)
kaempferol 3-O-rutinoside
Kaempferol-3-O-Rhamnosyl-(1→2)-galactoside



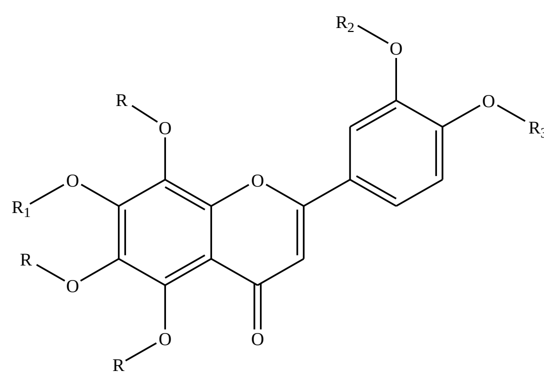
Vitexin-glucoside



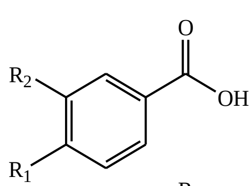
Vicenin-2



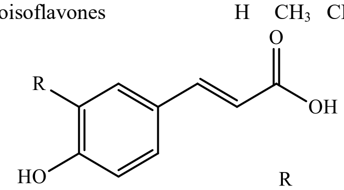
5-hydroxy-6,7,8-trimethoxy-flavanone



	R	R_1	R_2	R_3
5,6,7,8,3',4'-hexamethoxyflavone	CH_3	CH_3	CH_3	CH_3
5,6,7,8,4'-pentamethoxyflavone	CH_3	CH_3	H	CH_3
7,3'-dihydroisoflavones	H	CH_3	CH_3	H

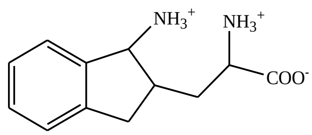


	R_1	R_2
p-Hydroxy benzoic acid	OH	H
Porotocatechuic acid	OH	OH
Vanillic acid	OH	OCH_3

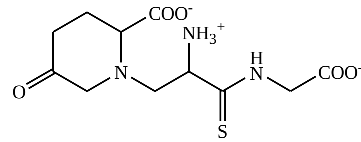


	R
Caffeic acid	OH
Ferulic acid	OCH3
P-Coumaric acid	H

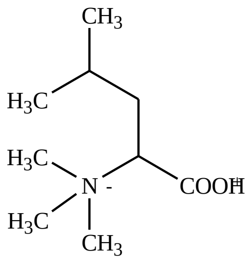
Figure 2. (Cont.)



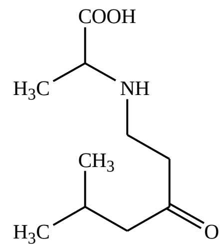
*Cycas*indene



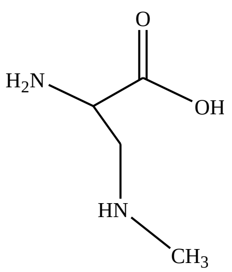
Cycathioamide



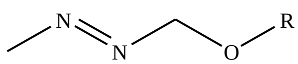
Leucine betaine



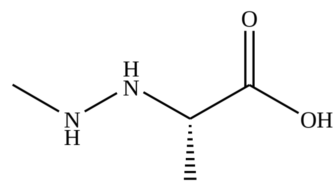
N-(3'-one-5'-methyl)-hexyl-alanine



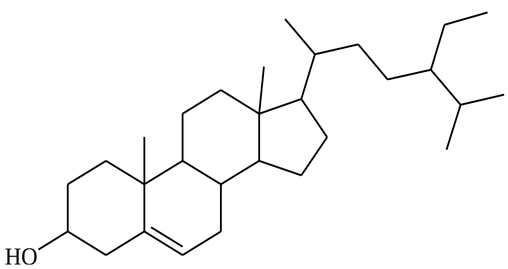
α-amino-β-methylaminopropionic acid (L-BMAA)



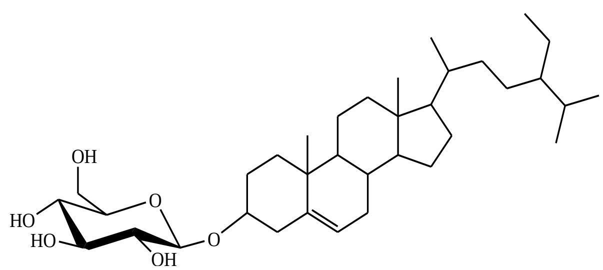
R= H MAM
R= B-D-glucose Cycasin



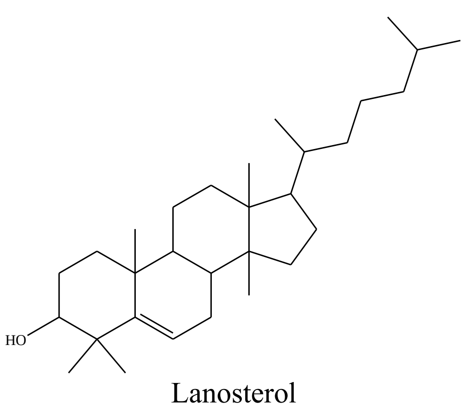
Methylaminoalanine



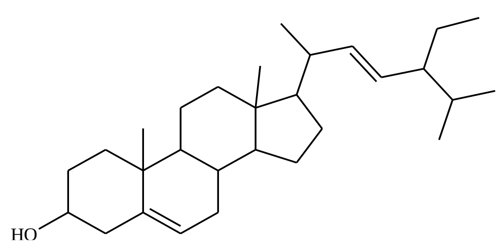
β-sitosterol



β-sitosterol glucoside

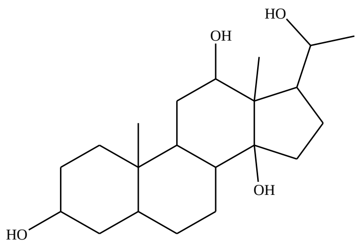


Lanosterol

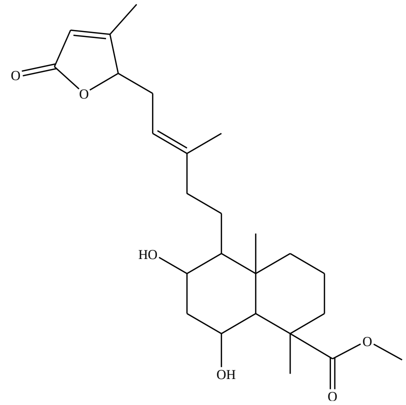


Stigmasterol

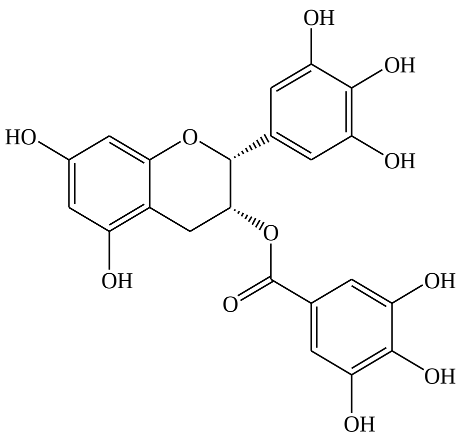
Figure 2. (Cont.)



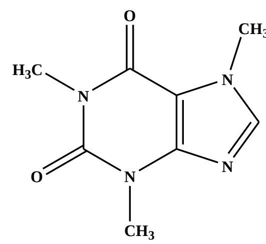
Pregnane-3,12,14,20-tetrol



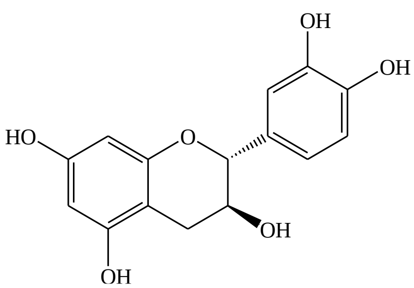
Salvileucolide methyl ester



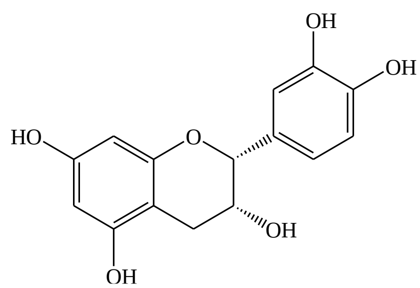
Epigallo-catechin 3-gallate



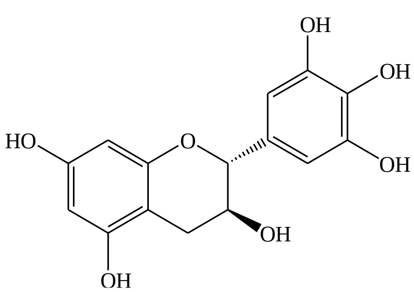
Caffeine



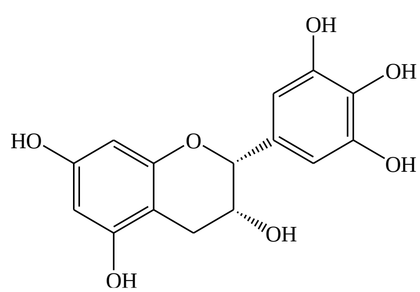
Catechin



Epicatechin

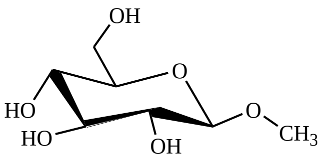


Gallocatechin

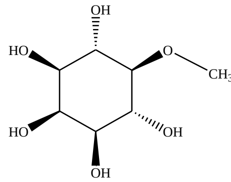


Epigallocatechin

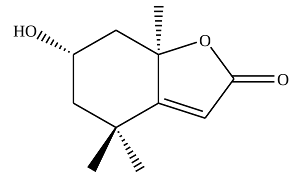
Figure 2. (Cont.)



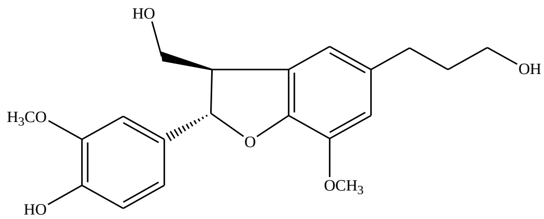
Methyl glucose



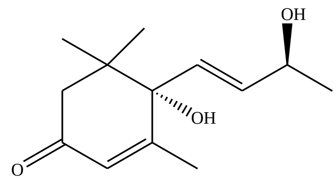
Sequoyitol



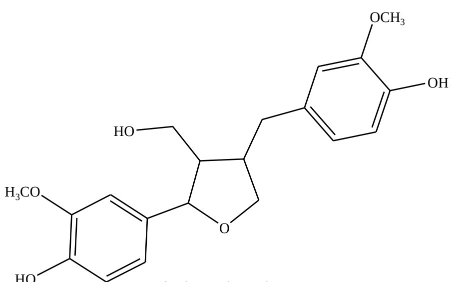
Loliolide



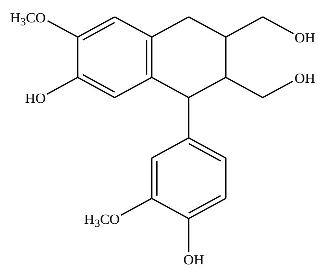
Dihydrodehydrodiconiferyl alcohol



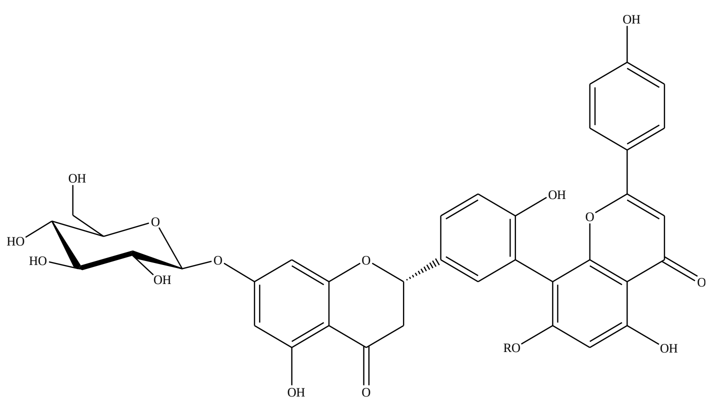
Vomifoliol



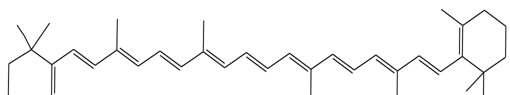
Lariciresinol



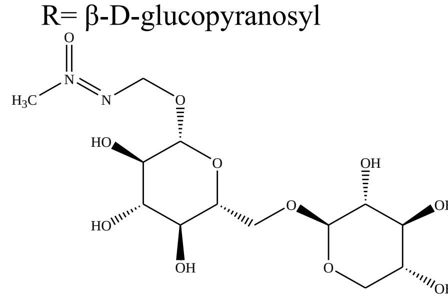
Isolariciresinol



Dihydroamentoflavone monoglucoside R= H
Dihydroamentoflavone diglucoside R= β-D-glucopyranosyl

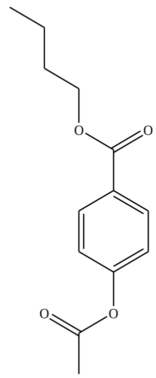


β-carotene

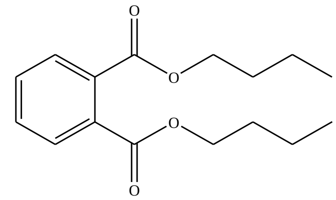


Macrozamin

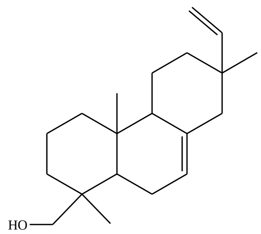
Figure 2. (Cont.)



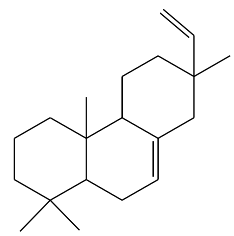
4-Acetoxybenzoic acid butyl ester



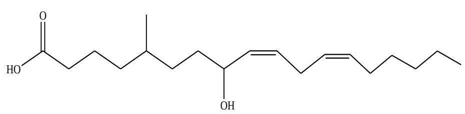
Phthalic acid dibutyl ester



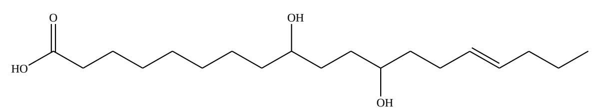
Isopimara-7,15-dien-19-ol



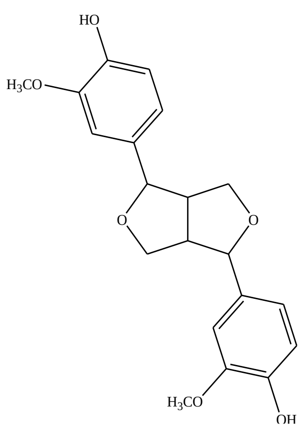
Isopimara-7,15-diene



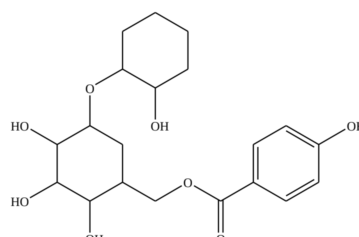
5,8-Dihydroxy-9,12-octadecadienoic acid



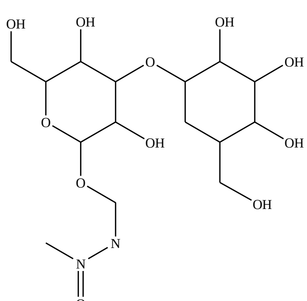
9,12-Dihydroxy-15-nonadecenoic acid



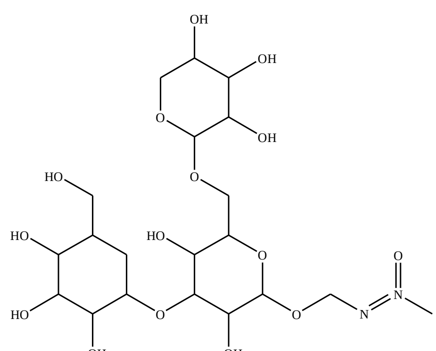
Pinoresinol



Glanduloidin C



Neo*Cycas*in A



Neo*Cycas*in J

Figure 2. (Cont.)

Conclusion

Cycas plants are abundantly found in tropical and subtropical regions of the world. The species are used for their pharmacologically established properties, including those against cancer, tumors, broad-spectrum microbes, viruses, and fungi, have all been described and demonstrated. Several additional verification of pharmacological efficacy are necessary, even though the physiological illnesses share common symptoms. Out of nine species of this genus distributed in Middle East, just three species have been phytochemically investigated. Phytochemical work on this genus seems to be by no means exhaustive and there still remains a vital scope for study of active molecules. Biflavonoids are widely distributed throughout this genus which suggests that these compounds may be chemotaxonomic markers of the genus *Cycas*.

Finally, the genus *Cycas* is revealed as a botanical treasure trove that is not limited by time. The review's compilation of collective knowledge encourages more multidisciplinary investigation and emphasizes the value of comprehensive strategies for comprehending, protecting, and maximizing *Cycas*' potential. This review highlights *Cycas* species as a potential source of bioactive molecules. As we traverse the delicate interplay between ecological resilience, cultural richness, and chemical variety within this species, we are reminded of the urgency to maintain and appreciate the priceless contributions of *Cycas* to the natural and cultural legacy of our world.

Methodology

Limited phytochemical studies on *Cycas* Middle Eastern species made a challenge for collecting enriched data. A deep search in many websites as Google Scholar, Research gate with aid of a database library engine of The Egyptian Knowledge Bank; EKB.

CRediT authorship contribution statement

AI: Conceptualization, Writing – original draft, data curation, Investigation, Validation.

Declaration of Competing Interest: The author declares that he has no competing interests.

Funding: No funding resources.

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