ISSN: 2357-0547 (Print)
ISSN: 2357-0539 (Online)

Review Article / JAPR / Sec. A
Sobhy et al., 2022, 6 (3), 94-106

Journal of Advanced Pharmacy Research

Section A: Natural Products & Metabolomics

Phytochemical and Pharmacological Values of Two Major Constituents of *Asparagus* Species and their Nanoformulations: A Review

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Submitted on: 30-05-2022; Revised on: 12-06-2022; Accepted on: 18-06-2022

To cite this article: Sobhy, Y.; Mady, M. S.; Mina, S. A.; Abo-zeid, Y. Phytochemical and Pharmacological Values of Two Major Constituents of *Asparagus* Species and their Nanoformulations: A Review. *J. Adv. Pharm. Res.* **2022**, *6* (3), 94-106. DOI: 10.21608/aprh.2022.141715.1176

ABSTRACT

Objectives: This review article highlights two of the major chemical classes and their derivatives frequently isolated from different species of genus *Asparagus* and the diversity of their biological activities in addition to different applications of genus *Asparagus* in nanoformulation. The species belonging to this genus are well known for their nutritional and medicinal benefits and are considered one of the promising sources of biologically active natural compounds. Among the major constituent detected in the genus *Asparagus* are saponins and flavonoids to which most of the biological activities are attributed. **Methods:** This review includes a collection of articles between 2000 to 2022, reviewed by internationally accepted databases and scientific journals. **Results:** This review demonstrates the structural and biological diversities of fifty-three saponin aglycones and glycosides and nineteen flavonoids and flavonoid glycosides isolated from different *Asparagus* species highlighting their structural diversity along with the biological activities of the reviewed species highlighting their structural diversity along with the biological activities of the reviewed species. Moreover, the application of *Asparagus* extracts for green synthesis of metal-based nanoparticles to minimize the hazardous effect on the environment and humans observed with metal-based nanoparticles chemically synthesized. **Conclusion:** The structural and biological diversities and potency of the reviewed saponins and flavonoids isolated from *Asparagus* along with their use in the production of stable nanoformulations made them a perfect candidate for future drug discovery of new pharmaceutically active agents.

Keywords: *Asparagus, Saponins, Polyphenols, Nanoformula*

INTRODUCTION

Plants are considered the major source of powerful drugs that have been used either for medical treatment or used as a precursor for semi-synthesis of effective analogs against several diseases. The Asparagaceae family is a large group of herbaceous plants including around 114 genera, and the most famous one is *Asparagus*, including other several genera, genus *Asparagus* is one of its well-known plant genera, it comprises about 300 species of herbaceous perennials and woody shrubs all over the world [1] such as *Asparagus*

INTRODUCTION

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Nanoparticles (NPs) have been applied previously for diagnosis, prevention, and treatment of several diseases such as viral infections with promising results[27, 30-33], and and also, they demonstrated a good antibacterial activity against multidrug resistant bacteria,[17, 34-39] and for treatment of cancer, Alzheimer's, tuberculosis, wound healing repairing damaged tissue[40-42], and inflammation [43] .

Literatures reported nano formulations of natural products were characterized by a remarkable improvement of the stability of the prepared formula (due to protection of active ingredients from physical and chemical degradation), solubility, bioavailability, and thus biological activity, as well as reduction of toxicity [15, 44]. Metal-based nanoparticles such as gold and silver were extensively studied due to their unique physicochemical properties rendering them massively applied in different disciplines including chemistry, biology, and biochemical [17]. Silver nanoparticles are considered one of the most formulated nanoparticles for various biomedical applications[45]. However, they were commonly synthesized by a chemical method, which includes the administration of toxic chemicals, high energy, and pressure for successful production of nanomaterials. Toxic materials are hazardous to the surrounding environment and Humans [46]. Thus, researchers adopted other strategies for green synthesis of metal-based nanoparticles including silver nanoparticles to make benefit of unique properties of nanomaterials as well as minimize any harmful or toxic effects on the environment and humans [17]. Several researchers have reported the use of plant extracts for the green synthesis of nanoparticles [47] and among its best strategies are either nano-suspension or nano-emulsion of plant extracts [48, 49].

This review study covering a period of 22 years, aims to evaluate the content of different species of the genus *Asparagus* of saponins and phenolic compounds and their pharmacological effect along with the reported nanoformulations prepared with their extracts. The findings of this review study are categorized into different subclasses of the studied compounds as well as the collection of the reported biological activities of *Asparagus* species and its nano-applications.

MATERIAL AND METHODS

Search criteria

Original articles, research papers published in journals and PubMed Central, Google scholars on *Asparagus* species, and medicinal uses were collected and studied. The recorded collected data were selected when the keywords "Phytochemical, pharmacological significance, nanoformulations, *Asparagus* species"were typed in the search engines.

RESULTS AND DISCUSSION

Several reports indicated that saponins especially those with steroidal nucleus, flavonoid, and phenols are among the major constituents isolated from the genus *Asparagus*. Several other minor classes such as alkaloids, tannins, minerals, and amino acids were also reported from *Asparagus* species [50-52].

Steroidal saponin isolated from genus *Asparagus*

The main saponin of *A. officinalis* L., and some other *Asparagus* species, is protodioscin ($C_{51}H_{84}O_{22}$), which is a derivative of diosgenin of the spirostane, and furostanoid type (**Figure 1**) in a glycoside form [53, 54]. Structural activity relationships (SAR) of the steroidal saponins were extensively studied and the reports indicated that structural diversity of the saponin glycoside leads to functional alterations. The SAR of steroidal saponins were found to be due to the monosaccharide's residues constituting the sugar part and their sequences, as well as to the structures of the aglycones. [55, 56]. According to previous reports, saponins identified from *Asparagus* species, have different substitutions in the sapogenin (Aglycone part) as well as differences in their types, linkage, and the number of sugar residues. This tremendous structural variability opens the gate for diverse bioactivities. **Table 1-6** illustrates the steroidal saponin of the spirostane and the furostane type and their derivatives isolated from *Asparagus* species (**Figure 1-2**). We noticed that they are dominated by the hexacyclic spirostane nucleus. The chemical structure of this group of compounds has a perhydrocyclopentanophenanthrene nucleus. Most of the natural spirostane saponins have the R configuration at C-22. The spirostanes also differ in the configuration at C-25 and 27-Me which can acquire an R/S configuration [57]. The pentacyclic furostanols are characterized by a hemiacetal at C-22 and a C-26 glycosidic bond. Other steroidal compounds of androstane and cholestane nuclei isolated from *Asparagus* species are illustrated in **Table 7**.

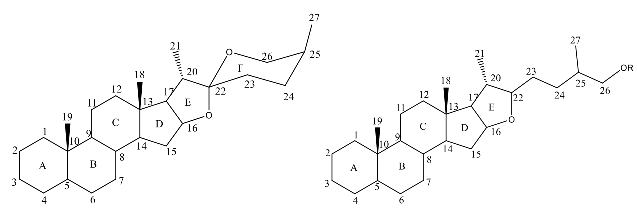
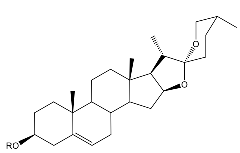


Figure 1. Spirostanol (left) and furostanol (right) saponins



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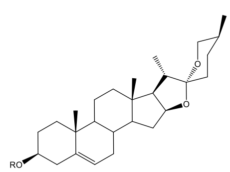

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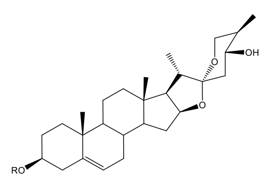

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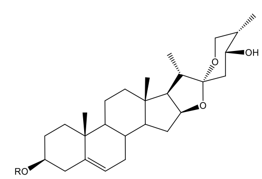

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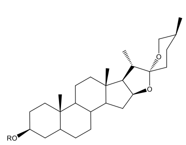

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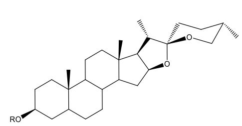

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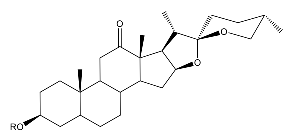

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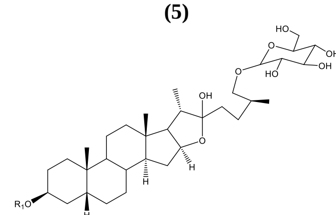

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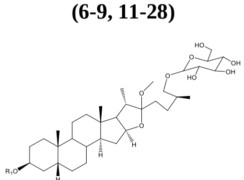
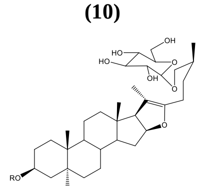


(33, 40-42)



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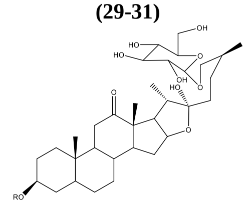

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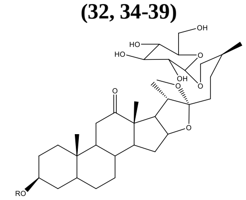


(45)

Figure 2. Spirostanoid, and furostanoid steroidal saponin isolated from *Asparagus* species.

Table 1. Spirosten saponin derivatives isolated from *Asparagus* species

Species(s)	Compound	R	Reference
A. racemosus	Diosgenin (25R) **(1)**	H	58
A. Officinalis	Yamogenin (25S) (**2**)		59
A. adscendens	Adscendin A (**3**)	*β*-D-Glu(1→6)*α*-L-Rha	60, 61
A. cochinchinensis	Asparagusoside C (**4**)	*α*-LRha-(1→2)-[*α*-L-Rha-(1→4)]-*β*-D-Glu	62
	Asparagusoside D (**5**)	*α*-L-Rha-(1→ 4)-*β*-D-Glu	

Table 2. Spirostan saponin derivatives isolated from *Asparagus* species

Species(s)	Compound	R	Reference
A. cochinchinensis	(25S)-5*β*-spirostan-3*β*-ol-3- O-*β*-D-glucopyranoside (**6**)	*β*-D-Glu	63
A. racemosus *A. adscendens*	Shatavarin IV (Asparanin B, Curillin H) (**7**)	*β*-D-Glu(1→2)*β*-D-Glu (1→4)*α*-L-Rha	64
A. racemosus	Asparanin A (**8**)	*β*-D-Glu(1→2)*β*-D-Glu	1, 58, 65
	Shatavarin V (**9**)	*β*-D-Glu(1→2)*α*-L-Rha(1→4) *β*-D-Glu	
	Shatavarin VI (**10**)	*β*-D-Glu(1→2)*β*-D-Glu (1→4)*α*-L-Rha	
	Shatavarin VIII (**11**)	*β*-D-Glu(1→2)*β*-D Glu(1→4)α-L-Ara(1→6) *β*-D-Glu	
	Shatavarin IX (**12**)	*β*-D-Glu(1→2)*β*-D-Glu(1→4) *β*-D-Glu	
	Shatavarin X (**13**)	*β*-D-Glu (1→2) *α*-L-Rha(1→4)*β*-D-6-acetylGlu	
	Shatavaroside A (**14**)	*β*-D-Glu(1→2)*α*-L-Ara (1→6)Rha	1
	Shatavaroside B (**15**)	*β*-D-Glu(1→2)*β*-D-Glu(1→4)*α*-L-Xyl(1→6) *α*-L-Rha	
	Immunoside (**16**)	*β*-D-Glu(1→2)*α*-L-Rha(1→4) *α*-L-Rha	1
A.filicinus	Filicinin A (**17**)	*β*-D-Glu(1→4){*β*-D-Glu(1→4)*β*-D-Gal(1→6)-*β*-D-Xyl}	66
	Filicinin B (**18**)	*β*-D-Glu(1→4){*β*-D-Glu(1→2)*β*-D Glu(1→4)*β*-D-Gal (1→6)*β*-D-Xyl}	
A. racemosus *A.filicinus*	Filiasparoside C (**19**)	*β*-D-Glu(1→2)*β*-D-Xyl(1→4) *α*-L-Rha	1, 67, 68
	Filiasparoside D (**20**)	*β*-D-Glu (1→6) *α*-L-Ara	68
	Aspafilioside A (**21**)	*β*-D-Glu (1→4) *β*-D-Xyl	69, 70
	Aspafilioside B (**22**)	*β*-D-Glu(1→4)*β*-D-Xyl(1→6) *α*-L-Rha	
A.racemosus *A.curillus*	Curillin H (**23**)	*β*-D-Glu (1→2) {*α*-L-Rha} (1→6)-*β*-D-Glu	71
	Racemoside A (**24**)	*β*-D-Glu(1→4){ *α*-L-Rha (1→ 6)-*β*-D-Glu } (1→6) *β*-D-Glu	1, 72
	Racemoside B (**25**)	*β*-D-Glu (1→6){ *α*-L-Rha(1→6)-*β*-D-Glu**}**	
	Racemoside C (**26**)	*β*-D-Glu (1→4) *α*-L-Rha (1→ 6)-*α*-L-Rha	
A.acutifolius	(25S)-5β- spirostan-3*β*-ol-3-O-*β*-D-xylopyranosyl-(1→2)-[*β*-D-xylopyranosyl-(1→4)]-*β*-D-glucopyranoside (**27**)	*β*-D-Glu(1→2)*β*-D-Xyl (1→ 4)-*β*-D-Xyl	73
A. africanus	(25R)-5b-spirostan-3*β*-ol 3-O-{ *β* -Dglucopyranosyl-(1→2)-[*α*-L-arabinopyranosyl-(1→6)]- *β* -D-glucopyranoside} **28**)	*β*-D-Glu(1→2)*β*-D-Glu(1→ 6)-*α*-L-Ara	74

Table 3. Spirostan-12-one saponin derivatives isolated from *Asparagus* species

Species(s)	Compound	R	Reference
A.filicinus	Filiasparoside A (**29**)	*α*-Glu(1→4)*α*-Xyl-(1→6)R-Ara	69, 70
	Filiasparoside B (**30**)	*α*-Glu(1→6)R-Ara	
A. africanus	(25R)-3*β*-hydroxy-5*β*-spirostan-12-one 3-O-{*β*-D-glucopyranosyl-(1→2)-[*α*-L-arabinopyranosyl-(→ 6)]-*β*-D-glucopyranoside} (**31**)	*β*-D-Glu(1→2)*β*-D-Glu(1→ 6) *α*-L-Ara	74

Table 4. Saponins with furostan nucleus isolated from *Asparagus* species

Species(s)	Compound	R	Reference
A. racemosus	Shatavarin I (**32**)	*β*-D-Glu(1→2)*β*-D-Glu(1→ 6) *α*-L-Rha	1, 58
A. curillus	Curilloside G (**33**)	*β*-D-Glu(1→ 2)*α*-L-Rha (1→ 4)-*β*-D-Glu	71
A. filicinus	Aspafilioside C (**34**)	*β*-D-Glu (1→2)-*β*-D-Xyl (1→ 4) *α*-L-Ara	70
A. acutifolius	(25S)-3*β*-5*β*,22*α*-furostane-3,22,26–triol-3-O-*β*-D-xylopyranosyl(1→2)-[*β*-D-xylopyranosyl(1→4)]- *β*-D-glucopyranosyl-26-O-*β*-D-glucopyrnoside (**35**)	*β*-D-Glu (1→2)-*β*-D-Xyl (1→ 4) *β*-D-Xyl	73
A. cochinchinensis	(25S)-26-O-*β*-D-glucopyranosyl-5*β*-furstan-3*β*, 22*α*,26-triol-3-O-*β*-D-glucopyranoside (**36**)	*β*-D-Glu	63
	(25S)-26-O-*β*-D-glucopyranosyl-5*β*-furostan-3*β*, 22*α*,26-triol-3-O-*α*-L-rhamnopyranosyl-(1,4)-*β*-D-glucopyranoside (**37**)	*β*-D-Glu(1→ 4) *α*-L-Rha	
A.curillus	Curilloside H (**38**)	*β*-D-Glu(1→2) *α*-L-Rha (1→ 6) *β*-D-Glu	71
A.racemosus	Asparoside A (**39**)	*β*-D-Glu(1→2) *β*-D-Glu (1→4) *α*-L-Rha	
A. africanus	26-O-*β*-D-glucopyranosyl-22*α*-methoxy-(25R)-furostan-3*β*,26-diol-3-O-{*β*-D-glucopyranosyl-(1→2)-*β*-D-glucopyranoside (**40**)	*β*-D-Glu-(1→2) *β*-D-Glu	74
A. acutifolius	(25R)-3*β*-5*β*,22*α*-22-methoxyfurostane -3,26-diol-3-O-*β*-D-xylopyranosyl(1→2)-[*β*-D-xylopyranosyl(1→4)]- *β*-D-glucopyranosyl-26-O-*β*-D-glucopyrnoside (**41**)	*β*-D-Glu(1→2)*β*-D-Xyl (1→4) *β*-D-Xyl	73
A. acutifolius	(25R)-3*β*-5*β*,22*α*-22-methoxyfurostane -3,22 –diol-3-O-*β*-D-xylopyranosyl(1→2)-*β*-D-xylopyranosyl-26-O-*β*-D-glucopyrnoside (**42**)	*β*-D-Glu(1→2)*β*-D-Xyl	73

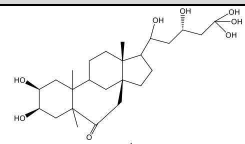
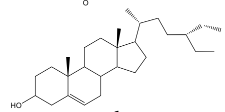
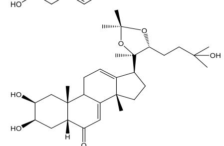
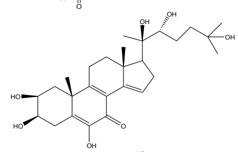
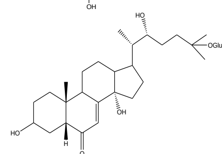
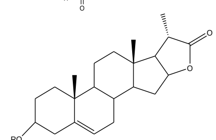
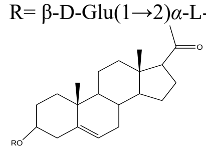
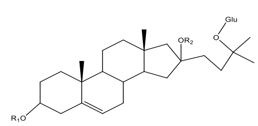
Table 5. Furostene saponin derivative isolated from *Asparagus* species

Species(s)	Compound	R	Reference
A. filicinus	Filiasparoside G (**43**)	*β*-D-Glu(1→4)*β*-D-Xyl(1→6)*α*-L-Ara	69

Table 6. Furostan-12-one saponin derivative isolated from *Asparagus* species

Species(s)	Compound	R	Reference
A. cochinchinensis	(25S)-26-O-*β*-D-glucopyranosyl-5*β*-furostan-3*β*,22 *α*, 26-triol-12-one-3-O-*β*-D-glucopyranoside (**44**)	*β*-D-Glu	63
	(25S)-26-O-*β*-D-glucopyranosyl-22*α* -methoxy-5*β*-furostan-3*β*, 26-diol-12-one-3-O-*β*-D-glucopyranoside (**45**)	*β*-D-Glu	

Table 7. Other steroidal compounds from *Asparagus* species

Species(s)	Compound	Structure	Reference
A. filicinus	Aspafilisine (**46**)		75
A. Officinalis	*β*-Sitosterol (**47**)		59
A.filicinus	Ecdysterone [stachysterone-α-20,22-acetonide] (**47**)		60, 61
A. dumosus	Calonysterone (**48**)		76
	Blechnoside (**49**)		77
	Dumoside I (**50**)	 R= β-D-Glu(1→2)*α*-L-Rha (1→6)*α*-L-Rha	
	Dumoside II (**51**)	 R= β-D-Glu(1→2)*α*-L-Rha (1→6)*α*-L-Rha	
			
	Dumoside III (**52**)	**R_1**= β-D-Glu (1→2)*α*-L-Rha (1→6)*α*-L-Rha **R_2**= H	
	Dumoside IV (**53**)	**R_1**= β-D-Glu (1→2)*α*-L-Rha (1→6)*α*-L-Rha **R_2**= CH_3	

Flavonoids reported from different species of the genus *Asparagus*

Several reports have demonstrated scarce information regarding the genus *Asparagus* flavonoids and phenolic investigations. Fuentes *et al* 2007 investigated the phenolic content of both white and green varieties of the genus *Asparagus*, and reported that white *Asparagus* contained hydroxycinnamic acid derivatives, on the other hand, flavonoids were the major phenolics in green *Asparagus*[78]. **Table 8** and **Figure 3** are illustrating different flavonoid classes identified from *Asparagus* species including classes such as flavones (e.g., luteolin), flavanols (e.g., quercetin, kaempferol), flavanones (e.g., naringenin), and others.

Pharmacological studies

Several therapeutic potentials of *Asparagus* are well documented in the literature. The therapeutic activity is due to the possession of significant pharmacological activities such as antioxidant, anti-inflammatory, analgesic, antiulcer anti-aging, antifungal, and antimicrobial properties. **Table 9** describes the reported pharmacological activities of genus *Asparagus*.

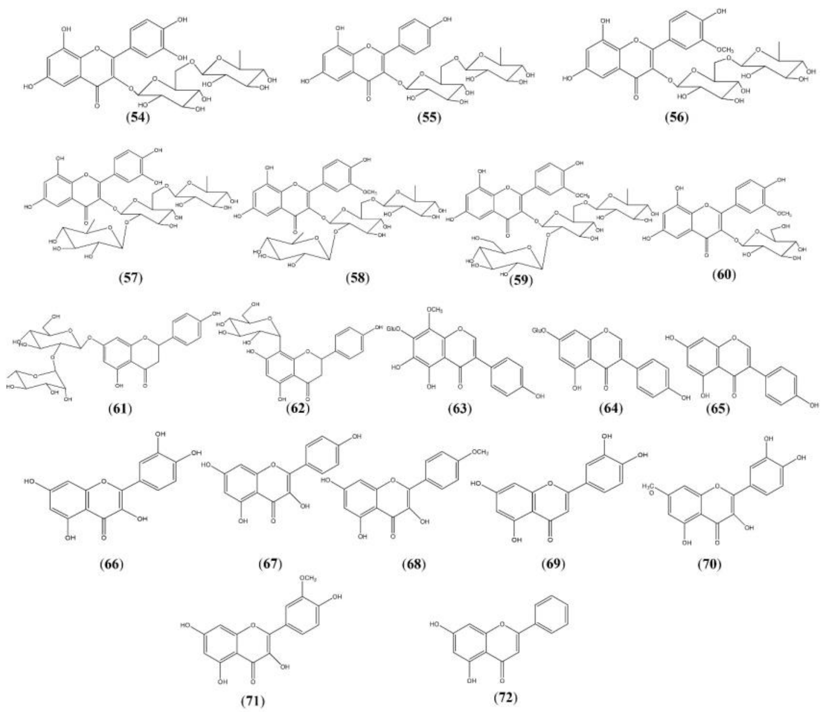


Figure 3. Flavonoids isolated from *Asparagus* species.

Table 8. Flavonoids reported from different *Asparagus* species

Compounds	Reference
Rutin (**54**)	1, 3, 78, 79
Kaempferol-3-O-rutinoside (**55**)	78
Isorhamnetin-3-O-rutinoside (**56**)	78
Quercetin-3-rhamnosyl-rutinoside (**57**)	79, 80
Isorhamnetin-3-rhamnosyl-rutinoside (**58**)	80
Isorhanetin-3-glucosyl-rutinoside (**59**)	79, 80
Isorhamnetin-3-O-glucoside (**60**)	79, 80
Naringin (**61**), Vitexin (**62**)	81
8-Methoxy-5,6,4-trihydroxy isoflavone-7- O-β-glucopyranoside (**63**)	1
Genistin (**64**), Daidzein (**65**)	81
Quercetin (**66**)	1, 58, 78, 80
Kaempferol (**67**)	1, 78, 80, 81
Kaempferide (**68**), Luteolin (**69**)	81
Rhamnetin (**70**)	78
Isorhamnetin (**71**)	78, 79
Chrysin (**72**)	81

Nanoparticle formulation from extracts of genus *Asparagus*

Several reports have demonstrated the usage of the extracts of different species of the genus *Asparagus* in the synthesis of several metal-based nanoparticles due to the oxidative or reducing potential of active ingredients in the plant extracts [100]. Moreover, the plant extract enriched with biologically active macromolecules (e.g. saponin, flavonoids, etc) was also encapsulated into nanoformulations such as liposomes, suspension, or alternatively adsorbed onto the surface of metal-based nanoparticles to act as a targeted drug delivery system to target the plant extract to diseased organ. Nanoformulations of plant extracts as previously discussed had superior advantages over conventional plant extract and it includes increasing the solubility, enhancing the bioavailability, reducing toxicity, and increasing the biological activity of the drug, in addition to increasing the sustainability and the protection against physical and chemical degradation[101]. However, literature reported that nanoparticles formulated using plant extracts for preparation are most likely to have biological activities similar to that of the original plant extracts but with the added benefit of optimizing the biological activity of the secondary metabolites[102]. Different nanoformulations prepared from extracts of different species of genus *Asparagus* and their biological activities were presented in **Table 10**.

Table 10. Biological activities of extracts of genus *Asparagus*

Biological activity	Species	Reference
Antioxidant	*A. racemosus*	82-84
	A.cochinchinenss	85
	A.albus	86
	A.suaveolens	87
	A.stipularis	88
Anti-aging	*A.cochinchinenss*	85
Anti-inflammatory	*A. racemosus*	58
	A.pubescens	89
	A.cochinchinenss	90, 91
	A. africanus	92
	A.laricinus	
Anti-microbial	*A. racemosus*	93-95
	A.laricinus	92
	A.albus	86
Anti-fungal	*A.retrofractus*	73, 96
	A.acutifolius	
	A.setaceous	
Anti-bacterial	*A. suaveolens*	87, 97
	A. racemosus	
Anti-ulcer	*A.pubescens*	98, 99
	A. racemosus	58, 98
Analgesic	*A. africanus*	92

Table 11. Nano formulations and biological significance of extracts of genus *Asparagus*

Species	Nanoformulation	Biological significance	Reference
A. racemosus	Silver nanoparticles	Antibacterial activity	103
		Bactericidal and Cytotoxic	104, 105
	Silver nanoparticles Gold nanoparticles	Antibacterial and Immunomodulatory Potentials	100
	Silver nanoparticles	Ant mycobactericidal and Cytotoxicity	106
	Silver nanoparticles	Anti-diabetic activity	107
	Cobalt nanoparticles	Antibacterial activity	108
A. officinalis	Silver nanoparticles	Bactericidal and Cytotoxic	109
A. adscendens	Copper Nano-Particles	Antimicrobial Activities	110-112
A. racemosus	Liposomes	Anti-inflammatory activity	113
A. stipularis	Nanoencapsulation	Antioxidant	114

CONCLUSION

This review illustrated the structural diversity of two of the major classes of secondary metabolites separated from the genus *Asparagus*, including saponins and flavonoids. It also describes the diversity of their biological activities in addition to all nanoformulation application trials applied to different *Asparagus* extracts. The efficient comprehension of *Asparagus*`s steroidal saponins/flavonoids structural diversity and their biosynthetic pathways has scientific importance for further future studies of the possible use of the naturally occurring saponins and flavonoids as a chemical structural entity to prepare a library of semisynthetic derivatives for optimization of their biological activity and drug design research. Phytochemicals reported in *Asparagus* extracts were shown to be efficient in green synthesis of metal-based nanoparticles, where they can reserve the biological activity of these nanoparticles but with no harmful effect on the environment and humans that was previously identified with metal-based nanoparticles synthesized chemically. In addition, nano-encapsulation of *Asparagus* extracts into one of the promising drug delivery systems e.g. liposomes, suspension, emulsion, etc was shown to have various merits compared to conventional *Asparagus* extracts such as improving solubility, stability, bioavailability, and hence, pharmacological activity.

Funding Acknowledgment

No external funding was received.

Conflict of interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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