Journal of Applied Pharmaceutical Science Vol. 15(07), pp 027-036, July, 2025
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2025.234398
ISSN 2231-3354

Review on phenolic constituents and pharmacological activities of genus *Ononis*

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ARTICLE HISTORY

Received on: 28/12/2024
Accepted on: 16/04/2025
Available Online: 05/06/2025

Key words:
Ononis, phytochemical constituents, flavonoids, pharmacological activities, structure-activity relationship.

ABSTRACT

Plants of genus *Ononis* belong to family Fabaceae and are distributed in Europe, Atlantic Islands, West Asia, and North Africa and more than 75 species in the genus have been identified worldwide. Previous phytochemical studies showed a diversity of bioactive constituents, specifically flavonoids and isoflavonoids, that have been responsible for the different actions exerted by plants of this genus. This study represents a comprehensive review of all data present in literature related to the phenolic constituents isolated from *Ononis* plants and their pharmacological activities. The study revealed also the essential structure-activity relationship of *Ononis* compounds and briefly highlighted some toxicity studies. Data was collected by searching journals, books, periodicals, and databases. The results demonstrated a wide variety of flavonoids and isoflavonoids, isocoumarins, and resorcinols reported from different *Ononis* species. Flavonoidal compounds were the main constituents responsible for the various pharmacological activities such as antioxidant, anti-inflammatory, antimicrobial, cytotoxic, enzyme inhibitory, and antidiabetic effects. The reason behind these activities was mainly the degree and position of hydroxylation and methoxylation on the flavonoids' rings. The findings of this study suggest *Ononis* plants and/or their components are promising candidates for treatment of wide range of ailments as a preventive measure or in combination with conventional therapies. Further studies would be required to describe the detailed mechanistic pathways for promising compounds and their clinical applications.

INTRODUCTION

Papilionaceae, Leguminosae, or Fabaceae, also named the pea, legume, or bean family, belongs to the Fabales order. With 19,400 species and 740 genera, Fabaceae is the third-largest plant family after Orchidaceae (orchid family) and Asteraceae (aster family), and it is one of the world's estimated 12 flowering plants [1]. The Fabaceae family has over 490 species, making it the second-largest family of medicinal plants, the majority of which have been utilized as traditional medicines, making it one of the most interesting families in research [2]. The family features aquatic plants, woody lianas, climbing annuals, shrubs, subshrubs, trees, and herbs. Stems are twining, erect, or climbing. Leaves are rarely simple and mostly compound [3]. Flowers are rarely zygomorphic, actinomorphic, or unisexual. They are bisexual, mainly in corymbs, heads, racemes, panicles, or spikes [4].

The genus *Ononis*, commonly named restharrow, is part of the Fabaceae family. It is widely spread in West Asia, the Atlantic Islands, North Africa, and Europe, and more than 75 species in the genus have been identified worldwide, particularly near the coasts of the Mediterranean Sea [5]. The scientific interest in the genus *Ononis* has increased recently as it contains several active components that have therapeutic benefits and are cost-effective. Mainly, phenolic compounds, particularly flavonoids, have been extracted. Mainly, phenolic compounds, particularly flavonoids, have been extracted. Genus *Ononis* exhibits diverse pharmacological activities, including diuretic, antitussive, anti-inflammatory, analgesic, antioxidant [6,7], antimicrobial [6], and anticancer effects [8]. Additional uses include the treatment of urinary tract infections, rheumatism, wound healing, eczema, and other skin diseases

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[9]. In this work, we attempt to summarize and review the phenolic constituents of plants belonging to the genus *Ononis*, their pharmacological effects, structure–activity relationship, and reported mechanisms of action.

METHODS

The keywords *Ononis*, phytochemical constituents, pharmacological activities, and structure-activity relationship were searched. The search was obtained from journals and books in databases, such as Scopus, ScienceDirect, Web of Science, PubMed, Google Scholar, and The Cochrane Library, from 1990 to 2024.

RESULTS AND DISCUSSION

Phytochemical profile

Ononis species are the source of several pharmacologically important flavonoids and isoflavonoids. Flavonoids are classified as secondary metabolites. Their primary structural components are phenolic or polyphenolic groups found at different positions of a benzopyrone ring. They are divided into several categories based on the oxidation of the carbon ring, their degree of unsaturation, and their chemical structure. The several subclasses of flavonoids comprise isoflavonoids, flavanones, anthoxanthins (flavanol and flavanone), flavans , flavanones, flavanonols, chalcones, and anthocyanidins [10].

Flavonoids and isoflavonoids have been described from *Ononis* species so far, including the isoflavones and the less prevalent isoflavonones and pterocarpans. In addition to flavonoids and isoflavonoids, other types of constituents, including resorcinol derivatives [11], isocoumarins [12], phenolic lactones [13], and terpenoids [7,14], have been isolated from *Ononis* species. According to most data in the literature, flavonoids are very abundant in herbs, stems, fruits, flowers, vegetables, and seeds. It is highly suggested they are found in chloroplasts. Table 1 summarizes the phenolic profile of different *Ononis* species.

Pharmacological effects of some *Ononis* plants

Antioxidant and anti-inflammatory effects

Crude extracts (ethyl acetate, n-butanol, and petroleum ether) of *Ononis mitissima* plant showed moderate antioxidant activities. In addition, at 500 µg/ml, these extracts exhibited medium anti-inflammatory activity, with inhibition percentages of 33%, 11%, and 22% in comparison to diclofenac (86%) for ethyl acetate, n-butanol, and petroleum ether extracts, respectively [15]. Another study showed that ethyl acetate and methanolic root extracts of *O. spinosa* reduced inflammation by 40.4% and 35.4%, respectively [5]. Moreover, the leaf extract of Tunisian *Ononis natrix* demonstrated a high reducing power (ED50 = 100 µg/ml), with a low IC_{50} value (29 µg/ml) corresponding to an increased 2,2-diphenyl-1-picrylhydrazyl scavenging ability. With 60.94 mg of GAE/g DW, it also demonstrated a high level of overall antioxidant activity. [6].

Antimicrobial effects

Many studies reported on the antimicrobial effect of the *Ononis* species. *Ononis natrix* extract demonstrated efficacy against strains of gram-positive bacteria, particularly against *Staphylococcus aureus ATC 25923* and *Staphylococcus epidermidis* strains [16]. Similarly, *O. spinosa* stopped *Bacillus subtilis, S. aureus*, *Pseudomonas aeruginosa, and Escherichia coli* growth. Moreover, potential antimicrobial activity against *Candida albicans, MRSA*, *P. aeruginosa, Bacillus cereus, E. coli, Salmonella typhimurium*, and *Aspergillus niger* has been reported from *Oxalis hirta* and *Oxalis sicula* ethanolic extracts [17]. The same study showed that chloroform extract of *Oxalis arvensis* leaves had significant inhibitory activity against *E. coli* and *C. albicans*, showing respective MIC values of 12.75 µg/ml and 51 µg/ml. [17].

Cytotoxic effect

By stopping the growth of MDA MB-231 breast cancer cells, Jordanian *O. natrix* revealed a potential antitumor effect with an IC_{50} of 29–41 µg/ml compared to that of tamoxifen (IC_{50} 11 µg/ml) [18]. Turkish *O. natrix* extracts, on the other hand, exhibited an apoptotic effect against PC3 cancerous cell line at a very small concentration (0.1 µg/ml) [16].

Enzyme inhibitory effect

The dichloromethane extract of *O. spinosa* demonstrated a concentration-dependent suppression of TNF-α and IL-8 production from lipopolysaccharide-stimulated human neutrophils [19]. In addition, the ethyl acetate extract revealed high inhibitory activity of cholinesterase on both BChE (0.93 mg GALAE/g extract) and AChE (1.46 mg GALAE/g extract), unlike the water extract, which was ineffective on BChE. Conversely, the ethyl acetate extract had no inhibitory activity on tyrosinase, but the water extract had significant activity (52.81 mg KAE/g extract). Regarding glucosidase and amylase inhibition, the most effective extracts were the ethyl acetate (0.74 mmol ACAE/g and 17.52 mmol ACAE/g) and methanol extracts (0.59 mmol ACAE/g and 19.94 mmol ACAE/g) [16].

Antidiabetic effect

Preclinical studies on *O. natrix* decoction have demonstrated its effectiveness in lowering blood glucose levels in rats [20]. Ononis extracts can improve glucose and starch tolerance by activating the glucose transporter type-4 (Glut-4) receptor in experimental rats [21]. Moreover, aqueous extracts of *O. natrix* had the ability to restore the islets of Langerhans suffering from alloxan-induced tissue damage in albino Swiss mice [22].

Structure–activity relationship of phenolic constituents from *Ononis*

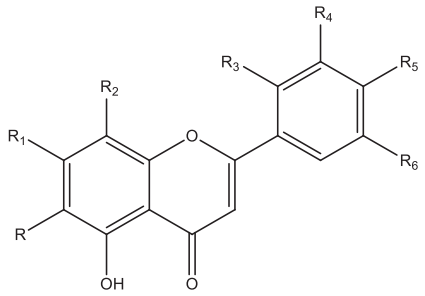
The medicinal importance of *Ononis* plants is explained by their phenolic contents, mainly flavonoids. These compounds account for the anti-inflammatory, antioxidant, and anticancer characteristics of *Ononis* plants [23].

Anticancer

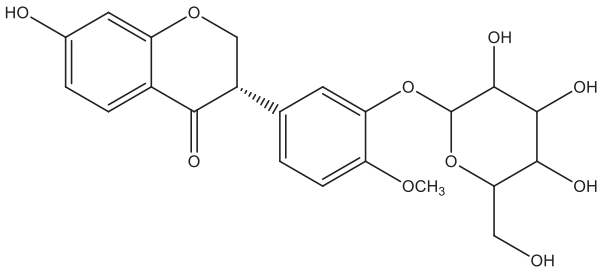
Formononetin, one of the most known isoflavones in the *Ononis* species, revealed anticancer activity against various types of cancers such as colon, breast, prostate, nasopharyngeal,

Table 1. Phytochemistry of *Ononis* species and their chemical structures.

Flavonoids

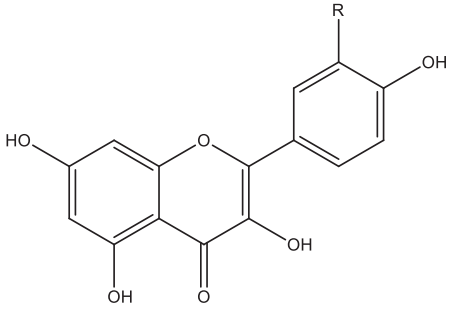


Compound	R	R_1	R_2	R_3	R_4	R_5	R_6	Plant Species	References
Gardenin B	OCH_3	OCH_3	OCH_3	H	H	OCH_3	H	*Ononis natrix* (aerial parts)	[24]
Xanthomicrol	OCH_3	OCH_3	OCH_3	H	H	OH	H		
Hemopexin	OCH_3	OH	OCH_3	H	H	OCH_3	H		
5,4'-diOH-6,7,8,3'-tetraOMe	OCH_3	OCH_3	OCH_3	H	OCH_3	OH	H		
Sideritoflavone	OCH_3	OCH_3	OCH_3	H	OH	OH	H		
Acrosin	OCH_3	OH	OCH_3	H	OH	OCH_3	H		
5,2',4'-triOH-6,7,8,5'-tetraOMe (Agecorynin D)	OCH_3	OCH_3	OCH_3	OH	H	OH	OCH_3		
Pectolinarigenin	OCH_3	OH	H	H	H	OCH_3	H	*Ononis natrix* (aerial parts)	[25]
Hispidulin	OCH_3	OH	H	H	H	OH	H		
Desmethylsudachitin	OCH_3	OH	OCH_3	H	H	OH	H		
Nevadensin	OCH_3	OH	OCH_3	H	H	OCH_3	H		
Nepetin	OCH_3	OH	H	H	OH	OH	H		
Jacoesidin	OCH_3	OH	H	H	OCH_3	OH	H		
Cirsiliol	OCH_3	OCH_3	H	H	OH	OH	H		



Compound	Plant Species	Reference
(3S)-7-hydroxy-4′-methoxy-isoflavanone 3′-β-d-glucopyranoside	*Ononis angustissima* (aerial parts)	[7]

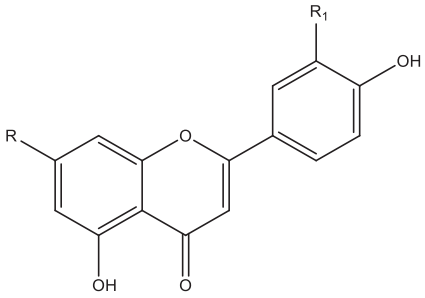
Flavonols



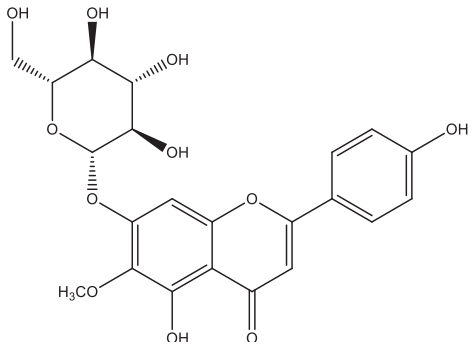
Continued

Compound	R	Plant Species	References
Quercetin	OH	*Ononis natrix* subsp. *hispanica* (aerial parts)	[16]
Kaempferol	H	*Ononis natrix* (leaves)	[26]

Flavones

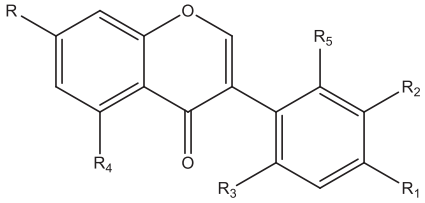


Compound	R	R1	Plant Species	References
Apigenin	OH	H	*Ononis natrix* subsp. *hispanica* (aerial parts)	[16]
Luteolin	OH	OH		
Luteolin 7-methyl ether	OH	OCH_3		
Chryseriol	OH	OCH_3	*Ononis natrix* (aerial parts)	[25]
Velutin	OCH_3	OCH_3		



Compound	Plant Species	Reference
Tectoridin (tectorigenin 7-O-glucoside)	*Ononis spinosa* (roots)	[27]

Isoflavones



Compound	R	R_1	R_2	R_3	R_4	R_5	Plant Species	References
Formononetin	OH	OCH_3	H	H	H	H	*Ononis spinosa* (roots)	[27]
Ononin (formononetin 7-O-glucoside)	Glucosi-de	OCH_3	H	H	H	H	*Ononis angustissim* (aerial parts)	[7]
Calycosin	OH	OCH_3	OH	H	H	H	*Ononis spinosa* (roots)	[28]
Genistein	OH	OH	H	H	OH	H	*Ononis spinosa* (roots)	[27]

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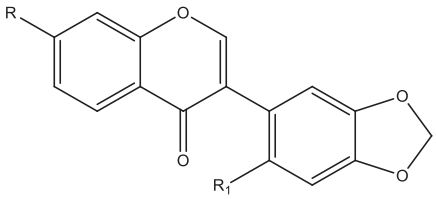
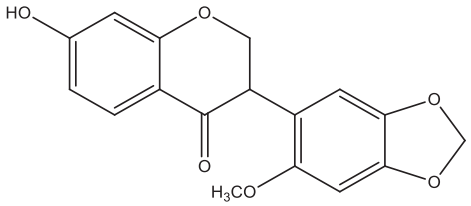
Genkwanin	OCH_3	OH	H	H	OH	H	*Ononis natrix* (aerial parts)	[25]

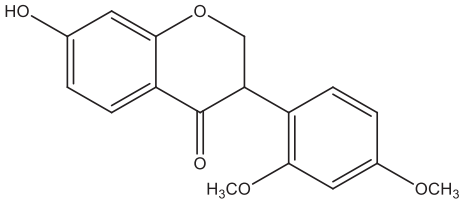


Compound	R	R_1	Plant species	References
Pseudobaptigenin	OH	H	*Ononis spinosa* (roots)	[28]
Pseudobaptigenin glucoside	O-glucoside	H	*Ononis spinosa* (roots)	[13]
Cuneatin	OH	OCH_3	*Ononis arvensis* (roots and aerial parts)	[28]

Isoflavanones

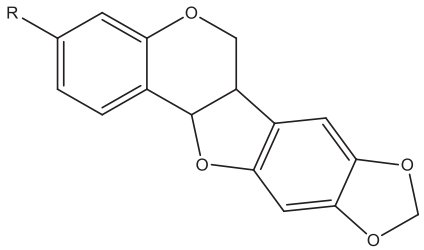


Compound	Plant species	Reference
Onogenin	*Ononis spinosa* (roots)	[27,28]

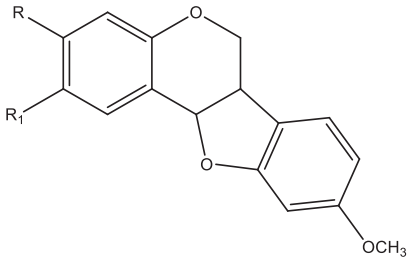


Compound	Plant species	Reference
Sativanone	*Ononis spinosa* (roots)	[28]

Pterocarpans



Compound	R	Plant species	References
Maackiain	OH	*Ononis spinosa* (roots)	[27,28]
Trifolirhizin (maackiain 7-O-glucoside)	O-glucose	*Ononis vaginalis* (roots)	[7]



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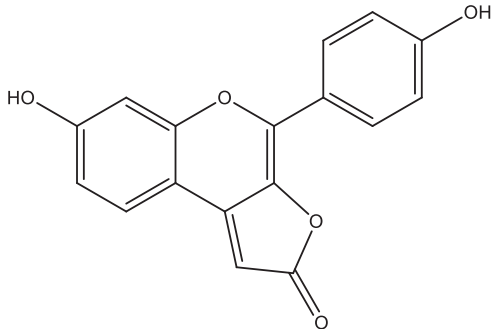
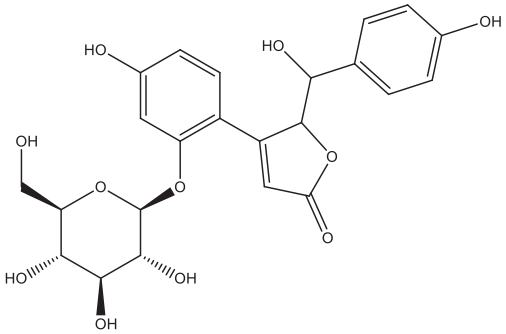
Compound	R	R_1	Plant species	References
Medicarpin	OH	H	*Ononis spinosa* (roots)	[27,28]
3,4,9-trimethoxypterocarpan	OCH_3	OCH_3	*Ononis vaginalis* (roots)	[29]

Phenolic Lactones

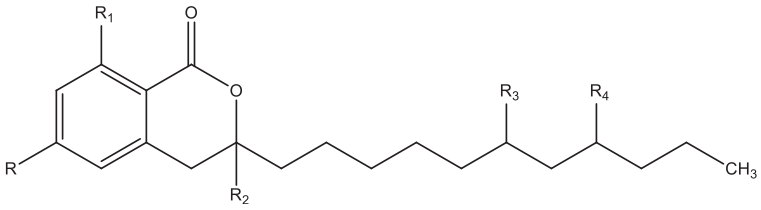


Compound	Plant species	Reference
Ononilactone	*Ononis spinosa* *Ononis arvensis* (hairy root cultures)	[13]



Compound	Plant species	Reference
Bulatlactone 2″-O-β-d-glucoside	*Ononis spinosa & Ononis arvensis* (hairy root cultures)	[13]

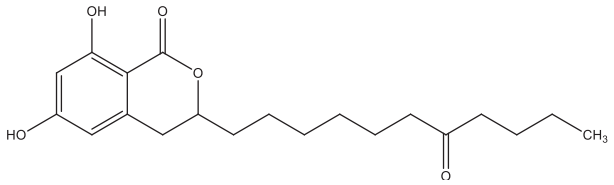
Dihydroisocoumarins



Compound	R	R1	R2	R3	R4	Plant Species	References
3,4-Dihydro-8-hydroxy-6-methoxy-3-(6-hydroxyundecyl)-1H-2-benzopyran-1-one	OCH_3	OH	H	OH	H	*Ononis natrix* (aerial parts)	[24]
6,8-Dihydroxy-3-(8'-hydroxyundecyl)-3,4-dihydroisocoumarin	OH	OH	H	H	OH	*Ononis natrix* (aerial parts)	[30]
3,8-Dihydroxy-6-methoxy-3-undecyl-3,4-dihydroisocoumarin	OCH_3	OH	OH	H	H		
6,8-dihydroxy-3-(6-oxoundecyl)-3,4-dihydroisocoumarin	OH	OH	H	H	H		
8-hydroxy-3,6-dimethoxy-3-undecyl-3,4-dihydroisocoumarin	OCH_3	OH	OCH_3	H	H		

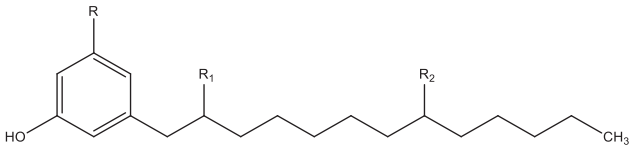
Continued

8-Hydroxy-6-methoxy-3-undecyl-3,4-dihydroisocoumarin	OCH_3	OH	H	H	H		
6,8-Dihydroxy-3-undecyl-3,4-dihydroisocoumarin	OH	OH	H	H	H		
6,8-Dihydroxy-3-(6-hydroxyundecyl)-3,4-dihydroisocoumarin	OH	OH	H	OH	H		
8-Hydroxy-6-methoxy-3-(6-hydroxyundecyl)-3,4-dihydroisocoumarin	OCH_3	OH	H	OH	H		
6,8-Dimethoxy-3-undecyl-3,4-dihydroisocoumarin	OCH_3	OCH_3	H	H	H	*Ononis natrix* (aerial parts)	[12]
6,8-Dihydroxy- 3-(6-oxoundecyl)-3,4-dihydroisocoumarin	OH	OH	H	=O	H		
8-Hydroxy-6-methoxy-3-(6-oxoundecyl)-3,4-dihydroisocoumarin	OCH_3	OH	H	=O	H		
6,8-Dimethoxy-3-(6-oxoundecyl)-3,4-dihydroisocoumarin	OCH_3	OCH_3	H	=O	H		
6,8-Diacetoxy- 3-(6-acetoxyundecyl)- 3,4. dihydroisocoumarin	$O\text{-}COCH_3$	$O\text{-}COCH_3$	H	$O\text{-}COCH_3$	H		

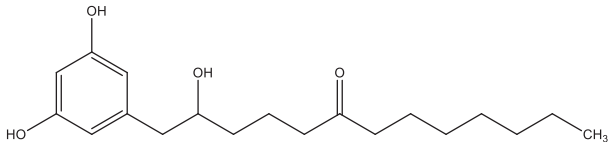


Compound	Plant Species	Reference
6,8-Dihydroxy-3-(7'-oxoundecyl)-3,4-dihydroisocoumarin	*Ononis natrix* (aerial parts)	[30]

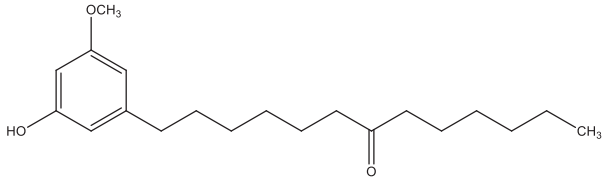
Resorcinol derivatives



Compound	R	R_1	R_2	Plant species	Reference
5-(2'-acetoxytridecyl) resorcinol methyl ether	OCH_3	$O\text{-}CH_3CO$	H	*Ononis natrix* subsp. *hispanica* (aerial parts)	[31]
5-(2'-acetoxy-tridecyl) resorcinol	OH	$O\text{-}CH_3CO$	H		
5-(2'-hydroxytridecyl) resorcinol methyl ether	OCH_3	OH	OH		
5-(2',8'-dihydroxytridecyl) resorcinol	OH	OH	OH		
5-(2',8'-dihydroxytridecyl) resorcinol methyl ether	OCH_3	OH	OH		



Compound	Plant species	Reference
5-(2'-hydroxy-8'-oxytridecyl) resorcinol	*Ononis natrix* subsp. *hispanica* (aerial parts)	[31]



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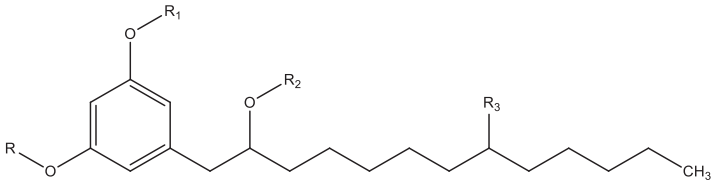
Compound	Species Found In	Reference
5-(7'-Oxotridecyl)-3-methoxyphenol	*Ononis natrix* (aerial parts)	[30]



Compound	R	R_1	R_2	R_3	Plant species	Reference
1-O-Methyl-5-(2'-acetoxytridecyl) resorcinol	CH_3	H	CH_3CO	H	*Ononis natrix* (aerial parts)	[11]
1-O-Methyl-5-(2'-acetoxy-8'-oxotridecyl) resorcinol	CH_3	H	CH_3CO	=O		
1-O-methyl-5-(2'-acetoxy-8'-hydroxytridecyl) resorcinol	CH_3	H	CH_3CO	OH		
1-O-Methyl-5-(2'-hydroxytridecyl) resorcinol	CH_3	H	H	H		
1-O-Methyl-5-(2'-hydroxy-8'-oxotridecyl) resorcinol	CH_3	H	H	=O		
1-O-Methyl-5-(2',8'-dihydroxytridecyl) resorcinol	CH_3	H	H	OH		
5-(2'-Acetoxy-8'-oxotridecyl) resorcinol	H	H	CH_3CO	=O		
5-(2'-Acetoxy-8'-hydroxytridecyl) resorcinol	H	H	CH_3CO	OH		
5-(2'-Acetoxy-8'-oxotridecyl) resorcinol diacetate	CH_3CO	CH_3CO	CH_3CO	=O		
5-(2',8'-Diacetoxytridecyl) resorcinol diacetate	CH_3CO	CH_3CO	CH_3CO	O-CH_3CO		

bladder, cervical, lung, laryngeal, glioma, adrenal medulla, multiple myeloma, and osteosarcoma cancer. It arrests the G0/G1 phase of the cell cycle in ES2 and the G1 phase in human ovarian and lung cancerous cells and triggers apoptosis in breast cancerous cells [32]. Data about formononetin structure–activity relationships are extremely limited. One study suggested that the presence of a 2–3 double bond, a 4-carbonyl group, and ortho- as opposed to meta-hydroxylation in the B ring greatly increased the cytotoxic activity. Comparing 3-hydroxylated molecules to their non-hydroxylated counterparts, the latter showed noticeably greater cytotoxicity [33].

As for the antioxidant activity, the total number of hydroxyl groups has a significant influence. For example, apigenin, kaempferol, luteolin, and quercetin reduced nitric oxide and phagocytosis in a dose-dependent manner, and the phenolic hydroxyl groups number was proportional to their antioxidant effect [34]. Additionally, the presence of a 3',4'-catechol structure in the B ring greatly increased the potential to inhibit lipid peroxidation. Thus, flavonoids are most efficient in scavenging peroxynitrite, superoxide, and peroxyl radicals. Due to oxidation on the flavonoid B ring with a catechol group, a relatively stable ortho-semiquinone radical that acts as a potent scavenger is produced. In contrast, flavones without a catechol system form unstable radicals when oxidized, showing less scavenging potential [35]. It is worth to mention that flavones and catechins appear to have the most potent activity against reactive oxygen species [35].

Concerning the antimicrobial activity, several structurally distinct flavonoids, such as isoflavones, flavones, isoflavanones, and flavanones, show that *Streptococcus sobrinus* and *Streptococcus mutans* growth was inhibited by 5-hydroxyisoflavanones and 5-hydroxyflavanones with one, two, or three additional hydroxyl groups at the 7, 2′, and 4′ positions, with position 2′ hydroxylation being crucial for the anti-staphylococcal activity. Additionally, hydroxyl groups at position 5 of flavones and flavanones are critical for their anti-MRSA action. It was also evident that chalcones work better than flavanones or flavones against MRSA. On the contrary, it has been observed that methoxy groups significantly reduce flavonoids' antibacterial activity [36].

For type 2 diabetes mellitus, quercetin has the highest IC_{50} value to inhibit α-glucosidase and dipeptidyl peptidase IV. The existence of the C-2-C-3 double bond and the C-4 ketonic group is crucial to its antidiabetic properties. However, acetylation, methylation, and hydroxyl groups reduce the antidiabetic *in-vitro* effects of flavonoids [37].

Toxicity and safety assessments

Till this date, no studies assessing the toxicity and safety of the *Ononis* species have been reported, so the literature is lacking in this regard. However, there are several investigations that have evaluated the safety of *Ononis*-based compounds. For example, quercetin, one of the most common and known flavonoids in the *Ononis* species, has shown conflicting results. One study proved the safety of quercetin when taken orally for 98 days in male and female mice (doses ~12.5, 25, or 50 mg/kg of body weight) [38]. On the other hand, higher doses of quercetin >2,000 mg/kg were associated with hepatotoxic stress in mice liver [39], and a dose of 3807 mg/kg was lethal 22 hours after administration to mice [40]. Moreover, sodium formononetin-30-sulphonate, a water-soluble derivative of formononetin, was considered safe and showed no side effects at doses <100 mg/kg in dogs [41], and formononetin was safe at a dose of 1.5 mg/kg in mice [42]. The lethal dose of 50% was

also considered to be 103.6 mg/kg, and no side effects were exhibited at doses <50 mg/kg [43].

The findings of the collected studies showed no discrepancies, contraindications, or conflicting viewpoints concerning pharmacological activities and associated structure–activity relationships. On the contrary, the main results of the different studies were consistent, enhancing the credibility of the available literature. However, it is important to mention that while most biological activities of *Ononis* flavonoids and their structure–activity relationship are well documented, there is a lack of studies investigating their cytotoxic activity. Accordingly, the cytotoxic activity of *Ononis* flavonoids needs to be thoroughly investigated to determine a detailed structure–activity relationship that could pave the way in the process of drug discovery. In addition, the available studies are mostly *in vitro* evaluations except for the antidiabetic activity, which has been studied *in vivo*. In addition, it is noteworthy to mention that the toxicity of some *Ononis* flavonoids has been assessed, but the *Ononis* plants or their extracts have not been studied in this aspect, thereby necessitating the need for further investigations. All in all, this is the first review article that summarizes the constituents of different *Ononis* species and their pharmacological activities, as well as highlighting their structure–activity relationship, thereby offering a collective review of these species. The use of several recent studies emphasizes the growing interest in the *Ononis* species and the importance of their therapeutic potential in various diseases and stimulates further investigations of these plants.

CONCLUSION

This review of genus *Ononis* highlights the presence of diverse bioactive compounds, mainly flavonoids and isoflavonoids, responsible for the pharmacological potential of these species. Based on the study findings, *Ononis* species could be considered important therapeutic remedies in curing oxidative stress, inflammation, infections, diabetes, and some cancers. It opens the gates for researchers to prepare more potent derivatives from the phenolic and flavonoid content of the *Ononis* plant. These derivatives could serve as novel molecule in the process of drug discovery. Furthermore, the study highlighted the therapeutic potential of the *Ononis* plant as preventive, treatment, and even adjuvant measures for various diseases. Preclinical and clinical studies will be recommended to support its clinical applications.

ACKNOWLEDGMENTS

The authors thank Beirut Arab University for providing the support throughout the manuscript preparation. The authors thank Acdlabs.com (ChemSketch free version) for making it possible to create all of the figures.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

FINANCIAL SUPPORT

This research was not supported by funding sources in the public, private, or not-for-profit sectors.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

The data supporting the results of this research are accessible in standard research databases such as PubMed, Scopus, ScienceDirect, Google Scholar, The Cochrane Library, Web of Science, and/or public domains that are accessible via keywords or DOI numbers.

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors state that they have not utilized artificial intelligence (AI) tools for writing and editing of the manuscript, and no pictures were modified using AI.

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How to cite this article:
Chouman A, El-lakany A, Aboul-ela M, Ali Hijazi M. Review on phenolic constituents and pharmacological activities of genus *Ononis*. J Appl Pharm Sci. 2025;15(07):027–036. DOI: 10.7324/JAPS.2025.234398