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The Traditional Uses, Constituents and Pharmacological Effects of *Ononis Spinosa*

Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, Thi qar University, Iraq.
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Abstract: *Ononis spinosa* was traditionally used as antitussive, aperient, diuretic and lithontripic. *Ononis spinosa* infusion was used in the treatment of dropsy, urinary tract infections, inflammations and rheumatism, while, it externally, used for the healing of wounds, eczema and the other skin disorders. It contained flavonoids, phenolic acids, volatile oil, spinonin glycoside, sterols, lectins, tannins and minerals. The pharmacological studies showed that it possessed diuretic, antimicrobial, anti-inflammatory, analgesic, antioxidant, dermatological, anticancer and hepatoprotective effects. The current review highlighted the traditional uses, chemical constituents and pharmacological effects of *Ononis spinosa*.
Keywords: *Ononis spinosa,* traditional uses, constituents, pharmacological effects

I. INTRODUCTION:

Recent reviews revealed that the medicinal plants possessed central nervous, cardiovascular, antioxidant, reproductive, gastro-intestinal, respiratory, antidiabetic, antimicrobial, antiparasitic, dermatological, anticancer, anti-inflammatory, antipyretic and analgesic, immunological, hepato and reno-protective[1-30] and many other pharmacological effects. *Ononis spinosa* was traditionally used as antitussive, aperient, diuretic and lithontripic. *Ononis spinosa* infusion was used in the treatment of dropsy, urinary tract infections, inflammations and rheumatism, while, it externally, used for the healing of wounds, eczema and the other skin disorders. *It* contained flavonoids, phenolic acids, volatile oil, spinonin glycoside, sterols, lectins, tannins and minerals. The pharmacological studies showed that it possessed diuretic, antimicrobial, anti-inflammatory, analgesic, antioxidant, dermatological, anticancer and hepatoprotective effects. The current review will highlight the traditional uses, chemical constituents and pharmacological effects of *Ononis spinosa*.

Plant profile:
Synonyms:
Ononis campestris, *Ononis repens subsp. spinosa*, *Ononis spinosa subsp. spinosa*, *Ononis vulgaris*[31].
Taxonomic classification:
Kingdom: Plantae, **Subkingdom**: Tracheobionta, **Superdivision**: Spermatophyta, **Division**: Magnoliophyta, **Class**: Magnoliopsida, **Subclass**: Rosidae, **Order**: Fabales, **Family**: Fabaceae, **Genus**: Ononis, **Species**: *Ononis spinosa*[32].
Common names:
Arabic: Ononis, Shabraq, Lateen; **English**: restharrow, spiny restharrow, thorny restharrow; **German**: Dornige Hauhechel; **Swedish**: busktörne; **Turkey**: kayıskıran[33].

Distribution:
The plant is distributed in **Africa** (Algeria, Libya, Morocco, Tunisia), **Asia** (Afghanistan, Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, Armenia, Azerbaijan, India) and **Europe** (Denmark, Norway, Sweden, United Kingdom, Austria, Belgium, Czechoslovakia, Germany, Hungary, Netherlands, Poland, Switzerland, Estonia, Lithuania, Moldova, Russian Federation- European part, Albania, Bulgaria, Former Yugoslavia, Greece, Italy, Romania, France, Portugal, Spain)[33].

Description:
Perennial shrubs, 30-60 cm tall, with long and short glandular hairs, often arranged in 2 opposite lines. Stem erect, branched at base, spiny. Leaves 3-foliolate, sometimes 1-foliolate toward tip of stem, terminal leaflet oblong-elliptic, 5-10 × 3-5 mm, base rounded, margins irregularly serrulate, apex acute. Flowers in lax, leafy racemes, solitary at nodes, subsessile. Calyx 7-8 mm; teeth longer than tube. Corolla pale red to mauve, 10-20 mm. Legume oblong to rhomboid, 8-9 mm, equal to or slightly exserted from persistent calyx, apex beaked. Seeds 2 or 3, brown to black, tuberculate[34-35].

Traditional uses:

The roots, leaves and flowers were used as antitussive, aperient, diuretic and lithontripic. The plant infusion was used in the treatment of dropsy, urinary tract infections, inflammations and rheumatism[36].
Externally, it was used for the healing of wounds, eczema and the other skin disorders[37]. In Iraq, the aerial part decoction was used as diuretic and mild laxative, and the roots were used as diuretic, blood purative and expectorant[38].

Parts used medicinally:

The roots and aerial parts were used medicinally[39-40].

Chemical constituents:

The plant contained flavonoids: daidzin (0.944 x 10^{-3}%), genistin (1.173 x 10^{-3}%), formononetin 7-O-glucoside (ononin) (175.7 x 10^{-3}%), formononetin (9.499 x 10^{-3}%), formononetin 7-O-glucoside 6"-malonate (3.2-5.9 mg/100g), biochanin A 7-O-glucoside, biochanin A 7-O-glucoside 6"-malonate (biochanin A) (0.08-0.70 mg/100g), trifolirhizin, onogenin, sativanone, calycosin, pseudobaptigenin, calycosin; pterocarpans (maackiain and medicarpin); phenolic acids (p-hydroxybenzoic, vanillic acid, caffeic acid, syringic acid, p-coumaric acid, cinnamic acid, sinapin acid, homopipecolic acid, salicylic acid and gentisin acid); volatile oil: (0.02-0.2%) (*trans*-anethole, *cis*-anethole, carvone, menthol, menthone, isomenthone, linalool, estragole, borneol); triterpenoid saponin (3-*O*-[α-L-rhamnopyranosyl-(1→2)-β -D-xylopyranosyl-(1→2)- β -D-glucurono pyranosyl]-3β ,22α-dihydroxyolean-13-en-11-one); spinonin glycoside, sterols (β-sitosterol, stigmasterol, campesterol, cholesterol, α-spinasterol); deoxybenzoines (especially ononetin); lectins; tannins and minerals[39, 41-52].

GC-MS analysis of chloroform fraction of ethanolic root extract showed that it contained triterpene 9,19-cyclo-27-lanostan-25-on as the major constituent (13.17%), followed by ß-sitosterol (9.61%), medicarpin (9.4%), maackiain (8.01%) and linolic acid (7.98%)[53].

Pharmacological effects:

Diuretic effect:

The ethanolic extract at a dose corresponding to 2 g/kg bw, orally, significantly increased urinary volume by 103% ($p<0.05$) in mice and rats during 2 h observation time compared to saline control. No effect on sodium or potassium elimination was recorded. The diuretic activity was not confirmed by intraperitoneal administration of the extract at a dose up to 500 mg/kg[54].

The dried methanolic *Ononis spinosa* root extract (0.3 g/animal), ash (0.3 g/animal) and a mixture of methanolic extract and ash (0.3 g/animal) were intragastrically administered to determine their diuretic effects. There was significant difference between the effect of methanolic extract and ash, but the mixture of methanolic extract and ash showed the most potent diuretic effect. However, ash treatment associated with more excretion of sodium in urine 32.69 mg compared with 20.31 mg by dried methanolic extract, and 20.97 mg by the mixture of methanolic extract and ash, while potassium levels in urine were 95.50 mg for dried methanolic extract, 78.89 for ash and 65.87 mg for the mixture of methanolic extract and ash[55].
The essential oil and genistein constituents may be responsible for the diuretic action of the plant[49, 56].

Antimicrobial effects:

The antimicrobial effect of *Ononis spinosa* was investigated against *Escherichia coli*, *Pseudomonas aeruginosa, Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans*, *Candida galabrata* and *Candida krusei*. The results showed that it possessed good antimicrobial effect against *Escherichia coli*, *Pseudomonas aeruginosa, Staphylococcus aureus*, *Candida albicans* and *Candida krusei*, with diameters of the inhibition zones of 11, 11, 11, 16 and 16 mm, respectively[57].

The antibacterial activity of the root aqueous extract of *Ononis spinosa* was investigated against Gram-negative strains: *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*; Gram-positive strains: *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Staphylococcus epidermidis;* and fungi: *Candida albicans*, *C. tropicalis*, *C.parapsilosis*, *C. krusei T. rubrum E. floccosum* and *M. gypseum*. The extract was also tested against *Mycobacterium tuberculosis* and *M. avium.* Its MICs against *S. pneumonia S. pyogenes S. aureus S. epidermidis, M. tuberculosis*, *M. avium*, *K. pneumoniae H. influenzae P. aeruginosa*, *A. baumannii*, *C. albicans C. tropicalis C. parapsilosis, C. krusei*, *T. rubrum E. floccosum* and *M. gypseum* were 32, 16, 32, 32, 16, 8, 64, 64, 32, 32, 16, 16, 8,32, 16- 32, 64, 16-32 µg/ml respectively[58].

Spinonin glycoside isolated from from *Ononis spinosa* subsp. leiosperma showed weak activity against *Pseudomonas aeruginosa*[44].

The butanol extracts at 4 mg/disc of *Ononis spinosa*, possessed moderate antifungal activity against *Aspergillus flavus*, *Fusarium moniliforme* and *Candida albicans* relative to miconazole nitrate at 40 µg/disc[59].

The antifungal activity of *Ononis spinosa* ashes was investigate against 10 Candida isolates, of which one was a *Candida albicans* standard strain (ATCC 95071), and the others were clinical isolates (*Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida guilliermondii*, *Candida parapsilosis*, *Candida pelliculosa*) as well as against *Trichosporon asahii* and *Trichophyton rubrum*. Both aqueous and ethanol extracts of *Ononis spinosa* ash showed antifungal activity against *Candida albicans* ATCC 95071 (diameter of inhibition zones were 16 and 15 mm; MIC = 1.25 µg/ml, MFC = 1.25 µg/ml, respectively). Only ethanol extract exhibited antifungal activity against *Candida glabrata* (diameter of inhibition zone = 10 mm, MIC = 5.00 µg/ml, MFC = 40.00 µg/ml). No antifungal effect was detected against the other clinical *Candida* spp, *Trichosporon asahii* and *Trichophyton rubrum* isolates[36].

Antiinflammatory and analgesic effects:

Ononis spinosa root ethanolic extract was tested for anti-inflammatory activity using carrageenan-induced rat paw oedema test, the extract significantly reduced oedema (46%) after 3 hours ($p<0.05$) at a dose corresponding to 500 mg/kg bw, intraperitoneally. However, no significant anti-inflammatory effect was noted at 100 mg/kg bw[54].

The dichloromethane extract caused concentration- dependent inhibition of IL-8 and TNF-α release from LPS pre-stimulated human neutrophils. This inhibitory activity attributed to norneolignan clitorienolactone B and the triterpene α-onocerin. In addition, extract as well as clitorienolactone B and α-onocerine significantly decreased the expression of adhesion molecules CD11b/CD18 and conversely increased the expression of CD62L in LPS-stimulated human neutrophils, a finding that parallel with reduction in the inflammatory response by inhibition of adhesion and migration of immune cells. However, TLR4 transfected HEK293 cells and non-transfected HEK293 cells incubated with the dichloromethane extract showed that the anti-inflammatory effects in part mediated *via* TLR-4 receptor antagonism. These results rationalized the traditional use of extracts from *Ononis spinosa* in the treatment of urinary tract infections and rheumatic conditions, due to its anti-inflammatory effects[60].

The antiinflammatory effect methanolic extracts of of 43 plants were determined using the cytosolic phospholipase $A_2\alpha$ (cPLA2α) inhibitory activity. *Ononis spinosa* methanolic extract was one of the most active extracts (IC_{50}: 39.4 µg/ml). The phospholipase $A_2\alpha$ inhibitory activity was positively correlated with its phenolic content[61].

The methanolic *Ononis spinosa* root extract selectively inhibited 5-lipoxygenase *in vitro* with an IC_{50} of 7.8 µg/ml, and the isolated pterocarpan medicarpin inhibited leukotriene B4 formation with an IC_{50} of 6.7 µM[62].

The analgesic activity of a water extract of *Ononis spinosa* was studied in mice. Analgesic activity was investigated on the pain thresholds measured with the tail-flick test at 30, 90 and 150 min. The extract of *Ononis spinosa* showed analgesic activity equivalent to aspirin at 30 and 90 min, and even higher than aspirin at 50 mg/kg. At a dose of 100 mg/kg, *Ononis spinosa* extract possessed analgesic effect equivalent to aspirin at all time points[63].

The analgesic effect of ethanolic *Ononis spinosa* root extract was evaluated using phenylquinone writhing test in mice. The extract reduced reaction to pain by up to 80% at doses of 100 and 500 mg/kg bw, intraperitoneally. However, no analgesic effect was observed after oral administration and no analgesic effect was observed in the hot plate test in mice after oral and intraperitoneal administration of the extract[54].

TRPM3 (melastatin-related transient receptor potential 3) was blocked by ononetin, a deoxybenzoin from *Ononis spinosa*. By this inhibition it attenuate thermal nociception[64].

Antioxidant effect:

Methanol extract of *Ononis spinosa* possessed concentration dependent antioxidant effect. The percent of the inhibitory effects of *Ononis spinosa* extracts (0.5, 1, 2.5, 5 and 10 mg/ml) on superoxide anion formation were 79 ± 1, 61 ± 3, 21 ± 1, 27 ± 1 and 5 ± 1% respectively. While, the inhibitory effects of *Ononis spinosa* extracts (2.5, 5, 10 mg/ml) on lipid peroxidation were 38.45 ± 2.62, 36.62 ± 0.10 and 38.45 ± 2.64 nmol MDA/g tissue, respectively[65].

Extracts and fractions from *Ononis spinosa* roots were investigated for their radical scavenging activity using two different *in vitro* assays (DPPH and ABTS). The chloroform fraction possessed the highest radical scavenging activity (RSA) in both assays, DPPH (0.235 mmol/g) and ABTS (0.264 mmol/g). The greatest total phenolic content was detected in the ethyl acetate and chloroform fractions of ethanol extract (108.7 mg/g GAE and 102.1 mg/g GAE, respectively). A correlation between radical scavenging capacities of samples with total phenolic compound content was not observed[53].

The antioxidant activities of methanolic extracts were determined with the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. EC_{50} value for DPPH reduction of *Ononis spinosa* methanolic extract was 271.07 ± 13.13 µg/ml. The antioxidant activity was positively correlated with its phenolic content[61].

The aqueous extract of the root of *Ononis spinosa* was tested for antioxidant effect using DPPH radical scavenging assay. The DPPH inhibition was 20.5±0.8% and the total phenolic content was 3.09±0.01 mg GAE/g extract[58].

Dermatological effect

The efficacy of *Ononis spinosa* extract and glycerin on facial sagging and wrinkles, with a special focus on immediate and delayed effects was tested clinically. Thirty-nine women applied the product daily during an eight-week treatment period. Clinical grading by experts and a new 2-D imaging method (measured the upper eyelid lifting effect) were performed at different time points. The results showed an immediate and significant improvement in sagging and wrinkle parameters seven hours after the first application, in addition to significant long-term improvement. The lifting effect calculated from the 2-D pictures was 1.08 mm immediately after application, and 1.80 mm lifting effect following the eight-week treatment period[66].

The root extract of *Ononis spinosa* inhibited hyaluronidases, the inhibition of Hyal-1 was a promising target for improved wound healing, tissue regeneration, and for induction of dieresis. Two non-polar fractions of *Ononis spinosa* roots were found to be the most active, caused 86±3 % and 96±13 % inhibition of Hyal-1 at a concentration of 1mg/ml, respectively. Chemical analysis revealed 3 main components which were identified as onogenin, sativanone and medicarpin. Percentage inhibitions for 250 µM concentrations of these compounds were 25.3±18, 61.20 ± 20.6 and 22.4±16 respectively. The IC_{50} of sativanone was determined to be 151 µM[67].

Hot water and hydroalcoholic *Ononis spinosa* root extracts showed moderate hyaluronidase-1 (Hyal-1) inhibiting effects (IC_{50} 1.36 resp. 0.73 mg/ml) while dichloromethane extract exerted (Hyal-1) inhibiting effect with IC_{50} of 190 µg/ml[50].

Anticancer effect:

Formononetin, the bioactive isoflavones identified in the *Ononis spinosa* showed anticancer effects against ovarian, breast, colon, liver, cervical, lung, bladder, gastric, esophagus, nasopharyngeal, adrenal medulla tumor, multiple myeloma, osteosarcoma and glioma. It induced apoptosis in many kinds of cancer[68].

The methanol extract of *Ononis spinosa* was screened for cytotoxic activity against MCF-7, A-549, Hep-G2, HT-29 and MDBK cell lines. The extract exhibited potent cytotoxic activity against some of the tested cell lines[69].

Hepatoprotective effect:

The hepatoprotective effect of a water extract of *Ononis spinosa* was studied using carbon tetrachloride (CCl_4)-induced acute liver toxicity in mice. The extract had no significant effect on the increased levels of aspartate aminotransferase, alanine aminotransferase and bilirubin in CCl_4 treated animals ($p>0.05$)[63].

Side effects and contraindications:

Oral or intraperitoneal administration of ethanolic extract 2g/kg bw for 14 days to rats or mice did not cause any visible toxic effects[54].

No health hazards or side effects were known in conjunction with the proper administration of designated therapeutic dosages. The drug should not be used in the presence of edema of cardiac or renal origin. It should not be used during pregnancy and lactation without medical advice[39, 42].

The cytogenetic effects of the aqueous extract from *Ononidis radix* was investigated in the micronuclei formation *in vitro* using irradiated human blood lymphocytes obtained from healthy, non-smoking, young male donor. *Ononidis radix* at a concentration of 0.2 mg/ml, potentiated the yield of radiation- induced micronuclei up to 1.7-fold[70].

II. CONCLUSION:

Human beings have depended on nature for their simple requirements as being the sources for medicines, shelters, food stuffs, fragrances, clothing, flavors and fertilizers. There is a promising future of medicinal plants as there are about half million plants around the world, and most of them are not investigated yet for their medical activities. The pharmacological studies showed that *Ononis spinosa* possessed diuretic, antimicrobial, anti-inflammatory, analgesic, antioxidant, dermatological, anticancer and hepatoprotective effects. Accordingly, it represents a promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

REFERENCES:

[1]. Al-Snafi AE. The Pharmacological importance of *Bauhinia variegata*. A Review. Journal of Pharma Sciences and Research 2013; 4(12): 160-164.
[2]. Al-Snafi AE. The medical benefit of *Gnaphalium luteoalbum*-A review. IOSR Journal of pharmacy 2019; 9(5): 40-44.
[3]. Al-Snafi AE. Chemical constituents and pharmacological effects of *Lythrum salicaria* - A review. IOSR Journal of Pharmacy 2019; 9(6): 51-59.
[4]. Al-Snafi AE. Medical benefit of *Malva neglecta* - A review. IOSR Journal of Pharmacy 2019; 9(6): 60-67.
[5]. Al-Snafi AE. A review on *Lagerstroemia indica*: A potential medicinal plant. IOSR Journal of Pharmacy 2019; 9(6): 36-42.
[6]. Al-Snafi AE. Pharmacological and Therapeutic effects of *Lallemantia royleana*- A review. IOSR Journal of Pharmacy 2019; 9(6):43-50.
[7]. Al-Snafi AE. Chemical constituents and pharmacological effects of *Lathyrus sativus*- A review. IOSR Journal of Pharmacy 2019; 9(6): 51-58.
[8]. Al-Snai AE. Iraqi medicinal plants with antifungal effect- A review. IOSR Journal of Pharmacy 2019; 9(7): 16-56.
[9]. Al-Snai AE. Iraqi medicinal plants with antiviral effect- A review. IOSR Journal of Pharmacy 2019; 9(7): 57-75.
[10]. Al-Snai AE. A review on *Lycopus europaeus*: A potential medicinal plant. IOSR Journal of Pharmacy 2019; 9(7): 80-88.
[11]. Al-Snai AE. *Lemna minor*: Traditional uses, chemical constituents and pharmacological effects- A review. IOSR Journal of Pharmacy 2019; 9(8): 6-11.
[12]. Al-Snai AE. Chemical constituents and pharmacological effects of *Lithospermum officinale*. IOSR Journal of Pharmacy 2019; 9(8): 12-21.
[13]. Al-Snai AE. Iraqi medicinal plants with antibacterial effect- A review. IOSR Journal of Pharmacy 2019; 9(8): 22-103.
[14]. Al-Snai AE, Talab TA. A review of medicinal plants with nephroprotective effects. GSC Biological and Pharmaceutical Sciences 2019; 8(1): 114-122.
[15]. Al-Snai AE, Al-Kamel ML, Esmael ME. Antifungal effect of *Alhagi maurorum* phenolic extract. IOSR Journal of Pharmacy 2019; 9(8): 7-14.
[16]. Al-Snai AE. Pharmacological and therapeutic effects of *Lippia nodiflora* (*Phyla nodiflora*). IOSR Journal of Pharmacy 2019; 9(8):15-25.
[17]. Al-Snai AE, Mousa HM, Majid WJ. Medicinal plants possessed hepatoprotective activity. IOSR Journal of Pharmacy 2019; 9(8): 26-56.
[18]. Al-Snafi AE. Medical benefit of *Lallemantia iberica*- A review. To Chemistry Journal 2019; 3: 97-102.
[19]. Al-Snafi AE. Constituents and pharmacological effects of *Leontice leontopetalum*- A review. To Chemistry Journal 2019; 3: 103-108.
[20]. Al-Kamel ML and Al-Snafi AE. Antibacterial effect of the phenolic extract of *Alhagi maurorum*. IOSR Journal of Pharmacy 2019; 9(9):47-55.
[21]. Al-Snafi AE. A review on *Luffa acutangula*: A potential medicinal plant. IOSR Journal of Pharmacy 2019; 9(9):56-67.
[22]. Al-Snafi AE. Constituents and pharmacology of *Luffa cylindrica*- A review. IOSR Journal of Pharmacy 2019; 9(9):68-79.
[23]. Al-Snafi AE. A review on *Lawsonia inermis*: A potential medicinal plant. International Journal of Current Pharmaceutical Research 2019; 11(5):1-13.
[24]. Al-Snafi AE. Medicinal value of *Lagerstroemia speciosa*: An updated review. International Journal of Current Pharmaceutical Research 2019; 11(5):18-26.
[25]. Salehi B, Krochmal-Marczak B, Skiba D, Patra JK, Das SK Das G, Popović- Djordjević JB, Kostić AZ, Kumar NV, Tripathi A, Al-Snafi AE, Arserim-Uçar DK, Konovalov DA, Csupor D, Shukla I, Azmi L, Mishra AP, Sharifi-Rad J, Sawicka B, Martins N, Taheri Y, Fokou BVT, Capasso R and Martorell M. *Convolvulus* plant- A comprehensive review from phytochemical composition to pharmacy. Phytotherapy Research 2019;1–14.
[26]. Al-Snafi AE. Chemical constituents and pharmacological activities of *Lantana camara*- A review. Asian J Pharm Clin Res 2019; 12912):10-20.
[27]. Al-Snafi AE. Chemical constituents and pharmacological effects of *Lepidium sativum*- A review. International Journal of Current Pharmaceutical Research 2019; 11(6):1-10.
[28]. Al-Snafi AE. Constituents and pharmacology of *Fumaria officinalis*- A review. IOSR Journal of Pharmacy 2020; 10(1):17-25.

[29]. Al-Snafi AE. Chemical constituents and pharmacological effects of *Melilotus Officinalis*- A review. IOSR Journal of Pharmacy 2020; 10(1):26-36.
[30]. Al-Snafi AE. Bioactive metabolites and pharmacology of *Cistanche tubulosa*- A review. IOSR Journal of Pharmacy 2020; 10(1): 37-46.

[31]. The plant list, *Ononis spinosa*, http://www.theplantlist.org/tpl1.1/record/ild-29429
[32]. Uniprot. Taxonomy - *Ononis spinosa* (Spiny restharrow), https://www. uniprot. org/ taxonomy/ 58890
[33]. U.S. National Plant Germplasm System, *Ononis spinosa*, https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?id=105027
[34]. Plants for a future, *Ononis spinosa*, https://pfaf.org/user/Plant.aspx? Latin Name=Ononis+spinosa
[35]. Flora of China, *Ononis spinosa*, http://www.efloras.org/florataxon.aspx? flora_id= 2&taxon_id=220009481
[36]. Altuner EM, Ceter T and Işlek C. Investigation of antifungal activity of *Ononis spinosa* L. ash used for the therapy of skin infections as folk remedies. Mikrobiyol Bul 2010; 44(4): 633-639.
[37]. Toglu GS and Altanlar N. Antimicrobial activity of some plants used in folk medicine. J Fac Pharm, Ankara 2003; 32(3): 159-163.
[38]. Al-douri NA. A survey of medicinal plants and their traditional uses in Iraq, Pharmaceutical Biology 2000; 38(1): 74-79.
[39]. PDR for Herbal Medicines. Medical Economics Company, Inc. at Montvale, 2000: 713.
[40]. Kooperation Phytopharmaka, Restharrow, https://www.koop-phyto.org/en/ medicinal - plants/restharrow.php
[41]. Fayyazi N, Naghibi F, Keramatian B and Taheri S. Phytochemical analysis and purification of chief components of *Ononis spinosa*. MAGNT Research Report 2014; 2(2):69-73.
[42]. Mills S and Hutchins R. The scientific foundation for herbal medicinal products, Ononidis radix. ESCOP 2009.
[43]. Benedec D, Vlase L, Oniga I, Toiu A, Tamas M and Tiperciuc B. Isoflavonoids from *Glycyrrhiza Sp*. and *Ononis spinosa*. Farmacia 2012; 60 (5):615-620.
[44]. Kirmizigül S, Gören N, Yang SW, Cordell GA and Bozok-Johansson C. Spinonin, a novel glycoside from *Ononis spinosa* subsp. leiosperma. J Nat Prod 1997; 60(4):378-381.
[45]. Háznagy A, Tóth G and Tamás J. Über die Inhalsstoffe des wäßrigen Extraktes von *Ononis spinosa L*. Arch Pharm (Weinheim) 1978; 311:318-323.
[46]. Pietta P and Calatroni A. High performance liquid chromatographic analysis of flavonoids from *Ononis spinosa* L. J Chromatogr 1983; 280:172-175.
[47]. Blaschek W, Hansel R, Keller K, Reichling J, Rimpler H and Schneider G (Editors). Ononidis radix. In: Hagers Handbuch der pharmazeutischen Praxis: 5th ed. Volume 3: Drogen L-Z. Springer-Verlag, Berlin 1998: 263-270.
[48]. Luczak S and Swiatek L. GC-MS investigation of phenolic acids in *Ononis spinosa* roots. Fitoterapia 1991; 62: 455-456.
[49]. European medicines agency. Assessment report on *Ononis spinosa* L., radix. 2014. https://www.ema.europa.eu/en/documents/herbal-report/final-assessment - report-ononis-spinosa-l-radix_en.pdf
[50]. Addotey JN, Lengers I, Jose J, Gampe N, Béni S, Petereit F and Hensel A. Isoflavonoids with inhibiting effects on human hyaluronidase-1 and norneolignan clitorienolactone B from *Ononis spinosa* L root extract. Fitoterapia 2018;130:169-174.
[51]. Gampe N, Darcsi A, Kursinszki L and Béni S. Separation and characterization of homopipecolic acid isoflavonoid ester derivatives isolated from *Ononis spinosa* L. root. J Chromatogr B Analyt Technol Biomed Life Sci 2018; 1091: 21-28.
[52]. Gampe N, Darcsi A, Lohner S, Béni S and Kursinszki L. Characterization and identification of isoflavonoid glycosides in the root of Spiny restharrow (*Ononis spinosa* L.) by HPLC-QTOF-MS, HPLC-MS/MS and NMR. J Pharm Biomed Anal 2016;123:74-81.
[53]. Valyova M, Hadjimitova V, Stoyanov S, Ganeva Y, Traykov T and Petkov I. Radical scavenger and antioxidant activities of extracts and fractions from Bulgarian *Ononis spinosa* L. and GC-MS analysis of ethanol extract. The Internet Journal of Alternative Medicine 2008; 7(2): 1-5.
[54]. Bolle P, Faccendini P, Bello U, Panzironi C and Tita B. *Ononis spinosa* L. Pharmacological effect of ethanol extract. Phamacol Res 1993; 27(suppl 1): 27-28.
[55]. Rebuelta M, San Roman L and Serra Nillos M. Étude de l'effet diurétique de différentes préparations de l' *Ononis spinosa* L. Plantes Méd Phytothér 1981; 15:99-108.
[56]. Hilp K, Kating H and Schaden G. Inhaltsstoffe aus *Ononis spinosa* L., 1.Mitt. Das ätherische Öl der Radix Ononidis. Arch Pharmaz 1974; 308 (75):429-433

[57]. Citolu G and Altanlar N. Antimicrobial activity of some plants used in folk medicine. J Fac Pharm, Ankara 2003; 32(3): 159-163.
[58]. Orhan DD, Ozcelik B, Hosbas S and Vural M. Assessment of antioxidant, antibacterial, antimycobacterial, and antifungal activities of some plants used as folk remedies in Turkey against dermatophytes and yeast-like fungi. Turk J Biol 2012; 36: 672-686.
[59]. Mahasneh AM and El-Oqlah AA. Antimicrobial activity of extracts of herbal plants used in the traditional medicine of Jordan. J Ethnopharmacol 1999; 64: 271–276.
[60]. Spiegler V, Michalack B, Addotey J, Jose J, Kiss AK and Hensel A. Root extracts from *Ononis spinosa* exert anti-inflammatory activity *in vitro* on IL-8 and TNF-α release by inhibition of TLR-4 receptor. Planta Med 2019; 85(18): 1410.
[61]. Arnold E, Benz T, Zapp C and Wink M. Inhibition of cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) by medicinal plants in relation to their phenolic content. Molecules 2015; 20(8): 15033-15048.
[62]. Dannhardt G, Schneider G and Schwell B. Identification and 5-lipoxygenase inhibiting potency of medicarpin isolated from roots of *Ononis spinosa* L. Pharm Pharmacol Lett 1992, 2:161-162.
[63]. Yılmaz BS, Ozbek H, Citoglu GS, Ugra S, Bayram I and Erdogan E. Analgesic and hepatotoxic effects of *Ononis spinosa* L. Phytother Res 2006; 20: 500-503.
[64]. Straub I, Krugel U, Mohr F, Teichert J, Rizun O, Konrad M, Oberwinkler J and Schaefer M. Flavanones that selectively inhibit TRPM3 attenuate thermal nociception *in vivo*. Molecular Pharmacology 2013; doi: https://doi.org/ 10.1124/mol.113.086843
[65]. Çoban T, Saltan-Çitoglu G, Sever B and Iscan M. Antioxidant activities of plants used in traditional medicine in Turkey. Pharm Biol 2003; 41: 608-613.
[66]. Roure R, Lanctin M, Nkengne A, Nollent V, Dayan L and Bertin C. Cosmetic lifting effect of a formula combining tetrahydroxypropyl ethylene diamine, *Ononis spinosa* and glycerin as shown by a new 2-D imaging method. JCDSA 2013;3(3): 209-215.
[67]. Addotey J, Lengers I, Jose J, Gampe N, Béni S, Petereit F and Hensel A. Roots of diuretic plant *Ononis spinosa* L. contain Hyal-1 inhibitors. Conference: Münster Conference on Biomolecule Analysis 2018, doi: 10.13140/RG.2.2.13186.12482
[68]. Jiang D, Rasul A, Batool R, Sarfraz I, HussainG , Tahir MM, Qin T, Selamoglu Z, Ali M, Li J and Li X. Potential anticancer properties and mechanisms of action of formononetin. Bio Med Research International 2019; 5854315, https://doi.org/ 10.1155/ 2019/5854315
[69]. Irani M, Shahrestani R, Bahmani B, Esmaeili S and Nader N. Cytotoxic activity of plants from east Azarbaijan province, Iran. Research Journal of Pharmacognosy (RJP) 2017; 4(Supplement): 1.
[70]. Joksić G, Stanković M and Novak A. Antibacterial medicinal plants *Equiseti* herba and *Ononidis radix* modulate micronucleus formation in human lymphocytes *in vitro*. J Environ Pathol Toxicol Oncol 2003, 22:41-48.

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