



CAROB (*Ceratonia siliqua*): HEALTH, MEDICINE AND CHEMISTRY

Abdullatif Azab^{[a,b]*}

Keywords: Carob, antimicrobial, antioxidant, chemical composition, polyphenols, nutritional value.

Carob (*Ceratonia siliqua*) is one of the important crops over western Asia and North Africa. Its nutritional value has been acknowledged for millennia but its medicinal properties were practically studied only in the last four decades, despite the fact that some of them were used in traditional medicines for centuries. Modern food industry is just starting to discover the great potential of this plant. Carob has outstanding antioxidant capacity along with other important medicinal activities. Some of these have been extensively studied and reported in the last decades, but very few review articles were published about this plant, that summarize and discuss the findings. In this comprehensive review article, we present these reports and discuss them with special attention to traditional medicine, modern research findings, natural products and recommendations for future research subjects.

*** Corresponding Authors**

Telephone: +972-(0)4-6357011

Fax: +972-(0)4-6356168

E-Mail: eastern.plants@gmail.com

[a] Triangle Research & Development Center, Box 2167, Kfar-Qari, Israel 30075

[b] Eastern Plants Company, Box 868, Arara, Israel 30026

Introduction

Carob (*Ceratonia siliqua*) is an evergreen tree that belongs to the legume (Fabaceae) family. Its original habitats are the western parts of Asia, but after its domestication, it spread to all Mediterranean basin and then to the western shores of the Americas, South Africa and southern regions of Australia.¹ Until 1980, the genus *Ceratonia* was considered to include only one species, Carob, *C. siliqua*, but in 1980, another species, *C. oreoethauma*, was identified in the eastern region of Africa and Arabian Peninsula.² So far, *C. oreoethauma* has not been reported to have medicinal or nutritional properties.

According to archeological studies, Carob was used by human beings since very ancient times. But the accurate time of domestication remains debatably unclear. Some scholars reported that it was as late as the Roman era,^{3,4} other studies indicate much earlier use.^{5,6} However, due to its economic and nutritional value, especially in North Africa, many studies were conducted to investigate the various conditions that effect growth of the plant,⁷ and the quantity and the qualities of the fruits (pods) of various wild and domesticated varieties.^{8,9}

As far as we could find, three comprehensive review articles were published so far about chemical and medicinal properties of carob. R. Sundararajan and his colleagues mentioned *C. siliqua* among other plants that contain phytoconstituents with nephroprotective activity.¹⁰ The authors designate Carob as a an important plant that has natural products with nephroprotective activity, and they cite "Ben *et al.*, 2011". But reading the reference list revealed no Ben. The article of Nasar-Abbas focuses only on Carob, it is much more comprehensive and more reliable.¹¹ This article has two weaknesses. First, it does not refer to traditional medicinal knowledge which is the base of many of modern research studies. Secondly, it does not refer to medicinal activities of various extracts and other

Table 1. Ethnomedicinal uses of Carob

Region	Ethnomedicinal use	Method/Reference
Cyprus	Laxative	NI ^{a, 13}
Egypt	Diarrhea	Infusion ¹⁴
Greco-Arab	Diabetes, herpes, lip sores	Leaf decoction ¹⁵
India	Antiobesity	NI ¹⁶
Iran	Menorrhagia	Patient should sit in a container of a decoction of several plants. Including Carob Details in reference ¹⁷
Iraq	Abdominal pain, diarrhea	Eating ripe fruits ¹⁸
Israel	Antidiabetic; Against viral and bacterial infections and fevers	Leaves decoction: 50 g in 1 L; ¹⁹ Fruit syrup mixed with sesame paste ²⁰
Italy	Animal food; Emollient	Dry fruits, ²¹ Fruits decoction with <i>Ficus carica</i> and <i>Malva sylvestris</i> ²²
Jordan	Antidiabetic; Cough	Leaves decoction, ²³ Hot/cold infusion of fruits ²⁴
Lebanon	Sweetener; medicinal	Molasses of ripe fruits, ²⁵ NI ²⁶
Morocco	Diarrhea, fish killer, kills intestinal parasites, Relief of skin, digestive system, nervous system	Fruit, bark, leaves, ²⁷ Fruits/leaves decoction, ²⁸ Infusion/decoction of fruit powder, oral. ²⁹ Fruit powder. ³⁰
Palestine	Food	Fruits eaten raw(cooked) or ripe ³¹
Sicily	Food	Fruits eaten raw(cooked) or ripe ³²
Spain	Chocolate, coffee substitute, olive preservative	Ripe fruits, leaves ³³
Tunisia	Food	Ripe pods ³⁴
Turkey	Diuretic, purgative	Fresh pods ³⁵

^aNI= not indicated

materials produced from the tree leaves, which are drawing more and more research attention. Finally, an excellent yet a short review article was published by an internationally leading researcher of Carob, K. Rtibi and his colleagues from Tunisia.¹² But in addition to being a relatively short article, it also focuses on the fruits of the plant, hardly mentioning leaves and other parts of the tree. It also presents all data from the gastrointestinal tract point of view. But it displays some important phenolic compounds in clear and useful figure (page 3 in article).

Ethnomedicinal and other traditional uses of Carob

As mentioned above, Carob is being used by humans as food source and for medicinal purposes since antiquity. Most nations of the Mediterranean basin have such recorded uses as shown in table 1, but other nations discovered its qualities as well.

Modern research of Carob uses, composition and biological activities

Comparing with other fruiting wild trees with very important nutritional value, modern research has neglected Carob. This is to say that most publications of its medicinal/biological activities date from the 2000's. Most of the few earlier publication focus on chemical composition of the pods. We summarized below the findings of modern research of the properties and health uses of Carob. It is important to advise readers that when looking for a specific activity, it is worthy to look for it not only in designated columns, because many publications include reports of more than one activity. Moreover, many publications about Carob are not cited in this review because they studied subjects that are out of the interest of this article.

Antiatherogenic

Aqueous extracts of fruits inhibits lipid peroxidation, inflammation and enhances cholesterol efflux.³⁶

Antibacterial, antimicrobial, antifungal and related activities

Methanolic extract of *C. siliqua* was tested for antibacterial activity, compared with methanolic extract of *Plantago major*, which was found more active for most bacteria. The extract of *C. siliqua* was more active for *Enterococcus sp.*³⁷ Aqueous and methanolic extracts were tested for antibacterial activity, alone and in combination with other antibacterial agents (ampicillin, gentamicin, amikacin and clindamycin). The combination of extracts and antibacterial agents was more efficient than each separately. The extracts were analyzed and some pure compounds were isolated and characterized (Figure 1).³⁸ Ethanolic and acetone extracts were tested for antibacterial activity against *P. atrosepticum* in potato soft rot. Acetone extract was more active.³⁹ Methanolic extract of leaves found to be active against *Listeria monocytogenes*. HPLC analysis of extract yielded seven compounds with antibacterial activity, especially epigallocatechin-3-gallate (Figure 2).⁴⁰

Dichloromethane-methanol (1:1, v/v) extract of dried pods was tested against 14 types of bacteria and fungi.

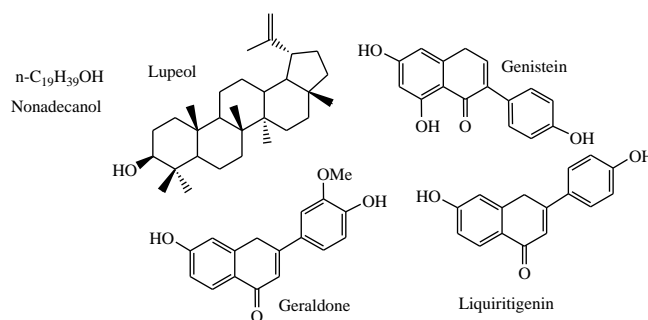


Figure 1. Some compounds isolated from the extract of *C. siliqua*

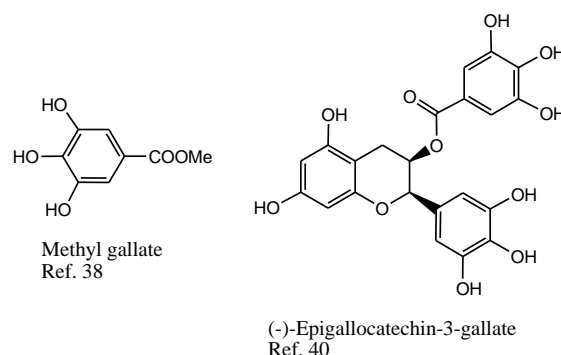


Figure 2. Some compounds isolated from *C. siliqua* by HPLC.

It was found highly active against 11 of them, in concentrations of 1000 and 500 $\mu\text{g/ml}$.⁴¹ Chloroform and hydroalcoholic (no ratio indicated) extracts of dry leaves were prepared and found active against 15 species of bacteria and fungi, including 3 species of *C. albicans*.⁴²

Dried powder of the plant (part not indicated) was soaked in methanol and the suspension was centrifuged, filtered and tested for antibacterial and antifungal activities results were positive. Its photosensitizing capacity was also tested and found sufficient. No analysis for natural products was done.⁴³

Hexane, chloroform, ethyl acetate and methanolic extracts of dry leaves were prepared and tested for antifungal activity against citrus sour rot agent *G. candidum*. First two were inactive and methanol extract more active than ethyl acetate extract.⁴⁴ Methanolic extract of dry pods was prepared and tested against 13 different microbes and 8 different fungi. It was active against all. Total phenolic content was found as 465.5 mg g^{-1} with reference to gallic acid, and total flavonoid content was found as 24.6 mg g^{-1} compared with quercetin.⁴⁵ Fresh fruits were extracted with 80 % methanol in water. The extract was found antimicrobial and moderate antioxidant (DPPH).⁴⁶ Dry leaves were extracted with n-hexane, ethanol, methanol, ethyl acetate and water. Extracts were tested for antimicrobial, antifungal and cytotoxic activity (brine shrimp assay). n-Hexane was the most cytotoxic and it had the highest antimicrobial activity along with methanolic extract.⁴⁷

Antidiabetic and related activities

Ethanol/water (96 %) extract of dry pods was tested for streptozotocin-induced diabetes in rats. It decreased blood glucose and lipids.⁴⁸ Mixture of dried flowers of Roselle (*Hibiscus sabdariffa*) and dry pods of Carob, was water extracted and administered to alloxan-induced diabetic rats. The extract was tested with or without Gamma radiation of the plants mixture powder. In both cases it was found active.⁴⁹

Aqueous extract of immature pod was tested in alloxan-induced diabetic rats for antidiabetic activity. It was found more active than the aqueous extract of mature pods.⁵⁰ Powder of dry pods was extracted with n-hexane for phytosterols. The dry extract was found active against alloxan-induced diabetes in pregnant female rabbits.⁵¹ Same extract was used by the same group to test the same activity, but female rabbits were not pregnant.⁵² Fiber purified aqueous extract of seed-free dry pods, was prepared and tested for antidiabetic activity by α -glucosidase inhibition. Sufficient activity was found.⁵³

Antiviral activity

Ethanol extract of leaves was tested against Newcastle Disease Virus and found partially active.⁵⁴

Anticancer, antiproliferative and related activities

Ethanol and ethyl acetate extracts of propolis that was collected in an area (Morocco) with Carob as a major tree were prepared, and tested against three mammalian tumor cell lines. Medium activity was measured.⁵⁵ Dry pods were extracted with ethanol, and it was analyzed for reductive components (very detailed), antioxidant, anticancer and anticalpain activities. It was found moderately active for the three activities.⁵⁶ Aqueous extracts of dry pods or leaves were tested against mouse hepatocellular carcinoma cell line, and both found active, but leaves extract was more active. Authors attribute this activity to the presence of gallic acid and some of its esters.⁵⁷ Methanolic extracts of pods and leaves were prepared and tested for antiproliferative and apoptotic activities in MDA-MB-231 human breast cancer cells, and both found active, with higher activity of leaves extract. Authors relate these activities to the presence of phenolic compounds.⁵⁸

Antidepressant

Acetone extract of fresh pods was prepared and analyzed for tannins content, and tested as antidepressant by tail suspension test and forced swim test. It was active in both and the proposed mechanism of action is by an interaction with the adrenergic and dopaminergic systems.⁵⁹

Antifibrotic

Seed and fibre free dry pods were extracted with water and tested for *Schistosoma mansoni*-induced liver fibrosis and reduction of oxidative stress in mice. Significant activity was found.⁶⁰

Anti-inflammatory and related activities

Methanol extract of bark was tested for antioxidant (DPPH), acute toxicity (rats) and chemical (Carrageenan) or mechanical paw oedema. It was analyzed for major compound families and flavonoids, tannins, sterols, quinones and mucilages were found.⁶¹ A galactomannan extracted from pods, authors refer to as LBG (locust bean gum) was used as contrast material in magnetic resonance enteroclysis (MRE) for imaging of Crohn's disease (bowels chronic inflammatory disease). It gave best results when used with water and mannitol.⁶² Leaves were extracted with dichloromethane:methanol, 1:1 v/v. The extract was tested for anti-inflammatory and cytotoxic activities and found inactive in both.⁶³

Antioxidant and related activities

Methanol extracts of leaves and pulps (all sexes of the tree) were tested for radical scavenging (DPPH) and antioxidant (carotene-linoleate) activities and leaves extract found to be more active.⁶⁴ Leaves were extracted successively with hexane, methanol/water (8:2, v/v), diethyl ether, dichloromethane and ethyl acetate. The extracts of three varieties of the tree were tested for antioxidant activity (DPPH) and total phenolic content was determined.⁶⁵

Ethanol extract of dry pods was tested for antioxidant activity (BHA, highly active) and analyzed for polyphenols and carotenoids.⁶⁶ 80 % Aqueous methanol extract was prepared from pods and tested for antioxidant activity (3 methods) and analyzed by reverse phase HPLC.⁶⁷ Immature pods were extracted (without seeds) with water, methanol, ethanol, acetone, petroleum ether and hexane. Extracts were tested for antioxidant activity (ABTS), analyzed for total phenolic content and tested *in vitro* and *in vivo* (rats) for cerebral and myocardial lipid peroxidation. Polar extracts were more active than non-polar ones.⁶⁸

Methanol extract of leaves was tested for antioxidant activity by various methods and found highly active compared with other fruiting plants.⁶⁹ Total phenolic content and antioxidant (DPPH, FRAP) capacity of dry leaves methanolic extract were determined. Compared with other studied plants (3), Carob showed moderate activities.⁷⁰ Dry Carob pods powder aqueous extract was prepared and its total phenolic content and antioxidation activity were determined. Both were found relatively high.⁷¹ Aqueous and methanolic extracts were prepared (plant part not indicated) and were tested for antioxidant activity and total phenolic content. Both extracts showed similar results and were relatively high compared with other (94) plants.⁷² Methanolic extract of leaves was prepared and tested for radical scavenging activity (DPPH, high), antioxidant activity (linoleic acid system assay, high) and antitumor activity (remarkable). It was also analyzed for polyphenolic content.⁷³

Aqueous extract of dry pods was prepared and analyzed for major nutritional materials and minerals. Its antioxidant activity and total phenolic content were determined. An infusion was made that contained Carob extract with other plants and antifungal and antibacterial activities were measured and found high.⁷⁴

Methanolic and ethyl acetate extracts were prepared from bark and were analyzed for major compound families, total phenolic content and antioxidant activity (DPPH) were measured. Methanolic extract was more active.⁷⁵ Dry leaves were extracted with 80 % ethanol-water, and the extract was fractionated with n-hexane, DCM and ethyl acetate. The ethyl acetate fraction showed the highest antioxidant (DPPH, β -carotene bleaching assay) and antimicrobial activities.⁷⁶ Carob seeds were ground and supplied, without further treatment, to female rats to test antioxidant and hepatoprotective activities of the powder against ethanol-induced oxidative stress. Results were measured by serum enzymes.⁷⁷ Aqueous extract of dry pods (or leaves) was prepared and found active inhibitor of neutrophils myeloperoxidase.^{78,79} Dry leaves aqueous extract was found protective against cell DNA oxidative stress caused by H_2O_2 and it had no genotoxicity.⁸⁰ Fresh pulp was extracted by ultrasonic-assisted 80 % aqueous ethanol. The effect of the free/encapsulated extract was tested for antioxidant and nutritional value of yogurts. The free form had higher antioxidant activity (shorter shelf-life) and both forms did not alter nutritional value.⁸¹ Ground pods were defatted with hexane and the dry residue was added to Kefir (yogurt). It improved its antioxidant capacity and increased bacteria growth.⁸² Dry pods powder was added to pasta flour. The antioxidant activity (ABTS, FRAP) was improved and the nutritional values were increased.⁸³ Powdered Carob pods were added directly to rats food to test its hepato- and nephroprotective effect against oxidative stress induced by CCl_4 . Positive results were obtained.⁸⁴ Pulp powder was extracted with acetone/water (7:3) and encapsulated with polycaprolactone. Encapsulated and non-encapsulated extract of ripe and unripe pulp was tested for antioxidant activity (ORAC, DPPH, FRAP) after *in vitro* digestion model. The encapsulation provided slow release of phenolic compounds and protection against digestive fluids.⁸⁵ Pod powder was fed to rabbits and its antioxidant activity was monitored through the activity of three oxidizing enzymes. It also promoted the growth of the animals.⁸⁶

Antiatherosclerotic

Commercial insoluble dietary fibre (81 % w) from carob pod was found antiatherosclerotic in rabbits.⁸⁷

Anxiolytic-sedative and antiproliferative

Methanolic extracts of leaves and pods were prepared and tested for central and peripheral benzodiazepine receptors binding. Leaf extracts, especially young leaves, found more active. No active compounds are indicated.⁸⁸

Chemical composition and some related activities

Methanolic and aqueous extracts of sapwood were prepared and analyzed for phenolic contents and their components. The extracts were also tested for antioxidant (H_2O_2) and antitumor activities, where methanolic extract was more active.⁸⁹ Pods of trees from various locations in Morocco were analyzed for fibre, sugar and polyphenolic content.⁹⁰ Seeds-free pod syrup was prepared from trees that grow in Bulgaria and in Turkey, analyzed for sugar content and compared. Turkish product had higher sugar content.⁹¹

Chemical composition of pods from different localities was determined for major compound families, minerals and nutritional ingredients. Aqueous extracts were prepared with hot and cold water, and higher temperatures yielded higher concentrations.⁹² Determination of the tannins, pectins, hemicellulose, cellulose, nitrogen, mineral elements, sugars and fat contents was carried out on carob pods.⁹³ Major chemical composition was determined with detailed extraction (aqueous) conditions of time and temperature.⁹⁴ Composition of Carob pods was determined in terms of carbohydrates, protein, fat, polyphenols and tannins. 70 % acetone/water was the most effective solvent for the extraction and recovery of tannins.⁹⁵ Detailed report of major nutrients determination in pods, with results and methods.⁹⁶ Pods were analyzed for carbohydrates, protein, fat, minerals, vitamins (6), phenolics (11) and fatty acids (17).⁹⁷ Major nutritional components of pulp and detailed amino acid composition is reported.⁹⁸ Methanolic extract of green pods and leaves was prepared, analyzed for chemical composition (major categories) and tested for antibacterial activity.⁹⁹ Three pulp extracts were prepared: 70% ethanol/water, 80 % methanol and aqueous. All were analyzed for chemical composition and tested for *in vitro* antioxidant activity. Ethanolic extract found most active and it was tested *in vivo* (rats, $AlCl_3$ -induced oxidative stress), and found active antioxidant.¹⁰⁰ This study focused on carbohydrate and fatty acid content of pods during different development stages of Carob trees. It also compared wild and domestic cultivars.¹⁰¹ This study compares between phenolic content (mainly) of ripe and unripe pods.¹⁰² Effect of seasonality and its relation with CO_2 assimilation and photosynthesis is reported in terms of changes in chemical composition of major nutrients.¹⁰³ Detailed study of determination of compounds in methanolic pod extract by Liquid Chromatography–Electrospray Ionization–Tandem Mass Spectrometry. Details include conditions (solvents, positive, negative), compounds and their fragmentation.¹⁰⁴ Essential oil was prepared from fresh whole pods and extracted from aqueous phase with DCM. Its analysis showed mainly long chain hydrocarbons, unpolar acids and other unpolar compounds. It was found active against several types of bacteria and cytotoxic against cancer cell line.¹⁰⁵ A short review article about chemical composition of Carob with some interesting uses that are usually ignored by other reports has appeared.¹⁰⁶ Total flavonoid content of leaves was determined by 70 % ethanol/water extraction. The extract was analyzed by HPLC and nine compounds were detected, with myricetin as major.¹⁰⁷ New acylated flavonol glycoside was isolated and characterized from methanolic extract that was fractionated and chromatographed by various solvents. Authors name the new compound ceratoside (Figure 3). Full spectroscopic data is reported.¹⁰⁸

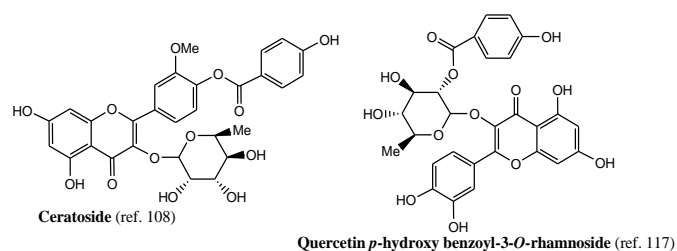


Figure 3. New compounds isolated from Carob.

Experimental and theoretical method for reducing isobutyric acid content in pods by roasting is required, since its foul smell decreases Carob uses for food products.¹⁰⁹ Seed oil was analyzed and the major constituents are: fatty acids, tocopherols and phytosterols.¹¹⁰ Defatted pods of two types (natural and commercial flour) were extracted with methanol and phenolic acids content was determined. Gallic acid was the major constituent.¹¹¹

Dry leaves were extracted with 70 % ethanol/water and analyzed by different methods for polyphenols. No new compounds are reported.¹¹² Leaves, bark, skin and pulp were oven-dried (500 °C) and their mineral content (Ca, K, Mg, Na, P, Cl, Cu, Fe, Zn, Se) was measured by atomic absorption spectrophotometry.¹¹³ Nitrogen and ash content of pods was measured in wild and grafted Carob trees.¹¹⁴ Mineral content (Mg, Cu, Fe, Zn, Se, Mn) of pods was determined by ICP-OES.¹¹⁵ Partial mineral content (K, Ca, Cl, Mg, Na) was determined by neutron activation analysis.¹¹⁶ Kinetic study of the extraction of polyphenols from pods using environment friendly solvents (best, 30 % ethanol/water, 1 % citric acid), and a new compound reported (Figure 3).¹¹⁷

Three types of domesticated Carob were analyzed for sugars, minerals and fatty acids.¹¹⁸ Phytochemical analysis of methanolic extract of pods has been done and antioxidant (DPPH) and cytotoxic activities were tested. Polyphenolics (gallic acid) comprised most of the extract, that had high antioxidant activity and low cytotoxic activity.¹¹⁹ D-pinitol content in various commercial Carob syrups was determined to be around 90 g Kg⁻¹ on an average of the dry weight.¹²⁰ A detailed report of isolation, quantification and identification of polyphenols in pods has appeared.¹²¹ 70 % Acetone/water was used to extract pods and the extract was analyzed for polyphenols and tested for antioxidant activity. Gallic acid was major compound.¹²² A short report of quantification of polyphenolic content of different Carob cultivars in Portugal has been published.¹²³ Total phenolic content of pods from different areas and different domesticated cultivars in Morocco was determined in this report.¹²⁴

Comparison between ripe and unripe pods and using three solvents for extraction of the content of leucoanthocyanins (3,4-dihydroxy flavans).¹²⁵ In this report, 137 compounds were identified in the volatile phase of Carob seeds. During roasting, more than 50 % of them are evaporated, mostly those that have unpleasant odors.¹²⁶ Later study discovered 169 compounds with clear dominance of short chain acids (77.5 %).¹²⁷ Use of advanced isolation and detection method (headspace solid-phase micro extraction, HD-SPME) revealed new yet known volatile compounds in pods, that were not reported in ref. 126, 127.¹²⁸ The extraction, isolation, quantification and characterization of galloyl glucose compounds have been reported.¹²⁹

Deseeded pods of cultivated and wild varieties were analyzed for sugar content. Domesticated plants had higher sugar content. Monosaccharide compositions were also reported.¹³⁰ Alkaline hydrolysis of condensed tannins separated sugars from polyphenols in pods, gave (+)-gallo catechin, (-)-epicatechin and (-)-epicatechin gallate as major compounds.¹³¹ Tannins isolated from ripe pods were hydrolysed with thioglycolic acid to yield free polyphenols and sugars (Scheme 1).¹³² It has been claimed that part of sweet taste of pods is due to 6-deoxymannose and 1-

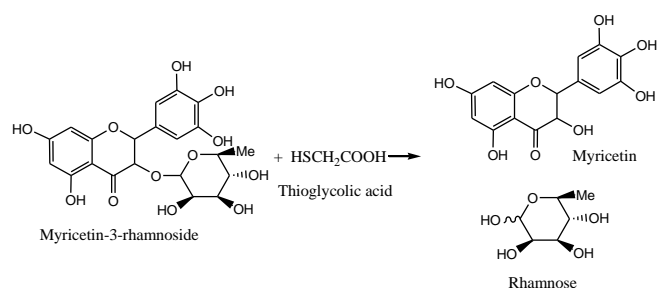
methoxy-6-deoxygalactose but no evidence has been provided.¹³³

Ethanol production

Ethanol was produced from pods that were extracted with water. Details of extraction and fermentation conditions have been presented. Maximum yields were around 45 %.¹³⁴

Heavy metals related activities

Silver nanoparticles were prepared from AgNO₃ solution, using Carob aqueous extract as reductant. The AgNP's have antibacterial activity against *E. coli*.¹³⁵ Dry pod methanolic extract found to be active corrosion inhibitor of copper and brass in aqueous 1 M HNO₃.¹³⁶ Bark was cleaned and treated for biosorption of heavy metals (Zn⁺², Ni⁺², Cu⁺² and Cd⁺²). Different variables are discussed and pH, metal concentration, contact time, adsorbent dose have been optimized. Kinetics of adsorption has been presented.¹³⁷ Ethanol extract of pods was found protective against lead (Pb) poisoning in *Oreochromis niloticus* fish. In this report, all along the article ether extract is mentioned but in the experimental section, alcohol extraction is described.¹³⁸



Scheme 1. Hydrolysis of tannins.

Human nutrition, nutritional sources and risk assessment

Carob flour was added to Tarhana (yogurt-wheat based food), and fibre, ash, Ca, K, Cu, total phenolic content and total antioxidant capacity were determined. All nutritional values and antioxidant property increased.¹³⁹ Powder of Carob pods was added to wheat biscuits. Their mineral and total phenolic content was found higher than biscuits without addition.¹⁴⁰ Risk assessment (Italy) of toxic metals (Pb, Cd) and pesticides (organochlorines, organophosphates, pyrethrins and pyrethroids, in honey of bees that feed on Carob trees) were done. No risk was detected.¹⁴¹ Heavy metals (Cd, Pb, Fe, Cu, Mn, Ni, Cr, Se) in honey of bees that fed from Carob trees (Turkey) among other plants have been determined.¹⁴²

Honey of bees that feed on Carob flowers (Italy) has been physicochemically characterized. Most important presented value is sugar content.¹⁴³ Honey of bees that feed on Carob flowers (Morocco) was physicochemically characterized. Most important presented value is mineral content. Antioxidant activity (DPPH) was tested and found high.¹⁴⁴ Human volunteers, fed with tannates rich carob-fibre that was added to dairy food, had improved cardiovascular functions and significantly lowered cholesterol levels.¹⁴⁵ Extraction of pods with refluxing methanol resulted in high

content of condensed tannins extract, that was added to kids' diet. Lowering of cholesterol level was significant.¹⁴⁶ Snacks that contained Carob with the same amount of available carbohydrates as chocolate snacks were compared in terms of glycemic index (GI). Carob snacks resulted in much lower GI.¹⁴⁷ This study aimed on the finding of optimal ratio of Carob flour in snack to achieve acceptable taste and texture in order to compete with chocolate snacks.¹⁴⁸ Nutritional content was tested and compared between homemade and commercial Carob flour. In all nutritional aspects, soluble sugars, amino acids, fatty acids and mineral content, homemade flour was better.¹⁴⁹ Carob pods are fermented in to produce a special type of wine in Serbia.¹⁵⁰

Animal food and nutrition

Aqueous extract of Pod was tested against cellulolysis and proteolysis of rumen bacteria activity. Its inhibition of cellulolysis was related by authors to high carbohydrate content, while anti-proteolysis activity was related to tannin compounds.¹⁵¹ Deseeded pods and seeds were analyzed for mineral, protein and energy content. Seeds have higher values but tests showed that they are harder to digest for animals. So, pods have higher nutritional importance.¹⁵² Sugar content of Carob pods help both nursing ewes and lambs in the growth process.¹⁵³ Effect of feeding quails with Carob seed powder as food additive was tested. It was found that mortality of birds decreased, egg quality and fatty acid content increased, and cholesterol levels decreased.¹⁵⁴

Gastroprotection and other digestive system related activities

Pods were extracted with 70 % methanol/water and extract was tested against HCl-ethanol induced gastric ulcer and found moderately active, compared with other plants used in this study.¹⁵⁵ Aqueous extract of pods was tested for antioxidant activity (DPPH) and against ethanol-induced oxidative gastric stress (lipoperoxidation and hydrogen peroxide increase) in rats and found active.¹⁵⁶ Aqueous extract of pods was tested against dextran sulfate sodium-induced sub-acute experimental ulcerative colitis in adult Wistar rats. Results were positive and authors attributes this to phenolic compounds in Carob.¹⁵⁷ Aqueous extract of pods was prepared, analyzed (RP-HPLC) for tannins and dietary fiber, total sugar and total phenolics content. It was also tested against small intestinal motility in rats and jejunal permeability in mice, and found active in both tests.¹⁵⁸ Soluble galactomannans were water extracted from Carob seeds, and formulated to treat gastric reflux of infants. Results were positive after three days treatment.¹⁵⁹

Hepatoprotective

Aqueous extract of dry pods was tested against ethanol-induced oxidative stress in rat liver and found active.¹⁶⁰

Inhibition of enzymes and other medicinally active materials

Ethyl acetate extract of immature pods inhibits the growth of peas (*Pisum sativum*) promoted by gibberellic acid.¹⁶¹ Growth inhibition of peas by different extracts of Carob was compared with the same activity of abscisic acid. This

natural growth inhibitor is stronger than Carob extracts.¹⁶² Carob extracts inhibit natural growth promoter indol-3-acetic acid, but this inhibition is weaker than inhibition of gibberellic acid (ref. 161).¹⁶³ Pods were extracted with 60 % ethanol/water and the extract moderately inhibited protease action. This was done in search of anti-infectious plant extracts.¹⁶⁴ Decoctions of different parts of Carob tree were prepared and tested for antioxidant activity (DPPH, ABTS and FRAP), and enzyme inhibition (AChE, BuChE, α -amylase and α -glucosidase). All decoctions were highly active in all tests.¹⁶⁵

Nephroprotection and urinary system related activities

Carob honey (syrup) was tested as diuretic in rats and found very active. Authors attribute this activity to flavonoid content of Carob pods.¹⁶⁶ Pods were extracted with 70 % ethanol/water and the extract was administered to diabetic (STZ-induced) rats. Results showed moderate improvement in kidney function.¹⁶⁷ Aqueous extract of pods was prepared and tested against dextran sulfate sodium-induced injuries in rat liver and kidney, and found active. Polyphenolic content of extract is probably responsible for the antioxidant and anti-inflammatory properties.¹⁶⁸ Leaves and pods were extracted with 70 % ethanol-water, and the extract was tested for reduction of oxidative nephrotoxicity of synthetic anticancer agent cisplatin, and found active.¹⁶⁹ Leaves were extracted with 80 % ethanol/water and the extract was fractionated with ethyl acetate, n-hexane and DCM. All fractions, including the remaining aqueous phase, were analyzed for total phenolic content and tested for antioxidant activity (3 methods). It was also against renal failure caused by oxidative stress that was CCl₄-induced. All tested fractions were active, where the ethyl acetate fraction was most active.¹⁷⁰

Glycemic response

Carob seeds were extracted with methanol and petroleum ether. Both extracts were tested *in vivo* (rats) for glycemic response. Crude polyphenols of Carob were also tested. No positive results were obtained.¹⁷¹ Healthy human volunteers were supplied with tablets of Carob flour. Glycemic index showed clear improvement.¹⁷²

Neuroprotection

In a short review article attempts have made to link the active compounds in Carob with neuroprotection against monosodium glutamate damages. No direct link is established.¹⁷³

Reproductive system related activities

Monosodium glutamate caused damage to reproductive organs of female Wistar rats. When fed with Carob powder, the damages were less.¹⁷⁴ Pods were extracted with 50 % ethanol/water and the extract was tested for its effect on fertility of male rats. Results indicate that it can increase testosterone synthesis and increases sperm density in seminiferous tubules.¹⁷⁵ A review article mentions Carob as a medicinal plant (decoction) for treatment of abnormal uterine bleeding by Avicenna.¹⁷⁶

Phytoestrogens, bone recovery

Seed flour was screened for chemical composition, especially lignans. The detected phytosterols were secoisolariciresinol, lariciresinol, isolariciresinol and pinoresinol (Figure 4).¹⁷⁷ Rats that were fed with Carob pod powder showed improvement in osteoporosis bone model in rats.¹⁷⁸

Skin depigmentation

Various parts of Carob were extracted with ethanol and the dry extract was fractionated with other solvents. Methanolic fraction of bark extract was most active inhibitor of tyrosinase, the enzyme responsible for oxidation of amino acid tyrosine, that causes hyperpigmentation. The extract was also tested in L-dopa model and found active. It was also tested with human volunteers for irritation and found non-irritant. Three isolated gallates were active.¹⁷⁹

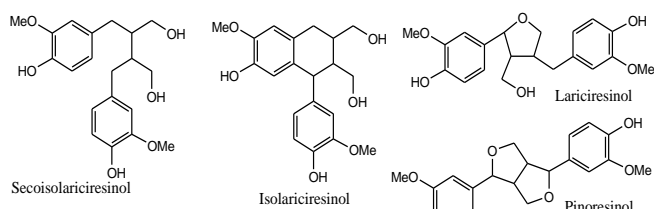


Figure 4. Phytosterols detected in the seed flour of Carob.

Toxicological evaluation

Goats fed with Carob leaves showed no signs of illness.¹⁸⁰ Seeds aqueous extract was prepared and supplied to rabbits in drinking water. No physical or behavioral adverse effects were recorded.¹⁸¹

Metabolism of proanthocyanins

Proanthocyanidins (condensed tannins) in unripe pods were radiolabelled by ¹⁴C, they were extracted with acetone-water (3:1 v/v), isolated and fed to rats. Proanthocyanidins were partially metabolized and they are not inert within the animal gut.¹⁸²

Neutralization of toxicity of Egyptian horned viper venom

Aqueous extract of seeds was tested for neutralization of toxicity of Egyptian horned viper (*Cerastes cerastes*) venom *in vitro* (hyaluronidase inhibition) and *in vivo* (rats). It had weak activity.¹⁸³

Waterpipe smoke and amiodarone toxicity amelioration

Aqueous extract of pods ameliorates impairments in liver, kidney and lung functions and decreased the oxidative stress induced by exposure to water pipe smoke and amiodarone in rats.¹⁸⁴

Discussion

Reading the literature of ethnomedicinal and other traditional uses of Carob (Table 1) reveals an interesting, yet a strange fact. The plant (molasses of ripe pods) is very well known in Palestinian traditional medicine to have strong anti-inflammatory activity, especially mouth inflammations; and modern research approves this property. But articles of ethnomedicine of Carob do not mention this at all. S. A. Baydoun and her colleagues from Lebanon (Ref. 26), mention many traditional uses of Carob but not a clue of anti-inflammatory activity.

Antibacterial/antifungal activity of various extracts of *C. siliqua* was reported by many research groups (ref. 38-47). A. H. Ibrahim and her colleagues, prepared aqueous and methanolic extracts of *C. siliqua* and tested them for antibacterial activity.³⁸ They isolated nine pure compounds from these extracts. All the nine compounds are known to have antibacterial activities. The structures of five of them are shown in Figure 1.

These five compounds were reported by other groups for having antibacterial activities. For example, n-nonadecanol from *Schinus lentiscifolius*,¹⁸⁵ lupeol from *Albizia adianthifolia*,¹⁸⁶ genistein from soybean (*Glycine max*),¹⁸⁷ geraldone from *Flourensia oolepis*,¹⁸⁸ and liquiritigenin from *Dalbergia odorifera*.¹⁸⁹ N. Aissani *et al.* isolated (–)-epigallocatechin-3-gallate (Figure 2) from the methanolic extract of Carob leaves. It is interesting to notice that in reference 38 the same extract was prepared and analyzed but this compound was not isolated. Methyl ester of gallic acid was isolated. Epigallocatechin-3-gallate is the major antibacterial agent in green tea (*Camellia sinensis*).¹⁹⁰

One general fact can be noticed, methanolic extract of leaves has the highest antibacterial capacity. But it is also important to notice the contradiction between the reports of I. Talibi *et al.*⁴⁴ and B. Kivcak and T. Mert⁴⁷: while the first reports that n-hexane extract of dry leaves was inactive antimicrobial, the second reports that the very same extract had the highest activity, along with methanolic extract. The weak antimicrobial activity reported by C. Tassou *et al.*,¹⁹¹ can not be explained or compared with later reports since Carob tree part was not indicated and extraction solvent was 80 % ethanol/water.

But Carob can be a medium for bacteria growth also. A. Hariri and his colleagues reported the growth of *L. bulgaricus* from Carob pods syrup.¹⁹² Despite the fact that this bacterium is a "friendly" one that is used for cheese production from milk, the sugar rich Carob pods syrup, that has high nutritional value, can potentially help growing harmful bacteria. Fungi can also grow on nutritional Carob trees. M. El-Neketi and her colleagues have isolated and characterized six new interesting compounds, including alkaloids and polyketides from the fungi *Penicillium citrinum*, that grows on Carob trees in Morocco.¹⁹³ The structures of these compounds are shown in Figure 5.

Among the reported Carob extracts tested for antidiabetic activity, it seems that the report of F. Mounce and M. Al-Saeed (ref. 51) is the less understandable.

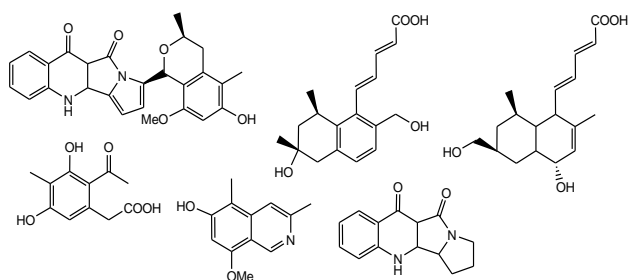


Figure 5. Alkaloids and polyketides from the fungi *Penicillium citrinum*, that grows on Carob trees.

They claim to find n-hexane extract of dry pods to be active against alloxan-induced diabetes in pregnant female rabbits. They claim that this extraction method yields "phytosterol extract". Obviously, phytosterols are highly soluble in hexane, but this extract naturally contains many other non-polar compounds that are found in Carob pods. So, it is scientifically inaccurate to refer the biological activity to a single compound or compound family, while the extract is crude and not fractionated.

Anticancer and related activities of Carob have been studied partially. Anyhow, some of these published studies must be considered very carefully. For example, H. A. Mouse and his colleagues tested ethanolic and ethyl acetate extracts of popolis extract from Morocco. They claim that the raw material was prepared by bees from mailny three trees, including Carob. But when they analyzed these extracts by HPLC, they did not find a single compound that is solely conatined in Carob.

Anti-inflammatory activity of Carob extracts reported in references 61-63, are to the best our knowledge, underestimating the capacities of this plant. Based on very pesonal experience and many others, we can state that molasses of Carob are very active against *mouth* infalamations. As we mentioned above, this is very well known activity in Palestinian traditional medicine, and its very strange that even publications about ethnomedicine of *C. siliqua* do not mention it.

Most reports about medicinal activities of Carob extracts, especially antioxidant activity and its related properties (ref. 64-86) indicate very clearly that extracts of polar solvents have higher activity than those of non-polar solvents. In most cases, extraction was done with methanol. This can be understood on the basis of the nature of the active compounds in Carob, most of them are polyphenols, that are relatively polar compounds. Even though other powerful antioxidants such as carotenoids are present in Carob, their amounts are much lower than that of polyphenols, and so, their contribution to the total antioxidant capacity is low. Special attention can be paid to the report of A. Ben Hsouna and his colleagues (ref. 76), where they state that the ethyl acetate leaves "extract" had the highest antioxidant and antimicrobial activities among the "extracts" that they prepared. As far as we can understand this, introducing the results this way is misleading. Leaves were originally extracted with 80 % aqueous ethanol, a very polar solvent. The dry extract was fractionated with ethyl acetate, DCM and n-hexane, where ethyl acetate is the most polar solvent among the three. HPLC analysis of this fraction yielded

polyphenolic compounds: 1,6-di-galloyl-glucose, 1,2,6-tri-galloyl-glucose, myricetin glucoside, 1,2,3,6-tetra-galloyl-glucose, myricetin rhamnoside and syringic acid. To conclude this part, it is important to pay attention to two additional reports. First, S. Klenow and her colleagues,¹⁹⁴ raised the question: does an extract of Carob have chemopreventive potential related to oxidative stress? And after a fundamental research they conclude that the answer is not clearly "yes". So, the antioxidant quality of Carob is superb but its anticancer properties are not the same. This doubt is strengthened by the report of N. Khalifa and her colleagues who found high antioxidant of extracts of leaves and pods of Carob, but zero and very weak cytotoxic activity, respectively.^{195*} Second, V. Goulas *et al.* published a comprehensive review article about "functional components of Carob fruit".¹⁹⁶ Its not clear why the most important medicinal and food value of Carob pods, antioxidant activity, was so clearly ignored there.

The chemical composition of Carob was widely investigated. Locality, seasonality and stage of development can influence the chemical composition of plants, and Carob is not an exception (ref. 90-92, 101-103). These effects are well known for other plants, and many studies of Carob indicate this, including the report of A. Haddarah and her colleagues from Lebanon.¹⁹⁷ One of the important reports of chemical composition of Carob was published by Y. M. Boufdi and her colleagues.¹⁰⁰ They prepared three extracts of pulp, and while the vast majority of composition studies report approximate compositions, this study reports a very detailed composition (Table 2, page 79 in the article). Most of the identified compounds are polyphenols and their derivatives.

Polyphenolic compounds are major components of Carob. They are responsible for most of its medicinal and other activities, such as antioxidant-reductive activity. This property enable extracts of Carob being corrosion inhibitors.¹³⁶ One of the new polyphenolic that were isolated for the first time from Carob is ceratoside, that its structure is shown in Figure 3.¹⁰⁸

Hydrolysis (degradation) of condensed tannins which are polyphenols attached by glycosyl bonds to sugars can be done in several reactions. One of the convenient reactions that is performed under mild conditions, is hydrolysis with thioglycolic acid, that can also hydrolyse other ether bonds.¹³² This reaction was discussed by Sears and Casebier.¹⁹⁸ In scheme 1, we illustrate the application of this reaction to myricetin-3-rhamnoside.¹⁰²

Carob extracts are being studied in recent years for gastroprotective activities, and they were found highly active, so far.¹⁵⁵⁻¹⁵⁹ Most studies were done *in vivo* after induction of gastric disorder in animals. These diorders were induced by various chemicals such as ethanol, hydrochloric acid, sodium chloride or dextran sulfate sodium. In most reports, authors link the medicinal activity to polyphenols found in Carob pods. One of these compounds is pyrogallol (1,2,3-trihydroxy benzene).¹⁵⁸ A short summary of these activities can be found in a recent review article that was published by I. C. Theophilou and her colleagues.¹⁹⁹ Some activities however, have been attributed to soluble galactomannans.¹⁵⁹ A general structure of Carob galactomannan, polysaccharide composed of mannose in major chain, with galactose branching, is shown in figure 6 (short form).²⁰⁰

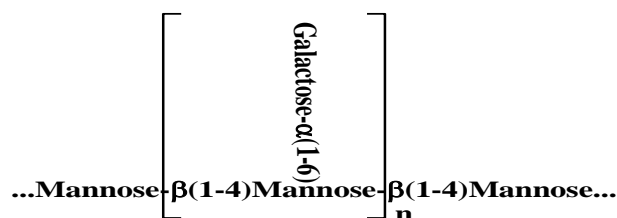


Figure 6. General structure of galactomannan found mainly in Carob beans

Carob phytoestrogens were found active in bone recovery.^{177,178} These compounds are shown in figure 4. This activity is very well known and it was finely presented in a comprehensive review article by Lagari & Levis.²⁰¹

Finally, Carob tree is a very important nutritional source, both for humans and animals, and relying on its potential and safety, even its used parts and by-products can have nutritional and medicinal important uses.²⁰² It is important to indicate here that in this review article we tried to focus our attention on major natural products found in Carob, despite the fact that some compounds that are found in trace amounts, might be of some interest.²⁰³ But these compounds are found in other plants in higher amounts and were studied in that context.²⁰⁴

Conclusions and suggested future research

(1) Carob has very important nutritional and medicinal qualities. Some were reasonably studied but others should be studied more thoroughly.

(2) Some of the reports concerning antibacterial activity of Carob are contradicting. Further studies are needed to clear these confusions. It is also recommended to use modern tools such as ionic liquids for extraction.

(3) There is a need to perform more studies of antiviral capacity of Carob.

(4) It is highly desirable to expand the research of anti-inflammatory activity of Carob since it is very well based in Palestinian ethnomedicine and almost was not studied so far.

(5) Works of actual research of neuroprotective effect of Carob were never published. This field should be extensively studied.

(6) There is an importance to expand the studies of the medicinal studies of the potential of Carob products as nutritional sources, especially in terms of antiobesity agents.

References

- ¹Battle, I., Tous, J., Promoting the conservation and use of underutilized and neglected crops. 17. Institute of Plant Genetics and Crop Plant Research, **1997**, 92 pages, <https://www.scribd.com/document/79689913>
- ²Hillcoat, D., Lewis, G., Verdcourt, B., *Kew Bull.*, **1980**, 35, 261-271. DOI: 10.2307/4114570

- ³Zohary, D., *Isr. J. Plant Sci.*, **2002**, 50, 141-145. DOI: 10.1560/BW6B-4M9P-U2UA-C6NN
- ⁴Jahns, S., *Veg. Hist Archaeobot.*, **2003**, 12, 127-130. DOI 10.1007/s00334-003-0013-8
- ⁵Lipshitz, N., *Isr. J. Bot.*, **1987**, 36, 191-197. DOI: 10.1080/0021213X.1987.10677083
- ⁶Sahin, G., Tasligil, N., *Turk. J. Agric. Food Sci. Technol.*, **2016**, 4, 1192-1200. <https://doi.org/10.24925/turjaf.v4i12.1192-1200.979>
- ⁷Bostan, S. Z., Kili, D., *Turk. J. Agric. Nat. Sci.*, **2014**, 1, 706-708. <http://www.mulkiyedergi.org/ttdb/article/view/5000090881/500084283>
- ⁸Sidina, M. M., El Hansali, M., Wahid, N., Ouattmane, A., Boulli, A., Haddaoui, A., *Sci. Hort.*, **2009**, 123, 110-116. <https://doi.org/10.1016/j.scienta.2009.07.009>
- ⁹Gharnit, N., Ennabili, A., *Int. J. Fruit Sci.*, **2016**, 16, 259-274. <http://dx.doi.org/10.1080/15538362.2015.1102674>
- ¹⁰Sundararajan, R., Bharampuram, A., Koduru, R., *Pharmacophore*, **2014**, 5, 160-182. <http://www.pharmacophorejournal.com/index/AbstractView/302>
- ¹¹Nasar-Abbas, S. M., Huma, Z., Vu, T-H., Khan, M. K., Esbenshade, H., Jayasena, V., *Compr. Rev. Food Sci. Food Saf.*, **2016**, 15, 63-72. DOI: 10.1111/1541-4337.12177
- ¹²Rtibi, K., Selmi, S., Grami, D., Amri, M., Eto, B., El-benna, J., Sebai, H., Marzouki, L., *Biomed. Pharmacother.*, **2017**, 93, 522-528. <http://dx.doi.org/10.1016/j.biopha.2017.06.088>
- ¹³Ozkum, D., Aki, O., Toklu, H. Z., *J. Med. Plants Res.*, **2013**, 7, 1652-1664. DOI: 10.5897/JMPR12.1207
- ¹⁴Abou Zid, S. F., Mohamed, A. A., *J. Ethnobiol. Ethnomed.*, **2011**, 7, 6 pages. DOI: 10.1186/1746-4269-7-18
- ¹⁵Saad, B.; Said, O. Greco-Arab and Islamic Herbal Medicine; Hoboken, New-Jersey; John Wiley & Sons, Inc.; **2011**, pp. 308
- ¹⁶Fatima, S., Shahid, M., Mand, D., Parveen, S., Naaz, I., *World J. Pharm. Res.*, **2017**, 6, 1475-1485. DOI: 10.20959/wjpr201710-9472
- ¹⁷Tansaz, M., Memarzadehzavareh, H., Qaraaty, M., Eftekhari, T., Tabarraei, M., Kamalinejad, M., *J. Evid. Based Complement. Alternat. Med.*, **2016**, 21, 71-76. DOI: 10.1177/2156587215589522
- ¹⁸Ahmed, H. M., *J. Ethnobiol. Ethnomed.*, **2016**, 12, 17 pages. DOI 10.1186/s13002-016-0081-3
- ¹⁹Said, O., Khalil, K., Fulder, S., Azaizeh, H., *J. Ethnopharmacol.*, **2002**, 83, 251-265. [https://doi.org/10.1016/s0378-8741\(02\)00253-2](https://doi.org/10.1016/s0378-8741(02)00253-2)
- ²⁰Landau, S. Y., Muklada, H., Abu-Rabia, A., Kaadan, S., Azaizeh, H., *Small Ruminant Res.*, **2014**, 119, 161-171. <http://dx.doi.org/10.1016/j.smallrumres.2014.01.004>
- ²¹Guarrera, P. M., Giovanni Salerno, G., Caneva, G., *J. Ethnobiol. Ethnomed.*, **2016**, 12, 17 pages. DOI: 10.1186/1746-4269-2-37
- ²²Montesano, V., Negro, D., Sarli, G., De Lisi, A., Laghetti, G., Hammer, K., *J. Ethnobiol. Ethnomed.*, **2012**, 8, 10 pages. DOI: 10.1186/1746-4269-8-15
- ²³Affifi-Yazar, F. U., Kasabri, V., Abu-Dahab, R., *Planta Med.*, **2011**, 77, 1210-1220. <http://dx.doi.org/10.1055/s-0031-1279983>
- ²⁴Oran, S. A., Al-Eisawi, D. M., *J. Bio. Env. Sci.*, **2015**, 6, 381-400. <http://www.innsipub.net/wp-content/uploads/2015/03/JBES-Vol6No3-p381-400.pdf>
- ²⁵Baydoun, S., Chalak, L., Dalleh, H., Arnold, N., *J. Ethnopharmacol.*, **2015**, 173, 139-156. <http://dx.doi.org/10.1016/j.jep.2015.06.052>

- ²⁶Baydoun, S.A., Kanj, D., Raafat, K., Aboul Ela, M., Chalak, L., Arnold-Apostolides, N., *J. Ecosys. Ecogr.*, **2017**, *S7*, 8 pages. DOI: 10.4172/2157-7625.S7-001
- ²⁷Ennabili, A., Gharniti, N., El Hamdouni, E., *Stud. Bot.*, **2000**, *19*, 57-74. <http://revistas.usal.es/index.php/0211-9714/article/viewFile/6081/6101>
- ²⁸El-Hilaly, J., Hmamouchi, M., Lyoussi, B., *J. Ethnopharmacol.*, **2003**, *86*, 149-158. [https://doi.org/10.1016/S0378-8741\(03\)00012-6](https://doi.org/10.1016/S0378-8741(03)00012-6)
- ²⁹Ouhaddou, H., Boubaker, H., Msanda, F., El Mousadik, A., *J. Appl. Biosci.*, **2014**, *84*, 7707-7722. <http://dx.doi.org/10.4314/jab.v8i4.1.5>
- ³⁰Orch, H., Zidane, L., Douira, A., *Int. J. Recent Sci. Res.*, **2017**, *8*, 15213-15220. <http://www.recentscientific.com/sites/default/files/6806.pdf>
- ³¹Ali-Shtayah, M. S., Jamous, R. M., Al-Shafie', J. H., Elgharabah, W. A., Kherfan, F. A., Qarariah, K. H., Khdaif, I. K., Soos, I. M., Musleh, A. A., Isa, B. A., Herzallah, H. M., Khlaif, R. B., Aiash, S. M., Swaiti, G. M., Abuzahra, M. A., Haj-Ali, M. M., Saifi, N. A., Azem, H. K., Nasrallah, H. A., *J. Ethnobiol. Ethnomed.*, **2008**, *4*, 13 pages. doi:10.1186/1746-4269-4-13
- ³²Lentini, F., Venza, F., *J. Ethnobiol. Ethnomed.*, **2007**, *3*, 12 pages. DOI:10.1186/1746-4269-3-15
- ³³Tardio, J., Pardo-de-Santayana, M., Morales, R., *Bot. J. Linn. Soc.*, **2006**, *152*, 27-71. <https://doi.org/10.1111/j.1095-8339.2006.00549.x>
- ³⁴Kaderi, M., Ben Hamouda, G., Zaeir, H., Hanana, M., Hamrouni, L., *Phytothérapie*, **2015**, *13*, 144-147. DOI 10.1007/s10298-014-0904-4
- ³⁵Fakir, H., Korkmaz, M., Guller, B., *J. Appl. Biol. Sci.*, **2009**, *3*, 33-43. <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.45.9.6995&rep=rep1&type=pdf>
- ³⁶Berrougui, H., Loued, S., Elghmari, A., Bouadili, A., Haddadi, B., Khalil, A., *Chem. Phys. Lipids*, **2008**, *154*, S53-S54. <https://doi.org/10.1016/j.chemphyslip.2008.05.147>
- ³⁷Abd Razik , B. M., Hasan , H., A., Murtadha, M. K., *Iraqi Postgraduate Med. J.*, **2012**, *11*, 130-135. <https://iasj.net/iasj?func=fulltext&afid=30208>
- ³⁸Ibrahim, A. H., Abd El-Baky, R. M., Desoukey, S. Y., Abd-Lateff, A., Kamel, M. S., *J. Adv. Biotechnol. Bioeng.*, **2013**, *1*, 3-13. <https://doi.org/10.12970/2311-1755.2013.01.01.1>
- ³⁹Meziani, S., Oomah, B. D., Zaidi, F., Simon-Levert, A., Bertrand, C., Zaidi, Yahiaoui, R., *Microb. Pathog.*, **2015**, *78*, 95-102. <http://dx.doi.org/10.1016/j.micpath.2014.12.001>
- ⁴⁰Aissani, N., Coroneo, V., Fattouch, S., Caboni, P., *J. Agric. Food Chem.*, **2012**, *60*, 9954-9958. DOI: 10.1021/jf3029623
- ⁴¹Kumar, V. P., Chauhan, N. C., Padh, H., Rajani, M., *J. Ethnopharmacol.*, **2006**, *107*, 182-188. DOI: 10.1016/j.jep.2006.03.013
- ⁴²Rahmoun, N. M., Ziane, H., Boucherit-Otmani, Z., *J. Coast. Life Med.*, **2014**, *2*, 975-979. DOI: 10.12980/JCLM.2.2014APJTB-2014-0072
- ⁴³Al-fawwaz, A. T., Al-Khaza'leh, K. A., *Eur. Sci. J.*, **2016**, *12*, 147-157. <http://dx.doi.org/10.19044/esj.2016.v12n6p147>
- ⁴⁴Talibi, I., Askarne, L., Boubaker, H., Boudyach, E. H., Msanda, F., Saadi, B., Ben Aoumar, A. A., *Lett. Appl. Microbiol.*, **2012**, *55*, 155-161. DOI: 10.1111/j.1472-765X.2012.03273.x
- ⁴⁵Ben Hsouna, A., Alayed, A. S., Abdallah, E. M., *Afr. J. Microbiol. Res.*, **2012**, *6*, 3480-3484. DOI: 10.5897/AJMR11.1613
- ⁴⁶Jamous, R. M., Abu Zaitoun, S.Y., Husein, A. I., Qasem, I. B., Ali-Shtayah, M. S., *Eur. J. Med. Plants*, **2015**, *9*, 1-13. DOI: 10.9734/EJMP/2015/17429
- ⁴⁷Kivcak, B., Mert, T., *Turk. J. Biol.*, **2002**, *26*, 197-200. <http://journals.tubitak.gov.tr/biology/issues/biy-02-26-4/biy-26-4-2-0111-4.pdf>
- ⁴⁸Mokhtari, M., Sharifi, S., Tabatabaee, M. S., *Int. Proc. Chem. Biol. Environ. Eng.*, **2011**, *3*, 82-86. <http://www.ipcbee.com/vol3/22-L10002.pdf>
- ⁴⁹Hamza, R. G., Al-Seeni, M. N., *Int. J. Pharm. Bio. Sci.*, **2015**, *6*, 951 - 960. <http://www.ijpbs.net/details.php?article=4022>
- ⁵⁰Rtibi, K., Selmi, S., Grami, D., Saidani, K., Sebai, H., Amri, M., Eto, B., Marzouki, L., *J. Sci. Food Agric.*, **2017**, *97*, 2664-2670. DOI: 10.1002/jsfa.8091
- ⁵¹Mounce, F. S., Al-Saeed, M. H., *Bas. J.Vet.Res.*, **2017**, *16*, 219-242. <http://www.basjvet.com/wp-content/uploads/2017/05/219-242.pdf>
- ⁵²Mounce, F. S., Al-Saeed, M. H., *Bas. J.Vet.Res.*, **2017**, *16*, 219-242. *IAJMR*, **2017**, *3*, 1094-1102. DOI: 10.22192/iajmr.2017.3.2.6
- ⁵³Macho-Gonzalez, A., Garcimartin, A., Lopez-Oliva, M. E., Bertocco, G., Naes, F., Bastida, S., Sanchez-Muniz, F. J., Benedi, J., *Food Funct.*, **2017**, *8*, 2258-2265. DOI: 10.1039/c7fo00166e
- ⁵⁴Khaldoun J. Al-Hadid, K. J., *Am. J. Agric. Biol. Sci.*, **2016**, *11*, 157-163. DOI: 10.3844/ajabssp.2016.157.163
- ⁵⁵Mouse, H. A., Tilaoui, M., Jaafari, A., M'barek, L. A., Aboufatima, R., Chait, A., Ziad, A., *Rev. Bras. Farmacogn.*, **2012**, *22*, 558-567. <http://dx.doi.org/10.1590/S0102-695X2012005000030>
- ⁵⁶Amessis-Ouchemoukh, N., Ouchemoukh, S., Meziant, N., Idiri, Y., Hernanz, D., Stinco, C. M., Rodriguez-Pulido, F. J., Heredia, F. J., Madani, K., Luis, J., *Ind. Crops Prod.*, **2017**, *95*, 6-17. <http://dx.doi.org/10.1016/j.indcrop.2016.10.007>
- ⁵⁷Corsi, L., Avallone, R., Cosenza, F., Farina, F., Baraldi, C., Baraldi, M., *Fitoterapia*, **2002**, *73*, 674-684. [https://doi.org/10.1016/s0367-326x\(02\)00227-7](https://doi.org/10.1016/s0367-326x(02)00227-7)
- ⁵⁸Custodio, L., Fernandes, E., Escapa, A. L., Lopez-Aviles, S., Fajardo, A., Aligue, R., Albericio, F., Romano, A., *Planta Med.*, **2008**, *74*, PA48. DOI: 10.1055/s-0028-1084046
- ⁵⁹Agrawal, A., Mohan, M., Kasture, S., Foddiss, C., Frau, M. A., Loi, M. C., Andrea Maxia, A., *Nat. Prod. Res.*, **2011**, *25*, 450-456. DOI: 10.1080/14786419.2010.527447
- ⁶⁰Al-Olayan, E. M., El-Khadragy, M. F., Alajmi, R. A., Othman, M. S., Bauomy, A. A., Ibrahim, S. R., Abdel Moneim, A. E., *BMC Complement. Altern. Med.*, **2016**, *16*, 11 pages. DOI 10.1186/s12906-016-1389-1
- ⁶¹Lachkar, N., Al-Sobarry, M., El Hajaji, H., Lamkins, T., Lachkar, M., Cherrah, Y., Alaoui, K., *J. Chem. Pharm. Res.*, **2016**, *8*, 202-210. <http://www.jocpr.com/articles/antiinflammatory-and-antioxidant-effect-of-ceratonia-siliqua-l-methanol-barks-extract.pdf>
- ⁶²Narin, B., Sungurlu, F., Balci, A., Arman, A., Kurdas, O. O., Simsek, M., *Saudi J. Gastroenterol.*, **2009**, *15*, 253-257. DOI: 10.4103/1319-3767.56104
- ⁶³Kaileh, M., Berghe, W. V., Boone, E., Essawi, T., Haegeman, G., *J. Ethnopharmacol.*, **2007**, *113*, 510-516. DOI:10.1016/j.jep.2007.07.008
- ⁶⁴Custodio, L., Fernandes, E., Romano, A., *Acta Hort.*, **2009**, *841*, 507-510. DOI: 10.17660/ActaHortic.2009.841.70
- ⁶⁵El Hajaji, H., Lachkar, N., Alaoui, K., Cherrah, Y., Farah, A., Ennabili, A., Bali, B., Lachkar, M., *Rec. Nat. Prod.*, **2010**, *4*, 193-204. http://www.acgpubs.org/RNP/2010/Volume%204/Issue%201/23_RNP_1001_181.pdf
- ⁶⁶El-sherif, G., El-sherif, M. A., Tolba, K. H., *Nat. Sci.*, **2011**, *9*, 108-115. <http://connection.ebscohost.com/c/articles/69683741>

- ⁶⁷Akkaya, H., Yilmaz, O., *Ekoloji*, **2012**, 21, 9-16. DOI: [10.5053/ekoloji.2011.822](https://doi.org/10.5053/ekoloji.2011.822)
- ⁶⁸Sebai, H., Souli, A., Chehimi, L., Rtibi, K., Amri, M., El-Benna, Sakly, M., *J. Med. Plants Res.*, **2013**, 7, 5-90. DOI: [10.5897/JMPR12.915](https://doi.org/10.5897/JMPR12.915)
- ⁶⁹Uysal, S., Zengin, G., Aktumsek, A., *J. Med. Herbs Ethnomed.*, **2015**, 1, 97-102. DOI: [10.5455/jmhe.2015.09.022](https://doi.org/10.5455/jmhe.2015.09.022)
- ⁷⁰Al-Qaraleh, S., Tarawneh, K. A., *Am-Euras. J. Agric. Environ. Sci.*, **2016**, 16, 479-486. DOI: [10.5829/idosi.aejaes.2016.16.3.12847](https://doi.org/10.5829/idosi.aejaes.2016.16.3.12847)
- ⁷¹Kumazawa, S., Taniguchi, M., Suzuki, Y., Shimura, M., Kwon, M-S., Nakayama, T., *J. Agric. Food Chem.*, **2002**, 50, 373-377. DOI: [10.1021/jf010938r](https://doi.org/10.1021/jf010938r)
- ⁷²Alali, F. Q., Tawaha, K., El-Elimat, T., Syouf, M., El-Fayad, M., Abulaila, K., Nielsen, S. J., Wheaton, W. D., Falkinham, J. O., Oberlies, N. H., *Nat. Prod. Res.*, **2007**, 21, 1121-1131. DOI: [10.1080/14786410701590285](https://doi.org/10.1080/14786410701590285)
- ⁷³Custodio, L., Fernandes, E., Escapa, A. L., Lopez-Aviles, S., Fajardo, A., Aligue, R., Albericio, F., Romano, A., *Pharm. Biol.*, **2009**, 47, 721-728. DOI: [10.1080/13880200902936891](https://doi.org/10.1080/13880200902936891)
- ⁷⁴Hussein, A. M., Shedeed, N. A., Abdel-Kalek, H. H., Shams El-Din, M. H., *Pol. J. Food Nutr. Sci.*, **2011**, 61, 201-209. DOI: [10.2478/v10222-011-0022-8](https://doi.org/10.2478/v10222-011-0022-8)
- ⁷⁵El Hajaji, H., Lachkar, N., Alaoui, K., Cherrah, Y., Farah, A., Ennabili, A., El Bali, B., Lachkar, M., *Arab. J. Chem.*, **2011**, 4, 321-324. DOI: [10.1016/j.arabjc.2010.06.053](https://doi.org/10.1016/j.arabjc.2010.06.053)
- ⁷⁶Ben Hsouna, A., Trigui, M., Jarraya Mezghani, R., Damak, M., Jaoua, S., *J. Med. Plants Res.*, **2015**, 9, 479-485. DOI: [10.5897/JMPR2011.685](https://doi.org/10.5897/JMPR2011.685)
- ⁷⁷Temiz, M. A., Temur, A., Celik, I., *J. Food Nutr. Res.*, **2015**, 3, 57-61. DOI: [10.12691/jfnr-3-1-10](https://doi.org/10.12691/jfnr-3-1-10)
- ⁷⁸Rtibi, K., Jabri, M. A., Selmi, S., Souli, A., Sebai, H., El-Benna, J., Amri, M., Marzouki, L., *RSC Adv.*, **2015**, 5, 84207-84215. DOI: [10.1039/c5ra14719k](https://doi.org/10.1039/c5ra14719k)
- ⁷⁹Rtibi, K., Jabri, M. A., Selmi, S., Souli, Sebai, H., Amri, M., El-Benna, J., Marzouki, L., *RSC Adv.*, **2015**, 6, 65483-65493. DOI: [10.1039/c6ra11297h](https://doi.org/10.1039/c6ra11297h)
- ⁸⁰Sassi, A., Bouhlef, I., Mustapha, N., Mokdad-Bzeouich, I., Chaabane, F., Ghedira, K., Chekir-Ghedira, L., *Regul. Toxicol. Pharmacol.*, **2016**, 77, 117-124. [http://dx.doi.org/10.1016/j.yrtph.2016.02.009](https://doi.org/10.1016/j.yrtph.2016.02.009)
- ⁸¹Rached, I., Barros, L., Fernandes, I. P., Santos-Buelga, C., Rodrigues, A. E., Ferchichi, A., Barreiro, M. F., Ferreira, I. C., *Food Funct.*, **2016**, 7, 1319-1328. DOI: [10.1039/c6fo00100a](https://doi.org/10.1039/c6fo00100a)
- ⁸²Mahtout, R., Zaidi, F., Saadi, L. O., Boudjou, S., Oomah, B. D., Hosseinian, F., *Int. J. Eng. Techniq.*, **2016**, 2, 168-177. <http://www.ijetjournal.org/Volume2/Issue2/IJET-V2I2P28.pdf>
- ⁸³Seczyk, L., Swieca, M., Gawlik-Dziki, U., *Food Chem.*, **2016**, 194, 637-642. [http://dx.doi.org/10.1016/j.foodchem.2015.08.086](https://doi.org/10.1016/j.foodchem.2015.08.086)
- ⁸⁴Suzek, H., Celik, I., Abdulahad Dogan, A., *Indian J. Pharm. Educ. Res.*, **2017**, 51, 312-320. DOI: [10.5530/ijper.51.2.37](https://doi.org/10.5530/ijper.51.2.37)
- ⁸⁵Ydjedd, S., Bouriche, S., Lopez-Nicolas, R., Sanchez-Moya, T., Frontela-Saseta, C., Ros-Berruazo, G., Rezgui, F., Louaileche, H., Kati, D-E., *J. Agric. Food Chem.*, **2017**, 65, 827-835. DOI: [10.1021/acs.jafc.6b05103](https://doi.org/10.1021/acs.jafc.6b05103)
- ⁸⁶Abu Hafs, S. H., Ibrahim, S. A., Hassan, A. A., *J. Anim. Physiol. Anim. Nutr.*, **2017**, AHEAD OF PRINT. DOI: [10.1111/jpn.12651](https://doi.org/10.1111/jpn.12651)
- ⁸⁷Valero-Munoz, M., Martin-Fernandez, B., Ballesteros, S., Lahera, V., de las Heras, N., *J. Nutr.*, **2014**, 144, 1378-1384. doi: [10.3945/jn.114.196113](https://doi.org/10.3945/jn.114.196113)
- ⁸⁸Avallone, R., Cosenza, F., Farina, F., Baraldi, C., Baraldi, M., *Fitoterapia*, **2002**, 73, 390-396. [https://doi.org/10.1016/s0367-326x\(02\)00115-6](https://doi.org/10.1016/s0367-326x(02)00115-6)
- ⁸⁹Custodio, L., Escapa, A. L., Patarra, J., Aligue, R., Albericio, F., Neng, N. R., Nogueira, J. M., Romano, A., *Rec. Nat. Prod.*, **2013**, 7, 225-229. <https://sapientia.ualg.pt/bitstream/10400.1/6456/1/Sapwood%20of%20carob%20tree.pdf>
- ⁹⁰El Kahkahi, R., Zouhair, R., Diouri, M., Ait Chitt, M., Errakhi, R., *Int. J. Biol. Med. Res.*, **2015**, 6, 4946-4952. <https://www.researchgate.net/publication/277774794>
- ⁹¹Fidan, H., Petkova, N., Sapoundzhieva, T., Abanoz, E. I., *CBU Int. Conf. Proc.*, **2016**, 4, 796-802. <http://ojs.journals.cz/index.php/CBUIC/article/view/855/pdf/118>
- ⁹²Khlifa, M., Bahloul, A., Kitane, S., *J. Mater. Environ. Sci.*, **2013**, 4, 348-353. https://www.jmaterenvironsci.com/Document/vol4/vol4_N3/43-JMES-307-2013-khlifa.pdf
- ⁹³Calixto, F. S., Canellas, J., *J. Agric. Food Chem.*, **1982**, 33, 1319-1323. DOI: [10.1002/jsfa.2740331219](https://doi.org/10.1002/jsfa.2740331219)
- ⁹⁴Karkacier, M., Artik, N., *GIDA*, **1995**, 20, 131-136. <http://www.gidadernegi.org/EN/Genel/BelgeGoster.aspx?17A16AE30572D3137A2395174CFB32E16AF944CADCF2DC3>
- ⁹⁵Avallone, R., Plessi, M., Baraldi, M., Monzani, A., *J. Food Comp. Anal.*, **1997**, 10, 166-172. DOI: [10.1006/jfca.1997.0528](https://doi.org/10.1006/jfca.1997.0528)
- ⁹⁶Ayaz, F. A., Torun, H., Ayaz, S., Correia, P. J., Alaiz, M., Sanz, C., Gruz, J., Strand, M., *J. Food Qual.*, **2007**, 30, 1040-1055. DOI: [10.1111/j.1745-4557.2007.00176.x](https://doi.org/10.1111/j.1745-4557.2007.00176.x)
- ⁹⁷Youssef, M. K., El-Manfaloty, M. M., Ali, H. M., *Food and Public Health*, **2013**, 3, 304-308. DOI: [10.5923/j.fph.2013030606](https://doi.org/10.5923/j.fph.2013030606)
- ⁹⁸Baston, O., *Ann. Food Sci. Technol.*, **2016**, 17, 50-54. http://www.afst.valahia.ro/images/documente/2016/issue1/full/w06_full.pdf
- ⁹⁹Meziou-Chebouti, N., Merabet, A., Behidj, N., Kirouani, M., Aliouat, S., *Int. J. Agric. Biosys. Eng.*, **2015**, 12, 96-99. <http://www.inase.org/library/2015/vienna/bypaper/BICHE/BI-CHE-14.pdf>
- ¹⁰⁰Boufadi, Y. M., Elaoufi, M., Tabet, F., Benali, M., Riazi, A., *South Asian J. Exp. Biol.*, **2015**, 5, 76-83. <http://sajeb.org/index.php/sajeb/article/view/20060>
- ¹⁰¹Vekiari, A. S., Ouzounidou, G., Gork, G., Ozturk, M., Asfi, M., *Bull. Chem. Soc. Ethiop.*, **2012**, 26, 343-351. [http://dx.doi.org/10.4314/bcse.v26i3.3](https://doi.org/10.4314/bcse.v26i3.3)
- ¹⁰²Benchikh, Y., Paris, C., Louaileche, H., Charbonnel, C., Ghoul, M., Chebil, L., *SDRP J. Food Sci. Technol.*, **2016**, 1, 7 pages. <http://www.dx.doi.org/10.25177/JFST.1.3.1>
- ¹⁰³Ouzounidou, G., Vekiari, S., Afsi, M., Gork, M. G., Sakcali, M. S., Ozturk, M., *Pak. J. Bot.*, **2012**, 44, 1689-1695. [https://www.pakbs.org/pjbot/PDFs/44\(5\)/30.pdf](https://www.pakbs.org/pjbot/PDFs/44(5)/30.pdf)
- ¹⁰⁴Owis, A. I., El-Naggar, E., *Pharmacogn. Mag.*, **2016**, 12, S1-S6. DOI: [10.4103/0973-1296.176108](https://doi.org/10.4103/0973-1296.176108)
- ¹⁰⁵Ben Hsouna, A., Trigui, M., Ben Mansour, R., Mezghani Jarraya, R., Damak, M., Jaoua, S., *Int. J. Food Microbiol.*, **2011**, 148, 66-72. doi: [10.1016/j.ijfoodmicro.2011.04.028](https://doi.org/10.1016/j.ijfoodmicro.2011.04.028)
- ¹⁰⁶Bulca, S., *Sci. Bull. Ser. F Biotechnol.*, **2016**, XX, 142-147. <http://biotechnologyjournal.usamv.ro/index.php/scientific-papers/current?id=296>
- ¹⁰⁷Vaya, J., Mahmood, S., *BioFactors*, **2006**, 28, 169-175. <https://doi.org/10.1002/biof.5520280303>
- ¹⁰⁸Gohar, A., Gedara, S. R., Baraka, H. N., *J. Med. Plants Res.*, **2009**, 3, 424-428. <http://www.academicjournals.org/journal/JMPR/article-full-text-pdf/C8F546A15251>

- ¹⁰⁹Berna, A., Perez-Gago, M. B., Guardiola, V. G., Salazar, D., Mulet, A., *J. Agric. Food Chem.*, **1997**, 45, 4084-4087. DOI: [10.1021/jf970136p](https://doi.org/10.1021/jf970136p)
- ¹¹⁰Matthaus, B., Ozcan, M. M., *Sci. Hort.*, **2011**, 130, 181-184. DOI: [10.1016/j.scienta.2011.06.034](https://doi.org/10.1016/j.scienta.2011.06.034)
- ¹¹¹Torun, H., Ayaz, F. A., Colak, N., Gruz, J., Strnad, M., *Food Nutr. Sci.*, **2013**, 4, 547-553. <http://dx.doi.org/10.4236/fns.2013.45070>
- ¹¹²Eldahshan, O. A., *Curr. Res. J. Biol. Sci.*, **2011**, 3, 52-55. <http://pakacademicsearch.com/pdf-files/bio/390/52-55%20Vol.%203,%20Issue%201%202011.pdf>
- ¹¹³El Hajaji, H., Farah, A., Ennabili, A., Boustia, D., Greche, H., El Bali, B., Lachkar, M., *J. Mater. Environ. Sci.*, **2013**, 4, 165-170. http://www.jmaterenvironsci.com/Document/vol4/vol4_N2/1-JMES-281-2010-Elhajaji.pdf
- ¹¹⁴Oziyici, H. R., Tetik, N., Turhan, I., Yatmaz, E., Ucgun, K., Akgul, H., Gubbuk, H., Karhan, M., *Sci. Hort.*, **2014**, 167, 149-152. <http://dx.doi.org/10.1016/j.scienta.2014.01.005>
- ¹¹⁵Fidan, H., Sapundzhieva, T., *Sci. Bull. Ser. F. Biotechnol.*, **2015**, XIX, 136-139. <http://biotechnologyjournal.usamv.ro/pdf/2015/Art23.pdf>
- ¹¹⁶El Bouzdoudi, B., Saidi, R., Embarch, K., El Mzibri, M., Nejjar El Ansari, Z., El Kbiach, M. L., Badoc, A., Patrick, M., Lamarti, A., *Int. J. Food Sci. Nutr. Eng.*, **2017**, 7, 91-103. DOI: [10.5923/j.food.20170704.04](https://doi.org/10.5923/j.food.20170704.04)
- ¹¹⁷Cavdarova, M., Makris, D. P., *Waste Biomass Valor.*, **2014**, 5, 773-779. DOI: [10.1007/s12649-014-9298-3](https://doi.org/10.1007/s12649-014-9298-3)
- ¹¹⁸Gubbuk, H., Kafkas, E., Guven, D., Gunes, E., *Span. J. Agric. Res.*, **2010**, 8, 1129-1136. DOI: [10.5424/sjar/2010084-1209](https://doi.org/10.5424/sjar/2010084-1209)
- ¹¹⁹Custodio, L., Escapa, A. L., Fernandes, E., Fajardo, A., Aligue, R., Albericio, F., Neng, N., Nogueira, J. M., Romano, A., *Plant Foods Hum. Nutr.*, **2011**, 66, 78-84. DOI: [10.1007/s11130-011-0214-8](https://doi.org/10.1007/s11130-011-0214-8)
- ¹²⁰Tetik, N., Turhan, I., Oziyici, H. R., Karhan, M., *Int. J. Food Sci. Nutr.*, **2011**, 62, 572-576. DOI: [10.3109/09637486.2011.560564](https://doi.org/10.3109/09637486.2011.560564)
- ¹²¹Papagiannopoulos, M., Wollseifen, H. R., Mellenthin, A., Haber, B., Galensa, R., *J. Agric. Food Chem.*, **2004**, 52, 3784-3791. DOI: [10.1021/jf030660y](https://doi.org/10.1021/jf030660y)
- ¹²²Makris, D. P., Kefalas, P., *Food Technol. Biotechnol.*, **2004**, 42, 105-108. http://hrcak.srce.hr/index.php?show=clanak&id_clanak_jezik=163267&lang=en
- ¹²³Custodio, L., Fernandes, E., Romano, A., *Acta Hort.*, **2009**, 841, 503-506. DOI: [10.17660/ActaHortic.2009.841.69](https://doi.org/10.17660/ActaHortic.2009.841.69)
- ¹²⁴El Bouzdoudi, B., Nejjar El Ansari, Z., Mangalagiu, I., Mantu, D., Badoc, A., Lamarti, A., *Am. J. Plant Sci.*, **2016**, 7, 1937-1951. <http://dx.doi.org/10.4236/ajps.2016.714177>
- ¹²⁵Joslyn, M. A., Nishira, H., Ito, S., *J. Sci. Food Agric.*, **1968**, 19, 543-550. DOI: [10.1002/jsfa.2740190912](https://doi.org/10.1002/jsfa.2740190912)
- ¹²⁶Cantalejo, M. J., *J. Agric. Food Chem.*, **1997**, 45, 1345-1350. DOI: [10.1021/jf960468e](https://doi.org/10.1021/jf960468e)
- ¹²⁷McLeod, G., Forcen, M., *Phytochemistry*, **1992**, 31, 3113-3119. DOI: [10.1016/0031-9422\(92\)83456-9](https://doi.org/10.1016/0031-9422(92)83456-9)
- ¹²⁸Farag, M. A., El-Kersh, D. M., *J. Adv. Res.*, **2017**, 8, 379-385. DOI: [10.1016/j.jare.2017.05.002](https://doi.org/10.1016/j.jare.2017.05.002)
- ¹²⁹Nashira, H., Joslyn, M. A., *Phytochemistry*, **1968**, 7, 2147-2156. DOI: [10.1016/S0031-9422\(00\)85671-X](https://doi.org/10.1016/S0031-9422(00)85671-X)
- ¹³⁰Biner, B., Gubbuk, H., Karhan, M., Aksu, M., Pekmezci, M., *Food Chem.*, **2007**, 100, 1453-1455. DOI: [10.1016/j.foodchem.2005.11.037](https://doi.org/10.1016/j.foodchem.2005.11.037)
- ¹³¹Nachtomi, E., Alumot, E., *J. Sci. Food Agric.*, **1963**, 14, 464-468. DOI: [10.1002/jsfa.2740140703](https://doi.org/10.1002/jsfa.2740140703)
- ¹³²Tamir, M., Nachtomi, E., Alumot, E., *Phytochemistry*, **1971**, 10, 2769-2774. DOI: [10.1016/S0031-9422\(00\)97277-7](https://doi.org/10.1016/S0031-9422(00)97277-7)
- ¹³³Alani, W. M., Abdullaheem, E., *World J. Pharm. Pharm. Sci.*, **2016**, 5, 105-108. DOI: [10.20959/wjpps20165-6652](https://doi.org/10.20959/wjpps20165-6652)
- ¹³⁴Turhan, I., Bialka, K. L., Demirci, A., Karhan, M., *Bioresour. Technol.*, **2010**, 101, 5290-5296. DOI: [10.1016/j.biortech.2010.01.146](https://doi.org/10.1016/j.biortech.2010.01.146)
- ¹³⁵Awwad, A. M., Salem, N. M., Abdeen, A. O., *Int. J. Ind. Chem.*, **2013**, 4, 6 pages. <https://doi.org/10.1186/2228-5547-4-29>
- ¹³⁶Fouda, A. S., Shalabi, K., Idress, A. A., *Green Che. Lett. Rev.*, **2015**, 8, 17-29. <http://dx.doi.org/10.1080/17518253.2015.1073797>
- ¹³⁷Farhan, A. M., Salem, N. M., Ahmad, A. L., Awwad, A. M., *Am. J. Chem.*, **2012**, 2, 335-342. DOI: [10.5923/j.chemistry.20120206.07](https://doi.org/10.5923/j.chemistry.20120206.07)
- ¹³⁸Said, A. A., Kairy, M. H., Shalaby, A. M., Ismail, H. T., *Zagazig Vet. J.*, **2017**, 45, 19-28. DOI: [10.5281/zenodo.803909](https://doi.org/10.5281/zenodo.803909)
- ¹³⁹Herken, E. N., Aydin, N., *Pol. J. Food Nutr. Sci.*, **2015**, 65, 167-174. DOI: [10.1515/pjfn-2015-0010](https://doi.org/10.1515/pjfn-2015-0010)
- ¹⁴⁰Youssef, M. K., Ali, H. M., El-Manfaloty, M. M., *Food and Public Health*, **2013**, 3, 336-340. DOI: [10.5923/j.fph.20130306.11](https://doi.org/10.5923/j.fph.20130306.11)
- ¹⁴¹Naccari, C., Macaluso, A., Giangrosso, G., Naccari, F., Ferrantelli, V., *J. Food Res.*, **2014**, 3, 107-117. DOI: [10.5539/jfr.v3n2p107](https://doi.org/10.5539/jfr.v3n2p107)
- ¹⁴²Pehlivan, T., Gul, A., *J. Appl. Pharm. Sci.*, **2015**, 5, 42-45. DOI: [10.7324/JAPS.2015.50807](https://doi.org/10.7324/JAPS.2015.50807)
- ¹⁴³Ferrauto, G., Pavone, P., *Int. J. Food Sci. Technol.*, **2013**, 48, 1596-1602. DOI: [10.1111/ijfs.12129](https://doi.org/10.1111/ijfs.12129)
- ¹⁴⁴El-Haskoury, R., Kriaa, W., Lyoussi, B., Makni, M., *J. Food Drug Anal.*, **2017**, In press, 1-7. <http://dx.doi.org/10.1016/j.jfda.2016.11.016>
- ¹⁴⁵Martínez-Rodríguez, R., Navarro-Alarcón, M., Rodríguez-Martínez, C., Fonolla-Joya, J., *Nutr. Hosp.*, **2013**, 28, 2107-2114. DOI: [10.3305/nh.2013.28.6.6952](https://doi.org/10.3305/nh.2013.28.6.6952)
- ¹⁴⁶Silanikove, N., Landau, S., Or, D., Kababya, D., Bruckental, I., Nitsan, Z., *Livest. Sci.*, **2006**, 99, 29-38. doi: [10.1016/j.livsci.2005.05.018](https://doi.org/10.1016/j.livsci.2005.05.018)
- ¹⁴⁷Kapetanakou, A. E., Makariti, I. P., Grivokostopoulos, N., Ha, M.-A., Skandamis, P. N., *Nutrition*, **2017**, 42, 12-19. <http://dx.doi.org/10.1016/j.nut.2017.05.011>
- ¹⁴⁸Aydin, S., Ozdemir, Y., *J. Food Qual.*, **2017**, Article ID 5028150, 7 pages. <https://doi.org/10.1155/2017/5028150>
- ¹⁴⁹Ayaz, F. A., Torun, H., Glew, R. H., Bak, Z. D., Chuang, L. T., Presley, J. M., Andrews, R., *Plant Foods Hum. Nutr.*, **2009**, 64, 286-292. DOI: [10.1007/s11130-009-0130-3](https://doi.org/10.1007/s11130-009-0130-3)
- ¹⁵⁰Miljic, U., Puskas, V., *Acta Agric. Serb.*, **2012**, XVII, 83-92. <http://scindeks-clanci.ceon.rs/data/pdf/0354-9542/2012/0354-95421234083M.pdf>
- ¹⁵¹Tagari, H., Henis, Y., Tamir, M., Volcani, R., *Appl. Microbiol.*, **1965**, 13, 437-442. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1058268/pdf/applmicro00359-0147.pdf>
- ¹⁵²El-Shantawi, M. K., Ereifej, K. I., *J. Range Manage.*, **2001**, 54, 669-673. https://doi.org/10.2458/azu_jrm_v54i6_el-shatnawi
- ¹⁵³Obeidat, B. S., Alrababah, M. A., Alhamad, M. N., Gharaibeh, M. A., Abu Ishmais, M. A., *Small Ruminant Res.*, **2012**, 105, 9-15. <http://dx.doi.org/10.1016/j.smallrumres.2012.01.001>
- ¹⁵⁴Calislar, S., Kaplan, Y., *R. Bras. Zootec.*, **2017**, 46, 113-117. <http://dx.doi.org/10.1590/S1806-92902017000200005>
- ¹⁵⁵Bakhtaoui, F.-Z., Lakmichi, H., Chait, A., Gadhi, C. A., *Am. J. Phytomed. Clin. Ther.*, **2014**, 2, 1262-1276. <https://www.academia.edu/17571150>

- ¹⁵⁶Rtibi, K., Jabri, M. A., Selmi, S., Souli, A., Sebai, H., El-Benna, J., Amri, M., Marzouki, L., *BMC Complement. Alter. Medi.*, **2015**, *15*, 8 pages. DOI: [10.1186/s12906-015-0819-9](https://doi.org/10.1186/s12906-015-0819-9)
 - ¹⁵⁷Rtibi, K., Jabri, M. A., Selmi, S., Sebai, H., Marie, J-C., Amri, M., Marzouki, L., El-Benna, J., *RSC Adv.*, **2016**, *6*, 19992-20000. DOI: [10.1039/c5ra21388f](https://doi.org/10.1039/c5ra21388f)
 - ¹⁵⁸Rtibi, K., Selmi, S., Jabri, M-A., Mamadou, G., Limas-Nzouzi, N., Sebai, H., El-Benna, J., Marzouki, L., Eto, B., Amri, M., *RSC Adv.*, **2016**, *6*, 44345–44353. DOI: [10.1039/c6ra03457h](https://doi.org/10.1039/c6ra03457h)
 - ¹⁵⁹Georgieva, M., Manios, Y., Rasheva, N., Pancheva, R., Dimitrova, E., Schaafsma, A., *World J. Clin. Pediatr.*, **2016**, *5*, 118-127. DOI: [10.5409/wjcp.v5.i1.118](https://doi.org/10.5409/wjcp.v5.i1.118)
 - ¹⁶⁰Souli, A., Sebai, H., Chehimi, L., Rtibi, K., Tounsi, H., Boubaker, S., Sakly, M., El-Benna, J., Amri, M., *Toxicol. Ind. Health*, **2013**, *31*, 802-810. doi: [10.1177/0748233713475506](https://doi.org/10.1177/0748233713475506)
 - ¹⁶¹Corcoran, M. R., West, C. A., *Plant Physiol.*, **1968**, *43*, 859-864. DOI: [10.1104/pp.43.6.859](https://doi.org/10.1104/pp.43.6.859)
 - ¹⁶²Corcoran, M. R., *Planta (Berl.)*, **1970**, *95*, 95-102. <https://doi.org/10.1007/bf00387242>
 - ¹⁶³Corcoran, M. R., *Plant Physiol.*, **1970**, *46*, 531-534. <https://doi.org/10.1104/pp.46.4.531>
 - ¹⁶⁴Ali-Shtayeh, M. S., Jamous, R. M., Abu Zaitoun, S. Y., *J. Biodivers. Biopros. Dev.*, **2015**, *2*, 13 pages. <http://dx.doi.org/10.4172/2376-0214.1000151>
 - ¹⁶⁵Custodio, L., Patarra, J., Albericio, F., Neng, N. R., Nogueira, J. M., Romano, A., *Nat. Prod. Res.*, **2015**, *29*, 2155–2159. <http://dx.doi.org/10.1080/14786419.2014.996147>
 - ¹⁶⁶El-Haskoury, R., Zizi, S., Touzani, S., Al-Waili, N., Al-Ghamdi, A., Lyoussi, B., *Afr. J. Tradit. Complement. Altern. Med.*, **2015**, *12*, 128-133. <http://dx.doi.org/10.4314/ajtcam.v12i4.19>
 - ¹⁶⁷Mokhtari, M., Mohammadi, B., Sharifi, E., Tabatabaee, M. S., *Yafte*, **2011**, *13*, 74-82. <http://yafte.lums.ac.ir/article-1-444-en.html>
 - ¹⁶⁸Rtibi, K., Selmi, S., Jabri, M-A., El-Benna, J., Amri, M., Marzouki, L., Sebai, H., *J. Med. Food*, **2016**, *19*, 882–889. DOI: [10.1089/jmf.2016.0020](https://doi.org/10.1089/jmf.2016.0020)
 - ¹⁶⁹Ahmed, M. M., *Nat. Sci.*, **2010**, *8*, 41-47. <https://www.researchgate.net/publication/228632173>
 - ¹⁷⁰Ben Hsouna, A., Saoudi, M., Trigui, M., Jamoussi, K., Boudawara, T., Jaoua, S., El Feki, A., *Food Chem. Toxicol.*, **2011**, *49*, 3183–3191. doi: [10.1016/j.fct.2011.09.034](https://doi.org/10.1016/j.fct.2011.09.034)
 - ¹⁷¹Mohamed, D. A., Hamed, I. M., Al-Okbi, S. Y., *Dtsch. Lebensmitt. Rundsch.*, **2008**, *104*, 25-29. <https://www.researchgate.net/publication/279545372>
 - ¹⁷²dos Santos, L. M., Tulio, L. T., Campos, L. F., Dorneles, M. R., Kruger, C. C., *Nutr. Hosp.*, **2015**, *31*, 482-487. DOI: [10.3305/nh.2015.31.1.8011](https://doi.org/10.3305/nh.2015.31.1.8011)
 - ¹⁷³El-Sayyad, H. H., Elkholy, W. M., Hamed, W. A., *Glob. J. Zool.*, **2017**, *2*, 024-032. <https://www.researchgate.net/publication/318493992>
 - ¹⁷⁴El-Beltagy, A. B., Elghaweet, H. A., *J. Biosci. Appl. Res.*, **2016**, *2*, 170-184. <http://jbaar.org/2016/03/29>
 - ¹⁷⁵Mokhtari, M., Sharifi, E., Azadian, S., *Adv. Environ. Biol.*, **2012**, *6*, 2778-2783. <https://www.researchgate.net/publication/281761331>
 - ¹⁷⁶Mobli, M., Qaraaty, M., Amin, G., Haririan, I., Hajimahmoodi, M., Rahimi, R., *Arch. Gynecol. Obstet.*, **2015**, *292*, 21–35. DOI: [10.1007/s00404-015-3629-x](https://doi.org/10.1007/s00404-015-3629-x)
 - ¹⁷⁷Durazzo, A., Turfani, V., Narducci, V., Azzini, E., Maiani, G., Carcea, M., *Food Chem.*, **2014**, *153*, 109-113. DOI: [10.1016/j.foodchem.2013.12.045](https://doi.org/10.1016/j.foodchem.2013.12.045)
 - ¹⁷⁸Sharaf, H. A., Shaffie, N. M., Morsy, F. A., Badawi, M. A., Abbas, N. A., *J. Arab Soc. Med. Res.*, **2015**, *10*, 65–75. DOI: [10.4103/1687-4293.175880](https://doi.org/10.4103/1687-4293.175880)
 - ¹⁷⁹Lall, N., Kishore, N., Momtaz, S., Hussein, A., Naidoo, S., Ngqophe, M., Crampton, B., *Phytother. Res.*, **2015**, *29*, 1729–1736. DOI: [10.1002/ptr.5420](https://doi.org/10.1002/ptr.5420)
 - ¹⁸⁰Silanikove, N., Gilboa, N., Perevolotsky, A., Nitsan, Z., *Small Ruminant Res.*, **1996**, *21*, 195-201. [http://dx.doi.org/10.1016/0921-4488\(95\)00833-0](http://dx.doi.org/10.1016/0921-4488(95)00833-0)
 - ¹⁸¹Gulay, M. S., Yildiz-Gulay, O., Ata, A., Balic, A., Demirtas, A., *J. Animal Vet. Adv.*, **2012**, *11*, 1853-1857. DOI: [10.3923/javaa.2012.1853.1857](https://doi.org/10.3923/javaa.2012.1853.1857)
 - ¹⁸²Abia, R., Fry, S.C., *J. Sci. Food Agric.*, **2001**, *81*, 1156-1165. DOI: [10.1002/jsfa.924](https://doi.org/10.1002/jsfa.924)
 - ¹⁸³Wahby, A. F., Mahdy, E. M., EL-mezayen, H. A., Salama, W. H., Ebrahim, N. M., Abdel-Aty, A. M., Fahmy, A. S., *J. Genet. Eng. Biotechnol.*, **2012**, *10*, 213-219. doi: [10.1016/j.jgeb.2012.10.001](https://doi.org/10.1016/j.jgeb.2012.10.001)
 - ¹⁸⁴Abdel-rahman, M., Salem, F-A., Bauomy, A. A., Khalifa, M. A., *Int. J. Pharm. Pharm. Sci.*, **2017**, *9*, 246-253. <https://innovareacademics.in/journals/index.php/ijpps/article/view/15470/8725>
 - ¹⁸⁵Gehrke, I., Neto, A., Pedroso, M., Mostardeiro, C., Da Cruz, I., Silva, U., Ilha, V., Dalcól, I., Morel, A., *J. Ethnopharmacol.*, **2013**, *148*, 486-491. <https://doi.org/10.1016/j.jep.2013.04.043>
 - ¹⁸⁶A2Abubakar, M. N., Majinda, R. R., *Medicines*, **2016** *3*, 9 pages. DOI: [10.3390/medicines3010003](https://doi.org/10.3390/medicines3010003)
 - ¹⁸⁷Hong, H., Landauer, M. R., Foriska, M. A., Ledney, G.D., *J. Basic Microbiol.*, **2006**, *46*, 329-335. DOI: [10.1002/jobm.200510073](https://doi.org/10.1002/jobm.200510073)
 - ¹⁸⁸Joray, M. B., Trucco, L. D., Gonzalez, M. L., Diaz Napal, G. N., Palacios, S. M., Bocco, J. L., Carpinella, M. C., *J. Evid. Based Complement. Alternat. Med.*, **2015**, Article ID 912484. 11 pages. <http://dx.doi.org/10.1155/2015/912484>
 - ¹⁸⁹Zhao, X., Mei, W., Gong, M., Zuo, W., Bai, H., Dai, H., *Molecules*, **2011**, *16*, 9775-9782. DOI: [10.3390/molecules16129775](https://doi.org/10.3390/molecules16129775)
 - ¹⁹⁰Steinmann, J., Buer, J., Pietschmann, T., Steinmann, E., *Br. J. Pharmacol.*, **2013**, *168*, 1059-1073. DOI: [10.1111/bph.12009](https://doi.org/10.1111/bph.12009)
 - ¹⁹¹Tassou, C. C., Drosinos, E. H., Nychas, G. J., *World J. Microbiol. Biotechnol.*, **1997**, *13*, 479-481. DOI: [10.1023/A:1018544821143](https://doi.org/10.1023/A:1018544821143)
 - ¹⁹²Hariri, A., Ouis, N., Bouhadi, D., Ould Yerou, K., *Banats J. Biotechnol.*, **2017**, *8*, 105-112. DOI: [10.7904/2068-4738-VIII\(15\)-105](https://doi.org/10.7904/2068-4738-VIII(15)-105)
 - ¹⁹³El-Neketi, M., Ebrahim, W., Lin, W., Gedara, S., Badria, F., Saad, H-E. A., Lai, D., Peter Proksch, P., *J. Nat. Prod.*, **2013**, *76*, 1099–1104. DOI: [10.1021/np4001366](https://doi.org/10.1021/np4001366)
 - ¹⁹⁴Klenow, S., Jahns, F., Pool-Zobel, B. L., Gleis, M., *J. Agric. Food Chem.*, **2009**, *57*, 2999–3004. DOI: [10.1021/jf802872b](https://doi.org/10.1021/jf802872b)
 - ¹⁹⁵Khalifa, N. S., El-Hallouty, S. M., Barakat, H. S., Salim, D. M., *Egypt J. Exp. Biol. (Bot.)*, **2013**, *9*, 137 – 144. <https://www.ejmanager.com/mnstemp/15/15-1429989346.pdf>
- * It is interesting enough to remark that the previous reference was published one year before (in 2012) in Russian: *Rev. Clin. Pharmacol. Drug Ther.*, **2012**, *10*, 50-57. DOI: [10.17816/RCF10250](https://doi.org/10.17816/RCF10250)
- ¹⁹⁶Goulas, V., Stylos, E., Chatziathanasiadou, M. V., Mavromoustakos, T., Tzakos, A. G., *Int. J. Mol. Sci.*, **2016**, *17*, 20 pages. DOI: [10.3390/ijms17111875](https://doi.org/10.3390/ijms17111875)
 - ¹⁹⁷Haddarah, A., Ismail, A., Bassal, A., Hamieh, T., Ioannou, I., Ghoul, M., *Eur. Sci. J.*, **2013**, *9*, 353-369. <https://www.researchgate.net/publication/275957562>
 - ¹⁹⁸Sears, K. D., Casebier, R. L., *Phytochemistry*, **1970**, *9*, 1589-1594. DOI: [10.1016/S0031-9422\(00\)85281-4](https://doi.org/10.1016/S0031-9422(00)85281-4)

- ¹⁹⁹Theophilou, I. C., Neophytou, C. M., Kakas, A., Constantinou, A. I., *J. Hepatol. Gastroenterol.*, **2017**, *1*, 5 pages. <http://www.scientificajournals.org/pdf/jhge.1005.pdf>
- ²⁰⁰Mulimani, V. H., Prashanth, S. J., *Biochem. Molec. Biol. Edu.*, **2002**, *30*, 101-103. DOI: [10.1002/bmb.2002.494030020044](https://doi.org/10.1002/bmb.2002.494030020044)
- ²⁰¹Lagari, V. S., Levis, S., *Curr. Opin. Endocrinol. Diabetes Obes.*, **2010**, *17*, 546-553. DOI: [10.1097/MED.0b013e32833f4867](https://doi.org/10.1097/MED.0b013e32833f4867)
- ²⁰²Drouliscos, N. J., Malefaki, V., *Br. J. Nutr.*, **1980**, *43*, 115-123. DOI: [10.1079/bjn19800071](https://doi.org/10.1079/bjn19800071)
- ²⁰³Baumgartner, S., Genner-Ritzmann, R., Haas, J., Amado, R., Neukom, H., *J. Agric. Food Chem.*, **1986**, *34*, 827-829. DOI: [10.1021/jf00071a015](https://doi.org/10.1021/jf00071a015)
- ²⁰⁴Chiera, J. M., Streeter, J. G., Finer, J. J., *Plant Sci.*, **2006**, *171*, 647-654. <https://doi.org/10.1016/j.plantsci.2006.06.006>

Received: 08.10.2017

Accepted: 13.11.2017.