CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Review Article

CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL EFFECTS OF *FRAXINUS ORNUS*- A REVIEW

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Abstract:
Chemical analysis of Fraxinus ornus revealed the presence of many compounds belonging mainly to the groups of hydroxycoumarins, secoiridoid glucosides, phenylethanoids and flavonoids, in addition to carbohydrate, trace elements and oils. Pharmacological studies showed that Fraxinus ornus possessed antiinflammatory, antimicrobial, antiprotozoal dermatological, antioxidant and many other effects. This review will highlight the chemical constituents and pharmacological effects of Fraxinus ornus.

Keywords: *chemical constituents, pharmacology, Fraxinus ornus*

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Please cite this article in press Ali Esmail Al-Snafi., ***Chemical Constituents and Pharmacological Effects of Fraxinus Ornus- A Review,*** *Indo Am. J. P. Sci, 2018; 05(03).*

INTRODUCTION:

During the last few decades there has been an increasing interest in the study of medicinal plants and their traditional use in different parts of the world. Many previous reviews revealed the wide range of the pharmacological and therapeutic effects of medicinal plants [1-33]. Chemical analysis of *Fraxinus ornus* revealed the presence of many compounds belonging mainly to the groups of hydroxycoumarins, secoiridoid glucosides, phenylethanoids and flavonoids, in addition to carbohydrate, trace elements and oils. Pharmacological studies showed that *Fraxinus ornus* possessed antiinflammatory, antimicrobial, antiprotozoal dermatological**,** antioxidant and many other effects. This review was designed to highlight the chemical constituents and pharmacological effects of *Fraxinus ornus*.

Plant profile:

Synonyms:

Fraxinus argentea Loisel., *Fraxinus cappadocica* Juss. ex Bosc, *Fraxinus diversifolia* Rochel ex Boiss., *Fraxinus florifera* Scop., *Fraxinus halepensis* Steud., *Fraxinus mannifera* [Raf.] Steud., *Fraxinus mille-lacuum* K.Koch, *Fraxinus mille-lacuum* K. Koch, *Fraxinus ornus* var. *acuminata* Kárpáti, *Fraxinus ornus* var. *americana* Bosc, *Fraxinus ornus* var. americana Bosc, *Fraxinus ornus* var. *angustifolia* Ten., *Fraxinus ornus* var. *argentea* [Loisel.] Gren. & Godr., *Fraxinus ornus* f. *argentea* [Loisel.] Beissn., *Fraxinus ornus* subsp. *argentea* [Loisel.] Arcang., *Fraxinus ornus* subsp. *argentea* [Loisel.] Javorka, *Fraxinus ornus* var. *danubialis* Borbás, *Fraxinus ornus* var. *diversifolia* Rochel, *Fraxinus ornus* f. *emarginata* [Kárpáti] Jovan.-Dunj., *Fraxinus ornus* var. *emarginata* Kárpáti, *Fraxinus ornus* var. *garganica* Ten., *Fraxinus ornus* subsp. *garganica* [Ten.] Hegi, *Fraxinus ornus* f. *grandifoliolata* Jovan.-Dunj., *Fraxinus ornus* var. *juglandifolia* Ten., *Fraxinus ornus* var. *latifolia* Aiton ex Dippel, *Fraxinus ornus* f. *linearis* Jovan.-Dunj., *Fraxinus ornus* subsp. *ornus*, *Fraxinus ornus* var. *oxyptera* Borbás, *Fraxinus ornus* var. *paniculata* [Mill.] Weston, *Fraxinus ornus* f. *platiptera* Jovan.-Dunj., *Fraxinus ornus* f. *rachilanata* Jovan- Dunj., *Fraxinus ornus* var. *rotundifolia* Ten., *Fraxinus ornus* subsp. *rotundifolia* [Ten.] Arcang., *Fraxinus ornus* subsp. *rotundifolia* [Ten.] Wesm., *Fraxinus ornus* f. *rufescens* Heimerl, *Fraxinus ornus* var. *Salicifoliolata* Jovan- Dunj., *Fraxinus ornus* var. *sanguinea* Hausm. ex Lingelsh., *Fraxinus ornus* var. *stenocarpa* Kárpáti, *Fraxinus ornus* f. *Sublinearis* Jovan- Dunj., *Fraxinus ornus* var. *ulmiifoliolata* Jovan. -Dunj., *Fraxinus paniculata* Mill., *Fraxinus pseudo-ornus* Steud., *Fraxinus rotundifolia* var. *argentea* [Loisel.] Dippel, *Fraxinus rotundifolia* f. *heterophylla* Lingelsh., *Fraxinus rotundifolia* f. *variegata* Lingelsh., *Fraxinus thrysantha* St.-Lag., *Ornanthes florida* Raf., *Ornanthes lutea* Raf., *Ornanthes mannifera* Raf., *Ornus cappadocica* [Juss. ex Bosc] A.Dietr., *Ornus corymbosa* Lavallée, *Ornus europaea* Pers., *Ornus lanceolata* Rouy & Foucaud, *Ornus nana* Lavallée[34].

Common names:

Arabic: Shajarat El-mann, American Derdar**; English**: flowering ash, manna, manna ash; **French**: frêne à fleurs, frêne à manne, orne à manne; **German**: Blumen-Esche, Manna-Esche; **Spanish**: fresno de flor, maná de Calabria; **Swedish**: manna-ask[35].

Taxonomic classification:

Kingdom: Plantae, Subkingdom: Viridiplantae, **Infrakingdom**: Streptophyta,Superdivision : Embryophyta, **Division**: Tracheophyta, **Subdivision:** Spermatophytina, **Class**: Magnoliopsida, **Superorder**: Asteranae, **Order**: Lamiales, **Family**: Oleaceae, **Genus**: *Fraxinus*, **Species**: *Fraxinus ornus*[36].

Distribution:

It grows wild in the Mediterranean region and south central Europe, northwards to the south Czech Republic and north- eastern Romania [37].

Description:

Fraxinus ornus is a small to medium sized deciduous tree, growing rarely up to 25 m tall and 1 meter in diameter. The bark is dark grey, usually very smooth even in old trees. The buds are grey-brown densely covered by short grey hairs. The foliage is olive-green and changes to yellow and deep pink in autumn. The leaf is compound, 25-30 cm long, odd-pinnate, arranged in 5-9 leaflets, obovate, acuminate, serrated, grooved above and pubescent at the joints, 7-10 cm long. The flowers are abundant and grouped in large inflorescences 10-20 cm long; appear in late spring at the same time as the leaves. The single narrow flowers are creamy white with four linear petals, 6 mm long. The fruits are 15-25 mm long, slender, green in colour until leaf fall, then brown when ripening in autumn [38-41].

Traditional uses:
Fraxinus ornus bark was used in the traditional medicine for wound healing and treatment of inflammation, arthritis and dysentery [37]. Bark was also used as antimicrobial, antiparasitic and insect repellent[42]. A decoction of the flowers, leaves and bark of *Fraxinus ornus* was used to hens in the case of pediculosis [43]. It was also used as dye plants[44].

The manna of commerce was collected from cultivated trees. The collection of Manna is begun in July and August, when the trees have ceased to put forth leaves freely, a vertical series of oblique incisions were made in the bark on alternate sides of the trunk. Dry, warm weather was essential for a good crop of the Manna which exudes. The larger pieces of incrustation those forms, and which were collected in September and October, when the heat has begun to moderate, were known as Flake Manna, and this was the best. Manna has a peculiar odour and a sweetish taste. It was used as laxative. It was a nutritive and a gentle tonic, usually operating mildly, but in some cases produced flatulence and pain. It was generally given dissolved in water or some aromatic infusion, in doses of a teaspoonful up to 1 or 2 oz. Usually it was prescribed with other purgatives, particularly senna, rhubarb, magnesia and the neutral salts, the taste of which it conceals while it added to the purgative effect. Syrups of Manna were prepared with or without other purgatives. The Codex of the British Pharmacopceia contained a Syrup of Manna to be prescribed as a mild laxative for children, in the proportion of 1 part of Manna to 10 of water[45].

Part used medicinally:
Bark, flowers, leaves and manna [37, 42-45].

Chemical constituents:
Chemical analysis of bark, leaves and flowers of *Fraxinus ornus* revealed the presence of many compounds belonging mainly to the groups of hydroxycoumarins, secoiridoid glucosides, phenylethanoids and flavonoids. *Fraxinus ornus* was rich in hydroxycoumarins. Esculin, esculetin, fraxin and fraxetin were the main components of the bark [37].

β-sitosterol, fatty acids, ursolic acid, rhamnetin, quercetin, quercetin-3, 7-O-digalactoside, quercetin-3-O-galactoside [hyperoside], quercetin-3-O-rhamnoside [quercitrin] and rutin were isolated from flowers of *Fraxinus ornus*[46].

Secoiridoid glucosides, hydroxyframoside A, hydroxyframoside B, ornoside; secoiridoids hydroxyornoside, ligstroside, framoside, oleuropein, the lignan l-hydroxypinoresinol glucoside, tyrosol derivative [ornosol] and coumarin-secoiridoid [escuside] were isolated as a mixture from the ethanolic extract of *Fraxinus ornus* bark [47-49].

Fraxinus ornus was rich in hydroxycoumarins. They occur free or as glucosides. Esculin, esculetin, fraxin and fraxetin were the main components of the bark, while coumarins were present in small amounts. The highest total contents of coumarins were found during the period of fruit ripening: 4.6% in the leaves, 2.7% in the shoots and in the bark. The leaves and the flowers contain cichoriin **as** a main component and esculin, esculetin, fraxin and fraxetin as minor ones. A seasonal variation of esculin, esculetin, fraxin and cichoriin **in** bark, shoots and leaves was observed. Oleoside type secoiridoid glucosides were found in the bark and the leaves. The bark contained ligstroside, insularoside, hydroxyornoside, oleuropein, framoside, hydroxyframoside A and hydroxyframoside B. Only ligstroside, insularoside and hydroxyornoside were isolated from the leaves. Flavonoids apigenin, quercetin, rutin, quercetin 3-*O*-galactoside and quercetin 3-*O*-glucoside were isolated from the leaves. Rhamnetin, quercetin, rutin, quercetin 3-*O*-galactoside, quercetin 3-*O*-digalactoside and quercetin 3-*O*-rhamnoside were obtained from the flowers. Quercetin, quercetin 3-*O*-rhamnoside and quercetin 3-*O*-galactoside were detected in the bark. Caffeic acid esters identified as a phenylethanoid glucoside [isolugrandoside], five phenylethanoid glycosides [2-[4-hydroxyphenyl]-ethyl-[6-O-caffeoyl]-beta-D-glucopyranoside, calceolarioside B, verbascoside, isoacteoside and lugrandoside] were isolated from *Fraxinus ornus* bark. Calceolarioside was isolated from the leaves. Tyrosol and ornosol were isolated from the bark. Organic acids, caffeic, gallic and *p*-coumaric acids were isolated from the bark. Caffeic, *p*-coumaric, gallic and ursolic acids were detected in the leaves. Ursolic acid was isolated from the flowers. Tannins 2%. and lignan 1-hydroxypinoresinol-4-β-D-glucoside was isolated from the bark. Bark and leaves contained Mg, Ca, Zn, Mn, Cu, Co and Ni. Plant manna contained mannitol, glucose, fructose and oligosaccharides [37, 50-51].

The chemical analysis of the plant flowers showed the presence of the following groups: tannins, 8 amino acids, polyphenols [flavonoids and

coumarins], free sugars, triterpenes, mucilage. The petroleum ether extracts revealed the presence of β -sitosterol, iauric, myristic, palmitic, palmitoleic, steatic, oleic, linoleic and linolenic aids. Ursolic acid was isolated from ether extracts. Quercetin-3-7-O-diagalactoside, aesculetin, fraxin, aesculin, cichoriin, phamnetin, guercetin, guercetin-3-galactoside, guercetrin and rutin were isolated from ethanolic extracts[52-53].

GC/MS analysis of the unsaponifiable fraction of *Fraxinus ornus* seeds hexane extract showed that it was constituted of 16 compounds. Hydrocarbons presented in high percentage, 46.378%, where *n*-hexacosane was the major one represented [13.614%]. Sterols represented [10.26%] of the total unsaponifiable fraction; the major sterol was β-sitosterol [9.008%]. As well as hydrocarbon content, triterpenoids were identified to represent high percentage of the unsaponifiable fraction [43.35%]; identified as lupeol and α-amyrin, [32.99 and 10.36, respectively]. However, the sixteen compounds isolated from *Fraxinus ornus* seeds were included: n-Heptadecane 1.769%, n-octadecane 2.185%, n-nonadecane 1.883%, n-eicosane 2.043%, n-heneicosane 5.552%, n-docosane 1.575%, n-tricosane 2.535%, n-tetracosane 8.238%, n-pentacosane 4.237%, n-hexacosane 13.614%, n-heptacosane 1.249%, n-octacosane 1.498%, 5α-cholestane 1.249%, β- sitosterol 9.008%, α-amyrin 10.366% and lupeol 32.992%[54].

Manna contained approximately 70% mannite or manna sugar, a crystalline, sweet compound. Mannite was white, inodorous, and crystallizable in semi-transparent needles of a sweetish taste. It also contained a fluorescent compound called fraxin, which occasionally gave a greenish colour to manna sugar. Manna also contained some true sugar, a small quantity of mucilage and minerals. Manna-ash [bark] contained: hydroxycoumarins; the coumarin, esculin; secoiridoid glucosides; phenylethanoids and flavonoids[42].

Pharmacological effects:

Antiinflammatory effects:

The total ethanol extract of the stem bark of *Fraxinus ornus* and its constituent esculin inhibited classical pathway and alternative pathway of complement activation in mouse serum. Intraperitoneal administration the total ethanol extract displayed antiinflammatory activity in both zymosan- and carrageenan-induced paw oedema in mice. The antiinflammatory effects were at least partially due to coumarin constituents of *Fraxinus ornus* [55].

The anti-inflammatory effect of boiling 96% alcoholic extract of stem bark of *Fraxinus ornus* was studied using zymosan and carrageenan induced odema in mice. After intraperitoneal administration the total extract displayed antiinflammatory activity in both zymosan- and carrageenan-induced paw oedema. The effective dose of about 5-15 mg/kg was comparable to the effect of other lipoxygenase inhibitors like phenidone. The total ethanol extract from *Fraxinus ornus* bark contained substances of high potency capable of inhibiting classical pathway and alternative pathway complement activity. The comparison between the effects obtained with total ethanol extract and esculin in the haemolytic inhibitory assay indicated that the anticomplementary action of total extract was not due only to esculin[55-56].

Antimicrobial effects:

Esculetin, fraxin and fraxetin were the compounds mainly responsible for the antimicrobial properties of *Fraxinus ornus* bark extracts[57].

The antibacterial investigation of the ethanolic extract and decoction from the bark of *Fraxinus ornus* revealed antibacterial effect against *Staphylococcus aureus* and *Bacillus subtilis*, as well as a marked activity against *Leptospira ponoma*[58].

The antimicrobial activity of the *n*-hexane fraction from the seeds of *Fraxinus ornus* was studied against Streptococcus *pneumonia, Bacillus subtilis, Streptococcus pyogenes, Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, Klebsiella penumoniae, Neisseria gonorrhoeae, Asperagillius fumigatus* and *Candida albicans*. The *n*-hexane fraction from the seeds of *Fraxinus ornus* possessed both antibacterial and antifungal activities. Its antibacterial activity against Gram positive bacteria was higher than that against Gram negative bacteria and fungai. The antibacterial activity against *N. gonorrhoeae* was the highest followed by *B. subtilis*, *K. penumoniae* and E. *faecalis*. Mild antibacterial activity was recorded against *S. Pneumoniae*, *S. pyogenes* and *E. coli*. Furthermore it exerted antifungal activity against both *C. albicans* and *A. fumigates* [54].

In studying of antimicrobial activity of different bark constituents [coumarins, secoiridoids and phenylethanoids], It appeared that there was a clear correlation between structure and antibacterial activity against *S. aureus* and *E. coli*. Compared to the aglucones [MIC=500 and 125 µg/ml, the glucosides showed a negligible activity [MIC= 1000

µg/ml]. It was appeared that methylation of phenolic OH decreased the activity, while acetylation does not alter the activity. Fraxetin **and** its diacetate appeared the most potent inhibitors of *S. aureus.* The secoiridoid glucosides **and** the phenylethanoid ornosol **inhibited** the growth of *S. aureus* and *Cladosporium cucumerinum*. The caffeoyl esters of phenylethanoid glycosides **showed** no activity against *Pseudomonas stutzeri* [59-60].

Esculetin [6,7-dihydroxycoumarin] islated from dried stem bark from mature trees of *Fraxinus ornus,* and its diacetate exhibited a marked inhibitory effect on Newcastle disease virus replication in cell cultures at concentrations of 36 µm and 62 µm, respectively [52].

Antiprotozoal effect:
The potential protective effects of *Fraxinus ornus* against experimental infection with *Eimeria tenella* was investigated in broiler chickens. Treatment with lasalocid or *Fraxinus ornus* at a lesser extend incorporated into the ration revealed significant reduction in the oocyst excretion whereas this effect was not significant when *Fraxinus ornus* was incorporated into drinking water. The caecal lesion score was also depressed by *Fraxinus ornus* and lasalocid supplementation but not significantly. In addition, the dietary *Fraxinus ornus* supplementation induced a significant growth promoting effect on un-infected broilers [61].

Dermatological effects:
The skin regenerating properties of the ethanolic bark extract and its main component esculin **was** investigated in male rats with standard oval wounds. The wounds were evenly coated, once a day for 15 days, with propylene glycol [solvent], 14.2% extract solution or 3.45% esculin solution. Rats treated with the bark extract, exhibited a more intense epithelization of the wounds in comparison with the control groups in all stage of the investigation. A weaker regenerating effect was found in group treated with esculin [62].

Four bark extracts include total methanolic extract and its petroleum ether, ethylacetate and methanol-water soluble parts, prepared by solvent-solvent partition of total methanolic extract were assayed for prevention of photodynamic yeast cell damage. The protection factor for the aglucones [94.7-97.6] at a concentration of 20 mg/l was higher than that of the corresponding glucosides **[**72.8-26.3] at a concentration of 50 mg/l. The protective effect of compounds caffeic acid was 98.2 at 25 mg/l which was comparable to that of *p*-aminobenzoic acid [92.6] at 25 mg/l. However, the activity of the extracts was depends on their hydroxycoumarin composition. Ethylacetate extract, which richer exerted the highest protection [63].

Antioxidant effects:
The antioxidative activity and strength of different concentrations of ethanolic extract from *Fraxinus ornus* bark, as well as of esculetin, esculin, fraxetin and fraxin was studied during the autoxidation at 100°C of kinetically pure triacylglycerols of lard [TGL] and triacylglycerols of sunflower oil [TGSO]. The extract exhibited a pronounced antioxidative activity. Esculetin and fraxetin considerably retarded the process in both lipid systems, this being more significant in the less oxidizable lipid substrate [TGL]. Fraxetin proved to be a more efficient and stronger inhibitor than esculetin. Fraxin and esculin displayed a very weak antioxidative action[64].

Side effects and toxicity:
The acute toxicity of the ethanolic bark extract and esculin was studied in experimental animals. Orally administered extract [50 to 8000 mg/kg] and esculin, to mice and rats showed no toxicity. The highest dose produced no lethality up to the 21st day. No significant changes were found in the behaviour and the reflexes of the animals. No pathological changes were recorded in hematological and biochemical indices [65].

CONCLUSION:
This review discusses the chemical constituent, pharmacological and therapeutic effects of *Fraxinus ornus* as promising herbal drug because of its safety and effectiveness.

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