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Fritillaria Imperialis- A Review

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Abstract: Fritillaria imperialis is a source of various pharmaceutically active components included steroidal alkaloids, saponins, terpenoids, glycosides and many other compounds. It possessed anticholinergic, cardiovascular, anticancer, insecticidal, platelet aggregation inhibition and many other pharmacological effects. The current review discussed the chemical constituents and pharmacological effects of Fritillaria imperialis.

Keywords: chemical constituents, pharmacological effects, Fritillaria imperialis

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I. INTRODUCTION

Medicinal plants have formed the basis of traditional medicine systems that have been in existence for thousands of years and continue to provide mankind with new remedies. Molecular biology has become essential to medicinal plant drug discovery through the determination and implementation of appropriate screening assays directed towards physiologically relevant molecular targets. Natural products and their derivatives represent more than 50% of all the drugs in clinical use in the world today. Recent reviews showed that medicinal plants possessed a wide range of pharmacological activities including antimicrobial, antioxidant, anticancer, hypolipidemic, cardiovascular, central nervous, respiratory, immunological, anti-inflammatory, analgesic antipyretic and many other pharmacological effects[1-15]. *Fritillaria imperialis* is a source of various pharmaceutically active components included steroidal alkaloids, saponins, terpenoids, glycosides and many other compounds. It possessed anticholinergic, cardiovascular, anticancer, insecticidal, platelet aggregation inhibition and many other pharmacological effects. The current review was designed to highlight the chemical constituents and pharmacological effects of *Fritillaria imperialis.*

Synonyms:

Fritillaria aintabensis, *Fritillaria corona-imperialis*, *Fritillaria corona-imperialis*, *Fritillaria imperialis* var. *imperialis*, *Fritillaria imperialis* var. *longipetala*, *Fritillaria imperialis* var. *maxima*, *Fritillaria imperialis* var. *rubra-maxima*, *Imperialis comosa*, *Imperialis coronata*, *Imperialis superba*, *Lilium persicum*, *Petilium imperiale*, *Imperialis comosa*, *Imperialis coronata*, *Imperialis superba*, *Lilium persicum*, *Petilium imperiale* and *Petilium imperiale*[16].

Taxonomic classification:

Kingdom: Plantae**; Subkingdom**: Tracheobionta; **Superdivision**: Spermatophyta; **Division**: Magnoliophyta; **Class**: Liliopsida; **Subclass**: Liliidae; **Order:** Liliales**; Family:** Liliaceae**; Genus:** *Fritillaria***; Species:** *Fritillaria imperialis*[17]**.**

Common names:

Arabic: Eklil El-Malik**, English:** crown imperial, imperial fritillary; **French**: couronne impériale; **German** Kaiserkrone; **Italian**: meleagride imperiale **Portuguese:** coroa-imperial, diadema; **Swedish:** kejsarkrona[18].

Distribution:

The genus Fritillaria comprises more than 100 species and has a distribution in the temperate regions of the northern hemisphere[19]**.**

Fritillaria imperialis was distributed in Asia: Afghanistan, Iran, Iraq, Turkey, India, Pakistan and some parts of the Himalaya; and in Eastern European[18,20-21].

Description:

Fritillaria imperialis grows to about 70 cm in height. The plant commands attention with their regal bearing and crown of bell shaped flowers. Each bulb produces one 3 to 4 foot stem. The base of each stem is graced with whorls of glossy green wavy lance-shaped leaves. Above the leaves, the maroon colored stem shoots leafless upward to form a whorl of downward facing flower buds and top-knot of leaves[22-23].

Traditional uses:

Fritillaria imperialis were used traditionally for the treatment of sore throat, cough, asthma, bronchitis, scrofula, gland tumor, dysuria and haemoptysis[24-26].

The bulb was used as diuretic, emollient and resolvent. It has been used as an expectorant and to encourage increased breast milk production. The bulb is poisonous raw, it contains low concentrations of a toxic alkaloid[27].

Part used medicinally:

The bulb was used medicinally[27].

Chemical constituents:

The genus *Fritillaria* is a botanical source for various pharmaceutically active components including steroidal alkaloids, saponins, terpenoids, glycosides and many other compounds[28].

Many steroidal bases were isolated from the bulbs of *Fritillaria imperialis* included, ebeinone, eduardine, edpetilidine, verticinone and isoverticine[24,29-30]. Cevanine steroidal alkaloids, impericine, forticine, delavine, persicanidine A, imperialine and isobaimonidine were isolated from the bulbs of *Fritillaria imperialis*[30-32]. As well as imperialine, two other alkaloids of molecular formula C27H41N02 and C27H45N03 were obtained from bulbs of *Fritillaria imperialis* L. var. *rubra maxima* ; the latter is identical with verticine[33]. A crystalline base was obtained from *Fritillaria imperialis*, it was elucidated as (20R, 25R)-5alpha,17beta-cevanine-3beta,6 beta-diol,. The base was found to be identical with persicanidine B and also with harepermine[34]. A new class of *C*-nor-d-homo steroidal alkaloids (impranane), impranine and dihydroimpranine, a new pyridyl-pregnane-type steroidal alkaloid, fetisinine and the base korsevine were isolated from the bulbs of *Fritillaria imperialis*[35].A diterpenoid isopimara-7,15-dien-19-oic acid was isolated from the nonpolar fraction of ethanolic extract of *Fritillaria imperialis* [36]

The component causing the foxy odor, characteristic for some *Fritillaria imperialis* cultivars, was studied, The headspace of flower bulbs was analyzed using gas chromatography-olfactometry (GC-O) and GC-mass spectrometry (GC-MS). Six Fritillaria species and cultivars were selected. GC-O revealed that the foxy odor was caused by a single component, identified as 3-methyl-2-butene-1-thiol on the basis of smell in GC-O analyses , mass spectra, and retention times. However, the volatile content of the flower bulbs of *Fritillaria imperialis* was included: acetic acid, 2-nitroethanol, 3-hydroxy-2-butanone, 3-methylpentanol, 2,3-butanediol, n-hexanal, 3-methyl-2-butene-1-thiol, 3-pentene-2-ol, 1-hexanol, 1,2-dimethyl benzene, cyclohexanone, dihydro-3-methyl 2(3H)-furanone, benzaldehyde, 3-methyl-2(5H)-furanone, 3-hydroxy-4,4,dimethyl 2(3H)-furanone, acetophenone, 2-nonene-1-ol, octanoic acid, decanal, nonanoic acid, ,4,6-trichlorophenol, tetradecane, pentadecane, 3,4-dimethyl-1,5-heptadiene and hexadecane[37].

Pharmacological effects:

Anticholinergic effects:

Ebeinone isolated from the bulbs of *Fritillaria imperialis* exhibited anticholinergic activity and completely blocked inhibitory responses of acetylcholine[29]. Ebeinone at concentration of (1µg/ml) exhibited anticholinergic activity as manifested by blocking of acetylcholine response in isolated guinea pig ileum and atria[24]. The steroidal bases (impericine, forticine, delavine, persicanidine A, and imperialine) isolated from the ethanol extract of the air-fried bulbs of *Fritillaria imperialis* showed anti-acetylcholinesterase and anti-butyrylcholinesterase inhibitory activity[31].

In order to check the structure-activity relationship and prepare more potent derivatives of imperialine with anticholinergic activity, imperialinol, 3 beta-acetoxyimperialine, 3 beta-propionoxyimperialine, and 3 beta-butyroxyimperialine were prepared. 3 beta-propionoxyimperialine, and 3 beta-butyroxyimperialine displayed better anticholinergic activity against muscarinic receptors of the heart and brain than imperialine. The decrease in activity in imperialinol showed the importance of the 6-keto functionality in imparting the anticholinergic activity[38].

The ability of the alkaloid, ebeinone, isolated from *Fritillaria imperialis*, for binding with muscarinic M2 and M3 acetylcholine receptors was investigated. In functional studies with guinea-pig left atrium, ebeinone was found to be 10-fold more active as an antagonist of responses to carbachol (CCh) than in either guinea-pig ileum or trachea. The estimated dissociation constants (KB values) in the three tissues were 77.3, 931.1 and 547.0 nM, respectively. Inhibition binding studies in rat atria with the non-selective antagonist [3H]N-methylscopolamine ([3H]NMS) showed that ebeinone have a KI value of 80.9 nM. Comparison of ebeinone with pancuronium, with a similar KB value at the muscarinic M2 receptor, found both compounds able to retard the dissociation rate of [3H]NMS in atria, indicating an allosteric mode of interaction at the M2 receptor[39].

Imperialine (cervane alkaloid), was assessed at M_1, M_2 and M_3 receptors in functional assays and at M_1, M_2, M_3 and putative M_4 sites in binding studies. In functional assay, imperialine appeared as a selective

surmountable antagonist at M_2 receptors in guinea-pig isolated atria and uterus ($-\log K_B$ = 7.7 and 7.4, respectively), in comparison to M_1, receptors in canine isolated saphenous vein ($-\log K_B$ = 6.9) or M3 receptors in a range of guinea-pig isolated smooth muscles including ileum, trachea, fundus, seminal vesicle or oesophagus ($-\log K_B$ = 6.6–6.8). In rat aorta, the $-\log K_B$ value at the M_3 receptor (5.9) was slightly, but significantly, lower. In competition radioligand binding studies, imperialine was also selective toward to M2 sites in rat myocardium ($-\log K_i$ = 7.2) with respect to M_1 and M_3 sites (rat cerebral cortex, rat submaxillary gland; $-\log K_i$ = 6.1 and 5.7, respectively). However, it did not significantly discriminate between rat cardiac M_2 sites and putative M_4 sites in rabbit lung ($-\log K_i$ = 6.9)[40].

Cardiovascular effects:

In anesthetized dogs, the alkaloidal fraction isolated from the corms of *Fritillaria imperialis* showed an appreciable fall in blood pressure due to cardiac depression and peripheral vasodilatation. Hypotensive effect is also observed in experimental hypertension. On frog's heart the alkaloidal fraction exhibited cardiotonic effect. The alkaloidal fraction also exhibited anti-arrhythmic activity resembling that of quinidlne and spasmolytic activity similar to that of papaverine[41].

Platelet aggregation inhibitory effects:

The effect of some Turkish medicinal plants against human platelet aggregation induced by AA, collagen and PAF have been examined. The ethanolic extracts of *Fritillaria imperialis* appeared one of the most potent inhibitors with minimal concentration[29].

Anticancer effects:

The anti-cancer potentials of Isopimara-7,15-Dien-19-oic acid, extracted from the bulbs of *Fritillaria imperialis* was evaluated in cervical cancer cell line, HeLa cells. Flow cytometry analysis of cell death, gene expression analysis via cDNA microarray and protein array were performed. The results revealed that Isopimara-7,15-Dien-19-Oic acid simultaneously induced cell death and promoted cell survival. The execution of apoptosis was apparent based on the flow cytometry results and regulation of both pro and anti-apoptotic genes. Furthermore, the regulation of anti-oxidant genes were up-regulated especially thioredoxin, glutathione and superoxide dismutase- related genes. Isopimara-7,15-Dien-19-oic acid also induced the activation of pro-survival heat shock proteins[21].

In evaluation of general toxicity of Turkish plants, using the brine shrimp, crude extracts of *Fritilluria imperialis* caused complete mortality within 24 hours[42].

Insecticidal activity:

In evaluation of insecticidal activity of Turkish plants, crude extracts of *Fritilluria imperialis* possessed significant insecticidal activity against the milkweed. Insecticidal activity of crude extracts of *Fritilluria imperialis* recorded as 90% or greater mortality within six days against Milkweed bug[42].

Endopeptidase inhibitory activity:

The ethanolic extract of the bulbs of *Fritillaria imperialis* was subjected to fractionation by solvent-solvent extraction. The nonpolar fraction showed inhibitory activity against prolyl endopeptidase (PEP) (EC.3.4.21.26), a large intracellular enzyme that preferentially hydrolyze proline-containing oligopeptidase at the carboxylic side of a prolyl residue. A diterpenoid isopimara-7,15-dien-19-oic acid was isolated from the nonpolar fraction of *Fritillaria imperialis*, to which the prolyl endopeptidase inhibitory activity was attributed[36].

Toxicity and side effects:

Imperialine and other steroid alkaloids of *Fritillaria imperialis* could induced spasms, disturbances of GI tract and kidneys, hypotension, cardiac arrest [43]. The analgesic effect of aqueous extract of *Fritillaria imperialis* bulbs (50 , 100, and 200 mg/kg, po) was evaluated in rats using (Tail- Flick pain model) in comparison with with morphine. Administration of 50 and 100 mg/kg of aqueous extract of *Fritillaria imperialis* bulbs did not show analgesic effect in the Tail- Flick test. However, aqueous extract of *Fritillaria imperialis* bulbs (200mg/kg) reduced pain significantly ($P<0.05$) in a potential comparable to morphine (2 mg/kg, Sc). It seems that the analgesic effect of AEFb was related to the presence of some alkaloids such as impericine and forticine[44].

II. CONCLUSION

The review highlighted the chemical constituent, pharmacological and therapeutic effects of *Fritillaria imperialis* as promising source of drugs because of its safety and effectiveness.

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