CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

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

PHARMACOLOGICAL AND THERAPEUTIC IMPORTANCE OF *ECHIUM ITALICUM*- A REVIEW

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Received: 01 February2017 **Accepted:** 08 February 2017 **Published:** 28 February 2017

Abstract:
Echium italicum contained naphthoquinone pigments such as alkannin and shikonin derivatives. However, nine shikonin pigments: shikonin, acetylshikonin, propionylshikonin, isobutyrylshikonin, tiglylshikonin, 3,3-dimethylacrylshikonin, angelylshikonin, 2-methyl-n-butyrylshikonin and isovalerylshikonin were isolated from the root epidermis of Echium italicum. The total phenolic content of the herb and root of Echium italicum was 11.46 ± 0.08 mg GA/g. The chemical analysis of three different stages (early, middle and late stage) of maturity of the seeds of Echium italicum from Turkey revealed that they contained total oil 15.22, 26.25 and 28.78 g/100 consisted of palmitic, stearic, oleic, linoleic, α-linolenic, Ɣ-Linolenic, heneicosanoic acids, while stigmasterol and brassicasterol were recorded only in the last stage. pharmacological studies showed that the plant possessed anxiolytic, sedative, antimicrobial, insecticidal, antioxidant, analgesic, anti-inflammatory, wound healing and other effects. The current review discussed the chemical constituents and pharmacological effects of Echium italicum.

Keywords: *pharmacology, medicinal plant, chemical constituents, Echium italicum*

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*Please cite this article in press as Ali Esmail Al-Snafi, **Pharmacological and Therapeutic Importance of Echium Italicum- A Review**, Indo Am. J. P. Sci, 2017; 4(02).*

INTRODUCTION:

Plants have been used as drugs by humans since thousands of years ago. As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Chemical analysis showed that Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-20]. *Echium italicum* contained naphthoquinone pigments such as alkannin and shikonin derivatives. However, nine shikonin pigments: shikonin, acetylshikonin, propionylshikonin, isobutyrylshikonin, tiglylshikonin, 3,3-dimethylacrylshikonin, angelylshikonin, 2-methyl-n-butyrylshikonin and isovalerylshikonin were isolated from the root epidermis of *Echium italicum*. The total phenolic content of the herb and root of *Echium italicum* was 11.46 ± 0.08 mg GA/g. The chemical analysis of three different stages (early, middle and late stage) of maturity of the seeds of *Echium italicum* from Turkey revealed that they contained total oil 15.22, 26.25 and 28.78 g/100 consisted of palmitic, stearic, oleic, linoleic, α-linolenic, ϒ-Linolenic, heneicosanoic acids, while stigmasterol and brassicasterol were recorded only in the last stage. pharmacological studies showed that the plant possessed anxiolytic, sedative, antimicrobial, insecticidal, antioxidant, analgesic, anti-inflammatory, wound healing and other effects. The current review will discuss the chemical constituents and pharmacological effects of *Echium italicum*.

Synonyms:

Echium altissimum Jacq., *Echium balearicum* Porta, *Echium collinum* Salisb., *Echium elongatum* Lam., *Echium glomeratum* Ledeb., *Echium italicum* var. balearicum (Porta & Rigo) O. Bolòs & Vigo, *Echium linearifolium* Moench, *Echium luteum* Lapeyr., *Echium pyramidale* Lapeyr., *Echium pyramidatum* A. DC., *Echium pyrenaicum* L., *Echium ramosum* Gaterau, *Echium strictissimum* Schur, *Isoplesion italicum* (L.) Raf. and *Isoplesion pyrenaicum* Raf [21].

Taxonomic classification:

Kingdom: Plantae, **Subkingdom:** Tracheobionta, **Superdivision**: Spermatophyta, **Division:** Magnoliophyta, **Class:** Magnoliopsida, **Subclass:** Asteridae, **Order**: Lamiales, **Family:** Boraginaceae, **Genus:** *Echium*; **Species:** *Echium italicum* [22].

Common names:

Arabic: Ward Lisan Althor, Musais, Sak al-Hamam, Zahrat alefaa al-Italia; **English**: Italian-bugloss, Lady Campbell-weed, Pale-bugloss, Yellow-bugloss; **German**: Hoher Naternkopf; **Portuguese**: Borrago-italiano; **Swedish**: Italiensk snokört [23].

Distribution:

The plant is distributed in: Africa (Egypt and Libya); Asia (Armenia, Georgia, Russian Federation – Dagestan, Russian Federation-Ciscaucasia – Ciscaucasia, Afghanistan, Iran, Iraq, Lebanon and Turkey); Europe (Moldova, Ukraine, Austria, Hungary, Slovakia, Albania, Bulgaria, Croatia, Greece, Italy, Romania, Serbia, Slovenia, France, Spain and Switzerland) and Australia [23].

Description:

Biennial or perennial herbs, to 80 cm high, usually single-stemmed, hairs spreading, short and dense. Leaves oblanceolate in the rosette, becoming linear-lanceolate or elliptic above, 6–30 cm long, 1–3.5 cm wide, base cuneate, lamina densely hairy, petiolate. Inflorescence conical with many spreading cymes. Sepals linear-lanceolate, 6–7.5 mm long, becoming longer in fruit. Corolla ± actinomorphic, 10–12 mm long, cream to yellow; lobes half the length of the tube. Mericarps greyish-brown, wrinkled [24].

Traditional uses:

In Turkey, the aerial parts of *Echium italicum* were used traditionally for wound healing, as diaphoretic, emollient and diuretic, while, the roots of the plant were used for wound healing, ulcer, rheumatic pain, blister and to treat bruises [25-26].

In Italy, the decoction of aerial parts of *Echium italicum* were used as depurative, diaphoretic, diuretic and as emollient for healing respiratory infections [27].

Chemical constituents:

The chemical compositions of three different stages (early, middle and late stage) of maturity of the seeds of *Echium italicum* from Turkey were analysed, They contained total oil 15.22, 26.25 and 28.78 g/100 respectively; palmitic acid 8.59%), 7.30% and 7.28%; stearic acid 2.81%, 2.54% and 2.42%; oleic acid 13.16%, 15.40% and 15.36%; linoleic acid 12.45%, 11.83% and 12.50%; α-linolenic acid 40.24%, 42.21% and 41.90%, ϒ-Linolenic acid 9.59%, 7.47% and 7.55%; heneicosanoic acid 13.16%, 13.25% and 12.99%, α-Tocopherol (mg/100 g) 9.00% (11.823), 5.92% (11.575) and 1.25% (11.186) respectively. However, stigmasterol and brassicasterol were recorded only in the last stage in concentration of 49.55% and 49.23%, while, cholesterol and campesterol were not recorded in all stages [28].

However, different populations of *Echium italicum* showed different oil composition. Total oil concentrations were ranged from 19.3- 23.5 % among the different *Echium italicum* populations in Turkey. Significant variations were detected between fatty acid concentrations. The major unsaturated fatty acids were alpha-linolenic, linoleic, oleic, stearidonic and gamma-linolenic acids respectively. The highest values for stearidonic (15.48 %) and gamma-linolenic

acid (7.66 %) were recorded in some population [29].

The oil content and fatty acid composition in Iranian *Echium italicum* (Boumehen, Kaleybar and Alamut populations) seed were: total oil % (w) 6.2-28.4, the γ-linolenic acid percent reached 0.61-2.19%, γ-linolenic acid 3.94-9.79%, palmitic acid 6.51-18.93%, stearic acid 3.67-4.30%, oleic acid 12.63-16.23%, linoleic acid 14.09-20.15%, α-linolenic acid 22.12-36.61% and stearidonic acid 4.33-12.45 [30].

However, the oil of the aerial parts of *Echium italicum* from the suburb of Geloogah, Mazandaran Province, North of Iran, comprised 4 monoterpenoids (17.1%), one sesquiterpene (3.8 %) and 17 non-terpenoids (69.2 %). Twenty-two components were identified in the oil of *Echium italicum* collected from the suburb of Geloogah, North of Iran. The major constituents of the essential oil were hexadecanol (27.1 %) and pulegone (8.8 %) [31].

Echium italicum contained naphthoquinone pigments such as alkannin and shikonin derivatives. An *in vitro* cell suspension culture of *Echium italicum* was assayed for the production of shikonin and alkannin derivatives. The production and/ or accumulation of these compounds in the *Echium italicum* cells was examined using fluorescence microscopy as the naphthoquinone molecules display autofluorescent properties. Phytochemical analysis of the n-hexane extract of the medium showed shikonin and alkannin derivatives [32]. Furthermore, shikonin derivatives acetylshikonin, deoxyshikonin, (2-methyl-n- butyryl shikonin and Isovalerylshikonin were isolated and determined from *Echium italicum* roots [33].

However, nine shikonin pigments: shikonin, acetylshikonin, propionylshikonin, isobutyrylshikonin, tiglylshikonin, 3,3-dimethylacrylshikonin, angelylshikonin, 2-methyl-n-butyrylshikonin and isovalerylshikonin were isolated from the root epidermis of *Echium italicum* [34-35].

The total phenolic content of the herb and root of *Echium italicum* and *E. vulgare* was 11.46 ± 0.08 and 19.97 ± 0.01 mg GA/g respectively, while, the total flavonoit content of the herb and root of *Echium italicum* and *E. vulgare* were 19.97 ± 0.01 and 47.11 ± 0.01 mg Quercetin /g respectively [36].

Pharmacological effects:

Anxiolytic and sedative effects:

The anxiolytic and hypnotic effects of the aqueous and ethanolic extracts of aerial parts of *Echium italicum* was evaluated in mice. Mice were administered the extracts intraperitoneally for evaluation of hypnotic activity (induced by sodium pentobarbital, 30 mg/kg, ip). Anxiolytic activity was elevated by plus-maze [EPM] test, locomotor activity by open field test, and motor coordination by rotarod test. The ethanolic and aqueous extracts of *Echium italicum*, at doses of 1.2 and 2.1 g/kg, increased the percentage of time-spent and the percentage of arm entries in the open arms of the EPM and decreased the percentage of time-spent in the closed arms of the EPM. Both extracts decreased the pentobarbital-induced latency to sleep and significantly increased the total sleeping time induced by pentobarbital. Locomotor activity was affected by aqueous extracts and ethanolic extract (at higher doses). Both extracts showed no effect in the rotarod test. According to these results, both ethanolic and aqueous extracts of *Echium italicum* psessed anxiolytic and sedative activity but they were free from muscle relaxant activity [37].

Antimicrobial effects:

Echium italicum extracts caused a zone of growth inhibition of at least 4 mm against *Pseudomonas solanaciarum* and 1 cm^2 against *Cladosporium cucumerinum* [38].

The antimicrobial activity of *Echium italicum* oil was studied using the disk diffusion method and determination of minimal inhibitory concentration values against *Bacillus subtilis* PTCC 1023, *Staphylococcus aureus* PTCC 1112, *Escherichia coli* PTCC 1330, *Salmonella typhi* PTCC 1639, *Pseudomonas aeruginosa* PTCC 1074, *Aspergilus niger* PTCC 5011 and *Candida albicans* PTCC 5027. *Echium italicum* oil exhibited concentration-dependent antimicrobial activity against all the tested microorganisms [31].

Insecticidal effects:

Echium italicum showed good insecticidal activity, its extract caused 100 % mortality within six days against Yellow Fever mosquito [38].

The insecticidal efficacy of aqueous extract of *Echium italicum* was investigated against Indian meal moth (IMM). Three concentrations of extract were used: 1%, 2% and 5%. The number of dead larvae/Petri dish was counted daily after 1, 2, 3 and 4 days after treatment. The extract showed insecticidal activity (dead larvae) in low concentration 1% extracts [39].

Antioxidant effects:

The antioxidant effect of the ethanol extracts from the roots and herbs of *Echium italicum* and *E. vulgare* was investigated by DPPH free-radical scavenging, Fe^{2+}- chelating ability, total phenolic contents and total flavonoid contents methods. Extracts showed a concentration-response relationship in DPPH scavenging activity. An increase in the concentration is synonymous with an increase in scavenging capacity. But root extracts of the plant showed more potent DPPH scavenging activity and Fe^{2+}- chelating ability than the herb extracts. DPPH free radical scavenging activities (%) for 50, 100, 500 and 1000 µg/ml of herb ethanolic extract were 3.18 ± 0.02, 16.49 ± 0.01, 25.90 ± 0.06 and 33.44 ± 0.03, and of root ethanolic extract were 11.93± 0.01, 13.83 ± 0.02, 57.24 ± 0.01 and 81.43 ± 0.01 respectively. The ferrous Ion chelating activities % of the ethanol

extracts for 200 and 400 µg/ml of herb ethanolic extract were 5.93 ± 0.04 and 7.26 ± 0.06 , and of root ethanolic extract were 25.93 ± 0.02 and 32.0 ± 0.06 respectively [36].

Analgesic and anti-inflammatory effects:
The analgesic effect of the ethanol extracts from the roots and herbs of *Echium italicum* and *E. vulgare* was investigated in mice using acetic acid-induced writhing and tail flick methods. The analgesic effect of root extracts of *Echium italicum* (0.5 mg/g) was comparable with the standard drugs, aspirin and morphine. The findings imply the involvement of both peripheral and central antinociceptive mechanisms [36].

Wound healing effects:
The wound healing activity of ethanolic extract 1% ointment of the roots of Echium species was evaluated by linear incision experimental models. The tissue samples were examined histopathologically. The healing potential was comparatively assessed with a reference ointment Madecassol®, which contains 1% extract of *Centella asiatica*. Significant wound healing activity was observed from the ointment prepared with ethanol extract at 1% concentration. The ethanol root extract of *Echium italicum* showed a significant increase (37.38%) wound tensile strength in the incision wound model [33].

Effects of Alkannin and shikonin:
Alkannin (S-enantiomer), shikonin (R-enantiomer) and related derivatives are potent pharmacological compounds, they were used to enhance wound healing, as antithrombotic, antibacterial, anti-HIV, anti-tumor, anti-inflammatory, antioxidant and as colorants in cosmetics and food industries [37, 40].

Toxicity:
The LD50 and maximum tolerated dose values of the aqueous extract were 4 and 3 g/kg, respectively. The ethanolic extract showed no mortality up to a dose of 5g/ kg [37].
Echium italicum was used as the only diet in calves and the histo-toxicological effects were compared with the control group that was fed just by hay. The animals were slaughtered after 2 monthes and tissue samples were collected for next histological examination. Microscopically evaluation of tissue sections showed many histological changes changes including: the hepatic cells were dissociated and showed necrosis. Kidney showed tubular cloudy swelling and the Bowman's capsular spaces were extended due to urine accumulation. In some, hydropic degeneration was seen in the Purkinje fibres of heart. In two cases, the animal's heart had focal necrosis and in another one showed cardiomyolysis lesions. Intestine showed edema, severe inflammation and patchy mucosal necrosis and the lymph nodes showed reduction of cellular population in germinal centers of lymphatic follicles. One of the animals died during the examination period [41].

CONCLUSION:
The current review discuss the chemical constituents and pharmacological effects of *Echium italicum* to open the door for its uses for many pharmacological purposes as a results of effectiveness and safety.

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