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Review Article

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The Pharmacological and Toxicological Effects of *Coronilla varia* and *Coronilla scorpioides*: A Review

Ali Esmail Al-Snafi

Department of Pharmacology, College of Medicine, Thi qar University, Iraq

Abstract *Coronilla varia* and *Coronilla scorpioides* were the species of *Coronilla* grown in Iraq. They contained many pharmacologically active metabolites. Coumarins (scopoletin, daphnoretine, umbelliferon), cardiotonic glycosides (deglucohyrcanoside, hyrcanoside), a toxic constituent, β-nitropropionic acid and potent neurotoxin, were also isolated from *Coronilla varia*. *Coronilla scorpioides* produced several compounds included cardenolide glycoside (hyrcanoside, hyrcanogenine, coronillin, corotoxigenin, frugosid, glucocorotoxigenin, scorpioside, and coronillobioside), hydroxycoumarins (umbelliferone, scopoletin and daphnoretin), dihydro-furanocoumarin marmesin, and the furocoumarin psoralen. The previous pharmacological studies revealed that *Coronilla varia* possessed cardiac, antimicrobial, insecticidal and cytotoxic effects; while *Coronilla scorpioides* induced cardiac effects. This review will cover the pharmacological and toxicological effects of *Coronilla varia* and *Coronilla scorpioides.*

Keywords constituents, pharmacology, toxicology, *Coronilla varia*, *Coronilla scorpioides*

Introduction

Medicinal plants are the Nature's gift to human beings to help them pursue a disease-free healthy life. 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 [1-30]. *Coronilla varia* and *Coronilla scorpioides* were the species of *Coronilla* grown in Iraq. They contained many pharmacologically active metabolites. Coumarins (scopoletin, daphnoretine, umbelliferon), cardiotonic glycosides (deglucohyrcanoside, hyrcanoside), a toxic constituent, β-nitropropionic acid and potent neurotoxin, were also isolated from *Coronilla varia*. *Coronilla scorpioides produced* several compounds included cardenolide glycoside (hyrcanoside, hyrcanogenine, coronillin, corotoxigenin, frugosid, glucocorotoxigenin, scorpioside, and coronillobioside), hydroxycoumarins (umbelliferone, scopoletin and daphnoretin), dihydro-furanocoumarin marmesin, and the furocoumarin psoralen. The previous pharmacological studies revealed that *Coronilla varia* possessed cardiac, antimicrobial, insecticidal and cytotoxic effects; while *Coronilla scorpioides* induced cardiac effects. This review will cover the pharmacological and toxicological effects of *Coronilla varia* and *Coronilla scorpioides.*

Plants Profile

I-*Coronilla varia*

Synonym: *Securigera varia* (L.) Lassen [31-33].

Taxonomic Classification

Kingdom: Plantae, **phylum**: Magnoliophyta**, Class**: Magnoliopsida, **Subclass**: Rosidae**, Order:** Fabales, **Family**: Fabaceae, **Genus**: *Coronilla* (*Securigera*), **Species**: *Coronilla varia* [31-33].

Nomenclature and Common Names

The genus name (*Coronilla*) is derived from the Latin (*corona*) meaning crown. (*Coronilla*) means little crown. The flowers and fruits are arranged in rings, suggesting little crowns. The species epithet (*varia*) means difference or variation, and refers to the plant's multi-colored flowers [34].

Common names**: Arabic**: scorgera mutaghiera**,** Coronilla; **English:** axseed, crown-vetch, trailing crown-vetch; **French:** coronille bigarrée, coronille variée; **German:** bunte kronwicke; **Spanish**: arvejilla morada, coronilla morada, ruda inglesa; **Swedish:** rosenkronill [31].

Distribution

It was native to Mediterranean region, Asia (Iran, Iraq, Lebanon, Syria, Turkey, Armenia, Azerbaijan, Georgia, Russian Federation, Turkmenistan); Europe: (Austria, Czechoslovakia, Germany, Hungary, Poland, Switzerland, Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation, Albania, Bulgaria, Former Yugoslavia, Greece, Italy, Romania, France, Spain) and North Africa. It was naturalized in New Zealand, North America, Canada and United States [31-36].

Description

Coronilla varia, crownvetch, is a herbaceous, perennial legume introduced from the Mediterranean region. Leaves are dark green and pinnately compound, usually with 15 ovate-oblong leaflets. It has coarse, strongly branched stems that are 2 to 6 feet long and upright to trailing. Crownvetch has a multi-branched root system and spreads by strong fleshy rhizomes. Flowers are pinkish-white to deep pink in long-stalked clusters. Seed pods are segmented, pointed, borne in crown-like clusters. It is not a true vetch and does not have tendrils for climbing. It normally grows to a height of 1½ to 2 feet [32, 37].

Traditional Uses

It was used traditionally as cardio-tonic, diuretic and in prostate diseases. However, it should be used with extreme caution because of toxicity [38]. A decoction of the bark has been used as an emetic. The crushed plant has been rubbed on rheumatic joints and cramps [39].

Part with Pharmacological and Toxicological Effects: all parts including seeds [38-39].

Chemical Constituents

Coumarins (scopoletin, daphnoretine, umbelliferon) and cardiotonic glycosides (deglucohyrcanoside, hyrcanoside) were isolated from the seeds of *Coronilla varia* [40-43]. A toxic constituent, β-nitropropionic acid, potent neurotoxin, was isolated from *Coronilla varia* [44]. Total number of flavonoids in *Coronilla varia* leaves was five, (four flavonoid sulphates and one flavone glucosides) [45].

However, flavonoids isolated from *Coronilla varia* leaves were included isovitexin, isovitexin-4'-o-glucoside, isovitexin-2"-o-xyloside, isoorientin, isoorientin-4'-o-glucoside, isoorientin-2"-o-xyloside, isoorientin 2″-*o*-rhamnoside, isoorientin 4′-*o*-glucoside, and isoorientin 7-*o*-glucoside [46-47].

Inflorescences of *Coronilla varia* also contained kaempferol and astragalin [48]. Two isoflavon compounds were isolated from *Coronilla varia*, 1.10 µg/ml Genistin and 0.34 µg/ml Genistein [49].

Coronilla varia had low saponin content and the content of total saponin in leaf was much higher than in stem [50].

The hydroxycoumarins umbelliferone, scopoletin, and daphnoretin were found in *Coronilla varia*, although they were not present in all plant organs [51].

The condensed tannin (Proanthocyanidins) concentration in *Coronilla varia* was 16.0 (g/ kg of dry weight) [52-53].

A group of 3-nitropropanoyl-D-glucopyranoses was isolated from active fractions of the crude extracts of the root of *Coronilla varia*. 3-nitropropanoyl-d-glucopyranoses isolated from the aerial parts of *Coronilla varia* were included 2,3,6-tri(3-nitropropanoyl)-α-d-glucopyranose (corollin), 1,2,6-tri(3-nitropropanoyl)-α-d-glucopyranose (coronillin), 2,6-di(3-nitropropanoyl)-α-d-glucopyranose (coronarian), triester karakin, diesters coronarian and cibarian, in addition to Di- and tri-nitropropanylgluco-pyranoses [54-57].

The oil yield of the plant was determined as 0.94% v/w. Twenty three compounds were identified by the GC-MS analysis of the essential oil of the *Coronilla varia* aerial parts representing 98.8% of the total oil. The isolated compound were included Z-Citral 1.800%, Nerol 1.86%, Trans-beta-Farnesene 1.02%, 3-Butenamide1.13%, (-)-Caryophyllene oxide 8.62%, Caryophyllene oxide 44.08%, Aromadendrene Veridiflorol 2.41%, 3-Cyclohexen-1-caroxaldehyde 1.96%, cis-3a,4,5,6,7,7a-Tetrahydro-1H-inden-1-one 1.21%, TAU-Muurolol 1.75%, alpha-Cadinol 4.13%, 1-Homoadamantaneca 2.13%, Tricyclo[4.3.1.13,8]undecane-1-car boxylic acid 2.13%, 6-butyl-3,6-dihydro-2-(1h)-pyridinone 3.31%, Palustrol 1.83%, 2-Dimethylamino-3-methyl-4-(3H)Pyrimidinone 1.94%, Benzenemethanol 1.44%, (E,Z)-Alpha-Farnesene 4.04%, 2-Pentadecanone 2.22%, 1,2-Benzenedicarboxylic acid 1.91% and Di-(2—etylhexyl)phthalate 1.95% [58].

Pharmacological Effects

Cardiac Effect

The Cardiotonic and cardiotoxic effects of two cardiac glycosides, hyrcanoside and deglucohyrcanoside isolated from the seeds of *Coronilla varia* were evaluated in comparison with the effect and toxicity of digoxin and ouabain. Evaluation of the cardiotonic effect using the methods of heart (in situ) and the isolated heart (Langendorff) proved that deglucohyrcanoside was more effective than hyrcanoside and that its effect was equal to that of digoxin as well as ouabain. The efficacy of deglucohyrcanoside at least equal to that of digoxin, while the toxicity of the former was several times lower, which indicated that the glycoside a potential candidate for therapeutic use [59-63].

Antimicrobial and Insecticidal Effects

Coronilla varia aerial parts extracts were tested for their antibacterial activity against *Streptococcus pyogenes* (ATCC 19615), *Staphylococcus aureus* (ATCC 25923), *Staphylococcus epidermidis* (ATCC 12228), *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 13883) and *Escherichia coli*. Two agar diffusion methods, well diffusion assay and disc diffusion assay were used to compare the susceptibility of the bacterial strains to the plant extracts. *Coronilla varia* extracts showed antibacterial activity against *Streptococcus pyogenes* (ATCC 19615), *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 13883) and *Escherichia coli* [64].

Antibacterial activity of plant extract was determined by disc diffusion method against three Gram negative bacteria (*Proteus mirabilis* PTCC (1076); *Enterobacter cloacae* PTCC (1003), and *Klebsiella pneumonia* PTCC (1290)) and two Gram posetive (*Staphylococcus aureus* PTCC (1112) and *Bacillus subtilis* PTCC (1023)). The extracts from *Coronilla varia* had interesting activity against *Proteus mirabilis* in the concentration of 700 µg/disc and did not show any activity against *Staphylococus aureus, Bacillus subtillis, Klebsiella pneumonia* and *Entrobacter cloacae* [58, 65].

A group of 3-nitropropanoyl-D-glucopyranoses was also isolated from active fractions of the crude extracts of the root. These compounds were toxic when administered orally to 3rd instar *Costelytra zealandica* larvae [55].

Cytotoxic Effect

Antitumour activity of *Coronilla varia* aerial parts extracts was assessed with the potato disc method. *Coronilla varia* extracts caused 66.7% growth inhibition and significantly decreased the mean number of tumours to 11.92 ± 2.15 in comparison with the negative control (water) 35.75 ± 4.54 [64].

The cytotoxic effect of extracts from *Cornilla varia* was investigated on MCF7 cancer cell line by MTT assay. *Corohilla varia* ethanol extract inhibited the proliferation of MCF7 cell line in RPMI 1640 medium. 5mg/ml was the optimum concentration of extract of *Coronilla varia* which inhibited cell line growth [58, 65].

An alcoholic extract of the seeds of *Coronilla varia* showed inhibitory activity against KB cells in culture and was fractionated through a series of partitions, column chromatography, and preparative layer chromatography to yield hyrcanoside, daphnoretin, scopoletin, and umbelliferone. Hyrcanoside, extract from the seeds of *Coronilla varia* showed inhibitory activity against KB cells in culture [64, 66].

Toxicology

Coronilla varia was toxic to human, the signs and symptoms of toxicity included vomiting, diarrhea, abdominal pain, slow pulse and death [38]. Glycosides of the plant appeared to have similar activities as cardiac glycosides and caused similar symptoms, the nitro compounds inhibited enzymes of citric acid cycle [67].

β-glycoside of 3-nitropropanol (NPOH) and (or) glucose ester of 3-nitropropionic acid (NPA) were highly toxic ingredients. These compounds were contained in crownvetch (*Coronilla varia*) and many species of Astragalus. The toxicology of NPA in nonruminant animals has been studied; the symptoms produced by NPA, including methemoglobinemia, which support the hypothesis that NPA exerts its toxic effect by irreversibly inhibiting the mitochondrial enzyme, succinate dehydrogenase. During this event, nitrite ion was released, resulted in methemoglobinemia. In contrast to nonruminants, ruminants rarely exhibit toxic symptoms, because NPA was metabolized to nontoxic products by rumen microorganisms [54, 68-69]. Several strains of anaerobic ruminal bacteria have been shown to degrade NPOH and NPA to nitrite, and the rate of degradation depends on the particular numbers and strains of bacteria present. These results may explain why NPOH and NPA are metabolized more effectively in cattle. Toxicity symptoms after NPOH administration include increased heart and respiration rates, frothy salivation and incoordination. Blood methemoglobin and nitrite concentrations are also increased [70-72].

Accordingly, crownvetch may be safely fed to ruminants but, if fed to nonrnminants, its concentration should not exceed 5% of the diet [54, 68-72].

A 9-month-old, male budgerigar (*Melopsittacus undulatus*) was presented with an acute onset of weakness and vomiting. The bird had ingested leaves of freshly harvested crown vetch (*Coronilla varia*) from a fresh cutting of the plant placed next to the bird's cage. During the following 10 hours, the bird exhibited tachypnea and showed progressive neurologic signs of weakness, incoordination, tremors, and depression. The bird was treated with supportive care and activated charcoal. Its condition stabilized in the following 8 hours, with improvement within 48 hours and complete recovery in 2 weeks. The toxic constituent of crownvetch was the nitrotoxin, β-nitropropionic acid, a potent neurotoxin [44].

II- *Coronilla scorpioides*

Synonyms:

Arthrolobium scorpioides (L.) DC., *Arthrolobium tauricum Kalen., Astrolobium scorpioides (L.) DC., Ornithopus scorpioides* L., *Ornithopodium scorpioides* (L.) Scop [73-78].

Taxonomic Classification

Kigdom: Plantae, **Phylum**: Magnoliophyta, **Class**: Magnoliopsida, **Order:** Fabales, **Family**: Fabaceae, **Genus**: *Coronilla* L., **Species**: *Coronilla scorpioides* [79].

Common Names

Arabic: Coronilla; **Armenian**: Kararvuit Volorvatz; **Brazilian**: Coronil**l**e; English: Annual Scorpion Vetch; Annual Scorpion-vetch; Yellow Crown Vetch; **French**: Coronille faux-scorpion; **German**: Skorpionskraut; **Italian**: **Cornetta coda di scorpione; Russian**: Vyazel Zavitoi**; Portuguese**: Pascoínhas; **Spanish**: Alacranera común; **Swedish:** Maskkronill and **USA**: Yellow crownvetch [73, 80]**.**

Distribution

The plant was distributed in **Africa** (Egypt, Algeria, Libya, Morocco, Tunisia and Ethiopia); **Asia** (Iran, Iraq, Jordan, Lebanon, Syria, Palestine, Turkey, Azerbaijan, Georgia, and Russian Federation); **Europe** (Ukraine, Albania, Bulgaria, Former Yugoslavia, Greece, Italy, Romania, France, Portugal and Spain) [80].

Description

It is a glabrous herb. Stems up to 35 cm tall, erect-ascending. Succulent leaves; baseline of up to 30 mm, simple, elliptical or suborbicular; cauline trifoliate, with lateral leaflets resembling stipules deciduous; stipules membranous, welded. Inflorescences with 2-4 flowers with longer stems than leaves. Goblet of 2 mm, with small teeth. Corolla 4-6 mm, with all the pieces about the same size. Legume up to 55 x 2.5 mm, pendulous, curved, tetragona. Flowering and fruiting from April to June [81-82].

Traditional Uses

It was used as stimulant and applied externally to bites of venomous animals [83]. *Coronilla scorpioides* was applied as a poultice for people who have been stung by a scorpion [84-85]. The twigs and leaves were used as diuretic, cardiac, cathartic and laxative [86].

Chemical constituents

Coronilla scorpioides produced several compounds with pharmaceutical interest, such as the cardenolide glycoside (hyrcanoside, hyrcanogenine, coronillin, corotoxigenin, frugosid, glucocorotoxigenin, scorpioside, and coronillobioside), hydroxycoumarins (umbelliferone, scopoletin and daphnoretin), the dihydro-furanocoumarin marmesin, and the furocoumarin psoralen [87-89].

Two species *Coronilla scorpioides* and *Coronilla repanda* of the genus *Coronilla* were investigated for coumarins and cardenolides. In both the same constituents were found. Five cardenolides (corotoxigenin, frugosid, glucocorotoxigenin, scorpioside, and coronillobioside) and four coumarins (psoralene, daphnoretin, scopoletin and umbelliferon) were isolated from *Coronilla repanda* and *Coronilla scorpioides* [90].

Scorpioside-A which obtained from the plant, has the structure of 3-β-(β-D-glucofuranosyloxy)-5, 14β-dihydroxy-19-oxo-5β-card-20(22)-enolide [91].

Glucocoroglaucigenin was also isolated from the seeds of *Coronilla scorpioides*, it has the structure of 3-beta-(o-beta-D-glucopyranosyl)-14-beta,19-dihydroxy-5-alpha-card-20(22)-enolide [92].

The seeds of *Coronilla scorpioides* have yielded a new cardenolidic bioside (coronillobiosidol) which has the structure of 3ß-o-[o-ß-D-glucopyranosyl-(1→4)-ß-D-glucopyranosyl]-14ß, 19-dihydroxy-5a-card-20(22)-enolide [93].

The relative levels of total phenolic content of 110 selected Egyptian plants were studied. The highest total phenolic contents were estimated in aqueous extracts 916.70 ± 4.80 mg% and methanol extracts of *Coronilla scorpioides*, 915.60±4.86 mg% [94].

The within-plant distribution of the coumarin compounds was investigated in Coronilla (C. *vaginalis, C. scorpioides, C. viminalis* and Securigera (*S. varia*) species with regard to improving the extraction procedure allowing better furocoumarin recovery. The hydroxycoumarins umbelliferone, scopoletin, and daphnoretin, the dihydrofurocoumarin marmesin, and the furocoumarin psoralen were detected. The hydroxycoumarins umbelliferone, scopoletin, and daphnoretin were found in all investigated species although they were not present in all the different plant organs. The dihydrofurocoumarin marmesin detected in the genus Coronilla, occured, only in the bound form, in leaves and roots of both *Coronilla scorpioides* and *C. vaginalis*. Also in these two species the furocoumarin psoralen was detected in all the plant parts in both free and bound forms. The preliminary acid hydrolysis of the plant material allowed psoralen recoveries substantially higher than the simple methanolic extraction, showing that in *Coronilla scorpioides* and *C. vaginalis* the bulk of the psoralen occurs in the bound form [51].

In vitro callus cultures of *Coronilla scorpioides* were established from hypocotyl, leaf, stem internode and root explants in order to evaluate the possibility of *in vitro* production of active secondary metabolites. Calli were obtained in B5 and MS medium. After the third subculture, B5 medium, giving the best results, and was selected for subsequent transfers. Homogeneous calli were kept either in darkness or in light. Chemical analyses showed that scopoletin and the intermediate products of the biogenetic pathway of psoralen, umbelliferone and marmesin, were always present in the calli and excreted into the media, while daphnoretin was never detected. Light seemed to be a prerequisite for psoralen biosynthesis. Root-derived calli produced a significantly higher amount of psoralen (137.5 microg/g DW). Component analysis showed that umbelliferone, marmesin and psoralen contents were related to variables associated with different explant types [87].

Pharmacological Effects

In 1886 Cardot, announced that the *Coronilla scorpioides* (Medic.) Koch, was an active cardiac poison. In 1889 Schlagdenhauffen and Reeb isolated a glucoside, *coronillin.* The physiological studies have demonstrated that the effect of coronillin on the heart in a manner similar to digitalis. In small doses it slowed the pulse through

stimulation of the inhibitory ganglia, and in larger quantity increased the tonicity and contractility of the heart, eventually leading to systolic spasm of the ventricle. This action upon the heart was accompanied by increase in the arterial pressure, followed after a time by lowering of the pressure, which apparently was the result of failure of diastole, causing the amount of blood forced out of the heart at each systole to be insufficient to fill the arteries. The drug also depressed the spinal cord, and lowered the respiratory movements by an action which was believed to be partly centric and partly peripheral. Death was produced by cardiac arrest. The dose of the commercial coronillin was commonly stated to be one and one-half grains (0.096 gm.) from four to six times a day, but it must be noted that Schlagdenhauffen mentioned that three-fourths of a grain (0.048 gm.) was a toxic dose. *Coronilla varia* of Europe also contained coronillin [88].

The acute toxicity studies of the cardiac glycosides which were also isolated from other plants, were examined by brine shrimp. Their lethal concentration 50 (LC_{50}) was 18.84ppm. The antitumor activity potato disk assays of the cardiac glycosides had shown good activity − 30.8% [95].

Investigation of the antioxidant potentials of 110 selected Egyptian plants revealed that the most potent plants was *Coronilla scorpioides* with calculated antioxidant values of 454.80 ± 4.83% for methanol extracts [94].

Screening of *Ae. aegyptii* larvicidal activity of 110 selected Egyptian plants proved that *Coronilla scorpioides* exhibited highest larvicidal activity, calculated as 22.53 ± 2.01 mg% for aqueous extracts and 18.53 ± 1.95 mg% for methanol extract [94].

Conclusion

This review was design to cover the pharmacological and toxicological effects of *Coronilla varia* and *Coronilla scorpioides.*

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