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REVIEW ARTICLE

A Review of Phytochemical Properties and Therapeutic Activities of *Glebionis coronaria*

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ABSTRACT

Glebionis coronaria, formerly *Chrysanthemum coronarium*, is one of the medicinal herbs that belong to the Asteraceae family. This review paper aims to provide information regarding the botanical description, distribution, and phytochemical properties which contribute to the medicinal properties of *Glebionis coronaria*. Various studies have reported the presence of tannins, vitamins, macro- and microelements, beta-carotene, carbohydrates, protein, and other bioactive compounds in the plant's essential oil, extract, or plant parts. Researchers have uncovered the potential pharmaceutical activities of the plant, including antibacterial, antifungal, antioxidant, anti-inflammatory, anti-cholesterol, to the anticancer properties. Based on the scientific evidence collected, *G. coronaria* has the potential to be used in many clinical areas for medicinal purposes. However, appropriate clinical testing should be pursued to evaluate the medicinal effects of this plant.

Keywords: *Glebionis coronaria*; *Chrysanthemum coronarium*; botanical; phytochemicals; pharmacological activities.

INTRODUCTION

Throughout the world, there are hundreds of thousands of plant species, distributed all over the map. Some of these plants have been known for their medicinal activity. These medicinal plants are widely used in many developing countries as a part of primary health care and are often used by patients who have chronic diseases such as cancers, liver diseases, and asthma. These facts correspond to the bioactive compounds contained in the medicinal plants, as well as its availability for the local area (Keskin, 2018). The World Health Organization (2002) stated that there are approximately 20,000 different plant species that have been used as a medicinal plant in many countries. These medicinal plants are commonly prepared in different dosage forms, such as powders, pills or tablets, infusions, and ointments (Yudharaj *et al.*, 2016).

Asteraceae, or generally known as an aster or crown daisy, is one of the most cultivated plant families that is commonly used for medicinal purposes. This family has more than 23,600 recognized species which further spread into 13 subfamilies. One of the most widely used medicinal plants in this family is *Glebionis coronaria* or *Chrysanthemum coronarium*. This medicinal plant has been used in decades, due to many of its functional properties, such as antibacterial, antifungal, antioxidant, immunomodulatory activity, and many other functional effects (Attard and Cuschieri, 2009; Tamokou *et al.*, 2017). Moreover, according to Williams (2013), *Glebionis coronaria* can be used to treat haematemesis (vomiting blood), blood in the stool, and it has a protective effect against lung cancer development.

Despite their potential, the use of medicinal herbs may lead to several side effects in many cases of herbs misuse, contamination, or undesired interaction with other medicines and plants (Keskin, 2018). This review article aims to provide information regarding the botanical description, distribution, phytochemical properties, as well as the general functions of *Glebionis coronaria*.

BOTANICAL DESCRIPTION

Chrysanthemum (Annual)

Common names	: Annual Chrysanthemum, Corn Marigold, Crown Daisy, Tricoloured Chrysanthemum
Origin	: Chrysanthemum segetum
Domain	: Eukaryota
Kingdom	: Plantae
Subkingdom	: Tracheobionta
Phylum	: Spermatophyta
Subphylum	: Angiospermae
Class	: Dicotyledonae
Order	: Asterales
Family	: Asteraceae
Genus	: Glebionis
Species	: *Glebionis coronaria*

(Randhawa and Mukhopadhyay, 1986)

PLANT MORPHOLOGY

*G. coronari*a is an annual, herbaceous plant, characterized by its upright, highly brachiferous stems. This plant was considered as ornamental, even though it was often found as a common weed. When cultivated in Polesia (in Zhytomyr) area, this plant will grow up to 60-143 cm height. Its leaves are bipinnately lobed and sessile, and the inflorescence is anthodium. The corolla on the disk flowers is yellow-colored, while the yellow on the ray florets has a different tone. The fruit of this plant is achene. Though, this plant is not usually cultivated in Polesia, Zhytomyr (Haouas *et al.*, 2016; Ivashchenko, 2017).

The result from a comparison study of pollen mother cells of *G. coronaria* with 3 other plants (*Matricaria recutita*, *Anacyclus monanthos*, and *Cotula barbata*) showed 9 bivalents at diakinesis, with a mean number of rod and bivalents is 2.795 and 6.205, respectively for *G. coronaria*. It also has an oblate-spheroidal shape with spines provided in the pollen walls. The size is ranging at 22.23- 29.95 µm polar axes with 24.65- 31.79 µm equatorial axes. Thus, *G. coronaria* can be differentiated from the structure of its pollen (Atta *et al.*, 2017).

Puglia *et al.* (2015) pointed out two factors that impede water uptake in and germination of *G. coronaria* seeds: directed water uptake via a channel-like structure spanning across the pericarp (peel), and mechanical stress exerted by the hard pericarp on embryo growth, thereby rejecting the hypothesis of physical dormancy of the cypselae of *G. coronaria*. Evidence supporting the rejection include the incomplete imbibition of pericarp-coated seeds compared to naked seeds, no increase in germination due to after-ripening and cold stratification, loss of viability during warm stratification at 35/20°C, higher germination rates in seeds with scarified pericarp tissue (and reaching full throttle upon its complete removal), and the absence of macrosclereids palisade layers in the pericarp tissue.

PLANT DISTRIBUTION

G. coronaria, whose common names are garland chrysanthemum, edible chrysanthemum, and crown daisy, is included in the Asteraceae family, in the Anthemideae class. This plant originally thought to be only found in the region of Mediterranean and probably China. This plant could be cultivated from Africa, Europe (in Belarus, Moldova, Russia, Ukraine), North America (in USA and Mexico), South America (in Uruguay, Chile, etc.), and occasionally found in New Zealand and Australia. It can also be cultivated in Romania, France, Slovakia, Estonia, and some other countries (Ivashchenko *et al.*, 2019). Furthermore, the flowering plant of genus Glebionis is known to be widely distributed throughout the Mediterranean region.

Cano *et al.* (2017) reported that *G. coronaria* L., formerly known as *Chrysanthemum coronarium* L., comprises two varieties, *G. coronaria var. coronaria* and *G. coronaria var. discolor*, which are found in the lower (warmer) and upper (cooler) regions of the thermo-Mediterranean bioclimatic belt, respectively. These varieties are distinguished by the arrangement of the sessile non-mucilaginous glands, which present between the ribs of cypselae; those in *G. coronaria var. coronaria* (yellow ray florets) were arranged in an orderly fashion. On the other hand, those found in *G. coronaria var. discolor* (white ray florets) were disordered. The other differences between the two varieties lie in the shape and width of the abaxial wing on the disc floret cypselae; it is wider and upward-facing in the yellow-ray floret variety, and narrower and not upward-facing in the white ray floret variety.

CHEMICAL COMPONENTS OF THE PLANT AND THEIR FUNCTIONS

G. coronaria has been widely used in Asia, especially in China, Korea, Japan, and India, as a dietary food product (Ivashchenko *et al.,* 2019). The same report also stated that *G. coronaria* is known to be an important vegetable, medicinal plant, and ornamental crop. Furthermore, this study stated that the aerial parts of the plant contain vitamins (especially B1, B2, C, B3), macro- and microelements (such as potassium, iron, calcium, selenium, iodine, etc.), beta-carotene, simple and complex carbohydrates, lactones, proteins, essential oil, and phenolic compounds (including flavonoids).

Antioxidant

Ivanshchenko *et al.* (2019*)* reported that *G. coronaria* has been reported to contain beta-carotene, a precursor of vitamin A. This compound was shown to have antioxidant properties, which at the cell membrane level, worked by neutralizing the free radical effects formed in the body. This vitamin A precursor could also stimulate the mucus formation by the epithelial cells of the mucous membranes, which affect the function of vision organs.

Anti-inflammatory, Astringent, Antimicrobial

Tannin, belonging to a complex group of high- and low- molecular weight natural polyphenols, was also found in *G. coronaria*, as the characteristic component of Asteraceae family (Ivashchenko *et al.,* 2019). The study stated that this compound has been used as an anti-inflammatory, astringent, and antimicrobial. Due to its tannin content, the plant preparation can be used for acute and chronic colitis, gastritis, enteritis, as a hemostatic agent, and to treat the inflammation in the nose, oral cavity, larynx, in the form of burns, rinses, ulcers, bedsores.

Dietary Food

G. coronaria has also been used as dietary food products, as it has been reported to contain a low amount of fat, but a high amount of protein and carbohydrates (Ivashchenko *et* *al.*, 2019). Furthermore, the same study mentioned that vitamin C content in the plant also played a role in activating the enzymes for carbohydrate metabolism and for endocrine glands function.

Findings from Guzelsoy *et al.* (2017) revealed that 100 g of edible parts of *G. coronaria* L. Spach contained 0.31 ± 0.03 g of fat, 1.58 ± 0.10 g of proteins, 0.84 ± 0.02 g of carbohydrates, 5.71 ± 0.30 g of dietary fibers, 10.2 ± 2.9 g of vitamin C, and energy of 23.9 ± 0.7 kcal. Furthermore, it was also known to contain high levels of potassium, calcium, and sodium with values of (per 100 g) 555 ± 11 mg, 239 ± 11 mg, and 198 ± 48 mg, respectively. It also provided an adequate amount of copper ions at 1.77 ± 0.37 mg per 100 g of serving.

Body General Function Enhancement

Ivashchenko *et al.* (2019) reported that *G. coronaria* contained calcium and was especially higher in the *G. coronaria var. discolor* compared to *G. coronaria var. coronaria*. This calcium may play a role in the skeleton formation, blood coagulation, muscle contraction, glycogen cleavage, etc. In addition, the report also stated that the aerial parts of this plant contained phosphorus which may contribute to the cell formation and regeneration, vitamin assimilation, teeth and bones development, energy exchange, acid-base balance, nerves, kidney, and heart muscle function.

Food Production

The flower heads of *G. coronaria* are known as chamomile adulterers, while its leaves are used to suppress fishy odors in Japanese-style soup, yuzu, and Japanese pepper (Haouas *et al.*, 2016). These authors also mentioned that the plant could also increase the level of fatty acid, such as vaccenic acid and linoleic acid in milk and cheese. Furthermore, the report also stated that *G. coronaria* could improve the volatile fraction composition in milk and cheese, which was attributed to the terpene contents, such as tricylene, α-pinene, β-citronellene, terpinolene, and camphene.

CHEMICAL COMPONENTS OF THE PLANT ESSENTIAL OIL AND ITS FUNCTION

G. coronaria essential oil was reported to contain several components, including camphor (29.2%), alpha-pinene (14.8%), lyratyl acetate (9.8%), beta-pinene (9.8%) and flavonoid (Hosni, *et al.,* 2013). According to the study, *G. coronaria* also contained an essential quinic acid, which is a phenolic compound that is classified as an aromatic compound.

Antimicrobial

According to Bardaweel *et al.* (2015), essential oil of *G. coronaria* L. possessed antimicrobial activities against Gram-positive bacteria. The study stated that the inhibition zone towards the Gram-positive bacteria was similar to the antimicrobial agent norfloxacin. In contrast, the essential oil showed less inhibition for Gram-negative bacteria. This might be attributed to the presence of a restrictive outer layer membrane in Gram-negative bacteria, which according to Moyo et al. (2011), contains lipopolysaccharides and matrix that consists of peptidoglycan, resulting in higher resistance of Gram-negative bacteria towards the essential oil. Based on Hosni *et al.* (2013), the antimicrobial effect shown was contributed by the compound in the essential oil, which mainly is camphor.

Insecticidal

The *G. coronaria* essential oil was also known to elicit insecticidal activity (Marongiu *et* *al*., 2009). The high insecticidal activity of the Chrysanthemum species could be elaborated by the collective synergistic effect of the phytochemical compounds present in the oil, such as santolinatriene, camphor, yomogi alcohol, bornyl acetate, cis-chrysanthenyl acetate, and hexadecanoic acid (Polatoğlu *et al.*, 2017). However, according to the study, not all *G. coronaria* possesses high insecticidal activity. This might be due to lower amount of hexadecanoic acid in some species, which has low volatility, a very high boiling point, and able to generate the fumigant insecticidal activity. Another study by Dalila Haouas *et al.* (2008) demonstrated that the flower head metabolic extract from the *G. coronaria* was more toxic than the leaves. This was due to the fact that the flower head contains more sesquiterpene lactones, which is known to be toxic to insects (Dalila Haouas *et al.,* 2008).

Antifungal

A study by Alvarez-Castellanos *et al.* (2001) reported that the essential oil of the *G. coronaria* possessed antifungal activity. This was due to the fact that the essential oil contains monoterpenoids, sesquiterpenoid, and non-terpenoids compounds, which are known for their ability to inhibit fungal growth. Even though the detailed antifungal mechanism of the terpenoid extracted from *G. coronaria* is yet to be elucidated, according to Zore *et al.* (2011), it was reported that terpenoids can modulate mevalonate pathways, alter the cellular levels of intermediate molecules, and modify the associated functions in eukaryotic cells. In addition, the terpenoids have the ability to destabilize membranes and modulate the functions associated with the membranes, such as permeability and cell signalling, which can lead to cell death. However, Alvarez-Castellanos *et al.* (2001) pointed out that the essential oil obtained from *G. coronarium* was less effective to inhibit fast-growing fungal such as *S. sclerotiorum, R. solani,* and *B. cinerea*.

Antioxidant

According to Bardaweel *et al.* (2015), *G. coronaria* L. essential oil demonstrated a moderate antioxidant effect, though it was mild compared to the strong antioxidant properties of ascorbic acid. This antioxidant activity could be related to vitamin C content in *G. coronaria*, especially in the flowering mass, which might work as a natural antioxidant (Ivashchenko *et al.*, 2019). A study by Bardaweel *et al.* (2015) reported that *G. coronaria* L. essential oil exhibited some level of AChE inhibitor. Despite its potential, it did not show any dose-dependent inhibitory action, and thus the IC_{50} could not be determined. Camphor, as one of the major constituents of monoterpenoids in *G. coronaria* L., was believed to contribute to this activity.

Anticancer

A study by Bardaweel *et al.* (2015) reported that the essential oil of *G. coronaria* was reported to have anticancer properties against several cancer cells. The result of the study showed that the inhibition of human breast cancer (MCF-7), human ductal breast epithelial tumor (T47D), human colon adenocarcinoma (Caco-2), human epithelial carcinoma (HeLa) were increased along with the increased of the extract concentration. According to the LD_{50} result, the inhibition of the extract was considered as potent with 43 - 110 µg/mL range of inhibition on various tumors (Bardaweel *et al.* 2015).

CHEMICAL COMPONENTS OF THE PLANT EXTRACTS AND THEIR FUNCTIONS

The aerial parts of *G. coronaria* were known to contain flavonoids and polyphenolic compounds that are responsible to help the plant to face biotic and abiotic stress (Wan *et al.,* 2017). In the preliminary study by Chuda *et al.* (1998), 3-5-di-O-caffeoyl-4-succinyl quinic acid, chlorogenic acid, and 3,5-di-O-caffeoylquinic were successfully extracted from the aerial parts of *G. coronaria*. While based on the study by Wan *et al.* (2017) on the ethanolic extract of *G. coronaria* aerial parts, more structures of caffeoylquinic acid was revealed for the first time, which include 3-O-caffeoylquinic acid, 4-O-caffeoylquinic acid, 3,4-di-O-caffeoylquinic acid, 1,5-di-O-caffeoylquinic acid, and 4,5-di-O-caffeoylquinic acid.

Immunomodulatory

Study by Attard and Cuschieri (2009) showed the difference between ethanol and chloroform extracts of *G. coronaria* towards their immunomodulatory activity. By using WST-1 tetrazolium test, the chloroform extract of *G. coronaria* had IC_{50}/SC_{50} (the half-maximal inhibitory/modulatory concentration) of 17.677 ± 0.830 µg/ml, while the ethanolic extract had IC_{50}/SC_{50} of 27.794 ± 5.465 µg/ml. The difference might be attributed to the different constituents that present in the extracts, in which the chloroform extract contained protein, terpenoids, and flavonoids, while the ethanolic extract contained protein, terpenoids and flavonoids with the addition of alkaloid content. However, it could not be concluded whether it has immunosuppressive or immunomodulatory effects due to the possibility of both (Attard and Cuschieri, 2009).

Antimicrobial

Based on the study by Ivaschenko (2017), the ethanolic extract of *G.coronaria* exerted an antimicrobial effect against Gram-positive bacteria, but not against Gram-negative bacteria such as *E. coli* or *P. aeruginosa*. Meanwhile, its fungicidal effect was only found effective against *C. albicans*. These 2 effects were suggested to be strongly correlated with the essential oil and phenol content in the plant (Ivashchenko, 2017).

Anti Nematicidal

The aqueous extract of *G. coronaria* was reported to inhibit the activity of root-knot nematodes during the egg masses, separated eggs, or J2 life stage (Bar-Eyal *et al.*, 2006). The same author stated that the nematicidal activity of root-knot nematodes corresponded to the generation of singlet oxygen which involves photoactivation of α-terthienyl. *Meloidogyne incognita* and *M. javanica* were used as root-knot nematodes in that study to evaluate the anti nematicidal activity of *G. coronaria* aqueous extract. The study stated that the *G. coronaria* aqueous extract was able to inhibit the activity of nematode control significantly. It was also found that the low molecular weight extract in acidic condition led to the more effective inhibition of the root-knot nematodes. The study also found that *G. coronaria* aqueous extract demonstrated a nematostatic activity towards other plant-parasitic nematodes, while showing no effect on beneficial nematodes. According to the study, the effect of the aqueous extract of *G. coronaria* towards the root-knot nematodes was considered to be irreversible.

Anti-cholesterol

Heterocyclic compounds extracted from the *G. coronaria* L. with MeOH and partitioned with EtOAc, n-BuOH, and water were tested in order to evaluate the inhibition properties of hACAT-1 and hACAT-2, and LDL-oxidation activity (Song *et al*., 2008). hACAT is an allosteric enzyme which involves the esterification of cholesterol, facilitates intracellular storage, and intercellular circulation (Song *et al.,* 2008). The study stated that 5,5'-dibutoxy-2,2'-bifuran from EtOAc and n-BuOH fractions, which was obtained as a yellow amorphous powder, was able to inhibit the activity of hACAT-1 and hACAT-2. This inhibition later would reduce the rate of cholesterol esterification and the development of foam cells, thereby preventing atherosclerosis. However, the inhibitory rate was lower compared to the oleic acid anilide as the positive control. Nevertheless, the relative paucity of naturally occurring hACAT-1 and hACAT-2 by 5,5'-dibutoxy-2,2'-bifuran are worth further studies. According to the same study, methyl trans-ferulate from EtOAc and n-BuOH fractions was also able to inhibit the LDL antioxidant activity. It was evident that 5,5'-dibutoxy-2,2'-bifuran and methyl trans-ferulate were effective to treat hypercholesterolemia and atherosclerosis.

Anti-angiogenesis

Campesterol is the most common sterol that is contained in *G. coronaria* (Choi *et al.,* 2007). The study stated that this compound was isolated from the extract of the aerial parts of the plant and has been proven to have antiangiogenic activity. Theoretically, the campesterol works by interfering the endothelial cell proliferation, migration, or tube formation that occurs in bFGF (basic fibroblast growth factor)-stimulated HUVECs (human umbilical vein endothelial cells). Five campesterol solutions at concentrations of 10 µg/mL, 20 µg/mL, 30 µg/mL, 40 µg/mL, and 50 µg/mL were tested to the bFGF-stimulated HUVECs. The study stated that campesterol at concentration of 10 µg/mL and 20 µg/mL exhibited weak toxicity against HUVECs, meanwhile, all of the concentrated campesterol were able to inhibit the bFGF-induced proliferation of HUVEC. Therefore, pathological angiogenesis was not able to be regulated. Moreover, campesterol significantly suppressed the capillary tube formation and inhibited the development of vascularization in CAM which can lead to angiogenesis. The study concluded that campesterol might inhibit the differentiation of the HUVECs and disrupt the development of new blood vessels.

COMMON USAGE IN SOME COUNTRIES

G. coronaria has been widely used in many countries, either as the whole plant, plant parts, essential oil, or as extracts, for a lot of therapeutic benefits (Ivashchenko *et al.*, 2019). The therapeutic effects include hepatoprotective, antioxidant, anti-angiogenic, antitumoral, nematocidal, insecticidal, and antimicrobial activity, which were attributed to the presence of beta-carotene, vitamin C, tannin, calcium, phosphorus, etc. Moreover, the same author also reported that in Asia, especially China, Korea, Japan, and India, this plant has been used as a dietary food product.

In China, this plant is often used to treat syphilis, gonorrhoea, chronic constipation, for metabolism normalization, and also works as a stomachic mediation and expectorant (Ivashchenko, 2017). According to this report, the Japanese use this plant as a medicine to prevent cancer and treat headaches. In addition, it can also be used to treat eye diseases, ears ringing, alcoholism, cardiovascular disease, swamp fever, kidney stone disease, radiation sickness, rheumatism, and hypertension. Ivashchenko (2017) also stated that this plant showed an activation of the immune system, antioxidative, hepatoprotective, antitumoral, insecticidal, nematocidal, and antimicrobial effects.

It is also worth noting that certain wild plants, including *G. coronaria*, are, for generations and regardless of region, widely used in cuisine, dyes, medicine, and ornamentals. These plants are also used as ingredients in certain dishes and are of economic importance to local people who mainly rely on said commodities (Guzelsoy *et al.*, 2017).

In addition, it has been reported that *G. coronaria* L. can be a good precursor in the preparation of activated carbon for heavy carbon removal, due to its availability and its physicochemical characteristic (Tounsadi *et al.*, 2016). Heavy metals are a common problem in the area of environmental pollution (Abbas *et al.,* 2018). Most metals are mobile in aqueous systems and non-biodegradable, which can cause disorders and diseases if not removed accordingly. Therefore, various treatments have been conducted for the removal of the toxic metal ions from the water, such as precipitation, ion exchange, membrane filtration, electrocoagulation, electrochemical treatment, adsorption, and activated carbon (Azimi *et al.*, 2017). According to Tounsadi *et al.* (2016), the activated carbon obtained from *G. coronaria* L. was able to remove heavy metals such as cadmium ion and cobalt from aqueous solution. According to that study, the best removal for both cobalt and cadmium could be attained at a carbonization temperature of 600°C in one hour with an impregnation ratio of 1.5 g/g.

According to Zollinger (2003), a major concern associated with the use of dyes in industrial settings is their ability to contaminate not only the soil in the facility where dyes are used in the production process but also the water bodies (e.g. canals, ponds) that are situated near the said facility. The usage of dyes could contaminate the environment because some dyes, especially the organic ones, possess carcinogenicity, toxicity, and mutagenicity, which could pose serious pollution problems (Barka *et al.*, 2016). In the search for natural alternatives on dye removal from aqueous solutions, Tounsadi *et al.* (2016) reported the dye-absorbing activity of *G. coronaria* against methylene blue and malachite green, both dyes of environmental concern. Although little to no influence on biosorption yield was exerted by the environmental temperature, higher pH levels significantly improved the yield. Interestingly, according to the study, more of methylene blue was absorbed by the plant compared to malachite green.

CONCLUSION

Plant material of *Glebionis coronaria* presented various nutritional and pharmacological effects, thereby finding a wide use in cuisine and traditional medicine. The plant in its entirety is rich in tannins, vitamins, carbohydrates and calcium, thereby making it eligible as a dietary food and a medicinal herb. Furthermore, not only its essential oil exhibited antimicrobial, antifungal, insecticidal, and antioxidant activity due to the presence of camphor, mono- and sesquiterpenoids, flavonoids, and quinic acids, plant extracts of *G. coronaria* exhibited antifungal, cholesterol-lowering (attributed to 5,5'-dibutoxy-2,2'-bifuran), immunomodulatory, nematicidal (attributed to α-terthienyl), antiangiogenic (attributed to campesterol), and anti-cancer activity. The plant can also be used as a natural alternative for the removal of soil contaminants. It is suggested that in order to unravel the pharmacokinetics of the plant extract and the essential oil of *G. coronaria*, a suitable subject-testing method to obtain necessary data should be pursued.

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