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Review Article

Phytochemistry, Traditional Uses and Pharmacological Properties of the Genus Opopanax W.D.J. Koch: A Mini-Review

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Abstract

The genus *Opopanax* W.D.J. Koch is a member of the Apiaceae family, distributed throughout the Mediterranean region and comprises only three recognized and well-defined species, *O. chironium* (L.) W.D.J. Koch, *O. hispidus* (Friv.) Griseb. and *O. persicus* Boiss. The species of this genus with yellow flowers are well-known in traditional medicine and consumed as food. This review critically appraises published literature on the phytochemistry, traditional usages, and pharmacological activities of the genus *Opopanax*. In addition, it provides evidence to suggest that the plants from this genus have potential phytotherapeutic applications. Previous phytochemical and bioactivity studies revealed that the genus *Opopanax* predominantly produces coumarins, diterpenes, phenolics, and phthalides, and possesses various biological and pharmacological properties, including anticancer, antioxidant and antimicrobial activities. The phytochemical profile and pharmacological activities of the genus *Opopanax* could be useful for further study and might find additional medicinal applications in evidence-based phytotherapy.

Introduction

The term "Opopanax," referring to the genus *Opopanax* W.D.J. Koch, evokes confusion in pharmacognosy due to the existence of three different products with the same name, which are in use in the perfumery, as a commercially available bitter medicinal product and as a gum resin. A gum resin obtained from *Commiphora erytraea* var. *glabrescens* Engler, an endemic tree to the Horn of Africa,[1,2] is used in the perfumery industry as "opopanax," which should not be confused with the genus *Opopanax*. The "bursa-opopanax," or "bisabol-myrrh," is a commercially available opopanax, because "umba-opopanax," a bitter medicinal product, is not available in the market as a commercial product.[3] This opoponax does not have a sweet burning smell like that of *Opopanax persicus* Boiss. of Persian origin.[1] The ambiguous definition of ancient writers makes it impossible to define the exact source of the so-called "true opopanax." On the other hand, "Opopanax gum resin" was mentioned in the Greek and Latin scientific articles in medicine, which was probably obtained from various plants from the family Apiaceae (*alt.* Umbelliferae) such as *Ferula*, *Peucedanum*, *Laserpitium,* and *Heracleum,*[4] besides *Opopanax chironium* (L.) W.D.J. Koch and *Opopanax hispidum* (Friv.) Griseb. However, the oldest literature describes the term "opopanax" as "all-healing juice",[3] with specific medicinal properties.

The genus *Opopanax* W.D.J. Koch belongs to the Apiaceae family and mainly grows in the temperate regions. The Apiaceae family is known as the carrot or parsley family and represents around 450 genera and more than 3700 species worldwide.[5,6] It is one of the most prominent plant families in the world, representing many genera and a rich source of pharmacologically active secondary metabolites, with high economic and medicinal values.[5-8] The famous members of this family are *Anethum graveolens* (dill), *Anthriscus cerefolium* (chervil), *Angelica spp.* (angelica), *Apium graveolence* (celery), *Carum carvi* (caraway), *Coriandrum sativum* (coriander), *Cuminum cyminum* (cumin), *Foeniculum vulgare* (fennel), *Ferula gummosa* (galbanum) and *Pimpinella anisum* (anise), well-known vegetables and/or spices. The species of this family generally have a characteristic pungent or aromatic odor due to the presence of essential oil/oleoresin.[9,10]

The genus *Opopanax* consists of three aromatic plant species. These are *Opopanax hispidus* (Friv.) Griseb, *O. chironium* (L.) W.D.J. Koch and *O. persicus* Boiss., distributed throughout the Mediterranean, and Central Asia (Iran, Afghanistan, western Pakistan, northern Iraq,

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Azerbaijan, and Turkmenistan).[11,12] In the *Flora of Turkey*, it is also represented by three species as mentioned above: *O. chironium* (L.) W.D.J. Koch (Syn. *Laserpitium chromium* L.); *O. hispidus* (Friv.) Griseb [Syn. *Pastinaca opopanax* L., *Ferula hispida* Friv., *Pastinaca hispida* (Friv.) Fenzl, *Opopanax orientale* Boiss.] and *O. persicus* Boiss. (Syn. *Opopanax armeniacum* Bordz.);[13] the characteristics of the genus and the species are well described there. The genus is specifically characterized for the presence of vittae on the dorsal and commissural surfaces of its fruits[11,14] containing essential oils as aromatic plants. On the other hand, *O. hispidus* is a perennial plant, up to 300 cm tall, and has lobes generally 2–4 cm ovate to lanceolate with hispid (like the rhachis). The schizocarp fruit is broad and thin-edged, broadly elliptical. The species is widely distributed in the South of Balkan Peninsula, Aegean Region, South Italy, and Sicilia.[13,15] The other species, *O. chironium,* is a large indigenous plant of the Western Mediterranean zone.[16] Dioscorides described *O. chironium* from post-Linnaean scholars,[17] recorded as a perennial plant with 1-3 m stems,[13] and registered as an expectorant and antispasmodic used in folk medicine.[18] *O. persicus* differs from *O. hispidus* in its glabrous leaf lamina and shorter narrowly elliptic fruit.[13] In addition to the above three accepted species, there are also a few other "unresolved" species included in the genus *Opopanax*, *e.g., O. armeniacus* Bordz., *O. armenus* Fisch. & C. A. Mey. ex Bordz, *O. chironius* Guss., *O. glabrus* Bernh., *O. hispidium* Griseb., *Opopanax horidus* Miq. Ex Dippel, O. *orientalis* Boiss., *O. siculus* A. Huet ex Nyman and *O. syriacus* Boiss.[19] Most recently, although a new species, *O. bulgaricus* Velen. has been cited by the European Environmental Agency, too little information is available about this species to consider it as a real species of this genus. The coverage of this review is confined to well-defined and well-recognised species of the genus *Opopanax* species, which are used effectively in traditional medicine. This review will also provide useful information for researchers who want to work on these species in the future. Therefore, an extensive literature survey was carried out using various electronic databases, *e.g.,* Web of Knowledge, Science Direct, Medline/PubMed, Scopus, Scifinder, Embase, and Google Scholar. This review appraises published literature on the phytochemistry, traditional uses, and pharmacological activities, and provides evidence to suggest that the plants from this genus have potential phytotherapeutic applications.

Traditional Usage

Systematic literature research has demonstrated the multiple uses of the genus *Opopanax* in traditional medicine, as shown in Table 1. For example; the stem, leaves, and inflorescence of *O. hispidus* have been used as an antiseptic in Iranian folk medicine.[9] In Turkey, this species is locally known as "Kekire" in Erzurum in the Eastern side of Turkey;[20] "Çördük, Çörtük" in Isparta (Eğirdir)/ Turkey;[21,22] "Kaymecik, Gaymecik" in Madra mountain (Balikesir/Izmir/Turkey);[23] and "Kaymaklık" in a rural village on Kazdağı (Mount Ida).[24,25] This plant is known by many other different names such as "çördük otu, çörtlük otu, halız, heliz, kaymak otu, kaymaklık, kekire, kirkora zar, mayasıl otu, sarı çiçek, or sarı ot"; in many localities of Turkey.[26] Some of the other plants are also called as çördük in Turkey, such as *Pyrus* sp., *Echinophora* sp., sometimes this name has been given as a village name.

The Turkish folkloric medicine describes a wide variety of applications of this species as both medicine and food.[23] For example, the fresh stems by eating are used to treat infertility in women.[20] The leaves in powder form are taken to cure hemorrhoids in internal use, 1-2 times a day.[21,22] The plant is also recorded in a plant list for the treatment of

Table 1. Traditional uses of *Opopanax* species.

Species	Local name	Using part	Usage and Purpose	Locality	Ref.
O. hispidus	-	Stem, leaves, inflorescence	Antiseptic	Iran	9
O. hispidus	Kekire	Fresh plant	Food (Pickle)	Turkey/Erzurum/ Muğla/Malatya	20, 26
O. hispidus	Çördük, Çörtük	Fresh stems,leaves as a decoction or powder	Infertility in women	Turkey/Isparta	21, 22
O. hispidus	-	-	Haemorrhoid	Turkey/Çanakkale	27
O. hispidus	Kaymecik, Gaymecik	-	Medicine and food	Turkey/Balıkesir	23
O. hispidus	Kaymaklik	-	Food	Turkey/Kazdağları	24, 25
O. hispidus	-	Young shoots, leaves, young stems	Cooked with milk in or mixed with yogurt	Turkey/Muğla	26
O. hispidus	Kaymak otu, cördük otu, cörtlük otu, halız, heliz, kaymak otu, kaymaklık, kekire, kirkora zar, mayasıl otu, sarı çiçek, or sarı ot	-	Vegetable and tea	Turkey/Aegean Region	28, 29
O. chironium	Jāvshir	Gum (resinoid part)	Epilepsy (children)	Iran	30
O. chironium		-	Antipyretic	-	31
O. chironium		-	Sensory neuropathy (tablet form)	Persian Canon of Medicine	32

hemorrhoids in the Canakkale district.[27]

Inhabitants of Kazdağı (Mount Ida) consume this plant during the winter as a custom. This information was compiled from the answers received by asking various questions to people living in the region.[25] Another report that the young shoots and leaves are cooked with milk; young leaves are cooked or mixed with yogurt; sometimes, young shoots have also been prepared as a meal (Muğla). The young stems of the plant have been consumed freshly after peeling in Erzurum, Malatya, and Muğla, and/or used for the preparation of pickle in Malatya.[26] In almost all the Aegean region, *O. hispidus* (Kaymak otu) is one of the wild edible plants and traditionally used as a vegetable and a tea.[28,29] It is apparent that this plant is utilized in many localities in Turkey as a food and spice.[26]

On the other hand, *Opopanax chironium* has been known for its medicinal properties for a long time.[33] For instance, *O. chironium,* an ancient Iranian herb, found in the Iranian Traditional Medicine references such as Al-Abniah'an Haqaeq al Adwia, Canon, Al-Hawi, Makhzan ul-Adwia, and Tuhfat al-Mu'minin, has been prescribed to treat epilepsy in children.[31] Dioscorides also mentioned that this plant could be used as an antipyretic.[32] Moreover, this species is one of the main ingredients of "Habb al-Sheitaraj," a tablet, used for sensory neuropathy. In addition, in the same manner, it is also the main ingredients of "Ayarej-e Jalinus," a medicinal substance mixed with honey or another sweet substance used for the same purposes in the Persian Canon of Medicine.[33] Injured branches and enlarged roots cause exudation of yellowish latex with a pleasant and permanent licorice odor. Because of its poisonous properties, animals keep away from this plant.[16] Only one old literature has been mentioned that the plant is poisonous addressed resinous part, and it is used traditionally in the healing of many diseases in the other references. As a result, it is evident that the genus *Opopanax* is an important edible plant and used as vegetable and tea. In some literature, the used parts of the plant are not fully specified, and how these parts are used is not emphasized. However, in many articles, it is clear that the aerial parts of the plants have been used for many applications.[25,26]

Phytochemistry

When the literature is examined, it is frequently stated that *Opopanax* species contain coumarins predominantly. Besides, the genus comprises phthalates, diterpenes, and simple phenolics (Table 2). Previously, there is also a compilation of information on the presence of similar compounds belonging to some species of the Apiaceae family.[5] In the previous studies, three main species were emphasized, and no other species were found. The phytochemistry of the *Opopanax* species is discussed under the following subsections.

Opopanax chironium (L.) W.D.J. Koch

Opopanax chironium (Syn: *Pastinaca opopanax* L. and *Ferula opopanax* Spreng.) is a rich source of coumarins,[34] mainly furanocoumarins, and simple prenylated coumarins. Furthermore, a series of C-17 acetylenes,[16] and various phthalides (Figure 1) including *Z*-butylidenephthalide (**1**), butylphthalide (**2**), cnidilide (**3**), *Z*-ligustilide (**4**), senkyunolide A (**5**) and senkyunolide I (**6**)**,** were identified from the petroleum ether and diethyl ether extracts of the roots of this plant.[35,36] These compounds constituted a rather unusual phytochemical profile for any member of the Peucedaneae tribe of the Apiaceae.

In addition to the presence of coumarins such as gaudichaudin (**7**), columbianadin (**8**), peucedanin (**9**), officinalin isobutyrate (**10**) (Figure 2), an irregular diterpene skeleton called as peucelinenoxide acetate

Table 2. Phytochemical composition of the *Opopanax* species.

Species	Phythalides	Ref.	Coumarins	Ref.
O. chironium	*Z*-butylidenephthalide (**1**) Butylphthalide (**2**) Cnidilide (**3**) *Z*-ligustilide (**4**) Senkyunolide A (**5**) Senkyunolide I (**6**)	35, 36	Gaudichaudin (**7**) Columbianadin (**8**) Peucedanin (**9**) Officinalin isobutyrate (**10**) Umbelliprenin (**11**) Imperatorin (**12**) Xanthotoxin (**13**) Bergapten (**14**) Heraclenin (**15**) Heraclenol (**16**) Suberosin (**17**) Marmesin (**18**) Dehydromarmesin methyl ether (**19**) Prantschimgin (**20**) Smirniorin (**21**).	4, 18, 37
O. hispidus	-	-	4'-Acetyl-3'-senecioyl-3'-hydroxymarmesin (**22**) 4'-Acetyl-3'-isobutyryloxy-marmesin (**23**) (+)-3'-Hydroxyprantschimgin (**24**) Smirniorin (**19**)[4] Peucedanin (**8**) Officinalin (**25**) Oreoselon (**26**)	4, 8, 28, 39, 40, 41, 42

(Figure 3) was also obtained from an ethereal extract of the roots and seeds of *O. chironium*.[18,37] The absolute stereochemistry of the compound was not determined, and irregular diterpene scaffolds are extremely rated and seem to be rather confined in the family Apiaceae. Coniferyl esters of long-chain acyl groups such as palmitoyl (C16:0), stearoyl (C18:0), and oleoyl (C18:1) were also found in the *O. chironium*.[38] The constituents of various collections of *O. chironium* growing in Sardinia and Sicily were investigated, and surprisingly it was observed that none of the groups had any phthalides, but had large amounts of coumarins with significant qualitative and quantitative differences among collections. However, among the samples collected from two different places, there were many coumarins in common.

It can be considered as a good example that the same species growing in various areas show chemical diversity. Furthermore, this may be chemotaxonomically important. It should be noted here that unlike the previous work, the *O. chironium* roots were extracted here with acetone, which might have preferentially extracted furano- and dihydrofurano-coumarins avoiding phthalides. The acetone extract of the roots of *O. chironium* from the Sardinian collection was fractionated by column chromatography

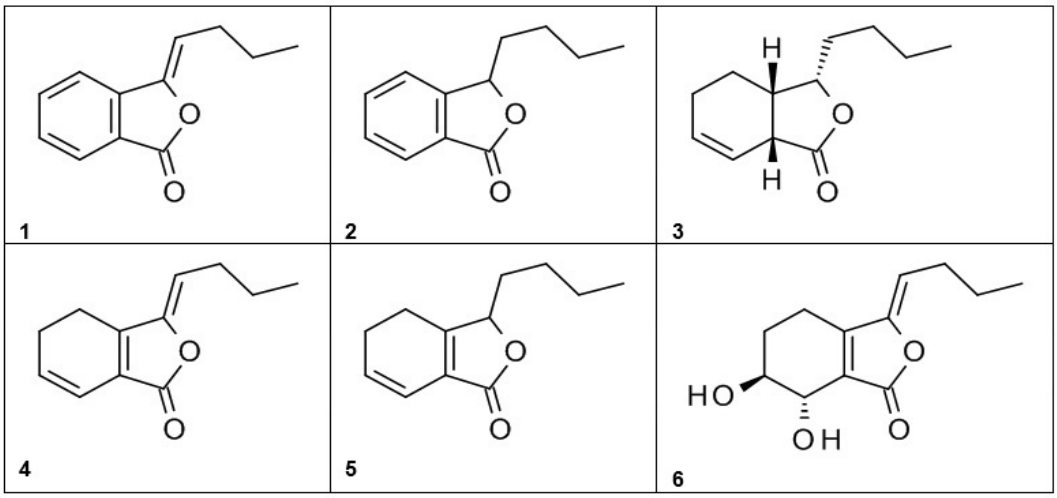

Figure 1. Phthalides from *Opopanax chironium*.

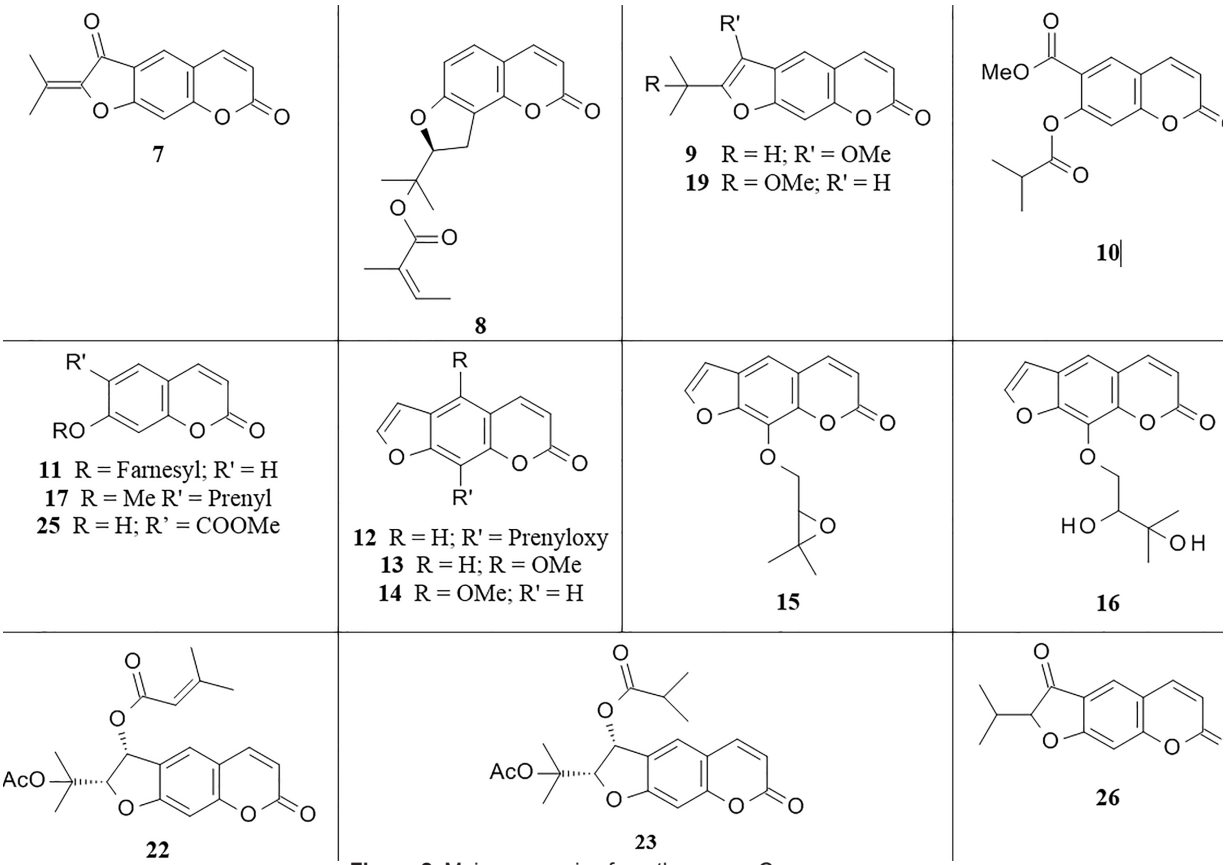

Figure 2. Major coumarins from the genus *Opopanax*.

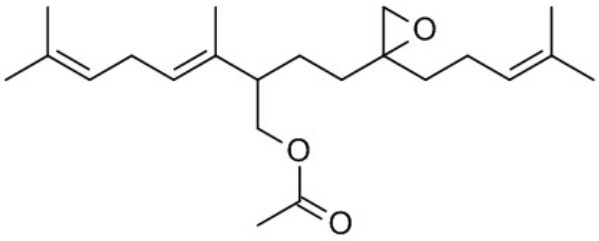

Figure 3. An unusual diterpene, peucelinenoxide acetate, from *Opopanax chironium.*

on silica gel to obtain umbelliprenin (**11**) (0.020%), imperatorin (**12**) (0.47%), a mixture of xanthotoxin (**13**) and bergapten (**14**) (3.4%), heraclenin (**15**) (0.40%) and heraclenol (**16**) (0.042%), while a prenylated coumarin, suberosin (**17**)**,** was found in the fruits (Figure 2). It was noticed that the Sicilian *O. chironium* (roots and seeds) possessed large amounts of coumarin derivatives, including the major constituent peucedanin (**9**) **(**0.56%), along with four other coumarins, marmesin (**18**)**,** dehydromarmesin methyl ether (**19**), prantschimgin (**20**) and smirniorin (**21**).[4] In addition to coumarins, the Sicilian collection of this plant afforded a mixture of saturated long-chain coniferates, including the main component coniferyl stearate.

Moreover, *O. chironium* produces (yield up to 16 L/ha) essential oil, originated from subalpine *Abies cephal-lonica* forests of mountain Parnassus at an altitude of 1450 m. In a study, whole fresh parts of the species were subjected to a Clevenger-type apparatus using a Microwave Accelerated Reaction System to obtain the essential oil. The components which are used in the cosmetic industry (in perfumes) and in plastic industry, called *E,E*-farnesyl acetate almost 20% of the total weight, and another ester, the 1-bornylacetate (a colourless liquid with a piny, camphor-like odour) were detected and obtained from the well-known pharmaceutical plant *O. chironium*.[30]

Opopanax hispidus (Friv.) Griseb.

The chloroform extract of the *O. hispidus* aerial parts afforded coumarins such as 4'-acetyl-3'-senecioyl-3'-hydroxymarmesin (**22**), 4'-acetyl-3'-isobutyryloxy-marmesin (**23**)[4], (+)-3'-hydroxyprantschimgin (**24**),[39] smirniorin (**19**),[40] peucedanin (**8**), officinalin (**25**)[41] and oreoselon (**26**) (Figure 2).[4,8,42] In addition to coumarins, flavonoids were also found in *O. hispidus*, based on qualitative analysis (121.18 mg Res/g extract).[28] To the best of our knowledge, there is no individual flavonoid, isolated and identified from this species. According to the information obtained from the unpublished results; coumarins have not been found in the aerial parts dichloromethane extract of the plant, which is collected from the southwest part of Turkey.

The essential oil from the fruits of *O. hispidus* from Serbian origin was obtained by hydro-distillation with a yield of 0.015% and analyzed by GC/FID and GC/MS, resulting in the identification of 79 compounds, making up over 96% of the oil. The labdane diterpenes (49.1%), acetate derivatives of diterpenes (22.2%), and sesquiterpenes (7.2%) were present in large amounts in the essential oil from the fruits of *O. hispidus;* torulosol (48.8%), geranyl geraniol acetate (17.9%), incensole acetate (4.3%) and germacrene D (4.0%) were the major components (Figure 4).[43]

Opopanax persicus Boiss.

Only a very limited phytochemical study has ever been carried out on this species. The phytochemical investigation on the dichloromethane extract of the aerial parts of *O. persicus* Boiss., an endemic species growing in some parts of Turkey, in Iran, Iraq, and

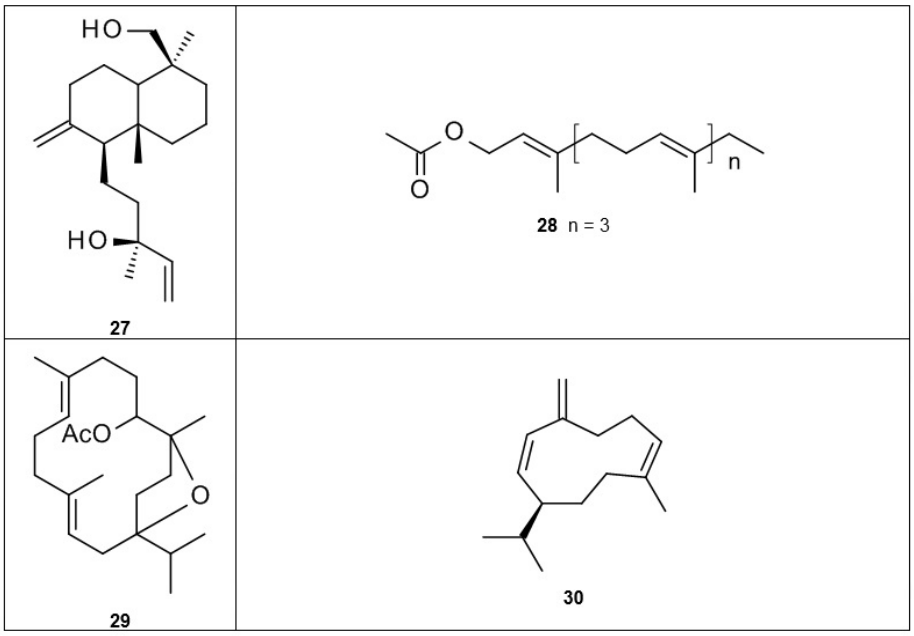

Figure 4. The major constituents from the essential oil of *Opopanax hispidus.*

Table 3. Pharmacological properties of *Opopanax* species.

Pharmacological Activities	Species	Compounds/Extracts	Outcomes	Ref.
Anticancer activity	*O. chironium*	Imperatorin **(12)** Heraclenin **(15)**	Induction of apoptosis in Jurkat leukemia cells	4
		Psoralen derivatives	Photodynamic therapy	4
Antimicrobial activity	*O. hispidus*	AcOEt extract	Fruits MIC/MBC=3.125/6.25 mg/mL Inflorescence MIC/MBC=6.25 mg/mL *Listeria monocytogenes* *Escherichia coli*	44
	O. persicus	Angular and linear dihydro-pyrano-coumarins	IC_{50}= 3.6 to 6.9 µg/mL *Plasmodium falciparum* K1 strain *Trypanosoma brucei rhodesiense*	19
Antioxidant activity	*O. hispidus*	MeOH extract AcOEt extract	MeOH extract: IC_{50}=1.157 mg/mL Inflorescence AcOEt extract IC_{50}=3.167 mg/mL	44
Psychoactivity	*O. hispidus*	Incensole **(29)**	Elicit by activating TRPV3 channel in the mice brains	45
Neuroprotective activity	*O. hispidus*	Incensole **(29)**	-	46
CNS effects (Paralysis)	*O. persicus*	Aqueous extract	-	47

Transcaucasia, has been performed. The dichloromethane extract of this species has been revealed the presence of many different types of compounds, mainly linear and angular dihydropyranocoumarins, via many types of chromatographic methods, and this was published as a conference abstract, not a full paper.[19]

Pharmacological Properties

Only a few studies on *Opopanax* genus regarding anticancer, antioxidant, antimalarial, and antimicrobial activity have ever been carried out (Table 3), despite its traditional medicinal uses in the folk medicines. However, in this section, all previously performed pharmacological studies on the genus *Opopanax* species are discussed.

Anticancer Activity

The high content of furanocoumarins, mainly psoralen derivatives, is believed to be responsible for the plant phototoxicity. However, the furanocoumarins, in the Sardinian chemo-type of *O. chironium,* imperatorin (**12**), and heraclenin (**15**), obtained from the acetone extract of the Sardinian collection of this plant, could induce apoptosis in Jurkat leukemia cells, suggesting the possible development of selectively toxic drug to treat cancers. Additionally, it was recommended that this Sardinian chemo-type could be a promising new source of psoralen derivatives for photodynamic therapy.[4]

Antimicrobial activity-Antioxidant activity

The antimicrobial activity of the ethyl acetate extracts of the fruits (MIC/MBC=3.125/6.25 mg/mL) and inflorescence (MIC/MBC=6.25 mg/mL) of *O. hispidus* was evident against *Listeria monocytogenes* and *Escherichia coli*. The methanolic extract had stronger antioxidant activity than that of the ethyl acetate extract, tested by the DPPH (methanol extract IC_{50}=1.157 mg/mL) and (ethyl acetate extract IC_{50}=3.167 mg/mL from the inflorescence) and the ABTS assay. The highest value of total phenolics (89.95±0.005 mg GA/g) and flavonoids (24.06±0.004 mg Qu/g) was measured in inflorescence extracts might have some importance as a therapeutic agent on prevention or deceleration of the oxidative stress-related degenerative diseases.[44] Incensole (**29**), one of the major components of the essential oil of *O. hispidus*, which is also present in *Boswellia* resin, was found to elicit psychoactivity by activating TRPV3 channel in the mice brains.[45] The neuroprotective property of this compound was also reported in the same year.[46] Some of the angular and linear dihydropyranocoumarins, isolated from *O. persicus*, showed moderate activity against *Plasmodium falciparum* K1 strain and *Trypanosoma brucei rhodesiense* (IC_{50}= 3.6 to 6.9 µg/mL) selectivity indices (SI) have been found on L-6 cells of 5.7 to 25, respectively.[19]

Miscellaneous Usages

Besides, the nasal formulations described in traditional Persian pharmacopeia categorized based on dosage forms, and diseases, indicated the use of the aqueous extract of *O. persicus* for different *Central nervous system* (CNS) disorders including Paralysis.[47] Despite its traditional use for haemorrhoids and infertility in women, there are no studies found on this subject. On the other hand, an ester, 1-bornylacetate isolated from *O. chironium* is used primarily either as a scent in perfumes manufacturing or as a plasticizer.[30] It is important to perform the studies on this topic and to investigate whether it will support traditional use. In light of this review, it is hoped that such a study can be organized in the near future.

Conclusion

Based on the available literature, albeit limited, the genus

Opopanax has emerged as a good source for several bioactive coumarins and phthalides showing potential anticancer, antioxidant, antimalarial and antimicrobial activities, justifying some of its traditional medicinal and culinary uses against various human ailments. Moreover, some of the species can be good sources for psoralens on photodynamic therapy in the industrial platform. The essential oils and their components of the *Opopanax* were also reported as a scent in perfumes manufacturing or as a plasticizer. Although the *Opopanax* has a good reputation for traditional, medicinal, and culinary uses, further studies are much needed. Thus, this review will provide the basis for future phytochemical and pharmacological studies.

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Conflict of Interests

There is no conflict of interest reported by the authors.

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