Pharmacological Role of *Ostericum koreanum*: A Short Viewpoint

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Abstract

*Ostericum koreanum* Maxim., a perennial medicinal plant native to Asian countries, is traditionally exploited in Korean Oriental and Chinese Herbal Medicine. It has been used in the treatment of neuralgia, respiratory problems, and joint pain due to its rich content of phytochemicals. Therefore, the significant role of compounds present in *O. koreanum* should not be overlooked to explore and develop drugs against diseases. The purpose of this review is to provide a reference for researchers and to describe the phytochemical constituents and pharmacological activity of *O. koreanum*. In this mini review, we have collected the data from 1980 to 2020 regarding the phytochemicals present and pharmacological activities of this plant. Our findings indicated that this plant possesses a rich source of phytochemicals that have significant pharmacological activities, such as anti-microbial, anti-inflammatory, anti-pyretic, anti-influenza, anti-cancer, and neuroprotective. These phytochemicals have promising pharmacological activity which should be further explored for the treatment of various diseases.

Keywords

medicinal plant, herbal medicine, phytochemicals, umbelliferae, pharmacological activity

Introduction

Historical records revealed that ancient civilizations had mastered the ability to use different plant parts such as stems, roots, leaves, and flowers to prepare therapeutic medication. Herbal medicines contain a wide variety of bioactive compounds which have been utilized against a wide range of diseases. The data regarding these therapeutic substances have been aggregated and compiled in Traditional Chinese Medicine (TCM). Nowadays, about 90% of the population in Asia and other countries rely upon herbal medicine and its market is expected to increase by more than 50 billion US dollars. In the 21st century, advanced chemical and physical techniques allowed us to obtain several bioactive compounds from medicinal plants.

Traditional Chinese medicine was introduced to Korea in the sixth century. Many substances in Korean herbal medicines have been modified and developed separately from traditional Chinese medicines due to differences in location, climate, culture, and politics. As a result, quality control of active components in herbal extracts is critical in both medical and nutritional applications. The importance of medicinal plants in the lives of most people around the world should not be underestimated. Herbal medicines have a long history in Korean Peninsula and are widely used around the world to prevent and treat human sickness. One of the most important perennial traditional herbal medicine is *Ostericum koreanum*, which belongs to the Umbelliferae family and has been used to cure the common cold, fever, relieve rheumatic articular pains, headaches, and neuralgia (Figure 1). Its features include a pungent and warm sensation. The biological and pharmacological properties of this plant include anti-tumor, anti-bacterial, anti-microbial, anti-inflammatory, antioxidant, acaricidal activity, vasorelaxant effects, and antiasthmatic. *Osterici Radix*,

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the root of *O. koreanum*, is grown in Kangwon Province, Korea, where it is known as “Kanghwal.” The origins of this plant have been portrayed differently in Korean, Chinese, and Japanese pharmacopoeias. The Chinese and Japanese pharmacopoeias only include *Notopterygium incisum* and *N. forbesii* as sources of “Kanghwal”, but the Korean pharmacopoeias also include *Ostericum koreanum*.

*O. koreanum* is known as Kang Bow in South Korea, but also goes by the names of Hogangsaja, Howangsaja, Ganghwa, Gangbori, Ganggol, Gangecheong, Jamgang, and Dokyocho. The plant thrives in cold areas in mountain valleys in Korea. Harvesting takes place between the end of October and the beginning of November. Furthermore, there are two methods for raising this plant in Korea. One is a seeding method known as “Nam-kangwhoal (OK(S))”, while the other is a root splitting method known as “Buk-kangwhoal (OK(N)).” However, this plant has received limited scientific investigation due to its vague taxonomical classification. Therefore, in this mini review, we have compiled the literature from the 1980s to 2021 about *O. koreanum*, including a list of its constituents, and its pharmacological activity in the treatment of various diseases.

**Assessment of Compounds**

An HPLC-UV detection method published by Lee et al. was the simplest and most sensitive approach for the simultaneous identification of four marker chemicals: bisabolangelone (I), oxypeucedanin (2), imperatorin (3) and isoimperatorin (4) (Figure 2) in *O. koreanum*.

**Constituents of Ostericum koreanum and Their Pharmacological Activities**

The constituents of the root and stem of *O. koreanum* are summarized in Table 1. Caffeic acid, aesculin, uracil, cimifugin, and adenosine were identified in the root, and bergapten (5), xanthotoxin (6), hamaudol (7), auraptenol (8) (Figure 3), and a combination of phytosterols in the stem. They also reported for the first time the isolation of hamaudol. Kang et al isolated bisabolangelone (I), an acaricidal constituent, from the methanolic extract of the roots.

Jeon et al extracted essential oil and identified the components using gas chromatography-mass spectrometry (GC-MS). β-Phellandrene (38.1%), α-bisabolol (9.4%), 3-methylphenol (6.7%), α-terpinolene (5.5%), 1-acetoxy-1,2-epoxy cyclohexane (5.0%), 4′-hydroxy-3′-methylaceto phenone (4.8%), isosafrole (4.1%), 2-methyl-3-ethylpentane (3.9%), isopentyl-3-methyl butanoate (3.6%), 2,5-dimethyl-3-hexanol acetate (3.4%), (+)-3-carene (2.8%), limonene (2.3%), tridecanolide (2.3%), 2,5-dimethyl-3-vinyl-1,4-hexadiene (2.1%), α-pine (1.5%) and 4,7-dimethyl-5-decyn-4,7-diol (1.3%) were detected. The essential oil included terpene hydrocarbons, oxygenated terpene hydrocarbons, phenols, alcohols, and aliphatic hydrocarbons.

Another GC-MS study of the essential oil of *O. koreanum* was carried out in 2015. This reported β-phellandrene (38.1%), α-bisabolol (9.4%), m-cresol (6.7%), terpinolene (5.5%), 1-acetoxy-1,2-epoxy cyclohexane (5.0%), 4′-hydroxy-3′-methyl acetophenone (4.8%), 2-methyl-3-ethylpentane (3.9%), isopentyl-3-methyl butanoate (3.6%), 2,5-dimethyl-3-hexanol acetate (3.4%), 3′-dimethyl-13,6-octatriene (2.8%), limonene (2.3%), tridecanolide (2.3%), 2,5-dimethyl-3-vinyl-1,4-hexadiene (2.1%), α-pine (1.5%) and 4,7-dimethyl-5-decyn-4,7-diol (1.3%). Shin used steam distillation and diethyl ether extraction to isolate thirty-four essential oil components from the dried roots, which were identified using GC-MS. The main components of this oil were α-pine (41.1%), p-cresol (18.0%), 4-hydroxy-2-methylacetophenone (7.9%) sabine (7.6%), α-bisabolol (2.0%), p-cymen-8-ol (2.0%), and camphene (1.9%). The variation between the reported results may have been caused by several factors, including plant part used (flower, leaves, root, and stem), the different conditions of the plant material used, the geographical location, climate, and soil type.

From the benzene-soluble and n-butanol-soluble portions of *O. koreanum* root, Kwon et al extracted four furocoumarins (imperatorin, isomperatorin, oxypeucedanin and oxypeucedanin hydrate) and two dihydrofurocoumarin glycosides (marmesin and 4′-O-β-D-glucopyranosyl-3′-hydroxymarmesin). Kang et al isolated oxypeucedanin (2), with *in vitro* activity against human prostate carcinoma DU145 cells. Raza et al isolated and characterized isomperatorin (4) from the ethyl acetate fraction of the roots.

Park et al used the ethyl acetate fraction of *O. koreanum* roots to isolate 11-hydroxy-sec-O-glucosylhamaudol (9), three chromones (sec-O-glucosylhamaudol (10), prim-O-glucosylcimifugin (11) and cimifugin (12)), three coumarins (marmesin (13), oxypeucedanin hydrate (14) and bergapto-O-β-D-glucopyranoside (15)), six phenolic compounds (ligusti phenol (16), 2-methoxy-2-(4′-hydroxyphenyl)-ethanol (17),
Figure 2. The chemical structures of bisabolangelone, oxypeucedanin, imperatorin, isoimperatorin.

Table 1. Constituents of *Ostericum koreanum*.

| No. | Compounds                                      | Part of Plant | Fraction of methanol extract | Classification   |
|-----|-----------------------------------------------|---------------|------------------------------|------------------|
| 1   | Caffeic acid                                  | Root          | n-Butanol                    | Hydroxycinnamic acid |
| 2   | Uricil                                        | Root          | n-Butanol                    | Uricil           |
| 3   | Aesculin                                      | Root          | n-Butanol                    | Coumarin         |
| 4   | Bergapten                                     | Stem          | n-Hexane                     | Coumarin         |
| 5   | Xanthotoxin                                   | Stem          | n-Hexane                     | Coumarin         |
| 6   | Auraptenol                                    | Stem          | n-Hexane                     | Coumarin         |
| 7   | Marmesinin                                    | Root          | Ethyl acetate                | Coumarin         |
| 8   | Oxypeucedanin hydrate                         | Root          | Ethyl acetate                | Coumarin         |
| 9   | Bergaptol-O-β-D-glucopyranoside               | Root          | Ethyl acetate                | Coumarin         |
| 10  | Imperatorin                                   | Root          | Benzene- n-Butanol           | Coumarin         |
| 11  | Isoimperatorin                                | Root          | Benzene- n-Butanol           | Coumarin         |
| 12  | Oxypeucedanin                                 | Root          | Benzene- n-Butanol           | Coumarin         |
| 13  | 4′-O-β-D-Glucopyranosyl-3′-hydroxymarmesin    | Root          | Benzene- n-Butanol           | Coumarin         |
| 14  | Cimifugin                                     | Root          | n-Butanol                    | Chromone         |
| 15  | Hamaudol                                      | Stem          | n-Hexane                     | Chromone         |
| 16  | 11-Hydroxy-sec-O-glucosylhamaudol             | Root          | Ethyl acetate                | Chromone         |
| 17  | sec-O-Glucosylhamaudol                        | Root          | Ethyl acetate                | Chromone         |
| 18  | prim-O-Glucosylcimifugin                      | Root          | Ethyl acetate                | Chromone         |
| 19  | Cimifugin                                     | Root          | Ethyl acetate                | Chromone         |
| 20  | Ligustipheno                                  | Root          | Ethyl acetate                | Phenolic         |
| 21  | 2-Methoxy-2-(4′-hydroxyphenyl)-ethanol        | Root          | Ethyl acetate                | Phenolic         |
| 22  | 4-(2-Hydroxy-vinyl)-2-methoxy-phenol          | Root          | Ethyl acetate                | Phenolic         |
| 23  | 3-Methoxy benzene-1,4-diol                    | Root          | Ethyl acetate                | Phenolic         |
| 24  | 4-(2-Hydroxyvinyl)-benzene-1,2-diol           | Root          | Ethyl acetate                | Phenolic         |
| 25  | Protocatechuic acid                           | Root          | Ethyl acetate                | Phenolic         |
| 26  | 5-Caffeoyquinic acid methyl ester             | Root          | Ethyl acetate                | Quinic acid      |
| 27  | 3,5-Dicaffeoyquinic acid                      | Root          | Ethyl acetate                | Quinic acid      |
| 28  | 4,5-Dicaffeoyquinic acid                      | Root          | Ethyl acetate                | Quinic acid      |
| 29  | Bisabolangelone                               | Root          | n-Hexane                     | Benzo-furan      |
| 30  | Adenosine                                     | Root          | n-Butanol                    | Furan            |
Figure 3. The structures of bergapten, xanthotoxin, auraptenol and hamaudol.

Figure 4. Compounds isolated from EtOAc extract of the roots of *Ostericum koreanum*. 
Table 2. Summary of Pharmacological Activities Showed by *Ostericum koreanum*.

| Part used | Extract    | Dose            | Model                  | Time duration | Results                                                                 | References |
|-----------|------------|-----------------|------------------------|---------------|-------------------------------------------------------------------------|------------|
| Root      | Methanol   | 50.9 µg/cm²     | *D. farina* and *D. pteronyssinus* | 24 h          | Significant acaridical activity (compared to three acaricides such as benzyl benzoate, N,N-diethyl-m-toluamide (DEET), and dibutyl phthalate) | Kang et al. (2006)²² |
| Oil       | —          | 3.09 and 3.31 µg/cm² | *D. farina* and *D. pteronyssinus* | 24 h          | Highly useful as mite control agent for house dust mites or highly useful for protection of humans from allergic diseases | Jeon et al. (2012)²³ |
| Root      | Methanol   | 50 µM           | Inflammatory property of bisabolangelone in RAW 264.7 cells | 24 h          | Strong anti-inflammatory activity (inhibiting LPS-stimulated inflammation-associated gene expression) | Jung et al. (2010)³⁶ |
| Root      | Diethyl-ether | —               | Antibiotic-resistant and antibiotic-susceptible | —             | Significant antibiotic activity (*O. koreanum* oil) against the bacterial strains | Shin (2005)¹² |
| Root      | Methanol   | —               | Antioxidant activity   | —             | Significant DPPH radical scavenging activity superoxide anion radical scavenging activity (4-(2-Hydroxy-vinyl)-benzene1,2-diol) | Park et al. (2007)¹⁴ |
| Root      | Methanol   | 0.516, 2.884, 1.514 mM/g | Antioxidant and free radical scavenging activities | 24 h          | Significant antioxidant activity (based on TEAC, ORAC and DPPH) | Mahesh et al. (2011)³⁷ |
| Root      | Methanol   | —               | Inflammatory mediators in LPS-stimulated RAW264.7 Cells | 24 h          | Anti-inflammatory activity (ethyl acetate fraction) | Kim and Park (2009)³⁸ |
| Root      | Methanol   | 10 to 50 µg/mL  | Inflammatory responses in PMA/ A23187-stimulated mast cells | 24 h          | Anti-inflammatory activity (ethyl acetate fraction) | Seo et al. (2008)³⁹ |
| Root      | Distilled water | 0 to 25 µg/mL  | Lipopolysaccharide [LPS]-induced bone loss in mice | 24 h          | Significant amelioration of bone-destructive diseases | Kim et al. (2015)⁴¹ |
| Root      | Methanol   | 50 and 100 mg/kg| Allergic responses in ovalbumin-induced allergic rhinitis mice | 24 h          | Significant anti-allergic properties, improving rhinitis symptoms | Jung et al. (2011)³² |
| Root      | Water      | 10 and 50 mg/kg | Anti-allergic effect in human mast cell | —             | anti-allergic agents for use in a number of allergic diseases | Jung et al. (2010)⁴³ |
| Root      | Ethanol    | —               | Vasorelaxant activity  | 2 h           | Useful for treating cardiovascular diseases such as hypertension | Lee et al. (2012)⁴⁴ |
| Root      | Ethanol    | 50 and 100 mg/kg| Learning and memory impairments induced by scopolamine | —             | Useful in cognitive impairment treatment, enhancing the cholinergic nervous system | Kim et al. (2011)⁴⁷ |
4-(2-hydroxy-vinyl)-2-methoxy-phenol (18), 3-methoxy benzene-1,4-diol (19), 4-(2-hydroxyvinyl)-benzene-1,2-diol (20) and protocatechuic acid (21) and three quinic acids (5-caffeoylquinic acid methyl ester (22), 3,5-dicaffeoylquinic acid (23) and 4,5-dicaffeoylquinic acid (24)). The structures are shown in Figure 4. All the isolated compounds were tested for antioxidant activity using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and superoxide anion radical scavenging assay systems, and it was discovered that chromosomes containing 11-hydroxy-sec-O-glucosylhamamelide (9) and the coumarins did not have significant antioxidant activity, whereas the phenolics and caffeoylquinic acids did.

In LPS-stimulated RAW264.7 cells, the ethyl acetate fraction of the methanol extract of O. koreanum root inhibited nitric oxide (NO) and prostaglandin E2 (PGE2) production efficiently. It was believed that the extract had anti-inflammatory and therapeutic activities by decreasing the generation of inflammatory mediators in activated macrophages. Park et al. conducted another study on the anti-inflammatory and inhibitory effects of O. koreanum root. They evaluated the down-regulated LPS-induced NO and cytokines production via repressing activation of mitogen-activated protein kinase (MAPKs) and degradation of inhibitory kappa Ba (Iκ-Ba). In 2008, the effects were studied of the ethyl acetate extract of O. koreanum on allergic inflammation in activated human mast cells. The extract showed anti-inflammatory properties by lowering the output of inflammatory mediators in activated mast cells, and that the blockage of the nuclear factor kappa-B (NFκB) route was due to its molecular mechanism. Hee and Young reported LPS-induced NO and PGE2 synthesis produced by the ethanol extract of O. koreanum and concluded that the extract could be used for its analgesic and anti-inflammatory properties.

The effects of O. koreanum root extract on lipopolysaccharide (LPS) induced bone loss in mice were investigated by studying bone structure and the levels of Receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) in serum and bone marrow fluid (BMF). Therefore, for the first time, a link between O. koreanum and bone diseases, particularly osteoporosis, was established, and the extract was shown to have the capacity to ameliorate bone-damaging diseases caused by extreme bone resorption.

O. koreanum root extract showed anti-allergic characteristics, improved rhinitis symptoms, inhibited histamine and IL-4 production in ovalbumin-induced allergic rhinitis mice, and inhibited mast cell degranulation in compound 48/80-stimulated mast cells. The root water extract was tested in a human mast cell line and shown to have anti-allergic properties.

An ethanol extract of O. koreanum root was studied for its mechanism of action and effect on vasorelaxant activity. The effects of the extract on several vasorelaxant and vasoconstriction variables were studied using isolated rat aortic rings. The induction of NO synthesis from l-arginine and NO-cGMP routes was thought to be produced by the vasorelaxant activity of the extract. According to their findings, Osterici Radix may be a useful herbal medicine for the treatment of cardiovascular illnesses such as hypertension.

Fascinating results were obtained on the effect of the ethanolic extract of O. koreanum root on better learning and memory deficits generated by scopolamine in an in vivo and in vitro investigation. Beneficial effects were attributed to boosting the cholinergic nervous system.

**Conclusions and Future Directions**

In this mini review, the therapeutic activity of O. koreanum was highlighted, and essential phytochemicals found in this plant were summarized (Table 2). These phytochemicals play a vital role in providing anti-inflammatory properties through downregulation of inflammatory markers (PGE2, NO, cytokines and interleukins) and inflammatory pathways (NFκB, MAPK) implicated in the inflammation. These phytoconstituents also reduce the growth of pathogenic microorganisms and cancer cells. In addition to these properties, they are recognized as neuroprotective, gastroprotective and cardioprotective. However, there are potential shortfalls which need to be addressed in future studies. The pharmacological activity and phytochemical exploration from other plant components (leaves, flower, stem) are necessary to map and discover new promising compounds for various diseases. To the best of our knowledge, this plant’s pharmacological activity has been explored between 1982 to 2017, but, recently, Ko et al. identified new phytochemicals from the stem of this plant, but their biological activity is unknown yet. The acute toxicity and safety profile of these phytochemicals has not been determined in most of the studies, which is a major setback to introduce them for clinical trials. The anticancer effects of this plant have only been researched in one study, but its activity against different cancer cells should be investigated further.

**Acknowledgments**

This work was supported by the National Research Foundation of Korea (NRF) funded by the Korean Government (MEST) (2020R1I1A3069699).

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Research Foundation of Korea (grant number 2020R111A3069699).

Ethical Approval
Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent
Not applicable, because this article does not contain any studies with human or animal subjects.

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Trial Registration
Not applicable, because this article does not contain any clinical trials.

Supplemental Material
Supplemental material for this article is available online.

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