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MIN-REVIEW ARTICLE

Bioactive Furanocoumarin 'Alloimperatorin': Therapeutic Importance and Pharmacological Activities in Medicine

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Abstract:

Background:

Plants and their derived phytochemicals commonly called secondary metabolites have been used in medicine as a good source of medicine for the treatment of numerous kinds of human disorders and associated complications. Herbal medicines have been used in modern medicine for the treatment of some chronic disorders, including cancer. Coumarins class phytochemicals are important in medicine and mainly derived from plant sources, including Angiosperms. Coumarins have numerous biological activities including antimicrobial, antibacterial, antifungal, antioxidant, antitumor, anti-HIV, antihypertension, anticoagulant, anticancer, antiviral, anti-inflammatory, analgesics, antidiabetic, and anti-depressive.

Methods:

Here in the present work, numerous scientific data were collected from different scientific databases and analyzed in order to know the biological potential of alloimperatorin in medicine. Google, Google Scholar, PubMed, and Scopus databases were searched and analyzed to know the medicinal properties and therapeutic potential of alloimperatorin. Therapeutic potential of alloimperatorin was investigated in the present work through scientific data analysis of different scientific research work. Pharmacological activities of alloimperatorin were analyzed in the present work to know the beneficial health aspects of alloimperatorin against various forms of human disorders.

Results:

Scientific data analysis of different research work revealed the therapeutic potential of alloimperatorin in medicine. Alloimperatorin is a coumarin class phytochemical found in the *Angelica dahurica*. Alloimperatorin revealed significant therapeutic potential in medicine mainly due to its anti-oxidative, anti-inflammatory, anti-apoptotic potential, however its biological potential in breast cancer and their photosensitization effect were also discussed in the present work. Analytical data signified the presence of alloimperatorin in different medicinal plants.

Conclusion:

Present work signified the biological importance and therapeutic potential of alloimperatorin in medicine.

Keywords: *Angelica dahurica*, Alloimperatorin, Anti-oxidative, Anti-inflammatory, Anti-apoptotic, Breast cancer, Photosensitization.

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1. INTRODUCTION

Herbal medicines have numerous advantages in modern medicine as well as in the different types of traditional medicine. Herbal medicines are being used by human beings in different geographical locations for the treatment of numerous human health complications. Herbal medicines are a rich source of nutrients and active phytochemicals of different classes, including alkaloids, glycosides, terpenoids and flavonoids. Human body needs these phytochemicals in considerable amounts for better growth, maintenance and reproduction. Phytochemicals, commonly called secondary metabolites, are pure active phytoconstituents mainly responsible for the different biological activities in medicine. Phytoconstituents are also responsible for the different types of shades of plants and also for the flavors, colors, and orders. Some of the nutraceuticals, perfumes, beverages and medicines were mainly prepared in the modern age by the application of various classes of phytoconstituents and their derived pure active phytochemicals [1 - 6]. Plants are a good source of active phytochemicals which have been utilized in medicine for the treatment of human disorders and associated secondary

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complications. Plants and their derived secondary metabolites were used in modern medicine for the treatment of human diseases, including bacterial and fungal infections, cancer and associated complications. Most of the drugs used for the treatment of cancerous disorders in modern healthcare systems mainly derived from plants and their derived secondary metabolites. For the treatments of both curable and incurable diseases in modern medicine, more than 3000 species of the plants have been reported to have biological potential and therapeutic benefits. More than 80% of populations of the world rely on herbal remedies for their primary health care need in developed and undeveloped countries. *Ammi majus* is widely cultivated in India and other tropical countries for its medicinal application in modern medicine, especially in the skincare products development. Coumarins possess numerous biological activities in medicine and are found to be present in *Ammi majus*. Marmesin, alloimperatorin, khellin, isopimpinellin, nonhydroxylic coumarins, isoimperatorin, heraclenin, ammirin, and visnagin are the main active phytochemicals of the *Ammi majus*. *Ammi majus* is widely used in medicine for regulating menstruation and associated complications. *Ammi majus* has been also used for the treatment of leprosy, kidney stones and urinary tract infections [7]. Asian countries such as China and India rely on plant-based products for their primary health care. Plants and herb-based products have been used in medicine, perfumery, beverages, cosmetics, and nutraceuticals. A large number of prescribed drugs in the USA and Europe were mainly derived from plants. Coumarins are an important class of heterocyclic compounds consisting of 1, 2-benzopyrones ring. Coumarins are classified into simple coumarins, furanocoumarins, dicoumarins, phenylcoumarins and pyranocoumarins [8 - 12]. Phenylpropanoid pathways were mainly responsible for the production of coumarins class phytochemicals in the plants. Presence of furanocoumarins in the Apiaceae, Fabaceae, Rutaceae, and Moraceae is the specific feature which is largely reported in the genus Ficus. Furanocoumarins have been historically used in medicine for the treatment of skin disorders [13]. Coumarins are found in higher plants like Rutaceae and Umbelliferae and essential oils of cinnamon bark, cassia leaf, and lavender oil. Coumarin compounds have numerous biological potentials in the medicine, including antimicrobial, antibacterial, antifungal, antioxidant, antitumor, anti-HIV, antihypertension, anticoagulant, anticancer, antiviral, anti-inflammatory, analgesics, antidiabetic, and anti-depressive properties. Coumarin and its derivatives possess anticancer activity against different types of cancers such as prostate, renal, breast, laryngeal, lung, colon, CNS, leukemia, and malignant melanoma [14]. Coumarins have been used as food material and cosmetic additives in medicine, which have inhibitory potential on microbes, antiplatelet coagulation, inducing cell differentiation and protecting effect on the liver against hepatic injury and steatosis. Furanocoumarins were present in high concentrations in bergamot, lime and lemon oils. Some furanocoumarins have photogenotoxic and phototoxic activities in different organisms. Furanocoumarins have been used for the treatment of psoriasis and atopic eczema in some traditional Chinese medicine. Some furanocoumarin containing herbal medicines may alter the pharmacokinetic parameters of co-ingested drugs in the human body [15]. Coumarins are also found to be present in the Angiosperms and consist of 1, 2-benzopyrones ring and are classified into simple dicoumarins, furanocoumarins, phenylcoumarins, coumarins, and pyranocoumarins. Coumarins have antioxidant, anti-allergic, anti-cancer, anticoagulant, antimicrobial, anti-inflammatory, and anticancer potential [8 - 11, 16]. Furanocoumarins are natural coumarin derivatives produced in plants in response to stress and to protect plants against fungal, bacterial and insect attacks. Furanocoumarins are basically used in medicine in combination with ultraviolet radiation for the treatment of autoimmune skin diseases like psoriasis, vitiligo, eczema, alopecia, and lichen planus and primary T-cell lymphomas. Health beneficial effects of furanocoumarins in the medicine for their analgesic, anticonvulsive, sedative, anticoagulant and hypotensive effects were well investigated and observed. Further, anti-bacterial, anti-fungal, anti-depressants, anti-oxidants, anti-inflammatory, anti-allergic, anti-cancer, and anti-viral properties of furanocoumarins have been well investigated in medicine [17]. Furanocoumarins possess a variety of biological activities, including acetylcholine esterase, antimicrobial, estrogenic, inhibitory effects on cytochrome P-450 enzymes and on prostaglandin E2 production in the medicine [18]. Plants families, including Moraceae, Rutaceae, Apiaceae, and Fabaceae contain coumarins produced by prenylation of the precursor of furanocoumarins – umbelliferone at C6 or C8 followed by cyclization and closure of the furan ring leads to the generation of furanocoumarins constituting a sub-family of coumarin compounds. Both simple coumarins and furanocoumarins exhibited anticancer, antioxidant, or anti-inflammatory activity. Furanocoumarins exhibit phototoxic properties resulting in skin burns or erythema. Coumarins in plant material have mostly been determined using normal or reverse phase high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), and gas chromatography (GC). Application of different variants of capillary electrophoresis such as zone capillary electrophoresis (CZE), pressurized capillary electrochromatography (pCEC), or non-aqueous capillary electrophoresis for the separation of coumarins has been also mentioned in the scientific fields [19].

Furanocoumarins are a group of coumarin derivatives with furan rings, and examples are angelicin, pimpinellin, psoralen, methoxypsoralen, xanthotoxin, and bergapten. Furanocoumarins are found to be present in the plants belonging to umbelliferae, sankoh, legumes, rutaceae, asteraceae, etc., Furanocoumarins possess extensive phototoxic and photo-genotoxic activities on organisms. However, in some traditional Chinese herbs, such as *Angelica dahurica*, furanocoumarins were found to have multifaceted anti-tumour, anti-inflammatory and analgesic and anti-depressant properties [20]. Grapefruit juices contain limonin, nomilin, and furanocoumarins. In the human body, furanocoumarins affect the metabolism of other important classes of drugs [21]. Furanocoumarins are a group of bioactive chemicals naturally existing in Radix Angelica dahuricae having analgesic, anti-inflammatory, antioxidative, antihypertensive, anticancer, and antiproliferative activities in the medicine [22]. Scientific studies have reported that furanocoumarins from grapefruit interacted with medications by interfering with the haptic and

intestinal enzyme cytochrome P450 [23]. Fabaceae, Amaranthaceae, Goodeniaceae, Guttiferae, and Solanaceae contain furanocoumarins class phytochemicals and are widely present in the Apiacae, Rosaceae, Samydaceae, Dipsacaceae, Rutaceae, Compositae, Cyperaceae, Moraceae, and Pittosporaceae [24]. Furanocoumarins and their derivatives are plant defense compounds active against a range of predators and pathogens [25]. Alloimperatorin (Fig. **1**) is a natural coumarin class phytochemical isolated from *Angelica dahurica* and its epoxide derivative 13 was synthesized and evaluated for its antitumor and apoptotic effects against acute myeloid leukemia HL-60 cells in the scientific field [26]. Some scientific studies have revealed that alloimperatorin isolated from *Angelica dahurica* has anticancer activity in leukemia HL-60 cells. The antiproliferative activity alloimperatorin on cervical cancer cells has been investigated with its underline mechanism [27]. To date, more than 100 coumarins have been isolated from *Angelica dahurica* which exhibiting diverse pharmacological potential including anti-tumor, anti-inflammatory, anti-oxidative, and acetylcholinesterase inhibitory potential. Furanocoumarins, including dimers, trimers, and tetramers, have been isolated from *Heracleum candicans, Pleurospermum rivulorum*, and *Ferula sumbul* [28].

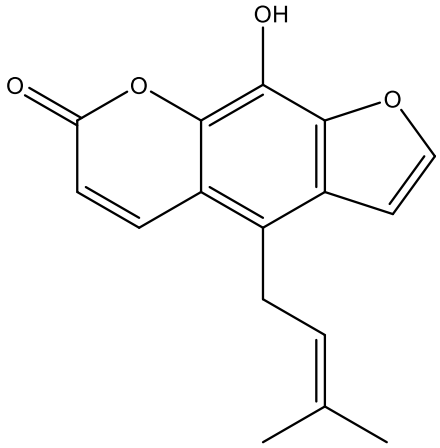

Fig. (1). Chemical structure of alloimperatorin.

2. PHARMACOLOGICAL ACTIVITIES

2.1. Anti-oxidative, Anti-inflammatory, and Anti-apoptotic Activities

Biological potential of alloimperatorin isolated from *Ammi majus* for their protective potential at a dose level 25 mg/kg body weight against Px-induced gastric ulceration and hepatorenal toxicity have been investigated in rats. Biochemical parameters such as serum prostaglandin E2 (PG-E2) and liver and kidney functions have been investigated. Oxidative stress markers were also evaluated with their histopathological features and caspase-3 immunoexpression in the tissues in order to know the biological potential in the medicine. Piroxicam triggered increased indices of liver and kidney functions, provoked oxidative stress, gastric ulceration, decreased PG-E2 levels, and activated caspase-3 immunoexpression. Co-treatment with alloimperatorin has demonstrated protective potential in the medicine and exhibited anti-inflammatory, anti-oxidative, and anti-apoptotic potential [29].

2.2. Breast Cancer Cells

Biological potential of alloimperatorin from *Angelica dahurica* has been investigated in medicine for its effectiveness on breast cancer cells and found to inhibit breast cancer cell viability in a concentration and time dependent manner. Alloimperatorin increased the activities of caspase-8, caspase-9, caspase-3, and poly (ADP-ribose) polymerase and induced breast cancer cell apoptosis. However, alloimperatorin also caused significant mitochondrial shrinkage, promoted the accumulation of Fe^{2+}, reactived oxygen species and malondialdehyde contents. Alloimperatorin significantly reduced mRNA and protein expression levels of SLC7A11 and GPX4. In addition, alloimperatorin significantly promoted Kelch-like ECH-associated protein 1 (Keap1) expression and inhibited the invasion of breast cancer cells. Results revealed that alloimperatorin induced ferroptosis, and oxeiptosis, breast cancer cell apoptosis [30].

2.3. HeLa cell Apoptosis

Biological potential of alloimperatorin-induced apoptosis of cervical cancer cells has been investigated with its molecular mechanism. Cytotoxicity of alloimperatorin on HeLa, SiHa, and MS-751 cells was investigated using cholecystokinin octapeptide. Alloimperatorin reduced the activity of HeLa cells and the IC_{50} at 48 hours was found to be 116.9 μM. Further, it increased the apoptotic rate of HeLa cells and reduced the mitochondrial membrane potential of HeLa cells. Further, alloimperatorin promoted the expression of caspase3, 8, 9 and that Bax apoptotic proteins reduce PARP expression, procaspase3, 8, 9, and BCL-2 proteins and reduced the cyt-c in the mitochondria expression signifying their biological potential on HeLa cell [27].

2.4. Photosensitized Effects

Biological potential of alloimperatorin methyl ether and its photooxygenation product alloimperatorin hydroperoxide for their photosensitized effects has been investigated on human erythrocytes. Alloimperatorin methyl ether photosensitizes efficiently the hemolysis of erythrocytes and the rate of photohemolysis increases on raising the temperature. Alloimperatorin methyl ether increased the erythrocyte membrane permeability and photosensitized lipid peroxidation. The rate of hemolysis induced by alloimperatorin hydroperoxide increased with incubation temperature and decreased in the presence of tert-butanol and BHT [31].

3. ANALYTICAL ASPECTS

Repeated column chromatographic methods on silica gel and HPLC techniques have been used to separate and identify the chemical constituents of the roots of *Angelica dahurica* cv. Yubaizhi. Further, chemical structures of the phytocompounds, including alloimperatorin, were determined by spectral data analysis [32]. Various chromatographic techniques were used for the separation of chemical compounds of *Goodyera schlechtendaliana* and identified by spectroscopic analysis.

Seven chemical compounds, including alloimperatorin, have been separated and identified from 95% ethanol extract of *Goodyera schlechtendaliana* [33]. Chemical constituents of the roots of *Angelica dahurica* var. formosana cv. Chuanbaizhi were separated and purified by repeated column chromatographic methods on silica gel and HPLC methods. Further, chemical structures of isolated phytocompounds were determined by spectral data analysis. Twenty-nine compounds were obtained and identified, including alloimperatorin in the *Angelica dahurica* [34]. Chemical constituents of the root of *Angelica dahurica* cv. Qibaizhi were isolated and purified by solvent extraction and chromatographic technique, and their structures were identified on the basis of the spectral data analysis. Twenty-seven compounds, including alloimperatorin were isolated and identified in the *Angelica dahurica* [35]. The fluorescence properties of psoralen derivatives, 8-methoxypsoralen, imperatorin and alloimperatorin were investigated in different solvent and micellar solutions. The result revealed the photoionization efficiencies of imperatorin and alloimperatorin, which were found to be similar [36]. In another scientific investigation, photooxygenation of alloimperatorin gave hydroperoxide in medicine [37]. Supercritical fluid extraction techniques have been used for the separation of chemical components of *Angelica dahurica*. Further, chemical components of *Angelica dahurica* oils were analyzed by gas chromatography-mass spectrometry (GC-MS). A total of 50 chemical compounds were identified, including alloimperatorin in the *Angelica dahurica* as major coumarin [38]. Four antioxidative furanocoumarins were isolated from *Dracocephalum heterophyllum* by medium- and high-pressure liquid chromatography in combination with on-line high-performance liquid chromatography-1,1-diphenyl-2-picrylhydrazyl recognition. Thereafter, the antioxidative peaks were separated and purified through high-pressure liquid chromatography to obtain four furanocoumarins with purities greater than 95%; namely isodemethylfuropinarine, demethylfuropinarine, alloimperatorin, and alloisoimperatorin which can be efficiently utilized for isolating antioxidants from other natural products [39].

CONCLUSION

Coumarin is an important class of phytochemicals that belongs to the benzopyrone family and has great scientific interest in medicine due to its medicinal importance and pharmacological activities. Due to the biological importance of coumarin class phytochemicals in medicine, its different synthetic derivatives have been prepared in the scientific field to meet potential demands. Coumarin and its derivatives are well-known in medicine for their photosensitizing properties. The major subtypes of coumarin available in nature are furanocoumarins, simple coumarins, pyranocoumarins and pyrone substituted coumarins. Coumarins and furanocoumarins are a class of phytochemicals found to be present in citrus, including grapefruit, pummelo, limes, parsley, parsnips, celery and lemons. There is substantial growth and interest in the field of natural products for furanocoumarins which consists of a furan ring fused with coumarin. Due to the numerous biological potentials of furanocoumarins, it has huge application in the pharmaceutical industry. Furanocoumarins enhanced ultraviolet therapy for skin diseases, including psoriasis and vitiligo, as they are well known to cause photosensitivity of the skin [40]. Furanocoumarins are found to be present in different plant materials including citrus fruits like lemons, grapefruit and vegetables, such as parsnips, parsley, and celery. These furanocoumarins class phytochemicals compounds interact with different systems in the human body, particularly the P450 enzymes [41]. Furanocoumarins class phytochemical has limited solubility in water and has lipophilic nature. Liposomal dosage form of furanocoumarin can provide good biodistribution in the tissues of the human body [42]. Present work summarized the medicinal importance and pharmacological activities of alloimperatorin in medicine. Numerous scientific data on alloimperatorin were collected from Google, PubMed, Google Scholar, and Scopus and analyzed it in order to know the medicinal importance and therapeutic potential of coumarins class phytochemical in medicine. Therapeutic effectiveness of alloimperatorin has been investigated in the present work through scientific data analysis of different scientific research work. Pharmacological activity data of alloimperatorin were collected and analyzed in the present works to know the beneficial health aspects of alloimperatorin against various forms of human disorders. Scientific data analysis of different research work revealed the biological importance and therapeutic potential of alloimperatorin in medicine. Alloimperatorin is a coumarin class phytochemical found to be present in the *Angelica dahurica* (Table **1**). Alloimperatorin revealed significant therapeutic potential in medicine mainly due to its anti-oxidative, anti-inflammatory, anti-apoptotic potential (Fig. **2**), however, its biological potential in breast cancer and its photosensitization effect were also discussed in the present work. Analytical data signified the presence of alloimperatorin in different medicinal plants.

Table 1. Biological source of alloimperatorin.

S. No.	Biological Source	Refs
1.	*Angelica dahurica*	[32, 34, 35, 38]
2.	*Goodyera schlechtendaliana*	[33]

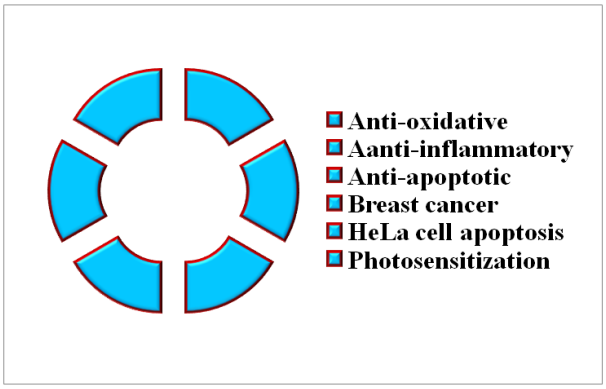

Fig. (2). Pharmacological activities of alloimperatorin.

LIST OF ABBREVIATIONS

BHT = 2,6-di-tert-butyl-p-cresol

AIFM1 = Apoptosis-inducing factor mitochondria associated 1

CZE = Capillary zone electrophoresis

GC = Gas chromatography

GC-MS = Gas chromatography-mass spectrometry

HPLC = High-performance liquid chromatography

PARP = Poly (ADP-ribose) polymerase

pCEC = Pressurized capillary electrochromatography

PG-E2 = Prostaglandin E2

TLC = Thin-layer chromatography

UV = Ultraviolet

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The author reports no conflict of interest.

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