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A PHYTOCHEMICAL AND PHARMACOLOGICAL REVIEW ON *ANISOMELES INDICA*

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Abstract

This review presents up-to-date phytochemical information and pharmacological activities of medicinal plant *Anisomeles indica*. The leaves, flowers, stems and essential oils of the plant possess a number of important phytochemical moieties and significant biological activities, including antimicrobial, antioxidant, anticancer, neuroprotective, and antimalarial activities. The herb is also found to show potent harbicidal activity against *Phalaris minor, Bidens pilosa, Cassia occidentalis, Amaranthus viridis* and *Echinochloa crus-galli*. Apigenin, an important compound isolated from this herb, is evident to upregulate BAK and suppress MMP-2 and MMP-9 in many cancer cells. In conclusion, *A. indica* and its derived compound apigenin, may be potential therapeutic agents.

Keywords: *Anisomeles indica; phytochemicals; biological activities; apigenin; cancer*

Introduction

Anisomeles indica (commonly known as Catmint; **Taxonomy and Image: Box 1**), an ethnomedicinally important perennial woody shrub belongs to the family Lamiaceae (Vivek et al., 2013). It is an annual herb of about 1-2 m in height, with a 4-angled, pubescent stem. The leaves are thin, ovate, 3-12 cm, long-stalked, and pointed at the tip, with round-toothed margins.

The plant is widely distributed in Southeast Asia and the tropical region of the world, including India, China, Taiwan, Indonesia, Thailand, Philippines, Australia, and Vietnam (Anonymous, 2003). The plant grows as a weed in higher altitude, wild area, agricultural field and the flowering and fruiting period of this plant is from august to April (Ulhe and Narkhede, 2013). To date, numerous phytochemicals were isolated from the crude extracts of the different parts of the plant, including terpenoids, diterpenoids, alkaloids, flavones, arachnoids, ovatodiolide, stigmasterol, β-sitosterol, stigmasterol, anisomlic acid, paraffins and fatty acids derivatives (Kundu et al., 2013; Basappa et al., 2015). Extracts from various parts of the plant (e.g., leaves, flowers, stems) have shown extensive biological activities such as anticancer, antimicrobial, antiviral, antioxidant, anti-HIV, anti-inflammatory, antiplatelet, antiepileptic activity (Chen et al., 2008; Basappa et al., 2015). *A. indica* also exhibits a significant phytotoxic effect to certain weeds of wheat crops and produce a natural harbicidal effect (Batish et al., 2007). Moreover, traditionally this herb is widely used in the treatment of inflammatory skin disorders, liver diseases, abdominal pain, intestinal infections and immune system deficiencies, rheumatism, cold, and fever (Huang et al., 2003).

This review aims to sketch a current scenario on the phytochemical and pharmacological activities of *A. indica* on the basis of database (PubMed, Science Direct and Google Scholar) information.

Methods

A search (till September 2018) was done in the following databases: *PubMed, Science Direct, MedLine, Scopus,* and *Google Scholar* with the keyword '*Anisomeles indica*', pairing with 'phytochemicals', 'biological activities/effects', or 'pharmacological activities/effects'. No language restrictions were imposed. Articles were assessed for the information about the extracts or fractions and isolated compounds of the plant or its parts, concentration or dose (route of administration), test systems, results or possible mechanism of action, and final conclusion. Inclusion and exclusion criteria of evidences found in databases have been given below.

Inclusion criteria:

1. Studies carried out *in vitro*, *ex vivo* or *in vivo* with or without using experimental animals, including humans and their derived tissue and cells;
2. Studies with *A. indica*'s and its other parts's crude extracts, isolated compounds or their derivatives or preparations;
3. Studies with or without proposing activity mechanisms;
4. Studies with extracts without phytochemical analysis, but having biological activities;
5. Studies with extracts, with phytochemical analysis, but having no report for biological activities.

Exclusion criteria:

1. Duplication of data and titles and/or abstracts not meeting the inclusion criteria;
2. *A. indica* with other studies uncovering the current topic;
3. Studies on other Genus or Species of the plant.

Findings

Among the vast evidences, 45 published articles found in the databases that contain screening reports on the phytochemical and/or pharmacological activities of *A. indica* or its crude extracts/fractions or isolated compounds have been summarized below:

Phytochemicals

The entire plant has various medicinal usefulness (Dharmasiri et al., 2003). The plant consists of flavones, alkaloids, arachnoids and terpenoids like, anisomelic acid, ovatodiolide, 4,7-oxycycloanisomelic acid, iso-ovatodiolide, β-sitosterol and stigmasterol (Burkill, 1985; Baranwal

et al., 2012). The major phytochemicals in leaves include alkaloids, tannin, glycosides, carotenoids and saponin (Ulhe and Narkhede, 2013). The seeds contain stigmasterol, β-sitosteroltetracosine, tetracoranel-β-amyrin and macrocylicditerpenes, while the flowers contain macrocylic diterpenes, ovatodiolide and anisomlic acid (Yadava and Barsainya, 1998). The essential oils isolated from the plant contain a number of bioactive chemicals like D-limonene, D-α-thujone, citral, borneol, α–terpineol, 1-8, cineole, azulene, caryophyllene, α–pinene, β–pinene, myrcene, bornyl acetate, P- cymene, nerol and camphene (Ulhe and Narkhede, 2013). Some important phytochemicals isolated from *A. indica* extract are shown in **Figure 1**.

Pharmacological activities

Antimicrobial Activity

Antibacterial activity: The epidemiological studies reported that approximately 75% of the risk for gastric cancer is caused by *Helicobacter pylori* (Herrera and Parsonnet, 2009). Recent studies indicate that inhibition of *H. pylori* infection is one of the best targets for prevention of gastric cancer (Peek and Blaser, 2002). Ethanol extract of whole plant (*A. indica*) at 0.1-0.5 mg/mL showed potent anti-*H. pylori* activity with inhibition zone ranging from 0 to 21 mm. Ovatodiolide isolated from the extract exhibited significant inhibitory effect against *H. pylori* growth at 0.5 mg/mL is 20 ± 4 mm (Rao et al., 2011; Lien et al., 2012). Essential oil of flowers of this plant was found to act against the bacterial strains *Proteus vulgaris*, *Bacillus subtills, Bacillus anthracis*, *Salmonella* sp., *Salmonella newport*, *Salmonella pullorum*, *Streptococcus agalacties*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* with the zone of inhibition within 10 to 29 mm (Yadava and Barsainya, 1998). Methanolic extract of leaves at 100 µL showed an inhibitory effect against antibiotic resistant urinary tract pathogens *S. aureus, Enterococcus faecalis, Escherichia coli, P. aeruginosa* and *K. pneumoniae* with the zone of inhibition range 0.1 to 2.3 cm (Vivek et al., 2013).

Antifungal activity: The medicinal plants are the good source of novel anti-fungal agents (Bhengraj et al., 2008; Vuuren et al., 2010). *A. indica* is evident to show strong antifungal activity against a number of pathogenic fungi. Essential oil obtained from the fresh leaves is effective against *Rhizoctonia solani*, *R. bataticola*, *Sclerotium rolfsii*, *Fusarium udum*, *F. oxysporum*, *Alternaria solani*, *Pythiumaphani dermatum* and *Aspergillus flavus* at 62.5 to 500 µg/mL. Maximum activity was obtained against *P. aphanidermatum* (ED_{50}: 51.58 µg/mL) followed by *R. bataticola* (ED_{50}: 72.80 µg/mL) (Kundu et al., 2013). Essential oil from the flowers of the herb showed appreciable anti-fungal activity within the zone of inhibition 12 to 27 mm against *A. flavus, A. niger, A. fumigatus*, and *F. oxysporum* (Yadava and Barsainya, 1998; Basappa et al., 2015).

Antioxidant activity

About two-third of the world's plant species have medicinal importance and most of them have excellent antioxidant potentials (Krishnaiah et al., 2011). Plant-derived antioxidants in the form of raw extracts or chemical constituents are very efficient to block reactive oxygen species (ROS)-induced oxidative damage by neutralizing free radicals (Rezaeian et al., 2015). In a study, the antioxidant capacity of the plant extracts was measured by its free radical scavenging activity using DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2′-azinobis-(3-ethylbenzothiaziline-6-sulfonate) assay, suggesting potent free radical scavenging capacity (Proestos et al., 2013). The methanolic extract of whole plant of *A. indica* possesses strong antioxidant potential in a dose dependent manner. The methanolic extract of the herb was also evident to show DPPH and hydroxyl radical ($^{\bullet}OH$) scavenging activity (IC_{50}: 12.67 and 18.61 mg/mL, respectively) (Uddin et al., 2016). Moreover, the essential oil from the fresh leaves of the herb exhibited strong antioxidant activity (IC_{50}: 9.86 µL/mL) (Basappa et al., 2015).

Anticancer activity

Cancer is considered as one of the major causes of death all over the world now-a- days (Behzad et al., 2014). In recent years, cytotoxicity of medicinal plant extracts and their isolated compounds are capturing the researchers' interest for their antitumor and anticarcinogenic potentials (John, 2013). About 25% of prescribed drugs originate from medicinal plants in the world and more than 3000 species of plants have been

recorded to have anticancer properties (Uddin et al., 2009). In this review, the cytotoxic activity of *A. indica* has been identified on different tumor cell lines. The hexane extract of *A. indica* exhibited significant cytotoxicity toward the human pharynx squamous cancer (FaDu) cells in a dose- and time-dependent manner. The extract induced FaDu cell apoptosis by down-regulating Bcl-2 and Bcl-xL protein expression, while up-regulating BAX, BAK expression and activating caspase-9/3 (Hsu et al., 2012a). The hexane extract also possesses potential anticancer activity through inhibition of matrix metalloproteinases (MMP)-9 and MMP-2 expression, which effectively suppressed cell migration and invasion (Hsu et al., 2012b). The aqueous extract of whole plant and its isolated compounds exhibited potential anti-metastatic activities against human breast cancer (MCF-7) cell lines through inhibition of MMP-9 and its mRNA expression *via* c-Fos and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) p65/activator protein (AP)-1 signaling pathway (Liao et al., 2012). The cytotoxic effects of methanol extract of whole plant were recorded against human liver cancer (Hep G2, Hep 3B), lung cancer (A549), breast cancer (MDA-MB-23), colon cancer (Colon 205), and prostate cancer (PC3)cell lines (Chen et al., 2008; Hsieh et al., 2008). The cytotoxic activities of essential oil from the fresh leaves were screened on tumor cell lines, such as human embryonic kidney (HEK-293), HepG2, A549, human immortalized myelogenous leukemia (K562) by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Basappa et al., 2015). The possible mechanism by which the plant exerts its anticancer activity is structurally presented in **figure 2**.

Neuroproyectctive activity

Recent studies suggested that various natural products play an important role in the prevention and treatment of different neuronal diseases and disorders (Mohebbati et al., 2017). In Ellman method the ethyl acetate extracts of *A. indica* showed significant inhibitory activity against both the acetylcholinesterase and butyrylcholinesterase enzymes with IC_{50} values of 176.02 and 143.78 mg/mL, respectively (Uddin et al., 2016). The enhanced production of nitric oxide (NO) radicals, pro-inflammatory cytokines (tumor necrosis factor alpha (TNF-α), interleukin (IL)-12) are significantly inhibited by the methanolic extract of whole plants in a dose-dependent manner (Hsieh et al., 2008; Rao et al., 2009). The oral administration of decoction of leaves and stems to rat exhibited significant dose-dependent anti-inflammatory activity by cyclooxygenase (COX)-I inhibition, plasma membrane stabilization and scavenging free radical (Dharmasiri et al., 2002). The chloroform, ethyl acetate, aqueous extract of areal part of the plant possess significant antiepileptic potential against both maximal electroshock (MES) and pentylenetetrezole (PTZ) model at 200-400 mg/kg with reduced neuronal complications (Sundriyal et al., 2013).

Herbicidal activity

Weed is the key limiting factors of crop production, which compete with crops for water, nutrients, light and harm the crops. Today's agriculture highly depends on chemical herbicide that causes different environmental effects and scientists are searching for, finding alternative methods for weed management (Miri and Armin, 2013). In this study, the essential oil from leaves of *A. indica* exhibit noticeable harbicidal activity by inhibiting the radicle growth, seedling elongation and dry weight accumulation of *B. pilosa*, *C. occidentalis*, *A. viridis* and *E. crus-galli* in a dose-response manner (0.125-2.0 mL/mL). Aqueous extracts from dried leaf and root powder of the plant also produce potential herbicidal activity by reducing the emergence and growth of *Phalaris minor* and other weeds of wheat crop (Batish et al., 2007).

Miscellaneous effects

Antimalarial activity: Mosquitoes act as key vectors for devastating parasites and pathogens, including malaria, yellow fever, dengue, chikungunya, filariasis, encephalitis etc (WHO, 1996). The eco-friendly control of mosquitoes is an important alternative approach in order to develop safer insecticides of botanical origin (Govnindarajan, 2011). *A. indica* leaf extract and biosynthesized silver nanoparticle (AgNPs) represents dose-depended acute toxicity against larvae of the malaria vector

Anopheles subpictus, the dengue vector *Aedesalbopictus* and the Japanese encephalitis vector *Culex tritaeniorhynchus* at 50-250 (µg/mL) of extract, 15-75 (µg /mL) of AgNPs (Govindarajan et al., 2015).

Antiplatelet aggregation activity: Selective antiplatelet aggregation activities toward collagen and inhibitory effects on antiplatelet aggregation induced by thrombin was exhibited by the methanolic extract of *A. indica* (Chen et al., 2008).

Anti-HIV activity: Ovatodiolide, a diterpenoid isolated from *A. indica* extracts exhibited moderate cytotoxic effect (EC_{50}: 0.10 µg/mL; IC_{50}: 1.20 µg/mL) on HIV-1 at 5.0-6.0 µg/mL (Alam et al., 2000).

In summary, the recent research claims that *A. indica* is a very beneficial medicinal plant. This review combines phytochemical and pharmacological properties of the plant. The plant contains some important phytoconstituents, including ovatodiolide, apigenin, stigmasterol, β-sitosterol, D-limonene, citral, p-cymene, and nerol. The plant exhibits various biological activities such as antimicrobial, antioxidant, anticancer, neuroprotective, and herbicidal activity. The possible mechanism of action is very important that would help to design drugs with potent healing activity as well as negligible side effects. Apigenin, a known compound of this herb has significant anticancer activity and it could be a potential source of drug target for future researchers.

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Conflict of Interest

None declared.

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Box 1. Taxonomy of *A. indica*

Kingdom: **Plantae**
Order: **Lamiales**
Family: **Lamiaceae**
Genus: **Anisomeles**
Species: ***Anisomeles indica***

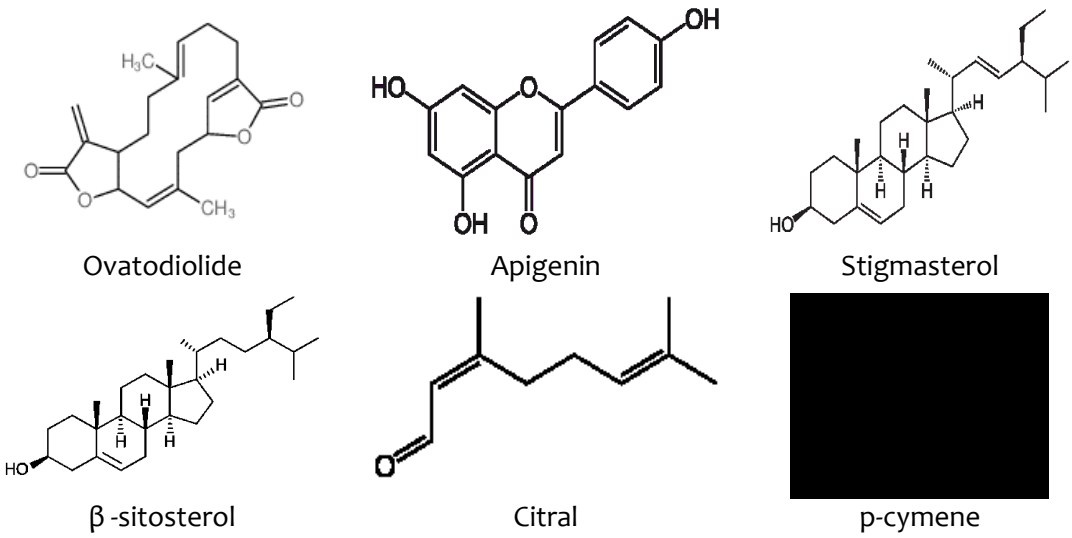

Figure 1. Structure of some important phytochemicals isolated from *A. indica*

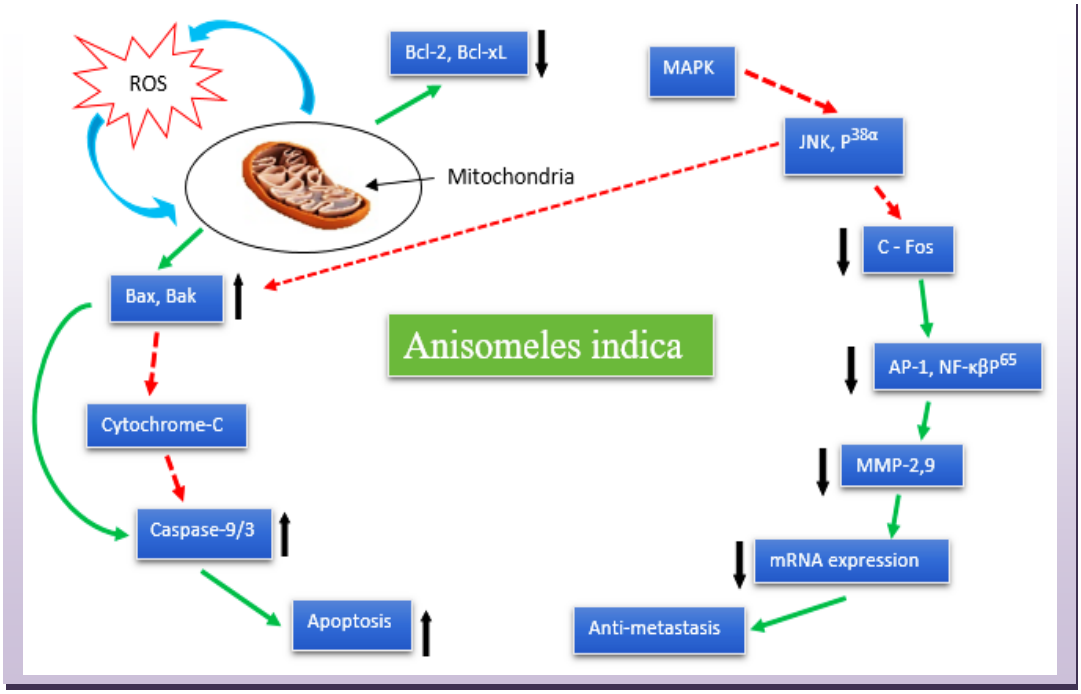

Figure 2. Possible anticancer mechanism of action of *A. indica* by inducing apoptosis and inhibiting metastasis.