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ETHNOBOTANY, CHEMISTRY AND PHARMACOLOGY OF AN AROMATIC GENUS *ANISOMELES* LINN. IN INDIA

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ABSTRACT

Anisomeles is an aromatic genus that belongs to the family Lamiaceae. The members of this genus are characterized by the presence of camphor-scented flowers. Members of this genus are widely used in folklore medicine in countries like India to cure various diseases like fever, anti-inflammatory, antiseptic, skin diseases, abdominal pain, psoriasis etc. In the present review traditional uses, phytochemistry and pharmacology of members belongings to this genus are presented. A wide range of chemical constituents were isolated from different species of *Anisomeles*. Among all the constituents that were isolated from these species anisomelic acid and ovatodiolids are the more abundant bioactive compounds, which show greater biological significance. They show a wide range antimicrobial, antipyretic, anti-inflammatory, antioxidant, cytoprotective, anticancer, insecticidal, and herbicidal properties. These species have strong cytotoxicity and anticancer properties which should be further evaluated. The literature presented in this review will provide a platform for further research on this genus to develop new safe plant based drugs to cure cancer.

KEYWORDS: ***Anisomeles indica, A. malabarica, A. heyneana, A. salviaefolia, ethnobotany, phytochemistry, pharmacology***

INTRODUCTION

The genus *Anisomeles* is one of the old world Asian-Australian genus that belongs to the family Lamiaceae. The members of this genus are characterized by the presence of glandular hairs on the floral parts. The exact number of species that belong to this genus is not known, however according to the available literature very few species are found in this genus. The members that are found in this genus are *Anisomeles heyneana, A. indica, A. malabarica* and *A. salviaefolia*. Among these *A. indica* and *A. malabarica* are native to Asia where as *A. heyneana* and *A. salviaefolia* are native to the Australia. In *A. indica* another variety *A. indica* var. *albiflora* was reported from India [1]. The taxonomic basis of this genus was developed based on the detailed investigation of Asian species. The information regarding this valuable genus *Anisomeles* that is found in India was presented in t his paper.

DISTRIBUTION

Anisomeles indica and *A. malabarica* are of Asiatic origin and the remaining *A. heyneana* and *A. salviaefolia* are of Australian origin. *A. indica* was distributed in countries like Sri Lanka, China, Indonesia, India, Japan, Philippines and in Australia. Among all the places it occurs, widespread distribution was found in India particularly in Indian Himalayas. The other species of Asiatic origin *A. malabarica* was limited in its distribution and is found only in south India, Sri Lanka and Australia. Whereas *A. heyneana* whose origin is not exactly known, but its distributions was found to occur in both Australia and in south India [2].

HABIT AND HABITAT

Members of this genus are perennial shrubby herbs. They may be the tall or under shrubs. These plants occupy various weedy habitats and can grow on both moist and arid soils. *A. indica* grows in moist sandy loam, lateritic and granitic soils. In India

particularly in Andhra Pradesh, it is restricted to stream edges of irrigated rice fields. *A. malabarica* grows in relatively arid sandy loam soils in India. Where as in Ceylon this species grows particularly in lateritic soils. In Australia sandy flats or coastal dunes are more suitable for this species. In south India *A. heyneana* seems to grow on sandy loam soils and on sandy flats in Australia [2].

ANISOMELES INDICA (LINN.) KUNTZE

Anisomeles indica is locally known as in Hindi: Kala bhangra, Gobara, Manipuri: Thoiding angouba; Marathi: Gopali; Malayalam: Chedayan; Telugu: Adabeera; Kannada: Mangamari soppu; Bengali: Gobura, gopali, apang; Konkani: Gopali in India. Where as in other countries it is named as - in Malaysia: Babadotan; Indonesia: Javanese; Philippines: Kabling parang; Thailand: Komko huai; Laos: San nga. The synonyms of *A. indica* are *Nepeta indica*, *Anisomeles ovata* and *Phlomis indica*. *Anisomeles indica* is a camphor-scented large perennial woody shrubby herb, which can reach up to 2 m tall. The stems are quadrangular and sparsely hairy to densely hairy. The leaves are (broad) ovate, measuring 5-12 x 2-7 cm, hairy on both sides and with 5-celled hairs. The petiole is 1.5-4 cm long and covered with soft hairs. The inflorescence is a terminal spike, accompanied by more than 2 lateral spikes. The sepal measures 6 mm x 6.5 mm with the longest teeth 1.7-2 mm long. The fruit is 9-10 mm long where the upper part of the tube and teeth are hairy inside and the petal is up to 11 mm long while the lower lip measures about 8 mm x 3 mm, greenish to whitish, and with dark red lines inside but sometimes purple or blue. The filaments are didymous and 5-6 mm long with the style about 9 mm long. The nutlets are subglobular, measuring 1.2 mm x 1 mm and shiny black.

ANISOMELES MALABARICA (L.) R.BR.

Anisomeles malabarica are locally known as Malabar catmint in English, Kalpanath, Codhara, Gopoli in Hindi, Kannu thumbai in Irula, Karitumbi, Gandubirana Gida in Kannada, Kaktumbo in Konkani, Karintumpa, Karithumba, Karimthumba, Perumtumpa in Malayalam, Gojibha in Marathi, Vaikuntha in Oriya, Mahadronah, Vaikunthah in Sanskrit, Aruvaachadachi, peyimarutti in Tamil, where as in Telugu it is named as Mogabheri or Moga- biran. The synonyms of *A. malabarica* are *Anisomeles salviifolia*, *Nepeta malabarica*, *Stachys mauritiana*, *Craniotome mauritiana*, *Nepeta pallida* and *Ajuga fruticosa*. Perennial, semi-shrubby herb; stem to about 2 m high, much branched from base, subquadrangular, thickened below to 1.8 cm in diam., densely lanate. Leaves ovate-lanceolate to oblong-lanceolate, 3.6-16 x 1.3-7 cm, narrowed and rounded at base, acute, crenate-serrate, slightly bullate and velvety lanate above, densely so beneath; petioles 0.7-3.5 cm long, stout, lanate. Racemes to 34.5 cm long; verticils close, dense; peduncles densely lanate. Floral leaves 8-10 mm long, densely lanate. Bracts linear, to 5 mm long. Calyx to 9 mm long; tube to 5 mm long, lanate without, glabrous within; lobes lanceolate, to 4 mm long, acuminate. Corolla 1.4-2 cm long; tube to 9 mm long, white, glabrous without; throat pilose towards base of lower lip; Upper lip oblong, 4-6 mm long, obtuse at apex, slightly arched, whitish; lower lip to 1 cm across, coral pink, with 2 white streaks towards base, pilulose without with gland-tipped hairs, the lateral lobes shallowly rounded, the median one larger, broadly orbicular, 2-fid. Style glabrous; branches linear, unequal. Nutlets ovoid, 2.5 x 1.5 mm, trigonous, glabrous, blackish-brown and shining.

ANISOMELES HEYNEANA BENTH.

This species is commonly known as western hill catmint, Chandhara in Hindi, Gopali in Marathi and in Sanskrit it is named as Oshthaphala *Anisomeles heyneana* is a tall, erect herb, growing to 1-1.5 m high. Slender stems and branches are quadrangular. Oppositely arranged ovate lance-like leaves are 5-12 cm long. Flowers occur in cymes which are 10-30 cm long. Small 2 cm flowers are white, tinged with pink, and 2-lipped. Upper lip is 5 mm. The lower lip is 3-lobed. The flowers resemble cow's earlobes, which gives it its Marathi name. Flowering: October-November.

ETHNOBOTANY

Anisomeles Linn. Is an ethnomedicinally important aromatic genus and widely used for the treatment of various kinds of ailments in various parts of world. Among all the species of this genus *A. indica* has distinct role in traditional medicine in curing various diseases [3]. *A. indica* possesses aromatic astringent, carminative and tonic properties and is employed as a cure in gastric catarrh and intermittent fevers. Decoction prepared from this species is used to cure convulsions. The essential oil obtained from this plant is useful in urine infection [4]. The leaves of this species are used to cure diseases like inflammation and they have antiseptic and antibiotic properties[5,6,7]. In Thailand the volatile oils of *A. indica* are used in preparation of dermatological products[8]. The fresh leaves as

well as greenish parts containing volatile oil used to cure ailments like stomachache, cough and cold [9, 10]. *A. indica* is commonly used in numerous conditions of immune system deficiencies in treating diseases such as gastrointestinal and liver disorders [11]. The juice of the leaves is administrated to children for colic dyspepsia and fever caused by teething. Inhaling the vapor of the hot infusion induces copious perspiration. A decoction of this plant is an excellent fomentation and used externally as an embrocation in rheumatism arthritis[12]. Bantar tribes of Bhaudaha, Morang, Nepal use leaf extract of *A. indica* to cure stomachache[13]. Leaves are considered useful to cure skin diseases, abdominal pain and psoriasis. Bruised leaves are applied in snake bites[14]. According to Sri Lankan traditional medicine, a decoction made from stems and leaves of *A. indica* possesses analgesic activity[15]. Leaf juice of *A. indica* is given to fever and dyspepsia. The leaf paste is applied on snake bites and scorpion sting[16]. It is reported that leaf extract of *A. indica* is used to cure fever[17]. *Anisomeles malabarica* is useful in halitosis, epilepsy, hysteria, amentia, anorexia, dyspepsia, colic, flatulence, intestinal worms, fever arising from teething children, intermittent fever, gout, swelling, diarrhea and rheumatism [18, 19]. This species is reported to possess anticancer, allergenic, antihelmintic, antibacterial, antiplasmodial and antiperotic properties [20]. The plant also shows other properties like antiperotic, diaphoretic, emmenagogue etc.[6, 21]. Ethnobotanically, the leaves of *A. malabarica* are used against convulsions, dyspepsia, intermittent fever, colic, boils, tetanus [21, 22, 23, 24]. The plant is also used in curing various ailments like anticancer, allergenic, anthelmintic, antiallergic, antianaphylactic, antibacterial, anticarcinomic, antiedemic, antihistaminic, anti-inflammatory, antileukemic, antinociceptive, antiplasmodial, antiseptic and antiperotic properties[25]. *A. malabarica* was investigated for its pharmacognostical and various biological activities[26]. Recently the valued plant was investigated for its herbicidal activity [27]. Mixture of *A malabarica* and *Alangium salvifolium* leaves made in to paste and applied externally to cure chronic wounds[28]. Stem paste of *A. malabarica* mixed with coconut oil is applied topically over the wounds[29]. Leaves of *A. malabarica* are used to treat Eczema[30].

PHARMACOGNOSTIC STUDIES

The proper identification of this valuable species is very important because they have great medicinal importance. For this purpose it is very important to carry out pharmacognistic studies. Pharmacognostic studies of *A. malbarica* were carried out by Brindha[31]. The pharmocognostical studies of *A. malbarica* were also conducted by studying morphological and anatomical characteristics of the leaf with the determination of physio chemical constants[32]. Pharmacognostic studies on leaves of other species *A. indica* were studied by Ushir et al., [26]. Comparative Pharmacognostical studies in between the species of genus *Anisomeles* that are found in India were carried out by Ushir[33]. Further histological and phytochemical characteristics of leaves of *A. indica* was reported for proper identification of this species[34].

PHYTO-CHEMISTRY

Two acylated flavone glucosides were isolated from *A. indica* [35]. The presence of 6-methoxy flavones in *A. indica* was also reported by Rao *et al.*,[36]. Later the same group reported the presence of 5,6-Dimethoxy-7,3 ,4 - trihydroxyflavone in *A. indica* [37]. *A. indica* is well documented to possess phytoconstitutents like glycosides, flavonoids, terpenoides and steroids[38]. The same group latter reported the occurrence of flavonoid glycosides in *A. indica* [39]. Preliminary chemical examination of *A. indica* revealed presence of triterpenoids in entire plant. Whole plant is reported to contain anisomelic acid (terpenoid) (Fig – 1A), ovatodiolide (terpenoid) (Fig – 1B), 4,7-oxycycloanisomelic acid (terpenoid), iso-ovatodiolide, β sitosterol stigmasterol, flavones and apigenin and yields an essential oil [40, 41]. Constituents of the essential oils of *A. indica* are found to be α- pinene (Fig – 1D), β- pinene (Fig – 1E), d- limonene, methyl chavicol, d- alpha - thujene, citral, borneol, 1,8 cineole, α- terpineol eugenol, azullene, and caryophyllene (Fig – 1C)[42]. Complete chemical syntheses of anisomelic acid were reported[43]. Presence of terpenoides in entire plant, *A. indica* was reported[44]. Five new cembrane-type diterpenoids with a trans-fused alpha-methylene-gamma-lactone, a new flavonoid glucoside, and with some other compounds were isolated from a methanol extract of *A. indica*[45]. 14 constituents were isolated from the methanolic extract of the whole plant of *A. indica* among them one is cembrane-type diterpenoid, two are benzenoids, five are flavonoids, and six are phenyl propanoids [46]. They are 7- methoxy-3,4,5,6-tetrahydroxyflavone (pedalitin), apigenin, ovatodiolide, methylgallate, 3,4- dihydroxybenzoic acid, scutellarein 7-*O*-d-glucuronide methyl ester, apigenin 7-*O*-glucuronide, desrhamnosylverbascoside (calceolarioside),

cistanoside F, betonyoside A, campneoside II, acteoside, isoacteoside and apigenin 7-*O*-d-(6-*O*-*p*-coumaroylglucopyranoside) (terniflorin) respectively [46, 47]. 27 components were resolved from essential oil obtained from aerial parts and roots of *A. indica* by GC-MS analysis [48]. The ^{1}H- and ^{13}C-NMR spectral studies reported the presence of ovatodiolide, a diterpenoid in *A. indica* [49]. The presence of stigmasterol, β-sitosterol tetra cosine, tetra coranel β-amyrin in seed along with macrocylic diterpenes, ovato-diolide and anisomlic acid in the flowers was reported[20, 50]. The ovatodiolide compound showed cytotoxicity effects by causing apoptosis with producing reactive oxygen species and down-regulation of FLICE inhibitory protein leading to cell cycle arrest towards oral squamous cell carcinoma. The major components that present in essential oil of *A. indica* are eugenol, α-terpeneol (α-terpineol,), β-pinene, bornyl acetate[51]. In *Anisomeles malabarica* preliminary phytochemical analysis revealed that the presence of alkaloids, steroids, proteins, flavonoids, saponins, mucilage, carbohydrates, tannins, fats and oils [52]. The ethanolic and diethyl ether extracts of *A. malabarica* revealed the presence of alkaloids, flavonoids, tannins, saponins, and glycosides [53]. The hexane extract derived from the whole plant of *A. malabarica* reported to contain beta sitosterol [54] (Fig – 1F). Anisomelic acid is one of the major compounds in *A. malabarica* which is a cembrane type diterpenoid [20]. Ovatodiolide and Anisomelic acid are two diterpenoid lactones isolated from *A. malabarica* [55] and *A. indica*. It has been shown to be cytotoxic to KB cells [40, 41]. *A. malabarica* has been shown to possess many other compounds viz., anisomelolide (Fig – 1G), malabaric acid (Fig – 1H), 2-acetoxymalabaric acid, anisomelyl acetate, anisomelol [56] and some other flavones glucosides [57]. New phyllocladane diterpene, phyllocladan-16α, 17-dihydroxy-19-oic acid, together with known phyllocladane diterpene, phyllocladan-16α, 19-diol, cembrane diterpene ovatodiolide, sitosteryl-3-*O*-β-D-glucoside and verbascoside, were isolated from aerial parts of *A. heyneana*. The structure of compound 1 was elucidated by 1D and 2D NMR analyses which included HSQC, HMBC, and nuclear overhauled effect spectroscopy (NOESY) experiments as well as X-ray crystallography. Compounds 1, 3, 4, and 5 significant biological properties like inhibition of *Mycobacterium tuberculosis* and 3 was found to exhibit anti-mycobacterial activity with IC_{90} 6.53 µg/ml. Compounds 1, 3, and 5, at 100 µg/ml, were also evaluated for inhibition of Thp-1 cell lines, and compounds 1 and 3 showed 59.02% and 96.4% inhibitions respectively [58].

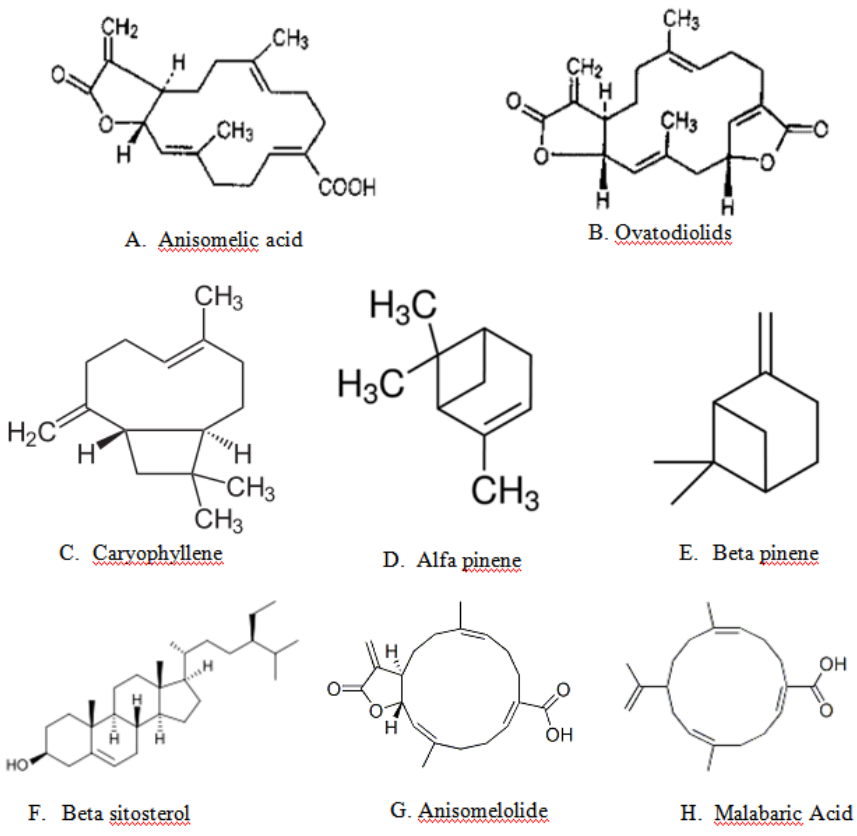

Figure 1
Chemical constituents of the aromatic Genus *Anisomeles* Linn.

PHARMACOLOGY

The members of *Anisomeles* have been prescribed for their antipyretic, carminative, antirheumatic, and analgesic activities [59]. Scientific evidence revealed that a decoction from pre-flowering leaves and stems of *A. indica* has anti-histaminerigic, free-radical scavenging, membrane stabilizing, and cyclooxygenase-I inhibitory activities. Moreover, its aqueous extract was also shown to have analgesic and anti-hyperalgesic activities [15, 60]. The ethanol extract of the whole *A. indica* exhibited strong anti-*Helicobacter pylori* activity [61] and it possessed significant anti-inflammatory activity by inhibiting the enhanced production of nitric oxide (NO) radicals, and pro-inflammatory cytokines (TNF- and IL-12) induced by LPS/IFN- on murine peritoneal macrophages [62].

ANTIMICROBIAL

The potent antimicrobial activity of essential oils obtained from the flowers of *A. indica* was reported by Yadava and Barsainya [42]. The essential oil from aerial parts and roots of *A. indica* showed potent microbiological activity on *E. coli, P. aeruginosa, B. pumilus* and *S. aureus* with a range of minimum inhibitory concentration values extended from 31.25 to 250 µg/ml [33]. The microbiological activity of the isolated essential oils from *A. indica* was investigated; it was found that the essential oil show strong activity on *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus pumilus* and *Staphylococcus aureus* with a range of minimum inhibitory concentration values extended from 31.25 to 250 µg/ml [63]. Among petroleum ether, ethyl acetate, methanol extracts of *A. malabarica* tested for Antimicrobial efficacy against gram positive and gram negative bacterial and fungal organisms, The methanolic extract exhibited maximum antibacterial and anti fungal activity when compared with other two extracts [64]. The significant antibacterial effect of *A. indica* leaf extract against various pathogenic bacteria like *E. coli, Proteus vulgaris, Klebsiella pneumoniae* and *P. aeruginosa* was reported [12]. *In vitro* antibacterial activity of leaf extracts of *A. malabarica* against *E.* coli, *S. aureus, P. mirabilis, P. aeruginosa, K. pneumoniae* was evaluated and found that the ethanolic extract exhibited a strong antibacterial activity at 200 µg/ml and produced 25mm zone of inhibition against *S. aureus* whereas Diethyl ether extracts produced 30 mm zone of inhibition at the same concentration [53]. Among all the constituents of *A. indica* tested for antibacterial activity, ethanol extract, pure constituents ovatodiolide followed by acteoside, isoacteoside, and terniflorin showed potent antimicrobial activity. Ovatodiolide demonstrated bactericide activity against *H. pylori* reference, as well as multidrug-resistant strains. On the other side, *in vitro H. pylori* infection model revealed that ovatodiolide inhibited the *H. pylori* bacteria adhesion and invasion to human gastric epithelial cells [65]. The antibacterial effect of leaf extract against five drug resistant urinary tract pathogenic isolates viz., *S. aureus*, *Enterococcus faecalis*, *E. coli*, *P. aeruginosa* and *K. pneumoniae* was evaluated [66]. They found that gram positive bacteria have shown higher susceptibility to leaf extract than gram negative bacteria. *S. aureus* and *E. coli* were inhibited to high extent among gram positive and gram negative bacteria respectively. *K. pneumoniae* was inhibited to least extent. The Antifungal activity of essential oil obtained from *A. indica* was evaluated by poisoned food technique and maximum activity against *Pithium aphanidermatum* (ED 50 51.58 µg/ml) followed by *Rhizoctonia bataticola* (ED50 72.80 µg/ml) was noticed [51]. The synthesized silver nanoparticles from leaf and boiled leaf extracts of *A. malabarica* showed prominent growth inhibition on *Pseudomonas* species [67]. The *in vitro* antimicrobial activity of *A. malabarica* was performed by agar well diffusion method against the clinically important multi drug resistant bacterial strains *S. aureus, B. subtillis* and *K. pneumoniae* with the concentration of extracts ranging from 25 to 75µL; it was found that the activity was varied with depending upon the concentration [68]. The ethanol, methanol, petroleum ether and aqueous extract from the leaf and boiled leaf of *A. malabarica* were investigated for antibacterial property. In polar studies the maximum zone of inhibition were found against *S. aureus*. Whereas in non-polar studies the maximum zone of inhibition were found against *p. aeruginosa* [69]. The aqueous, petroleumether, acetone and methanolic extracts of *A. indica* showed potent antibacterial activity against *S. citreus*, *P. vulgaris* and *K. pneumoniae* [70]. *In vitro* antibacterial activity of leaf extracts of *A. malabarica* was tested against *E. coli, S. aureus, P. mirabilis, P.aeruginosa, K.pneumonia* by Rajarajan et al. [71]. They reported that the ethanolic extract exhibited a potent antibacterial activity at 200µg/ml and produced 25mm zone of inhibition against *S. aureus* whereas Diethyl ether extract produced 30 mm zone of inhibition in the same concentration.

WEED MANAGEMENT

A. indica was assessed for its potential inhibitory activity against *Phalaris minor* and other weeds of

the wheat crop leaf and root powder applied as mulch at 1 and 2 t ha-1 significantly reduced the emergence and growth of *P. minor* and other weeds of wheat crop similar to herbicide, without any negative effect on the wheat growth and yield. At 2 t ha-1 dose of root powder, there was an enhancement in the grain yield of wheat and suppression of weeds under natural field conditions [27].

ANTIPLASMODIAL ACTIVITY

Among 10 experimental plant extracts tested, the leaf methanol extracts of *A. malabarica*, and *Ricinus communis* showed good antileishmanial activity (IC (50)=126±19.70 and 184±39.33 µg/mL), respectively against promastigotes of *Leishmania donovani* [72].

ANTIINFLAMATORY ACTIVITY

The members of *Anisomeles* have potent antiinflamatory properties [73]. The anti-inflammatory activity of decoctions of leaves and stems of *A. indica* at pre-flowering and flowering stages and possible toxic effects of the decoctions were evaluated [60]. Decoctions of pre-flowering stage demonstrated a significant and dose-dependent anti-inflammatory effect in all three models, while decoctions during flowering stages did not demonstrate significant anti-inflammatory activity. Decoctions of pre-flowering stage demonstrated a significant dose-dependent antihistamine activity and free radical scavenging activities in addition to the membrane stabilizing and cyclooxygenase-I inhibitory activities. However, decoctions of pre-flowering stage failed to impair significantly the *in vitro* activity of lipoxygenase. A 30-day treatment with 500 mg/kg of decoction of pre-flowering stage was not liver toxic or renotoxic, and it did not have a significant effect on body weights. It was noticed that the anti-inflammatory activity of decoction of pre-flowering stage is contributed by cyclooxygenase-1 inhibition, plasma membrane stabilization, antihistamine and free radical scavenging activities, but not by the inhibition of lipoxygenase [60]. Among different compounds examined for their inhibitory effects on the inflammatory mediator's enhanced production from LPS/IFN-gamma-stimulated macrophages, ovatodiolide exhibited potent inhibition on NO, TNF-alpha and IL-12 enhanced production at a concentration of 5 micro M, followed by pedalitin, scutellarein 7-O-beta-d-glucuronide methyl ester and acteoside at 40 micro M. Furthermore, 2 micro M of ovatodiolide, and 20 micro M of 7-methoxy-3,4,5,6-tetrahydroxyflavone and scutellarein 7-O-*B*-d-glucuronide methyl ester significantly arrested the cell cycle of Con A-stimulated spleen cells at the G0/G1 stage[46] different extracts of *A. indica* significantly inhibited the enhanced production of NO radicals, and pro-inflammatory cytokines (TNF-α, and IL-12) induced by LPS/IFN-γ in a dose-dependent manner. Furthermore, methanolic extracts of leaves and flowers significantly and dose-dependently arrest nitrogen-stimulated spleen cells in G0/G1 stage, in addition to their cell proliferation inhibition against Colon 205, MCF 7 and PC 3 by 94, 82; 98, 71; 82, 98%, respectively, at 200 µg/mL concentration [62]. An *in vitro H. pylori* infection model revealed that 95% ethanol extract attenuated *H. pylori*-induced nuclear factor kappa B (NF-κB) activity and interleukin (IL)-8 secretions of gastric epithelial cells [74]. The antiinflammatory activity of the various extracts of *A. malabarica* was evaluated based on their effects on carrageenan-induced paw oedema and cotton pellet granuloma in rats, among the extracts tested ethanol and aqueous extracts of leaves of *A. malabarica* produced significant anti-inflammatory activities in a dose-dependent manner [52]. Presence of *In-vitro* anti-Inflammatory, anti-platelet and anti-arthritic activities to the leaves of *A. malabarica* was reported[75]. Ovatodiolide isolated from *A. indica* inhibited the *H. pylori*-induced inflammatory response by the reduced nuclear factor (NF)-κB activation and interleukin (IL)-8 expressions in *H. pylori*-infected AGS cells. Furthermore, Ovatodiolide attenuated the cytotoxin-associated gene A (CagA) functions by reduced CagA translocation, phosphorylation, and caused hummingbird phenotype of AGS cells [65].

ANTI-PYRETIC ACTIVITY

Anti-pyretic activity of various extracts of *A. malabarica* was evaluated using the brewer's yeast-induced pyrexia in rats. The extracts in dose levels of 50,100 and 200 mg/kg orally were used for anti-pyretic studies. The three extracts have shown a good anti-pyretic effect with all the doses used [52].

ANALGESIC AND ANTIHYPERALGESIC ACTIVITY

Water extracts were made from leaves and stems of both pre flowering (E1) and flowering plants (E2). E1 showed a dose-dependent analgesic effect up to 6 h in rats. Further, the analgesic effect of E1 was not accompanied by toxic effects. This effect was neither gender dependent nor dependent on the stage of the estrous cycle. E1 also showed a dose-dependent antihyperalgesic activity in rats. In contrast, E2 did not show any analgesic effect event

at higher concentration 500 mg/kg. E1 dose-dependently retarded the amplitude of the spontaneous contractions of isolated dioestrous rat uterus. Further, E1 induced a dose dependent plasma membrane stabilization effect on rat erythrocytes. The analgesic and antihyperalgesic effects of E1 are mediated from inhibition of COX-1, thus impairing the synthesis of prostaglandins. A change in chemical contents that accompanies during flowering may be reason for the inability of E2 to demonstrate analgesic effect [15]).

ANTI CANCER ACTIVITY

Among all the extracts of *A. indica* tested 95% ethanol extract significantly inhibited lipopolysaccharide (LPS)-induced expression of inducible nitric oxide synthase (iNOS), as well as production of nitric oxide (NO) and tumor necrosis factor α (TNF-α) by macrophages [74]. The ethnolic extract of *A. malbarica* at a oral dose of 100 mg/kg body weight exhibited a significant protective effect by reduce in liver and serum levels of total protein glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, acid phosphatase, and alkaline phosphatase [76]. Treatment of Ca9-22 cells with ovatodiolide led to cell cycle arrest at G2/M phase. Ovatodiolide treatment also induced apoptosis, as indicated by caspase activation, DNA fragmentation, and poly (ADP-ribose) polymerase (PARP) cleavage. By using specific inhibitors of caspase-9 and -8, they demonstrated that the ovatodiolide-induced apoptosis is dependent on both intrinsic and extrinsic pathways. The action of ovatodiolide was correlated with a rapid and sustained increase in ROS production and down-regulation of FLICE inhibitory protein (FLIP), which is an endogenous caspase-8 inhibitor and is sensitive to intracellular redox status. Pretreatment of Ca9-22 cells with N-acetylcysteine, a thiol antioxidant, abolished all of ovatodiolide-induced effects, including ROS generation, down-regulation of FLIP, caspase activation, apoptosis as well as cell cycle arrest[77]. *n*-hexane and chloroform extracts of *A. malabarica* were cytotoxic to the cervical cancer cells in dose- and duration-dependent manner. The cells that responded to the treatments revealed typical apoptotic features. Early features of apoptosis, phosphatidyl serine translocation and loss of mitochondrial trans-membrane potential, were noticed in the treated cells and comet assay revealed DNA damage. In the FACS analysis, the cells accumulated in the sub-G0/G1 phase of the cell cycle, except in *n*-hexane- and chloroform extract–treated SiHa cells at 24 h, which showed arrest in S- and G2/M phases [20]. Anisomelic acid (AA) was tested for its cytotoxicity and apoptosis-inducing potential in breast and cervical cancer cells. The MTT assay for cell viability indicated that AA is cytotoxic to all types of cell lines tested in a dose- and duration-dependent manner. Acridine Orange and Ethidium Bromide (AO & EB) and Hoechst 33258 staining of AA-treated cells revealed typical apoptotic morphology such as condensed chromatin and formation of apoptotic bodies. The comet assay revealed DNA strand break(s), indicating that AA induces DNA damage which culminates in apoptosis [78]. The antioxidant capacities of *A. indica* methanol extract increased in a dose-dependent pattern. The ovatodiolide purified from the extract of *A. indica* inhibited melanogenesis in B16F10 cells. It was noticed by observing the inhibited mushroom tyrosinase activity (IC (50) = 0.253 mM), the compound also effectively suppressed intracellular tyrosinase activity (IC (50) = 0.469 mM) and decreased the amount of melanin (IC (50) = 0.435 mM) in a dose-dependent manner in B16F10 cells [79]. The effect of *A. malabarica* whole plants methanol extract (AMME) has been studied on cellular redox status during hamster buccal pouch carcinogenesis. Administration of AMME to DMBA - painted hamsters reduced the incidence of SCC and mean tumour burden in addition to preneoplastic lesions. In the buccal pouch, AMME reversed the susceptibility to lipid peroxidation while simultaneously increasing GSH-dependent antioxidant enzyme activities, whereas in the liver and erythrocytes, the extent of lipid peroxidation was reduced with elevation of antioxidants. Thus, modified oxidant status together with antioxidant adequacy in the target organ as well as in the liver and erythrocytes induced by AMME may significantly reduce cell proliferation and block tumour development in the HBP. AMME has been shown to prevent the increase in lipid peroxidation and protect against oxidative DNA damage by improving antioxidant defenses. Among the doses used in the present study, the medium dose and higher dose of AMME (250 mg/kg bw and 500 mg/kg bw) were found to be more effective in inhibiting HBP carcinogenesis compared to low dose. They also reported that the protective role of AMME against HBP carcinogenesis may be related to the antioxidant and anti proliferative properties of phytochemicals such as flavonoids present in the plant [80]. Hsu *et al*. [81] reported that *A. indica* hexane extract (AIE) can induce cellular death in FaDu human pharynx squamous cancer cells by apoptosis. They found that AIE significantly inhibited migration and invasion of FaDu cells in a

dose-dependent manner under non-cytotoxic concentrations. Western blotting analysis revealed that AIE treatments inhibited the expression of matrix metalloproteinase-9 (MMP-9) and MMP-2 proteins dose-dependently. Moreover, according to enzyme-linked immunosorbent assay (ELISA) and gelatin zymographic assay. The expression of MMP-9 and MMP-2, both proteins declined significantly with an increasing AIE dose. AIE can inhibit the migration and invasion of FaDu cells by suppressing the expression of MMP-9 and MMP-2. AIE also exhibited potent cytotoxicity toward FaDu cells in a time-dependent manner (IC50 = 60.1 μg/ml for 24 h treatment and 29.7 μg /ml for 72 h. in comparison, AIE displayed lower sensitivity to normal lung fibroblast MRC-5 cells (IC50 = 102.7 μg/ml for 24 h treatment). They also observed typical morphological changes of apoptosis, such as cell shrinkage, rounding, apoptotic vacuoles and forming majority of the floating cells through microscopically. Cytometric analysis revealed that FaDu cells were arrested at the G2/M phase. Moreover, AIE induced FaDu cell death mainly via the apoptosis pathway and partly via the necrosis pathway. The extract induced FaDu cell apoptosis by down-regulating Bcl-2 and Bcl-xL protein expression, up-regulating Bax and Bak protein expression, and activating caspase-9 and caspase-3 [82]. The anti-metastatic potential of *A. indica* aqueous extract (AI) and its isolated compounds apigenin, ovatodiolide, β-sitosterol and acteoside in 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced human breast adenocarcinoma MCF-7 cells was evaluated. Among the test agents, crude extract AI and pure compound apigenin potently suppressed the TPA-induced MCF-7 cells migration and invasion. In addition, AI and apigenin time- and dose-dependently down regulated the matrix metalloproteinase (MMP)-9 enzymatic activities and its mRNA expression. Furthermore, AI and apigenin also down regulated the nuclear factor (NF)-κB subunit p65, and activator protein (AP)-1 subunit c-Fos proteins expression in nucleus and, transcriptional activity of NF-κB and AP-1[83]. The anti-rheumatic and immunomodulatory properties of the methanolic extract of the plant *A. malabarica* was evaluated [84]. The three extracts i.e., aerial parts, leaves and roots inhibited TNF-α production in 1 μg/mL concentration. 38.75 % inhibition of TNF-α was noticed at 200 μg extracts of the aerial parts of the plant followed by 17.64 and 14.94 % by the roots and leaves respectively. .

ANTIOXIDANT ACTIVITY

The members of the genus *Anisomeles* have potent antioxidant properties [85]. Among different plants tested for antioxidant properties *Cassia occidentalis, Clitoria ternatea, Trianthema decandra, Capparis zeylanica, Anisomeles malabarica* and *Plumbago zeylanica* exhibited strong antioxidant characteristics, when compared to other plants [86]. The ethyl-cetate extract of leaves from *A. malabarica* was tested for antioxidant property by using Free radical scavenging assays such as hydroxyl, superoxide anion radicals, 2,2-diphenyl-1-picryl hydrazyl (DPPH) and 2,2'-azinobis-(3-ethyl-enzothiazoline-6-sulfonic acid) (ABTS) radical scavenging. They found that the extract effectively scavenged hydroxyl and superoxide anion, DPPH and ABTS radicals. All the concentrations of leaf extract have prominent free radical scavenging and antioxidant power and the preventive effects were in a dose-dependent manner [87]. The methanolic extract of whole plant of *A. malabarica* contains significant quantities of the antioxidant principles compared to the other solvent extracts [64]. The antioxidant capacities of *A. indica* methanol extract was evaluated by using DPPH assay, ABTS radical scavenging assay, reducing capacity and metal ion chelating capacity and found that the antioxidant capacities of *A. indica* methanol extract increased in a dose-dependent pattern [79]. Methanolic extract of *A. indica* shows the better free radical scavenging property when compared to aqueous extract [12]. The antioxidant activity of whole plant (*A. malabarica*) was assessed by hydroxyl radical scavenging activity, FRAP assay, nitric oxide radical scavenging activities. The significant free radical scavenging activity was found in methanolic extract than that of standard. The radical scavenging activity of the extract was increased with increasing concentration [87]. Prominent *in vitro* antioxidant potential of ethanolic extract of *A. malabarica* was reported [88]. Significant antioxidant activity of the essential oil obtained from *A. indica* was reported [51]. *In vitro* antioxidant assay by DPPH free radical scavenging activity and reducing ability with leaf extracts of *A. malabarica* was evaluated. It was found that methanol and hexane extracts showed good potency of antioxidant property. Comparative study of these crude extracts revealed that methanol extract was more effective than hexane [89]. Methanol and hexane leaf extracts of *A. malabarica* showed good potency of antioxidant activity. Comparative study of these crude extracts revealed that methanol extract was more effective than

hexane. Methanol extract showed very good antiradical activity and reductive ability [89].

ANTI-EPILEPTIC AND ANTICONVULSANT ACTIVITY

The anticonvulsant potential of chloroform, ethyl acetate and methanol extracts of leaves of *A. malabarica* against pentylenetetrazole (PTZ) and maximal electroshock (MES) induced convulsions was tested. All the three extracts were administered (i.e. 100, 200, 400 mg/kg, p.o.) for 7 days and at the end of the treatment convulsions were induced experimentally. High doses (400 mg/kg, p.o.) of chloroform and ethyl acetate extracts both significantly decreased the extent of MES- and PTZ-induced convulsions. On the other hand, ethyl acetate extract at lowest and medium selected doses (i.e. 100 mg/kg, p.o. and 200 mg/kg, p.o., respectively, for 7 days) had also significantly attenuated PTZ-induced convulsions. However, methanol extract at any of the doses used (i.e. 100, 200 and 400 mg/kg, p.o.) did not show any significant effect on PTZ- and MES-induced convulsions [90]. Single dose pretreatment with total flavonoids fraction of *A. malabarica* (25 and 50 mg/kg, i.p.) has found to be effective against both maximal electroshock and pentylenetetrazole - convulsions, but associated with a marked decrease in locomotor activity and motor activity performance (i.e., neurotoxic effects), similar to that of diazepam treatment. Interestingly, chronic treatment with total flavonoids fraction at lower doses (6.25 and 12.5 mg/kg, i.p., 1 week) has also produced significant antiepileptic activity, but without causing neurotoxic effects [91]. Pretreatment with ethyl acetate extract of *A. indica* at concentrations of 200, 400 mg/kg, po, for 1 week showed significant antiepileptic activity against pentylenetetrazole induced convulsions. Isolated flavonoid fraction showed more potent antiepileptic activity as compared to ethyl acetate extract, without any neurotoxic effect [92].

LARVICIDAL ACTIVITY

The acetone, chloroform, ethyl acetate, hexane, and methanol dried leaf, flower, and seed extracts of *Achyranthes aspera, Anisomeles malabarica, Gloriosa superba, Psidium guajava, Ricinus communis* and *Solanum trilobatum* were tested against the larvae of cattle tick *Rhipicephalus microplus*, sheep internal parasite *Paramphistomum cervi* at 2,000 ppm and fourth instar larvae of *Anopheles subpictus* and *Culex tritaeniorhynchus* at 1,000 ppm. All plant extracts showed moderate effects after 24 h of exposure; however, the highest parasite mortality was found in the leaf ethyl acetate extract of *A. aspera*, leaf methanol extract of *A. malabarica*, flower methanol extract of *G. superba* and leaf methanol extract of *R. communis* were potent against the larvae of *R. microplus* (LC_{50} = 265.33, 95.97, 153.73 and 181.49 ppm; LC_{90} = 1,130.18, 393.88, 1,794.25, and 1,829.94 ppm); leaf acetone and chloroform of *A. malabarica*, flower acetone extract of *G. superba*, and leaf chloroform and methanol of *R. communis* were toxic against the adult of *P. cervi* (LC_{50} = 108.07, 106.69, 157.61, 69.44, and 168.24 ppm; LC_{90} = 521.77, 463.94, 747.02, 256.52, and 809.45 ppm); leaf ethyl acetate extract of *A. aspera*, leaf chloroform extract of *A. malabarica*, flower methanol of *G. superba* and leaf methanol extract of *R. communis* were active against the larvae of *A. subpictus* (LC_{50} = 48.83, 135.36, 106.77, and 102.71 ppm; LC_{90} = 225.36, 527.24, 471.90, and 483.04 ppm); and leaf ethyl acetate extract of *A. aspera*, leaf chloroform extract of *A. malabarica*, flower methanol extract of *G. superba*, and leaf methanol extract of *R. communis* were effective against the larvae of *C. tritaeniorhynchus* (LC_{50} = 68.27, 95.98, 59.51, and 93.94 ppm; LC_{90} = 306.88, 393.83, 278.99, and 413.27 ppm), respectively [93]. The larvicidal activity of two indigenous plants, *A. malabarica* and *Phyllanthus emblica* against the larvae of economically important malarial vector, *Anopheles stephensi* under laboratory condition was evaluated and found that the methanol extract of both the plants showed significant larvicidal activity and also combined extracts (synergistic) exhibit highest larval mortality [94]. The egg hatching and larvicidal effect of indigenous plant extracts were investigated against the sheep parasite, *Haemonchus contortus*. The efficacy of leaf, bark, and seed ethyl acetate, acetone and methanol extracts of *Andrographis paniculata*, *Anisomeles malabarica*, *Annona squamosa*, *Datura metel* and *Solanum torvum* were tested against *H. contortus* using egg hatch assay (EHA) and larval development assay (LDA). All plant extracts showed moderate parasitic effects after 48 and exposure for egg hatching and LDA, respectively [95]. Dharmasiri et al., [96] studied the gastroprotective effects of *Anisomeles indica.*

CONCLUSION

Members of the genus *Anisomeles* are widely used in traditional system of medicine from several decades in many countries like India. Now the scientific research on these species suggests that these plants have pharmaceutical importance.

Presence of chemicals which support various biological activities are presented in this paper providing evidence for use of these plants in developing new drugs for curing various ailments. There is a need to standardize methods for isolation of active principles in pure forms to produce new standardized drugs. The active principles which are present in these plants showing strong antioxidant, antiinflammatory and anticancer properties. In these days it is very essential to develop natural drugs against cancer. Development of natural antioxidants from these plants help the food and pharmaceutical industries.

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