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Review

Ethnobotany, phytochemistry and pharmacology of *Ageratum conyzoides* Linn (Asteraceae)

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In the present review, an attempt has been made to congregate the traditional, phytochemical and pharmacological studies done on an important medicinal plant, *Ageratum conyzoides* Linn. (Family Asteraceae) which is widely spread all over the world, especially in the tropical and subtropical region. There are many reports on folk and traditional uses that include wound dressing, skin diseases, ophthalmic, colic, ulcers treatment, diarrhoea, dysentery, fever, gynecological diseases, sleeping sickness, mouthwash, anti-inflammatory, insecticides, etc. Phytochemical investigations have revealed that many components are bioactive due to the presence of broad range of secondary active metabolites such as terpenoids, flavonoids, alkaloids, steroids, and chromene. The plant has been examined on the basis of the scientific *in vitro*, *in vivo* or clinical evaluations possessing the major pharmacological activities that includes analgesic activity, antimicrobial activity, anti-inflammatory activity, spasmolytic effects, gamma radiation effects, anti cancer and radical scavenging activity, anti-malarial activity and others activities. The information summarized here is intended to serve as a reference tool to practitioners in the fields of ethnopharmacology, natural product chemistry and drug discovery related research.

Key words: *Ageratum conyzoides,* terpenoids, flavones, isoflavone.

INTRODUCTION

The genus *Ageratum* is derived from the Greek words '*a geras'* meaning non-aging which refers to long life-time of plant and the species epithet '*konyz*' is the Greek name of *Inula helenium* which resembles the plant. *Ageratum conyzoides* Linn. (Family Asteraceae, Tribe Eupatoriae) is an annual herb with a long history of traditional medicinal use in the tropical and sub-tropical region of the world, commonly known as Billy goat weeds. The stems and leaves of the plant are covered fully with fine white hairs.

The leaves are ovate in shape and grow up to 7.5 cm long. The flowers are arranged in terminal inflorescences which are white in colour. The fruits are achaenes and easily dispersed by air. The mature plant is used for its haemostatic, anti-inflammatory, antispasmodic, antiasthmatic, properties for the treatment of wounds and in bacterial infections (Kokwaro, 1976; Gonzalez et al., 1991). The essential oil found in it can inhibit the growth and production of toxigenic strain of *Aspergillus parasiticus* (Patil et al., 2010), a new biological activity which indicates as a useful tool for a better understanding of the complex pathway of aflatoxin biosynthesis (Nogueira et al., 2010). The plant extract is found to have cardiovascular depressant activity, has antispasmodic effects (Achola et al., 1994), antioxidant activity and insecticidal activities (Amal et al., 2010). *A. conyzoides* has larvicidal and growth inhibitory activity exhibited in the 2nd and 4th instar larvae of the *Anopheles stephensi* (Neetu et al., 2011). The water soluble fraction (WSF)

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obtained from a hydroalcohol extract of *A. conyzoides*, was evaluated for possible analgesic and anti-inflammatory activities (Jose et al., 1997). It was also demonstrated that WSF (20 to 50 mg/kg; i.p.) treatment reduced the articular incapacitation induced by carrageenin (300 µg) in rats. A number of flavones have been isolated including 8-hydroxy-5, 6, 7, 3, 4, 5-hexamethoxy flavones (Gill et al., 1978). Besides these, the genus is well known for its chromenes and flavonoids contents (Gonzalez et al., 1991). In India, ayurvedic study has found out that the root of the plant is useful in fever and possesses anti-helmintic and anti-dysentric properties (Kirtikar and Basu, 1991). However, studies reveal that the plant contains toxic properties and inhibits the growth of other native plants of the invaded area, thereby leading to declination of the productivity (Perumal et al., 1999). The essential oil obtains by steam distillation has been reported to have a powerful nauseating odour (Sood, 1973). The plant is not eaten by humans except when taken as medicinal purposes; however, it is used to feed fish, domestic guinea pigs, cattle and horses. In Manipur, India, the whole plant is used traditionally as hair lotion known as '*Cheng- hi'* which is prepared by boiling the plant with rice water. The plant has also been found to be poisonous to rabbits due to the presence of coumarin and hydrogen cyanide (HCN) (Abbiw, 1990). It has also been reported that the plant might contain allelochemicals when the acetone extract residue of the plant inhibits the germination and growth of the roots and shoots of other plants (Kato-Naguchim, 2001). It has been said that crude extracts from *A. conyzoides* offer the possibility of biocontrol of plant pathogenic fungi (Iqbal et al., 2004). The leaves of the plant are reported to have anti-inflammatory properties, with no apparent hepatotoxicity (Moura et al., 2005). The released water-soluble phenolic acids contents from the leaf debris of the plant into the soil environment affect the early growth of rice to a worst extent (Daisy et al., 2009). The essential oil of *A. conyzoides* has very strong smell and has been tested for its anti-inflammatory, analgesic and anti-pyretic activities (Abena et al., 1996b).

This review is aimed to summarize on pharmacological, biological activities of this valuable herbs.

ETHANOBOTANY AND TRADITIONAL USES OF *A. CONYZOIDES*

Traditionally, *A. conyzoides* has been used in various parts of the world like Africa, Asia and South America as folk medicine. The whole plant produces volatile strong smelled oil which also possesses various biological activities. It is used for wound dressing, curing various skin diseases, ophthalmic, colic, ulcers treatment, as purgative and febrifuge (Girthens, 1948). The decoction or infusion of the herb is given in stomach ailments such as diarrhoea, dysentery, intestinal colic, flatulence, rheumatism fever (Chopra et al., 2002), and gynaecological diseases (Sharma and Sharma, 1995). Other folk remedies include anti-itch, sleeping sickness, and mouthwash for toothache, antitusive, vermifuge, tonic and killing lice (Burkill, 1985; Kapur, 1993). The leaves are used for application on cuts, sores (Ahluwalia, 1968; Gangwar and Ramakrishnan, 1990; Dutta and Nath, 1998; Sudhakar and Chetty, 1998; Upadhay et al., 1998), anti-inflammatory agent, haemostatic (Jain and Puri, 1990; Banerjee and Banerjee, 1986; Jamir, 1990; Suresh et al., 1995; Kumar and Jain, 1998), insecticide (Ramachandran and Nair, 1981), skin diseases (Sankaran and Alagesaboopathi, 1995), ringworm infection (Upadhye et al., 1986), antidote to snake poison (Neogi et al., 1989; Jain and Sahu, 1993), malarial fever, antitetanus, uterine problems (Rajwar, 1983), prolaps of anus (Siddiqui and Husain, 1992), swollen piles (Singh, 1988), throat infection, painful gums, abscess for early suppuration, wound healing and leucorrhoea (Sharma et al., 1985; Sahoo and Mudgal, 1993; Dagar and Dagar, 1996; Katewa and Arora, 1997) and infant diarrhoea (Hemadri and Rao, 1989). It has been reported to have nematocidal activity and potential used in controlling pests (Gravena et al., 1993). The plant has an antienteralgic and antipyretic, for cuts as a wound dressing (Nair et al., 1977). In India, it is used for leprosy treatment and as an oil lotion for purulent opthalmia. Besides these, it is used for preparing local hair lotion in Manipur, India for treating dandruffs. In some parts of Africa, the plant is used for headaches, dyspnoea, mental and infectious diseases. The leaves crushed in water are applied intravaginally for uterine troubles and also given as emetic. In Central Africa, the plant is applied for treating burnt wounds, while in Kenya it is used as antiasthmatic, antispasmodic and for haemostatic effects traditionally. In Brazil, the leaves of this plant are served as anti-inflammatory, analgesic and anti-diarrhoeic. The plant is also particularly used for treatment of gynecological diseases in Vietnam (Nair et al., 1977). The plant also has a number of magical and superstitious attributes, like against snake bites. In western part of Nigeria, it is believed that incantations help against witches and bad medicine. In Congo, the leaf sap is believed to improve luck of card players (Burkill, 1985). The leaf of the plant is reported to have hematopoietic potentials which could possibly cure anaemia (Burkill, 1985) and further reported to have gastroprotective activity (Shirwaikar et al., 2003).

The plant is reported to be one among the selective weeds which can be used successfully as substrate for oyster mushroom cultivation and also helps to increase its protein content and production time (Nirmalendu and Mina, 2007). It was further reported to yield high value of improved vegetative growth and numerous open flowers when *Ageratum* was grown for a time period of 28 days under a radiation mixture of blue, red or far-red light and within a controlled closed system which is very helpful in

the field of horticulture for higher profit (Jeong et al., 2006).

PHYTOCHEMISTRY OF *A. CONYZOIDES*

Monoterpenes and sesquiterpenes

So far, a total of 51 constituents have been reported from the analysis of the *Ageratum* oil sample from Nigeria as the highest which include 20 monoterpenes (6.6%) of which 1% of it contains sabinene, 1.6% contains β-pinene and β-phellandrene, 2.9% contains 1.8-cineole and limonene, 0.6% contains terpenen-4-ol and 0.5% contains α-terpineol and further found 20 sesquiterpenes (5.1%) and that of single substance were found to be in traces approximately 0.1%. Indian *Ageratum* oil is found to contain 5.3% ocimene which was found in traces from Nigerian plant, 6.6% α-pinene, 4.4% eugenol and 1.8% methyleugenol (Rao and Nigam, 1973).

The major sesquiterpenes are beta-caryophyllene, 1.9 to 10.5% from an oil sample obtained from Cameroon and 14 to 17% in a Pakistani oil sample. Another sesquiterpene, δ- cadinene occurred in approximately 4.3% in the oil received from Indian plants (Rao and Nigam, 1973). Sesquiphellandrene and caryophyllene epoxide have been obtained in 1.2 and 0.5%, respectively from leaves (Ekundayo et al., 1988). The summary is as shown in Table 1.

Benzofuran, chromene, chromone and coumarin

Precocene I (Figure 1a) or 7-methoxy-2,2-dimethlchromene ranging from 30 (Vietnamese oil) to 93% (Congo oil) (Pham et al.,1976; Sharma et al., 1980; Wandji et al., 1996) while Precocene II (Figure 1b) ranging from 0.7% (Quijano et al., 1982) to 55% (Pham et al.,1976) while cumarine (5.01%) and trans-caryophyllene (3.02%) are the most common components of essential oil of *A. conyzoides*. They are found to have *Aspergillus flavus* suppressing activity and also completely inhibit the growth of *Rhizoctonia solani* and *Sclerotium rolfsii*. Ageratochromene dimer is also reported from the essential oil (Burkill, 1985) which believes the genus is chemically closer to the Ageritanae subtribe and possesses chemotaxonomic activity to the Piqueriiae group (Burkill, 1985).

Seven other chromene derivatives are isolated from oil in the aerial part of the plant. They are 2,2-dimethylchromene-7-o-β-glucopyranoside (Figure 1c) (Nair et al., 1977); 6-(1-methoxyethyl)-7-methoxy-2,2-dimethylchromene; 6-(1-hydroxyethyl)-7-methoxy–2,2-dimethylchromene; 6-(1-ethoxyethyl)-7-methoxy-2,2-dimethylchromene; 6-angeloyloxy-7-methoxy-2,2-dimethylchromene, 3-(2-methylpropyl)-2-methyl-6,8-demothoxychrom-4-one, 2-(2-methylethyl)-5,6-dimethylbenzofuran and a mixture of ageratochromene dimer (Figure 2a) and encecanescin (Figure 2b) (Nair et al., 1977). 1.219% of coumarin and a minor amount of benzo-uran and its derivatives are yielded from its essential oil.

Flavonoids and alkaloids

A total of 21 polyoxygenated flavonoids have been reported from the species which includes 119 polymethoxylated flavones, namely scutellarein-5,6,7,1-tetrahydroxyflavone, quercetin, quercetin-3-rhamnopiranoside, kaempferol, 14 polymethoxy flavones (Figure 3a), Eupalestin (Figure 3b), quercetin-3-rhamnopiranoside (Figure 3c) and kaempferol 3,7-diglucopiranoside (Nair et al., 1977). A novel isoflavone glycoside, 5,7,2,19-tetrahydroxy-6,3-di-(3,3-dimethylallyl)-isoflavone 5-O-α–L-rhamnopyranosyl–(1→19)–α-L-rhamnopyranoside was isolated from the stems (Gill et al., 1978).

Some alkaloids found in *Ageratum* species are lycopsamine (Figure 4a), echinatine (Figure 4b), caffeic acid (Figure 4c), phytol (Figure 4d), 2-(2'-methylethyl) 5,6-dimethyoxybenzofuran (Figure 4e), 2-(2-methylprop-2-enyl)-2-methyl-6,7-dimethoxychromane-4-one, 2-(1'-oxo-2'methypropyl)-2- methylpropyl)-2-methyl-6,7-dimethoxychromene (Figure 4f) and 3-(2'-methylpropyl)-2-methyl-6,8-demothoxychrom-4-one (Figure 4g) (Adewole, 2002).

Pyrrolizidine alkaloids (PA_S) are widely distributed in Asteraceae family (particularly in tribes Senecioneae and Eupatorieae), but only lycopsamine and echinatine (isomeric) are isolated from this plant (Nair et al., 1977). Other common compounds isolated are sesamin, aurantiamide acetate, fumaric acid, caffeic acid, phytol and hydrocarbons $nC_{27}\ H_{56}$ to $nC_{32}\ H_{66}$ (Nair et al., 1977; Pari et al., 1998). The flowers were reported to contain vitamins A and B (Nair et al., 1977; Tyagi et al., 1995).

Triterpenes and steroids

The oil from leaves and stems of this plant is reported to contain sterols like friedeline (Figure 5a), beta-sitosterol (Figure 5b) and stigmasterol as major constituents and minor sterols include brassicasterol (Figure 5c) (Okunade, 2002). The presence of beta-sitosterol and stigmasterol in various tissue samples and plants parts of *A. conyzoides* were confirmed by thin layer chromatography (TLC) for beta-sitosterol (Rf 0.95, Melting point 139 to 140) and stigmasterol (Rf 0.89, Melting point 142 to 144). Sterols content were found to be higher in 6 weeks old tissue of *A. conyzoides*. In case of *in-vivo* plant parts, *A. conyzoides* was observed slightly higher in stem (0.0868%) followed by leaves (0.0656%) and roots (0.0533%) (Sarin and Bansal, 2011).

Table 1. Compounds isolated from A. *conyzoides*.

Compound	Class	Source	Country	Reference
Ageratochromene dimer	Chromene	Oil	India	Katsuri et al. (1973)
B-caryophyllene	Sesquiterpene	Oil	India	Ekundayo et al. (1988)
Brassicasterol	Sterol	Oil	India	Dubey et al. (1989)
Caffeic acid	Secondary metabolites	Oil	India	Nair et al. (1977)
Caryophyllene epoxide	Sesquiterpene	Oil	India	Ekundayo et al. (1988)
Dihydrobrassicasterol	Sterol	Oil	India	Dubey et al. (1989)
Echinatine	Alkaloids	Whole plant	Mexico	Wiedenfeld and Roder (1991)
Eugenol	Terpenes	Oil	India	Ekundayo et al. (1988)
Fumaric acid	Secondary metabolites	Oil	India	Nair et al. (1977)
Kaempferol-3,7- diglucopiranoside	Flavonoid	Oil	India	Nair et al. (1977); Gill et al. (1978)
Lycopsamine	Alkaloids	Oil	Mexico	Wiedenfeld and Roder (1991)
Methyleugenol	Terpenes	Oil	India	Ekundayo et al. (1988)
Ocimene	Terpenes	Oil	India	Rao et al. (1973)
Precocene I(7-methoxy-2,2´-dimethylchromene)	Chromene	Oil	Brazil	Wandji et al. (1996)
Precocene II (ageratochromene)	Chromene	Oil	India	Quijano et al. (1980); Iqbal et al. (2004)
Sesquiphellandrene	Sesquiterpene	Oil	India	Ekundayo et al. (1988)
Spinasterol	Sterol	Oil	India	Dubey et al. (1989)
Vitamins A& B	Vitamin	Flower	India	Tyagi et al. (1995)
α-pinene	Terpenes	Oil	India	Rao et al. (1973)
β-pinene	Terpenes	Oil	India	Ekundayo et al. (1988)
δ- cadinene	Sesquiterpene	Oil	India	Rao et al. (1973)
2-(1´-oxo-2´-methylpropyl)-2- methyl-6,7-dimethoxy- chromene	Chromene	Oil	India	Pari et al. (1998)
2-(2´-methylprop-2´-enyl)-2-Methyl-6,7-dimethoxychroman-19-one	Chromene	Oil	India	Pari et al. (1998)
-(2´-methylpropyl)-2-methyl-6,8-dimethoxychrom-19-one	Chromene	Oil	India	Pari et al. (1998)
2-(2´-methylethyl)-5,6- Dimethoxybenzofuran	Benzofuran	Oil	India	Pari et al. (1998)
5,7,2´,19´- tetrahydroxy-6,3´-di-(3,3-dimethylallyl)- isoflavone 5-o-α-L- rhamnopyrosyl-(1→19)-α L-rhamnopyranoside	Isoflavone	Stem	India	Yadava et al. (1999)
Methyl-6,7-dimethoxy chromene	Chromene	Oil	India	Pari et al. (1998)
(+) –sesamin	Alkaloids	Oil	-	Gonzalez et al. (1991)

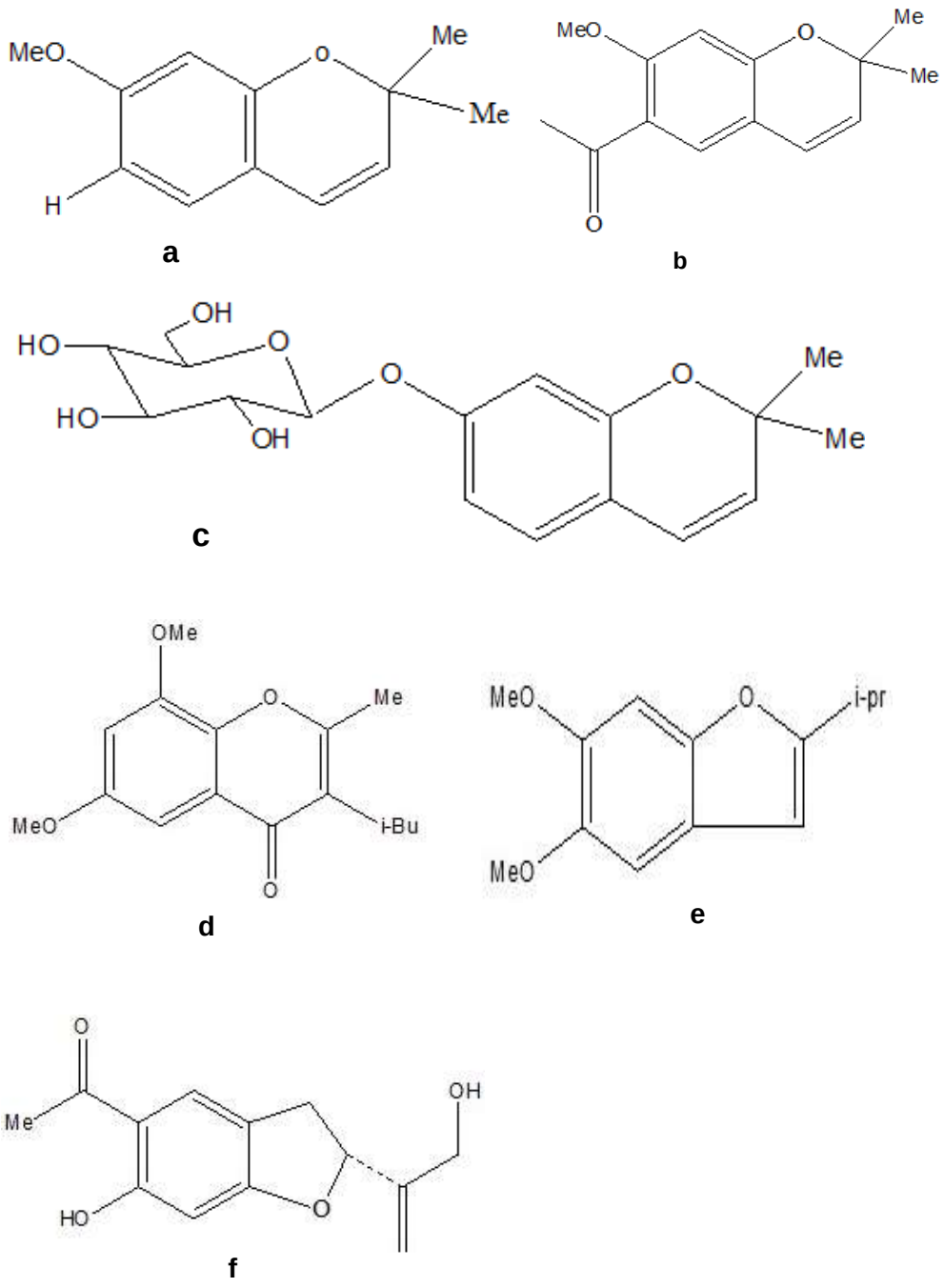

Figure 1. Organic structures of (a) Procene I; (b) Procene II; (c) 2,2-dimethylchromene-7-O-beta-glucopyranoside; (d) 3-(2'-methylpropyl)-2-methyl-6,8-demethoxychrom-4-one; (e) 2-(2'-methylethyl)-5,6-dimethoxybenzofuran; (f) 14-Hydroxy-2H beta3-dihydroeuparine.

Yield of essential oils

The oil content was found to be 0.2% from water distillation of the fresh flowers (Sood, 1973) and that of leaves and root were found to be 0.11 to 0.58% and 0.03 to 0.18%, respectively, depending on the seasons. The oil yielded from petroleum ether extract was reported to be 26% (Devdhar and Rao, 1970).

PHARMACOLOGICAL PROPERTIES OF *A.CONYZOIDES*

Analgesic activity

A. conyzoides extract showed strong indications of biological activity in *in vitro* receptor radio ligand binding assays (Bradykinin II) expressed in Chinese hamster

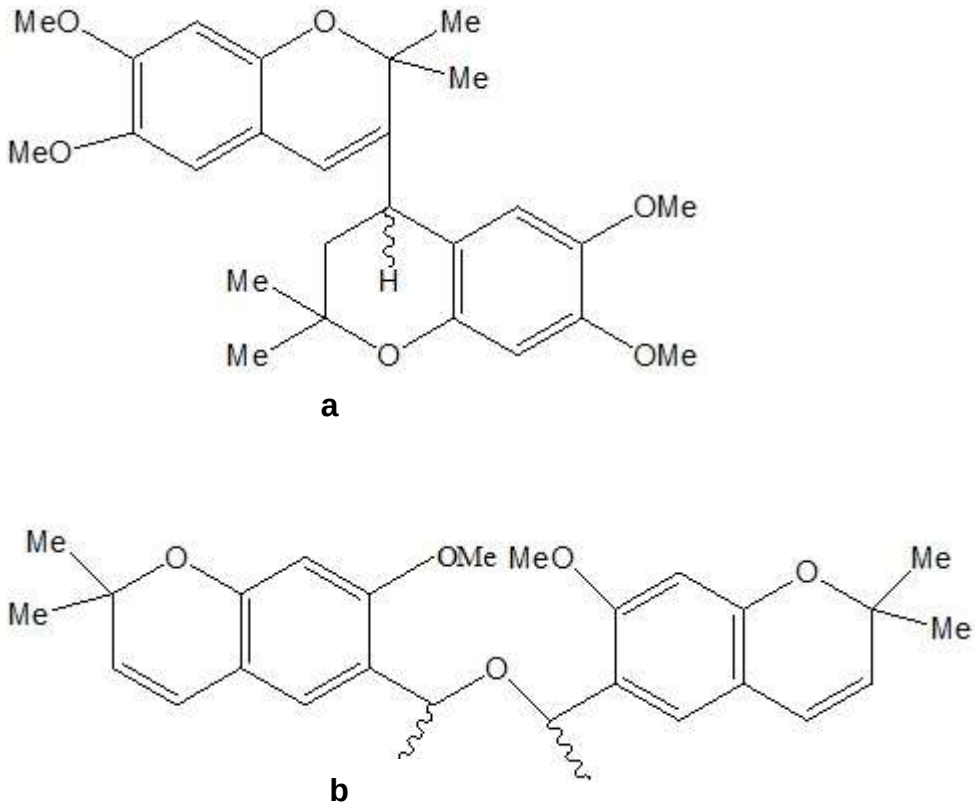

Figure 2. Organic structures of (a) Ageratochromene dimer; (b) Encecanescin.

ovary cells, Neurokinin1 expressed in astrocytoma cells and calcitonin gene related peptide. The WSF of the plant extract produces peripheral analgesic activity and an anti-inflammatory action, which seems to occur in leucocyte-dependent inflammatory events (Magalhaes et al., 1997). They are implicated in the mediation of acute pain in the mammalian central nervous system (Sampson et al., 2000).

Antimicrobial activity and wound healing effects

Essential oil has strong toxicity against the fungi causing ringworm, *Epidermophyton floccosum, Trichophyton mentagrophytes* and *Microsporum gypseum*, with the inhibition of the mycelia being 80.28, 78.43 and 68.24%, respectively (Mishra et al., 1991). The extract of leaves, however, had no effect on the conidial germination of the fungus *D. oryzae* (Ganesan and Krishnaraju, 1995). Aqueous extract was tested against three Gram-positive bacteria and seven Gram-negative bacteria and evaluated by the filter paper disc diffusion method. Results showed a significant control of the growth of *Alcaligenes viscolactis, Klebsiella aerogenes, Bacillus cereus* and *Streptococcus pyogenes* (Moody et al., 2004). *In vitro*, the minimum inhibition concentration (MIC) and anti-methicillin resistant *Staphylococcus aureus* test (MRSA) for ethanol and water extracts were recorded as 30.6 to 193.0 and 195.19 to 71.0 µg/kg, respectively, while the minimum bactericidal concentration (MBC) for both extracts was found to be higher (Akinyemi et al., 2005). Petroleum ether extract was found to be effective against *S. aureus*. However, a study in Nigeria reported that methanolic extract has no inhibition for various strains of *S. aureus* (four strains), *Escherichia coli* (two strains), *Pseudomonas aeruginosa* (one strain), *Proteus* species (three strains), and *Shigella* species (one strain) using the well diffusion method (Chah et al., 2006). The essential oil has antimicrobial and anticonvulsant activities (Whittle and Turner, 1981). The oil was reported to inhibit 20 bacteria out of 22 bacteria (Gram positive cocci and rods and Gram negative rods) and 4 fungi namely *Candida albicans* SP-14*, Cryptococcus neoformas* SP-16*, S. rolfsii* SP-5 and *T. mentagrophytes* SP-12 out of 12 fungi (3 yeast like and 9 filamentous) (Pattnaik et al., 1999). Further, the oil is effective against *Penicillium chrysogenum* and *Penicillium javanicum* (Rao and Nigam, 1973; Ekundayo et al., 1988). The oil also provides 100% inhibition of the mycelial growth and germination of the spores of *Didymella bryoniae* (Fiori et al., 2000). Wound healing properties were also determined using the excision wound model. More than 90% wound healing was recorded in the extract, whereas 72% healing was observed in the distilled water-treated group

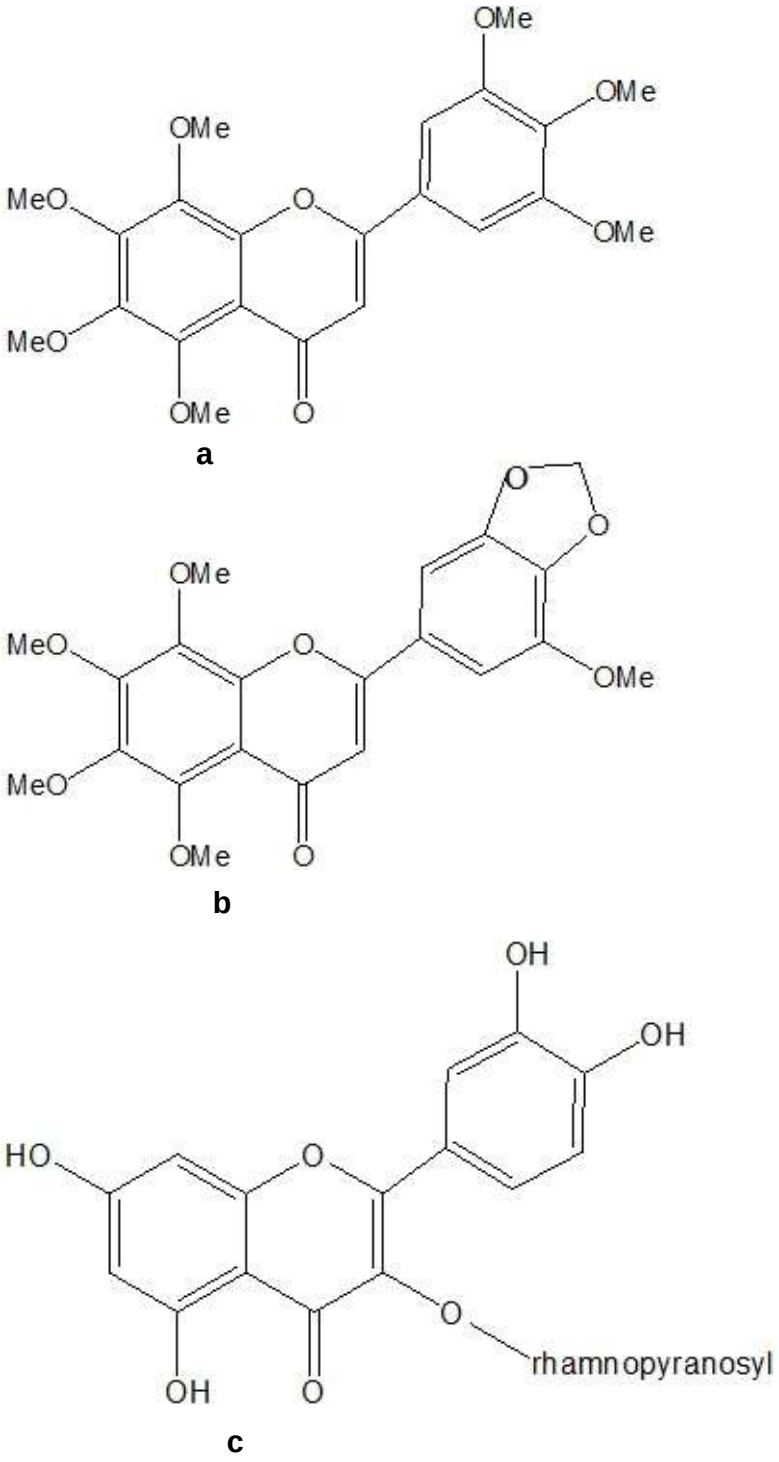

Figure 3. Organic structures of (a) 14 Polymethoxy flavones; (b) Eupalestin; (c) Quercetin-3-rhamnopiranoside

(Almagboul et al., 1985). Methanolic extract was found to have wound healing property (Chah et al., 2006). On the other hand, it showed very potent antibacterial activity against *Helicobacter pylori*, a Gram negative micro-aerophilic bacterium which is a major etiological agent in duodenal, peptic and gastric ulcers (Roland et al., 2007). The wound healing effect of the *A. conyzoides* methanolic extract was studied in Wistar rats (n=10). Wounds prepared in excised areas of the skin were packed with gauze soaked by the extracts and were determined

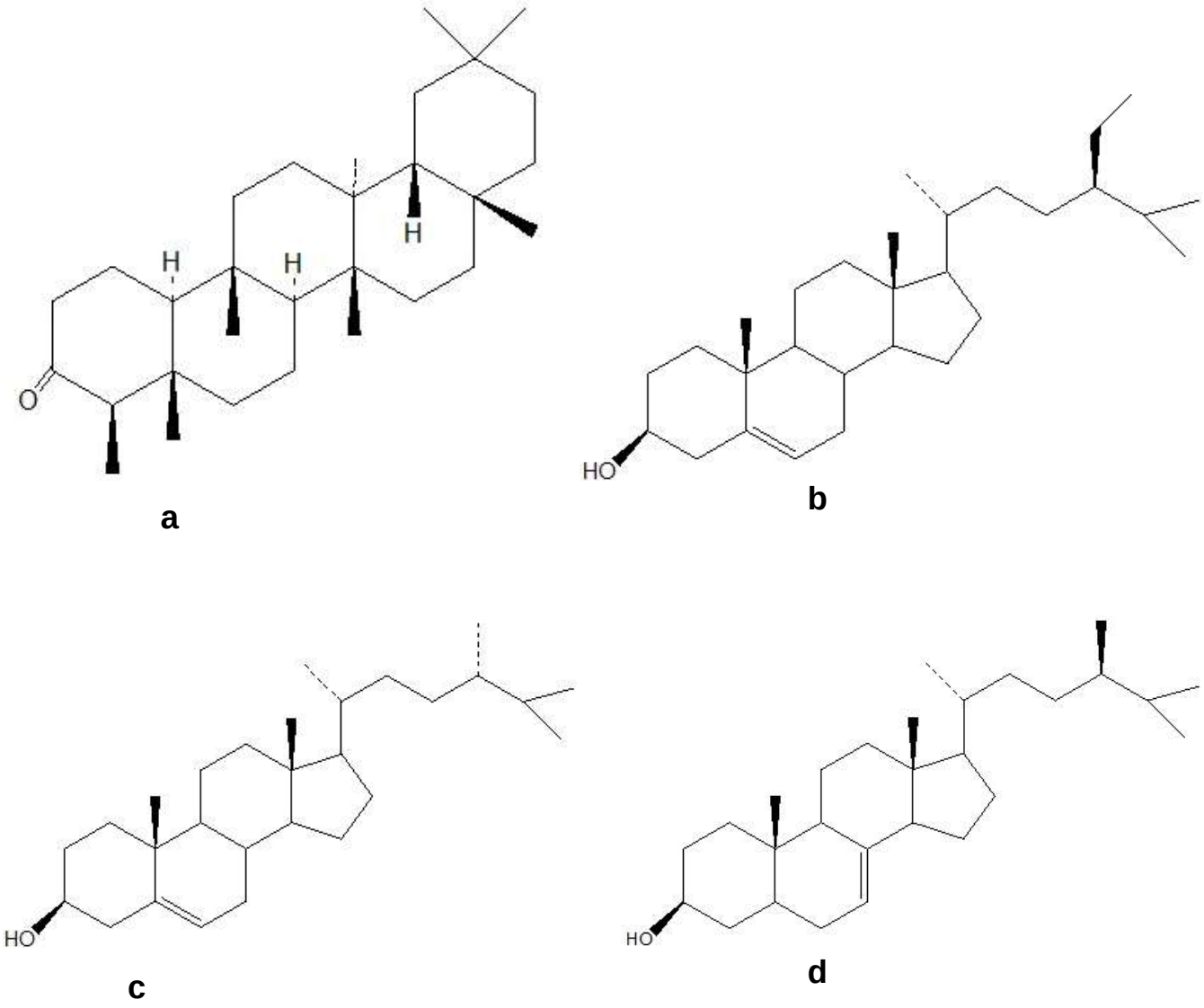

Figure 4. Organic structures of (a) Friedeline; (b) Beta-Sitosterol; (c) Brassicasterol; (d) Spinasterol.

histologically after 10 days. The *Ageratum* sections showed fewer inflammatory cells and more fibrosis than the controls. In a study, it was found that wounds treated with aqueous leaves extract in combination with honey and with solcosery ointment significantly accelerate wound healing process and the rates of wounds sterility compared to wounds treated with honey alone (Mustafa et al., 2005).

Anti-inflammatory activity

A group of rats was orally treated with 250 mg/kg extract for anti-inflammatory test using hydro alcoholic extract and was found to have a 38.7% reduction in the cotton pellet-induced granuloma ($p<0.05$) (Tailor and Goyal, 2012). The leaves have been used on cuts, sores, as an anti-inflammatory agent (Abena et al., 1993a; Moura et al. 2005). Aqueous extract of an association of *A. conyzoides*, *Cymbopogon citrates* and *Lippia multiflora* produced a significant reduction in mouse of writhings induced by acetic acid and an increase of pain threshold in the hot plate test in mice.

The presence of saponins and flavonoids supports the observed activities and suggests that this association of three plants could be used as traditional improved preparation (Okemy et al., 2006). The development of chronically induced paw edema was also reduced significantly ($p<0.05$) and serum glutamic pyruvic transaminase (SGPT) activity in the blood of rats treated with 500 mg/kg was reduced to 30.2% ($p<0.05$) which confirm the anti-inflammatory properties of *A. conyzoides* (Moura et al., 2005). The biochemical and haematological analysis of the blood of rats treated with daily doses of

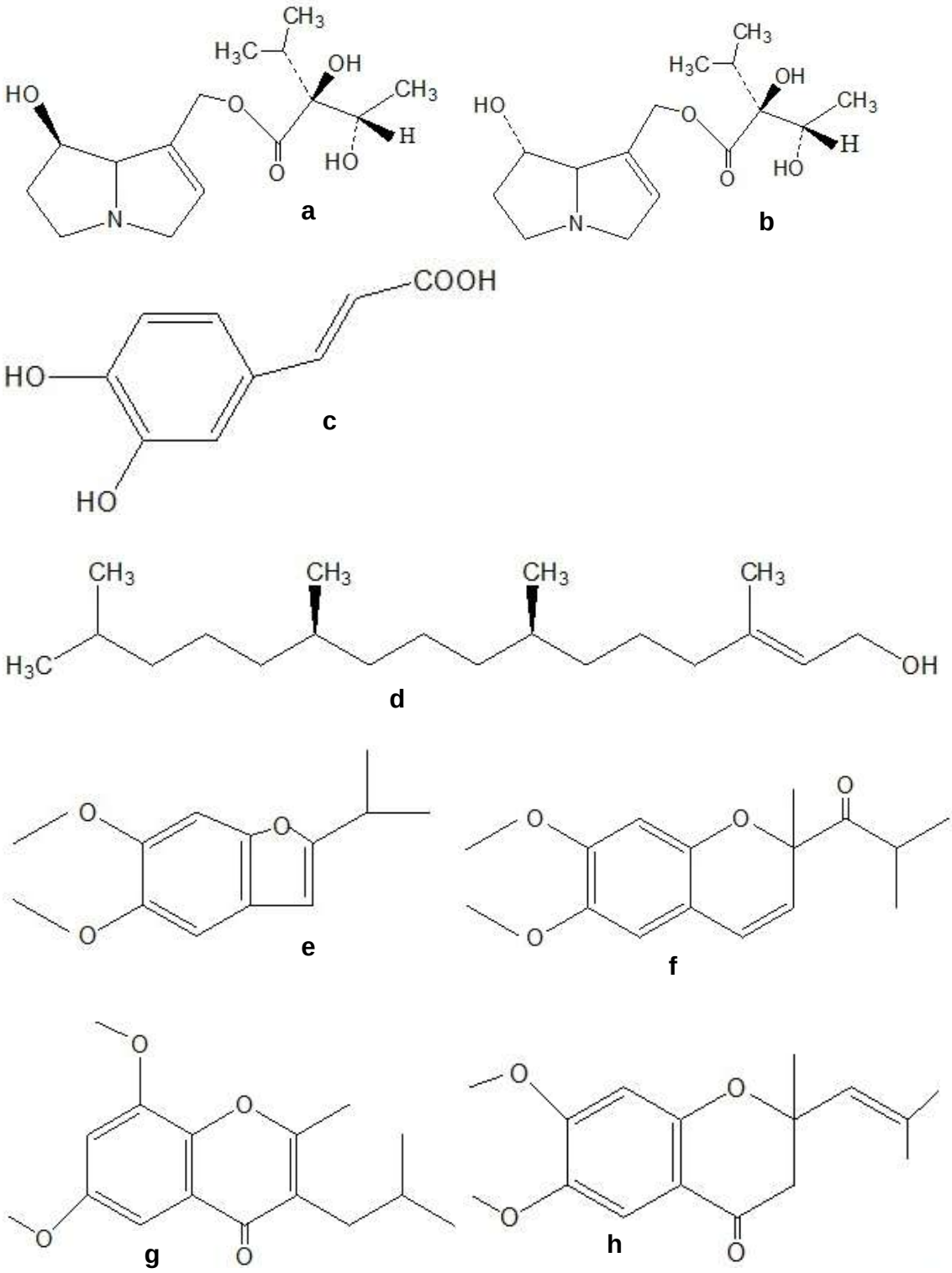

Figure 5. Organic structures of (a)Lycopsamine; (b) Echinatine; (c) Caffeic acid; (d) Phytol; (e) 2-(2'-Methylethyl)5,6-dimethoxybenzofuran; (f) 2-(1'-oxo-2'methylpropyl)-2-methyl-6,7-dimeyhoxychromene; (g) 3-(2'-Methypropyl)-2-methyl-6,8-dimethyoxychrom-4-one; (h) 2-(2'-Methylpropyl)-2-methyl-6,7-dimethyoxychroman-4-one

250 or 500 mg/kg extract for 90 days did not show any treatment-related abnormalities in the biochemical or haematological parameters towards toxicity. Therefore, no indications were found for an apparent hepatoxicity

(Moura et al., 2005). It has been reported that WSF obtained from a hydroalcohol extract of *A. conyzoides* had analgesic and anti-inflammatory activities. It was demonstrated that WSF (20 to 50 mg/kg) treat-ment reduced the articular incapacitation induced by carrageenin (300 µg) in rats (José et al*.,* 1997). The effect on smooth muscles using isolated rat uterus and intestine smooth muscles, concluded that the fraction possesses substances, which provoke direct relaxing effect on smooth muscles and inhibit contraction induced by several agonists possibly by blocking the entry of calcium and/or inhibiting cAMP phosphodiesterase (Margort et al., 2000). Microscopically, pre-treated rats with aqueous extract showed significantly marked inhibition of gastric lesions and marked reduction of submucosal oedema as compared to the control group (Mahmood et al., 2005). The ethanolic root extract of plant in a dose of 100 and 300 mg/kg significantly reduced the carrageenin-induced hind paw oedema in rats with no acute toxic effect in mice (Tandon et al., 1994). The anti-inflammatory effect of *A. conyzoides* methanol extract depends on the flavonoid fraction, which could produce a protective action against free-radical mediated damage in cells and tissue. Therefore, it is possible to hypothesize that flavonoids influence inflammatory gene protein expression (Galati et al., 2001).

Spasmolytic effects

The WSF (0.2 and 0.19 mg/ml) studied in the rat uterus and intestinal smooth muscles showed increase in the EC50 values and decreased the maximum responses to acetylcholine and calcium chloride. The WSF (0.5 to 3.3 mg/ml) produced direct relaxant effect on smooth muscle preparations. Theophylline (10^{-3} M) potentiated the relaxant action of the WSF and also prevented the decrease in maximum response promoted by the WSF in acetylcholine concentration-effect curves which seems to be partially connected to calcium mobilization which helped to inhibit the cyclic AMP phosphodiesterase (Yamamoto et al., 1991; Silva et al., 2000).

Gamma radiation effects

The study of the mortality rate of mice exposed to 10 gray of gamma radiations was found to be most effective at a dose of 75 mg/kg alcoholic extract which is considered to be the optimal dose for radio protection which reduce the severe symptoms of sickness caused by radiation and mortality at all exposure doses of radiation, thus increase survivors rate at all doses and also protected mice against the effects of the lethal gastrointestinal and bone marrow depressions. The protection effects of the extract against gamma radiation may be caused by scavenging reactive free radicals of oxygen molecules. Thus, the plant has appreciable anti-oxidant property (Jagetia et al., 2003).

Anti-cancer, anti-radical scavenging activity and gastric properties

Ethanol extract showed an IC_{50} values of 1.73 µg/ml in P-388 cell line, while petroleum ether extract had IC_{50} values of 14.06, 13.77 and 0.71 µg/ml in A-549 (human non-small cell lung cancer cell line), SGC-7901(human gastric cell line) and P-0.0003 µg/ml in A-549, DU-145 (human prostrate carcinoma cell line), SGC-7901 and P-388 (mouse leukemia cell line) cells, respectively. Similarly, ethyl acetate extract had IC_{50} value of 0.68, 9.97, 14.88 and 0.0003 µg/ml in A-549, DU-145, SGC-7901 and P-388 cells, respectively. The result therefore showed that it possesses anti-cancerous and antiradical properties (Adebayo et al., 2010).

Anti-malarial properties

Petroleum ether extracts of *A. conyzoides* with LC_{50} values 1925.60 and 267.90 ppm was found effective against the mosquito, *Culex quinquefasciatus* larvae (Preeti et al., 2009). The uses of each extraction parts of this plant are shown in Table 2.

Anticoccidial activity

A recent study revealed that essential oil has efficacy in treating caecal coccidiosis of broilers (Nweze and Obiwulu, 2009). Acute toxicity test was done using 28 days old broiler chicks (250 to 3000 mg of extract/kg body weight orally) which were divided into six groups of five birds each in which group VI were given equal volumes of distilled water where the observation was done for 219 h for signs of toxicity. Acute toxicity test gave no sign of toxicity, but it was found decreasing steadily in all the treatment groups until it became zero for the faecal oocyst per gram of faeces. Finally, the packed cell volumes, weight and red blood cell counts of the treated birds were found to be significantly ($P< 0.05$) higher than those of the infected untreated control which confirms the plant's ethno-veterinary use in the treatment of coccidiosis.

Schistosomicidal activity

For *in vitro* condition, *A. conyzoides* oil was studied for its schistosomicidal activity against adult worms of *Schistosoma mansoni.* It was found to be active which leads to reduction in the number of eggs of the adult worms in a dose-dependent manner even though less than the positive control (praziquantel, PZQ) in terms of separation of coupled pairs, mortality, decrease in motor activity, and tegumental alterations. Precocene I (74.3%) and (*E*)-caryophyllene (14.23%), the constituents of the oil were found to be much less effective than the

Table 2. The bioactivities of the extracts.

Extract	Source	Concentration used	Bioactivity	Reference
Alcoholic extract	Leaves	75 mg/kg	Scavenging reactive radicals of oxygen	Jagetia et al. (2003)
Alcoholic extract	Whole plant	0.25-900 mg/kg	Protection effects against gamma radiation	Jagetia et al. (2003)
Aqueous	Leaves	-	Analgesic activity	Abena et al. (1993)
Aqueous	Leaves	-	Prevent coagulation of whole blood	Abena et al. (1993)
Aqueous	Leaves	-	Treatment in chronic pain in osteoarthrotic Patients	Marques et al. (1988)
Aqueous	Root	-	Anti-tumour activity	Rosangkima et al. (2004)
Aqueous	Whole plant	-	Active against certain selected microrganisms	Perumal et al. (1999)
Aqueous	Whole plant	-	Dermatological remedy	Adolfo (2009)
Aqueous	Whole plant	-	Prostate problems	Cheryl (2007)
Ethanol	Leaf	200,1900, and 500 mg/kg	Haematopoitic properties (remedy anaemia)	Ita et al. (2007)
Ethanol	Whole plant	500 and 750 mg/kg	Gastro-protection in rats	Shirwaikar et al. (2003)
Ethanol	Whole plant	30.6 - 193.0 µg/kg	Acts against *Staphylococcus aureus*	Akinyemi et al. (2005)
Ethanol	Whole plant	500 -1000 mg/kg	Anti-coccidial effects	Nweze et al. (2009)
Ethanol	Leaf	200, 1900, and 500 mg/ml	Haematopoietic properties	Ita et al. (2007)
Hydro alcoholic	Whole plant	250 mg/kg	Anti-inflammation	Moura et al. (2006)
Lyophilized powder	Leave juice	50 and100 mg/kg	Precocious ataxia, sedation and slight ptosis	Abena et al. (1993)
Methanol	Whole plant	-	Wound healing	Chah et al. (2006)
Methanol	Aerial part and root both	100 mg/ml	Broncho-dilating and uterine activities	Achola et al. (1998)
Methanol	Whole plant	p<0.036	Wound healing material	Oladejo et al. (2003)
Methanol	Whole plant	15.1- >90 g/ml	Antiprotozoal and cytotoxic	Amal et al. (2010)
Petroleum ether	Whole plant	-	Acts against *S. aureus*	Durodola et al. (1977)
Petroleum ether	Whole plant	-	Active against against the mosquito *C. quinquefasciatus* larvae	Preeti et al. (2009)
Water	Leaves	0.1-0.5 g/kg	Induced quietness and reduced the spontaneous motility in rats and mice	Abena et al. (1993)
Water	Whole plant	0.01-10 mg/ml	Tonic contractions of the smooth muscles	Yamamoto et al. (1991)
Water soluble fraction (WSF)	Whole plant	0.2 and 0.19 mg/ml	Spasmolytic medicine	Yamamoto et al. (1991); Silva et al. (2000)
Water	Whole plant	195.19 to 71.0 µg/kg	Acts against *S. aureus*	Akinyemi et al. (2005)

essential oil and PZQ when tested both individually as well as in mixture form in the ratio similar to that found in the essential oil suggesting that the oil may help to develop a new schistosomicidal agents (de Melo et al., 2011).

Miscellanious activities

The crude extract of *A. conyzoides* is found to have antioxidant property and is superior to vaseline gauze as a wound dressing material. The ethanolic leaf extract is reported to have haemopoietic properties in albino rats (Ita et al., 2007) and reported to have gastroprotective activity in rats by determining mean ulcer size, ulcer number and ulcer index and found that the oral administration of ethanol extract at dose level 500 and 750 mg/kg significantly protected gastric lesions by 80.59 and 89.33%, respectively as compared to Misoprostol (719.193%) in the Ibuprofen model; by 97.09 and 99.219%, respectively in rats (Shirwaikar et al., 2003). The root and aerial part extracts were reported to inhibit 86 and 79% activities of histamine and 5-hydroxy tryptamine (5-HT), respectively which could be the reason of inducing tracheal relaxant. They are also found to have activities on isolated

uterus of rat by inhibiting uterine contractions induced by 5-HT which suggest that the plant extract exhibits specific antiserotonergic activity on isolated uterus (Lans, 2007). The leaf extract is also used as pain relief in osteoarthrotic patients (Marques et al., 1988) showing analgesic effect and articulation mobility improvement without side effects. The aqueous leaves extract are reported to act as anti-coagulant which also decreases bleeding time (Akah, 1988). The leaf extract has analgesic activity and was detected by hot plate method (Abena et al., 1993a). *A. conyzoides* is also found in the treatment of abdominal and menstrual pains (Nair et al., 1977). *In vitro* receptor radio ligand assay of the extract showed that it produced positive results (> 50% inhibition) in the bradykinin (BK II) responsible for the initial bioactivity. The aqueous extract of *A. conyzoides* roots was reported to decrease glutathione in the liver and in the lymphoma cells of the tumour-bearing mice which could be one step of producing the anti-tumour effect (Rosangkima and Prasad, 2001). The leaf extract was reported to change the electrocardiogram, atrial impulse velocity and coronary vessel resistance in the isolated guinea pig heart, but its effects disappeared after wash. The plant (leaves and root) was devoid of *in-vivo* cholinesterase activity (Gupta and Gupta, 1997). The leaves extract changes the electrocardiogram, atrial impulse velocity and coronary vessel resistance on isolated guinea-pig heart (Garcia and Carvalho, 1999). Aqueous extract of an association of *A. conyzoides*, *C. citrates* and *L. multiflora* produced a significant reduction in mouse of writhings induced by acetic acid and an increase of pain threshold in the hot plate test in mice. The presence of saponins and flavonoids supports the observed activities and suggests that plants could be used as traditional improved preparation (Okemy et al., 2006).

Allelopathic property of *A. conyzoides*

Both the volatile oil and the aqueous extract of *A. conyzoides* have been shown to have allelopathic effects on a number of cultivated crops. These include radish, mungbean and ryegrass (Xu et al., 1999). The saturated aqueous solution of the isolated and purified precocenes I and II have been reported to have significant inhibitory effect on the seedling growth of radish, tomato and rye-grass (Hu and Kong, 2002). The allelopathic potential of the aqueous extract from different organs of *A. conyzoides* and from its different development stages, especially from different habitats, was different (Kong et al., 2002). It showed strong inhibition on *Raphanus sativus* L. germination and growth in a bioassay. It showed strong inhibition on *R. sativus* L. germination and growth in a bioassay. The whole plant show high potential of allelopathic property against intercropped in citrus orchards. This activity may be due to reversible transformation between ageratochromene and its dimers in the *A. conyzoides* intercropped citrus orchard soil (Kato-Naguchim, 2001; Kong et al., 2005). Flavones released by the plant acts as a natural fungicide in citrus orchids which is comparable with commercial fungicide, carbengin (Kong et al., 2005). The residue of the plant is believed to contain allelochemicals since it inhibited the germination and the growth of roots and shoots of *Amaranthus caudatus, Digitaria sanguinalis, Lactuca sativa.* This plant may have potent allelochemicals which may act as inhibiting agents which may be economically useful (Saito et al., 2008). In India, further study found that the leaf debris of the plant released water soluble phenolic acids into the soil environment (not through soil nutrient depletion) which affects the early growth of rice (*Oryza sativa*) deleteriously. However, it was reported that the effects of such weeds can be reduced by planting legume fallows like *Leucaena* and pigeon pea. Not only this, it was found to increase soil nitrogen and phosphorus contents, but not upland rice yields (Kuldip et al., 2009). The invasion of *A. conyzoides* on the flora of the Shivalik hills of Himachal Pradesh, India was reported to affect the diversity and productivity of the invaded areas and found that the amount of phenolic acids in the soil invaded area was 60.90% more than the control area.

Insecticidal property

The most important considerable biological activity of this plant is in fact, its insecticidal activity which may play a valuable role in agriculture economically as well as effectively. Both the oil as well as its extracts has insecticidal activity. The oil and precocenes I and II, the chromenes, the major constituents of its oil are reported to have anti-juvenile hormonal activity (Vyas and Mulchandani, 1980) and have been assayed on varieties of insects namely *Sitophilus oryzae, Thlaspida japonica, Leptocarcia chinesis* and *Disdercus flavidus* which results to metamorphosis of the larvae, production of sterile, moribund and dwarfish adults (Fagoonee and Umrit, 1981). It can exhibit insecticidal property against cowpea weevil, *Callosobruchus maculatus* F. (Gbolade et al., 1990) and high nymphal mortality, that is, 91% to the nymphs of *Schistocerca gregaria* (Pari et al., 1998). Petroleum ether extract is active against the mosquito, *C. quinquefasciatus* larvae (Preeti et al., 2009). The crude plant extract also showed insecticidal and pesticidal activities against various types of insects and pests. Calle et al. (1990) showed that the hexane extract of the whole plant showed activity against *Musa domestica* larvae. The methanolic extract of the plant was found to suppress the population of the malaria vector *A. stephensi* in higher dosage, whereas in lower dosage it was found to induce several developmental defects and ultimately decrease the growth index to a considerable extent (Saxena and Saxena, 1992), whereas the lower concentrations were found to induce developmental defects ultimately decreasing the growth index of the treated second and fourth instar larvae of *C. quinquefasciatus* (Saxena et al.,

1994). The crude extract of the plant showed insecticidal activity against nymphs of mustard aphid *L. erysimi* (Bhathal et al., 1994). It might be a natural herbicide for weed control in paddy fields to reduce the dependence on synthetic herbicides (Xuan et al., 2004).

Toxicity

The presence of pyrrolizidine alkaloids in this plant has been reported in the previous literature review; these compounds are hepatotoxic and cause lung cancer and variety of other ailments in rats (Couet et al., 1996). This may be hazardous to human health. The toxicity was observed in alcoholic extract of whole plant in mice at >3000 mg/kg body weight (Jagetia et al*.,* 2003). However, the hydroalcoholic extract (HAE) does not show any toxicity in rat during sub-acute treatment, but found reduction of SGPT value during chronic treatment of HAE (500 mg/kg body weight) significantly by $p<0.05$. Further reports found that the cytotoxicity of the plant may be due the oxidative dealkylation process.

CONCLUSIONS AND FUTURE PROSPECTS

Among the weeds, members of *Ageratum* seem to be the most commonly spreading in agricultural areas throughout the world. The species is believed to possess various biological activities starting from its various phytochemical contents. It offers many opportunities to investigate the various functions and prospects in pharmaceutical studies. A number of studies have been carried out using this plant as weed controlling agent. It is believed that detailed information as presented in this review on its phytochemistry and various pharmacological properties of the extracts and the constituents might provide incentive for proper evaluation of the use of the plant in medicine and in agriculture. Activities like its effects on spasmolytic and anti-inflammatory properties of the flavonoids isolated from the plant need to be studied. Further studies in this area could serve as a means of controlling the *Anopheles* mosquitoes and *L. donavani.* The ability to inhibit the aflatoxin production is a new biological activity of *A. conyzoides* L. which indicates that it may be considered as a useful tool for a better understanding of the complex pathway of aflatoxin biosynthesis and controlling of fungal growth in agriculture.

Although, the pharmacological properties of *A. conyzoides* seem to have been determined, the mechanism of these principles is still unknown. The bioassay guided for isolation and identification of the bioactive components are still needed and detailed researches are also required to reveal the structure activity relationship of these active constituents. Outcome of the future research in the aforementioned areas will provide a convincing support for the future clinical uses of *A. conyzoides* in modern medicine.

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