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REVIEW ARTICLE

A Review on Traditional Uses, Chemical Constituents and Pharmacology of *Ageratum conyzoides* L. (Asteraceae)

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ABSTRACT

Ageratum conzoides L. (Family: Asteraceae) is a widely available plant in India. The plant has been employed in various conventional systems of medicines to cure a wide array of disorders including asthma, wounds, malaria, piles, dysentery, etc. Various chemical constituents belonging to chemical classes such as sterols, flavonoids, terpenoids, lignan, pyrrolone, chromenes and pyrrolizidine alkaloids have been found in the plant. This review compiles the available data on the traditional uses, chemical constituents, pharmacology and toxicity studies reported from *Ageratum conyzoides* in a systematic order so as to highlight the medicinal worth of the plant.

Keywords: *Ageratum conyzoides*, Asteraceae, Chromenes, Goat weed, Wounds.

INTRODUCTION

Ageratum conyzoides L. commonly known as Goat weed or White weed is a member of the family Asteraceae, also known as sunflower family. The plant is native of Tropical America and is found throughout India, upto an altitude of 1,800 m. [1-3] It is an annual erect, aromatic herb with 1 m height; leaves are broadly ovate or rhomboid-ovate to triangular; stem is branched and more or less hairy bearing pale blue or white malodorous flowers. Achenes are either glabrous or thinly hairy, with aristate, serrulate pappus-scales. Various parts of the plant have been conventionally used in several countries for healing wounds, boils, sores, tetanus, skin diseases, fever, eye ailments, rheumatism, stomach disorders etc. [4,5] This review focuses on the traditional uses, chemical constituents pharmacological and toxicological aspects reported from the plant so as to encourage the researchers to develop this plant into a potential herbal medicine.

TRADITIONAL USES

Since ages various parts of *A. conyzoides* have been used in different folkloric system of medicine to treat a variety of diseases such as, skin disorders, stomach ailments, chronic ulcer, intra-uterine problems, frontal headache, rheumatism, colic, pneumonia, sleeping sickness, wounds, boils, malaria and sore throat. [3, 6-9] The plant is also used as a purgative, febrifuge, emetic, antispasmodic and antiasthmatic. [10] The leaves of the plant are consumed as a vegetable [11] and also for preventing tetanus. [4] Traditional preparations employing various parts of the plant are described in (**Table 1**).

CHEMICAL CONSTITUENTS

The secondary metabolites identified from *A. conyzoides* comprise of terpenoids (**87**), sterols (**8**), flavonoids (**23**), chromenes (**23**), pyrrolizidine alkaloids (**1**), coumarin (**1**), pyrrolone (**1**) and lignan (**1**). [26-28] Chemical constituents identified from *A. conyzoides* are briefly described below:

Sterols: Sterols namely β-sitosterol, stigmasterol, brassicasterol, dihydrobrassicasterol, spinasterol, dihydrospinasterol, stigmast-7-en-3β-ol and cholesterol (**8**) were reported from various parts of the plant. [4, 29-31]

Flavonoids:

5,6,7-trimethoxy-3,4-methylene dioxyflavone (ageconyflavone A), 4-hydroxy-5,6,7,3-tetramethoxyflavone (ageconyflavone B), 4'-hydroxy-5,6,7,3',5'-pentamethoxyflavone (ageconyflavone C), 5,6,7,3',4'-pentamethoxy flavone (sinensetin), 5,6,7,8,5'-pentamethoxy-3',4'-methylenedioxyflavone (eupalestin; 5'-methoxylucidin dimethyl ether), 5,6,7,8-

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tetramethoxy-3',4'-methylenedioxyflavone (linderoflavone B; lucidin dimethyl ether), 5,6,7,8,3'-pentamethoxy-4',5'-methylenedioxy flavone, 5,6,7,8,3',4'-hexamethoxyflavone (nobiletin), 5,6,7,8,3',4',5'-heptamethoxyflavone (5'-methoxynobiletin), 5,6,7,5'-tetramethoxy-3',4'-methylenedioxyflavone, 4'-hydroxy-5,6,7,8,3'-pentamethoxyflavone, 4'-hydroxy-5,6,7,8,3',5'-hexamethoxyflavone, 5,6,7,3',4'5'-hexamethoxy flavone, kaempferol 3,7-diglucoside and kaempferol 3-rhamnoglucoside were identified from *A. conyzoides*. Quercetin (3,5,7,3',4'-pentahydroxyflavone), kaempferol (3,5,7,4'-tetrahydroxyflavone), 5,6,7,4'-tetrahydroxy flavone (scutellarein), 8-hydroxy-5,6,7,3',4'5'-hexamethoxyflavone and 5,6,8,3',4'5'-hexamethoxyflavone were reported from the leaves of the plant. [4, 17, 32-38] Catechin was also identified from the leaves. [39] An isoflavone glycoside, 5,7,2',4'-tetrahydroxy-6,3'-di-(3,3-dimethylallyl)-isoflavone-5-O-α-L-rhamno pyranosyl-(1→4)-α-L-rhamnopyranoside was reported from stems. [40]

Table 1: Traditional uses of *Ageratum conyzoides* L.

Country	Traditional use (s)	Plant part (s)	Preparation (s)
Bangladesh	Hepatic disorders, antidote to poison, fever	NS	NS [12]
	Wounds, cuts, bruises	Leaves	Poultice [12,13]
	Diarrhoea and dysentery, boils, skin diseases, joint pain		Decoction, paste [14]
Cameroon	Syphilis	Leaves	Mixed with other herbs [15]
India	Cuts, wounds	Leaves	Mixed with other herbs [16]
	Bleeding, antiseptic		Juice [16,17]
	Piles		Paste [18]
Nepal	Cuts, wounds	Leaves	Juice [19]
Nigeria	Diabetes	Whole plant, leaves	Juice, decoction [20]
	Insecticide	Leaves	NS [21]
	Wounds, sores		Poultice [22]
Tanzania	Eye drops	Leaves	Juice [23]
Trinidad and Tobago	Prostate, female complaints	NS	NS [24]
Zimbabwe	Mosquitocidal	Leaves	Smoke made by burning leaves [25]

NS- Not stated

Chromenes:

6-(1-methoxyethyl)-7-methoxy-2,2-dimethyl chromene, encecanescins, 6-(1-ethoxyethyl)-7-methoxy-2,2-dimethylchromene, 6-vinyl,7-methoxy-2,2-dimethylcromene, 6-(1-hydroxy ethyl)-7-methoxy-2,2-dimethylchromene, encecalol methyl ether, 7-methoxy-2,2-dimethylchromene (6-demethoxy ageratochromene; precocene I), 6,7-dimethoxy-2,2'-dimethylchromene (ageratochromene; precocene II), 2,2-dimethylchroman-7-ol, encecalol angelate, 6-angeloyloxy-7-methoxy-2,2-dimethylchromene, 6,7,6',7'-tetramethoxy-2,2,2',2'-tetramethyl-3'(4')-dehydro-3'-4(S)-bichroman, (RS)-1(7-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethanol (encecalol), 1-(7-hydroxy-2,2-dimethyl-2H-chromen-6-yl)ethanone, 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone, eupatoriochromene and a dimer of ageratochromene were isolated from aerial parts of *A. conyzoides*. 1-(7-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethanone (encecaline; 6-acetyl-7-methoxy-2,2-dimethylchromene), androencecalinol, 6-acetyl-2,2-dimethylchromene (demethoxy-encecalin), 6-acetyl-7-hydroxy-2,2-dimethylchromene (demethylencecaline), 6-acetyl-2,2-dimethylchroman (dihydromethoxy encecaline) and 6-acetyl-7-methoxy-2,2-dimethylchroman (dihydroencecaline) were reported from the leaves. [4, 31, 32, 34, 38, 41-55]

Terpenoids:

Terpenoids are the major phytoconstituents present in *A. conyzoides*. Four types of terpenoids were reported:

Monoterpenes:

So far **39** monoterpenes have been reported from the essential oil of *A. conyzoides*; α-phellandrene, α-thujene, (E)-β-ocimene, α- and β-pinene, δ2-carene, myrcene, thymol, thymyl acetate, limonene, nerol, p-cymene, linalool, camphene, carvacrol, carvacryl acetate, sabinene, sabinene acetate, (E)-sabinene hydrate, linalool, myratenal, trans-pinocarveol, trans-pulegol, α-terpineol, α- and γ-terpinene, terpinen-4-yl acetate, terpinolene, 1,8-cineole, methyl eugenol, eugenol, α-fenchone, fenchene, fenchyl acetate, borneol, bornyl acetate, bornyl formate, isobornyl formate and isobornyl acetate. [4, 41-48, 51-53, 55, 56]

Sesquiterpenes:

Till date **45** sesquiterpenes namely; α-muurolene, α-copaene, α- and β-gurjunene, α-trans-bergamotene, β-sesquiphellandrene, β-bourbonene, cis-β-guaiene, α- and β-cubebene, α- and β-farnesene, farnesol, elemol, α- and β-selinene, α-, β-, γ- and δ-elemene, α-humulene, humulene epoxide II, (Z)-α-bisabolene, γ-bisabolene, α- and γ-muurolene, α-, γ- and δ-cadinene, 1-epi-cubenol, cadina-1,4-diene, guaiol, nerolidol, (Z)-jasmone, cedrene, germacrene D, germacrene D-4ol, bicyclogermacrene, spathulenol, α-cadinol, epi-α-cadinol, β-

caryophyllene, caryophyllene alcohol, caryophyllene oxide, caryophyllene epoxide were isolated from *A. conyzoides*. [4, 31, 41-48, 51-56]

Diterpene and triterpenes:

Only one diterpene (phytol) [54] and two triterpenes (squalene and friedelin) [28, 54] have been identified from the plant.

Miscellaneous compounds:

Two pyrrolizidine alkaloids (lycopsamine and echinatine), [57] a coumarin (cumarine), [41, 43] a natural pyrrolone (5-ethoxy-1H-pyrrol-2[5H]-one) [58] and a lignan (sesamin) [31] have been reported from *A. conyzoides*. Fumaric acid, gallic acid, coumalic acid, protocatechuic acid, p-hydroxybenzoic acid, p-coumaric acid, sinapic acid, benzoic acid, cis-hexen-3-en-1-ol, phenyl ethyl acetate, resorcinol, hexadecanoic acid, methanazulene and tricycoundecane were also identified from the plant. [17, 39, 42, 46-48, 50, 53-55]

PHARMACOLOGICAL REPORTS

A. conyzoides has a wide range of pharmacological activities. The pharmacological effects reported highlighted antiulcerogenic, [59] analgesic, [60] anti-inflammatory, [61, 62] anti-cataleptic, [63] antidiabetic, [64] antitumor, [65] cytotoxic, [50] hepatoprotective, [66] anticonvulsant, [67] radioprotective, [68] antidotal, [69] antioxidant, [70] antiprotozoal, [25,32] antimicrobial, [43] anthelmintic, [71] allelopathic, [72] insecticidal, [73] haematopoietic, [74] wound healing, [22, 75] gastroprotective, [76] uterine and bronchodilating [77] potential of *A. conyzoides*. Apart from these uses, the ethnoveterinary use of the plant in the management of diarrhoea and coccidiosis in livestock has also been scientifically confirmed. [78, 79]

Mostly crude extracts and to a smaller extent fractions of *A. conyzoides* have been employed to demonstrate the pharmacological activities. The bioactive constituents along with their structures and pharmacological activity are described in (**Table 2**). A few pharmacological reports are described below:

Antimicrobial activity:

Mostly *in vitro* studies were carried out using disc diffusion and broth dilution method. [22, 41, 80, 81] The crude methanolic extract of the plant showed antibacterial activity against *Bacillus subtilis*, *Staphylococus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. [19] Various researchers have reported the antimicrobial activity exhibited by essential oil of the plant. The essential oil was found to demonstrate moderate (60%) fungitoxicity against the test fungus, *Botrytis cinerea* at 500 ppm. [82] It also showed prominent antifungal activity against toxigenic strain Saktiman 3NSt of *Aspergillus flavus* at 1µl/ml and completely inhibited aflatoxin production at 0.5 µl/ml. [83] Pure fractions of the plant have also exhibited significant *in vitro* antimicrobial activity against *Helicobacter pylori*. [84] A formulation developed using aerial parts of the plant was found to show better antimicrobial activity than the crude extracts. [54]

Antioxidant activity:

The antioxidant activity of crude extracts has been mostly determined using DPPH assay. [22] The crude methanolic extract of the stems showed concentration-dependent scavenging of DPPH (IC_{50}- 46.01±2.23 µg/ml) [85] whereas ethanol extract demonstrated antioxidant activity with EC_{50} of 15.19 µg/ml. [65, 86] The flavonoid fraction of *A. conyzoides* produced significant DPPH radical scavenging effect (52.18%) at a concentration of 100 µg/ml. [62]

Anticancer activity:

The antitumor activity of ethanolic leaf extract of *A. conyzoides* was analysed using carrot disc infected with *Agrobacterium tumefaciens*. The extract showed activity after 3 weeks of incubation at 1000 ppm dose. [86] Ethylacetate extract of the leaves showed highest anticancer activity against A-59 and P-388 cancer cell lines with IC_{50} of 0.68 and 0.0003 µg/ml respectively. [37] The crude ethanol extract and various fractions of the leaves were found to be cytotoxic against human lung cancer cells lines (SK-MES 1 cells) with IC_{50} ranging from 10-38.5 µg/ml. [81]

Antidiabetic activity:

The crude aqueous extract along with biaoactive fractions of *A. conyzoides* leaves exhibited hypoglycaemic and antihyperglycaemic activities in normoglycaemic and streptozotocin- induced diabetic rats. [87, 88]

Anti-inflammatory:

Crude alcoholic extract of *A. conyzoides* showed a time-dependant anti-inflammatory activity in carrageenan-induced paw edema model at an oral dose of 1.0 and 1.5 g/kg. The activity was comparable to the standard (diclofenac sodium). [60] The water soluble fraction (30 and 50 mg/kg, s.c.) of hydroalcoholic leaf extract of the plant significantly reduced the carrageenan-induced neutrophil migration into peritoneal cavities and

subcutaneous 6 day old air pouches. At the same dose the fraction inhibited carrrageenan-induced paw edema and blocked increase in cutaneous vascular permeability. [89]

Antiulcerogenic activity:

The antiulcer potential of aqueous and ethanolic extracts of *A. conyzoides* alone and in combination with honey was investigated in rats against ethanol-HCl-induced gastric ulcer. Honey in combination with extracts (10% w/w 5 ml/kg, p.o.) increased the resistance of gastric mucosal cells. [90]

Analgesic activity:

The antinociceptive activity of water soluble fraction of *A. conyzoides* leaf extracts were determined using rat articular incapacitation model. The fractions significantly decreased the paw elevation time with doses of 30 and 50 mg/kg, i.p. or 90 and 150 mg/kg, p.o. [89]

Wound healing activity:

Methanol and aqueous extracts of *A. conyzoides* leaves showed faster rate of wound healing in rats than corresponding petroleum ether and chloroform extracts. [91] Topical administration of ethanolic extract (40 mg/kg, body weight) of *A. conyzoides* in rats with open excision wound showed increased cellular proliferation, tensile strength and collagen synthesis along with improved rate of epithelialization and wound contraction of the treated tissue. [92] Polyherbal formulation containing leaf extracts of *A. conyzoides* along with other plant extracts have shown better results than the plant extract alone. [93, 94] The aqueous and methanol extract of the leaves demonstrated haemostatic activity by decreasing bleeding time, prothrombin time and clotting time. [95, 96]

Anthelmintic activity:

The leaf extract of *A. conyzoides* showed detrimental effect against root-knot nematode, *Meloidogyne incognita* at different concentrations (2-10 ppm). [97] Interestingly the essential oil obtained from the plant demonstrated dose-dependant reduction in the number of eggs of *Schistosoma mansoni* while the isolated compounds, precocene I and β-caryophyllene were found to be less effective than the essential oil. [56]

Antiprotozoal activity:

The volatile oil obtained from the leaves of *A. conyzoides* showed 100% mortality of *Culex* specie mosquito at dose level of 15 µl. [98] Hexane and methanol extract of the plant showed repellent effect against malarial fever mosquito *Anopheles stephensi*. [21, 99] The aqueous extract and fractions of leaf extract showed significant antimalarial activity against mice infected with *Plasmodium berghei* at tested oral doses (100, 200 and 400 mg/kg, p.o.). [100] Thus an herbal product employing *A. conyzoides* should be developed so as so provide a safer and a cheaper alternative to synthetic antimalarial drugs.

Allelopathic activity:

On thorough literature survey numerous reports depicting allelopathic potential of *A.* conyzoides were found. [34, 51, 55, 101] *A. conyzoides* was found to retard the root length, height, biomass and nodulation of chickpea (*Cicer arietinum*). [102, 103] Aqueous extracts of the plant have also shown allelopathic effects on a variety of other cultivated crops. [104]

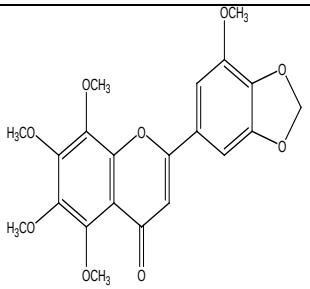
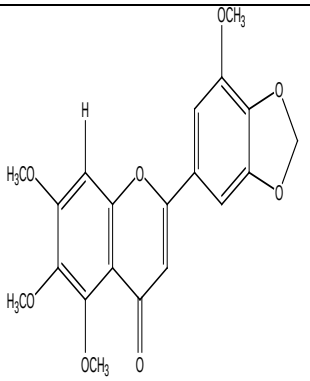
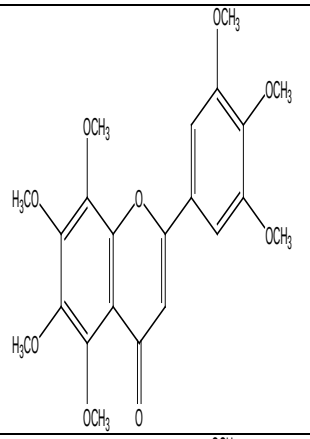
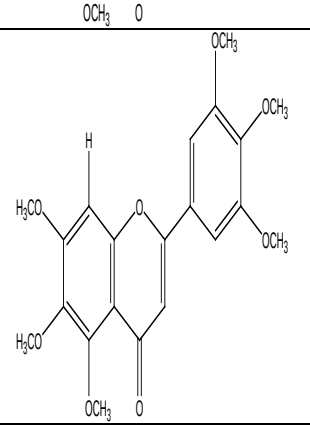
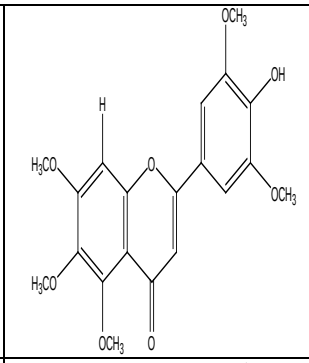
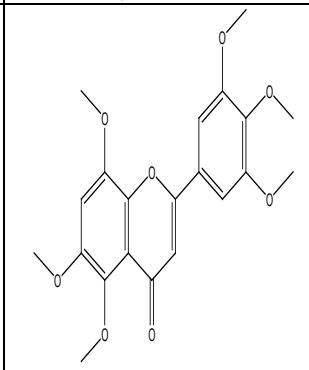
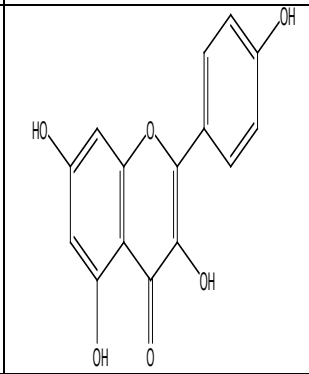
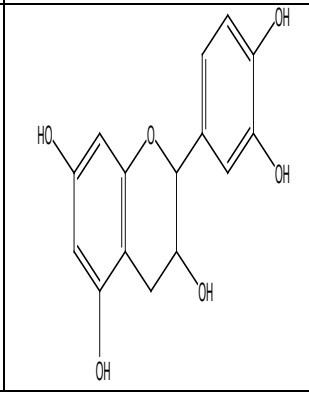
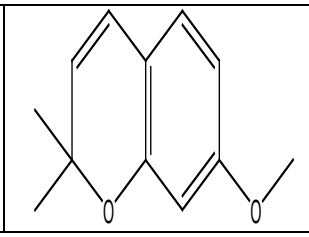
Insecticidal activity:

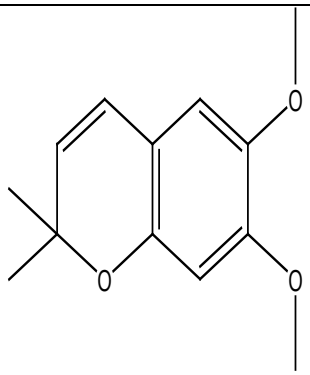
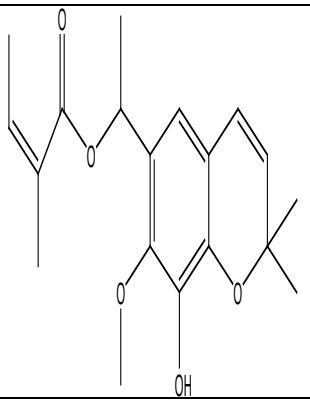
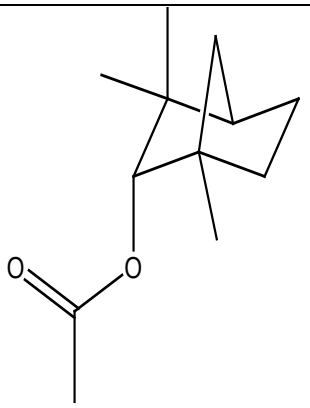
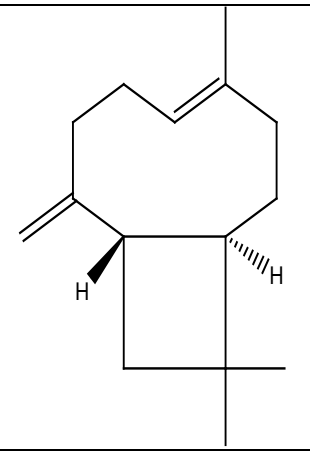
The essential oil obtained from the leaves of the plant should be harnessed as an effective insecticide, as the volatile oil has shown promising results in the management of a number of grain insect pests such as, *Callosobruchus maculatus*, *Sitophilus zeamais*, *Tribolium castaneum*. [46, 105, 106] The hexane extract caused 88.67% mortality of *Rhyzopertha dominica* F. while coumarin showed insecticidal activity against all the tested insect pests; *R. dominica*, *S. zeamais*, *Diaphania hyalinata*, *Musca domestica*, *Periplaneta americana* and *Oryzaephilus surinamensis* L. with LD_{50} ranging from 2.49-39.72 mg/g. [33, 35] Petroleum ether extract of the plant showed strong larvicidal activity against *M. domestica*, *Cynthia carye* and *Acanthoscelides obtectus*. [38]

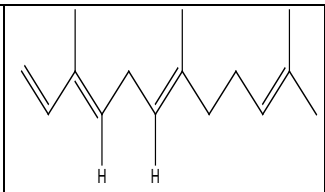
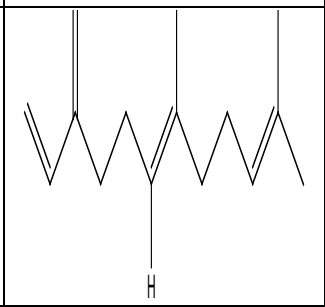
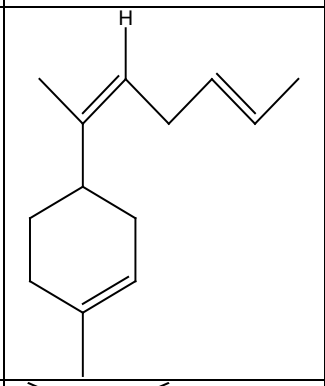
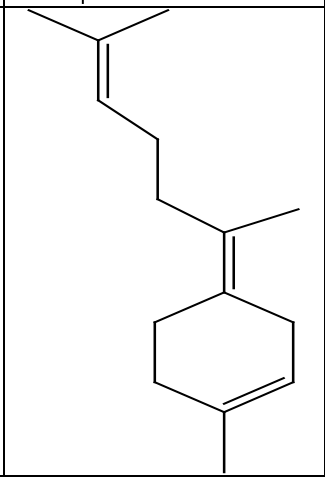
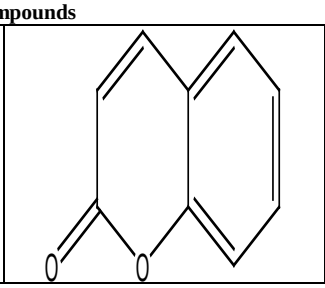
Radioprotective activity:

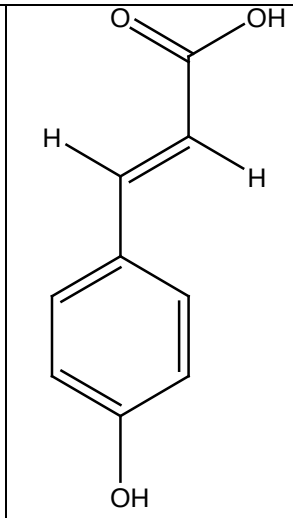
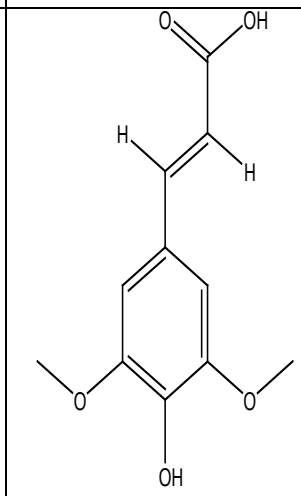
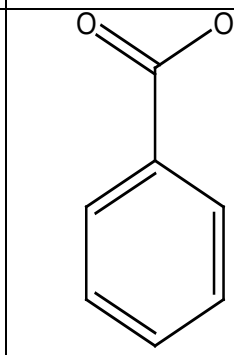
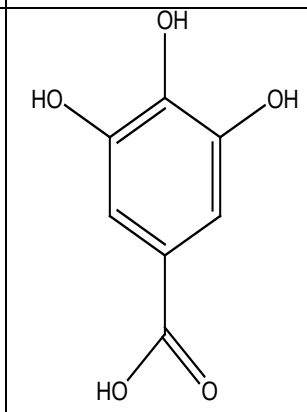
Alcoholic extract of *A. conyzoides* caused dose-dependant decline in radiation-induced mortality upto a dose of 75 mg/kg, i.p. The extract further demonstrated concentration-dependant scavenging of DPPH which indicates that the radioprotective activity may be due to scavenging of reactive oxygen species. [107]

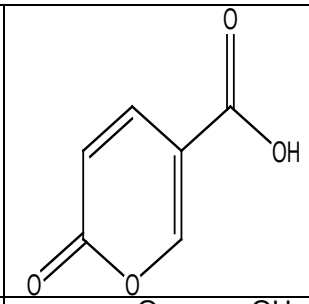
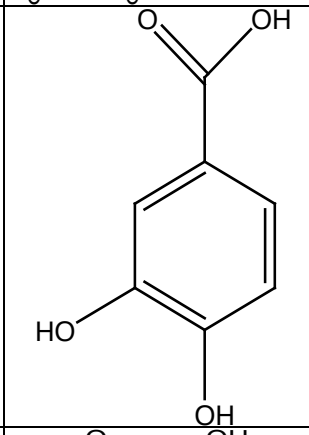
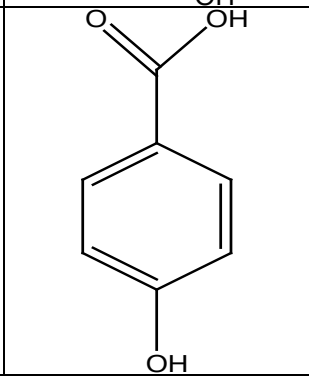
Table 2: Bioactive constituents identified in *Ageratum conyzoides* L. along with their structures and pharmacological activity

Class and bioactive constituents(s)	Structure	Pharmacological activity reported
Flavonoids		
5,6,7,8,5'-pentamethoxy-3',4'-methylenedioxyflavone (eupalestin)		Antiprotozoal [32]
5,6,7,5'-tetramethoxy-3',4'-methylene dioxyflavone		Antiprotozoal [32]
5,6,7,8,3',4',5'-heptamethoxy flavones (5'-methoxy nobiletine)		Antiprotozoal, [32] allelopathic, [34] insecticidal [35]
5,6,7,3',4'5'-hexamethoxy flavone		Antiprotozoal, [32] allelopathic [34]
4'-hydroxy-5,6,7,3',5'-pentamethoxy flavone (ageconyflavone)		Antiprotozoal [32]
5,6,8,3',4'5'-hexamethoxy flavone		Allelopathic [34]
Kaempferol		Antioxidant [37]
Catechin		Allelopathic [39]
Chromenes		
Precocene I		Antiprotozoal, [98] allelopathic, [47, 51, 55] anthelmintic [56]

Precocene II (6,7-dimethoxy-2,2-dimethyl-2-chromene)		Allelopathic, [47] hypoglycaemic, [110] insecticidal [38, 55]
Encecalol angelate		Antiprotozoal, cytotoxic [50]
Monoterpene		
Fenchyl acetate		Allelopathic [47, 55]
Sesquiterpenes		
β-caryophyllene		Allelopathic, [47, 51, 55] anthelmintic [56]

α-farnesene		Allelopathic [51, 55]
β-farnesene		Allelopathic [51, 55]
α-bisabolene		Allelopathic [51, 55]
γ-bisabolene		Allelopathic [47]
Miscellaneous compounds		
Coumarin		Insecticidal [33, 35]

p-coumaric acid		Allelopathic [39]
Sinapic acid		Allelopathic [39]
Benzoic acid		Allelopathic [39]
Gallic acid		Allelopathic [39]

Coumalic acid		Allelopathic [39]
Protocatechuic acid		Allelopathic [39]
p-hydroxybenzoic acid		Allelopathic [39]

TOXICITY STUDIES

Several studies were carried by researchers to determine the toxicity of *Ageratum conyzoides*, and have generally found it to be safe. [61, 99, 108] Brine shrimp larvae lethality test was used to evaluate *in vitro* toxicity of crude ethanol extract. LC_{50} for acute (6 h exposure) and chronic toxicity (24 h exposure) was 2005.07 and 768.72 ppm respectively. [65] Crude methanolic extract of *A. conyzoides* stem was found to be cytotoxic (LC_{50}-1.32 µg/ml). [85] The safety potential of ethanolic leaf extracts was determined in Sprague Dawley rats by evaluating biochemical, haematological and histological indices. Significant reduction in biochemical markers along with elevated levels of WBC count and mean platelet volume and hepatocellular necrosis was observed in groups treated with extracts (1000 and 1500 mg/kg). [109] Sub-chronic toxicity study of Precocene II (25 and 50 mg/kg, gastric intubation) was carried out in Sprague Dawley rats and it was observed that the compound altered some haematopoietic elements

but was non toxic to liver, kidney and spleen tissues. [110]

CONCLUSION

Ageratum conyzoides has been used in traditional system of medicine of various countries to manage different ailments. So far 160 compounds have been identified from this plant and the crude fractions have shown multifarious pharmacological activities and have generally found to be safe. Despite the extensive phytochemical research not many compounds have been related to the pharmacological activities and still the mechanism responsible for the activity of crude extracts/fractions have not been established. This review would hopefully encourage researchers to explore the plant with respect to its use in pharmaceutical, biotechnological and agriculture fields.

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