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AN UPDATED REVIEW ON INVASIVE NATURE, PHYTOCHEMICAL EVALUATION, & PHARMACOLOGICAL ACTIVITY OF *AGERATINA ADENOPHORA*

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ABSTRACT: *Ageratina adenophora*, often known as Crofton Weed, is one of the common invasive weeds which first originated from Mexico and Central America and gradually invaded numerous parts of the world. Because of its ability to alter the soil microbial communities and its allelopathic competition with other plant species, this plant colonizes forest margins, stream banks and disturbed areas in large dense clumps and is found to possess potent toxicological effects on livestock; the lethal chronic pulmonary disease has been reported in horses while liver complications have been reported in mice. Despite this, the plant has been studied more extensively for its therapeutic uses as phytochemicals *viz.* steroids, tannins, triterpenes, coumarins and saponins (7-hydroxy-dehydrotremetone, 7, 10,1 1-trihydroxy-dehydrotremetone, 10-oxo-7-hydroxynordehydro-tremetone,Eupatorone, 2-deoxo-2-(acetyloxy)-9-oxoagera-phorone(DAOA), 9-oxoagerophorone(OA), etc.) which have been reported are found to possess antimicrobial activity, antipyretic activity, wound healing, antioxidant activity, analgesic activity, anti-tumor activity, insecticidal activity, antiviral activity, anti-inflammatory activity, larvicidal activity. This present review is an effort to give a detailed survey of the literature on invasive nature, pharmacological study, phytochemical review, and ethnobotanical and therapeutical uses of the plant *A. adenophora*, which could help researchers for advanced qualitative research on it.

INTRODUCTION: *Ageratina adenophora* (Spreng.) (adenophora = ‘aden’ (a gland) + ‘phoros’ (bearing); refers to oil-producing glands in the leaves), one of the species of the Asteraceae family is a perennial, semi-shrubby herbaceous plant which grows up to 3m tall in moist conditions, such as on the edges of slow-flowing streams in waterlogged soaks, on steep slopes and in high rainfall areas.

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FIG. 1: ***AGERATINA ADENOPHORA***

Crofton weed, its most common vernacular name out of many (*Eupatorium adenophorum*, Eupatory, Mexican Devil, sticky snakeroot, Banmara,

Catweed, hamp agrimony, Maui pāmakani, pāmakanihaole, *etc*.), is named after the councilor in Lismore Shire, New South Wales, Australia, when the species first became identified as an invasive weed [1].

Originally from Mexico & Central America, this species was first introduced as an ornamental species, but its ability to alter the soil microbial communities and its allelopathic competition with other plant species helped this species to invade numerous areas and is now a worldwide invasive. In terms of the Alien and Invasive Species Regulations (AIS), National Environmental Management: Biodiversity Act (Act No 10 of 2004), Crofton weed was declared a category 1b species, and is supposed to be eradicated or at least controlled by the landowners [2]. This plant has numerous smooth, terete, purplish, glandular puberulent stems that arise from a short, thick, pale-yellow rootstock which give a carrot-like odor when broken. They give rise to numerous branching secondary roots extending laterally to a radius of 1 m and downwards to 40 cm; adventitious roots may form on the first 3 cm of the stem. Leaves are dark-green (purple underneath), opposite, trowel shaped with serrated edges, which grow to about 10cm in length. They have an acuminate apex and obtuse to very broadly cuneate/truncate base with a 2-4cm slender stalk; each leaf being 3-nerved, glabrous or slightly pubescent with 4-5cm long petiole.

Flowers comprise about 50 to 70 white, tubular florets about 3.5 mm long; grouped into heads 5-6 mm diameter within a row of green bracts and arranged in flat clusters up to 10 cm across at the end of the branches. The seed is an achene, varying from elliptic to oblanceolate, often gibbous, 1.5–2 mm long, 0.3–0.5 mm wide, with five prominent ribs and five to 40 pappi with slender scabrous bristles. Their bodies are hairless (glabrous) however, they are trapped with a ring (pappus) of numerous whitish hairs (3-4mm long), which are readily shed. Dispersal occurs by wind-borne seeds, and each plant produces about 100,000 seeds per season (15-30% seeds are usually not viable) [1, 3].

As far as its medicinal importance is concerned, this plant is known to possess antimicrobial, antiseptic, astringent, analgesic, and antipyretic properties. Based on folklore, its leaf extract is used to stop bleeding of cut & wounds, forming clots & root extract is prescribed to treat fever. Leaf juice is also used in the treatment of dysentery and is also poured in the eye to treat insomnia. However, there are some significant negative environmental impacts that this plant brings for which it is suggested to be controlled or not to be introduced. This plant colonizes forest margins, stream banks, and disturbed areas, preferring shaded wetter areas but also growing in open sunny sites. It grows in large dense clumps and will eventually out-compete all other plants in an area, choking out native vegetation and forming a monoculture. It is also poisonous to livestock, being particularly toxic to horses. In fact, this species is the cause of an acute pulmonary disease in horses, which is known as "Tallebudgera horse disease" in Queensland and "Numinbah horse sickness" in New South Wales [4].

Using the reliable sources like PubMed, Science Direct, Springer, and pertinent research papers(from 1991-2019), this paper highlights all the evidence-based information, related to its invasive nature, pharmacological activity, phyto-chemical constituent, ethnomedicinal properties and its potential in the medicinal industry, revealed till date, in a compiled and a systematic way.

Invasive Nature: First introduced into Yunnan Province in China in 1940, this species has extensively colonized southwestern China & is spreading rapidly (20 km/yr.) eastward & northward. Globally, *A. adenophora* is invasive in southern and south-eastern Asia (China, Nepal, Pakistan, Thailand, India, Philippines, Malaysia, Singapore), eastern Australia, New Zealand, and South Africa [5]. In terms of the Alien and Invasive Species Regulations (AIS), National Environmental Management: Biodiversity Act (Act No 10 of 2004), Crofton weed was declared a category 1b species, and is supposed to be eradicated or at least controlled by the landowners. In many of these countries, it invades crop fields, plantations, and pastures [6]. It prefers moist conditions, such as the edges of slow-flowing streams and waterlogged sites on steep slopes in high rainfall areas [2]. China is one of the worst-hit countries, with *A. adenophora* classified as one of their worst invasive alien species [5].

In South Africa, the first record of *A. adenophora* was from Limpopo province in 1958. *A. adenophora* is also naturalized in parts of the Western Cape, Mpumalanga, North–West and Gauteng provinces [2, 7], but was expected to be most invasive in the mist-belt region of KwaZulu-Natal, where it is a weed of roadsides, railway embankments, riverbanks and commercial timber plantations around Pietermaritzburg [6]. In California, it was introduced around 1849, and the first field collection was made in 1878. By 1920, it had spread throughout the mountains on the northern side of the Los Angeles Basin. Its occurrence in tropical countries such as India, Nepal, Philippines & Thailand is limited to elevations between 1000 & 2000m in the hills [3].

To invade successfully, invasive plants have developed complex strategies to cope with both neighboring plants and pathogens. Synthesizing specialized metabolites that have a phytotoxic activity to disturb the growth of neighbors is one of the most important strategies for the successful invasion of plants. These specialized metabolites can retard or inhibit seed germination, induce root cell death, and disturb the growth of tested plants. In the recent study, it was confirmed that the allelopathy of *A. adenophora*was due to leachates, with three compounds isolated and identified as the main allelochemicals *i.e*. 4,7-dimethyl-1-(propan-2-ylidene)-1,4,4a, 8a tetrahydronaphthalene-2, 6(1H, 7H)-dione (DTD) and 6-hydroxy-5-isopropyl-3, 8-dimethyl-4a, 5, 6, 7, 8, 8a-hexahydronaphthalen-2(1H)-one (HHO). When the physiological and morphological impacts of these allelochemicals on upland rice (*Oryza sativa* L.) seedlings were investigated to test the allelopathic mechanism of *A. adenophora,* it was found that the two allelochemicals (HHO & DTD) reduced the chlorophyll contents in leaves, while significantly increasing the contents of malondialdehyde and the activities of peroxidase in upland rice seedlings, indicating that DTD and HHO treatments induced peroxidation in root cells of upland rice seedlings.

In addition, root treatment of upland rice seedlings with the two allelochemicals enhanced abscisic acid, while reducing indoly-3-acetic acid and zeatin riboside. This effect increased with the treatment length and treatment concentration. Balanced changes of the concentration ratios of the three phytohormones in rice seedling roots showed inhibition of growth and development of rice plants when treated with DTD or HHO [5, 8].

The ability of *A. adenophora* to alter the underground microbial community in invaded areas & modify the soil biota, another factor for the plant invasion, helps to facilitate its continued invasion which is a self-reinforcing mechanism. From the recent study, it has been found that with the invasion, *A. adenophora* selectively accumulates bacteria, primarily Clostridium and Enterobacter, from the rhizosphere soils in the invaded ranges, suggesting that the recognition mechanism between plant host and certain bacteria in the roots may be conserved and not require a long-term interaction between invasive plants and local soil bacteria. Similarly, according to another report, the *A. adenophora* invasion highly increased soil fungi, azotobacteria, ammonia-oxidizing bacteria, and soil NO_3^-/-N, NH_4^+/-N, available P and available K contents, which were abundant in heavily invaded sites. Soil fungi, azotobacteria, and ammonia-oxidizing bacteria were associated with most of the measured soil physical and chemical properties. The results further indicated that *A. adenophora* changed soil microbial communities, especially the soil nutrition cycling-related soil microbial groups and created a favorable soil environment to benefit itself [9-11].

Similarly, the ecosystem heterogeneity (diversity & complexity within the ecosystem) also plays a crucial role in determining the fate of invasive plant species. As far as previous results are concerned, habitats with high diversity and complexity possessed strong resistance to the *A. adenophora* invasion, while disturbed habitats favored invasion. *A. adenophora* seedlings are adaptable to various soil types and fertilizers, with high adaptation to soil conditions being one aspect of its successful invasion. The number of *A. adenophora* seedlings was positively correlated with both the degree of disturbance and soil moisture in the microhabitats. Roadsides and wasteland were most sensitive to the *A. adenophora* invasion, Masson pine forestland was less resistant and shrubbery land the most resistant. High moisture habitats are fragile with regard to *A. adenophora* invasion. Scrutiny of characteristics of community structure of various ecosystems revealed that wasteland was sensitive to

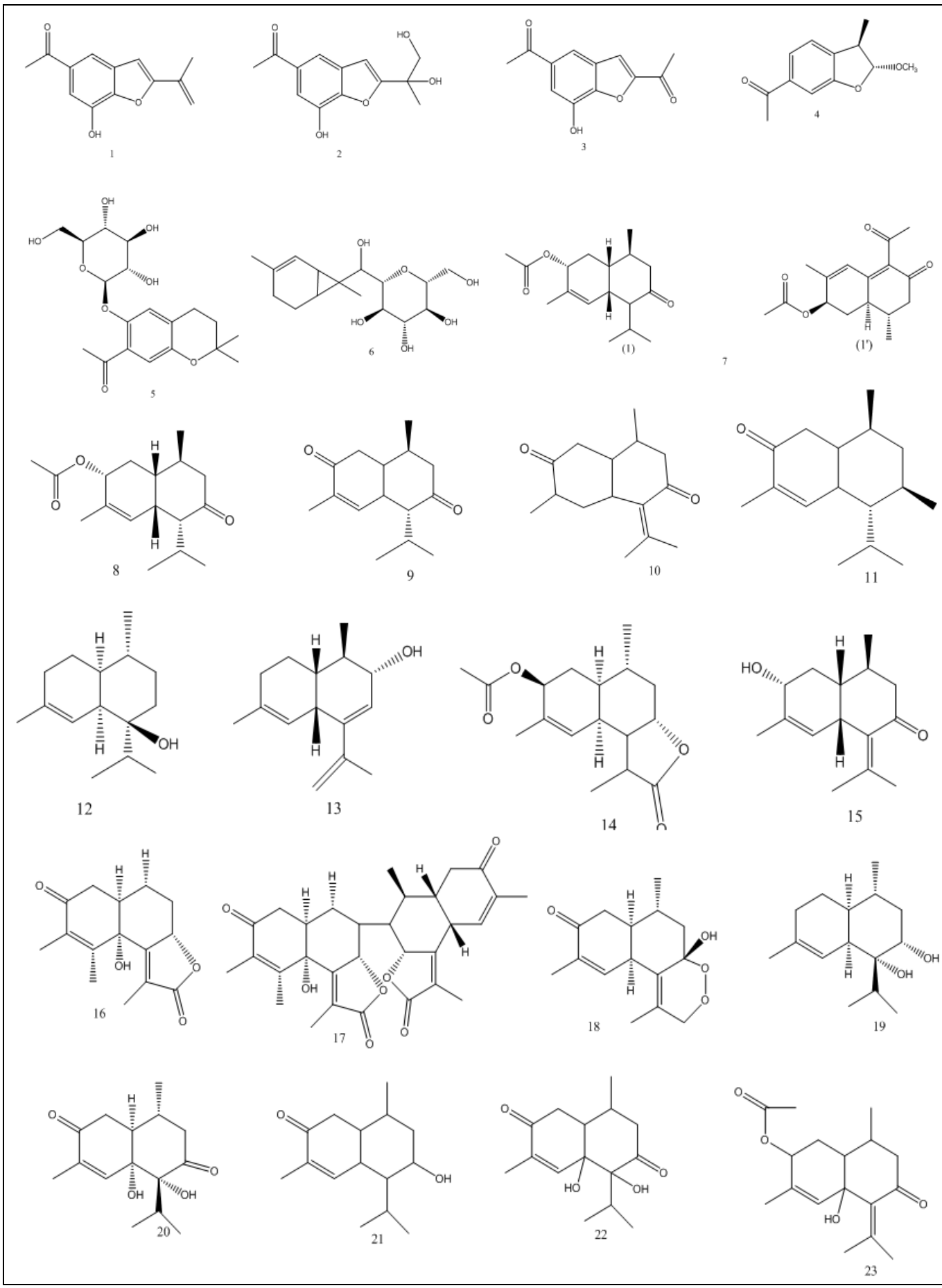
A. adenophora owing to low vegetation diversity and more niche space resulting from overgrazing and higher habitat disturbance [5, 12].

As this plant species has been threatening native vegetation in majority of the areas, the issue needs to be addressed. For this purpose, ecological restoration by competitive replacement of *A. adenophora* and use of biological control agents seem to be very effective measures. The competitor *S. sphacelata*, at the planting density of 45 m^{-2}, was an effective replacement plant that out-competed and replaced native plants, and therefore prevented *A. adenophora* from re-colonization after being uprooted. Similarly, the results of competition experiments on activities of soil enzymes and nutrients had also indicated that *S. sphacelata* was more effective than *A. adenophora* in activation of soil nitrogen, phosphorous, and potassium compounds, which showed its strong competitive ability with *A. adenophora.* Apart from these, classical biological control has also been proved to be one of the effective approaches for controlling invasive plant species. One report demonstrated that the imported fruit fly, *Procecidochares utilis* Stone (Tephritidae, Diptera), infected the weed at high rates and reduced its seed germination rates, but it did not produce significant impacts on weed height. Parasitism by the *P. utilis* was significantly affected by habitats where the weed was attacked (Parasitism was higher in open fields (55.4%) than under forest trees (41.2%)). Similarly, the mycelia of 19 strains of *Alternaria alternate* (Fr.) Keissler from the natural pathogenic fungus were found to be more pathogenic than the conidia, which caused brown spotted leaf disease in *A. adenophora*. The cause of pathogenicity was attributed to the AAC-toxin, identified as tenuazonic acid. The toxin is a broad-spectrum and high activity under illumination. It rapidly killed weeds and was easily degradable, thus beneficial. It significantly reduced the photosynthetic oxygen evolution rate, and the apparent quantum efficiency of *A. adenophora* leaves [5, 12].

Phytochemical Evaluation: To talk about its phytochemicals, *A. adenophora* mainly contains (mono-, sesqui-, di-, and tri-) terpenoids, phenylpropanoids, flavonoids, coumarins, essential oils, Sterols, phenolic acids, and alkaloids have also been reported as secondary metabolites. Following are some of the principles, along with their classes and their respective chemical structures that have been identified in this plant [13-18].

TABLE 1: PHYTOCHEMICALS AND THEIR RESPECTIVE CLASS

S. no.	Chemical Class	Phytochemicals
1	Benzofuran derivatives	7-hydroxy-dehydrotremetone (1); 7,10,11-trihydroxy dehydrotremetone (2); 10-oxo-7-hydroxy-nordehydrotremetone (3), 2αmethoxyl-3β-methyl-6-(acetyl-O-methyl)-2,3-dihydrobenzofuran(4)(BI Luo, 2018)
2	Chromene derivative	5-b-glucosyl-7-demethoxy-encecalin (5)
3	Monoterpene glucoside	8-hydroxy-8-b-glucosyl-2-carene (6)
4	Rare norsesquiterpene and Cadinene type of sesquiterpenes	Eupatorone (7); 2-deoxo-2-(acetyloxy)-9-oxoageraphorone(DAOA) (8), 9-oxoagerophorone(OA) (9), (Euptox A) 9-oxo-10,11-dehydro-agerophorone (10)(Pedro et.al 2019), 9 Beta-hydroxy-ageraphorone (11), muurol-4-en-7-ol (12), 8-beta-hydroxy-9,12-dehydroverbocciolenten(13) ,eupatoranolide (14), 3-hydroxymuurola-4,7 (11)- dien-8-one (15)(Wang et.al,2006;Bohlman and Gupta, 1981) (+)-(5R,7S,9R,10S)-2-oxocandinan-3,6(11)-dien-12,7-olide,(16) (+)-7,7'-bis[(5R,7R,9R,10S)-2-oxocadinan-3,6(11)-dien-12,7-olide,(17) (+)-(5R,7S,9R,10S)-7-hydroxy-7,12-epidioxycadinan-3,6(11)-dien-2-one,(18) (-)-(5R,6R,7S,9R,10S)-cadinan-3-ene-6,7-diol,(19) (+)-(5S*,6R*,9R*,10S*)-5,6-dihydroxycandinan-3-ene-2,7-dionel,(20) 7-hydroxycandinan-3-ene-2-one,(21) 5,6-dihydroxy candinan-3-ene-2,7-dione,(22) 2-acetyl-candinan-3,6-diene-7-one,(23) Candinan-3-ene-2,7-dione,(24) Candinan-3,6-diene-2,7-dione(25).
5	Monoterpene	1,6-dihydroxy-1-isopropyl-4,7-dimethyl-3,4dihydronaphthalen-2(1H)-one (26) (BI Luo, 2018),(Wang et al, 2006, (BI Luo, 2018)), (4R,5S)-4-Hydroxy-5-isopropyl-2-methyl-2-cyclohexehone (27)
6	New sesquiterpenes	chlorogenic acid (5-O-caffeoylquinic acid, 5-CQA)(28)and aerial parts also contains Neochlorogenic acid (3-O-caffeoylquinic acid, 3-CQA (29)) and cryptochlorogenic acid (4-O-caffeoylquinic acid, 4-CQA (30)
7	Quinic acid derivates	5-O-trans-o-coumaroylquinic acid methyl ester (31), chlorogenic acid methyl ester (32), macranthoin F (33) and macranthoin G (34).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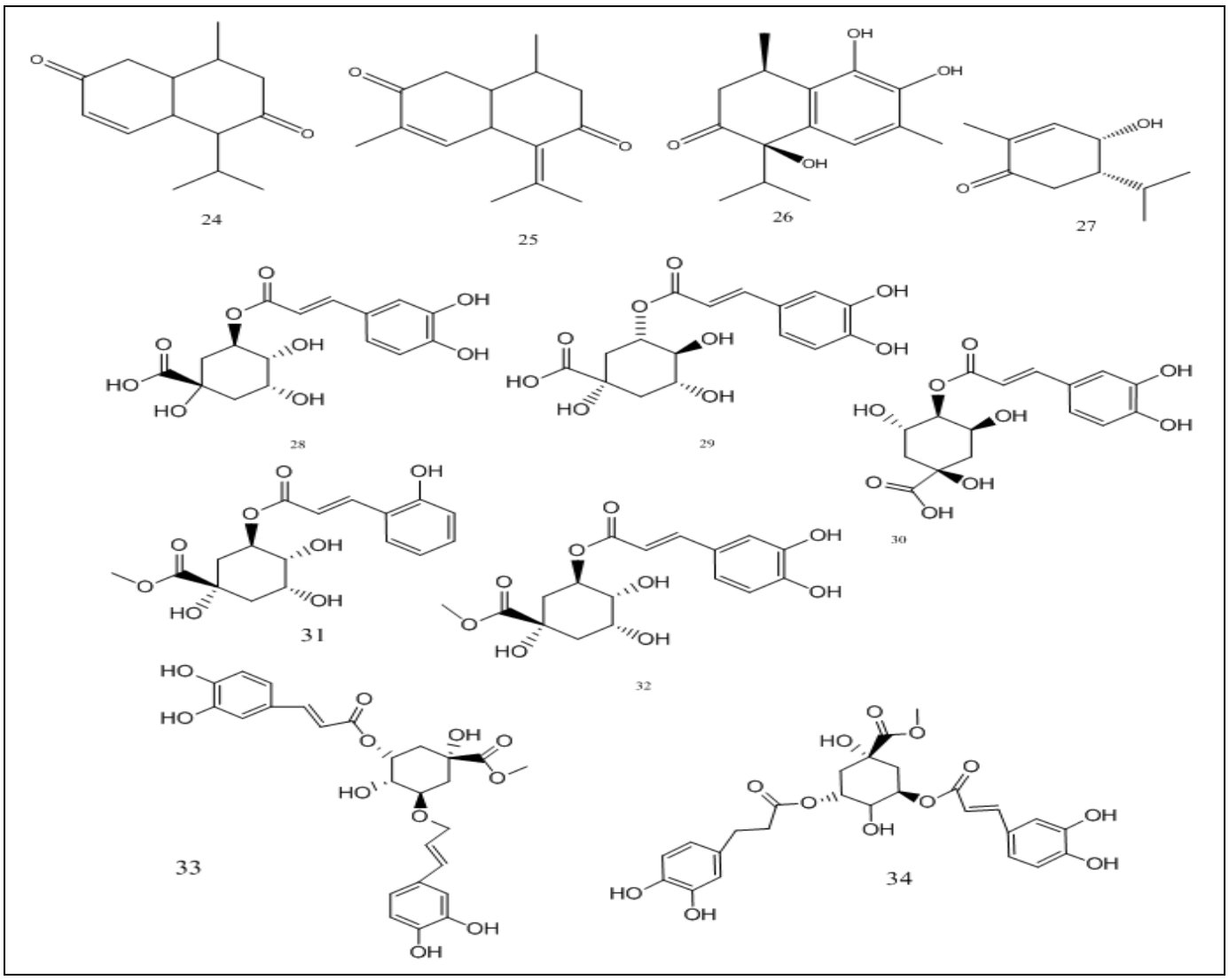

FIG. 2: CHEMICAL STRUCTURES OF SOME OF THE PHYTOCHEMICALS REPORTED IN *A. ADENOPHORA*

In addition, *A. adenophora* leaves and aerial parts are also found to be rich in various essential oils, among which some of them are mentioned in the following table [19-21, 36-38].

TABLE 2: VOLATILE OILS FOUND IN *A. ADENOPHORA*

S. no.	Volatile Oils
1	2-Pentanone, 4-hydroxy-4-methyl- (CAS) Diacetone alcohol
2	Bicyclo[2.2.1]heptane, 2,2-dimethyl-3-methylene- (CAS) 3,3-Dimethyl-2-methylenenorbornane
3	p-Mentha-1,4(8)-diene
4	Benzene, methyl(1-methylethyl)- (CAS) Cymol
5	1,3-Cyclohexadiene, 2-methyl-5-(1-methylethyl)- (CAS) p-Mentha-1,5-diene
6	β-Linalool
7	p-Mentha-1,5-dien-8-ol
8	Bornyl acetic ether
9	Camphene
10	Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-, [1R-(1R*,4E,9S*)]
11	Bicyclo[2.2.1]heptane, 2,2-dimethyl-3-methylene- (CAS) 3,3-Dimethyl-2-methylenenorbornane
12	2-Norpinene, 2,6-dimethyl-6-(4-methyl-3-pentenyl)-
13	beta.-Sesquiphellandrene
14	(6Z)-7,11-Dimethyl-3-methylene-1,6,10-dodecatrien
15	1H-Benzocycloheptene, 2,4a,5,6,7,8-hexahydro-3,5,5,9-tetramethyl-, (R)-
16	δ-Cadinene
17	Germacrene D
18	trans-Caryophyllene

19	1,2,3,4,5-Pentamethylcyclopentadiene
20	β-Bisabolene
21	Tricyclo[7.2.0.0(3,8)]undec-4-ene, 4,8,11,11-tetramethyl
22	β-Sesquiphellandrene
23	Naphthalene, 1,2,3,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-, (1S-cis)- (CAS) (+)-.delta.-Cadinene
24	5-Isopropyl-2-methylbicyclo[3.1.0]hex-3-en
25	(3E)-4,4-Dimethyl-3-(3-methyl-3-butenylidene)-2-m
26	Cyclohexene, 4-(1,5-dimethyl-1,4-hexadienyl)-1-methyl-
27	Androstan-17-one, 3-ethyl-3-hydroxy-, (5.alpha.)
28	(6E)-3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol
29	Andrographolide
30	(-)-Spathulenol
31	Caryophyllene oxide
32	α-Cedrol
33	Biphenylene, 1,2,3,6,7,8,8a,8b-octahydro-4,5-dimethyl
34	Guaiol
35	Torreyol
36	Isoledene
37	Azulene, 1,2,3,4,5,6,7,8-octahydro-1,4-dimethmethylethylidene)-, (1S-cis)- (CAS) Guaiene
38	α-Bisabolol
39	4,6,6-Trimethyl-2-(3-methylbuta-1,3-dienyl)-3-oxatricyclo[5.1.0.0(2,4)]octane
40	9H-Cycloisolongifolene, 8-oxo
41	Cyclodecacyclotetradecene, 14,15-didehydro-1,4,5,8,9,10,11,12,13,16,17,18,19,20-tetradecahydro
42	Bicyclo[4.4.0]dec-5-ene, 1,5-dimethyl-3-hydroxy-8-(1-methylene-2-hydroxyethyl-1)
43	1,4,4,7a-Tetramethyl-2,4,5,6,7,7a-hexahydro-1H-indene-1,7-diol
44	Di-epi-α-cedrene
45	9oxoageraphorone
46	Epifriefdelinol
47	Stigmasterol
48	octacosanoic acid
49	hydroxycinnamic acid
50	ferulic acid
51	Caffeic acid
52	2-isopropenyl-5-acetyl-6-hydroxybenzo-furan acetate

Pharmacological Activity & its Toxicity:

Antimicrobial Activity (Silver Nanoparticles): In the present study, the silver nanoparticles synthesized using the methanolic leaf extract of *Ageratina adenophora* were analyzed for their antimicrobial potential [22].

When the antibacterial activity of silver nanoparticles was tested at 10µg concentration based on the zone of inhibition, they were found to be more effective against *Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Salmonella typhi*, while moderately effective against *Klebsiella pneumoniae* and *Shigella flexneri* [22].

When the antifungal activity of silver nanoparticles was tested based on agar plug method, they showed 100% activity against *Aspergillus niger*, *Aspergillus flavus*, and *Candida albicans*, while > 50% but not full activity against *Rhizopus indicus*, *Aspergillus fumigatus* and *Mucor oryzae* [22].

Larvicidal Activity (Crude Leaf Extracts): In the present investigation carried out by Samuel *et al.* where the crude solvent extracts prepared from the flowers & leaves of *Ipomoea cairica* & *Ageratina adenophora* using petroleum ether, chloroform & methanol solvents were tested for their larvicidal activity against third instar larvae of *C. quinquefasciatus* as target species, *I. cairica* and *A. adenophora* plant extracts were found to be effective against third instar larvae of *C. quinquefasciatus* causing 77–100% mortality at 48 h. The highest mortality was observed at 500 ppm, and the order of larvicidal action was observed to be of methanol extract of *I. cairica* flower > petroleum ether extract of *A. adenophora* leaf > chloroform extract of *I. cairica* leaf.

A significant correlation (three-way factorial ANOVA) was also noticed among concentration of the plant extracts, exposure time and solvent extraction in relation to larval mortality (P <

0.0001), which indicates that larval mortality is concentration-dependent as well as time-dependent [23].

Anti-inflammatory Activity (Ethanolic Leaf Extracts): According to the recent study conducted by Chakravarty *et al.*, the ethanolic leaf extract of *A. adenophora* was investigated for its anti-inflammatory effect by administering intravenously & in other cases topically at the site of delayed-type hypersensitivity (DTH) reaction in mouse foot paw induced with dinitrofluorobenzene. The leaf extract was found to effectively inhibit DTH reaction and bring back normalcy to the paw much earlier than the controls. Intravenous administration of the leaf extract increased the number of CD_4^+ T cells in spleen and tumor necrosis factor (TNF)-α in the serum of DTH mice. The leaf extract also induced higher expression of TNF-α gene, TGF-β encoding a cytokine involved in tissue repair mechanism, and amount of the cytokine in serum. It also inhibited expression of another proinflammatory cytokine gene IL-1β and down-regulates cyclooxygenase 2 (COX-2) gene responsible for the metabolism of inflammatory mediators like prostaglandins; however, there was no effect in the expression of other inflammation-related genes such as IL-6, IL-10 and IKK [24].

Anti-pyretic Activity (Aqueous Leaf Extracts): The aqueous extracts of leaves of *A. adenophora* have been found to show antipyretic activity. In the recent research study, the aqueous extracts at doses of 300 & 400mg/kg body weight showed a significant decrease in pyretic temperature in second hours of treatment, respectively. This result was similar to that of the standard drug (150mg/kg body weight) on the comparison. Similarly, at the 500 mg/kg body weight, the body temperature came to normal within one hour. Thus, the dose of 500mg/kg body weight proved to be a significant dose than the standard paracetamol that, too, without any adverse effects [25].

Wound Healing Activity (Ethanolic Leaf Extract): In the present study, the ethanolic extract of *Ageratina adenophora* formulated as the gel was tested for its wound healing potential by excision & incision wound models. When the gel was applied on excision & incision wounds and left for 13-day study, the ethanol extract of *Ageratina adenophora* showed strongly significant ($p<0.01$) wound healing potential in excision as 90.98% wound contraction and 36.16% reduction in epithelialization time while in incision model, the plant extract showed significant increase (37.86%) in tensile strength on 13th day when compared to pure gel control. This study, hence provided experimental support to the traditional claim that this plant species is an effective wound healer [26].

Anti-oxidant Activity (Methanolic Leaf Extract): In the current work, the methanolic extracts of *Ageratina adenophora* and *Ageratum conyzoides* leaves were evaluated for their *in-vitro* antioxidant activity based on DPPH (2,2-diphenyl-1-picrylhydrazy) and hydrogen peroxide radical scavenging activity. In the scavenging assays, the extracts showed a significant DPPH activity as compared to the standard butylated hydroxyl toluene (IC_{50} for *A. conyzoides* was 70.489, for *A. adenophora* was 92.791 and for butylated hydroxyl toluene was 68.043). Similarly, they also showed a comparable H_2O_2 scavenging activity as compared to the standard ascorbic acid (*A. conyzoides* = 63.15%, *A. adenophora* = 79.32%, Ascorbic acid = 86.84%) [27].

Analgesic Activity (Methanolic Leaf Extract): In the recent study, the methanolic extract of *A. adenophora* leaves showed significant analgesic activity as compared to standard drugs diclofenac sodium and pentazocine in an acetic acid-induced writhing test, tail immersion test, and tail-flick test models. The leaf extract significantly increased the required induction time to produce the writhing movements and demonstrated significant analgesic activity in tail-flick and tail immersion tests, respectively. Under an acetic acid-induced writhing reflex model of analgesic activity, the number of writhing movements was significantly less in the mice treated with the methanol extracts of leaves when compared to that of the vehicle-treated control group thereby suggesting it's both peripheral and central analgesic effect [28].

Anti-tumor activity (Essential Oil- 9-Oxo10,11-Dehydroageraphorone or Euptox A): In the recent investigation, it was found that the essential oil from *A. adenophora* promoted HCC (hepatocellular carcinoma) apoptosis via activation of the apoptotic signaling pathway in mitochondria

and endoplasmic reticulum, as well as repressed the activity of STAT3 (Signal transducer and activator of transcription 3) and AKT(Protein kinase B) in HCC cells [29].

In another study, when the crude 9-oxo10,11-dehydroageraphorone (euptox A), a cadenine sesquiterpene from *A. adenophora*, was tested for its cytotoxicity to human lung cancer A549 cells, Hela cells & Hep-2 cells *in-vitro* by 4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, it was found that euptox A had significant antitumor activity against the three tumor cell lines *in-vitro* in a dose-dependent manner. When the concentration of euptox A was at 500 μg/mL, the percent inhibition of human lung cancer A549 cells, Hela cells, and Hep-2 cells were 76.42, 68.30 and 79.05%, respectively while the 50% inhibitory concentration (IC_{50}) of euptox A for the three tumor cell lines were 369, 401 and 427 μg/mL (A549, Hela and Hep-2 cells, respectively). This study suggested that euptox A may be considered as a potential candidate for developing a novel low toxicity antitumor agent [30].

Insecticidal Activity (Leaf Extracts): In the recent study done by Yunshou *et al*, the insecticidal activity of extracts from *A. adenophora* Spreng against the adults of the rice weevil *Sitophilus oryzae* (L.), maize weevil S. zeamais Motschulsky, Chinese bean weevil *Callosobruchus chinensis* (L.), and European bean weevil *Bruchus rufimanus* Boheman was evaluated. The results showed that the mortality of the four species reached 100.00% when treated with a fumigant concentration of 44.44mg/L. The further bioassay revealed that the LC_{50} (median lethal dose) after treating the four species for 24h were 14.65, 12.80, 25.07 and 12.20mg/L respectively, and the LC_{50} (median lethal dose) after treatment for 48h were 11.79, 9.67, 13.29 and 9.76mg/L respectively [31].

Antiviral Activity (Leaf Extract): According to the present research study, an *A. adenophora* extract was tested for antiviral activity against the tobacco mosaic virus (TMV) using the local lesion assay method, and also characterized. The *A. adenophora* leaf extract was able to strongly inhibit TMV infection, with electron microscopic observations indicating that the virus particles had been disaggregated. This result-the first reported observations of antiviral activity from leaf extracts of *A. adenophora* - suggests that this species provides an excellent source of antiviral substances for medicinal use [32].

Toxicity: *Ageratina adenophora* is an invasive weed with potent toxicological effects on livestock. Regular consumption of *Ageratina adenophora* causes chronic pulmonary disease in horses, which is characterized by pulmonary interstitial fibrosis, emphysema, alveolar epithelization, and reduced tolerance to exercise. This horse disease, a significant negative impact of *A. adenophora*, is known in Australia as 'Numimbah horse sickness' in New South Wales and 'Tallebudgera horse disease' in Queensland and as 'blowing disease' in Hawaii, USA. It may take several years to become evident but is always fatal. Similarly, in a recent report, intragastric administration of the freeze-dried leaf powder or methanol extract of *A. adenophora* resulted in multiple focal parenchymal necrosis and liver degeneration in mice. Rats fed with chow containing 25% (w/w) freeze-dried *A. adenophora* leaf powder developed jaundice, characterized by increased levels of plasma bilirubin, alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP). The electron microscopic study revealed a number of lesions in the liver rather than the lungs. The hepatic injury in these animals was characterized by multiple areas of focal necrosis of the parenchyma associated with degeneration and loss of the epithelium lining the small bile ducts, and the active principle 9-oxo-10, 11 dehydro-agerophorone was found to be responsible for these lesions.

Furthermore, rumination suspension and photosensitization have been caused by cattle. The toxic effects of *A. adenophora* ingestion on the liver, spleen, and kidney of goat have also been demonstrated, with dose-dependent apoptosis and autophagy seen in goat tissues. Another study has demonstrated that *A. adenophora* induced significant mice oxidative stress characterized by upregulating mRNA levels of antioxidants, including superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH). Thus, the invasive nature of *Ageratina adenophora* has reduced not only the number of local plants but also the number of grazing animals by indirect means [33, 34].

CONCLUSION: To sum up, this plant is one of the most threatening invasive species with potent detrimental effects on livestock (particularly horses and mice). Despite these negative features, this plant has been at the fore of the research interest as it has been shown to possess various novel constituents (7- hydroxy-dehydrotremetone, 7, 10, 11-trihydroxy dehydrotremetone, 10-oxo-7-hydro-xy-nordehydrotremetone, Eupatorone, 2-deoxo-2-(acetyloxy)- 9- oxoageraphorone (DAOA), 9-oxo-agerophorone (OA), *etc*.) with promising thera-peutic uses like anti-microbial , anti-viral, anti-tumor, anti-oxidant, larvicidal, anti-inflammatory, anti-pyretic, analgesic, *etc*.

This plant is also used in folklore medicine for the treatment of dysentery, insomnia, and fever. However, since the recent findings are based on a small array of samples, there needs to be a further evaluation for its safe and effective use in the therapeutic industry.

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