

Review Article

Pharmacological Profile, Phytochemicals and Toxic Effects of *Ageratina adenophora*: A Comprehensive Review

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ARTICLE INFO

Article history:
Received: 27/04/2025
Revised: 29/04/2025
Accepted: 29/04/2025

Key Words:
Ageratina adenophora,
pharmacological
activity, toxicology,
traditional medicine,
Invasive plant,
Phytochemicals.

Please cite this article as:
Goikane R, Pharmacological
Profile, Phytochemicals and
Toxic Effects of *Ageratina
adenophora*:A
Comprehensive Review, 7(2)
6-12

ABSTRACT

Ageratina adenophora, commonly known as Crofton weed, is an invasive perennial plant belonging to the family Asteraceae. Originally native to Central America, it has spread widely across Asia, Africa, and Australia, where it poses ecological and agricultural challenges. Despite its invasive nature and known toxic effects—particularly hepatotoxicity in livestock *A. adenophora* has garnered scientific interest due to its rich phytochemical profile and diverse pharmacological potential. This review provides a comprehensive overview of the plant's bioactive constituents and their associated pharmacological activities, including antimicrobial, antioxidant, anti-inflammatory, anticancer, and hepatoprotective effects. Simultaneously, it highlights the plant's toxicological aspects, emphasizing its adverse effects on animal health, mechanisms of toxicity, and dose-dependent responses. The dual nature of *A. adenophora*—as both a promising source of therapeutic agents and a toxic invasive species—underscores the need for further in-depth studies to assess its safety, efficacy, and possible applications in medicine and agriculture. This review aims to bridge the gap between its traditional uses, scientific evidence, and toxicological concerns to guide future research and utilization strategies.

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Introduction:

Natural products offer a wide range of structures with strong biological activity and appealing pharmacological characteristics, making them an appealing source. Throughout history, numerous novel medications have been derived from natural ingredients. For instance, natural goods are the source of 75% of medications for infectious diseases and 60% of medications for cancer[1]. The perennial, semi-shrubby herb *Ageratina adenophora* (Spreng.) can reach a height of three meters in damp conditions. It typically grows in places with a lot of water, on steep slopes, along the banks of

slow-moving streams, and in areas with a lot of rainfall. The word "adenophora" refers to "aden" (a gland) + "phoros" (bearing); refers to oil-producing glands in the leaves[2]. *Ageratina adenophora* the highly invasive alien plant known as "Crofton weed," R. King & H. Rob, is native to Mexico. It is extensively found in Europe, Africa, Asia, and Oceania and has progressively grown to be one of the world's most prominent invasive alien plants. In the United States and Australia, *A. adenophora* is a harmful weed[3]. The worst invasive weed is *A. adenophora*, sometimes known as Crofton weed or the "forest killer plant." Due to the release of

allelochemicals, this plant has been known to cause harm to other plants, including native wild species and crops within its invasive area[4]. Allelopathy is one way that Crofton weed impacts other plants. In its aboveground and belowground sections, it produces a number of substances called allelochemicals or secondary metabolites that aid in preventing the growth of other plants. Numerous experimental studies have substantiated that leachates prepared from above and belowground parts of Crofton weed have a strong allelopathic effect on native species as well as in crops[5]. *A. adenophora* is utilized in traditional medicine as an insect repellent, blood coagulant, analgesic, antipyretic, astringent, stimulant, and anti-acetylcholinesterase agent. In *A. adenophora*, the following compounds were identified: biologically active flavonoid glycosides; sesquiterpene lactones; sesquiterpenoids, cadinenes, chromenes; amorphenes, p-cymene; bornyl acetate; camphene; and thymol derivatives[6]. A widespread and very invasive weed, can cause serious respiratory problems in horses, including oedema and permanent pulmonary fibrosis. Although reports of lung poisoning in horses are still common in Australia and New Zealand, they are less common in other nations where Crofton weed is native and less well-known. For horses with Crofton weed-associated pneumotoxicity, there are no reliable diagnostic procedures or effective therapies[7]. Terminal clusters of little white flowers are produced by *A. adenophora* from late winter to April. Approximately 10,000 seeds can be produced by a normal plant, 70% of which are viable but short-lived, and distributed by wind and water[8]. Galls in the stem of *A. adenophora* are formed by the Mexican gall fly *Procecidochares utilis*. When the larvae hatch; they burrow into the stem from the eggs they lay on the top of the stem. The stem develops a gall in reaction to the presence of larvae, which may have one to twenty-three larvae inside. Significant stunting, decreased flowering and seed set, and possibly even the plant's eventual death have all been linked to galls when they occur in high quantities[9]. The partly purified fraction and the methanolic extract significantly increased the levels of transaminases, alkaline phosphatase, 50 nucleotidase, and total and conjugated bilirubin. These rat 'livers' histopathological examinations showed proliferative alterations and dilated bile ducts. Using the method outlined, the hepatotoxin found

in *E. adenophorum* leaves can be extracted using methanol and then further partially purified[10].

Botanical description

The leaves grow in opposite pairs and have a trowel shape with serrated edges. Their usual dimensions are 3–6 cm in width and 6–10 cm in length. The leaves taste harsh and have a subtle, unique scent. The stems are reddish, and they are dark green. The flowers are creamy white coloured followed by a small brown seed with a white feathery parachute[11]. The plant is a huge perennial herb or under-shrub that grows to a height of 1-2 meters on several upright, glandular, hairy burgundy stems. Its leaves are dark green, broad, trowel-shaped, with serrated edges and burgundy petioles. They grow in an opposite orientation and range in length from 2.5 to 5 cm. When crushed or disturbed, the leaves releases a strong, unique perfume. Flowers develop as small, dense heads at the tips of branches in the spring. They are 5–8 mm across and grow in white clusters of disc florets. The blooms are surrounded by bracts, which are tiny, leaf-like appendages. Croton weed is an abundant source of pollen even though it is apomictic—that is, able to create female clones from asexual seed production. A fully grown plant can yield between 100,000 and 1,000,000 seeds annually[7]. Each little blossom has a brown seed that looks like a dandelions and has a white feathery "parachute" that the wind can distribute[12].

Taxonomical study

| | |
|---------------|-----------------------------|
| Species | <i>Ageratina adenophora</i> |
| Family | Asteraceae |
| Genus | <i>Ageratina</i> |
| Kingdome | Plantae |
| Sub-kingdom | Viridiplantae |
| Infra-kingdom | Streptophyta |
| Division | Tracheophyta |
| Superdivision | Embryophyta |
| Sub-division | Spermatophytina |
| Class | Magnoliopsida |
| Order | Asterales |
| Superorder | Asteranae |

[12].

Table 1: Taxonomy of *Ageratina adeanophora*.



Fig 2: *Ageratina adenophora*

TRADITIONAL USES

The Portuguese term "Abundância" refers to *Ageratina adenophora* (Spreng.) R. King & h. Rob., which is used in traditional medicine to treat conditions of the stomach, liver, gallbladder, diabetes, cancer, and indisposition as a juice or herbal tea. Numerous investigations revealed that a number of its secondary metabolites have pharmacological effects, antiviral, anticancer, antibacterial, and antioxidant properties[13]. Throughout history, people have utilized *E. adenophorum* in traditional medicine. It is used as a blood coagulant, analgesic, cytotoxic agent, antipyretic, antibacterial, and antiseptic by local practitioners in many underdeveloped countries. *E. adenophorum* has been utilized in traditional Chinese medicine in China to treat phyma, traumatism, fever, and desinsectization. Native Americans in the Himalayan region applied raw leaf extract on bruises or injuries to cause clots and halt the bleeding[3].

Phytochemical study

Bioactive phytochemicals found in crofton weed include alkaloids, phenylpropanoids, polysaccharides, coumarins, phenolic acids, phenylfuran, sterols, quinic acid, and mono-, sesqui-, di-, and tri-terpenoids. 34 phytochemicals and 52 volatile oils that were extracted from Crofton weed were identified in a 2020 assessment. Numerous studies have looked into the potential pharmacological uses of the chemical extracts and phytotoxins found in Crofton weed, including their potential for treating wounds, promoting wound healing, reducing inflammation, promoting

analgesia, preventing cancer, and exhibiting antimicrobial, antiviral, insecticidal, larvicidal, and acaricidal properties[7]. *A. adenophora* was found to contain the biologically active flavonoid glycosides, sesquiterpene lactones, sesquiterpenoids (copaen, a-bisabolol, 4,4-dimethyl-3-(3-methylbut3-enylidene)-2-methylene bicyclic, heptane, and azulene), cadinenes, chromenes, amorphenes (amorph-4-en-7-ol and 3-acetoxyamorph-4,7(11)-dien-8-one and amorph-4,7(11)-dien-8-one), p-cymene, bornyl acetate, camphene, and thymol derivatives[6].(component that was extracted from the plant: euptox A, also known as 9-oxo-10-11-dehydroageroforone. This substance is a cadinene sesquiterpene, one of the more than 20 sesquiterpenes that have been found in this plant thus far, the most of which share a structural resemblance. In bottom-up investigations that target those particular proteins, euptox A has been shown to interfere with the cell cycle and the production of important proteins in the cell cycle and carcinogenesis[13].

Toxicity study

The pathophysiological mechanisms and phytotoxins responsible for the deadly pneumotoxicity in horses caused by Crofton weed are yet unknown. Equine Crofton Weed Pneumotoxicity, also called "Crofton Weed Poisoning," "Numinbah Horse Sickness," and "Tallebudgera Disease," was first thought to be caused by an allergic reaction or the hematogenous spread of an unidentified phytotoxin following intake[7]. In this work, mice were employed in an effort to identify the toxin in question. Liver lesions occurred when 50g male mice were gavaged with 1 mg or more of freeze-dried powdered *E. adenophorum* leaf suspended in regular saline[14]. A methanolic extract of *Eupatorium adenophorum* (*Ageratina adenophora*) leaf powder that had been oven-dried at 60°C and a partially purified fraction from that extract were administered to a group of rats. Administration of the methanolic extract and the partially purified fraction elicited a significant increase in total and conjugated bilirubin, alkaline phosphatase, 50 -nucleotidase and transaminases. and causes a hepatotoxicity[10]. Two cadinene sesquiterpenes, 2-deoxo-2-(acetyloxy)-9-oxoageraphorone (DAOA) and 9-oxo-10,11-dehydro-agerophorone (ODA), were assessed for their immunotoxicity in vitro and in vivo in Kunming mouse lymphocytes and natural killer

cells utilizing histopathology and toxicology techniques[15]. In rodents, 9-Oxo-10, 11-dehydroagerophorone (euptox A) showed hepatotoxicity[16]. Reactive oxygen species and malondialdehyde were markedly elevated by *Ageratina adenophora*, while antioxidants such as catalase, superoxide dismutase, glutathione, and glutathione peroxidase were dramatically reduced. Furthermore, treatment with *A. adenophora* also resulted in a decrease in the antioxidant enzymes' activity. *A. adenophora* causes pyroptosis and oxidative stress damage in mice, which compromises spleen function[17].

Invasive nature

A. adenophora, which is native to Mexico and Costa Rica, is one of the most significant invasive plant species in China. It has been known to effectively colonize environments all over the world. In addition to urban open spaces, open woods, and forest edges in subtropical and milder temperate climates, *A. adenophora* is typically found along roadsides, pastures, fence lines, waste areas, and riparian zones[18]. It prefers damp environments, such as the waterlogged spots on steep slopes in high rainfall regions and the borders of streams with a slow flow. Two. One of the worst-hit nations is China, where *A. adenophora* is regarded as one of their worst invasive alien species[19]. Another aspect contributing to the plant invasion is *A. adenophora*'s capacity to modify the soil biota and change the subterranean microbial community in invaded areas. This ability serves as a self-reinforcing process that aids in the plant invasion's continuous spread. In order to benefit itself, *A. adenophora* altered the soil microbial populations, particularly those connected to soil nutrition cycling, and produced a favorable soil environment[2].

Pharmacological activity

Anti-inflammatory activity

There are two types of inflammation: acute (the first stage) and chronic (the damage that exceeds the level of protection). Inflammation is frequently characterized by elements like heat, redness, swelling, discomfort, and impaired cell activity. In reaction to bodily inflammation brought on by microbial infections, mechanical trauma, and other stimuli, human living cells automatically generate defense systems[20]. In mice's footpads, *Eupatorium adenophorum* leaf extract (EEA) was

administered both intravenously and directly at the location of a delayed-type hypersensitivity (DTH) reaction that was brought on by dinitrofluorobenzene. In comparison to the control group, the extract significantly accelerated the paw's return to normal and successfully decreased the DTH reaction. Additionally, EEA administered intravenously increased the number of CD4⁺ T cells in the spleen and tumor necrosis factor[21][2]. Cryptochlorogenic acid extracted from *Adenophora* reduced inflammation by blocking the phosphorylation of NF- κ B proteins[22].

Wound Healing Activity

Any loss or disturbance of the cells, structure, or regular function of live tissue is referred to as a wound. The body's normal process of replacing dermal and epidermal tissue is known as wound healing or wound repair. Bite, burn, surgical wound abrasion, laceration, and acute inflammatory phase wounds are examples of wounds that can be broadly classified as having an acute or a chronic origin[23]. With 90.98% wound contraction and a 36.16% reduction in the time it took for new skin to grow, the plant *Ageratina adenophora* demonstrated a robust wound healing effect in the excision model. These results were statistically significant ($p < 0.01$). In the incision model, the plant extract notably enhanced tensile strength by 37.86% on the 13th day compared to the pure gel control[24].

Anti-tumor activity

A class of disease known as cancer is characterized by abnormal cell growth that spreads throughout the body. This spread, referred to as metastasis, can be lethal if it is not stopped. In addition to internal causes including inherited genetic mutations, hormone fluctuations, immune system problems, and random mutations, cancer can also result from a variety of external factors like chemical exposure, radiation, tobacco use, and infections[25]. Using increasing dosages ranging from 20 to 100 μ g/mL, the cytotoxic effect of *A. adenophora* extract on A549 cells was tested over a 24-hour period using the MTT assay. The results showed that *A. adenophora* methanolic extract significantly and dose-dependently induces cytotoxicity. With IC₅₀ values of 60.13 ± 0.11 , 50.08 ± 0.14 , and 43.28 ± 0.27 at doses of 20, 40, and 60 μ g/mL against A549 cells, respectively, *A. adenophora* showed substantial antiproliferative activity[26]. Using flow cytometry (FACS analysis), the effects

of Eupatorium adenophorum essential oil (EAEO) on the cell cycle of liver cancer (HCC) cells were investigated. For a whole day, HepG2 cells were exposed to 0, 10, 30, and 50 µg/mL of EAEO. The fraction of HepG2 cells in the G₂/M phase was shown to be dose-dependently reduced by EAEO treatment, and this was accompanied by a concurrent rise in G₀/G₁ cells[27]. A. adenophora-derived Euptox A altered the protein and metabolic profiles of HeLa cells. The decline in the 40S ribosomal protein RP8 raises the possibility of a drop in total protein synthesis, which may help offset traits typically linked to the development of cancer. The observed qualitative changes in lipid and protein composition, along with quantitative shifts in lipids, glycogen, and nucleic acids, indicate that euptox A could be inducing apoptosis[13].

Anti Bacterial activity

Erwinia herbicola and Pseudomonas putida, two bacteria related to plants, were used to assess the antibacterial properties of essential oils derived from plants in the Asteraceae family. According to the findings, oils from Blumea eriantha and Artemisia nilagirica Linn. were the next most hazardous to both bacteria, behind Eupatorium adenophorum Spreng oil.

[28]. GC-MS analysis was used to perform chemical profiling on the essential oil, resulting in the identification of 14 potential chemical components. α-Muurolol, which made up 24.56% of the composition overall, was the most prevalent of these chemicals. The highest zone of inhibition seen in relation to an essential oil's antibacterial activity against Staphylococcus subsp. aureus. In vitro antibacterial activity was demonstrated by all five compounds, including 5-O-trans-o-coumaroylquinic acid methyl ester, a novel quinic acid derivative, and three previously identified ones, namely macranthoin F, macranthoin G, and chlorogenic acid methyl ester, which were extracted from the aerial sections of the invasive plant Ageratina adenophora[29].

Anti pyretic activity

One of the most prevalent symptoms of sickness is pyrexia, or fever. It is described as a rise in body temperature over the average (37.0° C) for that specific person at that time of day. One Antipyretics are substances that lower elevated body temperature. Aspirin, acetaminophen, and other non-steroidal anti-inflammatory medicines, which

are used as analgesics and antipyretics, are currently synthetically derived medications[30]. The aqueous extract of A. adenophora leaves is a great antipyretic agent. Within the second hour of treatment, the aqueous extract significantly reduced fever temperature at dosages of 300 and 400 mg/kg body weight. Its effects were comparable to those of the commonly used medication, paracetamol. At doses of 500 mg/kg weight, the pyretic temperature decreased within an hour[31][19].

Anti fungal activity

At a dose of 50 mg per disk, 7-hydroxydehydrotremetone, the most frequently isolated chemical from A. adenophora roots, had potent, broad-spectrum efficacy in preventing the growth of all tested fungal strains. The diameter of the inhibitory zone varied between 13.90 ± 1.05 mm and 17.28 ± 0.46 mm. Encecalin had only mild inhibitory effect against Fusarium oxysporum f. sp. niveum, while other compounds were inactive.

[32]. sesquiterpenes, the main components of which are bornyl acetate, c-cadinene, c-muurolene, and 3-acetoxyamorpha-4,7(11)-diene-8-one.

Sesquiterpenes and monoterpenes were present in nearly equal amounts in the root oil, with the main components being α-phellandren-8-ol, β-cadinene, isothymol, c-muurolene, and E,E-cosmene. When both oils were applied to five phytopathogenic fungus, they showed notable antifungal efficacy. The antibacterial activity of the inflorescence oil was greater against Klebsiella pneumoniae, whereas the root oil was more efficacious against Staphylococcus aureus[33]. A cadinene sesquiterpene called 9-Oxo-10,11-dehydroageraphorone (ODA) was extracted from Eupatorium adenophorum. Four bacterial and four fungus strains were evaluated in vitro to determine the antibacterial activity of ODA. Bipolaris sorokiniana, Fusarium oxysporum, Fusarium proliferatum, and Alternaria tenuissima, with all examined strains exhibiting a notable reduction in mycelia size[34].

Conclusion

The invasive plant Ageratina adenophora is physiologically rich and possesses a variety of pharmacological properties, such as antimicrobial, antioxidant, anti-inflammatory, anti-tumor, antibacterial, antipyretic, and antifungal properties. These activities are attributed to its diverse phytochemical constituents such as

flavonoids, terpenoids, alkaloids, mono-, sesqui-, di-, and tri-terpenoids and. While traditional uses and experimental studies have demonstrated promising therapeutic potential, the plant also poses ecological and toxicological risks due to its invasive nature and toxicity in livestock. Therefore, further in-depth studies, including clinical trials and toxicological evaluations, are essential to validate its safety and efficacy for future pharmaceutical applications. Harnessing its bioactive compounds in a controlled and sustainable manner could offer new avenues for drug development while mitigating its environmental impact.

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