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Biological properties of active compounds from *Ageratina adenophora*

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Abstract

Ageratina adenophora is an invasive weed with widespread distribution. During the last several decades, many biologically active secondary metabolites have been isolated and characterized from *A. adenophora*, some of them having inspired the research and development of new therapeutic agents. This review mainly focuses on biological properties of *A. adenophora*, including the toxicity, antibacterial, antifungal, insecticidal, antiviral activities and others. In addition, the current limits and potentials of *A. adenophora* and its extracts are also discussed.

Keywords

Ageratina adenophora, active compounds, phamaceutical effects, application

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Introduction

Ageratina adenophora, also known as *Eupatorium adenophorum*, belongs to the genus *Agerina* in the *Compositae* family including multiple variants, such as *E. adenophorum* var. *adenophorum*, *E. adenophorum* var. *peruvianum* Hieron, *Eupatorium glandulosum* Michx, *E. glandulosum* Hort. ex Kunth [Illegitimate] and *Eupatorium pasadenense* Parish. *A. adenophora* is a perennial semi-herbaceous plant, originating in Mexico and Costa Rica, and has successfully invaded Europe, Oceania and Asia.[1] In 1940, Eupatorium adenophorum invaded Yunnan Province of China from the China-Myanmar border and spread widely to Sichuan, Guangxi, Guizhou, Hubei and Tibet provinces, as well as Chongqing and even Taiwan.[2] As one of the most important invasive plants in China, *A. adenophora* affects more than 30 million hectares in China.[3] It is estimated that *A. adenophora* will spread further north and east at an average speed of 20 kilometers per year.[2] However, there are no effective methods available at present to prevent and control its spread.

A. adenophora is rich in bioactive compounds, including monoterpenes, sesquiterpenes, diterpenes, triterpenes, flavonoids, polysaccharides, pyrrolizidine alkaloids, essential oils, phenylpropanoids etc., of which terpenes are the predominant component.[4] Those compounds from *A. adenophora* exhibit a wide range of biological activities, playing an important role in discovering clues to drug development for human disease treatment. For example, in India, *A. adenophora*, as a common folk medicine, has the property of antibacterial, sterilization, coagulation, analgesia and antipyretic.[5] In this review, we have mainly discussed the current research on *A. adenophora* extracts and their biological activities (Table 1).

Toxicity

A. adenophora is highly toxic to animals and affects many organs of animals. Studies have shown that horses feeding on *A. adenophora* will develop respiratory diseases.[6] Multifocal parenchymal necrosis and liver degeneration can be caused by intragastric injection of freeze-dried *A. adenophora* leaf powder or methanol extract in mice.[7] In another study, rats fed with 25% (w/w) freeze-dried *A. adenophora* powder will induce jaundice, mainly manifested by increased plasma bilirubin, ALP, ALT and AST levels.[8] Furthermore, studies have proved that *A. adenophora* has toxic effects on the liver, spleen and kidney by inducing autophagy and

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Table 1. Biological properties of *Ageratina adenophora* and its extracts.

No.	Activity	Source or Compound Name	Effect and Application	References
1	Toxicity	Whole grass Methanol extract DAOA, OA and Euptox A	– Respiratory disease in horses. – Extensive inflammation on mice. – Toxicity of liver, spleen and kidney in goat. – Hepatotoxicity, jaundice to mice and rat. – Immuno-toxic and hepatotoxicity to mice.	[6–15]
2	Antibacterial effects	Oil extract Organic and aqueous extracts Euptox A Thymol derivatives	– Against *Erwinia herbicola* and *Pseudomonas putida* from plants. – Inhibition of the growth of *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella aerogenes* and *Pseudomonas aeruginosa.* – Against the *Ralstonia solanacearum* – Against both Gram-negative and Gram-positive bacteria	[16–21]
3	Antifungal effects	Leaf extracts Euptox A Oil extract	– Inhibited the formation of *Pythium myriotylum* mycelial. – Against *Fusarium oxysporum*, *Bipolaris sorokiniana*, *Fusarium proliferatum* and *Alternaria tenuissima* as well as spore production in *F. oxysporum* and *B. sorokiniana.* – Against *Phytophthora capsici.*	[5,19,22–25]
4	Antiviral effects	Leaf extract Euptox A	– Inhibition of tobacco mosaic virus infection by disaggregating virus particles. Inhibition of H5N1 subtype of influenza virus and alleviate the flu symptoms by enhancing anti-viral immune response. – Inhibition Newcastle Disease Virus infection of chicken embryo fibroblasts.	[26–29]
5	Anti-nematode and insecticidal effects	Aqueous extract Acetone extract Ethanol extract and Euptox A 5,6-dihydroxycadinan-3-ene-2,7-dione	– Against *Oncomelania hupensis* in humans and livestock. – Against coccidian oocysts in chickens and *Aphis gossypii*. – Against cabbage aphids and *Brevicoryne brassicae.* – Against *Psoroptes cuniculi* and *Sarcoptes scabiei* in rabbit. – Against *Meloidogyne incognita.*	[30–40]
6	Other effects	Sesquiterpene Whole grass	– Antitumor effects and inhibition of cancer cell proliferation. – Animal feed after detoxification. – - Inhibit the inflammatory reaction	[41–43]

apoptosis of cells in goats and mice, respectively.[9] In addition, after feeding *A. adenophora* with a dose of more than 20%, the liver index of mice increased and caused extensive inflammation, in addition to the decrease of antioxidant activity, increasing the production of reactive oxygen species, and activating pyroptosis via the NLRP3-dependent pathway. This indicated that *A. adenophora*-induced liver damage was mediated via increased oxidative stress.[10]

The structural and functional characteristics of the liver determine its increased susceptibility to pathogens and toxins.[11] The major toxin isolated from *A. adenophora* is 9-oxo-10, 11-dehydro-agerophorone (Euptox A), one of the twenty sesquiterpenes with the same molecular skeleton of cadinene present in the weed. Euptox A is a major hepatotoxin for rodents, with a median lethal dose (LD50) of 1470 mg/kg body weight in mice.[12] Two more toxic sesquiterpenes isolated from *A. adenophora*—2-deoxo-2-(acetyloxy)-9-oxo-ageraphorone (DAOA) and 9-oxo-agerophorone (OA)—are also hepatotoxic in mice with respective LD_{50} 926 mg/kg BW and 1470 mg/kg BW.[13] DAOA and Euptox A are also immuno-toxic to mice, leading to decreased numbers and irregular arrangement of splenocytes and thymocytes. Consistent with this, we found that Euptox A arrested splenocyte proliferation in G0/G1 phage and induced autophagy in a dose-dependent manner when administered to mice via the gastric route.[14] In addition, three sesquiterpenes (amorpha-4, 7 (11)—diene-8—a DTD), eupatoranone and 9-oxo-radinone) and two esters, dibutyl phthalate and di (2-ethylhexyl) phthalate (DEHP), were purified from the root of *A. adenophora* as phytotoxic compounds and played a key role in allelopathy.[15]

Antibacterial effects

In recent decades, the emergence of drug-resistant strains has prompted researchers to pay more and more attention to the development of novel antibacterial agents. Plant extracts are potentially rich sources of antimicrobial compounds, and are considered clinically and ecologically safer compared to synthetic chemicals.[16] In Vietnam, *A. adenophora* is used to treat various skin infections, and its oil-extract has obvious inhibitory effect on *Erwinia herbicola* and *Pseudomonas putida*, two phyto-pathogenic bacteria.[17] The organic phase and water extracts from the crude leaves of *A. adenophora*

have inhibitory effects on the growth of *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella aerogenes* and *Pseudomonas aeruginosa.*[18] In addition, Euptox A has a strong inhibitory effect on *Ralstonia solanacearum* (R1-4), which is widely distributed in plant pathogens, with a minimum inhibitor of 0.25 to 1 mg/ml, while OA has moderate toxicity to animals.[19] The thymol derivatives of *A. adenophora* have also exhibited inhibitory effects on both gram-negative and gram-positive bacteria.[20] Furthermore, bioactive quinic acid derivatives from *A. adenophora* have in vitro antibacterial activity toward five assayed bacterial strains.[21]

Antifungal effects

Secondary metabolites refer to compounds that are synthesized under stress conditions, and primarily inhibit pathogens. A number of secondary metabolites, mainly sesquiterpenes, have been isolated from the inflorescence and roots of *A. adenophora* that show potent antifungal activity. A study shows that the crude extract of *A. adenophora* has inhibitory effect on pathogenic fungi.[22] A later research demonstrated that sesquiterpenoids, the main active component of *A. adenophora*, mainly isolated from inflorescence and root.[5] In addition, Liu et al.[23] reported that the leaf extracts of *A. adenophora* (mainly 10Hβ-9-oxo-agerophorone, 10Hα-9-oxo-agerophorone and Euptox A) inhibited the formation of *Pythium myriotylum* mycelial biomass at the minimum inhibitory concentration of 100 μg/ml. Euptox A also inhibited germination of *Fusarium oxysporum*, *Bipolaris sorokiniana*, *Fusarium proliferatum* and *Alternaria tenuissima* as well as spore production in *F. oxysporum* and *B. sorokiniana*.[19] Furthermore, a bioactive quinic acid derivatives from *A. adenophora* has in vitro anti-fungal activity against spore germination of Magnaporthe grisea with an IC_{50} value 542.3 μM.[21] Six compounds isolated from the root of *A. adenophora* have antifungal activity against Alternaria alternata and four other agricultural pathogenic fungi Colletotrichum gloesporioides, C.musae, Rhzoctonia solani and Fusarium oxysporum f.sp.niveum.[24] Finally, the mycelial growth of *Phytophthora capsici* was inhibited by *A. adenophora* oil extraction after incubation 7 d at the concentration of 500 μg/mL.[25]

Antiviral effects

Pathogenic viruses affect humans, farm animals and plants, resulting in considerable mortality, morbidity and economic losses worldwide.[26] Furthermore, the frequent emergence of new vaccine-resistant mutant strains render most vaccination and treatment regimens ineffectual. Herbal formulations have been used since millennia to prevent and treat viral infections and enhance immunity, and much of the current research on developing antiviral drugs is focused on medicinal plants. *A. adenophora* inhibits the growth of other plants via allelopathy, indicating its potential as an anti-viral agent as well.[27] For example, leaf extract from *A. adenophora* inhibited tobacco mosaic virus infection by disaggregating virus particles, as observed under by electron microscopy.[27] In addition to plant virus, *A. adenophora* is also effective against animal virus. In addition, the polysaccharides in *A. adenophora* leaf extracts inhibited the highly pathogenic H5N1 subtype of influenza virus, and alleviated the flu symptoms by enhancing anti-viral immune response via IL-6, TNF-α and IFN-γ.[28] Xu et al.[29] reported that Euptox A extracted from *A. adenophora* neutralizes the Newcastle disease virus, then inhibited the infection of chicken embryo fibroblasts.

Anti-nematode and insecticidal effects

In recent years, the potential of *A. adenophora* as anti-nematode agent and insecticide has been gradually recognized, and its extract has been approved for clinical application in Vietnam.[30] Aqueous extracts of *A. adenophora* inhibited *Oncomelania hupensis* and controlled schistosomiasis spread in humans and livestock.[31] It is also significantly effective against coccidian oocysts and *Aphis gossypii*.[32] In addition, the *A. adenophora* acetone extraction has a strong inactivation effects against cabbage aphids and *Brevicoryne brassicae*.[33] Acariasis is a highly infectious skin disease caused by mites, which frequently affects livestock and can lead to decreased productivity and even death.[34] Although several chemical acaricidic drugs are available to treat and control ectoparasitic acariasis,[35] their therapeutic utility is limited by bioaccumulation and the emergence of resistant strains. In contrast, botanical acaricides are biodegradable and do not have the risk of resistance.[36] The ethanol extract of *A. adenophora* showed potent toxicity against the mites *Psoroptes cuniculi* and *Sarcoptes scabiei* in a time and concentration-dependent manner,[40] and its crude extract has shown satisfactory clinical outcome on rabbits with spontaneous and induced mite infection.[32] Euptox A, was recently characterized by silica gel column chromatography, thin-layer chromatography and ^{1}H, ^{13}C nuclear magnetic resonance, and makes up a considerable proportion of *A. adenophora*-derived toxins.[37] It showed potent toxic effects against *S. scabiei* and *P. cuniculi*.[38] Four cadinene sesquiterpenes were isolated from *A. adenophora* leaves with ethyl acetate and identified by gas chromatography-mass spectrometry, of which 5,6-dihydroxycadinan-3-ene-2,7-dione exhibited significant antinemic activity against *Meloidogyne incognita*.[39]

Others

It is reported that the extract and secondary metabolites of *A. adenophora* have anti-inflammatory activity. For example, the ethanol leaf extract of *A. adenophora* shows anti-inflammatory activity by inhibiting gene expression of IL-1β and cyclooxygenase 2 (COX-2).[41] In addition, the ethanol leaf extract of *A. adenophora* can effectively inhibit the

inflammatory reaction of foot paw caused by injection of DNFB. Furthermore, intravenous injection of *A. adenophora* leaf extract can increase the number of $CD4^+$T cells in spleen and induce TGFβ gene coding and inhibiting IL1β And COX-2 expression.[42]

The study also found that the extract of *A. adenophora* has anti-tumor activity. In vitro tests showed that the inhibition rate of 9-oxo10,11-dehydroezelanone isolated from *A. adenophora* on human lung cancer A549 cells, Hela cells and Hep-2 cells were 76.42%, 68.30% and 79.05% at a dose of 500 μg/mL, respectively.[43]

Summary and future perspectives

Due to its easy absorption, the liver is one of the main target organs of *A. adenophora* toxins, especially sesquiterpenoids.[11] In addition, the terpenoids and terpened that have not been isolated so far could exert hepatotoxic effects. *A. adenophora* or its extracts induce liver toxicity by activating oxidative stress, pytoptosis,[10] and atoptosis,[9] although the exact mechanism, as well as the metabolic effects of *A. adenophora* are unknown. The intestine is colonized by a large number of microorganisms, defined as gut microbiome or microbiota.[44] Because the liver and intestine are closely connected through the portal vein, intestinal microbes and toxins can easily enter the liver, with pathogenic implications.[45] Intestinal microflora is closely related to liver disease, and relevant research reports are extensive,[46] but it remains to be elucidated whether any disturbance in the gut microbiota is directly linked to hepatotoxicity induced by *A. adenophora*.

Despite its toxicological action, *A. adenophora* contains many bioactivity with potential therapeutic applications. For instance, the extract from *A. adenophora* has antitumor effects,[47] and inhibits cancer cell proliferation by triggering the apoptotic pathway.[48] Furthermore, *A. adenophora* can also be used as a livestock feed after detoxification. However, a number of bioactive compounds still remain to be identified and characterized, before incorporating *A. adenophora* in clinical use. The invasiveness of *A. adenophora* in arable lands is difficult to control, and will require extensive efforts.[40]

At present, there are many basic studies on the comprehensive development and utilization of *A. adenophora*. However, the extracts of functional active components from *A. adenophora* are mostly crude extracts. The identification technology, active mechanism and in-depth utilization of monomer chemical components need to be further strengthened. In addition, *A. adenophora* has a wide range of biological activities, and the specific mechanism of its function needs further detailed study.

Conclusions

The toxicity and potential utilization of *A. adenophora* were reviewed in this paper. Our concluding recommendation would be to utilize the double attributes of toxicity and drug properties of *A. adenophora*, and turn waste into treasure through reasonable development in the future!

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