INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Ethnopharmacological Potential and Bioactive Compound of *Ageratum conyzoides*

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ARTICLE INFO

Published: 26 Apr 2026
Keywords:
Ageratum conyzoides, Ethnopharmacology, Phytochemistry, Anti-inflammatory activity, Antimicrobial activity, Bioactive compounds.
DOI:
10.5281/zenodo.19788447

ABSTRACT

Ageratum conyzoides has great value as a palliative agent for people in need, as it has a major contribution to ethnopharmacology and has many bioactive compounds. This review attempts to describe the botany of this plant, its uses in different traditional medicine systems, its chemical composition, its pharmacological activities, the mechanisms by which it acts, and the problems related to it. Wound healing, treatment of infection, fever and inflammation as well as the management of different systemic diseases have traditionally focused on this plant in the different traditional medicine systems of Ayurveda, Chinese and African medicine. The presence of a wide variety of flavenoids, alkaloids, terpenoids, chromenes, coumarins and also the volatile oils of this plant, speak of a broad range of biological activities of the plant. It has been documented that this plant is an anti-inflammatory, antimicrobial, antioxidant, anticancer, antidiabetic, analgesic, antipyretic, insecticidal and promotes wound healing. This plant is said to cause these effects by Ageratum conyzoides through a variety of pathways which includes the NF-κB, MAPK, and PI3K/Akt pathways and the inhibition of cyclooxygenase and lipoxygenase, and the balance of stress in the body to oxidative

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

stress by the antioxidant systems of the body. The presence of pyrrolizidine alkaloids, lack of standardization and clinical validation are major barriers to its deployment. The standardization of clinical trials, isolation of the active compounds, detailed evaluation of mechanisms of action and the development of novel delivery systems for the compounds from this plant is of utmost need.

INTRODUCTION

1.1 Background and significance of medicinal plants

From ancient to modern times, medicinal plants have formed the basis of almost all healthcare systems and, by extension, almost all modern pharmaceuticals [1]. Medicinal plants have been important to all the world's ancient civilizations and their medicinal systems, which incorporated natural, plant-based medicines to treat, and even prevent, illness and disease. In the twenty-first century, herbal medicine continues to be the first, and often only, form of health care for about 70-80% of the population in developing countries, largely due to the cultural, social, and even health perceptions of natural medicine [2]. Medicinal plants have an almost limitless variety of natural, bioactive, and eco-safe compounds with an equally vast variety of medicinal properties; many modern pharmaceuticals are derived directly or indirectly from plant materials. This is especially true of morphine, paclitaxel, and artemisinin [3]. Phytochemicals of plants have excellent translational and therapeutic potential, since there are very few pharmaceutical plant based medicines and even less synthetic medicines that are safe, effective, and economically beneficial. Additionally, the existing supply of synthetic medicines is inadequate and the demand for effective, plant-based medicines is further exacerbated by modern, yet untreatable diseases such [4]. The last of chronic diseases, cancer, and the beginning of the age of resilience to all treatment, safety, and all issues relating to western medicine, pharmaceutical industry. The significant importance of ethnopharmacology, science, and research, is the potential to identify safe therapeutic medicinal compounds that are validated by old, traditional, and integrated systems of plant-based medicines [5].

Furthermore, high-performance liquid chromatography (HPLC), gas chromatography–mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy have made analyzing complex phytochemicals easier. These technologies have closed the gaps between traditional and modern pharmacological knowledge and provided systematic methods for research on medicinal plants [6]. The use of medicinal plants, despite their potential, has been associated with a range of challenges such as heterogeneity of the constituent phytochemicals due to changes in the environment, absence of standardization, deficient clinical information, phytotoxicity, and herb–drug interactions [7]. Thus, ethnopharmacological information with far-reaching potential ought to be synthesized in a thoroughly detailed way to integrate phytochemical and pharmacological information, to elucidate the medicinal usefulness of such plants and the holistic potential of medicinal plants [8].

1.2 Overview of *Ageratum conyzoides*

Ageratum conyzoides (goat weed) plantain is a vibrant shrub representing the Asteraceae family. As it thrives in tropical to subtropical environments, it circulates mainly in Asia, Africa, and parts of southern America [9]. The adaptive and robust features of the shrub are seen with its persistence in the growth of shrub along sites of environmental disturbance, including roadsides and construction sites. Botanically, this species is characterized by its hair-coated stems, ovate, serrated leaves, and small, fluffy flowers varying

in blue, lavender, and white colors. The plant produces odor due to the presence of volatile compounds which contribute to its biological activity [10]. The resinous odor attributed to its volatile compounds gives it a sharp, distinct odor. Its rapid growth and invasive nature have often led to its classification as a weed; however, this same adaptability has made it readily available for traditional medicinal use. It is believed that traditional and folk medicine, especially Ayurveda, has for a long time utilized *Ageratum conyzoides* to treat wounds, febrile conditions and/or inflammation, and gastroenteritis and/or cutaneous pathologies [11]. Especially in African traditional medicine, *Ageratum conyzoides* is famed for its antimicrobial and analgesic attributes. It is also popular in Chinese medicine to control bleeding (hemostatic) and inflammation. The species is also used by traditional veterinarians to treat a variety of pathological conditions (infections and injuries) in farm animals. As with many medicinal plants, the phytochemical analysis of *Ageratum conyzoides* has demonstrated the presence of wide range of bioactive ingredients, including the chromenes (precocenes I and II), the flavonoids (quercetin and kaempferol), the alkaloids, the terpenoids and the essential oils [12].

The antimicrobial, anti-inflammatory, antioxidant, anticancer, and insecticidal activities of these compounds are a result of their incorporation of chromene. Due to their high potential as lead drug candidates, these compounds are of great importance. Besides its medicinal value, biopesticide properties of *Ageratum conyzoides* are of great value. *Ageratum conyzoides* and its larvicidal and insecticidal activities are attractive as biopesticides [13]. As a result of the need for sustainable agricultural practices, biopesticides are presented as substitutes for synthetic biopesticides. *Ageratum conyzoides* shows its health benefits, however, the presence of pyrrolizidine alkaloids, imply safety risks, since they are harmful to the liver. The promising nature together with potential risk of *Ageratum conyzoides* shows that appropriate and careful research should be done [14].

1.3 Rationale and Objectives of the Review

The global interest in 'greener' pharmaceuticals and the resurgence in the use of traditional medicines necessitate more thorough reviews of the scientific evidence backing the use of plants in traditional medicines. The presence of *Ageratum conyzoides* in almost all parts of the planet, the diverse ethnomedicinal applications, and the complexity of the phytochemicals it contains makes it an ideal candidate for such studies. The presence of both ethnomedicinal, pharmacology, chemical, and mechanism of action data in literature makes it an ethnobotanically rich plant, but the literature on *Ageratum conyzoides* seems to be scattered [15]. The chemical compounds that have been described as bioactive in the plant are also incompletely described in the literature with respect to the structure and activity of the compounds, and the molecular action pathways to which, the compounds are involved [16]. Limited knowledge on this aspect keeps the use of traditional medicines in this respect spiritually symbolic, and not practically scientific. Concern about the safety of this plant and the presence of liver-damaging pyrrolizidine alkaloids in the plant, raise questions regarding the mechanism of action and the dosage and the formulations of it in traditional medicines for safety evaluation [17]. The use of pyrrolizidine alkaloids in medicine for long periods also warrants the need of systematic review of the toxicology data on. The use of traditional and modern scientific methodologies can be a valuable strategy to harness the full

potential of *Ageratum conyzoides* as a source of novel pharmaceuticals [18].

2. Botanical profile of *Ageratum conyzoides*

2.1 Taxonomy and Classification

Ageratum conyzoides is a widely distributed annual herb belonging to the family Asteraceae, one of the largest families of flowering plants characterized by composite inflorescences and diverse phytochemical profiles. The taxonomic classification of this species reflects its evolutionary placement within angiosperms and provides a systematic framework for its identification and comparative botanical studies [19]. The accepted taxonomic hierarchy of *Ageratum conyzoides* is as follows:

- **Kingdom:** Plantae
- **Clade:** Angiosperms
- **Clade:** Eudicots
- **Clade:** Asterids
- **Order:** Asterales
- **Family:** Asteraceae (Compositae)
- **Genus:** *Ageratum*
- **Species:** *Ageratum conyzoides* L.

The genus Ageratum has an estimated 30 species, with most species endemic to Central America and widely naturalized in tropical and subtropical areas. *Ageratum conyzoides* belongs to the family Asteraceae and is classified in the tribe Eupatorieae, which has a number of species that are rich in secondary metabolites, particularly, flavonoids and terpenoids [20]. The taxonomy of Ageratum also draws interest in the field of pharmacognosy, since it is often indicative of specific biosynthetic pathways as well as profiles of bioactive compounds. Carl Linnaeus was the first to understand and appreciate the taxonomy of *Ageratum conyzoides* and thus conyzoides was named to mirror plants of the genus Conyza [21]. The identified plant was often mistaken for the related species owing to their morphological affinity, yet flower morphology, foliar morphology and, chemical content also greatly resolved the dilemma in the Ageratum taxonomy. Taxonomy systems that are critically and rightly placed in ethnopharmacological research are not just a welfarism [22].

2.2 Morphological characteristics

Ageratum conyzoides has features that easily catch the eye, making them easy to spot even in the wild. They are usually anywhere from 30 to 100 cm tall and grow as annual, erect, and branched herbs. They grow in a variety of conditions that are indicative of their size and health. Their texture is unique and soft and almost all of their above-ground parts have some kind of hairy growth [23].

Stem: Their stems are cylindrical in shape, have some green and purple hues, and have some fine hairs covering them. Young plants have relatively soft and juicy stems, while older stems become a little more rigid and woody. The branches are also irregularly distributed, making the plants look bushy.

Leaf: The leaves of *Ageratum conyzoides* are petiolate and grow in pairs on the stem. Their shapes vary from being ovoid to triangular. They also have a variety of growth along the margins of the leaves, which could be serrated, or crenate, and end with a sharp and pointy tip. The surfaces are all hairy and have glandular trichomes. This particular kind of zombie hair is responsible for the plant's odor and some of the texture of the plant. Hair also serves the dual purpose of providing

shade to the plant and acting as a natural insect repellent [24].

Infloroscence & flowers: Plants in the Asteraceae family all produce a type of floral cluster known as a capitula, which can be found on the terminal and side branches/internodes. The colors of the florets inside the capitulum can be blue, lavender, white, or even some combination of the three. *Ageratum conyzoides* differs from a lot of other Asteraceae in that they completely lack ray florets. This also contributes to the fluffy or powdered-puff look of their floral heads. The arrangement of the involucral bracts that surround the capitulum is also quite specific and is typically characteristic for that particular species [25].

Fruits and Seeds: The fruit is a small, dry achenes that contains a single seed, which is usually black or brown. It is also equipped with a pappus that aids with wind dispersal. Having this efficient method of seed dispersal, the species exhibits an invasive nature and wide distribution.

Root System: The plant has a shallow but fibrous root system which aids with the quick uptake of nutrients and moisture. Due to this adaptation, the species is able to thrive within disturbed and nutrient-poor environments [26].

The great adaptation features and the high potential both in the pharmaceuticals and in the production of raw materials (due to high reproductive and growth rate) of *Ageratum conyzoides*, say a lot of the species. A good example in this regard could be the presence of glandular trichomes connected to the secretion and the storage of essential oils besides other bioactive materials [27].

2.3 Geographical distribution and habitat

Ageratum conyzoides has one of the most extensive ranges among all plant species. It is believed to have originated in the Central and South American region but is now fully established in the tropics and subtropics of the world across all continents, including Asia, Africa, and Oceania [28]. In Asia, *Ageratum conyzoides* grows in almost the entire continent, including the Indian, Chinese, Indonesian, and the Philippine subcontinents. In India, the plant is present in almost all the landscape of the entire country. It is found in the plains, the hills, and the forests, even in urban areas where roads, gardens, fields, and garbage land have disturbed the ecology. *Ageratum conyzoides* has naturalized in all the climate zones of the world, from the high subtropics to the humid tropics [29]. In Africa, *Ageratum conyzoides* has fully established itself and is used extensively in the folk medicine of most countries. The same can be said for the plant's continued establishment in both the wild and settled environment of its country of origin in South America. Humans have been responsible for the dissemination of the plant in all other continents, especially in the fields of trade and farming [30]. *Ageratum conyzoides* is also adapted to the humid warm climates with a mean annual rainfall of about 950mm and growing conditions within the average range which include all types of soil, including sandy, loamy, clay, and even poor, disturbed, and residuals; however the plant grows best in rich, fertile, well-drained soils [31]. The plant is a weed in almost all the agricultural systems in the world because of its invasive character and its high allelopathic and seed-producing effects. *Ageratum conyzoides* is categorized as a serious invasive plant in many ecologies in the world due to its rapid and aggressive growth with a high seed-producing rate and its allelopathic effects, which inhibit the growth of all its neighboring plants. This plant is abundant and problematic for farming practices.

The phytochemistry of this plant is considerably impacted by its growth conditions. The soil, climate, elevation, and season may affect the concentration and the variety of the active chemical constituents. This variability demonstrates the need for standardization in pharmacological research and the design of herbal drugs [32].

3. Traditional and ethnopharmacological uses of *Ageratum conyzoides*

3.1 Use in ayurveda and traditional indian medicine

For a long time, *Ageratum conyzoides* has been used in the traditional medicine systems of India, primarily Ayurveda and various folk traditions. It is often used, especially when considering the Ayurvedic traditions of ethnomedicine, due to its wide-ranging effects and availability, even though its use is not as prevalent as some of the "big" Ayurvedic medicines mentioned in the classical texts. Under the Ayurvedic system, *Ageratum conyzoides* is seen as a medicine that is anti-inflammatory (Shothahara), pain-relieving (Vedanasthapana), and promotes healing of (Vrana Ropana) and closure of wounds [33]. Furthermore, the leaves are used to make a fresh paste to be topically applied to skin wounds, cuts, and burns, as well as to skin infections, which helps to reduce swelling and infection as well as to promote overall healing. The traditional use of this plant in Ageratum for its hemostatic activity is also seen in its use for controlling bleeding. In some remote areas, *Ageratum conyzoides* is used to descale pyrexia, diarrhea, dysentery, and respiratory tract infections. Some plant use ethnobotanists note that this plant is primarily used in the treatment of jaundice [34]. The pyrrolizidine alkaloids that are hepatotoxic, for example, are included, but it can be seen as "holistic hepatotoxic" Ageratum. These ethnobotanists also note that this plant is primarily used in some tribal medicine systems for the treatment of liver diseases, and some traditional practitioners elaborate on the use of this plant in the treatment of liver diseases, primarily in some tribal systems of medicine. Some *Ageratum conyzoides* ethnobotanists, in some traditional medicine systems of some tribes, actually used *Ageratum conyzoides* combined with other plants to provide a more synergistic use of *Ageratum conyzoides* in traditional medicine systems for the treatment of skin diseases [35]. For example, some ethnobotanists that are specifically Ayurvedic ethnobotanists describe the use of Ageratum in the combined use of Ageratum with other ethnobiologic plants to describe *Ageratum conyzoides* along with the other plants to be used in some traditional medicine systems for *Ageratum conyzoides* combined with the use of other ethnobiologic plants. Some traditional Ayurvedic medicine systems describe the use of Ageratum in some form of combined use of some traditional tribal systems of medicine to the treatment of Ageratum in some form of combined use of some traditional systems of Ayurveda [36]. India's ethnopharmacological engagement with *Ageratum conyzoides* is validated by its presence as a common weed with a high availability. Low-income groups, among others, easily access it and employ it as a primary health care option. However, absence of standard dosage forms and differences in methods of preparations make therapeutic outcomes consistent [37].

3.2 Use in chinese and african traditional systems

Medicinal application of *Ageratum conyzoides* ranges from India to numerous traditional systems, including Chinese and numerous African ethnomedicine, where it has been integrated into local healing frameworks. In traditional Chinese

medicine (TCM), this plant, which is known as "Huo Xiang Rong," has been used for herpetic and bleeding conditions due to its property as a heat-clearing, detoxifying and bleeding stopping/controlling agent. It is consumed as boil, infusion, or balm to treat skin disease, to treat and prevent enteric and outbreak infections; and in some cases, to treat and prevent pyrexia and digestive abnormalities, as seen in other therapeutic traditions [38]. Chinese herbal medicine is concerned with the balance of the Yin and Yang; and *Ageratum conyzoides* is considered to possess cooling properties to dispel the Yang heat, or excess heat, in the body. The observed anti-inflammatory and anti-microbial activities of the plant helps justify the therapeutic tradition. In African ethnomedicine, especially in numerous parts West, East, and Central Africa, there has been a significant ethnomedicinal tradition of utilizing *Ageratum conyzoides* for the management and treatment of a wide variety of disorders, including cutaneous diseases and inflammation. In West Africa, especially in Nigeria and Ghana, the plant has been employed as a medicine with antimicrobial properties for cutaneous infections and to treat ulcers, pyrexial and malarial illnesses [39]. It has also been employed in the management of cephalgia, odontalgia, and rheumatism, emphasizing its pain-relieving properties. In some cultures, it is applied for gynecological issues, like menstrual and postpartum care. An interesting part of usage for African systems is in the treatment of malaria. It is used, either on its own or synergistic with other medicinal plants. While more scientific research is required for its antimalarial properties, its usage is still extensive. The application of *Ageratum conyzoides* in Chinese system of medicine with African systems show the considerable ethnopharmacological scope of this plant system. Even with differing medical systems, real application can be seen for its use in control of bleeding, inflammation, infection, and healing [40].

3.3 Folk medicinal applications

The largest and most varied domain of *Ageratum conyzoides* applications are found in folk medicine. These applications draw from folk practices and vary from region to region. Therapeutic themes of folk practices are typically the same. Wound healing is where the majority of folk practices of the plant are centered. Leaves are crushed to make a paste and are spread to bother cuts and burns to help heal and create a barrier to infection and to soothe pain and offer protection from the appearance of inflammation. This plant and its several varieties are widely relied upon for the treatment of fevers and for control of and relief from inflamed and other infection symptomatic states [41]. Decoctions of the leaves, sap, and/or stem are consumed to help control and offer relief to inflamed infection symptomatic states. This plant is used for the control of dysentery, diarrhea, and for the control of pain and inflammation in the abdominal region. This plant is believed to have microbial and in fold antispasmodic and other qualities. The plant may be used in the treatment of intestinal parasites. Cough, asthma, and bronchitis are diseases of the respiratory system that may be treated with infusions of *Ageratum conyzoides*. It is believed that the volatile compounds in the plant contribute to the plant's bronchodilatory and expectorant qualities [42]. The plant is used to treat eczema, and other skin fungi, as is the case of other skin fungi and diseases, due to its anti-microbial and anti-inflammatory properties the plant is used to heal skin diseases. It can also be used as an analgesic for headaches, tooth pain, and pain related to muscular, and skeletal injuries. Even more interesting, the plant has been used as an ingredient for repellents and insecticides [43]. The

bioactive compounds and essential oils from the plant, including precocenes, have insecticidal properties, defending against mosquito bites and other agricultural pests. International use of *Ageratum conyzoides* in traditional medicine demonstrates the broad applications and potential of this plant. Nonetheless, the existing empirical data is insufficient to determine its effectiveness and safety to be used as a medicine, thus the formulations, and mechanisms of the applications need to be scientifically validated.

4. Phytochemical composition of *Ageratum conyzoides*

4.1 Overview of phytoconstituents

Chemically diverse and rich in secondary metabolites, *Ageratum conyzoides* is ethnomedically functional and therapeutic. Phytochemical studies show that several classes of bioactive secondary metabolites occur in the species and include: alkaloids, flavonoids, terpenoids, steroids, coumarins, chromenes, and terpenoids. These compounds occur in the species stem, roots, leaves, and flowers, though the aerial parts usually have a higher concentration of phytochemical constituents that are ethnomedicinally and pharmaceutical important. The phytochemical constituents of *Ageratum conyzoides* are affected by a combination of intrinsic and extrinsic factors, including, genetic variability, geographical location, climatic and soil type, and time of harvest. The differentiation of constituents is more effective and practical when complemented by the modern chemical analysis methods such as, high-performance liquid chromatography, gas chromatography-mass spectrometry, and nuclear magnetic resonance spectroscopy. The presence of various classes of secondary metabolites is an indicator of a plant's phytochemical synergism **Fig.1**. It is indicative of the myriad medicinal properties a plant possesses, which are often anti-inflammatory, anti-microbial, anti-oxidative, and insecticidal in nature [44].

4.2 Alkaloids

Alkaloids are a major category of secondary metabolites containing nitrogen found in *Ageratum conyzoides*. Pyrrolizidine alkaloids (PAs) fall within this category and serve important bioactive functions but are also considered potentially toxic. These alkaloids are a known method of a plant's defense against herbivore and pathogen attacks and also serve important and varied pharmacologic functions [45]. Several pyrrolizidine alkaloids are found in *Ageratum conyzoides* such as lycopsamine and their derivatives. These alkaloids contain significant antimicrobial and anti-inflammatory functions. This is likely the reason for this plant's use in traditional medicine for use in cases of infection and inflammatory disorders. These PAs are known to possess the potential for hepatotoxicity due to their capability of being metabolically activated to reactive intermediates in the liver that result in damage to hepatic tissue. This illustrates the reason for the concern in terms of therapeutic use about PA dosage and the method of formulation. In addition to pyrrolizidine alkaloids, this plant also likely contains other secondary alkaloids that are minor in concentration and also contribute to the overall bioactivity profile of this plant. The overall alkaloid content of *Ageratum conyzoides* is within a lower range when compared to other similar plants, but the alkaloids found within *Ageratum conyzoides* are significant in terms of pharmacologic activity. The properties of these compounds require a balanced approach that promotes both the potential therapeutic use and the safety of these compounds [46].

4.3 Flavonoids

Ageratum conyzoides houses many phytochemicals, one significant and many times the most requested, are flavonoids. They are an important subclass of polyphenolic antioxidants that are dispersed in the plant kingdom. In addition to free radical sequestration, modified oxidative stress, and chelation of metal flavonoids that baloney iron, quercetin, kaempferol, and tyrosine derivatives are found in *Ageratum conyzoides*. This spectrum of oxidation related chronic degenerative diseases, like cancer and cardiovascular problems, invoicing oxidation of the neurodegenerative mechanism [47]. These flavonoids' anti-inflammatory activities include the inhibition of the cyclooxygenase and lipoxygenase enzymes as well as the good team NF-kB signaling pathways. *Ageratum conyzoides* plant, its significant application of flavonoids is directed toward its wound healing statistical activities. Flavonoids are known to improve the quantifiable healing of damaged tissue with their ability to boost collagen healing and inhibit oxidative stress through their anti-microbial effects. Multiple flavonoids will also show multiple interactions, which indicate they will work together in a substantial therapeutic way [48].

4.4 Terpenoids and steroids

Another key class of phytochemicals present in *Ageratum conyzoides* is terpenoids and steroids. Terpenoids, which derive from isoprenes, are known for causing structural divergent, wide-ranging, pharmacological activity, and antiinflammatory, antimicrobial, and anticancer properties that, are of course, active in many of the activities of *Ageratum conyzoides*. Many monoterpenes, sesquiterpenes, and diterpenes are present in *Ageratum conyzoides* and are commonly linked to the essential oil fraction of the plant and active constituents in its biological activity [49]. Terpenoids disrupt and damage microbial cell membranes, inhibit the activity of enzymes, and modulate/influence the signaling pathways used in inflammation and cell division/proliferation. The presence of steroids is shown to assist in determining the effects that *Ageratum conyzoides* has, especially, in the treatment of metabolic and inflammatory disorders. The extant, structural resemblance, anti-inflammatory, immunomodulatory, and cholesterol lowering effects, of phytosterols, such as β-sitosterol and stigmasterol, are high in steroids. The presence of both steroids and terpenoids has the potential to boost the pharmacological characteristics of *Ageratum conyzoides* and defend the validity of its traditional use in the treatment of a wide range of disorders. These factors, in addition to being lipophilic, assist in determining the effects *Ageratum conyzoides* has in the treatment of metabolic and inflammatory disorders, as well [50].

4.5 Coumarins and chromenes

Coumarins and chromenes are sizable groups of phytochemicals, one of which is found in *Ageratum conyzoides*, with chromenes being the most representative of the species in question. Of these, precocene I and precocene II are recognized chromene derivatives and have been the focus of much research. Precocenes are active with biological and insecticidal and anti-juvenile hormone activities, thus of great value for obvious reasons, which act as endobiological insecticides [51]. They interfere with the endobiological mechanisms in insects, inhibiting their growth and reproductive development. This is in agreement with the fact that *Ageratum conyzoides* have a traditional use as insect deterring and pest controlling plants. Apart from their insecticidal activity, chromenes and coumarins are proven to have antimicrobial, anti-inflammatory and

antioxidant activities. Coumarins are proven to have a modulating effect of enzyme activities and are able to interact with a number of molecular signaling targets which is great for their use in pharmacological science. The structural variety that is found in these compounds is also a center of great interest in drug development, with the promise that they have in the creation of drug derivatives that have high efficacy and lesser toxicity [52].

4.6 Essential oils and volatile compounds

The fraction of essential oils from *Ageratum conyzoides* is part of its phytochemical profile made up of a myriad of the volatile components which give the plant its distinct smell and biological activity. The fragrance of the essential oil is due to the presence of monoterpenes and sesquiterpenes and their oxygenated counterparts [53]. Gas chromatography coupled with mass spectrometry has characterized the essential oil of *Ageratum conyzoides*, and cassumunarins A and I, caryophyllene, citronellal, and limonene were determined to be part of the essential oil of *Ageratum conyzoides*. The essential oils of *Ageratum conyzoides* have antimicrobial, antifungal and insecticidal activity, and the presence of these essential oils may be the reason for the increased antimicrobial activity. The antiseptic activity of *Ageratum conyzoides* is due to the rupture of the integrity of the cell wall. The insecticidal properties combined with the volatile components, make these plants ideal in the fields of agriculture and vector control. Essential oils composition also depends on environmental conditions, the part of the plant being used and the method of extraction. The presence of bioactive compounds in *Ageratum conyzoides* essential oils offers considerable potential for their application in the fields of medicine, agriculture, and cosmetics [54].

4.7. Other secondary metabolites

Besides the above classifications of phytochemicals, *Ageratum conyzoides* has also been shown to possess various other secondary metabolites that help to augment the pharmacological activity of the plant. These include but are not limited to, phenolic acids, tannins, saponins, and glycosides, which all contribute to the broad spectrum of biological activities of the plant. Phenolic acids have antioxidant activity. Therefore, they help to prevent damage caused by oxidative stress by eliminating free radicals [55]. Tannins are said to have an astringent and anti-microbial activity thereby aiding in the healing of wounds and soothing the digestive tract. The unique surfactive property combined with their provision of enhanced immunity and antimicrobial properties makes saponins highly beneficial. Glycosides are structurally diverse and depending on their varying structure, glycosides exhibit a broad assortment of pharmacological effects that include the anti-inflammatory and cardioprotective activities. The various secondary metabolites, which in their right testify to the broad chemical nature of *Ageratum conyzoides*, also expound on the potential synergism that may be obtained from the various metabloites. Therefore, these provide a good foundation to assume that the various coupled activities may yield enhanced therapeutic potential along with decreased resistance, especially when it comes to the anti-microbial activities [56].

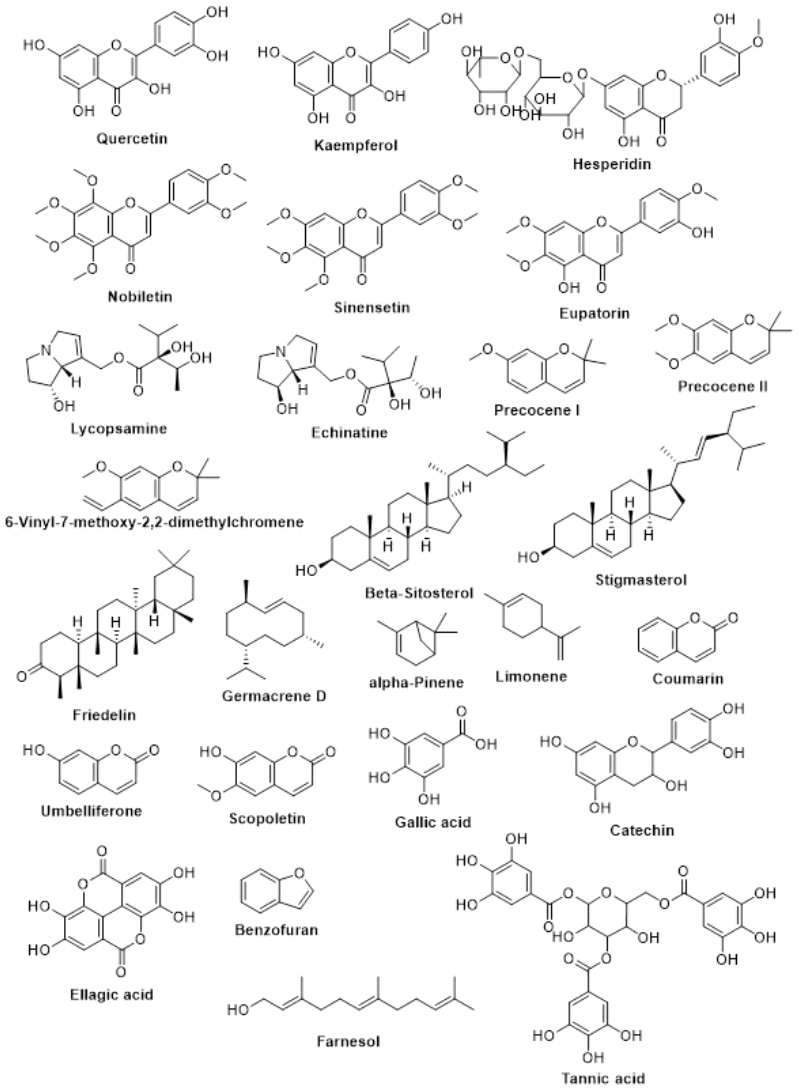

Fig.1: Phytochemistry of *Ageratum conyzoides*

5. Pharmacological activities of *Ageratum conzyoides*

Ageratum conyzoides has diverse, bioactive phytochemicals, comprising of flavonoids, alkaloids, terpenoids, chromenes, coumarins, tannins, and essential oils. These phytochemicals contribute to a variety of this plant and its extracts of the plant sample are able to reduce pain and inflammation. The specimen has been proven to posses a variety of fungal and bacterial activities that has been used to support its historical healing properties to treat a variety of skin and drift infection and disorders. *Ageratum conyzoides* can neutralize free radicals and oxidative stress due to the presence of antioxidents and Flavonoids. Of worthy mention, is its analgesic and antipyretic properties that support *Ageratum conyzoides* utility in pain, and fever therapy. The plant specimen is credible in enhancing the healing of wounds by increasing tissue regenerate, increasing speed to the epithelization and enhancing the synthesis of collagen. Research supports the plant's anti diabetic virtue proving its efficacy in enhancing glucose metabolism, as well as reducing plasma glucose concentration in several experimental models. *Ageratum conyzoides* has also proven its liver protective properties by shielding the liver tissues from adverse effects of several chemical agents. There were anti-cancer

potential as a plant due to the presence of the cytotoxic effects that can induce the characteristics of certain cancer cell lines by apoptosis, as well as, the inhibition of the proliferation of cancer cells. The specificity of the plant *Ageratum conyzoides* can be seen by its anti ulcer, anti malaria, and insecticidal properties that can be seen in its pharmaceutical and agricultural diversification. The various therapeutic properties of *Ageratum conyzoides* requires further clinical and toxicological studies for proving its safe medicinal usage **Fig.2**.

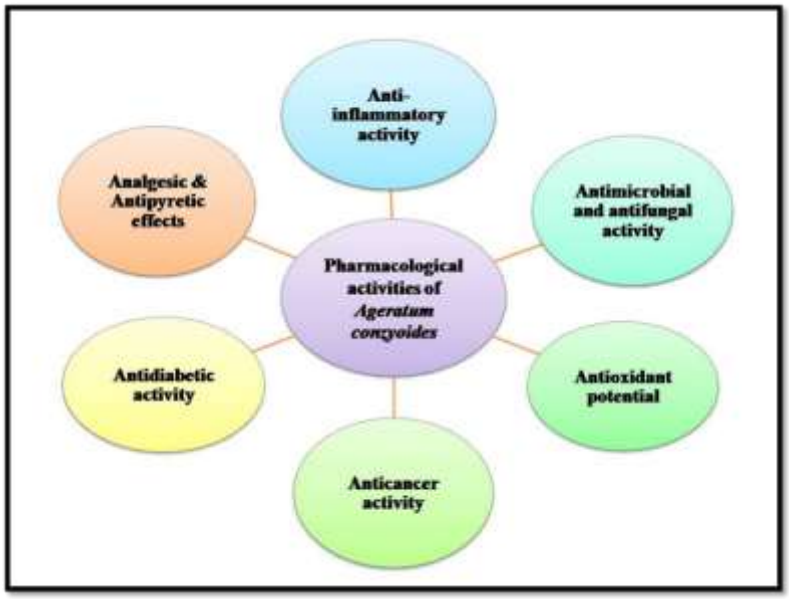

Fig.2: Pharmacological activities of *Ageratum conzyoides*

5.1 Anti-inflammatory activity

The considerable anti-inflammatory effect exhibited by *Ageratum conyzoides* underpins its empiric application for the treatment of inflammatory diseases. Inflammation is an immune response that involves the proliferation of immune cells and production of inflammatory mediators known as cytokines (TNF-α and IL-1β) and an inflammatory enzyme (cyclooxygenase and lipoxygenase) among many. Extracts from the leaves and the *Ageratum conyzoides* aerial parts seem also to mitigate these processes [57]. Many of the bioactive compounds that appear to be largely responsible for the anti-inflammatory effect of *Ageratum conyzoides* include the flavonoids quercetin and kaempferol that are known to modulate oxidative stress and inhibit activation of NF-kB. In addition, the terpenoids and chromene derivatives of *Ageratum conyzoides* seem to stabilize cellular membranes and inhibit the synthesis of prostaglandins. Many of the animal experiments appear to support the effect of Ageratum on decreasing inflammation and formation of edema. These compounds support the ethnobotanical claims of *Ageratum conyzoides* use to treat inflammation including that of the skin, wounds, inflammation, and arthritis. The use and application of *Ageratum conyzoides* vehemently propose a safer and potent anti-inflammatory alternative to the contemporary synthetic drugs that are used globally to treat inflammation, having far less adverse reactions than most of the synthetic drugs [58].

5.2 Antimicrobial and antifungal activity

The phytochemistry of *Ageratum conyzoides* confirmed the abilities of the plant to manifest evident antimicrobial and antifungal activities.

Plant extracts were reported to possess broad-spectrum activities against pathogenic bacteria of both Gram-positive and Gram-negative categories, and pathogenic fungi. Antimicrobial activities among these crude extracts are due to the presence of some levels of flavonoids, alkaloids, essential oils, and chromenes which work together to prevent the growth and multiplication of microbes [59]. These phytochemical compounds break up the microbial cell membrane, disrupt their enzymatic systems, and inhibit the synthesis of nucleic acids. The constituents of essential oils, namely caryophyllene and limonene, attest to a large percentage of the activity by facilitating an increase in permeability of the cell membrane which in turn induces cell lysis. *Ageratum conyzoides* has antifungal activity and has been reported to act against a number of common fungal and bacterial pathogens namely Staphylococcus aureus, Escherichia coli, and many fungal genus of Aspergilli and Candida. Due to this antifungal and antibacterial activity, the traditional uses of this plant in the management of skin problems, infections, and gut health are justified. This suggests A. conyzoides antimicrobial activity, along with antibiotic resistance attribute, establishes A. conyzoides as a relevant candidate phytomedicine in the recent case of noticeable antimicrobial resistance among some classical antibiotic sources [60].

5.3 Antioxidant potential

Ageratum conyzoides has high antioxidant potential from its phenolic compounds and flavonoids, allowing them to neutralize reactive oxygen species and lessen oxidative stress. Oxidative stress contributes to many chronic illnesses, including cancers, cardiovascular disease, and neurodegenerative diseases. Plant extracts have demonstrated a considerable activity to scavenge free radicals in the DPPH, ABTS and FRAP assays [61]. Flavonoids like quercetin and kaempferol donate electrons to free radicals, thereby stabilizing them and preventing oxidative damage to cells. Furthermore, the antioxidant activity of phenolic acids and tannins includes metal ion chelation and inhibition of lipid peroxidation. The antioxidant actions of *Ageratum conyzoides* support its anti-inflammatory and wound healing properties, as the antioxidants help to lessen the oxidative damage that occurs in inflammation and injury. This aspect further enhances its therapeutic activities and defend its claim of use in the treatment and management of diseases that are caused by and/or associated with oxidative stress [62].

5.4 Anticancer activity

There is increasing evidence for the anticancer potential of *Ageratum conyzoides* due to target multiple pathways in cancer cell death by regulating apoptosis, hindering cancer cell growth, and changing the cancer cell signaling pathways. Some of the bioactive molecules found in this plant are cytotoxic for a variety of cancerous cell lines. It has been substantiated that flavonoids, terpenoids, and chromenes can provoke apoptosis of cancer cells in three different ways [63]. They can activate caspases, alter membrane potential within varying mitochondria, and alter the balance of pro-apoptotic and anti-apoptotic proteins within cells during their apoptosis. Also, Cancer can spread to other organs in the body due to a process called angiogenesis. The plant extracts can alter both the PI3K/Akt and the MAPK pathways to inhibit that process. The *Ageratum conyzoides* can be an antioxidant. It helps the body to bear less reactive oxygen species and hence minimize the oxidative stress which causes cancerous cells. Though limited studies are mostly in vitro and preclinical models these studies provide ample opportunity for *Ageratum conyzoides* to be used

for the development of novel anticancer medicines. More detailed studies, preclinical studies, and clinical studies to substantiate the evidence and their results are needed [64].

5.5 Antidiabetic activity

Ageratum conyzoides has presumable hypoglycemic influences owing to its active phytoconstituents, which modules synaptic functioning as well as stimulatory insuletic secretion. Extraction of lagustilide saponins has been observed to hinder the activity of glycemic level-changing digestive enzymes, as an example, glucosidases. Lagustilide described as a flavonoid has also been observed to change glycosidic activity as well as oxidative stress modulation which is a characteristic of diabetes mellitus [65]. Additionally, the extract also influences the storage of hepatic medication and production of glycogen which helps his glycemic modulation. The extracts of *Ageratum Conyzoides* have been used to support its antidiabetic activity in animal testing settings. The antioxidant and anti-inflammation characteristics of the plant disparage and tackle the diabetes complications and stress that is oxidative. Despite offering anticancer, antidiabetes, and anti-inflammation benefits, there are no organized and conformed studies that have been provided [66].

5.6 Analgesic and Antipyretic Effects

Ageratum conyzoides has both analgesic and antipyretic properties, and these properties are also dependent on its anti-inflammatory activity. The analgesic property of *Ageratum conyzoides* is generally reported to occur due to inhibition of the synthesis of the pain mediators, prostaglandins. The leaves have nalgesic pathways and or modulate pain perception. *Ageratum conyzoides* leaves have been experimentally shown to significantly reduce pain, evidenced by the decreased pain responses associated with the use of chemical pain models or thermal pain models [67]. Fever is managed as the leaves of the plant have shown to exhibit antipyretic property via inhibition of the production of pyrogenic cytokines and prostaglandins in the hypothalamus. This consequently leads to the hypothalamic set point. This activity supports its traditional use in treating fever and febrile conditions. The combined analgesic and antipyretic properties make *Ageratum conyzoides* a natural healer to the pain and fever in the communities which otherwise people have no access to the synthetic pain and fever managing medicine [68].

6. Mechanisms of action of *Ageratum conzyoides*

6.1 Molecular targets and signaling pathways

Like many other herbs, *Ageratum conyzoides*, or billygoat weed, interacts with many biochemical pathways within a cell, most likely due to the complex biochemistry of the herb, particularly phenols, chromenes (for example, precocene), flavanoids, terpenoids, and other phenolic compounds [69]. They bio-active compounds are likely to interfere with the complex pathways of cell survivability, inflammation, apoptosis, defense against microbes, and many other biochemical pathways. One of the biochemicals pathways that respond to the herb *Ageratum conyzoides*, billygoat weed, in most herbs is the nuclear factor kappa B (NF-kB) pathway. This pathway is critically involved in the regulation and control of immune and inflammation response. When there is an activation of NF-kB, a state of inflammation is transmitted via transcription of many inflammatory cytokines such as TNF-α, IL-6, and the adhesion molecules. In addition to the enzymes such as COX-2 and inducible nitric oxide synthase (iNOS), there are likely several other constituents that control the activation and nuclear translocation of NF-kB, which stack on the other

side of the bibliographic chain. Furthermore, ERK, JNK, and P38 kinases, are all involved in the MAPK pathway which control a cell and its response to proliferation and stress or inflammation. *Ageratum conyzoides* has been shown to modulate MAPK signaling to prevent inflammation and control cell proliferation, which is relevant to the development of cancer [70]. The Bioactive constituents of *Ageratum conyzoides* also influence the Phosphoinositide 3 Kinase/Protein Kinase B (PI3K/Akt) pathway. This pathway is involved in the control of cellular survivability and metabolism, as well as the induction of apoptosis. In Cancer cell lines, especially the cancer of *Ageratum conyzoides*, bioactive constituents that control apoptosis and induction of apoptosis, are likely to down regulate the PI3K/Akt pathway and tumorigenesis. Additionally, the herb also impinges upon other practices such as the orchestration of apoptosis, signaling pathways, particularly those that are intrinsic as in the case of the mitochondria, and those that are extrinsic. Compounds like flavonoids may affect the equilibrium of pro-apoptotic (Bax) and anti-apoptotic (Bcl-2) proteins, resulting in the disruption of the mitochondrial membrane, the release of cytochrome c, and the subsequent activation of caspases. This is the basis for its possible anticancer activity. Taken together, the capability of *Ageratum conyzoides* to engage with various molecular targets demonstrates its promising potential as a multitarget therapeutic agent, to alter intricate pathways of disease [71].

6.2 Role in oxidative stress modulation

Middle oxidative stress describes the state when reactive active oxygen species (ROS) over scales the balancing born body-nourished anti-active oxygen species (AOA). Overproduction of ROS causes considerable (lipid, protein, and DNA) damage at the cellular level and promotes chronic diseases, including diabetes, cancer, and neurodegenerative diseases. *Ageratum conyzoides* contributes substantially to resolving high oxidative stress state by 'donating' (richly) anti-microactive oxidants [72]. A certain large subclass of phytochemical constituents such as flavonoids and phenolic compounds describes there 'donating' (scavenging) capacity to act as anti-microactive oxidants (to neutralize) the ROS of superoxide and hydroxy and/or hydrogen peroxide. Since in vitro (shuffled microorganisms) aid in sampling and shuffling, these constituents also exhibit in vivo (donating) metal-chelating capacity, thereby reducing (neither in oxides nor in free ions) availability of the detrimental iron and copper ions that serve as high catalytic microactive oxidants necessary for free radical formation via (Fenton) reactions. The phytocomponents also motivate shapeware endogenous antioxidant enzymes like (in expert reduction) superoxide dismutase (SOD), and (under) catalase (CAT), amd (donating) glutathione peroxidase (GPx). Through these, *Ageratum conyzoides* 'donates' the relieving endogenous artillery to combat stress. The 'donating' also contributes to activating the (N)otif (r)-2–related factor (Nrf2) pathway, the relating switch on antioxidant's genetic relaying. High depth to 'donating' (donating by phytochemicals) of *Ageratum conyzoides*, Nrf2 activation, and cellular oxide stress resilience to chronic diseases is considerable [73].

6.3 Anti-inflammatory Pathways (COX and LOX Inhibition)

The anti-inflammatory properties of *Ageratum conyzoides* can be attributed to the ability to block certain pathways in the body where COX-1 and LOX-1 inflammatory substances are produced. COX pathways transform Arachidonic acid to COX inflammatory substances. COX-1 is the

COX isomer in tissues produced and maintained in the body and COX-2 is the inflammatory COX isomer [74]. The *Ageratum conyzoides* extracts have the ability to inhibit COX-2 and therefore the production of the COX-2 isomer while leaving COX-1 unaffected. This is needed to eliminate the gastro-intestinal side effects that are caused by the harmful effects that other COX inhibitors have. The other pathway, LOX, converts Arachidonic acid to leukotrienes, and is also associated with the inflammatory response and LOX-1 and COX-2 lead to allergic response. The anti-inflammatory response can be performed by preventing leukotriene production by the PL. The LOX, COX and other inflammatory agents, and also the allergic response can be further avoided by using a selective COX and LOX. COX pathway mediators also have negative effects which can be avoided by a selective COX and LOX approach to COX and LOX pathways. The Ageratum extracts also have the ability of inducing LOX and COX inhibitors restoration which can also have anti-inflammatory and analgesic effects. This is basically the compounds that alter NF-κB to cause a disruption in inflammation and their effects that inflammatory mediators have [75].

6.4 Antimicrobial mechanisms

Ageratum conyzoides demonstrates antimicrobials efficiency stemming from several pathways that facilitate targeting of various elements of pathogenic bacteria and fungi. One well-studied mechanism is disruption of microbial cellular membranes. The essential oils and lipophilic compounds of the plant disrupt the structure of microbial membranes by increasing permeability that results in active leakage of cellular contents. Eventually, cellular integrity is compromised and results in cell death [76]. The plant also demonstrates the capacity to inhibit various microbial processes by a diverse group of enzymes and microbial metabolic pathways. Phytochemicals that include but are not limited to flavonoids and alkaloids are documented to inhibit various the pathways that are critical to energy and nucleic acid synthesis, and protein. The synthesis of protein for example, is induced by enzymes including DNA gyrase and RNA polymerase that facilitate enzymatic processes for replication. The plant is also antifungal by increasing permeability of the fungal cell walls. It results in the cell contents oozing out and biosynthesis of ergosterol, a critical component of fungal cell membranes [77-79].

It forms pores and ose the cell to increased permeability of the environment. Additionally, *Ageratum conyzoides* may exert antimicrobial effects through oxidative pathways, whereby oxidative species are formed that are detrimental to the microbial organisms [80]. Additional mechanisms of antimicrobial effects include the inhibition of biofilm and the breaking of existing biofilm that is often encountered amongst various structural microbial aggregates. The ability of multiple phytochemicals in synergistic interaction to reduce the chance of resistance formation adds to the value of the overall antimicrobial activity of the plant. Hence, *Ageratum conyzoides* can be considered an excellent source for the development of new antimicrobial agents.

7. Challenges and limitations

Ageratum conyzoides has numerous ethnopharmacological applications and promising pharmacological activities, but it has limitations that impede its movement from traditional use to documented clinical use. One major limitation is the phytochemical compositions that vary due to geographical location, climatic condition, types of soil, harvesting season, and harvesting time. The concentration of the bioactive compounds is not consistent due to these factors, and consequently,

reproducibility, efficacy, and standardization of the therapeutic outcomes is compromised. The inconsistency also makes it difficult to produce dependable herbal medicine formulations, and to fulfill the underlying legal requirements of herbal medicine. Furthermore, the pharmacological activities have not been well documented clinically. There has been limited human clinical studies reported despite the various reported *in vivo* and *in vitro* studies that support anti-inflammatory, antimicrobial, antioxidant, and anticancer properties of *Ageratum conyzoides*. The major abridgement in this gap implies that therapeutic efficacy, dosing parameters, and pharmacovigilance including risks associated with the long-term safety of the drug is dispersed, without clinical substantiation. The public need for this medicine remains unmet. There are also limited safety studies, despite the compounds having the potential of disrupting the liver and of having antitumoral and anti-genotoxic properties. The associated risks also answer the concerns on safe dosing parameters, use duration, and detoxification. Thus, *Ageratum conyzoides* use therapeutically does in fact pose various health hazards. In addition to these gaps, extraction and methods used for formulations remain heterogeneous. The variation in extraction techniques, solvent systems, and processing methods may affect the phytochemical profile and thereby may limit the reproducibility of phytopharmaceuticals as a whole. The variable drug–herb interactions and the reported effects further limit the herbal formulation's ease of use. The bioactive constituents found in *Ageratum conyzoides*, for example, may cause alterations in the bioactive properties and efficacy of synthetic drugs through the induction and/or inhibition of cytochrome P450 enzymes. However, the number of studies conducted to understand the manageable and/or unavoidable interactions of phytopharmaceuticals with the constituents of *Ageratum conyzoides* is limited. The invasive nature and influence of this plant species on the ecosystems of the region negatively impact the use of *Ageratum conyzoides* in a sustainable way. The easy of access to *Ageratum conyzoides* is because of how abundant *Ageratum conyzoides* is, and due to how aggressive its growth is, it can negatively harm an ecosystem as a whole and negatively harm the ability of crops to grow. To fully understand the unexplored therapeutic properties, there should be more mechanistic and molecular studies implemented in the future. Researchers should be integrating pharmacology, biotechnology, and toxicology into their studies, as *Ageratum conyzoides* can be used as a safe and effective therapeutic agent.

8. Future perspectives

Ageratum conyzoides has significant potential as a novel source of active therapeutics; however, its maximum benefits will only be achieved through greater cross-disciplinary research. The bioactive molecules of *Ageratum conyzoides* i.e. the chromenes, flavonoids, and terpenoids, need to be isolated and evaluated in terms of their structure-activity relationship in order to develop molecules with lead efficacy and minimized toxicity. This strategy also needs to be extended to ensure a thorough clinical validation. The initial steps will include the development of randomized control clinical trials to establish safety, efficacy, and the pharmacokinetic profiles of the novel therapeutics. *Ageratum conyzoides* will enhance its evidence-based acceptance in the legal (Modern) healthcare systems. During this time, the toxicity of *Ageratum conyzoides* will need to be assessed, especially that of its pyrrolizidine alkaloids, ensuring that the novel therapeutics will be safe and to enhance the detoxification of alkaloids or their selective removal from the extracts. *Ageratum conyzoides* also has the ability to

enhance therapeutic potential through the improved drug delivery and bio-availability of its therapeutics. The advanced use of drug biotechnologies has demonstrated the use of liposomes and nano-phytosomes to enhance the stability of phytactive systems. Further biotechnologies like the genomics and bioinformatics will also help in the discovery of the therapeutic potential of *Ageratum conyzoides*. The synergistic use of *Ageratum conyzoides* with other plant medicines is also another area of research that needs exploring. Finally, *Ageratum conyzoides* has the ability to act as a noval natural biopesticide and/or a natural antimicrobial agent and can replace synthetic chemical interventions and their redundancies. Finally, the implementation of standardization protocols, sustainable cultivation methods, and regulation will guarantee quality, safety, and environmental balance. Combined, these future steps will change *Ageratum conyzoides* from a natural medicinal weed to a clinically relevant and scientifically validated therapeutic resource.

CONCLUSION

Ageratum conyzoides is a plant that is gaining interest due to its diversity and abundance of phytochemicals with biological activities of therapeutic interest. The plant has significant pharmacological activities that serve a wide variety of applications such as analgesic, wound healing, anti-inflammatory, anti-cancer, anti-microbial, and anti-oxidant activities. The pharmacological potential of the plant is further augmented by the insights provided by ethnopharmacology stemming from the Indian, Chinese, and African cultural traditions. The traditional uses of the plant and the ethnomedicinal claims of therapeutical relevance are increasingly validated by a variety of experimental studies that explain different molecular mechanisms and pharmacological activities of the plant. The main mode of actions of the plant are modulation in the NF-kB signaling pathway, MAPK signaling pathway, PI3K/Akt signaling pathway, and its ability to inhibit the action of cyclooxgenases and lipoxgenases. Additionally, this plant serves to be a good candidate for the development of further therapeutic agents due to its potential to ameliorate oxidative stress and to inhibit the growth of different types of microbes. Nonetheless, the presence of phytochemicals that are of a pyrrolizidine structure raises the need for safety. Thus, more rational and systematic studies of the plant will be required. Once this is done this will widen the scope of therapeutic options of the plant. For top-down research, bilayer compounds research suggests the conyzoides has the ability to catalyze numerous bioactive compounds, and the creation of bioactive compounds and the creation of standard formulations. Additionally, the discovery of bioactive compounds and the subsequent formulations may use bioactive combinetrials and may involve the use of bioactive controls. The use of biopesticides in agriculture and the management of natural ecosystems demonstrate extending the range of bioactive compounds. *Ageratum conyzoides* is a wellness asset, and the potential is high. The research and formulation of the herb will add to the bioactive of care to all patients, and will create standard control bioactive protocols, thus, balancing the new health bioactive with the old health bioactive.

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HOW TO CITE: Mohammed Aashik, Shakthi L, Ajinkya Chavan, Prerona Das, Chandresh Maurya, Snega Boopathy, J. Ambika, Ethnopharmacological Potential and Bioactive Compound of Ageratum conyzoides, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 4, 4419-4442. https://doi.org/10.5281/zenodo.19788447