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FORMULATION AND EVALUATION OF AGERATUM CONYZOIDES LINN-BASED TOPICAL AGENTS

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Abstract

Ageratum conyzoides is a traditional medicine herb used to treat a wide range of illnesses in South America, Asia, and Africa. Purgative, febrifuge, anti-colic, anti-ulcer, anti-inflammatory, antipyretic, wound dressing, and for cuts and scrapes. The aromatic, straight, hairy, thin, branching annual plant A. conyzoides is native to the tropics. Its maximum height is around 1 meter. Its deep, fibrous roots have a deep yellowish-brown color and are poorly attached. The stem is slender, green, aerial, and cylindric while a plant is young; as it matures, it becomes strong and somewhat brown.

Keywords: Ageratum microbial, antifungal, affects, network**,** people.

INTRODUCTION

Invasions by bacteria, fungi, viruses, or parasites may lead to skin infections, which constitute a dermatological emergency. An infection of the skin may be somewhat uncomfortable or very painful, depending on the microbe, its bioburden, and the length of time it has been exposed to. Bacterial infections are the most common kind, impacting around 155 million individuals every year (Vos et al., 2015). A number of bacterial infections are prevalent, including acne vulgaris, cellulitis, impetigo, folliculitis, and others. Worldwide, around 650 million individuals deal with acne, according to many studies (Garcines et al., 2016; Garg, 2016). This makes acne the eighth most frequent cutaneous illness.

Acne may not be life-threatening, but it severely diminishes the self-esteem of those who suffer from it, particularly adolescents. People who are affected sometimes feel hopeless about how they look, and they may even suffer from severe pain and deformities (Frank, 1971). Acne vulgaris, according to the World Health Organization (WHO), is a multifactorial skin disorder that affects people of all ages and is widely distributed over the sebaceous glands of the face, neck, chest, and upper back (Bowe and Shalita, 2011; Raza et al., 2012; Hay et al., 2014; Vos et al., 2016). Acne is more prevalent in girls and occurs more often in boys throughout adolescence (15 years and above), although it usually clears itself by maturity for girls.

Keeping up with the appearance and regulation of new microorganisms is a major problem for contemporary science. Opportunistic infections of various fungal strains have been documented to cause a number of deadly illnesses globally. A large number of mycological investigations have shown that candidemia cases have increased dramatically throughout the last decade. There are about 1.5 million annual fatalities due to fungal infections, which impact over one billion people worldwide. This is more than three times the number of deaths caused by malaria and on par with TB. A single fungus spore may initiate a fatal process in individuals with impaired immune systems, in addition to inducing minor fungal infections in healthy participants. Patients undergoing chemotherapy, having bone marrow or other organ transplants, and those with chronic conditions including diabetes, cystic fibrosis, AIDS, or recurring infections are also at a greater risk.

People think of herbal medicinal resources as an integral aspect of nature. Because of their unique chemical structures and powerful bioactivities, researchers have long been interested in discovering new active components, especially those with a natural origin.

As evidence, consider that the vast majority of the therapeutic medicines authorized in the last century originated from plants or other naturally occurring sources. This highlights the significance of plant actives in the creation of new medications. The above suggests that natural chemicals have promise as anti-infective and anti-inflammatory agents. Furthermore, other secondary metabolites or extracts have been shown to be efficient antifungals, including terpenoids from essential oils, alkaloids, flavonoids, etc. [9]. In comparison to the synthetic alternatives available today, novel herbal fungicides should ideally provide enhanced target specificity, broad-spectrum activity, a variety of action mechanisms, and no cross-resistance. There have been reports in the literature suggesting that oils and extracts from certain allelopathic weeds might be used as alternatives to dangerous synthetic fungicides.

LITERATURE REVIEW

M. micrantha has remarkable phenotypic flexibility and does better at lower altitudes, according to research by Prabhu et al. (2014), which found that its photosynthetic capacity is unaffected by differences in altitude.

Hossain et al, (2013) A. Following an ethanol extraction, a battery of chemical tests identified tannins, saponins, alkaloids, gums, reducing sugars, steroids, and an abundance of flavonoids in the leaves of Conyzoides.

Biavatti et al. (2016) The antinociceptive and anti-inflammatory activities of the plant's standardized poly methoxy flavone extract (SEPAc) were investigated. They improved our understanding of the anti-inflammatory and pain-relieving effects of polymethoxyflavones by developing a standardized extract of these compounds from A. conyzoides after removing the harmful pyrrolizidine alkaloids.

Fröde et al. (2016) investigated the anti-inflammatory effects of eupalestin, 1,2-benzopyroneas, 5'-methoxy nobiletin, and other phytochemicals found in A. conyzoides L.'s aerial parts, as well as the crude extract and its fractions, which included ethanol, hexane, and ethyl acetate.

Nyunai, et al. (2015) This information was compiled. In this study, the anti-diabetic effects of an aqueous extract of Ageratum conyzoides leaves were evaluated. Ageratum conyzoides aqueous extract's antidiabetic activity was investigated in male adult albino rats with streptozotocin-induced hyperglycemia (at doses of 100, 200, and 300 mg/kg, respectively). Throughout the research, the diabetic rats were housed in metabolic cages. We measured participants' weights three times: once at the beginning of the experiment and again on days 7, 14, and 21. The quantity of food and water ingested, along with the amount of urine output, were also measured.

BOTANICAL DESCRIPTION

One member of the Asteraceae family is the little herbaceous Ageratum conyzoides (Fig. 1). This annual weed may grow to a height of 80 to 90 cm, has soft hairs, and grows upright and branching. The tropical plant has a long history of medicinal usage in a variety of African, Asian, and South American countries. Fine white hairs cover the stems and leaves; the leaves are oval and may reach a length of 7.5 cm. Located in a terminal inflorescence, the blooms vary in color from purple to white and have a diameter of less than 6 mm. The fruits are readily spread and have a pleasant taste.Its ability to spread makes it an invasive weed that ecologists and farmers alike have to deal with. The viability of seeds often disappears after a year since they are positively photoblastic. Goat weed, also known as billy goat weed, has a foul odor that males avoid eating because it smells like a male goat.The whole plant has a lengthy history of use in traditional medicine throughout several nations, and its therapeutic properties are its exclusive application.

Physical-Chemical Properties

The secondary metabolites of A. conzyoide, which include of tannins, essential oils, cumarins, flavonoids, and alkaloids, exhibit a great deal of variation. Quite a few of them have biological effects. The oil content fluctuates seasonally, ranging from 0.11 to 0.58% in the leaves and from 0.03 to 0.18% in the roots.The fresh flowers have an oil content of 0.2% according to the results of water distillation. A 26% oil yield was achieved by extracting the seed with petroleum ether.The GC-MS study of the essential oil of Ageratum conyzoides 7-8 has shown a plethora of components. The study of a plant oil sample yielded the highest number of components to yet, with 51 identified components. Twenty monoterpenes (6.4%) and twenty sequiterpenes (5.1%) are the components that have been discovered. Trace amounts (0.1%) of the mono- and sesquiterpenes are obtained. About 1% of the oil contains monoterpenes, including 1.6% sabinene and β-pinene, 2.9% β-phellandrene, 0.6% terpinen-4-ol, and 0.5% α-terpineol. The percentage of ocimene in the oil extracted from the plant in India is 5.3%, whereas it is only present in trace amounts in the oil extracted from the plant in Nigeria. The Indian plant oil 8 also contains α-Pinene 6.6%, eugenol 4.4%, and methyleugenol 1.8%.

The primary constituent of Ageratum conyzoides essential oil is precocene-I, which is 7-methoxy2,2-dimethylchromene (1). This oil also contains encecalin(6), 6-vinyl-7-methoxy-2,2- dimethylchromene(7), dihydroencecalin(9), dihydrodemethoxyencecalin(10), demethoxyencecalin(11), demethylencecalin(12), and 2(1-oxo-2-methylpropyl, among other related chemicals.-2- methyl-6,7-dimethoxychromene(14). According to chemotaxonomic experts, Ageratum conyzoides contains acetyl chromenes.

The hexane extract of the plant's aerial parts yields seven more chromene derivatives, in addition to the chromenes derived from the oil. The compounds in question are 2,2-dimethylchromene-7-O-glucopyranoside (13) and 6-(1-methoxyethyl).6-(1- ethoxyethyl)-7-methoxy-2,2 dimethylchromene(4), 6-(1-hydroxyethyl)-(7-methoxy-2,2-dimethylchromene(3)).6-angeloyloxy seven-methoxy-2,2-dimethylchromene(5)encecanescins (20-22) and -7-methoxy-2,2-dimethylchromene (8) in an inseparable combination. Benzofuran derivatives, 3-(2-methylpropyl) benzofuran (17), 14-hydroxy-2H, β-3-dihydroeuparine(18), and chromone derivativesand 2-(2 methylprop-2-enyl)-2-methyl-6,8-dimethoxychrom-4-one (15).Additionally, the plant 8 has been discovered to contain -2-methyl-6,7-dimethoxychroman-4-one (16).

There are twenty-one polyoxygenated flavonoids found in Ageratum conyzoides. Fourteen of these flavones are polymethoxylated (23–36). The glycosides of quercetin and kaempferol are also polyhydroxyflavones. The triterpene friedelin(41) was identified with two main common sterols, stigmasterol and sitosterol, as well as a minor sterol. Phytol, fumaric acid, caffeic acid, sesamine, and long chain hydrocarbons are among the other typical compounds. Scutellarein-5,6,7,4_- tetrahydroxyflavone, quercetin, kaempferol, kaempferol -3- rhamnopiranoside, kaempferol 3,7- diglucopiranoside, and curcumin are all polyhydroxyflavones. An Indian study team documented the isoflavone content of the plant in their findings.

PHARMACOLOGICAL ACTIVITIES

Crude extract

It has been discovered to inhibit neuromuscular transmission. Osteoarthritis sufferers have found relief from their persistent pain with the use of the leaf extract. It has also shown anticonvulsant and antibacterial properties. Additionally, the antibacterial action is seen in the methanolic extract of the whole plant. The hot plate technique was used to detect the analgesic activity of the leaf extract.

Medicinal oil

Animal studies in mice and rats have shown that the essential oil of A. conyzoides possesses anti-inflammatory, analgesic, and antipyretic effects. The oil had a notable anti-inflammatory effect (cotton pellet granuloma) at dosages of 3 and 4 ml kg per os11.

Chemical Compounds

There has been no identification of the pharmacological activity of the most important metabolites responsible for the therapeutic effects of this plant, except from its essential oil. The families of chemicals derived from this plant, however, exhibit a broad range of pharmacological actions. There have been reports of the anti-depressant, analgesic, and antipyretic activities of simple chromenes and chromans, particularly the 6-amino and 6-acetamido variants. 12-13. There are also simple 2,2-dimethyl chromene derivatives that exhibit antibacterial properties. These include 6-hydroxy-7,8- dimethoxy-2,2 dimthyl chromene and 6-(1-hydroxyethyl.)-7,8- dimethoxy-2,2-dimethylchromene. There is strong evidence that the sterols, and stigmasterol in particular, have anti-inflammatory effects. A broad variety of biological functions are shown by the flavonoids. It is well-known that flavonoids have anticancer and free radical scavenging properties. Regardless, research into the biological effects of the Ageratum conyzoides flavonoids has been lacking.

Ageratum conyzoides Linn displays a number of significant pharmacological characteristics, including:

A) The impact on bacteria

The bactericidal activity of water and ethanol extracts from the freshly harvested, shredded plant was examined. The minimum inhibitory concentration (MIC) for ethanol extracts ranged from 30.6 to 43.0 µg/kg, while for water extracts it ranged from 45.4 to 71.0 µg/kg, as measured in an in vitro anti-methicillin resistant Staphylococcus aureus (MRSA) assay. There was a significant increase in the minimum bactericidal concentration (MBC) for both extracts.

B) Effects on inflammation

There was an investigation on the anti-inflammatory benefits of a hydroalcoholic extract in rats. The cotton pellet-induced granuloma was reduced by 38.7 percent in rats that were given 250 mg/kg of extract orally. The plant extract also rendered chronically induced paw edema far less likely to develop.

(C) Effects on wound healing

Ten Wistar rats were used to study the wound healing efficacy of the methanolic extract of Ageratum conyzoides. After 10 days, the histology of the wounds created by the extracts were assessed by packing gauze into the incisions made in the skin. There were greater fibrosis and fewer inflammatory cells in the Ageratum sections compared to the controls.

D) Actions on spasms and gastrointestinal protection

Using the ibuprofen, ethanol, and cold restraint ulcer stress paradigm, the gastroprotective effects of the Ageratum conyzoides ethanol extract were examined in rats. The effectiveness was evaluated by finding the average size of the ulcers, the total number of ulcers, and an ulcer index of 15.

E: Anticancer action

With in vivo Dalton's lymphoma in a mouse model of ascites Ageratum conyzoides root aqueous extract reduced glutathione levels in tumor-bearing mice's liver and lymphoma cells.

Insecticidal Activities

The bioactivity of Ageratum conyzoides suggests it could be useful in agriculture. Perhaps the most significant biological function of this species is its ability to kill insects. There have been reports of antijuvenile hormonal action in both the essential oil and its main components, namely the precocenes.

The disease known as hemopathy

Several farmed crops have been shown to be allelopathic to Ageratum conyzoides, either in the form of its volatile oil or its water extract. Radish, tomato, and ryegrass seedlings were shown to be significantly stunted in their development when exposed to a saturated water solution containing the separated and purified precocene I and II. The aqueous extract of Ageratum conyzoides showed varying allelopathic potency throughout its many organs, developmental phases, and environments.

Many studies have been conducted on Ageratum conyzoides. This study presents thorough information on the plant's phytochemistry as well as the numerous biological features of its extracts and components. The hope is that this will encourage scientists to properly evaluate the plant's medicinal and agricultural uses. While some research has suggested that flavonoids like quericitin may have an antilithiatic effect in mice, further research on the plant's toxicity is necessary.

Fig.1: Ageratum conyzoides Linn., Asteraceae

Chromene, Chromone, Chromanone and Benzofuran

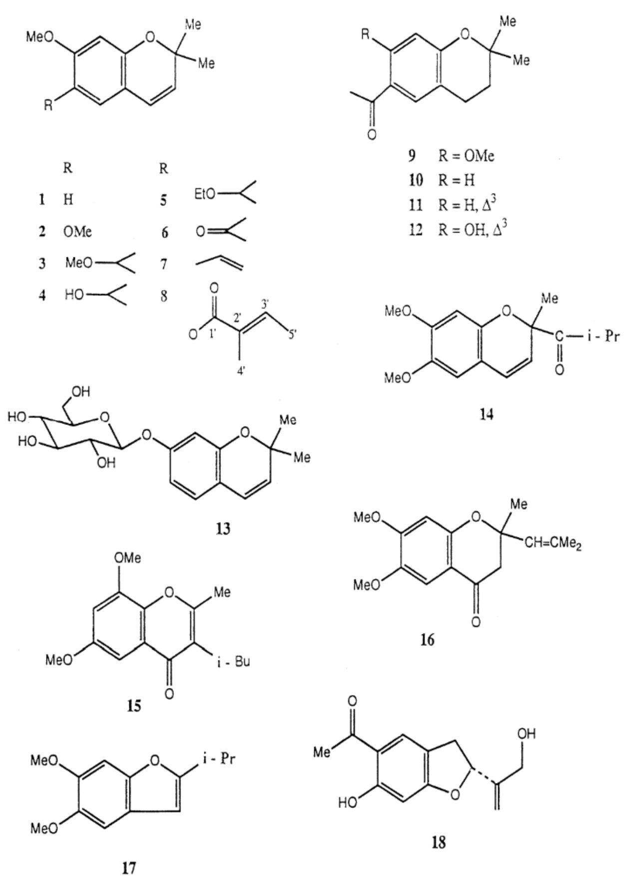
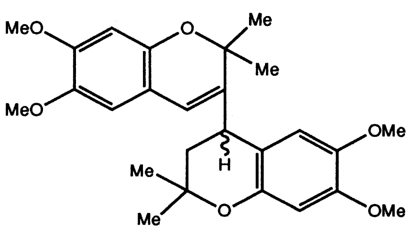


Fig.2: Phytochemical structures

Chromene Dimer



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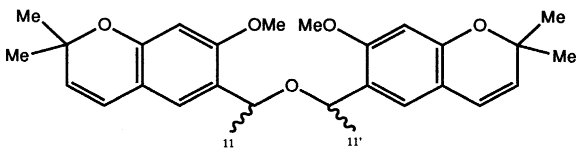

20 11α - Me, 11'β - Me
21 11β - Me, 11'β - Me
22 11β - Me, 11'α - Me

Fig.3 Phytochemical Structures

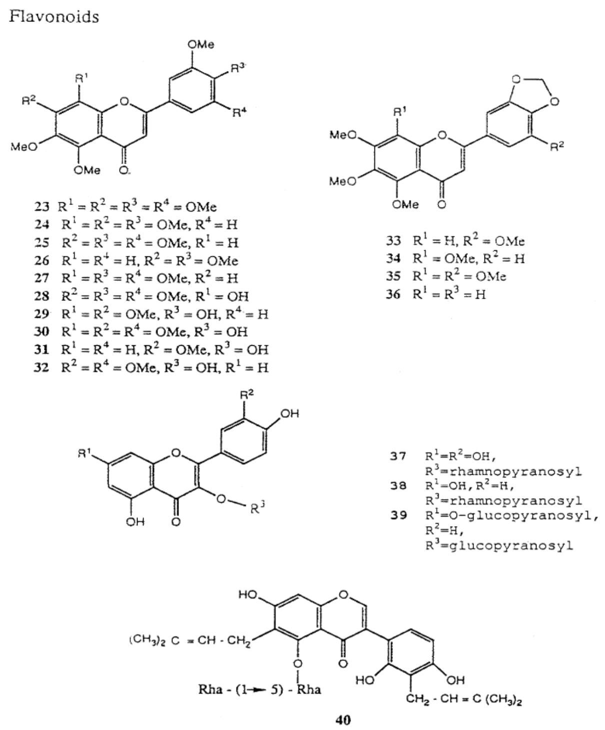

Fig.4: Phytochemical Structures

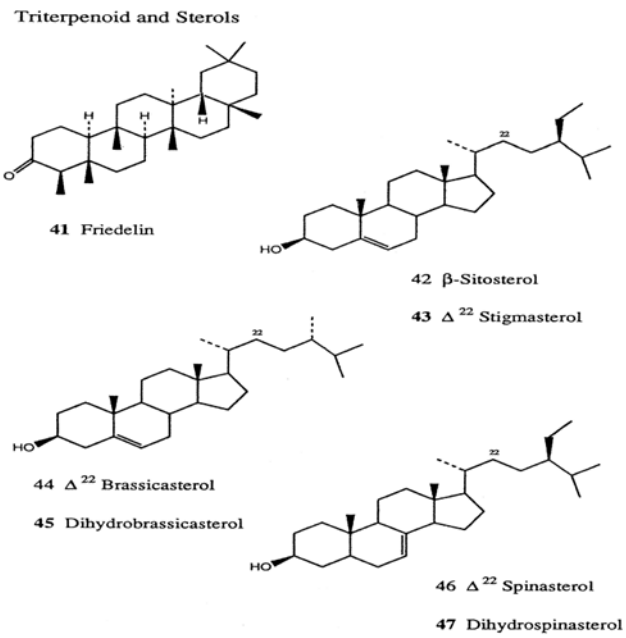

Fig.5: Phytochemical Structures

Evaluation of Traditional Medicinal Uses by Molecular Tools

There is a wide variety of items derived from plants. Plants have been used as medicinal ingredients by many cultures from prehistoric times. Modern pharmaceutical companies rely heavily on this body of information about ancient cures when creating new drugs. Nowadays, ethnomedicinal plant formulations and new medication discoveries rely on a plethora of cutting-edge biotechnological interventions, such as tissue-culture, marker-assisted breeding, DNA microarrays, metabolomics, proteomics, functional genomics, bioanalytics, and many more. Indigenous communities throughout the world have long relied on A. conyzoides as a medicinal remedy for a wide range of conditions.

In addition to its uses as a febrifuge and purgative, the plant is known to alleviate dyspnea, skin ailments, ulcers, wounds, and so on. Traditional African medicine makes use of the plant's anti-asthmatic, antispasmodic, and hemostatic characteristics. From their crude or tissue-specific fractions, the many phytochemical substances found in ACE may have a wide range of potential medicinal uses, including antioxidant, antibacterial, antimicrobial, anticancer, and so on. Traditional medicine has long made use of it to treat problems with the prostate and urinary tract. Nevertheless, research evaluating the pharmacological efficacy of A. conyzoides and gene expression studies employing modern molecular methods are lacking. One kind of pharmaceutical therapy for benign prostatic hypertrophy (BPH) is 5-α-reductase inhibitors.

These drugs relax the muscles around the urethra and bladder, which helps with urine retention. For the purpose of evaluating the safety and effectiveness of ACE in treating BPH, the impact on 5-α-reductase gene expression was measured. The amount of human 5-α-reductase mRNA in prostate epithelial cells was found to be considerably lower in the extract. Therefore, A. conyzoides may have therapeutic promise for benign prostatic hyperplasia (BPH) since it reduces 5-α-reductase enzyme activity. It may also be utilized after extracting the active ingredient from ACE and undergoing further clinical trials.

Bioinformatics advancements have made it easier to use computational methods to identify target drug molecules and their interactions prior to their usage in further tests. The use of in silico analysis has many applications, including the identification and prediction of the metabolic fate of isolated phytochemicals and the screening and creation of prospective therapeutic targets for different illnesses. Potential biopharmaceutical uses of phytochemicals extracted from ACE have been investigated via in silico research. Isolated from ACE, a number of compounds including precocene I, β-sitosterol, precocene II, 6-vinyl-7-methoxy-2,2-dimethyl chromene (VMDC), stigmasterol, polymethoxyflavone, pyrrolizidine, neophytadiene, phytol, and caryophyllene have been investigated for possible use in treating diseases such as malaria, diabetes, breast cancer, and cervical cancer, among others.

Isolated important secondary metabolites from ACE, including as kaempferol and quercetin, have recently shown promise as possible anti-SARS-CoV-2 therapeutic candidates. These metabolites may interact with the active site residues of the major protease enzymes, which inhibits the replication of the virus, according to in silico molecular docking research. As a result, molecular dynamic simulations and virtual screenings may play an essential role in the future of drug development for a wide range of disorders.

Inflammation results in the production of many mediators, some of which promote inflammation and others of which inhibit it. The anti-inflammatory activities of three compounds isolated from A. conyzoides leaves were studied: eupalestin, 1, 2-benzopyrone, and 5'-methoxy nobiletin (MeONOB). Furthermore, we looked at a number of enzymes, cytokines, and genes that are part of the inflammatory response. The levels of myeloperoxidase, nitric oxide, adenosine deaminase, leukocyte influx, etc., were considerably decreased ($p < 0.05$) by isolated substances and other ACE fractions. Additionally, the levels of p-p38 MAPK and p-p65 NF-κB were decreased. Isolated chemicals may have contributed to A. conyzoides' anti-inflammatory response by preventing MAPK and NF-κB activation.

Osteoarthritis (OA) is characterized by inflammation of the joints, which limits mobility and causes discomfort. The impact of ACE on OA in rats has been investigated, which might provide light on how TNF-α and MMP-9 influence the swelling and breakdown of proteoglycans during OA. At a dosage of 160 mg/200 g body weight, the MMP-9 and TNF-α levels were considerably reduced by the leaf ACE. This indicates that ACE may suppress the activities of TNF-α and MMP-9, respectively, which in turn decreases cartilage inflammation and breakdown. Additionally, the most important factor in diagnosing triple-negative breast cancer is the degree of MMP-9 expression.

As a result of its enhanced MMP-9 selectivity, OTC shows promise as a non-toxic treatment option for triple-negative breast cancer [78]. Future targeted research using the amazing advancements in molecular technology should reveal a plethora of useful applications confirming the biomedicinal characteristics of A. conyzoides.

CONCLUSION

Traditional medicine practitioners across the world use A. conyzoides L. to cure a variety of illnesses and conditions, despite the fact that it is invasive. The existence of various pharmacological characteristics is the reason for this. As a result, pharmacologists and researchers throughout the globe need to learn more about A. conyzoides in order to raise awareness of the plant and its medicinal use. Writing updated reviews and conducting experiments on different areas of A. conyzoides are the only ways to pique scientists' attention and close this gap.

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