



# **Importance of Dermal Antioxidant Property of *Ageratum conyzoides* Linn and Related Criterion**

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## **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## **ABSTRACT**

Different plant items have been utilized in the treatment of wounds throughout the years. Wound recuperating phytochemical mixes battle contamination, enhanced blood coagulation, and quicken the recuperating process. Various phytochemical mixes have been recognized and incorporated from therapeutic plants that have one of a kind properties related with the system of wound mending. Curiously, a considerable lot of these injury mending plants explored showed cancer prevention agent potential as their significant one of a kind properties. A plenty of instances of restorative plants shows up in writing to have indicated both injury mending and cancer prevention agent properties. There are certain criteria to consider a plant for wound healing and antimicrobial purposes- the phytochemical constituents of the plant should exhibit significant antioxidant properties and phenolic content of the plant should be adequate, the plant should exhibit significant cytotoxic properties. Interestingly *Ageratum conyzoides* L., possesses all the required criteria as

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was evident from literature. Lesser amounts of reactive oxygen species (ROS) and stress due to oxidation dictates the terms of normal wound healing process. Repeated exposure to stress of oxidation results in impediment of healing of wounds and as the free radicals are immensely unstable, they try to pull electrons from a variety of moieties in the cell and ultimately inducing changes in structure and functions of those moieties.

*Keywords: ROS; free radical; antioxidant; phytochemical; NSAID.*

## 1. INTRODUCTION

The pace at which globalization is accelerating permitted the exchange of processes of treatment between global and local pharmacopoeias not only through multinational commercial interests but also through many social media platforms as well. Thus the infiltration of global pharmacopoeial and biomedical knowledge into traditional system of medicine paved the way for more standardization and observance of stringent protocols during the practice of indigenous or traditional system of medicine [1].

The perceptions of the western societies have been changing during the last few decades and they are of the that medicinal plants and flora based products are free of side effects in comparison to pharmaceutical based products and due to this change in perceptions, local medicines or traditional medicines have gained recognition on the global platform and this in turn lead to the emergence of alternative medicine or the complementary medicine [2].

The traditional medicine use a complex poly-herbal formulations and poly-compound extracts and this poly-phytochemical approach of curing the chronic and degenerative ailments is a multi factorial approach in treating various ailments. The logic behind such a treatment is "complex diseases- multiple factors- multiple targets – multiple herbal formulations" [3,4].

ROS are also included in free radicals because they contain oxygen atom and other reactive moieties like superoxides and peroxides. These free radicals are usually formed as by-products during metabolic processes and are natural defenders against invading species as they are also reactive towards invading species. Never the less the deluge of free radicals results in oxidative stress [5]. The action of free radicals on the cell moieties in turn have a harmful effect on the process of wound healing. At some point of fundamental level of wound healing, ROS are infact necessary and this is true because even

complete inhibition of ROS also resulted in impediment of wound healing process. ROS are found to be prime mediators of cell signaling and swelling in the process of repairing of wounds. Even though the ROS are produced by normal physiological processes, detrimental effects can be observed due to over production.

Antioxidants are compounds that block oxidation and also nullify the inherent properties of ROS (detrimental effects) by various mechanisms. Antioxidants avert disease by suppressing lipid peroxidation and also by scavenging free radicals [6].

Many synthetic antioxidants are being used by pharmaceutical, cosmetic and food industries like 'butylated hydroxyanisole (BHA), butylated hydroxytoulene (BHT), and tertiary butylhydroquinone (TBHQ)', which scavenge the free radicals, but because of the attachment of 'synthetic antioxidants' in chronic diseases and severe outputs like carcinogenicity, researcher attention was turned towards natural antioxidants, that too specifically of plant origin [7,8].

There is extraordinary enthusiasm for the utilization of normal items, which incorporate mixes got from organic products, plants, and herbs.

The normal capacity of nutrient E is available in edible oils, nuts, and other greasy floristic nourishments is to avert oxidation. Nutrient E in this manner goes about as cancer prevention agent when devoured. It forestalls corruption of cell films in locales containing olefins. Some different cancer prevention agents work by various systems, responding with oxygen particles to avert the creation of free radicals. Moreover, various fibrous cancer prevention agents that can be devoured which add to an upgraded cell assurance.

As of late, center around plant examine has expanded everywhere throughout the world, and a huge assemblage of confirmations has been

gathered to appear the enormous capability of therapeutic plants utilized in different customary frameworks. Green tea, for model, contains catechin parts that are denoted to animate cell reinforcement movement by rummaging free radicals, hindering genius oxidant compounds and invigorating cancer prevention agent chemicals [9].

## 2. MEDICINAL PLANTS WITH ANTIOXIDANT PROPERTIES

'*Ageratum conyzoides* Linn.', belongs to the family 'Asteraceae' and is a annual herb. The term *Ageratum conyzoides* (A.C.) is existed from two Greek words- *Ageras* & *Konyz*, *ageras* meaning- 'non-aging' and *Konzy* for the plant '*Inula helenium*', since the A.C resembles this plant *Inula helenium*. Larger part of these are blessed with free radical rummaging particulates, e.g. 'nutrients, terpenoids, phenolic acids, lignins, stilbenes, tannins, flavonoids, quinones, coumarins, alkaloids, amines, betalains, and different metabolites', which are wealthy in cancer prevention agent exercises [10].

Amusingly a significant number of these injury mending plants examined showed cancer prevention potential as their significant exceptional properties. Incidentally during our literature survey, ample plants have been found to possess antioxidant and injury mending and cell reinforcement properties.

**Table 1. Taxonomic classification of A.C**

Kingdom	Plantae-Plants
Subkingdom	Tracheobionta-Vascular Plants
Superdivision	Spermatophyta-Seed plants
Division	Magnoliophyta-Flowering plants
Class	Magnoliopsida-Dicotyledons
Subclass	Asteridae
Order	Asterales
Family	Asteraceae-Aster family
Genus	<i>Ageratum</i> L.-whiteweed
Species	<i>Ageratum conyzoides</i> L.-tropical whiteweed

It is a pronounced fact that tannins are 'polyphenols' and are infact astringent and 'phenols' are free radical scavengers. Hence phenol containing diversities are considered to be antioxidants as well as anticarcinogenic.

## 3. LITERATURE REVIEW

This makes *A.conyzoides* as the lead plant species for our excogitate.

'Girthers, has found that A.C has found its way into the folk medicine in manifold continents i.e. South America, Africa and Asia. Volatile pungent smelling oil is produced from the plant which has got several biological properties inherent to the plant oil. It was being used for dressing of wounds, curing of dermatological diseases, in ocular, colic, ulcers treatment, and also as purgative and febrifuge [10]. Chopra et al., had reviewed that the decoction or infusion of the herb is given in several gastric problems like diarrhea, dysentery, intestinal colic, flatulence, rheumatic fevers [11]. Sharma and Sharma, 2015, had proved that the infusion of the plant was being used for Gynaecological diseases also. [12] Kapur, had demonstrated that the plant was being used in folk medicine for itching, sleeping sickness, as mouthwash for toothache, antitussive, vermifuge, tonic and for killing lice [13]. But as per *Akinmeyi* et al., [14] the Minimum Inhibitory Concentrations (MIC) of both ethanol and hydro extracts were too high against MRSA and hence they suggested immediate stoppage of *A.conyzoides* for use in traditional medicine against MRSA infections. The most common microbe for surgical bruise infection is *S. aureus* and the MRSA [methicillin resistant *S. aureus*] form of this species is the notorious one and this particular form is spreading at an alarming rate' [15].



**Image 1. *Ageratum conyzoides* L.**

## 4. MATERIALS AND METHODS

The A.C. plant was forwarded to decoction and alcoholic extraction under descending weight and further fractionation was done on the ethanolic leaf separate utilizing distinctive solvents. Add up to cell reinforcement capability of the unrefined fluid and ethanolic concentrates was researched with the expectation of complimentary radical searching movement, for the nearness of glutathione and additionally add up to phenolic substance. The Skin Infection study was

conducted utilizing the tetrazolium-based colorimetric, 3-(4, 5-dimethylthiazol-2-yl) - 2, 5-diphenyltetrazolium bromide (MTT) test, on leukemia, prostate and bosom tumors, and prostate ordinary cell lines (Jurkat, LNCap, MCF-7, and PNT2), individually, utilizing the unrefined watery and ethanolic separates and also divisions of the ethanolic leaf remove. Curcumin was utilized as standard.

## 5. RESULTS AND DISCUSSION

The outcomes demonstrated that the unrefined concentrates rummaged **2,2-diphenyl-1-picryl hydrazyl (DPPH)** free radical in a measurement subordinate way contrasted with the positive control, **butylated hydroxy toluene (BHT)**. Phenolic mixes were available; however glutathione was not distinguished in any of the unrefined concentrates. The watery leaf concentrate was the most grounded forager of DPPH, with half successful focus (EC50) of  $0.091 \pm 0.024$  mg/ml. It additionally marked the escalation of aggregated phenol content,  $1678.86 \pm 40.67$  mg/g likeness Gallic corrosive. The counter disease comes about apparent that the ethanolic leaf separate had similarly bring down cytotoxic consequences for the phone lines, with half maximal **inhibitory concentration (IC50)** estimations of  $15.08 \pm 0.28$ ,  $304.22 \pm 71.54$  and  $934.94 \pm 105.91$  µg/ml on Jurkat, LNCap and MCF-7 cells individually. Simultaneously, the chloroform and ethylacetate divisions displayed more grounded cytotoxic impacts with IC50 estimations of  $6.36 \pm 1.56$ ,  $35.28 \pm 6.46$  and  $74.27 \pm 8.15$  µg/ml for the previous and  $4.6 \pm 0.12$ ,  $37.28 \pm 2.09$  and  $67.38 \pm 1.71$  µg/ml for the last in Jurkat, LNCap and MCF-7 cell lines separately. All concentrates and divisions were not cytotoxic to the PNT2 cell lines. The C<sub>2</sub>H<sub>5</sub>OH leaf remove and the CHCl<sub>3</sub> and ethylacetate portions were firmly particular against Jurkat cell lines, with selectivity files (SI) estimations of 66.33, 15.72 and 21.74 separately. The similarity of tannins, saponins and terpenoids were gathered in the leaf and

blossom of the plant. The present contrive urged that the *Ageratum conyzoides* has striking antioxidative agent and Skin Infection characteristics and the synthetic mixes adversely affected the objective and endeavor depends parallel on following criterion: [16].

**Wounds and the process of Healing:** Wounds are absolute result of comprehensive severance of the skin – which is the major intervene for the infection to establish itself by microbial pathogens in visceral tissues. Infection inferences when the microbes breach this membrane barrier [17,18].

Trauma is the usual aetiological factor for wound formation. Trauma may be induced intentionally or accidentally. The leading causes of nosocomial morbidity and additional medical expenses are the contamination of the hospital-acquired wounds [19,20].

In the process of wound recuperation, macrophages play multiple roles. Cytokines are released by macrophages initially, wound and these promote inflammatory response by employing and activating additional leukocytes. Macrophages pave the way for resolution of inflammation by inducing and clearing apoptotic cells. As the apoptotic cells are being cleared by the macrophages, these apoptotic cells undergo phenotype regularize correction phase that in turn stimulate keratinocytes, angiogenesis, and fibroblasts that promote tissue regeneration. Thus macrophages aid in the promotion of the healing from the proliferative stage [21,22].

Additionally the skin also contains prominent T-cells called  $\gamma$ - $\delta$  T-cells which regulate the process of wound rehab, like- regulating inflammation, sustained tissue entity, and conquering against pathogens. These  $\gamma$ - $\delta$  T-cells are devoted as **dendritic epidermal T-cells (DETC)** because of identical dendritic morphology.

**Table 2. Phytochemical constituents in different extracts of A.C**

S. No.	Constituent	Hydro extract	Hydro-ethanolic extract (50/50)	Methanolic extract	Ethyl acetate extract
1	Alkaloids	√	√	√	√
2	Terpenoids	√	√	√	√
3	Flavonoids	√	√	√	√
4	Tannins	√	√	√	√
5	Saponins	√	√	√	√

Optimum level of oxygenation is crucial for proper healing of wound. Wound healing is stimulated by hypoxia with the release of expansion factors and angiogenesis and also oxygen itself is needed for sustaining the steps of healing. **Hyperbaric oxygen therapy [HBOT]** can overcome the impression of tissue hypoxia and can be effective in the treatment of hypoxic wounds [23,24].

**Age:** The proportion of the elderly in the population is rapidly increasing when compared to other age groups and at the same time, increasing age is an important assessment for lagged wound healing. Recent molecular and cellular level investigation at clinical and in animal models on age in relation to changes in wound cureness have noted that in healthy older adults as age increases there is a transient delayed recovery and not an factual interference in the quality of healing.

**Effect of sex hormones on wound healing:** When comparisons were made among aged males and aged females concerning healing process in acute conditions, it was revealed that the former have a slow healing and the logic behind this is that the sex hormones have a tremendous effect on healing processes. The male and female sex like the dehydroepiandrosterone and its derivatives - testosterone, di-hydrotestosterone, estrone, estradiol exhibit some influential effects on the activity of healing. This research have concluded that androgens have a negative effect on cutaneous injury healing while estrogens augment wound healing in both the elderly males and females.

**Stress:** Strain has a tremendous effect on human fitness and social conduct. Many sicknesses like- cardiovascular ailments, most cancers, compromised wound restoration, and diabetes- are linked with strain. Numerous scrutinizes have showed that strain brought about disruption of neuroendocrine immune equilibrium is consequential to health.

**Diabetes:** Globally diabetes is the major reason behind the poor quality of life index and affects millions. Impedance in remedy of infected wounds is usually observed in people suffering from diabetes. Also these people frequently develop chronic non-healing wounds on foot called as **diabetic foot ulcers (DFUs)**. These DFUs occur in almost 15% of the people suffering from diabetes and are also a serious

complication of diabetes. Hypoxia always accompanies DFUs and prolonged hypoxic conditions are a result of insufficient perfusion and inadequate angiogenesis. This prolonged hypoxic condition is another factor that delays wound healing.

**Medications:** Several drugs that are used routinely for treating various ailments also concurrently have effects on normal physiological processes like platelet function, clot formation, inflammatory responses, and proliferation of cells.

**Glucocorticoids:** Hypoxia-inducible factor-1(HIF-1) is a chief transcriptional messenger for wound wellness and systemic glucocorticoids suppress the production of HIF-1. Apart from interfering with healing, the systemic use of these drugs may increase infection risk. Studies have suggested that low-dose glucocorticoid when administered topically, alleviate pain, decrease exudates, enhances wound healing, and inhibit the formation of hypergranulation tissue [25].

**NSAIDs:** NSAIDs like ibuprofen are being broadly employed for the relief of pain, **rheumatoid arthritis (RA)**, and also in inflammation. Aspirin even though it can be employed as a pain killer and an anti-inflammatory drug, it has got anti-platelet activity and is not recommended at higher doses as a pain killer, but at lower-doses this aspirin has got cardiac activity and hence is being used in cardiac patients. Meta-analysis has demonstrated that short term use of NSAIDs interferes with healing, and nonavailability of data concerning the effect of long term use of NSAIDs on healing process. This will ensure that NSAIDs does not interfere with wound repair.

**Chemotherapeutic Drugs:** Several chemotherapeutic agents interfere with wound healing process because of their inherent activities like- Inhibiting metabolism of the cell, Suppressing or killing of rapidly dividing cells, Suppressing angiogenesis.

These agents bring about a decrease in fibroplasias, and neovascularisation of wounds through inhibition of DNA, RNA, or ultimately the protein synthesis. Also these agents delay chemotaxis, inhibit early matrix formation in the wound, decrease collagen production, impair proliferation of fibroblasts, and restricted wound contraction.

**Obesity:** Obesity is another risk factor for several ailments and these include impaired wound healing also. Obese individuals are more prone for wound complications like- infections, dehiscence, seroma and hematoma formation, venous and pressure ulcers. Surgical site infections and wound complications are on an increase in obese patients and in also those obese patients who undergo either bariatric or non-bariatric surgical procedures. Hypoperfusion and ischemia of the subcutaneous adipose tissue may lead to many of these complications [25].

**Alcohol consumption:** Biochemical proof and animal interactions have shown that unweaving to R-OH impairs wound recovery and ascending the occurrence of infection.

Intake of alcohol not only increases the incidence of infection but also affects the proliferative section of wound healing. Animal studies have demonstrated that even a single dose consumption of ethanol equivalent to blood levels of 100 mg/dl have disturbed collagen synthesis, closure of wound, new blood vessel formation, and re-epithelialization. It is a well known fact that smoking is the etiological factor for many diseases and it also affects the process of wound healing. Delay in post-operative wound healing was observed in smokers and also such individuals develop certain complications like infection, leakages from blood vessel interconnections, necrosis of wound and flap, rupture of epidermis, decreased tensile wound strength.

**Carbohydrates, Proteins and Amino acids:** The process of wound requires energy and this energy is primarily derived from carbohydrates and fats. For the deposition of new tissues and angiogenesis energy is required and this energy is supplied by cellular ATP which in turn is produced by glucose, a major source of fuel for the production of the cellular ATP. Glucose is used as a primary source for the synthesis of ATP consequently to prevent depletion of other protein substrates and amino acids.

Protein deficient nutrition impairs many stages of wound healing like- angiogenesis, proliferation of fibroblasts, synthesis of proteoglycans, synthesis of collagen and wound remodeling. Thus protein in nutrition is an important factor that affects the process of wound healing.

**Fatty acids:** In critically ill and post-operative patients, there is a huge demand for energy which is essential for wound healing and tissue

repair. This energy demand can be met by nutritional supplementation of lipids which provides the building blocks for both tissue repair and wound healing. Mammals cannot synthesize 'polyunsaturated fatty acids (PUFAs)' on their own and depend on dietary sources for them. There are 2 classes of polyunsaturated fatty acids- omega-6 class found in soybean oil and omega-3 class ingredient of fish oil.

**Vitamins, Micronutrients, and Trace elements:** Vitamins A, C, and E are potent anti-oxidants and also exhibit anti-inflammatory effects. The contribution of vitamin C in wound healing is well acknowledged. A deficiency of vitamin C has got its toll on tissue repairing.

## 6. CONCLUSION

The knowledge gained and being used for manufacturing modern pharmaceuticals can be applied to plant based medicine also. There are several advantages with plant based medicines, viz. they are easily available, economical, and safe. Now a days it has become a trend to look for plant based medicines for minor ailments to that of life threatening ailments. Also globally the share of plant based medicines is increasing at a rapid pace. At this juncture it is necessary to propagate the economic importance of medicinal plants and also bring into practice the principles of plant based medicine.

- ✚ Other methods of extraction processes may be carried out using other solvents for evaluating the wound healing and antibacterial properties.
- ✚ Many species of A.C do exist and it is recommended that all these species are evaluated, as they do differ in their active constituents and their concentrations.
- ✚ Newer compounds are being isolated from A.C and their pharmacological activities can be studied in depth for newer pharmacological actions.

## DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT etc.) and text to image generators have been used during the writing or editing of this manuscript.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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