

## ETHNOMEDICINAL IMPORTANCE, PHYTOCHEMISTRY AND PHARMACOLOGICAL POTENTIAL OF *ACALYPHA WILKESIANA*: A REVIEW

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### ABSTRACT

*Acalypha wilkesiana* Müll. Arg., commonly known as copper leaf, Joseph's coat or red acalypha, is a member of the Euphorbiaceae family with significant medicinal properties. It has been traditionally utilized in various parts of the world, particularly in Africa and Asia. The present review compiles the ethnopharmacological uses, phytochemical composition, pharmacological activities and toxicological aspects of *Acalypha wilkesiana*. The plant exhibits considerable antimicrobial, antioxidant, anti-inflammatory, antidiabetic and anticancer activities, as demonstrated in several in vitro and in vivo studies. Major bioactive constituents identified include ellagitannins such as geraniin and corilagin, along with flavonoids eg quercetin and rutin, phenolic acids, and phytosterols. Despite its promising therapeutic potential, toxicological studies indicate that organ toxicity may occur in a dose-dependent manner; therefore, its use in herbal medicinal formulations should be carefully evaluated.

**KEYWORDS:** *Acalypha wilkesiana*, Phytochemistry, Pharmacological activities, anticancer, toxicity, traditional medicine.

### 1. INTRODUCTION

Copper leaf or *Acalypha wilkesiana*, is a shrub that's common in the South Pacific. You can find it in tropical and subtropical places around the world now. People grow it mainly for its leaves, which come in different colors, like copper-red and other blends, depending on the kind you get.<sup>[1]</sup> Besides being a nice plant to look at, copper leaf is also

used in traditional medicine. People say it can help with things like stomach problems, fungal infections, high blood pressure, diabetes and skin issues.<sup>[2]</sup> The red *Acalypha* group has a lot of different plants somewhere between 450 and 570.

That makes it one of the biggest in the Euphorbiaceae family. Among these, *Acalypha wilkesiana* has been the most extensively studied, owing to its widespread traditional medicinal use and its reported therapeutic properties. This section provides an overview of the traditional uses of the plant, its phytochemical composition, mechanisms of action and safety profile.<sup>[3]</sup>

The plant have significant activity like antidiabetic, antioxidant, antimicrobial, hepatoprotective, and anti-inflammatory properties mediated by its rich phytochemical profile, particularly phenolics, flavonoids, alkaloids and tannins. Other side preclinical studies show some therapeutic potential comparable or exceeding standard pharmaceutical dose, clinical trials are limited but, necessitating further investigation to establish safe dosing regimens and optimize therapeutic applications for human populations.<sup>[4,5]</sup>

This review bridges traditional knowledge to preclinical validation, highlighting *A. wilkesiana*'s multitarget potential against antimicrobial resistance and oxidative stress-related diseases outperforming standards in key assays while identifying gaps like clinical RCTs and standardization. By compiling cultivar variations (e.g. *Hoffmanii* antifungal superiority) and dose-toxicity profiles, it guides phytomedicine development for affordable, accessible therapies in resource-limited settings, potentially reducing reliance on synthetic drugs amid rising T2DM (global prevalence 10.5%) and fungal infections. Our critical analysis underscores translational pathways, making this beneficial for researchers, herbal formulators and policymakers advancing evidence-based herbal interventions.

## 2. Botanical Taxonomy, Distribution and Morphological Characteristics

### 2.1 Taxonomic Classification and Nomenclature

The plant name *Acalypha wilkesiana* is a member of the Euphorbiaceae, or spurge family, which is large and includes many other medicinally useful species. The plant was named scientifically as *Acalypha wilkesiana* Müll. Arg. in botanical nomenclature. It decays in mulch and like most species blessed with many forms, some cultivars are significantly different to others, so you need to know your botany.<sup>[4]</sup>

### 2.2 Morphological Description and Physical Characteristic

Description *Acalypha wilkesiana* is a evergreen shrub growing to be 3 meters tall and spreading 2 meters wide with compact crown, erect stem and many branches. Stems and foliage are hairy which gives them their distinctive texture and look. The leaves are big and broad, 10–20 cm long, some 15 cm wide with characteristic teeth along its margins. The most outstanding trait of the *A. wilkesiana* is its leaves which are predominantly coppery green with conspicuous red splashes, giving it a beautiful patterned or variegated-like appearance that makes it look different from other members of the species. This aesthetic potential has made it a popular choice for gardens in the tropics and subtropics.<sup>[4,5]</sup>

### 2.3 Geographic Distribution and Ecological Habitat

*Acalypha wilkesiana* has been evolved in island ecosystems, and is endemic to paciffic island this is a tropical and subtropical plant that spreads naturally in Vanuatu and Pacific Islands there for grew up with very warm climate which

has humid characteristics. The plant has been naturalized in ornamental gardens and within several ecosystems throughout various tropical regions like Africa, America and Asia. It prefers light, well-drained soil and does well in sheltered, shady places but is also quite tolerant of shade or sun depending on the cultivar. The plant has exactly the right requirements such as being sensitive to drought but also to stress, requiring a minimum temperature of at least 10°C (50°F).<sup>[5,6]</sup>

#### 2.4 Traditional Uses

In Southern Nigeria and also other region of West African and some Asian country, *Acalypha wilkesiana* has been used for long days as a traditional remedy. Used as Management of hypertension and diabetes mellitus.

- Used as Treatment of gastrointestinal disorders and diarrhoea.<sup>[2]</sup>
- Used as Antifungal therapy for skin infections.<sup>[2]</sup>
- Used as Wound healing and dermatological conditions.<sup>[3]</sup>
- Used as Management of asthma and dysentery.<sup>[3]</sup>

The aqueous or ethanolic extract of red/brown varieties, particularly "Red Acalypha," has been used as traditionally applied topically for treating various skin problems including eczema, seborrheic dermatitis and pityriasis versicolor like disease.<sup>[5]</sup>

The survey that leaves represent the most commonly utilized plant part, for 93% of preparations, while roots only 7% of traditional formulations. The preparation follow *Acalypha wilkesiana* have decoction (54%), maceration (40%) and infusion methods 5 to 6%.<sup>[6][8]</sup> It is use for diarrhoea, scabies, abscesses and cardiovascular diseases.<sup>[10,11,13]</sup>

#### 2.5 Plant Parts Used

Different plant parts are utilized in traditional medicine as shown in below:

**Leaves:** Most commonly used part, administered as decoctions, infusions or topical preparations it use on skin.

**Stem bark:** Used as a certain preparations for systemic conditions.

**Root bark:** used in specific traditional formulations.

**Seeds:** mostly used in traditional healers in Southwest Nigeria as part of powder mixtures.<sup>[8,11,13]</sup>



**Fig no. 1: Different parts *Acalypha wilkesiana* of including seeds, roots, stem bark and leaves used in traditional medicine.**

### 3. Phytochemical Composition and Chemical Characterization

#### 3.1 Major Phytochemical Constituents

Biochemical fingerprinting of *Acalypha wilkesiana* has led to the confirmation that this plant has a complex and varied phytochemical profile.

#### Phytochemical content

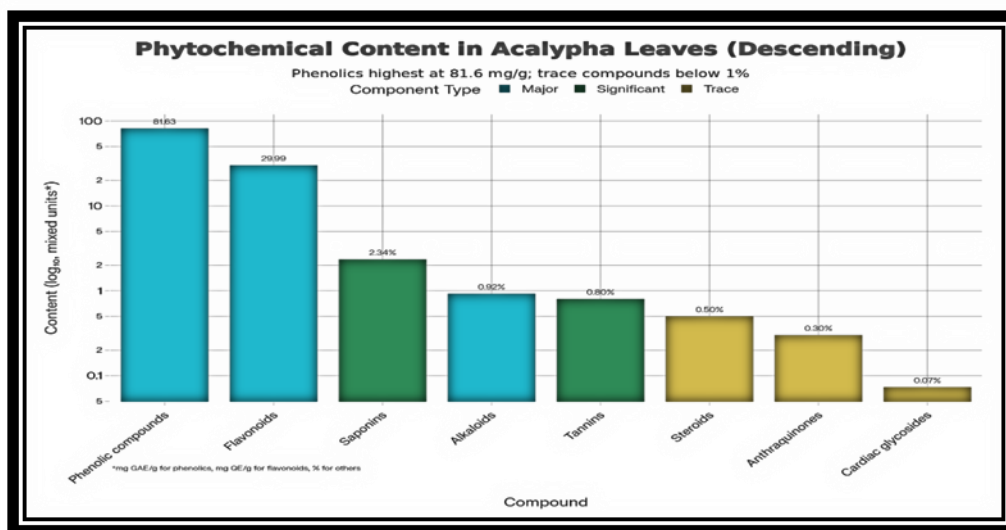


Fig no. 2: Quantitative phytochemical composition of *Acalypha wilkesiana* leaves showing major bioactive constituent. [6,7,11,13]

Table no.1: Representation of major bioactive compounds identified in *Acalypha wilkesiana* and their associated pharmacological properties.

Phytochemical Class	Alkaloids		Flavonoids		Phenolic Compounds		
	Identified Alkaloids	Total Alkaloids	Flavones/ Flavonols	Total Flavonoids	Phenolic Acids	Hydrolysable Tannins	Total Phenolics
Identified Constituents	Akuammidine, Voacangine, Echitamine, etc.	—	Apigenin, Quercetin, Naringin, Kaempferol	—	Gallic, Caffeic, Chlorogenic, Ferulic, Protocatech ic, p-Coumaric, Syringic	Geraniin, Corilagin	—
Quantitative Content	Relative %	0.92–3.20%	% composition	29.988± 0.089mg QE/g	Qualitative	—	81.627±0.321mg GAE/g extract (~12% DW)
Analytical Method	GC-MS	Gravimetric/ GC-MS	Chromatography	AlCl3 method	HPLC, GC-MS	Chromatography	Folin–Ciocalteu
Pharmacological Activities	Antidiabetic, Antimicrobial	Hypoglycemic, Antimicrobial	Antioxidant	Antioxidant, Anti-inflammatory	Antioxidant, Antimicrobial	Wound healing, Antimicrobial	Antioxidant, Anti-inflammatory
Remarks / Key Findings	Akuammidine major	Higher in ethanol extract	Apigenin dominant	Second largest class	Diverse phenolic acids	Geraniin major antioxidant	Major bioactive class
References	[15],[16]	[15],[16]	[3],[19]	[15]	[14],[15]	[19]	[15],[16]

Phytochemical Class	Steroids & Polyphenols	Terpenoids	Saponins	Tannins
Category / Subclass	Mixed	Mono-, Sesqui-, Diterpenes	Triterpenoid	General
Identified Constituents	—	—	—	Tannic acid
Quantitative Content	Qualitative	Qualitative	0.22–0.44%	Qualitative
Analytical Method	Screening	GC-MS	Screening	Phytochemical tests
Pharmacological Activities	Hormonal, Anti-inflammatory	Anti-inflammatory	Anti-inflammatory	Astringent, Antimicrobial
Remarks / Key Findings	Often co-present	Detected widely	Limited structure data	Present in extracts
References	[15],[16]	[15],[16]	[15],[16],[20]	[15],[16]

### 3.2 Mineral and Nutrient Composition

Other beyond the organic phytochemicals, *acalypha wilkesiana* plant leaves are more in essential minerals and micronutrients it is contribute to the nutritional value as well as likely health benefits. Mineral analysis show that the *acalypha wilkesiana* plant leaves present more quantities of sodium (na) =  $(3.96 \pm 0.05 \text{ mg/g})$ , potassium(k) =  $(2.89 \pm 1.79 \text{ mg/g})$ , phosphorus =  $(2.73 \pm 0.25 \text{ mg/g})$ , magnesium =  $(1.94 \pm 0.08 \text{ mg/g})$ , manganese =  $(1.40 \pm 1.01 \text{ mg/g})$ , calcium =  $(1.31 \pm 0.42 \text{ mg/g})$ , and zinc =  $(0.30 \pm 0.14 \text{ mg/g})$  this phytochemical as make this plant more in micronutritional.<sup>[22]</sup>

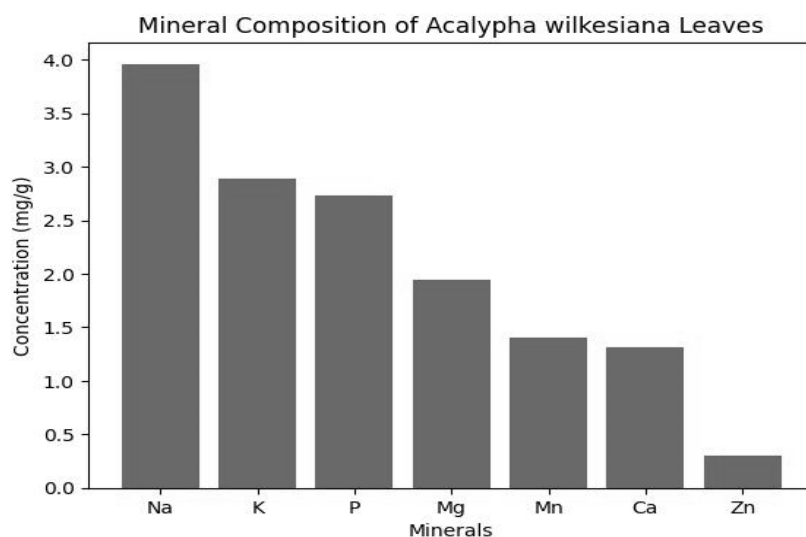


Fig no. 2: Graphical representation of Mineral composition of A.wilkesiana.

Vitamins are present in this plant as follow Fat\_soluble vitamins in *Acalypha wilkesiana* plant leaves have present  $4.12 \pm 0.26 \text{ mg/kg}$  for vitamin D, and  $17.28 \pm 1.00 \text{ mg/kg}$  for vitamin E. Water soluble vitamins range to  $0.05 \pm 0.02 \text{ mg/100g}$  for vitamin B<sub>2</sub> and  $69.61 \pm 1.77 \text{ mg/kg}$  for Vitamin C.<sup>[22]</sup>

## 4. Pharmacological Activities and Mechanisms of Action:

### 4.1 Antioxidant Activity and Mechanisms

Excessive accumulation of radicals causes oxidative stress, which have key pathological factor in many chronic diseases, such as cancer, cardiovascular disease and neurodegeneration. *Acalypha wilkesiana* possesses high signaling activity by the use of several standardized assay systems. In the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay of methanolic leaf extract of A. wilkesiana showed 47.21% scavenging percentage with an IC<sub>50</sub> value of  $24.21 \mu\text{g/mL}$ , representing moderate to good antioxidant activity. The FRAP (ferric reducing antioxidant power) assay demonstrated that the extract was an effective reducer of oxidative species exhibiting a FRAP value of  $113.61 \mu\text{mol Fe}^{2+}/\text{g}$ .<sup>[19,21]</sup>

The antioxidant activities of A.wilkesiana may be mediated via diverse phytochemicals through multiple pathways. It is important to observe that high concentration of ellagic acid in *Acalypha wilkesiana* extracts used for its powerful antioxidant activity, due primarily to the presence of phenolic hydroxyl groups which directly donate protons to free radicals and complex with oxidized forms of metal ions Flavonoids and tannins in the extract show DPPH radical scavenging activity, due to donation of proton neutralizing radicals free and as well as preventing ferryl-perferryl

complex formation and by scavenging superoxide radicals and hydroxyl. Saponins, flavonoids and tannins also contribute to free radical scavenging effects in a concentration dependent manner as shown by the DPPH assay.<sup>[21,36]</sup>

#### 4.2 Antimicrobial and Antifungal Activities.

Microbial infections are difficult challenges to global health problems, during in the developing country where resistance to the conventional antibiotics has continued to be used. *Acalypha wilkesiana* has anti-bacterial activity to different bacterial organisms. The results of this study suggest that methanolic extracts and fractions of *A. wilkesiana* leaves have inhibitory effects on bacteria unresponsive to certain standard antibiotics, signifying potential for treatment against antibiotic-resistant organisms. The extract was active against clinical isolates as well as laboratory reference strains, indicating universal antimicrobial activity among the divergent bacterial populations.<sup>[20,23]</sup>

Studies on MIC of crude *A. wilkesiana* extracts observed varying MIC (0.25-8 mg/ml) against different fungal strains, and for herbal cream formulations (0.31-8 mg/ml). *Candida albicans* was the most susceptible to *A. wilkesiana* Hoffmannii and *A. wilkesiana* Macrophylla types, showing a low MIC value when compared to other fungal pathogens tested suggesting specific sensitivity to antifungal phenolic compounds of this plant. The best antifungal activity was shown by the *A. wilkesiana* Hoffmannii leaves against *Candida albicans* and *Malassezia furfur*; this difference in effect may reflect the biological variability between different plant cultivars,<sup>[24]</sup> 73.3% clinical cure rate overall, with impressive efficacy against mycoses: *Tinea pedis* exhibit 100% cure rate.<sup>[25,38]</sup>

#### 4.3 Anti-inflammatory Activity and mechanisms

Chronic inflammation is a central pathological cause of cardiovascular disease, autoimmune diseases, metabolic syndrome and oncogenesis, so anti-inflammatory agents are promising for treatment. Ellagic acid, highly concentrated in *Acalypha wilkesiana* extracts, inhibits the expression of pro-inflammatory mediators such as nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2), consequently decreasing the production of inflammatory prostaglandins and nitric oxide.<sup>[35,36,37]</sup>

Liver disease and hepatic injury are so common in human living conditions due to chemical exposure, viral infection or metabolic disorders that they have become an important health problem worldwide which leads to morbidities and mortalities.<sup>[29]</sup>

#### 4.4 Hepatoprotective activity and mechanism

Hepatoprotective activity *Acalypha wilkesiana* in vivo Hepatoprotective activities of *Acalypha wilkesiana* has been reported through screening based on carbon tetrachloride (CCl<sub>4</sub>)-induced liver injury models. The ANOVA showed that pretreatment with *Acalypha wilkesiana* aqueous extract significantly ( $p < 0.05$ ) dose-dependently reduced the activities of alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT) compared to CCl<sub>4</sub> - treated control animals, with percentage-protection in dosage-dependent manner ranging between 83.21 - 92.45 % for ALP, 19.65 - 57.56 % for AST and 3.23 - 60.47 % for ALT activity respectively.<sup>[16,21]</sup>

#### 4.5 Antidiabetic Activity and mechanism

Antidiabetic Activity and Mechanisms T2DM, characterized by insulin resistance and the progressive failure of pancreatic  $\beta$ -cell function, is one of the most common chronic diseases worldwide, having devastating effects on human health and healthcare systems. *Acalypha wilkesiana* exerts significant antihyperglycemic and antidiabetic effect

via multiple mechanisms of action. In vitro  $\alpha$ -glucosidase inhibitory evaluations showed that the ethanol-extract of *A. wilkesiana* root bark extracts had lower inhibitor concentrations for acarbose (control) when compared is by the control, suggesting that *A. wilkesiana* might relatively exert anti-hyperglycaemic property by suppressing the postprandial glucose spikes in treating diabetes.<sup>[26,27,28]</sup>

#### 4.6 Anticancer Activity and Mechanisms:

Several in vitro studies had shown anticancer activity for *Acalypha wilkesiana*. Several extracts displayed cytotoxic activity against cancer cells, implying possible antiproliferative properties. It is believed that these effects have been mediated by its biological active components consisting of flavonoids, phenolic compounds and alkaloids.<sup>[28]</sup>

Potential anticancer mechanisms proposed include induction of apoptosis (programmed cell death), suppression of cell proliferation, antioxidant activity and inhibition of inflammatory pathways contributing to tumor progression. The endogenous alkaloid is well known to interfere with cell cycle timing and reduced oxidative stress in the initiation and promotion phases of tumorigenesis. These findings showed that the *Acalypha wilkesiana* could be a potential candidate for cancer treatment requires more in-depth investigation.<sup>[30]</sup>

#### 4.7 Analgesic Activity and Mechanisms:

It is typically with treated non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics but the long-term use of these medications may produce detrimental effects. Experimental studies have shown high analgesic activity in *Acalypha wilkesiana*. The ethanolic leaf extract has shown dose-dependent pain inhibition in vivo that was similar to standard drugs such as Diclofenac sodium when tested using methods like the acetic acid-induced writhing test and the hot plate method. The analgesic mechanism is thought to be related to the inhibition of prostaglandin synthesis and subsequently peripheral pain signalling. Flavonoids, tannins, and phenolic compounds content also might induce peripheral and central analgesics effects. These results validate the traditional use of *A. wilkesiana* in pain and inflammatory conditions management.<sup>[30,31]</sup>

#### 4.8 antiulcer activity and mechanisms

*Acalypha wilkesiana* has been reported to exhibit significant antiulcer activity in experimental animal models. Ethanolic leaf extracts have shown protective effects against ulcer induction models such as ethanol-induced and indomethacin-induced gastric ulcers. The extract demonstrated a reduction in ulcer index and gastric lesion formation compared to the control group. The antiulcer mechanism is believed to involve multiple actions, including reduction of gastric acid secretion, enhancement of mucus production, antioxidant activity, and cytoprotective effects on the gastric mucosa. Phytoconstituents such as flavonoids, tannins, and saponins may contribute to mucosal protection and free radical scavenging. These findings support the potential therapeutic role of *A. wilkesiana* in the management of peptic ulcer disease.<sup>[29,31]</sup>

#### 4.9 Antipyretic Activity and mechanism

Aqueous extract of leaves exhibits marked dose-dependent antipyretic activity similar to that of standard drugs (e.g., aspirin). It is effective in reducing yeast-induced pyrexia in wistar rats as per studies, however maximum results at higher doses eg. possibly due to flavonoids, saponins and alkaloid.

Activity: Methanolic and ethanolic leaf extracts of *A. wilkesiana* reduce body temperature significantly, usually using a control group as comparison. The Activity is ascribed to Phytochemical constituents, including flavonoids, alkaloids and saponin. Traditional Uses for Treating Fever Research says the plant's influence on fever is similar to regular medicines like aspirin, also proving its traditional consumption for treating fever.<sup>[27,29]</sup>

#### 4.10 Additional Pharmacological Activities for this plant

Another study revealed that the major pharmacological effect of this plant, some research has done that identified additional therapeutic effect this plant of *Acalypha wilkesiana*. Cytotoxic and anticancer properties have been list in study related *Acalypha* species (*Acalypha indica*), with hexane leaves powder extract demonstrating inhibitory effects on MCF-7 breast cancer cell lines with IC<sub>50</sub> values of 50 µg/ml. The antioxidant phytochemicals include flavonoids and tannins present in *Acalypha wilkesiana* plant cancer chemoprevention.<sup>[29,30,31]</sup>

#### Pharmacological Activities of *Acalypha wilkesiana*

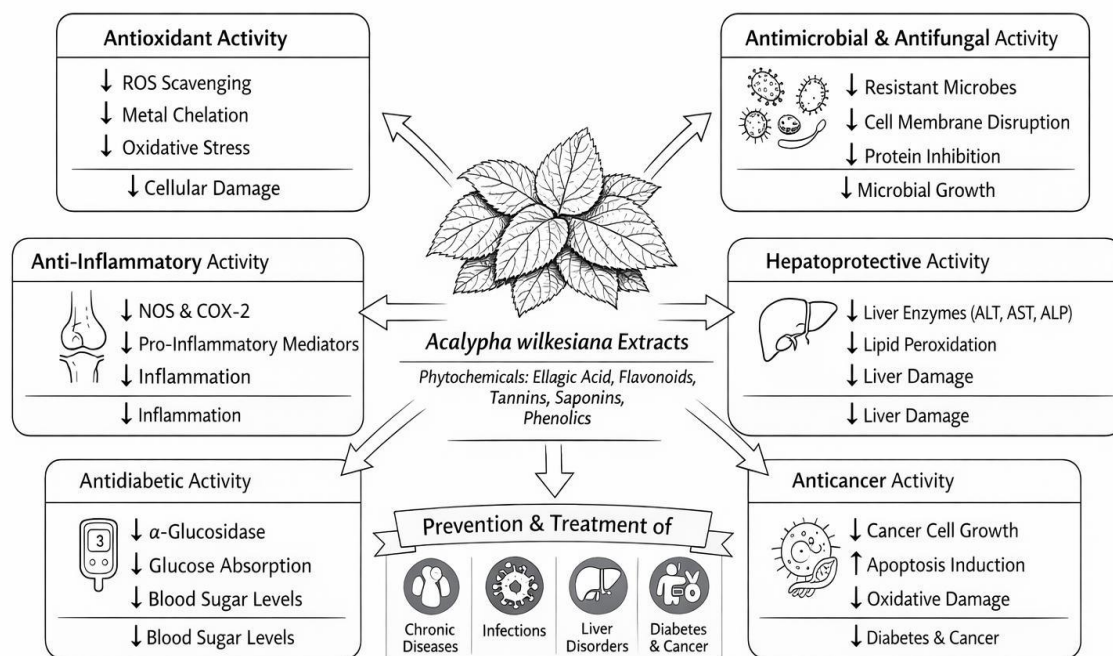


Fig no. 3: Schematic representation of the major pharmacological activity of *Acalypha wilkesiana*.

## 5. Formulation and Pharmaceutical Development

### 5.1 Topical Cream and Ointment Formulations

Pharmaceutical research of *Acalypha wilkesiana* has mainly focus to its topical application for healing skin diseases. Creams containing 0.5%, 1% and 2% w/w of the ethanol extract of *Acalypha wilkesiana* leaves suspended in cetomacrogol, zinc oxide emulsifying wax, and emulsifying ointments was formulated successfully. Stability testing of the formulations with temperature fluctuation (-10, 4, 30, 37 and +45°C), freeze-thaw cycles, centrifuge tests, pH measurement as well as its exposure to UV light showed that the *A. wilkesiana* extract-based cream with a concentration of 2% was more effective in terms of stability and antimicrobial activity than the other lower extract concentrations.<sup>[20,32,40]</sup>

Antimicrobial activities of the formulated creams against bacteria (*Bacillus subtilis*, *Escherichia coli*, *Salmonella typhi*) and fungi (*Candida albicans*) demonstrated that cetomacrogol based cream formulations containing *Acalypha wilkesiana* extract have better antimicrobial activities at 4% w/v concentration than zinc oxide or emulsifying wax vehicle. The formulations showed significant ( $P < 0.05$ ) activity against all test organisms pointing to good antimicrobial preservation in the topical vehicle and release of bioactive from them for long periods. Some analysis of dermatophyte-infected skin tissue treated with 2% *Acalypha wilkesiana* cream formulations did atrophy and improved microfungus healing which converts observed in vitro antimicrobial activity into relevant clinical tissue healing.<sup>[20,33,35,36,40]</sup>

## 6. Safety Profile and Toxicological Considerations

### 6.1 Acute and Sub-chronic Toxicity

*Acute Toxicity:* Studies found no mortality in rats at doses up to 3,000–5,000 mg/kg, with the determined to be 2,828.34 mg/kg in one study, indicating low acute risk.<sup>[17,18]</sup>

*Organ Toxicity:* While generally safe at low doses, high doses over extended periods have shown potential for hepatotoxicity (liver damage) and nephrotoxicity (kidney damage), causing symptoms like necrosis, hemorrhage and cell degeneration.<sup>[42]</sup>

Safety evaluation is paramount for any botanical medicine under development for clinical use, requiring systematic toxicological assessment across multiple endpoints. Acute toxicity studies of *A. inferno* (a closely related *Acalypha* species) in mice revealed that no adverse effects were observed at doses up to 5000 mg/kg, with estimated  $LD_{50} \geq 5000$  mg/kg, indicating exceptionally low acute toxicity and favorable safety margins. This  $LD_{50}$  value exceeds those of many conventional pharmaceutical agents, suggesting excellent biocompatibility.

In subchronic toxicity studies in rats, *A. inferno* administration produced dose-dependent increases in body weight in male animals and dose-dependent decreases in female animals at 500 mg/kg. Diarrheal symptoms were observed in female rats administered doses of 250 mg/kg and 500 mg/kg on the fourth day of administration, representing the primary adverse effect at higher doses. These findings indicate that while *A. wilkesiana* demonstrates excellent acute safety, prolonged high-dose administration requires monitoring for gastrointestinal effects and hormonal perturbations.<sup>[17,37,42]</sup>

### 6.2 Clinical Safety and Tolerability

Human clinical studies are small, but in general favorable Results from human data showed that positive directing effects. A clinical trial of *Acalypha wilkesiana* ointment in 32 Nigerian patients with superficial fungal infections gave maximum tolerability, only one patient had the treatment discontinued because intolerable excoriation occurring at the site of lesion.<sup>[39,41]</sup> This is a 96.9% tolerability rate. It's interesting to note that *Acalypha wilkesiana* preparations, when formulated and administered properly, display good safety and effect profiles in human populations according to this clinical experience have been done on this plant.<sup>[25,34]</sup>

## 7. CONCLUSION

Our review concludes that *Acalypha wilkesiana*'s rich phytochemical profile dominated by ellagitannins (geraniin, corilagin), flavonoids (quercetin at 0.97 mg/g) and phenolics (81.6 mg GAE/g) supports its broad bioactivities, as

evidenced by DPPH scavenging (47% at IC<sub>50</sub> 24 µg/mL) and FRAP (113 µmol Fe/g). We accomplish potent antimicrobial/antifungal efficacy (MIC 0.25-8 mg/mL vs. *Candida/Malassezia*; 73-100% cure in models and 96.9% clinical tolerability) from in vitro, in vivo and small human trials, validating traditional topical uses for skin infections.

Findings from a some study the number of preclinical studies to evidence the plant is rich in antioxidant, antimicrobial, anti-inflammatory, hepatoprotective and antidiabetic potential several activities showing potencies comparable to or greater than those to a number of conventional drugs. This review concludes low acute toxicity (LD<sub>50</sub> >5000 mg/kg) but dose-dependent risks (hepatotoxicity/nephrotoxicity >250 mg/kg subchronically), derived from rat/mouse studies showing necrosis at high exposures. We also conclude favorable clinical safety for topical use (one trial: 96.9% tolerability), yet systemic applications require caution. Some clinical study of *Acalypha wilkesiana* from its ethnobotanical study towards evidence based medicinal formulation to this end is incomplete and appropriately designed dose escalation proof that studies are required for testing at safe effect on human relevant doses. Our analysis identifies critical gaps like limited large-scale clinical trials to confirm preclinical potencies (e.g. only small antifungal study); absence of human dose-escalation for antidiabetic/hepatoprotective claims; undefined therapeutic windows amid toxicity variability; lack of standardized extracts/markers (e.g. geraniin quantification) and insufficient data on cultivar differences (e.g. *Hoffmanii* vs. *Macrophylla* antifungal variance). Future work should prioritize RCTs, pharmacokinetic studies, and quality protocols for phytomedicine translation.

## 8. Conflict of Interest

Authors declare no conflicts of interest.

## Abbreviations

DPPH: (2,2-diphenyl-1-picrylhydrazyl);

FRAP: (ferric reducing antioxidant potential);

MIC: (minimum inhibitory concentration);

IC<sub>50</sub>: (half maximal inhibitory concentration);

LD<sub>50</sub>: Lethal Dose 50%;

T2DM: Type 2 diabetic mellitus.

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