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From weed to wonder: Anti-inflammatory applications of *Amaranthus spinosus* in modern medicine

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Abstract
Amaranthus spinosus L., commonly known as spiny amaranth, is a medicinally important plant that has been widely recognized in traditional systems of medicine for the treatment of inflammatory conditions, wounds, fever, and gastrointestinal disorders. The plant is rich in diverse phytoconstituents such as flavonoids, alkaloids, phenolic compounds, terpenoids, saponins, and glycosides, which are largely responsible for its broad spectrum of pharmacological activities. Among these, its anti-inflammatory potential has drawn significant scientific interest in recent years.

Several experimental studies have demonstrated that extracts of *A. spinosus* possess potent anti-inflammatory activity in both *in vitro* and *in vivo* models. The underlying mechanisms are attributed to modulation of multiple molecular targets including cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, inhibition of nitric oxide (NO) and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, along with enhancement of antioxidant defences. These actions result in the attenuation of oxidative stress and the suppression of acute as well as chronic inflammatory responses. Additionally, the synergistic effect of various phytochemicals may contribute to its overall therapeutic efficacy.

Despite these promising findings, most studies on *A. spinosus* remain confined to preliminary pharmacological investigations and preclinical evaluations. Limited data are available on standardized dosage forms, toxicity profiles, bioavailability, and clinical trials, which restrict its translation into modern evidence-based medicine. Future research focusing on phytochemical isolation, molecular docking, and Nano formulation approaches, and well-designed clinical studies will be essential to validate its therapeutic role and promote its utilization in phytopharmaceutical development.

This review integrates ethnomedicinal knowledge and modern pharmacological evidence, providing a comprehensive outlook on the anti-inflammatory potential of *Amaranthus spinosus*. It highlights its relevance as a promising candidate for developing safe, effective, and affordable herbal therapeutics targeting inflammatory disorders.

Keywords: *Amaranthus spinosus*, anti-inflammatory, ethnomedicine, phytoconstituents, traditional medicine, pharmacology, herbal formulation

Introduction

Amaranthus spinosus Family: *Amaranthaceae*, also called "spiny amaranth" or "pig weed," is a plant that has long been valued for its therapeutic benefits.

Amaranthus spinosus Linn. (*A. spinosus* L) is one such medicinal plant of India. Belongs to the family of *Amaranthaceae*, the plant is believed to originate from South and Central America and then introduced into various regions of Africa specially south tropical African countries such as Zimbabwe, Botswana, Malawi, Zambia and Namibia. The plant is also widely distributed in waste places, roadsides and fields in Bangladesh, Ghana, Cambodia, Philippines Maldives, Japan, Sri Lanka, Myanmar, Indonesia, Australia and India.[1] *A. spinosus* L. grows annually as an erect perennial herb with many branches. Stems are hard, terete or obtusely angular and greenish to purple in colour. Leaves are alternate, have bitter taste with a characteristic odour. Flowers are numerous, appear throughout the year. Fruit is ovoid shaped. Seed is shiny, black or brownish-black in colour [2, 3].

Plant Profile

- **Synonyms:** *Prickly Amaranthus*
- **Botanical Name:** *Amaranthus spinosus*
- **Family:** Amaranthaceous

- **Natural Distribution:** The plant is also widely distributed in waste places, roadsides and fields in Bangladesh, Ghana, Cambodia, Philippines Maldives, Japan, Sri Lanka, Myanmar, Indonesia, Australia and India.

Classification of *Amaranthus spinosus*

- **Kingdom:** Plantae.
- **Subkingdom:** *Viridaeplantae*.
- **Phylum:** *Magnoliophyta*.
- **Subphylum:** *Euphyllophytina*.
- **Division:** *Magnoliophyta*.
- **Class:** *Magnoliopsida*.
- **Subclass:** *Caryophyllidae*.
- **Order:** *Caryophyllales*.
- **Suborder:** *Chenopodiineae*.
- **Family:** *Amaranthaceae*.
- **Genus:** *Amaranthus*.
- **Species:** Spinous [4-6]

Botanical Description

An erect glabrous herb of 30-60 cm in height; stems are hard, often reddish in colour, with many grooved branches and with sharp divaricate spines, often exceeding 1.3 cm long in the leaf-axils. Leaves are 3.2-7.5 of 1.3-3.8 cm, ovate or lanceolate. Petioles are 2-6.3 cm in length. Flowers very numerous, sessile, in dense axillary. Clusters and in terminal and axillary dense and interrupted spikes; bracteoles linear, bristle-pointed, usually longer than the sepals. Perianth of male flowers 2.5-3 mm, long; sepals 5, ovate, acute, bristle-pointed. Perianth of female flowers scarcely 1.5 mm long, sepals 5. Capsules were 1.5 mm long, ovoid, thickened at the top, circumscissile about the middle, membranous, rugose; styles, divaricate, pubescent [7, 8].

In recent years the pharmacological actions of *Amaranthus spinosus* have been investigated by various researchers. The plant is has found various pharmacological activities which include antihyperlipidemic, antidiabetic, antitumor, Immuno-modulatory properties, antimicrobial, antibacterial, anti-peptic ulcer, anti-inflammatory, analgesic, bronchodilator and spasmolytic, hepato-protective, antifertility, anti-nociceptive, anti-helminthic, Haematological activity, antimalarial, antidiarrheal, gastrointestinal activity, antigenic and allergenic activity, antipyretic, diuretic, antioxidant properties [9].

Materials and Methods

A comprehensive review of literature was carried out through search engines, various journals and data bases available till date. Published Scientific data and reports available offline and online journal were collected and reviewed. The main source of data collection was research and review articles published by reputed publishers such as Elsevier, Informa, Springer, Taylor and Francis, and several others; online databases such as PubMed, Google scholar, Science hub, Research gate, Scopus and Science Direct; and various books from the libraries of RTM Nagpur University, Nagpur. Data regarding the morphological identification and characteristics of the plant was compared with herbarium specimen number 11217 in the Department of Botany, RTM Nagpur University, Nagpur with the help of expert botanist Dr. Nitin Dongarwar of the same department.

Traditional and Ethnomedicinal use

Amaranthus spinosus, commonly known as spiny amaranth, is a plant with a rich history of ethnomedicinal uses and demonstrated therapeutic activities supported by phytochemical analysis [11]. Its widespread distribution in tropical and subtropical regions, particularly in South Asia, has led to its integration into various traditional medicine systems, such as Ayurveda [11, 12].

Ethnomedicinal Uses

Traditional applications of *Amaranthus spinosus* are diverse, reflecting its perceived efficacy across a spectrum of ailments:

- **Menstrual disorders:** The leaves of *A. spinosus* are traditionally used to treat menstrual disorders [13].
- **Gastrointestinal issues:** It is employed in folklore medicine for gastroenteritis and is also investigated for its gut modulatory (laxative and spasmolytic) activities [13, 14].
- **Inflammation:** Traditionally, *A. spinosus* has been used to address general inflammation [13, 12].
- **Hepatic disorders:** The leaves are recognized in the Ayurvedic system for treating hepatic disorders [12].
- **Fever**: Traditional remedies utilize *A. spinosus* for fever.
- **Skin conditions:** It is applied for conditions such as leprosy and eczema.
- **Respiratory ailments:** The plant is used for bronchitis.
- **Other conditions:** Traditional uses also include gall bladder inflammation, abscesses, arthritis, snakebites, and leucorrhoea [13, 12]. In some African folklore, it's used to treat several illnesses, including those potentially requiring antiepileptic intervention [15].

Therapeutic Activities and Pharmacological Potentials:

Modern scientific investigation has begun to validate many of these traditional uses by identifying specific bioactive compounds and evaluating their pharmacological effects. The plant's therapeutic potential is largely attributed to its complex phytochemical profile, which includes alkaloids, carbohydrates, glycosides, saponins, phenolic compounds, phytosterols, proteins, amino acids, flavonoids, and tannins [13, 16].

- **Antioxidant Activity**: *A. spinosus* exhibits significant antioxidant properties, largely due to its high content of phenolic compounds and flavonoids. These compounds act as efficient radical scavengers and chain-breaking antioxidants, which are crucial for mitigating oxidative stress and combating various degenerative diseases [17, 18]. Quantitative analysis using RP-HPLC has identified 21 health-promoting bioactive polyphenolic antioxidants in *A. spinosus* extracts.
- **Anti-inflammatory Activity:** Extracts of *A. spinosus* have shown anti-inflammatory properties [17]. This aligns with its traditional use for inflammatory conditions [12].
- **Anti-diabetic Activity**: The plant demonstrates anti-diabetic potential, suggesting its utility in managing blood sugar levels [17].
- **Antiepileptic Potential**: Methanol leaf extracts of *A. spinosus* have been experimentally studied for their antiepileptic potential in albino mice, indicating promising central nervous system effects [15].

- **Wound Healing Activity:** Studies have shown that ethanol extracts of the whole *A. spinosus* plant promote wound healing. In vitro efficacy was observed on HaCaT and MEF cells, demonstrating effects on clonogenic and scratch assays. Acute oral and dermal toxicity studies conducted in accordance with OECD guidelines have also indicated a favorable safety profile for the extract when applied topically [19].
- **Antimicrobial Activity:** Leaf extracts of *A. spinosus* have demonstrated antimicrobial activity, which is typically linked to the presence of secondary metabolites such as alkaloids, flavonoids, and terpenoids that can inhibit microbial growth [16].
- **Gut Modulatory Effects:** Investigations into aqueous-methanolic extracts of the whole plant have revealed laxative, spasmolytic, and bronchodilator activities, supporting its traditional use for gastrointestinal complaints [14].
- **Cytotoxic and Apoptotic Activities:** Extracts have also shown cytotoxic and apoptotic activities in Allium cepa root meristematic cells and human erythrocytes, indicating potential anticancer properties that warrant further investigation [18].

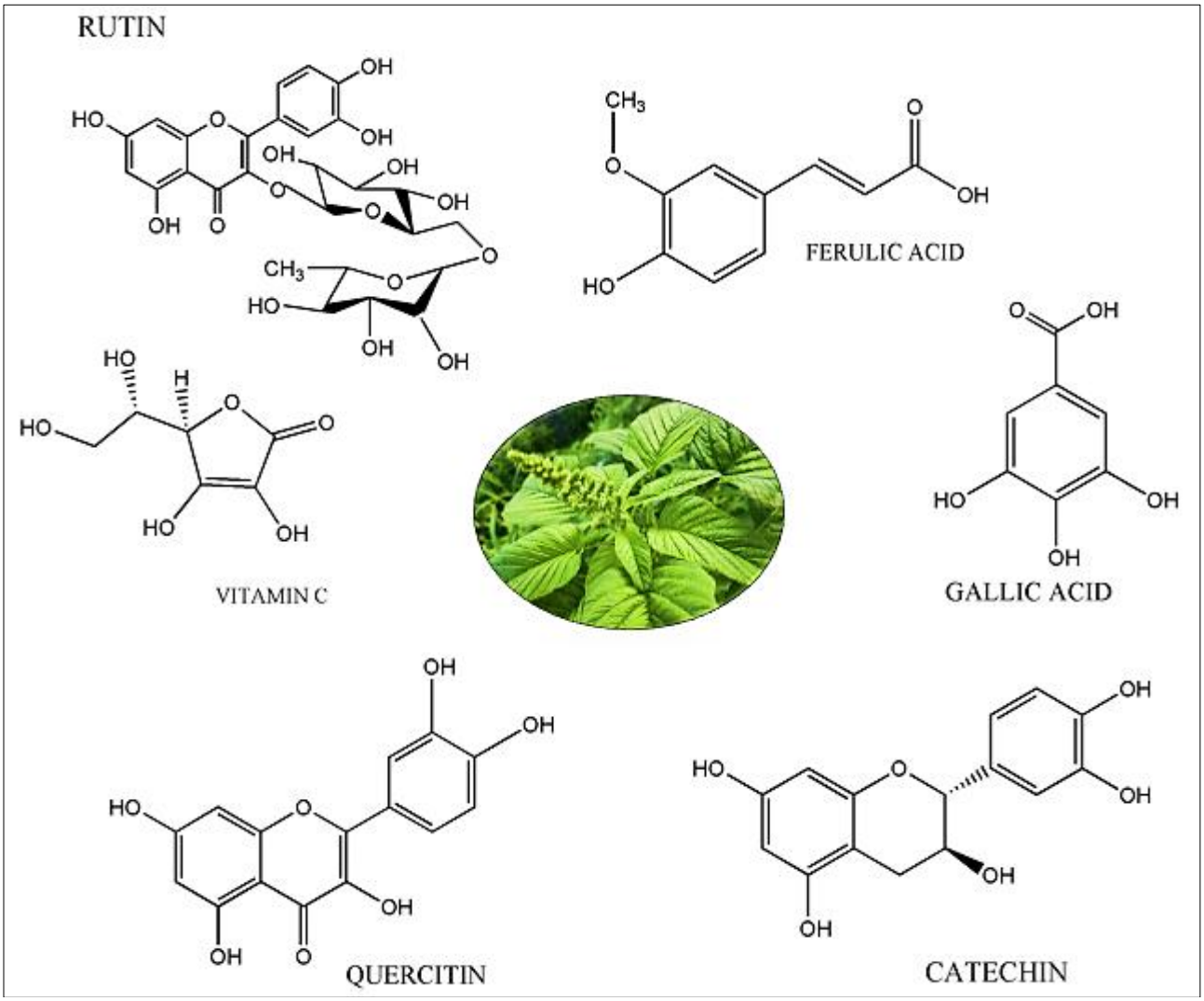
The therapeutic activities of *A. spinosus* are closely linked to its rich and diverse phytochemical composition. Further research, including detailed clinical trials, is essential to fully validate its traditional uses and develop standardized herbal formulations for broader application [11].

Phytochemical constituents related to anti-inflammatory activity

The therapeutic potential of *Amaranthus spinosus* is attributed to its rich phytochemical profile [12]. Extensive phytochemical analysis has confirmed the presence of several classes of compounds known for their anti-inflammatory effects, including flavonoids, alkaloids, terpenoids, and phenolic compounds [12-15].

Flavonoids

Flavonoids are a large and diverse group of polyphenolic compounds widely distributed in plants, recognized for their significant anti-inflammatory, antioxidant, and anti-cancer properties [16-19]. *Amaranthus spinosus* is a rich source of flavonoids [13, 20-23]. Specific flavonoids identified in *A. spinosus* include hesperidin and rutin [24]. Flavonoids exert their anti-inflammatory effects through multiple mechanisms, including the elimination of free radicals, modulation of carcinogen metabolism, regulation of gene expression in oncogenes and tumour suppressor genes, induction of cell cycle arrest and apoptosis, and modulation of enzymatic activities involved in detoxification, oxidation, and reduction [19]. They also inhibit the production of pro-inflammatory mediators [17].



Alkaloids
Alkaloids are a diverse group of nitrogen-containing organic compounds often recognized for their biological activities [18, 25, 15]. *Amaranthus spinosus* contains alkaloids [13, 14, 22, 25]. Some alkaloids contribute to hepatocyte detoxification and exhibit anti-inflammatory properties [18].

Terpenoids
Terpenoids are a large class of organic compounds derived from isoprene units, known for their antimicrobial and anti-inflammatory properties [26-28]. *Amaranthus spinosus* contains terpenoids [12, 14, 29].

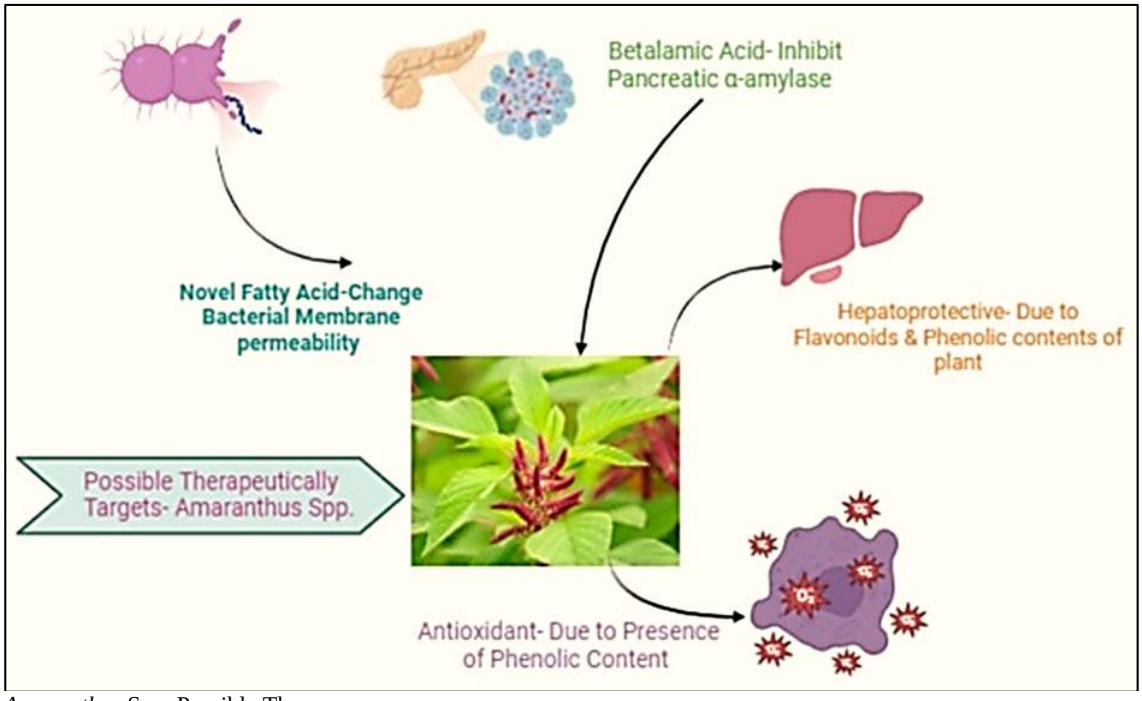
Phenolic compounds
Phenolic compounds, including phenolic acids, are a major group of plant secondary metabolites with well-known antioxidant and anti-inflammatory activities [21, 22, 25, 30, 31, 23, 32-35]. Studies indicate that the phenolic compounds present in *A. spinosus* are primarily responsible for its pharmacological activities, including potent antioxidant and radical scavenging effects [13, 32]. (E)-ferulic acid is one such phenolic acid isolated from *A. spinosus* [24]. Phenolic acids exhibit antioxidant, anticarcinogenic, antimutagenic, and anti-inflammatory effects [16].

Other bioactive molecules
Beyond these major categories, *Amaranthus spinosus* also contains saponins, glycosides, phytosterols, proteins, amino acids, and tannins, all of which can contribute to its overall health benefits [22, 25, 15]. For instance, saponins have been associated with hepatocyte detoxification and anti-inflammatory properties [18].

Experimental studies on anti-inflammatory activity
The anti-inflammatory potential of *Amaranthus spinosus* has been investigated through various experimental studies.

***In vitro* studies (cell-line based)**
While specific cell-line based studies for *A. spinosus* are not detailed in the provided literature, the general approach to evaluate anti-inflammatory activity *in vitro* often involves methods like the HRBC (Human Red Blood Cell) membrane stabilization method and egg albumin denaturation assays [36, 37]. These methods assess the ability of plant extracts to stabilize cell membranes and inhibit protein denaturation, which are indicators of anti-inflammatory action [36].

***In vivo* studies (animal models)**
Several *in vivo* studies have confirmed the anti-inflammatory activity of *Amaranthus spinosus* extracts. For example, methanol extracts of *A. spinosus* leave inhibited carrageenan-induced rat paw edema and significantly reduced acetic acid-induced increased vascular permeability in rats. Inhibition of cotton pellet granuloma was also observed with *A. spinosus* extract [38]. These findings demonstrate its efficacy in animal models of acute and chronic inflammation [38]. Another study evaluated the analgesic, anti-inflammatory, and anti-pyretic activities of *Amaranthus spinosus* stem extracts. Till here.



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Mechanisms of anti-inflammatory action
The anti-inflammatory effects of *Amaranthus spinosus* are likely mediated through multiple pathways involving its diverse phytochemicals.

Inhibition of pro-inflammatory mediators (TNF-α, IL-6, IL-1β)
Although direct evidence for *A. spinosus* inhibiting TNF-α, IL-6, and IL-1β is not explicitly detailed in the provided sources, many anti-inflammatory compounds, including flavonoids and phenolic acids found in *A. spinosus*, are known to suppress the production of these pro-inflammatory cytokines. For instance, anti-inflammatory secondary metabolites can inhibit inflammatory pro-inflammatory cytokines like IL-1β and IL-6 [48].

Cyclooxygenase (COX) and lipoxygenase (LOX) pathway modulation

Inflammation involves the production of prostaglandins and leukotrienes through the cyclooxygenase (COX) and lipoxygenase (LOX) pathways, respectively [36, 39]. Modulation of these pathways is a common mechanism for anti-inflammatory agents [36, 48]. For example, studies on other medicinal plants have shown that some compounds can modulate arachidonic acid metabolism and prostaglandin synthesis, thereby inhibiting inflammation [48]. Molecular docking studies for other plant extracts have investigated binding to cyclooxygenase-2 (COX-2) to understand anti-inflammatory mechanisms [36].

Antioxidant and free radical scavenging effects

Oxidative stress and reactive oxygen species (ROS) play a critical role in the initiation and propagation of inflammation [32]. *Amaranthus spinosus* extracts have demonstrated significant antioxidant and free radical scavenging activities, which contribute to their anti-inflammatory properties [13, 32]. The presence of phenolic compounds and flavonoids is strongly linked to these antioxidant capacities [13, 17, 32]. By neutralizing free radicals, *A. spinosus* can mitigate oxidative damage and reduce the inflammatory response [17, 19].

NF-κB pathway regulation

The Nuclear Factor-kappa B (NF-κB) pathway is a crucial regulator of immune and inflammatory responses. Its activation leads to the transcription of numerous pro-inflammatory genes. Inhibition of NF-κB expression is a key mechanism for many anti-inflammatory compounds. While not explicitly detailed for *A. spinosus* in the provided texts, general anti-inflammatory mechanisms include the inhibition of NF-κB expression [48].

Comparative Studies with Standard Anti-inflammatory Agents

The provided literature primarily focuses on establishing the anti-inflammatory efficacy of *Amaranthus spinosus* itself rather than direct comparative studies with synthetic drugs [13, 38, 45]. However, the growing interest in natural alternatives is driven by concerns over the adverse effects associated with conventional synthetic anti-inflammatory drugs. Medicinal plants, like *A. spinosus*, offer potential advantages such as fewer side effects, economic viability, and improved patient compliance [41]. Further research into comparative efficacy and safety profiles against established synthetic agents would be valuable.

Formulation and Pharmaceutical Prospects

The traditional uses of *Amaranthus spinosus* suggest its potential for modern pharmaceutical formulations. Currently, studies typically involve extracts, such as methanol or ethyl acetate extracts, which are prepared from various parts of the plant [18, 38, 23]. These extracts could serve as starting materials for developing various dosage forms. The rich phytochemical content positions *A. spinosus* as a candidate for tablet, capsule, or even topical gel formulations, especially given its traditional application for external inflammatory conditions like eczema [9]. As according to novel drug delivery, the formulation can also prepare as Nanoparticles for increase in efficacy of the dosage. However, specific studies on the development of such formulations for *A. spinosus* are not elaborated upon in the provided sources.

Toxicological and Safety Profile

The use of *Amaranthus spinosus* as a food source in many cultures suggests a degree of safety [47]. While comprehensive acute and chronic toxicity studies for *A. spinosus* are not explicitly detailed in the provided literature, safety is a critical consideration for any herbal medicine. Generally, plant-based medicines are sought for their "lesser side effects" compared to synthetic drugs [40]. Establishing safe dosage ranges through rigorous toxicological assessments would be crucial for clinical application.

Challenges and Future Perspectives

Despite the promising evidence, several challenges and research gaps remain for *Amaranthus spinosus*. There is a need for more in-depth research to fully elucidate its mechanisms of action at the molecular level, particularly concerning specific inflammatory pathways. Standardization of extracts based on their active anti-inflammatory compounds is essential for ensuring consistent efficacy and quality across different preparations [46]. Clinical validation through human trials is a significant step required to translate traditional knowledge and preclinical findings into accepted therapeutic interventions [41]. Finally, exploring commercialization potential through novel drug discovery and development requires addressing these scientific and regulatory hurdles [45].

Conclusion

Amaranthus spinosus possesses significant anti-inflammatory activity, substantiated by both traditional uses and experimental studies [38]. Its efficacy is primarily attributed to a diverse array of phytochemicals, including flavonoids, alkaloids, terpenoids, and phenolic compounds, which exert their effects through antioxidant properties, free radical scavenging, and likely modulation of key inflammatory pathways [13, 32]. While preclinical evidence is encouraging, further research focusing on detailed mechanistic studies, standardized formulations, and rigorous clinical trials is essential to fully realize its potential as a natural and safe anti-inflammatory agent.

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