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Review Article

Phytochemical Composition and Neuroprotective Potential of *Amaranthus tricolor*: A Scientific Rationale for Its Evaluation in Epilepsy Models

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ABSTRACT

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures, affecting millions worldwide. Despite advances in pharmacotherapy, current antiepileptic drugs often have limited efficacy, significant side effects, and do not address the underlying neuronal damage caused by oxidative stress and neuroinflammation. Amaranthus tricolor, a leafy vegetable with traditional medicinal uses, is rich in bioactive phytochemicals such as flavonoids, phenolic acids, betalains, vitamins, and essential minerals. These compounds exhibit potent antioxidant, anti-inflammatory, and neuroprotective activities, suggesting a mechanistic basis for their potential anticonvulsant effects. This review consolidates existing evidence on the phytochemical composition and neuroprotective properties of A. tricolor and presents a scientific rationale for its systematic evaluation in experimental epilepsy models. Future studies exploring its efficacy, safety, and underlying molecular mechanisms could pave the way for the development of novel plant-based interventions in epilepsy management.

INTRODUCTION

Epilepsy is a chronic neurological disorder marked by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain. It affects over 50 million individuals worldwide, representing a major public health concern. The pathophysiology of epilepsy is complex and involves a combination of genetic predisposition, neuronal hyperexcitability, synaptic dysfunction, and imbalance between excitatory and inhibitory neurotransmission. Despite the availability of numerous antiepileptic drugs (AEDs), about 30% of patients remain refractory to treatment, and long-term use of AEDs is often associated with adverse effects such as hepatotoxicity, sedation, cognitive deficits, and teratogenicity. These limitations underscore the need for alternative or adjunct therapies that not only control seizures but also protect neurons from ongoing damage.[1]

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Oxidative stress, neuroinflammation, and excitotoxicity are recognized as key contributors to epileptogenesis. Excessive production of reactive oxygen species (ROS) can damage neuronal membranes, proteins, and DNA, leading to neurodegeneration. Simultaneously, chronic neuroinflammation, mediated by activated microglia and pro-inflammatory cytokines, exacerbates seizure susceptibility. Glutamate-mediated excitotoxicity further amplifies neuronal injury and seizure propagation. Therapeutic strategies targeting these pathways may therefore provide both seizure suppression and neuroprotection.[2]

In this context, plant-based neuroprotective agents have gained significant attention due to their multimodal mechanisms, safety profile, and traditional use in neurological disorders. *Amaranthus tricolor*, commonly known as red amaranth, is a leafy vegetable widely consumed in Asia and Africa. Ethnomedicinally, it has been used for its antioxidant, anti-inflammatory, hepatoprotective, and nutritional properties. Phytochemicals such as flavonoids, phenolic acids, betalains, vitamins, and essential minerals contribute to its potential neuroprotective effects.[3]

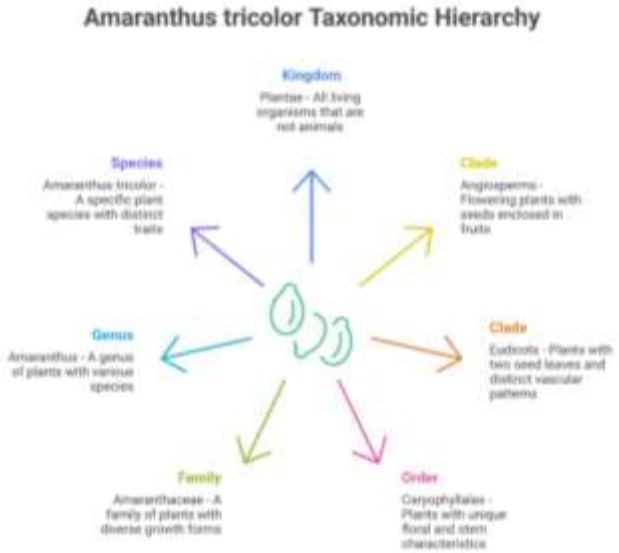
The aim of this review is to provide a comprehensive analysis of the phytochemical composition of *A. tricolor* and its neuroprotective mechanisms, and to establish a scientific rationale for its evaluation in experimental epilepsy models. By consolidating existing evidence, this review highlights the potential of *A. tricolor* as a novel plant-based intervention for seizure management and neuronal protection.

2. Botanical Description and Taxonomy of *Amaranthus tricolor*

2.1 Taxonomic Classification

Amaranthus tricolor L. belongs to the family Amaranthaceae, which comprises approximately 60 species in the genus *Amaranthus*. Its accepted taxonomic hierarchy is as follows:

- **Kingdom:** Plantae
- **Clade:** Angiosperms
- **Clade:** Eudicots
- **Order:** Caryophyllales
- **Family:** Amaranthaceae
- **Genus:** *Amaranthus*
- **Species:** *Amaranthus tricolor* L



2.2 Morphological Characteristics[4]

Amaranthus tricolor is an annual, fast-growing herbaceous plant typically 30–100 cm in height. It is characterized by:

- **Leaves:** Broad, ovate to lanceolate, often displaying vibrant red, green, or variegated colors.
- **Stem:** Erect, succulent, and branching, with a reddish tinge in many cultivars.
- **Flowers:** Small, inconspicuous, greenish or reddish, clustered in terminal or axillary inflorescences.
- **Seeds:** Tiny, rounded, and black or dark brown, containing a high nutritive value.

2.3 Geographical Distribution and Cultivation

Amaranthus tricolor is widely distributed in tropical and subtropical regions of Asia, Africa, and the Americas. It thrives in a variety of soil types but prefers well-drained, fertile soils with adequate sunlight. The plant is cultivated for both its edible leaves and seeds. In many countries, it is grown in home gardens, farms, and as a seasonal crop due to its rapid growth and high nutritional yield.[5]

2.4 Traditional Uses in Food and Medicine

The leaves of *A. tricolor* are commonly consumed as a vegetable in soups, salads, and stir-fried dishes. Traditional medicinal uses include:

- **Anti-inflammatory:** Used in folk remedies for swelling and pain relief.
- **Hepatoprotective:** Employed in decoctions to support liver health.
- **Antioxidant and general tonic:** Consumed to boost immunity and overall well-being.
- **Other uses:** Management of gastrointestinal disorders, anemia, and skin ailments.

2.5 Nutritional Significance

Amaranthus tricolor is nutritionally rich and contributes essential nutrients to the diet:

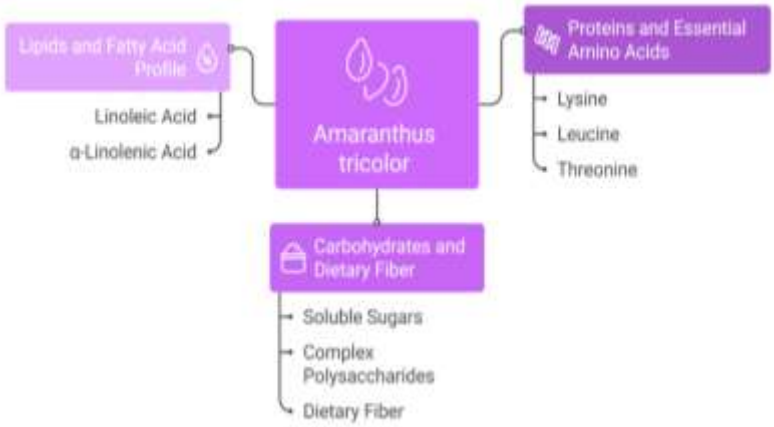
- **Vitamins:** High in vitamin A, C, and folate
- **Minerals:** Iron, calcium, magnesium, and zinc
- **Proteins:** Contains essential amino acids
- **Dietary fiber:** Supports gastrointestinal health
- **Phytochemicals:** Flavonoids, phenolic acids, and betalains with potential neuroprotective properties

These nutritional and phytochemical attributes make *A. tricolor* a promising candidate for neuroprotective and therapeutic applications, supporting its evaluation in experimental epilepsy models.[6]

3. Phytochemical Composition of *Amaranthus tricolor*

The therapeutic and neuroprotective potential of *Amaranthus tricolor* is largely attributed to its rich phytochemical profile. Its metabolites are broadly categorized into primary and secondary metabolites, both contributing to nutritional and pharmacological effects.[7]

3.1 Primary Metabolites



Proteins and Essential Amino Acids: *Amaranthus tricolor* leaves contain a significant amount of proteins (approximately 2–4 g/100 g fresh weight), including essential amino acids such as lysine, leucine, and threonine, which are vital for neuronal function and repair.

Carbohydrates and Dietary Fiber: The plant is a source of carbohydrates, primarily in the form of soluble sugars and complex polysaccharides, along with dietary fiber that supports metabolic health and gut–brain axis modulation.

Lipids and Fatty Acid Profile: Although low in total fat, the lipids present contain essential fatty acids, including linoleic and α-linolenic acids, which are important for neuronal membrane integrity and cognitive function.[9]

3.2 Secondary Metabolites

Flavonoids: Key flavonoids include quercetin, kaempferol, and rutin. These compounds exhibit potent antioxidant, anti-inflammatory, and neuroprotective activities, which may counteract oxidative stress and excitotoxicity in epilepsy.

Phenolic Acids: Gallic acid, ferulic acid, and caffeic acid are present and contribute to radical scavenging activity, modulation of neuroinflammation, and protection against neuronal apoptosis.

Betalains: Pigments such as amaranthin and betacyanins provide antioxidant effects and may regulate mitochondrial function and cellular redox balance in neurons.

Alkaloids and Saponins: These secondary metabolites possess neuroprotective, anti-inflammatory, and membrane-stabilizing properties, supporting neuronal health.[10]

Vitamins and Minerals with Neurorelevance:

- **Magnesium (Mg):** Involved in NMDA receptor regulation and seizure suppression
- **Zinc (Zn):** Modulates neurotransmission and antioxidant defense
- **Iron (Fe):** Essential for neuronal metabolism but requires balance to prevent oxidative stress
- **Folate (Vitamin B9):** Supports neuronal development and DNA methylation

Table 1. Key Phytochemicals in *Amaranthus tricolor* and Their Neuroprotective Relevance

Phytochemical Class	Major Compounds	Neuroprotective Relevance
Flavonoids	Quercetin, Kaempferol, Rutin	Antioxidant, anti-inflammatory, neuroprotective, modulates excitotoxicity
Phenolic acids	Gallic acid, Ferulic acid, Caffeic acid	Radical scavenging, neuroinflammation inhibition, neuronal apoptosis prevention
Betalains	Amaranthin, Betacyanins	Antioxidant, mitochondrial protection, redox balance regulation
Alkaloids	Various minor alkaloids	Neuroprotection, anti-inflammatory, membrane stabilization
Saponins	Steroidal and triterpenoid saponins	Neuroprotective, anti-inflammatory
Vitamins	Folate, Vitamin C, Vitamin A	Cognitive support, antioxidant activity, DNA repair
Minerals	Mg, Zn, Fe	Neurotransmission modulation, seizure suppression, antioxidant defense

4. Pharmacological Activities Relevant to Neuroprotection

The neuroprotective potential of *Amaranthus tricolor* is closely associated with its antioxidant, anti-inflammatory, and neuromodulatory activities. These properties may contribute to seizure suppression and protection against epilepsy-induced neuronal damage.

4.1 Antioxidant Activity

Amaranthus tricolor exhibits strong free radical scavenging activity, primarily due to flavonoids, phenolic acids, and betalains. These compounds neutralize reactive oxygen species (ROS), preventing lipid peroxidation and oxidative damage to neuronal membranes. Additionally, extracts of *A. tricolor* can enhance endogenous antioxidant defense systems by upregulating enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). This dual mechanism of direct scavenging and enzyme modulation is particularly relevant to seizure-induced oxidative stress, which contributes to neuronal loss and epileptogenesis.[11]

4.2 Anti-Inflammatory Effects

Neuroinflammation is a key contributor to epilepsy, mediated by microglial activation and release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Bioactive constituents of *A. tricolor* can inhibit these inflammatory mediators and suppress microglial activation. By attenuating neuroinflammation, the plant may reduce excitotoxic neuronal injury and modulate seizure susceptibility.

4.3 Neuroprotective and Cognitive-Enhancing Effects

Several studies suggest that *A. tricolor* protects neurons against degeneration through its antioxidant and anti-inflammatory actions. Flavonoids and phenolic compounds may prevent apoptosis, enhance synaptic plasticity, and maintain neuronal integrity. Moreover, the plant's bioactive molecules may improve cognitive functions by modulating neurotrophic factors and supporting neuronal signaling pathways, which are often impaired in chronic epilepsy.

4.4 Modulation of Neurotransmitter Systems

Neuronal hyperexcitability in epilepsy is largely associated with an imbalance between excitatory

glutamatergic and inhibitory GABAergic neurotransmission. Compounds in *A. tricolor* may help restore this balance by enhancing GABAergic activity and regulating glutamate release. Additionally, ion channel stabilization by these phytochemicals could contribute to membrane potential regulation, reducing seizure initiation and propagation.[12]

Table 2. Summary of Neuroprotective Mechanisms of *Amaranthus tricolor*

Mechanism	Active Constituents	Neuroprotective Effect
Antioxidant	Flavonoids, Phenolic acids, Betalains	ROS scavenging, lipid peroxidation inhibition, upregulation of SOD, CAT, GPx
Anti-inflammatory	Flavonoids, Alkaloids, Saponins	Inhibition of TNF-α, IL-1β, IL-6; suppression of microglial activation
Neuroprotection & Cognitive Enhancement	Flavonoids, Phenolic acids	Prevention of neuronal apoptosis, enhanced synaptic plasticity, cognitive improvement
Neurotransmitter Modulation	Flavonoids, Alkaloids, Minerals (Mg, Zn)	GABAergic activation, glutamate regulation, ion channel stabilization

5. Mechanistic Basis for Antiepileptic Potential

The antiepileptic potential of *Amaranthus tricolor* can be mechanistically explained by its ability to target multiple pathways implicated in seizure initiation and neuronal damage. Its phytochemicals exert complementary effects that collectively reduce seizure susceptibility and protect neural tissue.

5.1 Oxidative Stress Suppression

Seizures induce excessive generation of reactive oxygen species (ROS), leading to lipid peroxidation, DNA damage, and neuronal apoptosis. Bioactive compounds in *A. tricolor*, such as flavonoids, phenolic acids, and betalains, directly scavenge ROS and enhance endogenous antioxidant defenses (e.g., SOD, CAT, GPx). This dual antioxidant action mitigates oxidative damage in neurons, a major contributor to epileptogenesis.

5.2 Attenuation of Neuroinflammation

Chronic neuroinflammation contributes to seizure progression by activating microglia and promoting pro-inflammatory cytokine release (e.g., TNF-α, IL-1β, IL-6). Phytochemicals in *A. tricolor* can inhibit these mediators and reduce microglial activation, thereby limiting inflammatory-induced neuronal hyperexcitability.[13]

5.3 Anti-Excitotoxic Mechanisms

Excessive glutamate release and impaired GABAergic inhibition lead to excitotoxicity, which triggers neuronal injury during seizures. *A. tricolor* compounds may restore the balance between excitatory and inhibitory neurotransmission, enhance GABAergic activity, and regulate glutamate signaling, reducing excitotoxic neuronal damage.

5.4 Mitochondrial Protection

Mitochondrial dysfunction contributes to seizure-induced neuronal damage through impaired ATP production and increased ROS generation. Betalains and flavonoids in *A. tricolor* may stabilize mitochondrial membranes, preserve mitochondrial function, and prevent apoptosis, thereby maintaining neuronal energy homeostasis.

5.5 Synaptic Stabilization

Seizure activity disrupts synaptic function, affecting neurotransmitter release, receptor

sensitivity, and ion channel regulation. Phytochemicals in *A. tricolor* may stabilize synaptic structures, regulate ion channel activity, and enhance neuroplasticity, supporting both seizure control and cognitive function.[14]

Table 3. Mechanistic Pathways Targeted by *Amaranthus tricolor* in Epilepsy

Mechanism	Key Phytochemicals	Potential Effect on Epilepsy
Oxidative Stress Suppression	Flavonoids, Phenolic acids, Betalains	Reduces ROS, prevents lipid peroxidation, protects neurons
Neuroinflammation Attenuation	Flavonoids, Alkaloids, Saponins	Suppresses microglial activation, decreases pro-inflammatory cytokines
Anti-Excitotoxicity	Flavonoids, Minerals (Mg, Zn)	Modulates glutamate and GABA balance, prevents excitotoxic damage
Mitochondrial Protection	Betalains, Flavonoids	Maintains ATP production, prevents apoptosis, reduces ROS generation
Synaptic Stabilization	Flavonoids, Phenolic acids	Enhances neuroplasticity, stabilizes ion channels, supports neurotransmission

6. Evidence from Preclinical Studies

Preclinical studies provide essential insights into the neuroprotective and potential antiepileptic effects of *Amaranthus tricolor* and related species. Although direct studies in epilepsy models are limited, evidence from in vitro and in vivo research supports its therapeutic relevance for central nervous system (CNS) disorders.

6.1 In Vitro Neuroprotective Studies

In vitro studies demonstrate that extracts of *A. tricolor* exhibit potent antioxidant activity, scavenging free radicals and reducing oxidative stress in neuronal cell lines. Flavonoids and phenolic acids in the extracts have been shown to protect neurons from hydrogen peroxide-induced cytotoxicity and excitotoxicity, supporting their potential role in mitigating seizure-induced oxidative damage. Additionally, anti-inflammatory effects were observed in microglial cultures, where *A. tricolor* constituents reduced the production of pro-inflammatory cytokines such as TNF-α and IL-6.[16]

6.2 In Vivo Studies of *Amaranthus* Species Relevant to CNS Disorders

Animal studies with *Amaranthus* species indicate neuroprotective and cognitive-enhancing effects:

- **Neuroprotection:** Rodent models of oxidative stress and neurodegeneration showed improved neuronal survival after administration of *A. tricolor* leaf extracts.
- **Antioxidant Activity:** Treated animals exhibited increased levels of endogenous antioxidant enzymes (SOD, CAT, GPx) and reduced markers of lipid peroxidation in brain tissue.
- **Anti-inflammatory Effects:** Extracts decreased microglial activation and pro-inflammatory cytokines in CNS tissues.
- **Cognitive Function:** Behavioral tests, such as the Morris water maze and passive avoidance tests, suggested enhanced learning and memory in rodents treated with *Amaranthus* extracts.

Although studies directly evaluating seizures are scarce, these findings suggest a mechanistic basis for antiepileptic activity via antioxidant, anti-inflammatory, and neuroprotective pathways.

6.3 Comparative Analysis with Other Plant-Based Anticonvulsants

Several medicinal plants, including *Bacopa monnieri*, *Withania somnifera*, and *Ginkgo biloba*, have demonstrated anticonvulsant effects in preclinical models via similar mechanisms:

- Antioxidant activity reduces seizure-induced ROS
- Anti-inflammatory effects suppress neuroinflammation
- Modulation of GABAergic and glutamatergic systems prevents excitotoxicity

The phytochemical profile of *A. tricolor*—rich in flavonoids, phenolic acids, betalains, and neurorelevant minerals—shares mechanistic similarities with these established plant-based anticonvulsants. This comparative perspective strengthens the rationale for evaluating *A. tricolor* in experimental epilepsy models.

Table 4. Summary of Preclinical Evidence Supporting Neuroprotective Effects of *Amaranthus tricolor* and Related Species

Study Type	Model / Species	Key Findings	Mechanism
In vitro	Neuronal cell lines	Protection against H_2O_2-induced cytotoxicity	Antioxidant, anti-inflammatory
In vivo	Rodent oxidative stress model	Increased SOD, CAT, GPx; reduced lipid peroxidation	Oxidative stress suppression
In vivo	Behavioral/ cognitive tests	Improved memory and learning	Neuroprotection, synaptic stabilization
Comparative plants	*Bacopa*, *Withania*, *Ginkgo*	Anticonvulsant effects in PTZ/MES models	Antioxidant, anti-inflammatory, neurotransmitter modulation

7. Relevance of *Amaranthus tricolor* Phytochemicals in Epilepsy Models

The bioactive compounds present in *Amaranthus tricolor* provide a strong mechanistic rationale for evaluation in standard experimental epilepsy models. Although direct studies of *A. tricolor* in seizure models are limited, its phytochemicals—flavonoids, phenolic acids, betalains, vitamins, and neurorelevant minerals—have demonstrated anticonvulsant and neuroprotective effects in related models.

7.1 Pentylenetetrazole (PTZ)-Induced Seizures

PTZ is widely used to induce generalized tonic-clonic and myoclonic seizures in rodents by antagonizing GABA_A receptors, leading to neuronal hyperexcitability. Flavonoids such as quercetin and kaempferol, present in *A. tricolor*, have shown protective effects in PTZ-induced models by enhancing GABAergic neurotransmission and reducing oxidative stress. Phenolic acids and betalains may further contribute to seizure suppression via antioxidant and anti-inflammatory mechanisms.[17]

7.2 Maximal Electroshock Seizure (MES) Model

The MES model is used to mimic generalized tonic-clonic seizures and screen for anticonvulsant drugs that inhibit seizure propagation. Compounds capable of stabilizing neuronal membranes and modulating ion channels are effective in this model. Minerals such as magnesium and zinc in *A. tricolor*, along with flavonoids, may contribute to ion channel regulation and membrane stabilization, potentially reducing seizure severity in MES-induced convulsions.

7.3 Kindling Models

Kindling models replicate the progressive development of epilepsy following repeated subthreshold stimulation. Neuroinflammation, oxidative stress, and excitotoxicity are critical in kindling-induced epileptogenesis. The combined antioxidant, anti-inflammatory, and neuroprotective activities of *A. tricolor* phytochemicals make it a promising candidate for modulating epileptogenesis in these models.

7.4 Comparison of Known Phytochemicals Active in Epilepsy Models

Phytochemical	Presence in *A. tricolor*	Reported Activity in Epilepsy Models	Mechanistic Insight
Quercetin	High	PTZ, MES	Antioxidant, GABAergic modulation, anti-inflammatory
Kaempferol	Moderate	PTZ, kainic acid	Neuroprotection, excitotoxicity inhibition
Rutin	Moderate	PTZ	ROS scavenging, anti-apoptotic
Gallic acid	High	PTZ, kainic acid	Reduces oxidative stress and neuronal apoptosis
Betalains	High	Limited data	Mitochondrial protection, antioxidant
Magnesium & Zinc	High	MES, PTZ	Ion channel regulation, seizure threshold modulation

These mechanistic correlations highlight the potential of *A. tricolor* phytochemicals to exert anticonvulsant effects across multiple experimental epilepsy models, justifying systematic preclinical evaluation.

8. Safety Profile and Toxicological Considerations

A comprehensive understanding of the safety and toxicological profile of *Amaranthus tricolor* is crucial before considering its evaluation in epilepsy models. Available evidence suggests that the plant is generally safe, but careful consideration of dose, extract type, and potential interactions is essential.[18]

8.1 Acute and Sub-Chronic Toxicity Studies

Acute toxicity studies in rodents indicate that *A. tricolor* leaf extracts have a high safety margin, with no mortality or significant behavioral changes observed at doses up to 2000 mg/kg body weight. Sub-chronic studies (28–90 days) report no major histopathological alterations in vital organs such as the liver, kidney, or brain. Hematological and biochemical parameters generally remain within normal ranges, suggesting low systemic toxicity.

8.2 Dietary Safety and Traditional Consumption

Amaranthus tricolor has a long history of dietary consumption in many Asian and African countries. Its use as a leafy vegetable provides vitamins, minerals, and antioxidants with minimal risk. Traditional culinary preparations, such as boiling, steaming, or stir-frying, may reduce potential antinutrients such as oxalates, enhancing its safety for regular intake.[19]

8.3 Potential Herb–Drug Interactions

Although direct interaction studies are limited, the antioxidant and enzyme-modulating properties of *A. tricolor* phytochemicals could theoretically influence the pharmacokinetics of conventional antiepileptic drugs (AEDs). For instance, flavonoids may inhibit cytochrome P450 enzymes or modulate drug transporters, affecting AED metabolism. Therefore, careful preclinical

assessment is warranted when considering combination therapy.[20]

8.4 Limitations and Safety Gaps

- Lack of systematic toxicity studies specifically targeting CNS or seizure models.
- Limited data on chronic or long-term consumption at high doses.
- Insufficient studies on herb–drug interactions with common AEDs.
- Variability in phytochemical composition due to geographical, seasonal, and cultivation factors, which may influence safety and efficacy.

Despite these gaps, the overall safety profile and historical dietary use of *A. tricolor* provide a strong foundation for its evaluation in preclinical epilepsy models, provided appropriate dose optimization and monitoring are applied.[21]

9. Future Research Directions

Although preclinical evidence suggests significant neuroprotective potential of *Amaranthus tricolor*, systematic evaluation in epilepsy models is currently lacking. Future research should focus on:

- **Systematic Anticonvulsant Evaluation:** Conducting studies in established seizure models such as PTZ, MES, and kindling to directly assess anticonvulsant efficacy.
- **Standardization of Extracts:** Developing standardized extracts with defined phytochemical profiles to ensure reproducibility and accurate dose-response relationships.
- **Dose-Response and Mechanism-Based Studies:** Determining optimal doses for efficacy and safety, and elucidating molecular mechanisms underlying anticonvulsant effects.
- **Translational Potential and Clinical Relevance:** Evaluating pharmacokinetics, bioavailability, and potential interactions with conventional antiepileptic drugs to support future clinical applications.

10. Limitations of Current Evidence

- **Lack of Direct Epilepsy-Focused Studies:** Most existing studies focus on antioxidant, anti-inflammatory, or cognitive effects rather than direct anticonvulsant evaluation.
- **Variability in Phytochemical Composition:** Differences in cultivar, cultivation conditions, and extraction methods can affect the bioactive content and biological activity.
- **Need for Robust Experimental Designs:** Standardized, well-controlled in vitro and in vivo studies are required to strengthen the evidence base.

CONCLUSION

Amaranthus tricolor is a nutrient-rich leafy vegetable with a diverse phytochemical profile, including flavonoids, phenolic acids, betalains, vitamins, and neurorelevant minerals. Preclinical evidence highlights its antioxidant, anti-inflammatory, and neuroprotective activities, which collectively provide a mechanistic rationale for anticonvulsant potential. While direct studies in epilepsy models are limited, the current findings support systematic preclinical evaluation. With appropriate standardization, dose optimization, and mechanistic studies, *A. tricolor* holds promise as a functional neurotherapeutic agent for seizure management and neuronal protection, bridging traditional dietary use with modern pharmacological research.

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