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REVIEW ARTICLE

A Review on Phytochemical Diversity and Therapeutic Applications of *Annona muricata* L

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Abstract: *Annona muricata* L., a prominent member of the Annonaceae family, possesses a diverse repository of bioactive secondary metabolites with documented therapeutic utility across tropical and subtropical regions. Historical applications across various cultures involve the utilization of leaves, bark, roots, and fruit to address a wide spectrum of pathological conditions including parasitic infections, inflammatory disorders, and metabolic diseases. Quantitative analysis of scientific literature spanning four decades reveals a predominant research focus on the plant's antineoplastic properties, followed by significant investigations into its gastroprotective, hypoglycemic, and antimicrobial capabilities. The physiological efficacy of *A. muricata* originates primarily from Annonaceous acetogenins unique polyethers characterized by tetrahydrofuran rings and gamma-lactone moieties which exhibit potent cytotoxic effects via the inhibition of mitochondrial complex I. The presence of isoquinoline alkaloids, flavonol triglycosides, and essential oils contributes to its multi-targeted pharmacological profile. Clinical and preclinical data substantiate the plant's ability to modulate oxidative stress, induce apoptosis in malignant cells, and inhibit key digestive enzymes associated with type 2 diabetes. While the therapeutic potential is vast, toxicological assessments indicate a narrow safety margin regarding long-term consumption of specific acetogenins, which may correlate with neurodegenerative risks. Consequently, *A. muricata* is a significant candidate for pharmaceutical development, provided that standardized extraction methods and rigorous safety protocols are established to harness its medicinal benefits effectively.

Keywords: *Annona muricata*; Acetogenins; Cytotoxicity; Ethno-pharmacology; Bioactive Metabolites.

1. Introduction

The global shift toward natural product-based therapeutics has revitalized interest in plant-derived compounds, many of which provide the structural foundation for modern pharmacotherapy. *Annona muricata*, commonly known as Soursop or Graviola, stands as a premier example of a medicinal plant whose traditional reputation is increasingly validated by rigorous scientific inquiry. Historical records indicate that various morphological parts of the plant, including the seeds, fruit, and foliage, have served as primary treatments for ailments ranging from simple febrile conditions to complex parasitic infestations and chronic inflammatory states [1].

Recent analytical perspectives emphasize the role of specific bioactive fractions, particularly Annonaceous acetogenins, in defining the medicinal identity of the species. These compounds have been the subject of intensive research due to their ability to interfere with cellular bioenergetics, a mechanism that holds profound implications for oncology and metabolic health [2]. As chronic degenerative diseases including diabetes, cardiovascular disorders, and various malignancies continue to escalate globally, the requirement for accessible and effective therapeutic agents becomes more pressing. *A. muricata* emerges in this context as a versatile biological resource [3].

The characterization of its phytochemical profile is indispensable for the transition from traditional usage to standardized clinical application. Identifying the precise concentrations of triterpenoids, flavonoids, and alkaloids allows for the verification of ethnopharmacological claims and the development of quality-controlled preparations [4]. Modern predictive modeling and structure-activity relationship (SAR) studies are being employed to determine how the chemical architecture of these metabolites dictates their physiological interactions and potential toxicity [5]. The current literature suggests that *A. muricata* is not merely a dietary supplement but a complex chemical system with significant allelopathic and therapeutic properties that merit granular investigation [6]

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Figure 1. Leaves and Fruits of *Annona muricata*

2. Taxonomical Classification and Nomenclature

The botanical identity of *Annona muricata* is rooted in the Magnoliales order, representing one of the more primitive lineages of flowering plants.

2.1. Classification

Kingdom: Plantae
Division/Phylum: Tracheophyta (vascular plants)
Class: Magnoliopsida (dicotyledons)
Order: Magnoliales
Family: Annonaceae (custard-apple family)
Genus: Annona L.
Species: *Annona muricata* L.

2.2. Family and Genus Characteristics

As a member of the Annonaceae family, *A. muricata* shares characteristics with approximately 130 genera and over 2,300 species. The genus *Annona* L. is the type genus of the family, characterized by its distinct floral structures and syncarpous fruits. The species name *muricata* refers to the "muricate" or rough, prickly surface of the fruit, which distinguishes it from other closely related custard apples [7].

3. Botanical Description and Geographic Distribution

Understanding the physical characteristics and environmental requirements of *A. muricata* is essential for sustainable cultivation and the standardization of raw medicinal materials [8].

3.1. Morphological Features

A. muricata is characterized as a slender, evergreen tree reaching heights of approximately 5 to 8 meters. The tree typically develops a broad, rounded canopy. Its leaves are notable for their aesthetic and medicinal value, appearing as large, glossy, dark green structures with an obovate to elliptic shape [9].

The flowers are large and typically solitary, appearing on the branches or the trunk (cauliflory). The most distinctive feature is the fruit, a large, heart-shaped or ovoid syncarp that can reach 15 to 20 cm in diameter. The exterior is covered in soft, pliable spines, while the interior consists of a white, fibrous, and juicy pulp embedded with numerous dark brown or black seeds. The taste profile

of the pulp varies significantly across different cultivars, ranging from highly acidic to sweet, which influences its local classification as either a "sweet" or "sour" custard apple [10, 11].

3.2. Global Distribution and Ecology

While indigenous to the tropical regions of the Americas and the Caribbean, the plant has achieved a pantropical distribution. It is now widely naturalized in India, Malaysia, Nigeria, and other humid tropical zones.

The species thrives in low-to-middle elevations, typically up to 1150 meters above sea level, requiring high humidity and warm temperatures. A notable ecological feature of *A. muricata* is its allelopathic potential. The tree produces secondary metabolites that are released into the surrounding soil, which can inhibit the germination and growth of competing plant species, indicating its competitive biological advantage in diverse ecosystems [12-14].

4. Ethnomedicinal and Traditional Applications

The historical utilization of *A. muricata* provides a roadmap for modern pharmacological screening, with different cultures applying specific preparations for targeted health outcomes.

4.1. Regional Therapeutic Practices

In South and North America, as well as West Africa, the plant serves as a foundational element of local pharmacopeias. Preparations range from simple infusions and decoctions to topical poultices and expressed juices.

In the South Pacific and Indonesia, the leaves are traditionally used in medicinal baths to treat various dermatological conditions. Conversely, in Brazil and Mexico, the leaves are more frequently utilized as an infusion to manage respiratory distress, including asthma and bronchitis. In East Africa, particularly Tanzania, the leaves have gained prominence as a traditional treatment for diabetes. Local practitioners often prescribe specific dosages of leaf decoctions to regulate blood glucose levels, emphasizing the need for caution to prevent hypoglycemic episodes [15].

Table 2. Ethnomedicinal Applications of *A. muricata* by Region and Plant Part

Plant Part	Region / Country	Traditional Therapeutic Use
Leaves	Indonesia & South Pacific	Treatment of skin ailments and medicinal baths.
Leaves	Mexico & Brazil	Respiratory conditions (Asthma, Bronchitis, Cough).
Leaves	Tanzania (East Africa)	Management of Type 2 Diabetes; regulation of blood glucose.
Fruit / Juice	South America	Liver and kidney diseases; treatment of urethritis and hematuria.
Bark / Roots	West Africa	Potent antiparasitic, insecticide, and treatment for fever.
Seeds	Tropical Americas	Astringent; crushed seeds used to treat internal and external parasites.

4.2. Systems-Based Traditional Use

The versatility of the plant is reflected in its use for systemic infections and chronic conditions. It has been historically employed as an antimalarial agent, a sedative for nervous disorders, and a cardiac tonic. The fruit juice is frequently consumed to treat liver and kidney ailments, while the bark and roots are favored for their potent antiparasitic and insecticidal properties. This wide-ranging ethnomedicinal use suggests a multi-factorial mechanism of action that warrants detailed chemical analysis [16, 17].

5. Phytochemical Composition

The pharmacological versatility of *A. muricata* is a direct result of its intricate chemical composition, which includes over 212 bioactive compounds identified across different morphological parts. These secondary metabolites are synthesized through complex primary and secondary metabolic pathways, serving as defense mechanisms for the plant while providing therapeutic benefits for human health [18, 19].

5.1. Annonaceous Acetogenins (AGEs)

Annonaceous acetogenins represent the most significant class of bioactive compounds within the *Annona* genus. These are C-32 or C-34 long-chain fatty acid derivatives combined with a 2-alkanol-4-cyclopentyl-1,4-lactone or a gamma-lactone ring.

5.1.1. Structural Diversity

AGEs are characterized by the presence of one, two, or three tetrahydrofuran (THF) or tetrahydropyran (THP) rings. Key examples isolated from *A. muricata* include annomuricins (A–E), annonacin, and various muricins (J, K, L, M, N). Their biological potency is highly dependent on the stereochemistry and the number of hydroxyl groups present along the aliphatic chain [20, 21].

5.1.2. Mechanism of Action

The primary biological activity of acetogenins involves the potent inhibition of the mitochondrial NADH:ubiquinone oxidoreductase (Complex I). By blocking the electron transport chain, AGEs deplete cellular adenosine triphosphate (ATP) levels. While this mechanism is lethal to high-energy-demanding malignant cells, it also defines the boundary for potential neurotoxicity, as prolonged inhibition in healthy neurons can lead to ATP deficiency and proteostatic stress [22, 23].

5.2. Alkaloids

The seeds, roots, and bark of *A. muricata* are particularly rich in isoquinoline alkaloids. Notable compounds include reticuline, coclaurine, coreximine, and xylopine [24].

The alkaloid profile varies significantly between plant parts. The roots primarily contain xylopine and reticuline, which have showed potent cytotoxic effects against leukemia and lung adenocarcinoma cell lines. In contrast, the fruit peel contains higher concentrations of nornuciferin and anonaine. These compounds exhibit high affinity for dopamine receptors and have been investigated for their potential impact on the central nervous system [25, 26].

5.3. Phenolic Compounds and Flavonoids

Flavonoids and other phenolic derivatives are prevalent in the leaves and fruit pulp, contributing significantly to the plant's antioxidant capacity.

Isolated polyphenols such as quercetin, rutin, and kaempferol-3-O-glucoside serve as potent radical scavengers. These compounds modulate the activity of digestive enzymes, specifically inhibiting alpha-amylase and alpha-glucosidase, which has direct implications for postprandial glucose regulation. The high phenolic content in the fruit pericarp correlates with enhanced protection against oxidative lipid peroxidation [27, 28].

Table 3. Major Phytochemical Constituents and Biological Significance

Chemical Class	Representative Compounds	Biological Significance
Acetogenins	Annonacin, Annomuricins (A–E), Muricins (J–N)	Inhibition of mitochondrial Complex I; potent cytotoxicity.
Alkaloids	Xylopine, Reticuline, Coreximine, Coclaurine	Cytotoxic activity against leukemia and lung cancer cells.
Flavonoids	Quercetin, Rutin, Kaempferol-3-O-glucoside	Antioxidant; inhibition of alpha-glucosidase and ACE enzymes.
Phenolic Acids	Chlorogenic acid, Gallic acid	Free radical scavenging; gastroprotective effects.
Essential Oils	Sesquiterpenes (beta-caryophyllene)	Anti-inflammatory and antimicrobial properties.

6. Pharmacological Activities

Research spanning four decades has validated the efficacy of *A. muricata* extracts in modulating various pathological pathways.

6.1. Antineoplastic and Cytotoxic Potential

Approximately 25% of current research into *A. muricata* focuses on its role in oncology. The plant extracts show selective toxicity, targeting malignant cells while sparing healthy counterparts in many *in vitro* models [29, 30].

Extracts from the leaves and fruit induce apoptosis in human leukemia (HL-60) and colorectal cancer cells. This is achieved through the generation of reactive oxygen species (ROS), the reduction of mitochondrial membrane potential (MMP), and the subsequent release of Cytochrome C. These events trigger the caspase cascade (Caspase-3, 7, and 9). Additionally, the compounds arrest the cell cycle at the G0/G1 phase, effectively halting the proliferation of malignant populations [31, 32, 33].

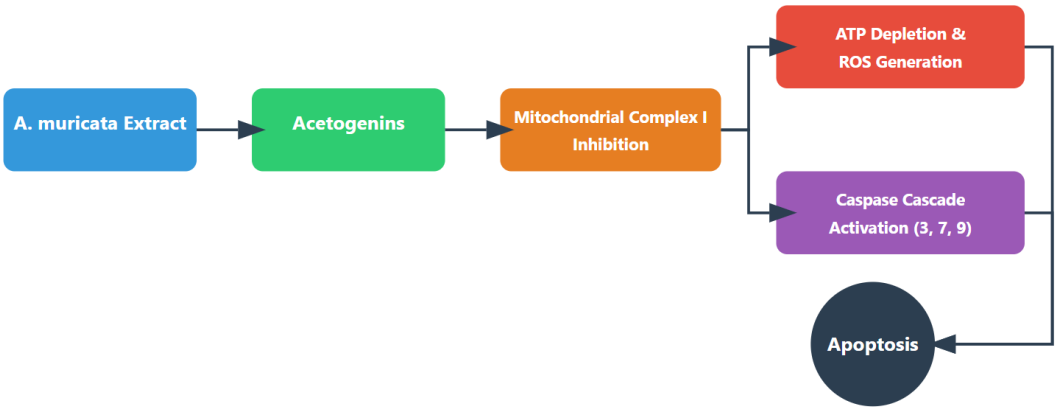

Figure 2. Molecular Mechanism of Antineoplastic Action

6.2. Gastroprotective and Anti-ulcerogenic Properties

Traditional use of soursop for digestive distress is supported by findings that emphasize its ability to reinforce the gastric mucosal barrier.

The hydroalcoholic extract of the leaves significantly reduces the formation of gastric lesions. This gastroprotective effect is mediated by the upregulation of prostaglandins (PGE2) and the expression of Heat Shock Protein 70 (Hsp70). *A. muricata* modulates inflammatory biomarkers by suppressing pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β), while simultaneously increasing levels of endogenous antioxidants like Superoxide Dismutase (SOD) and Glutathione (GSH) [34, 35].

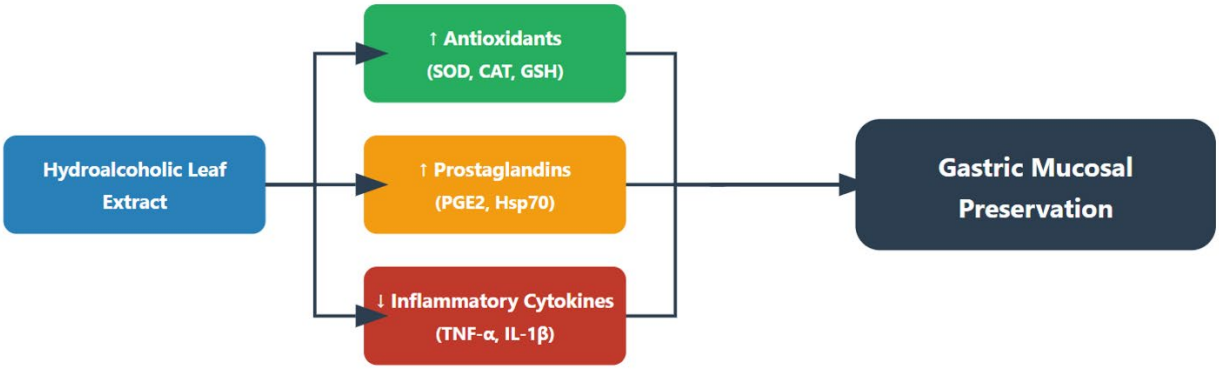

Figure 3. Gastroprotective and Anti-ulcerogenic Properties of A. muricata

6.3. Hypoglycemic and Antidiabetic Effects

The antidiabetic potential of *A. muricata* is largely attributed to its ability to preserve pancreatic integrity and modulate carbohydrate metabolism.

Flavonoids within the fruit and leaves act as natural inhibitors of alpha-glucosidase and alpha-amylase, thereby slowing the rate of glucose absorption into the bloodstream. In animal models of type 1 diabetes, seed oil and leaf extracts have shown the capacity to protect pancreatic beta cells and reduce oxidative stress in hepatocytes, leading to more stable serum lipid profiles and glucose levels [36, 37].

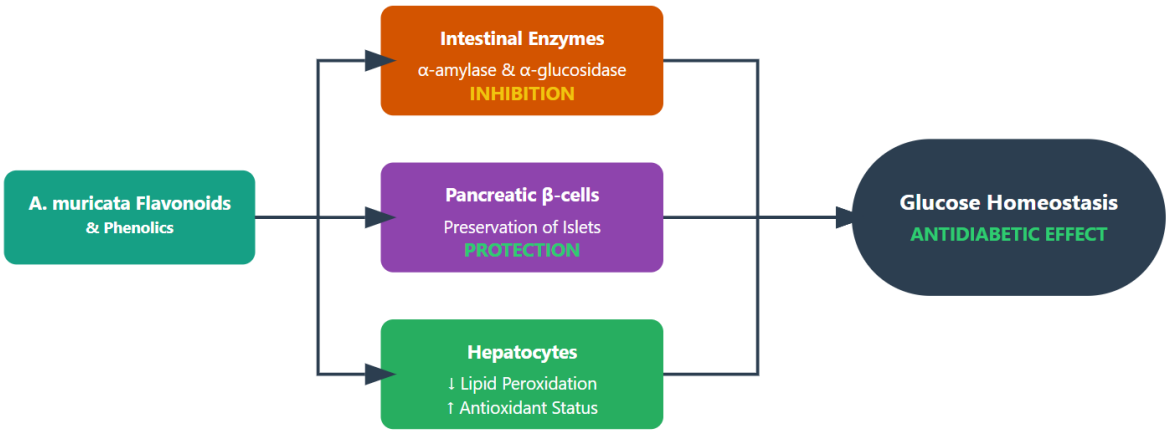

Figure 4. Antidiabetic effects of *A.muricata*

Table 4. Reported Pharmacological Activities of *A. muricata*

Pharmacological Activity	Model / Study Type	Molecular Mechanism	Effects
Anticancer	HL-60, Colorectal (*In vitro*)	ROS generation; Caspase-3/7/9 activation; G0/G1 arrest.	Selective apoptosis of malignant cells.
Anti-ulcer	Ethanol-induced ulcers (*In vivo*)	Upregulation of PGE2 and Hsp70; Suppression of TNF-α.	Significant reduction in gastric lesions.
Antidiabetic	Streptozotocin rats (*In vivo*)	Alpha-glucosidase inhibition; protection of Beta cells.	Stabilization of blood glucose and lipid profile.
Antihypertensive	Normotensive rats (*In vivo*)	Calcium channel blockade; ACE inhibition.	Dose-dependent reduction in blood pressure.
Antimicrobial	S. aureus, E. coli (*In vitro*)	Bacterial membrane disruption.	Broad-spectrum efficacy; synergistic with antibiotics.

6.4. Antimicrobial and Antiviral Efficacy

A. muricata exhibits broad-spectrum activity against a diverse range of pathogens, including multidrug-resistant bacterial strains.

Compounds such as annonaine and asimilobine are thought to disrupt bacterial cell membranes, showing efficacy against Gram-positive (S. aureus) and Gram-negative (E. coli) bacteria. In virology, extracts have shown the ability to inhibit the replication of Herpes Simplex Virus and HIV-1. Recent computational modeling suggests that specific acetogenins, notably cis-annonacin, may inhibit the SARS-CoV-2 spike protein by binding to critical protease sites, although clinical validation is required [24].

6.5. Cardiovascular and Antihypertensive Properties

The cardiovascular benefits of *A. muricata* involve both direct vasodilation and the inhibition of regulatory enzymes.

Leaf extracts produce a hypotensive effect by blocking calcium channels, which leads to reduced peripheral resistance and lowered blood pressure. Additionally, fruit extracts inhibit the angiotensin-converting enzyme (ACE), a key regulator in the renin-

angiotensin-aldosterone system. Some studies suggest that combining *A. muricata* with other tropical extracts like *Persea americana* (avocado) may result in synergistic antihypertensive effects [21, 28, 29]

6.6. Antidiarrheal and Gastrointestinal Regulatory Effects

Beyond its anti-ulcerogenic properties, *A. muricata* serves as a traditional intervention for acute diarrheal diseases. The bark and fruit extracts have been scientifically evaluated for their ability to modulate intestinal motility.

Experimental models indicate that the methanol-soluble fraction of the fruit pulp reduces the frequency of loose stools and slows intestinal transit time at concentrations of 400 mg/kg. These effects are likely mediated by the plant's bioactive metabolites, which inhibit excess fluid secretion and reduce the hypermotility of the smooth muscles in the gastrointestinal tract [15, 16, 17].

6.7. Antiprotozoal and Antiparasitic Efficacy

The necessity for novel antiprotozoal agents has led to the investigation of *A. muricata* against various widespread parasitic infections, including malaria and leishmaniasis.

Ethanolic and ethyl acetate fractions of the leaves have showed significant inhibitory activity against *Toxoplasma gondii*, *Trypanosoma cruzi*, and various *Leishmania* species. Specifically, the extract exhibits an IC_{50} of approximately 46.1 μg/mL against *Plasmodium falciparum*, suggesting that it interferes with the metabolic pathways of the parasite during its erythrocytic stage [30, 31].

6.8. Wound Healing and Tissue Regeneration

The ability of *A. muricata* to accelerate tissue repair is linked to its antioxidant and anti-inflammatory profile. Topical application of ethyl acetate leaf extracts in ointment form has been shown to significantly enhance the rate of wound contraction. This process is accompanied by an increase in the expression of Hsp70 and a reduction in malondialdehyde (MDA) levels, indicating a decrease in oxidative damage during the inflammatory phase of healing. The presence of tannins and flavonoids further aids in protein precipitation and the formation of a protective layer over the damaged tissue [32, 33].

7. Toxicology and Safety Profile

While the therapeutic applications of *A. muricata* are extensive, its safety profile must be critically analyzed due to the presence of neurotoxic acetogenins.

7.1. Acute and Sub-chronic Toxicity

General toxicological assessments suggest that aqueous extracts have a relatively wide safety margin for short-term use, with LD_{50} values exceeding 2 g/kg to 5 g/kg in rodents. However, excessive administration (above 1 g/kg) has been associated with physiological imbalances, including unintended hypoglycemia and potential kidney stress [34, 35].

Table 5. Toxicological Profile and Dosage Safety Limits

Extract Type	Animal Model	Dosage / Parameter	Observed Effect / Safety Note
Aqueous (Leaf)	Mice / Rats	LD_{50} > 211 mg/kg – 5 g/kg	Generally safe in acute doses; excessive use causes hypoglycemia.
Ethanolic (Leaf)	Mice	LD_{50} > 2 g/kg	Lower safety margin compared to aqueous; potential for kidney stress.
Annonacin (Isolated)	Neuronal Cultures	High-frequency exposure	Inhibition of mitochondrial energy; potential tau cell dysfunction.
Fruit Pulp	Human Data (Observed)	Daily consumption for 1 year	Correlated with neurodegenerative symptoms (atypical Parkinsonism).

7.2. Neurotoxicity and Mitochondrial Stress

The most significant safety concern involves annonacin, a major acetogenin. As a potent mitochondrial Complex I inhibitor, annonacin can lead to ATP depletion in the striatum. Long-term, high-frequency consumption of *A. muricata* modeled as daily intake for an extended period has been linked to the development of atypical Parkinsonism and tau pathology. These neurodegenerative

effects result from the impairment of mitochondrial energy production and subsequent cellular dysfunction. Therefore, while the plant offers significant medicinal value, prolonged or excessive consumption should be approached with caution to avoid cumulative neurotoxic risks [36, 37, 38].

8. Conclusion

Annona muricata has a documented history of multi-factorial therapeutic efficacy. Scientific analysis identifies that approximately 25% of research efforts are dedicated to its antineoplastic capabilities, with significant secondary focus on gastroprotective (17%), antidiabetic (14%), and antiprotozoal (10%) activities. The presence of Annonaceous acetogenins, which constitute nearly half of its identified bioactive components, underscores its potential as a source for potent cytotoxic agents. When combined with its diverse alkaloid and flavonoid profile, the plant offers a comprehensive pharmacological spectrum that addresses both infectious and chronic degenerative diseases. However, the transition from traditional use to clinical pharmacology requires a balanced understanding of its toxicological limits. The same mechanisms that enable its anticancer properties specifically the inhibition of mitochondrial Complex I pose risks for neurotoxicity upon chronic exposure. Research should prioritize the isolation of therapeutic fractions that minimize neurotoxic potential and the establishment of standardized dosing protocols.

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