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PRECLINICAL PHARMACOLOGICAL INVESTIGATION OF THE ANXIOLYTIC EFFECTS OF *ABELMOSCHUS MANIHOT* AND *ACALYPHA INDICA* IN EXPERIMENTAL ANIMALS: A COMPREHENSIVE REVIEW

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ABSTRACT

Anxiety disorders represent a significant global health burden, characterized by excessive fear, apprehension, and physiological arousal. While conventional pharmacotherapies, such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs), are effective, their utility is often limited by side effects, including sedation, cognitive impairment, and dependency. Consequently, research into herbal alternatives has intensified. This review examines the preclinical pharmacological profiles of two significant medicinal plants: *Abelmoschus manihot* (Malvaceae) and *Acalypha indica* (Euphorbiaceae). Both plants have traditional histories of use in treating central nervous system (CNS) disorders. Recent studies using experimental animal models such as the Elevated Plus Maze (EPM), Light/Dark Box (LDB), and Open Field Test (OFT), suggest that extracts from these plants possess potent anxiolytic properties. This paper synthesizes the phytochemical constituents, predominantly flavonoids and alkaloids, and the hypothesized GABAergic mechanisms through which these botanicals exert their effects, providing a foundation for future clinical evaluation.

KEYWORDS: *Abelmoschus manihot*, *Acalypha indica*, Anxiolytic, GABA, Preclinical Pharmacology, Flavonoids, Medicinal Plants.

INTRODUCTION

Anxiety disorders are among the most prevalent mental health conditions worldwide, affecting approximately 10-15% of the population at any given time. These disorders encompass generalized anxiety disorder (GAD), panic disorder, social phobia, and post-traumatic stress disorder (PTSD). Pathophysiologically, anxiety is linked to dysregulation in neurotransmitter systems, specifically the gamma-aminobutyric acid (GABA), serotonin (5-HT), and norepinephrine pathways, as well as overactivity in the hypothalamic-pituitary-adrenal (HPA) axis.[1]

Currently, the primary pharmacological interventions involve benzodiazepines, which act as positive allosteric modulators of the GABA-A receptor. While effective for acute relief, long-term use is associated with tolerance, withdrawal syndromes, and motor incoordination. SSRIs and buspirone offer alternatives but often require weeks to reach therapeutic efficacy and can cause sexual dysfunction or gastrointestinal distress.[2]

Given these limitations, ethnopharmacological research focuses on secondary metabolites from plants that may offer anxiolytic effects with a more favorable safety profile. *Abelmoschus manihot* (known as Sunset Hibiscus) and *Acalypha indica* (Indian Acalypha) are two such candidates. Traditionally used in Asian and African medicine for conditions ranging from inflammation to nervous exhaustion, these plants have become subjects of rigorous preclinical investigation.[3]

Among Southeast Asian and Indian medicinal flora, *Abelmoschus manihot* (Sunset Hibiscus) and *Acalypha indica* (Indian Nettle) have emerged as significant subjects of investigation. *A. manihot* is widely utilized in traditional Chinese medicine for its anti-inflammatory and restorative properties, while *A. indica* is a staple in Ayurvedic systems for treating various ailments, including respiratory and neuro-inflammatory conditions.[4] This review provides a detailed examination of the evidence supporting their anxiolytic properties in animal models.

Botanical and Phytochemical Profiles

A. Abelmoschus manihot (L.) Medik

Abelmoschus manihot, belonging to the Malvaceae family, is widely distributed in Eastern Asia and the Pacific Islands. It is particularly noted in Traditional Chinese Medicine (TCM) as "Huang Shu Kui."

The therapeutic potential of *A. manihot* is largely attributed to its rich flavonoid content, particularly in the flowers. Phytochemical screening has identified:[5]

- **Flavonoids:** Myricetin, quercetin, rutin, and hyperoside.
- **Specific Glycosides:** Hibifolin and myricetin-3-O-beta-D-glucopyranoside.[6]
- **Polysaccharides and Sterols:** Including beta-sitosterol.

Flavonoids are known to cross the blood-brain barrier (BBB) and exhibit a high affinity for the benzodiazepine binding site of the GABA-A receptor complex, making them prime candidates for anxiolytic activity.



Fig. 1: Abelmoschus manihot.

B. Acalypha indica L.

Acalypha indica, a common annual herb from the Euphorbiaceae family, is found throughout the tropical regions of India and Southeast Asia. In the Indian Siddha and Ayurvedic systems, it is referred to as "Kuppaimeni."

The phytochemical landscape of *A. indica* includes:[7]

- **Alkaloids:** Acalyphine and acalyphamide.
- **Cyanogenic glycosides:** Acalyphin.
- **Phenolics and Flavonoids:** Kaempferol and various tannins.

- **Saponins and Steroids**

While traditionally used for its emetic and expectorant properties, the presence of specific alkaloids and flavonoids suggests a significant impact on CNS activity, specifically through the modulation of monoamine levels and GABAergic signaling.[8]



Fig. 2: Acalypha indica.

Preclinical Models for Assessing Anxiolytic Activity

To evaluate the efficacy of *A. manihot* and *A. indica*, researchers utilize several validated rodent behavioral assays. These models rely on the conflict between the innate curiosity of rodents to explore new environments and their natural aversion to open, brightly lit spaces.

- **Elevated Plus Maze (EPM):** The gold standard for anxiolytic screening. An increase in the time spent and the number of entries into the "open arms" (relative to the closed arms) indicates reduced anxiety.
- **Light/Dark Box (LDB):** This test measures the transition between a dark compartment and a brightly lit one. Anxiolytic agents increase the time spent in the light zone and the frequency of transitions.[9]
- **Open Field Test (OFT):** Used to assess both anxiety and locomotor activity. Anxiolytic drugs increase the time spent in the "center zone" of the arena without significantly depressing overall movement (which would suggest sedation).
- **Vogel Conflict Test:** A punished-drinking paradigm where anxiolytics increase the number of licks despite the presence of a mild electrical shock.[10]

Pharmacological Investigation of *Abelmoschus manihot*

A. Experimental Evidence

Several studies have investigated the ethanol and aqueous extracts of *A. manihot* flowers. In a pivotal study using Swiss albino mice, the administration of a flavonoid-rich fraction of *A. manihot* (50, 100, and 200 mg/kg) demonstrated a dose-dependent increase in open-arm entries in the EPM model.[11]

Researchers observed that the 200 mg/kg dose was comparable in efficacy to Diazepam (2 mg/kg, i.p.), the standard reference drug. Furthermore, in the LDB test, treated mice showed a significant increase in the duration of stay in the light compartment and a decrease in the number of "rearing" incidents, which are indicative of exploratory behavior without fear.

B. Mechanism of Action

The anxiolytic effect of *A. manihot* is primarily hypothesized to be mediated through the GABAergic system. GABA is the major inhibitory neurotransmitter in the brain. When GABA binds to the GABA-A receptor, it opens a chloride channel, leading to hyperpolarization of the neuron and reduced excitability.[12]

The total flavone content of the flower (TFA) has been shown to compete with flumazenil (a GABA-A receptor antagonist). This suggests that the flavonoids in *A. manihot*, specifically myricetin, act as partial agonists or positive allosteric modulators at the benzodiazepine binding site.[13] Unlike full agonists, these plant-derived compounds may cause fewer side effects related to motor impairment and sedation.

C. Neuroprotective and Antioxidant Contributions

Anxiety is often exacerbated by oxidative stress in the hippocampus and amygdala. The high antioxidant capacity of *A. manihot*'s quercetin and rutin components helps neutralize reactive oxygen species (ROS). Recent studies have shown that *A. manihot* extracts reduce lipid peroxidation and increase levels of endogenous antioxidants like Superoxide Dismutase (SOD) and Glutathione (GSH) in the brain tissue of stressed rodents.[14]

Pharmacological Investigation of *Acalypha indica*

A. Experimental Evidence

The CNS-depressant and anxiolytic activities of *Acalypha indica* have been documented using various solvents for extraction. Methanolic and hydro-alcoholic extracts (200–400 mg/kg) have shown the most significant results.

In the EPM model, animals treated with *A. indica* leaf extract spent significantly more time in the open arms compared to the control group. In the Open Field Test, the center-square entries were increased, while the defecation rate (a biomarker for autonomic stress) was significantly reduced.[15]

A unique aspect of *A. indica* is its dual effect. While it reduces anxiety, higher doses have been observed to possess sedative properties, evidenced by a reduction in spontaneous locomotor activity. This suggests it might be particularly useful for anxiety-induced insomnia.[16]

B. Phytochemical Correlation

The anxiolytic effects of *A. indica* are attributed to the synergistic action of its alkaloids and flavonoids. Acalyphine, the plant's signature alkaloid, has been investigated for its affinity for CNS receptors. Furthermore, the presence of kaempferol identifies a pathway for modulating the serotonin system. It is hypothesized that *A. indica* might influence the 5-HT1A receptors, which play a crucial role in the modulation of emotional states.[17]

C. Safety and Locomotor Coordination

One critical finding in the study of *A. indica* is its effect on the "Rotarod" test. Unlike high-dose benzodiazepines which cause mice to fall off the rotating rod due to muscle relaxation, standardized doses of *A. indica* provided anxiolytic relief without significant motor impairment.[18] This "functional selectivity" is a major advantage in drug development.

Comparative Neuropharmacological Mechanisms

The anxiolytic effects of both plants appear to converge on the modulation of the hypothalamic-pituitary-adrenal (HPA) axis. By regulating corticosterone levels, these plants prevent the hyperactivation of the stress response. Furthermore, evidence suggests that *A. manihot* acts predominantly via the GABA-benzodiazepine receptor complex, whereas *A. indica* exhibits a more nuanced effect, potentially involving modulation of 5-HT1A receptors.[19]

Proposed Mechanisms: A Molecular Perspective

To understand how these plants work at a cellular level, we must look at the GABA-A Receptor Complex.

1. **Direct Binding:** Flavonoids like hyperoside (*A. manihot*) bind to the α and γ subunits of the GABA-A receptor. This facilitates the entry of chloride ions into the postsynaptic neuron.
2. **Modulation of GABA Synthesis:** There is evidence suggesting that certain plant extracts increase the activity of Glutamate Decarboxylase (GAD), the enzyme responsible for converting glutamate (excitatory) into GABA (inhibitory).[20]

3. **HPA Axis Regulation:** Anxiety involves a hyperactive HPA axis, resulting in high corticosterone levels in rodents (cortisol in humans). Preliminary data suggests that *A. manihot* reduces the secretion of Corticotropin-Releasing Hormone (CRH) from the hypothalamus, thereby blunting the physiological stress response.[21]

Toxicity and Safety Profile

Preclinical investigation is incomplete without toxicity assessment.

- **Acute Toxicity:** Studies on *A. manihot* have shown a high (exceeding 2000 mg/kg in mice), indicating a wide safety margin.
- **Chronic Toxicity:** Long-term administration of *A. indica* extracts (up to 28 days) showed no significant changes in liver enzymes (ALT, AST) or renal markers (creatinine), suggesting that the plant is well-tolerated at therapeutic doses.[22]
- **Behavioral Toxicity:** Neither plant, at moderate doses, induced the "paradoxical aggression" sometimes seen with synthetic anxiolytics.

Challenges and Future Directions

While the preclinical data is promising, several hurdles remains before these plants can be transitioned into clinical practice:

1. **Standardization:** Plant chemistry varies based on geography, soil quality, and harvest time. Standardizing the extracts for "active markers" (e.g., a specific percentage of Myricetin) is essential for consistent dosing.[23]
2. **Pharmacokinetics:** We need more data on the bioavailability of these compounds. How much of the orally administered flavonoid actually reaches the brain?
3. **Human Clinical Trials:** Most current evidence is limited to Swiss albino mice or Wistar rats. Phase I and Phase II clinical trials are necessary to determine if the anxiolytic effects translate to humans without causing adverse reactions.
4. **Interaction Studies:** Given that many patients with anxiety may already be taking medication, it is vital to study the herb-drug interactions, particularly between these plants and existing antidepressants or anticonvulsants.[24]

CONCLUSION

The preclinical pharmacological investigation of *Abelmoschus manihot* and *Acalypha indica* reveals significant anxiolytic potential. *A. manihot*, through its rich flavonoid content, offers a potent modulation of the GABAergic system with added neuroprotective benefits. Similarly, *Acalypha indica* provides an effective reduction in anxiety-related behaviors, possibly

through a combination of GABAergic and monoaminergic pathways. Both plants exhibit efficacy in validated models like the Elevated Plus Maze and Light/Dark Box, often matching the performance of standard drugs like Diazepam without the concomitant motor deficits. As the global demand for "Green Medicine" grows, these two species represent promising candidates for the development of novel, safer therapeutic agents for the management of anxiety disorders.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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