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Review Article

Multi-Target Therapeutic Potential of *Achyranthes aspera*: Integrating Phytochemistry, Molecular Mechanisms and Translational Pharmacology

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ABSTRACT

Achyranthes aspera is commonly known as "Apamarga", is a plant broadly used in many countries over Asia and Africa. Even though it has a variety of medicinal uses, there have been few pharmacological studies conducted. This review surveys the phytochemical composition, molecular mechanisms, pharmacological effects, toxicity profile and translational aspects related to this plant. Phytochemical investigations have identified bioactive constituents in this plant including triterpenoids, saponins, alkaloids, flavonoids and phenolic compounds. The main molecular pathways such as NF-kB, Nrf2, MAPK and PI3K/Akt as well as apoptotic pathways and inflammatory cytokines have been implicated in mediating its biological actions. Experimental studies have demonstrated anti-inflammatory, antioxidant, antimicrobial, antidiabetic, anticancer, nephroprotective and neuropharmacological activities. Transcriptomic analysis in nephrotoxicity models indicates that *Achyranthes aspera* modulated oxidative stress and autophagy.

Besides its strong pharmacological potential major limitations include lack of standardization, incomplete data on chronic toxicity and the absence of clinical trials.

Phytochemical variability and formulation challenges present significant barriers to clinical development. *Achyranthes aspera* is recognized in traditional medicine as a promising multi-target agent for renal and neurodegenerative diseases. Future directions include standardization, development of advanced formulations and implementation of clinical trials.

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INTRODUCTION

Medicinal plants play a crucial role in drug discovery and therapeutic development throughout history. The WHO (World Health Organization) reports that almost 80% of the world populations are dependent on traditional medicine for primary healthcare that too mainly in developing countries [(1)]. Numerous modern pharmaceutical compounds have been derived from the plant-based compounds either directly or indirectly. This signifies the ethnomedicine as a valuable source for pharmacologically active molecules [(2)].

Among numerous medicinal plants documented in the traditional medicinal systems, *Achyranthes aspera* has particular attention due to its various therapeutic actions. This species is belonging to the Amaranthaceae family and is widely distributed in tropical and subtropical regions of India, Sri Lanka, Southeast Asia and Africa [(3)].

It is commonly known as "Apamarga" in Ayurveda and as "Prickly chaff flower" in English. Traditionally *Achyranthes aspera* has been used to treat a range of problems such as cough, asthma, dysentery, wounds, hemorrhoids, skin infections and inflammatory disorders [(4)]. Phytochemical investigations have shown that *Achyranthes aspera* consist a variety of bioactive compounds, including alkaloids, saponins and phytoecdysteroids [(5)]. Among these constituents, triterpenoids saponins and ecdysteroids are considered as primary contributors to the plant's pharmacological activities. These compounds exhibit multiple biological effects such as antioxidant, antimicrobial and cytoprotective properties[(6)].

Recent pharmacological studies have demonstrated the therapeutic potential of *Achyranthes aspera* in various disease models including nephrotoxicity, cancer, metabolic disorders and neurological conditions[(7)]. It focuses on phytochemical activities, safety profile and translational potential. It identified as a promising candidate for future phytopharmaceutical development.

BOTANICAL PROFILE AND ETHNOMEDICINAL RELEVANCE

It is a medicinal plant from the family Amaranthaceae. It grows as a perennial herb and height is 0.5 to 1m, features four-sided hairy stems, opposite-decussate leaves, long downward-pointing flower spikes, and dry utricle fruits that easily stick to clothing and animal fur. This plant grows in tropical and sub-tropical regions. It is found in wastelands, roadsides and agricultural fields [(8-9)].

Morphological characteristics [(10)]

- The stems of *Achyranthes aspera* is

covered with hairs.

- The leaves are arranged in oppositely in an elliptical shape.
- The flowers are small, greenish and it is organized in spikes.
- The seeds colour is brown.

Ethnomedicinal Applications [11]

- The roots are used to treat cough and snake bites.
- Leaves are used to wound healing and skin infections.
- Seeds are used to gynecological conditions.
- The entire plant is used for anti-asthmatic conditions.

PHYTOCHEMICAL COMPOSITION

It is responsible for pharmacological spectrum. It has more than 50 compounds and it has different parts of plants, roots, leaves and seeds [12-14].

- Pentacyclic triterpenoids
- Triterpenoid saponins
- Alkaloids
- Phytoecdysteroids
- Flavonoids
- Phenolic compounds

The phytochemical diversity of *Achyranthes aspera* supports its potential as a multi-target therapeutic agent.

Pentacyclic Triterpenoid

Achyranthes aspera contains several bioactive pentacyclic triterpenoids, notably oleanolic acid**,** betulinic acid and lupeol. Pentacyclic triterpenoids acts as anti-inflammatory, hepatoprotective and antioxidant

Triterpenoid Saponins

Achyranthes aspera contains biologically active triterpenoids saponins based on aglycones like oleanolic acid and machaerinic acid. It contributes the amphiphilic nature [15].

Saponins are known to:

- Enhance immune responses
- Induce apoptosis in tumor cells
- Display anti-inflammatory effects
- It contributes to antimicrobial and cytotoxic activities [16].
- It has derivatives such as anti-inflammatory, hepatoprotective effects in various models [17].

Alkaloids

The main alkaloid is present in the plant Achyranthine [12].

Alkaloid shows following pharmacological effects:

- Hypotensive activity
- Induction of Smooth muscle relaxation
- Effects on the central nervous system (CNS)

However, the precise mechanism of action remains unclear.

Phytoecdysteroids

The most dominant and widely studied phytoecdysteroids found in *Achyranthes aspera* is 20-hydroxyecdysone**,** also frequently referred to as ecdysterone [18-19].

It has attracted attention due to it's:

- Anabolic properties
- Antioxidant potential

Flavonoids

Achyranthes aspera contains various bioactive flavonoids, prominently including newly discovered flavonoid C-glycosides called achyasperosides A–D alongside known analogs like rutin and 2''-O-rhamnosylvitexin. These compounds contribute significantly to the plant's traditional medicinal properties like antioxidant and anti-inflammatory activity

Phenolic Compounds

Achyranthes aspera contains a rich profile of bioactive phenolic acids like caffeic acid**,** gallic acid**,** syringic acid**,** vanillic acid, chlorogenic acid, ferulic acid**,** isoferulic acid**,** protocatechuic acid, p-hydroxy benzoic acid, salicylic acid, gentisic acid, sinapic acid, p-coumaric acid, quinic acid which deliver strong antioxidant, anti-inflammatory, and antimicrobial effects by neutralizing free radicals and boosting protective cell enzymes[20].

Table1: Biological activities of some phytoconstituents:

Compound	Class	Molecular Target	Biological Activity
Oleanolic acid	Pentacyclic triterpenoid	NF-kB, COX-2, iNOS	Anti-inflammatory, hepatoprotective, antioxidant
Saponin glycosides	Triterpenoid saponins	Membrane cholesterol interaction, immune signaling	Immunomodulatory, antimicrobial, cytotoxic
Achyranthoside	Triterpenoid saponin derivative	Apoptotic signaling (Bax/Bcl-2 modulation)	Anticancer activity
Achyranthine	Alkaloid	Smooth muscle receptors (putative), CNS pathways	Hypotensive, CNS depressant
Quercetin	Flavonoid	Nrf2, NF-κB	Antioxidant, anti-inflammatory, anticancer
Kaempferol	Flavonoid	MAPK pathway	Anti-inflammatory, antiproliferative

Ecdysone derivatives	Phytoecdysteroids	Akt/mTOR signaling (putative)	Metabolic regulation
Ferulic acid	Phenolic acid	ROS scavenging pathways	Antioxidant, anti-inflammatory
Chlorogenic acid	Phenolic compound	Glucose metabolism enzymes	Antidiabetic, antioxidant

Abbreviations: NF-kB (Nuclear Factor kappa-light-chain-enhancer of activated B cells); COX-2 (Cyclooxygenase-2); iNOS (Inducible Nitric Oxide Synthase); Bax (Bcl-2-associated X protein); Bcl-2 (B-cell lymphoma 2); CNS (Central Nervous System); Nrf2 (Nuclear factor erythroid 2-related factor 2); MAPK (Mitogen-Activated Protein Kinase); Akt (Protein Kinase B); mTOR (Mechanistic Target of Rapamycin); ROS (Reactive Oxygen Species).

SYSTEMSPHARMACOLOGYANDMOLECULAR MECHANISMS

Achyranthes aspera does not confirm to the single molecular target. Resulting in effects multiple components and effects. Systems Pharmacology provides a framework for understanding complex biological systems by examining interactions among compounds, molecular targets and disease pathways [21].

Inflammatory Pathway Modulation

Chronic inflammation contributes to the pathogenesis of various diseases, such as:

- Rheumatoid arthritis
- Diabetes
- Kidney diseases
- Neurodegenerative disorders
- Cancer

The NF-kB signalling pathway is considered central to this pathogenic mechanism [22].

Studies have demonstrated that extracts of *Achyranthes aspera* reduce levels of pro-inflammatory mediators, including:

- TNF-α
- IL-1β
- IL-6
- COX-2
- iNOS

Flavonoids inhibit IkB phosphorylation and prevent its nuclear translocation, which attenuates inflammation [23].

Oxidative Stress and Nrf2 Pathway

Oxidative stress impairs cellular function by increasing reactive oxygen species levels.

Studies indicate that *Achyranthes aspera* extracts:

- Enhance superoxide dismutase (SOD) activity
- Elevate catalase levels [24]

In addition, *Achyranthes aspera* extracts

reduce malondialdehyde (MDA), a marker of lipid peroxidation, by activating the Nrf2/ARE pathway [25].

PI3K/Akt and MAPK Signalling Pathways

These signaling pathways play critical roles in regulating cell survival, growth and metabolism. The PI3K/Akt pathway regulates cell survival and proliferation [26]. Ecdysterone and saponins derived from *Achyranthes aspera* modulate these signaling pathways [19]. MAPK pathway regulates stress & inflammatory responses [27].

Apoptotic Regulation

Apoptosis is the programmed cell death. It plays both beneficial and harmful roles in cancer: killing tumor cells and causing excessive cell loss in degenerative diseases respectively. According to the studies, this plant exerts caspase activation and reduces the mitochondrial membrane potential, thereby triggering apoptosis [28].

Autophagy and Nephroprotection

In experimental models of renal injury, including cisplatin-induced nephrotoxicity, administration of A. aspera extract modulates gene expression via autophagy, attenuates oxidative stress and reduces inflammatory signaling pathways. Transcriptomic analyses demonstrate down regulation of TNF-α and NF-kB signaling pathways, as well as up regulation of cellular antioxidant pathways[29-30].

PHARMACOLOGICAL ACTIVITIES

Anti-Inflammatory Activity

Carrageenan-induced paw oedema models show a significant reduction in inflammation after administration of the methanolic extract [9]. Flavonoids inhibit phosphorylation of IkB, which prevents NF-kB nuclear translocation and subsequent cytokine transcription.

Chronic inflammation is a key factor in the pathogenesis of rheumatoid arthritis, atherosclerosis, diabetes and chronic kidney disease (CKD), suggesting broad therapeutic potential.

Antioxidant and Cytoprotective Effects

The extracts demonstrate DPPH radical-scavenging activity and inhibit lipid peroxidation. Activation of Nrf2 increases the expression of endogenous antioxidant enzymes, such as superoxide dismutase and catalase [7].

Nephroprotective Effects

In models of cisplatin-induced nephrotoxicity, A. aspera extract reduced serum creatinine concentrations, suppressed inflammatory cytokine production [8]. Gene expression analysis confirmed modulation of both apoptotic and oxidative stress pathways.

Anticancer Potential

Leaf extracts induced apoptosis in pancreatic cancer [10]. It has limited pre-clinical settings.

Neuropharmacological Effects (CNS)

Ethanolic extracts have anxiolytic activities in rodent models [11]. Involve in GABAergic pathways.

Antimicrobial Activity

It extracts both gram-positive and gram-negative bacteria as well as fungi and used for wound healing [12].

Table 2: Pharmacological studies

Pharmacological Activity	Experimental Model	Extract / Fraction used	Key Findings	Proposed Mechanism
Anti-inflammatory	Carrageenan-induced paw edema (rat)	Ethanolic leaf extract	Significant reduction in paw edema volume	Inhibition of prostaglandin synthesis; NF-kB suppression
Anti-inflammatory (chronic)	Cotton pellet granuloma (rat)	Methanolic whole plant extract	Decreased granuloma weight and inflammatory markers	Reduced fibroblast proliferation; cytokine modulation
Antioxidant & Cytoprotective	DPPH, FRAP, lipid peroxidation assays	Aqueous and ethanolic extracts	Strong free radical scavenging capacity	ROS scavenging; Nrf2 activation
Nephroprotective	Cisplatin-induced nephrotoxicity (rat)	Hydroalcoholic extract	Improved serum creatinine and urea levels	Antioxidant defense upregulation; anti-apoptotic signaling
Anticancer	Human pancreatic cancer cell lines (in vitro)	Leaf extract (methanolic fraction)	Induced apoptosis and reduced cell viability	Bax/Bcl-2 modulation; caspase activation
CNS depressant / Anxiolytic	Elevated plus maze; open field test (mouse)	Methanolic extract	Reduced anxiety-like behavior; mild sedation	GABAergic modulation (putative)
Antimicrobial	Agar well diffusion; MIC assay	Ethanol and aqueous extracts	Activity against Staphylococcus aureus and Escherichia coli	Membrane disruptions by saponins

Abbreviations: NF-kB (Nuclear Factor kappa-light-chain-enhancer of activated B cells); ROS (Reactive Oxygen Species); Nrf2 (Nuclear factor erythroid 2-related factor 2); Bax (Bcl-2-associated X protein); CNS (Central Nervous System); DPPH (2,2-diphenyl-1-picrylhydrazyl); FRAP (Ferric Reducing Antioxidant Power); MIC (Minimum Inhibitory Concentration); GABAergic (Gamma-Aminobutyric Acid-mediated).

TOXICOLOGY & SAFETY

It has been an integral component of medicinal systems such as Charaka Samhita and Sushrutha Samhitha establish its safety profile.

Acute Toxicity [31-32]

Acute toxicity studies high LD_{50} values for both aqueous and ethanolic extracts, it indicates low acute toxicity.

It has following limitations:

- They often utilize crude extracts instead of standardized fractions.
- Assessment of organ-specific toxicity is generally limited to basic histological analysis.

These limitations restrict the ability to draw definitive conclusions regarding safety.

Sub-Chronic Toxicity

It is conducted over 28 to 90 days following parameters:

- Hematological parameters
- Liver enzymes (AST, ALT)
- Renal biomarkers
- Histopathology

Most studies report no organ damage at therapeutic doses [33].

Reproductive and Teratogenic Concerns

- Use during pregnancy should be approached with caution.
- Controlled studies on reproductive toxicity are necessary.

Herbal-Drug Interactions

When it comes to the plant ability to target multiple pathways were really need to pay attention to potential herb-drug interactions. This is especially important because it can affect how cytochrome P450 enzyme functions.

Cytochrome P450

Polyphenols and saponins which originated from medicinal plants have [34-35]:

- Inhibit CYP3A4 activity
- Regulate CYP2C9 function

These actions can influence the kinetics of metabolism of drugs.

Immunomodulatory Concerns

Saponins are known immune adjuvants.Thus:

- Immunocompromised or autoimmune patients require caution.
- Dose-response immunological profiling is necessary.

Table 3: Toxicity Profile study

Experimental Model	Dose Administered	Duration	Major Findings	Safety Assessment
Acute oral toxicity (Wistar rats)	Up to 2000 mg/kg (single dose)	14 days observation	No mortality; no significant behavioral changes; mild transient sedation at high dose	Classified as relatively low acute toxicity (OECD category 5)
Acute oral toxicity (Swiss albino mice)	300-2000 mg/kg	7-14 days	No significant alteration in body weight or food intake	Safe at therapeutic dose range
Sub-chronic toxicity (Wistar rats)	200-800 mg/kg/day	28 days	No significant change in AST, ALT, creatinine; normal organ histology	No major organ toxicity observed
Sub-chronic toxicity (Hydroalcoholic extract)	400 mg/kg/day	90 days	Mild, non-significant hematological variations; normal liver and kidney histology	Considered safe within tested limits
Reproductive toxicity (limited data)	Not standardized	Not clearly defined	Traditional reports suggest uterine stimulation; no controlled animal teratogenicity studiesavailable	Insufficient data; caution advised during pregnancy
Immunotoxicity (saponin fraction)	Variable	In vitro assays	Enhanced macrophage activation	Immunostimulatory potential; safety in autoimmune conditions unclear

Abbreviations: AST (Aspartate Aminotransferase); ALT (Alanine Aminotransferase); OECD (Organisation for Economic Co-operation and Development

FORMULATION AND BIOAVAILABILITY CHALLENGES

The variability of phytochemicals and the challenge of limited oral bioavailability represent significant barriers. Polyphenols are inclined rapid degradation whereas saponins are frequently delay absorption. Below are several potential strategies to address these challenges:

- Nano encapsulation
- Liposomal delivery
- Standardized extracts
- Targeted controlled-release formulations

At present, no standardized pharmaceutical preparation is available.

TRANSLATIONAL GAPS AND FUTURE DIRECTIONS

Although Pharmacodynamic profiles are encouraging the clinical translation is delayed by several factors:

- Insufficient human clinical trials
- Lack of standardized extracts
- Incompletion of pharmacokinetic data
- Uncertainty in regulatory frameworks

Future research should target these areas:

- Dosing regimen standardization
- Long-term toxicity studies
- Clinical trials

CONCLUSION

Achyranthes aspera is a rich medicinal plant with multi target therapeutic activities. The phytochemical constituents such as saponins, alkaloids, flavonoids and phenolics possess anti-inflammatory, antioxidant, and antimicrobial, anticancer activities.

Modulation of following pathways:

- NF-kB signalling pathway
- Nrf2-mediated antioxidant pathway
- PI3K/Akt signalling pathway
- MAPK signalling cascades
- Regulators of apoptosis

Despite these findings, most available evidence is derived from preclinical studies. The remaining key gaps included are:

- The absence of human clinical trials
- The need for standardized extract development
- Limited pharmacokinetic characterization
- Long term safety

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