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PHARMACOLOGICAL AND FORMULATION ADVANCES IN THE MANAGEMENT OF HEPATIC AND INFLAMMATORY DISORDERS: A REVIEW OF *ACALYPHA FRUTICOSA* AND *TRIBULUS TERRESTRIS*

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ABSTRACT

Background: The increasing global burden of liver diseases and chronic inflammatory conditions necessitates the exploration of effective, plant-based therapeutics. *Acalypha fruticosa* and *Tribulus terrestris* are two medicinal plants deeply rooted in traditional ethnomedicine, widely recognized for their diverse biological activities. **Objective:** To systematically review the current literature surrounding *Acalypha fruticosa* and *Tribulus terrestris*, focusing on their antioxidant, anti-inflammatory, and hepatoprotective mechanisms, and to explore recent advances in standardizing these extracts into modern pharmaceutical dosage forms. **Methods:** A comprehensive review of recent literature was conducted. *In vitro*, *in vivo*, and formulation studies evaluating the phytochemical composition, metabolic modulation, and drug delivery systems of both plant extracts were analyzed. **Discussion:** Pharmacological evaluations confirm that *Acalypha fruticosa* possesses potent antioxidant and anti-inflammatory properties, driven by compounds like acalyphin that activate PPAR receptors and inhibit NF-κB pathways. Concurrently, *Tribulus terrestris* demonstrates profound hepatoprotective effects by neutralizing oxidative stress and restoring endogenous antioxidant enzymes. Furthermore, recent pharmaceutical advancements have successfully standardized these hygroscopic extracts into modern dosage forms, including tablets, capsules, and effervescent formulations, significantly enhancing patient compliance and bioavailability. **Conclusion:** The literature robustly validates the pharmacological efficacies of *A. fruticosa* and *T. terrestris*. Their complementary mechanisms of action—coupled with modern formulation technologies—highlight their significant potential for integration into advanced therapeutic regimens for liver and inflammatory disorders.

KEYWORDS: *Acalypha fruticosa*; *Tribulus terrestris*; Hepatoprotection; Phytopharmacology; Herbal Formulation; Effervescent Technology.

1. INTRODUCTION

In recent years, the paradigm of treating chronic inflammatory and hepatic disorders has increasingly shifted toward the integration of phytotherapy. The limitations of conventional synthetic drugs have driven researchers to explore natural alternatives. *Acalypha fruticosa* and *Tribulus terrestris* are two prominently utilized medicinal plants with extensive ethnomedical histories. Modern pharmacological evaluations have begun to map the complex phytochemical profiles of

these plants, revealing secondary metabolites capable of modulating oxidative stress and inflammatory signaling pathways. Concurrently, pharmaceutical technologists are developing advanced delivery systems to overcome the physical limitations of crude herbal extracts. This review comprehensively synthesizes the current literature surrounding the pharmacological activities and formulation advancements of these two botanicals.

2. Pharmacology of *Acalypha fruticosa*

2.1 Antioxidant Potential and Cytotoxicity

The therapeutic versatility of *Acalypha fruticosa* is heavily attributed to its robust antioxidant capabilities. Rajkumar et al. conducted a pivotal evaluation of the antioxidant potential, cytotoxicity, and DNA cleavage protective properties of methanolic and aqueous extracts of the plant.[1] Their findings demonstrated that the methanolic extract exhibited superior free radical scavenging activity in FRAP, DPPH, and OH assays due to its higher phenolic content. Furthermore, the extracts showed marginal cytotoxicity against MDA-MB-435S and Hep3B cell lines and provided significant protection against UV-photolysed H_2O_2-induced oxidative damage to pBR322 DNA.[1]

Gupta et al. provided a foundational evaluation of the plant's leaf extracts, confirming high concentrations of phenols, triterpenoids, and steroids. Utilizing a carrageenan-induced paw edema model in rats, they established that the methanolic extract possessed potent anti-inflammatory properties comparable to the standard synthetic drug, Indomethacin.[2]

2.2 Phytochemistry and Anti-inflammatory Mechanisms

Chemical characterization by Fawzy et al. isolated four specific compounds from Saudi Arabian *A. fruticosa*: 2-methyl-5,7-dihydroxychromone 5-O-β-D-glucopyranoside, acalyphin, apigenin, and kaempferol 3-O-rutinoside.[3] Their investigation revealed that these compounds exhibited dual PPARα and PPARγ agonistic activity. These compounds effectively inhibited NF-κB and iNOS, confirming their role in reducing cellular oxidative stress and suppressing inflammation.[3] Malathi et al. further corroborated this through qualitative pharmacognostic evaluations and fluorescence analysis, identifying a rich matrix of flavonoids, cardiac glycosides, fatty acids, phlobatannins, and emodins.[4]

Beyond anti-inflammatory properties, the plant exhibits broad therapeutic utility. Shanmugalingam et al. reviewed the plant's extensive *in vivo* and *in vitro* effects, documenting its ability to reduce tumor cell size, lower blood glucose, and provide antiepileptic protection against convulsions, alongside potent antileishmanial and antimalarial activities.[5] A comprehensive systematic review by Al-Massarani et al. reported that the high phenolic content in the aerial parts correlates directly with the plant's ability to scavenge superoxide and hydroxyl radicals, validating its broad-spectrum antimicrobial defense against pathogens like *Staphylococcus aureus* and *Escherichia coli*.[6]

2.3 Hepatoprotection

The direct hepatoprotective mechanisms of *A. fruticosa* have been validated in robust animal models. Nambiar et al. investigated the effects of ethanolic leaf extracts on carbon tetrachloride (CCl_4)-induced hepatotoxicity in rats.[7] The study demonstrated a dose-dependent reduction in serum liver enzyme markers (ALT, AST, and ALP) and the restoration of total protein levels. Histopathological examinations proved that the extract effectively preserved lobular architecture and significantly reduced fatty degeneration and necrosis.[7] A recent global ethnobotanical review by Villaescusa-González et al. further highlighted that the plant is historically utilized for 17 distinct disease types, confirming its versatility across multiple contemporary experimental models.[8]

3. Pharmacology of *Tribulus terrestris*

3.1 Phytopharmacology and Phytochemistry

Tribulus terrestris has a well-documented history in ethnomedicine. Chhatre et al. conducted an extensive phytopharmacological overview, synthesizing early evidence that the plant's steroidal saponins exert highly protective effects on visceral organs by modulating oxidative stress. They noted that the geographical sourcing of the plant significantly alters its saponin profile.[9]

3.2 Hepatoprotective and Antioxidant Effects

The efficacy of *T. terrestris* in treating acute hepatic damage is strongly supported by literature. Harraz et al. examined the total ethanolic extract against CCl_4-induced hepatotoxicity. They discovered that the ethyl acetate fraction significantly decreased elevations in serum ALT, AST, and total bilirubin to levels comparable with silymarin.[10] The fraction lowered malondialdehyde (MDA) levels while elevating glutathione (GSH) content and superoxide dismutase (SOD) activity.[10] Abdel-Kader et al. independently evaluated these hepatoprotective activities, confirming that the ethyl acetate fraction exhibited the most significant hepatoprotective activity.[11]

The systemic benefits of *T. terrestris* extend into complex metabolic pathways. El-Shaibany et al. evaluated the methanol extract of aerial parts in glucose-loaded normal rabbits. A single oral dose (250 mg/kg) significantly lowered fasting blood glucose levels, presenting efficacy comparable to glibenclamide.[12] Naseri et al. detailed the plant's potent free radical scavenging and lipid peroxidation inhibition properties, emphasizing its role in reducing chemotherapy side effects.[13]

3.3 Anti-inflammatory and Renal Protection

Ștefănescu et al. provided a comprehensive review demonstrating that *T. terrestris* extracts successfully downregulate NF-κB, inhibit COX-2, and reduce cytokine production, supporting its use in inflammatory disorders.[14] Saeed et al. similarly explored its nutritional potential, noting its ability to strongly modulate inflammatory mediators via its rich matrix of saponins and flavonoids.[15]

Renal protection is also evident; Shetty et al. explored the nephroprotective and hepatoprotective properties of the aqueous extract against carboplatin-induced toxicity in rats, noting a significant downregulation of the pro-inflammatory cytokine IL-6.[16] Similarly, Al-Mohamadi et al. demonstrated that the ethanol extract provided full recovery from gentamicin-induced nephrotoxicity at 450 mg/kg.[17] At a genetic level, Gao et al. utilized advanced transcriptomics to identify an active fraction (TTAI) capable of reversing the expression of 40 metabolic biomarkers and regulating 235 genes associated with inflammation through the PI3K/AKT and MAPK signaling pathways.[18]

4. Herbal Formulation Studies and Delivery Systems

Transitioning crude herbal extracts into stable pharmaceutical dosage forms is essential for clinical efficacy. Srinath et al. provided a comprehensive review of effervescent technology, detailing the fundamental chemistry of organic acids and bicarbonates, and highlighting the rapid onset of action these formulations provide for geriatric patients.[19] Aslani et al. established critical methodologies for fusion and wet granulation methods, providing validated protocols for evaluating angle of repose, Carr's index, and moisture content in effervescent powders.[20]

Specifically regarding these herbs, Venkatachalam et al. successfully developed a polyherbal floating effervescent tablet containing *Pedalium murex* and *Tribulus terrestris* fruit extracts, which enhanced bioactivity and prolonged gastric retention.[21] Alburyhi and El-Shaibany formulated *Acalypha fruticosa* extract tablets using wet granulation to overcome the poor flowability of the crude powder. The optimized formulation demonstrated an 89.5% drug release within 60 minutes, representing a major milestone in standardizing this medicinal plant.[22]

The complexities of herbal effervescence were recently reviewed by Butar-Butar et al., who identified that the hygroscopicity of crude extracts can trigger premature effervescent reactions, necessitating specific moisture-protective packaging and precise acid balancing.[23] Furthering these advancements, Alburyhi and El-Shaibany optimized *Tribulus terrestris* capsules for controlling diabetes, achieving 94% drug release within 60 minutes.[24] Dovchinsuren et al. also successfully optimized a tablet formulation strategy for *Tribulus terrestris* dry extract yielding standardized dioscin content that met all pharmacopoeial standards.[25]

Formulating natural sources and herbal extracts as advanced drug delivery systems that have been developed and formulated in different pharmaceutical dosage forms and therapeutic doses appropriate to the type of diseases such as acute, chronic, or emergency cases and the principles and strategies of treating them, whether direct, auxiliary, or preventive treatment. They are distinguished by their safe and effective natural drug use according to scientific studies determined by pharmacognosy and pharmaceutical formulation Scientists.[26-34]

5. CONCLUSION

A comprehensive review of the current pharmacological literature clearly establishes the potent therapeutic profiles of *Acalypha fruticosa* and *Tribulus terrestris*. *Acalypha fruticosa* exerts powerful anti-inflammatory and antioxidant actions primarily through the activation of PPAR receptors and the inhibition of NF-κB/iNOS pathways. Concurrently, *Tribulus terrestris* provides robust hepatoprotective benefits by neutralizing oxidative stress, restoring critical endogenous enzymes, and suppressing pro-inflammatory cytokines. Furthermore, recent advancements in formulation technology—such as the development of standardized tablets, capsules, and effervescent delivery systems—have successfully overcome the physical limitations of crude plant extracts. The convergence of these complementary pharmacological mechanisms with modern pharmaceutical design holds immense potential for the development of advanced, multi-target therapeutics in the management of complex liver diseases and chronic inflammatory disorders.

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