EJPMR, 2026, 13(4), 520-524 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

A HEPATOPROTECTIVE AND ANTI-INFLAMMATORY POLYHERBAL APPROACH: THE SYNERGISTIC POTENTIAL OF *ACALYPHA FRUTICOSA* AND *TRIBULUS TERRESTRIS* EXTRACT

Amina El-Shaibany[1,3]*, Maged Alwan Noman[2,3], Mahmoud Mahyoob Alburyhi[2], Abdalwali Ahmed Saif[2], Alaa Al-Deen Fahd Al-Khulaidi[3], Naif Sultan Al-Qawati[3], Taha Mohammed Al-Kebsi[3], Hussam Hasan Al-Twiti[3]

[1]Professor Dr. of Pharmacognosy, Department of Pharmacognosy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.
[2]Professor Dr. of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.
[3]Department of Pharmacy, Faculty of Medical Sciences, Al-Yemenia University, Sana'a, Yemen.

***Corresponding Author: Prof. Dr. Amina El-Shaibany**

Professor Dr. of Pharmacognosy, Head of Pharmacy Department, Faculty of Medical Sciences, Al-Yemenia University, Sana'a, Yemen. **Email Id:** amina.doc.pharm@gmail.com, **DOI:** https://doi.org/10.5281/zenodo.19703809

How to cite this Article: Amina El-Shaibany[1,3]*, Maged Alwan Noman[2,3], Mahmoud Mahyoob Alburyhi[2], Abdalwali Ahmed Saif[2], Alaa Al-Deen Fahd Al-Khulaidi[3], Naif Sultan Al-Qawati[3], Taha Mohammed Al-Kebsi[3], Hussam Hasan Al-Twiti[3] (2026). A Hepatoprotective And Anti-Inflammatory Polyherbal Approach: The Synergistic Potential Of Acalypha Fruticosa And Tribulus Terrestris Extract. European Journal of Pharmaceutical and Medical Research, 13(4), 520–524.

Article Received on 05/03/2026 **Article Revised on 20/03/2026** **Article Published on 04/04/2026**

ABSTRACT

Background: Liver diseases and chronic inflammatory disorders represent a profound global health challenge, significantly contributing to morbidity and mortality. In resource-limited settings such as Yemen, this burden is compounded by high rates of viral hepatitis, metabolic liver disorders, and inadequate access to modern synthetic therapies. **Objective:** To systematically review the epidemiology of hepatic and inflammatory disorders in Yemen and provide a comprehensive ethnobotanical and pharmacological rationale for a polyherbal intervention combining *Acalypha fruticosa* and *Tribulus terrestris*. **Methods:** A detailed review of the literature was conducted, mapping the phytochemistry, traditional uses, and molecular mechanisms of both plants to identify synergistic hepatoprotective and anti-inflammatory properties. **Discussion:** The integration of multiple herbs addresses the multifactorial nature of liver injury. *Acalypha fruticosa* offers robust anti-inflammatory action by activating PPAR-α and PPAR-γ receptors via its cyanogenic glycoside, Acalyphin. Concurrently, *Tribulus terrestris* protects hepatocytes from oxidative stress and downregulates the NF-κB pathway via steroidal saponins and Tribulusamides. The amphiphilic nature of *Tribulus* saponins theoretically enhances the bioavailability of antioxidant flavonoids from *Acalypha*. **Conclusion:** A dual-herb approach combining *A. fruticosa* and *T. terrestris* presents a scientifically justified, multi-target strategy for managing hepatic inflammation. This synergism offers a sustainable, cost-effective, and safe alternative to single-target synthetic hepatoprotectives.

KEYWORDS: Hepatoprotection; Anti-inflammatory; *Acalypha fruticosa*; *Tribulus terrestris*; Polyherbal Formulation; Yemen.

1. INTRODUCTION

The liver is a vital organ responsible for critical physiological functions, including the metabolism of carbohydrates, proteins, and lipids, detoxification of xenobiotics, and the production of bile.[1] Due to its central role in processing foreign substances, the liver is highly susceptible to injury from agents such as viral infections, alcohol consumption, and hepatotoxic drugs.[2] Liver damage frequently manifests as inflammation (hepatitis), which, if left unchecked, progresses to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[3]

Chronic inflammation is a pathological driver of many liver disorders. The inflammatory cascade triggers the release of pro-inflammatory cytokines such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α), exacerbating tissue damage.[2] Consequently,

therapeutic strategies offering dual hepatoprotective and anti-inflammatory activities are highly desirable.

Globally, liver diseases account for approximately 2 million deaths annually, representing 4% of all worldwide mortality.[3] Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has emerged as a leading cause of chronic liver disease, affecting 1.5 to 2 billion people as of 2021.[4] In the Middle East and North Africa (MENA) region, the burden is particularly severe, with countries reporting some of the highest prevalence rates of metabolic liver diseases globally.[4] In Yemen, the crisis is compounded by limited advanced healthcare infrastructure, leading to frequent cirrhosis complications such as jaundice, hepatic encephalopathy, and renal failure.[5]

2. Epidemiology of Hepatic and Inflammatory Disorders in Yemen

The burden of liver and inflammatory diseases in Yemen has reached alarming levels, exacerbated by environmental factors, infectious agents, and specific lifestyle habits. Hospital-based studies at tertiary centers in Sana'a indicate that liver diseases account for 30% of all gastroenterology admissions. Among these, autoimmune hepatitis is the most common diagnosis (27.7%), followed closely by MASLD (22.6%) and viral hepatitis (20.6%).[6]

Viral hepatitis remains a persistent public health threat. Recent data shows that the prevalence of Hepatitis B Virus (HBV) among blood donors is approximately 6.56%, while Hepatitis C Virus (HCV) is around 0.82%.[7] Furthermore, intra-familial transmission of HBV is critically high, with a 19% prevalence among family members of infected index cases in Aden, highlighting gaps in prevention and surveillance.[8]

Lifestyle factors also drive hepatic morbidity. The widespread habit of chewing Khat (*Catha edulis*) is a documented risk factor for liver injury, frequently complicating the prognosis of pre-existing viral hepatitis or leading to drug-induced liver injury (DILI) due to inherent alkaloids and pesticide residues.[9] Moreover, chronic inflammatory conditions extend beyond the liver. *Helicobacter pylori* infection is hyper-endemic in Yemen, with up to 98.7% of endoscopy patients testing positive.[10] Autoimmune disorders like Rheumatoid Arthritis (RA) severely impact women aged 30–50 years, who frequently suffer from unmanaged, severe systemic inflammation.[11]

3. Traditional Herbal Medicine: A Shift Towards Polyherbalism

To combat these challenges, Yemen relies heavily on its rich tradition of herbal medicine. Traditional healers have historically utilized plant-based remedies to treat digestive and hepatic disorders, a practice that remains the primary healthcare source in rural areas where synthetic pharmaceuticals are unaffordable.[12]

In modern medicine, conventional treatments—such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs)—carry severe adverse effects, including gastrointestinal ulceration and further hepatotoxicity with long-term use.[1] The concept of polyherbalism—combining multiple medicinal herbs to achieve superior therapeutic results—provides an alternative. Unlike the single-target approach of synthetic drugs, polyherbal formulations utilize a multi-target approach, modulating various signaling pathways simultaneously to provide holistic treatment for complex diseases like chronic hepatitis.[1]

4. Botanical and Pharmacognostic Profile of *Acalypha fruticosa*

4.1 Botany and Distribution

Acalypha fruticosa Forssk., belonging to the Euphorbiaceae family, is an aromatic, resinous, deciduous shrub growing 1.5 to 3 meters tall. The leaves are simple, ovate-rhombic, with crenate-dentate margins and a glandular-punctate underside that produces a strong characteristic odor.[13, 14, 15] The plant is monoecious, bearing axillary spikes with minute male flowers clustered at the tip and female flowers at the base protected by dentate bracts. It produces a three-lobed capsule containing smooth, globose seeds.[14]

The species is highly drought-resistant and prominent across the Arabian Peninsula. In Yemen, it is widely distributed across escarpment zones, dry bushlands, rocky slopes, and wadis (300 to 2,500 meters above sea level), particularly in the Taiz, Ibb, Dhale, Sana'a, and Hajjah governorates.[16, 17]

4.2 Traditional Uses and Phytochemistry

Locally known as "Arn" or "Zafra," the fresh leaves of *A. fruticosa* are crushed and applied topically for skin infections, fungal ailments, and ulcers.[12] Internally, infusions are consumed for dyspepsia, jaundice, and liver complaints, providing ethnomedical evidence for its hepatoprotective potential.[12]

The plant's pharmacological versatility stems from its diverse secondary metabolites. The primary lipid fractions contain palmitic and linoleic acids, which stabilize cell membranes.[18] The antioxidant and hepatoprotective activities are predominantly driven by flavonoids, including Apigenin, Kaempferol 3-O-rutinoside, and 2-methyl-5,7-dihydroxychromone 5-O-beta-D-glucopyranoside.[13] It also features a specific cyanogenic glucoside marker, Acalyphin (a 3-cyanopyridone derivative).[13] Non-polar fractions are rich in sesquiterpenes (α-Humulene, β-Caryophyllene) and phytosterols (β-Sitosterol, Stigmasterol).[18]

4.3 Mechanisms of Action

Groundbreaking research indicates that Acalyphin and its phenolic derivatives act as potent agonists for Peroxisome Proliferator-Activated Receptors (PPAR-α and PPAR-γ). The activation of these receptors regulates

lipid metabolism and directly inhibits the expression of pro-inflammatory genes.[13] Flavonoids within the plant boost endogenous antioxidant enzymes (Superoxide Dismutase [SOD] and Catalase [CAT]), neutralizing free radicals and preventing lipid peroxidation of the hepatocyte membrane.[1] Furthermore, β-Caryophyllene selectively binds to cannabinoid receptor type 2 (CB2) to exert analgesia and reduce inflammation, while flavonoids suppress TNF-α and IL-6.[2]

5. Botanical and Pharmacognostic Profile of *Tribulus terrestris*

5.1 Botany and Distribution

Tribulus terrestris L. (Zygophyllaceae), commonly known as "Puncture Vine," is a prostrate annual or perennial herb. It possesses opposite, paripinnate leaves with 5–8 pairs of leaflets and a deep, cylindrical taproot.[14,19] The plant produces solitary, yellow hermaphroditic flowers that mature into a distinct woody schizocarp splitting into five mericarps armed with sharp spines.[20]

In Yemen, it is a ubiquitous, drought-tolerant species distributed abundantly across the Tihama coastal plains (Hodeidah, Zabid) and the lower western escarpments of Taiz, Ibb, and Hajjah.[14]

5.2 Traditional Uses and Phytochemistry

Locally named "Qutiba" or "Hassak," the plant is a revered diuretic, lithotriptic, and aphrodisiac.[17] Liver-specific applications include the use of infusions as a general hepatic tonic to treat conditions associated with jaundice and to detoxify the body.[12]

The efficacy of *T. terrestris* is primarily attributed to steroidal saponins (furostanol and spirostanol types), with Protodioscin serving as the principal bioactive marker. Other vital saponins include Prototribestin, Pseudoprotodioscin, Dioscin, Tribulosin, and Diosgenin.[21] The plant also contains powerful flavonoids (Quercetin, Rutin, Astragalin)[19] and distinct lignanamides, specifically Tribulusamides A, B, and D.[14]

5.3 Mechanisms of Action

The therapeutic actions of *T. terrestris* are mediated through targeted molecular pathways. Protodioscin increases the release of nitric oxide (NO) from the endothelium, modulating oxidative stress pathways and improving blood flow.[21] Tribulusamides inhibit the production of inflammatory mediators by blocking the NF-κB signaling pathway.[21] Synergistically, Tribulosin and Quercetin maintain intracellular levels of SOD, CAT, and Glutathione Peroxidase (GPx), preventing hepatic injury by scavenging free radicals and stopping the leakage of AST and ALT enzymes into the bloodstream.[2] Furthermore, Diosgenin suppresses Cyclooxygenase-2 (COX-2) and Inducible Nitric Oxide Synthase (iNOS).[14]

6. Scientific Rationale for Polyherbal Combination

The strategic combination of *Acalypha fruticosa* and *Tribulus terrestris* leverages their distinct yet complementary pharmacological profiles. *Tribulus terrestris* regenerates hepatocellular integrity and restores depleted antioxidant enzyme levels, addressing the core pathology of liver injury.[1] *Acalypha fruticosa* directly targets the inflammatory cascade that exacerbates liver damage.[13]

Combining these extracts offers profound pharmacodynamic synergism. The amphiphilic steroidal saponins (e.g., Protodioscin) from *Tribulus* act as natural bio-enhancers by modifying mucosal membrane permeability, theoretically facilitating the superior absorption of the antioxidant-rich flavonoids in *Acalypha.*[20] Mechanistically, *Acalypha* suppresses inflammation upstream via PPAR-α/γ activation[13], while *Tribulus* complements this downstream by inhibiting NF-κB signaling and suppressing TNF-α and IL-6 release.[14] Together, they provide a dual-blockade against the inflammatory cascade.

This synergism accelerates the liver's natural regeneration process, neutralizing circulating reactive oxygen species via *Acalypha's* phenolic content[18] and restoring intracellular glutathione via *Tribulus.*[2] Furthermore, the potent antimicrobial properties of *Acalypha* provide vital protection against secondary bacterial infections that frequently complicate cirrhotic liver diseases.[22]

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.[23-39]

7. CONCLUSION

There is a critical unmet need for effective, safe, and accessible hepatoprotective agents, particularly in regions burdened by high rates of viral and metabolic liver diseases. The strategic combination of *Acalypha fruticosa* and *Tribulus terrestris* represents a scientifically rigorous translation of Yemeni traditional medicine into a targeted polyherbal therapy. By synergistically activating PPAR receptors, inhibiting the NF-κB cascade, and restoring endogenous antioxidant enzymes, this botanical combination comprehensively addresses both hepatic inflammation and cellular necrosis. Future research must continue to standardize these extracts into modern delivery systems, ultimately providing a sustainable healthcare solution for liver disorder management.

REFERENCES

1. Aladejana EB, Aladejana AE. Hepatoprotective activities of polyherbal formulations: A systematic review. Journal of Medicinal Plants for Economic Development, 2023; 7(1): Article a206.
2. Shetty N, Holla S, Nayak V, Shenoy VB, Mohandas RKG. Antioxidant and anti-inflammatory activity by modulating IL-6 as a potential mechanism in the nephroprotective and hepatoprotective properties of Tribulus terrestris. Research in Pharmaceutical Sciences, 2024; 19(4): 376–386.
3. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. Journal of Hepatology, 2023; 79(2): 516–537.
4. Kan C, Zhang K, Wang Y, Zhang X, Liu C, Ma Y, Hou N, Huang N, Han F, Sun X. Global burden and future trends of metabolic dysfunction-associated steatotic liver disease: 1990-2021 to 2045. Annals of Hepatology, 2025; 30(2): Article 101898.
5. El-Sayed GGM, Al-Awlaqi MH. Clinical patterns and outcomes in cirrhotic Yemeni patients with acute-on-chronic liver failure. Electronic Journal of University of Aden for Basic and Applied Sciences, 2024; 5(3): 309–319.
6. Mutahar DJA, Al-Khamesy KSA, Al-Moyed KAA, Al-Shamahy HA, Al-Shehari MM. Pattern of liver disease admissions at a tertiary government hospital in Sana'a, Yemen. Universal Journal of Pharmaceutical Research, 2022; 7(4): 38–43.
7. Al-Mohani SKM, Al-Huthaifi OAA, Al-Nahham DSAM, Al-Sharai AAS, Al-Deen ANS. The prevalence of hepatitis B and C viruses among blood donors attending blood bank in Jiblah University Hospital, Ibb, Yemen. Journal of Community Medicine and Public Health Reports, 2024; 5(7): Article 454.
8. Gubran ANM. Intra-familial transmission of hepatitis B virus in Aden-Yemen. Electronic Journal of University of Aden for Basic and Applied Sciences, 2024; 5(2): 210–216.
9. Patanwala IM, Burt AD, Bassendine MF, Hudson M. Khat associated end stage chronic liver disease: A case report. Journal of Medical Cases, 2011; 2(3): 104–106.
10. Al-Shamahy HA. Seroprevalence of Helicobacter pylori among children in Sana'a, Yemen. Annals of Saudi Medicine, 2005; 25(4): 299–303.
11. Alhaj AY, Al Wazeer A, Abdulhafed SA, Al-Zandani M. Rheumatoid arthritis: Prevalence, patterns of presentations and associated factors among arthritis patients in Military Hospital, Sana'a, Yemen 2019-2021. Journal of 21 September University of Medical and Applied Sciences, 2022; 1(1).
12. Hehmeyer I, Schönig H (Eds.). Herbal medicine in Yemen: Traditional knowledge and practice, and their value for today's world. Brill; 2012.
13. Fawzy GA, Al-Taweel AM, Perveen S, Khan SI, Al-Omary FAM. Bioactivity and chemical characterization of Acalypha fruticosa Forssk. growing in Saudi Arabia. Saudi Pharmaceutical Journal, 2017; 25(1): 104–109.
14. Zhu W, Du Y, Meng H, Dong Y, Li L. A review of traditional pharmacological uses, phytochemistry, and pharmacological activities of Tribulus terrestris. Chemistry Central Journal, 2017; 11(1): Article 60.
15. Alabyadh M, Sharaf H, Mazen R, Saeed A, Al-salmi M, Masood N, Nagy H. Evaluation of antimicrobial and antioxidant in Acalypha fruticosa leaves: A natural source of bioactive compounds. Yemeni Journal for Medical Sciences, 2025; 19(3): Article 2762.
16. Al-Khulaidi AW. Flora of Yemen. Sustainable Natural Resource Management Project (SNRMP), Environmental Protection Authority (EPA) & United Nations Development Programme (UNDP); 2013.
17. Al-Fatimi M, Wurster M, Schröder G, Lindequist U. Antioxidant, antimicrobial and cytotoxic activities of selected medicinal plants from Yemen. Journal of Ethnopharmacology, 2007; 111(3): 657-666.
18. Gopalakrishnan S, Saroja K, Elizabeth JD. Chemical investigation of aerial parts of Acalypha fruticosa Forssk. Der Pharmacia Lettre, 2010; 2(3): 290–295.
19. Chhatre S, Nesari T, Somani G, Kanchan D, Sathaye S. Phytopharmacological overview of Tribulus terrestris. Pharmacognosy Reviews, 2014; 8(15): 45–51.
20. Semerdjieva IB, Zheljazkov VD. Chemical constituents, biological properties, and uses of Tribulus terrestris: A review. Natural Product Communications, 2019; 14(8).
21. Dinchev D, Janda B, Evstatieva L, Oleszek W, Aslani MR, Kostova I. Distribution of steroidal saponins in Tribulus terrestris from different geographical regions. Phytochemistry, 2008; 69(1): 176–186.
22. Al-Massarani S, El-Sayed MIK, El-Shaibany A. Antioxidant and anti-proliferative activities of Acalypha fruticosa: Possible elucidated mechanism. Pakistan Journal of Pharmaceutical Sciences, 2019; 32(5): 2041–2050.
23. Noman MA, Alburyhi MM, Saif AA, Yahya TAA. Formulation and evaluation of polyherbal extract for skin hyperpigmentation as gel advanced delivery systems. World Journal of Pharmaceutical Research, 2024; 13(22): 1260-1280.
24. Alburyhi MM, Noman MA, Saif AA. Formulation and evaluation of natural herbal anti-acne as gel delivery systems. World Journal of Pharmaceutical Research, 2024; 13(21): 1447-1467.
25. Alburyhi MM, El-Shaibany A. Formulation and evaluation of anti-peptic ulcer capsules of Curcuma longa herbal product. World Journal of Pharmaceutical Research, 2023; 12(22): 76-96.
26. Noman MA, Alburyhi MM, El-Shaibany A, Alwesabi NA. Formulation and evaluation of Pandanus odoratissimus L extract for treatment of nocturnal enuresis as orodispersible tablets delivery system. World Journal of Pharmaceutical Research, 2024; 13(5): 56 -71.

27. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of Pandanus odoratissimus extract capsules delivery system as an advanced phytotherapy approach for hepatoprotective. European Journal of Pharmaceutical and Medical Research, 2024; 11(4): 06-13.
28. Alburyhi MM, El-Shaibany A. Recent innovations of novel drug delivery systems for formulation, development and evaluation of Aloe rubroviolaceae extract capsules as naturaceutical for hepatoprotective. European Journal of Biomedical and Pharmaceutical Sciences, 2024; 11(4): 53-61.
29. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of celery extract capsules delivery system as an advanced phytotherapy approach for gout. World Journal of Pharmaceutical Research, 2024; 13(11): 2383-2404.
30. Alburyhi MM, El-Shaibany A. Formulation and evaluation of effervescent granules of Artemisia arborescence herbal product for foodborne illness. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(12): 1429-1444.
31. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of chamomile extract capsules delivery system as an advanced phytotherapy approach for gout. World Journal of Pharmaceutical and Life Sciences, 2025; 11(04): 215-228.
32. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of Tribulus terrestris extract capsules delivery system as an advanced phytotherapy approach for controlling diabetes. World Journal of Pharmaceutical Research, 2024; 13(7): 1264-1282.
33. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of Plicosepalus acacia extract capsules delivery system as an advanced phytotherapy approach for hepatoprotective. World Journal of Pharmaceutical Research, 2025; 14(8): 1309-1334.
34. Alburyhi MM, El-Shaibany A. Formulation and evaluation of antibacterial orodispersible tablets of Artemisia arborescence extract herbal product. European Journal of Pharmaceutical and Medical Research, 2024; 11(2): 409-417.
35. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of Acalypha fruticosa extract tablets delivery system as an advanced phytotherapy approach for controlling diabetes. World Journal of Pharmaceutical Research, 2024; 13(8): 1073-1091.
36. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of Ginger extract capsules delivery system as an advanced phytotherapy approach for controlling diabetes. World Journal of Pharmaceutical and Medical Research, 2025; 11(6): 400-415.
37. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of Tribulus terrestris extract capsules as naturaceutical novel drug delivery systems for kidney stones. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(5): 1425-1443.
38. Alburyhi MM, El-Shaibany A. Formulation, development and evaluation of Capsicum extract capsules delivery system as an advanced phytotherapy approach for tonic and natural stimulant. European Journal of Pharmaceutical and Medical Research, 2025; 11(6): 323-337.
39. Noman MA, Alburyhi MM, Saif AA. Formulation and evaluation of skin whitening naturaceutical composition gel as advanced drug delivery systems. World Journal of Pharmaceutical and Medical Research, 2025; 11(10): 400-414.