International Journal of Medical and Pharmaceutical Sciences
Open access peer-reviewed Journal
Volume 2, Issue 11, Page 82-84.
https://doi.org/10.5281/zenodo.24413580

Review Article

Natural Therapeutics in Non-Alcoholic Fatty Liver Disease: A Comprehensive Review

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Non-alcoholic fatty liver disease (NAFLD), recently redefined as metabolic dysfunction-associated steatotic liver disease (MASLD), represents the hepatic manifestation of metabolic syndrome and is the leading cause of chronic liver disease globally. The disease spectrum extends from simple steatosis (NAFL) to non-alcoholic steatohepatitis (NASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Given the multi-targeted pathomechanisms of NAFLD—including insulin resistance, lipid dysregulation, oxidative stress, and pro-inflammatory signaling—herbal therapeutics have gained substantial interest. Plants belonging to the genus Ficus (family Moraceae), notably Ficus amplissima, are rich sources of bioactive flavonoids, polyphenols, and terpenoids that exhibit protective metabolic effects. This review synthesizes current insights into the pathophysiology of NAFLD, evaluates natural dietary and herbal interventions, and highlights the therapeutic mechanisms of Ficus amplissima in mitigating hepatic steatosis, dyslipidemia, oxidative stress, and structural liver injury.

Keywords: NAFLD, dyslipidemia, Ficus amplissima, oxidative stress.

INTRODUCTION

1. Introduction and Epidemiology

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver conditions characterized by lipid accumulation exceeding 5% of liver weight in individuals without excessive alcohol consumption or secondary causes of steatosis. Globally, NAFLD affects approximately 25%–30% of the adult population, with rising prevalence in parallel with global obesity and type 2 diabetes mellitus (T2DM) epidemics. While lifestyle modifications—including dietary calorie restriction and exercise—remain the cornerstone of management, long-term patient compliance is notoriously low. Furthermore, pharmacotherapeutic options directly approved for liver-specific protection in NAFLD remain limited, driving research toward plant-derived natural compounds capable of multi-target physiological regulation.

2. Pathophysiology

The progression of simple steatosis to NASH and advanced fibrosis is described by the "multiple-hit" hypothesis, replacing the outdated "two-hit" model.

- **Insulin Resistance & Lipolysis:** Uncontrolled peripheral lipolysis floods the portal vein with free fatty acids (FFAs), driving hepatic *de novo* lipogenesis (DNL).
- **Lipotoxicity & Mitochondrial Dysfunction:** Intracellular overload of saturated FFAs and diacylglycerols impairs mitochondrial β-oxidation, resulting in excessive reactive oxygen species (ROS) formation and mitochondrial permeability transition.

- **Endoplasmic Reticulum (ER) Stress & Inflammation:** ROS and oxidative stress activate nuclear factor-kappa B (NF-κB), triggering pro-inflammatory cytokines such as TNF-α and IL-6, which exacerbate hepatocyte ballooning and leukocyte infiltration.

- **Fibrogenesis:** Chronic injury activates hepatic stellate cells (HSCs), leading to extracellular matrix accumulation and fibrosis.

3. Phytochemical Strategies and Natural Products in NAFLD

Plant-derived bioactives act on multiple signaling nodes in the liver, offering systemic protective benefits:

Class	Key Compounds	Primary Molecular Targets / Mechanisms
Flavonoids	Quercetin, Rutin, Epicatechin	Activates AMPK/PPAR-α; inhibits SREBP-1c; scavenges ROS; suppresses NF-κB.
Phenolic Acids	Gallic acid, Ferulic acid, Chlorogenic acid	Reduces hepatic lipid uptake; enhances endogenous glutathione (GSH) and Catalase (CAT).
Alkaloids	Berberine	Enhances insulin sensitivity; activates AMPK pathway; reduces serum triglycerides and LDL.
Terpenoids & Steroids	Ursolic acid, Lupeol, β-Sitosterol	Suppresses hepatic inflammatory responses; downregulates lipogenic enzymes.

4. The Potential of Genus *Ficus* with Focus on *Ficus amplissima*

The genus *Ficus* (Moraceae family) comprises over 800 species distributed throughout tropical and subtropical regions. Species such as *Ficus religiosa*, *Ficus racemosa*, and *Ficus carica* have demonstrated substantial hypolipidemic, hypoglycemic, and anti-inflammatory activities. *Ficus amplissima* Smith, an ethnomedicinal plant native to India, contains a rich profile of bioactive secondary metabolites:

- **High Flavonoid Content:** Up to ~60% flavonoid content in crude ethanolic extracts, contributing to robust free-radical scavenging and lipid peroxidative inhibition.

- **Phenolic Abundance:** Promotes expression of endogenous enzymes (Catalase and GSH) while mitigating serum transaminase elevation (ALT, AST, ALP).

5. Summary of Pharmacological Evidence for *Ficus amplissima*

Experimental evaluation in combined streptozotocin (STZ) and high-fat diet (HFD) preclinical models demonstrates the multi-target efficacy of *Ficus amplissima* leaf extract:

1. **Lipid Homeostasis:** Reverses HFD-induced dyslipidemia by lowering total cholesterol, triglycerides, and LDL, while restoring protective HDL cholesterol.

2. **Glycemic Control:** Reduces fasting blood glucose levels and attenuates hyperphagia-associated weight changes in metabolic models.

3. **Hepatoprotection & Structural Integrity:** Lowers elevated liver enzymes (ALT, AST, ALP) and total bilirubin, protecting hepatocyte membranes and cellular protein synthesis.

4. **Histological Reversal of Steatosis:** Prevents and reverses macrovesicular lipid accumulation and vacuolation within hepatocytes, preserving central vein and sinusoidal cord structures.

CONCLUSION

Natural products, particularly rich flavonoid sources like *Ficus amplissima*, represent promising multi-target candidates for managing complex metabolic conditions like NAFLD. Future directions include:

- Characterization and isolation of individual active constituents responsible for metabolic regulation.

- Detailed mapping of specific downstream molecular pathways (e.g., AMPK, PPAR-γ, SREBP-1c, and Nrf2 pathways).

Preclinical toxicological safety profiling and translational clinical trials to determine human efficacy and dosage regimens.

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Cite: Arshi Khan*, Richa Agarwal, Rajesh Asija, Natural Therapeutics in Non-Alcoholic Fatty Liver Disease: A Comprehensive Review, Int. J. Med. Pharm. Sci., 2026, 2 (11), 82-84. https://doi.org/10.5281/zenodo.24413580