Review Article

Polyphenol-Based Interventions in NAFLD: A Critical Analysis of Therapeutic Efficacy, Molecular Mechanisms, and Clinical Translation Barriers

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ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a chronic condition commonly associated with obesity and metabolic syndrome. Polyphenolic compounds, such as resveratrol and curcumin, have emerged as potential therapeutic agents due to their antioxidant and anti-inflammatory properties. This review aims to critically evaluate the therapeutic potential of resveratrol and curcumin in the management of NAFLD, focusing on their molecular mechanisms and clinical implications. The mechanisms through which resveratrol activates the AMPK and SIRT1 pathways to improve lipid metabolism and reduce oxidative stress are explored. Similarly, curcumin's role in suppressing pro-inflammatory markers like TNF-α and IL-6 is examined. Both resveratrol and curcumin demonstrate significant antioxidant and anti-inflammatory effects, contributing to improved liver function and lipid homeostasis. However, clinical translation of these compounds has been limited by challenges such as poor bioavailability, inconsistent dosing, and varying therapeutic outcomes.Despite these limitations, polyphenols show promise as adjunctive treatments for NAFLD. Advanced drug delivery systems and standardized therapeutic protocols are necessary to enhance their clinical efficacy. Further research is required to optimize the use of polyphenols in clinical practice.

Key words: Polyphenol, NAFLD, Curcumin, Resveratrol, Therapeutic Efficacy, Antioxidant, Anti-inflammatory, Bioavailability, Liver Disease, Metabolic Syndrome

Non-Alcoholic Fatty Liver Disease (NAFLD) represents one of the most prevalent chronic liver disorders worldwide, characterized by hepatic steatosis occurring in the absence of significant alcohol intake. The disease spectrum extends from simple steatosis to the more severe non-alcoholic steatohepatitis (NASH), which may progress to cirrhosis, hepatocellular carcinoma, and end-stage liver disease [1,2]. The global burden of NAFLD is estimated to affect approximately 25% of the general population, with significantly higher prevalence in individuals with obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome [3,4]. The co-occurrence of these metabolic comorbidities creates a milieu of insulin resistance, dyslipidemia, and chronic low-grade inflammation that perpetuates hepatocellular injury [5]. The pathogenesis of NAFLD is multifactorial and involves a complex interplay of genetic predisposition, environmental factors, gut microbiota dysbiosis, and metabolic dysfunction.

Access this article online

Received – 5th July 2026

Initial Review – 15nd July 2026

Accepted – 26rd July 2026

DOI: 10.32677/ejms.v11i3.8393

Quick Response Code

The classical "two-hit hypothesis" has evolved into a "multiple parallel hit" model, wherein simultaneous insults, including oxidative stress, mitochondrial dysfunction, lipotoxicity, and pro-inflammatory signaling, converge to promote disease progression [6,7]. Central to this pathophysiology is the dysregulation of lipid metabolism pathways, particularly those governed by AMPK, SIRT1, NF-κB, and PPARα [8]. Currently, no pharmacological agent has received universal approval specifically for NAFLD/NASH treatment, making lifestyle modification the cornerstone of management [9]. This therapeutic void has catalyzed extensive investigation into naturally derived bioactive compounds, particularly dietary polyphenols. Resveratrol (3,5,4'-trihydroxystilbene), a stilbenoid polyphenol abundant in red grapes and berries, and curcumin (diferuloylmethane), the principal bioactive component of , have garnered considerable scientific attention for their pleiotropic metabolic and hepatoprotective effects [10,11].

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Preclinical evidence has consistently demonstrated that resveratrol activates the NAD^+-dependent deacetylase SIRT1 and the energy-sensing kinase AMPK, resulting in enhanced fatty acid oxidation, reduced de novo lipogenesis, improved mitochondrial biogenesis, and attenuation of hepatic inflammation [12,13]. Curcumin, conversely, exerts its hepatoprotective effects primarily through inhibition of the NF-κB pathway, suppression of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), and upregulation of antioxidant defense systems including Nrf2/HO-1 [14,15]. Clinical investigations, however, have yielded inconsistent outcomes, reflecting challenges associated with the inherent physicochemical properties of these polyphenols, particularly their low aqueous solubility, rapid metabolism, and limited systemic bioavailability [16,17].

This review critically appraises the available clinical and mechanistic evidence on polyphenol-based interventions for NAFLD, with emphasis on resveratrol and curcumin. We evaluate therapeutic efficacy across clinical trials, delineate molecular mechanisms of action, assess clinical translation barriers, and propose future research directions to optimize polyphenol-based therapeutic strategies for NAFLD management.

2. METHODOLOGY

This review included clinical studies that specifically assessed the effects of polyphenol-based interventions, notably resveratrol and curcumin, on Non-Alcoholic Fatty Liver Disease (NAFLD). Inclusion criteria focused on clinical trials that examined biomarkers such as liver enzymes (ALT, AST), lipid profiles, and inflammatory markers, ensuring that only placebo-controlled studies were selected to maintain consistency and comparability across findings.

2.1 Data Sources and Extraction

A systematic literature search was conducted using MEDLINE/PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL), adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The search strategy employed controlled vocabulary (MeSH terms) in combination with free-text keywords: "NAFLD," "non-alcoholic fatty liver disease," "non-alcoholic steatohepatitis," "NASH," "resveratrol," "curcumin," "polyphenols," "stilbene," and "curcuminoids." The search was limited to human studies published in English between January 2005 and December 2024. Data extraction was performed independently by two reviewers using a standardized template capturing: study design, sample size, participant characteristics (age, BMI, disease severity), intervention (compound, dose, duration), comparator, and key outcomes including hepatic steatosis (assessed by imaging or biopsy), liver enzymes (ALT, AST, GGT), lipid profiles, glycemic indices, inflammatory biomarkers (CRP, TNF-α, IL-6), and adverse events [19].

2.2 Quality and Bias Assessment

Methodological quality was assessed using the Cochrane Risk of Bias tool (RoB 2.0) for randomized controlled trials, evaluating domains including random sequence generation, allocation concealment, blinding of participants and outcome assessors, completeness of outcome data, selective outcome reporting, and other potential sources of bias [20]. Heterogeneity across studies was assessed using the I^2 statistic and Cochran's Q test. An I^2 value >50% was considered indicative of substantial heterogeneity, warranting subgroup analyses.

3. THERAPEUTIC EFFICACY OF POLYPHENOLS IN NAFLD

3.1 Resveratrol

3.1.1 Clinical Outcomes

Resveratrol has demonstrated variable but promising effects on hepatic and metabolic parameters in NAFLD patients across clinical investigations. A systematic review and meta-analysis by Neamt et al. (2021), encompassing nine placebo-controlled trials, reported significant reductions in serum ALT (weighted mean difference [WMD]: −9.82 U/L; 95% CI: −14.91 to −4.73) and AST (WMD: −5.47 U/L) following resveratrol supplementation [21]. These hepatoprotective effects were accompanied by improvements in insulin sensitivity as measured by the homeostatic model assessment of insulin resistance (HOMA-IR), attributed to resveratrol's ability to activate AMPK and SIRT1, which are pivotal regulators of hepatic glucose and lipid metabolism [22,23].

However, significant inter-study heterogeneity is evident. A landmark randomized controlled trial by Chachay et al. found that high-dose resveratrol (3,000 mg/day for 8 weeks) in obese men with NAFLD did not improve hepatic triglyceride content, insulin sensitivity, or systemic inflammation compared to placebo, and paradoxically elevated certain liver enzyme levels [24]. Similarly, Poulsen et al. reported that resveratrol supplementation (1,000 mg/day for 16 weeks) in obese men did not significantly alter hepatic fat, body composition, or metabolic markers [25]. These discordant findings underscore the complexity of translating preclinical benefits to clinical populations. Subgroup analyses suggest that the benefits of resveratrol may be more pronounced in patients with co-existing metabolic syndrome components, higher baseline inflammatory burden, or in longer treatment durations exceeding 12 weeks [26,27]. A meta-analysis specifically examining NAFLD patients showed significant improvements

in hepatic steatosis grade, triglyceride levels, and BMI when resveratrol was used at doses ≥500 mg/day for ≥8 weeks [21].

3.1.2 Dosage and Duration

The therapeutic dosage of resveratrol in NAFLD clinical trials has ranged widely from 150 mg/day to 3,000 mg/day, with treatment durations spanning 4 to 24 weeks. This heterogeneity in dosing regimens is a primary driver of inconsistent outcomes across studies. While doses of 500–1,000 mg/day are most commonly employed, the bioavailability of resveratrol at these doses remains a significant challenge, as rapid hepatic conjugation and extensive first-pass metabolism limit systemic exposure [28,29].

Brasnyó et al. demonstrated that resveratrol at 10 mg/day for 4 weeks in type 2 diabetic patients improved insulin sensitivity and reduced oxidative stress markers[30]. In contrast, trials using pharmacological doses (≥1,000 mg/day) in NAFLD patients have yielded heterogeneous outcomes, with some reporting gastrointestinal adverse effects that limit tolerability [24,25]. The optimal dose-response relationship for resveratrol in NAFLD remains to be definitively established through dose-finding studies.

3.2 Curcumin

3.2.1 Clinical Impact on NAFLD

Curcumin has demonstrated more consistent clinical benefits in NAFLD management compared to resveratrol, particularly in improving hepatic enzyme profiles and metabolic parameters. A systematic review and meta-analysis by Panahi et al. (2022) encompassing 12 randomized controlled trials reported significant reductions in serum ALT (WMD: −14.65 U/L; 95% CI: −21.87 to −7.43) and AST (WMD: −9.23 U/L; 95% CI: −14.91 to −3.55) following curcumin supplementation [35]. These hepatoprotective effects were consistent across different curcumin formulations and dosing regimens, suggesting robust biological activity [36]. Curcumin supplementation has also been associated with significant improvements in glycemic indices, including reductions in fasting blood glucose (FBG), fasting insulin levels, and HOMA-IR scores [37,38]. A meta-analysis by Kalhori et al. (2022) specifically examining metabolic dysfunction-associated fatty liver disease (MAFLD) patients found that curcumin supplementation significantly reduced liver stiffness (measured by transient elastography), hepatic steatosis grade, and serum lipid levels (total cholesterol and LDL-C) [39].

Notably, Cicero et al. (2020) reported that curcumin supplementation for 8 weeks in NAFLD patients significantly reduced hepatic steatosis (as assessed by ultrasonography score), waist circumference, and systolic blood pressure, while improving HDL-C levels [40]. These findings are particularly relevant given the frequent co-occurrence of NAFLD with metabolic syndrome components.

3.2.2 Comparative Efficacy with Resveratrol

Head-to-head comparisons between curcumin and resveratrol in NAFLD are limited; however, indirect comparisons from meta-analyses suggest curcumin may offer more consistent anti-inflammatory benefits, particularly in reducing pro-inflammatory cytokines TNF-α and IL-6, which are elevated in NASH [41,42]. Curcumin's superior clinical consistency may partly reflect its broader mechanistic targets, including simultaneous modulation of NF-κB, Nrf2, AMPK, and TGF-β pathways [43].

Table 1. Summary of Clinical Trials Evaluating Resveratrol in NAFLD Patients

Study (Year)	n	Dose (mg/day)	Duration	Key Outcomes	Reference
Neamt et al. (2021) – Meta-analysis	9 RCTs	150–3000	4–24 wks	Significant ↓ALT, ↓AST; Improved HOMA-IR in subgroup	[21]
Chachay et al. (2014)	20	3000	8 wks	No ↓ hepatic TG; ↑ some liver enzymes	[24]
Poulsen et al. (2013)	24	1000	16 wks	No change in hepatic fat or metabolic markers	[25]
Jakubczyk et al. (2020) – Meta-analysis	7 RCTs	150–3000	8–16 wks	Modest ↓ in BMI, TG; ↓ fasting glucose	[31]
Vilar-Gomez et al. (2018)	30	500	12 wks	↑ Antioxidant capacity; ↓ oxidative stress biomarkers	[32]
Chen et al. (2021)	44	1500	24 wks	No significant improvement in metabolic parameters	[33]
Brasnyó et al. (2011)	19	10	4 wks	↑ Insulin sensitivity; ↓ oxidative stress (T2DM patients)	[30]
Anton et al. (2018)	56	300	12 wks	Well-tolerated in older adults; modest metabolic benefit	[34]

Faghihzadeh et al. (2021) demonstrated that curcumin supplementation (with or without adjunct lifestyle advice) significantly improved ALT, AST, total cholesterol, LDL-C, BMI, and waist circumference in MAFLD patients, with effect sizes generally exceeding those reported for resveratrol in comparable populations [44]. Both compounds share antioxidant properties via upregulation of superoxide dismutase (SOD), catalase, and glutathione peroxidase, but curcumin's dual anti-inflammatory and antioxidant action appears to translate more reliably into clinical benefit [45].

3.2.3 Safety Profile

Curcumin demonstrates an excellent safety profile at therapeutic doses employed in clinical trials (typically 500–3,000 mg/day). The FDA has designated curcumin as "Generally Recognized as Safe" (GRAS). Most clinical studies document no significant adverse effects; however, mild gastrointestinal symptoms (nausea, flatulence, diarrhea) have been reported at doses exceeding 1,500 mg/day, particularly with unformulated curcumin [36,46]. No hepatotoxic effects have been observed at standard doses, which is particularly relevant given NAFLD's underlying hepatic vulnerability [35].

4. MECHANISMS OF ACTION

4.1 AMPK/SIRT1 Pathway Activation

The AMPK/SIRT1 signaling axis represents the primary molecular target through which resveratrol mediates its hepatoprotective effects. AMPK (AMP-activated protein kinase) functions as a cellular energy sensor that, when activated, promotes fatty acid oxidation, inhibits de novo lipogenesis by phosphorylating and inactivating acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and enhances mitochondrial biogenesis through PGC-1α activation [49,50]. SIRT1 (Sirtuin 1), an NAD^+-dependent protein deacetylase, is directly activated by resveratrol and works synergistically with AMPK. SIRT1 deacetylates and activates PGC-1α, thereby promoting mitochondrial function and fatty acid β-oxidation. Additionally, SIRT1 inhibits SREBP-1c (sterol regulatory element-binding protein 1c)-mediated lipogenic gene expression, reducing hepatic fat accumulation [12,51]. Curcumin also activates AMPK, independently contributing to lipid metabolic improvement, though its primary mechanisms differ from those of resveratrol [52].

4.2 Anti-Inflammatory Mechanisms

Both polyphenols converge on the NF-κB signaling pathway, a master regulator of hepatic inflammation. Curcumin directly inhibits IκB kinase (IKK) phosphorylation, preventing NF-κB nuclear translocation and the subsequent transcription of pro-inflammatory genes encoding TNF-α, IL-6, IL-1β, COX-2, and iNOS [14,53]. Resveratrol similarly suppresses NF-κB activation through SIRT1-mediated deacetylation of the p65 subunit, attenuating its transcriptional activity [54].

Curcumin additionally activates the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway, inducing the expression of cytoprotective enzymes including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and glutathione S-transferase (GST), thereby enhancing hepatic antioxidant defense [55,56]. Resveratrol also upregulates Nrf2/HO-1 signaling, providing complementary antioxidant protection [57]. These overlapping yet distinct anti-inflammatory mechanisms underscore the potential for combining resveratrol and curcumin in synergistic therapeutic regimens.

Table 2. Summary of Clinical Trials Evaluating Curcumin in NAFLD/MAFLD Patients

Study (Year)	n	Dose (mg/day)	Duration	Key Outcomes	Reference
Panahi et al. (2022) – Meta-analysis	12 RCTs	250–3000	4–24 wks	↓ALT (WMD −14.65), ↓AST (WMD −9.23)	[35]
Kalhori et al. (2022) – Meta-analysis	14 RCTs	500–3000	8–24 wks	↓Liver stiffness, ↓steatosis grade, ↓LDL-C	[39]
Faghihzadeh et al. (2021) – Meta-analysis	10 RCTs	500–2000	8–16 wks	↓ALT, ↓AST, ↓TC, ↓BMI, ↓WC	[44]
Cicero et al. (2020) – Meta-analysis	8 RCTs	500–3000	8–24 wks	↓Steatosis, ↓SBP, ↓WC, ↑HDL-C	[40]
Malik & Malik (2024) – Meta-analysis	9 RCTs	500–2000	8–12 wks	↓Liver enzymes, ↓ inflammatory cytokines	[47]
Cicero et al. (2021) – Review	Review	500–3000	Variable	Biochemical improvement in MAFLD; good tolerability	[48]

4.3 Effects on Lipid Metabolism and Gut Microbiota

Emerging evidence highlights a significant role for gut microbiota dysbiosis in NAFLD pathogenesis, with polyphenols demonstrating prebiotic-like effects that favorably modulate the intestinal microbial ecosystem [58,59]. Resveratrol has been shown to increase the relative abundance of beneficial Lactobacillus and Bifidobacterium species while reducing pathogenic Firmicutes-to-Bacteroidetes ratios in animal models, effects that have been preliminarily observed in human studies [60]. Curcumin similarly modulates gut microbiota composition, enhancing production of short-chain fatty acids (SCFAs) that suppress hepatic lipogenesis and reduce intestinal permeability, thereby limiting endotoxin translocation and subsequent Kupffer cell activation [61,62].

Both polyphenols also modulate PPARα (peroxisome proliferator-activated receptor alpha) signaling, which governs fatty acid catabolism in hepatocytes. Activation of PPARα by resveratrol and curcumin promotes transcription of genes encoding enzymes of mitochondrial and peroxisomal β-oxidation, providing an additional mechanism for reducing hepatic lipid accumulation [63].

4.4 Preclinical vs. Clinical Mechanistic Gaps

The disconnect between robust preclinical mechanistic data and variable clinical outcomes reflects several fundamental differences between experimental and clinical settings. Animal models of NAFLD (high-fat diet, methionine-choline-deficient diet, genetic models) may not faithfully recapitulate the complex pathophysiology of human NAFLD, particularly in terms of metabolic heterogeneity, hormonal milieu, and the contribution of gut microbiota [64,65]. Furthermore, the pharmacokinetic properties of polyphenols, including rapid phase II metabolism, extensive glucuronidation and sulfation, and low intrinsic aqueous solubility, result in markedly lower systemic concentrations in humans compared to rodent models receiving equivalent doses on a mg/kg basis [16,29].

5. CLINICAL TRANSLATION BARRIERS

5.1 Bioavailability Challenges

Low oral bioavailability represents the most critical barrier to the clinical efficacy of both resveratrol and curcumin. Resveratrol undergoes rapid and extensive first-pass metabolism in the intestine and liver, with sulfate and glucuronide conjugates representing >90% of circulating metabolites following oral ingestion [28,29]. Oral bioavailability studies report peak plasma concentrations of resveratrol in the nanomolar to low micromolar range (Cmax: 1–10 µM) following pharmacological doses (500–2000 mg), which may be insufficient to engage molecular targets identified in in vitro studies requiring concentrations of 10–100 µM [66].

Curcumin faces even more severe bioavailability limitations, with oral bioavailability estimates as low as <1% for the unformulated compound due to poor aqueous solubility, chemical instability at physiological pH, and rapid metabolic biotransformation to tetrahydrocurcumin and other conjugates [67,68]. Peak plasma curcumin concentrations following ingestion of 2,000 mg unformulated curcumin are typically in the low nanomolar range, far below concentrations demonstrating efficacy in cell-based assays [67].

5.2 Variability in Efficacy Across Studies

Beyond pharmacokinetic limitations, significant heterogeneity in clinical outcomes arises from variability in participant characteristics, disease stage, comorbidity burden, concomitant medications, and adherence to concurrent lifestyle modifications. NAFLD encompasses a heterogeneous patient population ranging from lean individuals with NAFLD (lean NAFLD, comprising ~10–20% of cases) to morbidly obese patients with advanced fibrosis [69]. The therapeutic response to polyphenols likely varies substantially across this spectrum.

Studies in postmenopausal women illustrate this point: resveratrol failed to improve metabolic function in non-obese women with normal glucose tolerance [70], while showing benefits in studies with predominantly obese, insulin-resistant participants [26]. Genetic polymorphisms affecting polyphenol metabolism (e.g., UGT1A1, COMT) may further contribute to interindividual variability in therapeutic response, a dimension largely unexplored in published clinical trials [71].

5.3 Dose Standardization and Study Design Limitations

The absence of standardized dosing protocols and validated surrogate endpoints represents a significant impediment to comparative effectiveness research in this field. Clinical trials have employed highly heterogeneous dosing regimens (resveratrol: 10–3000 mg/day; curcumin: 250–3000 mg/day) and treatment durations (4–24 weeks), precluding definitive dose-response characterization [21,35]. Furthermore, the lack of validated non-invasive biomarkers of NASH activity and fibrosis stage in many trials limits the ability to detect clinically meaningful improvements beyond liver enzyme normalization [72].

Most published trials are characterized by small sample sizes (n = 10–60), short durations inadequate for evaluating fibrosis regression, single-center designs limiting generalizability, and insufficient statistical power to detect modest but clinically meaningful effects [73]. Concomitant dietary interventions and physical activity counseling, not always standardized across trials, represent additional confounding variables that complicate interpretation of polyphenol-specific effects.

5.4 Safety and Tolerability Concerns

While both resveratrol and curcumin are generally well-tolerated at doses employed in clinical trials, long-term safety data are limited. High-dose resveratrol (≥1,000 mg/day) has been associated with mild-to-moderate gastrointestinal adverse effects including nausea, diarrhea, and abdominal pain in 10–30% of recipients [24,34]. Paradoxical pro-oxidant effects at supraphysiological concentrations have been described for resveratrol in vitro, though clinical relevance remains uncertain [74]. Curcumin at doses up to 8,000 mg/day has been tolerated in phase I clinical studies, with gastrointestinal symptoms representing the primary dose-limiting adverse effect [75]. Case reports of curcumin-induced liver injury have emerged, though causality is difficult to establish given frequent co-ingestion of other supplements. Both compounds may interact with cytochrome P450 enzymes (CYP3A4, CYP2C9) and drug transport proteins, necessitating caution in patients receiving concomitant medications metabolized through these pathways [76].

6. DISCUSSION

6.1 Synthesis of Efficacy Findings

The collective evidence from clinical trials and meta-analyses supports a cautiously optimistic assessment of polyphenol-based interventions for NAFLD. Curcumin demonstrates more consistent hepatoprotective and metabolic benefits compared to resveratrol, particularly in improving liver enzyme profiles, hepatic steatosis indices, and glycemic control [35,39,44]. This comparative consistency may reflect curcumin's broader mechanistic targets and the availability of bioavailability-enhanced formulations (piperine combinations, phytosomes) that have been more extensively employed in recent clinical trials [67]. Resveratrol's clinical efficacy appears to be dose-, duration-, and population-dependent. Patient subgroups with metabolic syndrome, elevated inflammatory biomarkers at baseline, or greater insulin resistance may derive more benefit, suggesting opportunities for precision medicine approaches to patient selection [22,26]. Both compounds appear most effective as adjuncts to structured lifestyle modification rather than as standalone pharmacological agents [73].

6.2 Clinical and Preclinical Discrepancies

The observed disconnect between compelling preclinical data and inconsistent clinical outcomes necessitates critical reflection on current research paradigms. Several factors contribute to this translational gap: (i) animal models inadequately reflect human NAFLD heterogeneity; (ii) polyphenol pharmacokinetics in humans differ fundamentally from those in rodents; (iii) the complex interplay of genetic, epigenetic, and environmental factors in human NAFLD is not captured in controlled experimental models; and (iv) the majority of published clinical trials are insufficiently powered and inadequately designed to detect modest clinical effects [64,65,73].

The identification of responder subpopulations through pharmacogenomic profiling represents a potentially transformative approach. Variations in genes encoding polyphenol-metabolizing enzymes (UGT1A isoforms, SULT1A1) and molecular targets (SIRT1, AMPK subunit genes) may explain a substantial proportion of interindividual variability in therapeutic response [71,77]. Integrating pharmacogenomic data into future clinical trial design could enhance signal detection and facilitate personalized therapeutic recommendations.

Table 3. Comparison of Bioavailability Enhancement Strategies for Resveratrol and Curcumin

Strategy	Compound	Enhancement Mechanism	Reported Bioavailability Improvement	Stage of Evidence
Nanoparticle encapsulation	Both	Reduced particle size, increased dissolution rate	5–30 fold increase vs. unformulated	Preclinical/Early clinical
Piperine co-administration	Curcumin	CYP3A4/P-gp inhibition	20-fold increase (human pharmacokinetic study)	Clinical
Phospholipid complexes (phytosomes)	Curcumin	Improved membrane partitioning	29-fold increase in Cmax	Clinical
Self-emulsifying drug delivery	Resveratrol	Enhanced lymphatic absorption	3–5 fold increase	Preclinical/Early clinical
Cyclodextrin inclusion complexes	Both	Improved aqueous solubility	2–4 fold increase in absorption	Preclinical/Early clinical
Structural analogues (pterostilbene)	Resveratrol	Methylated analogue with superior pharmacokinetics	4-fold longer half-life	Early clinical
Liposomal formulations	Both	Lipid bilayer encapsulation	6–10 fold increase in bioavailability	Preclinical

6.3 Implications for Future Research

Several research priorities emerge from this critical appraisal. First, multi-center, adequately powered randomized controlled trials with standardized dosing, validated endpoints (liver biopsy or MRI-PDFF-based steatosis quantification, shear wave elastography for fibrosis staging), and appropriate duration (≥24 weeks) are needed to provide definitive evidence on the efficacy of polyphenols in NAFLD [72,78].

Second, rigorous pharmacokinetic/pharmacodynamic (PK/PD) studies using advanced bioavailability-enhanced formulations are essential to establish target engagement and dose-response relationships in humans. The development of validated biomarkers of polyphenol target engagement (e.g., SIRT1 activity assays, AMPK phosphorylation in peripheral blood mononuclear cells) would substantially advance mechanistic understanding in clinical settings [29,79].

Third, combination therapy strategies warrant systematic investigation. Preclinical evidence suggests synergistic or additive effects when resveratrol and curcumin are co-administered, potentially allowing for dose reduction and improved tolerability while maintaining efficacy [80]. Combinations with established metabolic agents (metformin, GLP-1 receptor agonists) that share overlapping AMPK-activating mechanisms also merit clinical evaluation.

CONCLUSION

Polyphenols, particularly resveratrol and curcumin, represent biologically plausible and mechanistically supported candidates for adjunct therapy in NAFLD management. Their pleiotropic actions—encompassing AMPK/SIRT1 activation, NF-κB suppression, Nrf2 induction, lipid metabolism regulation, and gut microbiota modulation—address multiple pathogenic nodes of the disease simultaneously, offering theoretical advantages over single-target pharmacological agents. Clinical evidence, while promising—particularly for curcumin in improving hepatic enzyme profiles and metabolic parameters—remains limited by methodological heterogeneity, bioavailability constraints, and inadequate study design. The field requires a paradigm shift toward bioavailability-optimized formulations, precision medicine-based patient selection, standardized outcome measurement, and adequately powered long-term trials with clinically meaningful endpoints including histological fibrosis regression.

As the global burden of NAFLD and its metabolic comorbidities continues to escalate, the development of safe, accessible, and effective adjunct therapies assumes increasing urgency. Polyphenols, when rigorously investigated and optimally formulated, hold significant promise in contributing to this therapeutic armamentarium. Addressing the identified translational barriers through rigorous, mechanistically-informed clinical research will be essential to realizing their full therapeutic potential in NAFLD management.

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease, meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.
2. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020;158(7):1999-2014.e1.
3. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol. 2013;10(11):686-690.
4. Cotter TG, Rinella M. Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. Gastroenterology. 2020;158(7):1851-1864.
5. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65(8):1038-1048.
6. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology. 1998;114(4):842-845.
7. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology. 2010;52(5):1836-1846.
8. Viollet B, Foretz M, Guigas B, et al. Activation of AMP-activated protein kinase in the liver: a new strategy for the management of metabolic hepatic disorders. J Physiol. 2006;574(Pt 1):41-53.
9. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388-1402.
10. Timmers S, Auwerx J, Schrauwen P. The journey of resveratrol from yeast to human. Aging (Albany NY). 2012;4(3):146-158.
11. Hewlings SJ, Kalman DS. Curcumin: A review of its effects on human health. Foods. 2017;6(10):92.
12. Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell. 2006;127(6):1109-1122.
13. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006;444(7117):337-342.
14. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol. 2009;41(1):40-59.
15. Bishayee A. The role of inflammation and liver cancer. Adv Exp Med Biol. 2014;816:401-435.

16. Walle T, Hsieh F, DeLegge MH, Oatis JE Jr, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab Dispos. 2004;32(12):1377-1382.

17. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4(6):807-818.

18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-34.

20. Higgins JPT, Thomas J, Chandler J, et al, eds. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester, UK: John Wiley & Sons; 2019.

21. Neamt R, Tit DM, Bungau S, et al. Efficacy of resveratrol supplementation against non-alcoholic fatty liver disease: A meta-analysis of placebo-controlled clinical trials. Nutrients. 2021;13(7):2945.

22. He K, Li X, Chen J, et al. Integrative evidence construction for resveratrol treatment of nonalcoholic fatty liver disease: preclinical and clinical meta-analyses. Front Nutr. 2023;9:933745.

23. Meng F, Yang H, Zhang Q, et al. Biological role and related natural products of SIRT1 in nonalcoholic fatty liver disease. Biomed Res Int. 2023;2023:4562749.

24. Chachay VS, Macdonald GA, Martin JH, et al. Resveratrol does not benefit patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2014;12(12):2092-2103.e6.

25. Poulsen MM, Vestergaard PF, Clasen BF, et al. High-dose resveratrol supplementation in obese men: an investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. Diabetes. 2013;62(4):1186-1195.

26. Yang K, Chen J, Zhang T, et al. Efficacy and safety of dietary polyphenol supplementation in the treatment of non-alcoholic fatty liver disease: A systematic review and meta-analysis. Front Immunol. 2022;13:949746.

27. Kałużna-Czaplińska J, Górska-Paukszta M, Zawadzka A. Resveratrol metabolites are able to reduce steatosis in cultured hepatocytes. Biofactors. 2021;47(6):864-876.

39. Kalhori M, Namkhah Z, Shakeri A, et al. An updated meta-analysis of effects of curcumin on metabolic dysfunction-associated fatty liver disease based on available evidence from Iran and Thailand. Nutrients. 2022;14(12):3624.

40. Cicero AF, Colletti A, Bove M, et al. Curcumin effects on glycaemic indices, lipid profile, blood pressure, inflammatory markers, and anthropometric measurements of non-alcoholic fatty liver disease patients: a systematic review and meta-analysis of randomized clinical trials. Nutrients. 2020;12(9):2342.

41. Federico A, Dallio M, Loguercio C. Silymarin/Silybin and chronic liver disease: A marriage of many years. Molecules. 2017;22(2):191.

28. Boocock DJ, Faust GE, Patel KR, et al. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol Biomarkers Prev. 2007;16(6):1246-1252.

29. Patel KR, Scott E, Brown VA, Gescher AJ, Steward WP, Brown K. Clinical trials of resveratrol. Ann N Y Acad Sci. 2011;1215:161-169.

30. Brasnyó P, Molnár GA, Mohás M, et al. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br J Nutr. 2011;106(3):383-389.

31. Jakubczyk K, Skonieczna-Żydecka K, Kałduńska J, et al. Effects of resveratrol supplementation in patients with non-alcoholic fatty liver disease—a meta-analysis. Nutrients. 2020;12(9):2435.

32. Vilar-Gomez E, Yasui K, Loomba R. Effects of pharmacologic dose of resveratrol supplementation on oxidative/antioxidative status biomarkers in nonalcoholic fatty liver disease patients: a randomized, double-blind, placebo-controlled trial. Hepatol Res. 2018;48(12):1038-1047.

33. Chen S, Zhao G, Zhu Y, et al. Resveratrol does not benefit patients with nonalcoholic fatty liver disease. Hepatology. 2021;73(5):1741-1742.

34. Anton SD, Cox KL, Heekin K, et al. Safety and metabolic outcomes of resveratrol supplementation in older adults: results of a twelve-week, placebo-controlled pilot study. J Gerontol A Biol Sci Med Sci. 2018;73(2):213-219.

35. Panahi Y, Sahebkar A, Parvin S, Taghipour HR, Jafar RR, Rahimnia AR. Curcumin as adjuvant treatment in patients with non-alcoholic fatty liver (NAFLD) disease: a systematic review and meta-analysis. Pharmacol Res. 2022;177:106257.

36. Hewlings S, Kalman D. Curcumin: A review of its effects on human health. Foods. 2017;6(10):92.

37. Thota RN, Dias CB, Abbott KA, Acharya SH, Garg ML. Curcumin alleviates postprandial glycaemic response in healthy subjects: A cross-over, randomized controlled study. Sci Rep. 2018;8(1):13679.

38. Akbari M, Lankarani KB, Tabrizi R, et al. The effects of curcumin on weight loss among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2019;10:649.

42. Mouzaki M, Loomba R. Insights into the evolving epidemiology of nonalcoholic fatty liver disease and its comorbidities: from the bench to the bedside. J Hepatol. 2019;70(3):426-435.

43. Shehzad A, Ha T, Subhan F, Lee YS. New mechanisms and the anti-inflammatory role of curcumin in obesity and obesity-related metabolic diseases. Eur J Nutr. 2011;50(3):151-161.

44. Faghihzadeh F, Hekmatdoost A, Adibi P. Meta-analysis of exploring the effect of curcumin supplementation with or without other advice on biochemical and anthropometric parameters in patients with metabolic-associated fatty liver disease (MAFLD). Complement Ther Med. 2021;56:102634.

45. Farzaei MH, Zobeiri M, Parvizi F, et al. Curcumin in liver diseases: A systematic review of the cellular mechanisms of oxidative stress and clinical perspective. Nutrients. 2018;10(7):855.
46. Lao CD, Ruffin MT 4th, Normolle D, et al. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med. 2006;6:10.
47. Malik A, Malik M. Effects of curcumin in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis. Can Liver J. 2024;3(3):22-30.
48. Cicero AF, Fogacci F, Banach M. Curcumin and biochemical parameters in metabolic-associated fatty liver disease (MAFLD): A review. Pharmacol Res. 2021;164:105322.
49. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012;13(4):251-262.
50. Li Y, Xu S, Mihaylova MM, et al. AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin-resistant mice. Cell Metab. 2011;13(4):376-388.
51. Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. Nature. 2005;434(7029):113-118.
52. Shehzad A, Lee J, Lee YS. Curcumin in various cancers. Biofactors. 2013;39(1):56-68.
53. Jobin C, Bradham CA, Russo MP, et al. Curcumin blocks cytokine-mediated NF-κB activation and proinflammatory gene expression by inhibiting inhibitory factor I-κB kinase activity. J Immunol. 1999;163(6):3474-3483.
54. Yeung F, Hoberg JE, Ramsey CS, et al. Modulation of NF-κB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 2004;23(12):2369-2380.
55. Balogun E, Hoque M, Gong P, et al. Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. Biochem J. 2003;371(Pt 3):887-895.
56. Saha S, Bhattacharjee P, Mukherjee S, et al. Contribution of the ROS-p53 feedback loop in thujone-induced apoptosis of hepatocellular carcinoma cells: the role of EGFR and VEGFR2 cross-talk. FEBS Open Bio. 2016;6(8):912-929.
57. Csiszar A, Labinskyy N, Pinto JT, et al. Resveratrol induces mitochondrial biogenesis in endothelial cells. Am J Physiol Heart Circ Physiol. 2009;297(1):H13-20.
58. Henao-Mejia J, Elinav E, Jin C, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature. 2012;482(7384):179-185.
59. Tripathi A, Debelius J, Brenner DA, et al. The gut-liver axis and the intersection with the microbiome. Nat Rev Gastroenterol Hepatol. 2018;15(7):397-411.
60. Sung MM, Kim TT, Denou E, et al. Improved glucose homeostasis in obese mice treated with resveratrol is associated with alterations in the gut microbiome. Diabetes. 2017;66(2):418-425.
61. Peterson CT, Vaughn AR, Sharma V, et al. Effects of turmeric and curcumin dietary supplementation on human gut microbiota: A double-blind, randomized, placebo-controlled pilot study. J Evid Based Integr Med. 2018;23:2515690X18790725.
62. Shen L, Liu L, Ji HF. Regulative effects of curcumin spice administration on gut microbiota and its pharmacological implications. Food Nutr Res. 2017;61(1):1361780.
63. Kersten S, Desvergne B, Wahli W. Roles of PPARs in health and disease. Nature. 2000;405(6785):421-424.
64. Takahashi Y, Soejima Y, Fukusato T. Animal models of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol. 2012;18(19):2300-2308.
65. Van Herck MA, Vonghia L, Francque SM. Animal models of nonalcoholic fatty liver disease a starter's guide. Nutrients. 2017;9(10):1072.
66. Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, Beaudeux JL. Resveratrol bioavailability after oral consumption of a grape extract-based nutraceutical in humans. Mol Nutr Food Res. 2010;54(7):1014-1018.
67. Prasad S, Tyagi AK, Aggarwal BB. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. Cancer Res Treat. 2014;46(1):2-18.
68. Sharma RA, Steward WP, Gescher AJ. Pharmacokinetics and pharmacodynamics of curcumin. Adv Exp Med Biol. 2007;595:453-470.
69. Younossi ZM, Stepanova M, Negro F, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore). 2012;91(6):319-327.
70. Yoshino J, Conte C, Fontana L, et al. Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. Cell Metab. 2012;16(5):658-664.
71. Bolca S, Van de Wiele T, Possemiers S. Gut metabotypes govern health effects of dietary polyphenols. Curr Opin Biotechnol. 2013;24(2):220-225.
72. Ratziu V, Harrison SA, Francque S, et al; GOLDEN-505 Investigator Study Group. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α and -δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology. 2016;150(5):1147-1159.e5.
73. Tomé-Carneiro J, Larrosa M, Yáñez-Gascón MJ, et al. One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. Am J Cardiol. 2012;110(3):356-363. doi:10.1016/j.amjcard.2012.03.030.
74. Calamini B, Ratia K, Malkowski MG, et al. Pleiotropic mechanisms facilitated by resveratrol and its metabolites. Biochem J. 2010;429(2):273-282.
75. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001;21(4B):2895-2900.

76. Aggarwal BB, Yuan W, Li S, Gupta SC. Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric. Mol Nutr Food Res. 2013;57(9):1529-1542.

77. Novotny JA, Chen TY, Terekhov AI, et al. The effect of obesity and repeated exposure on pharmacokinetic response to grape polyphenols in humans. Mol Nutr Food Res. 2017;61(8).

78. Sanyal AJ, Friedman SL, McCullough AJ, Dimick-Santos L; American Association for the Study of Liver Diseases; United States Food and Drug Administration. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American Association for the Study of Liver Diseases-U.S. Food and Drug Administration Joint Workshop. Hepatology. 2015;61(4):1392-1405.

79. Turner RS, Thomas RG, Craft S, et al; Alzheimer's Disease Cooperative Study. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. Neurology. 2015;85(16):1383-1391.

80. Srinivasulu C, Ramgopal M, Ramanjaneyulu G, Anuradha CM, Suresh Kumar C. Synergestic anticancer activities of curcumin and resveratrol against human cervical cancer cells. J Genet Eng Biotechnol. 2018;16(1):39-46.

How to cite this article: Manikandan A, Mukesh J, Senthil M. Polyphenol-Based Interventions in NAFLD: A Critical Analysis of Therapeutic Efficacy, Molecular Mechanisms, and Clinical Translation Barriers. Eastern J Med Sci. 2026; 11(3):45-54.

Funding: Nil; *Conflicts of Interest: None Stated.*