e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2025; 17(8); 1502-1510

Original Research Article

Antioxidant Therapy with Vitamin E and Glutathione in Non-Alcoholic Steatohepatitis: Insights from Systematic Reviews

Patel Bhavya H.[1], Vaghasia Yagnik A.[2], Bhatt Dhruti G.[3]

[1]Independent Researcher
[2]Senior Resident, Department of Pharmacology, Dr. M. K. Shah Medical College & Research Centre, Ahmedabad, Gujarat, India
[3]Assistant Professor, Department of Pharmacology, Dr. M. K. Shah Medical College & Research Centre, Ahmedabad, Gujarat, India

Received: 04-06-2025 / Revised: 29-06-2025 / Accepted: 21-07-2025
Corresponding author: Dr. Vaghasia Yagnik A
Conflict of interest: Nil

Abstract

Background: Non-alcoholic steatohepatitis (NASH) is a serious liver condition caused by fat build up that triggers inflammation and damage. Over time, this can lead to fibrosis or cirrhosis. With no approved medicines available, researchers are testing antioxidants like vitamin E and glutathione (GSH), which reduce oxidative stress in the liver.

Aims and Objectives: This review summarizes evidence on vitamin E and GSH for NASH, evaluating their benefits, risks, and limitations.

Methods: We reviewed studies from 2010–2024, including 22 systematic reviews/meta-analyses and 10 primary studies, reporting effects on liver enzymes, tissue changes, oxidative stress, and safety.

Results: Vitamin E (400–800 IU/day) consistently lowered liver enzymes (ALT, AST), reduced liver fat and inflammation, and modestly improved fibrosis, especially in adults without diabetes. GSH (300–1200 mg/day, oral or injectable) reduced enzymes and oxidative stress markers in smaller pilot studies, suggesting promise. Some studies combining antioxidants showed better outcomes, but large trials are lacking. High-dose vitamin E may increase stroke or prostate cancer risk, while long-term GSH safety remains unclear.

Conclusion: Vitamin E shows proven benefits for NASH; GSH appears promising but needs further study. Antioxidant therapies could aid NASH, but larger, long-term trials are required to confirm safety and effectiveness.

Keywords: Non-alcoholic steatohepatitis, vitamin E, glutathione, oxidative stress, antioxidant therapy, systematic review.

Introduction

Non-alcoholic steatohepatitis (NASH) is a progressive form of metabolic dysfunction–associated steatotic liver disease (MASLD) that affects an estimated 3–6% of people worldwide [1]. Its burden continues to grow alongside rising rates of obesity, type 2 diabetes, and metabolic syndrome [1]. NASH is defined by excess fat in the liver accompanied by lobular inflammation, hepatocyte ballooning, and scarring of the liver tissue. Over time, it can advance to cirrhosis, hepatocellular carcinoma (HCC), and liver-related death, and accounts for about 10–20% of advanced liver disease cases [2].

The disease develops through a "multiple-hit" process, with insulin resistance, lipo-toxicity, gut microbiome imbalance, and oxidative stress all playing major roles [3]. Among these, oxidative stress is particularly important. When the production of reactive oxygen species (ROS) overwhelms the body's antioxidant defences, it triggers lipid peroxidation, stimulates inflammatory cytokines like TNF-α and IL-6, and activates hepatic stellate cells—key steps that drive fibrosis [4].

At present, the only proven management strategies are lifestyle changes, especially sustained weight loss of 7–10% and regular exercise. These can improve liver histology, but maintaining such changes is difficult for many patients [5]. No drugs have yet been approved by the FDA or EMA, highlighting the urgent need for new treatment options [6]. Antioxidant therapy has received particular attention. Vitamin E (α-tocopherol) and glutathione (GSH) are two candidates with

promising mechanisms: both reduce oxidative stress and influence inflammatory pathways [7]. Vitamin E is a lipid-soluble antioxidant that interrupts lipid peroxidation and stabilizes hepatocyte membranes [8], while GSH, a tripeptide produced in the body, regulates redox balance, detoxifies harmful compounds, and supports key antioxidant enzymes such as glutathione peroxidase [9].

Evidence to date is mixed but encouraging. Large systematic reviews and meta-analyses show that vitamin E can improve outcomes, particularly in non-diabetic adults, whereas GSH has supportive data from smaller clinical studies and preclinical research [10,11]. This review brings together results from 22 systematic reviews (2010–2024), 10 primary studies, and relevant experimental models to assess the therapeutic potential of vitamin E and GSH in NASH.

It discusses biochemical and histological endpoints, mechanisms of action, safety, and the role of combination therapies, while also identifying gaps in the evidence base. The aim is to provide clinicians and researchers with a clearer understanding of where these antioxidants stand in the search for effective NASH treatments.

Materials and Methods

Data Sources and Search Strategy: This review was conducted in accordance with PRISMA guidelines to evaluate the role of antioxidant therapy, specifically vitamin E and glutathione (GSH), in non-alcoholic steatohepatitis (NASH) [12].

A systematic search of PubMed, Scopus, and Web of Science was performed for studies published between January 2010 and October 2024. The search strategy combined the terms: “non-alcoholic steatohepatitis,” “NASH,” “vitamin E,” “glutathione,” “antioxidant therapy,” and “systematic review.”

Eligibility Criteria: Studies were eligible if they were systematic reviews, meta-analyses, or primary investigations (randomized controlled trials and pilot studies) that evaluated vitamin E or GSH in patients with biopsy-confirmed NASH, or in NAFLD populations with suspected NASH. Eligible studies were required to report at least one biochemical outcome (ALT, AST) or histological endpoint (steatosis, inflammation, fibrosis).

Inclusion and Exclusion

Inclusion: Systematic reviews, meta-analyses, randomized controlled trials, and pilot studies assessing vitamin E or GSH in NASH/NAFLD, with biochemical or histological endpoints.

Exclusion: Non-human studies, case reports, and studies lacking clear NASH-related outcomes.

Data Extraction

Two reviewers independently screened titles, abstracts, and full texts. Any discrepancies were resolved by consensus. Extracted data included:

- Study design and sample size
- Intervention details (dose, duration)
- Outcomes (ALT, AST, NAS, fibrosis)
- Safety profiles

Where available, quantitative data from meta-analyses were extracted, including mean differences (MD) and odds ratios (OR). For GSH, which lacked sufficient pooled analyses, data were synthesized narratively.

Risk of Bias Assessment: The methodological quality of included studies was assessed using AMSTAR-2 for systematic reviews and the Cochrane Risk of Bias tool for randomized controlled trials [13]. Heterogeneity across studies was evaluated with the I^2 statistic, and subgroup analyses (e.g., diabetic vs. non-diabetic, adult vs. pediatric) were summarized. Data on adverse events and outcomes from combination therapies were also reviewed to assess clinical applicability.

Results

This review brought together evidence from 22 systematic reviews, 10 primary studies, and supportive preclinical experiments published between 2010 and 2024. The findings are organized around four major themes: the role of oxidative stress in NASH, evidence for vitamin E, evidence for glutathione (GSH), and comparative or combination approaches.

Oxidative Stress and the Biology of NASH: Oxidative stress is not just a background feature of NASH—it is the engine that drives disease progression. When hepatocytes are overloaded with free fatty acids, mitochondrial β-oxidation cannot keep up, and excess electrons leak into the respiratory chain. This produces a surge of reactive oxygen species (ROS), which in turn trigger lipid peroxidation, protein oxidation, and DNA damage [14,15]. Other pathways add fuel to the fire: cytochrome P450 activity, peroxisomal oxidation, and endoplasmic reticulum stress all contribute to ROS production. The downstream result is inflammation (through NF-κB activation and cytokine release) and fibrogenesis (through hepatic stellate cell activation) [16]. Clinical data mirror these mechanisms. Patients with biopsy-confirmed NASH consistently show depleted hepatic glutathione stores and lower vitamin E availability compared to healthy or steatosis-only controls [17]. Biomarkers of oxidative injury—malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and 8-

hydroxy-2-deoxyguanosine (8-OHdG)—are consistently elevated, and their levels correlate with histological severity. One meta-analysis reported that MDA levels were more than double in NASH compared to simple steatosis, while 8-OHdG tracked closely with hepatocyte ballooning [18,19]. Importantly, improvements in these markers have been associated with better histological outcomes, highlighting their value as surrogate targets in trials [20].

Vitamin E: The Best-Studied Antioxidant in NASH

Biochemical Benefits: Vitamin E has the broadest evidence base among antioxidants for NASH. Across more than a dozen randomized trials and several meta-analyses, vitamin E consistently lowers transaminases. A 2022 meta-analysis of 15 RCTs (over 1,300 patients) found average reductions of about 11 IU/L for ALT and 7 IU/L for AST compared to controls [29]. These biochemical shifts are clinically meaningful, often paralleling improvements in liver histology.

Histological Improvements: Histological data show that vitamin E is most effective at reducing steatosis and lobular inflammation. The landmark PIVENS trial (n=247) demonstrated NASH resolution in 43% of vitamin E-treated patients compared with only 19% on placebo [30]. Other pooled analyses confirm these benefits, with odds ratios suggesting 60–80% greater improvement in steatosis and inflammation relative to controls [31]. That said, vitamin E has only modest or inconsistent effects on fibrosis, with most trials failing to demonstrate significant reversal of scar tissue [32].

Who Benefits Most?: The benefits appear strongest in non-diabetic adults and in those with higher baseline AST or NAS scores [32,33]. Pediatric data (such as the TONIC trial) suggest some benefit in children, but the magnitude is smaller and more gradual [39].

Mechanisms and Safety: Vitamin E's lipophilic nature allows it to stabilize hepatocyte membranes and halt lipid peroxidation. It also suppresses pro-inflammatory cytokines and influences nuclear receptors like PPAR-γ and Nrf2 [34–36].

However, long-term safety remains a concern. High-dose supplementation (>800 IU/day) has been linked with increased risk of hemorrhagic stroke and prostate cancer in some large-scale studies [40,41]. Most trials in NASH have not seen major safety signals, but the balance of benefit and risk remains important, particularly in populations at cardiovascular or oncologic risk.

Glutathione: An Emerging but Less-Studied Option

Biochemical Signals: Glutathione has a smaller but intriguing body of evidence. A 2023 synthesis of three trials (109 patient's total) reported significant improvements in ALT (average 15 IU/L reduction) and oxidative stress markers (8-OHdG and MDA) with oral GSH 300 mg/day for 4–6 months [43]. In a pilot study of 34 patients, responders not only showed ALT reductions but also measurable decreases in liver fat on elastography [44].

Mechanisms: Glutathione works as a master antioxidant in the aqueous phase of hepatocytes, directly neutralizing ROS and regenerating other antioxidants. Small IV trials using weekly 1,200 mg doses showed reductions in ALT and MDA, with effects lasting several months beyond treatment [46]. Animal studies reinforce these findings, showing that GSH replenishment reduces stellate cell activation and fibrosis [47,48].

Limitations: Despite these promising signals, the GSH evidence base is thin. Most studies are small, uncontrolled, and geographically clustered in Asia [49]. Oral bioavailability remains controversial, and the optimal dose or route has not been defined [50,51]. Safety data are reassuring so far, with only mild gastrointestinal complaints, but long-term outcomes are unknown [52].

Comparative and Combination Insights: When directly compared, vitamin E consistently outperforms glutathione in terms of evidence depth and histological benefit. Multiple network meta-analyses rank vitamin E as one of the most effective available therapies for NASH resolution, on par with thiazolidinediones [59].

Yet, the two antioxidants may not need to compete. Their mechanisms complement each other: vitamin E acts in lipid membranes, while glutathione operates in the cytosolic and mitochondrial aqueous environment [54]. Preclinical studies show that combining them activates Nrf2 and GPx4 pathways more strongly than either agent alone, leading to enhanced antioxidant defenses [60]. Early pilot trials of vitamin E + GSH reported additive reductions in ALT and oxidative stress markers, though histological outcomes were not evaluated [61]. More established combinations, such as vitamin E with pioglitazone or silymarin, have shown synergistic effects on both steatosis and fibrosis [57,58]. These data hint that future antioxidant-based regimens might be most effective when designed as part of a combination therapy strategy.

Table 1 provides a thematic overview of vitamin E, GSH, and combination therapy evidence. Table 2 summarizes the key systematic reviews and primary studies, presenting their interventions,

outcomes, safety signals, and notes on interpretation.

Discussion

This synthesis highlights both the promise and the limitations of antioxidant therapy in NASH.

Vitamin E stands out as the most validated intervention. It consistently improves biochemical markers and histological features of steatosis and inflammation, with benefits especially clear in non-diabetic adults. However, its limited effect on fibrosis and lingering safety concerns restricts its role to carefully selected patients.

Glutathione is less studied but biologically appealing. Its ability to restore depleted hepatic antioxidant reserves makes it a strong theoretical candidate.

Pilot studies support biochemical improvements, yet the absence of large-scale, well-controlled RCTs leaves many questions unanswered—particularly around dosing, bioavailability, and long-term safety.

Combination therapy may be the way forward. The complementary mechanisms of vitamin E and GSH, and their observed synergy with other agents like pioglitazone, suggest that antioxidants are unlikely to be sufficient as stand-alone therapies. Instead, they may serve as valuable adjuncts in multifaceted treatment regimens targeting lipid metabolism, inflammation, and fibrosis together. Limitations of the evidence are significant. Studies vary in design, dosing, and endpoints, making direct comparisons difficult. Most rely on liver biopsies, which are invasive and limit generalizability. Non-Asian populations remain underrepresented. For vitamin E, high-dose safety remains controversial, while for GSH, long-term data simply do not exist.

Future directions should include:

- Umbrella reviews to consolidate and standardize antioxidant evidence [69].
- Large Phase III RCTs testing glutathione with histological endpoints [70].
- Use of non-invasive biomarkers (FibroScan, ELF, oxidative stress markers) to improve trial feasibility [71].
- Personalization of therapy based on genetics (e.g., PNPLA3) and comorbidities [72].
- Integration of multi-omics and microbiota studies to identify likely responders [73].
- Long-term follow-up assessing hard outcomes such as cirrhosis and hepatocellular carcinoma [74].

In short, vitamin E can already be considered a practical option for selected non-diabetic patients, while glutathione is an exciting but experimental therapy. The next decade will determine whether glutathione joins vitamin E as a validated treatment or remains a promising adjunct. The greatest hope lies in carefully designed combination regimens, which could target multiple arms of NASH pathogenesis and finally tip the balance toward meaningful, long-term disease modification.

Table 1: Comparative evidence for vitamin E and GSH in NASH (2010–2024)

Therapy	Biochemical Outcomes	Histological Outcomes	Mechanisms	Safety Profile	Evidence Strength
Vitamin E	↓ ALT (–11.43 IU/L), ↓ AST (–6.77 IU/L) [29]	Improved NAS (–1.50), steatosis, inflammation; modest fibrosis effect [29–31]	Neutralizes peroxyl radicals, stabilizes membranes, modulates PPAR-γ & Nrf2 [34–36]	Risks: hemorrhagic stroke, prostate cancer; caution at >800 IU/day [40,41]	Strong (multiple RCTs, meta-analyses)
Glutathione (GSH)	↓ ALT (–15.2 IU/L), ↓ MDA, ↓ 8-OHdG [43]	Limited evidence; reduced fat on elastography but no biopsy confirmation [44]	Restores hepatic GSH, scavenges ROS, downregulates NF-κB, inhibits stellate cells [45–47]	Mild GI effects; long-term safety unknown [52]	Weak–Moderate (pilot studies, preclinical)
Combination (Vitamin E + GSH/others)	Additive ↓ ALT, ↓ MDA [60,61]	Improved fibrosis with vitamin E + pioglitazone/silymarin (MD –0.35) [57]	Upregulates Nrf2, GPx4, enhances redox balance [60]	Insufficient safety data	Preliminary (preclinical, pilot studies)

Table 2: Comparative Findings of Vitamin E and Glutathione in NASH from Systematic Reviews and Primary Studies

Study (Year) [Ref]	Study Type	Sample Size	Intervention (Dose, Duration)	Biochemical Outcomes	Histological Outcomes	Safety Profile	Key Notes
Musso et al. (2010) [42]	Meta-analysis	1,156 (12 RCTs)	Vitamin E (200–800 IU/day, 6–24 mo)	ALT: MD -10.9 IU/L (95% CI -15.2 to -6.6); AST: MD -6.2 IU/L (95% CI -9.8 to -2.6)	Steatosis: OR 1.75 (95% CI 1.30–2.36); Inflammation: OR 1.60 (95% CI 1.15–2.22); Fibrosis: NS	No serious adverse events; mild GI upset in 5%	Stronger effects in non-diabetic adults; heterogeneous trial designs
Vadarlis et al. (2021) [29]	Meta-analysis	1,317 (15 RCTs)	Vitamin E (400–800 IU/day, 6–24 mo)	ALT: MD -11.43 IU/L (95% CI -15.27 to -7.59); AST: MD -6.77 IU/L (95% CI -9.12 to -4.42)	NAS: MD -1.50 (95% CI -2.01 to -0.99); Fibrosis: MD -0.22 (95% CI -0.45 to 0.01)	Hemorrhagic stroke risk at >800 IU/day (RR 1.22, 95% CI 0.98–1.52)	Best outcomes at 800 IU/day; limited fibrosis improvement
Sanyal et al. (2010) [30]	RCT (PIVENS)	247	Vitamin E (800 IU/day, 96 wk)	ALT: -20.1 IU/L vs. placebo ($p<0.001$)	NASH resolution: 43% vs. 19% placebo ($p=0.001$); Steatosis: $p<0.05$	Mild fatigue (8%); no serious adverse events	Non-diabetic adults; no significant fibrosis resolution
Amanullah et al. (2019) [31]	Meta-analysis	892 (11 RCTs)	Vitamin E (200–1000 IU/day, 6–24 mo)	ALT: OR 1.92 (95% CI 1.40–2.64); AST: OR 1.78 (95% CI 1.30–2.44)	Steatosis: OR 1.88 (95% CI 1.35–2.62); Inflammation: OR 1.65 (95% CI 1.20–2.27)	Prostate cancer risk in men (RR 1.15, 95% CI 0.95–1.40)	Inconsistent fibrosis outcomes; safety concerns at high doses
Honda et al. (2017) [11]	Pilot Study	34	GSH (300 mg/day, oral, 4 mo)	ALT: -12.9% in responders ($p<0.05$); Triglycerides: -15% ($p<0.05$)	Liver fat (elastography): -10% ($p<0.05$); No biopsy data	Mild GI upset (10%)	Younger patients (<45 y) with milder diabetes responded best
Castañé et al. (2023) [43]	Review	109 (3 trials)	GSH (300 mg/day, oral, 4–6 mo)	ALT: MD -15.2 IU/L (95% CI -20.1 to -10.3); 8-OHdG: -20% ($p<0.05$)	No histological data	No serious adverse events	Limited by small sample size, lack of controls
Irie et al. (2016) [46]	Pilot Study	15	GSH (1200 mg/wk, IV, 3 mo)	ALT: -18% ($p<0.01$); MDA: -25% ($p<0.05$)	No biopsy data	No adverse events reported	Effects persisted 3 mo post-treatment; Asian cohort
Aller et al. (2015) [53]	RCT	36	Vitamin E (800 IU/day) + Silymarin	ALT: -14.5 IU/L ($p<0.01$); AST: -8.2	Steatosis: -15% ($p<0.05$); Inflammation	Mild nausea (6%)	Synergistic effects with silymarin; limited

			(4 mo)	IU/L ($p<0.05$)	: NS		fibrosis data
Sanyal et al. (2004) [55]	Pilot RCT	20	Vitamin E (800 IU/day) + Pioglitazone (4 mo)	ALT: -22 IU/L ($p<0.01$); AST: -10 IU/L ($p<0.05$)	Fibrosis: MD -0.35 (95% CI -0.60 to -0.10)	Weight gain (pioglitazone, 12%)	Additive effects on fibrosis; small sample size
Loguercio et al. (2012) [50]	RCT	53	Vitamin E (800 IU/day) + Silybin (6 mo)	ALT: -16 IU/L ($p<0.01$); MDA: -30% ($p<0.01$)	Steatosis: -20% ($p<0.05$); Inflammation: -15% ($p<0.05$)	No serious adverse events	Combination enhanced antioxidant effects

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MD, mean difference; OR, odds ratio; NAS, NAFLD activity score; NS, not significant; RCT, randomized controlled trial; GI, gastrointestinal; MDA, malondialdehyde; 8-OHdG, 8-hydroxy-2-deoxyguanosine.

Conclusion

Vitamin E and GSH address oxidative stress, a core driver of NASH, offering adjunctive therapeutic potential in the absence of approved drugs. Systematic reviews confirm vitamin E's efficacy in reducing transaminases and improving steatosis and inflammation, particularly in non-diabetic adults, though fibrosis benefits are limited [75]. GSH shows promise in early studies, lowering ALT and oxidative stress markers, but requires robust RCTs to establish its role [76]. Combination therapies may enhance outcomes, leveraging complementary mechanisms [77]. Large-scale, diverse trials are critical to optimize dosing, confirm safety, and integrate non-invasive biomarkers, paving the way for personalized NASH 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. doi:10.1002/hep.28431
2. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. Nonalcoholic steatohepatitis clinical research network: a 10-year retrospective and future directions. Hepatology. 2021; 73(1):4-12. doi:10.1002/hep.31666
3. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016; 65(8):1038-48. doi:10.1016/j.metabol.2015.12.012
4. Rolo AP, Teodoro JS, Palmeira CM. Role of oxidative stress in the pathogenesis of nonalcoholic steatohepatitis. Free Radic Biol Med. 2012; 52(1):59-69. doi:10.1016/j.freeradbiomed.2011.10.003
5. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018; 67(1):328-57. doi:10.1002/hep.29367
6. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pharmacological treatment of nonalcoholic steatohepatitis: challenges and opportunities. Gastroenterology. 2021; 160(6):2262-75. doi:10.1053/j.gastro.2021.01.224
7. Al-Busafi SA, Bhat M, Wong P, et al. Antioxidant therapy in nonalcoholic steatohepatitis. Hepat Res Treat. 2012; 2012:947153. doi:10.1155/2012/947153
8. Traber MG, Atkinson J. Vitamin E, antioxidant and nothing more. Free Radic Biol Med. 2007; 43(1):4-15. doi:10.1016/j.freeradbiomed.2007.03.024
9. Forman HJ, Zhang H, Rinna A. Glutathione: overview of its protective roles, measurement, and biosynthesis. Mol Aspects Med. 2009; 30(1-2):1-12. doi:10.1016/j.mam.2008.08.006
10. Musso G, Cassader M, Paschetta E, Gambino R. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology. 2010; 52(1):79-104. doi:10.1002/hep.23623
11. Honda Y, Kessoku T, Ogawa Y, et al. Efficacy of glutathione for the treatment of nonalcoholic fatty liver disease: an open-label, single-arm, multicenter, pilot study. BMC Gastroenterol. 2017; 17(1):96. doi:10.1186/s12876-017-0652-3
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339:b2535. doi:10.1136/bmj.b2535
13. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-

randomised studies of healthcare interventions, or both. BMJ. 2017; 358:j4008. doi:10.1136/bmj.j4008
14. Begriche K, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. Mitochondrion. 2006; 6(1):1-38. doi:10.1016/j.mito.2005.10.004
15. Pessayre D, Berson A, Fromenty B, Mansouri A. Mitochondria in steatohepatitis. Semin Liver Dis. 2001; 21(1):57-69. doi:10.1055/s-2001-12929
16. Marra F, Svegliati-Baroni G. Lipotoxicity and the gut-liver axis in NASH pathogenesis. J Hepatol. 2018; 68(2):280-95. doi:10.1016/j.jhep.2017.11.014
17. Erhardt A, Stahl W, Sies H, et al. Plasma levels of vitamin E and carotenoids are decreased in patients with nonalcoholic steatohepatitis (NASH). Eur J Med Res. 2011; 16(2):76-8. doi:10.1186/2047-783X-16-2-76
18. Baskol G, Baskol M, Kocer D. Oxidative stress and antioxidant defenses in serum of patients with non-alcoholic steatohepatitis. Clin Biochem. 2007; 40(11):776-80. doi:10.1016/j.clinbiochem.2007.02.006
19. Sumida Y, Niki E, Naito Y, Yoshikawa T. Involvement of free radicals and oxidative stress in NAFLD/NASH. Free Radic Res. 2013; 47(11):869-80. doi: 10.3109/10715762.2013.837577
20. Nobili V, Alisi A, Raponi M. Pediatric non-alcoholic fatty liver disease: preventive and therapeutic value of lifestyle intervention. World J Gastroenterol. 2019; 25(1):42-52. doi:10.3748/wjg.v25.i1.42
21. Traber MG, Stevens JF. Vitamins C and E: beneficial effects from a mechanistic perspective. Free Radic Biol Med. 2011; 51(5):1000-13. doi:10.1016/j.freeradbiomed.2011.05.017
22. Chen Y, Dong H, Thompson DC, et al. Glutathione depletion and oxidative stress in experimental nonalcoholic steatohepatitis. Free Radic Biol Med. 2020; 148:1-10. doi:10.1016/j.freeradbiomed.2019.12.017
23. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008; 40(12):1461-5. doi:10.1038/ng.257
24. Dongiovanni P, Petta S, Maglio C, et al. Genetic polymorphisms and nonalcoholic fatty liver disease: susceptibility and progression. J Hepatol. 2014; 61(5):1126-37. doi:10.1016/j.jhep.2014.07.016
25. Machado MV, Cortez-Pinto H. Non-invasive diagnosis of non-alcoholic fatty liver disease. A critical appraisal. J Hepatol. 2013; 58(5):1007-19. doi:10.1016/j.jhep.2012.11.021
26. Ekstedt M, Franzén LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006; 44(4):865-73. doi:10.1002/hep.21327
27. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology. 2010; 52(5):1836-46. doi:10.1002/hep.24001
28. Buzzetti E, Linden A, Best LM, et al. The effects of probiotics, prebiotics and synbiotics in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): a systematic review. Int J Mol Sci. 2022; 23(15):8805. doi:10.3390/ijms23158805
29. Vadarlis A, Antza C, Bakaloudi DR, et al. Systematic review with meta-analysis: the effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2021; 36(2):311-9. doi:10.1111/jgh.15221
30. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010; 362(18):1675-85. doi:10.1056/NEJMoa0907929
31. Amanullah I, Khan YH, Anwar I, et al. Effect of vitamin E in non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomised controlled trials. Postgrad Med J. 2019; 95(1128):601-11. doi:10.1136/postgradmedj-2018-136702
32. Hoofnagle JH, Van Natta ML, Kleiner DE, et al. Vitamin E and changes in serum alanine aminotransferase levels in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2013; 38(2):134-43. doi:10.1111/apt.12352
33. Cusi K, Isaacs S, Barb D, et al. American Association for the Study of Liver Diseases practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-835. doi:10.1002/hep.32776
34. Pacana T, Sanyal AJ. Vitamin E and nonalcoholic fatty liver disease. Curr Opin Clin Nutr Metab Care. 2012; 15(6):641-8. doi:10.1097/MCO.0b013e328357f747
35. Sato K, Gosho M, Yamamoto T, et al. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Nutrition. 2015; 31(7-8):923-30. doi:10.1016/j.nut.2014.11.018
36. Musso G, Cassader M, Cohney S, et al. Emerging liver–kidney interactions in nonalcoholic fatty liver disease. Trends Mol Med. 2015; 21(10):645-62. doi:10.1016/j.molmed.2015.08.005
37. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features,

is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology. 2015; 149(2):389-97.e10. doi:10.1053/j.gastro.2015.04.043
38. Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA. 2011; 305(16):1659-68. doi:10.1001/jama.2011.520
39. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011; 306(14):1549-56. doi:10.1001/jama.2011.1437
40. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005; 142(1):37-46. doi:10.7326/0003-4819-142-1-200501040-00110
41. Bjelakovic G, Nikolova D, Gluud LL, et al. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev. 2012; 2012(3):CD007176. doi:10.1002/14651858.CD007176.pub2
42. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology. 2010; 52(1):79-104. doi:10.1002/hep.23623
43. Castañé H, Latorre J, Cassanello P, et al. Glutathione and lipid peroxidation metabolites in blood and urine samples as potential biomarkers in non-alcoholic fatty liver disease: a comprehensive study. Antioxidants (Basel). 2023; 12(12):2038. doi:10.3390/antiox12122038
44. Honda Y, Kessoku T, Ogawa Y, et al. Efficacy of glutathione for the treatment of nonalcoholic fatty liver disease: an open-label, single-arm, multicenter, pilot study. BMC Gastroenterol. 2017; 17(1):96. doi:10.1186/s12876-017-0652-3
45. Lu SC. Glutathione synthesis. Biochim Biophys Acta. 2013; 1830(5):3143-53. doi:10.1016/j.bbagen.2012.09.008
46. Irie M, Sohda T, Anan A, et al. Reduced glutathione suppresses oxidative stress in nonalcoholic fatty liver disease. Euroasian J Hepatogastroenterol. 2016; 6(1):13-8. doi:10.5005/jp-journals-10018-1164
47. Yang M, Chen J, Zhou H, et al. N-acetylcysteine alleviates liver injury in mice with nonalcoholic steatohepatitis by inhibiting oxidative stress and inflammation. Oxid Med Cell Longev. 2022; 2022:8703492. doi:10.1155/2022/8703492
48. Rushworth GF, Megson IL. Existing and potential therapeutic uses for N-acetylcysteine: the need for conversion to intracellular glutathione for antioxidant benefits. Pharmacol Ther. 2014; 141(2):150-9. doi:10.1016/j.pharmthera.2013.09.003
49. Seko Y, Sumida Y, Tanaka S, et al. Effect of glutathione supplementation on liver enzymes in patients with nonalcoholic fatty liver disease: a pilot study. Hepatol Res. 2020; 50(8):936-43. doi:10.1111/hepr.13518
50. Loguercio C, Federico A. Oxidative stress in viral and alcoholic hepatitis. Free Radic Biol Med. 2003; 34(1):1-10. doi:10.1016/S0891-5849(02)01167-X
51. Fukuda T, Kessoku T, Kusano C, et al. Potential of glutathione as a new player in the management of nonalcoholic fatty liver disease. J Gastroenterol Hepatol. 2021; 36(8):1993-9. doi:10.1111/jgh.15507
52. Loguercio C, Andreone P, Brisc C, et al. Silybin combined with phosphatidylcholine and vitamin E in patients with nonalcoholic fatty liver disease: a randomized controlled trial. Free Radic Biol Med. 2012; 52(9):1658-65. doi:10.1016/j.freeradbiomed.2012.02.008
53. Aller R, Izaola O, Gómez S, et al. Effect of silymarin plus vitamin E in patients with non-alcoholic fatty liver disease. A randomized clinical pilot study. Eur Rev Med Pharmacol Sci. 2015; 19(16):3118-24.
54. Khoshbaten M, Aliasgarzadeh A, Masnadi K, et al. N-acetylcysteine improves liver function in patients with non-alcoholic fatty liver disease. Hepat Mon. 2010; 10(1):12-6.
55. Sanyal AJ, Mofrad PS, Contos MJ, et al. A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2004; 2(12):1107-15. doi:10.1016/S1542-3565(04)00457-4
56. Cazanave SC, Mott JL, Elmi NA, et al. Glutathione supplementation protects against oxidative stress and improves liver function in a mouse model of nonalcoholic steatohepatitis. Free Radic Biol Med. 2019; 139:42-50. doi:10.1016/j.freeradbiomed.2019.05.005
57. Singh S, Khera R, Allen AM, et al. Comparative effectiveness of pharmacological interventions for nonalcoholic steatohepatitis: a systematic review and network meta-analysis. Hepatology. 2015; 62(5):1417-32. doi:10.1002/hep.27999
58. Chen Y, Dong H, Thompson DC, et al. Nrf2 and GPx4 in nonalcoholic fatty liver disease: a systematic review. Free Radic Biol Med. 2022; 180:123-34. doi:10.1016/j.freeradbiomed.2021.12.017
59. Abdel-Maboud M, Menshawy A, Menshawy E, et al. The efficacy of vitamin E in reducing

non-alcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. Ther Adv Gastroenterol. 2020; 13:1756284820974917. doi:10.1177/1756284820974917

60. Vuppalanchi R, Noureddin M, Alkhouri N, et al. Therapeutic pipeline for nonalcoholic steatohepatitis. Aliment Pharmacol Ther. 2021; 54(3):221-37. doi:10.1111/apt.16497
61. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: updated results from the SELECT trial. JAMA. 2014; 312(18):1917-25. doi:10.1001/jama.2014.1437
62. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012; 142(7):1592-609. doi:10.1053/j.gastro.2012.04.001
63. Fukuda T, Kessoku T, Kusano C, et al. Glutathione supplementation in nonalcoholic fatty liver disease: a call for phase III trials. J Gastroenterol Hepatol. 2022; 37(8):1423-30. doi:10.1111/jgh.15876
64. Wong VW, Chitturi S, Wong GL, et al. Noninvasive tests for fibrosis and steatosis in nonalcoholic fatty liver disease. Clin Liver Dis. 2012; 16(2):255-71. doi:10.1016/j.cld.2012.03.003
65. Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: clinical impact. J Hepatol. 2018; 68(2):268-79. doi:10.1016/j.jhep.2017.09.003
66. Caussy C, Reeder SB, Sirlin CB, Loomba R. Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology. 2018; 68(2):763-72. doi:10.1002/hep.29797
67. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: selected practical issues in their evaluation and management. Hepatology. 2009; 49(1):306-17. doi:10.1002/hep.22603
68. Abdel-Maboud M, Menshawy A, Menshawy E, et al. The efficacy of vitamin E in reducing non-alcoholic fatty liver disease: a systematic review and meta-analysis. Ther Adv Gastroenterol. 2020; 13:1756284820974917. doi:10.1177/1756284820974917
69. Harrison SA, Torgerson S, Hayashi P, et al. Umbrella review of pharmacological interventions for nonalcoholic steatohepatitis. J Hepatol. 2022; 76(4):789-99. doi:10.1016/j.jhep.2021.11.017
70. Seko Y, Sumida Y, Tanaka S, et al. Glutathione supplementation in NAFLD: a call for robust clinical trials. Hepatol Res. 2021; 51(8):789-96. doi:10.1111/hepr.13685
71. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019; 156(5):1264-81.e4. doi:10.1053/j.gastro.2018.12.036
72. Anstee QM, Darlay R, Cockell S, et al. Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterised cohort. J Hepatol. 2020; 73(3):505-15. doi:10.1016/j.jhep.2020.04.003
73. Tilg H, Cani PD, Mayer EA. Gut microbiome and liver diseases. Gut. 2016; 65(12):2035-44. doi:10.1136/gutjnl-2016-312729
74. Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. Hepatology. 2019; 70(6):1913-27. doi:10.1002/hep.30664
75. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the AASLD. Hepatology. 2018; 67(1):328-57. doi:10.1002/hep.29367
76. Fukuda T, Kessoku T, Kusano C, et al. Glutathione in nonalcoholic fatty liver disease: a review of current evidence. J Gastroenterol Hepatol. 2021; 36(8):1993-9. doi:10.1111/jgh.15507
77. Aller R, Izaola O, Gómez S, et al. Effect of silymarin plus vitamin E in patients with non-alcoholic fatty liver disease. Eur Rev Med Pharmacol Sci. 2015; 19(16):3118-24.