Drug Corner

A Review on the Role of 21st Century Vitamin E : Tocotrienol in Nonalcoholic Fatty Liver Disease

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Nonalcoholic Fatty Liver Disease (NAFLD) is an increasingly prevalent condition associated with significant morbidity and mortality, closely linked to cardiovascular disease, malignancies, and cirrhosis. The role of oxidative stress in NAFLD's development and progression is well recognized. Despite the growing burden of NAFLD, there is no established pharmacotherapy. Apart from weight loss and lifestyle modifications, alpha-tocopherol, a specific form of Vitamin E, is currently recommended for steatohepatitis patients due to its ability to alleviate oxidative stress in NAFLD. Another member of the vitamin E family, tocotrienol (T3), possesses additional anti-inflammatory, antioxidant and anti-fibrotic attributes beyond those of alpha-tocopherol, making it a promising candidate for managing NAFLD. Tocotrienols have shown 40-60 times higher antioxidant activity than alpha-tocopherol. T3s can penetrate into tissues that have saturated fatty layers, such as the liver, more efficiently due to their unsaturated side chain.This review provides an overview of NAFLD management, focusing on the potential benefits of tocotrienol supplementation. Clinically, tocotrienols have shown normalization of hepatic echogenic response and reduction in fatty liver inhibition (FLI), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), serum hs-CRP, tumour necrosis factor-alpha (TNF-α), Alanine Transferase (ALT), Asparagine Transferase (AST), Malondialdehyde (MDA) parameters. Mechanistically, tocotrienol demonstrates improvements in lipid metabolism, protection against liver steatosis, and the reduction of mitochondrial and endoplasmic reticulum stress, inflammation, and liver fibrosis. In conclusion, tocotrienol shows promise as a potential therapeutic agent for NAFLD.

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Key words **: NAFLD, Tocotrienols, Antioxidants, Anti-inflammatory, Risk factors.**

Nonalcoholic Fatty Liver Disease (NAFLD) is a prevalent disease with a global occurrence of 25-30% in the adult population, making it the most common chronic liver disease and a major cause of liver transplantation in the Western world. In populations with Type 2 Diabetes Mellitus (T2DM) and/or morbid obesity, the prevalence of NAFLD is even higher, ranging from 50-90%[1]. In India, NAFLD is prevalent between 9-32% of the general population, with a higher occurrence in individuals with overweight or obesity and those with diabetes or prediabetes[2]. NAFLD is a heterogeneous disease that can progress from simple steatosis (NAFL, fat accumulation in the liver is >5% of hepatocytes) to nonalcoholic steatohepatitis (NASH; steatosis, hepatocyte ballooning and focal inflammation) and to liver fibrosis, cirrhosis and Hepatocellular Carcinoma (HCC) in the absence of alcohol consumption; the suggested daily limit is less than 20g for women and less than 30g for men[3]. NASH patients have a high risk of mortality due to liver cirrhosis, HCC, cardiovascular disease, and extra-hepatic cancers, making it a silent epidemic closely linked to obesity and T2DM[1]. The occurrence of NAFLD is significantly higher among patients with obesity and diabetes, ranging from 70% to 90%.NAFLD is anticipated to become the primary reason for liver transplantation worldwide by 2030[4]. Fig 1 depicts the progression of NAFLD.

Risk factors :

Obesity, particularly central abdominal obesity (waist circumference >102 cm in men, >88 cm in women), insulin resistance, diabetes mellitus, hypertension, and hypertriglyceridemia are major risk factors for NAFLD. It has been suggested that there is ethnic variation in the distribution of NAFLD. While the cause of this ethnic variation is unknown, both lifestyle and genetic predisposition may be contributing factors[5]. Studies have shown that NAFLD and NASH are more common in men, although women tend to develop NAFLD later in life[6].

Pathogenesis :

The pathophysiology of NAFLD is a complex process characterised by the accumulation of lipids in liver cells, which causes fatty infiltration. There are several pathways that can lead to the development of

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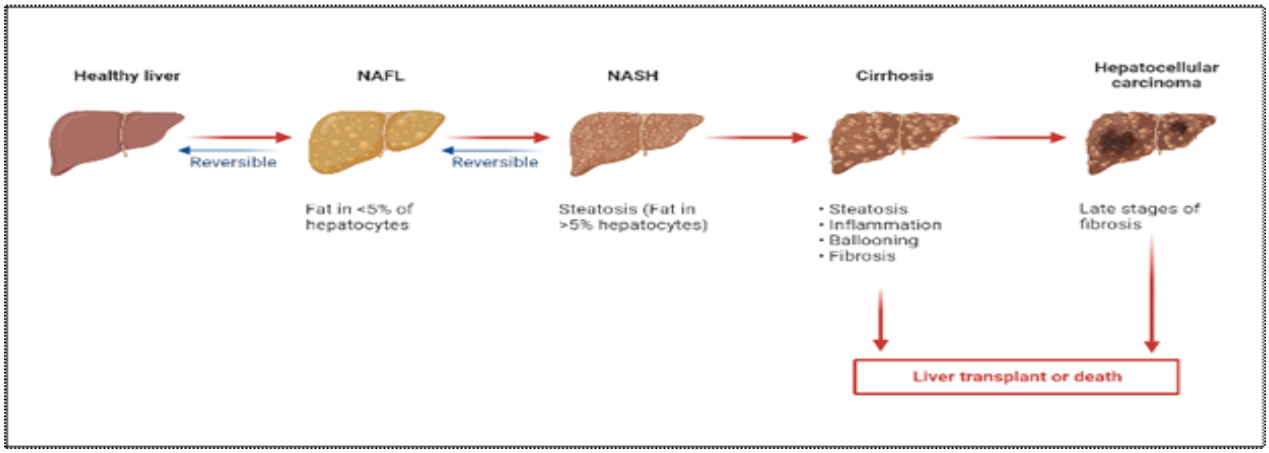

Fig 1 — Progression of Nonalcoholic fatty liver disease [Nonalcoholic Fatty Liver (NAFL); Nonalcoholic Steatohepatitis (NASH)]

hepatic steatosis. These include increased free fatty acid supply to hepatocytes, which can occur due to increased fat intake or increased lipolysis from adipose tissue[7].

Once hepatic steatosis has developed, the liver becomes more sensitive to inflammatory stimuli. There are two mechanisms that are believed to play a pivotal role in the pathogenesis of Non-alcoholic Steatohepatitis (NASH)[8]. The first mechanism involves oxidative stress and lipid peroxidation, which can result in cell death. The second mechanism involves pro-inflammatory and cytokine-mediated cell injury, which can also lead to cell death. These processes can result in fibrogenesis and collagen turnover, leading to hepatic fibrosis and, eventually, cirrhosis[8].

Management of NAFLD :

The mainstay of treatment for NASH and NAFL is lifestyle changes involving diet and exercise. This includes reducing calories, achieving moderate weight loss, and adjusting the types of nutrients consumed[3]. While there is currently no established pharmacotherapy for NASH, it is important to focus on the composition of the diet rather than simply restricting calories. Emphasizing the importance of carefully modulating the macro and micronutrient content of the diet is important. The Mediterranean Diet (MD) is a dietary option that can effectively lead to weight loss and provide metabolic benefits for individuals with NAFLD[9]. This diet is characterised by low levels of saturated fat and cholesterol and high levels of polyunsaturated fatty acids, carbohydrates, and fiber. Numerous cross-sectional and longitudinal studies have demonstrated the positive impact of MD on NAFLD[9,10].

There is a clear inverse relationship between coffee consumption and the risk of liver disease. A meta-analysis was conducted on 16 studies that involved more than 3,000 coffee consumers and over 13,000 non-consumers[11]. The pooled results indicated that coffee consumption significantly reduces the risk of hepatic fibrosis and cirrhosis. Furthermore, coffee intake has been linked to a lower risk of Hepatocellular Carcinoma (HCC). Another systematic review and meta-analysis involved 18 cohorts with more than 2 million participants, as well as 8 case-control studies comprising 1,825 cases and 4,625 controls[12]. The study discovered that an additional 2 cups of coffee led to a 35% decrease in the risk of HCC[7].

Apart from lifestyle modifications, the existing treatment options for individuals with NAFLD include the use of insulin sensitisers such as metformin and thiazolidinediones, weight loss medications like orlistat and sibutramine, and bariatric surgery, which is a viable option for morbidly obese patients[7]. However, liver transplantation remains the only definitive curative treatment option for end-stage cirrhosis[7].

Vitamin E :

Vitamin E has gained significant attention as a possible treatment for NAFLD due to its anti-inflammatory and antioxidant properties[13]. It also possesses anti-fibrotic properties in nonalcoholic steatohepatitis patients[14]. Vitamin E is a group of fat-soluble antioxidants that includes two types: tocotrienols (T3s) and tocopherols (TFs). Both types have four isomers, namely α (alpha), β (beta), δ (delta), and γ (gamma)[15]. Several meta-analysis reports have shown that vitamin E, particularly á-tocopherol (αTF), can enhance the metabolic profile, liver enzyme levels, and liver pathology in individuals with NAFLD[13,16-18]. Vitamin E has emerged as a potentially effective therapeutic strategy for NASH patients by targeting components related to oxidative stress. Guidelines

such as American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Asian Pacific Association for the Study of the Liver (APASL) have recommended lifestyle modifications as the first-line therapy for patients with NAFLD, and in pharmacotherapy for patients with advanced fibrosis or cirrhosis, vitamin E is the recommended agent. So, along with alpha-tocopherol, tocotrienol supplementation can also be explored for the same. However, despite the efficacy of α-tocopherol, the potential of tocotrienol (T3), another powerful member of the Vitamin E family, remains largely unexplored in NAFLD treatment[15].

Role of Tocotrienols (T3s) — The Vitamin E of 21st century :

Tocotrienols are unsaturated forms and have an isoprenoid side chain, which makes them more easily absorbed and better able to penetrate tissues with saturated fatty layers, such as the liver and brain[19]. Tocotrienols have been found to possess unique properties, such as powerful neuroprotective, anti-cancer, antioxidant, and cholesterol-lowering properties that differ from tocopherols[20].

α-Tocotrienol is 40-60 times more effective than α-tocopherol in countering lipid peroxidation of liver microsomes[21]. On the other hand, tocopherols are naturally lipophilic, which means they protect polyunsaturated fatty acids compounds such as lipoproteins, cellular membranes, and fat deposits from peroxidation reactions[19]. Interestingly, studies have shown that tocotrienols are more effective than tocopherols in reducing oxidative stress and inflammation[22]. Tocotrienols act as free radical scavengers, reducing oxidative stress in metabolic disorders and protecting cellular functions[23]. Tocotrienols have demonstrated superior anti-fibrotic effects compared to tocopherols in pre-clinical studies[24]. Since orally treated tocotrienols are mostly metabolised inside the liver, supplementing with tocotrienols has been shown to improve liver function in obese patients and increase the energy expenditure of the whole body through improved oxidation of hepatic fatty acids[25]. It has been observed that even micromolar amounts of tocotrienol can suppress HMG-CoA reductase activity, a hepatic enzyme responsible for cholesterol synthesis[22]. In addition, tocotrienols have been found to possess more potent antioxidant properties than α-tocopherol[26,27]. Due to the unsaturated side chain, tocotrienols can penetrate into tissues that have saturated fatty layers, such as the brain and liver, more efficiently[22]. Fig 2 depicts the reduction in FLI, and HOMA-IR parameters in tocotrienols group as compared to tocopherols, based on study conducted by *Pervez et al*. Table 1 presents the clinical trials demonstrating the effect of tocotrienol on NAFLD patients.

Anti-inflammatory activity :

Extensive research has been conducted on the anti-inflammatory properties of tocotrienols, with very promising results. Inflammation is closely linked to the activation of the transcription factor NF-κB[32,33], but tocotrienols have been found to suppress the expression of various mediators of inflammation, including TNF-α, IL-1, IL-6, IL-8, inducible nitric oxide synthase, and cyclo-oxygenase 2[22]. They have also been shown to suppress the STAT3 cell-signaling pathway, which is also involved in inflammation[34]. In a study, tocotrienols administered to streptozotocin-induced diabetic rats for 10 weeks significantly prevented the behavioral, biochemical, and molecular changes associated with diabetes through the suppression of NF-κB signaling pathway activation[35]. Additionally, non-toxic concentrations of tocotrienol have been found to attenuate TNF-α-induced NF-κB activation in human chronic myeloid leukemia cells, which are key steps in the development of inflammation[32]. Fig 3 depicts the properties of tocotrienol in management of NAFLD.

Antioxidant activity :

Oxidative stress is characterised by the production

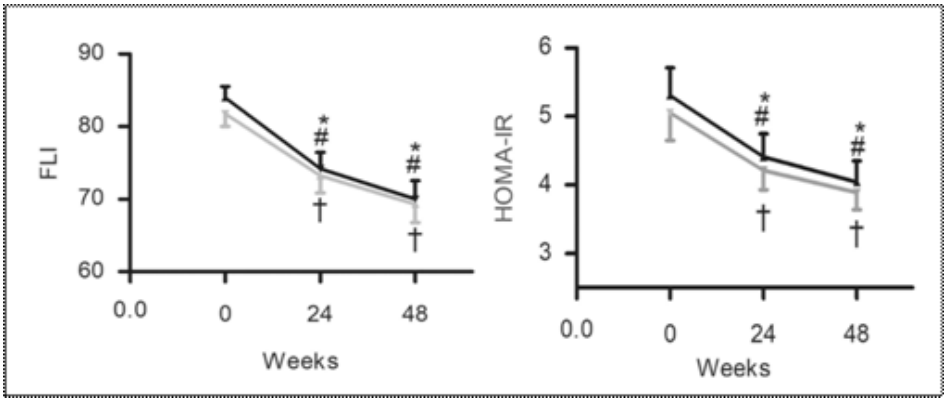

Fig 2 — Mean FLI and HOMA-IR at baseline, 24- and 48-weeks.
*p<0.001 versus baseline in the tocotrienol group.
#p<0.001 versus baseline in the tocopherol group, study conducted by *Pervez et al*

Table 1 — *Effects of tocotrienol administration in patients with NAFLD*

Study design	No of participants (n)	Treatment Groups	Results	References
Randomized placebo-controlled clinical trial	87	Treatment : tocotrienol twice daily for 1 year (oral). Placebo control group	Normalization of hepatic echogenic response *versus* placebo Worsening of steatotic grade in 2 cases in the placebo group, none in the T3 group.	Magosso, *et al* (2013)[28]
Randomized, double-blind, placebo-controlled pilot study	71	Treatment : tocotrienol twice daily for 12 weeks (oral). Placebo control : sucrose	Reduction inserumAST, hs-CRP, MDA and FLI score *versus* placebo No adverse effect detected.	Pervez, *et al* (2018)[29]
Randomized, placebo-controlled trial	71	Treatment : tocotrienol twice daily for 24 weeks (oral). Placebo control:sucrose	Reduction in FLI, HOMA-IR, hs-CRP, IL-6, TNF-α, MDA, AST, ALT. No adverse events reported.	Pervez, *et al* (2020)[30]
Randomized double-blind active-controlled trial	100	Treatment : tocotrienol (γT3) or tocopherol (αTF) twice daily for 24 and 48 weeks (oral).	Reduced FLI, HOMA-IR, serum hs-CRP, Reduced body weight, IL6, TNFα	Pervez, *et al* (2022)[31]

[TNF-α-tumour necrosis factor alpha; ALT - alanine transferase; AST - asparagine transferase; MDA – malondialdehyde; hs-CRP - high-sensitivity C-reactive protein; FLI - fatty liver inhibition; HOMA-IR - Homeostatic Model Assessment for Insulin Resistance; IL-6 - Interleukin 6]

of reactive species surpassing the capacity of antioxidant defense, which results in DNA damage and disruptions in cellular function[36]. Vitamin E is widely acknowledged as one of the most powerful natural antioxidants (Fig 3)[37]. The hydroxyl group of tocochromanols aromatic ring is credited with their antioxidant properties, as it donates hydrogen to scavenge free radicals or reactive oxygen species (ROS)[38].

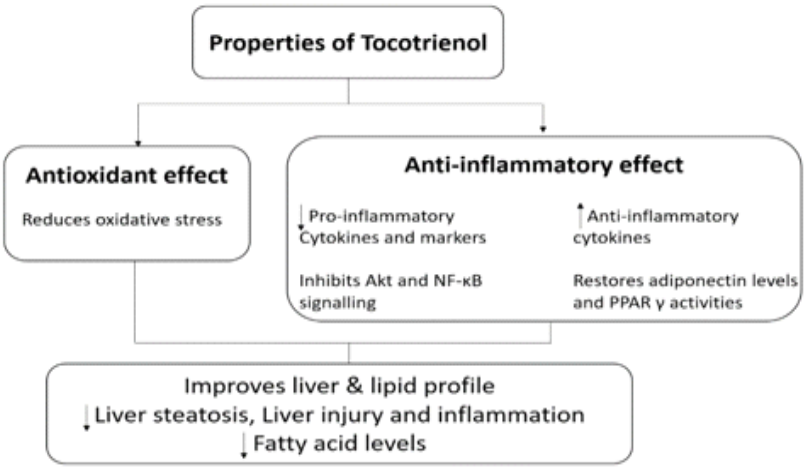

Fig 3 — The pharmacological properties of tocotrienol for the management of NAFLD

Conclusion :

Despite extensive research and its high prevalence, the treatment of Non-alcoholic Fatty Liver Disease (NAFLD) remains an unmet medical need. Tocotrienols demonstrates a potential agent for managing NAFLD. Studies indicatethat tocotrienols effectively safeguard against steatosis, inflammation, oxidative stress, and fibrosis, which are all associated with the progression of NAFLD. However, the level of protection varies depending on the severity of the condition and the duration of treatment. Considering its demonstrated protective effects on metabolic abnormalities in various clinical trials, tocotrienols could also serve as a preventive measure against the development of NAFLD.

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