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Editorial

Pharmacotherapeutic perspectives on nutraceuticals in the treatment of MASLD and MASH

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Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) continue to be serious global health concerns despite various concerted efforts. There has been significant progress in pharmacological treatments for these conditions. The recent FDA approval of resmetirom marks a milestone as the first medication specifically approved for MASH treatment.[1] Nonetheless, there is an unmet need for more efficacious or adjunctive approaches. Thus, exploration of various therapeutic approaches is ever increasingly needed. One avenue that has garnered attention in the fight against MASLD and MASH is the utilization of nutraceuticals. These are food-derived products that exhibit a plethora of health benefits beyond basic nutrition. They exert several beneficial effects in the battle against cardiovascular disease, cancer, inflammation, and metabolic disease, among others, especially since most of them are plant-derived or nature-inspired.[2–5] However, the current evidentiary basis for their efficacy remains limited and inconsistent. This necessitates a critical appraisal of the available literature before recommendations can be made. Recently, a consensus on the importance of diet and nutrition as integral elements of MASLD management has been published.[6] This report highlights the importance of a balanced healthy diet and body weight control, as well as the integration of personalized nutritional interventions (e.g. caloric restriction and intermittent fasting).[6] In addition, eating whole rather than refined grains and reducing fat/meat intake are strongly recommended. Interestingly, and in line with the premise of our perspective regarding nutraceuticals, eating healthy sources of protein, notably from plant sources, was one of the key recommendations.[6] Some of the molecules that received the most attention are omega-3 fatty acids, vitamin E, curcumin, in addition to probiotics and synbiotics.

Several studies have examined the effects of omega-3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), on liver health, with evidence suggesting improvements in liver fat content and some MASLD-associated biochemical markers.[7] For instance, significant reductions in alkaline phosphatase and liver fibrosis were reported with DHA supplementation.[8] However, such results are not consistent. For instance, in a larger study that lasted over 15 months, there was only a marginal improvement in liver fat percentage with DHA and EPA supplementation, with no significant impact on fibrosis scores.[9] These mixed results highlight the complexity of treating MASLD/MASH, at least as pertains to the use of omega-3 fatty acids therein. Interestingly, some meta-analyses suggest that omega-3 supplementation can lead to modest improvements in liver function, evident by favorable changes in certain enzymes or histological outcomes.[10] However, the inconsistencies or variabilities in study designs and patient populations complicate the interpretation of these findings. Furthermore, the long-term safety and efficacy of high-dose omega-3 supplementation, particularly regarding its impact on lipid profiles and potential gastrointestinal side effects, have been debated.

Vitamin E has also been suggested as a potential nutraceutical for MASLD/MASH, but the

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evidence is mixed at best. Part of vitamin E's potential ameliorative effects is owed to its ability to reduce oxidative stress and inflammation in nondiabetic patients with MASLD. Indeed, a meta-analysis found that vitamin E supplementation significantly improved liver function and histological changes in patients with MASLD, particularly those without diabetes.[11] However, the efficacy of this vitamin in diabetic individuals remains uncertain, largely due to conflicting results from various studies.[12] In addition, concerns regarding long-term safety, including potential adverse effects on cardiovascular health, warrant careful consideration before recommending vitamin E as a routine treatment for MASLD/MASH.

Another nutraceutical that has been considered in the management of MASLD/MASH is curcumin, which has numerous pharmacological actions.[13–16] Evidence shows that curcumin reduces chronic inflammation and oxidative stress, thereby protecting liver cells.[17,18] This is supported by a comprehensive meta-analysis of randomized controlled trials demonstrating that curcumin intake is associated with improvements in liver enzymes and steatosis.[19] However, these findings still need to be confirmed in larger and longer-term studies so that optimal dosing regimens can be determined, especially since some recent studies suggest curcumin does not favorably modulate levels of serum alanine aminotransferase.

It is crucial to mention here that curcumin's bioavailability is a significant challenge that limits its clinical application. Some formulations utilized nanoparticles or liposomal delivery systems to enhance absorption. However, further research is necessary to determine their effectiveness in clinical settings. In addition, while curcumin appears to have anti-inflammatory properties that could benefit liver health, its interactions with other medications must be carefully evaluated to avoid adverse effects.

The use of probiotics and synbiotics in MASLD/MASH management has also received particular attention. Probiotic supplementation has been proposed as a strategy to modulate gut microbiota and improve metabolic health. Some studies suggest that probiotics may help reduce liver fat accumulation by improving insulin sensitivity and reducing inflammation.[20] However, the evidence supporting their efficacy is still in its infancy and hence requires further investigation. It is therefore crucial to consider the potential synergistic effects of combining different nutraceuticals while emphasizing the need for more rigorous studies to validate these findings.

A large number of studies that have so far been conducted are limited by small sample sizes, short durations, and heterogeneous methodologies. As such, it becomes rather challenging to draw definitive conclusions about the potential efficacy of nutraceuticals in MASLD/MASH management. Furthermore, the lack of standardization in nutraceutical formulations and dosages complicates the interpretation of research findings. Together, these limitations underscore the need for more rigorous, standardized approaches in future studies. Nonetheless, despite these limitations, the potential of nutraceuticals as adjunctive therapies in MASLD/MASH management should not be overlooked. That is in small part due to the notion that the multifaceted pathophysiology of these conditions involves lipid accumulation, inflammation, and oxidative stress, all of which are mechanisms of action that could be ameliorated by many nutraceuticals.

Standardizing the doses and quantities of supplements in MASLD management, as well as the duration of treatment, remains a challenge in clinical practice. The lack of a universal agreement on optimal supplement regimens hinders the ability to make clear recommendations and compare results across studies. Variations in supplement quantity, bioavailability, and individual patient factors are yet another confounding factor in the efforts to establish standardized protocols. Therefore, it is imperative that future research addresses the current gaps in our understanding. Large-scale, well-designed randomized controlled trials with longer follow-up periods are needed. Such studies are expected to establish the efficacy and safety of promising nutraceuticals. In addition, these studies would help elucidate optimal dosing regimens and potential synergistic effects of different nutraceuticals. Likewise, long-term impacts on clinically relevant outcomes such as disease progression and quality of life can also be inferred from such studies. Therefore, despite their promise, nutraceuticals shall be integrated into clinical practice with caution. This is especially since these compounds are often perceived as "natural" and therefore safe. However, their potential interactions with other medications and long-term safety profiles need nothing less than a thorough evaluation.

In conclusion, while nutraceuticals represent an exciting avenue for expanding the therapeutic arsenal against MASLD and MASH, current evidence is insufficient to support their routine use as standalone treatments. They should be viewed as potential adjuncts to established lifestyle interventions and pharmacological therapies rather than replacements. As research continues to evolve, clinicians should remain cautiously optimistic but maintain a critical perspective when interpreting new findings. The future of MASLD/MASH management likely lies in a personalized multifaceted approach that combines lifestyle modifications, pharmacological interventions, and potentially carefully selected nutraceuticals. Ongoing research into novel therapies holds promise for further expanding treatment options and improving outcomes for patients facing these increasingly prevalent liver diseases.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Ali H. Eid: Conceptualization; Writing – original draft.

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