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Review Articles

An Update of Bioactive Compounds for Therapy of Metabolic Dysfunction-Associated Steatosis Liver Disease (MASLD) -- A Short Communication

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Abstract

Having reviewed the different significant etiopathogenesis and role of Vitamin D/its Receptor and Allyl Isothiocyanate (AITC)", with Prospective Therapies Like L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, as well as Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin, probiotics, prebiotics, and synbiotics., role of Resveratrol's Effects, natural products in the treatment of diabesity, inclusive of polyphenols along with flavonoids, dietary polyphenols, like resveratrol, curcumin, proteintyrosine phosphatase1 B (PTP1B) inhibitors, plant terpenes (specifically monoterpenes), flavonoids (querceetin, kaempherol), ursolic acid, besides epigenetic modes of certain plant agents antidiabetic action, like nonflavonoid polyphenols like curcumin, tannins, lignans as well as resveratrol, or flavonoids like anthrocyanins, epigallocatechin gallate (EGCG), quercetin, naringin, rutin along with kaempherol, astragaloside IV and other prospective agents, knowledge of Hepatic Macrophages and association of dietary fatty acids and gut microbiota alterations with Gut-Liver Axis with Gut Microbiome Dysbiosis correlated non alcoholic fatty Acid liver disease (NAFLD) along with non alcoholic steatohepapititis (NASH) alias metabolic dysfunction-associated steatosis liver disease (MASLD, alias NAFLD earlier) or MASH now, Curcumin Actions, role ofi) Obeticholic acid (OCA; Farsenoid X receptor [FXR] agonist) ii) Elafibranor (a Peroxisome Proliferator Activated Receptor [PPAR] α as well as δ agonist) iii) cenicriviroc (CVC-a dual antagonist of C-C chemokine receptor (cenicriviroc CCR) types 2 as well as 5 iv) resmetriom (THR-β- agonist) as well as aramchol (stearoyl-Co A desaturase [SCD1 inhibitor Yet no clearcut answer is there for therapy of, NAFLD,NASH metabolic dysfunction-associated steatosis liver disease (MAFLD), MASH. Herewe further detail, which herbal, plant products evaluated might work in therapy of such disorder. Other than silymarin, curcumin and probiotics, prebiotics, and synbiotics not much efficacy was seen with other bioactive compounds evaluated globally.

Keywords: Metabolic dysfunction-associated steatosis liver disease (MASLD; Probiotics and Synbiotics; Curcumin; Silybin

Introduction

Previously we reviewed the different significant etiopathogenesis and role of different factors in development of newer therapies for non alcoholic fatty Acid liver disease (NAFLD). By definition non alcoholic fatty liver disease (NAFLD), classificationcan be performed histologically into non alcoholic fatty liver or non alcoholic steatohepapititis (NASH). Role of Vitamin D /its Receptor and Allyl Isothiocyanate (AITC) ", with Prospective Therapies Like L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, as well as Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin, Probiotics and Synbiotics, role of Resveratrol's Effects Practical in multiple chronic inflammatory diseases and autoimmune diseases, natural products in the treatment of diabesity, inclusive of polyphenols along with flavonoids, dietary polyphenols, like resveratrol, curcumin, proteintyrosine phosphatase1 B (PTP1B) inhibitors, plant terpenes (specifically monoterpenes), flavonoids (querceetin, kaempherol), ursolic acid, besides epigenetic modes of certain plant agents antidiabetic action,like nonflavonoid polyphe-

nols like curcumin, tannins, lignans as well as resveratrol, or flavonoids like anthrocyanins, epigallocatechin gallate (EGCG), quercetin, naringin, rutin along with kaempherol, astragaloside IV and other prospective agents, knowledge of Hepatic Macrophages and association of dietary fatty acids and gut microbiota alterations with Gut-Liver Axis with Gut Microbiome Dysbiosis correlated NAFLD along with NAFLD- HCC, probiotics, prebiotics, Synbiotics. Actions of Curcumin –a magical agent for treatment of wide range of diseases varying from Neuroinflammatory disease (AD,PD) -IBD to DM and CVD,NAFLD,NASH along with various Cancers, De Novo lipogenesis inhibitors, of NAFLD including Organokines for early diagnosis and improvement of management and preventing early HCC development, immunomodulatory action of Food Plants, on Targeting Gut Microbiota (GM) for Avoidance of Metabolic dysfunction associated steatohepatitis propagation to Hepatocellular Carcinoma, Melatonin as prospective therapy for NAFLD]. Despite no FDA approved drugs for NASH, Vitamin E, Pioglitazone, along with Liraglutide escalated liver histology of patients with NASH in randomized controlled Clinical trial. Inspite of Vitamin E possessing potential advantages, it has been correlated with contradictory outcomes of total mortality, the haemorrhagic stroke as well as prostate cancer in males >than 50yrs age [Pioglitazone results in weight escalation, with its utility in NASH still getting evaluated although now Sodium –glucose cotransporter 2 (SGLT2) inhibitors are being evaluated in view of lack of above limitation,hence adversities need to get balanced with the potential advantages in NASH patients having no other option for therapy besides lifestyle changes. Currently weight reduction as well as lifestyle changes with the utilization of diet as well as exercise is advocated as the 1stline treatment. Nevertheless, long time compliance with lifestyle changes is tough for sustenance in target population. Thus, a main requirement that has not been resolved. We further detailed 5 Pharmacologic drugs-i) Obeticholic acid (OCA; Farsenoid X receptor [FXR] agonist) ii) Elafibranor (a Peroxisome Proliferator Activated Receptor [PPAR] α as well as δ agonist) iii) cenicriviroc (CVC-a dual antagonist of C-C chemokine receptor (cenicriviroc CCR) types 2 as well as 5 iv) resmetriom (THR-β- agonist) as well as aramchol (stearoyl-Co A desaturase [SCD1 inhibitor-resulted in enhancement of liver histology in phase 2 studies along with are going through evaluation of their long term effectiveness as well as safety. Extra a lot of innovative agents that target NASH-associated pathways are undergoing phase 1 as well as 2 trials are about 200 p Pharmacologic drugs are being analysed for NASH treatment therapy. Yet no clearcut answer is there for therapy of NAFLD, NASH metabolic dysfunction-associated steatosis liver disease (MAFLD), MASH [1-29]. Here we further detail, which herbal, plant products evaluated might work in therapy of such disorder.

Nowadays, there is presence of occasional pharmacological therapies for metabolic dysfunction-associated steatosis liver disease (MASLD, alias NAFLD earlier) or MASH, guaranteeing lifestyle intervening, weight reduction as well as escalated physical activity portray the underpinnings of management [30]. Thus, there is an escalating public value for dietary bioactive compounds for hepatic health, which are inclusive of MASLD. The working definition for bioactives of the US National Institutes of Health Office of Dietary Supplements is “components in food or dietary supplements, different from the ones whose requirement is to fullfill basic human nutritional needs, that are implicated in alteration of kinds of health status”. Additionally, there is a parameter for generating advocated consumption of dietary bioactive compounds [31]. Different examples of dietary bioactive compounds of public attraction in reference to MASLD are portrayed by curcumin (turmeric), silymarin (Milk Thistle), resveratrol, in addition to, polyphenols obtained from coffee along with green tea. The US National Institute of Diabetes as well as Digestive in addition to, Kidney Diseases (NIDDK) determine that as much as 40% of patients with clinical presentation at hepatology clinics, utilized certain of dietary bioactive substances [32]. Therefore, the aim of this validated asssessment Center scoping review was is to isolate as well as study the present properties of corroboration on dietary bioactive-compound-based intervening for adults, ≥18 years of age, with MASLD/NAFLD. Such scoping review by Handu etal. would impart knowledge in addition to research along with aid in future generation of randomized controlled trials (RCTs) along with systematic reviews (SRs) in this arena (Figure1,2).

Of the important findings from this scoping review was the geographical focus of research, with the maximum of studies performed in Iran. Whereas this concentration yielded attractive understanding, the queries evoked were in reference to the generalization of observations to variable populations. Liver diseases, MASLD, hepatitis, along with cirrhosis portray public health botherations in Iran. The escalating prevalence of MASLD is mainly guided by persistently escalating rates of obesity, metabolic syndrome (MetS), as well as type 2 diabetes (T2D), . Furthermore, hepatitis B in addition to, C persistently endemic in some areas, that aid in the load of liver disease [33]. Restricted characterization from others, for instance

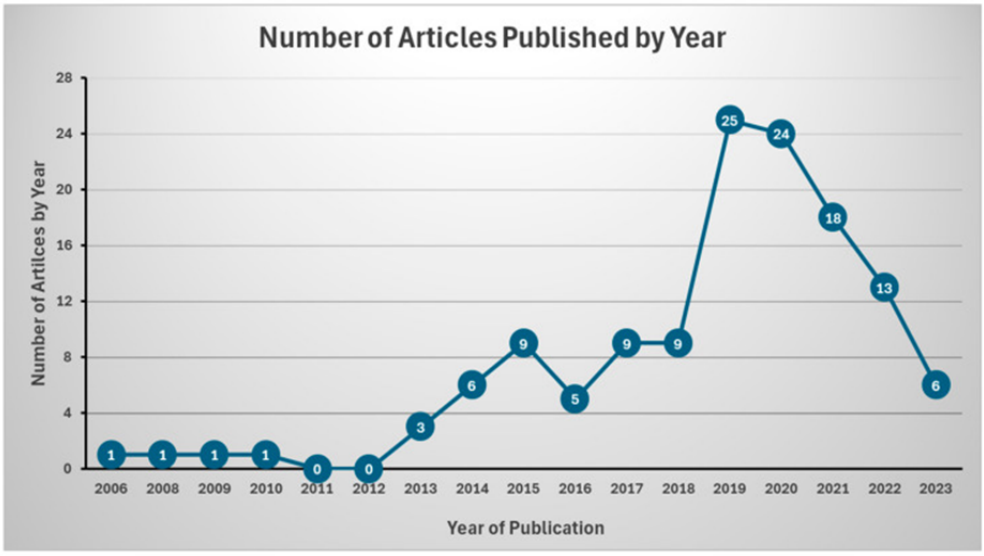

Figure 1: Courtesy ref no 39-Number of articles meeting inclusion criteria according to publication year.

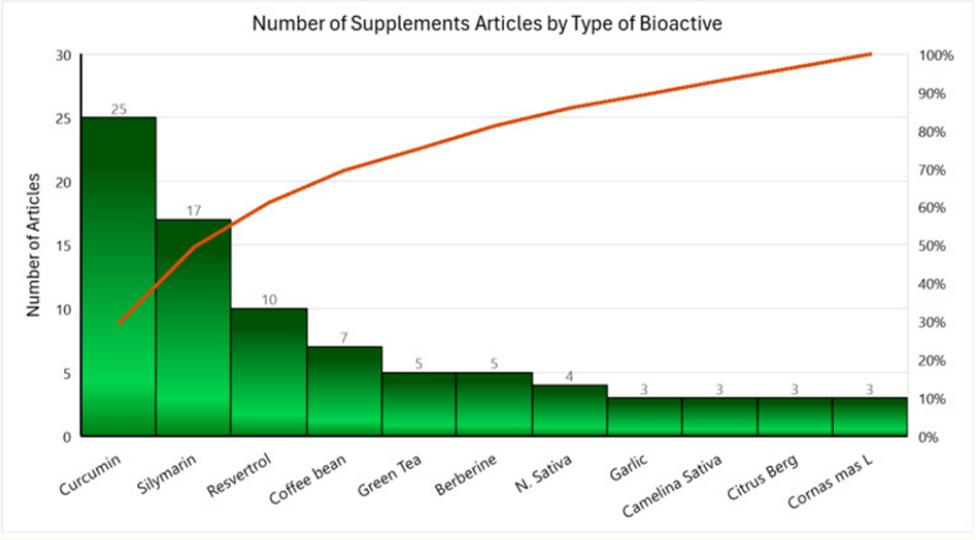

Figure 2: Courtesy ref no 39-Number of articles meeting inclusion criteria according to type of bioactive substance (bioactive reported in ≥3 articles) (n = 85).

Asia, North America, Latin America, along with Europe, pointed to the existence of a requirement for greater geographically variable research for guaranteeing wider application.

One further observation was the common inclusion of co- intervening for instance, dietary prescriptions or advocating for a healthy diet, in plethora of primary studies. Whereas this portrayed the sophisticated nature of MASLD/NAFLD management, it results in complexity of capacity of identification of the actions of dietary bioactive supplementation. Identification of the actions of bioactive compounds from concurrent lifestyle interventions poses a significant problem in research. This complicates nature of the origination of heterogeneous human behavior, physiology, as well as the crosstalk amongst intervening. Lurking variables are existent in the form of a main challenge, since overlapping actions from lifestyle alterations, for instance physical activity or dietary

interventions, might simulate or escalate the results of bioactive compounds. Behavioral alterations, for instance healthier habits embraced alongside supplementation, further conceal the contribution of actions found. Blinding, variability in personal reactions, in addition to, determination of botherations might take place. For tackling such hurdles, approaches- for instance study fashion by utilization of factorial or crossover strategies, objective determination via wearable gadgets along with biomarkers, as well as advancement of statistical methodologies for regulating diverting factors in addition to, crosstalk application might be attempted. Keeping a watch on compliance to interventions as well as performing studies of greater duration, further are capable of contributing in discriminating along with disentangle the autonomous as well as combination of actions of bioactive compounds in addition to, lifestyle amongst instant in addition to, postponed actions. By tackling such complicated d nature of research possesses the capability of causing advantageous interventions [34,35] . Future research needs to aim for advantageous estimation of the autonomous along with synergistic actions of such intervening to inform clinical advocating as well as practice (Figure 3).

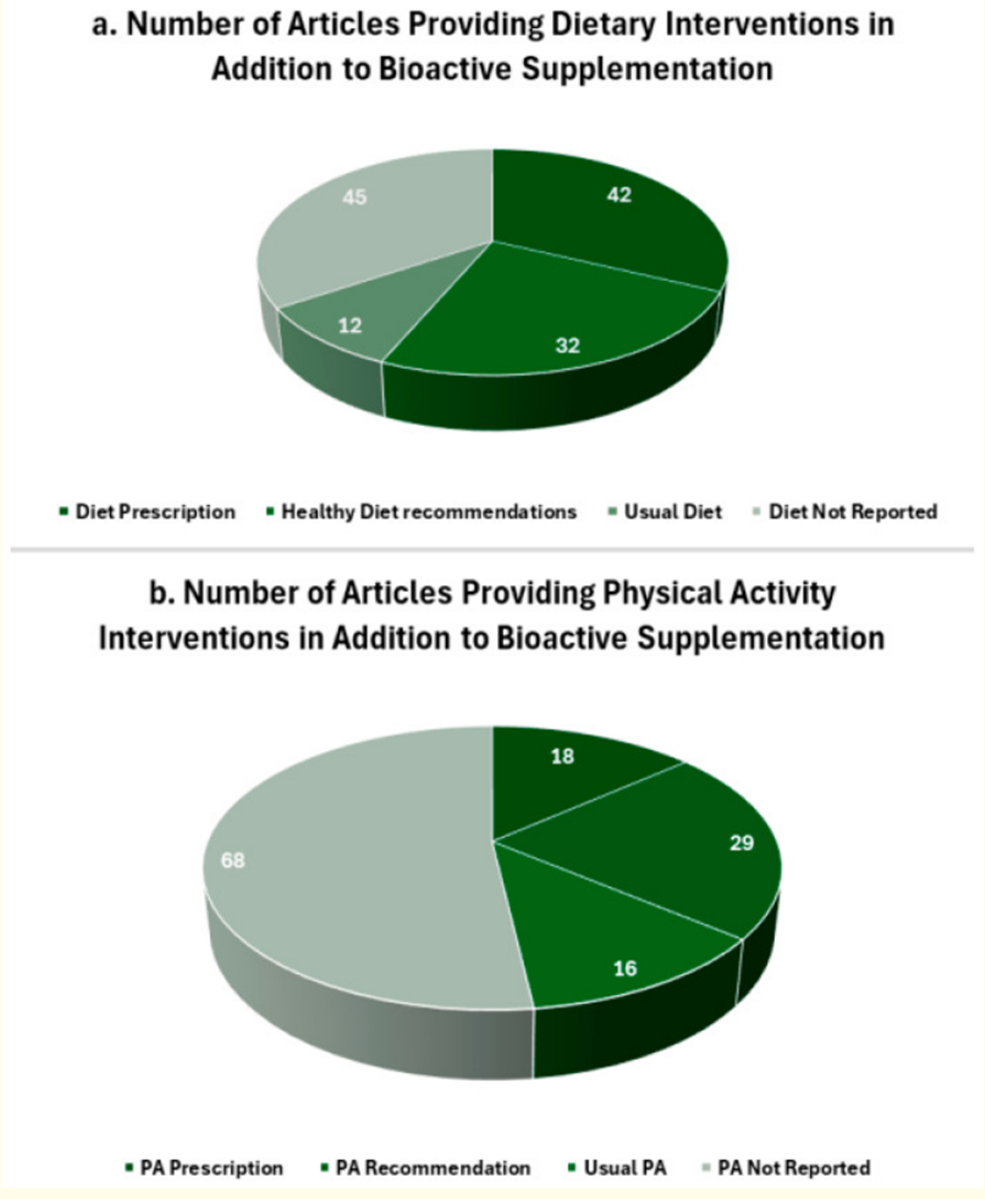

Figure 3: Courtesy ref no 39-Number of included articles providing dietary (a) and physical activity (b) co-interventions in addition to bioactive supplementation.

Intriguingly, practically 50%of the enrolled MASLD patients in primary studies did not display' associated comorbidities with MASLD, although MASLD/NAFLD usually take place in the backdrop of metabolic conditions for instance T2D as well as hypertension. Such absence of description restrict the capacity of getting insight on the manner they are capable of influencing interventions in greater manner in clinical scenarios, emphasizing, a significant lacuna in the literature. Scientific work that unequivocally targets populations with comorbidities or categorizes results dependent on such situations is imperative to generate customized dietary bioactive intervention strategies.

Amongst the broad variability of results displayed in the primary studies, the maximum works were inclusive of hepatic health (liver function tests, imaging tests, biopsies, etc.), body weight as well as body constitution, inflammatory in addition to, oxidative stress (OS) markers, along with biomarkers of cardiometabolic risk, for instance glycemic regulation as well as blood lipids. Energy in addition to, macronutrient consumption was further more commonly documented. In reference to safety outcomes for dietary bioactive compounds inimical sequelae were examined in 72% of the primary studies. Occasional primary studies displayed incident processes, generation of CVD, or mortality in view of the botherations of performing long-term research with RCTs (Figure 4).

TOTAL (n)	All (85)	Curcumin[1] (25)	Silymarin[2] (17)	Resveratrol[3] (10)	Coffee Bean[4] (7)	Green Tea[5] (5)	Berberine[6] (5)	Nigella sativa[7] (4)	Camelina sativa[8] (3)	Garlic[9] (3)	Cornus mas L.[10] (3)	Citrus bergamot[11] (3)
Prescribed:												
Diet	26	6	7	3	0	2	3	0	3	0	0	2
Exercise	15	6	3	2	0	1	3	0	0	0	0	0
Encouraged:												
Healthy Diet	15	7	3	1	2	0	0	2	0	0	0	0
Exercise	14	6	4	0	2	0	0	2	0	0	0	0
Hepatic Health[12]	75	22	16	9	7	4	5	3	2	3	1	3
Body Weight[13]	68	18	12	9	6	5	5	3	3	3	2	2
Adverse Events[14]	60	16	11	8	6	3	3	4	3	2	3	1
Glycemic Control[15]	54	14	14	6	4	4	5	1	2	2	-	2
Blood Lipids[16]	53	15	10	8	4	4	4	2	2	2	-	2
Body Composition[17]	45	13	7	8	3	4	4	2	1	1	1	1
I/OS Markers[18]	37	10	4	5	5	5	-	2	3	1	-	2
Dietary Intake[19]	30	10	-	6	6	1	-	2	2	-	3	-
Physical Activity[20]	21	9	1	5	1	-	-	2	-	-	3	-
Blood Pressure[21]	21	7	2	5	2	1	1	1	-	-	1	1
Renal[22]	13	3	2	3	1	1	1	-	-	-	-	2
Uric Acid[23]	6	1	-	-	-	1	-	-	2	-	-	2
CBC[24]	6	3	-	1	-	1	-	-	-	-	-	1
Serum Fatty Acids[25]	5	1	2	1	-	-	-	-	-	-	1	-
Other CVD[26]	4	2	-	-	-	-	-	-	1	-	1	-
Serum Vit/ Min[27]	2	1	-	-	-	1	-	-	-	-	-	-
Heart Rate[28]	1	-	-	1	-	-	-	-	-	-	-	-
Gastrointestinal[29]	-	-	-	-	-	-	-	-	-	-	-	-
Other[30]	19	6[A]	3[B]	-	1[C]	3[D]	2[E]	-	3[F]	-	-	1[G]

Heat map colors (as a percentage of total articles for each dietary intervention category): ≥75%; 50-74%; 25-49%; 1-24%; None

BMI=body mass index; CBC=complete blood count; CVD=cardiovascular disease; I/OS Markers=inflammatory and oxidative stress markers; MASLD=metabolic dysfunction-associated steatotic liver disease; Min=Minerals; NAFLD=non-alcoholic fatty liver disease; Vit=vitamins

Figure 4: Courtesy ref no 39--Heat map describing outcomes reported for each bioactive substance with at least n = 3 articles for adults with MASLD. Intervention descriptions: 1 Curcumin: Curcumin (n = 9), Nano-curcumin (n = 1), Curcuminoids + Piperine (n = 5), phospholipid Curcumin (n = 1), Phytosomal Curcumin (n = 3), Curcumin Complex + other bioactive substances (nutraceutical) (n = 1), Turmeric (n = 3), Turmeric, Chicory (n = 2); 2 Silymarin: Silymarin (n = 9), Silymarin + other substances (n = 8); 3 Resveratrol: (n = 10); 4 Coffee: Coffee components (n = 2), Green Coffee extract (n = 5); 5 Green Tea: Green Tea (n = 1), Green Tea extract (n = 4); 6 Berberine: Berberine (n = 2), Berberine + bicyclol (n = 1), Berberis integerrima (n = 1), Berberis aristate + other substances (n = 1); 7 Nigella sativa: N. Sativa oil (n = 2), N. Sativa (n = 2); 8 Camelina sativa: (n = 3); 9 Garlic: Garlic powder (n = 3); 10 Cornus mas L: Cornus mas L. fruit extract (n = 3); 11 Citrus bergamot: Bergamot citrus + wild cardoon (n = 1) and Citrus bergamias + Cynara cardunculus (n = 2); Outcome descriptions: 12 Hepatic health: includes liver function tests [e.g., alanine aminotransferase (ALT); aspartate aminotransferase (AST); gamma-glutamyl transferase (GGT); alkaline phosphatase (ALP)], various measures of hepatic steatosis and fibrosis [e.g., Controlled Attenuation Parameter (CAP) score, NAFLD grade, etc.], ballooning injury score, liver stiffness, liver volume, and bilirubin. 13 Body weight: includes body weight

and body mass index. 14 Adverse events: includes any self-reported adverse effect of intervention (e.g., nausea, constipation, bloating, etc.) or other adverse event identified by research staff (e.g., biliary disorder, abnormal lab values, etc.). 15 Glycemic control: includes blood glucose, total available glucose, hemoglobin A1c, Homeostatic Model Assessment of Insulin Resistance, insulin levels, quantitative insulin sensitivity check index (QUICKI), and C-peptide. 16 Blood lipids: includes total cholesterol, high-density lipoproteins, low-density lipoproteins, non-HDL-C, triglycerides, TC:HDL ratio, lipoprotein remnants. 17 Body composition: includes body fat, lean body mass, waist, hip and abdominal circumference, waist-to-hip ratio, fat mass, fat-free mass, and visceral fat. 18 I/OS markers: inflammatory and oxidative stress markers includes immunological, inflammatory, and oxidative stress markers such as C-reactive protein, interleukin-6, Tumor Necrosis Factor, adipokines and cytokines (leptin, adiponectin, etc.), malondialdehyde (MDA), total antioxidant capacity (TAC), fibroblast growth factor (FGF-21), glutathione peroxidase (GSH), superoxide dismutase (SOD), total glutathione, and many others. 19 Dietary intake: includes intake of energy, macro- and micronutrients, antioxidants, fiber, flavonoids, and caffeine. 20 Physical activity: includes any physical activity (aerobic, muscle-strengthening, stretching, balance, etc.). 21 Blood pressure: includes systolic and diastolic blood pressure. 22 Renal: includes renal function lab values (creatinine, blood urea nitrogen, etc.). 23 Uric acid: includes uric acid blood test. 24 CBC: includes albumin, hematocrit, hemoglobin, neutrophils, white blood cells, platelets, etc. 25 Serum fatty acids: includes lipid accumulation product (LAP), serum fatty acid profile (includes phospholipids, saturated and polyunsaturated fatty acids, etc.), and free fatty acids. 26 Other CVD: cardiovascular outcomes (other than lipids), including atherogenic index of plasma (AIP), homocysteine, coronary artery calcium (CAC), Castelli risk index I (CRI-I), CRI-II, and atherogenic coefficient (AC). 27 Serum vit/min: includes serum vitamin and minerals: 25-hydroxy vitamin D [25(OH)D3], potassium, iron, ferritin, transferrin, and magnesium. 28 Heart rate: includes heart rate and pulse. 29 Gastrointestinal: includes intestinal permeability and gut microbiota. 30 Other: other outcomes: A frequency of comorbidities, nesfatin, 8-Hydroxy-2′-Deoxyguanosine, methylation in MutL homolog 1, MutS homolog 2 (MSH2), carboxymethyl lisine (CML), 8-hydroxy-2′-deoxyguanosine, urea, liver-to-spleen CT attenuation ratio. B Thiobarbituric acid reactive substances (n = 2), tissue inhibitor of metalloproteinase-I/II, amino terminal propeptide of type III procollagen, endocan, high mobility group box-1, and thiobarbituric acid reactive substances. C Thyroid-stimulating hormone. D Liver-to-spleen computed attenuation ratio, nonprotein RQ, substrate oxidation. E Liver-to-spleen computed attenuation ratio, urea. F Mental health: general health questionnaire, depression, anxiety and stress scale. G Endothelial dysfunction parameters.

The Systematic Review'' (SRs) included in this scoping review yielded extra understanding, however displayed technological disparity. Whereas maximum SRs complied to PRISMA parameters along with performed risk of bias evaluation, occasional registered their protocols or assessed the surety of corroboration . This variability strengthens the requirement for greater technological standards in future SRs to underscore the credibility of consumption in dietary bioactive compounds research. Yates., *et al.* [31], generated exhaustive parameters for estimating advocated consumption of dietary bioactive compounds that yield health benefits. This parameter needs to be utilized to generate advocates since it is dependent on utilizing greater -quality scientific corroboration that comprehensively assesses efficaciousness as well as safety by personnel possessing qualification. Additionally, the specification embraced just yield quantified advocates with minimal moderate-quality corroboration [31].

The scoping review got buttressed by utilization of a stringent scientific strategy to explore the influence of dietary bioactive compounds in adults with MASLD/NAFLD. The protocol for this project complied to the PRISMA checklist for scoping reviews as well as is registered on Open Science Framework. Extra buttressing include the implications of a content expert, who was consulted all through full stages of the review for guaranteeing appropriate along with germane outcomes in addition to documenting along with, the attribution by a knowledge expert who performed a wide as well as deep literature search over six databases to comprehensively identify studies on dietary bioactive compounds associated with MASLD/NAFLD.

Nevertheless, need for recognizing, certain restrictions are existent . The limitations to English-language articles might have ruled out germane studies published in other languages. Furthermore, the lack of critical estimation of the studies that got included', technological quality as well as a absence of synthesis of observations or quantitative evaluation as well as an analysis of certainty of evidence (CoE), the manner is common for scoping reviews, restricts the capacity of examining the potency of individual observations [36-38]. Furthermore, the broad inclusion criteria in addition to, variable interventions captured in the review might in still variability that restricts the synthesis of particular conclusions.

The observations from this scoping review emphasize diverse opportunities for future research. First, there is a need for greater standardized documenting of study fashion designs, subject properties, along with data. Compatibility in definitions as well as documenting MASLD in addition to its comorbidities will escalate the similarity of observations across studies. Second, whereas this review isolated variable articles associated with consumption of dietary bioactive compounds, further greater -quality RCTs with rigid technologies are required to establish their effectiveness as well as safety. Third, the incorporation of interventions with lifestyle modifications, for instance diet in addition to, physical activity, requires greater concentrated evaluation to estimate the ideal combination for the management of MASLD. Lastly, as evolution of MASLD research takes place, the integration of outcomes associated with quality of life, healthcare utilization, as well as cost efficaciousness will be critical for translating observations into clinical practice in addition to policy.

Metabolic dysfunction-associated steatotic liver disease (MASLD) portray's a chronic disorder affecting a wide population. The is objective of such review was to isolate as well as provide a summary in reference to the present corroboration on bioactive-compounds - dependent interventions for adults with MASLD, acknowledged earlier in the form of nonalcoholic fatty liver disease (NAFLD), encompassing publications from 2000 to 2023 with utilization of 6 search engines for randomized controlled trials (RCTs) in addition to other study kinds (for instance prospective cohort studies, along with systematic reviews), portraying the scoping type of such review. The search was restricted to studies in adults (>18 years old), with an intervention of interest as well as a minimal of one comparator group. Overall they observed 4572 articles were fully extracted subsequent to screening of 201 full-text articles for eligibility. Out of them, 131 primary studies in addition to 49 systematic reviews got included in the scoping review. The maximum evaluated bioactive substances were curcumin (Turmeric) (n = 25), silymarin (Milk Thistle) (n = 17), resveratrol (n = 10), coffee (n = 7), green tea (n = 5), along with berberine (n = 5 each). Additionally, 46 studies documented on 36 other bioactive agents with 2 or lesser articles each. Among the included systematic reviews, 13 concentrated on curcumin, 12 on coffee/tea, 10 on combinations of bioactive compounds, 6 on resveratrol, as well as 2 each on silymarin in addition to artichoke leaf. The studies which had been included illustrated considerable multifaceted nature in documented outcomes, that basically concentrated on hepatic health, body weight, inimical sequelae, glycemic control, blood lipids, along with body constitution.

Conclusions

Thereby conclusions drawn by Handu., *et al.* [39], was such scoping review emphasizes on effectiveness of a variety of bioactive compounds utilized in the therapy of MASLD. Whereas enrichment of corroboration for bioactive compounds is present, for instance curcumin as well as silymarin, further research in addition to development of observations is imperative for generating the clinical efficacy of all bioactive compounds. They further emphasized on plausible regions of scientific research as well as critical lacunae. Such understanding further aid in driven methodologies for future research in addition to yield corroboration dependent approaches tackling the escalated load of MASLD.

Additionally, Perazza., *et al.* [40], further emphasized on gut microbiota (GM) alterations in the development of MASLD. We have already described the part played by GM, Short chain fatty acids (SCFA) for instance numerous studies illustrated the importance of another SCFA butyrate bacteria possessing the capacity of ameliorating NAFLD by controlling GM, intestinal tight junctions, hepatic glucagon like peptide 1 (GLP-1) receptor expression besides Toll-like Receptor 4 (TLR4) pathways, choline metabolic homeostasis along with escalated ethanol development, tryptophan metabolism in DM [41]. In normal situations numerous nutrients along with advantageous microbial metabolites arrive at the liver through the portal system.Like absorption of microbiota obtained SCFA followed by shifting in liver occurs via the portal system .In certain pathological situations like gut inflammation, dysbiosis, injured bacterial constitutents (alias damage –associated molecular patterns (DAMP) (LPS), along with proinflammatory bacterial

metabolites (like amonnia, besides ethanol). Via the portal system such toxic factors might reach liver directly, stimulate immune cells, proinflammatory cytokines pathways with ultimate NAFLD generation [rev in 21]. A preclinical study concentrated regarding mice fed HFD with intestinal inflammation escalated microbial obtained LPS quantities in the portal system along with facilitated NASH propagation [rev in 21]. It was illustrated that besides NASH metabolic changes in HCC patients had greater quantities of DL-3n phenyl acetic acid, L-tryptophan along with glycocholic acid detectable in portal vein contrasted to healthy controls [rev by us in ref no 21 and 28] . Besides direct connection amongst gut as well as liver via portal system/BA's circulation, GM possess the capacity of impacting liver metabolism via impacting the liberation of intestinal hormones with the capacity of escalating glucose stimulated insulin liberation while hampering glucagon liberation .Like the microbiome obtained SCFA have the capability of stimulating glucagon like peptide 1 (GLP-1) liberation, an intestinal hormone liberated from intestinal L cells [rev in 21] . Multiple GLP1 receptor agonists illustrated the capability of reversal of hepatic steatosis, thus acting as the newer alternate NAFLD therapy and role of probioticsetc. Perazza., *et al.* [40]. further elaborated on how digestion of *i*ndigestible carbohydrate takes place as well as alterations in MASLD along with the manner polyphenols contribute in its restoration to normal in addition to diminished quantities of tryptophan, butyrate, choline, escalated ethanol might result in greater nuclear factor κB (NFκB) quantities, causing escalated intestinal permeability, causing escalated lipopolysaccharide (LPS) translocation, escalated fataccrual. Furthermore diminished choline result in mitochondrial injury causing diminished β oxidation. Escalated polyphenols result in improvement of mitochondrial escalated β oxidation, diminished fataccrual,.Whereas correcting dysbiosis result in escalated butyrate bacteria possessing the capacity of i) escalated activation of Treg cells,ii) escalated expression of GLP-1 receptor result in diminished fataccrual, sustenance of structural intactness of intestinal wall, escalated tryptophan in addition to indole diminish lipogenesis along with fataccrual, as well as diminish LPS translocation. Moreover escalated activation of Treg cells further result in anti inflammatory actions. Collectively, these diminish MASLD propagation (Figure 5,6).

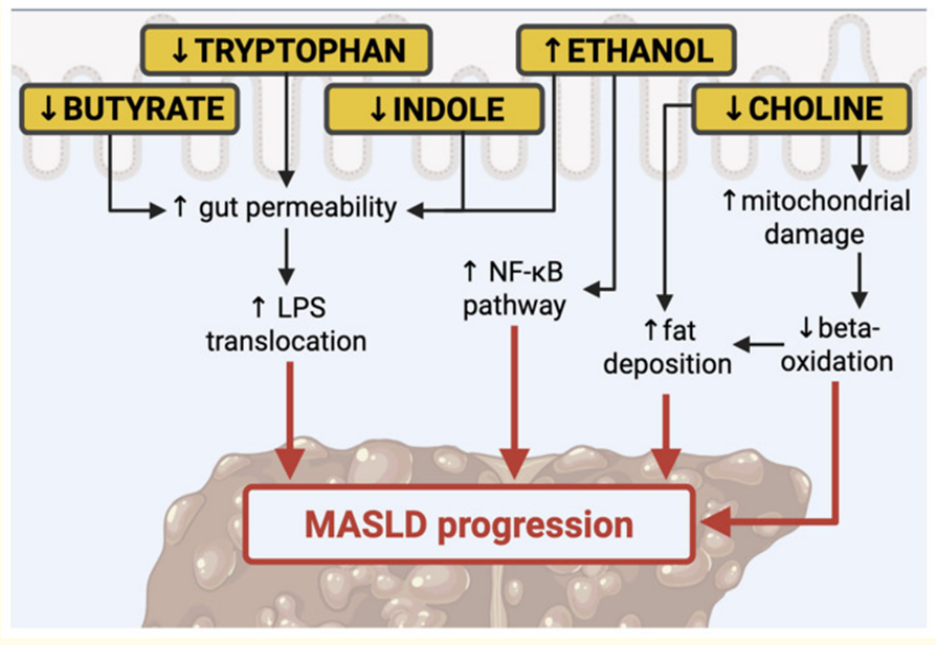

Figure 5: Courtesy ref no 40--Principal modulators of gut microbiota in the MASLD. Nuclear factor-κB (NF-κB), lipopolysaccharide (LPS).

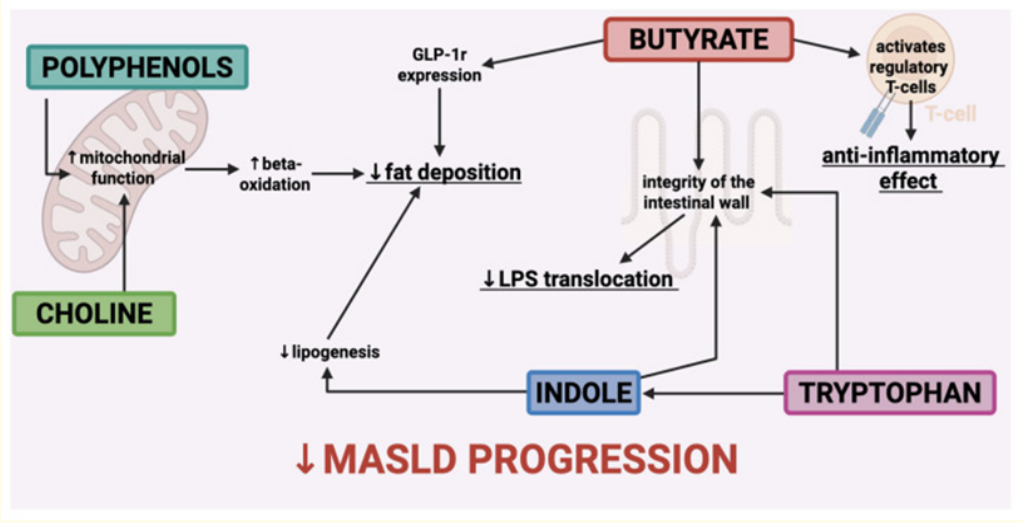

Figure 6: Courtesy ref no 40--The primary metabolites that contribute to the alteration of the microbiota exert a positive influence on the natural progression of MASLD. Receptor of Glucagon-Like Peptide-1 (GLP-1 r); lipopolysaccharide (LPS).

Sodium acetate (NaA) has illustrated plausibility of resulting in improvement of NAFLD by targeting hepatocytes as well as Kupffer cells. Nevertheless, hindering of its clinical applicability takes place by lesser oral bioavailability in addition to, inadequate liver quantities. Liposomes, possessing the capability of encapsulating water-soluble drugs along with surface-modification, yield a valuable answer in reference to targeted oral drug delivery. Hou et al. [42], fashioned modifications of NaA-loaded liposomes by utilization of sodium cholate (SC) as well as mannose (MAN) (NaA@SC/MAN-LPs) with idea of targeting hepatocytes in addition to Kupffer cells. Their observations were NaA@SC/MAN-LPs possessed an average diameter of about 100 nm with a positive surface charge. Contrasted to free NaA, NaA@SC/MAN-LPs significantly prolonged the serum half-life from 2.85 h to 15.58 h, extensively resulting in improvement of in vivo bioavailability. *In vivo* distribution studies displayed that NaA@SC/MAN-LPs prolonged the acetate peak time in the liver from 15 min to 60 min along with escalated hepatic acetate accrual to 3.75 fold that of free NaA. In *in vitro* cell experiments, NaA@SC/MAN-LPs significantly diminished the lipid droplet, triglycerides (TG), as well as total cholesterol (TC) in a fatty acid-stimulated hepatocyte steatosis model in addition to repressed proinflammation in a lipopolysaccharide (LPS) - induced Kupffer cell inflammation model. Free NaA efficaciously resulted in improvement of hepatic lipid accumulation in NAFLD mice. Additionally, NaA@SC/MAN-LPs diminished hepatic TG, TC, along with the germane area of lipid droplets by 30.44%, 15.26%, and 55.83%, contrasted to free NaA. Moreover, the liposomes diminished macrophage infiltration as well as pro-inflammatory response. Thereby NaA@SC/MAN-LPs illustrated efficacious double targeting effects on hepatocytes in addition to, Kupffer cells, significantly resulting in improvement of the pathogenesis of NAFLD, contrasted to free NaA. This study yields an innovative approach for generating efficacious along with safe oral agents for NAFLD.

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