International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

Vol. 45 No. 1 June 2024, pp. 315-352

Challenges of Non-alcoholic Fatty Liver (NAFLD) Management

Literature Review

Maged Naser [1], Mohamed M. Nasr [2], and Lamia H. Shehata [3]

1 Mazahmiya Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of ob/gyn,

2 Consultant of General and Endoscopic Surgery (MD, FRCS)

3 Care National Hospital, Department of Radiology

Abstract – Non-alcoholic fatty liver (NAFLD) is a common global disease, and its burden is predicted to increase because of the developing epidemic of obesity and diabetes. The key undertaking among NAFLD patients is to identify people with advanced fibrosis (F3,F4), who are at excessive threat of growing complications and will gain from specialized management and treatment with new pharmacotherapies whilst they may be approved. Liver biopsy seems unrealistic and unsuitable in practice, given the large number of excessive-risk patients and its well-known limitations. Non-invasive sequential algorithms using fibrosis-4 index as first-line test , accompanied with the aid of vibration-managed transient elastography or patented blood test, are the fine method for case finding of high-risk subjects. In truth, they may be now encouraged by way of numerous worldwide guidelines, and ought to be used and disseminated to increase awareness among physicians liver clinics wherein most NAFLD patients are seen.

Keywords – Non-Alcoholic Fatty Liver Disease; Elastography; Vibration Controlled Transient Elastography; Fibroscan; Liver Fibrosis.

I. Introduction

1. High-risk NAFLD patients

In NAFLD patients, NASH is the driving force of fibrosis development, but the presence of NASH without sizeable fibrosis isn't always related to increased liver-related mortality or overall mortality.[1,2] In all likelihood due to the competing mortality risks of cardiovascular disease and non-liver related cancers in these patients. Several studies have pronounced that, besides the excessive rate of liver-associated difficulty, the risk of all-cause mortality is absolutely multiplied in NAFLD patients with advanced fibrosis.[3,4] Further, 2 meta-analyses, primarily based mostly on longitudinal retrospective studies, have proven that, the principle prognosis driver for liver-related and overall mortality in NAFLD patients is the stage of liver fibrosis, specifically advanced fibrosis.[5,6] The findings had been lately showed prospectively inside the NASH CRN cohort (n=1,773 NAFLD patients), followed over an average duration of 4.0 years (total: 8,120 individual years).[7] Certainly, all-cause mortality improved with increasing fibrosis stages (0.32 deaths / 100 person-years for F0 to F2, 0.89 deaths per 100 person-years for stage F3, and 1.76 deaths for 100 person- years for stage F4. For this reason, it has now been nicely installed that the risk of liver-related complications in NAFLD exponentially will increase while transitioning to stage F3 and then F4. Advanced fibrosis is, consequently, the primary lesion to target when designing techniques to come across high-risk NAFLD patients who have the more severe clinical outcomes. No matter foremost efforts within the improvement of latest tablets.[8] No pharmacologic remedy has yet been accredited for NAFLD. The contemporary consensus is that pharmacotherapy need to be reserved for patients with NASH and at the least massive fibrosis. At-chance NASH (or fibrotic NASH) is described by means of the presence of NASH (NAFLD interest rating ≥4 with one object of each, at least) and sizable fibrosis (fibrosis stage ≥2).[9] Identification of those patients is vital in tertiary referral centers, as they are the principle goal population for ongoing NASH phase 2 and 3 trials.

Corresponding Author: Maged Naser

2. How to discover high -risk NAFLD patients?

2.1. Available non-invasive tests

2.1.1. Non-patented blood tests

ELFTM, Enhanced Liver Fibrosis; GPs, general practitioners; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NFS, NAFLD fibrosis rating; VCTE, vibration managed transient elastography; T2DM, type 2 diabetes mellitus.Context of use, mainly in a scientific putting, is critical whilst handling blood assessments, knowing that NFS isn't the nice take a look at for the screening of advanced liver fibrosis in patients with T2DM.[10-12] additionally, age[13] and BMI,[14] protected in the NFS components, have an effect on its performance in older patients with morbid weight problems. By way of assessment, FIB-4, which is most effective by age, seems a better option in those populations. Both FIB-4 and NFS can be calculated free of charge through websites and smartphone applications. FIB-4, however, is the maximum popular and maximum studied non-patented blood fibrosis test because of its simplicity and the fact that serum transaminases and platelet count are largely prescribed via general practitioners (GPs) in their check-up for metabolic diseases. In large populations of unselected patients, at a threshold of 1.30, FIB-4 has the strong advantage to very easily rule-out a big proportion (60–80%) of the subjects evaluated.[15] Furthermore, repeating FIB-4 measurement may want to evaluate the risk of liver related complication[16] within time.

2.2. Patented blood checks

The most studied patented blood fibrosis assessments in NAFLD encompass FibroTest®, FibroMeterTM, and Enhanced Liver Fibrosis (ELFTM) check.[17] The ones non-invasive tests integrate indirect and direct markers of liver fibrosis, the latter being additives of liver fibrosis or proteins at once worried inside the procedures of fibrogenesis and fibrolysis within the liver all through chronic liver diseases. Recent meta-analyses evaluating the accuracy of those exams in NAFLD patients said an AUROC for superior liver fibrosis of 0.77 for FibroTest®,[18] 0.83 for ELFTM,[19] and 0.89 for FibroMeterTM.[20] Direct comparison completed in 417 patients with biopsy-tested NAFLD has observed similar diagnostic accuracy among FibroMeterTM and ELFTM.[21] Patented blood checks are more correct than non-patented blood tests,[21,22] but their fee and limited availability limit their vast utility. therefore, they're extra suitable even as used as a 2nd-line desire, to similarly verify the danger of advanced liver fibrosis counseled via the primary-line nonpatented blood fibrosis test. Importantly, researches are concordant approximately the reality that negative predictive values (NPVs) for apart from enhanced fibrosis are higher than the corresponding postive predictive values (PPVs). Therefore, blood exams may be with a piece of good fortune used for first-line risk stratification to exclude enhanced fibrosis. however, maximum of those research were done in tertiary referral centers wherein the pre-take a look at possibility of advanced fibrosis is better (20–30%) than that during number one care (<5%), which can have a prime effect within the accuracy effects.[23]

2.3. Elastography

Elastography include ultrasound-based completely strategies, such as vibration-controlled transient elastography (VCTE) (FibroScan, Echosens, France), point shear wave elastography (pSWE), two-dimensional shear wave elastography (2D-SWE), and magnetic resonance elastography (MRE).[24] amongst them, VCTE is the approach with the largest amount of evidence.[17] two massive multicenter studies[25,26] said excessive VCTE applicability (96-97%) in NAFLD patients. Furthermore, the same cut offs can be used without further adjustment for steatosis whilst the M and XL probes are used consistent with an appropriate BMI (30 kg/m2). In a modern-day meta-analysis which include 5,489 NAFLD patients in 37 studies, VCTE had exquisite accuracy for diagnosing enhanced fibrosis and cirrhosis, with AU-ROCs of 0.85 and 0.90, respectively.[27]

As for the last strategies, a state-of-the-art systematic assessment of 82 studies (14,609 sufferers) and a meta-assessment of 70 research (12,547 patients) confirmed that simplest MRE and pSWE had a specificity greater than 80% for the analysis of enhanced fibrosis (89% and 86%, respectively).[28] Despite the fact that, all evaluated strategies had a great diagnostic accuracy. The mentioned summary AUROC for diagnosing enhanced fibrosis with VCTE, MRE, pSWE, and 2D-SWE have been 0.85, 0.92, 0.89, and 0.72, respectively.[28]

Although MRE had the pleasant diagnostic accuracy, it stays a research tool due to its confined availability and fee. Moreover, pSWE/ARFI and 2D-SWE aren't included within the modern-day recommendations on the control of NAFLD because of the confined amount of records. Taken together, these consequences advocate that VCTE is currently the method with the very first-

class stage of evidence to hopefully exclude enhanced fibrosis and cirrhosis with an excessive negative predictive value (around 90%) in NAFLD patients.[17] As an instance, VCTE had a 94% to 100% NPV at a cut-off <8 kPa. On the other hand, the PPV did not exceed 64% at a cut-off >10 kPa worldwide, and is accordingly the approach of desire for the second-line testing out of advanced fibrosis.

3. NAFLD patients with advanced fibrosis

what's the best approach?

The context of use is vital even as the use of non-invasive assessments, because it will strongly have an effect on their diagnostic performance. The pre-test possibility of the purpose scenario (advanced fibrosis) will affect PPV and NPV.[29] whilst coping with patients in primary care, where the prevalence of advanced fibrosis is low (<5%), non-invasive tests are far better for ruling out (high NPV) rather than for diagnosing (high PPV) the presence of advanced fibrosis. This indicates the need for at least two tiers of non-invasive fibrosis tests for selecting patients from low-prevalence populations for further investigations and follow-up to reduce false positive results.[30] Therefore, using widely available, easy-to-obtain, and cheap blood tests (nonpatented serum markers) as the first-line procedure followed, if positive, by a second-line confirmatory test (elastography or patented serum markers) seems the most appropriate strategy. The use of sequential algorithms is more effective than single tests in both low and high prevalence settings.[27,31]

3.1. Sequential strategies using blood tests followed by elastography

Several sequential strategies using non-invasive tests have been proposed to identify patients with advanced fibrosis in clinical practice.[29] The first algorithm proposed by the European Association for the Study of the Liver (EASL) targets patients at risk NAFLD observed in primary healthcare or diabetology clinics, using FIB-4 (single threshold 1.3) followed by VCTE (single threshold 8.0 kPa).[29] Patients with FIB-4 ≥1.3 are considered at intermediate-high risk of advanced fibrosis and should undergo TEVC, which may be performed before or after referral to a liver specialist depending on local availability and access routes. Finally, in patients with LSM ≥8.0 kPa, a third test (patented blood test) can be performed if available. If there are concordant results with VCTE, advanced fibrosis may be present. Otherwise, a liver biopsy may be considered when the results are negative or if a personal blood test is not available. Patients with FIB-4 <1.3 and/or LSM <8.0 kPa have a low risk of advanced fibrosis and can be evaluated by GPs using frequent measurements during follow-up. This algorithm was recently validated in "real life" in a retrospective, multicenter French cohort of 1,051 patients with biopsy-proven NAFLD.[32] Compared to the performance of a non-invasive test (NIT), agreement located between two NITs. (FIB4 and VCTE, VCTE and patented serum test) increased the specificity and PPV by 20%, thus supporting the methodology proposed in the EASL algorithm. The FIB-4/VCTE/FibroMeterTM and FIB-4/VCTE/FibroTest® algorithm performed the same, providing a diagnostic accuracy of 85% and a liver biopsy rate of only 10%. Interestingly, in a group of patients, the EASL algorithm can also predict the risk of liver-related events (LRE)[33]. Maintenance of 3.9 (95% confidence interval [95% CI] 1.3 to 10.9) in those with 8.0 < LSM < 12.0 kPa and 12.4 (95% CI 5.1 to 30.2) in those with LSM ≥12.0 kPa. Finally, the usefulness of the EASL algorithm was evaluated in 467 patients with type 2 diabetes seen in primary care, regardless of their transaminase levels.[34] 20 of 440 (4.5%) patients were found to have advanced liver disease, compared to three patients who were previously identified through standard care (odds ratio 6.71, 95% CI 2.0–22.7; P = 0.002). Alcohol consumption and obesity are predictors of higher morbidity, findings consistent with previous research.[35-37]

Other algorithms are recommended, including the American Gastroenterology Association (AGA) pathway[38] and the American Association of Clinical Endocrinology (AACE) algorithm.[39] The AGA pathway targets the same population as the EASL algorithm, and uses FIB-4 (dual cut-offs 1.3–2.67) followed by VCTE (two thresholds 8.0–12.0 kPa). Patients with FIB-4 between 1.3 and 2.67 are considered to be at undetermined risk and should undergo VCET. Patients with FIB-4 <1.3 and/or LSM <8.0 kPa are considered to be at low risk for advanced fibrosis and can be evaluated by their GP through repeated measurements during follow-up. Those with 8.0 <LSM <12.0 kPa are considered at undefined risk and should be referred to a hepatologist for liver biopsy or MRE. Those with FIB-4 ≥2.67 or LSM ≥12 kPa are considered high risk and should be referred to a hepatitis specialist. Regarding the AACE algorithm, it is very similar to the AGA method and consider the use of ELFTM (both thresholds 7.7-9.8) as an alternative to VCTE in patients with FIB-4 between 1 .3 and 2.67 . Patients with low risk (FIB-4 1.3-2.67 or LSM 8-12 kPa or ELFTM 7.7-9.8) and high risk (FIB-4 ≥ 2.67 or LSM ≥ 12 kPa or ELFTM ≥ 9.8) should be referred to a hepatologist for liver. pathology. biopsy or MRE. In summary, it should be noted that in the past year, the guidelines from the societies of

hepatology, gastroenterology, and endocrinology have recommended similar non-invasive procedures using the same tool and cut-offs. This may facilitate the diagnosis and case management of high-risk patients with NAFLD in clinical practice.

4. Identify NAFLD patients who are at risk for NASH

Several non-invasive serum concentrations and biomarkers have been proposed to identify NASH patients at risk. The first score is Fibro Scan-AST (FAST), A continuous and composite score, combining controlled attenuation parameters (CAP), LSM by VCTE and AST level.[40] The score varies from 0 to 1 and the limit 0.35 (sensitivity ≥90%) and the rule of 0.67 (specificity ≥90%). Patients with values between the two thresholds are in the gray area with no results. FAST has an AUROC of 0.85 for identifying high-risk NASH patients in the external support group, with a 94% NPV for exclusion and a 69% PPV for the diagnosis of high-risk NASH, respectively.

4.1 Procedures for blood tests followed by elastography

Several non-invasive serum concentrations and biomarkers have been proposed to identify NASH patients at risk. The first score is FibroScan-AST (FAST), a continuous and composite score, combining controlled attenuation parameters (CAP), LSM through VCTE and AST levels. 0.35 (sensitivity ≥90%) and a standard deviation of 0.67 (specificity ≥90%). Patients with values between the two thresholds are in the gray area with no results. FAST had an AUROC of 0.85 for identifying at-risk NASH patients in the external validation cohort, with a 94% NPV for exclusion and a 69% PPV for adjudication in high-risk NASH, respectively . In total, 60% of patients can be correctly segmented and avoid liver biopsy. It should be noted that the performance of FAST may vary depending on the number of NASH patients at risk and the included population. For example, in an American group with a population of 12%, FAST has an AUROC of 0.86, allowing 78% of patients to be classified, while in another group from Turkey with 57%, its AUROC is 0.74, and 43. % of patients. well divided.[40]

The second score, the Magnetic Resonance Imaging AST (MAST) score, is based on the FAST concept, but using MRI (PDFF and MRE) instead of VCTE. MAST has an AUROC of 0.93, NPV of 98% for exclusion and a. PPV of 50% for the determination of NASH risk, respectively . In total, 70% of patients can be successfully managed and avoid a liver biopsy. Finally, the MRE index combined with the FIB-4 index (MEFIB), a categorical score that combines MRE and FIB-4, was proposed, but with the main difference in the diagnosis of F2-4 fibrosis in NAFLD [41] After is checked for at-. NASH risk and MEFIB had AUROC of 0.77, NPV of 93% for exclusion, and PPV of 55% for trial and NASH risk, respectively . In total, 57% of patients could be correctly classified. A quick comparison of FAST, MAST and MEFIB showed conflicting results. One study suggested that MAST is superior to FAST[42], while another study suggested that MEFIB is superior to both MAST and FAST.[43] These results deserve several interpretations. First, one of the problems with these signs is treating patients in the gray area. It is interesting to note that in a study comparing three markers[53], the gray area of MAST was smaller than that of FAST and MEFIB (8.5% vs. 40.1% and 24.7%, respectively; P<0.001). Consequently, the proportion of patients correctly classified as NASH was at higher risk in MAST than in MEFIB and FAST (69.4% vs. 57.4% and 45.3%, respectively).[54] Second, comparing itself with the developers in a large group of T2DM patients with NAFLD, MAST and FAST exceeded MEFIB, and MAST collected the largest number of patients. [44] However, the cost is high and the end is limited. may undermine the widespread application of MRI-based quantification. More studies are needed.

There is an urgent need to introduce an effective treatment against MAFLD, especially in the early stages of its development. Currently, vitamin E and pioglitazone are recommended by the international scientific body [45], but these drugs are used in high levels of MAFLD (i.e. MASH), and the magnitude of improvement in steatosis seems frustrating. Therefore, there is great interest in other treatment options that can be used to treat MAFLD, especially in terms of drug regimens that are important for other co-existing conditions and patients with characteristics of metabolic syndrome (for example, diabetes and hyperlipidemia). In this case, the treatment and direction of the development of MAFLD pharmacotherapy should focus on finding drugs that improve the process of obesity, diabetes, insulin resistance, lipid disorders, hypertension and hyperuricemia. However, other potential therapeutic areas (endocrine system, microbiota and functional nutrition) will also be investigated.

One of the challenges associated with the introduction of new therapies is the proper evaluation of their clinical effectiveness. Despite better diagnostic tests, liver biopsies are not recommended in the early stages of MAFLD (e.g., steatosis). The most accurate method of non-invasive analysis of fatty liver is proton density fat fraction MRI (MRI-PDFF). However, the cost of the process and its limited scope means that it is almost exclusively for clinical trials. There are other ways to diagnose steatosis. Ultrasound techniques (for example, Fibroscan) are more accessible or more accurate than MRI. There are also several blood

markers that can be used to determine the extent or prognosis of MAFLD (Fib-4, etc.). However, most trials report simple liver function tests (LFT, i.e. alanine aminotransferase – ALT, aspartate aminotransferase – AST and gamma-glutamyl transferase – GGT). Here, we provide an in-depth narrative review of the potential use of investigational drug strategies to treat the onset of MAFLD, which is primarily hepatic steatosis, focusing on the most important findings reported .

5. Therapeutic lifestyle changes

The incidence of MAFLD is increasing alongside the global obesity epidemic. The pathophysiological link seems clear: high fat intake, obesity, insulin resistance and dyslipidemia [46]. Significant improvements in MAFLD can be achieved by implementing therapeutic lifestyle changes. Recent data show a positive correlation between the reduction of subcutaneous fat and the severity of hepatic steatosis [r = 0.42 (CI: 0.29-0.54)] [47]. This results in an increase in LFTs. The diet leads to a reduction in ALT activity [MD: (-4.48 IU/L)], and the effect is also evident in patients who exercise, ALT [(-13,27) UI/L; 95% CI: (-21.39)—(-5.16). In the patients and improvement are required in AST [(-7.02) ui / l; 95%: (-11.26) - (- 2.78). Do not sign a suggestion for the exercise increase in the instructions of many scientific companies deal with MAFLD. AASLD [48] Recommends encouraging patients with NAFLD to increase their activity level as much as possible. Personalized exercise counselling can improve support and provide benefits independent of weight loss. EASL also recommends a gradual increase in aerobic exercise and resistance training [46].

One of the systematic reviews published recently [49] showed that exercise is associated with improving inflammation and reducing steatohepatitis and fibrosis in experimental models. Additionally, in human studies, both aerobic and resistance exercise have been shown to reduce liver fat and improve insulin resistance and blood lipids, regardless of weight loss, with aerobic exercise possibly being more effective than resistance exercise. This review also shows that resistance training is more feasible for patients with NAFLD who have poor cardiorespiratory fitness (CRF). Meta-analysis by Wang [50] showed that exercise is associated with a decrease in LFT: ALT [SMD = (-0.17 IU/L), 95% CI: (-0.30) - (-0.05)], AST [SMD = (-0.25 IU / L), 95% CI: (-0.38) - (-0.13)] and GGT [SMD = (-0. 22 IU / L), 95% CI: (-0.36) - (- 0.08). Similar results were found in the meta-analysis and meta-regression conducted by Xiong et al. [51]. 5.73 IU/L), 95% CI: (-9.08) - (-2.38)] and BMI [WMD = (-0.85 kg/m2), 95% CI: (-1.19) - (-0.51)]. In addition, resistance exercise can significantly reduce AST activity [WMD = (-2.58 IU/L), 95% CI: (-4.79) – (-0.36)], while high-intensity interval training can reduce ALT activity significantly [WMD = (-6.20 IU/L), 95% CI: (-9.34) - (-3.06)] in patients with NAFLD. So now the reduction of 7-10% of the tissue follows the physical activity as a standard approach in overweight patients with Mafld [52].

6. The drugs affect carbohydrate metabolism

Diabetes mellitus type 2 (DMT2) is one of the metabolic diseases that increases the risk of developing MAFLD [53]. Important pathophysiological factors in DMT2, including hyperglycemia and insulin resistance, play an important role in the progression of MAFLD (54). Drugs that affect carbohydrate metabolism are considered to play a major role in the pathogenesis of MAFLD. The development of MAFLD, due to the prevalence of obesity and diabetes, has led to similar progress in the development of new antidiabetic drugs that simultaneously reduce obesity, contributing to the reduction and progression of MAFLD [55]. These drugs include SGLT-2 inhibitors (Sodium-Glucose Cotransporter-2) - leading to the excretion of glucose in the urine and reducing blood glucose levels; incretin analogues, such as GLP-1 (Glucagon-like Peptide-1) - stimulate insulin production, inhibit the release of glucose from the liver, and reduce gastric emptying - and GLP-1 + GIP (glucose-dependent insulinotropic peptide) — has an effect like GLP-1 affects blood glucose control; GLP-1 + glucagon (GCG) - can affect the metabolism and help in the management of diabetes; and the newest triple-incretin agonist, GLP-1/GIP/GCGR. The effect of other drugs for the treatment of diabetes in the context of MAFLD was also determined: metformin-reduces glucose production in the liver and increases tissue and insulin, DPP4i (Dipeptidyl Peptidase-4 inhibitors) - increases GLP-1 and GIP levels , ketohexokinase inhibitors. - a promising new area of research that can affect metabolism, as well as insulin sensitizers-glitazones. These drugs can improve the condition of patients with problems related to carbohydrates, including MAFLD. However, understanding the full extent of their impact and effectiveness in MAFLD therapy requires further clinical research.

6.1. Sodium/Glucose Cotransporter-2 Inhibitors

Sodium/glucose cotransporter-2 inhibitors (SGLT2is), also called flozins, are drugs which may be able to proscribing glucose reabsorption in renal proximal tubules. via inducing glucosuria, they in the long run lower serum glucose levels [56]. The primary drug from the group of SGLT2is (canagliflozin) come to be conventional by means of manner of the us food and Drug

management for the remedy of DMT2 in 2013. Over the last 10 years, different effective flozins had been done for the control of DMT2 e.g., dapagliflozin, empagliflozin, and ertugliflozin [57].Since the introduction of SGLT2 is, their variety of signs has hugely improved. capsules that at the start have been superior as antidiabetic medicinal drugs regarded to have aerobic and nephroprotective consequences. The results of clinical trials, collectively with DAPA-HF, DAPA-CKD, EMPEROR-reduced, EMPEROR-Preserved, and CREDENCE, allowed the utility of decided on SGLT2is in patients with coronary heart failure (HF) or continual kidney disease (CKD) even without concomitant DMT2 [60]. The useful consequences of SGLT2 is in cardiovascular and renal systems, for which no sufficiently effective capsules were available, brought approximately the studies in their capacity for boosting hepatic cell functioning. Records derived from research both on rodents and humans information the wonderful outcomes of remedy with SGLT2 is on MAFLD. The cell mechanisms answerable for the amelioration of liver abilities are nevertheless not fully elucidated expertise are concept to be connected with the activation of autophagy, endoplasmic reticulum stress reduction, and anti-apoptotic, anti-inflammatory, and antioxidant effects [59–62]. In a randomized controlled trial (E-elevate) in patients with DMT2 and NAFLD, empagliflozin decreased the serum ALT hobby (−10.9 IU/L; p = 0.05) and decreased the amount of liver fat assessed with MRI-PDFF. The advice reduction in liver fat content material become 4% in assessment with the control group (p < 0.0001) [49,63]. A scientific assessment of different randomized controlled trials (RCTs) confirmed that empagliflozin may want to ameliorate the plasma activity of AST [MD: (−3.10) IU/L; 95% CI: (−6.18)–(−0.02), p = 0.05]; liver stiffness, as assessed by using manner of an ultrasound exam [MD: (−0.49) kPa; 95% CI: (−0.93)–(−0.06), p = 0.03]; the homeostasis model evaluation of insulin resistance (HOMA-IR) [MD: (−0.45); 95% CI: (−0.90)–0.00, p = 0.05]; and the body mass index (BMI) [MD: (−0.98) Kg/m2; 95% CI: (−1.87)–(−0.10), p = 0.03] [60]. There were no statistically extensive versions within the reduction in different signs of liver fibrosis e.g., neither the controlled attenuation parameter (CAP) nor the fibrosis-4 (FIB-4) index [64].The facts from meta-analyses concerning dapagliflozin are similar, with large reduction within the ALT [WMD: (−6.62) IU/L; 95% CI: (−12.66)–(−0.58), p = 0.03] and AST [WMD: (−4.20) IU/L; 95% CI: (−7.92)–(−0.47), p = 0.03] levels, HOMA-IR [WMD: (−0.88); 95% CI: (−1.43)–(−0.33), p = 0.002], and BMI [WMD: (−1.33) Kg/m2; 95% CI: (−2.37)–(−0.28); p = 0.01] [47]. Dapagliflozin moreover decreased the CAP [MD = (−38.86) dB/m; 95% CI: (−73.39)–(−4.33)] [65] and liver fat content, as evaluated based totally at the liver attenuation index (LAI) in non-contrast computed tomography (CT) (5.5 ± 5.1 vs. 0. 5 ± 6.1 Hounsfield units, p = 0.006) [66].

Enhancements in liver feature were moreover located in patients with DMT2 and concomitant NAFLD handled canagliflozin based mostly on analyses from the CANVAS have a take a look at. Clinically good sized discounts inside the ALT stage or the normalization of ALT had been more common in subjects undergoing active remedy (OR = 1.52; 95% CI: 1.4–1.65), p < 0.001). furthermore, improvements, after 3 years of remedy, included an ALT degree discount (p < 0.001), as measured based on noninvasive assessments of fibrosis, e.g., NAFLD fibrosis score (NFS) [between-group difference (−0.062); 95% CI: (−0.116)–(−0.008); p = 0.002] and the fibrotic nonalcoholic steatohepatitis index (FNI) [between-group difference (−0.054); 95% CI: (−0.067)–((−0.041); p < 0.001] [67]. Moreover, SGLT2 is appear to save the development of liver illnesses and irritation [68]. even though it appears that the beneficial magnificence effect may be found in SGLT2 is, the presently available records show that dapagliflozin improves now not only LFTs however moreover the fats content material, as assessed based totally definitely at the CAP.

6.2 Agonists of Glucagon-like Peptide-1 Receptors

GLP-1 receptor agonists (GLP-1Ras) have shown large benefits in coping with diabetes and weight issues. The properties are contemplated by their action on pancreatic islets, beta cells, and the CNS [69–71]. However these benefits, the reaction rates to GLP-1Ras, in addition to other pharmaceutical remedies for liver steatosis in NAFLD, have not passed 50%. Studies data recommend that GLP-1Ras can also have useful outcomes on MAFLD via improving insulin sensitivity, lowering liver fat accumulation, and potentially exerting effects. Those tablets have confirmed promise in decreasing LFTs. additionally they should have a power on the liver histology. Liraglutide is the maximum appreciably investigated GLP-1 receptor agonist (GLP-1 RA) inside the context of NAFLD remedy. Numerous trials have evaluated its effectiveness in people, yielding amazing results. The multicenter, double-blinded, randomized, placebo-controlled phase 2 trial showed the benefits of a GLP-1 analogue (liraglutide). [72] In patients with MASH. A 48-week treatment with liraglutide at a dose of 1.8 mg (26 patients) ended in histological development, without exacerbating fibrosis, whilst in comparison to the placebo group (26 patients) (RR = 4.3; 95% CI: 1.0−17.7, p = 0.0190). The primary histological final results endpoint became a development in liver histology, which was defined due to the fact the choice of steatohepatitis characterised by way of the disappearance of hepatocyte ballooning. The secondary endpoint

blanketed changes in the normal NAFLD activity scoring (steatosis, hepatocyte ballooning, lobular infection, and fibrosis ranges) as well as the serum liver enzyme concentration. The variations within the lobular inflammation and preferred NAFLD activity scorings were no longer statistically tremendous between the 2 groups.

Semaglutide is being assessed for reducing liver steatosis in patients with NAFLD who are present process antiretroviral remedy [73]. Additionally, baseline parameters predicting the scientific response in NAFLD all through semaglutide remedy [74] and the applicability of semaglutide (oral or subcutaneous shape) as a powerful measure in improving NAFLD in patients with obesity and/or type 2 diabetes mellitus [75] are also being investigated. Orforglipron (additionally called LY3502970 or OWL833), a modern-day oral GLP-1 analogue, is presently below research in phase 1 and 2 of clinical trials [76,77] in sufferers with diabetes or obesity and who're overweight and characteristic weight-related comorbidities (inclusive of MAFLD) [78]. Most research investigating the efficacy of GLP-1 analogues are focused on their utility in weight troubles and MASH treatments, thereby leaving a big place for exploration concerning their effectiveness earlier ranges of NAFLD, as a protection measure in MASH development. currently, the AASLD recommendations [79] strongly recommend using semaglutide, 2.four mg/week (in step with the most effective assisting evidence), or liraglutide, three mg/day, for continual weight control for human beings with a BMI of ≥27 kg/m2 and both NAFLD or MASH, supporting their characteristic within the remedy of liver disease.

The power of GLP-1 agonists lies in their effectiveness in reducing body weight, which constitutes an essential element of MAFLD treatment. the constraints of the offered studies encompass, amongst others, small affected person group sizes (as located within the LEAN check on liraglutide) in addition to the assessed parameters. These researches normally focus on the efficacy of these tablets for treating MASH, which incorporates the reduction in fibrosis. in addition studies is wanted to provide strong proof of liver steatosis discount and elements worried inside the development from MAFLD to MASH (along with oxidative stress factors).

6.3. Dual Agonists of Incretin Receptors (Glucagon-like Peptide-1 and Glucagon)

The simultaneous activation of GLP-1 and glucagon receptors prevents the hyperglycemic reaction generally related to glucagon while also improving its catabolic outcomes and drastically amplifying hepatic glycolysis, glycogenolysis, and lipolysis. GLP-1 activation has been correlated with weight loss, anorexigenic residences, and hypoglycemic effects, at the equal time because the activation of GCGR is believed to particularly make a contribution to a reduction in hepatic steatosis and enhancement in mitochondrial respiratory; the twin agonist of GLP1/GCG receptors are believed to enhance the course of NAFLD and are currently being investigated for this indication. The currently published results of a section 2a energetic-comparator-managed study [85] on efinopegdutide (NCT: 04944992) installed that during 145 randomized sufferers with NAFLD, 24 weeks of treatment with a weekly dose of efinopegdutide at 10 mg (seventy two patients) ended in a big reduction ($p < 0.001$) in liver fat content material (LFC), as measured the usage of magnetic resonance imaging (LFC reduction of 72.7% [90% CI: 66.8–78.7]) while in comparison to a weekly dose of semaglutide at 1 mg (73 patients, LFC reduction of 42.3% [90% CI: 36.5–48.1]. In a phase 2b have a have a look at related to greater than 800 overweight diabetic with inadequate blood glucose manipulate, every other GLP1R/GCGR agonist, cotadutide, administered at dosages of 100–300 µg/d, yielded considerable upgrades in liver enzyme levels and indicators of liver fibrosis. in this observe, cotadutide done noteworthy reductions in HbA1c and body weight at both 14 and 54 weeks in comparison to the placebo institution (all $p < 0.001$). additionally, 300 µg of cotadutide verified improvements inside the lipid profile, AST and ALT degrees, propeptide of the type III collagen stage, fibrosis-4 index, and nonalcoholic fatty liver sickness fibrosis rating as compared to the placebo organization, however this impact changed into not determined with liraglutide. [86]. Currently, some other ongoing observe is assessing the protection and efficacy of cotadutide in contributors with non-cirrhotic MASH and fibrosis [87].In step with an overview article on scientific trials of MASH posted in July 2023 [50], cotadutide studied in seventy four patients tested a mild impact at the hepatic fats fraction, ALT, and AST after 19 weeks inside the cotadutide cohort compared to the placebo group. Different dual GLP1/GCGR agonists speculated to be utilized in NAFLD remedy are being investigated. Pemvidutide is underneath development as a treatment for obesity and MASH. In keeping with a scientific-degree biopharmaceutical agency assertion dated March 21, 2023 and the aforementioned examine article [88], a 12-week segment 1b trial for NAFLD patients showed that 65%, ninety four 4%, and 85% of patients dealt with pemvidutide (1.2 mg, 1.8 mg, and a pair of 4mg, respectively) executed a ≥30% reduction in hepatic fat on MRIPDFF in comparison with four.2% within the placebo institution. however, up to now, there had been no special courses to be had from those finished studies investigating pemvidutide and assessing its safety and impact at the hepatic fats fraction in subjects with NAFLD after 12 and 24 weeks of remedy (MOMENTUM 8 issues trials) [89,90].Every other candidate this is probably relevant

to NAFLD treatment [91] is a drug aggregate (HM14320) inclusive of HM15136 (a glucagon analogue) and efpeglenatide (a GLP-1 analogue), however there aren't any published studies concerning the mixture's effectiveness. Furthermore, the preclinical studies on weight problems and MASH had been discontinued in 2022 [92]. Furthermore, survodutide (BI 456906), a twin agonist of the GLP-1 and glucagon receptors, is being evaluated. medical trials compare its effectiveness via and large with semaglutide (weight issues). Presently, there aren't any ongoing research on survodutide in NAFLD remedy; the simplest ongoing study pertains to MASH [93]. Also, studies on the effectiveness of danuglipron in NAFLD treatment became discontinued due to the fact the sponsor determined to searching for its application only in patients with obesity and DMT2 (section 2 clinical trial) and no active liver disease [94].apparently, maximum studies related to this organization of medication in MAFLD remedy finish at preclinical investigations or early ranges of scientific trials. The destiny application of these tablets inside the remedy of MAFLD without concurrent diabetes currently appears now not going. Furthermore, the query of the amount to which the activation of the glucagon receptor influences the liver fats reduction and whether or no longer moves on the mitochondrial stage might also have a massive impact in this reduction remains to be settled.

6.4. Triple Incretin Receptor Agonists

The triple GLP1R/GCGR/GIPR agonist, efocipegtrutide (HM15211), distinguished with the resource of its prolonged period of interest, it is attributed to a non-peptidyl bendy linker, is being investigated in a phase 2 medical trial for MASH (217 contributors, elderly 18–70 years, throughout more than one US web sites with an predicted crowning glory date in November 2025) [95], and a phase 1 trial to evaluate the protection, tolerability, pharmacokinetics, and pharmacodynamics of a couple of doses of HM15211 in obese subjects with NAFLD has been cautioned (66 members, elderly 18–65 years) [96]. At present, no peer-reviewed articles supplying the consequences of research regarding efocipegtrutide are available.

Retatrutide (LY3437943), some other triple agonist, is presently in improvement for the treatment of DMT2, weight issues, and non-alcoholic fatty liver disease. Statistics emerging from the phase 2 study [97], particularly in the NAFLD subgroup, mean the ability for reversing initial liver disease stages and mitigating weight troubles-related coexisting situations. The consequences observed out inside the NAFLD population, liver fats normalization emerge as accomplished in 90% of cases subsequent to remedy with the 2 most extended doses. [98].The consequences of a newly posted network meta-assessment via Kongmalai et al. [61], regarding 2252 patients from 31 randomized controlled trials, examined that the addition of GLP-1 agonists to the same care in NAFLD patients' remedy brought about a full-size reduction in intrahepatic steatosis (IHS) at the same time as in comparison to the identical antique treatment . The effect size indicated a reduction of −3.93% (95% CI: −6.fifty four% to −1.33%) in steatosis. The cumulative rating curve (SUCRA) evaluation found out that GLP-1 receptor agonists had the fine possibility (SUCRA 88.5%) of reducing IHS. GLP-1 receptor agonists have been moreover discovered to be the only in decreasing liver enzyme levels, specially AST [MD (−5.04) IU/L; 95% CI: (−8.46)–(−1.62)], ALT (MD: (−9.84) IU/L; 95% CI: (−16.84)–(2.85)], and GGT [MD: (−15.53) IU/L; 95% CI: (−22.09)–(−8.97)] in evaluation to the same time of care, but they were more likely to be related to unfavourable activities in comparison to other interventions. Triple incretin agonists could probably end up useful inside the treatment of NAFLD; however, presently, the development of scientific applications is of their early ranges. consequently, we want to count on more strong evidence to provide medical pointers.

6.5. Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-four (DPP-4) inhibitors, which increases tiers of endogenous incretins, have additionally been investigated for their potential capability in MAFLD treatment. They may assist to improve insulin resistance and glucose metabolism, which might be primary factors in MAFLD development. A surface underneath the cumulative ranking curve evaluation (SUCRA) located out that DPP-4 inhibitors had the second highest (following GLP-1 agonists) possibility (SUCRA 69.6%) of decreasing intrahepatic steatosis, found through pioglitazone (SUCRA 62.2%) [99]. however, further research seem important to decide the total extent of their outcomes on MAFLD development.DPP-4 inhibitors represent a class of oblique incretin mimetics as they impede the enzymatic breakdown of GLP-1, GIP, and oxyntomodulin; however, within the available suggestions or pointers [79,100], there are nonetheless few research focusing on hard end-elements (anti-inflammatory markers or fibrosis) concerning DPP-4 inhibitors within the remedy of NAFLD, that modified into tested through dos Santos et al. [101], who indicated the overall terrible quality of the studies and heterogeneity of the analysed population. Even though, numerous limited-scale medical trials have investigated the ability efficacy of DPP-4 inhibitors in NAFLD treatment, each with and without accompanying DMT2.

Among these trials, sitagliptin (100 mg/d) displayed effectiveness in competition to hepatic steatosis and the hepatic collagen content material irrespective of DMT2, as demonstrated in a 1-year open-label randomized controlled trial [102]. Vildagliptin in DMT2 patients [103] and nondiabetic patients [104], omarigliptin [105], and teneligliptin (only in MASH) [106] exhibited enhancements in liver function and certain noninvasive markers of NAFLD. The preliminary statistics for saxagliptin patients with DMT2 and concomitant NAFLD verified that saxagliptin may want to attenuate insulin resistance damage via the downregulation of the hepatic and soluble shape of DPP-4 and, as an cease end result, reduce the degree of steatosis [107,108].Alogliptin showed simplest slight efficacy towards NAFLD (as measured primarily based on theNAFIC scoring—NASH, ferritin, insulin, and collagen 7S scoring) over a 12-month remedy period in patients with DMT2 and NAFLD [109]. other DPP-4 inhibitors, like evogliptin, anagliptin, trelagliptin, gemigliptin, and linagliptin, have showed first-class consequences in experimental rodent models, and their clinical utility remains to be explored in drawing close trials, as indicated by using Pirkhodko [91] in her evaluation.

6.6. Glitazones

The AACE (American association of clinical Endocrinology) [79] and AASLD [48] scientific exercising pointers suggest the usage of pioglitazone, a selective PPARγ (Peroxisome proliferator-activated receptor gamma) agonist, in cases of recognized MASH. This advice stems from the studies in which, regardless of the presence of DMT2, pioglitazone decreased the degree of liver steatosis and progressed disorder activity indicators [110–114]. in the field of NAFLD, a one year remedy with pioglitazone (as compared to sulfonylureas) at a low dosage notably ($p < zero.05$) superior liver steatosis and infection and systemic and adipose-tissue insulin resistance in patients with DMT2 [115]. Surrogate markers of NAFLD were advanced: the liver fat equation decreased with the aid of (−1.76) ± 3.84 ($p < 0.05$); the hepatic steatosis index by means of manner of (−1.35) ± 2.78 ($p < 0.05$); and the index of MASH via way of (−9.75) ± 43 ($p < zero.05$). other thiazolidinediones taken into consideration within the treatment of NAFLD–rosiglitazone [116] and lobeglitazone (to be simplest in Republic of Korea)— do now not have a substantial variety of studies confirming their effectiveness. thus far, there has been most effective paper that has emerged after the phase 4 clinical trial [79] DMT2 and NAFLD patients treated with lobeglitazone (43 who finished observe), showing a significant lowering in CAP values (313.4 dB/m at baseline vs. 297.8 dB/m at 24 weeks; $p = 0.016$), irrespective of the glycemic manage [80].

6.7. Ketohexokinase Inhibitors

KHK inhibitors (KHKis) are novel, promising compounds in the treatment of NAFLD. Fructose ($C_6H_{12}O_6$) is a keto-hexose (ketose-hexose) isomer of glucose, and it plays a good sized role within the improvement of NAFLD. KHK is an enzyme this is responsible for the preliminary and important step in fructose metabolism, that's thought to increase the intrahepatic lipid (IHL) content material. The pharmacological inhibition of KHK has led to a reduction in the IHL content material among people with NAFLD; but, the full scope of KHK inhibition stays to be elucidated. The protection and efficacy of PF-06835919 (a KHKi advanced via Pfizer) were assessed through several studies. KHK inhibition has been formerly investigated in a small phase 2 trial concerning people with NAFLD. PF-06835919 exhibited a widespread reduction in liver LFC after 6 weeks of treatment compared to the placebo institution. There had been facts indicating that people receiving PF-06835919 on the 300 mg dose showed good sized reductions in LFC in evaluation to the placebo institution, with a distinction of −18.73% ($p = 0.04$) [119] some different phase 2 have a examine carried out on a collection of patients with NAFLD and DMT2 demonstrated that at week 16, the least-squares suggest (90% CI) percent changes from baseline in LFC the usage of MRI-PDFF were as follows: (−5.26%) [(−12.86%)–2.99%] in the placebo organisation, (−17.05%) [(−24.01%)–(−9.46%)] within the 150 mg dose PF-06835919 institution, and (−19.13%) [(−25.51%)–(−12.20%)] within the 300 mg dose PF-06835919 group. considerably, the 300 mg dose PF-06835919 organization exhibited a statistically considerable significant in LFC in comparison to the placebo institution ($p = 0.0288$) [120]. The currently ongoing study [121] objectives to discover greater health results attributable to KHK inhibition with PF-0683591 in NAFLD patients without DMT2.

6.8. Metformin

Metformin, one of the primary drug for treating DMT2, which complements insulin sensitivity inside the liver and muscles, has moreover been broadly studied for NAFLD remedy. Steady with AASLD pointers [48] metformin (similarly to acarbose—an alpha glucosidase inhibitor) have to not be used for the treatment of steatohepatitis (as there can be no determined gain for hepatocyte necrosis or irritation), but, it is able to be persevered if needed for the remedy of hyperglycemia in human beings with

DMT2 and NAFLD or MASH [122]. As numerous meta-analyses of paired-biopsy studies associated with people with MASH have found, there was restrained clinical proof indicating advantages in terms of disorder activity or liver fibrosis [123,124] preliminary studies indicated that a slight effect became determined, specifically focused on hepatic steatosis and linked to weight loss [125,126]. Despite the fact that, a meta-evaluation of metformin trials revealed that the aggregated liver histologic scores for steatosis, ballooning, and fibrosis did not display off giant enhancements. moreover, lobular infection significantly worsened (weighted mean increase, 0.21; 95% CI: 0.11–0.31; $p < 0.0001$), it truly is consistent with findings from exclusive systematic opinions and meta-analyses. In summary, medications affecting carbohydrate metabolism are nicely-mounted in the AASLD tips [48]. Those include pioglitazone, liraglutide, semaglutide, tirzepatide, and SGLT-2 inhibitors because of their showed histological advantages in patients with biopsy-showed MASH and concurrent cardiac advantages. consistent with AASLD, none of these medicinal drugs are officially encouraged for the remedy of MASH, however they'll be employed in cautiously chosen individuals with MASH who have comorbidities, including diabetes or weight problems.

7. Capsules Affecting Lipid Metabolism

7.1. Core cholesterol-reducing therapy (Statins or/and Ezetimibe)

Hypercholesterolemia may also purpose the improvement of liver harm in MAFLD [127]. Statins play key roles within the remedy of hyperlipidemias [128]. However, many hepatotoxic properties had been attributed to their action. The cautious approach is contemplated inside the hints on the surveillance of statin therapy, which encompass ordinary check-ups of ALT at some point of the remedy of hyperlipidemia [129]. These pills need to no longer be used or need to be withdrawn even as the ALT ranges exceeds three instances the higher restriction of the reference degree. Liver steatosis is typically related to best a slight elevation in ALT levels. curiously, there had been reviews at the reduction in LFTs in the route of statin remedy [130]. this will stem from a right away reduction in intracellular cholesterol load in addition to the pleiotropic actions of statins [131].One of the first medical trials focusing at the effect of a 20 mg dose of atorvastatin LFTs in patients with MAFLD performed by Athyros et al. [132]. After 54 weeks of treatment, there had been no statistically giant effects of atorvastatin on ALT, AST, and ALP (alkaline phosphate) activities, which is probably attributed to a really small pattern size (63 patients). In a bigger trial (GRAECE) subjects with mildly extended aminotransferases (up to a 3× above the reference variety) had been additionally handled with the statin. at a few degree within the study at a sluggish discounts within the ALT, AST, and GGT activities were discovered. on the surrender of observation (3 years), the ALT interest dropped from 57 ± 8 to 37 ± 6 IU/L ($p < 0.0001$); the AST and GGT activities had been affected to a similar quantity. No full-size liver toxicity changed into reported for the statins.

This take a look at showed that surrogate markers of MAFLD might be advanced within the route of statin treatment [133]. In a modern-day paper (important study) on rosuvastatin (5 mg per day) in NAFLD treatment, there has been no change in the liver characteristic tests in some unspecified time in the future of the 24-week remark [134]. However, a massive reduction in fat accumulation modified into stated the use of MRI-PDFF (15.0 ± 7.3vs. 12.4 ± 7.4%; $p = 0.003$). Curiously, the reduction in the liver fat content modified into even more in patients subjected to blended therapy with 5 mg of rosuvastatin and 10 mg of ezetimibe (absolute imply difference = 3.2%; $p = 0.02$). but, the massive lipid-decreasing performance (LDL attention reduction from 171 ± 24 to 95 ± 36 mg/dl; $p < 0.001$) of the mixed remedy which encompass 10 mg of rosuvastatin and five mg of ezetimibe did now not bring about any significant modifications in aminotransferase activities (ALT:71 ± 37 vs.66± 37 IU/L; $p = 0.051$, AST: 47 ± 35 vs. 37 ± 17 IU/L; $p = 0.215$) in subjects with NAFLD at a few level within the 48-week remedy duration [135]. The CAP score become moreover no longer affected inside the direction of the trial (327 ± 76 vs. 307 ± 43 dB/m; $p = 0.302$). Great enhancements have been said best in subjects that, further to pharmacotherapy, introduced a healing life-style alternate. eventually, using ezetimibe as a monotherapy superior the NAFLD activity rating [SMD, (−0.30); 95% CI: (−0.57)–(−0.03)] however lacked an impact on the liver fats content cloth, as assessed the use of MRI-PDFF or a liver biopsy [SMD (−1.01); 95% CI: (−2.03)–0.01] [136].In keeping with nowadays aggregated statistics, the effect of statin in patients with NAFLD seems to seriously reduce the ALT (by means of 35.41%), AST (thru 31.78%), and GGT (thru 25.57%) [137]. The impact on the LFT is simultaneous with lipid profile enhancements. but it's miles possible that the pleiotropic outcomes of statins (e.g., anti-inflammatory and antioxidant) may additionally moreover have an extra critical contribution. Such an effect is probably, to a degree, responsible for the reduced propensity of hepatic cell carcinoma in NAFLD patients who are on statin remedy (OR = 0.59; 95% CI: 0.39−0.89) [138]. The available facts help the perception that patients with MAFLD ought to no longer be excluded from statin therapy due to a barely multiplied LFT previous to the initiation of the treatment. In truth, enhancements in LFTs can be expected in the route of extended remedies. Each atorvastatin and rosuvastatin appear like favourable in NAFLD treatment.

7.2. PCSK9 Inhibitors

Although statins and ezetimibe had been used for a long term, PCSK9 inhibitors(PCSK9i) are as an alternative new remedy of hypercholesterolemia. No direct link has been established between the circulating PCSK9 level and markers of NAFLD [139]. But, there are precise mutations within the PCSK9 gene which have been connected to liver steatosis (e.g., c.946 G.T and p. Gly316Cys) [140], but there has been no connection with the advancement toward liver fibrosis [141]. Seemingly, specific loss-of-feature mutations (e.g., rs11591147 R46L) within the PCSK9 gene seem to be protecting in opposition to the development of MASH [142]. During the therapy with PCSK9i, patients with familial hypercholesterolemia, regarded to advantage past the lipid-lowering effects of the treatment. In a subset of patients with NAFLD and a low TG (triglyceride)/HDL (high density lipoprotein) ratio, a 6-month treatment with PCSK9i significantly reduced the expression of the surrogate markers of liver steatosis; the triglyceride-glucose index became decreased with the aid of 7.5% ($p < 0.05$) and the hepatic steatosis index via 8.4% ($p < 0.05$) [143]. Real-global information from a single internet site showed lengthy-lasting (suggest duration of remedy 23.69 ± 11.18 months) resolution of the radiologic capabilities of liver steatosis in 8 out of 11 patients study, which changed into followed through the use of a sizable large ALT reduction (21.83 ± 11.89 vs. 17.69 ± 8.00 IU/L; $p = 0.042$) [144].

7.3. Peroxisome Proliferator-Activated Receptors Alpha Agonists

Fibrates belong to a circle of relatives of PPAR alpha-receptor agonists. The primary indication for those capsules is the treatment of hypertriglyceridemia. Their use since the introduction of the treatment has necessitated the periodical assessment of aminotransferases due to capability liver toxicity. but, studies in patients with MAFLD, who often have slightly elevated ALT stages, provide thrilling input. it seems that fenofibrate at a dose of 300 mg steady with day for 24 weeks in an RCT decreased LFTs, which incorporates ALT (114.6 ± 8.5 vs. 57.3 ± 7.8 IU/L, $p < 0.05$). moreover, indices of capability prevention inside the improvement in the course of more superior levels of NAFLD had been represented through a reduced TGF (transforming growth factor) beta level (15.2 ± 5.1 vs. 8.1 ± three.2 ng/mL; $p < 0.05$) and reduced liver stiffness (12.95 ± 5.1 vs. 9.eight ± three.7 kPa; $p < 0.05$) [145]. Comparable results had been noted in every different RCT (randomized controlled trial) with a 200 mg dose of fenofibrate. The ALT degree, on the stop of look at, emerge as decreased from 78 ± 11 to fifty three ± 26 IU/L ($p = 0.002$), and the extent of the reduction turned into just like that executed with the usage of pioglitazone [146]. contrary to the positive outcomes at the surrogate markers of NAFLD, a 12-week remedy of patients with recognized hypertriglyceridemia and an MRI-PDFF above 5.5% showed no have an effect on at the ALT stage and a moderate boom within the AST level in comparison to the placebo group. Additionally, in the path of remedy with fenofibrate, a big increase in liver fat volume changed into stated (23%), but it become nevertheless just like the placebo arm [147]. The ones results were incredibly unexpected, at the same time as the preceding effects showed a fashion inside the route of decreased lipid accumulation within the liver during fibrate remedy. Currently, fenofibrate is taken into consideration as a capability add-on to the radical treatment options for MASH: (1) acetyl-CoA carboxylase (ACC) inhibitors (e.g., firsocostat), which results in an elevation in TG. It appears that evidently fenofibrate no longer fine prevents the upward thrust in TG but additionally reduces the ALT (−37.three%; $p < 0.05$), GGT (−34%; $p < 0.05$) and ALP (−14.1%; $p < 0.001$) levels as compared to the baseline values ; and (2) farnesoid X receptor (FXR) agonists (e.g., cilofexor) [148].

7.4. Selective Peroxisome Proliferator-Activated Receptor Modulators

Fibrates, that are defined above and indicated in the remedy of hypertriglyceridemia, appear to have a few useful effect on the path of NAFLD. A comparable mechanism of activity, that is primarily based on selective PPAR alpha modulation (SPPARM), is used by a singular compound pemafibrate. The drug, itself, possesses triglyceride-lowering residences [149], but it excels at enhancing NAFLD. Early small-scale studies confirmed an extraordinary improvement within the reduction of ALT from 57.5 ± 8.8 to 30.3 ±5.8 IU/L ($p < 0.01$) and GGT from 63.9 ± 10.3 to 32.8 ± 6.6 IU/L ($p < 0.01$) in the course of a 6-month remedy [150]. Even shorter research with pemafibrate show substantial upgrades in LFT, as shown through the usage of Seko et al. [151]. The ALT degree have become reduced from 75.1 IU/L to 43.6 IU/L ($p = 0.001$) at week 12; however, even in the intermittent assessment at 4 weeks of remedy, ALT showed a giant bargain in LFTs in comparison to the baseline values. however, there has been no big trade within the more-strong NAFLD endpoints (FIB-4 index: 1.89 ± 1.17 vs. 1.95 ± 1.24; $p = 0.351$, CAP: 329.1 ± 35.6 vs. 314.6 ± 51.6 dB/m; $p = 0.329$, LSM [liver stiffness measurements]: 10.5 ± 8.8 vs. 9.2 ± 7.6 kPa $p = 0.080$). the ones facts underline the necessity of prolonged observations to evaluate drug efficacy. Comparable effects had been received through way of Shinozaki et al. [152]. A 3-month remedy with pemafibrate for 38 NAFLD patients resulted in massive reduction in ALT (63.9 ± 3.6 vs. 41.6 ± 3.6; $p < 0.001$), which changed into followed with the useful resource of upgrades inside the NAFLD fibrosis score

[(−2.27 ± 0.18) vs. (−2.38 ± 0.18); p = 0.009], however no exchange within the FIB-4 index become stated (1.51 ± 0.16 vs. 1.47 ± 0.12; p = 0.500). An extended, 6-month, observation moreover prompted enhancements in aminotransferases, that have been observed through a reduction in the FIB-4 score [2.26 (1.07–3.12) vs. 2.08 (0.97–2.67); p = 0.041]. nevertheless, CAP and LSM remained unchanged [153]. A 12-month treatment with pemafibrate also remained powerful in phrases of ALT and AST [154]. The abovementioned studies had been retrospective; however the outcomes had been additionally beneficial within the phase 2 RCT for a 0.2 mg dose of pemafibrate in NAFLD patients. At some point of the 72-week look at, a non-forestall reduction in ALT turned into advised (−33.6%) [(−46.5)–(−20.7); p < 0.0001] [155]. The liver fat content material did now not exchange considerably (−5.1%) [(−15.8)–5.6]; p = 0.35], whereas the liver stiffness, as assessed the use of MRI, have become reduced via the usage of 6.2% (0.8–11.5; p = 0.024). There were no changes inside the CAP and LSM in topics with NAFLD treated for 48 weeks [156,157], however a reduction in liver stiffness become determined [1.45 m/s at baseline vs. 1.32 m/s at week 48 (p < 0.001)] [158]. Despite the fact that most patients with MAFLD are obese, it seems that obviously an extra benefit from the therapy is probably determined in patients with a BMI of <25 kg/m2 [159].

7.5. Multiple Peroxisome Proliferator-Activated Receptor Agonists

Saroglitazar is used for the treatment of diabetic dyslipidemia because of its mechanism of action, it improves the lipid profile (PPAR alpha agonist) and glucose metabolism (PPAR gamma agonist). Additionally, when you consider that the start of its use, it's been referred to that saroglitazar may additionally enhance the course of comorbid MAFLD. A case series of 10 patients dealt with saroglitazar at 4 mg according to day and followed-up for 9 months led to good sized reduction in ALT (64.7 ± 15.56 vs. 46.2 ± 12.6 IU/l; p =0.0058) and AST (43.4 ± 10.48 vs. 35.4 ± 6.59 IU/l; p = 0.0321) activities. Those findings had been observed through a sizable reduction in SWV—Shear-Wave velocity (1.837 ± 0.0691 vs. 1.645 ± 0.0844; p =0.0004), which might be considered as a surrogate marker of fibrosis [160]. The venture of this remark have become its retrospective nature without a manipulate organization. In a bigger cohort of patients with NAFLD, even though although without control institution, saroglitazar also improved LFT, together with ALT (56.47 ± 15.17 vs. 42.3 ± 11.26 IU/l; p < 0.0001), AST (48.57 ± 13.15 vs. 36.63 ± 8.14 IU/l; p < 0.0001), and GGT (54.97 ± 9.52 vs. 45.33 ± 5.94 IU/l; p < 0.0001) [161].Moreover, a Fibroscan evaluation showed an outstanding discount in liver stiffness (13.93 ± 2.87 vs. 8.50 ± 1.86 kPa). Regrettably, no information on the CAP degree had been covered within the file. Continually, exquisite effects have additionally been shown in a truthful large institution of 107 patients sooner or later of 24 weeks of remedy with saroglitazar. similarly to improvements in LFTs [ALT: 94 (47–122) vs. 39 (31–49) IU/L; p< 0.0001, AST: 89 (43–114) vs. 37 (30–47) U/L; p < 0.0001] and LSM: 8.4 (7.1–9.3) vs. 7.5 (6.4–8.4) kPa; p = 0.0261], A giant reduction in liver steatosis became additionally observed [CAP 335 (281–392) vs. 256 (212–299) dB/m; p = 0.0076] [162]. Similar results have been said by using different researchers [163,164]. The most modern-day effects obtained from the actual-worldwide use of saroglitazar (4 mg regular with day) in patients with MAFLD offer in addition promising statistics for MAFLD patients, even the ones progressing in the path of cirrhosis [MD AST (IU/L): 40.78%, p < 0.001; ALT (IU/L): 52.21%, p < 0.001; LSM (kPa): 22.11%, p < 0.00; CAP (dB/m): 328 (46): 14.18%, p < 0.00]. but, there appears to be in the results of placebo-controlled double-blinded trials. no matter the reality that records in such research are available for LFT [165], We're despite the fact that awaiting consequences for CAP and LSM. Other dual agonists of PPAR (i.e., alpha and delta—elafibranor) and pan PPAR agonists (i.e., alpha, gamma, and delta—lanifibranor) display promise inside the treatment of MASH as opposed to steatosis [166,167].

7.6. Acetyl-CoA Carboxylase Inhibitors

Cellular lipid overload is a result of each exogenous and endogenous lipid excesses [168]. Experimental records strongly advocate that patients with MAFLD experience multiplied (over 3-fold) de novo fatty-acid synthesis [169]. Therefore, endogenous synthesis seems to be a crucial aim for the pharmacological approach to MAFLD treatment. One of the alternatives is the inhibition of hepatocyte-unique Acetyl-CoA carboxylases (ACC).Preliminary experiments on MK-4074, an ACC1 and ACC2 inhibitor, induced an outstanding reduction in the liver's fatty-acid content material, which reached 36% (8.6% in placebo organization) after a 4-week treatment [170]. lamentably, probable as a result of the concurrent inhibition of the PUFA3 elongation, a growth inside the TG degree grow to be noted (170 vs. 325 mg/dL). Similarly, phase II scientific trials on another ACC inhibitor (firsocostat) showed dose-based reduction in liver steatosis, as assessed based on MRI-PDFF, attaining 28.9% (vs. 8.4%; p = 0.002 in the placebo group) [171]. But, similar to the effects of the phase I medical trials, an elevation within the TG degree became located, accomplishing 11–13%. To mitigate the upward push inside the TG level and simultaneously take advantage of the high-quality effect of ACC inhibitors on steatosis, numerous strategies are being evaluated, which include (1) the

addition of fibrates, which have become noted in advance [110], and (2) blended remedy with every other experimental approach for DGAT2 inhibition (MIRNA observe); however the effects are predicted at the beginning of 2024 [172].

7.7. Fatty-acid Synthase Inhibitors

Fatty-acid synthase (FASN) is responsible for endogenous lipogenesis. because of its activity, cells are uncovered to an abundance of palmitate. This leads now not best to the accumulation of lipid droplets in hepatocytes however additionally to the activation of stellate cells, leading to fibrosis. therefore, the pharmacological inhibition of FASN seems to be a promising therapeutic goal [173]. As a give up end result, each lipid load and fibrosis might be inhibited, which may be critical pathological pathways in the development of MASH. In a phase I medical trial, the FASN inhibitor (TVB-2640) efficaciously decreased de novo lipogenesis within the liver, which was found by means of using a tremendous ALT reduction (15.8± 8.4%; $p = 0.05$) [174]. The recent results of a phase II scientific trial of TVB-2640 (denifanstat) in patients with MASH (FASCINATE-1), show even more promising findings [175]. In a group of 99 patients dealt with for three months, a substantial reduction in liver steatosis changed into noted the use of MRI-PDFF in a set receiving a 50 mg dose (28.1 + 28%; $p = 0.001$). The end result become observed by improvements in LFTs—ALT dropped by means of 22.3% ($p < 0.005$). The remedy modified into properly-tolerated with minor detrimental activity. Despite the fact that promising, those outcomes are preliminary in a segment II scientific trial which encompass an enormously small pattern period. despite the fact that, we're watching for brand spanking new clinical information from an ongoing examine with a larger study population and extended observation as plenty as 52 weeks [176].

7.8. Diacylglycerol Acyltransferase Inhibitors

A reduction in endogenous lipid synthesis is a promising healing approach in MAFLD treatment. The very last degree within the synthesis of triglycerides is mediated through diacylglycerol acyltransferases (DGATs). The inhibition of those enzymes, mainly DGAT2, shows promising outcomes. Ervogastat (PF-06865571) has been studied in phase I and phase II clinical trials. In patients with MAFLD, a 6-week remedy resulted in a −35.4% (−47.4,−20.7; $p = 0.0007$) reduction in liver fat, as determined using MRI-PDFF [177]. Moreover, a trend closer to improvement in LFT exams changed into determined. The ones consequences, although initial, are promising. we are eagerly searching ahead to the results of an ongoing, larger multicenter look at (MIRNA) at the results of DGAT2 inhibition (without or with the ACC inhibitor— clesacostat) in patients with MASH. The remark time is extended to 48 weeks [178]. An entire of 258 patients are blanketed inside the take a look at, which ought to complete via the cease of February 2024 [172]. Each other preference to reduce the effect of DGAT2 is to reduce its expression. This could be completed using antisense therapy. ION224 is a ligand-conjugated antisense compound that is presently underneath development in a phase II clinical trial on one a 160 patients with MASH, for which the finishing touch is predicted in March 2024 [179]. At the moment, DGAT2 inhibition is a capable, however still experimental, remedy.

7.9. Fibroblast Growth Factor 21

The relationship among the lipid overload and development of MAFLD is also contemplated inside the experimental usage of fibroblast growth factor 21 (FGF21). FGF21 participates drastically in lipid and glucose metabolism, and it's been counseled that FGF21 may additionally moreover enhance the route of MAFLD [180]. A pegylated FGF21 (pegozafermin), in a phase I/IIa clinical trial, showed a suitable safety profile and efficacy [181], and its efficacy modified into confirmed in a larger 24-week phase II clinical trial [182]. The look at become often targeted at the fibrosis assessed in liver biopsy specimens and showed enormous improvements in MASH. Furthermore, it appreciably reduced the liver fat content material up to 41.9 + 5.6% (vs. 5.0 + 5.2% within the placebo group), as assessed the usage of MRI-PDFF, and a concomitant ALT reduction through manner of as much as 31.8 + 5.4%. the ones promising effects warrant in addition lengthy-time period exploration in a phase III scientific trial in this indication. presently, pegozafermin is being evaluated in a phase III medical trial but in patients with extreme hypertriglyceridemia [183]. There are several special FGF21 analogues which can be presently being investigated. Efruxifermin showed promising results in phase II trials [184]; even though, despite assembly the treatment goals inside the FALCON application, every other long-appearing FGF21based drug—pegbelfermin, has been suspended from similarly development as a result of the sponsor’s choice [185].

8. The function of Ursodeoxycholic Acid in Metabolic-associated Fatty Liver Disease

UDCA, an agonist of the farnesoid X receptor, has been explored as a promising remedy opportunity for MAFLD. it's miles a hydrophilic bile acid going on evidently within the body, however its position however stays unsure, as emerge as proven in a

meta-assessment carried out with the useful resource of Zhang et al. [186]. The meta-assessment confirmed that UDCA remedy ended in a huge reduction in ALT degrees (p = 0.007), specifically within the European population (p = 0.003), aged over 50 years antique (p = 0.001). The effectiveness of UDCA inside the remedy of NAFLD changed into more reported at longer remedy durations (p = 0.008).A few other meta-evaluation carried out by way of the usage of Lin et al. [187], concerning 655 patients in 8 studies, showed the full-size reductions in ALT and GGT tiers after UDCA treatment but did now not show any extraordinary effect on the liver histology. Even though the undeniable impact of UDCA is the normalization of the liver feature parameters (ALT and GGT), its effect on hard endpoints, collectively with liver fibrosis and liver histology, has not been absolutely showed. in addition research is wanted to thoroughly check its potential outcomes in these regions.

9. The characteristic of the Microbiota within the Pathogenesis and management of Metabolic-related Fatty Liver disease

The characteristic of the intestinal microbiota within the pathogenesis and management of many issues (which includes MALFD) has been a subject of developing interest. The adjustments within the composition and feature of the intestine microbiota (described as dysbiosis) may additionally make contributions to the development of MAFLD. Dysbiosis may lead to improved intestinal permeability, resulting within the translocation of microbial products, including lipopolysaccharides (LPS), into the bloodstream. This device triggers irritation and oxidative strain within the liver through, amongst different pathways, growing the extent of circulating TNF-α (Tumor Necrosing element alpha), IL(interleukin)-1, and IL-6, thereby selling the improvement of hepatic steatosis and improvement of MAFLD [188,189] The involvement of the microbiota in the development of MAFLD has brought approximately the idea of the use of probiotics, prebiotics, and synbiotics (a combination of probiotics and prebiotics) inside the treatment of MAFLD. The modulation of the intestine composition through the usage of specific traces of probiotic bacteria can also possibly help to restore balance and decorate liver function in MAFLD [190,191]. Prebiotics (inclusive of fructans, galacto-oligosaccharides, starches and glucose-derived oligosaccharides, and peptic and non-carbohydrate oligosaccharides) are the materials that selectively stimulate the increase and interest of beneficial intestine bacteria and promote their useful effects [192].In the last few years, following the plethora of guides inside the fields of the microbiota and liver problems, some narrative and systematic opinions were posted. Capri et al. [190] provided outcomes of 13 studies, normally double-blinded, inclusive of 947 patients recognized with MASH or NAFLD (age 18−80 years), wherein probiotics (6 studies), prebiotics (3 research), and synbiotics (4 research) have been used. The intestinal microbiota intervention ended in an improvement inside the markers of inflammation, which encompass LPS, TNF-α, and IL-6, in addition to LFTs. the other parameters, just like the ranges of lipids, BMI, body weight, waist circumference, insulin sensitivity (as measured the use of HOMA-IR), fasting blood glucose, and vaspine stage, additionally confirmed development. The liver scores, such as the FLI (fatty-liver index) and steatosis, in addition to the fibrosis and NAFLD activity scores reduced.

A meta-evaluation of clinical trials involving 1403 patients, investigating the connection among NAFLD and probiotic supplementation, published via Huang et al. in 2022 [193], located that probiotic supplementation progressed liver harm in NAFLD patients. A huge reduction inside the aminotransferase interest changed into observed each for ALT (IU/L) [MD (−7.25); 95% CI: (−10.11)–(−4.39), p = 0.00001] and AST (IU/L) [MD (−3.53); 95%CI: (−5.62)–(−1.44), p = 0.0009], in addition to for GGT (IU/L) [MD (−2.27), 95% CI: (−4.49)–(−0.05), p = 0.04]. moreover, a full-size bargain turned into decided in the insulin level (μIU/mL) [MD (−1.27); 95% CI: (−2.39)–(−0.15), p = 0.003], insulin resistance (HOMA-IR) [MD (−0.61); 95% CI: (−1.02)–(−0.21), p = 0.03], and body-mass index (Kg/m2) [MD (−0.8)95% CI: (−1.51)–(−0.08), p = 0.03]. additionally, markers of systemic inflammation, consisting of TNF-α (pg/mL) [MD (−3.43); 95% CI: (−6.56)–(−1.71), p = 0.03] and CRP (mg/dL) [MD (−1.06); 95% CI (−1.94)–(−0.18), p = 0.02], were lower after probiotic supplementation. another meta-analysis of 21 randomized control trials with the useful resource of Sharpton et al. [153], executed on a collection of 1252 contributors, located out a large reduction in the ALT activity WMD: (−11.23 IU/L); 95% CI: [(−15.02)—(−7.44)] and liver stiffness dimension— WMD: (−0.70 kPa); 95% CI: [(−1.00)—(−0.40 kPa)], despite the fact that the analyses showed large heterogeneity (I2 = 90.6% and I2 = 93.4%, respectively) within the obtained outcomes. Probiotic and synbiotic administrations had been related to expanded odds of improvement in hepatic steatosis, as evaluated the usage of ultrasonography (OR: 2.40; 95% CI: 1.50, 3.84; I^2 = 22.4%). The reduction in the BMI changed into also related to probiotic management WMD: (−1.84); 95% CI: [(−3.30)—(−0.38); I2 = 23.6%], but there was no high first-class correlation with synbiotic management WMD: (−0.85); 95% CI: [(−2.17), 0.47; I2 = 96.6%]. Microbiota modulation gives a modest effect on LFTs; however the relative safety of such treatments is encouraging in medical practice.

9.1. The characteristic of Helicobacter pylori within the Pathogenesis and management of Metabolic-associated Fatty Liver disease

It's been postulated that H. pylori inflammation might be involved one of the many factors within the complex pathogenesis of MAFLD. H. pylori contamination can have an effect on the composition and characteristic of the intestine microbiota, insulin resistance, and systemic inflammation. [194] concerning the gut microbiota, H. pylori infection will have an impact on its composition and variety, potentially influencing the improvement of MAFLD. however, the proper mechanisms underlying this dating are not however absolutely understood. Furthermore, the systemic anti-inflammatory that contributes to the pathogenesis of MAFLD is associated with an H. pylori infection, at some point of which the awareness of pro-inflammatory markers will increase, doubtlessly influencing the development of MAFLD in a but-doubtful way [194].A meta-evaluation through Xu et al. based totally on 34 research (27 cross-sectional, three case control, and 4 cohort studies) found out a susceptible affiliation between H. pylori infection and NAFLD [195].

A few studies have shown a powerful association among H. pylori infection and markers of infection in humans with MAFLD. however, H. pylori is the number one aspect at the back of persistent gastritis and might result in capacity acute duodenal peptic ulcer disease, similarly to gastric cancer or gastric mucosa-associated lymphoid-tissue lymphoma. other ailments, inclusive of unexplained iron-deficiency anemia, food regimen B12 deficiency, and idiopathic thrombocytopenic purpura, may be related to H. pylori infection as well. There also are distinctive extra-gastric manifestations of H. pylori infection, together with neurodegenerative and cardiovascular disease, ischemic coronary heart sickness, diabetes mellitus, metabolic syndrome, and liver disease, consisting of non-alcoholic fatty liver disease [196]. The greater-gastric manifestations have been associated with persistent and subclinical systemic inflammation. The information commonly originate from observational research and are nevertheless constrained and inconsistent and, consequently, stay inconclusive. Other component contributing to the improvement of MAFLD—insulin resistance, has been shown to be related to H. pylori inflammation. A few research advocate a relationship among the eradication of H. pylori and a reduction in insulin resistance [197–199]. But, one of a kind research have no longer confirmed this affiliation [100].No matter the ones promising findings, it's far very critical to be aware that studies on the participation of dysbiosis in MAFLD is still evolving. similarly research had to set up the best mechanism in addition to most acceptable techniques for exploiting the microbiota for recovery use. one of the proposed mechanisms through which prebiotics may moreover act on MAFLD is thru the modulation of the PI3K-AKT/mTOR/AMPK (phosphatidylinositol 3 kinase-protein kinase B/mammalian goal of rapamycin/adenosine 5’-monophosphate (AMP)-activated protein kinase) pathway [201], at the same time as others spotlight the influences of prebiotics at the lipid profile, which includes decreased lipid accumulation in the liver (due to the downregulation of lipogenesis and upregulation of fatty-acid oxidation), the recuperation of the gut microbiota composition, and extra intestinal integrity [202].

9.2. Change of Microbiota

Antibiotics can put off destructive microbiota, and their efficacy has been showed in several liver disease [203]. For treating cirrhosis and encephalopathy, further to spontaneous bacterial peritonitis, fluoroquinolones (norfloxacin and ciprofloxacin), third generation cephalosporins (ceftriaxone and cefotaxime), and trimethoprim–sulfamethoxazole are endorsed; and neomycin, metronidazole, polymyxin B, and rifaximin have been used. βLactam/β-lactamase inhibitor mixtures (BLBLIs) and carbapenems are recommended as the first preference in empirical remedies. Rifaximin, as a eubiotic, has a potential impact at the liver thru modulating the bowels’ microbiota. Gangarapu et al. [204] located that the short-term management of antibiotics superior clinical signs in NAFLD/MASH patients through reducing circulating endotoxin and IL-10 levels (0.9 ± 0.34 vs. 0.8 ± 0.13 eu/mL, p = 0.03 and 4.08 ± 0.9 vs. 3.73 ± 0.7 pg/mL, p = 0.006, respectively) further to LFTs (AST: 50.4 ± 39 vs. 33 ± 14 IU/L, p = 0.01; ALT: 72 ± 48 vs. 45.2 ± 26.3 IU/L, p = 0.0001, GGT: 52 ± 33 vs. 41.2 ± 21.1 IU/L, p = 0.02). similarly, an examine via Abdal-Razik et al. [205] confirmed a giant decrease in transaminases and transferase enzyme [ALT: 64.6 ± 34.2 vs. 38.2 ± 29.2 IU/L, p = 0.017; AST: 66.5 ± 42.5 vs. 40.1 ± 20.1 IU/L, p = 0.042; GGT: 56.7 ± 31.6 vs. 34.8 ± 28.6 IU/L, p = 0.046]; endotoxins; and IL-10, TNF-alpha, and IL-6 levels [0.82 ± 0.22 vs. 0.7 ± 0.09 EU/mL, p = 0.001; 40.6 ± 18.78 vs. 58 ± 23.16 pg/mL, p = 0.009; 19.18 ± 9.29 vs. 13.34 ± 8.31 pg/mL, p = 0.045; 8.34 ± 1.8 vs. 6.67 ± 1.1 pg/mL, p = 0.004, respectively]; and the NAFLD Liver fat rating [from (−0.6) to (−0.2) vs. from (−0.7) to (−0.4) (p = 0.034)], following the management of rifaximin for 6 months however no longer after 1 month of remedy. The obtained results may be associated with the short period of the therapy or low drug dose, as determined via Ponziani et al. [206]. Furthermore, it is vital to renowned that rifaximin, as a eubiotic, can, indeed, impact the intestine microbiota with the aid of using selling the increase of useful microorganism, mainly Bifidobacteria and

Lactobacilli spp. but, it's far essential to bear in mind that despite the fact that quick-time period antibiotic treatment may additionally lead to top notch effects, extended and systemic antibiotic use can disrupt the stableness of intestine microbiota, leading to dysbiosis.

In summary, the consequences received from the ones studies can be related to the remedy duration, and the effectiveness of rifaximin for treating MASH might have been stimulated thru factors consisting of low drug dosages and small pattern sizables. moreover, despite the fact that several antibiotics can growth of useful gut microorganism, the lengthy-time period and systemic use of antibiotics should be approached with warning to avoid the functionality threat of gut dysbiosis [207].

10. Antioxidants

10.1. Diet E (Alpha-Tocopherol)

Modern-day worldwide recommendations for the management of liver disease (e.g., AASLD,AACE, the EU affiliation for the look at of Diabetes (EASD), and the EU association for the take a look at of weight problems (EASO)) advise the use of diet E (alpha-tocopherol) within the remedy of MASH in patients without diabetes [45]. Lipid accumulation in hepatocytes results in lipotoxicity and increases the level of oxidative stress, which ends up in liver harm and inflammation [208]. As a redox scavenger, nutrition E may also moreover prevent the damage due to excessive oxidative strain [209]. The off-label use of diet E is attached with upgrades in LFTs [210]. The contemporary-day pointers on the usage of food regimen E in NAFLD remedy are primarily based mostly on the effects supplied in RCTs regarding patients affected by MASH without or with type 2 diabetes mellitus (DMT2). inside the PIVENS trial, the antioxidative homes of nutrition E regarded to have a fine impact on the liver histology every in lowering the NAFLD activity scoring (NAS) and resolving MASH [110,211].Positive effects of diet E on rodent models of MAFLD had been referred to [212,213]. In patients with MASH and concomitant DMT2, such modifications were now not observed [214].additionally, a few RCTs finished in adult human patients with MAFLD indicated development within the stage of liver enzymes [ALT: −7.37 IU/L, 95% CI: (−10.11)–(−4.64); AST: (−5.71) IU/L, 95% CI: (−9.49)–(−1.93)] and histological functions (e.g., fibrosis rating, with a mean distinction of −0.26, ninety five% CI: (−0.4 7)–(−0.04) (I2 = 0%, p = 0.02)] [214,215] after remedy with weight-reduction plan E. though, thanks to the inconsistency of the records, to this point, there are despite the fact that a loss of strong hints for the use of vitamin E inside the control of earlier tiers of MAFLD [7].

11. Interactions between the Endocrine tool and NAFLD

The endocrine system participates, substantially, in lipid and glucose metabolisms [216].for many years, the course of hypothyroidism, hypogonadism, hypopituitarism, and hypercortisolism has been associated with the build-up of liver fats. consequently, screening (medical and/or laboratory) closer to endocrine problems in patients with NAFLD must be brought on an everyday basis to exclude functionality reversible reasons.

11.1. Thyroid Hormones

As referred to earlier (phase 1), hypothyroidism is an essential risk component forMAFLD [217]. using thyroid hormones to result in fats loss in the liver might be a promising healing alternative, however the burden of side outcomes precludes their use in local shape. however, it is probably viable to use particular agonists of thyroid receptor beta (TRb), which selectively have an effect on liver metabolism even as omitting maximum cardiac outcomes (e.g., tachycardia) because of TRa activation. presently, there are several compounds underneath assessment inside the remedy of NAFLD. Resmetirom halved liver fats content material, as assessed using MRI-PDFF, in patients with MASH during 36 weeks of remedy with an 80 mg every day dose of the drug [218]. This was followed by way of a large reduction in ALT [11.0 ± 6.8 vs. (−15.4) ± 4.7 IU/L; p = 0.0019] and AST [3.6 ± 2.8 vs. (−7.4) ± 1.9 IU/L; p = 0.0016] activities at week 36. The 72-week open-label extension trial moreover confirmed resmetirom's efficacy and enough tolerability. interestingly, no matter the reality that the fat content material material, as assessed using MRI-PDFF, became drastically decreased, the CAP dimension acquired at some stage in Fibroscan remained unaffected [219]. The results of a phase 3 clinical trial comparing the protection of resmetirom in NAFLD treatment are anticipated in 2024 [220].

11.2. Testosterone

Low testosterone levels (<346 ng/dL) in person males have been related with noninvasive markers of liver steatosis [221]. Prolonged-term observations strongly advocate enhancements in liver steatosis in hypogonadal men inside the path of testosterone substitute remedy. A 12-yr examine-up confirmed that keeping the greatest testosterone stage with testosterone undecanoate led to

a giant improvement within the Fatty Liver Index (from 83.6 ± 12.08 to 66.91 ± 19.38; p < 0.0001) and GGT (from 39.31 ± 11.62 to 28.95 ± 7.57 IU/L; p < 0.0005) however without a significant change inside the ALT or AST enzymes [184]. consequently, testosterone-alternative therapy is enhancing the metabolic popularity of persons with hypogonadism. Conversely, testosterone or anabolic androgenic steroids may also bring about liver harm in adult males with ordinary testosterone levels [223].

11.3. Estradiol

Estrogens play a vital function inside the metabolism of lipids [224]. Estradiol deficiency, which takes region after menopause, coincides with an extended propensity to increase NAFLD [225]. the shortage of the protecting consequences of estrogens is also pondered by using a discount within the sex-hormone binding protein (SHBG), which ends up in a relative "extra" in androgen levels [226]. Estradiol treatment is probably beneficial for the direction of MAFLD after menopause, however it is normally used with progestins, which may additionally alleviate the benefits [227]. moreover, because of common contraindications (e.g., thromboembolic events and breast cancers) this kind of treatment cannot be encouraged universally. consequently, in postmenopausal girls, estrogen/progestin-alternative remedy can also enhance the direction of MAFLD; but, currently, MAFLD must now not be the sole indication for the form of therapy [228]. Alternatively, more younger patients (<40 years of age) stricken by surgical hypogonadism have a progressed chance for developing MAFLD by way of the usage of 50% [229]. In this institution of patients, hormone-replacement treatment is normally really useful.

11.4. Growth Hormone

growth hormone (GH) has a multidimensional have an effect on at the human metabolism, together with that of the liver. Both deficiency and extra may additionally result in several pathologies [230]. GH deficiency is normally associated with liver steatosis, and the danger of NAFLD development in such patients is nearly -fold OR = 1.eighty five; 95% CI: [(1.05–3.28); p = 0.03] [231]. Patients with NAFLD generally tend to have a reduced top GH secretory reaction (9.2 ± 6.4 vs.15.4 ± 11.2 ng/mL; p = 0.001), and better IGF-1 (Insulin-like growth factor-1) levels are associated with an awful lot less-advanced FIB-4 scoring [232]. A small examine on young adults with NAFLD and without a selected GH deficiency, however with suboptimal IGF-1 levels, has no longer proven any sizeable impact on ALT, AST, and GGT stages. nonetheless, in some unspecified time in the future of the 24-week statement, a model towards a reduction in liver fat content (−3.3%); 90 5% CI: [(−7.8%)–1.2%; p = 0.14)] became stated [233]. The authors concluded that GH therapy can also moreover have a beneficial effect in obese NAFLD sufferers, but similarly research on a bigger population of patients are essential to find out this speculation.

12. Other recuperation strategies

12.1. Xanthine Oxidase Inhibitors

A superb correlation among hyperuricemia and the prevalence of MAFLD underlies the studies concerning the probable useful outcomes of remedy with xanthine oxidase inhibitors (allopurinol and febuxostat) on liver abilities [234].Within the mouse model of MASH, every xanthine oxidase inhibitors regarded to alleviate hepatic steatosis and fibrosis [235,236]. In a pilot interventional take a look at with febuxostat in patients with MAFLD, serum degrees of ALT [before: 73.0 (69.8–117.8); after: 70.5 (57.5–94.5) IU/L, p = 0.040] and AST [before: 50.5 (40.8–69.8); after: 44.5 (34.8–60.8) IU/L, p = 0.018] have been extensively decreased, and hepatic steatosis, as showed with the useful resource of sporting out a histopathological exam, become superior [235,236]. The results of an ongoing interventional randomized medical trial evaluating the effects of allopurinol and febuxostat on MAFLD (NCT05474560) can also make clear the ability use of xanthine oxidase inhibitors for the remedy of liver sicknesses in the destiny [237]. presently, there are not any pointers on using xanthine oxidase inhibitors in MAFLD treatment.

12.2. Lubiprostone

A gut–liver axis disease turned out to be one of the pathological mechanisms liable for the development of MAFLD. Therefore, disturbances in the intestinal permeability and dysbiosis have grown to be ability goals within the manipulate of MAFLD [238].Lubiprostone, an oral metabolite of prostaglandin E1, in order to growth intestinal fluid secretions via promoting the intraluminal chloride-anion efflux, grow to be at the start carried out for the remedy of idiopathic constipation and irritable bowel syndrome with constipation [239]. In mouse models, it appeared to improve plasma hepatic harm markers and liver steatosis in MAFLD [240]. In an RCT of 150 patients with constipation and MAFLD, after 12 weeks of treatment with lubiprostone, the ALT tiers have been drastically lower than those in the placebo MD: (−15) IU/L; 95% CI: [from (−23) to (−6), p = 0.0007)]. A significant development became additionally discovered inside the ranges of AST MD: (−9) IU/L; 95% CI: [from (−15) to (−6), p

= 0.006] and GGT MD: (−15) IU/L;95% CI: [from (−26) to (−6), p = 0.01]. The liver fats content material cloth, as assessed the use of MRI-PDFF, and liver stiffness, as assessed the usage of vibration-managed quick elastography, moreover improved [241]. The results of an ongoing RCT with a 100 patients (NCT05768334) laid low with MAFLD would possibly decide the usefulness of medicine that concentrate on the gut–liver axis within the treatment of MAFLD [242].

12.3. Pentoxifylline

Thinking about the multifactorial pathogenesis of MAFLD, which includes infection, drugs with capability outcomes, such as pentoxifylline, were evaluated to be used in the aforementioned liver dysfunction. As a nonspecific phosphodiesterase 4 (PDE-4) inhibitor with the capability to decrease the transcription of TNFa, that is considered as one of the main pro-anti-inflammatory agents responsible for the degradation of hepatocytes, the consequences of treatment with pentoxifylline had been tested each in rodents [243,244]. Despite the fact that early randomized trials in patients with MAFLD confirmed good sized improvements inside the ALT [WMD: (−13.64) IU/L, 95% CI: (−19.61)–(−7.66), p < 0.00001] and AST [WMD: (−9.70) IU/L, 95% CI: (−15.24)–(−4.16], p = zero.0006] stages and NAFLD activity score (NAS) [WMD: (−1.16), 95% CI: (−1.51)–(−0.81), p < 0.00001] and the regression of lobular infection in evaluation with the placebo group, similarly statistics concerning the fine consequences of pentoxifylline on liver functions have been inconsistent and, therefore, did not permit the implementation of this drug for the treatment of MAFLD [245–247].

12.4. Different Pills

The statistics from determined on meta-analyses may additionally endorse that several capsules generally used in patients with cardiovascular disease with concomitant MAFLD (e.g., losartan and acetylsalicylic acid) have tremendous impacts on hepatic enzyme ranges or guard closer to improvement to advanced fibrosis [248,249]. despite the fact that, currently, the quantity of evidence is underwhelming.

13. Realistic Components

13.1. Curcumin

Curcumin is the most common curcuminoid observed in turmeric, it is broadly used in herbal medicinal drug and has a pleiotropic effect . it's been shown that curcumin improves glucose and lipid metabolisms, reduces blood stress, has and antioxidant consequences, and has great effects on fats metabolism and weight loss [250]. It is nicely well worth mentioning that the lipid-decreasing homes of curcumin had been observed and protected inside the global Lipid professional Panel (ILEP) function paper [251,252] and the suggestions of the Polish Lipid association (PoLA) [253] .The exceptional efficiency of curcumin in the prevention of metabolic disorders is highlighted with the aid of a meta-analysis carried out via the use of Ashtary-Larky et al., which protected the outcomes of 9 randomized medical trials (n = 510 members). within the analyzed studies, nano-curcumin was used at a dose of 40–a 120 mg/day for a period of 6–12 weeks [254].The residences of curcumin advise that it is able to have a useful impact on the improvement of MAFLD. In a meta-analysis of 16 randomized medical trials carried out via Ngu et al., which incorporates 1028 patients with MAFLD, the impact of curcumin supplementation on severa metabolic parameters modified into assessed. Curcumin end up proven to reduce the severity of MAFLD (RR = 3.52; 95% CI: 1.27–9.72) and growth liver steatosis resolution (RR = 3.96; 95% CI:1.fifty four–10.17). moreover, curcumin turn out to be determined to lessen the concentrations of AST [MD = (−4.00); 95% CI: (−5.7 2)–(−2.28) and ALT [MD = (−7.02); 95% CI: (−9.83)–(−4.20)] [255]. The useful impact of curcumin at the direction of MAFLD have become additionally showed in the meta-analysis of 16 randomized scientific trials conducted thru Lukkunaprasit et al. It became confirmed that the use of curcumin via patients with MAFLD have become related to a decrease inside the attention of AST [MD = (−3.90); 95% CI: (−5.97)–(−1.82)], a lower in ALT [MD = (−5.61); 95% CI: (−9.37)–(−1.85)], an growth in the decision of hepatic steatosis (as measured using ultrasonography) (MD = 3.53; 95% CI: 2.01–6.22), and a discounted fasting blood sugar, body-mass index, and standard cholesterol level [256].The outcomes of those meta-analyses of randomized scientific trials advise that curcumin can be crucial in supporting the treatment of patients with MAFLD. however, understand that curcumin from the weight loss plan is poorly bioavailable and that you have to pick dietary supplements containing curcumin with improved bioavailability (e.g., nano-curcumin formulations [250].

13.2. Coffee

Espresso is the most-consumed beverage within the world after water and tea . Coffee incorporates over 1000 chemicals, and the maximum vital encompass caffeine, chlorogenic acid, trigonelline, caffeic acid, ferulic acid, and melanoidins, in addition to

kahweol and cafestol [257]. Espresso is characterised via using a multidirectional impact. It's been shown that the ordinary consumption of slight portions of coffee can be associated with anti- inflammatory and antioxidant results [258], antidiabetic outcomes [259], and antihypertensive outcomes [222], as well as enhancing the characteristic of the vascular endothelium [260]. The useful impact of coffee on health is showed by means of manner of the reality that the ordinary consumption of mild quantities reduces the threat of dying from any cause [261].The described pleiotropic activity mechanisms of espresso make it the problem of studies on its consequences on liver features. a scientific evaluation of the literature, achieved through Sewter et al., showed that coffee intake is inversely associated with the severity of hepatic fibrosis in people with MAFLD [262]. A meta-assessment of 11 observational studies, carried out by way of way of Hayat et al., showed an extensively decreased danger of liver fibrosis in individuals who drank espresso as compared to folks who did now not drink espresso amongst MAFLD sufferers (RR = 0.68; 95% CI: 0.68–0.79) [263]. This useful effect of espresso have become also showed in a meta-assessment of 5 research conducted with the resource of Kositamongkol et al. It will become proven that patients with MAFLD who consumed espresso had a lower possibility of liver fibrosis (OR = 0.67; 95% CI: 0.55–0.80) [264]. It is truly worth bringing up that patients with MAFLD who consume coffee have a decrease risk of death from liver cirrhosis (RR = 0.55; 95% CI: 0.35–0.74), as proven in a meta-assessment of nine studies carried out by means of Kennedy et al. [265].The outcomes of these studies and their meta-analyses imply that espresso intake, through patients with MAFLD, may additionally slow the development of MAFLD to cirrhosis. From a sensible point of view, patients with MAFLD who claim a choice to devour espresso ought to be encouraged espresso brewed with a paper clean out, that is because of the truth unfiltered espresso may also have a hyperlipemic impact [266], which, inside the case of MAFLD, is not an appropriate effect. Filtering coffee reduces the content of kahweol and cafestol, i.e., compounds with a hyperlipidemic impact [267] and, consequently, eliminates this doubtlessly negative effect for sufferers with MAFLD [266].

13.3. Resveratrol

Resveratrol is a polyphenolic by-product of stilbene and is normally determined in nuts, grapes (crimson wines), blueberries, tomato skins, and cocoa [267]. Resveratrol is characterized via, amongst different things, antioxidant, cardioprotective, and antidiabetic consequences [267].In spite of the several beneficial properties of resveratrol, the studies effects do now not indicate its giant position in assisting the treatment of MAFLD. In a meta-evaluation of 4 randomized scientific trials, accomplished with the resource of Zhang et al., covering 156 patients with MAFLD, it was proven that the usage of resveratrol did no longer have an impact at the body weight; BMI; systolic or diastolic blood strain; tissue sensitivity to insulin (HOMA-IR); or ALT, AST, GGT, bilirubin, or TNF-alpha levels [268]. Similar consequences have been obtained in a meta-assessment of 7 randomized clinical trials, conducted by Jakubczyk et al., which includes 302 patients with MAFLD. Resveratrol become administered daily over durations between 56 and 180 days in doses starting from 500 mg to 3000 mg in keeping with day. No effect of resveratrol supplementation (regardless of the dose and duration of the intervention) modified into observed on the AST, body weight, BMI, WC, glucose or insulin awareness, general ldl cholesterol, TG, LDL, HDL, or systolic or diastolic blood stress [269].The results of the meta-analyses of randomized clinical trials imply that the usage of resveratrol in patients with MAFLD does no longer offer any medical benefits.

13.4. Diet vitamin D

About 20% of the full vitamin D in the human body comes from the weight loss plan, at the same time as 80% comes from endogenous synthesis in pores and skin [270]. It is a steroid hormone concerned in the absorption of calcium and phosphate in the small gut. Several one of a kind mechanisms of activity also are attributed to diet D, which include reducing the activity of the renin–angiotensin tool, antioxidant results, and regulating the abilities of adipocytes and pancreatic beta cells [271].In a meta-assessment of 9 research, accomplished via Eliades et al., it became proven that patients with MAFLD have a 26% better hazard of diet D deficiency as compared to healthy people (OR = 1.26; 95% CI: 1.17–1.35) [272]. Therefore, it's miles critical whether or no longer weight loss plan D supplementation in patients with MAFLD can provide clinical advantages. In a meta-assessment of 7 studies, through Sindhughos et al., which include 735 patients with MAFLD, it became established that diet D supplementation became related to advanced tissue sensitivity to insulin [HOMA-IR: MD = (−1.06); 95% CI: (−1.66)–(−0.45)] and a decrease in AST [MD = (−4.44);95% CI: (−8.24)–(−0.65)] [273]. Ordinary consequences were received in a meta-assessment of 16 randomized medical trials, conducted by Rezaei et al., including patients with NAFLD. It became proven that nutrients D supplementation became associated with an increase in HDL-C($p = 0.008$) and decreases inside the body weight ($p = 0.007$), frame-mass index ($p = 0.002$), waist circumstance (WC) ($p = 0.02$), serum ALT ($p = 0.01$), fasting blood sugar ($p = 0.01$), and

tissue resistance to insulin (HOMA-IR; p = 0.004) [274].The outcomes of the meta-analyses of randomized trials imply that nutrients D supplementation also can contribute to the development within the metabolic profiles of sufferers with MAFLD.

13.5. Omega-3 Fatty Acids

Omega-3 fatty acids (ω-3 PUFA) are obviously determined in animals (fish, krill, eggs, and squid) and flora (algae, flaxseeds, walnuts, edible seeds, and clary sage) [275]. The mechanisms of motion of omega-3 fatty acids, which may additionally have a useful effect at the direction of MAFLD, encompass anti- inflammatory and antioxidant results, a discount in TG manufacturing, a decrease in fats accumulation within the liver, and an improvement inside the composition of the intestinal microbiota [74]. In a meta-evaluation of 18 randomized clinical trials, with the aid of manner of Yan et al., together with 1424 patients with MAFLD, omega-3 fatty acids had been related to enhancements in fats accumulation in the liver (RR = 1.56; 95% CI: 1.23–1.97) and ALT [SMD = (−0.50); 95% CI: (−0.88)–(−0.11)], decreases in AST [SMD = (−0.54); 95% CI: (−1.04)–(−0.05)] and GGT, [SMD = (−0.48); 95% CI: (−0.64)–(−0.31)], and improved tissue insulin sensitivity [HOMA-IR; WMD = (−0.40); 95% CI: (−0.58)–(−0.22)] [276]. Steady effects were acquired in a meta-evaluation of 6 randomized medical trials, with the resource of Moore et al., together with 362 MAFLD patients, which showed that omega 3 fatty-acid supplementation come to be associated with a reduction in ALT levels [MD = (−8.04); 95% CI: −14.70 to −1.38)] [277].The outcomes of the meta-analyses of randomized scientific trials imply that omega-three fatty-acid supplementation may additionally enhance the metabolic profiles and liver features of patients with MAFLD.

13.6. Silymarin

Silymarin is a flavone derivative acquired from milk-thistle fruit. by stabilizing the membranes of liver cells, it has a protecting impact at the liver parenchyma. It has stabilizing, regenerating, and defensive consequences at the membranes of liver cells; weakly relaxes clean muscle groups; stimulates the manufacturing and secretion of bile; and is anti-inflammatory and strongly detoxifying [278]. In a meta-assessment of 8 randomized clinical trials, performed via Kalopitas et al., which include 622 patients with MAFLD, it became positioned that silymarin supplementation modified into associated with a decrease in ALT ranges [MD = (−14.86); 95% CI: (−19.37)–(10.36)] and AST degrees [MD = (−7.11); 95% CI: (−14.16)–(−0.05)]. The small quantity of information does now not permit the elucidation of the impact of silymarin at the machine of liver fibrosis [279].The consequences of the meta-evaluation of randomized scientific trials indicate that silymarin supplementation can also moreover reduce the activity of liver enzymes in patients with MAFLD.

13.7. Garlic

The health benefits of garlic were known for a long term. Garlic is characterized by using anti-inflammatory, antioxidant, anti-aggregation, lipid-decreasing, antihypertensive effects, and so forth. [280]. In a meta-evaluation through Yu et al. for 139 patients with MAFLD, garlic supplementation end up related to decreases in ALT stages [MD = (−9.00) 95% CI: (−11.75)–(−6.24)] and AST [MD = (−5.03); 95% CI: (−7.15)–(−2.91)] [281]. The useful effect of garlic on the metabolic profiles of patients with MAFLD become additionally confirmed inside the meta-analysis by means of Rastkar et al. Their meta-evaluation included 186 patients with MAFLD, and it showed that garlic supplementation become associated with a massive reduction in the concentrations of ALT, AST, total ldl cholesterol, LDL-C, triglycerides, and fasting glucose. furthermore, the probability of a decrease in hepatic steatosis became 2.75 times decrease inside the garlic group in contrast to the placebo organization (RR = 2.75; 95% CI: 1.79–4.23) [282].

14. Future views

Due to the multifaceted pathophysiology of MAFLD, in current clinical trials, new capsules from considered one of a special agencies had been evaluated:

- farnesoid X receptor agonists—obeticholic acid and tropifexor;
- a lipogenesis inhibitor—aramchol;
- a galectin 3 inhibitor—belapectin;
- an A3 adenosine receptor agonist—namodenoson;
- a fatty acid—icosabutate;

- a cyclophilin inhibitor—rencofilstat; a changed bile acid—non-ursodeoxycholic.

In most of those medical trials, the primary endpoint concerns an improvement in liver fibrosis [283].

Summary

The pathogenesis of MAFLD is multifactorial, and the pathogenic drivers of MAFLD can feature recuperation objectives. the ones can consist of: the modulation of meals consumption, growth in power expenditure, development in adipocyte insulin sensitivity, inhibition of de novo lipogenesis, tapering of oxidative strain, and reduction in inflammation. MAFLD is probably considered as part of the clinical presentation of the metabolic syndrome. For numerous a long term, there were critical upgrades within the remedy options of diabetes, hyperlipidemia, and high blood strain. naturally capsules affecting incretin receptors, PPAR, and TRb have great influences on the surrogate markers of liver steatosis. primarily based at the to be had research findings and recommendations from liver sickness societies, evidently a number of the most huge factors are the success of an everyday body weight and the effective treatment of metabolic disorders. nevertheless, there may be a lack of a sufficient variety of studies indicating which of the cardiometabolic risk elements, included within the definition of MAFLD, most importantly lead(s) to illness improvement. consequently, the need for similarly studies on remedies in order to significantly and independently mitigate the outcomes and severity of liver steatosis appears vital. therefore, alongside the established roles of pioglitazone and nutrition E in MASH treatment, certainly capsules for weight reduction (which include incretin-based medicinal drugs that also have a glycemic-normalizing impact) and different drugs which have an impact on the cardiometabolic hazard will often benefit importance; subsequently, the incessant necessity for exploring pathophysiological pathways that would permit a not unusual mechanism of motion to be located for steatosis decision regardless of the shape of thing that induced it. consequently, we are anxiously looking for the outcomes of ongoing scientific trials no longer only regarding pharmacotherapy however also extra definitive research on the impact of the TLC and microbiota on the direction of MAFLD.

In precis, primarily based on our literature assessment, it seems that during sufferers with liver steatosis and concomitant diseases, a recommendation towards the subsequent healing itinerary may be supplied:

- physical activity and change of the modification are of the utmost importance;
- The strengthening of weight reduction with pharmacotherapy (preferably with GLP-1 analogues) is clearly helpful;
- The introduction of useful substances may additionally improve MAFLD;
- the eye of the usage of seasoned/prebiotics—change of microbiota (screening for H. pylori);
- The exclusion of hypothyroidism, hypogonadism, and GH deficiency;
- In patients with DMT2, a desire within the route of novel antidiabetic pills, i.e., SGLT-2i and incretin-based absolutely treatment options;
- In patients with lipid problems, the usage of lipid-decreasing tablets must be endorsed, at the same time as the risk of liver harm seems no longer to be more than that during patients without liver steatosis, and the capacity beneficial consequences on liver abilities seem to be concurrent with cardiovascular benefits.

II. Conclusion

The high-risk populace in NAFLD patients is now properly identified (i.e., patients with superior fibrosis), and simple non-invasive gear are to be had for case locating. Algorithms based on those non-invasive equipment are effective and endorsed by numerous international guidelines, but are on the whole confirmed to date in tertiary referral liver centers. the following step is to implement these algorithms beyond the liver health center , especially in number one care and diabetes clinics where most NAFLD patients are seen' the main barrier against is the lack of knowledge amongst physicians managing these patients.

Certainly, NAFLD remains largely unknown outside the fields of hepatology and gastroenterology, and is not noted by majority of physicians. As a result, much less than 10% of NAFLD patients are referred by specialist and possibilities for early interventions are overlooked, particularly in people with advanced fibrosis. in addition, NAFLD is absent from almost all national and worldwide techniques and guidelines for non-communicable diseases, including weight problems. Therefore, dissemination

of suggestions on the usage of non-invasive checks and multidisciplinary procedures are crucial to increase attention and to improve control of NAFLD patients.

Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors have equally participated and shared every item of the work.

List of Abbreviations

AACE	American Association of Clinical Endocrinology
AASLD	American Association for the Study of Liver Diseases
ACC	Acetyl-CoA Carboxylase
ALEH	Latin American Association for the Study of the Liver
ALP	Alkaline Phosphate
ALT	Alanine Aminotransferase
AMPK	Adenosine 5'-Monophosphate
(AMP)	Activated Protein Kinase
AST	Aspartate Aminotransferase
BLBLIs	β-Lactam/β-LactamaseInhibitor Combinations
BMI	Body-Mass Index
CAP	Controlled Attenuation Parameter
CK-18	Cytokeratin-18
CKD	Chronic Kidney Disease
CRF	Cardiorespiratory Fitness
CT	Computed Tomography
DGATs	Diacylglycerol Acyltransferases
DMT2	Type 2 Diabetes Mellitus
DPP4i	Dipeptidyl Peptidase-4 inhibitor
EASD	European Association for the Study of Diabetes
EASL	European Association for the Study of the Liver
EASO	European Association for the Study of Obesity
FASN	Fatty-Acid Synthase
FGF-21	Fibroblast Growth Factor 21
FIB-4	Fibrosis-4 Index

FLI	**Fatty Liver Index**
FNI	Fibrotic Nonalcoholic steatohepatitis Index
FXR	Farnesoid X Receptor
GCG	Glucagon
GCGR	Glucagon Receptor
GGT	Gamma-Glutamyl Transferase
GH	Growth Hormone
GIP	Glucose-Dependent Insulinotropic Peptide
GLP-1	Glucagon-like Peptide-1
GLP-1RA	GLP-1 Receptor Agonists
HCC	Hepatocellular Carcinoma
HDL	High-Density Lipoprotein
HF	Heart Failure
HIS	Intrahepatic Steatosis
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
IGF-1	Insulin-like Growth Factor-1
IHL	Intrahepatic Lipid
IL	Interleukin
KHKis	Ketohexokinase inhibitors
LAI	Liver Attenuation Index
LFC	Liver Fat Content
LFTs	Liver Function Tests
LPS	Lipopolysaccharides
LSM	Liver Stiffness Measurement
MAFLD	Metabolic-Associated Fatty Liver Disease
MASH	Metabolic Dysfunction-Associated Steatohepatitis
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
Met-ALD	Metabolic Alcohol-Related Liver Disease
MRI	Magnetic Resonance Imaging
MRI-PDFF	MRI-Proton Density Fat Fraction
mTOR	mammalian Target of Rapamycin
NAFIC score	NASH, Ferritin, Insulin, and type IV Collagen 7S score

NAFLD	Nonalcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic Steatohepatitis
NFS	NAFLD Fibrosis Score
PCSK9i	inhibitor of Proprotein Convertase Subtilisin/Kexin 9
PI13-AKT	Phosphatidylinositol 3 Kinase-protein Kinase B
PPAR9(α) alpha	Peroxisome Proliferator-Activated Receptors alpha
PPARγ	Peroxisome Proliferator-Activated Receptors gamma
Pro-C3	N-terminal type III collagen propeptide
PUFA	Polyunsaturated Fatty Acid
RCT	Randomized Controlled Trial
SGLT-2	Sodium-Glucose Cotransporter-2
SGLT-2is	Sodium-Glucose Cotransporter-2 inhibitors
SHBG	Sex-Hormone Binding Protein
SLD	Steatotic Liver Disease
SPPARM	Selective Peroxisome Proliferator-Activated Receptor Modulators
SUCRA	Surface Under the Cumulative Ranking Curve
SWV	Shear-Wave Velocity
TG	Triglyceride
TGF	Transforming Growth Factor
TLC	Therapeutic Lifestyle Change
TNF-alfa (α)	Tumor Necrosing Factor alpha
TRb	Thyroid Receptor beta
UDCA	Ursodeoxycholic Acid

List of Clinical Trials

CANVAS Study	Canagliflozin Cardiovascular Assessment Study
CREDENCE Study	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
DAPA-CKD Study	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease Study

DAPA-HF Study	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Study
E-LIFT Study	EndoBarrier(R) in Diabetes Trial
EMPEROR-Preserved Study	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure with Preserved Ejection Fraction
EMPEROR-Reduced Study	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure with Reduced Ejection Fraction
ENLIVEN Study	Study Evaluating the Safety, Efficacy and Tolerability of BIO89-100 in Subject with Biopsy-confirmed Nonalcoholic Steatohepatitis (NASH)
ESSENTIAL Study	Efficacy and Safety of Sparsentan in Patients with IgA Nephropathy
FALCON program	Two phase 2b randomized, double-blind, placebo-controlled studies to assess the efficacy and safety of pegbelfermin in the treatment of patients with nonalcoholic steatohepatitis and bridging fibrosis or compensated cirrhosis
FASCINATE–1 Study	TVB-2640 (FASN inhibitor) for the Treatment of Nonalcoholic Steatohepatitis
GRAECE Study	Greek Atorvastatin and Coronary-heart-disease Evaluation Study
LEAN Study	The Liraglutide Efficacy and Action in NASH
LUBIPRONE Study	Efficacy, safety, and tolerability of lubiprostone for the treatment of nonalcoholic fatty liver disease in adult patients with constipation: The LUBIPRONE, double-blind, randomized, placebo-controlled study design
MIRNA Study	Metabolic Interventions to Resolve NASH with fibrosis
MOMENTUM Trials	**Obesity** Multi-center.Randomized, Double-blind, Placebo-controlled, Parallel-group Studies Evaluating the Safety and Efficacy of Investigational Agents in Obese or Overweight Adult Participants
PIVENS Trial	Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis
SURPASS-3 MRI Study	Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomized, open-label, parallel-group, phase 3 SURPASS-3 trial
SURPASS-3 Trial	Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomized, open-label, parallel-group, phase 3 trial
SYNERGY-NAS Trial	A Study of Tirzepatide (LY3298176) in Participants with Nonalcoholic Steatohepatitis (NASH)

References

[1]- Angulo, Paul, et al. "Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease." *Gastroenterology* 145.4 (2013): 782-789.
[2]- Hagström, Hannes, et al. "Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD." *Journal of hepatology* 67.6 (2017): 1265-1273.
[3]- Ekstedt, Mattias, et al. "Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up." *Hepatology* 61.5 (2015): 1547-1554.
[4]- Younossi, Zobair M., et al. "Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality." *Hepatology* 53.6 (2011): 1874-1882.
[5]- Taylor, Rod S., et al. "Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis." *Gastroenterology* 158.6 (2020): 1611-1625.
[6]- Dulai, Parambir S., et al. "Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis." *Hepatology* 65.5 (2017): 1557-1565.
[7]- Sanyal, Arun J., et al. "Prospective study of outcomes in adults with nonalcoholic fatty liver disease." *New England Journal of Medicine* 385.17 (2021): 1559-1569.
[8]- Younossi, Zobair M., et al. "Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial." *The Lancet* 394.10215 (2019): 2184-2196.
[9]- Sanyal, A. J., S. L. Friedman, and A. J. McCullough. "Dimick-Santos LAmerican Association for the Study of Liver Diseases United States Food and Drug Administration Food and Drug Administration Joint Workshop." *Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American Association for the Study of Liver Diseases-US Hepatology* 61.04 (2015): 1392-1405.
[10]- Alkayyali, Tasnim, et al. "Clinical utility of noninvasive scores in assessing advanced hepatic fibrosis in patients with type 2 diabetes mellitus: a study in biopsy-proven non-alcoholic fatty liver disease." *Acta diabetologica* 57 (2020): 613-618.
[11]- Boursier, Jérôme, et al. "Impact of type 2 diabetes on the accuracy of noninvasive tests of liver fibrosis with resulting clinical implications." *Clinical Gastroenterology and Hepatology* 21.5 (2023): 1243-1251.
[12]- Patel, PreyaJanubhai, et al. "A pragmatic approach identifies a high rate of nonalcoholic fatty liver disease with advanced fibrosis in diabetes clinics and at-risk populations in primary care." *Hepatology communications* 2.8 (2018): 897-909.
[13]- McPherson, Stuart, et al. "Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis." *Official journal of the American College of Gastroenterology| ACG* 112.5 (2017): 740-751.
[14]- Qadri, Sami, et al. "Obesity modifies the performance of fibrosis biomarkers in nonalcoholic fatty liver disease." *The Journal of Clinical Endocrinology & Metabolism* 107.5 (2022): e2008-e2020.
[15]- Unalp-Arida, Aynur, and Constance E. Ruhl. "Noninvasive fatty liver markers predict liver disease mortality in the US population." *Hepatology* 63.4 (2016): 1170-1183.
[16]- Hagström, Hannes, et al. "Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease." *Journal of hepatology* 73.5 (2020): 1023-1029.
[17]- Castera, Laurent, Mireen Friedrich-Rust, and Rohit Loomba. "Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease." *Gastroenterology* 156.5 (2019): 1264-1281.

[18]- Vali, Yasaman, et al. "FibroTest for evaluating fibrosis in non-alcoholic fatty liver disease patients: a systematic review and meta-analysis." *Journal of clinical medicine* 10.11 (2021): 2415.
[19]- Vali, Yasaman, et al. "Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: a systematic review and meta-analysis." *Journal of hepatology* 73.2 (2020): 252-262.
[20]- Van Dijk, Anne-Marieke, et al. "Systematic review with meta-analyses: diagnostic accuracy of FibroMeter tests in patients with non-alcoholic fatty liver disease." *Journal of clinical medicine* 10.13 (2021): 2910.
[21]- Guillaume, Maeva, et al. "Direct comparison of the specialised blood fibrosis tests FibroMeterV2G and Enhanced Liver Fibrosis score in patients with non-alcoholic fatty liver disease from tertiary care centres." *Alimentary pharmacology & therapeutics* 50.11-12 (2019): 1214-1222.
[22]- Boursier, Jérôme, et al. "New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD." *Journal of hepatology* 71.2 (2019): 389-396.

[23]- Castera, Laurent, and Jérôme Boursier. "Noninvasive algorithms for the case finding of “at-risk” patients with NAFLD." *Seminars in Liver Disease*. Vol. 42. No. 03. Thieme Medical Publishers, Inc., 2022.
[24]- Friedrich-Rust, Mireen, Thierry Poynard, and Laurent Castera. "Critical comparison of elastography methods to assess chronic liver disease." *Nature reviews Gastroenterology & hepatology* 13.7 (2016): 402-411.
[25]- Eddowes, Peter J., et al. "Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease." *Gastroenterology* 156.6 (2019): 1717-1730.
[26]- Siddiqui, Mohammad S., et al. "Vibration-controlled transient elastography to assess fibrosis and steatosis in patients with nonalcoholic fatty liver disease." *Clinical Gastroenterology and Hepatology* 17.1 (2019): 156-163.
[27]- Mózes, Ferenc Emil, et al. "Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis." *Gut* 71.5 (2022): 1006-1019.
[28]- Selvaraj, Emmanuel Anandraj, et al. "Diagnostic accuracy of elastography and magnetic resonance imaging in patients with NAFLD: a systematic review and meta-analysis." *Journal of hepatology* 75.4 (2021): 770-785.
[29]- Panel, Clinical Practice Guideline, et al. "EASL Clinical Practice Guidelines on non-invasive tests for evaluation
[30]- Tsochatzis, Emmanuel A., and Philip N. Newsome. "Non-alcoholic fatty liver disease and the interface between primary and secondary care." *The lancet Gastroenterology & hepatology* 3.7 (2018): 509-517.
[31]- Majumdar, Avik, et al. "Defining the minimum acceptable diagnostic accuracy of noninvasive fibrosis testing in cirrhosis: a decision analytic modeling study." *Hepatology* 71.2 (2020): 627-642.
[32]- Canivet, Clémence M., et al. "Validation of the new 2021 EASL algorithm for the noninvasive diagnosis of advanced fibrosis in NAFLD." *Hepatology* 77.3 (2023): 920-930.
[33]- Boursier, Jerome, et al. "Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events." *Journal of Hepatology* 76.5 (2022): 1013-1020.
[34]- Mansour, Dina, et al. "Embedding assessment of liver fibrosis into routine diabetic review in primary care." *JHEP Reports* 3.4 (2021): 100293.
[35]- Glyn-Owen, Kate, et al. "The combined effect of alcohol and body mass index on risk of chronic liver disease: a systematic review and meta-analysis of cohort studies." *Liver International* 41.6 (2021): 1216-1226.
[36]- Harman, David J., et al. "Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography." *Alimentary pharmacology & therapeutics* 47.4 (2018): 504-515.
[37]- Innes, Hamish, et al. "Characterizing the risk interplay between alcohol intake and body mass index on cirrhosis morbidity." *Hepatology* 75.2 (2022): 369-378.
[38]- Kanwal, Fasiha, et al. "Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease." *Gastroenterology* 161.5 (2021): 1657-1669.
[39]- Cusi, Kenneth, et al. "American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD)." *Endocrine Practice* 28.5 (2022): 528-562.
[40]- Kanwal, Fasiha, et al. "Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease." *Gastroenterology* 161.5 (2021): 1657-1669.
[41]- Jung, Jinho, et al. "MRE combined with FIB-4 (MEFIB) index in detection of candidates for pharmacological treatment of NASH-related fibrosis." *Gut* 70.10 (2021): 1946-1953.
[42]- Noureddin, Mazen, et al. "MRI-based (MAST) score accurately identifies patients with NASH and significant fibrosis." *Journal of hepatology* 76.4 (2022): 781-787.
[43]- Kim, Beom Kyung, et al. "Head-to-head comparison between MEFIB, MAST, and FAST for detecting stage 2 fibrosis or higher among patients with NAFLD." *Journal of hepatology* 77.6 (2022): 1482-1490.
[44]- Noureddin, Mazen, Stephen A. Harrison, and Naim Alkhouri. "MEFIB vs. MAST and FAST: Not a competition but useful tools." *Journal of Hepatology* 80.1 (2024): e35-e36.
[45]- Castera, Laurent, Mireen Friedrich-Rust, and Rohit Loomba. "Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease." *Gastroenterology* 156.5 (2019): 1264-1281.
[46]- Sberna, A. L., et al. "European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the

management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes." *Diabetic Medicine* 35.3 (2018): 368-375.
[47]- Mátis, Dóra, et al. "Improved body composition decreases the fat content in non-alcoholic fatty liver disease, a meta-analysis and systematic review of longitudinal studies." *Frontiers in Medicine* 10 (2023): 1114836.
[48]- Rinella, Mary E., et al. "AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease." *Hepatology* 77.5 (2023): 1797-1835.
[49]- Barrón-Cabrera, Elisa, et al. "Physical activity protocols in non-alcoholic fatty liver disease management: A systematic review of randomized clinical trials and animal models." *Healthcare*. Vol. 11. No. 14. MDPI, 2023.
[50]- Wang, Shu-ting, et al. "Physical activity intervention for non-diabetic patients with non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials." *BMC gastroenterology* 20 (2020): 1-12.
[51]- Xiong, Yingzhe, et al. "Effect of different exercise methods on non-alcoholic fatty liver disease: a meta-analysis and meta-regression." *International Journal of Environmental Research and Public Health* 18.6 (2021): 3242.
[52]- Bischoff, Stephan C., et al. "European guideline on obesity care in patients with gastrointestinal and liver diseases–Joint ESPEN/UEG guideline." *Clinical Nutrition* 41.10 (2022): 2364-2405.
[53]- Gofton, Cameron, et al. "MAFLD: How is it different from NAFLD?." *Clinical and molecular hepatology* 29.Suppl (2023): S17.
[54]- Hazlehurst, Jonathan M., and Jeremy W. Tomlinson. "Mechanisms in endocrinology: Non-alcoholic fatty liver disease in common endocrine disorders." *European Journal of Endocrinology* 169.2 (2013): R27-R37.
[55]- Ranjbar, Golnaz, Dimitri P. Mikhailidis, and Amirhossein Sahebkar. "Effects of newer antidiabetic drugs on nonalcoholic fatty liver and steatohepatitis: Think out of the box!." *Metabolism* 101 (2019): 154001.
[56]- Rieg, Timo, and Volker Vallon. "Development of SGLT1 and SGLT2 inhibitors." *Diabetologia* 61.10 (2018): 2079-2086.
[57]- Jasleen, Bains, et al. "Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors: benefits versus risk." *Cureus* 15.1 (2023).
[58]- van der Aart-van der Beek, Annemarie B., Rudolf A. de Boer, and Hiddo JL Heerspink. "Kidney and heart failure outcomes associated with SGLT2 inhibitor use." *Nature Reviews Nephrology* 18.5 (2022): 294-306.
[59]- Nasiri-Ansari, Narjes, et al. "Empagliflozin attenuates non-alcoholic fatty liver disease (NAFLD) in high fat diet fed ApoE (-/-) mice by activating autophagy and reducing ER stress and apoptosis." *International journal of molecular sciences* 22.2 (2021): 818.
[60]- Shaaban, Hager H., et al. "Metformin, pioglitazone, dapagliflozin and their combinations ameliorate manifestations associated with NAFLD in rats via anti-inflammatory, anti-fibrotic, anti-oxidant and anti-apoptotic mechanisms." *Life Sciences* 308 (2022): 120956.
[61]- Shaaban, Hager H., et al. "Metformin, pioglitazone, dapagliflozin and their combinations ameliorate manifestations associated with NAFLD in rats via anti-inflammatory, anti-fibrotic, anti-oxidant and anti-apoptotic mechanisms." *Life Sciences* 308 (2022): 120956.
[62]- Sun, Lei, et al. "Effects of dapagliflozin in patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials." *Clinics and Research in Hepatology and Gastroenterology* 46.4 (2022): 101876.
[63]- Bellanti, Francesco, et al. "Impact of sodium glucose cotransporter-2 inhibitors on liver steatosis/fibrosis/inflammation and redox balance in non-alcoholic fatty liver disease." *World journal of gastroenterology* 28.26 (2022): 3243.
[64]- Kuchay, Mohammad Shafi, et al. "Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT Trial)." *Diabetes care* 41.8 (2018): 1801-1808.
[65]- Zhang, Yuyuan, et al. "Efficacy and safety of empagliflozin on nonalcoholic fatty liver disease: a systematic review and meta-analysis." *Frontiers in Endocrinology* 13 (2022): 836455.
[66]- Gu, Yunpeng, et al. "Comparative efficacy of 5 sodium-glucose cotransporter protein-2 (SGLT-2) inhibitor and 4 glucagon-like peptide-1 (GLP-1) receptor agonist drugs in non-alcoholic fatty liver disease: A GRADE-assessed systematic review and network meta-analysis of randomized controlled trials." *Frontiers in Pharmacology* 14 (2023): 1102792.
[67]- Phrueksotsai, Susrichit, et al. "The effects of dapagliflozin on hepatic and visceral fat in type 2 diabetes patients with non-alcoholic fatty liver disease." *Journal of gastroenterology and hepatology* 36.10 (2021): 2952-2959.
[68]- Arai, Taeang, et al. "Antifibrotic effect and long-term outcome of SGLT2 inhibitors in patients with NAFLD complicated by diabetes mellitus." *Hepatology communications* 6.11 (2022): 3073-3082.
[69]- Bułdak, Łukasz, et al. "Exenatide prevents statin-related LDL receptor increase and improves insulin secretion in pancreatic beta cells (1.1 E7) in a protein kinase A-dependent manner." *Journal of Applied Biomedicine* 20.4 (2022).

[70]- Bułdak, Łukasz, et al. "Exenatide improves antioxidant capacity and reduces the expression of LDL receptors and PCSK9 in human insulin-secreting 1.1 E7 cell line subjected to hyperglycemia and oxidative stress." *Postępy Higieny i Medycyny Doświadczalnej* 76.1 (2022): 16-23.
[71]- Bułdak, Łukasz, et al. "The impact of exenatide (a GLP-1 agonist) on markers of inflammation and oxidative stress in normal human astrocytes subjected to various glycemic conditions." *Experimental and therapeutic medicine* 17.4 (2019): 2861-2869.
[72]- Armstrong, Matthew James, et al. "Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study." *The Lancet* 387.10019 (2016): 679-690.
[73]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[74]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[75]- Kamata, Shotaro, Akihiro Honda, and Isao Ishii. "Current clinical trial status and future prospects of PPAR-targeted drugs for treating nonalcoholic fatty liver disease." *Biomolecules* 13.8 (2023): 1264.
[76]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[77]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[78]- Pratt, Edward, et al. "Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: a Phase 1b, multicentre, blinded, placebo-controlled, randomized, multiple-ascending-dose study in people with type 2 diabetes." *Diabetes, Obesity and Metabolism* 25.9 (2023): 2642-2649.
[79]- Cusi, Kenneth, et al. "American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD)." *Endocrine Practice* 28.5 (2022): 528-562.
[80]- El, Kimberley, et al. "The incretin co-agonist tirzepatide requires GIPR for hormone secretion from human islets." *Nature Metabolism* 5.6 (2023): 945-954.
[81]- Thomas, Melissa K., et al. "Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes." *The Journal of Clinical Endocrinology & Metabolism* 106.2 (2021): 388-396.

[82]-Thomas, Melissa K., et al. "Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes." *The Journal of Clinical Endocrinology & Metabolism* 106.2 (2021): 388-396.

[83]- Hartman, Mark L., et al. "Effects of novel dual GIP and GLP-1 receptor agonist tirzepatide on biomarkers of nonalcoholic steatohepatitis in patients with type 2 diabetes." *Diabetes Care* 43.6 (2020): 1352-1355.
[84]- Gastaldelli, Amalia, et al. "Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial." *The lancet Diabetes & endocrinology* 10.6 (2022): 393-406.
[85]- Romero-Gómez, Manuel, et al. "A phase IIa active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease." *Journal of Hepatology* 79.4 (2023): 888-897.
[86]- Nahra, Rajaa, et al. "Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: a 54-week randomized phase 2b study." *Diabetes care* 44.6 (2021): 1433-1442.
[87]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[88]- Harrison, Stephen A., et al. "Clinical trial landscape in NASH." *Clinical Gastroenterology and Hepatology* (2023).
[89]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[90]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[91]- Prikhodko, Veronika A., Natalia N. Bezborodkina, and Sergey V. Okovityi. "Pharmacotherapy for non-alcoholic fatty liver disease: emerging targets and drug candidates." *Biomedicines* 10.2 (2022): 274.

[92]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[93]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[94]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[95]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[96]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[97]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[98]- Jastreboff, Ania M., et al. "Triple–hormone-receptor agonist retatrutide for obesity—a phase 2 trial." *New England Journal of Medicine* 389.6 (2023): 514-526.
[99]- Kongmalai, Tanawan, et al. "New anti-diabetic agents for the treatment of non-alcoholic fatty liver disease: a systematic review and network meta-analysis of randomized controlled trials." *Frontiers in Endocrinology* 14 (2023): 1182037.
[100]- Valenzuela-Vallejo, Laura, Valentina Guatibonza-García, and Christos S. Mantzoros. "Recent guidelines for Non-Alcoholic Fatty Liver disease (NAFLD)/Fatty Liver Disease (FLD): Are they already outdated and in need of supplementation?." *Metabolism* 136 (2022): 155248.
[101]- dos Santos, Lucas R., et al. "Dipeptidyl peptidase IV inhibitors for nonalcoholic fatty liver disease-systematic review and metanalysis." *Current Diabetes Reviews* 17.5 (2021): 70-81.
[102]- Alam, Shahinul, et al. "Effect of sitagliptin on hepatic histological activity and fibrosis of nonalcoholic steatohepatitis patients: a 1-year randomized control trial." *Hepatic medicine: evidence and research* (2018): 23-31.
[103]- AKTAŞ, Ahmet, and O. Z. A. N. Zeynep. "The efficacy and safety of vildagliptin treatment for nonalcoholic fatty liver disease in type 2 diabetes mellitus." *Cumhuriyet Medical Journal* 42.4 (2020): 491-499.
[104]- Jin, Dachuan, et al. "Comparison of efficacy of anti-diabetics on non-diabetic NAFLD: A network meta-analysis." *Frontiers in Pharmacology* 13 (2023): 1096064.
[105]- Hattori, Sachiko, et al. "Beneficial effect of omarigliptin on diabetic patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis." *Diabetology & Metabolic Syndrome* 13 (2021): 1-6.
[106]- Gupta, Vishal Kumar. "1029-P: Teneligliptin Significantly Reduces Liver Fat Content (LFC) and Delays Progression of NASH in Type 2 Diabetes Mellitus Patients." *Diabetes* 68.Supplement_1 (2019).
[107]- Chen, Lin, et al. "Effect of saxagliptin, a dipeptidyl peptidase 4 inhibitor, on non-alcoholic fatty liver disease." *Diabetes, Metabolic Syndrome and Obesity* (2020): 3507-3518.
[108]- Li, Juan-Juan, et al. "The efficacy of saxagliptin in T2DM patients with non-alcoholic fatty liver disease: preliminary data." *Revista da Associação Médica Brasileira* 65 (2019): 33-37.
[109]- Mashitani, Tsuyoshi, et al. "Efficacy of alogliptin in preventing non-alcoholic fatty liver disease progression in patients with type 2 diabetes." *Biomedical reports* 4.2 (2016): 183-187.
[110]- Sanyal, Arun J., et al. "Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis." *New England Journal of Medicine* 362.18 (2010): 1675-1685.
[111]- Aithal, Guruprasad P., et al. "Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis." *Gastroenterology* 135.4 (2008): 1176-1184.
[112]- Belfort, Renata, et al. "A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis." *New England Journal of Medicine* 355.22 (2006): 2297-2307.
[113]- Cusi, Kenneth, et al. "Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial." *Annals of internal medicine* 165.5 (2016): 305-315.
[114]- Bril, Fernando, et al. "Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial." *Diabetes care* 42.8 (2019): 1481-1488.
[115]- Della Pepa, Giuseppe, et al. "Pioglitazone even at low dosage improves NAFLD in type 2 diabetes: clinical and pathophysiological insights from a subgroup of the TOSCA. IT randomised trial." *Diabetes research and clinical practice* 178 (2021): 108984.

[116]- Ndakotsu, Andrew, and Govinathan Vivekanandan. "The role of thiazolidinediones in the amelioration of nonalcoholic fatty liver disease: A systematic review." *Cureus* 14.5 (2022).
[117]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[118]- Lee, Yong-ho, et al. "Lobeglitazone, a novel thiazolidinedione, improves non-alcoholic fatty liver disease in type 2 diabetes: its efficacy and predictive factors related to responsiveness." *Journal of Korean medical science* 32.1 (2017): 60.
[119]- Kazierad, David J., et al. "Inhibition of ketohexokinase in adults with NAFLD reduces liver fat and inflammatory markers: a randomized phase 2 trial." *Med* 2.7 (2021): 800-813.
[120]- Saxena, Aditi R., et al. "A phase 2a, randomized, double-blind, placebo-controlled, three-arm, parallel-group study to assess the efficacy, safety, tolerability and pharmacodynamics of PF-06835919 in patients with non-alcoholic fatty liver disease and type 2 diabetes." *Diabetes, Obesity and Metabolism* 25.4 (2023): 992-1001.
[121]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[122]- Pinyopornpanish, Kanokwan, et al. "Effects of metformin on hepatic steatosis in adults with nonalcoholic fatty liver disease and diabetes: insights from the cellular to patient levels." *Gut and liver* 15.6 (2021): 827.
[123]- Li, Yan, et al. "Metformin in non-alcoholic fatty liver disease: A systematic review and meta-analysis." *Biomedical reports* 1.1 (2013): 57-64.
[124]- Musso, G., et al. "Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials." *Diabetologia* 55 (2012): 885-904.
[125]- Loomba, R., et al. "Clinical trial: pilot study of metformin for the treatment of non-alcoholic steatohepatitis." *Alimentary pharmacology & therapeutics* 29.2 (2009): 172-182.
[126]- Bugianesi, Elisabetta, et al. "A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease." *Official journal of the American College of Gastroenterology| ACG* 100.5 (2005): 1082-1090.
[127]- Ioannou, George N. "The role of cholesterol in the pathogenesis of NASH." *Trends in Endocrinology & Metabolism* 27.2 (2016): 84-95.
[128]- Bułdak, Łukasz. "The treatment of heterozygous familial hypercholesterolemia—A local perspective." *Endokrynologia Polska* 72.3 (2021): 189-190.
[129]- Okopień, Bogusław, Łukasz Bułdak, and Aleksandra Bołdys. "Current and future trends in the lipid lowering therapy." *Pharmacological Reports* 68.4 (2016): 737-747.
[130]- Boutari, Chrysoula, et al. "Statins' efficacy in non-alcoholic fatty liver disease: A systematic review and meta-analysis." *Clinical Nutrition* 41.10 (2022): 2195-2206.
[131]- Ahsan, Farah, et al. "Pleiotropic effects of statins in the light of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis." *Cureus* 12.9 (2020).
[132]- Athyros, Vasilios G., et al. "Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study." *Current medical research and opinion* 22.5 (2006): 873-883.
[133]- Athyros, Vasilios G., et al. "Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis." *The Lancet* 376.9756 (2010): 1916-1922.
[134]- Cho, Yongin, et al. "Ezetimibe combination therapy with statin for non-alcoholic fatty liver disease: an open-label randomized controlled trial (ESSENTIAL study)." *BMC medicine* 20.1 (2022): 93.
[135]- Lee, Won Myung, et al. "Effect of nutrition education in NAFLD patients undergoing simultaneous hyperlipidemia pharmacotherapy: A randomized controlled trial." *Nutrients* 13.12 (2021): 4453.
[136]- Lee, Hyo Young, et al. "Ezetimibe decreased nonalcoholic fatty liver disease activity score but not hepatic steatosis." *The Korean journal of internal medicine* 34.2 (2019): 296.
[137]- Pastori, Daniele, et al. "Statin liver safety in non-alcoholic fatty liver disease: A systematic review and metanalysis." *British Journal of Clinical Pharmacology* 88.2 (2022): 441-451.
[138]- Pastori, Daniele, et al. "Statin liver safety in non-alcoholic fatty liver disease: A systematic review and metanalysis." *British Journal of Clinical Pharmacology* 88.2 (2022): 441-451.

[139]- Wargny, Matthieu, et al. "Circulating PCSK9 levels are not associated with the severity of hepatic steatosis and NASH in a high-risk population." *Atherosclerosis* 278 (2018): 82-90.
[140]- Di Filippo, Mathilde, Benoit Vokaer, and Nabil G. Seidah. "A case of hypocholesterolemia and steatosis in a carrier of a PCSK9 loss-of-function mutation and polymorphisms predisposing to nonalcoholic fatty liver disease." *Journal of clinical lipidology* 11.4 (2017): 1101-1105.
[141]- Emma, Maria R., et al. "Hepatic and circulating levels of PCSK9 in morbidly obese patients: Relation with severity of liver steatosis." *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids* 1865.12 (2020): 158792.
[142]- Grimaudo, Stefania, et al. "PCSK9 rs11591147 R46L loss-of-function variant protects against liver damage in individuals with NAFLD." *Liver International* 41.2 (2021): 321-332.
[143]- Scicali, Roberto, et al. "Analysis of steatosis biomarkers and inflammatory profile after adding on PCSK9 inhibitor treatment in familial hypercholesterolemia subjects with nonalcoholic fatty liver disease: A single lipid center real-world experience." *Nutrition, Metabolism and Cardiovascular Diseases* 31.3 (2021): 869-879.
[144]- Shafiq, Muhammad, et al. "Effects of proprotein convertase subtilisin/kexin type-9 inhibitors on fatty liver." *World Journal of Hepatology* 12.12 (2020): 1258.
[145]- El-Haggar, Sahar Mohamed, and Tarek Mohamed Mostafa. "Comparative clinical study between the effect of fenofibrate alone and its combination with pentoxifylline on biochemical parameters and liver stiffness in patients with non-alcoholic fatty liver disease." *Hepatology international* 9 (2015): 471-479.
[146]- Yaghoubi, Malek, et al. "Comparison of fenofibrate and pioglitazone effects on patients with nonalcoholic fatty liver disease." *European Journal of Gastroenterology & Hepatology* 29.12 (2017): 1385-1388.
[147]- Oscarsson, Jan, et al. "Effects of free omega-3 carboxylic acids and fenofibrate on liver fat content in patients with hypertriglyceridemia and non-alcoholic fatty liver disease: A double-blind, randomized, placebo-controlled study." *Journal of clinical lipidology* 12.6 (2018): 1390-1403.
[148]- Lawitz, Eric J., et al. "Fenofibrate mitigates hypertriglyceridemia in nonalcoholic steatohepatitis patients treated with cilofexor/firsocostat." *Clinical gastroenterology and hepatology* 21.1 (2023): 143-152.
[149]- Araki, Eiichi, et al. "Effects of pemafibrate, a novel selective PPARα modulator, on lipid and glucose metabolism in patients with type 2 diabetes and hypertriglyceridemia: a randomized, double-blind, placebo-controlled, phase 3 trial." *Diabetes Care* 41.3 (2018): 538-546.
[150]- Ikeda, Suguru, et al. "Pemafibrate dramatically ameliorated the values of liver function tests and fibrosis marker in patients with non-alcoholic fatty liver disease." *Yonago acta medica* 63.3 (2020): 188-197.
[151]- Seko, Yuya, et al. "Effect of pemafibrate on fatty acid levels and liver enzymes in non-alcoholic fatty liver disease patients with dyslipidemia: a single-arm, pilot study." *Hepatology Research* 50.12 (2020): 1328-1336.
[152]- Shinozaki, Satoshi, et al. "Pemafibrate decreases markers of hepatic inflammation in patients with non-alcoholic fatty liver disease." *Clinical and experimental hepatology* 6.3 (2020): 270-274.
[153]- Hatanaka, Takeshi, et al. "Impact of pemafibrate in patients with hypertriglyceridemia and metabolic dysfunction-associated fatty liver disease pathologically diagnosed with non-alcoholic steatohepatitis: A retrospective, single-arm study." *Internal Medicine* 60.14 (2021): 2167-2174.
[154]- Shinozaki, Satoshi, et al. "Pemafibrate improves hepatic inflammation, function and fibrosis in patients with non-alcoholic fatty liver disease: A one-year observational study." *Clinical and Experimental Hepatology* 7.2 (2021): 172-177.
[155]- Nakajima, Atsushi, et al. "Randomised clinical trial: pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα), versus placebo in patients with non-alcoholic fatty liver disease." *Alimentary pharmacology & therapeutics* 54.10 (2021): 1263-1277.
[156]- Hatanaka, Takeshi, et al. "Effect of 48-week pemafibrate on non-alcoholic fatty liver disease with hypertriglyceridemia, as evaluated by the FibroScan-aspartate aminotransferase score." *JGH Open* 5.10 (2021): 1183-1189.
[157]-Morishita, Asahiro, et al. "Pemafibrate improves liver dysfunction and non-invasive surrogates for liver fibrosis in patients with non-alcoholic fatty liver disease with hypertriglyceridemia: A multicenter study." *Hepatology International* 17.3 (2023): 606-614.
[158]-Sugimoto, Ryosuke, et al. "Effect of pemafibrate on liver enzymes and shear wave velocity in non-alcoholic fatty liver disease patients." *Frontiers in Medicine* 10 (2023): 1073025.
[159]- Shinozaki, Satoshi, et al. "Pemafibrate therapy for non-alcoholic fatty liver disease is more effective in lean patients than obese patients." *Clinical and Experimental Hepatology* 8.4 (2022): 278-283.

[160]- Mitra, Asis. "An observational study of reduction in glycemic parameters and liver stiffness by saroglitazar 4 mg in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease." *Cureus* 12.7(2020).
[161]-Mitra, Asis. "An observational study of reduction in glycemic parameters and liver stiffness by saroglitazar 4 mg in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease." *Cureus* 12.7(2020).
[162]- Goyal, Omesh, et al. "Saroglitazar in patients with non-alcoholic fatty liver disease and diabetic dyslipidemia: a prospective, observational, real world study." *Scientific reports* 10.1 (2020): 21117.
[163]- Rajesh, N. A., et al. "Safety and Efficacy of Saroglitazar in Nonalcoholic Fatty Liver Patients With Diabetic Dyslipidemia—A Prospective, Interventional, Pilot Study." *Journal of Clinical and Experimental Hepatology* 12.1 (2022): 61-67.

[164]- Padole, Prateek, et al. "Saroglitazar for nonalcoholic fattyliver disease: a single centre experience in 91 patients." *Journal of Clinical and Experimental Hepatology* 12.2 (2022): 435-439.
[165]- Siddiqui, Mohammad Shadab, et al. "Saroglitazar, a dual PPAR α/γ agonist, improves atherogenic dyslipidemia in patients with non-cirrhotic nonalcoholic fatty liver disease: a pooled analysis." *Clinical Gastroenterology and Hepatology* 21.10 (2023): 2597-2605.
[166]- Malik, Adnan, Mahum Nadeem, and Muhammad Imran Malik. "Efficacy of elafibranor in patients with liver abnormalities especially non-alcoholic steatohepatitis: A systematic review and meta-analysis." *Clinical Journal of Gastroenterology* 14.6 (2021): 1579-1586.
[167]- Kotsiliti, Eleni. "Lanifibranor and NASH resolution." *Nature reviews Gastroenterology & hepatology* 18.12 (2021): 832-832.

[168]-Fabbrini, Elisa, Shelby Sullivan, and Samuel Klein. "Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications." *Hepatology* 51.2 (2010): 679-689.
[169]- Lambert, Jennifer E., et al. "Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease." *Gastroenterology* 146.3 (2014): 726-735.
[170]- Kim, Chai-Wan, et al. "Acetyl CoA carboxylase inhibition reduces hepatic steatosis but elevates plasma triglycerides in mice and humans: a bedside to bench investigation." *Cell metabolism* 26.2 (2017): 394-406.
[171]- Loomba, Rohit, et al. "GS-0976 reduces hepatic steatosis and fibrosis markers in patients with nonalcoholic fatty liver disease." *Gastroenterology* 155.5 (2018): 1463-1473.
[172]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[173]- O'Farrell, Marie, et al. "FASN inhibition targets multiple drivers of NASH by reducing steatosis, inflammation and fibrosis in preclinical models." *Scientific Reports* 12.1 (2022): 15661.
[174]- Syed-Abdul, Majid M., et al. "Fatty acid synthase inhibitor TVB-2640 reduces hepatic de novo lipogenesis in males with metabolic abnormalities." *Hepatology* 72.1 (2020): 103-118.
[175]- Loomba, Rohit, et al. "TVB-2640 (FASN inhibitor) for the treatment of nonalcoholic steatohepatitis: FASCINATE-1, a randomized, placebo-controlled phase 2a trial." *Gastroenterology* 161.5 (2021): 1475-1486.
[176]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[177]- Calle, Roberto A., et al. "ACC inhibitor alone or co-administered with a DGAT2 inhibitor in patients with non-alcoholic fatty liver disease: two parallel, placebo-controlled, randomized phase 2a trials." *Nature Medicine* 27.10 (2021): 1836-1848.
[178]- Amin, Neeta B., et al. "Efficacy and safety of an orally administered DGAT2 inhibitor alone or coadministered with a liver-targeted ACC inhibitor in adults with non-alcoholic steatohepatitis (NASH): rationale and design of the phase II, dose-ranging, dose-finding, randomised, placebo-controlled MIRNA (Metabolic Interventions to Resolve NASH with fibrosis) study." *BMJ open* 12.3 (2022): e056159.
[179]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[180]- Woo, Y. C., et al. "Fibroblast growth factor 21 as an emerging metabolic regulator: clinical perspectives." *Clinical endocrinology* 78.4 (2013): 489-496.
[181]- Loomba, Rohit, et al. "Safety, pharmacokinetics, and pharmacodynamics of pegozafermin in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 1b/2a multiple-ascending-dose study." *The Lancet*

Gastroenterology & Hepatology 8.2 (2023): 120-132.
[182]- Loomba, Rohit, et al. "Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH." *New England Journal of Medicine* 389.11 (2023): 998-1008.
[183]- To Evaluate the Efficacy and Safety of Pegozafermin in Subjects with Severe Hypertriglyceridemia (ENTRUST). Available online: https://classic.clinicaltrials.gov/ct2/show/NCT05852431 (accessed on 24 September 2023).
[184]- Puengel, Tobias, and Frank Tacke. "Efruxifermin, an investigational treatment for fibrotic or cirrhotic nonalcoholic steatohepatitis (NASH)." *Expert Opinion on Investigational Drugs* 32.6 (2023): 451-461. [185]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[186]- Zhang, Wenyue, et al. "Efficacy of ursodeoxycholic acid in nonalcoholic fatty liver disease: An updated meta-analysis of randomized controlled trials." *Asia Pacific Journal of Clinical Nutrition* 29.4 (2020): 696-705.
[187]- Lin, Xiaozhuan, et al. "Efficiency of ursodeoxycholic acid for the treatment of nonalcoholic steatohepatitis: A systematic review and meta-analysis." *Expert Review of Gastroenterology & Hepatology* 16.6 (2022): 537-545.
[188]- Ferro, Domenico, et al. "New insights into the pathogenesis of non-alcoholic fatty liver disease: gut-derived lipopolysaccharides and oxidative stress." *Nutrients* 12.9 (2020): 2762.
[189]- An, Lingxuan, et al. "The role of gut-derived lipopolysaccharides and the intestinal barrier in fatty liver diseases." *Journal of Gastrointestinal Surgery* 26.3 (2022): 671-683.
[190]- Carpi, Rodrigo Zamignan, et al. "The effects of probiotics, prebiotics and synbiotics in non-alcoholic fat liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): A systematic review." *International journal of molecular sciences* 23.15 (2022): 8805.
[191]- Sharpton, Suzanne R., et al. "Gut microbiome–targeted therapies in nonalcoholic fatty liver disease: A systematic review, meta-analysis, and meta-regression." *The American journal of clinical nutrition* 110.1 (2019): 139-149.
[192]- Davani-Davari, Dorna, et al. "Prebiotics: definition, types, sources, mechanisms, and clinical applications." *Foods* 8.3 (2019): 92.
[193]- Huang, Yuanshe, et al. "Effect of probiotics therapy on nonalcoholic fatty liver disease." *Computational and mathematical methods in medicine* 2022.1 (2022): 7888076.
[194]- Mavilia-Scranton, Marianna G., George Y. Wu, and Murali Dharan. "Impact of Helicobacter pylori infection on the pathogenesis and management of nonalcoholic fatty liver disease." *Journal of Clinical and Translational Hepatology* 11.3 (2023): 670.
[195]- Xu, Guangqin, et al. "Relationship of Helicobacter pylori infection with nonalcoholic fatty liver disease: a meta-analysis." *Canadian Journal of Gastroenterology and Hepatology* 2023.1 (2023): 5521239.
[196]- Malfertheiner, Peter, et al. "Helicobacter pylori infection." *Nature reviews Disease primers* 9.1 (2023): 19.
[197]- Aydemir, Selim, et al. "The effect of Helicobacter pylori on insulin resistance." *Digestive diseases and sciences* 50 (2005): 2090-2093.
[198]- Chen, Li-Wei, et al. "Helicobacter pylori infection increases insulin resistance and metabolic syndrome in residents younger than 50 years old: a community-based study." *PloS one* 10.5 (2015): e0128671.
[199]- Chen, Chen, et al. "Helicobacter pylori infection may increase the severity of nonalcoholic fatty liver disease via promoting liver function damage, glycometabolism, lipid metabolism, inflammatory reaction and metabolic syndrome." *European journal of gastroenterology & hepatology* 32.7 (2020): 857-866.
[200]- Azami, Mobin, et al. "Association of Helicobacter pylori infection with the risk of metabolic syndrome and insulin resistance: an updated systematic review and meta-analysis." *Diabetology & metabolic syndrome* 13.1 (2021): 145.
[201]- Tsuji, Ai, et al. "Tactics with prebiotics for the treatment of metabolic dysfunction-associated fatty liver disease via the improvement of mitophagy." *International Journal of Molecular Sciences* 24.6 (2023): 5465.
[202]- Arellano-García, Laura, et al. "Usefulness of probiotics in the management of NAFLD: evidence and involved mechanisms of action from preclinical and human models." *International Journal of Molecular Sciences* 23.6 (2022): 3167.
[203]- Dong, Yuzhu, et al. "Evaluation of the current guidelines for antibacterial therapy strategies in patients with cirrhosis or liver failure." *BMC Infectious Diseases* 22.1 (2022): 23.
[204]- Gangarapu, Venkatanarayana, et al. "Efficacy of rifaximin on circulating endotoxins and cytokines in patients with nonalcoholic fatty liver disease." *European journal of gastroenterology & hepatology* 27.7 (2015): 840-845.

[205]- Abdel-Razik, Ahmed, et al. "Rifaximin in nonalcoholic fatty liver disease: hit multiple targets with a single shot." *European journal of gastroenterology & hepatology* 30.10 (2018): 1237-1246.
[206]- Ponziani, Francesca Romana, et al. "Eubiotic properties of rifaximin: Disruption of the traditional concepts in gut microbiota modulation." *World journal of gastroenterology* 23.25 (2017): 4491.
[207]- Chen, Hui-Ting, et al. "Therapeutic advances in non-alcoholic fatty liver disease: A microbiota-centered view." *World journal of gastroenterology* 26.16 (2020): 1901.
[208]- Chen, Hui-Ting, et al. "Therapeutic advances in non-alcoholic fatty liver disease: A microbiota-centered view." *World journal of gastroenterology* 26.16 (2020): 1901.
[209]- Podszun, Maren C., and Jan Frank. "Impact of vitamin E on redox biomarkers in non-alcoholic fatty liver disease." *Redox Biology* 42 (2021): 101937.
[210]- Luo, Qian, et al. "Efficacy of off-label therapy for non-alcoholic fatty liver disease in improving non-invasive and invasive biomarkers: a systematic review and network meta-analysis of randomized controlled trials." *Frontiers in Medicine* 9 (2022): 793203.
[211]- An, Jihyun, and Joo Hyun Sohn. "Pharmacological advances in the treatment of nonalcoholic fatty liver diseases: focused on global results of randomized controlled trials." *Clinical and Molecular Hepatology* 29.Suppl (2023): S268.
[212]- Lahmi, A., et al. "Comparative effects of thymol and vitamin E on nonalcoholic fatty liver disease in male Wistar rats." *Brazilian Journal of Biology* 84 (2023): e268781.
[213]- Bai, Yaowei, et al. "Aerobic exercise and vitamin E improve high-fat diet-induced NAFLD in rats by regulating the AMPK pathway and oxidative stress." *European Journal of Nutrition* 62.6 (2023): 2621-2632.
[214]- Vadarlis, Andreas, et al. "Systematic review with meta-analysis: the effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease." *Journal of Gastroenterology and Hepatology* 36.2 (2021): 311-319.
[215]- Abdel-Maboud, Mohamed, et al. "The efficacy of vitamin E in reducing non-alcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression." *Therapeutic advances in gastroenterology* 13 (2020): 1756284820974917.
[216]- Bułdak, Łukasz, et al. "Endocrine diseases as causes of secondary hyperlipidemia." *Endokrynologia Polska* 70.6 (2019): 511-519.
[217]- Tanase, Daniela Maria, et al. "Hypothyroidism-induced nonalcoholic fatty liver disease (HIN): mechanisms and emerging therapeutic options." *International Journal of Molecular Sciences* 21.16 (2020): 5927.
[218]- Harrison, Stephen A., et al. "Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial." *The Lancet* 394.10213 (2019): 2012-2024.
[219]- Harrison, Stephen A., et al. "Effects of resmetirom on noninvasive endpoints in a 36-week phase 2 active treatment extension study in patients with NASH." *Hepatology communications* 5.4 (2021): 573-588.
[220]- Phase, A. "Study to Evaluate Safety and Biomarkers of Resmetirom (MGL-3196) in Patients with Non-alcoholic Fatty Liver Disease (NAFLD), MAESTRO-NAFLD-Open-Label-Extension (MAESTRO-NAFLD-OLE)." *ClinicalTrials. gov ClinicalTrials. gov https://clinicaltrials. gov/ct2/show/NCT04951219 Identifier: NCT04951219. Available at:(accessed 14 September 2022)* (3).
[221]- Polyzos, Stergios A., et al. "Nonalcoholic fatty liver disease in males with low testosterone concentrations." *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 14.5 (2020): 1571-1577.
[222]- Yassin, Aksam A., et al. "Long-term testosterone therapy improves liver parameters and steatosis in hypogonadal men: a prospective controlled registry study." *The Aging Male* 23.5 (2020): 1553-1563.
[223]- Patil, Vaibhav, et al. "Versatility of anabolic androgenic steroid–induced hepatotoxicity." *Journal of Clinical and Experimental Hepatology* 12.1 (2022): 216-221.
[224]- Palmisano, Brian T., Lin Zhu, and John M. Stafford. "Role of estrogens in the regulation of liver lipid metabolism." *Sex and gender factors affecting metabolic homeostasis, diabetes and obesity* (2017): 227-256.
[225]- Gutierrez-Grobe, Ylse, et al. "Prevalence of non alcoholic fatty liver disease in premenopausal, posmenopausal and polycystic ovary syndrome women. The role of estrogens." *Annals of hepatology* 9.4 (2010): 402-409.
[226]- Cao, Weijie, et al. "Associations between sex hormones and metabolic-associated fatty liver disease in a middle-aged and elderly community." *Endocrine Journal* 69.8 (2022): 1007-1014.
[227]- Polyzos, Stergios A., Irene Lambrinoudaki, and Dimitrios G. Goulis. "Menopausal hormone therapy in women with

dyslipidemia and nonalcoholic fatty liver disease." *Hormones* 21.3 (2022): 375-381.
[228]- DiStefano, Johanna K. "NAFLD and NASH in postmenopausal women: implications for diagnosis and treatment." *Endocrinology* 161.10 (2020): bqaa134.
[229]- Florio, Andrea A., et al. "Oophorectomy and risk of non-alcoholic fatty liver disease and primary liver cancer in the Clinical Practice Research Datalink." *European journal of epidemiology* 34 (2019): 871-878.
[230]- Oxley, Madisyn, Heather Francis, and Keisaku Sato. "Growth Hormone Signaling in Liver Diseases: Therapeutic Potentials and Controversies." *Seminars in Liver Disease*. Vol. 43. No. 01. Thieme Medical Publishers, Inc., 2023.
[231]- Hwang, Yoon-A., et al. "Positive association between nonalcoholic fatty liver disease and growth hormone deficiency in patients with nonfunctioning pituitary adenoma." *Frontiers in Endocrinology* 13 (2023): 1057769.
[232]-Dichtel, Laura E., et al. "The GH/IGF-1 axis is associated with intrahepatic lipid content and hepatocellular damage in overweight/obesity." *The Journal of Clinical Endocrinology & Metabolism* 107.9 (2022): e3624-e3632.
[233]- Pan, Chelsea S., et al. "Effect of recombinant human growth hormone on liver fat content in young adults with nonalcoholic fatty liver disease." *Clinical endocrinology* 94.2 (2021): 183-192.
[234]- Liu, Zhengtao, et al. "Dose-response relationship of serum uric acid with metabolic syndrome and non-alcoholic fatty liver disease incidence: a meta-analysis of prospective studies." *Scientific Reports* 5.1 (2015): 14325.
[235]- Nishikawa, Tomoki, et al. "Xanthine oxidase inhibition attenuates insulin resistance and diet-induced steatohepatitis in mice." *Scientific reports* 10.1 (2020): 815.
[236]- Kakimoto, Mai, et al. "Antioxidant action of xanthine oxidase inhibitor febuxostat protects the liver and blood vasculature in SHRSP5/Dmcr rats." *Journal of Applied Biomedicine* 21.2 (2023).
[237]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[238]- Kessoku, Takaomi, et al. "The role of leaky gut in nonalcoholic fatty liver disease: a novel therapeutic target." *International Journal of Molecular Sciences* 22.15 (2021): 8161.
[239]-Wilson, Nicholas, and Ron Schey. "Lubiprostone in constipation: clinical evidence and place in therapy." *Therapeutic advances in chronic disease* 6.2 (2015): 40-50.
[240]- Kim, Mi-Yeon, et al. "Lubiprostone significantly represses fatty liver diseases via induction of mucin and HDL release in mice." *Life Sciences* 311 (2022): 121176.
[241]- Kessoku, Takaomi, et al. "Lubiprostone in patients with non-alcoholic fatty liver disease: a randomised, double-blind, placebo-controlled, phase 2a trial." *The lancet Gastroenterology & hepatology* 5.11 (2020): 996-1007.
[242]- Bołdys, Aleksandra, et al. "Potential Therapeutic Strategies in the Treatment of Metabolic-Associated Fatty Liver Disease." *Medicina* 59.10 (2023): 1789.
[243]- El-Deen, Reham M., et al. "Comparative effectiveness of phosphodiesterase 3, 4, and 5 inhibitors in amelioration of high-fat diet-induced nonalcoholic fatty liver in rats." *Fundamental & Clinical Pharmacology* 34.3 (2020): 353-364.
[244]- Vachliotis, Ilias D., and Stergios A. Polyzos. "The role of tumor necrosis factor-alpha in the pathogenesis and treatment of nonalcoholic fatty liver disease." *Current obesity reports* 12.3 (2023): 191-206.
[245]- Du, Juan, et al. "Effects of pentoxifylline on nonalcoholic fatty liver disease: a meta-analysis." *World journal of gastroenterology: WJG* 20.2 (2014): 569.
[246]- Ipsen, David Højland, et al. "The effect of acetylsalicylic acid and pentoxifylline in guinea pigs with non-alcoholic steatohepatitis." *Basic & Clinical Pharmacology & Toxicology* 128.4 (2021): 583-593.
[247]- Mahjoubin-Tehran, Maryam, et al. "Non-alcoholic fatty liver disease and steatohepatitis: State of the art on effective therapeutics based on the gold standard method for diagnosis." *Molecular Metabolism* 50 (2021): 101049.
[248]- Malladi, Navya, et al. "The role of platelets in non-alcoholic fatty liver disease: From pathophysiology to therapeutics." *Prostaglandins & Other Lipid Mediators* 169 (2023): 106766.
[249]- Meng, Chang, et al. "Effects of losartan in patients with NAFLD: A meta-analysis of randomized controlled trial." *Open Life Sciences* 18.1 (2023): 20220583.
[250]- Surma, Stanisław, et al. "Curcumin-the nutraceutical with pleiotropic effects? Which cardiometabolic subjects might benefit the most?." *Frontiers in Nutrition* 9 (2022): 865497.
[251]- Cicero, Arrigo FG, et al. "Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid

Expert Panel." *Nutrition reviews* 75.9 (2017): 731-767.
[252]- Banach, Maciej, et al. "PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021." *Archives of Medical Science: AMS* 17.6 (2021): 1447.
[253]- Ruscica, Massimiliano, et al. "Impact of nutraceuticals on markers of systemic inflammation: Potential relevance to cardiovascular diseases–A position paper from the International Lipid Expert Panel (ILEP)." *Progress in cardiovascular diseases* 67 (2021): 40-52.
[254]- Ashtary-Larky, Damoon, et al. "The effects of nano-curcumin supplementation on risk factors for cardiovascular disease: a GRADE-assessed systematic review and meta-analysis of clinical trials." *Antioxidants* 10.7 (2021): 1015.
[255]- Ngu, M. H., et al. "Curcumin as adjuvant treatment in patients with non-alcoholic fatty liver (NAFLD) disease: A systematic review and meta-analysis." *Complementary Therapies in Medicine* 68 (2022): 102843.
[256]- Lukkunaprasit, Thitiya, et al. "An updated meta-analysis of effects of curcumin on metabolic dysfunction-associated fatty liver disease based on available evidence from Iran and Thailand." *Scientific Reports* 13.1 (2023): 5824.
[257]- Surma, Stanisław, and Franciszek Kokot. "Influence of chronic coffee consumption on the risk of kidney and other organ diseases. Review of the literature and clinical studies." *Renal Disease and Transplantation Forum*. Vol. 15. No. 1. 2022.
[258]- Surma, Stanisław, Amirhossein Sahebkar, and Maciej Banach. "Coffee or tea: Anti-inflammatory properties in the context of atherosclerotic cardiovascular disease prevention." *Pharmacological Research* 187 (2023): 106596.
[259]- Ding, Ming, et al. "Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis." *Diabetes care* 37.2 (2014): 569-586.
[260]- Ding, Ming, et al. "Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis." *Diabetes care* 37.2 (2014): 569-586.
[261]- Surma, Stanisław, and Maciej Banach. "Coffee and caffeine consumption and overall mortality. Pleasure with restrictions-where do we really stand in 2022?." *Nutrition (Burbank, Los Angeles County, Calif.)* 102 (2022): 111747.
[262]- Sewter, Rebecca, Susan Heaney, and Amanda Patterson. "Coffee consumption and the progression of NAFLD: a systematic review." *Nutrients* 13.7 (2021): 2381.
[263]- Hayat, Umar, et al. "The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis of 11 epidemiological studies." *Annals of hepatology* 20 (2021): 100254.
[264]- Kositamongkol, Chayanis, et al. "Coffee consumption and non-alcoholic fatty liver disease: an umbrella review and a systematic review and meta-analysis." *Frontiers in pharmacology* 12 (2021): 786596.
[265]- Kennedy, O. J., et al. "Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis." *Alimentary pharmacology & therapeutics* 43.5 (2016): 562-574.
[266]- Poole, Robin, et al. "Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes." *bmj* 359 (2017).
[267]- Salehi, Bahare, et al. "Resveratrol: A double-edged sword in health benefits." *Biomedicines* 6.3 (2018): 91.
[268]- Zhang, Chongyang, et al. "Efficacy of resveratrol supplementation against non-alcoholic fatty liver disease: a meta-analysis of placebo-controlled clinical trials." *PLoS One* 11.8 (2016): e0161792.
[269]- Jakubczyk, Karolina, et al. "Effects of resveratrol supplementation in patients with non-alcoholic fatty liver disease—A meta-analysis." *Nutrients* 12.8 (2020): 2435.
[270]- Adamczak, Marcin, Stanisław Surma, and Andrzej Więcek. "Vitamin D and arterial hypertension: facts and myths." *Current Hypertension Reports* 22 (2020): 1-8.
[271]- de la Guía-Galipienso, Fernando, et al. "Vitamin D and cardiovascular health." *Clinical Nutrition* 40.5 (2021): 2946-2957.
[272]- Eliades, M., et al. "Meta-analysis: vitamin D and non-alcoholic fatty liver disease." *Alimentary pharmacology & therapeutics* 38.3 (2013): 246-254.
[273]- Sindhughosa, Dwijo Anargha, et al. "Additional treatment of vitamin D for improvement of insulin resistance in non-alcoholic fatty liver disease patients: a systematic review and meta-analysis." *Scientific Reports* 12.1 (2022): 7716.
[274]- Rezaei, Shahla, Maryam Gholamalizadeh, and Saeid Doaei. "The effects of vitamin D supplementation on anthropometric and biochemical indices in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis." *Frontiers in Pharmacology* 12 (2021): 732496.
[275]- Rizzo, Manfredi, et al. "Nutraceutical approaches to non-alcoholic fatty liver disease (NAFLD): A position paper from the

International Lipid Expert Panel (ILEP)." *Pharmacological research* 189 (2023): 106679.
[276]- Yan, Jian-Hui, et al. "Omega-3 polyunsaturated fatty acid supplementation and non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials." *Medicine* 97.37 (2018): e12271.
[277]- Moore, Ella, et al. "A systematic review and meta-analysis of randomized controlled trials to evaluate plant-based omega-3 polyunsaturated fatty acids in nonalcoholic fatty liver disease patient biomarkers and parameters." *Nutrition Reviews* (2023): nuad054.
[278]- Federico, Alessandro, Marcello Dallio, and Carmelina Loguercio. "Silymarin/silybin and chronic liver disease: a marriage of many years." *Molecules* 22.2 (2017): 191.
[279]- Kalopitas, Georgios, et al. "Impact of Silymarin in individuals with nonalcoholic fatty liver disease: A systematic review and meta-analysis." *Nutrition* 83 (2021): 111092.
[280]- Surma, Stanisław, et al. "Garlic for arterial hypertension and hypercholesterolaemia. Review of literature studies and clinical studies." *Folia Cardiologica* 16.5 (2021): 296-302.
[281]- Yu, Leilei, et al. "Effects of garlic supplementation on non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials." *Journal of Functional Foods* 99 (2022): 105294.
[282]- Rastkar, Mohsen, et al. "Systematic review and meta-analysis of the effect of garlic in patients with non-alcoholic fatty liver disease." *Indian Journal of Gastroenterology* 41.6 (2022): 548-557.
[283]- Wiering, Leke, and Frank Tacke. "Treating inflammation to combat non-alcoholic fatty liver disease." *Journal of Endocrinology* 256.1 (2023).