

Nonalcoholic fatty liver disease: pathogenesis, the role of TNF- α , IL-6 in hepatic inflammation and future potential nutraceutical treatment

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a pathological condition characterized by the accumulation of triglycerides (TGs) in the hepatocytes and has usually been associated with hyperlipidemia, obesity, and insulin resistance. Besides, it is a progressive condition that has become one of the most common liver disorder in developed countries and is usually accompanied by increased cardiovascular and liver disease mortality. NAFLD is a spectrum of liver disorders, progressing from simple steatosis to non-alcoholic steatohepatitis which is characterized by inflammation and hepatocellular injury then fibrosis which finally results in cirrhosis and even hepatocellular cancer. However, the molecular mechanism contributing to NAFLD progression is not fully understood. Its pathogenesis has usually been recognized by the "double-insult" hypothesis. The "first insult" includes accumulation of TGs in the hepatocyte, followed by a "second insult" where inflammatory mediators convince hepatocellular injury, inflammation, and fibrosis. In NAFLD, insulin resistance initiates the hepatic steatosis by different mechanisms. Furthermore, it was shown that NAFLD is associated with an inhibition of fatty acid oxidation in the mitochondria and an increase in the release of very-low-density lipoproteins. This review discusses the pathophysiology of NAFLD and the role of insulin resistance, obesity and inflammatory markers in the initiation of NAFLD. In addition to the different Therapeutic approaches for NAFLD.

Keywords: NAFLD; Interleukin-6; Tumor necrosis factor- α ; Oxidative stress; Cranberry nutraceutical

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1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a pathological accumulation of TGs in the hepatocyte without alcohol intake. Non-alcoholic fatty liver disease can evolve from TGs accumulation in the hepatocyte to non-alcoholic

steatohepatitis (NASH), which is defined as steatosis accompanied by an inflammatory infiltrate, progressing to fibrosis then cirrhosis [1]. And finally hepatocellular carcinoma [2].

2. NAFLD etiology and prevalence

Obesity is a worldwide pandemic [3] and is

recognized as a major health problem. Notably, obesity exacerbates numerous health problems including insulin resistance (IR) and cardiovascular disease [4]. Metabolic changes accompanied by obesity have been gathered to describe the metabolic syndrome which is the main cause of mortality and morbidity in industrial countries [5]. Metabolic syndrome is characterized by the grouping of different disorders including, increase blood pressure, IR and obesity [6]. The growing epidemic of metabolic syndrome has been accompanied by an elevation in liver alterations including NAFLD [7]. Specifically, it has been shown that NAFLD is the hepatic manifestation of metabolic syndrome [8]. Non-alcoholic fatty liver disease is found in 22-30% of populations worldwide. The prevalence of NAFLD in normal weights persons, without complaining from a metabolic disorder, is stated to be about 16% [9]. In contrast, the prevalence of NAFLD is higher among obese patients, as it elevated to 73% in obese persons and 85% in very obese persons [10, 11].

3. NAFLD Pathogenesis

Nonalcoholic fatty liver disease pathogenesis has recognized as a major health problem. Notably, obesity exacerbates numerous health problems including insulin resistance (IR) and cardiovascular disease [4]. Metabolic changes accompanied by obesity have been gathered to describe the metabolic syndrome which is the main cause of mortality and morbidity in industrial countries [5]. Metabolic syndrome is characterized by the grouping of different disorders including, increase blood pressure, IR and obesity [6]. The growing epidemic of metabolic syndrome has been accompanied by an elevation in liver alterations including NAFLD [7]. Specifically, it has been shown that NAFLD is the hepatic manifestation of metabolic syndrome [8]. Non-alcoholic fatty liver disease is

found in 22-30% of populations worldwide. The prevalence of NAFLD in normal weights persons, without complaining from a metabolic disorder, is stated to be about 16% [9]. In contrast, the prevalence of NAFLD is higher among obese patients, as it elevated to 73% in obese persons and 85% in very obese persons [10, 11].

4. NAFLD Pathogenesis

Nonalcoholic fatty liver disease pathogenesis has usually been interpreted by the "double-insult" hypothesis [12]. The "first insult" shows that the TGs were accumulated in the hepatocyte leading to steatosis which in turn, increases the susceptibility of the liver to the "second insult", where oxidative stress and pro-inflammatory mediators induce liver injury and fibrosis [13].

5. Peripheral lipolysis

Obesity is considered as one of the main features of metabolic syndrome, which is usually associated with increase the release of pro-inflammatory cytokines by visceral adipose tissue (VAT), such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), which allow the hepatic diacylglycerols (DAG) deposition and activation of different inflammatory pathways linked with IR [14, 15] as illustrated in **Fig. 1**.

Moreover, mitochondrial β -oxidation overload and/or excessive deposition of triglycerides (TGs) in hepatocytes lead to an increase in the lipid intermediate DAG in the liver. After that DAG activates protein kinase ϵ (PKC ϵ), which in turn inhibits insulin receptor phosphorylation and causes a defect in insulin signaling, leading to hepatic IR. These processes, in turn, play a vital role in the initiation of NAFLD [16].

6. Inflammation

Metabolic syndrome and NAFLD are usually associated with inflammation. Notably, different inflammatory markers, such as TNF- α , IL-6,

nuclear factor-kappa B (NF-κB) are increased in NAFLD [17]. While, the level of the protective anti-inflammatory adiponectin (ADP) is decreased [18, 19].

6.1. The role of tumor necrosis factor-alpha in NAFLD

It was shown that the inflammatory tumor necrosis factor-α has a vital role in the initiation of peripheral and hepatic IR which results in NAFLD. Notably, the VAT expansion stimulates

the release of TNF-α, which activates the downstream inflammatory signaling pathways, including inhibitor of kappa B kinase (IKK) and C-Jun-N-terminal kinase (JNK). This, in turn, recruits the downstream molecules, NF-κB and activator protein-1 (AP-1) respectively, which inhibit the insulin receptor substrate (IRS) phosphorylation, which in turn impairs insulin signaling and leads to peripheral IR [20] as illustrated in Fig. 2.

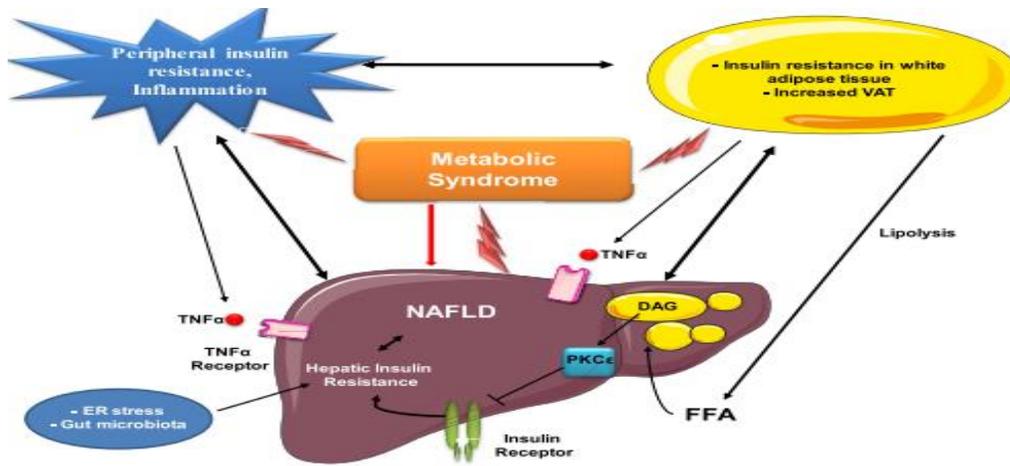


Fig. 1. Role of white adipose tissue and liver in the development of MetS and NAFLD [6]

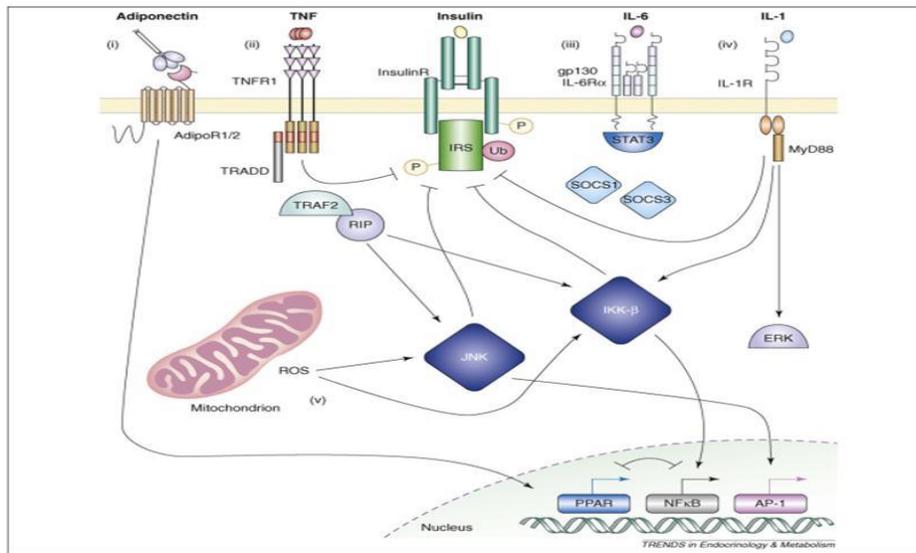


Fig. 2. Regulation of insulin resistance and involved pathways. Several inflammatory pathways involved in the regulation of IR have been identified [102]

Moreover, TNF- α decreases hepatocyte insulin sensitivity by reducing the expression of the insulin-dependent glucose transporter (GLUT-4) and by reducing the phosphorylation of IRS leading to hepatic IR [21]. Indeed, the accumulation of fat in the hepatocyte is modulated by several lipogenic and lipolytic genes. In particular, sterol regulatory element-binding protein-1c (SREBP-1c) and fatty acid synthase (FAS) has a major role in lipogenic

processes in the liver [22]. First of all, FAS is an important enzyme necessary for denovo-lipogenesis (DNL) of fatty acids, which is regulated in response to hormones [23, 24]. While, SREBP-1c is a transcription factor that plays an important role in maintaining lipid homeostasis and regulating gene expression related to fatty acid metabolism, including FAS [25, 26] as illustrated in Fig. 3.

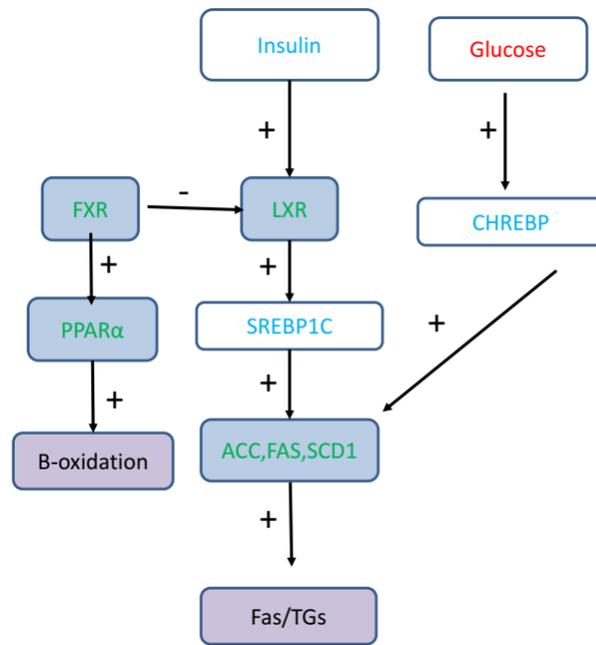


Fig. 3. Transcriptional control of lipogenesis and glycolysis [29]

It was shown that the increase in TNF receptor expression correlates the increases in the expression of SREBP1c, which induces hepatic lipogenesis. So TNF- α targeting NAFLD by impairing insulin sensitivity and also, by worsening the hepatic steatosis [27, 28].

The conversion of glucose into FA through DNL is nutritionally regulated by glucose and insulin signaling pathways, which induce the expression of glycolytic and lipogenic genes

synergistically in response to dietary carbohydrates. Insulin activates the transcription factor SREBP1c, which induces lipogenic enzymes (ACC1, FAS, SCD1), while glucose activates the transcription factor ChREBP, which induces both lipogenic (ACC1, FAS, SCD1) and glycolytic (G6PC, GCKR) enzymes. ChREBP is also a direct target of LXRs and modifies the ratio of MUFA/SFA in favor of MUFA by stimulating SCD1 activity. Recently, glucose was also identified as activating LXR's genes. Hepatic

FxR activation inhibits FA/TG synthesis by suppressing SREBP1c and LXR α activation and inducing the expression of PPAR α , which promotes mitochondrial oxidation of FAs. Abbreviations: ACC, acetyl-CoA carboxylase; ChREBP, carbohydrate-responsive element-binding protein; FA, fatty acid; FAS, fatty acid synthase; FFAs, free fatty acids; FxR, farnesoid X receptor; G6PC, glucose 6-phosphatase; GCKR, glucokinase regulatory protein; LXR, liver X receptor; MUFA, monosaturated fatty acids; PPAR α , peroxisomal proliferator-activated receptor alpha; SCD1, steroyl CoA desaturase 1; SFA, saturated fatty acids; SREBP1c, sterol regulatory element-binding protein 1c; TG, triglyceride

6.2. The role of Interleukin-6 in NAFLD

Interleukin-6 is an important inflammatory cytokine that regulates several biological processes including IR and inflammation [30] and for this reason, IL-6 is proposed as a potential mediator leading to NAFLD. Besides, hepatic IL-6 expression is also positively correlated with the severity of inflammation and fibrosis.

Also, IL-6 has been shown to activate the JNK signaling pathway, which in turn inhibits IRS phosphorylation and subsequently, the

development of hepatic IR [27]. Recently, IL-6 has been proposed to be a vital mediator in the activation of hepatic stellate cells (HSCs) and initiation of fibrosis. So, IL-6 plays a vital role in the pathogenesis of NAFLD by causing IR, inflammation and by increasing fibrosis [27, 31, 32].

7. Insulin resistance

Insulin is considered as a pleiotropic hormone that controls numerous cell functions, such as glucose transport stimulation, cell growth [33, 34]. It was shown that the failure of insulin to stimulate glucose transport into its target cells is termed IR, which plays an essential role in NAFLD [35, 36]. It was shown that any defects in insulin signaling pathways could lead to IR. Free fatty acids are recognized as an important risk factor contributing to the development of IR in several organs. Notably, hepatic IR correlates with increased accumulation of fat in the liver, the latter mainly initiating from peripheral lipolysis [37, 38]. Insulin resistance is a key factor in the initiation of steatosis. Insulin resistance induces both peripheral lipolysis and hyperinsulinemia. First of all, Peripheral lipolysis increases the serum level of FFAs and subsequently the uptake of these FFAs by the hepatocyte [1] as illustrated in Fig. 4.

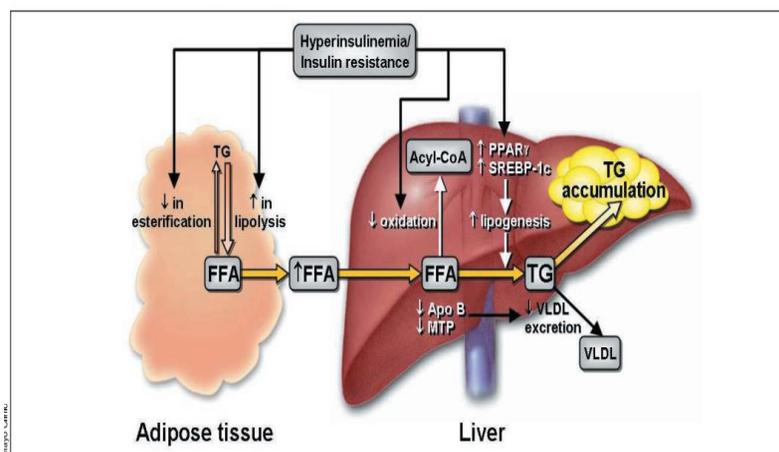


Fig. 4. Development of nonalcoholic hepatic steatosis [103]

Moreover, hyperinsulinemia increases the fat accumulation in the liver by inducing glycolysis and increasing the FFAs synthesis by DNL as illustrated in **Fig. 3**. On the other hand, hyperinsulinemia inhibits the mitochondrial β -oxidation of the fatty acids. Hyperinsulinemia also increases the accumulation of hepatic TGs by decreasing the re-esterification of the TGs and preventing them from leaving the hepatocyte and storing in the adipose tissue [39]. All-together, the accumulation of fats in the hepatocyte leads to NAFLD which finally leads to hepatic IR. So the possibility arises that the relationship between steatosis and IR is a vicious cycle in which systemic IR causes hepatic steatosis and hepatic steatosis exacerbate hepatic IR [40]. Therefore, IR is considered the missing link between metabolic syndrome and NAFLD, even in the absence of obesity [16]. An important transcriptional regulator of adipogenesis is peroxisome proliferator-activated receptor γ (PPAR γ), which has a vital role in the lipid storage process. On the contrary, PPAR α plays an important role in FFAs oxidation in the liver. Thus, PPAR α and PPAR γ have different functions in the regulation of fat metabolism [36, 41].

The protective effects of PPAR- γ are that it increases the level of ADP, which is a protein secreted from adipose tissue [42], causing an increase in the insulin sensitivity in adipose tissue and skeletal muscle leading to decrease in lipolysis rate and reduction in the deposition of the FFAs in the liver. Thus, ADP plays an important role in preventing liver steatosis. Moreover, ADP causes upregulation of PPAR α expression, which results in further FAs oxidation [29, 43]. It was shown that low levels of ADP play a vital role in the initiation of NAFLD by decreasing FAs oxidation in the liver. Besides, ADP decreases the DNL by decreasing the level of the enzymes involved in fatty acid

synthesis [44]. Furthermore, ADP has direct anti-inflammatory effects. These results collectively indicate that ADP might have hepatoprotective effects. The potential mechanism of protection includes the stimulation of hepatic fatty acid oxidation, the embarrassment of fatty acid synthesis, and the inhibition of TNF- α production in the liver. It was demonstrated that TNF- α and adiponectin suppress and antagonize each other's production and action in their target organs [45].

8. Oxidative stress

The antioxidant defense system in the liver maintains physiological levels of reactive oxygen species (ROS) and protects the cells from damage by ROS. It includes enzymatic components such as superoxide dismutase (SOD) and catalase (CAT), in addition to the non-enzymatic components including reduced glutathione (GSH) and vitamins C and E. Hereby, GSH-Px, SOD and CAT serve as the first line of defense opposing oxidative stress by converting superoxides and hydrogen peroxides to less toxic species [46-48]. Under normal physiological conditions, there is a balance between the rate of ROS generation and anti-oxidant but in NAFLD this balance is disturbed [49]. In NAFLD, once steatosis is established, the liver becomes susceptible to the "second hit", oxidative stress and multiple mechanisms contribute to lipid-induced cellular injury [50]. Oxidative stress is likely the cause of progression from steatosis to steatohepatitis. Mitochondria play an essential role in FFA oxidation. Increased mitochondrial β -oxidation of FFAs, as a result of an increase of peripheral lipolysis and excess FFAs accumulated in the liver, leads to mitochondrial defects and impairments of the respiratory chain. This produces ROS in the form of hydrogen peroxide and leads to extramitochondrial FFAs oxidation in the peroxisomes and microsomes, producing more ROS. The overall increase in oxidative stress leads to lipid peroxidation, DNA

and protein damage and finally cell death [39].

Moreover, lipid peroxidation increases the production of pro-inflammatory cytokines such as TNF- α , IL-6 and transforming growth factor- β (TGF- β) and recruits inflammatory cells into the liver. Activation of HSCs and inflammation result in collagen production and the initiation of fibrosis [50]. Nuclear factor erythroid-2-related factor-2 (Nrf-2) is considered a key transcription factor that combats cellular oxidative stress by up-regulation of antioxidant genes [51]. Also, it acts as a potent inhibitor of liver-x-receptor, which plays a crucial role in lipid hemostasis. Activation of this intracellular receptor stimulates a large number of transcription factors including SREPB-1c [52, 53]. Thereafter, this activated transcription factor translocates intra-nuclear to activate the DNA specific binding element that is responsible for increasing the expression of fatty acid synthase and acetyl-CoA carboxylase. Therefore, this DNL pathway can exaggerate the hepatic steatosis [54, 55]. On the other hand, Nrf-2 ameliorates hepatic steatosis induced by elevated SREBP and lipogenic gene expression [56-58]. Moreover, Nrf-2 has important anti-inflammatory and antifibrotic activity in response to oxidative stress and liver injury [59]. Collectively, Nrf-2 activation has a high potential role in inhibiting lipid-mediated oxidative stress and hepatic steatosis. Also, Nrf-2 attenuates inflammatory responses that occur with oxidative stress and tissue injury [51].

9. Fibrosis

The Increase of ROS generation induces lipid peroxidation which results in the activation and proliferation of HSCs [60] leading to fibrosis which is considered as one of the key features of fatty liver. The alpha isotype of smooth muscle actin (α -SMA) expressed by HSCs reflects their activation and has been directly related to liver fibrosis [60]. Moreover, activated HSCs are

responsible for TGF- β expression [61, 62]. Besides, the ongoing inflammation in the hepatocyte is associated with the production of TGF- β 1 [63, 64]. Also, activated HSCs are responsible for collagen production contributing to further liver damage and fibrosis [50].

10. Therapeutic approaches for NAFLD

10.1. Nonpharmacological therapy

The majority of NAFLD cases are associated with overweight so physical exercise and well balanced hypocaloric diet are recommended [65]. Up to the present time, there is no specific therapy for NAFLD either than the loss of body weight, increase physical activity and modification of the lifestyle, which still the most important and effective styles to recover from NAFLD [66, 67].

10.1.1. Weight loss

Inpatient with NAFLD, weight loss was accompanied by a significant improvement in all parameters of metabolic syndrome, liver function tests and steatosis [68-70], lobular inflammation, ballooning degeneration and fibrosis [71]. The improvement of liver function tests accompanied by weight loss was observed in 40% of overweight patients with NAFLD [72]. Moreover, weight loss is the only proven approach for pediatric NAFLD. However, weight loss should be gradual because too rapid weight loss may worsen of steatohepatitis [73].

10.1.2. Exercise

Exercise has been revealed to increase the oxidative capacity of the muscle cells and the consumption of FAs for oxidation [74]. It also decreases fatty acids and TGs accumulation in myocytes leading to improvement in insulin sensitivity. Moreover, the intensity of exercise is related to the improvement of insulin sensitivity [75].

10.2. Pharmacological approaches

Most of the current pharmacological approaches treating NAFLD aimed to inhibit fat absorption, inflammation, and insulin sensitivity [76].

10.2.1. Insulin sensitizers

10.2.1.1. Thiazolidinedione's (TZDs)

It is a class of insulin sensitizers that have been approved to increase both body and hepatic insulin sensitivity [77]. Thiazolidinedione's decrease FFAs leading to decrease FFAs delivery to the liver and improve liver steatosis. Moreover, TZDs increase the level of ADP [78] which increases the mitochondrial β -oxidation of the FFAs in the hepatocyte. In addition, TZDs have been approved to decrease the level of TNF- α [79] and C-reactive protein [80]. Besides, TZDs cause an improvement of liver functions in inpatient with NASH [81].

10.2.1.2. Metformin

The biguanide metformin is used widely in the management of diabetic patients worldwide, not only by reducing fasting hyperglycemia but also by increasing insulin sensitivity. Metformin reduces plasma glucose levels by reducing the liver production of glucose through activation of adenosine mono phosphate-kinase (AMP-kinase). The activation of AMP-kinase results in decrease lipid synthesis and increase fat oxidation [82] leading to a decrease of liver enzymes and improvement of the liver steatosis [83].

11. Statins

Reducing cholesterol and TGs is a logical approach when the diet fails, so statins are increasingly used in NAFLD. In addition to their ability to decrease serum levels of lipid, they can reduce the inflammatory cytokine TNF- α , thus

statins can ameliorate hepatic steatosis and further liver injury caused by inflammation [84].

12. Anti-inflammatory agents

12.1. L-Carnitine

It was shown that l-carnitine plays a vital role in controlling intracellular and metabolic functions, such as fatty acid transportation into the mitochondria, the reduction of serum lipid levels [85] and the modulation of the inflammatory response. It has been shown that L-carnitine improves insulin sensitivity and inflammatory biomarkers in patients with NASH. liver biopsies treated with l-carnitine showed a reduction in the NASH activity index and improvement in fibrosis scores. Thus, lifestyle changes in addition to l-carnitine could be considered as a positive treatment of NASH [86].

12.2. Adiponectin

It was approved that the administration of ADP produces positive effects on lipid metabolism, by improving lipid clearance from plasma and increasing the β -oxidation of the FFAs in muscles. In addition, ADP improves NAFLD by inhibiting glucose production through its direct action on hepatic tissue [87].

13. Anti-oxidant agents

Oxidative stress is considered an important mediator of hepatic injury and, based on the two-hit hypothesis, it is the main cause of worsening the NAFLD patient condition from the acute condition (steatosis) to NASH [88].

13.1. Anthocyanin

Anthocyanin-rich food improved hyperlipidemia, counteract oxidative stress and ameliorate liver steatosis in experimental NASH [86] Moreover, it improved IR and decreased plasma ALT in NAFLD patients [89]. These findings suggested several benefits of

anthocyanin supplementation in subjects with NAFLD, although further studies are needed [90].

13.2. Polyphenols

Polyphenols are members of a big family of plant-derived compounds [91, 92] classified as flavonoids and non-flavonoids. Polyphenols have an antioxidant effect. It reduces liver fat accumulation, mainly by inhibiting lipogenesis. Also, polyphenols have been proven to have a hepatoprotective effect as they increase FA oxidation, and decrease oxidative stress, IR and inflammation which are the main factors responsible for the progression of NASH [86]. Resveratrol improves insulin sensitivity and decreases plasma lipids, inflammation and oxidative stress [93]. Moreover, It reduces the level of ALT, steatosis and finally HOMA-IR in patients with NAFLD [94].

13.3. Cranberry nutraceutical as a future direction for NAFLD treatment

In 1989, nutraceutical was coined from pharmaceutical and nutrition by Stephen Defelice. According to him, a nutraceutical is considered as any substance that is a food or a part of the food and has medical or health benefits, including the treatment and prevention of disease. Since NAFLD is usually associated with inflammation, oxidative stress and IR, nutraceutical gain the attraction of the researchers as they could be potential therapies for NAFLD via improving insulin sensitivity which subsequently improves hepatic steatosis, oxidative stress, hepatic inflammation and finally hepatic fibrosis [86]. Interestingly, cranberry (*Vaccinium macrocarpon*) is an important nutraceutical source of phytochemicals, especially polyphenols [95], which has been approved to have an antioxidant effect [96]. In addition, cranberry showed anti-carcinogenic [97], anti-inflammatory [98], and anti-microbial

effects [99]. The intake of cranberry has been reported to ameliorate dyslipidemia, hyperglycemia as well as oxidative stress in individuals with MS [100]. Furthermore, cranberry administration significantly improved insulin sensitivity. Also, it was approved that Cranberry extract administration decreased diet-induced weight gain and visceral obesity. Also, it was shown that CE may have a hepatoprotective effect based on decrease hepatic and plasma TGs accumulation, blunted inflammation as well as reduced oxidative stress. Moreover, CE administration improved insulin sensitivity and decreased glucose-induced hyperinsulinemia during an oral glucose tolerance test [91, 101].

Conclusion

This review article highlights the main pathophysiological mechanisms of NAFLD focusing on the role of inflammatory markers, obesity, and IR in the initiation and progression of the disease in addition to the therapeutic approaches for the disease. Furthermore, this review highlighted the role of cranberry nutraceutical in the treatment of NAFLD as a future therapy. Further investigations recommended for differentiation the role of cranberry nutraceutical as a novel therapy for other organ toxicities.

Conflict of Interest

The authors declare no conflict of interest.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article in the

main manuscript.

Competing interests

The authors declare that no competing interests exist.

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