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Bioprotective Role of Phytocompounds Against the Pathogenesis of Non-alcoholic Fatty Liver Disease to Non-alcoholic Steatohepatitis: Unravelling Underlying Molecular Mechanisms

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Keywords
bioactive natural compounds, ethnomedicine, lipid metabolism, molecular targets, NAFLD, NASH

received December 22, 2023
accepted after revision March 7, 2024

Bibliography
Planta Med 2024
DOI 10.1055/a-2277-4805
ISSN 0032-0943

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD), with a global prevalence of 25%, continues to escalate, creating noteworthy concerns towards the global health burden. NAFLD causes triglycerides and free fatty acids to build up in the liver. The excessive fat build-up causes inflammation and damages the healthy hepatocytes, leading to non-alcoholic steatohepatitis (NASH). Dietary habits, obesity, insulin resistance, type 2 diabetes, and dyslipidemia influence NAFLD progression. The disease burden is complicated due to the paucity of therapeutic interventions. Obeticholic acid is the only approved therapeutic agent for NAFLD. With more scientific enterprise being directed towards the understanding of the underlying mechanisms of NAFLD, novel targets like lipid synthase, farnesoid X receptor signalling, peroxisome proliferator-activated receptors associated with inflammatory signalling, and hepatocellular injury have played a crucial role in the progression of NAFLD to NASH. Phytocompounds have shown promising results in modulating hepatic lipid metabolism and *de novo* lipogenesis, suggesting their possible role in managing NAFLD. This review discusses the ameliorative role of different classes of phytochemicals with molecular mechanisms in different cell lines and established animal models. These compounds may lead to the development of novel therapeutic strategies for NAFLD progression to NASH. This review also deliberates on phytomolecules undergoing clinical trials for effective management of NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD), a primary cause of cirrhosis and HCC, is a global concern for clinicians [1]. The Middle East has the greatest prevalence of NAFLD at 31.8%, followed by Europe at 23% and Africa at 13.5% [2, 3]. NAFLD is expected to become the largest cause of liver-related mortality and morbidity and a leading cause of hepatic transplantation within 20 years [4]. In non-alcoholics, NAFLD causes fat accumulation in liver [5]. Steatosis with or without moderate inflammation of the non-alcoholic fatty liver (NAFL) progresses to non-alcoholic steatohepatitis (NASH), leading to enhanced fibrosis progression [6]. Unlike other hepatic disorders, NAFLD is linked to metabolic syndromes [7].

Diabetes has assumed global proportions and affected 8.7% of adults worldwide in 2014 [8]. Type 2 diabetes mellitus (T2DM), cardiovascular disease, obesity, insulin resistance (IR), and hypothyroidism enhance the risk of cirrhosis and accompanying consequences (▶ **Fig. 1**). Reduced lipid oxidation and high FFAs cause IR and NAFLD. Dietary fat can cause hepatic steatosis (HS), which can worsen IR [9]. Another very interesting aspect of NAFLD, as pointed out by Tarantino et al., 2023, is the presence of sarcopenia in NAFLD patients, a pathological condition characterised by

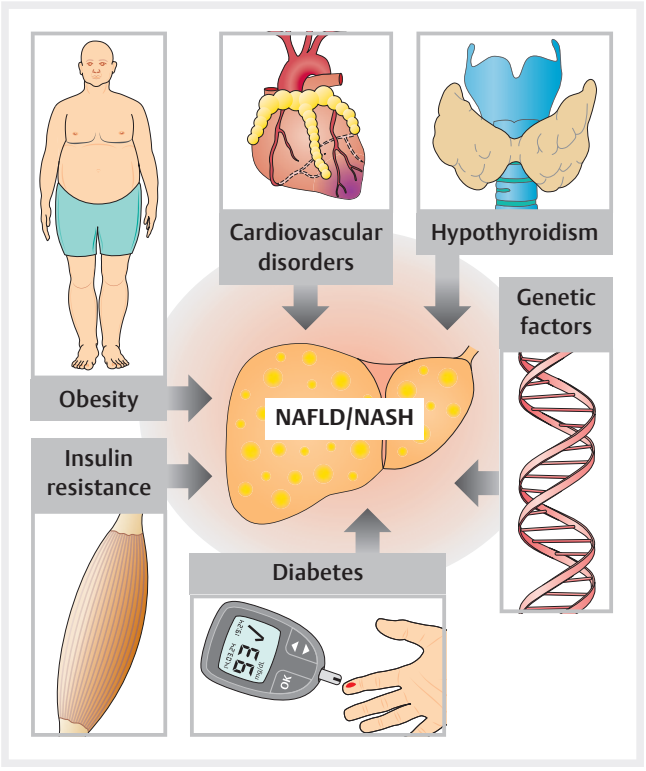
ABBREVIATIONS

ABCC2	ATP-binding cassette subfamily C member 2
ACADS	acyl-CoA dehydrogenases
ACC1	acetyl-CoA carboxylase 1
ACSL1	acyl CoA synthetase long-chain 1
AdipoR1	adiponectin receptor 1
AdipoR2	adiponectin receptor 2
ALK-1	anaplastic lymphoma kinase-1
ALK-5	anaplastic lymphoma kinase-5
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATF6	activating transcription factor 6
ATG5	autophagy related 5
ATG7	autophagy related 7
ATGL	adipose triglyceride lipase
ATP	Adenosine triphosphate
C/EBPα	CCAAT/enhancer binding protein α
CAV-1	caveolin-1
Co-SMAD	common-mediator SMAD 4 proteins
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CPT1A	carnitine palmitoyltransferase 1A
CPT2	carnitine palmitoyltransferase 2
CYP2E1	cytochrome p450 2E1
EIF2	eukaryotic initiation factor 2
ERR	estrogen-related receptor
ERRα	estrogen-related receptor α
FABP1	fatty acid-binding protein 1
FABP2	fatty acid-binding protein 2
FDFT1	farnesyl-diphosphate farnesyltransferase 1
FXR1	fragile X related 1
GLUT4	glucose transporter type 4
GPAT1	glycerol-3-phosphate acyltransferase 1
GRP78	glucose-regulated protein 78
HNF4-α	hepatocyte nuclear factor 4α
HSL	hormone-sensitive lipase
IFN-γ	interferon-γ
IL-10	interleukin-10
IL-18	interleukin-18
IL-1β	interleukin-1β
IL-6	interleukin-6
IRS-2	insulin receptor substrate 2
KEAP1	kelch-like ECH-associated protein 1
LC3-II	microtubule-associated protein light chain 3-II
LCAD	long-chain acyl-CoA dehydrogenase
LPL	lipoprotein lipase
MCAD	medium-chain acyl-CoA dehydrogenase
mRNA	messenger ribonucleic acid
mTORC1	mammalian target of rapamycin complex 1
NADPH	nicotinamide adenine dinucleotide phosphate
NR4A1	nuclear receptor 4A1
OA	oleic acid
PA	palmitic acid
PARP1	poly(ADP-ribose) polymerase 1
PCK1	phosphoenolpyruvate carboxykinase 1
PKB	protein kinase B
PPAR-α	peroxisome proliferator-activated receptor α
PPAR-δ	peroxisome proliferator-activated receptor δ
R-SMAD	receptor-activated SMAD
SCD1	stearoyl CoA desaturase 1
SMAD 2	suppressor of mothers against decapentaplegic homolog 2
SMAD 3	suppressor of mothers against decapentaplegic homolog 3
SREBF1	sterol regulatory element binding transcription factor 1
SREBP-2	sterol regulatory element-binding protein-2
SULT2A1	sulfotransferase 2A1
TAZ	transcriptional coactivator with PDZ-binding motif
TBXA2R	thromboxane A2 receptor
TIMP-1	tissue inhibitor of metalloproteinase-1
TIMP-2	tissue inhibitor of metalloproteinase-2
TNFR2	tumour necrosis factor receptor 2
UCP1	uncoupling protein 1
UCP2	uncoupling protein 2
VCAM-1	vascular cell adhesion molecule 1
VLDL	very-low-density lipoprotein
XBP-1	x-box binding protein 1
ZO-1	zonula occludens-1

loss of skeletal muscle and strength [10]. Oxidative stress–a disparity between ROS generation and antioxidant responses–is another important factor in NAFLD pathophysiology associated with inflammation and FFA lipotoxicity, as depicted in ▶ **Fig. 1** [11]. There are many co-morbidities linked to NAFLD that share the main mechanism of low-grade chronic inflammation, with the involvement of the immune system (primarily overexpression of cytokines) partly mediated by the spleen [12].

Pioglitazone, a thiazolidinedione derivative and PPAR-γ agonist, improves glucose and lipid metabolism in T2DM by reducing IR but has not received USFDA approval for the management of NAFLD [13, 14]. Obeticholic acid (OCA), a selective agonist of farnesoid X receptors (FXR), has been approved by the FDA to manage NAFLD [15]. Natural compound research has increased over the past decade, providing new insights into mechanisms involved in controlling dyslipidemia, improving liver function in NAFLD. Products of natural origin have been found to retard the progression towards NASH by their modulatory actions on inflammatory and fibrotic pathways. This review deliberates on the mechanism of many potent lead molecules with potential in the management of NAFLD and NASH. Certain lead molecules with noteworthy activity in clinical trials have also been discussed.

The novelty of this review lies in the fact that, to date, there have been no correlation studies of phytoconstituents with clinical and preclinical outcomes explicitly pointing to phytomarkers [16]. The preclinical and clinical studies of phytoconstituents ameliorating NAFLD and its progression have been reported separately without any correlation [11], whereas this review aims to explore



▶ **Fig. 1** Common risk factors associated with NAFLD.

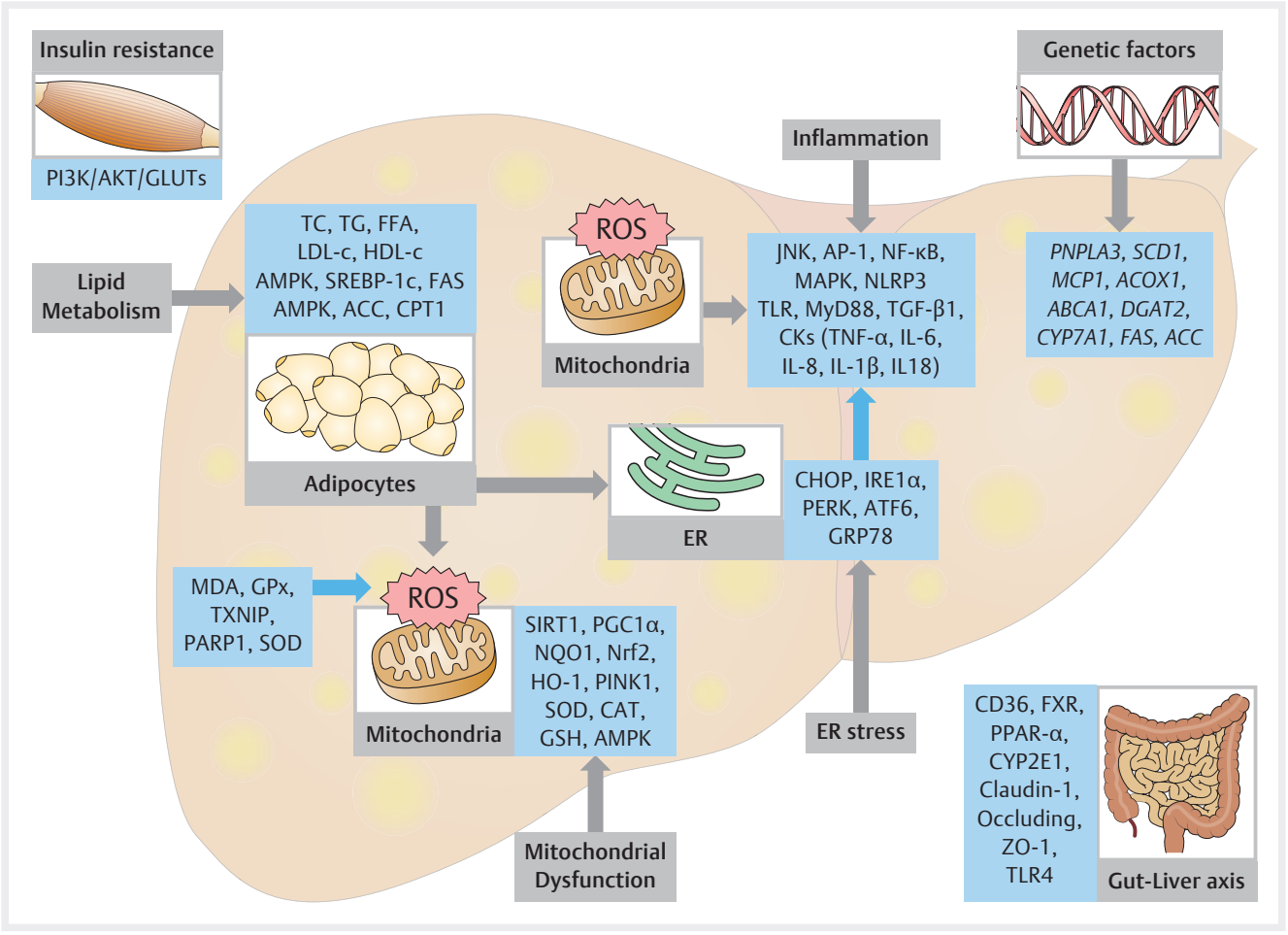
the mechanistic aspects of the lead phytotherapeutic molecules and map the mechanisms involved with the preclinical and clinical outcomes.

Pathophysiology of NAFLD Progressing to NASH

NAFLD is a medical disorder distinguished by the excessive build-up of adipose tissue inside the liver of individuals who exhibit little or no alcohol use. NAFLD is a prevalent hepatic illness on a global scale, exhibiting a range of severity levels from steatosis (simple fatty liver) to NASH, a more serious manifestation characterised by liver inflammation and damage. In the pathogenesis of NAFLD and the subsequent development of NASH, hepatic lipid build-up and inflammation play a pivotal role, as illustrated in ▶ **Fig. 2** [4]. The progression of NAFLD may be categorised into two distinct stages: non-alcoholic fatty liver (NAFL) and NASH. Nevertheless, NASH is characterised by not only the build-up of fat but also the presence of inflammation and damage to liver cells. Inflammation has a significant role in differentiating NASH from simple hepatic steatosis [1]. The immunological response is initiated in NASH due to the buildup of lipids inside hepatocytes. The precise processes behind this phenomenon remain incompletely elucidated; nevertheless, it is postulated that lipids originating from adipose tissue, together with cellular stress and injury, contribute to the attraction of immune cells, including macrophages, to the hepatic region. The immune cells secrete pro-inflammatory cytokines, including TNF-α and interleukins, which contribute to the amplification of the inflammatory response [17]. Hepatocellular death is a prominent indicator of NASH, as shown by the presence of enlarged hepatocytes seen during histological analysis of the liver. The condition is initiated by certain external and internal cellular stressors, such as the build-up of lipids in hepatocytes, leading to the occurrence of lipotoxicity. The phenomenon of lipotoxicity induces cellular apoptosis via the initiation of many intracellular processes, including endoplasmic reticulum stress and inflammation. Hepatocellular deaths are categorised into many routes, including apoptosis, necroptosis, and pyroptosis, based on their diverse underlying processes, which are characterised by specific morphological and molecular signs. Both the apoptosis and necroptosis signalling pathways are shown to be active in NASH, perhaps in a TNF-α-dependent manner. This is supported by the observed elevation in TNF-α levels, as well as the increased expression of its downstream effectors in the liver [18].

The occurrence of inflammation in NAFLD is initiated by the deposition of lipids inside hepatocytes, which then elicits an immune response. In response to hepatic inflammation, macrophages are attracted to the liver. Kupffer cells, which are specialised macrophages, reside in the liver. Macrophages serve as the primary barrier against invading microorganisms that gain access to the circulation through the portal vein, establishing a connection between the gastrointestinal tract and the liver. In the context of NAFLD and NASH, the activation of Kupffer cells occurs as a result of the presence of fatty acids and other inflammatory signals, hence playing a role in the promotion of hepatic inflammation [19]. The process of phagocytosis, facilitated by macrophages in the liver, aids in the removal of deceased or impaired liver cells. The liver cell death is heightened as a result of many variables, including oxidative stress and inflammation. Macrophages are recruited to eliminate these deceased cells; nevertheless, an excessive occurrence of cell death and subsequent macrophage activation might potentially exacerbate inflammation and fibrosis [20]. Fibrosis refers to the pathological process characterised by the accumulation of excessive scar tissue in the liver. This condition is primarily driven by the persistent activation of macrophages and the resulting inflammation. Notably, the activation of hepatic stellate cells assumes a pivotal role in the progression of liver fibrosis. Macrophages secrete several substances that induce hepatic stellate cells to synthesise collagen, so initiating the process of fibrosis, which is a characteristic feature of the course of NASH [21]. The role of oxidative stress in the pathogenesis and advancement of NAFLD is of considerable importance. Oxidative stress arises from a disparity between the generation of reactive oxygen species (ROS), often referred to as free radicals, and the organism's capacity to counteract their effects via the utilisation of antioxidants [22].

Lipid peroxidation is a process that may occur in NAFLD wherein an excessive build-up of lipids in hepatocytes can result in the peroxidation of these lipids. The aforementioned process encompasses the oxidative destruction of lipids, resulting in the production of very reactive compounds and free radicals. Reactive species can inflict harm against biological structures, including proteins, lipids, and DNA [23]. The impairment of mitochondrial activity, which is responsible for energy production inside hepato-



▶ **Fig. 2** Pathophysiology of NAFLD progressing to NASH.

cytes, may be caused by oxidative stress. The impairment of mitochondrial activity might result in an increased generation of ROS, initiating a cascade of oxidative stress that detrimentally affects hepatocytes and further aggravates the underlying pathology [24]. The liver may initiate an inflammatory response when exposed to oxidative stress. ROS have the capability to initiate inflammatory signalling pathways and facilitate the attraction of immune cells, namely macrophages, to the liver. Consequently, the presence of inflammation may exacerbate the levels of oxidative stress, establishing a self-sustaining feedback loop [25]. Transforming growth factor-beta (TGF-β) is a cytokine that assumes a pivotal role in the processes of tissue healing and fibrosis. In the setting of NAFLD, specifically NASH, it is widely postulated that TGF-β plays a significant role in the pathogenesis of liver fibrosis. The activation of hepatic stellate cells, which are involved in collagen production and the promotion of liver fibrosis, is stimulated. In the context of liver inflammation, it is noteworthy that TGF-β has immunosuppressive characteristics and has the ability to regulate the inflammatory reaction. In the context of NAFLD, inflammation plays a pivotal role, particularly during the progression from simple steatosis to NASH. TGF-β potentially plays a crucial role in the modulation of the equilibrium between pro-inflammatory and anti-inflammatory mechanisms [26].

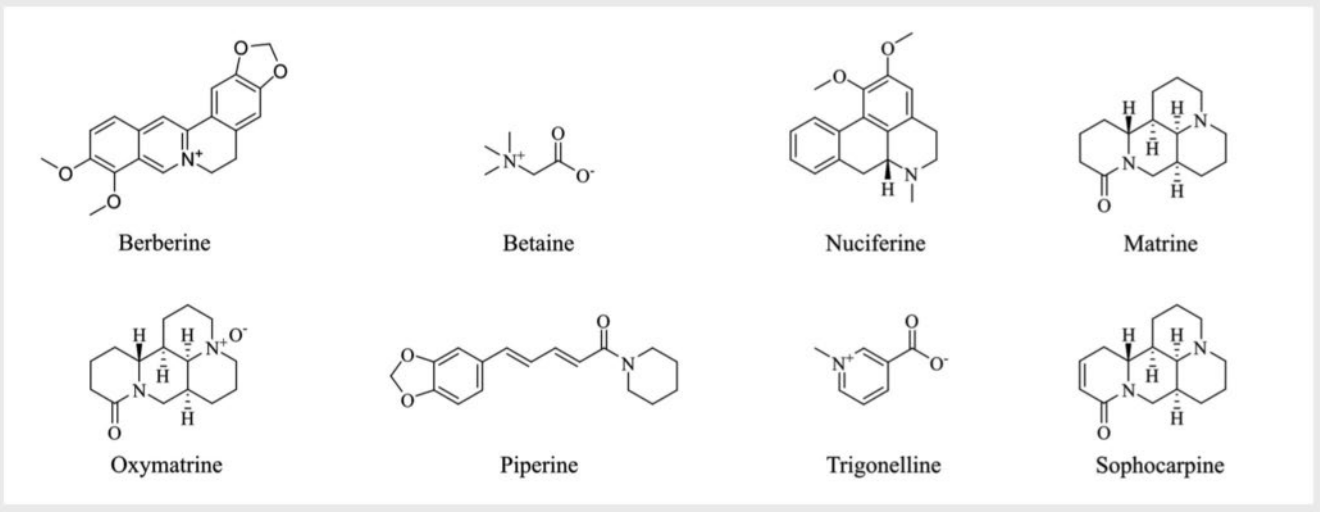
Satellite cells are a kind of stem cell found in skeletal muscle tissue. Satellite cells are a distinct population of stem cells that are specifically localised inside the skeletal muscle tissue. Skeletal muscle satellite cells are essential to the process of muscle repair and regeneration, particularly in response to instances of injury or physiological stress. Satellite cells are predominantly seen in muscle tissue, but their presence in the liver is often absent. The relationship between satellite cells and muscle tissue is of primary importance when examining the larger implications of physical exercise in the setting of NAFLD. Physical activity, including weight training and aerobic exercise, has been shown to have a beneficial influence on NAFLD. Engaging in regular physical exercise has been shown to enhance insulin sensitivity, diminish inflammation, and foster comprehensive metabolic well-being. These beneficial effects may contribute to the prevention and management of NAFLD [27]. Excessive caloric intake, especially from carbohydrates, is recognised as one of the main contributing factors to *de novo* lipogenesis (DNL) in NAFLD. When humans ingest excessive calories, particularly in the form of carbs such as sugars and starches, the surplus energy undergoes DNL in the liv-

er, resulting in the conversion of the extra energy into triglycerides (TG) [28]. IR is a prevalent metabolic anomaly seen in individuals with NAFLD. IR is characterised by a diminished responsiveness of the body's cells, particularly hepatocytes, to the physiological actions of insulin. Insulin plays a pivotal role in the regulation of glucose metabolism and acts as an inhibitor of DNL. Nevertheless, in individuals with IR, the liver exhibits reduced sensitivity to the suppressive impact of insulin on DNL, resulting in heightened lipid synthesis [29]. Increased intake of dietary carbohydrates, i.e., fructose, may lead to DNL. The metabolism of fructose occurs mostly in the liver, where it undergoes conversion into glucose and fatty acids, hence facilitating the process of lipid production. The liver can produce additional fatty acids from acetyl-CoA thanks to DNL. First, acetyl-CoA carboxylase (ACC) converts acetyl-CoA to malonyl-CoA, which fatty acid synthase (FAS) subsequently converts to palmitate. Following a variety of desaturation, elongation, and esterification processes, the newly formed fatty acid may either be evacuated as VLDL particles or retained as TG. As a result, elevated DNL may result in hypertriglyceridemia, hepatic steatosis, and/or steatohepatitis because saturated fatty acids, such as palmitate, can trigger apoptosis and inflammation. Research indicated that unusually increased DNL, independent of fasting, is a key feature of NAFLD patients [30].

Certain individuals may possess genetic predispositions that render them more susceptible to DNL. The development of NASH requires the presence of patatin-like phospholipase 3 (PNPLA3), a protein that facilitates the production of lipids. There exists a strong correlation between the severity of NAFLD and the presence of polymorphisms in the *PNPLA3* gene. The *PNPLA3* gene exhibits interaction with SREBP-1c, hence facilitating the promotion of gene expression [31]. An increase in the activity of AMPK leads to a decrease in DNL and an enhancement of fatty acid oxidation (FAO), which hinders the pathogenesis of NAFLD via the phosphorylation of ACC. The activation of malonyl-CoA decarboxylase occurs subsequent to phosphorylation by AMPK, resulting in a decrease in malonyl-CoA levels and a concomitant reduction in the synthesis of FFAs. In the context of gene regulation, it has been shown that the genes *FAS, ACC1*, and *SCD1* are known to be targeted by SREBP-1c. Notably, these genes have been found to be substantially inhibited by AMPK. This facilitates the promotion of the FAO and significantly adds to the regulation of lipogenesis balance [32]. In addition, it is essential to note that AMPK plays a crucial role in the maintenance of the mitochondrial matrix via the upregulation of carnitine palmitoyltransferase 1 (CPT1) in adipose tissue and hepatocytes. The AMPK functions by stimulating catabolic processes that generate ATP and suppressing ATP-utilising pathways to restore energy homeostasis. The efficiency of hepatic fat synthesis and storage may be influenced by genetic differences in enzymes associated with lipid metabolism [33]. Hormonal imbalances, characterised by elevated levels of hormones such as leptin and adiponectin, have the potential to disrupt lipid metabolism and have a role in DNL in NAFLD. The dietary choices made by individuals may have an impact on DNL since the specific kinds of lipids and carbs ingested play a significant role in this process. Diets that are rich in carbohydrates, particularly fructose, and saturated fats have a higher propensity to stimulate DNL and facilitate the storage of fat in the liver [34].

Hepatocyte ballooning is well recognised as a prominent and distinctive hallmark of NASH. Ballooning has been shown to be correlated with an increased risk for the development of NASH and fibrosis. Ballooned hepatocytes, while potentially progressing towards cell death and exhibiting increased susceptibility to apoptosis, are widely recognised as wounded but viable hepatocytes. Consequently, they have been referred to as "undead" hepatocytes. The hepatocytes that have undergone ballooning release sonic hedgehog (SHH), a protein that stimulates the activation of hepatic stellate cells (HSCs). However, it is probable that these hepatocytes also release other ligands that cause fibrosis. However, it is worth considering the possibility that ballooned "undead" hepatocytes may serve as an indicator of hepatocyte stress, suggesting that the progression of fibrosis in NASH can occur without hepatocytes reaching a state of ballooning or death [35]. The process of activating HSCs is crucial in the progression of fibrosis, since these cells are particular to the liver and have a pivotal role in this pathological condition. Upon receiving inflammatory signals and several other stimuli, dormant hematopoietic stem cells undergo activation and undergo a phenotypic transformation into cells resembling myofibroblasts. These activated cells then proceed to generate collagen and other constituents of the fibrous tissue. Cytokines and growth factors, including inflammatory cytokines (e.g., TNF-α and IL-6) and TGF-β, have been implicated in the promotion of fibrosis. These chemokines have a role in the activation of fibrogenic cells and promote the deposition of extracellular matrix components, leading to the formation of scar tissue [36]. The normal function of insulin involves its role as a hormone synthesised by the pancreas, which is crucial in the regulation of glucose levels in the bloodstream. The major role of this mechanism is to enhance the cellular absorption of glucose, with a particular emphasis on muscle and adipose cells, to support energy production. Additionally, it hinders the hepatic release of glucose. IR may be described as a physiological condition whereby the responsiveness of the body's cells, particularly those found in muscle, adipose tissue, and the liver, to the actions of insulin is diminished. Consequently, the impaired ability of cells to uptake glucose from the circulation and the ongoing hepatic glucose production contribute to the observed elevation in blood glucose levels [37].

Insulin plays a significant part in the metabolism of lipids, or fats. This process aids in the prevention of fat degradation inside adipocytes while also facilitating fat accumulation. IR gives rise to a compromised capacity of the body to control fat metabolism, resulting in heightened lipolysis (the breakdown of fat) and an elevation in circulating FFAs. These FFAs in the liver may be esterified to create TG as lipid droplets in hepatocytes, or they can be oxidised by β-oxidation in mitochondria to generate ATP or ketone bodies. Alternatively, they can be discharged into the bloodstream as very low-density lipoprotein (VLDL). Hepatic IR and lipid levels rise as a result of inadequate lipid oxidation. There is also a definite correlation between the quantity of visceral fat and hepatic IR. Different lipid intermediates, including ceramides and DAG, build up in cells of fatty livers and induce IR. Increased hepatic DAG concentration, which stimulates PKCε activity, might be a contributory factor of NAFLD-related hepatic IR. PKCε stimulation mediated by hepatic DAG is linked to the pathophysiology



▶ **Fig. 3** Alkaloids involved in the management of NAFLD [berberine (I), betaine (II), nuciferine (III), matrine (IV), oxymatrine (V), piperine (VI), trigonelline (VII), and sophocarpine (VIII)].

of hepatic IR linked to NAFLD. PKC activation caused by intracellular DAG closer to the cell membrane suppresses insulin receptor kinase, tyrosine phosphorylation of IRS-1 and −2 downstream, and phosphorylation of inositol 3-kinase (PI3K), all of which contribute to decreased insulin signalling. In the end, this results in decreased hepatic glycogen synthesis because glycogen synthase is not as activated and in enhanced hepatic gluconeogenesis because forkhead box protein O1 (FOXO1) is less inactivated. This causes an excessive amount of glucose to be released via glucose transporter 2 (GLUT2). Elevated generation and release of hepatocellular ceramide may promote hepatic IR in NAFLD. Ceramide plays a significant role in IR. For example, the reduction in ceramide synthesis decreases hepatic steatosis and fibrosis in NAFLD [38]. The intricacy of NAFLD therapy is reflected in its pathophysiology since effective treatment of NAFLD patients necessitates an integrated, multi-systemic approach. Referrals to liver disease may be made at any point, although they are most common when fibrosis is diagnosed. Since there are not many already authorised medicines, the field of treatment possibilities is ready for innovation. Although weight reduction might cause NASH and fibrosis to decline. NAFLD patients may benefit from various pharmacological therapies available as discussed later.

Natural Compounds from the Phytochemical Class Impeding NAFLD

Secondary metabolites such alkaloids, flavonoids, glycosides, terpenoids, and tannins have previously shown anti-microbial [39], anti-hyperglycemic, and anti-cancer properties [40,41]. There is an unmet, compelling need by physicians to use natural products to alleviate NAFLD, due to their large availability coupled with safety and low cost [42]. As shown in this section, several natural phytoconstituents that target lipid metabolism have demonstrated their effectiveness in treating fatty liver and can be used as therapies and natural remedies. This study describes the most current developments of isolated natural compounds and their chemotherapeutic characteristics in the prevention of NAFLD. The literature surveys for this review were performed using Scopus, PubMed, Web of Science, and Google Scholar. All the scientific data were collected from the years 2003 to 2023. The literature search was carried out using the following keywords: NAFLD, NASH, steatohepatitis, ethnomedicine for NAFLD, lipid metabolism, molecular targets for NAFLD & NASH, and novel phytocompound leads for NAFLD & NASH.

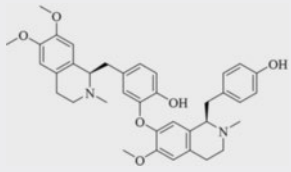
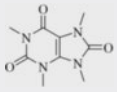
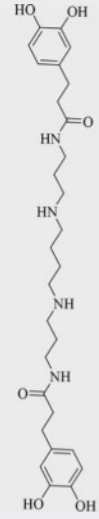
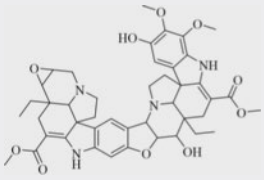
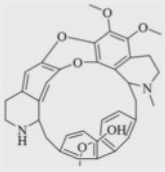
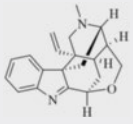
Alkaloids

Alkaloids are naturally occurring, alkaline, nitrogenous organic substances found in plants. Most alkaloids have complex cyclic structures and significant effects on lipid metabolism. The significant molecular target of alkaloids is AMPK, which increases the expression of PPAR-α and CPT1 and reduces the levels of SREBP-1c, ACC, PPAR-γ, and C/EBPα. Therefore, the availability of lipids like fatty acids might be restricted because natural substances in this class can boost lipid catabolic metabolism and hinder anabolic metabolism [43]. Some crucial alkaloids that have shown effect against NAFLD are briefly discussed below and depicted in ▶ **Fig. 3** and **Table 1**.

Berberine

From *Coptis chinensis* and *Phellodendron chinense*, berberine (BRB), an isoquinoline alkaloid, is isolated [44,45]. In HepG2 and 3 T3-L1 cells, BRB is said to activate AMPK, increasing FAO and decreasing lipid synthesis [46,47]. Turning on the sirtuin1 (SIRT1), forkhead box protein O1 (FOXO1) and SREBP-2 signalling pathways, BRB could prevent HepG2 cells from developing steatosis by FFA [48]. Furthermore, BRB lowered serum TG in rats fed a high-fat diet (HFD) and improved HS in mice with diet-induced obesity. Moreover, it reduced the phosphorylation of protein kinase C (PKC) on

▶ **Table 1** Structure of alkaloids targeting biomarkers involved in NAFLD.

Compound name with structure	Biological source	Research model	Biomarkers	Ref.
 Liensinine	*Nelumbo nucifera* Gaertn	*In vitro* PA-induced L02 and AML12 cells; *in vivo* HFD-fed mice	Downregulated NF-κB, TAK1, ROS, ACC, PPAR-γ, FAS, and KEAP1; upregulated AMPK, Nrf2, PPAR-α, CPT1A, and UCP2	[210]
 Theacrine	Camellia assamica var. kucha	*In vitro* OA-induced HepG2 and L02 cells; *in vivo* HFD-fed ApoE$^{-/-}$ and C57BL/6 J mice	Downregulated SREBF1, FAS, IL-1β, and IL-6; upregulated LCAD, and SIRT3	[211]
 Kukoamine A	*Lycium chinense* (*L. chinense*) Miller	*In vitro* PA-induced AML-12 cells; *in vivo* HFD-fed mice	Downregulated SREBP-1c, FAS, ACC1, TNF-α, IL-1β, and IL-6	[212]
 Conophylline	Tabernaemontana divaricate	*In vivo* HFD-fed BALB/c mice	Downregulated p62, TLR4, TGF-β, and TIMP-1; upregulated PPAR-α, CPT1, CPT2, LC3-II, and ACOX1	[213]
 Tiliamosine	*Tiliacora racemose*	*In vitro* PO-BSA- induced HepG2 cells; *in vivo* HFD N-Nitrosodiethylamine-induced rats	Downregulated TNF-α; upregulated FXR expression	[214]
 Koumine	*Gelsemium elegans*	*In vivo* HFD-fed rats	Downregulated IFN-γ, IL-6, IL-1β, IL-17A, and TNF-α; upregulated IL-10	[215]

Tyr311 and boosted the ATP-binding cassette transporter A1 (ABCA1), which regulated hepatic cholesterol and phospholipid transport [49]. Additionally, clinical studies supported the idea that BRB significantly reduced the amount of hepatic fat, specifically by inducing ceramide levels to decrease in NAFLD patients [50]. Overall, BRB therapy might be a natural alternative for treating NAFLD since it can increase FAO and decrease lipid build-up.

Betaine

Betaine (BET), a methyl derivative of glycine, is present in a wide range of foods, including spinach, mussels, wheat bread, and beets. It is also present in plants, animals, and microbes. According to reports, BET protects individuals against several metabolic diseases [51, 52]. For example, BET significantly reduced the severity of HS in C57BL/6 J mice by upregulating AMPK and downregulating SREBP-1c [53]. BET also lowered HS in HepG2 cells by preventing FOXO1/PPAR-α activation and reduced the effects of adenovirus-mediated FOXO1 overexpression, which noticeably elevated the mRNA expression levels of *PPAR-γ* and its target genes, including *FAS* and *ACC* [54]. Additionally, BET minimised methylation of the PPAR-γ promoter and increased PPAR-α expression, which brought down hepatic lipid build-up [55]. Similar outcomes were observed in rats with HFD, where BET increased hepatic lipid export and FAO by raising the expression of the *PPAR-α* and *CPT1* genes [56]. To slow the course of metabolic illnesses, BET seems to influence various metabolic processes, including lipid absorption, transportation, and FAO.

Nuciferine

The leaves of *Nelumbo nucifera* Gaertn are the prime source of nuciferine (NUF), an active aporphine alkaloid [57, 58]. In 3 T3-L1 adipocytes, NUF has drastically lowered intracellular TG levels and improved lipid metabolism. AMPK phosphorylation and activation mediated by NUF may be the cause of the pathways [59]. In mice with diet-induced HS, NUF may aid in hepatic lipid metabolism via activating the PPAR-α/PGC1α pathway [60]. Similarly, NUF protects golden hamsters on HFD from developing HS. Supplementing with this substance dramatically reduced blood and hepatic lipid levels and boosted PPAR-α and CPT1 expression levels, leading to more FAO. Additionally, NUF therapy significantly reduced the HFD-induced rise in SREBP-1c and FAS protein levels in the liver, indicating that NUF might delay the onset of HFD-induced HS [61].

Matrine

Matrine (MAT) is a tetracyclic quinoline alkaloid identified in the dried roots of *Sophora flavescens*. It reduces blood lipid levels and has anti-inflammatory, anti-fibrosis, and anti-cancer properties [62, 63]. In China, MAT has been used as a liver-protective drug, primarily for the treatment of liver tumours and viral hepatitis [64]. By triggering the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway, the researchers demonstrated that MAT had a protective impact against NAFLD and reduced HS. In addition to facilitating Nrf2 translocation to the nucleus, MAT may enhance the synthesis of the antioxidant enzyme protein [65]. In mice fed an HFD, MAT has been shown to reduce HS, hepatic lipid synthesis, plasma insulin levels, and liver TG content. The activation of heat shock protein 72 (HSP72), which prevents cellular stress in the liver, was surprisingly credited with the protective effect [66]. More significantly, researchers verified that the anti-NASH activity of MAT was connected to the overexpression of HSP72 and the downregulation of the mammalian target of rapamycin (mTOR) [67].

Oxymatrine

A bioactive alkaloid derived from the Sophora (Kushen) plant called oxymatrine (OXM) has a variety of pharmacological properties, which include anti-pathogen, anti-inflammation, anti-hepatitis B virus infection, and immunological modulation [68]. Recently, it was shown that OXM and lipid metabolism are closely related. Rats consuming OXM have reduced liver and serum TG and total cholesterol (TC) levels. In addition, PPAR-α, CPT1A, and microsomal TG transfer protein (MTTP), which is in charge of VLDL assembly and hepatic outflow, were all significantly upregulated by OXM [69]. It was also discovered that OXM might lessen HS and liver lipid build-up in rats with NAFLD. Increased expression of genes including *PPAR-α, CPT1A*, and acyl-CoA oxidase 1 (*ACOX1*) involved in FAO is thought to be the causative factor, as well as decreased expression of genes involved in DNL, including *SREBF1, ACC*, and *FAS* [70]. Thus, OXM should successfully treat NAFLD by focusing on mechanisms involved in lipoprotein transportation and lipogenic synthesis.

Piperine

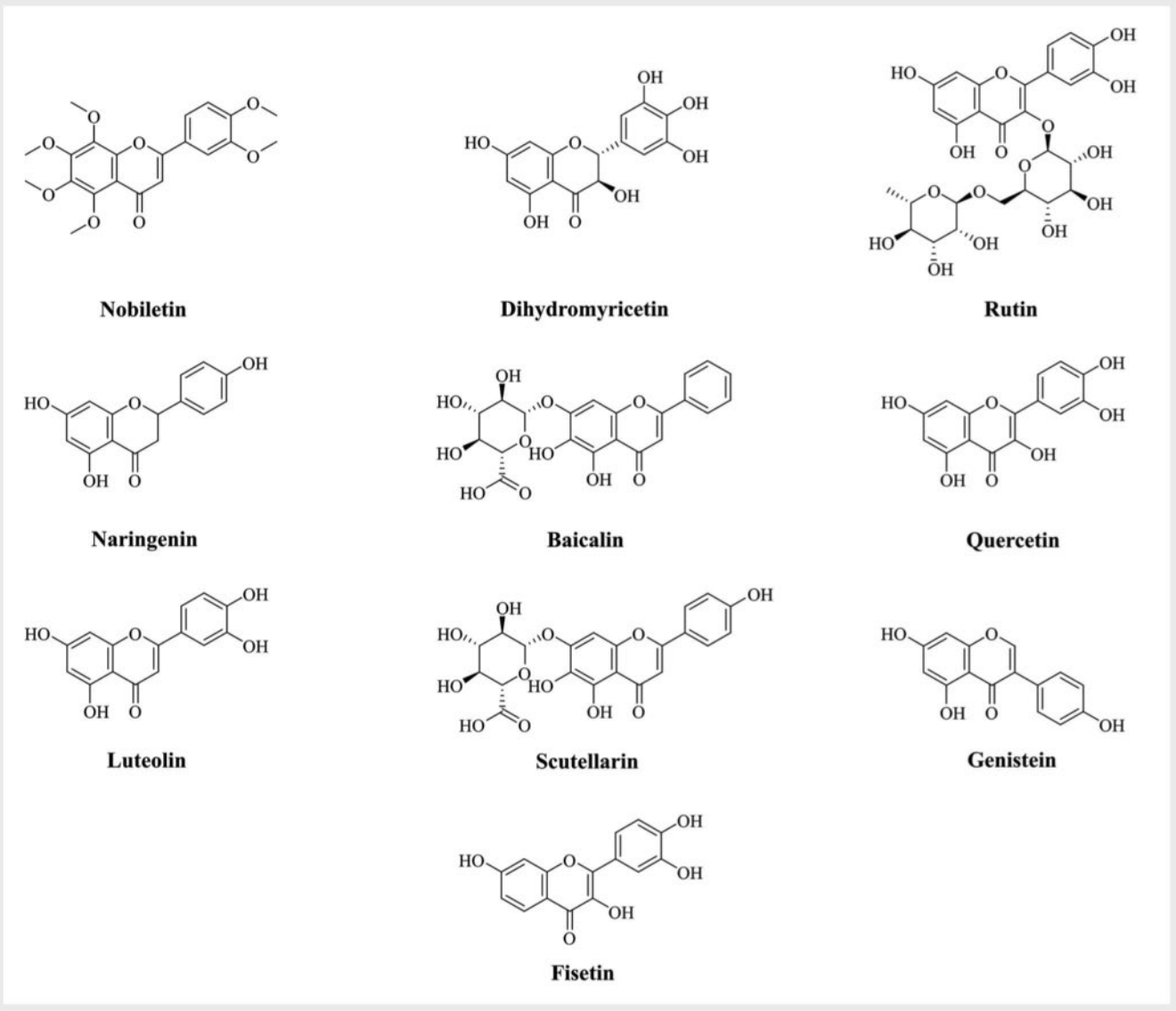
Piperine (PIP), a phytoconstituent present in black pepper, has anti-inflammatory, antioxidant, and anti-cancer activities [71]. The adipocyte differentiation and adipogenesis of 3 T3-L1 cells are significantly inhibited by PIP. The underlying molecular mechanism of PIP was revealed to be the inhibition of PPAR-γ expression and activity, as well as the downregulation of adipogenic transcription factors, such as SREBP-1c and C/EBP. Thus, the treatment of disorders linked to fat might benefit from using PIP [72]. Additionally, PIP might boost lipid catabolism by activating AMPK and PPAR-δ, and it can also prevent the onset of NAFLD by reducing hepatic TG build-up [73].

Trigonelline

Trigonella foenum-graecum is the principal source of the natural alkaloid known as trigonelline (TRG), which is also present in other food plants such as soybeans, onions, and maize. TRG demonstrates a range of therapeutic benefits, including anti-diabetic, anti-hypercholesterolemia, and anti-carcinogenic qualities [74, 75]. According to a study, TRG reduced adipocyte differentiation and fat accumulation in 3 T3-L1 cells by downregulating PPAR-γ and C/EBPα and could be effective in treating disorders connected with metabolism [76]. Western blot analysis showed that TRG markedly enhanced the expression of superoxide dismutase 1 (SOD1) in the hepatic tissues of rats receiving HFD. These proteins could protect the liver by hampering apoptosis and played a significant role in the treatment of NAFLD [77].

Sophocarpine

Sophocarpine (SPC), a member of the sophorae alkaloid (quinolizidines and pyridines) that is frequently used in traditional Chinese



▶ **Fig. 4** Flavonoids involved in the management of NAFLD [nobiletin (I), dihydromyricetin (II), rutin (III), naringenin (IV), baicalin (V), quercetin (VI), luteolin (VII), scutellarin (VIII), genistein (IX), and fisetin (X)].

medicine, apparently successfully lowers NASH in rats and adipocytokine production, demonstrating that adipocytokines can influence hepatic lipid metabolism through the AMPK pathway [78]. In primary hepatocytes derived from particular pathogen-free rats and treated with OA, a recent study showed that SPC therapy resulted in noticeable relief from HS, reductions in leptin expression, and increases in adiponectin expression. This study also showed that SPC therapy significantly increased AMPK phosphorylation and decreased the expression of the protein hepatocyte nuclear factor-4. Additionally, *SREBP-1c* mRNA expression was markedly reduced by SPC. The results showed that SPC reduced HS by activating the AMPK signalling pathway [79].

Flavonoids

Flavonoids are a class of organic compounds with varying phenolic structures present in various plant components, including fruits, barks, and aerial parts. The antioxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic qualities of flavonoids and their ability to influence important cellular enzyme activity are well known for positively impacting human health. Using FFA-induced HS in HepG2 and AML12 cells, the hepatoprotective effects of the flavonoids are discovered [80], and various flavonoids involved in retaliating against NAFLD are also enlisted below, shown in ▶ **Fig. 4**

Nobiletin

Nobiletin (NOB), a polymethoxy flavonoid abundant in citrus fruit and isolated from *Citrus depressa* and *Citrus reticulata* [81], attenu-

ated steatosis in high-glucose-treated HepG2 cells by downregulating SREBP-1c and FAS expression levels. Lipogenesis was restricted by inhibiting SREBP-1c activation and subsequent downregulation of FAS and ACC, which decreased malonyl-CoA generation upon AMPK activation. Therefore, the study concluded that NOB could effectively demolish hyperlipidemia and intracellular lipid accumulation in NAFLD [82]. Along with the upregulation of AdipoR1 expression, NOB substantially enhanced plasma levels of adiponectin. Lower amounts of malondialdehyde (MDA) in the plasma and liver tissue were associated with the downregulation of liver NADPH oxidase $gp91^{phox}$ subunit expression and thereby impaired ROS and MDA production in HFD-fed rats in NAFLD [83]. The activated NOD-like receptor family pyrin domain containing 3 (NLRP3) is likely to contribute to lipotoxicity and enhanced IL-1β and IL-18 expression in PA acid-induced AML-12 cells. NOB boosted the expression of SIRT1 while decreasing the expression of NLRP3, IL-1β, and IL-18. Additionally, it is proposed that SIRT1 might be a potential target to arrest the advancement of NAFLD [84].

Dihydromyricetin

Dihydromyricetin (DMY), a bioactive flavonoid isolated from *Ampelopsis grossedentata* and *Cedrus deodara* [85], was found to reduce lipid accumulation in OA-induced steatotic L02 and HepG2 cells. Additionally, OA-induced cell death was lessened by DMY, and peroxidation index generation was similarly reduced. By using qRT-PCR and Western blot analysis, DMY was shown to boost AMPK phosphorylation while lowering PPAR-γ expression and phosphorylating AKT. Therefore, DMY could efficiently treat NAFLD in the PPAR-γ, AMPK, and AKT signalling pathways [86]. DMY reduced NAFLD by enhancing redox homeostasis and mitochondrial respiratory capacity in PA-induced hepatocytes through a sirtuin 3 (SIRT3)-dependent mechanism by transfecting SIRT3 siRNA. Peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) and SIRT3 expressions increased AMPK activation in steatosis-induced HepG2 cells. PGC1α activated ERRα to facilitate ERR binding to ERRE in the SIRT3 promoter, which encouraged SIRT3 mRNA production. The experiment demonstrated that DMY might boost SIRT3 expression by stimulating the AMPK-PGC1α signalling pathway [87]. A study revealed that DMY decreased oxidative stress, inflammation, and apoptosis, preventing the onset of the NAFLD rodent model. The DMY therapy increased PPAR-α expression while decreasing albumin and collagen I levels and reducing NF-κB and p53 expression levels. It can be said that DMY preferentially protected the liver against NAFLD via NF-κB/p53 signalling pathways [88].

Rutin

Rutin (RUT), a flavonol initially isolated from *Ruta graveolens*, is a plant pigment found in various fruits and vegetables [89]. The report suggests that RUT increased the activity of SOD, an antioxidant enzyme, and decreased cellular MDA, a lipid peroxidation marker, in hepatocytes. Administering RUT decreased the expression of SREBP-1c, diglyceride acyltransferase 1 and 2 (DGAT1 and DGAT2), and ACC while enhancing the expression of PPAR-α and its downstream substrates CPT1 and CPT2. By decreasing the levels of the vital autophagy biomarkers TNF-α and IL-1β, RUT has also been demonstrated to suppress the autophagic activity of liver tissues. The capacity of RUT to promote fatty acid metabolism while inhibiting lipogenesis might be the cause of its hypolipidemic effects. RUT might therefore be the possible treatment option for NAFLD [90]. In rats, HFD generated metabolic syndrome, which included obesity, dyslipidemia, hypertension, and NASH. Increased levels of glutathione peroxidase (GPx) and MDA, both biomarkers of oxidative stress, demonstrated that these clinical states are influenced by oxidative stress. These stress parameters were blocked and turned around by the RUT administration. Therefore, RUT successfully prevented these diet-related alterations by lowering liver and cardiac inflammation and oxidative stress [91].

Naringenin

Naringenin (NGN), a colourless flavanone exclusively available in citrus fruits [92], is beneficial against liver diseases by targeting several molecular pathways [93]. In order to encourage fatty acid oxidation and prevent lipogenesis in the liver, NGN enhanced AMPK activation. A reduction in the activity of ACC, HMG-CoA reductase (HMG-CoAR), and lipogenesis due to AMPK activation protected the fatty liver by reducing the production of TGs. In addition, the NF-κB and PPAR-α were upregulated, leading to a significant elevation of heme oxygenase 1 (HO-1) expression decrease in VLDL production in NAFLD models [94]. Furthermore, NGN reduced inflammation and lipid build-up in the liver by preventing NLRP3 activation in primary hepatocytes and HepG2 cells. However, it was also evident that NGN decreased the expression of CD68 and CD64, macrophage markers, in the livers of wild-type mice given the methionine-choline deficient (MCD) diet. Additionally, NGN lowered inflammation by inhibiting NF-κB, IL-1β, and IL-18, reducing hepatic inflammation and steatosis [95].

Baicalin

Baicalin (BAI) is a monomeric flavonoid in the *Scutellaria baicalensis* Georgi plant [96], which restricted the toll-like receptor 4 (TLR4) expressed on the immune system cell surface and parenchymal hepatocytes in the MCD diet NAFLD mice model. TNF-α, IL-1β, IL-6, and C–X-C motif chemokine ligand 2 were among the pro-inflammatory indicators that BAI also suppressed when mitogen-activated protein kinase (MAPK) and NF-κB were turned down. Therefore, hepatocyte damage, intracellular lipid accumulation, and liver fibrosis were abolished upon BAI treatment [97]. Hepatic cholestasis was also diminished by BAI via activating crucial receptors such as FXR and takeda G-protein-coupled receptor 5 (TGR5), which regulated the gene expression responsible for lipid and bile acid synthesis. Furthermore, by overexpressing AMPK and downregulating SREBP-1c, BAI helps reduce the toxicity of FFAs by preventing fat build-up in the liver. Scientists determined that BAI performed a therapeutic effect in NAFLD via the regulation of endoplasmic reticulum (ER) stress and the thioredoxin-interacting protein (TXNIP)/NLRP3 pathway in an investigation of PA-induced NAFLD HepG2 cells [98]. In addition to providing good protection against the harmful effects of an HFC-rich diet on the liver, BAI significantly reduced oxidative stress and liver inflammation in NASH patients. Furthermore, BAI might protect the liver from damage by inhibiting the activity of JNK and downregu-

lating COX-2 and CYP2E1. Therefore, natural antioxidants like BAI might restrict NASH development [99].

Quercetin

Quercetin (QRC) is a bioflavonoid initially discovered in *Quercus* (oak genus) and reported to be available in a handful of plants, such as *Ginkgo biloba, Sambucus canadensis, Oryza sativa L.* [100], and *Hypericum perforatum*, with possible chemopreventive action and reverse lipid peroxidation [101]. In both *in vitro* and *in vivo* models of T2DM-induced NAFLD, the antioxidant QRC significantly reduced the production of IL-1β, IL-6, and TNF-α. Studies revealed that the lipid metabolism included the FXR1/TGR5 signalling pathways, which QRC enhanced to treat NAFLD [102]. Apart from possessing several beneficial effects in improving IR, QRC also ameliorated hyperlipidemia by downregulating SREBP-1c and FAS, thereby upregulating PPAR-α and LXRα expressions to accelerate cholesterol outflow from THP-1 macrophages and increasing the expression ATP-binding cassette transporter A1 (*ABCA1*) genes. Therefore, QRC can be a suitable molecule for NAFLD treatment [103]. In a study, QRC reduced excessive hepatic LDL-c accumulation and hepatic necrosis brought on by HFD in mice and enhanced autophagosome potential, which might have been involved in LDL-c degradation, in addition to blocking the expression of the receptors, such as macrophage scavenger receptor 1 (MSR1) and CD36, which are primarily involved in LDL-c uptake. An experiment revealed QRC has an impact on autophagy modification in the prevention of LDL-c and NAFLD [104].

Luteolin

Luteolin (LUT), a tetrahydroxyflavone with anti-inflammatory, anti-hypertensive, and anti-cancer properties [105], was observed to alleviate HS in the HFD-induced NAFLD mice model. The homeostatic model assessment of insulin resistance (HOMA-IR) was decreased upon LUT treatment, which was previously upregulated in the control group. Intestinal zonula occludens-1, occludin, and claudin-1 protein expressions were elevated following LUT treatment, as opposed to previously in the HFD group. Damage to the intestinal barrier allows lipopolysaccharides to reach the liver through the portal vein, activating TLR4 signalling to promote dyslipidemia and liver inflammation, exacerbating NAFLD. In addition to elevated IL-1β, IL-6, and TNF-α levels, the *TLR-4* and *NF-κB* mRNA expressions were upregulated after LUT administration [106]. Additional *in vitro* research has shown that LUT can inhibit the stimulation of the LXR. This inhibited TG accumulation in HepG2 cells and primary hepatocytes. Results showed that LUT could prevent lipid build-up by overexpression of SREBP-1c both *in vitro* and *in vivo*, suggesting that it could help treat NAFLD. To summarise, the LXR-SREBP-1c signalling pathway, which was initially upregulated in the hepatocytes of the NAFLD mice model, was downregulated by LUT to decrease hepatic DNL [107].

Scutellarin

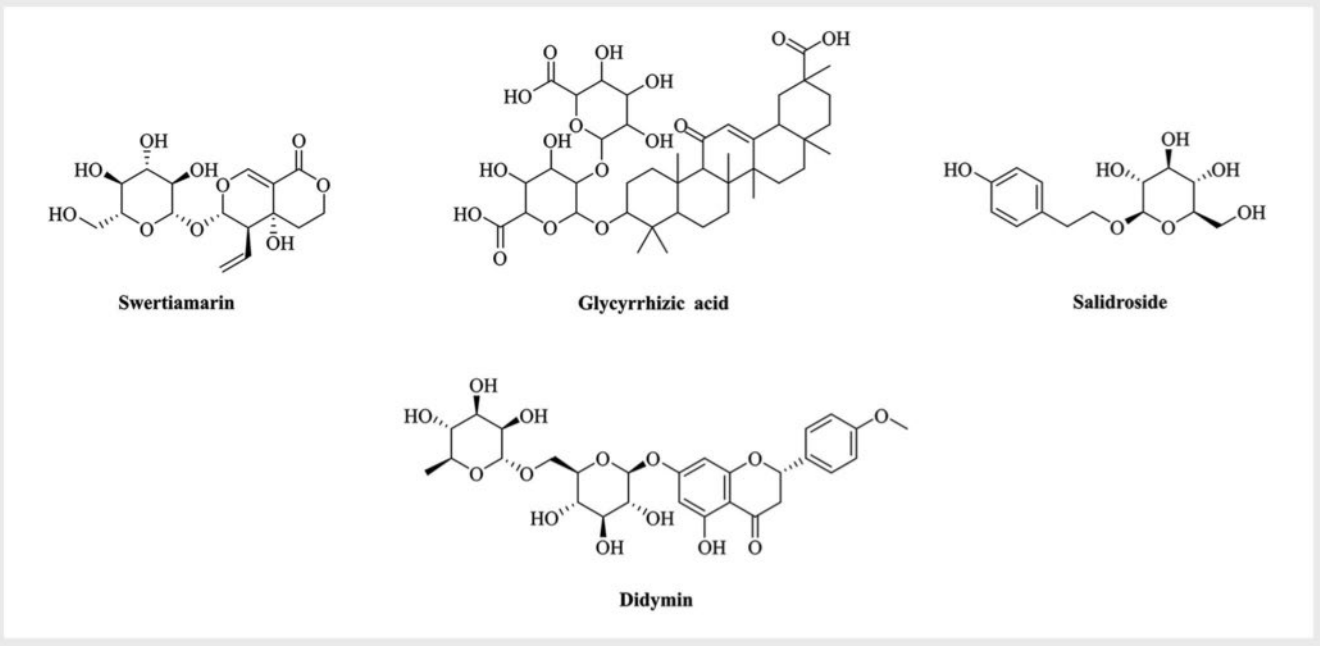
Scutellarin (SCU) is a flavonoid 7-O-glucuronide having cardioprotective attributes, mostly found in *Salvia splendens* and *Scutellaria baicalensis* [108]. In HFD rats, SCU prevented dyslipidemia via reducing oxidative damage. After one month of SCU treatment on the liver cells obtained from the established rat model, activated phosphoinositide 3-kinase (PI3K) and AKT expression with concomitant elevation of Nrf2 promoted the expression of HO-1 and NADPH quinone dehydrogenase 1 (NQO1). Therefore, the findings by Western blot suggested that SCU could be a necessary antioxidant in NAFLD treatment. Furthermore, these findings indicated that SCU prevented NAFLD by potentially reducing oxidative stress in the HFD rat model [109]. In the experiment conducted on *in vitro* HepG2 cells and *in vivo* HFD NAFLD mice models, SCU considerably lowered hyperlipidemia and boosted antioxidant capacity. Additionally, SCU administration markedly suppressed NF-κB and KEAP1 while activating PPAR-γ, Nrf2, PGC1α, HO-1, glutathione S-transferase (GST), and NQO1. The results indicated that SCU had potent antioxidative, hepatoprotective, and hypocholesterolemic properties that might effectively cure NAFLD via the PPAR-γ/PGC1α-Nrf2 signalling pathway [110].

Genistein

Genistein (GNT), an isoflavonoid isolated from *Glycine max*, commonly known as soybean, has been found effective in treating cancer and obesity, while currently showing a therapeutic role in retarding NAFLD [111]. An increase in plasma thromboxane A2 (TXA2) and the expression of TBXA2R in the HepG2 cells and liver of the HFD-induced NAFLD model were indicators that the TXA2 pathway was active. GNT, an isoflavonoid derived from soybean, targeted the COX-1 activity, inhibited TXA2 production, and affected NAFLD development by reducing insulin sensitivity. This research demonstrated the critical mechanism of GNT in the advancement of NAFLD in the TXA2 pathway [112]. Steatosis-induced primary human hepatocytes (PHHs) exhibited increased PPAR-α protein expression and elevated CPT1 and ACSL1. In addition, GNT therapy downregulated PPAR-α expression and reverted the activated SREBP-1c protein in steatotic PHHs [113].

Fisetin

Edible fruits and vegetables, including strawberries, grapes, and onions, contain the bioactive flavonol known as fisetin (FST), preventing LDL-c oxidation [114]. In the hepatocytes of HFD-induced obese mice, FST treatment also increased the production of SIRT-1 and CPT1 and decreased the levels of HS, FAS, and leptin. It also considerably boosted AMPK phosphorylation. Furthermore, FST accelerated lipolysis and β-oxidation in hepatocytes. According to this investigation, FST might improve NAFLD and hepatic lipid metabolism in mice via activating the SIRT1/AMPK and β-oxidation pathways [115]. Despite enhancing Nrf2 in the liver exposed to PA, FST substantially reduced cellular and mitochondrial ROS generation, inhibiting the inflammatory response and lipid deposition. Furthermore, FST strongly inhibited ER stress induced by PA. Surprisingly, ER stress inhibition governed by glucose-regulated protein 78 (GRP78) was substantially responsible for ROS production inhibited by FST [116]. In a rat model of NAFLD brought on by high fat/high sugar, FST decreased lipid accumulation in hepatocytes. The administration of FST resulted in an upregulation of HNF4-α gene expression and lipin-1 signalling. Additionally, it led to a decrease in oxidative stress, inhibition of ROS-induced synthesis of TXNIP, and activation of PARP1. Therefore, FST could offer protection from NAFLD and slow disease progression [117].



▶ **Fig. 5** Glycosides involved in the management of NAFLD [swertiamarin (I), glycyrrhizic acid (II), salidroside (III), and didymin (IV)].

Apart from the discussed compounds, some alkaloids that contribute to reverting NAFLD are listed in ▶ **Table 2**.

Glycosides

Glycosides are phytochemicals in which the sugar moiety has a glycosidic linkage with another functional group. They play various essential functions of glycosides in phytopharmacology. Inactive glycosides are the primary type of chemical storage in many plants. These can be made active by enzyme hydrolysis, which separates the aglycone part from the sugar component and makes it therapeutically active [118]. The crucial molecular targets of glycosides are sterol regulatory element-binding protein 1 (SREBP-1), ACC, FAS, NF-κB, PI3K-AKT pathway, PPAR-α, and several other pathways. Thus, this class of phytochemicals is a crucial player in controlling the progression of NAFLD. Some of the widely discovered glycosides are summarised below (▶ **Fig. 5**) and portrayed in ▶ **Table 3**.

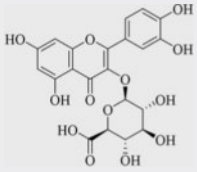
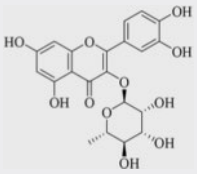
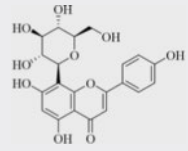
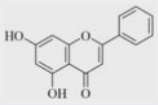
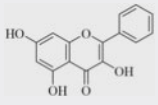
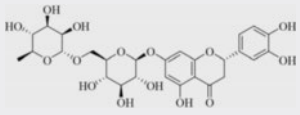
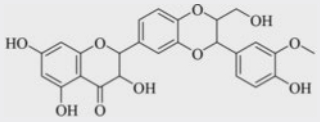
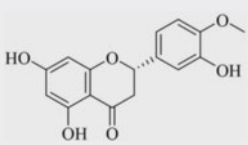
Swertiamarin

Swertiamarin (SWT), a bitter secoiridoid glycoside, improves IR in T2DM and has lipid-lowering properties. It is the main constituent in *Enicostemma littorale* Blume and other medicinal plants from the Gentianaceae family [119]. By maintaining membrane integrity and preventing apoptosis, as seen by decreased cleavage of caspase 3 and PARP1, SWT effectively lowered TG levels and drastically reduced lactate dehydrogenase release activity. With a concurrent decrease in p307 insulin receptor substrate 1 (IRS1), SWT also markedly boosted the expressions of essential insulin signalling proteins like IR, PI3K, and AKT. Noticeably, SWT controls hepatic glycemic load, fat deposition, IR, and ROS in HS by collectively targeting putative metabolic regulators AMPK and PPAR-α [120]. In a recent study, SWT was found to reduce weight gain, glucose intolerance, oxidative stress, and IR caused by HFD in mice and improve insulin signalling. The SWT-treated animals showed enhanced lipolysis and decreased adipocyte hypertrophy and macrophage infiltration in epididymal white adipose tissue (eWAT) compared to HFD-fed mice. In the liver of obese mice, SWT reduced HS and inflammation brought on by HFD by inhibiting p38 MAPK and NF-κB pathway activation in the eWAT [121]. In HFD, SWT administration to fructose-fed mice also decreased levels of ALT, AST, uric acid, blood glucose, and TGs. Histological analyses revealed that SWT therapy could reduce hepatic ballooning degeneration and steatosis. Additionally, SWT treatment reduced hepatic oxidative stress and hepatic pro-inflammatory cytokines, which was connected to a decline in hepatic xanthine oxidase activity and an increase in antioxidant defence system enzymes as activation of Nrf2 in mice fed fructose. Furthermore, SWT also reduced the expression of ACC1, FAS, and SREBP-1 in the liver of mice administered with fructose [122].

Glycyrrhizic acid

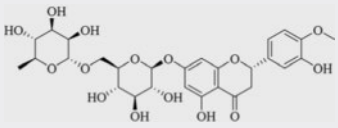
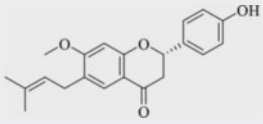
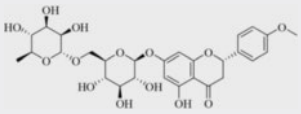
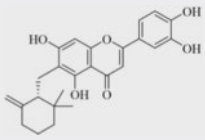
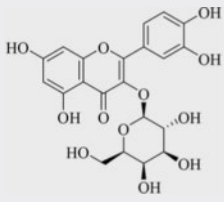
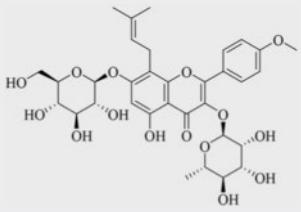
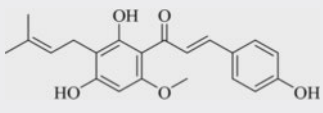
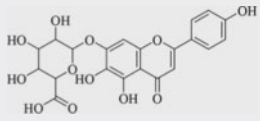
Glycyrrhiza glabra, an edible and medicinal plant with a long history of usage in Ayurveda and traditional Chinese medicine, yields a triterpene glycoside known as glycyrrhizic acid (GA) [123]. The relative liver weight, serum ALT and AST activity, lipid levels, blood glucose, and insulin levels were all dramatically decreased by GA therapy. In addition, GA reduced the build-up of lipids in the liver. Further research into the mechanism of action of GA revealed that it decreased the expression of SREBP-1c, FAS, and SCD1, raised the expression of PPAR-α, CPT1, and ACADS, and enhanced lipid metabolism via activating LPL. Additionally, GA boosted glycogen synthesis by inducing *PDase* and *GSK3β* gene expressions while decreasing gluconeogenesis by suppressing PEPCK and G6Pase. Fur-

▶ **Table 2** Structure of flavonoids targeting biomarkers involved in NAFLD.

Compound name with structure	Biological source	Research model	Biomarkers	Ref
 Quercetin-3-O-*β*-D-glucuronide	*Polygonum perfoliatum* and *Polygonum aviculare*	*In vitro* RAW264.7 cells; *in vivo* primary hepatocytes of HFD-fed rats	Downregulated SREBP-1c and FAS; upregulated PPAR-*α*, CPT1, and MCAD	[216, 217]
 Quercitrin	*Xylopia emarginata* and *Lotus ucrainicus*	*In vivo* ovariectomised mice	Downregulated TNF-*α*, IL-1β, and IL-6	[218, 219]
 Vitexin	*Prosopis cineraria* and *Acer palmatum*	*In vivo* liver tissue of HFD-fed mice	Downregulated PPAR-*γ*, SREBP-1c, ACC and FAS; up-regulated PPAR-*α*, CPT1A, and AMPK	[220–222]
 Chrysin	*Passiflora caerulea* and *Passiflora incarnata*	*In vitro* HepG2 cells; *in vivo* MCD mice, and HFD-fed rats	Downregulated PKC, HNF4-*α*, TNF-*α*, SREBP-1c and IL-6; upregulated PPAR-*α*	[223–225]
 Galangin	*Alpinia officinarum*	*In vitro* OA:PA (2:1)-induced HepG2 cells; *in vivo* streptozotocin-induced hyperglycaemic rats and HFD-fed rats	Downregulated CD36, SREBP-1c and ChREBP; up-regulated PPAR-*α*, CPT1A	[226, 227]
 Eriocitrin	*Citrus limon*	*In vitro* PA-induced HepG2 cells; *in vivo* diet-induced obesity zebrafish and HFD-fed obese mice	Downregulated FAS, PPAR-*γ*, ACC, SCD1, and CD36; up-regulated PPAR-*α*, CPT1A, PGC1*α*, and UCP1	[228, 229]
 Silymarin	*Silybum marianum* L.	*In vitro* PA-induced HepG2 cells; *in vivo* HFD-fed mice and fructose-induced mice	Downregulated PARP, SREBP-1, FAS, CPT1A, GRP78 and XBP-1; upregulated PPAR-*α*, PPAR-δ, SIRT1, and AMPK	[230–232]
 Hesperetin	*Citrus genus*	*In vitro* OA-induced HepG2 cells and *in vivo* HFD-fed and primary hepatocytes of rat	Downregulated NF-*κ*B, TNF-*α*, IL-6; upregulated Nrf2, PI3K, AKT, SOD, GPx, HO-1, XBP-1, and GRP78	[233–235]

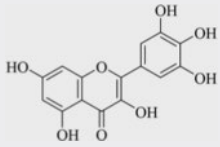
continued next page

▶ **Table 2** *Continued*

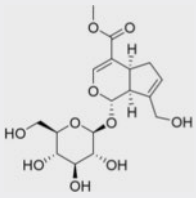
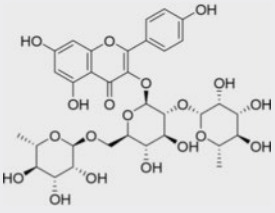
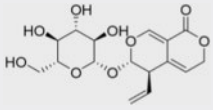
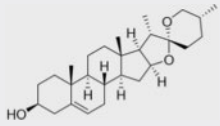
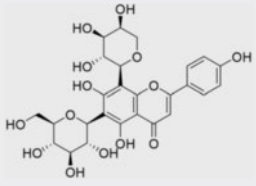
Compound name with structure	Biological source	Research model	Biomarkers	Ref
 Hesperidin	*Citrus sinensis*	*In vitro* OA-induced HepG2 cells; *in vivo* HFD-fed mice	Downregulated SREBP-1c, ACC and FAS; upregulated AMPK	[236, 237]
 Bavachinin	*Psoralea corylifolia* L. and *Fructus Psoraleae*	*In vitro* PA-induced HepaRG cells	Downregulated FDFT1, SREBP-2, AKT and mTOR	[238, 239]
 Didymin	*Citrus* genus and *Mentha spicata*	*In vitro* insulin-resistant HepG2 cells; *in vivo* HFD-fed mice	Downregulated SREBP-1c, ACC1, FAS, TLR4, NF-κB and LXRα	[132, 240]
 Ugonin J	*Helminthostachys zeylanica*	*In vitro* PA-induced HuS-E/2 cells; *in vivo* HFD-fed mice	Downregulated SREBP-1c; upregulated AMPK, ACC, AKT and CPT1	[241]
 Hyperoside	*Hypeticum perforatum* and *Artemisia capillaris*	*In vivo* HFD-fed mice	Downregulated SREBP-1, SREBP-2 and ACC; upregulated CYP7A1, FXR, LXRα, and NR4A1	[242, 243]
 Icariin	*Epimedium genus*	*In vivo* HFD-fed mice	Downregulated SREBP-1c and DGAT2; upregulated CPT1, ACC, PGC1α, and GLUT4	[244]
 Xanthohumol	*Humulus lupulus*	*In vivo* HFD-fed mice and T2DM-induced steatosis rats	Downregulated PPAR-γ and NF-κB; upregulated Nrf2	[245–247]
 Breviscapine	*Erigeron breviscapus* (Vant.) Hand. -Mazz.	*In vivo* HFD-fed, MCD, and HFHC diet-fed mice	Downregulated NF-κB, TAK1, FAS, ACC, SCD1, CD36, FABP1, and PPAR-γ; upregulated PPAR-α and CPT1A	[248, 249]

continued next page

▶ **Table 2** *Continued*

Compound name with structure	Biological source	Research model	Biomarkers	Ref
 Myricetin	*Euphorbia tirucalli* L.	*In vivo* HFD-fed, and ob/ob mice	Downregulated ChREBP, SREBP-1c, TNF-α, IL-6, and PPAR-γ; upregulated Nrf2, SOD, GPx, HO-1, and NQO1	[250–252]

▶ **Table 3** Structure of glycosides targeting biomarkers involved in NAFLD.

Compound name with structure	Biological source	Research model	Biomarkers	Ref.
 Geniposide	*Gardenia jasminoides*	*In vitro* OA and PA-induced HepG2 cells; *in vivo* tyloxapol (Ty)-induced mice	Downregulated SREBP-1c, MPO, mTORC, and PI3K; upregulated Nrf2, HO-1, PPAR-α, and AMPK	[253, 254]
 Clitorin	*Carica papaya* L.	*In vitro* OA-induced HepG2 cells; *in vivo* male Western diet-fed mice	Downregulated SREBP-1, PPAR-γ, C/EBPα, LXR and HMGCR, ACC, and FAS; upregulated PPAR-α, CPT1, and AMPK	[255]
 Gentiopicroside	Gentianaceae family	*In vitro* OA and PA at (2:1)-induced HepG2 cells; *in vivo* Ty-induced hyperlipidemia mice	Downregulated SREBP-1c and MDA; upregulated PI3K, AKT, Nrf2, NQO1, HO-1, PPAR-α, and SOD	[256]
 Diosgenin	*Dioscorea villosa* and *Rhizoma Dioscoreae Nipponicae*	*In vitro* high glucose treated HepG2 cells; *in vivo* HFD-fed rats	Downregulated SREBP-1c, LXR; upregulated AMPK, and ACC	[257]
 Schaftoside	Herba Desmodii Styracifolii	*In vitro* OA-induced Huh-7 cells and FXR knockout mice primary hepatocytes; *in vivo* HFD-fed mice	Downregulated SREBP-1 and CYP7A1; upregulated FXR	[258]

thermore, GA improved insulin sensitivity by upregulating IRS1 and IRS-2 phosphorylation [124]. Other research suggested that by lowering the levels of SREBP-1c, FAS, ACC1, and SCD1 in the liver, GA treatment decreased hepatic lipogenesis. It also increased lipid metabolism by inducing PPAR-α, CPT1A, ACADS, and LPL. Through a reduction in the expression of monocyte chemoattractant protein 1 (*MCP1*) and *VCAM-1* in the liver, GA also decreased hepatic inflammation. By limiting HSC activation and collagen deposition, GA also decreased liver fibrosis. In conclusion, GA significantly reduced the risk of NASH in mice brought on by the MCD diet [125].

Salidroside

Salidroside (SAD), a phenylpropanoid glycoside [2-(4-hydroxyphenyl)-ethyl-β-d-glucopyranoside], is the main bioactive phytoconstituent isolated from *Rhodiola rosea* L. SAD has been studied for its potential biological effects, including its anti-inflammatory, antioxidant, antifibrotic, and neuro- and cardioprotective activities [126]. Interestingly, SAD improved oxidative stress and mitochondrial damage while reversing the damage caused by PA in a dose-dependent manner in AML-12 cells. It also protected against hepatic lipotoxicity by inhibiting TLR4/MAPK and p53 activation in AMPK and AKT pathways. Furthermore, SAD-reduced lipid accumulation was likewise influenced by TLR4 suppression [127]. According to another study, SAD treatment significantly improved their insulin sensitivity by reducing obesity, hepatic fat deposition, and blood glucose fluctuation caused by HFD in mice. Moreover, SAD also reduced the production of TXNIP and the activation of the NLRP3 inflammasome in the liver by increasing AMPK activity and insulin sensitivity in cultured hepatocytes by regulating lipid accumulation, ROS formation, and NLRP3 inflammasome activation. The positive effects of SAD on hepatocytes were suppressed due to inhibiting AMPK activation by an inhibitor or short interfering RNA [128]. While reducing hepatic tissue vacuolation and steatosis, SAD also markedly decreased liver TG and FFA levels. Treatment with SAD improved serum dysregulation of fasting blood sugar (FBS), HOMA-IR, ALT, and AST. In addition, SAD significantly increased the levels of important insulin signalling pathway molecules such as phosphorylated IRS1, PI3K, and PKB in the liver while considerably lowering the levels of SREBP-1c, curing the NASH condition [129].

Didymin

Didymin (DYM) is an orally bioactive dietary flavonoid glycoside in citrus fruits, including oranges, lemons, etc. [130, 131], which was found to decrease lipid imbalance and hepatocyte damage dramatically. Furthermore, DYM significantly reduced hepatocyte apoptosis by controlling the expressions of the caspase family and the B-cell lymphoma-2 (BCL-2) family. It also reduced the expression of TLR4, as well as the phosphorylation of NF-κB, showing that DYM inhibits the TLR4/NF-κB pathway. DYM similarly suppressed the PI3K/AKT pathway, as evidenced by the reduction in PI3K and AKT phosphorylation levels [132]. Recent research suggested that DYM dramatically reduced hepatic damage and fibrogenesis by CCl_4, low transaminase activity, and reduced collagen build-up. In addition, it markedly reduced hepatocyte apoptosis by restoring the expression of the BCL-2 and caspase families and the mitochondrial dysfunction. It also significantly reduced the production of IL-1β and IL-6 while inhibiting the glycerophospholipid metabolism pathway by reducing the production of phosphatidylethanolamines and phosphatidylcholines [133].

Phenols and Polyphenols

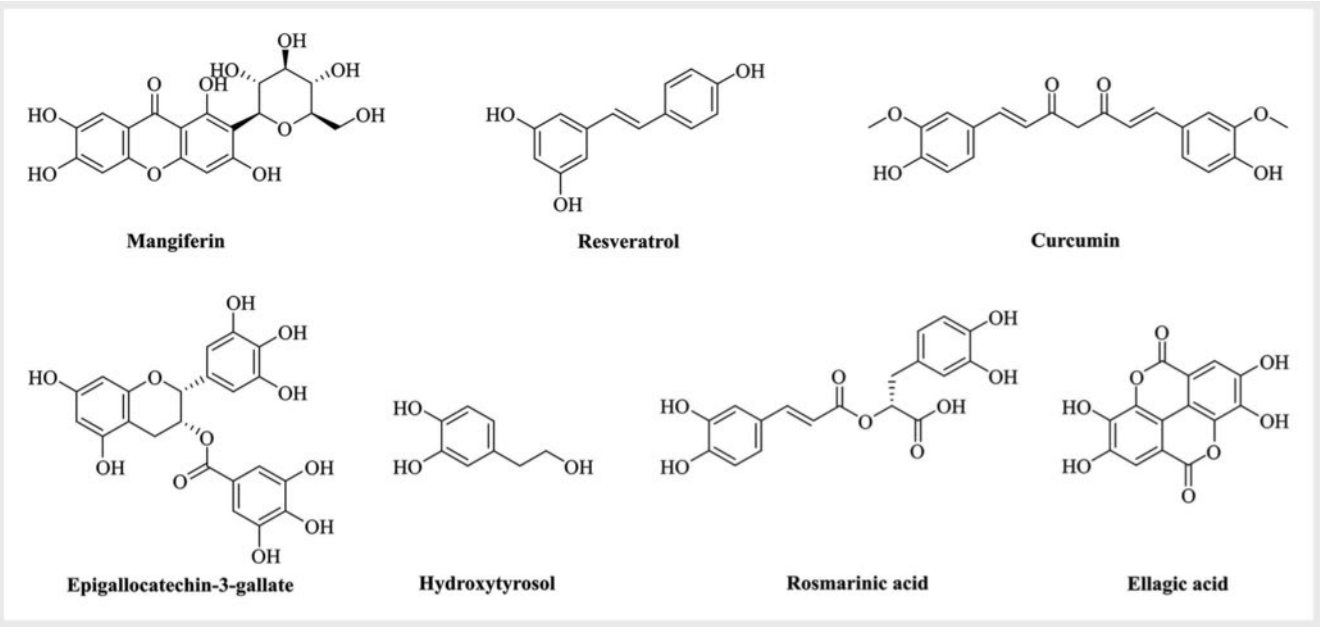
Phenolic compounds are the primary antioxidants and are essential for human health, and they primarily act as free radical scavengers by hindering lipid oxidation. This reduces the formation of rancidity-causing decomposition products like aldehydes and ketones [134]. Dietary polyphenols are secondary plant metabolites with antioxidant capabilities that work as antioxidants to prevent the development of chronic illnesses. The phytochemicals in the polyphenolic subclass might have anti-cancer, anti-diabetic, and anti-neurodegenerative properties [135]. This section extensively investigates phenolic and polyphenolic compounds proven beneficial in treating NAFLD, as illustrated in ▶ **Fig. 6** and **Table 4**.

Mangiferin

Mangiferin (MGN) is a glucosylxanthone polyphenol primarily isolated from *Mangifera indica* [136], possessing antioxidant as well as anti-diabetic, hypolipidemic, and cardioprotective properties [137]. This phytocompound promoted glucose metabolism and diminished hepatic TG accumulation by reducing NLRP3 and IL-1β transcription levels while upregulating phosphorylated AMPK in both *in vitro* HepG2 cells and *in vivo* HFD-induced mice models. The authors have also mentioned that by activating AMPK, MGN elevated IR, which could be a promising agent to cure NAFLD [138]. The effective concentration of MGN for inhibiting inflammatory cytokines NF-κB and activating PI3K was 30 mg per kg. The protein level of hepatic phosphorylated JNK was elevated in the HFD-induced NAFLD model, which was downregulated after MGN treatment to suppress HS. Deprivation of mTOR and AMPK stimulation led to the masking of SREBP-1, which prevented DNL. The findings demonstrate that MGN improved lipid accumulation in NAFLD by promoting autophagy and inhibiting lipogenesis via AMPK/mTOR pathway activation [139]. In the liver of seven-week-old male HFD hamsters, MGN elevated the mRNA expression of *PPAR-α, CD36*, and *CPT1* while downregulating *SREBP-1c, ACC, DGAT2*, and microsomal TG transfer protein genes responsible for lipogenesis [140].

Resveratrol

Resveratrol (RVT) is a polyphenol that is available in dietary plant sources such as grapes, apples, blueberries, and peanuts and is particularly abundant in *Polygonum cuspidatum*. Hyperlipidemia and inflammation have been cured by RVT [141]. Dephosphorylation of phosphatidic acid is catalysed by lipin-1 to produce DAG, which is necessary to produce lipids. RVT reduced HS and lipid deposition in HepG2 cells primarily by upregulating AMPK and ACC while suppressing SREBP-1c and lipin-1 expression [142]. Genes responsible for FAO, such as *CPT1* and *ACOX1*, were elevated in the HFD mice group, reversely expressed upon RVT treatment. In addition, lipogenic genes, viz., *GPAT1* and *DGAT2*, along with cytosolic FABP1 and FABP2 proteins, were suppressed by RVT. TLR4 and myeloid differentiation primary response 88



▶ **Fig. 6** Phenols and polyphenols involved in the management of NAFLD [mangiferin (I), resveratrol (II), curcumin (III), epigallocatechin-3-gallate (IV), hydroxytyrosol (V), rosmarinic acid (VI), and ellagic acid (VII)].

(MyD88), as well as inflammatory mediators IL-1β and TNF-α, were elevated in the liver of the NAFLD model, but these alterations were abolished in the RVT group [143]. Overfed zebrafish model exhibited higher TG in plasma by lowering AMPKα, SIRT1, and PGC1α expression, which were upregulated by RVT, suggesting that it could lower plasma TG primarily activating the AMPKα-SIRT1-PGC1α pathway. Finally, RVT also suppressed CAV-1 and PPAR-γ while elevating LC3-II protein levels [144].

Curcumin

Curcumin (CRM) is derived from the *Curcuma longa* rhizomes and has an extensive range of therapeutic benefits, including anti-inflammatory and anti-mutagenic effects [145, 146]. O-GlcNAc transferase (OGT) and O-GlcNAcase are the only two enzymes responsible for the crucial post-translational modification known as O-glcNAcylation. In MCD diet mice, O-linked β-N-acetylglucosamine (O-GlcNAc) modification is linked to developing HS into hepatitis. Administration with CRM reduces the degree of HS via reducing O-GlcNAcylation on NF-κB in inflammatory signalling. Conversely, CRM administration dramatically increased the expression of SOD1 and SIRT1 while downregulating ChREBP [147]. Besides lowering LDL-c and FFA levels in the serum of the NAFLD mice model, CRM suppressed SREBP-1c, extracellular-signal-regulated kinase (ERK), TNF-α, and JNK expressions, as confirmed by Western blot [148]. Eventually, CRM might enhance FAO via the elevation of AMPK and PPAR-α, decreasing SREBP-1 expression and FAS transcription [149]. A clinical study of subjects with evidence of HS had low AST and ALT values with reduced pro-inflammatory high-sensitivity C-reactive protein and TNF-α levels in the serum [150].

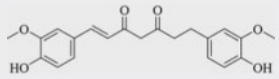
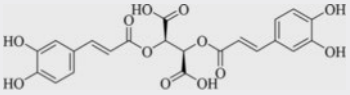
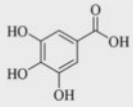
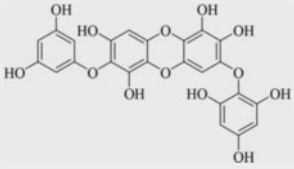
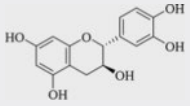
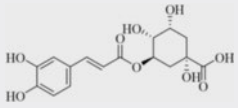
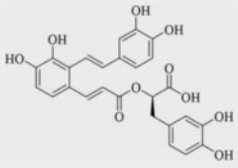
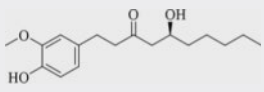
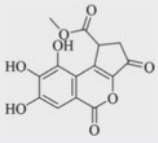
Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is an abundant polyphenol in green tea (*Camellia sinensis*) and possesses a potent antioxidant property that significantly blocked the expressions of TGF-β1, α-smooth muscle actin (α-SMA), SMAD 2, and SMAD 4, which were elevated in female HFD Sprague–Dawley rats. In the NAFLD model, EGCG reduced the expression of matrix metalloproteinase-2 (MMP-2) and the level of TIMP-2 protein. Moreover, EGCG therapy reversed NAFLD-induced changes in the expression of FOXO1 and p27kip and enhanced the phosphorylated PI3K and AKT [151]. A rate-limiting enzyme called glycogen synthase kinase 3β (GSK3β) controls many signalling pathways, including hepatic glycogen production and lipogenesis. In addition to triggering the enzymes involved in the insulin-signalling pathway, phosphorylation of GSK3β also controls glycogen production in the liver by raising glycogen synthase (GS) levels. This GS expression in HepG2 cells treated with EGCG was substantially increased; AMPKα and ACC expressions were significantly higher than in glucose-induced lipogenic cell lines [152]. The NAFLD progression could be restricted as the bile acid synthesis was hampered by the elevation of the cholesterol 7 alpha-hydroxylase (CYP7A1) enzyme by EGCG [153].

Hydroxytyrosol

Hydroxytyrosol (HT), the predominant phenolic compound in the fruit and leaves of *Olea europaea* L., showed a significant decrease in TC and TG and higher HDL-c levels in hyperlipidemic rabbits [154]. mRNA expression of *PPAR-α, CPT1A*, and fibroblast growth factor (*FGF21*) was elevated along with *ACC* in HT-treated rats. Interestingly, HT reduced hepatic inflammation and HIR on downregulation of TNF-α, IL-6, MDA, and COX-2 by HT to combat steatosis [155]. When mice on the HFD were given HT, the physiological changes that the diet caused in the liver were lessened by

▶ **Table 4** Structure of phenols and polyphenols targeting biomarkers involved in NAFLD.

Compound name with structure	Biological source	Research model	Biomarkers	Ref
 Dihydrocurcumin	*Curcuma longa*	*In vitro* OA-induced L02 and HepG2 cells	Downregulated PNPLA3, SREBP-1c; upregulated PPAR-α, CYP4A, PI3K, AKT, and Nrf2	[259]
 Cichoric acid	*Echinacea purpurea*	*In vitro* PA-induced L02, AML-12 and HepG2 cells; *in vivo* larval zebrafish and MCD mice	Downregulated MDA, NF-κB, KEAP1, SREBP-1c, DGAT1, FAS, and SCD1; upregulated SOD, AMPK, Nrf2, and HO-1	[260–262]
 Gallic acid	*Jatropha podagrica*	*In vivo* HFD rats	Downregulated TNF-α, NF-κβ, IL-6, IL-17, IL-1β, FAS, ACC-α, and HMGCR; upregulated Nrf2, HO-1, GST, SOD, and GPx	[263–265]
 Diphlorethohydroxycarmalol	*Ishige okamurae*	*In vitro* PA-induced HepG2; *in vivo* transgenic zebrafish	Downregulated SREBP-1c, ChREBP, FAS, IL-1β, and TNF-α; upregulated AMPK and SIRT1	[266]
 Catechin	*Camellia sinensis*	*In vitro* 3 T3-L1 preadipocytes and *in vivo* high fructose-fed rat	Downregulated TNF-α, MCP1, JNK, p38, AP-1, TLR4, TNFR1, and NF-κB; upregulated Nrf2	[267, 268]
 Chlorogenic acid	*Coffea arabica*	*In vivo* HFD and db/db mice	Downregulated SREBP-1c, LPL, PPAR-γ, FAS, C/EBPα, and TGF-β1; upregulated PPAR-α, AMPK, AdipoR1 and AdipoR2	[269–271]
 Salvianolic acid A	*Radix Salvia miltiorrhiza*	*In vitro* PA-induced HepG2 cells; *in vivo* HFD and high-carbohydrate diet mice	Downregulated ChREBP, FAS, MDA, TNF-α, TXNIP, NLRP3, IL-1β and IL-6; upregulated LC3-II AMPK, SIRT1, SOD	[272, 273]
 6-Gingerol	*Zingiber officinale*	*In vivo* HFD and high-cholesterol diet NMRI mice	Downregulated ChREBP, DGAT2, and FOXO1; upregulated AKT, PPAR-α, CPT1α, and SIRT3	[274, 275]
 Methyl brevifolincarboxylate	*Canarium album* and *Geranium carolinianum*	*In vitro* OA-induced SK-HEP-1 cells	Downregulated SREBP-1c, FAS, ACC1, TNF-α, NF-κβ, IL-6, IL-8, and IL-1β; upregulated PPAR-α, CPT1, ACOX1, and AMPK	[276, 277]

counteracting the pro-lipogenic, pro-inflammatory, and oxidative stress states. These impacts could be related to the PPAR-α and Nrf2 stimulation and the silencing of NF-κB [156]. Stress-induced mitochondrial dysfunction is prevented by PTEN-induced kinase 1 (PINK1). Ultimately, HT boosted PINK1 and AMPK expressions in the HFD zebrafish liver model, which suggested a reduction in hepatic lipid accumulation and mitochondrial dysfunction, activating the AMPK/PINK1 pathway [157].

Rosmarinic acid

Rosmarinic acid (RA) is named after rosemary, a polyphenol primarily isolated from *Rosmarinus officinalis* belonging to the Lamiaceae family [158]. Hepatic ROS generation was reduced as RA efficiently increases the activities of both enzymatic antioxidants, viz., SOD, CAT, and GPx, and non-enzymatic antioxidants, viz., GSH in HepG2 cells. RA significantly diminished ER stress to revert NAFLD by suppressing the expressions of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) and ATF6. With RA treatment in the steatotic HepG2 cells, overexpression of the vital autophagic markers, including LC3-II, Beclin-1, ATG5, and ATG7, was noticed [159]. Findings from both *in vivo* and *in vitro* experiments showed that the PGC1α level improved noticeably following RA treatment compared to levels in both NAFLD model groups. In contrast, the yes-associated protein 1 (YAP1) levels and TAZ considerably dropped. However, through silencing YAP1, the activity of RA was severely thwarted [160].

Ellagic acid

Ellagic acid (EA) is a bioactive polyphenol in various fruits and vegetables, including strawberries, almonds, and pomegranates. In streptozotocin-induced diabetic rats, EA reduced HS by triggering AMPK. This AMPK could cure NAFLD by reducing lipid synthesis by preventing SREBP-1/2, FAS, and HMG-CoAR from overexpressing and activating PPAR-α and CPT1A. EA also decreased NF-κB translocation into the nucleus, ROS, MDA, TNF-α, and IL-6 in the liver while increasing Nrf2, GSH, and SOD [161]. EA treatment lowered the level of AKT and reduced the activity of ribosomal protein S6 (RPS6) and SREBP-1, the two downstream effectors of the AKT/mTORC1 pathway. The results suggested that the EA-mediated reduction in SREBP-1, FAS, and ACC was suppressed both *in vitro* and *in vivo*. The research revealed a unique approach by which EA reduced AKT-triggered DNL [162]. By overexpressing Nrf2 and downregulating p47phox, EA demonstrated antioxidant advantages, which ultimately led to a decrease in HIF-α expression. Additionally, EA enhanced HIR by elevated AKT phosphorylation, therefore pointing to the possibility that EA could be used to treat HS in NAFLD [163].

Terpenoids

Terpenoids, which range in size from minor lipophilic cannabinoids to lipophilic pentacyclic triterpenes and polar saponins, are the largest class of chemicals that can modulate PPARs [164]. In addition, terpenes, which are chemically hydrocarbons, have been found to have antioxidant, anti-inflammatory, anti-hyperglycemic, and immunomodulatory properties in various plant secondary metabolites [165]. Some essential terpenoids with remarkable attributes to combat NAFLD are enlisted below and represented in ▶ **Fig. 7**.

Ursolic acid

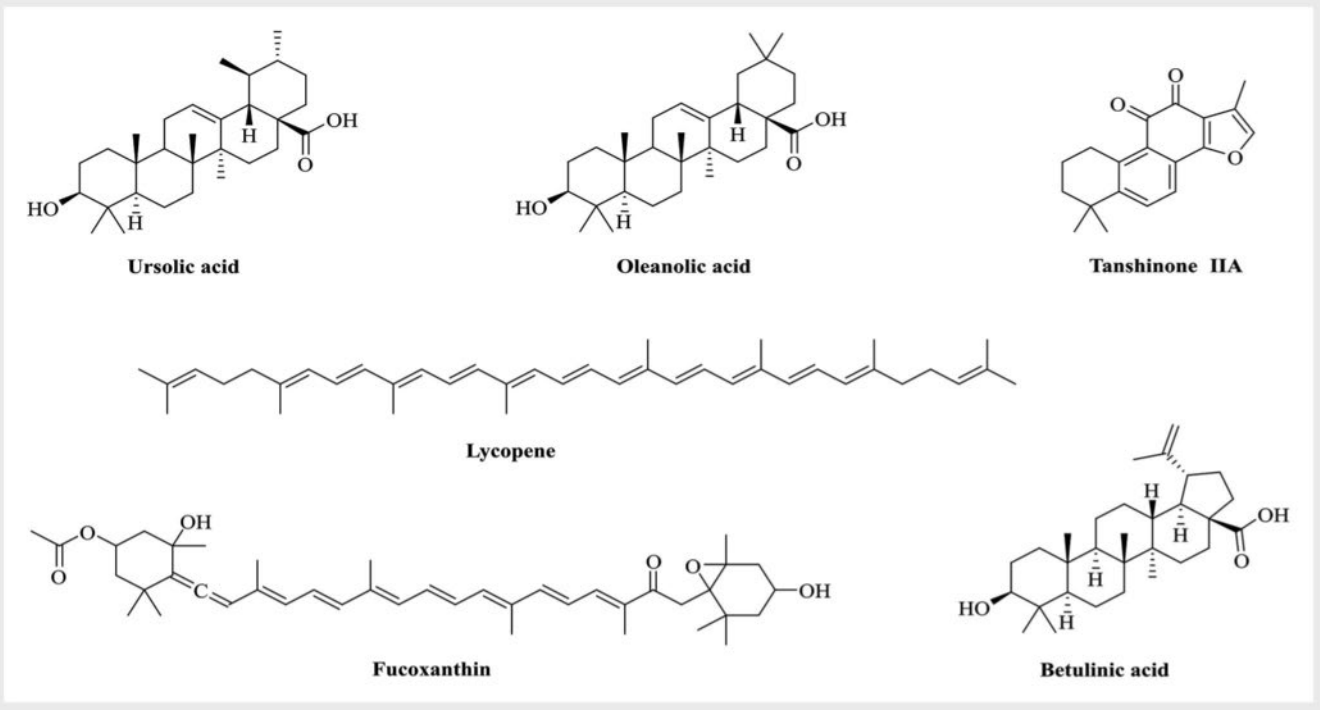
Ursolic acid (UA), a pentacyclic triterpenoid, is primarily present in *Fructus Ligustri Lucidi* and isolated from *Lantana camara* Linn. [166, 167]. Impairing hepatic ER stress and boosting β-oxidation of lipids are presumably the mechanisms by which UA supplementation greatly reduced the occurrence of NAFLD and liver damage in db/db mice with upregulation of PPAR-α. The UA treatment reduced inositol-requiring protein 1α (IRE1α) and phosphorylation of JNK. An important marker of ER stress, CHOP (C/EBP homologous protein), was also inhibited by UA. In PA-induced L02 cells showing elevated ER stress, proteins such as IRE1α, PERK, and JNK were significantly restricted with UA administration [168]. By decreasing DGAT-mediated processes in mRNA and protein levels, UA significantly decreased HS caused by HFD via the increase in PPAR-α, CPT1, and TGR5. Lipogenic enzymes like ACC and FAS, along with SREBP-1c, were downregulated by UA treatment. Pro-inflammatory cytokines such as TNF-α, MCP1, and interleukins were markedly reduced on UA administration. The oxidative stress-combating ability of UA was also analysed as serum SOD, and MDA levels were reversed [169]. T0901317 is a potent, high-affinity LXR agonist. In a T0901317-induced animal model, UA severely reduced the LXRα and SREBP-1c, lowering the hepatocellular fat level. The mRNA expression of *SREBP-1c, FAS, SCD1*, and *ACC* was markedly downregulated upon inducing UA. The small heterodimer partner-interacting leucine zipper protein (SMILE) and AMPK phosphorylation were influenced by UA in hepatocytes. However, steroid receptor coactivator-1 (SRC-1) binding to the SREBP-1c promoter area was suppressed [170].

Oleanolic acid

Oleanolic acid (OLA) is a pentacyclic triterpenoid abundant in *Olea europaea* [171, 172]. By lowering lipid accumulation and providing hepatoprotection in NAFLD, dietary supplementation with OLA delays the onset of high-fructose-induced NAFLD [173], which reduced the risk of developing pre-diabetes-related NAFLD by reducing HS, which lowered hepatic inflammation. Moreover, OLA controlled hepatic oxidative stress by reducing MDA levels and elevating GPx and SOD antioxidants. Plasma SREBP amount was also significantly lowered by OLA [174]. In hepatic cells, OLA confined SRC-1 to the SREBP-1c promoter region while increasing AMPK phosphorylation and SMILE. This phytonutrient OLA could be an antagonist of LXRα as it suppressed the expression of lipogenic genes such as *LXRE-* and *SREBP-1c* [175]. For lipid metabolism, OLA may overexpress genes including AMPK and GLUT-4. Noticeably, OLA highly expresses β-oxidation of fatty acids regulated by CPT1. Adiponectin was increased by onefold, and so was the *AdipoR1* gene expression upon OLA treatment. Inflammatory biomarkers, viz., TNF-α, IL-6, and MCP1, were enhanced to establish that OLA might be a powerful anti-NAFLD agent [176].

Tanshinone IIA

Tanshinone IIA (TSO) is a terpenoid primarily obtained from the roots of *Salvia miltiorrhiza* Bunge [177, 178], which markedly lessened lipid accumulation in the liver of HFD-fed Sprague–Dawley



▶ **Fig. 7** Terpenoids involved in the management of NAFLD [ursolic acid (I), oleanolic acid (II), tanshinone IIA (III), lycopene (IV), fucoxanthin (V), and betulinic acid (VI)].

rats by silencing TNF-α and IL-6 proteins. An *in vivo* study showed that TSO suppressed TLR4, as well as the NF-κB signalling pathways. The mRNA and protein expression of TLR4, MyD88, NF-κB, and IKKβ were suppressed by TSO. Deregulated PGC1α was enhanced upon TSO induction comparison to the HFD group [179]. By preventing the development of neutrophil extracellular traps linked to the production of MPO, TSO might diminish inflammatory TNF-α and IL-6 markers to control hepatocyte death in MCD diet-fed NASH mice. Overexpression of TGF-β was also reverted by TSO via SMAD signalling [180]. Furthermore, TSO minimised oxidative stress by reducing the formation of ROS and MDA while increasing the activities of SOD and GPx, which could also help to prevent cytotoxicity and improve HS [181].

Lycopene

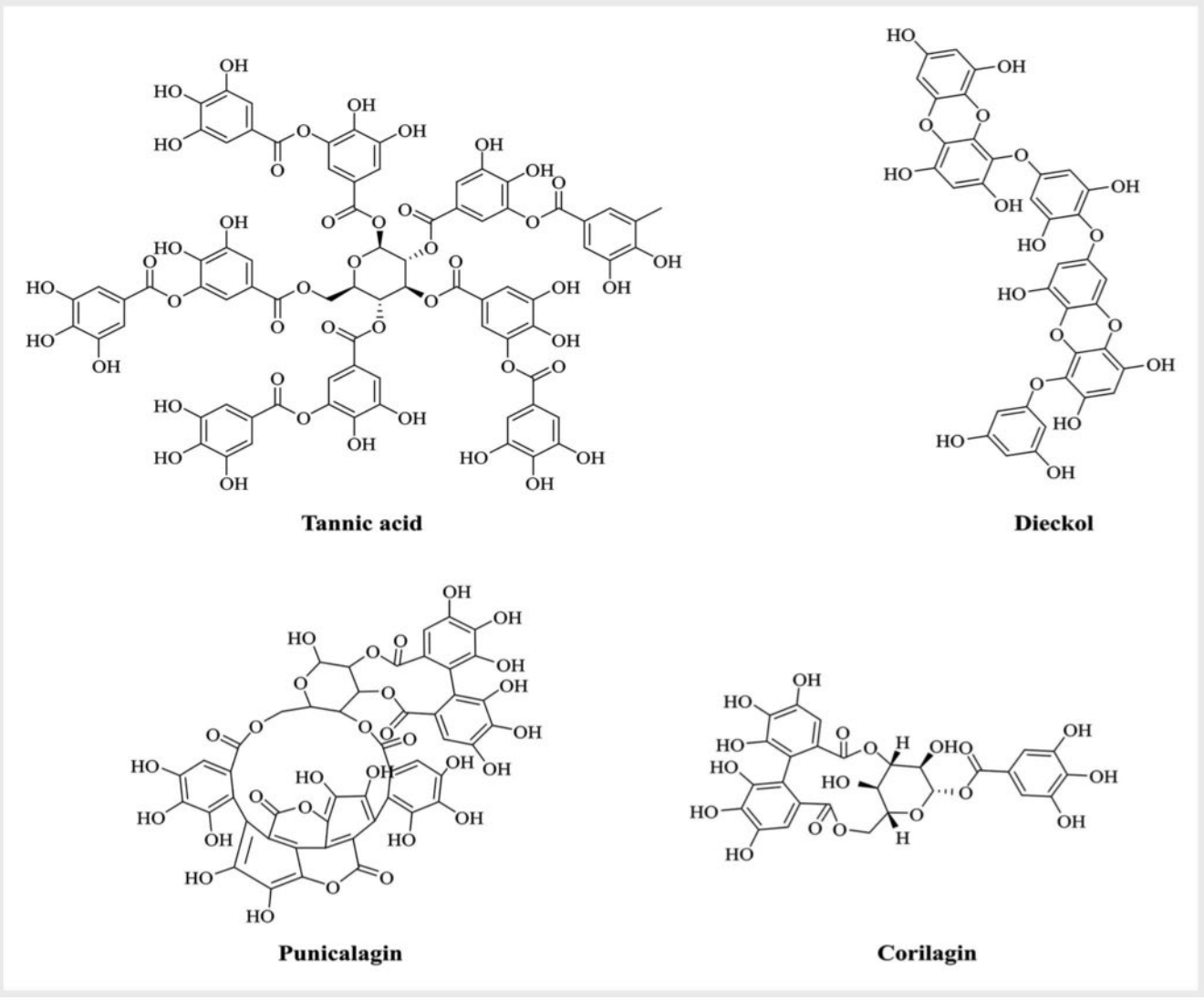
Lycopene (LP) is a tetraterpenoid found in a wide range of vegetables in the kitchen and has been found to lower health hazards like CVD, prostate cancer, and other malignancies [182]. HDL-c levels were raised by LP, which also reduced MDA levels with the capability to treat NAFLD. In addition, serum amyloid A and TNF-α promoting ROS generation contributing to liver damage were inhibited. Supplementing Wistar rats with a hypercaloric diet increased their levels of SOD and CAT enzymes [183]. The hepatoprotective action of LP against HFD-induced NAFLD was observed via inhibition of TNF-α, MDA, and CYP2E1 levels. In addition, LP also escalated the SOD and GSH [184]. By promoting PPAR-α activity, LP dramatically reduced the build-up of lipids in HepG2 cells exposed to PA. Additionally, it had been demonstrated that LP inhibited mitochondrial dysfunction by increasing the expressions of the AMPK, SIRT1, and PGC1α pathways for mitochondrial biogenesis. In mice given a Western diet, LP treatment significantly decreased fat accumulation by increasing PPAR-α activity. In order to demonstrate its antioxidant properties, LP also boosted the production of mitochondrial complexes, HO-1, and NQO1 [185].

Fucoxanthin

Fucoxanthin (FX), a carotenoid abundant in the brown marine algal family Phaeophyceae, has exceptional biological features [186]. Dietary FX treatment dramatically reduced the build-up of hepatic lipids, alleviating the symptoms of hepatic damage by suppressing mRNA expression of inflammatory cytokines, such as *TNF-α, IL-6, IL-1β,* and *MCP1*, as well as the expression of infiltration markers, such as *F4/80*, C–C chemokine receptor type 2 (*CCR2*), and *Ly6c*. Fibrogenic genes, viz., *TGF-β1*, collagen type I alpha 1 chain (*COL1α1*), and *TIMP-1*, were negatively expressed by FX. At both mRNA and protein levels, FX reduced α-SMA, thereby decreasing steatosis [187]. Interestingly, FX downregulated the essential lipid metabolism-operated transcription factors such as SREBP-1c and FAS while upregulating the downstream proteins, viz., PPAR-α, AMPK, ACC, and CPT1. After FX induction, antioxidant proteins like HO-1 and NQO1, along with Nrf2, were restored, while KEAP1 was elevated. The TLR4/MyD88 signalling pathway was significantly activated by FX [188].

Betulinic acid

Betulinic acid (BETA) is a pentacyclic triterpenoid isolated from the bark of *Betula alba* [189], which reversed the mRNA overexpression of *SREBP-1c, FAS, SCD1*, and *ChREBP*. Compared to the



▶ **Fig. 8** Tannins involved in the management of NAFLD [tannic acid (I), dieckol (II), punicalagin (III), and corilagin (IV).

HFD-fed mice group, TNF-α, IL-6, and IL-1β gene expression significantly decreased in the BETA-treated group. As determined by a Western blot study, BETA therapy lowered the levels of PERK, EIF2, XBP-1, and GRP78 proteins [190]. The BETA administration stimulated both CAMKK and AMPK. Hepatocytes exposed to BETA showed decreased SREBP-1, mTOR, and S6 kinase (S6K) protein contents, demonstrating that the CAMKK-AMPK-SREBP-1 signalling cascade was responsible for the BETA-induced decrease in HS [191]. The triterpenoid BETA behaved as an FXR agonist by directly binding to it in HepG2 cells to elevate *SHP, ABCC2, SULT2A1*, and *CYP7A1* gene expressions. Protein levels of PPAR-α and CPT1A were significantly increased upon BETA treatment. An *in vivo* study revealed that *SHP* and *PGC1α* mRNA levels dramatically rose after BETA exposure, whereas the expression quantities of the genes for *HNF4-α, PCK1*, and *SCD1* dropped significantly [192].

Some bioactive terpenoids suppressing NAFLD are also enrolled in ▶ **Table 5**.

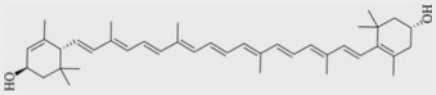
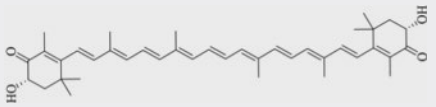
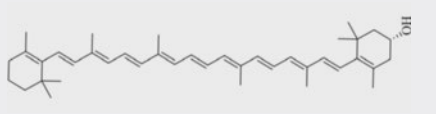
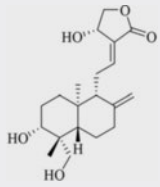
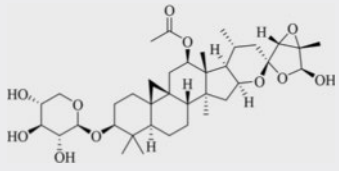
Tannins

Tannins are a diverse range of large-molecular-weight, water-soluble chemicals found naturally in various fruits, grains, and vegetables [193]. Tannins, potent antioxidant substances, serve as scavengers preventing harmful ROS effects [194]. Therefore, the compounds belonging to the tannin class with anti-NAFLD characteristics are enlisted in this section and outlined in ▶ **Fig. 8**

Tannic acid

Many nutritional plant products contain tannic acid (TA), a hydrolysable tannin primarily obtained from the Quercus genus that has appeared to resist inflammation as an antioxidant [195]. Histone H3 lysine 9 (H3K9) acetylation is a well-known epigenetic marker for NAFLD. Histone acetylation caused by histone acetyltransferase (HAT) inhibitors was inhibited by the TA, as demonstrated by *in vitro* and *in vivo* HAT experiments. Lipid-accumulation-induced increases in the acetylation levels of H3K9 were decreased by TA.

▶ **Table 5** Structure of terpenoids targeting biomarkers involved in NAFLD.

Compound name with structure	Biological source	Research model	Biomarkers	Ref.
 Lutein	*Chlorella vulgaris*	*In vivo* HFD-fed rats and hypercholesterolemic diet-fed guinea pigs	Downregulated MDA, TNF-α, NF-κB, and IL-1β; upregulated PPAR-α, SIRT1, IRS2, PI3K, and GLUT2	[278–280]
 Astaxanthin	*Haematococcus pluvialis*	*In vitro* OA and PA-treated L02 and HepG2 cells; *in vivo* HFD-fed mice	Downregulated SREBP-1c, ACC, FAS, CD36, CPT1α, FOXA, PGC1α, TNF-α, and IL-1β; upregulated AMPK and Nrf2	[281–283]
 β-cryptoxanthin	*Capsicum annuum* L.	*In vivo* high carbohydrate diet-fed mice	Downregulated ACC, FAS, and SCD1; upregulated PPAR-α, ACOX1, CYP7A1, SHP, SIRT1, and AMPK	[284, 285]
 Andrographolide	*Andrographis paniculata*	*In vitro* PA-induced HepG2 and OA-treated L02 cells; *in vivo* CDAA diet-fed and HFD-fed mice	Downregulated α-SMA, MMP-2, TIMP-1, TGF-β, MCP1, TNF-α, IL-1β, IFN-γ, NF-κB, and DGAT1	[286–288]
 Actein	*Cimicifuga foetida*	*In vitro* fructose-treated L02 cells; *in vivo* HFD-fed mice	Downregulated TNF-α, SREBP-1c, IL-1β, FAS, MCP1, SCD1, α-SMA, CD36, IRS1, FOXO1, AKT, and GSK3β	[289]

The rise in both mRNA and protein expressions of SREBP-1c, ATP-citrate lyase (ACLY), PPAR-γ, and FAS were inhibited by TA in HepG2 cells and Western-diet-fed mice. Moreover, TA decreased the genetic expression of *DGAT2* [196]. ATO-treated liver histopathological alterations were lessened by TA therapy, as primary observations revealed that increased serum levels of ALT and AST were reduced. As a result of TA therapy, MDA and ROS quantities were minimised. TA therapy reduced ATO-induced hepatic inflammatory reactions by lowering IL-1β, IL-6, and TNF-α. Additionally, TA treatment enhanced the concentrations of Nrf2, KEAP1, HO-1, and NQO1 proteins. Battling against oxidative stress and inflammation confirmed that TA had a preventive impact on hepatotoxicity and hepatic lipid accumulation, which seriously impacted NAFLD [197].

Dieckol

Dieckol (DK) is an eckol-type marine phlorotannin found in the marine brown algae *Ecklonia cava* possessing hypnotic behaviour [198], which was found to decrease IL-6 and TNF-α, which were elevated by HFD in mice. More importantly, DK restored vascular endothelial growth factor receptor-C and its receptor VEGFR-3. The PI3K, AKT, and ERK levels were also upregulated by DK treatment [199]. AMPK phosphorylation was significantly increased by DK, and this ultimately resulted in the suppression of FAS and SREBP-1c proteins. By inhibiting ACC, DK may have a major impact on hepatic fatty acid β-oxidation by activating CPT1A, SIRT1, PGC1α, and PPAR-α [200]. With the administration of DK, the TLR4 and NF-κB levels were suppressed, which lowered the NLRP3 inflammasome components, including ASC and NLRP3, in the liver. The expressions of lipogenic genes such as *FAS, SREBP-2, PPAR-γ*, and FFA-binding protein 4 (*FABP4*) were decreased, while *ATGL* and *HSL* lipolytic genes were enhanced with DK induction in the NAFLD mice model [201].

Punicalagin

Punicalagin (PCG) is one of the major ellagitannins found in pomegranate (*Punica granatum* L.) [202, 203]; it could preserve HepG2 cells against lipotoxicity induced by PA via stimulating Nrf2. By increasing MMP and lowering ROS generation caused by PA, PCG increased mitochondrial activity. The researchers observed that the

JNK activation and p38 were suppressed by PCG. Furthermore, PCG significantly impacted enhanced mitochondrial performance by inducing ERK and AKT phosphorylation. Therefore, PCG could influence cellular antioxidant mechanisms through the ERK/Nrf2 pathway, defending mitochondrial function [204]. Treatment with PCG significantly reduced the expression of DNL-related genes such as *CD36* and *PPAR-γ*. The *PPAR-α* expression was markedly increased in the PCG-treated animals, two genes involved in lipid clearance. AMPK phosphorylation, Nrf2, ZO-1, and HO-1 were enhanced by PCG. The mitochondrial biogenesis genes, viz., *PGC1* and *TFAM* expressions, were higher in the PCG-treated mice model [205]. Hepatic lipid production and the dyslipidemia caused by the HFD were significantly decreased by PCG. Downregulation of TNF-α and interleukins while Nrf2 stimulation was brought back to baseline with PCG administration to revert NAFLD. Lastly, PCG therapy decreased the expression of UCP2 and enhanced ATP levels in the hepatocytes. However, mitochondrial density remained unaffected at a high PGC1α level after PCG treatment [206].

Corilagin

Among the main active ingredients in many traditional medicinal plants, corilagin (CORI), a gallotannin isolated from *Caesalpinia coriaria* (Jacq.) Willd., was reported to possess hepatoprotective, anti-inflammatory, and anti-tumour properties [207]. An experiment showed that CORI therapy markedly decreased the gene expressions involved in fatty acid synthesis, such as *SREBP-1c, ACC1*, and *FAS*, and markedly increased the FAO-related genes, such as *PPAR-α, CPT1*, and *ACOX1*. Enhanced MMP suggested that CORI therapy improved mitochondrial dysfunction. Furthermore, *MCP1, TNF-α*, and *IL-6* genes were downregulated upon CORI therapy in HFD-induced animals. Among the antioxidant enzymes that CORI increased were SOD, GPx, and CAT [208]. Finally, FABP4 was lowered, while *CD36* and *CYP7A1* genes were upregulated upon CORI administration [209].

Clinical Trials on Potent Phytocompounds in NAFLD

Several natural compounds have shown specific termination of FFA synthesis and lipid accumulation on different *in vitro* cell lines and preclinical animal models targeting molecular levels. At the same time, Phase 1/2/3 clinical trials of numerous phytochemicals have shown encouraging results in diminishing NAFLD (▶ **Table 6**).

In 2019, a randomised controlled trial with an open label was carried out for seven weeks to investigate the effect of BRB on the metabolic profiles and liver function of 24 patients with NAFLD. Employees eligible for the study were randomised into one of two groups using a computer-generated random-allocation sequence. The treatment group was administered BRB at 6.25 g per day, while the second group received no intervention. The primary outcome measures considered changes from baseline in serum levels of ALT, AST, and ALP. In contrast, secondary outcome measures included changes from baseline in FBS, TC, LDL-c, HDL-c, and TG levels (https://clinicaltrials.gov/ct2/show/study/NCT04 049 396).

Patients suffering from NAFLD received two capsules regularly for three months. Each capsule comprised 700 mg of silymarin and the additives in a randomised, controlled trial conducted at the ambulatory care setting in a Brazilian hospital. The patients were split into two groups, including control and intervention. Primary outcome measures would scrutinise variations in NAFLD severity, while glycated haemoglobin, FBS, lipid profile, serum ferritin, AST, and ALT would be surveyed by secondary outcome measures (https://clinicaltrials.gov/ct2/show/study/NCT03 749 070).

Conclusion

The development of NAFLD and its progression involves various molecular signalling pathways, as well as genomic alterations, in the liver. Biological markers involved in different signalling pathways can portray the underlying mechanisms associated with NAFLD. Therefore, modulating the signalling pathways involved with NAFLD could be a viable option for arresting its progression. Although dietary and exercise-related lifestyle modifications are now the frontline of therapy for NAFLD, there is an impending need to mitigate this disorder through medication. The disease progression in NAFLD is multi-factorial in nature and involves a myriad of events like insulin resistance, oxidative stress, inflammation, and disrupted cellular energy metabolism, which contribute to the pathogenesis of NAFLD. A key aspect of management of NAFLD treatment could be preventing fibrosis, as well as ameliorating oxidative stress and inflammation. Natural products may offer new perspectives for novel therapeutic strategies aiming to reduce the development or progression of complications associated with diabetes mellitus, obesity, and NAFLD. Major lipogenic enzymes, viz., ACC, FAS, and DGAT2, are stimulated by SREBP-1c and ChREBP transcriptional factors to enhance hepatic lipogenesis. In addition, pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α play pivotal roles in various phases of liver ailments, influencing key features such as dyslipidemia, cholestasis, and fibrosis. The FAS, a crucial enzyme in DNL, has been observed at elevated levels in HS. Therefore, downregulation of FAS could control the biosynthesis of the FFAs.

OCA, a synthetic derivative of natural bile acid called chenodeoxycholic acid, has been exemplified to decrease HS, glucogenesis, and lipogenesis in the liver by stimulating the FXR. Despite having an influential role in combating NAFLD, unfortunately, OCA was reported to cause numerous adverse effects including dyslipidemia, oropharyngeal pain, thyroid hormone disorder, and hypersensitivity reactions. The case studies of the mentioned side effects have created severe challenges for OCA in achieving FDA approval. So, to avoid such undesired adverse events, larger numbers of bioactive phytocompounds are now being investigated for the management of NAFLD.

Naturally occurring substances derived from a variety of biological sources seemed to be extremely important in mitigating oxidative stress by reducing insulin resistance and fat accumulation. Altering the levels of hepatic enzymes and biochemical parameters such as serum TG, TC, HDL-c, and LDL-c by the bioactive plant molecules provides a primary perception in alleviating liver

▶ **Table 6** Clinical trials of phytocompounds from different classes engaged in the treatment of NAFLD.

Phytocompounds	Class	Phase	Clinical Trial ID	Primary outcome	Time frame	Ref.
Berberine	Alkaloid	Phase 4	NCT03198572	Improvement in histologic features of NASH by NAFLD activity score (NAS)	48 weeks	[290]
Silymarin	Flavonoid	Phase 2	NCT02006498	To determine the efficacy of silymarin on NAS	12 months	[291]
		Phase 1	NCT00389376	Determining the adverse effects	10 days	[292]
		Phase 2	NCT00680407	Improvement in NAS score	48–50 weeks	[293]
		Phase 4	NCT02973295	Lowering of liver steatosis and liver fibrosis	24–25 weeks	[294]
Resveratrol	Polyphenol	Phase 2/3	NCT02216552	Adverse effect profile	8 weeks	[295]
		N/A	NCT01446276	Hepatic VLDL-TG secretion and its clearance	6 months	[296]
		Phase 2/3	NCT02030977	ALT levels	12 weeks	[297]
		N/A	NCT01464801	Alteration in HS and inflammatory markers	6 months	[298]
		N/A	NCT01150955	Parameters related to glucose, protein and fat metabolism	5 weeks	[299]
Curcumin	Polyphenol	N/A	NCT03864783	Percentage of steatosis in the liver tissue	42 days ± 3 days	[300]
		Phase 2/3	NCT02908152	HS	12 weeks	[301]
Hydroxytyrosol	Phenol	Phase 3	NCT02842567	Improvement of markers for inflammation and oxidative stress	4 months	[302]
Anthocyanin	Flavonoid	Early Phase 1	NCT01940263	Oxidative stress and inflammatory biomarkers	12 weeks	[303]

disorders. Compounds from different chemical classes, viz., alkaloid, flavonoid, glycoside, polyphenol, tannin, and terpenoid, which have been proven to mitigate the onset of illness by modulating hepatic lipid metabolism through various molecular targets such as AMPK, TGF-β1, PPARs, etc., are discussed vividly in this present work. The preclinical studies (Table **1**, **2**, **3**, **4**, **5**), including *in vitro* assays against human cell lines like HepG2 and *in vivo* diet-fed animal NAFLD models of a significant number of compounds from each natural chemical class, have been discussed. Due to the promising efficacy exhibited by certain phytomolecules in preclinical studies, some of them have progressed to clinical trials, which has been depicted in ▶ **Table 6**. Due to the rising popularity of plant-based remedies globally, it is imperative that medical professionals be aware of both natural products and conventional therapies. Evidently, this review will serve as a springboard for additional research on the bioactive phytocompounds to scrutinise and create novel treatments that might serve as alternatives or supplements to existing ones in the battle against NAFLD.

Contributors' Statement

T. Banerjee, A. Sarkar, S. Z. Ali, R. Bhowmik; Design of the study: T. Banerjee, N. Ghosh; Analysis and interpretation: A. K. Halder, S. Karmakar; Drafting the manuscript: T. Banerjee, A. Sarkar, S. Z. Ali, R. Bhowmik, A. K. Halder, S. Karmakar, N. Ghosh; Critical revision of the manuscript: A. K. Halder, S. Karmakar, N. Ghosh".

Acknowledgements

We acknowledge the support of the Department of Science and Technology and Biotechnology (WBDSTBT), Govt. of West Bengal, India Vide Memo. 2027 (Sanc.)/STBT-11012 (19)/6/2023-ST SEC, dated 24–01–2024. We also thank the Central Council for Research in Unani Medicine, F.No. 3–72/2020-CCRUM/TECH, CCRUM (Ministry of AYUSH) India, AICTE, UGC-DSA, DST, UGC-UPE, RUSA 2.0, and the Swami Vivekananda Merit Cum Means Scholarship Scheme (SVMCM), Government of West Bengal, India for providing fellowship. We also acknowledge the State Government Research Fellowship Scheme (Ref. no.: P-1/RS/08/23, dated 19.01.2023). The authors gratefully acknowledge the scientific illustrations provided by the Smart Medical Art server (https://smart.servier.com/) and appreciate the support obtained from the Department of Pharmaceutical Technology, Jadavpur University, Kolkata.

Conflict of Interest

The authors declare no conflicts of interest.

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