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Review

Recent advances in the treatment of non-alcoholic fatty liver disease with astragaloside IV

HUI WANG[a]
YUNQIN JIANG[a]
SHIYUN WANG
CHANCHAN LU
LUMIN TANG
TINGTING GU
SHU SHI[*]

TCM Department, Shanghai Punan Hospital of Pudong New District, Shanghai, China

[*] Correspondence; e-mail: shushi_1123@163.com
[a] These authors contributed equally to this work.

ORCIDs. – HUI WANG 0000-0002-3230-3116; YUNQIN JIANG 0009-0004-9652-3427; SHIYUN WANG 0009-0004-3783-185X; CHANCHAN LU 0009-0009-3569-9177; LUMIN TANG 0009-0003-5076-9301; TINGTING GU 0009-0005-2861-421X; SHU SHI 0000-0001-5578-4090.

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a prevalent metabolic disorder that has become a global health challenge. With the lack of effective FDA-approved treatments, alternative therapies are being explored. Astragaloside IV (AS-IV), a bioactive compound derived from the plant *Astragalus membranaceus* (Fisch. ex Bunge) (Fabaceae/Leguminosae), native to Inner Mongolia and Siberia, has shown significant therapeutic potential in NAFLD. This review discusses the pharmacological effects and molecular mechanisms of AS-IV, highlighting its role in improving insulin resistance, regulating lipid metabolism, reducing oxidative stress and modulating inflammation. AS-IV acts through key molecular pathways, such as AMPK, Nrf2 and SREBP-1c, to mitigate liver steatosis and inflammation. Additionally, AS-IV influences gut microbiota and bile acid metabolism, contributing additionally to its therapeutic effects. Despite promising results from preclinical studies, clinical data supporting AS-IV's efficacy in NAFLD treatment are limited. Future research should focus on clinical trials, pharmacokinetics, and the combination of AS-IV with other therapeutic agents to optimize its therapeutic potential and reduce side effects.

Keywords: astragaloside IV, NAFLD, insulin resistance, lipid metabolism, gut microbiota

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a manifestation of multi-system metabolic dysfunction that affects the liver (1). Currently, the number of NAFLD patients accounts for 25 % of the global population, making it the most recognized chronic liver disease worldwide. The rapidly increasing prevalence of NAFLD has become a new challenge in the fields of liver disease and metabolism, posing a significant threat to public health and societal development globally (2, 3). Despite its rising prevalence, there is currently no FDA-approved treatment for NAFLD (4–6). Current management primarily focuses on lifestyle modifications, such as weight loss, as well as off-label use of drugs like pioglitazone and vitamin E. If left untreated, NAFLD can progress to liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC) (7).

The pathophysiology of NAFLD is complex, involving the interplay of genetic, metabolic and environmental factors (8, 9). Currently, the pathogenesis of non-alcoholic steatohepatitis (NASH) mainly focuses on insulin resistance (10, 11), oxidative stress-induced damage (12, 13), inflammatory responses (14, 15), and gut microbiota dysbiosis (16, 17). Characterized by liver inflammation, lipotoxicity, oxidative stress and fibrosis, the disease is typically driven by metabolic dysregulation, including lipid metabolism imbalance and mitochondrial dysfunction (8, 9). Although NAFLD is closely associated with metabolic factors such as obesity and insulin resistance, the specific mechanisms underlying its progression, especially from steatosis to hepatitis, fibrosis and cirrhosis, remain an area requiring further investigation (18, 19).

Given the limited treatment options and the increasing burden of NAFLD, there is an urgent need for new therapeutic approaches. Among the promising candidates, astragaloside IV (AS-IV), a bioactive compound derived from *Astragalus membranaceus* (Fisch. ex Bunge) (Fabaceae/Leguminosae) [syn. *Astragalus propinquus* Schischkin] primarily cultivated in Inner Mongolia, China, and Siberian regions, has been reported to regulate immune-inflammatory factors, modulate gut microbiota, act as an antioxidant, regulate blood lipid levels, and reduce hepatic lipid deposition (20–22). Recent studies suggest that AS-IV may play a role in alleviating NAFLD by regulating lipid metabolism and gut microbiota, as well as suppressing inflammation (23–25). However, the exact mechanism through which AS-IV affects the pathological progression of NAFLD is not yet properly and fully understood.

This review aims to explore the pharmacological effects of AS-IV on NAFLD and the molecular mechanisms underlying its actions. Specifically, we will discuss the latest advances regarding AS-IV's involvement in regulating key pathological pathways associated with NAFLD, including insulin resistance, apoptosis, gut microbiota, oxidative stress and inflammation. Additionally, we will assess the potential of AS-IV as part of the therapeutic strategy for NAFLD.

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NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Clinical features and pathological classification

NAFLD encompasses several stages of liver injury, which can be classified based on histological findings (26). Simple hepatic steatosis or non-alcoholic fatty liver (NAFL) is the early stage of NAFLD, characterized by the accumulation of triglycerides in hepatocytes without significant inflammation or hepatocellular injury (27). This stage is driven by an imbalance between lipid uptake (*via* CD36/FATPs), *de novo* lipogenesis (upregulated SREBP-1c), and impaired β-oxidation (PPAR-α suppression), creating a lipid-rich hepatic microenvironment (28, 29). This stage is typically considered benign and may be reversed through lifestyle changes such as introduction of modified diet pattern, eventual weight loss and proper exercise (27).

Additionally, NAFL can progress to NASH, defined by the presence of hepatic steatosis and inflammation, often accompanied by hepatocellular ballooning and varying degrees of fibrosis (30). Transition to NASH involves "two hits" such as mitochondrial dysfunction (ROS overproduction), ER stress (IRE1α/XBP1 activation), and inflammasome activation (NLRP3/IL-1β), which amplify hepatocyte apoptosis and Kupffer cell-driven inflammation (31 – 33). NASH is a more severe and progressive form of NAFLD, associated with an increased risk of liver-related complications, including cirrhosis and HCC (34). The degree of fibrosis in NASH is a key factor in determining disease progression and prognosis, with advanced fibrosis associated with significantly higher mortality and liver-related morbidity.

The final stage of NAFLD involves progression from NASH to cirrhosis, which, in some cases, may also include liver failure and HCC (35). Cirrhosis is characterized by extensive liver scarring that disrupts the normal liver architecture and impairs liver function. Fibrotic septa in cirrhosis distort hepatic vasculature, leading to portal hypertension and collateral circulation, while regenerative nodules reflect aberrant hepatocyte proliferation driven by Wnt/β-catenin signaling (36). NAFLD is the leading cause of liver transplantation worldwide, especially among patients with advanced NASH (34). As the disease progresses, patients may also experience extrahepatic complications, including cardiovascular diseases, which are often associated with metabolic dysfunction and insulin resistance (Table I) (35).

Table I. Clinical stages of non-alcoholic fatty liver disease (NAFLD) and histological features

Clinical stage	Histological features	Description	Reference
Non-alcoholic fatty liver (NAFL)	Hepatic steatosis, triglyceride accumulation in hepatocytes	Initial stage with triglyceride accumulation in liver cells, no significant inflammation or damage; reversible with lifestyle changes.	26, 27
Non-alcoholic steatohepatitis (NASH)	Hepatic steatosis, ballooning of hepatocytes,	More severe, with fat accumulation, liver cell ballooning, inflammation, and fibrosis. Higher risk of complications	28, 29

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	inflammation, varying degrees of fibrosis	like cirrhosis and hepatocellular carcinoma (HCC).	
Cirrhosis	Severe fibrosis, liver scarring, disrupted liver architecture	End-stage of NAFLD with significant liver fibrosis, potentially leading to liver failure, HCC, and the need for liver transplantation.	30, 31

Pathological mechanisms of NAFLD progression

The transition from simple hepatic steatosis to NASH involves complex pathological processes, including oxidative stress, inflammation, lipotoxicity and mitochondrial dysfunction (37). In NASH patients, the accumulation of fat in hepatocytes triggers an inflammatory response, leading to hepatocellular injury, apoptosis, and the activation of hepatic stellate cells (HSCs) (38). Upon activation, HSCs can transform into myofibroblasts, which secrete large amounts of extracellular matrix (ECM) proteins, such as collagen and fibronectin. The accumulation of these proteins leads to liver fibrosis (37, 38). This process is closely related to oxidative stress, inflammatory responses, and metabolic dysregulation, particularly in NASH, where the accumulation of fat and cellular damage in the liver activates the immune system, promoting HSC activation and the progression of fibrosis (39). Non-invasive biomarkers and imaging techniques, such as transient elastography and MRI-based methods, are increasingly being used to assess the severity of fibrosis and predict disease progression (40, 41).

In summary, NAFLD is a progressive liver disease, beginning with simple fat accumulation in the liver and potentially evolving into more severe conditions such as NASH, fibrosis, cirrhosis, and ultimately leading to liver cancer. The progression of the disease is influenced by multiple factors, including insulin resistance, gut microbiota dysbiosis, metabolic abnormalities and genetic susceptibility. Early identification of high-risk patients and timely intervention are critical for preventing the progression of NAFLD.

PHARMACOLOGICAL EFFECTS AND MOLECULAR MECHANISMS OF AS-IV IN NAFLD

AS-IV is a cycloartane-type saponin extracted from the roots of *Astragalus membranaceus* (Fisch. ex Bunge), a leguminous plant indigenous to temperate Northeast Asia including Inner Mongolia and Siberia, a plant widely used in traditional Chinese medicine (42). AS-IV is a triterpenoid saponin with a unique cycloartane structure, composed of a glycoside structure where the sugar portion is attached to the triterpene skeleton (43). This structural feature is crucial for its bioactivity, allowing it to interact with cell membranes and regulate various cellular pathways (42, 43) (Fig. 1). To date, numerous studies using cell and animal models have shown that AS-IV has effective protective effects on the cardiovascular (44), pulmonary (45), hepatic (46), renal (47) and brain (48) systems. Additionally, AS-IV has demonstrated antiproliferative/anticancer potential by inducing apoptosis, inhibiting tumor growth, and preventing metastasis in various cancer types (45, 49). These multifaceted effects make AS-IV

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a promising candidate for the treatment of various chronic diseases, including liver diseases, and provide a foundation for exploring its potential therapeutic role in NAFLD.

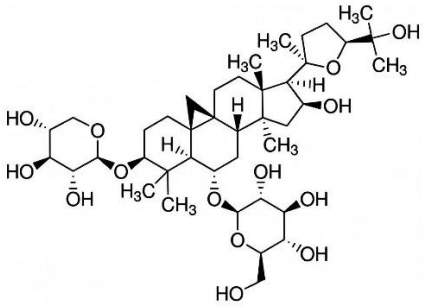

Fig. 1. The chemical structure of astragaloside IV.

Improvement of insulin resistance

Insulin resistance (IR) is a risk factor for NAFLD, characterized by the accumulation of lipids in hepatocytes (50). One of the mainstream theories explaining the complex pathogenesis of NAFLD, the "two-hit" hypothesis, posits that the "first hit" is caused by IR, which induces peripheral lipolysis and elevated insulin levels (51). The increased free fatty acids (FFAs) in the periphery lead to enhanced hepatic uptake of FFAs, while hyperinsulinemia promotes glycolysis, increases fatty acid synthesis, and ultimately results in hepatic lipid accumulation. Medium- and long-chain fatty acids are primarily oxidized in the mitochondria, whereas very long-chain fatty acids (VLCFAs) are almost entirely metabolized through β-oxidation in peroxisomes (52), a process that generates reactive oxygen species (ROS) such as hydrogen peroxide. Normally, the body has a well-established antioxidant mechanism to counteract ROS (51). However, in the case of hepatic lipid accumulation induced by IR, this balance is disrupted, and excess ROS triggers the onset of steatohepatitis through lipid peroxidation, cytokines and Fas ligand (FasL) activation. Fas (CD95/APO-1), a cell surface death receptor, binds to FasL, initiating caspase-dependent apoptosis (53). In NAFLD, ROS and lipid peroxidation products (*e.g.*, malondialdehyde) upregulate FasL expression, promoting hepatocyte apoptosis and amplifying inflammatory responses (53). This apoptotic signaling exacerbates liver injury and fibrosis, creating a vicious cycle in disease progression (53). Further, lipid peroxidation leads to cell death, increased collagen synthesis, and ultimately the development of hepatic fibrosis in NAFLD (51).

AS-IV has been shown to improve insulin sensitivity by inhibiting protein tyrosine phosphatase 1b (PTP1B), a negative regulator of insulin signaling. In insulin-resistant HepG2 cells, AS-IV treatment increased glucose consumption and enhanced insulin receptor phosphorylation, suggesting that AS-IV helps restore insulin signaling pathways (54) (Fig. 2). This effect was linked to a reduction in triglyceride (TG) and cholesterol levels, common metabolic disturbances in NAFLD. Furthermore, AS-IV alleviates IR and lipid accumulation by activating AMP-activated protein kinase (AMPK) (23). AS-IV promotes AMPK phosphorylation, which in turn reduces triglyceride production, indicating its role in improving lipid metabolism. Additionally, AS-IV inhibits the translocation of sterol regulatory element-binding protein-1c (SREBP-1c) into the nucleus by inducing phosphorylation of SREBP-1c at

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Ser372, a critical step for regulating lipid biosynthesis in the liver. These findings collectively suggest that AS-IV could be a promising therapeutic agent for treating hepatic steatosis and improving insulin sensitivity in NAFLD.

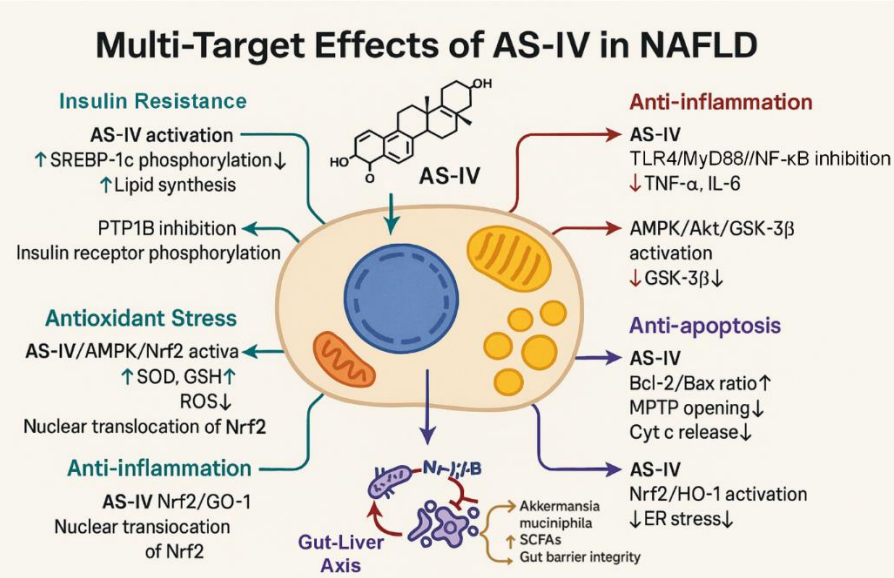

Fig. 2. Schematic diagram illustrating the multi-target mechanisms of astragaloside IV (AS-IV) in non-alcoholic fatty liver disease (NAFLD). AS-IV exerts therapeutic effects through five major mechanisms: (*i*) improving insulin resistance by inhibiting PTP1B and activating the AMPK pathway, leading to decreased SREBP-1c nuclear translocation and reduced lipogenesis; (*ii*) alleviating oxidative stress *via* activation of the AMPK/Nrf2 pathway, increasing antioxidant enzymes (SOD, CAT) and GSH levels; (*iii*) reducing inflammation through inhibition of the TLR4/MyD88/NF-κB pathway and regulation of the AMPK/Akt/GSK-3β axis, decreasing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α); (*iv*) suppressing hepatocyte apoptosis by modulating Bcl-2/Bax ratio, inhibiting cytochrome c release, and reducing caspase activation; (*v*) Restoring gut microbiota balance and bile acid metabolism by increasing beneficial bacteria (*Akkermansia muciniphila*, Lactobacilli), reducing harmful bacteria, inhibiting intestinal FXR, and activating hepatic FXR, ultimately improving lipid metabolism. Arrows indicate promotion (↑) or inhibition (↓).

AMPK – AMP-activated protein kinase, Akt – protein kinase B, Bcl-2 – B-cell lymphoma-2, Bax – Bcl-2-associated X protein, CAT – catalase, FXR – farnesoid X receptor, GSH – glutathione, GSK-3β – glycogen synthase kinase-3β, IL – interleukin, MyD88 – myeloid differentiation primary response 88, NF-κB – nuclear factor kappa B, Nrf2 – nuclear factor erythroid 2-related factor 2, PTP1B – protein tyrosine phosphatase 1B, SOD – superoxide dismutase, SREBP-1c – sterol regulatory element-binding protein-1c, TLR4 – toll-like receptor 4, TNF-α – tumor necrosis factor-alpha.

Antioxidant stress

Under long-term high-sugar and high-fat dietary habits, the liver increases the uptake of excess FFAs present in the circulating blood, which can undergo ectopic deposition, leading to an imbalance between oxidation and antioxidant mechanisms in the liver (55). This results in the accumulation of mitochondrial ROS, causing severe oxidative stress in the liver. Excess ROS can impair mitochondrial function in the liver, leading to significant damage, which exacerbates

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the deposition of lipid-related molecules in the liver. Nuclear factor E2-related factor 2 (Nrf2) is a key marker reflecting the body's ability to respond to oxidative damage (56). Under normal conditions, Nrf2 binds to the cytoplasmic protein partner molecule Keap1, existing as a complex outside the nucleus in a relatively stable state. When cells encounter harmful external signals, Nrf2 dissociates from Keap1 in the cytoplasm and translocate into the nucleus, promoting the expression of antioxidant-related proteins, including superoxide dismutase (SOD), glutathione peroxidase, and catalase (CAT), thereby increasing the intracellular levels of glutathione (GSH).

AMPK serves as an endogenous central metabolic sensor, regulating cellular energy metabolism, lowering the risk of metabolic-related diseases, and playing a significant role in antioxidant stress (57, 58). Research has shown that activation of the AMPK pathway can promote the expression of Nrf2 and its target genes, thus enhancing the intracellular levels of GSH and improving the body's ability to resist oxidative damage (59). Moreover, in cells experiencing oxidative stress, excess ROS accumulate, which inhibits AMPK activity. GSH can scavenge excess ROS and facilitate the *S*-glutathionylation of AMPK, further enhancing its activity and alleviating oxidative stress (23, 60). Studies have shown that AS-IV, by activating the AMPK/Nrf2 signaling pathway, increases liver GSH and SOD levels, alleviating the degree of liver oxidative stress and improving the excessive deposition of lipid-related molecules (61, 62). These studies provide evidence that AS-IV can inhibit the excessive accumulation of ROS in cells by activating the AMPK/Nrf2-related molecular pathways, thereby reducing the irreversible damage caused by oxidative stress and enhancing the body's ability to resist oxidative damage, which in turn alleviates the degree of hepatic steatosis.

Anti-inflammatory effects

Long-term high-sugar and high-fat diets can induce hepatic steatosis, triggering compensatory mechanisms to address excessive fat deposition (63). This leads to an increase in mitochondrial fatty acid oxidation. However, the enhanced fatty acid oxidation generates a large amount of ROS, which can promote the gene expression of harmful inflammatory factors such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), ultimately leading to liver inflammation. Glycogen synthase kinase-3β (GSK-3β) is known to be associated with the expression of pro-inflammatory factors like IL-6, IL-1β and TNF-α in tissues (64). However, the activity of GSK-3β is inhibited by phosphorylated Akt (p-Akt), which phosphorylates Ser9 of GSK-3β to suppress its activity. Studies have shown that activation of the AMPK signaling pathway increases p-Akt levels, inhibiting GSK-3β activity and subsequently reducing the expression of pro-inflammatory factors such as IL-1β, IL-6 and TNF-α (65). AS-IV can regulate the AMPK/Akt/GSK-3β signaling pathway (23, 66, 67), thereby reducing the expression of harmful pro-inflammatory substances like TNF-α, IL-1β and IL-6 in liver tissues and alleviating liver inflammation (62, 68).

The toll-like receptor-4 (TLR4)/myeloid differentiation factor 88 (MyD88)/nuclear factor kappa B (NF-κB) pathway is a classic signaling pathway mediating inflammation (69). This pathway is significantly activated in liver tissues when NAFLD progresses to NASH. TLR4 is expressed in all liver tissue cells, and in particular, it is the main pathway for Kupffer cells, which originate from the monocyte-macrophage system, to recognize danger signals (70). Under

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non-inflammatory conditions, NF-κB binds to IκB, forming a stable inactive complex in the cytoplasm (71). When the gut microbiota is disturbed by an unhealthy diet, circulating endotoxins such as lipopolysaccharides and FFAs can activate TLR4 and form a complex with MyD88 (71, 72). This activates the downstream molecule IκB kinase, allowing NF-κB to translocate into the nucleus and promote the expression of downstream inflammatory factors such as TNF-α and IL-6, thereby inducing liver inflammation. Relevant studies have shown that AS-IV can inhibit the gene expression of molecules in the TLR4/MyD88/NF-κB signaling pathway, reducing the levels of harmful inflammatory substances like TNF-α and IL-6 in the blood and alleviating the body's inflammatory response (25). These findings suggest that AS-IV can inhibit the expression of inflammatory factors by regulating the levels of molecules in the AMPK/Akt/GSK-3β and TLR4/MyD88/NF-κB signaling pathways, thereby suppressing the occurrence and progression of inflammation, including in NAFLD.

Anti-apoptosis

NAFLD patients often exhibit mitochondrial dysfunction and endoplasmic reticulum (ER) stress, both of which are major contributors to hepatocyte apoptosis (73). In steatotic hepatocytes, there is an accumulation of ROS that are not cleared in a timely manner. These ROSs inhibit the expression of genes related to the respiratory chain proteins by attacking mitochondrial DNA (mtDNA), leading to impaired respiratory chain function and the subsequent production of more ROS. ROS targets and attacks proteins in the mitochondrial permeability transition pore (MPTP) complex, causing a loss of mitochondrial membrane potential. Subsequently, cytochrome c (Cytc) is released from the mitochondrial intermembrane space into the cytoplasm, where it binds with apoptosis protease activating factor-1 (Apaf-1) and pro-caspase-9 to form an "apoptosome," further activating downstream caspase-3 and triggering apoptosis (73, 74). B-cell lymphoma-2 (Bcl-2) proteins are predominantly located on the outer mitochondrial membrane and the ER membrane (73, 75). These proteins can form heterodimers with the pro-apoptotic protein Bcl-2-associated X protein (Bax), preventing Bax from forming homodimers, thus stabilizing mitochondrial membrane permeability and inhibiting the release of Cytc. When ER homeostasis is disrupted, inositol 1,4,5-trisphosphate receptors (InsP3R) release stored Ca^{2+}, leading to intracellular Ca^{2+} overload, which then activates caspase-12 located on the ER membrane (76, 77). Activated caspase-12 enters the cytoplasm, where it acts on caspase-9, further activating caspase-3 and inducing apoptosis. Research has shown that Bcl-2 can reduce the excessive release of Ca^{2+} from the ER by inhibiting InsP3R, thereby alleviating ER stress-induced apoptosis (78).

AS-IV has been shown to inhibit hepatocyte apoptosis induced by oxidative stress and inflammatory signaling (79). In a study on NAFLD, AS-IV was found to inhibit the accumulation of lipids induced by palmitic acid (PA) in LO2 cells and to suppress PA-induced oxidative stress and apoptosis in these cells. Furthermore, AS-IV exerts its anti-apoptotic effects by modulating the JNK/p38 (80) and Nrf2/HO-1 (81) signaling pathways. By inhibiting the activation of these pathways, AS-IV reduces cell damage and apoptosis, particularly in response to stressors such as high-fat diets (80, 82). These findings are consistent with other studies, suggesting that AS-IV can reduce apoptosis in various tissues, including brain cells and cardiomyocytes. Additionally, the anti-apoptotic effects of AS-IV are partially mediated by its antioxidant properties, which reduce ROS production, a key initiator of apoptosis (83). By

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enhancing antioxidant defense, particularly through the Nrf2 pathway, AS-IV helps maintain cellular integrity and decreases the likelihood of apoptosis.

Regulation of gut microbiota dysbiosis and lipid metabolism abnormalities

The human gut harbors a large number of microorganisms, and under physiological conditions, the quantity and ratio of these microbial communities remain relatively stable (84). However, changes in the internal and external environment of the body can lead to gut dysbiosis. The gut and liver are closely connected due to their biological functions and anatomical relationships (85). Most of the liver's blood supply comes from the portal vein, which originates from the gut, linking the gut and liver through the portal circulation. This connection is referred to as the gut-liver axis. Emerging evidence highlights that gut-derived metabolites, such as lipopolysaccharides (LPS) and secondary bile acids, directly modulate hepatic inflammation and lipid metabolism *via* the portal vein (86). For instance, elevated LPS levels in portal blood activate hepatic Kupffer cells through TLR4 signaling, exacerbating oxidative stress and steatosis in NAFLD (87). Additionally, dysbiosis-induced alterations in bile acid metabolism impair FXR signaling, further disrupting hepatic lipid homeostasis (88). These mechanisms underscore the gut-liver axis as a pivotal therapeutic target for NAFLD.

This intricate crosstalk implies that liver metabolic dysfunction can reciprocally exacerbate gut dysbiosis. For example, impaired hepatic bile acid synthesis disrupts intestinal barrier integrity, allowing translocation of bacterial products like endotoxins into the portal circulation (89, 90). Xue *et al*. (91) found that fecal microbiota transplantation can effectively improve the treatment outcomes for NAFLD patients. Kaden-Volynets *et al*. (92) found that, compared to normal mice, germ-free mice fed a high-fat diet showed increased body weight and lipid metabolism abnormalities, although their livers remained normal without any signs of steatosis. Fu *et al*. (93) discovered that changes in the firmicutes/bacteroidetes ratio can alter blood lipid levels. This mechanism may be related to bile acids secreted by the gut microbiota, which promote fat absorption and activate G protein-coupled bile acid receptor 1 and other bile acid receptors, thus affecting lipid metabolism.

Several studies have shown that AS-IV can restore gut microbiota dysbiosis (94, 95). For example, AS-IV treatment has been shown to increase the abundance of beneficial bacteria such as *Akkermansia muciniphila*, lactobacilli and bifidobacteria strains, while reducing harmful bacteria such as *Escherichia coli* and streptococcus strains capable of causing different pathologies. These changes in the gut microbiota composition are associated with improvements in metabolic and inflammatory markers in NAFLD models (96). Specifically, AS-IV has been shown to increase the production of short-chain fatty acids (SCFAs) and regulate macrophage polarization, both of which play key roles in maintaining gut barrier integrity and modulating inflammation (21, 97). Furthermore, studies indicate that the effects of AS-IV on the gut microbiota may be mediated through the regulation of the NLRP3 inflammasome. By reshaping the gut microbiota and enhancing the production of bacteria such as *Butyricicoccus*, AS-IV not only alleviates the inflammatory burden but also contributes to the restoration of normal liver function (21). Zhai's study indicated that AS-IV alleviates diet-induced hepatic steatosis by regulating gut microbiota and bile acid metabolism (24). It reduces bile salt hydrolase (BSH) activity, increases taurine-β-muricholic acid levels, and inhibits intestinal farnesoid X receptor (FXR). This results in the activation of hepatic FXR, increased glucagon-like peptide-1 (GLP-

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1), decreased ceramide, and inhibition of SREBP-1c, ultimately reducing liver fat accumulation (24).

In conclusion, AS-IV exerts its therapeutic effects on NAFLD through multiple mechanisms, including improving insulin resistance, inhibiting oxidative stress, reducing inflammation, suppressing hepatocyte apoptosis, and regulating gut microbiota and bile acid metabolism. These actions, mediated through the regulation of key molecular pathways such as AMPK, Nrf2 and SREBP-1c, significantly improve lipid metabolism abnormalities and reduce hepatic steatosis, providing new potential strategies for the treatment of NAFLD (Table II).

Table II. Pharmacological effects and mechanisms of astragaloside IV in non-alcoholic fatty liver disease

Pharmacological effect	Molecular mechanism	Key signaling pathways/targets	Reference
Improve insulin resistance	Inhibit PTP1B, enhance insulin receptor phosphorylation; activate AMPK, reduce triglyceride synthesis; inhibit SREBP-1c nuclear translocation	AMPK/SREBP-1c/PTP1B	23, 47, 55
Antioxidative stress	Activate AMPK/Nrf2 pathway, increase GSH, SOD levels; clear ROS, alleviate mitochondrial dysfunction	AMPK/Nrf2/HO-1	23, 52, 54
Anti-inflammatory	Inhibit TLR4/MyD88/NF-κB pathway; regulate AMPK/ Akt/GSK-3β, reduce TNF-α, IL-6 expression	TLR4/NF-κB; AMPK/Akt/GSK-3β	25, 55, 62
Anti-apoptotic	Inhibit JNK/p38 and mitochondrial apoptotic pathways; activate Nrf2/HO-1 pathway, reduce Cytc -release and caspase activation	JNK/p38; Nrf2/HO-1; Bcl-2/Bax	72, 74, 76
Regulate gut microbiota	Increase beneficial bacteria (*e.g.*, *Akkermansia muciniphila*); lower BSH activity, inhibit gut FXR, activate liver FXR	FXR/GLP-1/SREBP-1c; NLRP3 inflammasome	24, 82, 84
Regulate lipid metabolism	Inhibit SREBP-1c-mediated lipid synthesis; reduce ceramide accumulation through bile acid metabolism	SREBP-1c; bile acid metabolism pathway	23, 24, 55

Akt – protein kinase B; AMPK – AMP-activated protein kinase, Bax – Bcl-2-associated X protein, Bcl-2 – B-cell lymphoma-2, Cytc – cytochrome c, FXR – farnesoid X receptor, GLP-1 – glucagon-like peptide-1, GSH – glutathione, GSK-3β – glycogen synthase kinase-3β, IL-6 – interleukin-6, NAFLD – non-alcoholic fatty liver disease, NF-κB – nuclear factor kappa B, NLRP3 – NLR family pyrin domain containing 3, Nrf2 – nuclear factor erythroid 2-related factor 2, PTP1B – protein tyrosine phosphatase 1B, ROS – reactive oxygen species, SOD – superoxide dismutase, SREBP-1c – sterol regulatory element-binding protein 1c, TLR4 – toll-like receptor 4, TNF-α – tumor necrosis factor-alpha.

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

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Currently, the mainstream treatments for NAFLD mainly include lifestyle interventions, pharmacological treatments and surgical procedures (97). Among them, lifestyle interventions that regulate basic dietary and exercise habits are widely promoted. However, achieving significant improvement in liver function requires at least a 5 % body weight reduction, while reversing liver fibrosis requires a weight loss of more than 10 %, which must be sustained for at least one year. Most patients find it difficult to maintain these changes. Surgical treatments primarily include bariatric surgery and liver transplantation; however, there is insufficient evidence to support the use of bariatric surgery for the treatment of NAFLD, and the recurrence rate of NAFLD after liver transplantation is as high as 50 %, with a higher risk of cardiovascular complications. Therefore, pharmacological treatments are highly anticipated.

Faced with the growing clinical demand, the pharmacological market for NAFLD still faces a significant gap (98, 99). Multiple NAFLD drugs are under development both domestically and internationally, but to date, only resmetirom (THRβ agonist), developed by Madrigal Pharmaceuticals (USA), has recently been approved by the U. S. Food and Drug Administration (FDA) for the treatment of NASH with liver fibrosis. Other promising drugs in development include lanifibranor (a pan-PPAR agonist) in phase III clinical trials (100), and semaglutide (a GLP-1 receptor agonist) (101). In addition to being used as monotherapy, a phase IIa clinical trial of a combination therapy (semaglutide + cilofexor + firsocostat) has also reached the primary endpoint and demonstrated good safety (102). Furthermore, drugs such as BIO89-100, efruxifermin and VK2809, have also shown potential in clinical trials for NAFLD and NASH, although they are still at different clinical stages and require further research to confirm their efficacy and long-term safety (103–105). At the same time, compared to monotherapy, combination therapies have shown statistically significant improvements in liver fat accumulation and liver injury. As with most disease treatments, the treatment of NAFLD/NASH requires weighing the benefits against potential side-effects (106). For example, resmetirom, while treating NASH and liver fibrosis, still carries a certain risk of liver toxicity, cholelithiasis and cholecystitis, and not all patients benefit from the drug, as 26 % of patients show no response. Additionally, in the early stages of the NAFLD disease spectrum, there are no obvious clinical manifestations, and NASH is often not detected promptly. This leads to some patients not seeking pharmacological treatments in a timely manner. Therefore, there remains a need to develop new drugs for NAFLD and explore new therapeutic targets (Table III).

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389 *Table III. Comparative data on astragaloside IV and other treatments against non-alcoholic fatty liver disease (NAFLD)*

Treatment	Mechanism of action	Effectiveness in NAFLD	Clinical status	API chemical composition	Producer/ developer	Country/origin	Pharmacological events (noticed/expected)	Reference
Astragaloside IV (AS-IV)	Improves insulin resistance, regulates lipid metabolism, reduces oxidative stress, modulates inflammation	Reduces liver steatosis, improves insulin sensitivity, alleviates oxidative stress, reduces inflammation	Preclinical studies, promising potential	Triterpenoid saponin (cycloartane glycoside)	Natural product (no specific manufacturer)	Native range: Inner Mongolia (China), Siberia	Multi-target effects on AMPK/Nrf2/TLR4 pathways; gut microbiota modulation; low systemic toxicity observed	23, 47, 55
Lifestyle interventions	Weight loss, exercise, dietary changes	Effective in early stages (NAFL), leads to liver function improvement and reversal of steatosis	Widely recommended	N/A	N/A	N/A	Sustainable weight loss (>5-10 %) improves steatosis; high dropout rates due to adherence challenges	26, 27
Vitamin E	Antioxidant properties, reduces oxidative stress	Improves liver function in early stages (NAFLD and NASH) by reducing oxidative stress and inflammation	FDA-approved for NASH (no cirrhosis)	α-Tocopherol	Various, *e.g.*, BASF-Germany, DSM-Netherlands	Multi-national	Reduced ALT/AST levels; potential long-term safety concerns (hemorrhage risk)	29, 30

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Resmetirom	THR-β agonist, reduces liver fat and improves metabolic markers	Reduces liver fat, improves metabolic markers, and reduces fibrosis in NASH	FDA approved for NASH with fibrosis	Resmetirom (MGL-3196) (liver-directed THR-β agonist)	Madrigal Pharmaceuticals	USA	Liver fat reduction (↓ 30-40 % in trials); side effects: liver enzyme elevation, cholelithiasis (26 % non-response)	86, 87
Semaglutide	GLP-1 receptor agonist, reduces appetite, improves insulin sensitivity	Significant reduction in liver fat, improves insulin sensitivity, and weight loss	Phase III for NASH	GLP-1 analog (acylated peptide)	Novo Nordisk	Denmark	Weight loss (≥10 %), improved glycemic control; gastrointestinal side effects (nausea, diarrhea)	88, 89
Lanifibranor	Pan-PPAR agonist	Improves hepatic steatosis and inflammation; antifibrotic effects	Phase III	Lanifibranor (PPAR-α/δ/γ agonist)	Inventiva Pharma	France	↑ Adiponectin, ↓ fibrosis markers; side effects: edema, weight gain	88
BIO89-100	FGF21 analogue, promotes hepatic fat metabolism	Reduces liver fat (↓ 25-30%) and improves lipid profiles in NASH patients	Phase IIb	Efruxifermin (FGF21-Fc fusion protein)	89bio	USA	Dose-dependent lipid reduction; mild injection-site reactions	91
Efruxifermin	Fc-FGF21 fusion protein, mimics FGF21 activity	Reduces liver fat (↓ 30-40%) and fibrosis in NASH patients	Phase IIb	Efruxifermin (FGF21-Fc)	Akero Therapeutics	USA	Improved fibrosis biomarkers (↓ Pro-C3); transient diarrhea	92
VK2809	THR-β agonist, enhances liver fat metabolism	Reduces liver fat (↓ 35-45%) and LDL-C in NAFLD patients	Phase II	VK2809 (liver-targeted THR-β agonist)	Viking Therapeutics	USA	↓ LDL-C (≥20 %), ↓ liver fat; mild transient hyperthyroidism risk	93

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Akt – protein kinase B, ALT – alanine aminotransferase (also known as serum glutamate-pyruvate transaminase, SGPT)/AST – aspartate aminotransferase (also known as serum glutamic oxaloacetic transaminase, SGOT), AMPK – AMP-activated protein kinase, AS-IV – astragaloside IV, FGF21-Fc – fibroblast growth factor 21, Fc fusion variant, GLP-1 – glucagon-like peptide-1, LDL-C – low-density lipoprotein cholesterol, NAFLD – non-alcoholic fatty liver disease, NAFL – non-alcoholic fatty liver, NASH – non-alcoholic steatohepatitis, Nrf2 – nuclear factor erythroid 2-related factor 2, PPAR – peroxisome proliferator-activated receptor, Pro-C3 – plasma Pro-C3 (N-terminal type III collagen propeptide), THR-β – thyroid hormone receptor beta, TLR4 – toll-like receptor 4, N/A – not applicable.

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AS-IV, the major bioactive component of *Astragalus membranaceus*, is recognized as a quality control marker for this herb in traditional medicine (107). Preclinical studies demonstrate that AS-IV reduces hepatic steatosis and inflammation in NAFLD models by targeting multiple pathological pathways (23, 24, 62). Specifically, it activates AMPK/Nrf2 signaling to mitigate oxidative stress and lipid accumulation, while suppressing TLR4/NF-κB-mediated inflammatory responses. Additionally, AS-IV modulates gut microbiota composition and bile acid metabolism, further contributing to its therapeutic efficacy (24, 94). These multi-target effects position AS-IV as a promising candidate for NAFLD treatment, particularly in addressing metabolic dysregulation and inflammation-driven liver injury.

Although AS-IV has demonstrated broad potential in the treatment of NAFLD, there are still some limitations in current research. First, most studies remain at the cellular and animal model stages, lacking clinical data to support its efficacy. While animal studies have shown that AS-IV effectively alleviates liver steatosis and improves metabolic disorders, its efficacy, safety and bioavailability in different populations still require further validation. Additionally, the specific mechanisms of AS-IV, particularly, how it coordinates between different molecular pathways, remain unclear. Future research should focus on clinical trials of AS-IV to confirm its therapeutic effects in NAFLD patients, explore the optimal dosage, treatment regimens, and assess the long-term safety of its use. Furthermore, as a component of TCM, the combined use of AS-IV with other drugs has not been fully explored. For example, the combination of AS-IV with other drugs, such as insulin sensitizers or anti-inflammatory agents, may have synergistic effects, justifying need for further investigation. Additionally, the pharmacokinetic properties of AS-IV and its metabolic processes in the liver need additional studies to enhance its therapeutic effects and reduce side-effects.

CONCLUSIONS

AS-IV, a naturally derived bioactive compound, has demonstrated significant therapeutic potential in the treatment of NAFLD. It improves the pathological state of NAFLD through multiple mechanisms, including enhancing insulin resistance, regulating lipid metabolism, inhibiting oxidative stress, exerting anti-inflammatory and anti-apoptotic effects, and modulating gut microbiota and bile acid metabolism. Its actions, mediated through the regulation of key molecular pathways such as AMPK, Nrf2 and SREBP-1c, reduce hepatic steatosis and related inflammation, offering a new strategy for the treatment of NAFLD. However, despite the promising results in animal models, there is still a lack of extensive clinical data to validate its efficacy and safety in diverse populations. Future research should focus on clinical trials, pharmacokinetic analysis, and the combined application of AS-IV with other drugs to further elucidate its mechanisms in treating NAFLD and enhance its clinical applicability.

List of acronyms, abbreviations, symbols. – Akt – protein kinase B, ALT – alanine aminotransferase (also known as serum glutamate-pyruvate transaminase, SGPT)/AST – aspartate aminotransferase (also known as serum glutamic oxaloacetic transaminase, SGOT), AMPK – AMP-activated protein kinase, AS-IV – astragaloside IV, Bax – Bcl-2-associated X protein, Bcl-2 – B-cell

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lymphoma-2, BSH – bile salt hydrolase, CAT – catalase, Cytc – cytochrome c, ECM – extracellular matrix, ER – endoplasmic reticulum, FasL – Fas ligand, FFA – free fatty acid, FGF21-Fc – fibroblast growth factor 21-Fc fusion variant, FXR – farnesoid X receptor, GLP-1 – glucagon-like peptide-1, GSH – glutathione, GSK-3β – glycogen synthase kinase-3β, HCC – hepatocellular carcinoma, HSC – hepatic stellate cell, IL-1β – interleukin-1β, IL-6 – interleukin-6, IR – insulin resistance, Keap1 – Kelch-like ECH-associated protein 1, LDL-C – low-density lipoprotein cholesterol, MPTP – mitochondrial permeability transition pore, MyD88 – myeloid differentiation factor 88, NAFLD – non-alcoholic fatty liver disease, NAFL – non-alcoholic fatty liver, NASH – non-alcoholic steatohepatitis, NF-κB – nuclear factor kappa B, NLRP3 – NLR family pyrin domain containing 3, Nrf2 – nuclear factor erythroid 2-related factor 2, PA – palmitic acid, PPAR – peroxisome proliferator-activated receptor, Pro-C3 – plasma Pro-C3 (N-terminal type III collagen propeptide), PTP1B – protein tyrosine phosphatase 1B, ROS – reactive oxygen species, SCFA – short-chain fatty acid, SOD – superoxide dismutase, SREBP-1c – sterol regulatory element-binding protein 1c, TG – triglyceride, THR-β – thyroid hormone receptor beta, TLR4 – toll-like receptor 4, TNF-α – tumor necrosis factor-alpha, VLCFA – very long-chain fatty acid.

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REFERENCES

1. R. Loomba, S. L. Friedman and G. I. Shulman, Mechanisms and disease consequences of nonalcoholic fatty liver disease, *Cell* **184**(10) (2021) 2537–2564; https://doi.org/10.1016/j.cell.2021.04.015
2. F. Bessone, M. V. Razori and M. G. Roma, Molecular pathways of nonalcoholic fatty liver disease development and progression, *Cell. Mol. Life Sci.* **76**(1) (2019) 99–128; https://doi.org/10.1007/s00018-018-2942-5
3. M. Papatheodoridi and E. Cholongitas, Diagnosis of non-alcoholic fatty liver disease (NAFLD): current concepts, *Curr. Pharm. Des.* **24**(38) (2018) 4574–4586; https://doi.org/10.2174/1381612824666181002105543
4. C. D. Byrne and G. Targher, NAFLD: a multisystem disease, *J. Hepatol.* **62**(1)(Suppl.) (2015) S47–S64; https://doi.org/10.1016/j.jhep.2014.12.012
5. A. Vadarlis, C. Antza, D. R. Bakaloudi, I. Doundoulakis, G. Kalopitas, M. Samara, T. Dardavessis, T. Maris and M. Chourdakis, Systematic review with meta-analysis: The effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease, *J. Gastroenterol. Hepatol.* **36**(2) (2021) 311–319; https://doi.org/10.1111/jgh.15221

Uncorrected proofs

6. M. Y. Wang, K. Prabahar, M. A. Găman and J. L. Zhang, Vitamin E supplementation in the treatment of nonalcoholic fatty liver disease (NAFLD): Evidence from an umbrella review of meta-analysis on randomized controlled trials, *J. Dig. Dis.* **24**(6–7) (2023) 380–389; https://doi.org/10.1111/1751-2980.13210

7. C. Gofton, Y. Upendran, M. H. Zheng and J. George, MAFLD: How is it different from NAFLD?, *Clin. Mol. Hepatol.* **29**(Suppl) (2023) S17–S31; https://doi.org/10.3350/cmh.2022.0367

8. S. L. Friedman, B. A. Neuschwander-Tetri, M. Rinella and A. J. Sanyal, Mechanisms of NAFLD development and therapeutic strategies, *Nat. Med.* **24**(7) (2018) 908–922; https://doi.org/10.1038/s41591-018-0104-9

9. L. Rong, J. Zou, W. Ran, X. Qi, Y. Chen, H. Cui and J. Guo, Advancements in the treatment of non-alcoholic fatty liver disease (NAFLD), *Front. Endocrinol.* (Lausanne) **13** (2023) Article ID 1087260 (18 pages); https://doi.org/10.3389/fendo.2022.1087260

10. M. J. Watt, P. M. Miotto, W. De Nardo and M. K. Montgomery, The liver as an endocrine organ—Linking NAFLD and insulin resistance, *Endocr. Rev.* **40**(5) (2019) 1367–1393; https://doi.org/10.1210/er.2018-00241

11. Y. Sakurai, N. Kubota, T. Yamauchi and T. Kadowaki, Role of insulin resistance in MAFLD, *Int. J. Mol. Sci.* **22**(8) (2021) Article ID 4156 (26 pages); https://doi.org/10.3390/ijms22084156

12. G. Paradies, V. Paradies, F. M. Ruggiero and G. Petrosillo, Oxidative stress, cardiolipin and mitochondrial dysfunction in nonalcoholic fatty liver disease, World J. Gastroenterol. **20**(39) (2014) 14205–14218; https://doi.org/10.3748/wjg.v20.i39.14205

13. J. Yang, M. Fernández-Galilea, L. Martínez-Fernández, P. González-Muniesa, A. Pérez-Chávez, J. A. Martínez and M. J. Moreno-Aliaga, Oxidative stress and non-alcoholic fatty liver disease: effects of omega-3 fatty acid supplementation, *Nutrients* **11**(4) (2019) Article ID 872 (37 pages); https://doi.org/10.3390/nu11040872

14. C. Luci, M. Bourinet, P. S. Leclère, R. Anty and P. Gual, Chronic inflammation in non-alcoholic steatohepatitis: molecular mechanisms and therapeutic strategies, *Front. Endocrinol.* (Lausanne) **11** (2020) Article ID 597648 (14 pages); https://doi.org/10.3389/fendo.2020.597648

15. R. Forlano, B. H. Mullish, S. K. Mukherjee, R. Nathwani, C. Harlow, P. Crook, R. Judge, A. Soubieres, P. Middleton, A. Daunt, P. Perez-Guzman, N. Selvapatt, M. Lemoine, A. Dhar, M. R. Thursz, S. Nayagam and P. Manousou, In-hospital mortality is associated with inflammatory response in NAFLD patients admitted for COVID-19, *PLoS One* **15**(10) (2020) e0240400; https://doi.org/10.1371/journal.pone.0240400.

16. A. A. Kolodziejczyk, D. Zheng, O. Shibolet and E. Elinav, The role of the microbiome in NAFLD and NASH, *EMBO Mol. Med.* **11**(2) (2019) e9302; https://doi.org/10.15252/emmm.201809302

17. A. Albillos, A. de Gottardi and M. Rescigno, The gut-liver axis in liver disease: pathophysiological basis for therapy, *J. Hepatol.* **72**(3) (2020) 558–577; https://doi.org/10.1016/j.jhep.2019.11.003

18. Z. Younossi, Q. M. Anstee, M. Marietti, T. Hardy, L. Henry, M. Eslam, J. George and E. Bugianesi, Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention, *Nat. Rev. Gastroenterol. Hepatol.* **15**(1) (2018) 11–20; https://doi.org/10.1038/nrgastro.2017.109

Uncorrected proofs

19. S. Wei, L. Wang, P. C. Evans and S. Xu, NAFLD and NASH: etiology, targets and emerging therapies, *Drug Discov. Today* **29**(3) (2024) Article ID 103910; https://doi.org/10.1016/j.drudis.2024.103910

20. Y. Sun, Y. Ma, F. Sun, W. Feng, H. Ye, T. Tian and M. Lei, Astragaloside IV attenuates lipopolysaccharide induced liver injury by modulating Nrf2-mediated oxidative stress and NLRP3-mediated inflammation, *Heliyon* **9**(4) (2023) e15436; https://doi.org/10.1016/j.heliyon.2023.e15436

21. S. Wu, F. Wen, X. Zhong, W. Du, M. Chen and J. Wang, Astragaloside IV ameliorate acute alcohol-induced liver injury in mice via modulating gut microbiota and regulating NLRP3/caspase-1 signaling pathway, *Ann. Med.* **55**(1) (2023) Article ID 2216942 (16 pages); https://doi.org/10.1080/07853890.2023.2216942

22. Y. Li, X. Yang, X. Li, S. Wang, P. Chen, T. Ma and B. Zhang, Astragaloside IV and cycloastragenol promote liver regeneration through regulation of hepatic oxidative homeostasis and glucose/lipid metabolism, *Phytomedicine* **135** (2024) Article ID 156165; https://doi.org/10.1016/j.phymed.2024.156165

23. B. Zhou, D. L. Zhou, X. H. Wei, R. Y. Zhong, J. Xu and L. Sun, Astragaloside IV attenuates free fatty acid-induced ER stress and lipid accumulation in hepatocytes via AMPK activation, *Acta Pharmacol. Sin.* **38**(7) (2017) 998–1008; https://doi.org/10.1038/aps.2016.175

24. Y. Zhai, W. Zhou, X. Yan, Y. Qiao, L. Guan, Z. Zhang, H. Liu, J. Jiang, J. Liu and L. Peng, Astragaloside IV ameliorates diet-induced hepatic steatosis in obese mice by inhibiting intestinal FXR via intestinal flora remodeling, *Phytomedicine* **107** (2022) Article ID 154444; https://doi.org/10.1016/j.phymed.2022.154444

25. Y.-L. Liu, Q.-Z. Zhang, Y.-R. Wang, L.-N. Fu, J.-S. Han, J. Zhang and B.-M. Wang, Astragaloside IV improves high-fat diet-induced hepatic steatosis in nonalcoholic fatty liver disease rats by regulating inflammatory factors level via TLR4/NF-κB signaling pathway, *Front. Pharmacol.* **11** (2021) Article ID 605064 (11 pages); https://doi.org/10.3389/fphar.2020.605064

26. J. M. Clark, Weight loss as a treatment for nonalcoholic fatty liver disease, *J. Clin. Gastroenterol.* **40**(Suppl. 1) (2006) S39–S43; https://doi.org/10.1097/01.mcg.0000168641.31321.fa

27. N. Hossain, P. Kanwar and S. R. Mohanty, A comprehensive updated review of pharmaceutical and nonpharmaceutical treatment for NAFLD, *Gastroenterol. Res. Pract.* **2016** (2016) Article ID 7109270 (17 pages); https://doi.org/10.1155/2016/7109270

28. S. Pouwels, N. Sakran, Y. Graham, A. Leal, T. Pintar, W. Yang, R. Kassir, R. Singhal, K. Mahawar and D. Ramnarain, Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss, *BMC Endocr. Disord.* **22**(1) (2022) Article ID 63 (9 pages); https://doi.org/10.1186/s12902-022-00980-1

29. M. F. Abdelmalek, Nonalcoholic fatty liver disease: another leap forward, *Nat. Rev. Gastroenterol. Hepatol.* **18**(2) (2021) 85–86; https://doi.org/10.1038/s41575-020-00406-0

30. G. Farrell, Insulin resistance, obesity, and liver cancer, *Clin. Gastroenterol. Hepatol.* **12**(1) (2014) 117–119; https://doi.org/10.1016/j.cgh.2013.07.040

Uncorrected proofs

31. N. Sodum, G. Kumar, S. L. Bojja, N. Kumar and C. M. Rao, Epigenetics in NAFLD/NASH: Targets and therapy, Pharmacol. Res. 167 (2021) Article ID 105484; https://doi.org/10.1016/j.phrs.2021.105484

32. S. A. Harrison, A. M. Allen, J. Dubourg, M. Noureddin and N. Alkhouri, Challenges and opportunities in NASH drug development, *Nat. Med.* **29**(3) (2023) 562–573; https://doi.org/10.1038/s41591-023-02242-6

33. S. J. Song, J. C. T. Lai, G. L. H. Wong, V. W. S. Wong and T. C. F. Yip, Can we use old NAFLD data under the new MASLD definition?, J. Hepatol. 80(2) (2024) e54–e56; https://doi.org/10.1016/j.jhep.2023.07.021

34. R. Younes and E. Bugianesi, The impact of metabolic syndrome on the outcome of NASH: cirrhosis, hepatocellular carcinoma, and mortality, *Curr. Hepatol. Rep.* **17**(4) (2018) 336–344; https://doi.org/10.1007/s11901-018-0422-x

35. T. Puengel and F. Tacke, Efruxifermin, an investigational treatment for fibrotic or cirrhotic nonalcoholic steatohepatitis (NASH), *Expert Opin. Investig. Drugs* **32**(6) (2023) 451–461; https://doi.org/10.1080/13543784.2023.2230115

36. K. Shree Harini and D. Ezhilarasan, Wnt/β-catenin signaling and its modulators in nonalcoholic fatty liver diseases, *Hepatobiliary Pancreat. Dis. Int.* **22**(4) (2023) 333–345; https://doi.org/10.1016/j.hbpd.2022.10.003

37. N. Bhala, R. Younes and E. Bugianesi, Epidemiology and natural history of patients with NAFLD, *Curr. Pharm. Des.* **19**(29) (2013) 5169–5176; https://doi.org/10.2174/13816128113199990336

38. H. Kojima, S. Sakurai, M. Uemura, H. Fukui, H. Morimoto and Y. Tamagawa, Mitochondrial abnormality and oxidative stress in nonalcoholic steatohepatitis, *Alcohol Clin. Exp. Res.* **31**(s1) (2007) S61–S66; https://doi.org/10.1111/j.1530-0277.2006.00288.x

39. N. Alkhouri, M. P. Berk, R. Lopez, T. Abu-Rajab Tamimi, L. Yerian, Y. Chung, R. Zhang, T. M. McIntyre, S. L. Hazen and A. E. Feldstein, OxNASH score correlates with histologic features and severity of nonalcoholic fatty liver disease, *Dig. Dis. Sci.* **59**(7) (2014) 1617–1624; https://doi.org/10.1007/s10620-014-3031-8

40. L. S. R. R. Okada, C. P. Oliveira, J. T. Stefano, M. A. Nogueira, I. D. C. G. da Silva, F. B. Cordeiro, V. A. F. Alves, R. S. Torrinhas, F. J. Carrilho, P. Puri and D. L. Waitzberg, Omega-3 PUFA modulate lipogenesis, ER stress, and mitochondrial dysfunction markers in NASH – proteomic and lipidomic insight, *Clin. Nutr.* **37**(5) (2017) 1474–1484; https://doi.org/10.1016/j.clnu.2017.08.031

41. J. S. Chang, J. H. Ahn, S. H. Kang, S. B. Koh, J. Y. Kim, S. K. Baik, J. H. Huh, S. S. Lee, M. Y. Kim and K. S. Park, Metabolic stress index including mitochondrial biomarker for noninvasive diagnosis of hepatic steatosis, *Front. Endocrinol.* **13** (2022) Article ID 896334 (8 pages); https://doi.org/10.3389/fendo.2022.896334

42. S. Seki, T. Kitada and H. Sakaguchi, Clinicopathological significance of oxidative cellular damage in non-alcoholic fatty liver diseases, *Hepatol. Res.* **33**(2) (2005) 132–134; https://doi.org/10.1016/j.hepres.2005.09.020

Uncorrected proofs

43. J. Zhang, C. Wu, L. Gao, G. Du and X. Qin, Astragaloside IV derived from Astragalus membranaceus: a research review on the pharmacological effects, *Adv. Pharmacol.* **87** (2020) 89–112; https://doi.org/10.1016/bs.apha.2019.08.002

44. L. Li, X. Hou, R. Xu, C. Liu and M. Tu, Research review on the pharmacological effects of astragaloside IV, *Fundam. Clin. Pharmacol.* **31**(1) (2017) 17–36; https://doi.org/10.1111/fcp.12232

45. Z. Zhuang, Z.-H. Wang, L.-H. Deng, Q. Zheng, G.-Q. Zheng and Y. Wang, Astragaloside IV exerts cardioprotection in animal models of viral myocarditis: a preclinical systematic review and meta-analysis, *Front. Pharmacol.* **10** (2019) Article ID 1388 (11 pages); https://doi.org/10.3389/fphar.2019.01388

46. F. Xu, W. Q. Cui, Y. Wei, J. Cui, J. Qiu, L. L. Hu, W. Y. Gong, J. C. Dong and B. J. Liu, Astragaloside IV inhibits lung cancer progression and metastasis by modulating macrophage polarization through AMPK signaling, *J. Exp. Clin. Cancer Res.* **37**(1) (2018) Article ID 207 (16 pages); https://doi.org/10.1186/s13046-018-0878-0

47. Z. Han, J. Zhu and Z. Han, Evaluation of astragaloside IV in hepatic fibrosis: a meta-analysis, *Medicine* **100**(13) (2021) e25105; https://doi.org/10.1097/MD.0000000000025105

48. H. Wang, Z. Zhuang, Y.-Y. Huang, Y. Zhuang, J. Jin, X. Ye, Z. Lin, J. Zheng and H. Wang, Protective effect and possible mechanisms of Astragaloside IV in animal models of diabetic nephropathy: a preclinical systematic review and meta-analysis, *Front. Pharmacol.* **11** (2020) Article ID 988 (17 pages); https://doi.org/10.3389/fphar.2020.00988

49. I. M. Costa, F. O. V. Lima, L. C. B. Fernandes, B. Norrara, F. I. Neta, R. D. Alves, J. R. L. P. Cavalcanti, E. E. S. Lucena, J. S. Cavalcante, A. C. M. Rego, I. A. Filho, D. B. Queiroz, M. A. M. Freire and F. P. Guzen, Astragaloside IV supplementation promotes a neuroprotective effect in experimental models of neurological disorders: a systematic review, *Curr. Neuropharmacol.* **17**(7) (2019) 648–665; https://doi.org/10.2174/1570159X16666180911123341

50. M. Marušić, M. Paić, M. Knobloch and A.-M. Liberati Pršo, NAFLD, insulin resistance, and diabetes mellitus type 2, *Can. J. Gastroenterol. Hepatol.* **2021** (2021) Article ID 6613827 (9 pages); https://doi.org/10.1155/2021/6613827

51. D. Xia, W. Li, C. Tang and J. Jiang, Astragaloside IV, as a potential anticancer agent, *Front. Pharmacol.* **14** (2023) Article ID 1065505 (15 pages); https://doi.org/10.3389/fphar.2023.1065505

52. K. Mehta, D. H. Van Thiel, N. Shah and S. Mobarhan, Nonalcoholic fatty liver disease: pathogenesis and the role of antioxidants, *Nutr. Rev.* **60**(9) (2002) 289–293; https://doi.org/10.1301/002966402320387224

53. F. Item, S. Wueest, V. Lemos, S. Stein, F. C. Lucchini, R. Denzler, M. C. Fisser, T. D. Challa, E. Pirinen, Y. Kim, S. Hemmi, E. Gulbins, A. Gross, L. A. O'Reilly, M. Stoffel, J. Auwerx and D. Konrad, Fas cell surface death receptor controls hepatic lipid metabolism by regulating mitochondrial function, *Nat. Commun.* **8**(1) (2017) Article ID 480 (10 pages); https://doi.org/10.1038/s41467-017-00566-9

54. L. Ding, W. Sun, M. Balaz, A. He, M. Klug, S. Wieland, R. Caiazzo, V. Raverdy, F. Pattou, P. Lefebvre, I. J. Lodhi, B. Staels, M. Heim and C. Wolfrum, Peroxisomal β-oxidation acts as a sensor

Uncorrected proofs

for intracellular fatty acids and regulates lipolysis, *Nat. Metab.* **3**(12) (2021) 1648–1661; https://doi.org/10.1038/s42255-021-00489-2

55. X. Zhou, L. L. Wang, W. J. Tang and B. Tang, Astragaloside IV inhibits protein tyrosine phosphatase 1B and improves insulin resistance in insulin-resistant HepG2 cells and triglyceride accumulation in oleic acid (OA)-treated HepG2 cells, *J. Ethnopharmacol.* **268**(11) (2021) Article ID 113556; https://doi.org/10.1016/j.jep.2020.113556

56. J. L. Rains and S. K. Jain, Oxidative stress, insulin signaling, and diabetes, *Free Radic. Biol. Med.* **50**(5) (2011) 567–575; https://doi.org/10.1016/j.freeradbiomed.2010.12.006

57. S. Vomund, A. Schäfer, M. J. Parnham, B. Brüne and A. Von Knethen, Nrf2, the master regulator of anti-oxidative responses, *Int. J. Mol. Sci.* **18**(12) (2017) Article ID 2772 (19 pages); https://doi.org/10.3390/ijms18122772

58. S. Herzig and R. J. Shaw, AMPK: guardian of metabolism and mitochondrial homeostasis, *Nat. Rev. Mol. Cell Biol.* **19**(2) (2018) 121–135; https://doi.org/10.1038/nrm.2017.95

59. H. Yun, S. Park, M. J. Kim, W. K. Yang, D. U. Im, K. R. Yang, J. Hong, W. Choe, I. Kang, S. S. Kim and J. Ha, AMP-activated protein kinase mediates the antioxidant effects of resveratrol through regulation of the transcription factor FoxO1, *FEBS J.* **281**(19) (2014) 4421–4438; https://doi.org/10.1111/febs.12949

60. Q. Lu, L. Yang, J.-J. Xiao, Q. Liu, L. Ni, J.-W. Hu, H. Yu, X. Wu and B.-F. Zhang, Empagliflozin attenuates the renal tubular ferroptosis in diabetic kidney disease through AMPK/NRF2 pathway, *Free Radic. Biol. Med.* **195** (2023) 89–102; https://doi.org/10.1016/j.freeradbiomed.2022.12.088

61. X. Li, D. Wu and T. Ye, Fibroblast growth factor 19 protects the heart from oxidative stress-induced diabetic cardiomyopathy via activation of AMPK/Nrf2/HO-1 pathway, *Biochem. Biophys. Res. Commun.* **502**(1) (2018) 62–68; https://doi.org/10.1016/j.bbrc.2018.05.121

62. X. H. Zhou, L. Q. He, S. N. Zuo, Y. M. Zhang, D. Wan, C. M. Long, P. Huang, X. Wu, C. R. Wu, G. Liu and Y. Yin, Serine prevented high-fat diet–induced oxidative stress by activating AMPK and epigenetically modulating the expression of glutathione synthesis-related genes, *Biochim. Biophys. Acta Mol. Basis Dis.* **1864**(2) (2018) 488–498; https://doi.org/10.1016/j.bbadis.2017.11.009

63. L. Li, W. X. Huang, S. K. Wang, K. Sun, W. Zhang, Y. Ding, L. Zhang, B. Tumen and L. Lang, Astragaloside IV attenuates acetaminophen-induced liver injuries in mice by activating the Nrf2 signaling pathway, *Molecules* **23**(8) (2018) Article ID 2032 (9 pages); https://doi.org/10.3390/molecules23082032

64. N. Cheng, S. Chen, X. Liu, H. Zhao and W. Cao, Impact of *Schisandra chinensis* bee pollen on nonalcoholic fatty liver disease and gut microbiota in high-fat diet induced obese mice, *Nutrients* **11**(2) (2019) Article ID 346 (16 pages); https://doi.org/10.3390/nu11020346

65. M. Martin, K. Rehani, R. S. Jope and S. M. Michalek, Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase 3, *Nat. Immunol.* **6**(8) (2005) 777–784; https://doi.org/10.1038/ni1221

66. D. Sag, D. Carling, R. D. Stout and J. Suttles, Adenosine 5′-monophosphate-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype, *J. Immunol.* **181**(12) (2008) 8633–8641; https://doi.org/10.4049/jimmunol.181.12.8633

Uncorrected proofs

67. R. Wei, H. Liu, R. Chen, Y. Sheng and T. Liu, Astragaloside IV combating liver cirrhosis through the PI3K/Akt/mTOR signaling pathway, *Exp. Ther. Med.* **17**(1) (2019) 393–397; https://doi.org/10.3892/etm.2018.6966 Spandidos Publications

68. D. Qin, D. N. Ma, Z. G. Ren, X. D. Zhu, C. H. Wang, Y. C. Wang, B. Ye, M. Cao, D. Gao, Z. Tang and Z. Tang, Astragaloside IV inhibits metastasis in hepatoma cells through the suppression of epithelial-mesenchymal transition via the Akt/GSK-3β/β-catenin pathway, *Oncol. Rep.* **37**(3) (2017) 1725–1735; https://doi.org/10.3892/or.2017.5389

69. X. Qu, H. Gao, L. Tao, Y. Zhang, J. Zhai, J. Sun, Y. Song and S. Zhang, Astragaloside IV protects against cisplatin-induced liver and kidney injury via autophagy-mediated inhibition of NLRP3 in rats, *J. Toxicol. Sci.* **44**(3) (2019) 167–175; https://doi.org/10.2131/jts.44.167

70. J. R. Ham, H.-I. Lee, R.-Y. Choi, M.-O. Sim, K.-I. Seo and M.-K. Lee, Anti-steatotic and anti-inflammatory roles of syringic acid in high-fat diet-induced obese mice, *Food Funct.* **7**(2) (2016) 689–697; https://doi.org/10.1039/C5FO01411A

71. G. Baffy, Kupffer cells in non-alcoholic fatty liver disease: the emerging view, *J. Hepatol.* **51**(1) (2009) 212–223; https://doi.org/10.1016/j.jhep.2009.03.008

72. S. Saravanan, V. I. Islam, N. P. Babu, P. Pandikumar, K. Thirugnanasambantham, M. Chellappandian, C. S. Raj, M. G. Paulraj and S. Ignacimuthu, Swertiamarin attenuates inflammation mediators via modulating NF-κB/IκB and JAK2/STAT3 transcription factors in adjuvant induced arthritis, *Eur. J. Pharm. Sci.* **56** (2014) 70–86; https://doi.org/10.1016/j.ejps.2014.02.005

73. Z. L. Bian, Y. Peng, Z. You, Q. Wang, Q. Miao, Y. Liu, X. Han, D. Qiu, Z. Li and X. Ma, CCN1 expression in hepatocytes contributes to macrophage infiltration in nonalcoholic fatty liver disease in mice, *J. Lipid Res.* **54**(1) (2013) 44–54; https://doi.org/10.1194/jlr.M026013

74. E. Radi, P. Formichi, C. Battisti and A. Federico, Apoptosis and oxidative stress in neurodegenerative diseases, *J. Alzheimers Dis.* **42**(Suppl. 3) (2014) S125–S152; https://doi.org/10.3233/JAD-132738

75. K. J. Campbell and S. W. G. Tait, Targeting BCL-2 regulated apoptosis in cancer, *Open Biol.* **8**(5) (2018) Article ID 180002 (11 pages); https://doi.org/10.1098/rsob.180002

76. C. A. Gregory, H. Singh, A. S. Perry and D. J. Prockop, Deletion of the BH1 domain of Bcl-2 accelerates apoptosis by acting in a dominant negative fashion, *J. Biol. Chem.* **278**(22) (2003) 19732–19742; https://doi.org/10.1074/jbc.M300373200

77. C. Cárdenas, R. A. Miller, I. Smith, T. Bui, J. Molgó, M. Müller, H. Vais, K.-H. Cheung, J. Yang, I. Parker, C. B. Thompson, M. J. Birnbaum, K. R. Hallows and J. K. Foskett, Essential regulation of cell bioenergetics by constitutive $InsP_3$ receptor Ca^{2+} transfer to mitochondria, *Cell* **142**(2) (2010) 270–283; https://doi.org/10.1016/j.cell.2010.06.007

78. J. A. Martinez, Z. Zhang, S. I. Svetlov, R. L. Hayes, K. K. Wang and S. F. Larner, Calpain and caspase processing of caspase-12 contribute to the ER stress-induced cell death pathway in differentiated PC12 cells, *Apoptosis* **15**(12) (2010) 1480–1493; https://doi.org/10.1007/s10495-010-0531-7

79. C. J. Hanson, M. D. Bootman, C. W. Distelhorst, R. J. H. Wojcikiewicz and H. L. Roderick, Bcl-2 suppresses Ca^{2+} release through inositol 1,4,5-trisphosphate receptors and inhibits Ca^{2+} uptake by

Uncorrected proofs

mitochondria without affecting ER calcium store content, *Cell Calcium* **44**(3) (2008) 324–338; https://doi.org/10.1016/j.ceca.2008.01.003

80. X.-Y. Liang, F.-F. Hong and S.-L. Yang, Astragaloside IV alleviates liver inflammation, oxidative stress and apoptosis to protect against experimental non-alcoholic fatty liver disease, *Diabetes Metab. Syndr. Obes.* **14** (2021) 1871–1883; https://doi.org/10.2147/DMSO.S304817

81. X. Liu, W. Chu, S. Shang, L. Ma, C. Jiang, Y. Ding, J. Wang, S. Zhang and B. Shao, Preliminary study on the anti-apoptotic mechanism of astragaloside IV on radiation-induced brain cells, *Int. J. Immunopathol. Pharmacol.* **34** (2020) Article ID 2058738420954594; https://doi.org/10.1177/2058738420954594

82. Z. Liu, Z. Zhou, P. Ai, C. Zhang, J. Chen and Y. Wang, Astragaloside IV attenuates ferroptosis after subarachnoid hemorrhage via Nrf2/HO-1 signaling pathway, *Front. Pharmacol.* **13** (2022) Article ID 924826 (13 pages); https://doi.org/10.3389/fphar.2022.924826

83. Z. Qi, P. Zhang, L. Yang, P. Song, J. Zhao, H. Wang, Y. Zhao and L. Cao, Astragaloside IV alleviates doxorubicin-induced cardiotoxicity by inhibiting cardiomyocyte pyroptosis through the SIRT1/NLRP3 pathway, *Am. J. Chin. Med.* **52**(2) (2024) 453–469; https://doi.org/10.1142/S0192415X24500198

84. X. Meng, G. Zhang, H. Cao, D. Yu, X. Fang, W. M. de Vos and H. Wu, Gut dysbacteriosis and intestinal disease: mechanism and treatment, *J. Appl. Microbiol.* **129**(4) (2020) 787–805; https://doi.org/10.1111/jam.14661

85. L. L. Deng, Astragaloside IV as potential antioxidant against diabetic ketoacidosis in juvenile mice through activating JNK/Nrf2 signaling pathway, *Arch. Med. Res.* **51**(7) (2020) 654–663; https://doi.org/10.1016/j.arcmed.2020.06.013

86. D. M. Chopyk and A. Grakoui, Contribution of the intestinal microbiome and gut barrier to hepatic disorders, *Gastroenterology* **159**(3) (2020) 849–863; https://doi.org/10.1053/j.gastro.2020.04.077

87. J. W. Jung, F. Wang, A. Turk, J. S. Park, H. Ma, Y. Ma, H.-R. Noh, G. Sui, D. S. Shin, M. K. Lee and Y. S. Roh, Zaluzanin C alleviates inflammation and lipid accumulation in Kupffer cells and hepatocytes by regulating mitochondrial ROS, *Molecules* **28**(22) (2023) Article ID 7484; https://doi.org/10.3390/molecules28227484

88. J. Fang, C.-H. Yu, X.-J. Li, J.-M. Yao, Z.-Y. Fang, S.-H. Yoon and W.-Y. Yu, Gut dysbiosis in nonalcoholic fatty liver disease: pathogenesis, diagnosis, and therapeutic implications, *Front. Cell. Infect. Microbiol.* **12** (2022) Article ID 997018 (12 pages); https://doi.org/10.3389/fcimb.2022.997018

89. D. Zhang, X. Hao, L. Xu, J. Cui, L. Xue and Z. Tian, Intestinal flora imbalance promotes alcohol-induced liver fibrosis by the TGFβ/Smad signaling pathway in mice, *Oncol. Lett.* **14**(4) (2017) 4511–4516; https://doi.org/10.3892/ol.2017.6762

90. A. Wieland, D. N. Frank, B. Harnke and K. Bambha, Systematic review: microbial dysbiosis and nonalcoholic fatty liver disease, *Aliment. Pharmacol. Ther.* **42**(9) (2015) 1051–1063; https://doi.org/10.1111/apt.13376

Uncorrected proofs

91. L. Xue, Z. Deng, W. Luo, X. He and Y. Chen, Effect of fecal microbiota transplantation on non-alcoholic fatty liver disease: a randomized clinical trial, *Front. Cell. Infect. Microbiol.* **12** (2022) Article ID 759306 (10 pages); https://doi.org/10.3389/fcimb.2022.759306

92. V. Kaden-Volynets, M. Basic, U. Neumann, D. Pretz, A. Rings, A. Bleich and S. C. Bischoff, Lack of liver steatosis in germ-free mice following hypercaloric diets, *Eur. J. Nutr.* **58** (2019) 1933–1945; https://doi.org/10.1007/s00394-018-1748-4

93. J. Fu, M. J. Bonder, M. C. Cenit, E. F. Tigchelaar, A. Maatman, J. A. M. Dekens, E. Brandsma, J. Marczynska, F. Imhann, R. K. Weersma, L. Franke, T. W. Poon, R. J. Xavier, D. Gevers, M. H. Hofker, C. Wijmenga and A. Zhernakova, The gut microbiome contributes to a substantial proportion of the variation in blood lipids, *Circ. Res.* **117**(9) (2015) 817–824; https://doi.org/10.1161/CIRCRESAHA.115.306807

94. Z. Li, E. Hu, F. Zheng, S. Wang, W. Zhang, J. Luo, T. Tang, Q. Huang and Y. Wang, The effects of astragaloside IV on gut microbiota and serum metabolism in a mice model of intracerebral hemorrhage, *Phytomedicine* **121** (2023) Article ID 155086; https://doi.org/10.1016/j.phymed.2023.155086

95. X. Q. Du, L. P. Shi, Z. W. Chen, J. Y. Hu, B. Zuo, Y. Xiong and W. F. Cao, Astragaloside IV ameliorates isoprenaline-induced cardiac fibrosis in mice via modulating gut microbiota and fecal metabolites, *Front. Cell. Infect. Microbiol.* **12** (2022) Article ID 836150 (11 pages); https://doi.org/10.3389/fcimb.2022.836150

96. T. Yang, S. Xie, L. Cao, M. Li, L. Ding, L. Wang, S. Pang, Z. Wang and L. Geng, Astragaloside IV modulates gut macrophages M1/M2 polarization by reshaping gut microbiota and short chain fatty acids in sepsis, *Shock* **61**(1) (2024) 120–131; https://doi.org/10.1097/SHK.0000000000002262

97. P. Golabi, H. Bush, M. Stepanova, C. T. Locklear, J. P. Weston, Z. Goodman, I. M. Younossi and Z. M. Younossi, Liver transplantation (LT) for cryptogenic cirrhosis (CC) and nonalcoholic steatohepatitis (NASH) cirrhosis: data from the Scientific Registry of Transplant Recipients (SRTR): 1994 to 2016, *Medicine* **97**(31) (2018) e11518; https://doi.org/10.1097/MD.0000000000011518

98. S. A. Harrison, M. R. Bashir, C. D. Guy, R. Zhou, C. A. Moylan, J. P. Frias, N. Alkhouri, M. B. Bansal, S. Baum, B. A. Neuschwander-Tetri, R. Taub and S. E. Moussa, Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial, *Lancet* **394**(10213) (2019) 2012–2024; https://doi.org/10.1016/S0140-6736(19)32517-6

99. A. R. Saran, S. Dave and A. Zarrinpar, Circadian rhythms in the pathogenesis and treatment of fatty liver disease, *Gastroenterology* **158**(7) (2020) 1948–1966.e1; https://doi.org/10.1053/j.gastro.2020.01.050

100. S. M. Francque, P. Bedossa, V. Ratziu, Q. M. Anstee, E. Bugianesi, A. J. Sanyal, R. Loomba, S. A. Harrison, R. Balabanska, L. Mateva, N. Lanthier, N. Alkhouri, C. Moreno, J. M. Schattenberg, D. Stefanova-Petrova, L. Vonghia, R. Rouzier, M. Guillaume, A. Hodge, M. Romero-Gómez, P. Huot-Marchand, M. Baudin, M.-P. Richard, J.-L. Abitbol, P. Broqua, J.-L. Junien and M. F. Abdelmalek, A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH, *N. Engl. J. Med.* **385**(17) (2021) 1547–1558; https://doi.org/10.1056/NEJMoa2036205

Uncorrected proofs

101. P. N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A. J. Sanyal, A.-S. Sejling and S. A. Harrison, A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis, *N. Engl. J. Med.* **384**(12) (2021) 1113–1124; https://doi.org/10.1056/NEJMoa2028395

102. N. Alkhouri, R. Herring, H. Kabler, Z. Kayali, T. Hassanein, A. Kohli, R. S. Huss, Y. Zhu, A. N. Billin, L. H. Damgaard, K. Buchholtz, M. S. Kjær, C. Balendran, R. P. Myers, R. Loomba and M. Noureddin, Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: a randomised, open-label phase II trial, *J. Hepatol.* **77**(3) (2022) 607–618; https://doi.org/10.1016/j.jhep.2022.04.003

103. R. Loomba, E. J. Lawitz, J. P. Frias, G. Ortiz-Lasanta, L. Johansson, B. B. Franey, L. Morrow, M. Rosenstock, C. L. Hartsfield, C.-Y. Chen, L. Tseng, R. W. Charlton, H. Mansbach and M. Margalit, Safety, pharmacokinetics, and pharmacodynamics of pegozafermin in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 1b/2a multiple-ascending-dose study, *Lancet Gastroenterol. Hepatol.* **8**(2) (2023) 120–132; https://doi.org/10.1016/S2468-1253(22)00347-8

104. S. A. Harrison, J. P. Frias, G. Neff, G. A. Abrams, K. J. Lucas, W. Sanchez, S. Gogia, M. Y. Sheikh, C. Behling, P. Bedossa, L. Shao, D. Chan, E. Fong, B. de Temple, R. Shringarpure, E. J. Tillman, T. Rolph, A. Cheng and K. Yale, Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial, *Lancet Gastroenterol. Hepatol.* **8**(12) (2023) 1080–1093; https://doi.org/10.1016/S2468-1253(23)00272-8

105. J. Zhou, L. R. Waskowicz, A. Lim, X.-H. Liao, B. Lian, H. Masamune, S. Refetoff, B. Tran, D. D. Koeberl and P. M. Yen, A liver-specific thyromimetic, VK2809, decreases hepatosteatosis in glycogen storage disease type Ia, *Thyroid* **29**(8) (2019) 1158–1167; https://doi.org/10.1089/thy.2019.0007

106. S. A. Harrison, R. Taub, G. W. Neff, K. J. Lucas, D. Labriola, S. E. Moussa, N. Alkhouri and M. R. Bashir, Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial, *Nat. Med.* **29**(11) (2023) 2919–2928; https://doi.org/10.1038/s41591-023-02603-1

107. Chinese Pharmacopoeia Commission, *Pharmacopoeia of the People's Republic of China*, 11th ed., China Medical Science Press, Beijing 2020.

Uncorrected proofs