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COMMENTARY

Research Progress on the Role and Mechanism of Flavonoids in Improving Metabolic Associated Fatty Liver Disease

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Abstract: Flavonoids are widely present in various plants and possess multiple biological activities, such as anti-inflammation, antioxidation and anticancer. In the realm of disease prevention and therapeutic interventions, a noteworthy function is assumed by these entities, evident from their significant research potentiality and intrinsic value. Characterized by an excessive lipid accumulation within the hepatic cells, metabolic associated fatty liver disease (MAFLD) manifests as a prevalent chronic ailment of the liver. The "multiple hits" theory suggests that its occurrence is the result of systemic homeostasis imbalance, influenced by factors such as abnormal lipid metabolism, inflammatory reaction, oxidative stress, insulin resistance, and gut microbiota. However, there are no effective clinical drugs for it. Recent studies have found that flavonoid active components can alleviate MAFLD through multiple pathways, including regulating abnormal lipid metabolism, inhibiting inflammatory response, alleviating oxidative stress, improving insulin resistance, regulating gut microbiota, and regulating liver autophagy. Therefore, this paper summarizes the pharmacological action and related mechanisms of flavonoid active components in improving MAFLD. This manuscript may provide a reference for seeking a novel therapeutic agent for MAFLD management.

Keywords: flavonoids, metabolic-related fatty liver disease, mechanism, research progress, literature review

Introduction

Non-alcoholic fatty liver disease (NAFLD) was renamed metabolic-associated fatty liver disease (MAFLD) in 2020.[1,2] It is primarily defined by the abnormal buildup of triglycerides (TGs) and other lipids in liver cells. This buildup can result in chronic liver inflammation, liver fibrosis, and liver cell damage. Liver cirrhosis and hepatocellular carcinoma are both significantly impacted by this key risk complications.[3] Research has shown that the active flavonoid components can effectively improve liver damage caused by MAFLD, and in - depth research has been conducted on its mechanism of action. This article reviews the research progress on the intervention effect and mechanism of active flavonoid components on MAFLD, and discusses the existing problems and solutions in current research, aiming to provide some references for the application and research of active flavonoid components in the prevention and treatment of MAFLD.

Methodology

To gain a more comprehensive understanding of flavonoid active substances, oxidative stress, and diseases related to lipid metabolic disorders as well as their interrelationships, relevant literature was collected from various medical databases. We utilized databases such as PubMed, Web of Science, and Google Scholar, selecting pertinent articles published between 2015 and 2025. However, to ensure the timeliness of the data, we prioritized literature from the most recent five years. Keywords included: MAFLD, NAFLD, flavonoid active substances, mechanisms, etc. To enhance the completeness and effectiveness of the search, these keywords were adjusted to meet the specific requirements of different

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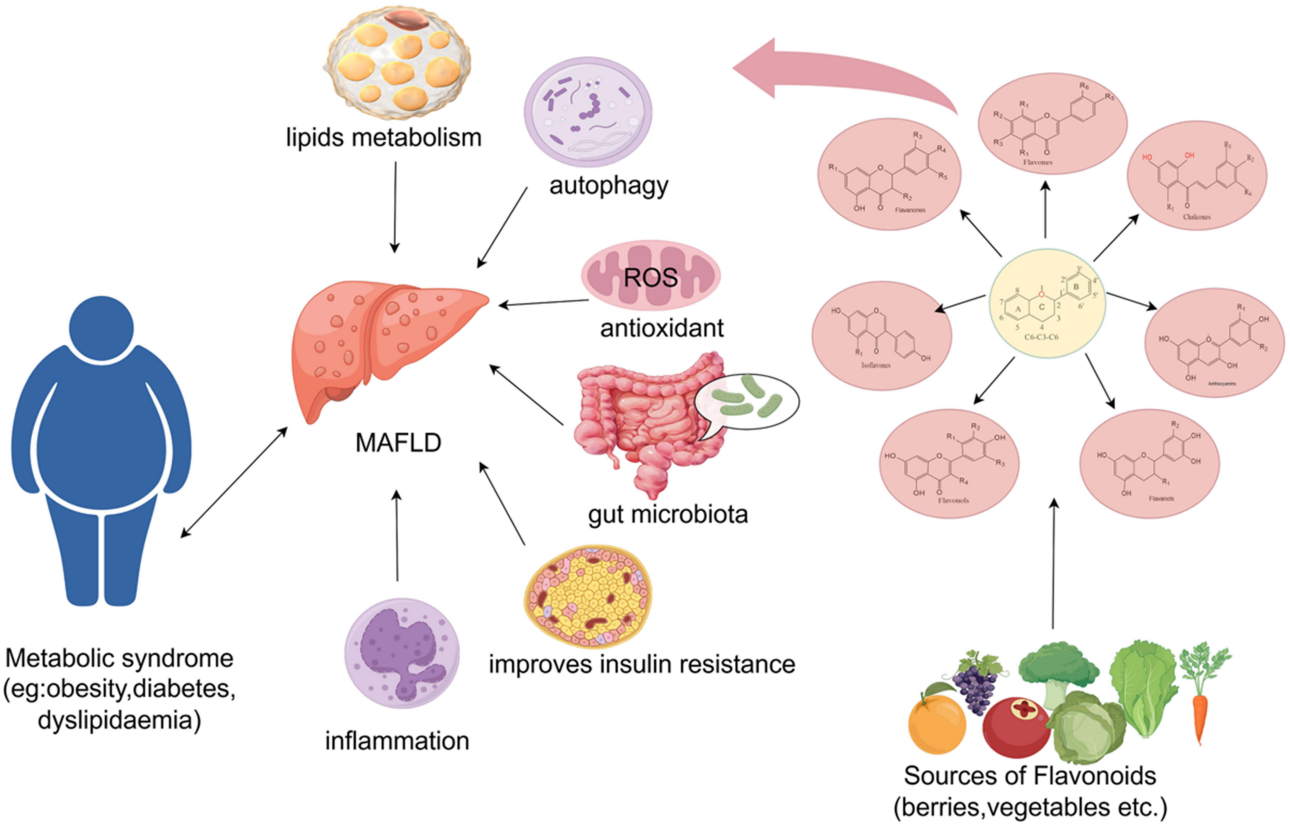
Graphical Abstract



databases. For the relevant articles identified during the search, preliminary screening was conducted based on titles and abstracts, excluding those with low or no relevance.

Pathogenesis and Treatment of MAFLD

MAFLD is a group of liver diseases that are characterized by the buildup of fat in the liver. It is a crucial step in the progression from simple steatosis to liver cirrhosis. Its occurrence can be increased by obesity, hypertension, type 2 diabetes, and metabolic syndrome.[4,5] The "multiple hits" theory suggests that the occurrence of MAFLD is the result of systemic homeostasis imbalance, which is influenced by multiple factors such as abnormal lipid metabolism, oxidative stress, insulin resistance, inflammation and gut microbiota.[6–8] Currently, there is no standard treatment for MAFLD. Intervention is mostly carried out by optimizing lifestyle through reasonable diet and exercise interventions. Therefore, it is urgent to discover drugs that can effectively intervene in MAFLD and conduct experiments in vitro and in vivo and clinical efficacy verification. Flavonoids provide new ideas and research directions for researchers.

Flavonoids with Efficacy in Improving MAFLD

Flavonoids constitute a category of naturally occurring polyphenolic compounds that are pervasive in the natural world, which are mainly divided into seven major categories, namely flavones (such as apigenin and luteolin), flavanones (such as naringenin and hesperetin), isoflavones (such as genistein, daidzein and glycitein), flavonols (such as quercetin, galangin, kaempferol and myricetin), flavanols (such as catechin, gallocatechin, epicatechin), anthocyanidins (such as delphinidin, cyanidin, malvidin, peonidin and pelargonidin), and chalcones (found in Leguminosae, Moraceae, Zingiberaceae and Cannabaceae), most exist in the form of glycosides or carbon-based bonds and are stored in the vacuoles of various plant roots, stems, leaves, and flowers. They

have antioxidant, anti-inflammatory, antiviral and anti - cancer activities.[9–15] Although the active flavonoid components are considered beneficial to health, such as having anti - inflammatory, antioxidant, and anti - cancer properties, they have relatively low oral bioavailability due to low water solubility, poor intestinal absorption, high hepatic first - pass effect, and rapid excretion in bile and urine.[12,16–18] Most active flavonoid components are not absorbed during the enterohepatic circulation and are more susceptible to the influence of gut microbiota compared with other active components.[19] To address these issues, researchers have begun to explore various innovative drug delivery systems, such as liposomes, nanoparticles, and solid dispersions, to enhance the stability and bioavailability of active flavonoid components. The clinical application of flavonoids is developing in multiple aspects, and new flavonoid drugs are becoming an important research direction for the treatment of MAFLD. Therefore, a thorough understanding of the mechanism of action of active flavonoid components can help people better prevent and treat MAFLD.

Intervention Effect and Mechanism of Flavonoids on MAFLD

Regulate Lipid Metabolism

Lipid metabolism dysfunction is a key link in the occurrence and development of MAFLD. Improving lipid metabolism disorders is an important way to delay or even block the progression of the disease. Lipid accumulation in the liver is the first step in the occurrence of MAFLD, which is regulated by mechanisms such as lipoprotein synthesis, lipid uptake and efflux, and fatty acid synthesis and oxidative metabolism.[20,21] The increased influx and synthesis of fatty acids in liver cells and the weakened fatty acid oxidation caused by factors such as a high-fat diet (HFD) are important links in inducing excessive lipid accumulation in the liver.[22] The production of toxic lipids can also result from a disturbance in the regulation of lipid homeostasis in hepatocytes, which in turn causes organelle dysfunction and induces inflammation, hepatocyte damage, and cell death, etc.[23] The active flavonoid components can inhibit the relevant pathways, reduce lipid production and lipid deposition to regulate liver lipid metabolism, improve liver lipid metabolism disorders, and decelerate the progression of MAFLD.

In mice fed with a high-fat diet (HFD), the protein levels of fatty acid synthase (FASN), sterol regulatory element-binding protein 1c (SREBP-1c), and acetyl-coenzyme A carboxylase (ACC) related to lipogenesis increase sharply, which exacerbates the disease progression of MAFLD. As one of the abundant flavonols, quercetin can reduce lipogenesis-related proteins. After treating HepG2 cells with overexpressed SREBP-1c with quercetin for 6 h, the levels of FASN and ACC proteins induced by HFD are effectively reduced, thus delaying the progression of MAFLD.[24,25] Fructus Aurantii Immaturus belongs to the citrus family and is rich in flavonoids, which have antioxidant and immune-enhancing effects.[26] Studies have confirmed that it can correct the gut microbiota dysbiosis induced by HFD, enhance the presence of beneficial microbial taxa related to lipid metabolism, including Alistipes and Parabacteroides, and increase the concentrations of anti-obesity short-chain fatty acids (including caproic acid and isocaproic acid). It can also improve the dysbiosis caused by HFD, boost the adenosine monophosphate-activated protein kinase (AMPK) / peroxisome proliferator-activated receptor alpha (PPARα) / carnitine palmitoyltransferase 1A (CPT-1A) signaling pathway to enhance fatty acid catabolism and prevent obesity in mice, thereby promoting the oxidation of free fatty acids and reducing hepatic lipid accumulation.[27,28] The species of the Chinese herbal medicine kudzu root can be extracted with natural flavonoid compounds.[29] The phosphatidylinositol 3-kinase (PI3K)/serine-threonine protein kinase (Akt)/mammalian target of rapamycin (mTOR) signaling pathway is involved in physiological processes such as apoptosis, hepatic gluconeogenesis, and the cell cycle, and is related to the development of MAFLD.[30] Animal experiments have shown that the PI3K/Akt/mTOR pathway is key to the significant reduction of abdominal lipid storage in rats caused by flavonoids from Radix Puerariae, decrease the levels of triglyceride (TG) and total cholesterol (TC) in the rat liver, and reduce intracellular lipid deposition, thereby improving lipid metabolism.[31] The peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor belonging to the nuclear hormone receptor superfamily. It is considered an important regulator of liver lipid metabolism and inflammation.[32] CCAAT/enhancer-binding protein alpha (CEBPA) is expressed in hepatocytes and regulates glycolipid homeostasis,[33] Inhibiting CEBPA activation can optimize glucose metabolism and reduce hepatic steatosis.[34] Both the PPAR-γ2 protein and the adipocyte protein 2 (aP2) are target genes of the PPAR-γ. Research has demonstrated that nobiletin has the capacity to reduce the levels of CCAAT/enhancer-binding protein β (C/EBPβ) expression and significantly inhibit the Ppar-γ2 protein that promotes fat production, thereby inhibiting the differentiation of adipocytes.[35] These findings indicate that the active

flavonoid components can improve metabolic dysfunction induced by a high-fat diet and delay the progression of MAFLD by reducing adipogenesis and intracellular lipid deposition.

Alleviate Oxidative Stress

Oxidative stress is the most important pathological event in the pathogenesis of MAFLD, which is defined as an imbalance between the production of reactive oxygen species (ROS) and the ability of antioxidant defenses to detoxify them.[36,37] This may lead to DNA damage, lipid peroxidation and dysregulation of intracellular signaling pathways.[38] In the case of lipid overload, theβ-oxidation of fatty acids produces a significant quantity of reactive oxygen species (ROS). Extensive or long-term exposure to ROS leads to oxidative stress, thereby exacerbating the progression of MAFLD.[24] Active flavonoid components can reduce oxidative stress damage to liver cells by regulating relevant pathways.

Research has demonstrated that PPARαis associated with the attenuation of oxidative stress during the treatment of MAFLD by downregulating ROS-generating enzymes. The nuclear factor erythroid-2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) signaling pathways are the core of the cellular antioxidant system, providing powerful multi-organ protection against a series of exogenous and endogenous damages and playing a key role in mediating anti-inflammatory, antioxidant, and anti-apoptotic responses.[39] Quercetin has a strong antioxidant capacity and can enhance the antioxidant capacity of mice on a high-fat diet by downregulating the Nrf2/HO-1 signaling pathway and upregulating superoxide dismutase (SOD) and glutathione peroxidase 1 (GPX1) expression,[40] It can also regulate and upregulate PPARα and CPT - 1A to promote fatty acid β- oxidation and reduce cell damage caused by lipid peroxidation.[24] Adiponectin receptor 1 (AdipoR1)/(AMPK) can regulate PPAR-γ to reduce hepatic lipogenesis and increase fatty acid oxidation. Luteolin is an effective flavonoid compound that can upregulate PPARγ through the AdipoR1/AMPK signaling pathway, increase the expression of PPARγ in the liver of HFD-fed rats, and play a key role in improving dyslipidemia.[41] It can also reduce the levels of inflammatory markers such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF-α), increase the activities of antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT), and reduce lipid peroxidation.[42] Research shows that Nrf2 is critical for defending against oxidative stress. Kelch-like ECH-associated protein (Keap1) is an inhibitory protein anchored in the cytoplasm, which can physically bind to Nrf2 and prevent its translocation to the nucleus. The Keap1/Nrf2 complex is considered to be the "oxidative stress sensor" of cells.[43,44] Apigenin is a flavonoid that occurs naturally in various fruits and leafy vegetables. It has antioxidant and anti - inflammatory effects and has a significant effect on constraining the progression of MAFLD.[45] Treatment with apigenin in HFD mice significantly increased the expression of Nrf2 in liver tissue, induced the dissociation of the Keap1/Nrf2 complex and activated Nrf2, disrupted the complex between Keap1 and Nrf2, released the Nrf2 protein to translocate into the nucleus, and improved the oxidative stress response.[46] Radix Scutellariae (SA) was first recorded in "Materia Medica of Southern Yunnan" and "Ancient Medical Books of Righteous Doctors". It is widely used as a medicine in many countries. Scutellaria flavonoids (SAF) have functions such as antibacterial, antioxidant, antiviral, and antitumor effects. They mainly include baicalein and other components.[47] Studies have confirmed that HFD mice treated with SAF can improve MAFLD and inhibit oxidative stress by regulating the Keap1/Nrf2/HO-1 signaling pathway.[48] These studies have confirmed that the active flavonoid components can weaken or eliminate the oxidative stress response through relevant mechanisms and protect liver cells, thereby achieving the goal of delaying the progression of MAFLD.

Inhibit the Inflammatory Response

The inflammatory response is a key part of the progression of MAFLD. Kupffer cells (KCs) are a type of macrophage found in the liver that acts as the organ's primary sensor. Once activated, KCs can recruit other immune cells, amplify inflammatory signals, exacerbate liver inflammation, and further aggravate MAFLD.[49,50] An increasing amount of evidence suggests that targeting pro-inflammatory cytokines is an important part of the treatment strategy for MAFLD. The active components of flavonoids reduce liver inflammation by regulating relevant inflammatory signaling pathways and reducing the expression of pro-inflammatory factors. This not only delays the progression of MAFLD but also further reduces the risk of liver fibrosis by influencing the interactions between inflammatory factors.[51]

Quercetin can effectively inhibit the abnormal expression of HFD-induced pro-inflammatory cytokines (IL-1β and IL-6). Additionally, the nuclear transcription factor κB (NF-κB) signaling pathway is inhibited, quercetin can also inhibit the activation of the inflammatory pathway and prevent MAFLD.[24,52] There is mounting evidence pointing to the critical role of M1 macrophage activation in the development of liver inflammation and fibrosis.[53] The Notch pathway is crucial for macrophage-

mediated obesity-induced liver inflammation and is a critical transcription factor associated with the activation of M1 macrophages.[54] The expression of the Notch1 gene and protein, as well as pro-inflammatory cytokines, was significantly reduced by quercetin, such as monocyte chemoattractant protein-1 (MCP-1), IL-1β, IL-6, and TNF-α.[55] The classical pathway of NF-κB activation is through activation of IκB-kinase (IKK) to induce phosphorylation and ubiquitination of IκB, which is then phosphorylated and translocated into the nucleus to activate NF-κB-responsive genes.[56] Myricetin is mainly derived from flavonoids and has effects such as anti - inflammatory, antioxidant, and liver - protecting. Its anti - inflammatory effect has been proven in other inflammation models. Its role in the treatment of MAFLD is considered crucial, and it is recognized as a new type of anti-inflammatory agent.[57] Studies have found that it can inhibit the acute inflammatory response of lipopolysaccharide (LPS)-induced macrophages by interfering with the PI3K/Akt and downstream IKK/IκB signaling pathways, thereby eliminating the nuclear translocation of NF-κB, decreasing the levels of TNF-α, IL-1β, and IL-6, and alleviating the inflammatory response in the liver.[58] TNF-α/receptor-interacting protein kinase 3 (RIPK3) signaling pathway has been recognized as a key regulator to many inflammation-related diseases.[59] Fisetin (Fn) is a bioactive flavonoid belonging to the flavonol class. It is widely present in fruits and vegetables and has anti-inflammatory and anti-tumor activities. HFD can trigger metabolic disorders and liver function loss, but these issues can be prevented by Fn intervention, downregulate liver inflammation related to TNF-α/RIPK3 signal transduction, balance the expression of genes related to lipid metabolism, and ultimately inhibit lipid accumulation and steatohepatitis.[60] Anthocyanins (ACN) are widely present in many vegetables and berries, such as corn, cherries, mulberries, blueberries, strawberries, cranberries, and Chinese bayberries. They have become a vital part of the human diet.[61] Colored corn contains a large amount of anthocyanins and has great anti-inflammatory and anti-adipogenic abilities.[62] Various chronic liver diseases are associated with the involvement of toll-like receptors (TLRs). They are a group of pattern recognition receptors responsible for activating the innate immune system and can play a crucial role in the progression of MAFLD by promoting pathophysiological mechanisms.[63,64] Some researchers have proposed that the active components of anthocyanins can regulate pro-inflammatory pathways.[65] Prevent obesity by regulating the TLR/AMPK signaling pathway, decreasing adipose inflammation, adipogenesis and promoting energy consumption.[66] Overall, flavonoids can exert anti - inflammatory effects through their diverse biological activities and related mechanisms of action, providing strong support for improving liver function and decreasing the progression of MAFLD. This also offers a promising direction for the treatment of MAFLD.

Improve Insulin Resistance

Patients with MAFLD are said to be among the populations with the highest risk of developing type 2 diabetes mellitus (T2DM).[67] Various changes are observed in the microenvironment of adipose tissue during the development of obesity. Under normal conditions, adipose tissue grows by effectively recruiting preadipocytes, having sufficient angiogenic responses, and undergoing appropriate extracellular matrix remodeling. In contrast, pathological adipose tissue expansion involves substantial enlargement of existing fat cells, limited angiogenesis, and hypoxia. These factors lead to the activation of hypoxia-inducible factor 1α (HIF-1α), induction of a fibrotic program, and systemic insulin resistance.[68] The defects in the action of insulin, in turn, affect the accumulation of visceral fat tissue levels.[69] Numerous pieces of evidence show that the active ingredients of flavonoids have demonstrated antioxidant and anti - inflammatory activities. Consuming flavonoids or foods rich in flavonoids can improve insulin by targeting inflammatory signals.[70]

Insulin resistance (IR) involves the response to insulin and the processing of metabolism through insulin receptor substrate (IRS) proteins and key mediators, such as Akt and PI3K.[71] The PI3K/Akt pathway is a classic insulin signaling transduction pathway.[72] The PI3K/Akt pathway in the liver has the capacity to impede gluconeogenesis and encourage glycogen synthesis.[73] Genistein belongs to isoflavones and is mainly found in soybeans, which can improve insulin. Genistein reduces the insulin sensitivity of normal mice by inhibiting the phosphorylation of insulin receptor substrate (IRS) and IRS-1 (insulin receptor substrate-1), leading to the inhibition of the translocation of the glucose transporter type 4 (GLUT4) in adipocytes. In contrast, in insulin-resistant mice, genistein improves the impaired insulin sensitivity induced by inflammatory stimulation restores the function of IRS1 and activating the AMPK signaling pathway, thereby improving GLUT4 translocation.[69] In addition, nobiletin and chrysin both belong to flavonoids, which can improve disorders of lipid metabolism and IR by regulating the AMPK/PI3K/Akt signaling pathway.[35,74,75] Kaempferol is a flavonol, a type of flavonoid that naturally occurs in various parts of plants.[76] Kaempferol Ameliorates insulin signaling pathway defects in diabetes by mediating IKK downregulation and inhibiting NF-κB pathway activation to reduce IR, enhancing insulin sensitivity in middle-aged obese diabetic mice, and improving hyperglycemia,

hyperinsulinemia, and circulating blood lipid levels. In addition, luteolin increases hepatic insulin sensitivity by inhibiting SREBP-1 expression, reducing IR by enhancing IRS2 expression, and inhibiting gluconeogenesis. It can also increase adipocyte uptake of free fatty acids (FFA) to activate peroxisome proliferator-activated receptor gamma (PPARγ), reducing dyslipidemia and improving hepatic insulin sensitivity.[72] Luteolin can prevent IR by targeting TLR signaling and downregulating the expression of adipocyte genes involved in inflammation, improving chronic low-grade inflammation, and increasing pancreatic β-cell mass and insulin levels.[77] A mixture of polyphenolic molecules, more precisely flavonolignans, is called silymarin.[78] The activation of the PPARγsignaling pathway can reduce blood glucose and boost insulin sensitivity.[79] In general, it can improve IR in MAFLD through relevant mechanisms. It is a potential therapeutic agent that benefits the MAFLD population.

Regulate the Gut Microbiota

Maintaining intestinal microecological balance is important for preventing and treating MAFLD. The development of MAFLD is closely related to an imbalance in intestinal flora. An increasing amount of evidence suggests that intestinal flora plays an important role in lipid metabolism, nutrition, and energy acquisition. It may also be responsible for metabolic diseases.[80] Consequently, concentrating on the gut microbiota through dietary modifications might be one of the most effective approaches for addressing metabolic diseases. Research has demonstrated a two-way interaction between dietary flavonoids and the symbiotic gut microbiota. First, flavonoid metabolites are produced when the gut microbiota metabolize flavonoids, which enhances bioavailability. Second, these components can regulate the population structure of the gut microbiota.[81]

The gut-liver axis uses environmental and host mediators for bidirectional crosstalk to control gastrointestinal health and disease. Nutrients, metabolites, microbial antigens, and bile acids regulate the metabolism and immune responses of the gut and liver, thereby mutually shaping the microbial community's structure and function. The disruption of communication between the gut and the liver is described in clinical evidence as it relates to MAFLD.[82,83] Naringenin can alleviate metabolic disorders caused by a HFD and improve intestinal barrier function. This inhibits the migration of gut microbiota and their products through the gut-liver axis. It also enhances the growth of beneficial symbiotic bacteria and inhibits the colonization of pathogenic bacteria. Thus, naringenin can prevent MAFLD.[84] Dysbiosis is accompanied by intestinal barrier dysfunction, endotoxemia, and alterations in the gut-liver axis, as well as subsequent overexpression of inflammatory genes. Dysbiosis-mediated activation of toll-like receptor 4 (TLR-4)-NF-κB signaling pathway correlates with inflammatory vesicle initiation response and reticular stress pathway induction. Quercetin can reverse the imbalance of gut microbiota and the endotoxemia-mediated activation of the TLR4 pathway, subsequently the inflammasome response and the activation of the unfolded protein response are both inhibited, leading to the blockade of the dysregulation of lipid metabolism gene expression and inhibiting the progression of MAFLD.[85,86] Wolfberry is the dried immature fruit of Rutaceae plants, naringin, naringin, hesperidin, and neohesperidin are the main components and are an important class of flavonoids.[87] Studies have shown that wolfberry extract can intervene in intestinal dysbiosis and obesity-related metabolic disorders by decreasing the ratio of the phylum Thick-walled Bacteria to the phylum Mycobacterium anthropophilum and by acting as a prebiotic in dietary supplements.[88] The active flavonoid components regulate intestinal flora disorder through relevant mechanisms, delay the progression of MAFLD, and reduce liver cell damage.

Regulate Liver Autophagy

Autophagy is a conserved catabolic metabolic pathway crucial for maintaining cellular homeostasis and promoting survival under stressful conditions.[89,90] The liver is a vital organ that controls energy metabolism in the body, and autophagy is particularly important for the liver.[91] The research has revealed the importance of autophagy as a key homeostatic process for clearing damaged proteins and organelles, and it is a promising approach for the treatment of MAFLD.[92] By promoting autophagy, natural products help clear damaged organelles and lipid droplets, thereby reducing lipid accumulation in hepatocytes.[93] A growing body of research has proven that the active flavonoid components can offer new hope for the treatment and protection of MAFLD by promoting autophagy, highlighting their potential as therapeutic drugs for liver health.

mTOR serves as the central hub regulating autophagy, through its upstream targets AMPK and Akt. Both the AMPK/mTOR and Akt/mTOR signaling pathways are involved in hepatic autophagy regulation and constitute key protective mechanisms of MAFLD.[94,95] A traditional Chinese tea known as tengcha (Ampelopsis grossedentata) is abundant in flavonoids and boasts a variety of biological activities. Studies have found that in HFD mice treated with Tengcha flavonoids (TFs), not only were the body weight and blood lipid levels significantly reduced, but also the AMPK/mTOR pathway was activated, autophagy was

initiated, and the levels of expression of proteins involved in lipid metabolism in mice that were fed a HFD.[96] Cherries are a kind of food rich in nutrients, with relatively low calorie content, and contain a large amount of active anthocyanin components, such as cyanidin-3-rutinoside and cyanidin-3-glucoside.[97] Studies have shown that cherry anthocyanins are a powerful autophagy inducer. It can lead to a significant increase in the expression level of the number of autophagosomes, participate in the induction of autophagy through the signaling pathway of AMPK/mTOR and Akt/mTOR, and confer their anti - lipid deposition effect by activating autophagy.[95] Sirtuin 1 (SIRT1) is a crucial regulator of the autophagy process.[98] Epigallocatechin-3-gallate (EGCG), a polyphenol from green tea, regulates lipid metabolism in male C57BL/6 (the C57BL/6 mouse strain is the most widely used in biomedical research) mice by promoting the formation of autophagosomes, enhancing autophagic flow, and phosphorylation of AMPK.[93] Various plants are natural sources of kaempferol, a flavonoid compound,[99] it can reduce the triglyceride content in cells and induce autophagy by rising the expression level of the autophagy protein recombinant human autophagy effector protein (Beclin-1) in fatty liver cells, which highlights its potential in the treatment of MAFLD.[100] Study shows that kaempferol is an active inhibitor of the AKT/mTOR pathway. It induces autophagy in mouse liver cells by inhibiting the AKT/mTOR signaling pathway and suppresses liver lipid accumulation by reducing SREBP-1 expression.[101]

Conclusions

With the advancement of technology and improvement in quality of life leading to a decline in the physical activity levels of Homo sapiens, this may have implications for their health and well-being. MAFLD has become a significant global health burden, lacking specific pharmacological interventions. In this context, the flavonoid active ingredients widely present in various plants have garnered considerable attention due to their anti-inflammatory, antioxidant, antiviral, anti-diabetes mellitus, anticancer, anti-aging, neuroprotective, and cardioprotective effects. It is well known that MAFLD pathology primarily encompasses six aspects, such as lipid metabolism dysfunction, oxidative stress, inflammatory response, insulin resistance, intestinal dysbacteriosis, and hepatic autophagy. Current research has confirmed that flavonoid active ingredients are beneficial for the treatment of MAFLD and can prevent its further progression. However, current studies still have certain limitations. First, the structure of flavonoids is

Table 1 Main Pathways or Targets of Major Active Flavonoid Components in MAFLD

Regulation Mechanism	Major Flavonoid Active Compounds	Related Pathways or Targets
Regulate lipid metabolism	Quercetin	SREBP-1c[24,25]
	Fructus Aurantii Immaturus	AMPK/PPARα/CPT-1A[27,28]
	Radix Puerariae	PI3K/Akt/mTOR[31]
	Nobiletin	CCAAT/(C/EBPβ)[35]
Alleviate oxidative stress	Quercetin	Nrf2/HO-1,SOD,GPX1[40]
	Luteolin	AdipoR1/AMPK[41]
	Apigenin	Keap1/Nrf2[47]
	Scutellariae	Keap1/Nrf2/HO-1[48]
Inhibit the inflammatory response	Quercetin	NF-κB,[24,52] Notch 1[55]
	Myricetin	PI3K/Akt, IKK/IκB[58]
	Fisetin	TNF-α/RIPK3[60]
	Anthocyanins	TLR/AMPK[66]
Improve Insulin Resistance	Genistein	AMPK[69]
	Nobiletin and chrysin	AMPK/PI3K/Akt[34,74,75]
	Kaempferol	IKK, NF-κB[72]
	Luteolin	SREBP-1, PPARγ[72]
	Silymarin	PPARγ[79]
Regulate the gut microbiota	Naringenin	Gut-liver axis[84]
	Quercetin	TLR-4 NF-κB[85,86]
	Wolfberry extract	Reducing the ratio of Firmicutes to Bacteroidetes[88]
Regulate liver autophagy	Tengcha flavonoids (TFs)	AMPK/mTOR[96]
	Cherry anthocyanins	AMPK/mTOR, Akt/mTOR[95]
	Kaempferol	AKT/mTOR[101]

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complex, and research on their structure-activity relationships remains limited. Additionally, the distribution and extraction methods of different flavonoid active ingredients require further exploration. Second, current research on the intervention effects and mechanisms of flavonoid active ingredients on MAFLD primarily focuses on animal experiments and in vitro cell studies, which differ from the effects and metabolism of flavonoids in Homo sapiens. Subsequent research should conduct scientifically standardized clinical trials to further validate and elucidate the clinical efficacy of flavonoids. Finally, flavonoid active ingredients can intervene in MAFLD through multiple signaling pathways and molecular mechanisms. However, current studies mostly focus on the upstream and downstream molecules of a single signaling pathway, with limited research on the interactions between multiple signaling pathway regulatory networks. This could serve as a future research direction, providing theoretical support for the development of novel drugs targeting multiple pathways and multiple targets for MAFLD treatment.

We have summarized the above content in more detail in the table, as shown in Table 1.

Data Sharing Statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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Author Contributions

Lala Qin, Qingsong Xiao: Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

Xin Deng: Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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