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Targeting AMPK Pathways with Plant Derived Phytocchemicals: A Multi-Mechanistic Strategy Against NAFLD

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Abstract: A major global health burden, non-alcoholic fatty liver disease (NAFLD) is strongly linked to obesity, metabolic syndrome, and sedentary lifestyles. Since there are now no FDA-approved drugs on the market, there is a growing need for safe, natural, and efficient medicinal substitutes. This review investigates how phytoconstituents produced from plants can help manage NAFLD by focusing on the AMP-activated protein kinase (AMPK) pathway, which is a key regulator of energy and lipid metabolism. The mechanisms involving the AMPK-ACC-PPARα, AMPK/Nrf2, Sirt1/AMPK, AMPK/mTOR/ULK1, and AdipoR1-AMPK signalling axes are described regarding important phytochemicals such as gallic acid, plantamajoside, kaempferol, methylsulfonylmethane, and atractylenolide III. These substances show promise in reducing oxidative stress, promoting fatty acid oxidation, inhibiting de-novo lipogenesis, restoring autophagy, and regulating inflammation. According to the results, phytoconstituents have the potential to be effective multi-targeted agents in the management and prevention of NAFLD. To convert these discoveries into successful treatment plans, more research on clinical validation, bioavailability, and formulation development is required.

Keywords: *Non-Alcoholic Fatty Liver Disease (NAFLD), AMP-Activated Protein Kinase (AMPK), Phytoconstituents, Lipid Metabolism, Oxidative Stress, Natural Products.*

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I. INTRODUCTION

As people's lifestyles have been changing to "eat more, move less," the number of overweight and obese people is skyrocketing. As a result, chronic disorders linked to obesity, including fatty liver disease (FLD), cardiovascular disease, and type 2 diabetes, are becoming more common. Excessive hepatic lipid accumulation is the hallmark of FLD, the most prevalent liver disease, and it can be brought on by a variety of causes besides alcohol consumption, drug use, viral infections, and autoimmune diseases. Benign steatosis is the only one of FLD's early symptoms. However, about 30% of FLD cases will develop into steatohepatitis (SH) if left untreated. About 5% to 25% of SH patients will pass away from advanced liver disorders within ten years, and roughly 30% to 40% of SH cases will subsequently develop into cirrhosis and fibrosis.(1) Without significant alcohol consumption, FLD is defined by an excessive lipid deposit in hepatocytes of 5–10%. Affecting 80–100 million people, it is the most prevalent type of chronic liver disease in the United States. It has been demonstrated that the main risk factor for the development of NAFLD is obesity.(2) Increased liver enzymes are primarily caused by FLD. The prevalence of FLD has been estimated to range from 25% to 45% in various groups, and it is on the rise due to the rising rates of diabetes and obesity worldwide. From mild hepatic steatosis to SH, which can result in cirrhosis, liver failure, and death, FLD covers a wide range of histological conditions. (3)

Lipid metabolism, including de novo lipogenesis, lipid oxidation, and lipoprotein uptake/secretion, depended on the liver's activity. The synthesis and deposition of lipids would increase in the liver and body when the excessive intake of dietary fat and energy exceeded the liver's ability to metabolize lipids. This would result in a lipid metabolic disruption, which is crucial to the pathophysiology of FLD.

The overabundance of lipids that coincides with the rise in free fatty acid levels may encourage the overproduction of reactive oxygen species (ROS) and the use of antioxidants. The progression of FLD could be accelerated by oxidative stress, which may further damage hepatocyte function and even destroy the hepatic structure. (4) According to epidemiological research, cigarette smoke exposure raises the likelihood of developing cellular hepatocarcinoma and speeds up the development of several liver conditions, such as MAFLD, hepatitis C, and primary biliary cirrhosis. Importantly, both obesity and dyslipidemia are independent risk factors for liver disease and, when linked to smoking, can work in concert to cause MAFLD. Therefore, exposure to

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cigarette smoke and metabolic stresses can exacerbate liver disease, particularly in obese people and those who already have other medical disorders, including hypertension and dyslipidemia. (5)

The best way to treat NAFLD at the moment is to adopt lifestyle modifications, such as managing weight and embracing healthy eating practices, as there is currently no FDA-approved treatment for the condition. (2) Consequently, NAFLD therapy and prevention are essential. However, given the limited effectiveness and possible adverse effects of chemically synthesized medications, several natural compounds have demonstrated powerful anti-obesity and/or antioxidant action, making them a viable substitute for the prevention of NAFLD and obesity. (4) Alongside a sharp rise in obesity, the prevalence of NAFLD has also significantly grown. It is believed that an imbalance between the transport of fat to the liver and its subsequent release or metabolism results in FLD-associated hepatic steatosis. (6)

II. OVERVIEW OF CURRENT TREATMENT LIMITATIONS FOR NAFLD

There is currently no FDA-approved pharmaceutical treatment for NAFLD, which includes simple steatosis to NASH. The first-line recommendation at the moment is lifestyle adjustment, which includes exercise and nutrition restriction. However, it might be difficult to maintain weight over the long term, and patient compliance is frequently low.(1)

Pioglitazone, a PPAR-γ agonist, is one of the pharmacological medicines that has demonstrated histological improvement in NASH, especially in insulin resistant individuals. However, adverse effects like weight gain, fluid retention, bone fractures, and possible cardiovascular risk limit its clinical use.(2)(3) Although vitamin E has also shown antioxidant advantages in non-diabetic NASH patients, its wider use is limited by long-term safety concerns, such as links to higher all-cause mortality and hemorrhagic stroke.(4)

Although medications such as fibrates, omega-3 fatty acids, statins, and metformin have been studied, the outcomes are mixed and frequently do not produce histological improvement.(5)(6) Furthermore, extensive trials have not shown ursodeoxycholic acid to be significantly effective.(7) The varied nature of NAFLD pathophysiology complicates the discovery of a single successful therapy, and many of the medicines being studied only target one pathogenic pathway, which renders them ineffective in multiple disease situations.

Therefore, the lack of approved medications, side effects, inconsistent effectiveness, and inability to address numerous disease pathways are among the therapy constraints. This underscores the necessity of multi-targeted therapies, including bioactive substances derived from plants, as viable substitutes.

III. AMPK-MEDIATED MECHANISMS OF PHYTOCHEMICALS IN NAFLD AMELIORATION

A. Gallic Acid Mitigates NAFLD via AMPK-ACC-PPARα Axis

Gallic acid (GA), also known as 3,4,5-trihydroxybenzoic acid, is a polyphenol chemical (7) that has steadily gained a lot of interest due to its widespread presence in fruits, vegetables, and herbal remedies, including grapes, (8)(9) (10) gallnuts, (11) pomegranates (12) and tea leaves (Table:1). (13)

The study explains how GA reprogrammed lipid metabolism by inhibiting DNL synthesis, raising β-oxidation, and enhancing mitochondrial function, so reducing OA/PA stimulated lipid accumulation in hepatocytes and HFD-induced hepatic steatosis in mice. The information makes it clear that GA's action in NAFLD depends on AMPK signaling activity. Because of its many uses, AMPK is an essential energy sensor of cellular metabolism.

Therefore, by controlling the inhibition of anabolic pathways (such as fatty acid, cholesterol, and protein synthesis pathways) and stimulating catabolic pathways (such as fatty acid oxidation and glycolytic pathways), AMPK activation has emerged as a promising treatment strategy for metabolic diseases like obesity, type 2 diabetes, cardiovascular disease, and NAFLD (Fig1).

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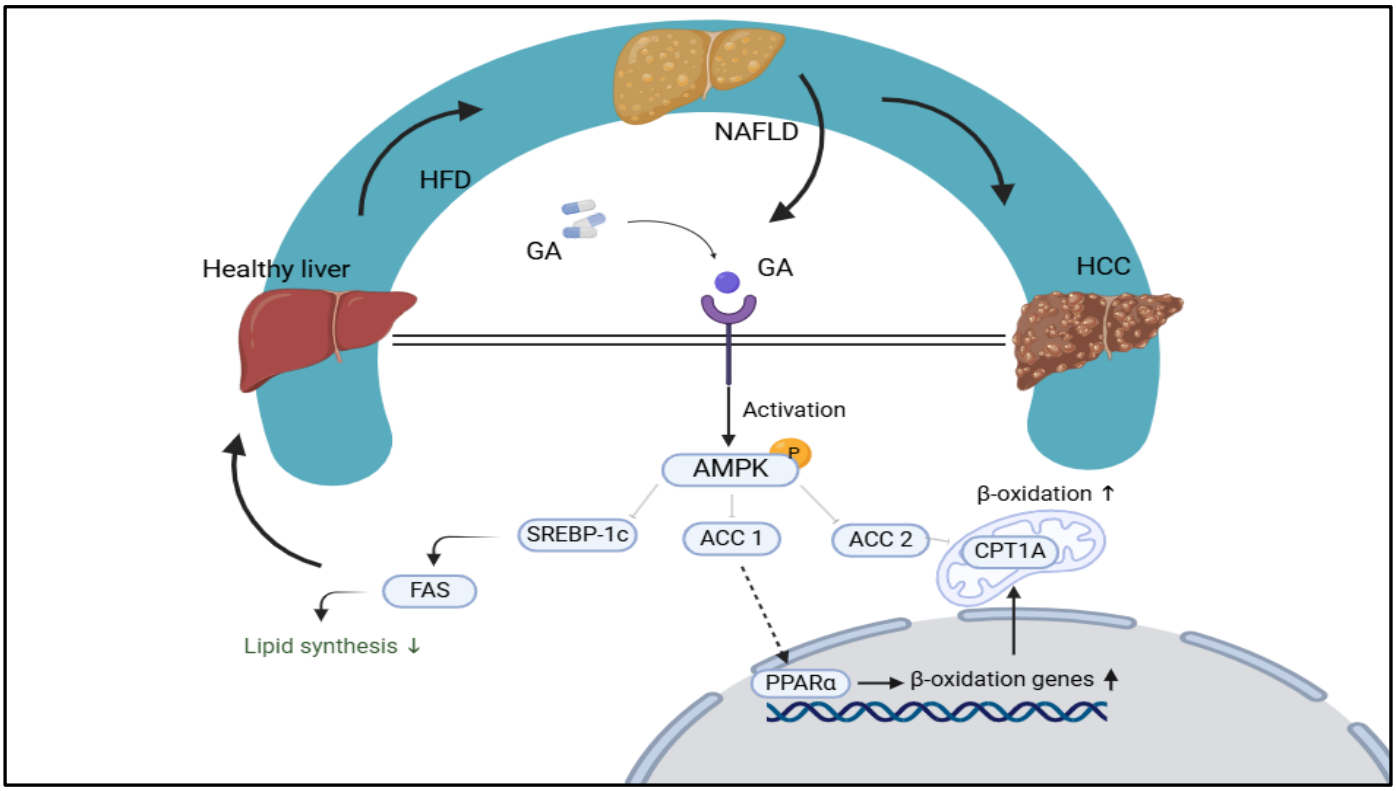

Fig 1 Gallic Acid Mitigates NAFLD via AMPK-ACC-PPARα Axis

A healthy liver can develop into non-alcoholic fatty liver disease (NAFLD) and even hepatocellular carcinoma (HCC) as a result of a high-fat diet (HFD). Gallic acid (GA) reduces lipid synthesis via activating AMP-activated protein kinase (AMPK), which in turn inhibits fatty acid synthase (FAS) and SREBP-1c. At the same time, AMPK increases PPARα and CPT1A and inhibits ACC1/2, which improves β-oxidation. GA's promise as a treatment for NAFLD is demonstrated by its dual impact of improving lipid metabolism and reducing hepatic fat buildup.

The study found that the administration of GA decreased FASN expression in participants with elevated AMPK, which helped to restrict lipid production. Increased flux of PPAR α and CPT1A from β-oxidation and up-regulated mitochondrial respiration were shown by the increased hepatic lipid metabolism. According to the results of molecular docking, GA may form hydrogen bonds with nearly identical binding energies to two distinct domains of AMPK α that contain the Val98 and Glu96 residues in AMPK in the AMPK α α 1β1 and Leu20 residues 1β2 pocket.

Following the administration of GA, those with elevated AMPK had decreased FASN expression, which helped to suppress lipid production. By blocking the conversion of Acetyl-CoA to malonyl-CoA, AMPK can phosphorylate and inactivate Acetyl-CoA (ACC), hence preventing the synthesis of fatty acids. Increased flux of PPAR α and CPT1A from β-oxidation and elevated mitochondrial respiration were indicated by the increased hepatic lipid metabolism. (14)

B. Plantamajoside Modulates Immunity and Lipid Metabolism via AMPK/Nrf2 in NAFLD

Plantamajoside (PMS), a distinct phenylethanoid glycoside component that is isolated from *Plantago asiatica*, with the formula C29H36O16. (15) PMS has been shown to possess a wide range of biological properties, including anti-inflammatory, antioxidant, anti-fibrotic, anti-cancer, antiviral, and immune boosting properties. (16) By inhibiting NF-κB and MAPK activation, PMS lowers the amount of pro-inflammatory factors in osteoarthritis. (17) Additionally, PMS exhibits anti-fibrotic properties in the heart and liver.(18)(19) Furthermore, PMS inhibits hepatocellular carcinoma's development, epithelial mesenchymal transition, and treatment resistance.(20)(21) In rats with HFD induced NAFLD, PMS reduced liver damage.

At the molecular level, PMS reduced immunological dysregulation and aberrant hepatic lipid metabolism in HFD-induced NAFLD rats. In HFD-feeding rats, PMS therapy mechanically reversed the downregulation of p-AMPK/AMPK, Nrf2, and HO-1 relative protein levels*(Table:1)*. Collectively, PMS reduced immunological dysregulation and aberrant hepatic lipid metabolism in rats with NAFLD via activating the AMPK/Nrf2 pathway.(22) Additionally, there is a wealth of research demonstrating that natural plant components reduce NAFLD through the AMPK/Nrf2 pathway *(Figure:2)*.(23)(24)(25) PMS, a phenylethanoid glycoside component derived from P.asiatica, has been demonstrated to impede hepatic fibrosis by deactivating hepatic stellate cells,[18] suppress liver cancer proliferation, epithelial–mesenchymal transition, and drug resistance[20][21] and induce hepatocellular carcinoma proliferation arrest, apoptosis, and autophagy.(26)

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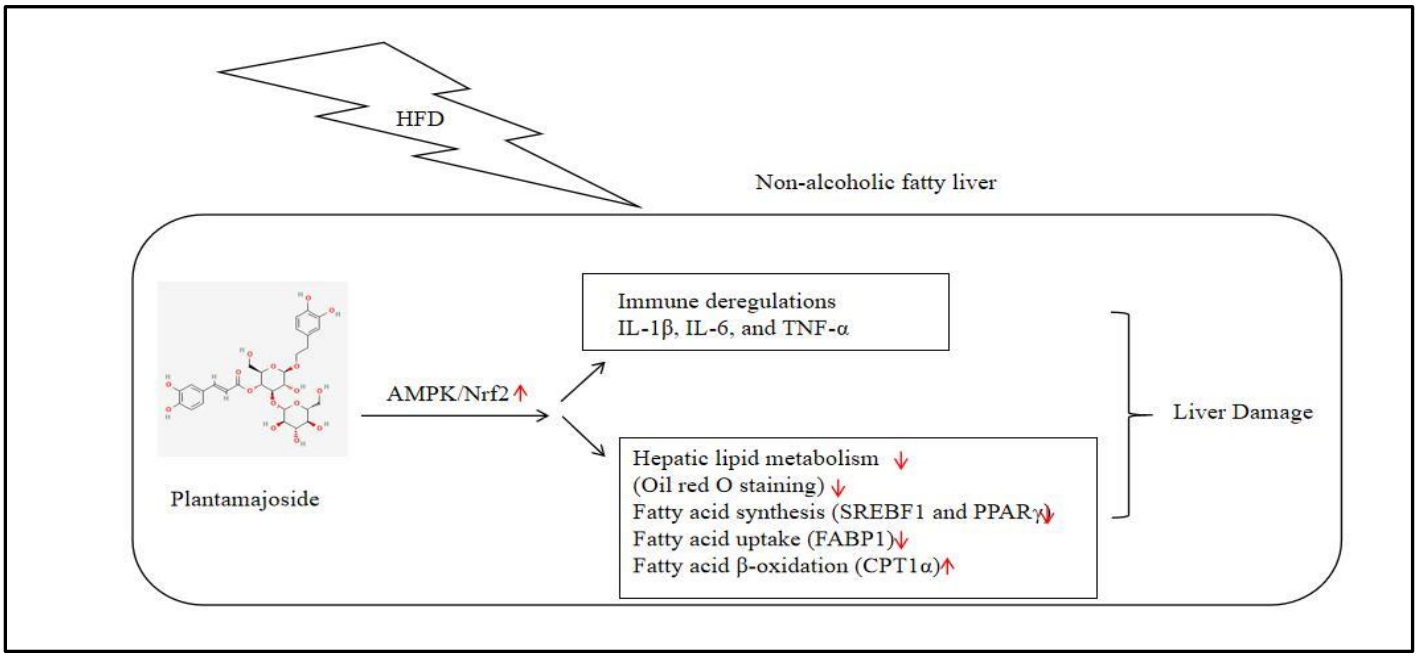

Fig 2 Plantamajoside Ameliorates NAFLD via AMPK/Nrf2 Pathway Modulation

Hepatic lipid buildup and immunological dysregulation are two symptoms of NAFLD, which is brought on by a HFD. Plantamajoside suppresses lipid metabolism markers like SREBP1, PPARγ, and FABP1 and reduces inflammation (IL-1β, IL-6, and TNF-α) by activating the AMPK/Nrf2 signaling pathway. Additionally, this activation promotes fatty acid β-oxidation mediated by CPT1α, which eventually shields the liver from injury and steatosis. Interleukin (IL), tumor necrosis factor alpha (TNF-α), sterol regulatory element-binding protein 1 (SREBP1), fatty acid-binding protein 1 (FABP1), and carnitine palmitoyltransferase 1A (CPT1α) are some of the abbreviations.

C. Kaempferol Attenuates NAFLD via Sirt1/AMPK Pathway

A flavonoid chemical with four hydroxyl groups, kaempferol (KAP), is found in many different plants, such as fruits, vegetables, medicinal herbs, and more *(Table:1)*. Numerous pharmacological effects, including antioxidative, anti-inflammatory, anticancer, antidiabetic, and antiatherosclerotic properties, have been shown by prior research to be present in KAP.(27) According to certain research, KAP inhibited liver damage by triggering Sirt1.(28) KAP has also been demonstrated to enhance insulin resistance and control the metabolism of fats and carbohydrates.(29)(30) According to a recent study, KAP has an anti-lipid deposition effect in-vitro.(31) Additionally, KAP may help NAFLD by reducing the buildup of hepatic lipids both in-vitro and in- vivo. The pharmacological mechanism of KAP may include improving Sirt1/AMPK signalling. KAP has been shown to enhance glucose and lipid metabolism, decrease lipid production, and encourage FAO.(32) The "double-hit hypothesis" has given way to the "multiple hit hypothesis" in the complicated pathophysiology of non-alcoholic fatty liver disease.(33)(34) Drugs that efficiently inhibit lipogenesis and increase FAO have been suggested as possible treatment strategies for NAFLD among the manipulations of these intricate pathological systems.(35)

AMPK and Sirt1 have a long-standing relationship in which they share numerous target molecules and regulate one another.(36) According to a recent study, in NAFLD illness, microRNA-122 downregulates Sirt1 to enhance hepatic lipogenesis.(37) In KKAy mice, resveratrol, a well-known Sirt1 agonist, inhibits hepatic steatosis by increasing Sirt1 expression and AMPK phosphorylation.(38) Another study showed that resveratrol reduces endoplasmic reticulum stress and regulates the Sirt1-autophagy pathway to improve hepatic lipid buildup in rats given a high-fat diet.(39)

According to one study, KAP increased the capacity of PGC1α to induce mitochondrial FAO by activating Sirt1 and AMPK. One important regulator of lipogenesis is the transcription factor SREBP1, which is negatively controlled by AMPK and contributes to the transcriptional activation of genes that encode rate limiting enzymes in lipogenesis, including ACC and FASN. In line with those conclusions, their investigation found that KAP-induced AMPK activation blocked SREBP1 signalling, which in turn suppressed the expression of its downstream FASN and ACC genes, lowering the synthesis of fatty acids.(40) These results imply that KAP may be a viable treatment agent for T2DM associated NAFLD, in addition to improving adipose tissue and metabolic disorders (Fig 3).(32)

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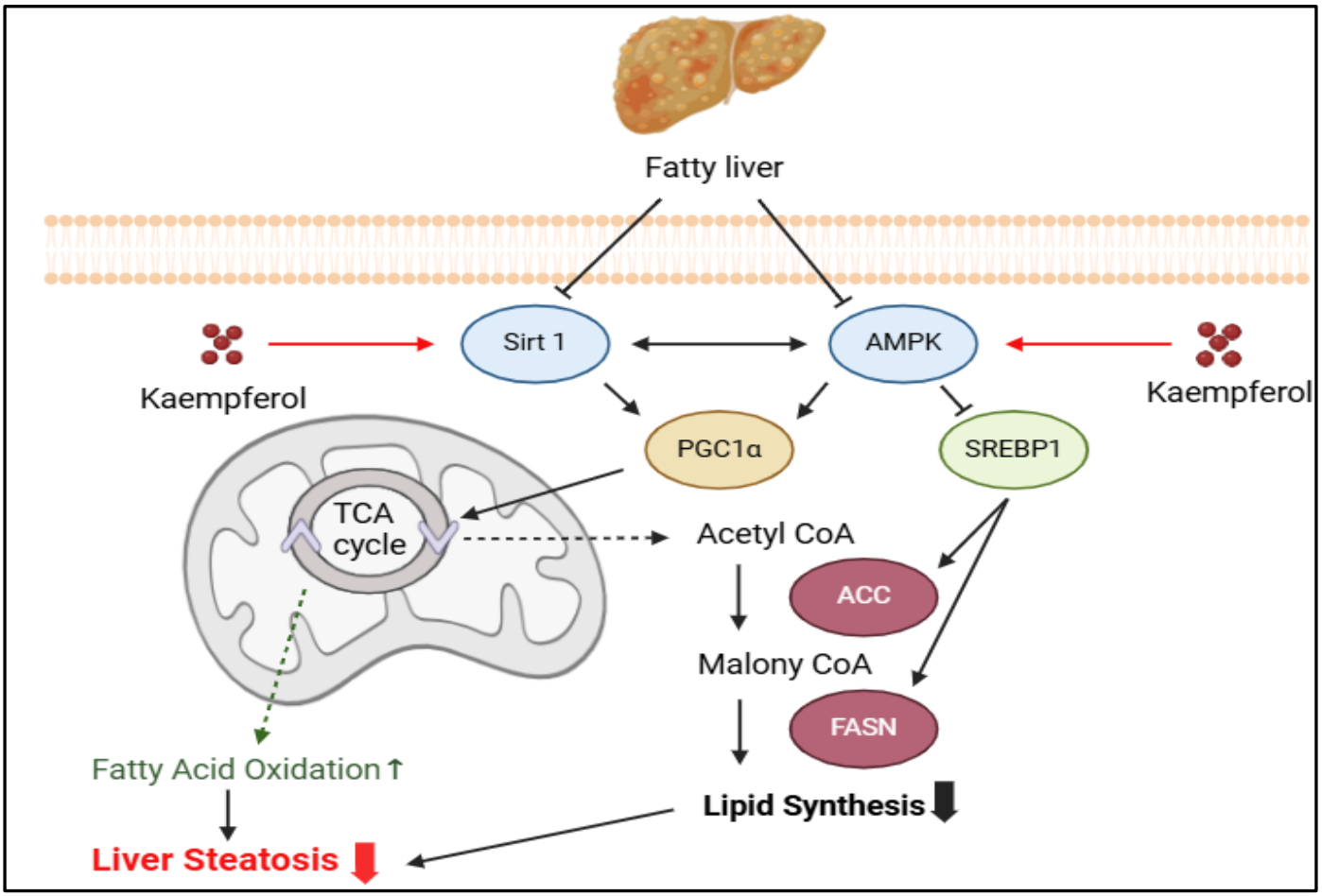

Fig 3 Kaempferol Attenuates NAFLD via Sirt1/AMPK Pathway

Kaempferol suppresses SREBP1-driven lipogenesis and increases PGC1α-mediated fatty acid oxidation by activating both AMPK and Sirt1 signaling. By blocking ACC and FASN activity, this lowers the conversion of acetyl-CoA to malonyl-CoA, which in turn lowers hepatic lipid synthesis and steatosis. PGC1α stands for peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ACC stands for acetyl-CoA carboxylase; FASN for fatty acid synthase; SREBP1 for sterol regulatory element-binding protein 1; and AMPK for AMP-activated protein kinase.

D. Methylsulfonylmethane Restores Autophagy in MAFLD via AMPK/mTOR/ULK1

Numerous plant and animal tissues contain the organosulfur molecule methylsulfonylmethane (MSM) *(Table:1)*, which has been studied for possible biological advantages such as its analgesic, antioxidant, and anti-inflammatory properties.(41)(42)(43) MSM improves insulin resistance and hepatic steatosis brought on by obesity.(44) MSM may be able to reduce hepatic steatosis by acting as a source of methyl donation. It's interesting to note that in many dietary models, methyl donors have been demonstrated to reduce hepatic fat buildup. MSM-treated obese mice in the study showed a decrease in hepatocellular ballooning and steatosis, which is consistent with this finding. One important aspect affecting MSM's bioavailability and effectiveness is its solubility.

Because of its high solubility in aqueous solutions with pH values ranging from neutral to slightly alkaline, MSM is easier to absorb and may have therapeutic benefits. In order to maximize MSM's solubility and subsequent absorption, it is crucial to take into account its formulation and delivery techniques. It usually has modest side effects, such as headache, bloating, and gastrointestinal discomfort.(45) Because autophagy controls the turnover of organelles and other macromolecules, such as proteins and lipids, it is essential for preserving cellular homeostasis.(46) Impaired autophagic flux contributes to the development of hepatic steatosis, hepatic inflammation, and the buildup of lipid droplets in hepatocytes in a number of liver disorders.(47) Additionally, MSM restored the autophagic flow in the liver tissues of mice given a high-fat diet and HepG2 cells treated with PA. MSM may encourage autophagic breakdown in MAFLD, as evidenced by the observed decrease in ubiquitinated protein and p62 levels in the detergent-insoluble fractions of cells and liver tissues in the MSM-treated group. This impact is likely to help improve liver function overall and reduce fat buildup.(45)

E. Atractylenolide III Activates AdipoR1-AMPK to Ameliorate NAFLD

The main bioactive ingredient in *Atractylode macrocephala* Koidz is a sesquiterpene lactone called atroptylenolide III (ATL III). Other therapeutic plants like *Codonopsis pilosula*, *Atractylode lancea*, and *Chloranthus*

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henryi Hemsl also contain ATL III *(Table:1)*. Numerous advantages of ATL III have been shown, including anti oxidant, anti-tumor, antiallergic response, antibacterial, and cognitive protective properties.

The identification of AdipoR1 as a possible binding target for ATL III is one of the study's key discoveries. It is commonly known that the AMPK signalling pathway is crucial in regulating the progression of NAFLD. In that investigation, AdipoR1 and AdipoR2 were discovered as possible targets of ATL III by the design and execution of a computational target fishing simulation based on molecular docking. Furthermore, their research showed that ATL III treatment restored the hepatic expression of AdipoR1, which had been significantly downregulated in the HepG2 cell model treated with FFAs and the HFD-induced NAFLD mouse model.(48)

The significant functions of adiponectin and its receptors in controlling insulin resistance and lipid metabolism have been extensively studied. Adiponectin is an adipocytokine that controls glucose and lipid metabolism by attaching to its receptors, AdipoR1 and AdipoR2.(49) In animal models, the AdipoR1/AdipoR2 dual agonist has been demonstrated to ameliorate fibrosis and NASH. On the one hand, ATL III therapy decreased the ROS and MDA levels, which were significantly elevated in the HFD animal model and the cell model treated with FFAs. The HFD animal model and the cell model treated with FFAs, on the other hand, demonstrated lower levels of GSH-Px and SOD, which were up-regulated by ATL III.

According to all of the study's findings, ATL III therapy reduces oxidative stress and intracellular lipid droplets, which in turn helps to improve hepatic steatosis.(48) One significant mechanism that controls hepatic lipogenesis-which is thought to be a potential therapeutic target for the treatment of NAFLD-is the AMPK/SIRT1 signalling system.(50) According to earlier research, ATL III enhanced downstream molecules such as Nrf2, SIRT3, CPT1A, and PGC1α after activating AMPK and SIRT1 signalling molecules. The elevated SIRT1 protein levels brought on by FFAs were partially offset by AMPK inhibition, indicating that AMPK was the downstream signalling molecule responsible for the SIRT1 activation brought on by FFAs. Furthermore, as SIRT1 inhibitors inhibited the activation of these pathways, these studies suggested that Nrf2, SIRT3, CPT1A, and PGC1α were the downstream signalling molecules of SIRT1. According to some research, ATL III reduces NAFLD by triggering several signalling pathways that are involved in fatty acid oxidation (CPT1A and PGC1α), oxidative stress (SIRT3 and Nrf2), and lipid buildup (LKB1 and AMPK) (Fig 4). (48)

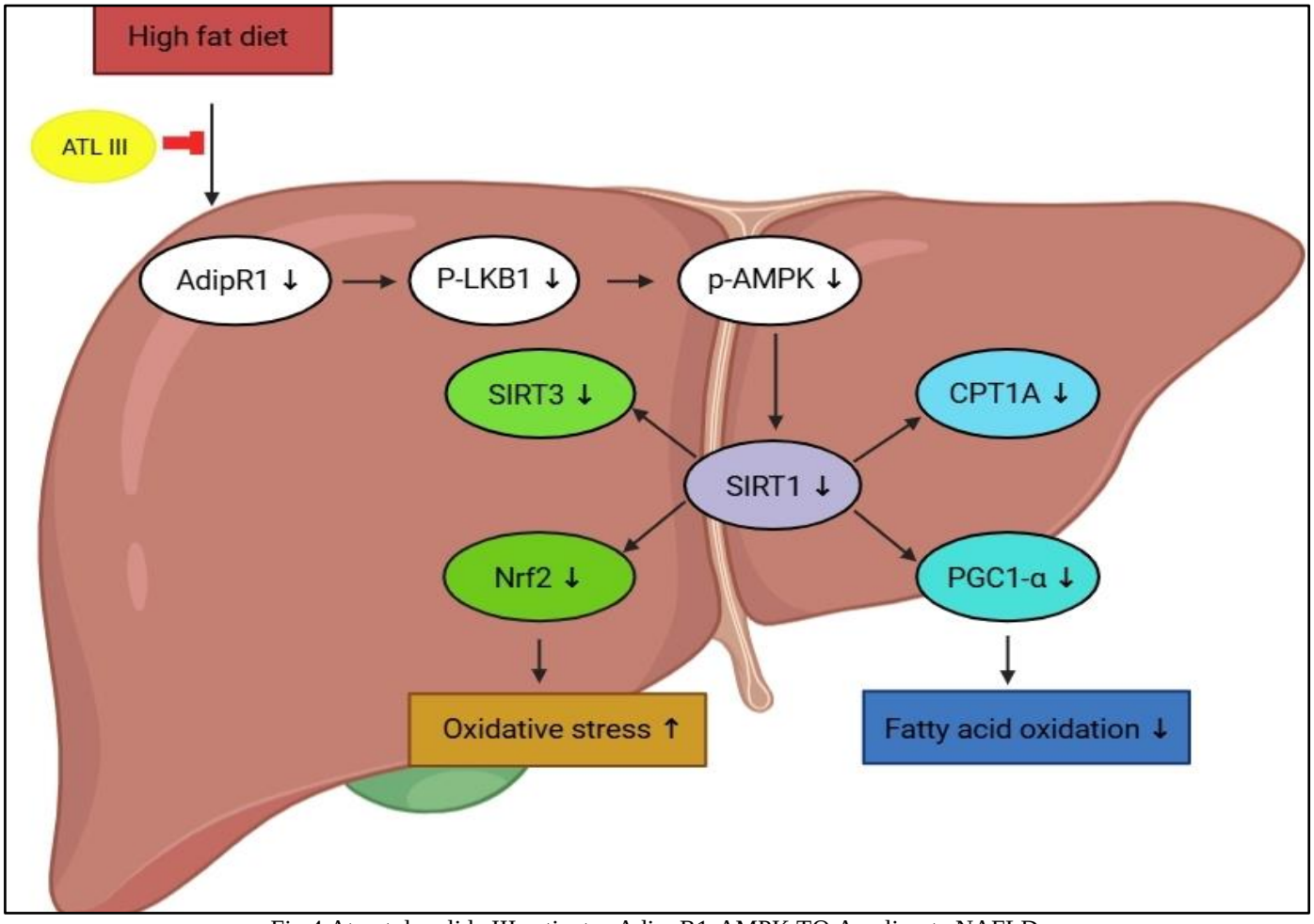

Fig 4 Atractylenolide III activates AdipoR1-AMPK TO Ameliorate NAFLD.

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ATL III reverses the suppression of important regulators such as SIRT1, CPT1A, and PGC1-α caused by HFD by activating the AdipoR1–AMPK–SIRT1 axis. This lowers oxidative stress and increases fatty acid oxidation.

IV. COMPARATIVE TABLE

Table 1 Summary of Key Plant-derived Phytoconstituents Targeting AMPK Signaling Pathways in NAFLD.

Active Compound	Plant Name	Target Pathway	Key Effects in Nafld	Experimental Model
Gallic Acid	Grapes, Tea, Pomegranate	AMPK–ACC–PPARα	↓ FASN, ↑ CPT1A & β-oxidation, ↓ lipid accumulation, ↑ mitochondrial respiration	HFD mice, hepatocytes
PMS	*Plantago asiatica*	AMPK/Nrf2	↓ Inflammation, ↑ HO-1, ↑ lipid metabolism, ↓ fibrosis, restores AMPK & Nrf2 activity	HFD-induced NAFLD rats
KAP	Fruits, vegetables,	Sirt1/AMPK	↓ Lipogenesis, ↑ FAO, ↓ SREBP1, FASN, ACC, ↑ glucose & lipid metabolism	*In-vitro*, KKAy mice
MSM	Plants and animal tissues	AMPK/mTOR/ULK1	Restores autophagy, ↓ lipid droplets, ↓ oxidative stress, improves insulin resistance	HFD mice, HepG2 cells
ATL III	*Atractylodes macrocephal*	AdipoR1–AMPK–	↓ ROS/MDA, ↑ SIRT3, CPT1A, PGC1α, restores AdipoR1, ↑ antioxidant enzymes	HFD mice, HepG2 cells

The main therapeutic benefits seen in NAFLD experimental models are highlighted in this table along with the active chemicals, their source plants, and related signaling pathways.

V. DISCUSSION

Hepatic steatosis, insulin resistance, inflammation, and oxidative stress are the hallmarks of NAFLD, a progressive metabolic illness. There are currently few therapeutic options available, mostly consisting of lifestyle changes and a few potentially harmful pharmaceuticals. Recent studies have demonstrated the potential therapeutic benefits of phytoconstituents derived from plants that target the AMPK pathway, a crucial regulator of energy and lipid metabolism.

This review describes a number of bioactive substances that have demonstrated effectiveness in NAFLD models through activation of AMPK and its downstream signalling cascades, including gallic acid, plantamajoside, kaempferol, MSM, and atractylenolide III. The actions of these phytochemicals are multifaceted and include fatty acid oxidation enhancement, antioxidant defence, de novo lipogenesis inhibition, and inflammatory pathway regulation. Their function as possible substitutes for synthetic pharmaceuticals is supported by their effects through the AMPK-ACC PPARα, AMPK/Nrf2, Sirt1/AMPK, AMPK/mTOR/ULK1, and AdipoR1–AMPK signalling pathways.

Despite encouraging preclinical data, there are still obstacles in converting these discoveries to clinical use because of a dearth of standardized formulations, bioavailability problems, and human research. For these phytoconstituents to be confirmed as efficacious treatment agents for NAFLD, more research concentrating on pharmacokinetics, safety profiles, and clinical trials is necessary.

VI. CONCLUSION

Future research should concentrate on clinical validation, bioavailability enhancement, and formulation strategies to optimize the therapeutic efficacy of these plant-derived compounds. Given the complexity of NAFLD pathophysiology, a multi-targeted approach that leverages the therapeutic potential of natural phytoconstituents could be an effective alternative or complementary strategy to current treatment modalities. By expanding our understanding of their molecular mechanisms, plant-based interventions could open the door to new, safe, and effective treatments for NAFLD and related metabolic disorders.

CONFLICT OF INTEREST

There are no conflicts of interest.

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