


## Review Article

# Impact of Phytochemicals on PPAR Receptors: Implications for Disease Treatments

Ayeshah Enayati,<sup>1</sup> Mobina Ghojoghnejad,<sup>1</sup> Basil D. Roufogalis,<sup>2,3</sup> Seyed Adel Maollem,<sup>4,5</sup> and Amirhossein Sahebkar <sup>6,7,8</sup>

<sup>1</sup>Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran

<sup>2</sup>Discipline of Pharmacology, School of Medical Sciences, University of Sydney, Sydney, NSW, Australia

<sup>3</sup>NICM Health Research Institute, Western Sydney University, Penrith, NSW, Australia

<sup>4</sup>Department of Pharmacology and Toxicology, College of Pharmacy, Al-Zahraa University for Women, Karbala, Iraq

<sup>5</sup>Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>6</sup>Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>7</sup>Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>8</sup>Department of Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence should be addressed to Amirhossein Sahebkar; [amir\\_saheb2000@yahoo.com](mailto:amir_saheb2000@yahoo.com)

Received 26 March 2022; Accepted 10 July 2022; Published 31 August 2022

Academic Editor: John P. Vanden Heuvel

Copyright © 2022 Ayeshah Enayati et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peroxisome proliferator-activated receptors (PPARs) are members of the ligand-dependent nuclear receptor family. PPARs have attracted wide attention as pharmacologic mediators to manage multiple diseases and their underlying signaling targets. They mediate a broad range of specific biological activities and multiple organ toxicity, including cellular differentiation, metabolic syndrome, cancer, atherosclerosis, neurodegeneration, cardiovascular diseases, and inflammation related to their up/downstream signaling pathways. Consequently, several types of selective PPAR ligands, such as fibrates and thiazolidinediones (TZDs), have been approved as their pharmacological agonists. Despite these advances, the use of PPAR agonists is known to cause adverse effects in various systems. Conversely, some naturally occurring PPAR agonists, including polyunsaturated fatty acids and natural endogenous PPAR agonists curcumin and resveratrol, have been introduced as safe agonists as a result of their clinical evidence or preclinical experiments. This review focuses on research on plant-derived active ingredients (natural phytochemicals) as potential safe and promising PPAR agonists. Moreover, it provides a comprehensive review and critique of the role of phytochemicals in PPARs-related diseases and provides an understanding of phytochemical-mediated PPAR-dependent and -independent cascades. The findings of this research will help to define the functions of phytochemicals as potent PPAR pharmacological agonists in underlying disease mechanisms and their related complications.

## 1. Introduction

Peroxisome proliferator-activated receptors (PPARs) are a subfamily of the ligand-dependent nuclear receptor family. PPARs consist of three distinct subtypes, namely, peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), and peroxisome proliferator-activated receptor beta or delta (PPAR $\beta$  or PPAR $\delta$ ), each exerting specific biological activi-

ties depending on the particular targeting ligands and tissue localization [1–3]. They regulate a wide range of biological processes, including fatty acid metabolism, metabolic pathways, cellular differentiation, insulin sensitivity, cell migration, and inflammation. Therefore, PPARs can provide unique beneficial effects on cancer, atherosclerosis, metabolic diseases, cardiovascular diseases, neurodegeneration, reproduction, and inflammation via activation or inhibition of various up/downstream signaling pathways, including

AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), Sirtuins, and oxidative and inflammatory responses [1, 2, 4].

PPAR $\alpha$  is mainly known as a metabolic regulator which is expressed in liver and brown adipose tissue. It is associated with energy storage, lipogenesis, fatty acid up-regulation and  $\beta$ -oxidation, ketogenesis, gluconeogenesis, and inflammation in these tissues [1]. PPAR $\beta/\delta$  is involved in energy expenditure in fatty acid (FA) uptake,  $\beta$ -oxidation, placenta and gut development, inflammation reduction, cell proliferation, differentiation, cell survival, tissue repair, and energy homeostasis in muscle and white adipose tissue. It is ubiquitously observed in renal, gut, gastrointestinal tract, liver, and the central nervous systems [1, 2]. PPAR $\gamma$  mediates energy storage-lipogenesis, glucose metabolism, and inflammation in white adipose tissue (WAT) and macrophages [1, 5]. Additionally, PPAR $\gamma$  is an important target to treat several types of cancer, neurodegenerative diseases, long-chain fatty acid processing in the intestinal epithelium, body adiposity, mucosal defenses, and hypotensive and anticoagulant effects [1, 2, 4, 5]. Moreover, the PPAR $\gamma$  isotype is expressed as two isoforms, PPAR $\gamma$ 1 and PPAR $\gamma$ 2. PPAR $\gamma$ 2 is expressed in adipose tissue, whereas PPAR $\gamma$ 1 occurs in adipose tissue, gut, vascular cells, brain, and special immune and inflammatory cells [1].

As a result of the broad and specific biological activities of PPARs, researchers have actively pursued the development of PPAR-targeting drugs. Some synthetic PPAR agonists, including thiazolidinediones (TZDs), pioglitazone, troglitazone, fibrates, glitazars, rosiglitazone, and gemfibrozil, were approved following several experimental and clinical studies [1, 2, 5]. Despite these advances, various studies have reported significant side effects of these PPAR agonists, such as heart failure, hepatotoxicity, fluid retention, edema, tumorigenesis, weight gain, and cardiotoxicity [2]. On the other hand, natural phytochemicals have shown promising potential as PPAR agonists, including endogenous unsaturated fatty acids, polyacetylenes, terpenoids, and polyphenols [3–6]. Hence, this review examines the impact of phytochemicals on PPAR receptors, with particular emphasis on the signaling pathways which PPARs enhance or inhibit in the management of various diseases. The mechanisms responsible for their toxicity are also discussed.

## 2. PPAR Mechanism of Action and Therapeutic Targets of Diseases

PPARs are involved in regulation of a wide spectrum of adverse reactions, including oxidative stress, inflammation, neuron degeneration, cardiovascular disease (CVD), multiple sclerosis (MS), Alzheimer's disease, diabetes, dyslipidemia, kidney dysfunction, gastrointestinal toxicity, cancer, autophagy, and immunity. This is associated with particular signaling pathways as well as the presence of specific coactivators/corepressors in each organ, such as inflammatory and antioxidant elements [1, 2, 6]. It is known that B-cell lymphoma 6 (BCL-6), the silencing mediator of retinoic acid and thyroid hormone receptor (SMRT), and the nuclear

corepressor 1 (NCoR1) act as PPAR corepressors. Additionally, enzymatic coactivators modulate PPAR activity, including histone acetylase activity (steroid receptor coactivator 1 (SRC-1), cAMP response element-binding protein/p300), helicases (PPAR A-interacting complex (Pric)285), and an ATPase (SWItch/sucrose non-fermentable (SWI/SNF)). Additionally, nonenzymatic coactivators that bind to PPAR complex, such as PGC-1 $\alpha$  (PPAR coactivator- (PGC-) 1 $\alpha$ ) and SMARCD1 (SWI/SNF related, matrix associated, actin-dependent regulator of chromatin subfamily d, member 1), have been reported [1, 6].

Mechanistically, PPARs heterodimerize with retinoid X receptors (RXRs) for binding to the peroxisome proliferator response elements (PPREs) as their upstream DNA binding site [1, 2, 6]. After a ligand binds to PPARs, and then making a heterodimer and binding to PPRE, PPARs regulate gene transcription by recruiting coactivators in transactivation, while they recruit corepressors in the transrepression of certain genes by activation of the heterodimer in the presence of RXR ligand. PPARs regulate gene transcription by recruiting coactivators in transactivation and coactivators/corepressors in the transrepression of certain genes. In transrepression function, PPARs recruit coactivators/corepressors and exert their negative regulation on certain genes by preserving or releasing corepressors, mitogen-activated protein kinase (MAPK) pathways, and physical interaction with transcription proteins (nuclear factor kappa B (NF- $\kappa$ B), Smad-3, activator protein 1 (AP-1), and signal transducer and activator of transcription (STAT)) and competing with target genes for binding their co-regulators [6]. Furthermore, PPARs show distinct functions in various pathways such as energy storage, modulating mTOR activity, flexible interaction with AMPK, regulation of insulin signaling and insulin sensitivity, tissue repair and remodeling, lipid metabolism, cell survival, and inflammatory cascades [1, 2, 6].

Although PPARs show mainly transcriptional activities (genomic action), they may also operate via the stimulation of nongenomic pathways (such as insulin-like growth factor- (IGF-) insulin receptor (IR), stress response, calcium influx, and MAPK). In light of these considerations, PPAR $\gamma$  down-regulates MAPK pathway as a main insulin/IGF axis cascade and reduces circulating insulin to prevent cell migration and proliferation [6]. In addition, PPAR $\gamma$  can inhibit production of inflammatory cytokines by MAPK suppression in colon mucosal [1]. It can also decrease angiotensin II-induced proliferation in vascular smooth muscle cells (VSMCs) through diminishing c-fos and via blocking MAPK signaling pathways. Moreover, activation of PPAR $\gamma$  suppresses MAPK pathway and its downstream signaling (Ets-1, matrix metalloproteinase (MMP)2, and MMP9) for inhibiting platelet-derived growth factor (PDGF) and thrombin-triggered VSMC migration [6].

It is therefore clear that PPARs play a critical role in management of diseases by genomic/nongenomic actions plus cross talk between PPARs and other key survival pathways and through their multiple functions with up-and downstream coactivators and co-regulators (Figure 1). To utilize these properties, multitask and safe PPAR agonists or antagonists are needed.

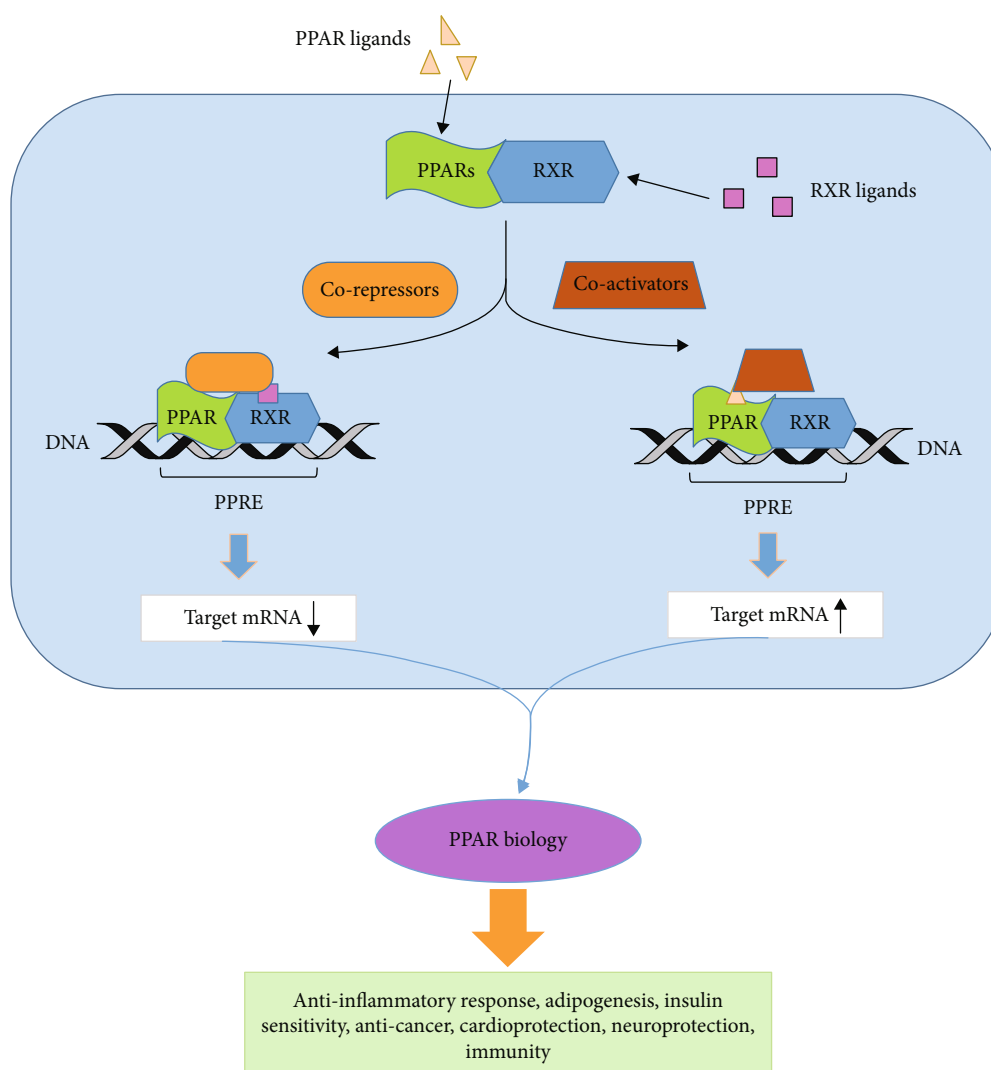


FIGURE 1: Concept map of PPARs icross-talk with RXR and PPRE.

### 3. Methods

A systematic search strategy was developed to identify the impact of phytochemicals on PPAR receptors and the implications for the treatment of diseases. Searches were undertaken in PubMed, Scopus, and Google Scholar (January 2010 to March 2021). The terms “diseases,” “phytochemicals,” “herbal medicine,” and “PPARs receptor” were incorporated into an electronic search strategy. For each selected nutraceutical, the plausible mechanism of action was identified from the *in vitro* and *in vivo* evidence, and their clinically observed effects and relevant tolerability information were reported.

### 4. Phytochemicals with PPAR Modulation Activities

Plant-derived phytochemicals are well-known as modulators of the PPAR family, and their mechanisms in the prevention and treatment of human diseases have been ascribed to their physiological effects on carbohydrate and lipid metabolism.

The versatile activities of phytochemicals are illustrated in Table 1 in terms of their PPAR activating abilities. The critical role of natural phytochemicals to human health in relation to their PPAR activating properties is discussed in the following section.

**4.1. Curcumin.** Curcumin is a natural lipophilic polyphenol from the rhizome of turmeric, *Curcuma longa* L. (Zingiberaceae), which can modulate a number of signaling pathways in its biological activities, including inflammation, atherosclerosis, and cardiovascular disease [7, 8]. Curcumin has been found to remarkably enhance peroxisome proliferator-activated receptor- $\alpha$  and  $\gamma$  (PPAR $\alpha$  and PPAR $\gamma$ ) in its anti-inflammatory, antioxidant, antihyperglycemic, and insulin sensitizer effects (Table 1) [8–10]. In this regard, it can initiate the PPAR $\gamma$ /liver X receptor (LXR)/ATP-binding cassette transporter A1 (ABCA1) pathway by up-regulation of ABCA1, ATP-binding cassette transporters G1 (ABCG1), LXR $\alpha$ , scavenger receptor (class B) (CD36), and cytochrome P450 oxidase or sterol 27-hydroxylase (Cyp27); this then leads to reverse cholesterol transport and cellular cholesterol efflux

TABLE 1: Modulatory effects of phytochemicals on the PPAR family in diseases.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
Polyphenols and simple phenols	Curcumin	Dyslipidemia	0.1% (w/w), oral feeding, 16 or 18 weeks	C57BL/6J obese mice	Antioxidant, anti-inflammatory, antihyperglycemic by reduction of lipid peroxidation, non-fasting blood glucose, oxidative stress, obesity, macrophage accumulation, and inflammation in eWAT	(+) PPAR $\gamma$ , C/EBP $\alpha$ (-) Surf, TNF- $\alpha$ , IFN- $\gamma$ , eIF2 $\alpha$ , CD206, ALOX5, GPAT1, DGAT1, Pnpl2, F4/80, CD11c, MCP-1, IL-10, Rela, Leptin, NF- $\kappa$ Bp65, SCD1	[9]
			100 mg/kg/day, feeding, 13 weeks	High-fat diet-induced obese mice	Antibesity, antiapoptotic, autophagy regulation, anti-insulin resistance, antihepatic steatosis	(+) PPAR $\alpha$ , PPAR $\gamma$ , AMPK (-) TG, Aig5, caspase 3, SREBP1	[10]
			10 $\mu$ M, 24 h treatment	Palmitic acid induced lipid droplet formation in AML12 cells	Autophagy regulation, antiapoptotic	(+) AMPK, LC3-Aig7, Bcl2/Bax (-) Lipid droplet formation	[10]
			80 mg/kg/BW, orally, 8 weeks	High fructose diet induced insulin resistance in rats	Antioxidant, antihyperglycemic	(+) PPAR $\gamma$ , CAT, GSH, hexokinase, HDL, SOD (-) TBARS, lipid hydroperoxides, fasting blood glucose, TC, TG, LDL	[8]
			50 mg/kg/BW, oral gavage, 8 weeks	Male C57BL/6J obese mice	Antibesity, antihyperglycemic	(+) PPAR $\gamma$ , C/EBP $\alpha$ , HSL, ATGL, adipose triglyceride lipase (-) TG, TC, HDL-C, LDL-C, FFA, fasting blood glucose	[206]
			10, 20, and 35 $\mu$ M, treat 48 h	3T3-L1 adipocytes	Antihyperglycemic	(+) PPAR $\gamma$ , PPAR $\alpha$ , C/EBP $\alpha$ Glucose uptake (-) Glycerol release	[206]
			100 mg/kg/BW + 1mg/kg/BW, orally, 21 days	Streptozotocin-induced diabetic rats	Anti-inflammatory, antioxidant, and lipid lowering	(+) PPAR $\gamma$ , GSH, adiponectin secretion (-) TC, TG, L-MDA, IL-6	[207]
			0.5%, 2% w/w, diet, 12 weeks	AApoAII female mice	Increasing hepatic lipid metabolism	(+) PPAR pathway, PPAR $\alpha$ , ApoA2 mRNA, CAT, CD36, Fabp, ApoE, HDL, amyloidosis, Scd-1 (-) TG	[208]
			50 and 100 mg/kg, IP, 16 weeks	HFD-fed C57BL/6J mice	Antibesity, antihyperglycemic, anti-inflammatory, antisteatosis, antidiabetes, anti-insulin resistance, antiatherosclerotic	(+) CREB (-) PPAR $\gamma$ , PPAR $\gamma$ 1, TG, hepatic steatosis, FFA, CD36	[25]
			10 $\mu$ M, 48 h treatment 80 mg/kg/BW, lavage, 5 weeks	Steatotic BRL cell, NAFLD rat	Antibesity, hepatoprotective, antihyperglycemic, anti-insulin resistant	(+) PPAR $\alpha$ (-) DNA methylation level, TG, TC, ALT, AST, HOMA-IR, Serum glucose	[209]
Liver disease	Curcumin-mPEG454		100, 200, and 300 mg/kg, gavage, 8 weeks	CCl4, olive oil-induced liver fibrosis rats	Antifibrotic, inducing hepatic stellate cell senescence, antiapoptotic	(+) PPAR $\gamma$ , P53/ $\alpha$ -SMA, Hmgal1/ $\alpha$ -SMA (-) HSC activation	[210]
			10, 20, and 40 $\mu$ M, 28 h treatment	HSC-T6 cell line	Antifibrotic, inducing hepatic stellate cell senescence, antiapoptotic	(+) P16, P21, Hmgal1, Senescence-associated $\beta$ -galactosidase-positive (-) $\alpha$ -SMA, $\alpha$ 1(I)-procollagen, G0/G1 phase-related cyclins/CDKs	[210]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
		Cancer	100 and 200 mg/kg/day, IP, 8 weeks	HFD rat	Antiatheroplipidemia, anti-inflammatory, fat degradation and suppression of lipogenesis, treat insulin resistance	(+) PPAR $\alpha$ , PPAR $\gamma$ , CPT-1 (-) TC, TG, LDL, insulin resistance, Notch-1, Hes-1, NF- $\kappa$ B, ACC, COX-2, TNF- $\alpha$ , SREBP-1c, FASN	[12]
		Cancer	2.5, 5, and 10 $\mu$ M, treat 24 h	TNBS-induced rat IEC-6 cell fibrosis	Antifibrotic	(+) PPAR $\gamma$ , E-cadherin (-) Smad3, EMT, FN, CTGF, $\alpha$ -SMA	[211]
		Renal diseases	50 and 100 mg/kg, gastro gavage, 14 days	UUO-induced renal fibrosis mice	Antifibrotic	(+) PPAR $\gamma$ , Smad2/3, ECM accumulation (-) FN, COL 1, PCNA, $\alpha$ -SMA, NRK-49F, cell cycle in G1 phase, cell proliferation	[30]
		Renal diseases	10, 20, and 30 $\mu$ M, treat 48 h	NRK-49F cells			
		Renal diseases	120 mg/kg, oral gavage, 5 days	Breast cancer-induced female Sprague-Dawley rats	Antifibrotic, anticancer, anti-inflammatory, antitumor	(+) PPAR $\gamma$ , HDL-C, GSH, myocardial marker (-) TNF- $\alpha$ , IL-6, IL-8, IL-10, BDNF	[212]
		Renal diseases	5 and 10 mg/kg, orally, 60 days	HFD-induced CMetS rats	Antioxidant, anti-inflammatory, Antifibrotic, collagen deposition, antihyperglycemic	(-) TNF- $\alpha$ , IL-6, NF- $\kappa$ B, I $\kappa$ -CRP, glucose, insulin, insulin resistant, TC, TG, LDL-C, TBARS	[31]
		Cardiovascular diseases	20 $\mu$ M, treat 1 h	Angiotensin II-induced inflammatory rat VSMCs	Anti-inflammatory, antioxidant, antiproliferative	(+) PPAR $\gamma$ (-) IL-6, TNF- $\alpha$ , NO, iNOS, p47phox, iROS,	[33]
		Cardiovascular diseases	150 mg/kg/BW, Intragastric, 4 weeks	Rat myocardial infarction	Anti-ischemic, anti-inflammatory, antiapoptotic, antioxidant, antinecrotic	(+) PPAR $\gamma$ , Bcl-2 (-) NF- $\kappa$ Bp65	[32]
		Cardiovascular diseases	100 mg/kg/day, orally, 12 weeks	Spontaneously hypertensive rats	Antihypertension, antifibrotic		[213]
		Cardiovascular diseases	5, 10, and 20 $\mu$ M, treat 1 h	Rat cardiac fibroblasts		(+) PPAR $\gamma$ (-) Ang II, CTGF, PAI-1, ECM production, TGF- $\beta$ /Smad2/3, systolic blood pressure, collagen III, fibronectin	
		Cardiovascular diseases	100 mg/kg/day, orally, 6 weeks	Diabetic rat cardiomyopathy	Cardioprotection, antioxidant, anti-inflammatory, regulate lipid metabolism, prevent heart failure	(+) PPAR $\gamma$ , TAC, GSH, HDL-C (-) CaMKII/NF- $\kappa$ B/TGF- $\beta$ , lipid peroxidation, Blood glucose level, CK-MB, troponin I, MDA, TNF- $\alpha$ , NF- $\kappa$ B, IL-6, TG, TC	[214]
		Cardiovascular diseases	0.02% w/w, diet, 18 weeks	LDLR <sup>-/-</sup> mice	antiatherogenic, lipid-lowering, antihyperglycemic, immunity	(+) PPAR $\alpha$ , LXRx, HDL-C, Apo A-1 (-) Cholesterol, TG, LDL-C, Apo B, CETP, HMG-CoA reductase, ACAT1, ACAT2, C6i, CRP, ICAM-1, VCAM-1	[11]
		Brain and nervous system diseases	10 $\mu$ M, treat 1 h	OGD/R-induced injury rat cortical neuron cells	Anti-ischemic, antiapoptotic, neuroprotection, antioxidant	(+) PPAR $\gamma$ , Bcl-2, Cyt c, AIF, JC-1, (-) LDH, I $\kappa$ B- $\alpha$ , NF- $\kappa$ Bp65, NF- $\kappa$ B, NO, Bax, caspase3, ROS, IKK, DCFDA	[215]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
			20 mg/kg/d, P.O., 14 days	STZ-induced Swiss albino mice dementia	Antidementia, antioxidant	(+) PPAR $\gamma$ , GSH, (-) AChE, TBARS	[216]
			1 or 5 $\mu$ M, treat 24 h	Rat OPs-myelin diseases	Protect against demyelination, anti-inflammatory	(+) PPAR $\gamma$ , PGC1- $\alpha$ , COX1, ERK1/2, Caspase3, MBP, O $_2$ , O $_2$ (-) OP metabolic, TNF- $\alpha$	[217]
			150 mg/kg, IP, 4 weeks	APPswe/PS1 $\Delta$ 9 transgenic mice	Anti-Alzheimer, anti-inflammatory, improved memory function, neuroprotection,	(+) PPAR $\gamma$ , ChAT, Ach (-) NF- $\kappa$ B, LDH, TNF- $\alpha$ , IL-1 $\beta$ , COX-2, NO, GFAP, Mac-1, I $\kappa$ B- $\alpha$ , NF- $\kappa$ B p65	[37]
			40 mg/kg, 4 weeks	Primary cultured mouse astrocytes	Anti-Alzheimer, anti-inflammatory, neuroprotection	(+) PPAR $\gamma$	[34]
			200 mg/kg, IP, 3 days	Rat middle cerebral artery occlusion	Anti-ischemic, anti-inflammatory, neuroprotection, decreased infarct volume	(+) PPAR $\gamma$ , PPAR $\gamma$ -PPRE, (-) IL-1 $\beta$ , I $\kappa$ B- $\alpha$ , TNF- $\alpha$ , NF- $\kappa$ B p65, PGE2, NO, iNOS, COX-2	[35]
			10 $\mu$ M, treat 24h	APOE4-induced neurological SH-SY5Y cell damage	Anti-inflammatory, neuroprotection	(+) PPAR $\gamma$ (-) TNF- $\alpha$ , IL-1 $\beta$ , NO, COX-2, iNOS, NF- $\kappa$ B p65	[36]
Respiratory			0-50 $\mu$ M, treat 48h	TGF- $\beta$ 1-induced human lung CCD-19Lu fibroblasts	Antifibrotic, anti-inflammatory,	(+) PPAR $\gamma$ , CatB, CatL, stefin B, (-) ERK, $\alpha$ -SMA, TGF- $\beta$ 1, collagen I, Colla1, Colla2, cystatin C,	[20]
			10, 30, and 100 $\mu$ M, treat 48 h	Preeclamptic PBMC	Anti-inflammatory	(+) PPAR $\gamma$ (-) IL-1 $\alpha$ , IL-6, TNF- $\alpha$ , NF- $\kappa$ B p50	[38]
Immunity			100 $\mu$ g, IP, 12 or 13 days	EAE C57BL/6 mice	Immunity, anti-inflammatory	(+) PPAR $\gamma$ , IL-10, CD4 $^{+}$ CD25 $^{+}$ Foxp3 $^{+}$ Treg, CD4 $^{+}$ Thelper	[218]
			0, 2.5, 5, 10, and 25 $\mu$ M,	Spleen cells of EAE mice	Immunity, antimalarial	(-) IFN $\gamma$ , IL-17, IL-12, IL-23	[219]
			10 $\mu$ M, treat 24h	Human THP-1 monocytes	Antiatherosclerotic, lipid-lowering, antioxidant	(+) PPAR $\gamma$ , CD36, monocyte ROS, Nr2 (-) SR-A, RAGE, foam cell formation, cholesterol accumulation	[40]
			1, 5, and 10 $\mu$ M, treat 2 h	Human monocytic leukemia THP-1 cells	Antiatherosclerotic, lipid-lowering, antioxidant, attenuate changes in carbohydrate metabolism and amino acid metabolism	(+) PPAR $\alpha$ , PPAR $\gamma$ , ABCA1, ABCG1, (-) monoglyceride accumulation, cholesterol accumulation, T.C, CE, neutral lipids	[41, 206]
			10 mg/kg/ twice a day, orally, 24 weeks	Male ApoE $^{-/-}$ atherosclerotic mice	Antioxidant, antidiabetes, antiobesity, improved endothelium-dependent relaxations	(+) PPAR $\delta$ , SIRT1, eNOS, Akt, PPRE luciferase	[220]
			1.5 $\mu$ g/ml, treat 24 h	Mice RAW264.7 macrophages	Antioxidative metabolism, anti-insulin sensitivity	(-) ROS, BW, HW, subcutaneous fat weight	[221]
Resveratrol		Dyslipidemia Metabolic syndrome	20 mg/kg/day, gavage, 2 weeks	HFD-induced obese/diabetes mice			
			20 $\mu$ M, treat 24 h	HUVECs			
			50 $\mu$ M, treat 24h	C2C12 myoblast hypoxic cell line			

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
			100 mg/kg/day, gavage, 12 weeks	Catch up growth rat	Anti-inflammatory, antiobesity, fat lowering, balance between lipid production and storage, ameliorating insulin sensitivity	(+) SIRT1, FSP27, GIR60-120, adipose tissues glucose, adiponectin (-) PPAR $\gamma$ , FINS, TNF- $\alpha$	[222]
	Resveratrol+ quercetin		10 or 50 mg/kg/day, orally	WAT from MetS rats	Improving lipid metabolism, antiobesity, antidiyslipidemia, antioxidant, anti-inflammatory	(+) PPAR $\alpha$ , MUFA, PUFA, UCP2 (-) UCP3, dihomo- $\gamma$ -linoleic, SFA	[223]
			4weeks 0.04%, feeding, 8weeks	HFD mice	Antioxidant, protect lifestyle-related diseases	(+) PPAR $\alpha$ , PPAR $\beta/\delta$ , cyp4a10, cyp4a14, FABP1, UCP3, PDK4 (-) ROS	[224]
			200 and 400 mg/kg/day, liquid diet feeding, 2 weeks	Alcoholic fatty liver mice	Reduced lipid synthesis, increased rates of fatty acid oxidation, prevented alcoholic liver steatosis	(+) SIRT1, AMPK, PGC-1 $\alpha$ , AdipoR1/R2, circulating adiponectin, FOXO1, CPT1a, MCAD, AOX	[225]
Liver disease			100 mg/kg/day, gavage, 8 weeks	HFD-induced NAFLD in rats	Antioxidant, improved lipid metabolism and mitochondrial respiratory chain activity	(-) SREBP-1, PPAR- $\gamma$ , TNF- $\alpha$ , SCD1, FAS, GPAT1, ACC $\alpha$ , ME (+) PPAR $\alpha$ , AMPK, PKA, CPT-1, SOD, CAT, T-AOC, complex I	[226]
			30 or 50 $\mu$ M, treat 24,48h	Human colon carcinoma cell lines SW480, HCT116, Caco-2, SW620	Antiapoptotic, cancer cell cycle arrest effect, antitumor, accumulation of tumor cells in the S phase	(-) SREBP-1 $\alpha$ , FAS, MDA, ALT, AST, LDL-C, TC, TG (+) PPAR $\gamma$ , caspase3, pCDNA3 (-) Cell survival	[227]
Cancer			5 g/kg, diet, 5 weeks	Ovariectomized female C57BL/6 mice	Antiobesity, anticancer, anti-inflammatory, antimammary adipocyte hypertrophy, prevented macrophage infiltration, CLS prevalence, and M-Wnt murine mammary tumor size	(+) PPAR $\gamma$ (-) IFN- $\gamma$ , IL-1 $\beta$ , IL-6, COX-2, MCP-1, TNF- $\alpha$ , Wnt/ $\beta$ -Catenin	[228]
	Resveratrol and Vaticanol C (resveratrol tetramer)		40 mg/kg, orally, 6 months 50 $\mu$ M, treat 24h	Male C57BL/6 mice HK2 cell	Antioxidant, anti-inflammatory, improved renal function, antifibrotic, prevents diabetic nephropathy, prevent lipotoxicity	(+) PPAR $\alpha$ , C/Cl, Bcl-2, Nr2f2, HO-1, NQO-1, SIRT1, AMPK, PGC-1 $\alpha$ , ERR-1 $\alpha$ , SOD1, SOD2, COX I/COX IV	[229, 230]
Renal diseases			20 mg/kg/day, gavage, 12 weeks	C57BLKS/J <i>db/db</i> mice	Antilipotoxicity, antiobesity, anti-inflammatory, antifibrotic	(-) HbA1c, albumin, SCr, eGFR, Col IV, TGF- $\beta$ 1, F4/80, Bax, $\delta$ -OH-dG, urinary isoprostane, Lys-PGC-1 $\alpha$ , SREBP1, PI3K, Akt, FOXO3a	[231]
			400 mg/kg/day orally, 12 weeks	HFD-C57BL/6j mice	Antihyperlipidemic, antihyperglycemic, cardioprotection, improved cardiac function	(+) PPAR $\alpha$ , AMPK, lipolysis (-) TG, lipid, 4-HNE, TNF- $\alpha$ , IL-6, iNOS, BUN, albumin, eGFR,	[232]
Cardiovascular diseases			100 mg/kg/day, IP, 6 weeks	<i>db/db</i> C57BL/6 mice	Antihyperlipidemic, antihyperglycemic, cardioprotection, improved cardiac function	(+) PPAR $\alpha/\gamma$ , SIRT1, mtDNA, FS (-) PGC-1 $\alpha$ , TG, glucose	[233]
			10 and 25 $\mu$ M, treat 18 h	<i>THP-1 monocytes</i> , <i>HAEc</i>	Antiatherosclerosis, antioxidant, lipid lowering	(+) PPAR $\gamma$ , cholesterol efflux, ABCA1, LXR- $\alpha$ , 27-OH, SR-B1, CD36, (-) Foam cell formation, oxLDL, lipid accumulation	[233]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
			50 mg/kg/day, IP, 5 days 50 $\mu$ M, treat 24	Hypertrophic neonatal rats NCMs	Cardioprotection, anti-inflammatory, lipid lowering, antioxidant	(+) PPAR $\alpha$ , SIRT1, PDK4, mCPT-1, MCAD (-) NF- $\kappa$ B, PGC-1 $\alpha$ , AdGF $\beta$ , ANF, $\alpha$ -SKA, MCP-1	[234]
			(0.01, 0.1, 1, 5, and 10) $\mu$ M, treat 48 h	EPCs	Antioxidant, enhanced re-endothelialization, inhibited EPC senescence, repaired endothelium	(+) PPAR $\gamma$ , h-TERT, HO-1, NO (-) NADPH, SIRT1, ROS (+) PPAR $\gamma$	[235]
	trans (t)-resveratrol		15 mg/kg/day, IV, 1 month	Ang-II-induced rat vascular inflammation Leukocyte-HUVECs MCAO mice	Cardioprotection, inhibition of ATI receptor, anti-inflammatory	(-) MCP-1, MIP-1 $\alpha$ , CAM, leukocyte, p38 MAPK, NF- $\kappa$ B p65, CD11b, CINC/KC, VCAM-1, P-selectin, IL-8, ICAM-1, RANTES	[236]
	Malibatol A (a resveratrol oligomer)	Brain and nervous system diseases	1-10 $\mu$ M, treat 1h 20 mg/kg, injection, 15 min after the onset reperfusion		Antioxidant, anti-ischemic, anti-inflammatory, immunity, neuroprotection	(+) PPAR $\gamma$ , IL-10, TGF- $\beta$ , CD206, YM-1	[237]
		Dyslipidemia	8.9 $\mu$ g/mL, treat, 48 h	Peritoneal macrophages of ApoE $^{-/-}$ mice	Anti-atherosclerotic, anti-inflammatory, prevented foam cells formation in peritoneal macrophages	(-) TNF- $\alpha$ , IL-1 $\beta$ , iNOS, IL-6, CD16, CD32, CD86 (+) PPAR $\gamma$ , ABCA1 (-) TC, free cholesterol, cholesterol ester, TNF- $\alpha$ , IL-1 $\beta$ , CD36,	[50]
		Metabolic syndrome	100 mg/kg/d, oral, 4 weeks	HFD mice	Antiobesity, anti-inflammation, body weight loss	(+) PPAR $\gamma$ , HDL, leptin (-) TC, adipose cell sizes, fat mass, TG, LDL, MCP-1, TNF- $\alpha$ ,	[238]
			100 mg/kg, P1, 12 weeks	HFD-ApoE $^{-/-}$ mice	Antiatherosclerotic, anti-inflammatory, reduced atherosclerotic plaques in aortic arch and sinus, down-regulation of cholesterol metabolism related gene transcription, losing blood lipids.	(+) HDL, T-SOD (-) TC, TG, LDL, ALT, AST, MDA, SREBP1, Fasn, HmgCR, PBEF, PPAR $\gamma$ ; cholesterol uptake, IL-6, TNF- $\alpha$ , hs-CRP,	[239]
			50, 100, and 200 $\mu$ g/mL, treat, 2h	RAW 264.7 cells			
			1, 3, and 10 $\mu$ mol/L, treat, 6 h	Rats aortas	Antihyperglycemia, improved the histological damage to endothelial cells, restored the relaxation under acetylcholine	(+) eNOS, NO, PPAR $\beta$ (-) iNOS	[52]
	Polydatin						
		Liver disease	50 and 100 mg/kg/d, intragastric, 4 weeks	STZ-HFD mice (diabetic hepatopathy mice)	Hepatoprotection, antidiabetes, anti-inflammatory, lipid lowering	(+) PPAR $\beta$ , PPAR $\alpha$ (-) TNF- $\alpha$ , IL-1 $\beta$ , TC, TG, ALT, AST, ALP, FBG, NF- $\kappa$ B p65, iNOS, COX-2	[53]
			7.5, 15, and 30 mg/kg, intragastric, 7 weeks	Fructose-associated liver inflammation and lipid deposition rats	Antioxidant, anti-inflammatory, antihyperlipidemic	(+) PPAR $\alpha$ , Keap1/Nrf2, miR-200a, CPT-1, GST, HO-1, NQO1, (-) ROS, TC, TG, TXNIP, NLR, NLRP3, SREBP-1, SCD-1, TNF- $\alpha$ , IL-1 $\beta$ , ASC, Caspase 1,	[54]
			10, 20, and 40 $\mu$ M, treat, 48 h	Buffalo rat liver cells, HepG2			
		Cardiovascular diseases	200 $\mu$ M/kg, gavage, 6 weeks	Rats	Increased arterial pressure and heart rate, decreased QRS interval and slightly reduce ST and QT intervals, attenuate myocardial pathological damage, improving energy metabolism	(+) AMPK- $\alpha$ 2, PPAR- $\alpha$ , SOD, GSH-Px, Na $^{+}$ -ATPase, Ca $^{2+}$ *Mg $^{2+}$ -ATPase, PCr, ATP, ADP, TAN, PCr/ATP (-) MDA, FFA	[240]



TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
		Brain and nervous system diseases	20 $\mu$ M, treat, 24h	Ischemic rat brain microvascular Endothelial cells	Anti-inflammatory, anti-ischemic, antiapoptotic	(+) PPAR $\gamma$ , MALAT1, CREB, PGC-1 $\alpha$ , C/EBP $\beta$ (-) LDH, TNF- $\alpha$ , IL-6, COX-2, Claudin-5, Occludin, ZO-1, ICAM-1, VCAM-1, MCP-1	[241]
		Respiratory	50, 100, and 200 mg/kg/d, intragastric, 28 days	Bleomycin-induced pulmonary fibrosis in SPF male mice	Antipulmonary fibrosis, anti-inflammatory	(+) PPAR-r (-) NF- $\kappa$ B, cytokines	[242]
			50 mg/kg, oral, 8 weeks	aPM2.5-induced rat lung injury	Anti-inflammatory, antioxidant	(+) PPAR $\gamma$ , GSH-Px, Nrf-2 (-) ROS, MDA, ICAM-1, MCP-1, IL-6	[243]
	Phlorotannins	Metabolic syndrome	12.5, 25, and 50 $\mu$ M, treat, 8 days	3T3-L1 adipocytes cells	Suppressed adipocyte-specific genes and lipid formation, antiadipogenic, reduced lipid accumulation, antiobesity	(-) PPAR $\gamma$ , C/EBP $\alpha$ , lipid content	[55]
	Phloroglucinol of <i>Potentilla longifolia</i>		10, 20, 40, and 80 $\mu$ M, treat, 96 h	3T3-L1 cells	Inhibited lipid accumulation	(+) AMPK, ACC (-) SREBP1c, FAS, SCD1, PPAR $\gamma$ , C/EBP $\alpha$ , TG	[58]
	<i>Ecklonia stolonifera</i> extract	Liver diseases	50, 100, and 200 mg/kg/day, gavage, 4 weeks	Ethanol-induced fatty liver Rat	Antioxidant, hepatoprotective, lipid lowering, anti-inflammatory	(+) PPAR $\alpha$ , CPT-1 (-) TG, SREBP-1, TC, ALT, AST, MDA, FFA	[244]
			0.19 and 0.95 mg/Kg/day, orally, 4 weeks	WAT from MetS rat	Reduced adipogenesis in preadipocytes, body weight, central adiposity, insulin concentration, and systolic arterial pressure	(+) PPAR $\gamma$ , HDL-C, SIRT 1, SIRT 2, PUFAs (-) TC, TG, SIRT 3, leptin, MUFAs, NEFAs	[68]
			0.05%, gavage, 9 weeks 10 $\mu$ M, treat 40–42 h	WAT of HFD-fed obese mice 3T3-L1 adipocytes	Antiobesity, thermogenic activator, induced browning of WAT, improved metabolic complication	(+) PPAR $\gamma$ , PGC1 $\alpha$ , Tfam, Tmem26, Cidea, Prdm16, Nr1h1, UCP1, PKA/AMPK, $\beta$ 3AR (-) -	[69]
			5, 10, and 50 $\mu$ M, treat, 24 h	OP9 cells	Prevented adipogenesis, regulated lipolysis enzymes, antiobesity, antiadipogenic	(+) ATGL, HSL (-) C/EBP $\alpha$ , PPAR $\gamma$ , SREBP-1c, lipid accumulation, FAS, LPL, ap2	[245]
	Quercetin	Metabolic syndrome	0.3, 1.5, 3, 15, and 30 $\mu$ M, treat, 8 h	THP-1 cells	Antiatherogenic, antihyperlipidemic	(+) PPAR $\gamma$ , LXR $\alpha$ , ABCA1, HDL, apoA1 (-) -	[70]
			25, 50, 100, and 200 $\mu$ M, treat, 4, 8, 16, 32 h	THP-1 cells	Decreased formation of foam cell derived, increased cholesterol efflux from macrophages	(+) PPAR $\gamma$ -LXR $\alpha$ , ABCA1, PPRE-luc reporter (-) TC, lipid droplets	[246]
			5, 10, and 30 $\mu$ M, treat, 6 days	Male F344 rat primary mSCs	Suppressed lipid accumulation, and mSC adipogenesis	(+) - (-) PPAR $\gamma$ , FABP4, TG	[247]
			0, 0.2, 0.4, and 0.6 g/kg/feeding, 42 days	AA broilers	Decreased abdominal fat, improved lipid metabolism	(+) PPAR $\alpha$ , PDK, AMPK $\alpha$ 1, AMPK $\alpha$ 2, AMPK $\beta$ 2, IKK1, PKB, AMPK $\gamma$ , CPT1, (-) PPAR $\gamma$ , SREBP1, ACC, HMGR	[248]
	Quercetin-3-O- $\beta$ -D-glucuronide		25 and 50 mg/kg/day, gavage, 8 weeks	HFD-male SD rats	Reduced bodyweight, liver weight, liver index, fat overload, lipid accumulation and dyslipidemia, anti-inflammatory, antiapoptotic, hepatoprotective	(+) PPAR $\alpha$ , HDL, CPT1, MCAD (-) TG, SREBP-1c, TNF- $\alpha$ , IL-6, ALT, AST, LDL, TC, FAS	[249]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
			1%, feeding, 16 weeks	HFD mice	Antiobesity, increased WAT browning, increased lipolysis, Enhanced lipid transportation and $\beta$ -oxidation of FA, reducing lipid deposition	(+) PPAR $\gamma$ , UCPI, PGC1 $\alpha$ , BAT, ACSL4, ACOT11, ADRB3 (-) TC, p38 [250]	
			5, 10, and 20 mg/L, treat, 24, 48, and 72 h	AA broiler hepatocytes		(+) PPAR $\alpha$ , ACSL, ApoA1, FABP, (-) ApoC3, VLDL, TG [251]	
			100 mg/kg/d, gavage, 2 weeks	<i>ob/ob</i> mice	Reduced body weight and fat, ameliorated insulin resistance, alleviated hepatic steatosis	(+) MRC II, III, IV, V (-) PPAR $\gamma$ , ap2, CD36, LPL, ACC, SREBP -1c, ap2, CD36, SCD1, AUC, FFA, Leptin, Insulin level, Blood glucose, TG, TC [252]	
			1% (W/W), diet, 4weeks	HFD-C57/BL6 mice			
	Isorhamnetin		12.5, 25, and 50 $\mu$ M	3T3-L1 preadipocyte	Antioxidant, augmented adiponectin expression, increased the concentration of circulating Adiponectin	(+) Plasma adiponectin, FFA (-) PPAR $\gamma$ , HOMA, 8-iso-PGF2 $\alpha$ , TG [253]	
			25 mg/kg/BW, gavage, 4 weeks				
			1, 5, 10, and 25 $\mu$ M, treat, 7 days	Mouse 3T3-L1 cells	Suppressed lipid accumulation, adipocyte area, antiobesity, attenuated adipogenesis	(+) PPAR $\gamma$ , cEBP $\alpha$ , HDL, adiponectin [254]	
	Q, Q2		0.26 mg/kg orally, 12 weeks	HFD rat		(-) BW, BMI, abdominal fat, heart weight, cardiac somatic index, glycemia, insulin, HOMA, TC, TG, LDL [254]	
			25 mg/kg/day, IP, 4 weeks	Male C57BL/6 mice	Antidiabetic, antiobesity, reduced hyperlipidemia, hyperglycemia, adipogenesis	(+) GLUT4, Akt, AMPK, insulin sensitivity, glucose tolerance [255]	
			1, 10, and 50 $\mu$ M, treat, 48 h	3T3-L1 adipocytes		(-) PPAR $\gamma$ , FABP4, cEBP $\alpha$ , BW, TC, TG, glucose, LDL [255]	
			10 <sup>-5</sup> M, diet, 5 days	HFD-C57BL/6N mice	Antioxidant, antiobesity, improved lipid and glucose metabolism, enhanced $\beta$ -oxidation	(+) PPAR $\alpha$ , Ehhadh, GK (-) gp91phox, FAS, GPAT, L-PK, G6Pase [256]	
			6.25, 12.5, and 25 $\mu$ M, treat, 24 h	3T3-L1, RAW 264.7 cells		(+) IL-10, adiponectin, insulin sensitivity, HDL [256]	
			25,50,100 mg/kg, oral, 10 weeks	HFD mice	Anti-inflammatory, antiobesity, inhibited adipogenesis and lipogenesis, inhibited lipid accumulation and body weight	(-) PPAR $\gamma$ , mTOR, P3K, Akt, p70S6K, C/EBP $\beta$ , C/EBP $\alpha$ , FABP4, DGATI, LPAAT $\beta$ , Lipin1, ERK, JNK, P38MAPK, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, AP-1, MCP-1, NF- $\kappa$ B, TG, LDL [257]	
	Q derivatives+1% catechin	Liver disease	10, 20 mg/kg/BW, gavage, 6weeks	Hepatocarcinogenesis rats	Antioxidant, prevented early stages of liver cancer and neoplastic foci, induced apoptosis	(+) CAT, SOD, Caspase3, p53, Bax/Bcl-2, cytochrome c (-) PPAR $\gamma$ , PPAR $\alpha$ , TARS, cyclin D1, cyclin A, cyclin B1, cdk1 [258]	
			50 and 100 mg/kg gavage, 4 weeks	NAFLD rat	Antioxidant, anti-inflammatory, decreased lipid accumulation, antiapoptotic	(+) PPAR $\alpha$ , MMP, SOD, TAC, Nuclear Nrf2, (-) NOX, TXNIP, ROS, H <sub>2</sub> O <sub>2</sub> , MDA, iNOS, XO, O <sub>2</sub> <sup>-</sup> , NLRP3, ASC, Caspase 1, IL-1 $\beta$ , IL-18, JAK2, STAT3, SOCS3, SREBP1, SCD1 [259]	
			20 $\mu$ M, treat, 24h	RHPCs			

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
			50 $\mu$ M, treat, 48h	Oleic acid-induced lipid accumulation Huh7.5 cells	Decreased intracellular lipids and LD size, downregulate hepatic lipogenesis, upregulate lipolysis, reduced steatosis	(+) PPAR $\alpha$ (-) TG, SREBP-1c, PPAR $\gamma$ , ACAT1, apoB, apoB	[260]
			0.08% in the AIN-93G diet, 10 weeks	<i>ob/ob</i> mice	anti-inflammatory, antioxidant, controlled hypercholesterolemia, alleviated hepatic steatosis, improved liver function, alleviation of insulin resistance, enhanced fatty acid oxidation, suppressed lipogenesis,	(+) PPAR $\alpha$ , AMPK, adiponectin, (-) FFA, ALT, SREBP-1c, PPAR $\gamma$ , TNF- $\alpha$ , MCP-1, cholesterol, TC, HOMA-IR, TG	[261]
			50 mg/kg, oral, 6 weeks	High-fat high-sucrose-rats	hypolipidemic action, modulated metabolic markers	(+) G6PDH, (-) PPAR $\gamma$ , TG, TC, lipase, G3PDH, Adipose, hepatic tissue	[262]
	QP	Cancer	100 mg/kg, gavage, once a week/12 weeks 2 and 10 $\mu$ M, treat, 24 h	Mongolian gerbils Human A549 lung cancer cells	Suppressed cell invasion and migration, anticancer, cell cycle arrest at the G2/M phase, antiproliferative	(+) PPAR $\gamma$ , nm23-H1, TIMP-2, PTEN	[263, 264]
			10, 25, and 50 $\mu$ M, treat, 24-72 h	Human AGS cell line	Anticancer, anti-inflammatory, antiproliferative, pro-apoptotic	(+) PPAR $\gamma$ , PPAR $\beta$ , caspase 3, caspase 9	[265]
		Renal diseases	50 and 100 mg/kg/day, gavage, 4 weeks	Cd-induced nephrotoxicity rats	Inhibited lipid accumulation, antihyperuricemic, antidiabetic, nephroprotective	(-) Bcl2, Cyclin D1, Bcl-xL, CD31 (+) PPAR $\alpha$ , Renal XDH, FEUA, CPT1, AMPK, OCTN2, (-) Urine RBP, Urine $\beta$ -MG, Urine ALB, Serum UA, uric acid, Renal XO, Renal RST, Renal OATI, TG, VLDL, SREBP-1, PGC-1 $\beta$ .	[266]
			50 mg/kg/d, gavage, 8 weeks	C57BL/6 mice	Antiatherosclerotic, increased lipid droplets and lipid uptake, antioxidant	(+) PPAR $\gamma$ , SR-BI, DiI-HDL, LXRo, SLU, HDL-C	[60]
			15 $\mu$ M, treat, 6, 12, 24 h	HepG2 cells		(-) Lipid accumulation, oxLDL level	
	Isorhamnetin		12.5 mg/kg, oral gavage, 12 weeks	HFD-apoE <sup>-/-</sup> mice	Antiatherosclerotic, anti-inflammatory, antioxidant, reduced the atherosclerotic plaque area, increased the collagen fibers in atherosclerotic plaques, improved hepatocyte microstructure	(+) PPAR $\gamma$ , LXRo, ABCA1, HDL, IL-10 (-) CD36, PCSK9, TC, TG, LDL, oxLDL, TNF- $\alpha$ , IL-6, lipid accumulation, FC	[63]
		Cardiovascular diseases	50, 100 mg/kg, gavage, 1 week	Hypertensive rats	Antioxidant, anti-inflammatory, antiapoptotic, increased cardiac and renal antioxidant enzymes, cardioprotective effects	(+) PPAR $\gamma$ , Hsp70, ERK, GSH, GPx, SOD, GST, (-) SBP, DBP, MAP, AST, PT, NPT, Cyt C, p38, MDA, AOPP, H <sub>2</sub> O <sub>2</sub>	[64]
			5 and 10 mg/kg, gavage, 12 weeks 100 $\mu$ g/ml, treat, 24 h	Spontaneously hypertensive rats Angiotensin II-induced H9C2 cells	Reduced hypertrophic surface area, reduced blood pressure and left ventricular weight	(+) PPAR $\gamma$ , LV/IDd (-) AP-1, ANP, BNP, SBP, IVSd, LVPWd, c-fos, c-jun, CVF	[65]
			250 mg/kg/d, gavage, 10 days 40 $\mu$ M, treat, 24 h	MI-C57/BL6-mice Hypoxia H9C2 cell lines	Anti-ischemic, increased ejection fraction and fractional shortening, antioxidant, anti-inflammatory, antiapoptotic	(+) PPAR $\gamma$ , SOD, GSH-PX, (-) CK-MB, AST, cTnT, IDH, iNOS, MDA, caspase-3, NF- $\kappa$ B p65, I $\kappa$ B $\alpha$	[66]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
			0.5% w/w, gavage, 4 weeks	Cardiac dysfunction in hyperglycemic rats	Anthyperlipidemia, improved cardiac function, inhibited cardiac cholesterol and heart weight, antioxidant	(+) HDL, Nr1z, HO-1, SOD, CAT, GSH, ATP levels, PGC-1 $\alpha$ , (-) PPAR $\gamma$ , TC, TG, glucose, VLDL, LDL, TBARS, UCP2	[267]
			5-20 $\mu$ g/mL, treat, 24 h 40 and 80 $\mu$ M, treat, 72 h 60 $\mu$ M, treat, 21 days	3T3-L1 adipocytes	Increased adiponectin, antiadipogenic, suppressed lipid accumulation, antiobesity, anti-inflammatory, antioxidant	Prp1a2, Lipe (-) PPAR $\gamma$ , C/EBP- $\alpha$ , FAS, leptin, SREBP-1c, adiponin, LPL, aP2, Dgat2, Agpat2, Scd1, Lsr, Cel, GLUT4, CD36, LPIN1, Resistin, LXRs, LXR $\beta$ , C/EBP- $\beta$	[76, 78, 80]
			1, 10, or 25 $\mu$ M, treat, 48 h	hMSCs	Antiadipogenic, delipidating effects, reducing lipogenesis	(+) Aktg (-) PPAR $\gamma$ , C/EBP- $\beta$ , TG	[81]
		Metabolic syndrome Dyslipidemia	0.15% dietary, 92 days	HFD-obese C57BL/6J mice	Antiobesity, antidiabetic, reduced adipose tissue accumulation, increased lipid metabolism	(+) Insulin resistance, (-) PPAR $\gamma$ , TNF- $\alpha$ , fasting blood glucose, HbA1c, SREBP-1c, body weight	[77]
	Kaempferol		20 $\mu$ M, treat, 24 h	Hek-293 cells transfected with luciferase reporter constructs	Antioxidant, longevity-associated transcription factors	(+) PPAR $\gamma$ , Nr1z, FoxO (-) ROS	[82]
			10 or 20 $\mu$ M, treat, 24 h 150 mg/kg/d, orally, 10 weeks	HepG2, THP-1, and Caco2 ApoE-deficient C57BL/6J mice	Promoted lipid metabolism, induced hepatic autophagy, motivated macrophage cholesterol efflux, stimulated fatty acid oxidation and uptake, blocked SREBP1 translocation to nucleus	(+) PPAR $\alpha$ , PPAR $\delta$ , Insig-2a, 2-NBD-cholesterol efflux, Lxr $\beta$ , ABCA1, ABCG5, ABCG8, Apoe, ACADL, CPT-1a, ACOX-1, APOC3, fatty acid uptake, LC3-II, LAMP-1, LAMP-2, AFG-7 (-) Akt, TG, SREBP-1, NCPL1, GSK-3, S6K1	[79]
			50, 100, and 200 mg/kg, IP, 5 weeks	db/db mice	Lipid lowering, reduced glucose	(+) PPAR $\gamma$ , LPL (-) Blood glucose, TG	[83]
			3, 10, 30, and 100 $\mu$ M, treat, every 2 days for 8 days	Mouse 3T3-L1 adipocytes	Increased lipid accumulation, stimulated adiponectin secretion, adipogenesis	(+) PPAR $\gamma$ , C/EBP $\alpha$ , aP2, adiponectin secretion, adiponectin (-) -	[84]
	Rutin	Metabolic syndrome	100 mg in 100 g HFD, 16 weeks	HFD-C57BL/6J mice	Restored glucose and insulin tolerance, reduced ER stress markers, adiponectin	(+) PPAR $\gamma$ ; DsbA-1, p-JNK, Akt (-) Adiponectin, GRP78, insulin	[85]
			0.11% diet, 16 weeks	HFD rat	Improved mitochondrial loss, increased functional capacity in skeletal muscle, decreased total weight, lipid-lowering, decreased adipogenesis, antiobesity	(+) HDL, AMPK, mtDNA, NRF1, Tfam, PGC-1 $\alpha$ , SIRT1, CPT1 (-) PPAR $\gamma$ , SREBP-1c, aP2, atherogenic index, TG, LDL	[86]
			2, 10, and 50 $\mu$ M, treat, 48 h	Murine 3T3-L1 cells	Antiadipogenic, suppressed lipid accumulation	(+) AMPK (-) PPAR $\gamma$ , C/EBP $\alpha$ , Lipin1, FAS, LPL, aP2	[87]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.		
Rutin and quercetin		Renal diseases	50 and 100 mg/kg, gavage	Fructose-fed rats	Anthyperuricemia, antidyplipidemia, restored renal dysfunction, antioxidant, anti-inflammatory, lipid accumulation	(+) PPAR $\alpha$ , rCPT1, rOCTN2, L-carnitine, rJAK2, rIR, rAkt, rIRS1(Tyr), rERK1/2 (-) rNLRP3, rASC, rCaspase-1, uric acid, TG, TC, VLDL, creatinine, BUN, insulin, leptin, rOb, p-rOb, p-rSTAT3, IL-1 $\beta$ , IL-6, IL-18, rTNF- $\alpha$ , rSOCS3, p-rOb-RL (Tyr1138), rIRS1(Ser)	[88]		
		Brain and nervous system diseases	30 mg/kg, oral, 14 days	Cisplatin induces neurotoxic rats	Neuroprotective, antioxidant	(+) PPAR $\delta$ , PON-1, PON-3, GPX, glutathione (-) PON-2, TBARS	[89]		
		Immunity	11.5 mg/kg bw, oral, 4 weeks 5-30 $\mu$ M, treat, 48 h	Ovalbumin-induced sensitive Balb/c mice PMA/ionomycin- in induced EL4 T cells	Immunity, antiallergy, reducing food hypersensitivities	(+) PPAR $\gamma$ (-) IL-4, Th2, GATA3, p-STAT6, NF-AT	[268]		
		Metabolic syndrome	10 $\mu$ M, treat, 72 h 50 $\mu$ M, treat, 24 h	3T3-L1 adipocytes	Decreased insulin, increased lipid accumulation, accelerated adipocyte differentiation, improved insulin resistance, lipid lowering	(+) PPAR $\gamma$ , adiponectin, C/EBP $\alpha$ , glucose uptake (-) TG	[90, 91]		
			1, 10, and 25 $\mu$ M, treat, 8 days	Adipocytes derived from hMSCs	Antiadiipogenic effect, antiobesity	(+) atgl (-) PPAR $\gamma$ , TG, C/EBP $\beta$ , SREBP1C, perilipin, lipogenesis, fastn	[81]		
			50, 100,200 mg/kg, gavage, 7 days	CCl4-inducedALI C57BL/6j mice	Hepatoprotective effects	(+) PPAR $\gamma$ (-) ALT, AST	[92]		
		Hesperetin		Liver diseases	25 and 50 mg/kg, orally, 11 days	CYP-induced hepatotoxicity in rats	Anti-inflammatory, antioxidant, decreased lipid peroxidation	(+) PPAR $\gamma$ , albumin, GSH, CAT, SOD, GPx (-) ALT, AST, $\gamma$ GT, bilirubin, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, MDA, iNOS, NO, NF- $\kappa$ B	[97]
				Cancer	1-16 $\mu$ M, treat, 48 h 10-50 $\mu$ M, treat, 24 and 48 h	LPS-induced inflammation in RAW264.7 Cells NALM-6 cells	Anti-inflammatory Antiproliferative effects, increased subG1 phase cells, induced a apoptosis	(+) PPAR $\gamma$ (-) TNF- $\alpha$ , IL-1 $\beta$ , IL-6, JAK1, STAT1	[92]
				Cardiovascular diseases	200 mg/kg, orally, 28 days	ISO-induced cardiac hypertrophy rat	Anti-inflammatory, antiapoptotic, antioxidant, attenuated pathological changes, improved cardiac hemodynamics	(+) PPAR $\gamma$ , CAT, SOD, GSH, +dP/dt, -dP/dt, Bcl-2 (-) Heart weight, MDA, LDH, CK-MB, LVEDP, TNF- $\alpha$ , IL-6, NF- $\kappa$ B, JNK, p-JNK, caspase-3	[93]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
			100 mg/kg/day, orally, 14 days	IR in diabetic rat	Cardioprotective, antiapoptotic, increased blood flow, antioxidant, anti-inflammatory, reduced edema, improved cardiac function	(+) PPAR $\gamma$ , Bcl2, SOD, CAT, GSH, MAP, +dp/dt, -dp/dt, CK-MB, LDH, inotropic and lusitropic function (-) IS, Bax, TNF- $\alpha$ , MDA, LVEDP, thiobarbituric acid reactive	[94]
		Brain and nervous system diseases	50 and 100 mg/kg	AMI-rat	Antioxidation, anti-inflammatory, antiapoptotic, cardioprotective	(+) PPAR $\gamma$ , Bcl2 (-) MDA, IS, HW/BW, CK-MB, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, MCP-1, ICAM-1, caspase-3/9, p53, Bax	[95]
		Brain and nervous system diseases	100 mg/kg/day, orally, 8 weeks	Fluoride-induced neurobehavioral rat	Antioxidant, neuroprotective, increased fall time, improved neurobehavioral impairment	(-) Fluoride, MDA, DCF, AChE	[98]
		Dyslipidemia	50-200 $\mu$ M, treat, 24 and 48 h	3T3-L1 adipocytes	Inhibited early stage of differentiation, antiadipogenic, anti-inflammatory, antioxidant, reduced lipid accumulation, antiobesity	(+) G0/G1, S population (-) PPAR $\gamma$ , C/EBP- $\alpha$ , SRERP-1c, FAS, TNF- $\alpha$ , IL-6, cell cycle progression, ROS	[99]
			15 and 30 mg/kg/day, SQ, 13 days	HFD-induced obese mice	Inhibited adipogenesis, anti-visceral obesity, reduced body weight	(+) STAT3 (-) PPAR $\gamma$ , VAT, SAT, EAT, CD36	[100]
		Metabolic syndrome	10, 30, and 50 mg/kg, IP, 21 days	HFD and ob/ob mice, RAW264.7 cells	Reduced liver and muscular steatosis in macrophage, improved glucose resistance, anti-inflammatory	(+) PPAR $\gamma$ , MGL1/2, Ym1, Arg1, MMP-9, CD206 (-) ALT, AST, TC, TG, IL-12, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , CCL2, CD80, MHCII, CCL3, CCL4, CCR2, p65	[101]
			30 mg/kg/day, IP, 3 weeks	HFD-induced mice NAFLD	Inhibited lipid accumulation, antioxidant, anti-inflammatory, attenuated liver steatosis	(+) Nr2f2, Keap1, SOD, CAT, GSH-Px, GST, NOO1, GCLc, GCLm, GSTA2, GSTA4 (-) PPAR $\gamma$ , PPAR $\alpha$ , TNF- $\alpha$	[103]
	Apigenin		20 and 40 mg/kg, gavage, three times a week, 8 weeks	CCl $_4$ -induced mouse liver fibrosis	Alleviated liver fibrosis, suppressed autophagy, inhibited hepatic stellate cell activation, reduced cell viability, anti-inflammatory, decreased mean of integrated optical density of fibrotic and autophagy proteins, liver-protective	(+) PPAR $\alpha$ , MMP2, p62 (-) ALT, AST, ECM generation, HSCs, TIMP1, IL-1 $\beta$ , Col-1, $\alpha$ -SMA, Beclin-1, LC3, TGF- $\beta$ 1, p38	[102]
		Liver diseases	20 and 40 mg/kg/day, gavage, 14 days	BDL-induced mouse liver fibrosis	Cardioprotective, improved cardiac hypertrophy, regulated abnormal myocardial glucolipid metabolism	(+) PPAR $\alpha$ , CPT-1, PDK-4 (-) PPAR $\gamma$ , SBP, angiotensin II, HFA, HIF-1 $\alpha$ , GPAT, GLUT-4, Heart weight, Heart weight index	[104]
		Cardiovascular diseases	75 mg/kg/day, orally, 14 days	MI-in diabetic rats	Attenuated myonecrosis, prevented edema, antiapoptotic, antioxidant, improved cardiac function, reinstated a balanced redox status, prevented hemodynamic perturbations	(+) PPAR $\gamma$ , DAP, MAP, CAT, SOD, GSH, -LVdp/dt $_{\text{min}}$ + LVdp/dt $_{\text{min}}$ (-) Blood glucose, ST, SAP, HR, LVDEP, CK-MB, LDH, MDA	[105]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
		Brain and nervous system diseases	20 mg/kg, intragastrically, 3 weeks	CUMS rat	Ameliorated behavioral abnormalities, decreased locomotor activity, inhibited microglia, antioxidant, anti-inflammatory, antidepressant	(+) PPAR $\gamma$ , GSH, sucrose consumption, number of crossing (-) NLRP3, IL-1 $\beta$ , MDA, IL-18, CD11b, ASC, caspase-1	[106]
		Immunity	150-300 mg/kg, gavages, 28 days	Bleomycin-induced mouse pulmonary fibrosis	Antifibrotic, antioxidant	(+) PPAR $\gamma$ , GSH, SOD, Smad-7, E-cadherin	[107]
		Metabolic syndrome	3%, 11 weeks	Ovariectomized female mice	Inhibited lipid accumulation, reduced intra-abdominal and subcutaneous adiposity	(-) NF- $\kappa$ B, TGF- $\beta$ 1, MMP-9, vimentin (+) SREBF1, PPARGC1A, CPT1a, PGC1 $\alpha$ , Pck2 (-) PPAR $\alpha$ , PPAR $\gamma$ , MCP1/Ccl2, IL-6/Il6, leptin, glucose, insulin, TAG LIPIDS,cholesterol,ACOX1	[108]
			12.5, 25, and 50 $\mu$ g/ml, treat, 24 h	HepG2 and HUVECs	Anti-inflammatory, reinforced metabolism, antihypercholesterolemia	(+) PPAR $\gamma$ , LDLR, CYP7A1, SREBP2, I- $\kappa$ B $\alpha$	[109]
			100 mg/kg, orally, 4 weeks	Obese diabetic mice	Attenuated hypoglycemic, reduced obesity-related adipokine, antidiabetes	(-) EL, CRP, TNF- $\alpha$ , ICAM-1, VCAM-1,ERK1/2, NF- $\kappa$ B, p65	[115]
			100 and 200 mg/kg, IV, 16 weeks	STZ-induced diabetes mellitus rat	Increased body weight, enhanced blood glucose levels, ameliorated cognitive deficits, antioxidant, anti-inflammatory	(+) PPAR $\gamma$ , TIMP-1, CRP (-) Glucose	[116]
	Naringenin		25, 50,100 mg/kg/d, orally, 28 days	HFD-STZ-induced type 2 diabetic rat	Antioxidant, anti-inflammatory, hepatoprotective, decreased kidney damage, antidiabetes, attenuated ER distension, preserved granule content, attenuated glomerular sclerosis, ameliorated hepatic steatosis	(+) PPAR $\gamma$ , adiponectin, $\beta$ -cell, HDL-C, P-IRS1(Tyrl62), HSP-72, HSP-27, SOD, GSH-Px (-) Insulin resistance, TNF- $\alpha$ , IL-6, hyperinsulinaemia, CRP, NF- $\kappa$ B, TC, TAG, LDL-C, NEFA, SREBP-1c, LXR $\alpha$ , dyslipidaemia, hyperglycaemia, TBARS	[117]
		Liver diseases	0.003, 0.006, and 0.012% of diet, oral, 6 weeks	Rat	Hypolipidemic, antiadiposity, lowered adiposity, upregulated fatty acid oxidation	(+) PPAR $\alpha$ , CPT-1, UCP2 (-) TC, TG, free cholesterol	[110]
			30 mg/kg, oral gavages,14 days	HBx-induced hepatic lipid accumulation mice	Decreased hepatic lipid accumulation, inhibited hepatic adipogenic and lipogenic, prevented HBx-infected hepatic steatosis	(+) - (-) PPAR $\gamma$ , LXR $\alpha$ , adipogenic, lipogenic, ALT,AST, TG, SREBP1c	[118]
			126 and 400 $\mu$ M, treat, 24	Huh7-rat hepatocytes cells	Increased fatty acid oxidation, decreased cholesterol and bile acid production, normalized lipid, inhibited HCV, decreased time-resolved fluorescence resonance energy transfer (TR-FRET)	(+) PPAR $\alpha$ , PPAR $\gamma$ , CYP4A, ACOX, UCP1, ApoA1, FGC1 $\alpha$ , SREBP2 (-) LXR $\alpha$ GAL4-fusion reporters, ABCA1, ABCG1, HMGR, FASN,LXRE, TG, bile acids, SREBP1, ApoB	[111]
		Renal diseases	25 or 75 mg/kg/d, 4 weeks	Diabetic nephropathy mice	Ameliorated the glomeruli and renal tubular injury, improved effect on diabetic nephropathy, alleviated the morphological changes, reduced the proliferation of NRK-52E cells	(+) PPAR $\alpha$ , PPAR $\beta$ , PPAR $\gamma$ , CYP4A-20-HETE (-) BUN, Scr, urinary albumin FBG	[119]
			0.01, 0.1, and 1 $\mu$ mol/L,	High glucose-induced proliferation and hypertrophy NRK-52E cells			

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
Cardiovascular diseases		Cardiovascular diseases	0.1, 1, and 10 $\mu\text{mol/L}$ , treat, 48 h	High glucose-induced cardiomyocyte hypertrophy H9c2 cells	Improved myocardial hypertrophy, antihypertrophic, cardioprotection	(+) PPAR $\alpha$ , PPAR $\beta$ , PPAR $\gamma$ , CYP2J3, 14,15-EET (-) -	[112]
			100 mg/kg/d, IP, 7 days	STZ-induced diabetic rat	Antioxidant, anti-inflammatory, antihyperglycemia, improved learning and memory performances, neuroprotective, reduced diabetes-associated cognitive decline	(+) PPAR $\gamma$ , SOD (-) MDA, TNF- $\alpha$ , IL-1 $\beta$ , IL-6	[114]
Brain and nervous system diseases		Brain and nervous system diseases	20, 40, and 80 mg/kg, orally, 28 days	Quinolinic acid-induced neurotoxicity rat	Neuroprotective effect, antioxidant, anti-inflammatory, decreased body weight and relative brain weight, antiapoptotic, decreased oxidative stress, increased mitochondrial complex	(+) PPAR $\gamma$ , SOD, GSH, NADH, complex I, complex II, complex III, complex-IV, Bcl-2 (-) Locomotor activity, rearing, grooming, neurological score, footprint analysis, grip strength, number of slips, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, NF- $\kappa\text{B}$ , MDA, NO, Bax, caspase 3	[113]
			25, 50, and 100 mg/kg/d, orally, 7 days 20 $\mu\text{M}$ , treat, 1 h	DSS-induced ulcerative colitis in mice RAW264.7 cells	Anti-inflammatory, alleviated colitis outcomes anti-UC activity, regulated ZO-1	(+) PPAR $\gamma$ (-) Histological score, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, NF- $\kappa\text{B}$ p65, I $\kappa\text{B}$ , p38, ERK, JNK, NLRP3, ASC, MAPK, caspase-1, DAI score, colonic shortening	[269]
Catechins (catechin, EGCG, ECG, EGC, proanthocyanidins)		Immunity	50 and 100 mg/kg/d, gavage, 20 weeks	HFD-C57BL/6J mice	Decreased obesity and epididymal fat accumulation, increased free fatty acids excretion, increased <i>de novo</i> fatty acids synthesis genes, antihyperlipidemia, EGCG adipogenesis, lipogenesis, and lipolysis effects appear partially via AMPK activation in both subcutaneous and epididymal adipose tissues, antioxidant	(+) In subcutaneous adipose tissues: PPAR $\alpha$ , PPAR $\gamma$ , ACC1, FAS, SCD1, SREBP1, ACO2, MCAD, AP2, PGCL $\alpha$ , lipolysis ( <i>Isi</i> , <i>atgl</i> ), lipid oxidation, In both: AMPK, HDL-C, FFA (-) In epididymal adipose tissue: PPAR $\gamma$ , ACC1, FAS, SCD1, <i>Cl</i> EBPB, SREBP1, <i>Isi</i> , FASN, CPT1 $\alpha$ , PPAR $\alpha$ , ACO2, MCAD, AP2, PGCL $\alpha$ , UCP2 In both: TG, cholesterol, LDL-C, TAG	[120]
			100 $\mu\text{M}$ , treat, 2 days	DMI-induced 3T3-L1 preadipocytes	Inhibited cell proliferation, suppressed differentiation of 3T3-L1 preadipocytes, blocked adipocytes clonal expansion, lowering fat accumulation, antioxidant	(+) S-phase population (-) PPAR $\gamma$ , <i>C/EBP<math>\alpha</math></i> , <i>FoxO1</i> , PI3K/Akt, MEK/ERK, TAG, ROS, $G_{\beta}/G_i$ population	[121]
Metabolic diseases		Metabolic diseases	1-10 $\mu\text{M}$ , treat, 24 h	db/db C57BL/6J mice macrophages RAW264.7 cells	Promoted macrophage M2 polarization, suppressed M1 polarization, anti-inflammatory, ameliorated obesity-related inflammation, anti-inflammatory	(+) PPAR $\gamma$ , CD36, ABCG1, CD206 <sup>+</sup> , Arg1, Ym1, Fizz1 (-) CD86 <sup>+</sup> , IL-6, TNF- $\alpha$	[122]
			5, 50, and 100 $\mu\text{M}$ , treat, 2 days	DMI-induced 3T3-L1 preadipocytes	Inhibited glucose uptake, reduced lipid accumulation, lowering adipokine secretion, blocked adipocyte's differentiation, suppression maturation and functions of adipocyte, inhibited adipocytes secretory activity, antiobesity	(+) - (-) PPAR $\gamma$ , FAS, P-FOXO1, PI3K/Akt, TNF- $\alpha$ , adiponectin, resistin, leptin	[123]
	Procyanidin B2						



TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
			25, 50, 75, and 100 $\mu$ M, treat, 24 h	Primary cultures of visceral preadipocytes from <i>Rattus norvegicus</i> strain Wistar	Inhibited preadipocytes differentiation into adipocytes, antiobesity, enhanced cell viability, inhibited preadipocytes differentiation	(+) Adiponectin (-) PPAR $\gamma$	[124]
			1, 5, and 10 $\mu$ M, treat, 14 days	Human adipose-derived stem cells	Increased cell proliferation, enhanced osteogenic differentiation, suppressed adipogenesis	(+) ALP, BSP, Runx2, OCN, STAT3 (-) PPAR $\gamma$ , P-STAT3, C/EBP- $\alpha$	[125]
			50, 100, 200, 300, 600, and 900 $\mu$ M, treat, 24 and 48 h	3T3-L1 preadipocytes	Inhibited preadipocytes differentiation, suppressed lipid decomposition, decomposed lipid, antidifferentiation, antiadipogenesis, antiobesity	(+) cAMP/PKA, HSL, ATGL (-) PPAR $\gamma$ , C/EBP $\alpha$ , FAS, TG, C/EBP $\beta$ , C/EBP $\delta$ , SREBP1C, PLIN	[126]
Cancer			0-300 $\mu$ M, treat, 24 h	PANC1, TE-1, MCF-7, A2780	Induced cell death, anticancer, increased luciferase activity, PPAR $\alpha$ activation suppressed HO-1 induction by EGCG	(+) PPAR $\alpha$ (-) HO-1, NF $\kappa$ B	[127]
Cardiovascular diseases			1,10, and 50 $\mu$ M, treat, 0, 6, 12, and 24 h	HUVECs	Antioxidant, anti-inflammatory, protected vascular, increased luciferase activity	(+) PPAR $\gamma$ , Pim-1, PPRE (-) -	[128]
Brain and nervous system diseases			5-100 $\mu$ M, treat, 24 h	N2a-APP695 cells	Antiaoptotic, anti-inflammatory, antioxidant, neuroprotective	(+) PPAR $\gamma$ , MnSOD (-) A $\beta$ , BACE1, Bax, caspase-3, NF- $\kappa$ B, ROS, MDA	[129]
Renal diseases			25 and 50 mg/kg/d, gavage, 3 weeks	Crescentic GN 129/svj mice	Anti-inflammatory, antioxidant, reduced mortality, ameliorated renal injury, improved renal histology and function	(+) PPAR $\gamma$ , SIRT1, Nr2, GSH, GCLC, GCLM, GPX1, NOO1 (-) p-Akt, p-JNK, p-ERK1/2, p-P38, proteinuria, serum creatinine, tubulointerstitial injury, glomerular in jury, lymphocyte, macrophages, MDA	[130]
			10, 20, and 40 mg/kg, orally, 8 weeks	n-STZ-induced diabetic/peripheral neuropathy rats	Neuroprotective, anti-inflammatory, antioxidant, inhibited aldose reductase, suppressed edema, ameliorated impaired allodynia, hyperalgesia, and nerve conduction velocity, decreased oxido-nitrosative stress	(+) PPAR $\gamma$ , IGF-1, BDNF, insulin, SOD, NO, GSH, Na-K-ATPase, Thr-172, AMPK (-) TG, cholesterol, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, glycated Hb, glycosuria, MDA, PP2C- $\alpha$ , myelin degeneration, unmyelinated fibers	[132]
Metabolic diseases	Berberine		75, 150, and 300 mg/kg, orally, 16-week	3T3-L1 diabetic adipocytes	Anthyperlipidemia, hypoglycemic, promoted differentiation, inhibited lipid accumulation, decreased white adipose tissue, increased adipocyte number	(+) PPAR $\alpha$ / $\delta$ / $\gamma$ , CDK9, cyclin T1, aP2, P-TEFb, lipoprotein lipase (-) TNF- $\alpha$ , FFA	[133]
			300 mg/kg/d, gavage, 4 weeks	HFD rat	Lowering epididymal adipose tissue (EAT) and subcutaneous adipose tissue, alleviated liver steatosis, down-regulated lipogenesis, increased fatty acid oxidation, body weight lowering, promoted mitochondrial $\beta$ -OX	(+) PPAR $\alpha$ , CPT-1 $\alpha$ , Acox1, HDL, fatty acid $\beta$ -OX, SIRT3, LCAD deacetylation (-) TG, TC, LDL, FBG, glucose, SREBP-1c, SCD1, FAS	[134]
			250 mg/kg/d, oral, 4 weeks	KKY mice	Moderated glucose and lipid metabolism, ameliorated oral glucose tolerance and insulin sensitivity, increased energy dissipation	(+) PPAR $\alpha$ , GLUT4, MAPK14, MAPK8, UCP2, HNF4 $\alpha$ , JNK, LDLR	[135]
Alkaloids			5 $\mu$ M, treat, 4 days				

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
				Mouse 3T3-L1 cells	Antiobesity, antidiabetic, lipid-reducing	(-) PPAR $\gamma$ , CEBP, PGC 1 $\alpha$ , resistin, TC, TG, LDL-C, FBG (+) AMPK, <i>Ddit3</i> , <i>Ahrb2</i> (-) PPAR $\gamma$ , C/EBP $\alpha$ , SREBP-1, <i>Adipog</i> , <i>Fatp4</i> , <i>Pffp1</i> , <i>Slc2a4</i> , <i>Fasn</i> , <i>Cpt1a</i> , <i>Cpt2</i> , <i>Lipe</i> , <i>Mlyed</i> , ACC	[136]
			10 nM-10 $\mu$ M, treat, 6-72h; 60-300 mg/kg/d, intragastrically, 12 weeks	HepG2 cells, HFD rat	Lipid-lowering, improved lipid metabolism, hypolipidemic effect	(+) PPAR $\alpha$ , PPAR $\delta$ , CPT-1 $\alpha$ , HDL (-) PPAR $\gamma$ , TC, TG, LDL	[137]
			25, 50, and 100 mg	NAFLD rat	Antihyperglycemic, improved insulin resistance, anti-inflammatory	(+) PPAR $\gamma$ , HDL, insulin resistance (-) TC, TG, LDL, AST, ALT, TNF $\alpha$ , IL-6	[138]
		Cancer	50, 100, and 200 mg/kg, oral, 21 days	Bleomycin-induced pulmonary fibrosis in female ICR mice	Direct antifibrosis effect in a gut-dependent manner, anti-inflammatory, reduced edema, infiltration, parenchymal distortion, collapsed alveolar spaces, thicker alveolar membrane, and collagen deposition	(+) PPAR $\gamma$ , HGF, PTEN, CD36, <i>ap2</i> (-) -	[270]
	13-Methylberberine	Renal diseases	1, 5, 10, 50, and 100 $\mu$ M, Treat, 24h	PA-induced lipotoxicity in HK-2 cells	Decreased lipid accumulation, anti-inflammatory, antiapoptosis, protected renal function, inhibited lipotoxicity	(+) PPAR $\alpha$ , CPT1, PERK (-) ER, EAS, ACC, IPL, CHOP, GRE78, TNF- $\alpha$ , IL-6, caspase3	[139]
			10, 30, and 100 $\mu$ mol/L, treat, 24 h	Angiotensin IV-induced VSMCs proliferation	Antiproliferative, inhibited OD value at the A490, decreased protein synthesis, regulated PPAR $\alpha$ -NOS-NO signaling pathway	(+) PPAR $\alpha$ , eNOS, NO (-) -	[140]
		Cardiovascular	15 and 30 mg/kg/day, intragastrically, 6 weeks	HSD/streptozotocin rat	Protected diabetic cardiomyopathy, promoted glucose transport, alleviated cardiac lipid accumulation, increased cardiac output, decreased ventricular wall thickness, interventricular septum thickness, and collagen content	(+) PPAR $\gamma$ , GLUT4, +dp/dmax, LVDP, fatty acid transport protein-1, fatty acid transport protein, fatty acid $\beta$ -oxidase (-) PPAR $\alpha$ , -dp/dmax, TG, LVEDP, nonesterified FFA, fructosamine,fast blood glucose, glycated hemoglobin, glycosylated serum protein	[271]
			1 g/kg/day, gavage, 8 weeks 10, 50, and 100 $\mu$ M, treat, 1h 0.1-100 $\mu$ M, treat, 30 min	Collar placement-induced atherosclerosis in ApoE $^{-/-}$ mice HUVECs	Antioxidant, increases carotid atherosclerotic plaque stability, decreased Oil Red $^{+}$ lipid area, increased Sirius Red $^{+}$ collagen area, protected endothelial function, attenuated endothelial dysfunction	(+) PPAR $\gamma$ , collagen, NO, SOD (-) CD68 $^{+}$ , vulnerability index, MDA, ROS	[272]
			1, 3, and 10 $\mu$ mol/L, treat, 0.5 h	HGF-induced cardiomyocyte hypertrophy in rat myocytes	Antihypertrophic, exhibited crosstalk between PPAR $\alpha$ /eNOS-NO transduction	(+) PPAR $\alpha$ , eNOS, NOS, NO (-) Cell surface area, protein level, ANF	[141]
		Brain and nervous system diseases		LPS-induced U251 cell death	Neuroprotective, increased cell viability	(+) PPAR $\alpha$ , CYP2J2, RXR $\alpha$ (-) -	[142]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
Phytochemicals	Cinnamic acid	Metabolic diseases	12.5, 25, 50, 100, and 200 $\mu$ M, treat, 24 h 20 mg/kg/BW, oral, 4 weeks	HepG2 cells <i>dbi/dbi</i> mice	Reduced lipid accumulation, suppressed hepatic lipogenesis, inhibited fatty acid intake, increased fatty acid oxidation, reduced body weight, liver mass and liver index, antidiabetic	(+) PPAR $\alpha$ , CPT1A, PGC1 $\alpha$ , HDL, IHTG, ChREBP, BDK/PPM1K (-) PPAR $\gamma$ , LXR, AGLY, ACC, FAS, SCD1, CD36, TG, glucose, SREBP1c	[144]
		Brain and nervous system diseases	100 mg/kg/day, oral, 30 days	B6SJL-Tg male and female mice (5 $\times$ FAD model of AD)	Stimulated lysosomal proteolysis, reduced A $\beta$ burden in hippocampus and cortex, improved memory and behavioral deficit	(+) PPAR $\alpha$ , TFEB, cathepsin B, TPP1 (-) A $\beta$ plaques, $\beta$ CTF	[143]
	Trans-Cinnamic acid	Brain and nervous system diseases	100 mg/kg/day, oral, 7 days	MPTP-induced PD in mouse	Neuroprotective, restored locomotor deficit, restored striatal neurotransmitters, protected dopaminergic neurons	(+) PPAR $\alpha$ , PPRE-luciferase, TH, TH+neuron, dopamine (-) -	[145]
			Different proportion, oral, 4 weeks	Ethanol-induced A1D in rat	Reduced ethanol-induced liver injury, decreased liver index, antioxidant, decreased hepatic steatosis, regulated lipid metabolism	(+) PPAR $\alpha$ , CPT1A, HDL, SOD, GSH (-) ALT, AST, ALP, GGT, TC, TG, LDL, MDA, SREBP-1c, ACC	[147]
Terpenoids	Glycyrrhizic acid (18 $\alpha$ -GA + 18 $\beta$ -GA)	Metabolic syndrome	100 mg/kg, oral, 24 h	Rat	Improved serum lipid, increased insulin sensitivity, decreased blood glucose, regulated glucose homeostasis	(+) PPAR $\gamma$ , LPL, HDL (-) HOMA-IR, TAG, TC, LDL, insulin	[148]
		Brain and nervous system diseases	5 mg/kg/day, injections, 6 days	Subarachnoid hemorrhage (SAH) rat	Antivasospastic, anti-inflammatory, increased body weight, decreased systolic blood pressure, regulated neuroinflammation	(+) PPAR $\gamma$ , PPAR $\delta$ (-) IL-6, IL-1 $\beta$ , TNF- $\alpha$ , IL-8, CD45 <sup>+</sup> , GOT, GPT, BUN/creatinine	[149]
	Metabolic syndrome	Metabolic syndrome	1-50 $\mu$ M, treat, 48 h, 15 min (gene), 2 h (protein)	C2C12 muscle cells 3T3-L1 Murine fibroblasts	Anthyperglycemic, inhibited lipid accumulation, reduced cell functionality at 30 $\mu$ M and 50 $\mu$ M (toxic), improved insulin sensitivity	(+) PPAR $\gamma$ , PPAR $\alpha$ , GLUT-4, GLUT-4 translocation, FATP-1, AdipoQ, ACSL (-) Lipid storage	[154]
			60 mg/kg, oral, 14 days	High fructose-fed rat	Antidiabetes, regulated glucose homeostasis	(+) PPAR $\gamma$ -1, GLUT-4, glucose, glucose-1-phosphate, glucose-6-phosphate, ribose-5-phosphate (-) -	[152]
Oleamonic acid	Oleamonic acid	Metabolic syndrome	0.1-50 $\mu$ M, treat, 24 h	High glucose-induced endothelial dysfunction in human vascular endothelial cells	Enhanced vasodilatation, increased arterial relaxation	(+) PPAR $\delta$ , NO, PDK4, ADRP, ANGPTL4, Akt-Ser <sup>473</sup> , eNOS-Ser <sup>1177</sup> (-) -	[153]
			20, 40, and 80 mg/kg, injection, 3 days	Concanavalin A-induced acute liver injury in mice	Anti-inflammatory, attenuated autophagy and apoptosis, decreased necrotic area, congestion and lymphocytic accumulation, improved immunity	(+) PPAR $\alpha$ , Bcl-2 (-) JNK, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, I $\kappa$ B, caspase-3, caspase-9, Bclin 1, LC3, ALT, AST, TRAF2	[155]
			10 mg/kg (rabbit), 25 mg/kg (mice), oral, 5 weeks	Atherogenic diet-induced atherosclerosis in rabbit, C57BL/6J and LDLR <sup>-/-</sup> mice	Reduced the thickness of intima, antiatherosclerotic, decreased lipid accumulation	(+) PPAR $\gamma$ , AdipoR1, HDL-C (-) AdipoR2, TG, LDL-C, TC	[156]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
		Metabolic syndrome	250 mg/kg/d, oral, 8 weeks	HFD rat	Ameliorated obesity and metabolic disorder, attenuated thermal hyperalgesia, decreased paw edema, anti-inflammatory, reduced body weight, inhibited spinal cord inflammation	(+) PPAR $\alpha$ , adiponectin, I $\kappa$ B $\alpha$ (-) Insulin, cholesterol, leptin, IL-1 $\beta$ , TNF- $\alpha$ , COX-2, iNOS, NF- $\kappa$ B p65	[160]
		Liver disease	25 mg/kg/d, oral, first 6 h	Term-type diet-induced hyperglycemia in rabbit	Improved hypolipidemic and antiatherosclerosis efficacy, reduced lesions area, increased lumen area	(+) PPAR $\alpha$ (-) TG, cholesterol, VCAM-1	[158]
			5-100 $\mu$ M, treat	HepG2 cells	Regulated lipid metabolism, enhances PPAR $\alpha$ binding to PPRE	(+) PPAR $\alpha$ , PPRE, fatty acid uptake, FATP4, ACS, CPT1, ACOX (-) TG, cholesterol, SCD1, SREBP1c	[163]
		Brain and nervous system diseases	25 mg/kg/d, gavage, 120 days	EAE and cuprizone-induced demyelination Female C57BL/6J mice	Enhanced remyelination, anti-inflammatory, promoted myelin repair, immunomodulatory, repaired neural, anti-multiple sclerosis, reduced remyelinated axons G-ratio, neurorepairation	(+) PPAR $\gamma$ , CREB, CNTF, MBP, CC1, GFAP (-) CD45 <sup>+</sup> , A2B5, CD11b <sup>+</sup> , CD11c <sup>+</sup> , IFN- $\gamma$ , IL-17 <sup>+</sup> , GM-CSF <sup>+</sup> , CD4 <sup>+</sup> T cell, Th17, Th1	[164]
	Ursolic acid		5, 10, and 20 mg/kg, gavage, 0.5, 24, and 47 h after reperfusion	Cerebral ischemia/reperfusion rat	Neuroprotective, improved neurological deficit score and general condition, decreased median neurological deficit score, alleviated histological damage, increased intact neuron number, attenuated cerebral ischemia/reperfusion injury	(+) PPAR $\gamma$ , TIMP1 (-) MMP2, MMP9, MAPKs, infarct size, pERK1/2, pJNK1/2, pp38	[159]
		Respiratory diseases	2 and 20 mg/kg, orally, 3 times a week for 5 weeks	Allergic asthma mouse	Suppressed eosinophil infiltration, anti-inflammatory, antiasthma, decreased blood basophil and eosinophils, reduced airway inflammation, reduced total bronchoalveolar lavage fluid cells, decreased eosinophils in bronchoalveolar lavage fluid, acted as antagonist of Th2 and Th17	(+) PPAR $\gamma$ , Foxp3 (-) IL-5, IL-13, IL-17, GATA-3, STAT6, NF- $\kappa$ B, CCR3, ovalbumin-IgE, CD4 <sup>+</sup>	[165]
			50 mg/kg/d, gavage, 4 weeks	PAH-induced RV in Sprague Dawley rat	Improved RV function, attenuates RV hypertrophy, inhibited RV fibrosis, reduced apoptosis, regulated metabolic abnormalities	(+) PPAR $\alpha$ , CPT1b (-) ANP, BNP, TGF- $\beta$ 1, COL3A1, COL1A1, collagen, Bax, apoptotic cell	[162]
		Immunity	250 mg/kg/day, orally, 8 weeks	HFD-induced inflammation	Anti-inflammatory, ameliorated obesity, regulated metabolic disorder, prevented thermal hyperalgesia and paw edema, restored spinal cord inflammatory response	(+) PPAR $\alpha$ , I $\kappa$ B $\alpha$ (-) NF- $\kappa$ B, BW, IL-1 $\beta$ , TNF- $\alpha$ , COX-2, iNOS	[160]

TABLE 1: Continued.

Phytochemical classification	Phytochemicals	General category of disease	Daily dose and treatment period	Experimental Model	Protective effect	Mechanism	Ref.
6-Shogaol		Cancer	0.1–100 $\mu$ M, treat, 72 h	MCF-7 and HT29 cells	Inhibited breast and colon cancer cell proliferation, antitumor effects, induced apoptosis and cell cycle arrest, exhibited binding to PPAR $\gamma$	(+) PPAR $\gamma$ , PPRE, Cdc2, Cdc25C, caspase3, caspase 9, CYP1A1, CDKN1A, GADD45A, Bax (-) NF- $\kappa$ B, G2/M cell cycle, G1, ASCL1, CAV1, CXCL12, Bcl-2, Bcl-X <sub>L</sub> , p65, PPAR $\gamma$ si-1, PPAR $\gamma$ si-2	[273]
		Brain and nervous system diseases	5, 10, and 20 $\mu$ g/mL, 1h before LPS	LPS-activated BV2 microglia	Antitumor, anti-inflammatory, protected neurodegeneration	(+) PPAR $\gamma$ (-) TNF- $\alpha$ , IL-1 $\beta$ , IL-6, PGE2, I $\kappa$ B $\alpha$	[167]
Oleic acid		Metabolic syndrome	50, 100, and 200 $\mu$ M, treat, 24h	Aorta smooth muscle cells	Antioxidant, anti-inflammatory, protected coronary artery	(+) MMP-1, MMP-3, iNOS, NO, TGF- $\beta$ 1, NF- $\kappa$ B (-) PPAR $\gamma$ , SIRT1	[169]
		Liver disease	0.1–1 mM, treat, 24h	HepG2 steatotic cells	Regulated insulin sensitivity, induced lipid accumulation, increased $\beta$ -oxidation, enhanced insulin sensitivity, antiosteosis	(+) PPAR $\delta$ /GPR40, Ca <sup>2+</sup> influx, PLC (-) PTEN	[171]
Fatty acids	n-3 polyunsaturated fatty acid	Renal diseases	1.25 $\mu$ M, treat, 45 min	OGD/R-HK-2 cells	Attenuated apoptosis, increased cell viability, restored nuclei shape, protected against ischemia/reperfusion	(+) PPAR $\gamma$ , p-Akt, p-GSK3 $\beta$ , cytochrome C, AIF (-) Caspase-3, Bax	[274]
		Brain diseases	10 and 30 mg/kg, intraperitoneally, 90min after model	Middle cerebral artery occlusion-induced ischaemic stroke in rat	Neuroprotection, anti-inflammatory, anti-cerebral ischaemic, enhanced functional outcomes, reduced infarct volume, increased neuronal densities	(+) PPAR $\gamma$ ; neuronal densities (-) Infarct size, COX-2, TNF- $\alpha$ , iNOS	[275]
n-6		Liver disease	0.2 g/kg/d, injection, 5 days	Hemorrhagic shock/resuscitation mice	Improved lipid oxidation in the liver	(+) PPAR $\alpha$ , CPT-1A, FATP-1 (-) TG	[174]
		Cancer	50 and 120 $\mu$ M, treat, 24, 48, and 72 h	MGC and SGC cells	Anticancer, anti-inflammatory, anticachectic; inhibited gastric tumor cells	(+) PPAR $\gamma$ , C/EBP $\alpha$ (-) TNF- $\alpha$ , VEGF	[175]
n-3		Cardiovascular diseases	50 mg/kg, orally, 4 weeks	EC <sub>50</sub> -induced thrombin in mice	Inhibited arterial thrombosis, antiplatelet	(+) PPAR $\alpha$ (-) Platelet aggregation, calcium mobilization, PKC, dense granule secretion, collagen	[176]
		Immunity	20 mg/kg/day, intragastric, 60 days	TNBS-induced Crohn's disease in rat	Anti-inflammatory, immunity, attenuated colonic inflammation	(+) PPAR $\gamma$ (-) NFAT, TC, IL-6, IL-12, IL-2, IL-4, TNF- $\alpha$	[177]
			5 kg FO, oral, 14 days	Mastitis rat	Decreased mammary inflammation	(+) PPAR $\gamma$ , IL-10 (-) PMN, XOR, IL-1 $\beta$ , TNF- $\alpha$	[178]

(+): Increasing or activation of target; (-): Decreasing or inhibition of target; \*: not significant (or no effect).

in the prevention of hyperlipidaemia and atherosclerosis. In fact, curcumin can bind directly to PPAR $\gamma$  or indirectly induce the production of intracellular ligands of PPAR $\gamma$  [11]. Therefore, the induction of PPAR $\gamma$  by curcumin could regulate glucose homeostasis and insulin resistance and also suppress inflammatory cytokines (including nuclear factor- $\kappa$ B (NF- $\kappa$ B) and matrix metalloproteinases (MMPs)) in macrophages and oxidative stress [9, 11]. Furthermore, curcumin drives PPAR $\alpha$  activation by regulating mitochondrial fatty acid  $\beta$ -oxidation, down-regulating sterol regulatory element-binding protein-1c (SREBP-1c) through suppression of LXR/RXR formation, inhibiting acyl-CoA:cholesterol acyltransferase (ACAT), interfering with NF- $\kappa$ B and AP-1, and upregulating apolipoprotein A-I (Apo-AI), apolipoprotein A-II (Apo-AII), and mitochondrial 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby protecting against hypercholesterolemia and subsequent atherosclerosis [11, 12].

In addition, curcumin exerts an influence on metabolism through the activation of PPAR $\gamma$  to ameliorate obesity/insulin resistance related disorders and certain inflammatory diseases. Some *in vitro* or *in vivo* studies indicated activity of curcumin on PPAR in the PPAR $\gamma$  gene regulatory region is able to attenuate inflammation by inhibiting NF- $\kappa$ B, tumor necrosis factor alpha (TNF- $\alpha$ ), c-Jun N-terminal kinase (JNK), interferon gamma (IFN- $\gamma$ ), nitric oxide (NO), inducible nitric oxide synthase (*i*NOS), and AP-1. As well, antidiabetic properties of curcumin revealed through its antioxidant, anti-inflammatory, and antiapoptotic activities via mediation of PPAR $\alpha/\gamma$  lead to regulation of insulin signaling and phosphodiesterase/cyclic adenosine monophosphate (PDE/cAMP) in metabolism [13, 14]. Likewise, promoting PPAR $\gamma$  ligand-binding activity by curcumin can stimulate free fatty acid catabolism, which can modulate glucose homeostasis, insulin resistance, and hemoglobin A1c (HbA1c) levels in related disorders such as diabetes and obesity [15]. Curcumin can also inhibit several inflammatory pathways and modulate obesity-related metabolic diseases by inhibiting low-density lipoprotein (LDL) and the level of intracellular cholesterol by activation of PPAR $\gamma$ , leading to the suppression of  $\alpha$ 1 collagen, alpha smooth muscle actin ( $\alpha$ -SMA), connective tissue growth factor (CTGF), transforming growth factor (TGF- $\beta$ ) receptors, platelet-derived growth factor subunit B (PDGF- $\beta$ ), interleukin-1 (IL-1), interleukin-13 (IL-13), and epidermal growth factor (EGF) [16]. Furthermore, molecular docking studies showed that curcumin as a PPAR $\gamma$  agonist binds with Ile(341), Arg(288), Ser(289), Ala(292), Leu(333), Ile(326), Leu(330), and Met(329) amino acids in the active site of PPAR $\gamma$  [8].

Curcumin has also demonstrated anticancer and apoptosis properties on many tumor cells. For instance, curcumin down-regulated the  $\beta$ -catenin/T-cell factors (Tcf) signaling pathway in the human colon cancer cell line HT-29, which leads to suppression of the expression of PPAR $\delta$ , 14-3-3 $\epsilon$ , and vascular endothelial growth factor (VEGF) and subsequent induction of apoptosis in HT-29 cells [17]. In MCF-7 breast cancer cells, curcumin activated AMPK as an upstream signal of PPAR $\gamma$  in 3T3-L1 adipocytes, resulting in the down-regulation of PPAR $\gamma$  and a decrease in differentiation of adipocytes [18]. Furthermore, curcumin as a cancer therapy

candidate is shown to exert its anticancer effect through PPAR $\gamma$  activation and down-regulation of the aberrant WNT/ $\beta$ -catenin pathway leads to activation of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), leading to the control of inflammation, proliferation, and angiogenesis in cancers [19]. Curcumin mediates its antifibrotic effects by the PPAR $\gamma$  upregulation of matrix-degrading proteases, cathepsin B/L (CatB and CatL) [20]. Recently, it has been reported that curcumin mediates organic cation transporter 2 (OCTN2) expression through activation of the PPAR $\gamma$ /RXR $\alpha$  pathway by binding to the peroxisome proliferator response elements (PPRE) in colorectal cancer SW480 cells [21].

Curcumin can suppress hepatic stellate cell (HSC) activation and modulate liver inflammatory injury by upregulation of PPAR $\gamma$ , which can increase apoptosis or decrease cyclin D1 and proliferation to inhibit angiogenesis/cell growth, and also can cause a reduction in TGF- $\beta$  signaling and extracellular matrix in regard to inhibition of HSC activation and liver fibrosis [22]. Much research shows that curcumin alleviates cholangiopathy and biliary fibrosis in multidrug resistance-2 gene (*Mdr2*<sup>-/-</sup>) mice via PPAR $\gamma$  activation, TNF- $\alpha$  inhibition, and the stimulation of vascular cell adhesion molecule-1 (VCAM-1) expression in cholangiocytes [23]. Likewise, it can attenuate liver injuries by PPAR $\gamma$  activation, the elevation of cellular glutathione (GSH) content, extracellular-signal regulated kinase (ERK) inhibition, and prevention of toll-like receptor 4 (TLR-4) expression leading to down-regulation of NF- $\kappa$ B in hepatic stellate cells [24]. Curcumin-low-molecular-weight PEGs (mPEG454) showed a therapeutic effect on dyslipidemia and nonalcoholic fatty liver disease via cAMP response element binding (CREB)/PPAR $\gamma$ /CD36 pathway, by which the activation of CREB triggered inhibition of PPAR $\gamma$  and CD36 expression in mediation of lipid homeostasis [25]. Meanwhile, curcumin improved lipid accumulation in non-alcoholic fatty liver disease via increasing PPAR $\alpha$  mRNA and protein levels in the liver and inhibition of DNA methylation at the PPAR $\alpha$  gene [26]. Thus, curcumin may prevent nonalcoholic steatohepatitis (NASH)/cirrhosis and nonalcoholic fatty liver disease through direct/indirect induction of PPAR $\gamma$  expression [27].

In lung inflammation, curcumin acts as a mediator of inflammation and oxidative stress by the upregulation of PPAR $\gamma$ , leading to the inhibition of TNF- $\alpha$  in acute lung injury and pulmonary diseases such as idiopathic pulmonary arterial hypertension [28]. PPAR $\gamma$  activation by curcumin causes the upregulation of heme oxygenase-1 (HO-1) and blocks pulmonary cell proliferation, remodeling, differentiation, and apoptosis by mediating the protein kinase C (PKC)/AMPK/p38MAPK/NAD-dependent protein deacetylase (SIRT1)/PPAR $\gamma$  pathway, and then, through attenuation of NF- $\kappa$ B, signal transducer and activator of transcription-1 (STAT-1) and AP-1, protecting against lung inflammation [29].

In addition, curcumin can ameliorate renal fibrosis, a common pathology in chronic kidney disease, and arrest the cell cycle in the G1 phase. It seems that curcumin reduces fibroblast proliferation and extracellular matrix (ECM) accumulation through up-regulation of PPAR $\gamma$  and down-

regulation of Smad2/3-dependent TGF- $\beta$ 1 signaling [30]. Other studies indicated that curcumin inhibited TGF- $\beta$ 1-induced epithelial mesenchymal transition (EMT) via the ERK/PPAR $\gamma$  signaling pathway in a Smad2/3-independent manner in renal tubular epithelial cells [25]. However, curcumin reveals its antifibrotic effect at the activation stage of renal fibrosis by reducing TGF/Smad, MAPK/ERK, and sphingosine kinase 1 (Sphk1)/sphingosine-1-phosphate (S1P), as well as increasing PPAR $\gamma$  pathways to block fibrosis.

Growing evidence showed that curcumin exhibited a therapeutic effect in cardiometabolic syndrome treatment by an increase/activation of PPAR $\gamma$  and suppressing the levels of inflammatory markers including NF- $\kappa$ B, TNF- $\alpha$ , IL-6, and high-sensitivity C-reactive protein (hs-CRP) in both animal model and molecular docking [31]. Curcumin also inhibited myocardial cell necrosis and apoptosis by abrogating NF- $\kappa$ B expression and stimulating expression of PPAR $\gamma$  and B-cell lymphoma 2 (Bcl-2) in myocardial cells in a rat myocardial infarction model [32]. In vascular smooth muscle cells, curcumin diminished AngII-induced inflammatory factors and oxidative stress by enhancing PPAR- $\gamma$  activity, leading to down-regulation of TNF- $\alpha$ , IL-6, NO, cell proliferation, p47phox, reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and reactive oxygen species (ROS) production. These beneficial effects of curcumin enabled an explanation of its molecular mechanisms on atherosclerosis [33].

Previous studies have demonstrated the protective potential of curcumin on neurological diseases such as Alzheimer's disease, ischemic stroke, central nervous system (CNS) injury, chronic pain, trauma, multiple sclerosis, and Parkinson's disease. Curcumin alleviates neuroinflammation and the production of microglia, astrocytes, and inflammatory cytokines due to PPAR $\gamma$  activation, leading to inhibition of amyloid- $\beta$  accumulation as well as inflammatory signaling cascades such as Janus kinase (JAK)/signal transducer and activator of transcription (STAT), NF- $\kappa$ B, and IL-12/IFN $\gamma$  [34–37].

In addition, curcumin has immune-modulatory properties in various pathological or age-related diseases such as cancer, Alzheimer's disease, atherosclerosis, and metabolic disorders. It can enhance the immune system by the activation of PPAR $\gamma$ , thereby decreasing the levels of proinflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , IL-12, IL-6, TNF- $\alpha$ , NF- $\kappa$ B) and up-regulation of CD36, HO-1, and NADPH quinone oxidoreductase-1 (NQ-1) can occur, revealing an immunomodulatory effect of curcumin [35, 38, 39].

**4.2. Resveratrol.** Resveratrol, a natural polyphenol (stilbene) found in several plants such as grapes, peanuts, and other berries, has been reported to have antioxidant, anticancer, anti-inflammatory, cardioprotective, hypolipidemic, and metabolic regulation properties [40, 41], though therapeutic effects have been questioned in some clinical studies [41–43]. Previous studies indicated that resveratrol acts as a natural PPAR agonist on isotypes of PPARs and regulates metabolism [40, 41]. Resveratrol ameliorates atherosclerosis, platelet aggregation, lipid homeostasis, and total cholesterol accumulation through its antioxidant, anti-inflammatory,

antiapoptotic, and lipid overload inhibition, and in addition improves endothelial function [42]. Interestingly, these effects have been shown to occur through activation of the PPAR $\gamma$ /LXR $\alpha$  cascade, SIRT1, endothelial nitric oxide synthase (eNOS), AMPK, ABCA1, and G1, ERK1/2, inhibiting TNF $\alpha$ , IFN $\gamma$  and NF- $\kappa$ B, and promoting cholesterol efflux [40–42].

Resveratrol also ameliorates carboxymethyllysine (CML-) induced pancreas damage and hyperglycemia through increasing insulin synthesis and upregulating pancreatic PPAR $\gamma$  and pancreatic and duodenal homeobox-1 (PDX-1), as well as activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway [43]. Resveratrol suppresses oxidative stress by activation of Nrf2 and PPAR $\gamma$  signaling pathways and their crosstalk.

In diabetic cardiomyopathy, resveratrol inhibits myocardial fibrosis during hyperglycemic conditions by suppressing the ROS/ERK/TGF- $\beta$ /periostin and TGF- $\beta$ 1/Smad3 pathways, along with modulating the SIRT1/CDK2-associated cullin 1 (CACUL1)/PPAR $\gamma$  axis [42]. It seems that anti-inflammatory, antioxidant, antiapoptotic, and antifibrotic properties of resveratrol play a pivotal role in the up/down-regulations of the signaling cascades involved.

In further actions, resveratrol protects retinal pigment epithelium (RPE) cells from sodium iodate injury via its antioxidant and anti-inflammatory effects, leading to regulation of PPAR $\alpha$  and PPAR $\delta$  conformation and suppression of ROS and IL-8 production, as well as GSH up-regulation to attenuate oxidative stress and progression of age-related macular degeneration [44]. Furthermore, resveratrol in dyslipidemia or metabolic syndrome decreases body weight, regulates lipid deposition, modulates adipocyte gene expression, and stimulates white adipose browning, via phosphatidylinositol-3kinase (PI3K)/SIRT1, Nrf2, PPAR $\gamma$ , TNF- $\alpha$ , and protein kinase A (PKA)/LKB1/AMPK signaling pathways [45]. Resveratrol exerts immunomodulatory effects through regulating PPAR $\alpha$ /RXR $\alpha$  activation, IL-10 signaling, natural killer cell signaling, leucocyte extravasation signaling, and IL-6 signaling, immune response pathways involved in disease [45]. Recently, a novel hybrid compound (PTER-ITC) was synthesized from trans-3,5-dimethoxy-49-hydroxystilbene (PTER), a natural dimethylated analog of resveratrol, and an isothiocyanate (ITC) conjugate. PTER-ITC revealed anticancer potential on breast cancer cell lines (MCF-7 and MDA-MB-231) through activation of PPAR $\gamma$ , PPAR $\beta$ , p38 MAPK, JNK, caspase 9, caspase 7, and caspase 3 pathways and downregulation of Bcl-2 and survivin [46]. Thus, resveratrol may be considered a natural PPAR agonist which qualifies as an effective candidate to prevent and treat a number of chronic diseases (Table 1).

**4.3. Polydatin.** Polydatin, also known as piceid, is a glycoside compound of resveratrol which exists in grape, *Polygonum cuspidatum*, *Fallopia japonica*, peanut, berries, and other sources [47–49]. Polydatin has shown biological activities, such as antagonist of platelet aggregation, cardioprotective, neuroprotective, hepatoprotective, antithrombotic, antiatherosclerotic, antitumor, antibacterial, protection of lungs, anti-inflammatory, antioxidant, nephroprotective, melanogenesis

inhibitor, and immunostimulant [47, 48, 50–52]. Moreover, polydatin restored vascular endothelial cells (VECs) functions in high glucose conditions by PPAR $\beta$ -NO signaling pathways which ameliorate diabetes-related cardiovascular diseases [52]. Polydatin addition exerted antiatherosclerotic effects by Pre-B cell colony enhancing factor (PBEF) downregulation and activation of PPAR $\gamma$  and SREBP-1, thereby regulating intracellular lipid metabolism in peritoneal macrophage, as well as decreasing cholesterol deposition and prevention of development of atherosclerosis [49, 50]. In diabetes mellitus-(DM-) associated liver disease, polydatin acts as PPAR $\alpha/\beta$  signaling pathway activator through its anti-inflammatory and antioxidant effects (Table 1) [53, 54]. To sum up, polydatin exerts a pronounced effect on oxidative stress and inflammatory-induced diseases through activation of PPAR subunits and associated signaling pathways.

**4.4. Phlorotannins.** Phlorotannins, polymers of phloroglucinol, are a group of polyphenolic bioactive compounds which were found in brown alga [55, 56]. They possess several biological activities including antimicrobial, antiviral, hepatoprotective, cardioprotective, anti-inflammatory, neuroprotective, anticarcinogenic, immunomodulatory, hypolipidemic, antidiabetic, and antioxidant properties [55–57]. *Ecklonia*, a genus of kelp and brown alga which has abundance of phlorotannins, especially of the eckol-type, has hepatoprotective activity by increasing PPAR $\alpha$  and carnitine palmitoyl-transferase 1 (CPT-1) along with decreasing SREBP-1 and triglyceride (TG) to prevent fatty acid oxidation and reducing lipogenesis in ethanol-induced fatty liver [57]. Furthermore, phloroglucinol compounds of the aerial parts of *Potentilla longifolia* Wild. Ex Schlecht. protected 3T3-L1 adipocyte cells against lipid accumulation by downregulating SREBP1c, fatty acid synthase (FAS), stearoyl CoA desaturase-1 (SCD1), glycerol-3-phosphate acyltransferase (GPAT), PPAR $\gamma$ , and CCAAT-enhancer-binding protein  $\alpha$  (C/EBP $\alpha$ ) adipogenesis-related proteins [58]. Although phlorotannins demonstrated several beneficial effects, there was evidence of side effects or toxicity in cell lines, both in animal and human studies. However, further studies should evaluate safety and toxicity of phlorotannins for use as functional foods and pharmaceuticals (Table 1) [59].

**4.5. Quercetin.** Quercetin is a common and important flavonoids that is widely distributed in tea, onions, peppers, plums, mangos, and various types of berries, fruits, and vegetables [60–62]. Quercetin plays an important role in anti-inflammation, antioxidation, antiviral, anticancer, anti-atherosclerotic, cardioprotection, and other biological activities in the prevention and treatment of diseases [60–62]. Quercetin can inhibit atherosclerosis-induced myocardial infarction (MI), heart failure, and hypertension by upregulation of PPAR $\gamma$  and the signaling cascades involved, including the antioxidant pathway and the downregulation of inflammatory cytokines (Table 1) [60–66]. However, the PPAR $\gamma$ 2 chemically activated luciferase gene expression (CALUX) culture study showed that quercetin (10  $\mu$ M) co-incubated with vitamin C (500 $\mu$ M, to prevent auto-oxidation) can potentially increase the effect of PPAR $\gamma$  ligands

and expression of PPAR $\gamma$ -cellular receptors leads to synergistic effects with endogenous PPAR $\gamma$  agonists [67].

In metabolic disorders such as obesity and metabolic syndrome, quercetin can enhance WAT browning and brown adipose tissue (BAT) activation due to activation of  $\beta$ 3-adrenergic receptor ( $\beta$ 3AR)/PKA/AMPK/PPAR $\gamma$ /peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 $\alpha$ ) pathways, by this means inducing expression of uncoupling protein 1 (UCP1) and ABCA1 to promote adenosine triphosphate (ATP) and inhibit fat accumulation [68–70]. Owing to its relevance in adipogenesis, it appears that the inhibition of PPAR $\gamma$ , C/EBP $\alpha$ , or SREBP plays a pivotal role in obesity treatment. Furthermore, quercetin may exert its antidiabetic and glucose uptake effects through activating SIRT1/PPAR $\gamma$ /AMPK signal cascades to improve the complications of insulin resistance and diabetes [71]. The combination of quercetin (0.1  $\mu$ M) and pioglitazone (0.1  $\mu$ M, a PPAR $\gamma$  agonist) inhibited the angiotensin II (Ang II)-induced contractile effect in fructose-streptozotocin (FSTZ)-diabetic rats via antioxidant and NO release properties [72]. In another study, quercetin showed anti-diabetic effects more than antiobesity effects in high-fat high-sucrose diet (HFHSD) animals which consumed quercetin (30 mg/kg/BW/day) for 6 weeks. Likewise, lipogenic enzymes and lipoprotein lipases, including acyl-coenzyme A oxidase (ACO), CD36, carnitine palmitoyltransferase-1b (CPT-1b), PPAR $\alpha$ , PGC-1 $\alpha$ , uncoupling protein 3 (UCP3), transcription factor A mitochondrial (TFAM) and cyclooxygenase-2 (COX-2), remained unchanged in adipose tissue, while quercetin treatment reduced fructosamine, basal glucose, insulin and homeostatic model assessment for insulin resistance (HOMA-IR), as accepted diabetic markers in rat models [73].

PPAR isoforms have gained significant attention in CVD treatment. Quercetin exhibited antiatherosclerosis effect by upregulating PPAR $\gamma$ /LXR $\alpha$ /ABCA1 and promoting cholesterol efflux in THP-1 derived foam cells [62]. Moreover, the administration of quercetin reduces ischemia/reperfusion injury by upregulating SIRT1/PPAR $\gamma$ /PGC-1 $\alpha$ , activating PI3K/Akt pathway, suppressing myonecrosis, increasing Bcl-2/Bax (pro-apoptotic protein), inhibiting the inflammatory cascade, scavenging ROS, and enhancing cardiac function [61, 66]. Therefore, quercetin, by increasing or activating PPAR $\gamma$  and associated signaling cascades in the heart, exerts cardioprotective effects in CVDs, including hypertension, heart failure, ischemia, and atherosclerosis due to antioxidant, anti-inflammatory, and antiapoptotic disease [60–66]. Also, quercetin inhibited activation of all three isoforms of PPAR through its anti-inflammatory and antioxidant properties in obesity-related disorders and inflammatory diseases and an enhanced immune system [74]. Likewise, quercetin displayed its beneficial effects such as lipid lowering and suppression of the lipid accumulation-induced chronic inflammation by the PPAR $\alpha$  cascade in cultured chicken hepatocytes [75]. Furthermore, quercetin treated neurodegenerative dysfunction in the mouse Parkinson's disease model through up-regulating PPAR $\gamma$ , PGC-1 $\alpha$ , and TFAM to activate the polycystin 1 (PKD1)/Akt pathway [75].



**4.6. Kaempferol.** Kaempferol is a flavonol that is abundant in fruits, vegetables, and various medical plants, such as grapefruit, tea, and berries [76, 77]. Numerous studies have supported diverse beneficial properties of kaempferol, including antioxidant, anti-inflammatory, anticarcinogenic, antiobesity, antiatherosclerotic, cardioprotective, antihyperlipidemia, antiosteoporotic, and antidiabetic and estrogenic/antiestrogenic activities [76–79]. In addition, it reduced cholesterol, glucose, and TG levels through liver X receptor (LXR) activation and inhibition of sterol regulatory element-binding proteins (SREBPs), and without the side effect of hepatic steatosis [76–80]. Kaempferol also enhanced the expression of ACO, cytochrome P450 - family4 - subfamily a - polypeptide 1 (CYP4A1) and PPAR $\alpha$ , thereby reducing fat and lipid accumulation in obesity [79]. Published data revealed that in metabolic disorders, especially obesity and fat, kaempferol increased PPAR $\alpha$ , PPAR $\delta$ , and target genes, thereby inducing autophagy and fatty acid uptake as well as decreasing PPAR $\gamma$  and SREBP-1c expression via activation/inhibition of related signaling pathways regulating obesity and metabolic dysfunctions (Table 1) [76–82]. Although beneficial antioxidant and anti-inflammatory effects of kaempferol have been reported, the precise molecular target and mechanism of kaempferol in the treatment of diseases remains unclear. Therefore, further study is needed to investigate the kaempferol mechanisms of action.

**4.7. Rutin.** Rutin, quercetin-3-O-rutinoside, is a flavonol with significant beneficial properties, such as antioxidant capacity, anticarcinogenic, cardioprotective, antiatherosclerotic, antiadipogenic, neuroprotective, and antihyperuricemia activities [83–89]. A number of *in vitro* and *in vivo* studies indicated that rutin can improve glucose uptake, hyperlipidemia, insulin resistance, lipid accumulation, obesity, and metabolic dysfunction through modifying the expression of PPAR $\gamma$  and SREBP-1c in adipose tissue, thereby promoting AMPK and Akt activities to regulate body fat deposition [83–87]. Also, rutin attenuated NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation through its anti-inflammatory and antioxidant effects in response to fructose-induced renal hyperlipidemia and injury [88]. Likewise, rutin, by stimulating insulin (Akt and ERK1/2) pathways and inhibiting leptin (JAK2/STATE3) cascades, triggered PPAR $\alpha$ , carnitine palmitoyl-transferase 1 (CPT1), and organic cation transporter 2 (OCTN2) up-regulation, resulting in renal urate and lipid lowering [88]. Moreover, rutin exhibited neuroprotective effects due to its ability to retard oxidative stress in brain tissue by stimulating PPAR $\delta$  (an abundant PPAR isoform in neural tissue and brain), leading to a promotion of antioxidant systems, including glutathione peroxidase (GPX), GSH, and paraoxonase (PON-1, PON-3) and a reduction of PON-2 in the cisplatin-neurotoxic rat model [89]. Taken together, rutin attenuated the metabolic dysfunction or other diseases induced by oxidative/inflammation stress through stimulation or inhibition of molecular mechanisms associated with a regulation of PPAR $\alpha$ /PPAR $\gamma$ /PPAR $\delta$  levels (Table 1).

**4.8. Hesperetin.** Hesperidin and its aglycone hesperetin, a methoxylated flavanone known as citrus flavonoid, have particular pharmacological activities associated with high permeability in cell membranes, such as anti-inflammatory, antioxidant, antihypertensive, cardioprotective, vasodilation, anticancer, immunomodulator, antiallergic, neuroprotective, antiepileptic, antidepressant, lipid lowering, capillary fragility-reducing, antiadipogenic, and PPAR $\gamma$  agonist properties (Table 1) [81, 90–98]. Furthermore, hesperidin/hesperetin exerted their beneficial effects through PPAR $\gamma$  activation and subsequently modulating both PPAR $\gamma$ -dependent/independent pathways in targeted tissue [90, 98].

These studies indicated that hesperidin restored oxidative stress and inflammation-induced hepatotoxicity via boosting hepatic PPAR $\gamma$  expression and antioxidant markers, as well as reducing liver function enzymes and inflammation cytokines [92, 97]. Also, hesperidin/hesperetin stimulated PPAR $\gamma$ , which is centrally involved in the mediation of antiapoptotic (diminishing JNK, caspase-3/9, p53, Bax), anti-inflammatory (attenuating TNF- $\alpha$ , IL-1 $\beta$ , IL-6, monocyte chemoattractant protein-1 (MCP-1), intracellular adhesion molecule-1 (ICAM-1)), and antioxidant (increasing superoxide anion dismutase (SOD), catalase (CAT), GSH) effects and improving inotropic and lusitropic cardiac function (rate of left ventricular systolic pressure (+dP/dt), rates of pressure fall (-dP/dt), mean arterial pressure (MAP)) in rat heart hypertrophy and IR models [93–95].

Interestingly, hesperidin showed antiadipogenic and delipidating effects by inhibiting PPAR $\gamma$ , CCAAT-enhancer-binding protein  $\beta$  (C/EBP $\beta$ ), SREBP1-C, and *perilipin*, that are involved in different stages of adipogenesis (lipolysis and lipogenesis). In addition, it increased adipose triglyceride lipase in preadipocytes derived from human mesenchymal stem cells but also acted as a PPAR $\gamma$  agonist and increased C/EBP $\alpha$  to decrease insulin and lipid in the 3T3-L1 adipocytes model [81, 90, 91]. It can be postulated that hesperidin/hesperetin, as a PPAR $\gamma$  agonist, leads to attenuation of the inflammatory response and is thus ultimately protective against diseases through activation of radical scavenging activity.

**4.9. Apigenin.** Apigenin, a flavone abundant in foods ingested daily, such as fruits, vegetables, and some medicines, possesses various biological activities including antioxidant, anti-inflammatory, anticancer, antihyperglycemic, antiadipogenic, antiobesity, cardioprotective, antifibrotic, antidepressant, antidiabetic, and hepatoprotective actions [99–103]. Moreover, apigenin can also downregulate PPAR $\gamma$  and CEBP- $\alpha$  in the early phase of adipogenesis in 3T3-L1 adipocytes and protect against high-fat diet- (HFD-) induced metabolic syndrome in rats. Apigenin also prevents lipid accumulation and enhances adipocyte differentiation, thereby having hepatoprotective effects [99–103]. Recent research has established that apigenin is a PPAR modulator that inhibits obesity-induced metabolic syndrome via suppressing PPAR $\gamma$  and PPAR $\alpha$ , resulting in activation/inhibition of upstream or downstream targets, such as STAT3, C/EBP- $\alpha$ , SREBP-1c, CD36, and Nrf2 in adipose tissues [99, 100, 103]. In addition, another study showed that

apigenin provoked expression of PPAR $\gamma$  in the macrophage to reduce metabolic abnormality and liver/muscular steatosis in HFD and diabetic rat [101]. Likewise, apigenin attenuated carbon tetrachloride (CCl<sub>4</sub>)- and bile duct ligation (BDL)-induced liver fibrosis by alleviating autophagy and activated hepatic stellate cells (HSCs) and extracellular matrix (ECM) formation via activating PPAR $\alpha$  and inhibiting TGF- $\beta$ 1/Smad3 and p38 pathways [102]. However, to further confirm the precise underlying mechanisms of apigenin on PPARs specifically in adipose, macrophage, or other tissues, *in vivo* models of obesity and ob/ob *in vitro* studies are needed.

In the cardioprotective effects of apigenin, previous studies reported that PPAR $\alpha$  and PPAR $\gamma$  were involved in ameliorating cardiac hypertrophy and myocardial abnormality [104, 105]. Herein, apigenin in diabetic rats increased PPAR $\gamma$  to attenuate MI-induced myonecrosis and cardiac dysfunction [105]. In renovascular hypertensive rats, it improved cardiac hypertrophy and glucolipid metabolism by directly inhibiting angiotensin II and hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), and subsequently diminishing PPAR $\gamma$  and increasing PPAR $\alpha$  led to modulation of myocardial CPT-1, pyruvate dehydrogenase lipoamide kinase isozyme 4 (PDK-4), glycerol-3-phosphate acyltransferase (GPA-T), and glucose transporter-4 (GLUT-4) proteins [104]. Furthermore, apigenin by its antioxidant and anti-inflammatory properties activated PPAR $\gamma$  to protect against depression or mice pulmonary fibrosis by decreasing NLRP3 inflammasome, microglia, malondialdehyde (MDA), and apoptosis [106] or TGF- $\beta$ 1, matrix metalloproteinase 9 (MMP-9), and vimentin [107] in rat depression or mouse pulmonary fibrosis models, respectively. Therefore, the pharmacological effect of apigenin on PPARs suggests a novel approach in the treatment of cardiovascular, brain/nervous system, and immunity complications (Table 1).

**4.10. Naringenin.** Naringenin (a flavanone glucoside) and naringenin (its aglycone) are major flavonoids of citrus fruit, grapefruit, tomato, and orange with various pharmacological activities, such as antioxidant, anti-inflammatory and anti-hypercholesterolemia, antiobesity, hypotensive, cardioprotective, neuroprotective, and metabolic syndrome therapy [108–113]. Naringenin improved metabolic disturbances via PPAR $\alpha$  and/or PPAR $\gamma$  up-regulation and stimulation (PGC1 $\alpha$ , CPT-1, UCP1, UCP2)/suppression (LXR $\alpha$ , adipogenic, lipogenic) of its related underlying up/downstream kinases, enzymes, genes, and receptors, thereby providing antioxidant and anti-inflammatory effects in diabetic, hypercholesterolemia, obesity, and lipid metabolism liver dysfunction models, as shown in Table 1 [109–111, 114–117]. Some researchers have reported naringenin as a PPAR $\alpha$ / $\gamma$  agonist [108, 111], but using naringenin supplementation had no significant effect on PPAR $\alpha$ / $\gamma$  (slightly decreased) in ovariectomy-induced metabolically disturbed female mice. Interestingly, it increased fatty acid oxidation (CPT1 $\alpha$ ) and lipogenesis *de novo* (SREBF1) but decreased acyl-CoA oxidase 1 (ACOX1), another fatty acid oxidation target [108]. Also, in a further study, naringenin blocked expression of adipogenic and lipogenic activity by inhibiting LXR $\alpha$ /

SREBP1c/PPAR $\gamma$  signaling cascade to restore hepatic lipid accumulation and liver dysfunction in HBx-induced hepatic steatosis [118].

PPAR isoforms ( $\alpha$ ,  $\beta$ , and  $\gamma$ ) seem to have pivotal actions in cardiac and renal injuries. Naringenin, through the activation of PPAR $\alpha$ , PPAR $\beta$ , and PPAR $\gamma$ , ameliorated diabetic nephropathy and cardiomyocyte hypertrophy, which was associated with an increase in CYP4A-20-Hydroxyecosatetraenoic acid (20-HETE), cytochrome P450-family2-subfamily j-polypeptide 3 (CYP2J3), and 14,15-epoxyecososa-5,8,11-trienoic acid (14,15-EET) levels, respectively [112–119]. Thus, naringin/naringenin may be effective as a potential complementary/alternative medicine PPAR modulator in the treatment of immune, brain, cardiac, metabolic, and renal diseases.

**4.11. Catechins.** Catechins are a large group of flavonoids, with flavan-3-ol structure, including catechin, epi-catechin, epigallocatechin, epigallocatechin-3-gallate, and proanthocyanidins found in many plants and also dietary foods such as apples, tea, cocoa beans, grape seed, and red wines [120–130]. Notably, catechins have multibeneficial biological effects, for instance antiobesity, lipid lowering, antioxidant, anti-inflammatory, antidiabetic, anticancer, antiatherosclerotic, cardioprotective, neuroprotective, and nephroprotective [120–130]. (-)-Epigallocatechin-3-gallate (EGCG), a green tea catechin, exhibited PPAR $\alpha$  and PPAR $\gamma$  agonist properties in subcutaneous adipose tissues, but PPAR $\gamma$  antagonist activity in epididymal adipose tissue to reduce obesity and epididymal white adipose tissue weight in HFD mice via activation of AMPK [120]. In addition, EGCG and catechins suppressed differentiation of adipocyte by reducing ROS, inflammation, insulin signaling, and the stress-dependent mitogen-activated protein kinase (MAPK) kinase, (MEK)/ERK, and PI3K/Akt pathways. Additionally, increasing cyclic adenosine monophosphate (cAMP)/PKA signaling led to inactivation of PPAR $\gamma$ , C/EBP $\alpha$ , and forkhead transcription factor O1 (FoxO1) as clonal expansion-related genes in 3T3-L1 cells or preadipocyte models [121, 123–126]. Interestingly, procyanidin B2 (a catechin type) activated PPAR $\gamma$  to regulate macrophage M2 polarization and manipulation of M1/M2 macrophage homeostasis in metabolic inflammatory diseases. Likewise, it induced M2 macrophage markers, including arginase (Arg1), Ym1, found in inflammatory zone (Fizz1) and cluster of differentiation 206 (CD206<sup>+</sup>) as well as PPAR $\gamma$  targets (CD36, ABCG1), but inhibited the M1 markers in diabetic mice macrophages [122].

EGCG exerted its beneficial anticancer effects via PPAR $\alpha$  activation and inactivation of HO-1/Nrf2 pathway on some cancer cell lines, including pancreatic, esophageal, MCF-7, and ovarian. However, as a consequence of EGCG-induced PPAR $\alpha$  expression, HO-1 is negatively regulated by PPAR $\alpha$  as its direct target, depending on cell type and ligand stimulation. Therefore, PPAR $\alpha$  activation attenuates EGCG-induced HO-1 up-regulation and sensitizes cancer cells to EGCG [127]. In addition, catechins activated PPAR $\gamma$  via their anti-inflammatory, antioxidant, and antiapoptotic effects to ameliorate cardiac, renal, brain, and nervous system injuries induced by their related diseases [128–130].

Additionally, catechins appeared to be critical regulators of PPARs (PPAR $\alpha$ , PPAR $\gamma$ , PPAR $\alpha/\gamma$ , and PPAR $\delta$ ) (Table 1) that are involved in protection of organs, and by inhibiting/stimulating their upstream or downstream targets improved each of the organ functions [129–131].

**4.12. Berberine.** Berberine is an isoquinoline alkaloid, which exists in plants such as *Berberis* spp. and *Rhizoma coptidis*. In addition, several previous studies have reported that berberine is considered anti-inflammatory, antidiabetic, cardioprotective, neuroprotective, antihyperlipidemic, antioxidant, hepatoprotective, and antiadipogenic potential [132–138]. Berberine exhibited its pharmacological effects through PPARs, especially as selective PPAR $\alpha$  agonist in regulation of metabolic, liver, renal, cardiac, and brain dysfunctions (Table 1) [135, 137, 139–142]. Berberine affects upstream or downstream signaling targets, resulting in activation of PPAR $\alpha$ , thereby reducing lipogenesis and promoting  $\beta$ -oxidation in animal metabolic dysfunction models [133–135, 137]. Interestingly, berberine activated PPAR $\alpha$ /nitrous oxide systems (NOS)/NO signaling pathway in cardiac animal experiments, which indicated that NO is a pivotal downstream target of PPAR $\alpha$  signaling cascade in cardiachypertrophy [140, 141].

**4.13. Cinnamic Acid.** Cinnamic acid is an organic and aromatic unsaturated plant-based carboxylic acid (with two cis and trans isoforms) exerting beneficial therapeutic effects such as antitumoral activity, antioxidant, anti-inflammation, antiatherogenic, hepatoprotection, cardioprotection, and neuroprotection [143–145]. Cinnamic acid exhibited a PPAR $\alpha$  agonist role to reduce lipid accumulation and neurodegeneration in cellular and animal models [143–145]. Interestingly, it acted as PPAR $\gamma$  antagonist, resulting in inhibition of hepatic lipogenesis and fatty acid intake in HepG2 cells and *db/db* mice (Table 1) [144]. A recent study indicated that poly lactic-co-glycolic acid (PLGA) nanoparticle of cinnamic acid at concentration of  $\geq 25$   $\mu$ M inhibited MCF-7 cellular proliferation via PPAR $\gamma$  signaling pathway, leading to a drop of metabolic activity and Ki-67 antigen to exert its cytotoxic effects on breast cancer [146]. Thus, cinnamic acid can act as agonist or antagonist of PPARs to regulate abnormality of various diseases.

**4.14. Glycyrrhizic Acid.** Glycyrrhizic acid (Glycyrrhizin) is a bioactive triterpenoid that was extracted from *Glycyrrhiza glabra* L. roots [147, 148]. Previous studies reported beneficial effects of glycyrrhizin treatment of diseases and some research investigated the relationship of glycyrrhizic acid and PPARs (Table 1) [147–149]. In addition, new synthetic derivatives of glycyrrhizic acid, 2-cyano-substituted analogues, and 19 glycyrrhetic acid exhibited promising potential for PPAR $\gamma$  activation to inhibit HT-29, HCT-15, MCF-7, and HepG2 carcinogen cell lines [150]. In addition, 19 glycyrrhetic acid derivative increased PPAR $\gamma$  and reduced MMP-2/MMP-9 to act as antitumor agent against MCF-7 cells [150]. In another study, intraperitoneal injection of 50mg/kg glycyrrhetic acid in male Sprague-Dawley rats fed *ad libitum* with standard diet improved insulin sensitivity,

reduced lipid (total cholesterol (TC), LDL, and triacylglycerol (TAG)), up-regulated PPAR $\alpha$  and PPAR $\gamma$  in the liver, and revealed antiglyucocorticoid effects [151]. Finally, glycyrrhetic acid exerts a role as PPAR $\alpha/\gamma$  agonist due to its antioxidant and anti-inflammatory properties.

**4.15. Oleanolic Acid.** Oleanolic acid is a natural pentacyclic triterpenoid found in medicinal plants, fruits, and vegetables [152, 153]. It showed some pharmacological potential through its dual agonist actions on PPAR in tissues [153, 154]. Likewise, oleanolic acid simultaneously activated PPAR $\gamma/\alpha$ , leading to an increase of fatty acid transport protein 1 (FATP-1) and long-chain acyl-CoA synthetase (ACSL) to regulate metabolic dysfunction in 3T3-L1 and C2C12 cells [154]. Also, oleanolic acid operated as a ligand of PPAR $\gamma$ -1 or PPAR $\delta$  for management of obesity or high glucose-induced metabolic abnormality in animal and cell line models [152, 153]. However, in the *in vivo* studies, it had cardioprotective and hepatoprotective effects by stimulation of PPAR $\alpha$  and PPAR $\gamma$ , respectively [155, 156]. In another study, isolated oleanane-type triterpenoid of *Pulsatilla koreana* root showed anti-inflammatory effects via activation of PPAR binding to PPRE luciferase reporter, thereby inducing an inhibition of NF- $\kappa$ B, iNOS, and ICAM-1 in HepG2 cells (Table 1) [157]. However, future studies are needed to identify the precise mechanism of the PPARs agonist role of oleanolic acid.

**4.16. Ursolic Acid.** Ursolic acid (UA), a pentacyclic triterpenoid that is found in bark, root, leaves, and fruits of numerous medicinal plants, showed a wide range of biological activities such as anti-inflammatory, anticancer, antioxidant, cardioprotective, antiviral, and metabolic disorders [158–161]. In addition, UA functioned as a PPAR $\alpha$  agonist to regulate metabolic syndrome, liver diseases, respiratory dysfunction, and exaggerated inflammatory response in the animal and cell line experiments [158, 160, 162–164]. Likewise, UA improved cerebral ischemia/reperfusion injury, central nervous system (CNS) neural dysfunction, remyelination, multiple sclerosis (brain/central nervous system irregularities), and also airway inflammation of allergic asthma via promotion of PPAR $\gamma$  signaling by its PPAR $\gamma$  agonist potential in *in vivo* studies [159, 165, 166]. A recent study showed that UA (0–50  $\mu$ M) may exert antiskin cancer effects by promoting AMPK and PPAR $\alpha$  in Ca3/7 and MT1/2 premalignant and malignant skin cancer cell lines [166]. Also, ursolic acid in combination with artesunate suppressed hyperlipidemia and atherosclerosis due to increasing low density lipoprotein receptor (LDLR), apolipoprotein A-I (apoA-I), and PPAR $\alpha$ , as well as SREBP1 reduction in a hyperglycemic rabbit model [7]. Therefore, UA, a PPAR ligand and coactivator (Table 1), could play a role in management of multiple diseases, but future animal or clinical studies are needed to prove its promising properties related to PPARs.

**4.17. Shogaol.** 6-Shogaol, the dehydrated form of 6-gingerols from dried *Zingiber officinale* (ginger) rhizomes, is a phenolic pungent compound which possesses numerous

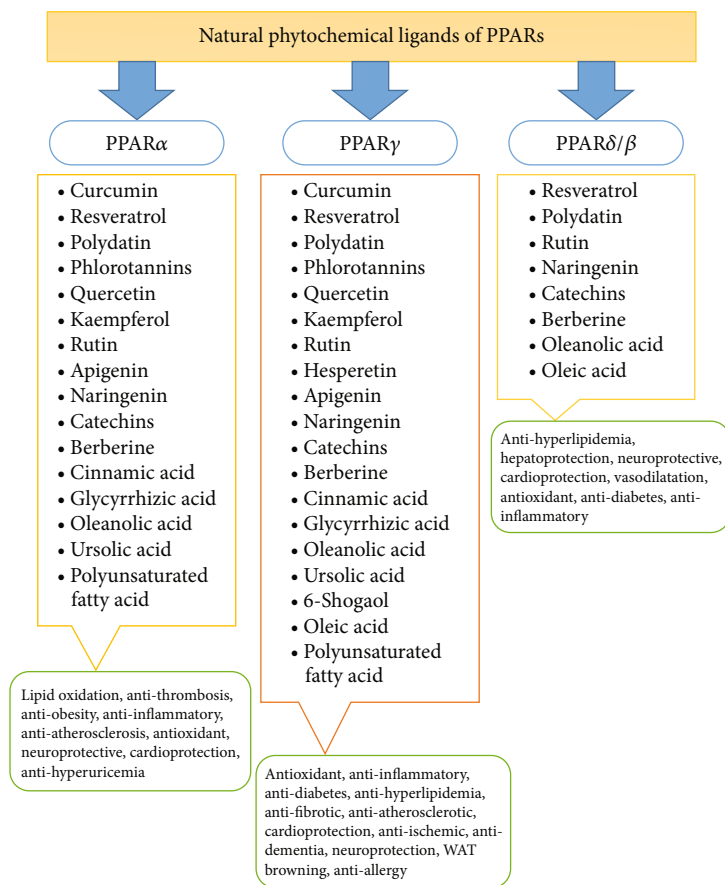


FIGURE 2: Phytochemical ligands of PPARs and their biological targets.

pharmacological properties, including anticancer, anti-inflammatory, and neuroprotective effects [167–169]. A number of studies reported that 6-shogaol acted as a PPAR $\gamma$  agonist in its anti-inflammatory, antitumor, and neuroprotective effects (Table 1) [167–169]. These studies suggest that 6-shogaol may have a role as a novel PPAR $\gamma$  agonist ligand to manage diseases such as inflammation, cancer, and neurodegeneration.

**4.18. Oleic Acid.** Oleic acid (OA) is the most abundant cis omega-9 monounsaturated fatty acid with 18 carbon atoms in olive oil, which exhibits antioxidant, cardioprotective, anti-inflammatory, antibacterial, and hepatoprotective effects [170, 171]. It has been reported that OA acts to enhanced PPAR $\gamma$  to reduce TNF- $\alpha$ , IL-6, IL-1 $\beta$ , iNOS, and MMP-9 in monocytes or macrophages [171, 172]. Interestingly, OA repressed expression of PPAR $\gamma$  and SIRT1 to protect coronary arteries in smooth muscle cells [170]. Also, OA boosted PPAR $\delta$  in HepG2 cells by provoking the G protein-coupled receptor 40-phospholipase C- (GPR40-PLC-) calcium pathway to regulate lipid metabolism and insulin sensitivity [172]. Thus, these results suggested that OA can function as a potential PPAR agonist (Table 1) and future work will be needed to investigate the relationship between PPARs and oleic acid on animal models and clinical trials.

**4.19. Polyunsaturated Fatty Acid.** Polyunsaturated fatty acids (PUFA) or essential fatty acids, known as n-3, n-6, or n-9, are found in fish and vegetable oils and have been shown to exert beneficial effects on human or animal health [173, 174]. Polyunsaturated fatty acids can act as PPAR signaling activators in the regulation of abnormalities in liver, cancer, cardiovascular, and inflammatory diseases (Table 1) [175–178]. In goats feeding with  $\alpha$ -linolenic acid enhanced PPAR $\alpha$  in the liver [172]. While a number of studies have investigated PUFA effects on PPARs results were contradictory, and therefore more studies are warranted to determine their precise effects.

**4.20. Other Phytochemicals.** In addition to the compounds mentioned above, other natural phytochemicals showed potential PPARs ligand activity in research studies (Table 1). Terpenoids such as 1,8-cineole [7, 179], gingerol [7], cinnamaldehyde [180], carvacrol [181], zerumbone [182], oridonin [183], tanshinone IIA [184], pedunculoside [185], and lycopene and  $\beta$ -carotene [186] acted as dual PPARs activators for exhibiting antiatherosclerotic, antiadipogenic, anti-inflammatory, anticancer, hepatoprotective, and anti-hyperlipidemia effects. Interestingly, betulinic acid (a triterpenoid) had PPAR $\gamma$  and PPAR $\alpha$  antagonist activity in 3T3-L1 cells to boost glucose uptake and osteogenesis, along with

TABLE 2: Summary of clinical studies of phytochemicals on the PPAR family in diseases.

Phytochemicals	Disease	Dose/route of administration	Assay	Protective effect	Mechanism	Ref.
Nano-curcumin	Diabetes on hemodialysis (HD)	80 mg/day, capsule, 12 weeks (RCT)	Gene expressions in PBMCs, blood sample	Antioxidant, antidiabetic, anti-inflammatory	(+) PPAR $\gamma$ mRNA, LDLR mRNA, HDL-cholesterol, TAC, total nitrite level (-) FPG, insulin level, TC, TG, VLDL-cholesterol, LDL-cholesterol, total-/HDL-cholesterol ratio, hs-CRP, MDA	[201]
Curcumin	Polycystic ovary syndrome	500 mg/day, supplementary, 12 weeks (RCT)	Fasting blood sample, insulin and lipid metabolism gene expressions	Antiobesity, antidiabetic, lipid lowering	(+) PPAR $\gamma$ mRNA, LDLR mRNA, HDL cholesterol (-) FPG, insulin level, HOMA-IR, TC, LDL-cholesterol, total-/HDL-cholesterol ratio	[202]
Resveratrol + curcumin	Postprandial inflammation response in high-fat meal	100/50 mg (Res/Cur), 2 capsule, 30 min before consuming the high-fat meal (RCT)	Blood sample, inflammatory markers, adhesion molecules, NF $\kappa$ B1, and PPAR $\alpha$	No impact on the postprandial inflammation response, have only small effects on endothelial function	(+) - (-) sVCAM-1 iAUC *: PPAR $\alpha$ and NF $\kappa$ B1 not changed	[203]
Resveratrol	Type 2 diabetes mellitus and coronary heart disease	500 mg/day, capsule, 4 weeks (RCT)	Fasting blood sample, lipid, inflammation and oxidative markers, related gene expression	Antidiabetic, antioxidant, regulated dyslipidemia *Not effect on inflammatory markers	(+) PPAR $\gamma$ , SIRT1, QUICKI, HDL-C, TAC (-) FPG, insulin, HOMA-IR, TC/HDL, MDA	[276]
Naringenin	Diabetes	150 mg, capsule, 3times/day, 8 weeks (a case)	Blood sample, respiratory quotient, insulin and metabolic markers	Reduced body weight and insulin resistance, increased metabolic rate	(+) PPAR $\alpha$ , PPAR $\gamma$ , serum glucose, UCP1, CPT1 $\beta$ (-) HOMA-IR, LDL-C	[204]
Epigallocatechin gallate	Obesity	150 mg, capsule, twice/day, 8 weeks (RCT)	Blood sample (enzyme and hormone assay), gene expression in adipocytes	Decreased blood pressure, no effects on obesity, lipolysis and browning of human white adipocytes	(+) - (-) TG, serum kisspeptin * not effect on PPAR $\gamma$ and UCP1 expressions	[205]

(+): Increasing or activation of target. (-): Decreasing or inhibition of target.

adipogenesis inhibition [187]. Also, fucosterol (a triterpenoid) [188], umbelliferone (a coumarin) [189], and chelerythrine (an alkaloid) [190] demonstrated PPAR $\gamma$  activation in remediation of liver injury, liver fibrosis, and diabetes in animal models, respectively. The phytochemical ligands of PPARs and their biological targets are shown in (Figure 2).

## 5. Clinical Finding

Although numerous *in vitro* and *in vivo* studies demonstrated beneficial therapeutic effects of phytochemicals via their PPARs activation/suppression roles on a wide range of diseases (Table 1), there are few clinical studies on the impact of phytochemicals on PPARs and their implications in diseases. Limited clinical evidence for some phytochemicals associated with PPARs and disease remediation is available and is mainly on metabolic syndrome (Table 2). For polyunsaturated fatty acids (PUFAs), known to be PPAR

ligands, most clinical trials have reported the role of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and  $\alpha$ -linolenic acid (*n*-3 PUFAs) on PPARs activation/suppression to modulate disease [191–200]. Additionally, blood sampling or gene assay of subjects demonstrated single nucleotide polymorphisms (SNPs) associated with impacts of PPARs and PUFAs on metabolic syndrome [202, 204]. Moreover, curcumin and resveratrol increased expression of PPAR $\gamma$  gene for regulation of metabolic syndrome and associated diabetes, coronary heart disease, and polycystic ovary syndrome [201–203]. In addition, administration of naringenin into a diabetic 53-year-old African American female (a case study) showed that naringenin exerted its regulatory effects on insulin resistance and metabolic rate via activation of PPAR $\alpha$  and PPAR $\gamma$ , leading to promotion of UCP1 and CPT1 $\beta$  [204]. In another study, effects of epigallocatechin gallate (EGCG) evaluated on Thai obese subjects (*n*=15) that reported consumption of 300 mg/day

EGCG for 4 and 8 weeks did not affect expression of UCPI and PPAR $\gamma$  in browning white adipocytes, but interestingly EGCG reduced TG, blood pressure, and kisspeptin levels in these obese human subjects (Table 2) [205]. Given the sparsity of such clinical studies, the exact activation/suppression effects of phytochemicals on PPARs in diseases warrant more clinical trial investigations with larger sample size with attention to pharmacokinetic, dosage, frequency, and treatment duration protocols.

## 6. Limitations

There are some limitations to this review which are highlighted here. The most important limitation for therapeutic evaluation is the lack of sufficient clinical studies on the majority of PPAR natural agonists to date. In addition, there is insufficient evidence of safety or adverse side effects and possible drug interactions in oral administration of phytochemicals both in clinical and animal studies. Thus, further studies are needed to evaluate pharmacokinetic characteristics and bioavailability of phytochemicals as PPAR agonists. Likewise, as genetic polymorphisms in different individuals may modify the phytochemical effects on PPARs and their dosage and treatment regimes, there are only genetic polymorphic considerations of PUFAs in the available studies. While a wide range of natural phytochemicals have been suggested as candidate PPAR regulators from *in vitro* and *in vivo* studies, the greatest number of clinical trials have been performed on polyunsaturated fatty acids.

## 7. Conclusions

Overall, based on adjunct therapy with natural products in numerous diseases, this review has highlighted the interplay between phytochemicals and PPARs in multiple regulatory mechanisms of disease (Table 1). Here, we have focused on regulation by phytochemicals of disease abnormalities through PPAR-targeted molecular mechanisms, mainly from available *in vitro* and *in vivo* experimental models. However, clinical trials which were reported on the impact of phytochemicals in management of diseases via PPARs activation or suppression pathways are summarized in Table 2.

Based on the information presented in this review, it is noteworthy that phytochemicals have demonstrated promising potential, with acceptable safety, as agonists or antagonists of PPAR subtypes in several diseases associated with PPAR signaling cascades. In addition, phytochemicals not only can act as PPAR ligands but also they are able to impact on interactions with coactivators and corepressors in order for PPARs to target gene activation or suppression. Furthermore, phytochemicals also affect RXR activity and pre- and post-transcription regulators by inducing the obligatory heterodimer PPARs/RXR interaction, thereby instituting binding to PPRE and the consequent DNA binding site.

To conclude, it can be proposed that further studies warrant evaluation of more details of phytochemical formulations mentioned on their pharmacokinetic parameters, oral administration dosage, frequency, and absorption to enhance and expand clinical applications. As natural

phytochemicals may represent favorable PPAR agonist/antagonist effects, it is expected that an understanding of phytochemical-mediated molecular mechanisms of PPAR-associated diseases will contribute to a safe approach to the therapeutic use of PPAR-targeted agents in the future.

## Abbreviations

A $\beta$ :	$\beta$ -Amyloid peptides
ABCA1:	ATP-binding cassette transporter A1
ABCG1/5/8:	ATP-binding cassette transporters G1/5/8
ACAA2:	Acetyl-coenzyme A acyltransferase 2
ACACA:	Acetyl-CoA carboxylase alpha
ACADL:	Acyl-CoA dehydrogenase long chain
ACAT:	Acyl-CoA cholesterol acyl transferase
ACC:	Acetyl-CoA carboxylase
AChE:	Acetyl cholinesterase
ACOT:	Acyl-CoA thioesterase
ACOX1:	Acyl-CoA Oxidase 1
ACSL:	Long-chain acyl-CoA synthetase
AdGFP:	AdCMV-GFP control vector
Agpat2:	1-Acylglycerol-3-Phosphate O-Acyltransferase 2
AIF:	Apoptosis-inducing factor
Akt:	Protein kinase B
ALB:	Albumin
ALOX5:	Arachidonate 5-lipoxygenase
ALP:	Alkaline phosphatase
ALT:	Alanine transaminase
AMPK:	AMP-activated protein kinase
ANF:	Atrial natriuretic factor
Ang II:	Angiotensin II
ANP:	Atrial natriuretic peptide
AP-1:	Activator protein 1
APG-7:	Autophagy protein 7
APOC3:	Apolipoprotein C3
Arg1:	Arginase
AOPP:	Advanced oxidation protein product
AOX:	Acyl-CoA oxidase
Apo-AI:	Apolipoprotein A-I
Apo-AII:	Apolipoprotein A-II
apoE <sup>-/-</sup> :	Apolipoprotein E-deficient
$\beta$ 3AR:	$\beta$ 3-Adrenergic receptor
ASC:	Apoptosis-associated speck-like protein
Atgl:	Adipose triglyceride lipase
ATGL:	Adipose triglyceride lipase
ATP:	Adenosine triphosphate
AUC:	Area under curve
BACE1:	$\beta$ -Site amyloid precursor protein-cleaving
BAT:	Brown adipose tissue
BDL:	Bile duct ligation
BDNF:	Brain-derived neurotrophic factor
BMI:	Body mass index
BNP:	Brain natriuretic peptide
BSP:	Bone sialoprotein
BUN:	Blood urea nitrogen
cAMP:	Cyclic adenosine monophosphate
CaMKII:	Ca <sup>+2</sup> /Calmodulin-dependent protein kinase II

CAT:	Catalase	FSP27:	Fat-specific protein 27
CatB/L:	Cathepsin B/L	FS:	Fractional shortening
CD36:	Scavenger receptor (class B)	GA:	Glycyrrhizic acid
CD11c:	Scavenger receptor	GCLC:	Glutamatergic cysteine ligase catalytic subunit
CD206:	Cluster of differentiation 206	GCLM:	Glutamyl cysteine ligase Modifier Subunit
cdk1:	Cyclin-dependent kinase 1	GIR60–120:	Glucose infusion rate between the 60th and 120th minute
C/EBP $\alpha$ :	CCAAT-enhancer-binding protein $\alpha$	GFAP:	Glial fibrillary acidic protein
CE:	Esterified cholesterol	GK:	Glycerol Kinase
Cel:	Carboxyl ester lipase	GLUT-4:	Glucose transporter-4
CETP:	Plasma cholesterol ester transferase	GOT:	Glutamic-oxaloacetic transaminase
Cfd:	Complement factor D	GPAT:	Glycerol-3-phosphate acyltransferase
ChAT:	Cholineacetyltransferase	G3PDH:	Glyceraldehyde-3-phosphate dehydrogenase
ChE:	Cholesterol efflux	GPR120:	G protein-coupled receptor 120
CHOP:	C/EBP-homologous protein	G6Pase:	Glucose 6-phosphatase
Cidea:	Cyclic adenosine monophosphate	GPT:	Glutamate pyruvate transaminase
CK-MB:	Creatine kinase on myocardial bundle	GPX3:	Plasmatic glutathione peroxidase
CNTF:	Ciliary neurotrophic factor	GRP78:	78 kDa glucose-regulated protein
Coll1 $\alpha$ 1/2:	Collagen type I alpha-1/2	GSH:	Glutathione
COX1:	Cytochrome C oxidase subunit 1	G0S2:	G0/G1 switch gene 2
COX-2:	Cyclooxygenase-2	GST:	Glutathione S-transferase
CPT1 $\beta$ :	Carnitine palmitoyl-transferase 1 $\beta$	$\gamma$ GT:	Gamma glutamyl transferase
CREB:	cAMP response element-binding	HbA1c:	Hemoglobin A1c
CRP:	C-reactive protein	HDL-C:	High-density lipoprotein cholesterol
CTGF:	Connective tissue growth factor	HFHS-D:	High-fat high-sucrose diet
CVD:	Cardiovascular disease	HGF:	Hepatocyte growth factor
CVF:	Collagen volume fraction	HIF-1 $\alpha$ :	Hypoxia inducible factor-1 $\alpha$
cTnT:	Cardiac troponin T	HK-2:	Normal human kidney epithelial
Cyt C:	Cytochrome CDAB	HMGCR:	3-Hydroxy-3-methylglutaryl-CoA reductase
CUMS:	Chronic unpredictable mild stress	4-HNE:	4-Hydroxynonenal
DAP:	Diastolic arterial pressure	HO-1:	Heme oxygenase-1
DCF:	2',7'-Dichlorofluorescein	H2O2:	Hydrogen peroxide
DGAT1/2:	Diacylglycerol O-Acyltransferase 1/2	HOMA-IR:	Homeostatic model assessment-insulin resistance
DsbA-L:	Disulfide-bond A oxidoreductase-like protein	HR:	Heart rate
EAT:	Epididymal adipose tissues	HSCs:	Hepatic stellate cells
ECM:	Extracellular matrix	hs-CRP:	High-sensitivity C-reactive protein
eGFR:	Estimated glomerular filtration rate	HSL:	Hormone-sensitive lipase
Ehhadh:	Enoyl-CoA hydratase and 3-Hydroxyacyl CoA dehydrogenase	Hsp70:	Heat shock protein70
EMT:	Epithelial-to-mesenchymal transition	HUVECs:	Human umbilical vein endothelial cells
ER:	Endoplasmic reticulum	iAUC:	Incremental AUC
ERK:	Extracellular signal-regulated kinase	ICAM-1:	Intracellular adhesion molecule-1
eIF2 $\alpha$ :	Phosphorylation of eukaryotic initiation factor-2 $\alpha$	IFN- $\gamma$ :	Interferon gamma
eNOS:	Endothelial nitric oxide synthase	IKK:	I $\kappa$ B kinase
ERR-1 $\alpha$ :	PPAR $\alpha$ -estrogen-related receptor	IL-1:	Interleukin-1
FABP1/4:	Fatty acid binding protein 1/4	IL-6:	Interleukin-6
FAS:	Fatty acid synthase	IL-10:	Interleukin-10
FBG:	Fasting blood glucose	IL-13:	Interleukin-13
FC:	Free cholesterol	iNOS:	Inducible nitric oxide synthase
FEUA:	Fractional excretion of uric acid	iROS:	Intercellular reactive oxygen species
FFA:	Free fatty acid	IS:	Infarct size
FINS:	Fasting insulin	IVSd:	End-diastolic interventricular septal thickness
FN:	Fibronectin	JNK:	c-JUN N-terminal kinase
Fitm1/2:	Fat-induced transcript 1/2	Keap1:	Kelch-like ECH-associated protein 1
Fizz1:	Found in inflammatory zone		
FoxO1:	Forkhead transcription factor O 1		
FPG:	Fasting plasma glucose		
FSI:	Fasting serum insulin		

LAMP-1/2:	Lysosome-associated membrane protein 1/2	PDE/cAMP:	Phosphodiesterase/Cyclic adenosine monophosphate
LC3:	Protein light chain 3	PDGF- $\beta$ :	Platelet-derived growth factor subunit B
LDH:	Lactate dehydrogenase	PDK-4:	Pyruvate dehydrogenase kinase-4
LDL-C:	Low-density lipoprotein cholesterol	PERK:	Prospective evaluation of radial keratotomy
LDLR <sup>-/-</sup> :	Lack the LDL receptor	PGC-1 $\alpha$ :	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
LPAAT $\theta$ :	Lysophosphatidic acid acyltransferase- $\theta$	PGE2:	Prostaglandin E2
LPL:	Lipoprotein lipase	PI3K:	Phosphatidylinositol-3 kinase
LPIN1:	Lipin1	PKA:	Protein kinase A
L-PK:	L-Pyruvate kinase	Plin2:	Perilipin 2
LSR:	Lipolysis-stimulated receptor	Pnpla2:	Adipose triglyceride lipase
LXR:	Liver X receptor	PON-1/2/3:	Paraoxonase-1/2/3
+LVdp/dt <sub>min</sub> :	Maximal positive rate of left ventricular pressure	PPAR $\alpha$ :	Peroxisome proliferator-activated receptor alpha
-LVdp/dt <sub>min</sub> :	Maximal negative rate of left ventricular pressure	PPAR $\gamma$ :	Peroxisome proliferator-activated receptor gamma
LVIDd:	Left ventricular end-diastolic internal diameter	PPAR $\delta$ :	Peroxisome proliferator-activated receptor delta
LVEDP:	Left ventricular end diastolic pressure	PP2C- $\alpha$ :	Protein phosphatase 2C- $\alpha$
LVPWd:	Left ventricular end-diastolic posterior wall thickness	PPRE:	Peroxisome proliferator response elements
MAP:	Mean arterial pressure	Prdm16:	PR domain containing 16
MAPK:	Mitogen-activated protein kinase	PT:	Protein thiol
MALAT1:	Metastasis-associated lung adenocarcinoma transcript 1	P-TEFb:	Positive transcription elongation factor b
MBP:	Myelin basic protein	PTEN:	Phosphatase and tensin homolog
MCAD:	Mitochondrial medium-chain acyl-CoA dehydrogenase	PUFA:	Polyunsaturated fatty acids
MCP-1:	Monocyte chemoattractant protein-1	QUICKI:	Quantitative insulin sensitivity check index
MDA:	Malondialdehyde	RAGE:	Advanced glycosylation end products receptor
ME:	Malic enzyme	rIR:	Insulin receptor
MI:	Myocardial infarction	ROS:	Reactive oxygen species
MMPs:	Matrix metalloproteinases	RST:	Renal-specific transporter
mTOR:	Mammalian target of rapamycin	RUNX2:	Runt-related transcription factor 2
MUFA:	Monounsaturated fatty acids	RXR:	Retinoid X receptor
NEFAs:	Nonesterified fatty acids	SAH:	Subarachnoid hemorrhage
NF- $\kappa$ B:	Nuclear factor- $\kappa$ B	SAP:	Systolic arterial pressure
NLRP3:	NOD-like receptor family pyrin domain containing 3	SAT:	Subcutaneous adipose tissue
NO:	Nitric oxide	SBP:	Systolic blood pressure
NOX:	NADPH oxidase	SCD-1:	Stearoyl CoA desaturase-1
NPT:	Non-protein thiol	Scr:	Serum creatinine
NQO-1:	NADPH quinone oxidoreductase	SFA:	Saturated fatty acids
Nrf2:	Nuclear factor erythroid 2-related factor 2	SIRT1:	NAD-dependent protein deacetylase
NRF-1:	Nuclear respiratory factor-1	S6K1:	Ribosomal S6 kinase 1
NRK-49F:	Rat renal interstitial fibroblasts	$\alpha$ -SKA:	$\alpha$ -Skeletal actin
O <sub>1</sub> :	Immature OL	SLU:	Selective lipid uptake
O <sub>4</sub> :	Pre-OL	$\alpha$ -SMA:	Alpha smooth muscle actin
OAT1:	Organic anion transporter 1	SOCS3:	Suppressors of cytokine signaling 3
OCN:	Osteocalcin	SOD:	Superoxide anion dismutase
OCTN2:	Organic cation transporter 2	SR-A:	Scavenger receptor-A
OP:	Oligodendrocyte progenitor	SR-BI:	Scavenger receptor class B type I
oxLDL:	Oxidized low-density lipoprotein	SQI:	Subcutaneous injection
PAI-1:	Plasminogen activator inhibitor	SREBP-1:	Sterol regulatory element-binding protein-1
PBEF:	Pre-B cell colony enhancing factor	STAT3:	Signal transducer and activator of transcription 3
PCNA:	Proliferating cell nuclear antigen	Surf:	Surfeit locus protein
PcSK9:	Proprotein convertase subtilisin/kexin type 9		



sVCAM-1:	Soluble vascular cell adhesion molecule-1
TAG:	Triacylglycerol
T-AOC:	Total antioxidative capability
TBARS:	Thiobarbituric acid reactive substances
3T3-L1 cells:	Mouse preadipocytes
TC:	Total cholesterol
TERT:	Antitelomerase reverse transcriptase
Tfam:	Transcription factor A
TG:	Triglyceride
TGF:	Transforming growth factor
TIMP-2:	Tissue inhibitor of metalloproteinase
TH:	Tyrosine hydroxylase
TNF- $\alpha$ :	Tumor necrosis factor alpha
Tmem26:	Transmembrane protein 26
TPP1:	Tripeptidyl-peptidase 1
TRAF2:	TNF receptor associated Factor 2
Treg:	Regulatory T cells
TR-FRET:	Time-resolved fluorescence resonance energy transfer
TXNIP:	Thioredoxin interacting protein
UA:	Uric acid
UCP 1/2:	Uncoupling protein 1/2
VAT:	Visceral adipose tissue
VLDL-cholesterol:	Very low-density lipoprotein-cholesterol
VSMCs:	Vascular smooth muscle cells
XDH:	Xanthine dehydrogenase
XO:	Xanthine oxidase
XOR:	Xanthine oxidoreductase
ZO-1:	Zonula occludens-1.

## Data Availability

There is no raw data associated with this article.

## Conflicts of Interest

The authors have no conflicts of interest.

## References

- [1] K. Duszka, A. Gregor, H. Guillou, J. König, and W. Wahli, "Peroxisome proliferator-activated receptors and caloric restriction—common pathways affecting metabolism, health, and longevity," *Cells*, vol. 9, no. 7, p. 1708, 2020.
- [2] Y. Xi, Y. Zhang, S. Zhu, Y. Luo, P. Xu, and Z. Huang, "PPAR-mediated toxicology and applied pharmacology," *Cells*, vol. 9, no. 2, p. 352, 2020.
- [3] M. Gamdzyk, D. M. Doycheva, J. Malaguit, B. Enkhjargal, J. Tang, and J. H. Zhang, "Role of PPAR- $\beta/\delta$ /miR-17/TXNIP pathway in neuronal apoptosis after neonatal hypoxic-ischemic injury in rats," *Neuropharmacology*, vol. 140, no. 140, pp. 150–161, 2018.
- [4] M. Royan and B. Navidshad, "Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), a key regulatory gene of lipid metabolism in chicken," *World's Poultry Science Journal*, vol. 72, no. 4, pp. 773–784, 2016.
- [5] F. Matrisciano and G. Pinna, "PPAR and functional foods: rationale for natural neurosteroid-based interventions for postpartum depression," *Neurobiology of Stress*, vol. 12, no. 12, article 100222, 2020.
- [6] M. Hamblin, L. Chang, Y. Fan, J. Zhang, and Y. E. Chen, "PPARs and the cardiovascular system," *Antioxidants & Redox Signaling*, vol. 11, no. 6, pp. 1415–1452, 2009.
- [7] A. Enayati, T. P. Johnston, and A. Sahebkar, "Anti-atherosclerotic effects of spice-derived phytochemicals," *Current Medicinal Chemistry*, vol. 28, no. 6, pp. 1197–1223, 2021.
- [8] V. Jayakumar, S. S. Ahmed, and K. K. Ebenezer, "Multivariate analysis and molecular interaction of curcumin with PPAR $\gamma$  in high fructose diet induced insulin resistance in rats," *Springerplus*, vol. 5, no. 1, pp. 1–5, 2016.
- [9] M. Kobori, Y. Takahashi, H. Takeda et al., "Dietary intake of curcumin improves eIF2 signaling and reduces lipid levels in the white adipose tissue of obese mice," *Scientific Reports*, vol. 8, no. 1, pp. 1–3, 2018.
- [10] E. S. Lee, M. H. Kwon, H. M. Kim, H. B. Woo, C. M. Ahn, and C. H. Chung, "Curcumin analog CUR5-8 ameliorates non-alcoholic fatty liver disease in mice with high-fat diet-induced obesity," *Metabolism*, vol. 103, article 154015, 2020.
- [11] S. K. Shin, T. Y. Ha, R. A. McGregor, and M. S. Choi, "Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism," *Molecular Nutrition & Food Research*, vol. 55, no. 12, pp. 1829–1840, 2011.
- [12] N. J. Zhao, M. J. Liao, J. J. Wu, and K. X. Chu, "Curcumin suppresses Notch-1 signaling: Improvements in fatty liver and insulin resistance in rats," *Molecular Medicine Reports*, vol. 17, no. 1, pp. 819–826, 2018.
- [13] S. S. Patel, A. Acharya, R. S. Ray, R. Agrawal, R. Raghuvanshi, and P. Jain, "Cellular and molecular mechanisms of curcumin in prevention and treatment of disease," *Critical Reviews in Food Science and Nutrition*, vol. 60, no. 6, pp. 887–939, 2020.
- [14] D. J. Den Hartogh, A. Gabriel, and E. Tsiani, "Antidiabetic properties of curcumin I: evidence from in vitro studies," *Nutrients*, vol. 12, no. 1, p. 118, 2020.
- [15] B. B. Aggarwal, "Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals," *Annual Review of Nutrition*, vol. 30, no. 1, pp. 173–199, 2010.
- [16] Q. Kang and A. Chen, "Curcumin suppresses expression of low-density lipoprotein (LDL) receptor, leading to the inhibition of LDL-induced activation of hepatic stellate cells," *British Journal of Pharmacology*, vol. 157, no. 8, pp. 1354–1367, 2009.
- [17] J. B. Wang, L. L. Qi, S. D. Zheng, H. Z. Wang, and T. X. Wu, "Curcumin suppresses PPAR $\delta$  expression and related genes in HT-29 cells," *World Journal of Gastroenterology*, vol. 15, no. 11, pp. 1346–1352, 2009.
- [18] Y. K. Lee, W. S. Lee, J. T. Hwang, D. Y. Kwon, Y. J. Surh, and O. J. Park, "Curcumin exerts antidifferentiation effect through AMPK $\alpha$ -PPAR- $\gamma$  in 3T3-L1 adipocytes and antiproliferatory effect through AMPK $\alpha$ -COX-2 in cancer cells," *Journal of Agricultural and Food Chemistry*, vol. 57, no. 1, pp. 305–310, 2009.
- [19] A. Vallée, Y. Lecarpentier, and J. N. Vallée, "Curcumin: a therapeutic strategy in cancers by inhibiting the canonical WNT/ $\beta$ -catenin pathway," *Journal of Experimental & Clinical Cancer Research*, vol. 38, no. 1, pp. 1–6, 2019.

- [20] A. Saidi, M. Kasabova, L. Vanderlynden et al., "Curcumin inhibits the TGF- $\beta$ 1-dependent differentiation of lung fibroblasts via PPAR $\gamma$ -driven upregulation of cathepsins B and L," *Scientific Reports*, vol. 9, no. 1, pp. 1–5, 2019.
- [21] J. Luo, J. Qu, R. Yang et al., "Phytochemicals mediate the expression and activity of OCTN2 as activators of the PPAR $\gamma$ /RXR $\alpha$  pathway," *Frontiers in Pharmacology*, vol. 7, p. 189, 2016.
- [22] F. Zhang, Z. Zhang, L. Chen et al., "Curcumin attenuates angiogenesis in liver fibrosis and inhibits angiogenic properties of hepatic stellate cells," *Journal of Cellular and Molecular Medicine*, vol. 18, no. 7, pp. 1392–1406, 2014.
- [23] A. Baghdasaryan, T. Claudel, A. Kusters et al., "Curcumin improves sclerosing cholangitis in Mdr2-/- mice by inhibition of cholangiocyte inflammatory response and portal myofibroblast proliferation," *Gut*, vol. 59, no. 4, pp. 521–530, 2010.
- [24] S. F. Nabavi, M. Daglia, A. H. Moghaddam, S. Habtemariam, and S. M. Nabavi, "Curcumin and liver disease: from chemistry to medicine," *Comprehensive Reviews in Food Science and Food Safety*, vol. 13, no. 1, pp. 62–77, 2014.
- [25] Y. Liu, F. Cheng, Y. Luo et al., "PEGylated curcumin derivative attenuates hepatic steatosis via CREB/PPAR- $\gamma$ /CD36 pathway," *BioMed Research International*, vol. 2017, Article ID 8234507, 11 pages, 2017.
- [26] Y. Y. Li, D. Tang, Y. L. Du et al., "Fatty liver mediated by peroxisome proliferator-activated receptor- $\alpha$  DNA methylation can be reversed by a methylation inhibitor and curcumin," *Journal of Digestive Diseases*, vol. 19, no. 7, pp. 421–430, 2018.
- [27] A. R. Buonomo, R. Scotto, S. Nappa et al., "The role of curcumin in liver diseases," *Archives of Medical Science*, vol. 15, no. 6, pp. 1608–1620, 2019.
- [28] K. Cheng, A. Yang, X. Hu, D. Zhu, and K. Liu, "Curcumin attenuates pulmonary inflammation in lipopolysaccharide induced acute lung injury in neonatal rat model by activating peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) pathway," *Medical Science Monitor*, vol. 24, pp. 1178–1184, 2018.
- [29] M. V. Carvalho, C. F. Gonçalves-de-Albuquerque, and A. R. Silva, "PPAR gamma: from definition to molecular targets and therapy of lung diseases," *International Journal of Molecular Sciences*, vol. 22, no. 2, p. 805, 2021.
- [30] X. Zhou, J. Zhang, C. Xu, and W. Wang, "Curcumin ameliorates renal fibrosis by inhibiting local fibroblast proliferation and extracellular matrix deposition," *Journal of Pharmacological Sciences*, vol. 126, no. 4, pp. 344–350, 2014.
- [31] Y. Y. Li, D. Tang, C. C. Y. Du YL, Y. Q. Nie, J. Cao, and Y. J. Zhou, "Fatty liver mediated by peroxisome proliferator-activated receptor- $\alpha$  DNA methylation can be reversed by a methylation inhibitor and curcumin," *Journal of Digestive Diseases*, vol. 19, no. 7, pp. 421–430, 2018.
- [32] F. H. Lv, H. L. Yin, Y. Q. He et al., "Effects of curcumin on the apoptosis of cardiomyocytes and the expression of NF- $\kappa$ B, PPAR- $\gamma$  and Bcl-2 in rats with myocardial infarction injury," *Experimental and Therapeutic Medicine*, vol. 12, no. 6, pp. 3877–3884, 2016.
- [33] H. Y. Li, M. Yang, Z. Li, and Z. Meng, "Curcumin inhibits angiotensin II-induced inflammation and proliferation of rat vascular smooth muscle cells by elevating PPAR- $\gamma$  activity and reducing oxidative stress," *International Journal of Molecular Medicine*, vol. 39, no. 5, pp. 1307–1316, 2017.
- [34] H. M. Wang, Y. X. Zhao, S. Zhang et al., "PPAR $\gamma$  agonist curcumin reduces the amyloid- $\beta$ -stimulated inflammatory responses in primary astrocytes," *Journal of Alzheimer's Disease*, vol. 20, no. 4, pp. 1189–1199, 2010.
- [35] Z. J. Liu, W. Liu, L. Liu, C. Xiao, Y. Wang, and J. S. Jiao, "Curcumin protects neuron against cerebral ischemia-induced inflammation through improving PPAR-gamma function," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 470975, 10 pages, 2013.
- [36] M. Wang, J. Kou, C. Wang, X. Yu, X. Xie, and X. Pang, "Curcumin inhibits APOE4-induced injury by activating peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) in SH-SY5Y cells," *Iranian Journal of Basic Medical Sciences*, vol. 23, p. 1576, 2020.
- [37] Z. J. Liu, Z. H. Li, L. Liu et al., "Curcumin attenuates beta-amyloid-induced neuroinflammation via activation of peroxisome proliferator-activated receptor-gamma function in a rat model of Alzheimer's disease," *Frontiers in Pharmacology*, vol. 7, p. 261, 2016.
- [38] B. Rahardjo, E. Widjajanto, H. Sujuti, and K. Keman, "Curcumin decreased level of proinflammatory cytokines in monocyte cultures exposed to preeclamptic plasma by affecting the transcription factors NF- $\kappa$ B and PPAR- $\gamma$ ," *Biomarkers and Genomic Medicine*, vol. 6, no. 3, pp. 105–115, 2014.
- [39] S. C. Funes, M. Rios, A. Fernández-Fierro et al., "Naturally derived heme-oxygenase 1 inducers and their therapeutic application to immune-mediated diseases," *Frontiers in Immunology*, vol. 11, p. 1467, 2020.
- [40] Y. Zhang, Z. Luo, L. Ma, Q. Xu, Q. Yang, and L. Si, "Resveratrol prevents the impairment of advanced glycosylation end products (AGE) on macrophage lipid homeostasis by suppressing the receptor for AGE via peroxisome proliferator-activated receptor gamma activation," *International Journal of Molecular Medicine*, vol. 25, no. 5, pp. 729–734, 2010.
- [41] G. Ye, G. Chen, H. Gao et al., "Resveratrol inhibits lipid accumulation in the intestine of atherosclerotic mice and macrophages," *Journal of Cellular and Molecular Medicine*, vol. 23, no. 6, pp. 4313–4325, 2019.
- [42] Y. J. Song, C. B. Zhong, and W. Wu, "Resveratrol and diabetic cardiomyopathy: focusing on the protective signaling mechanisms," *Oxidative Medicine and Cellular Longevity*, vol. 2020, Article ID 7051845, 19 pages, 2020.
- [43] C. Lee, "Collaborative power of Nrf2 and PPAR $\gamma$  activators against metabolic and drug- induced oxidative injury," *Oxidative MEDICine and Cellular Longevity*, vol. 2017, Article ID 1378175, 14 pages, 2017.
- [44] S. Qin, Y. Lu, and G. A. Rodrigues, "Resveratrol protects RPE cells from sodium iodate by modulating PPAR $\alpha$  and PPAR $\delta$ ," *Experimental Eye Research*, vol. 118, pp. 100–108, 2014.
- [45] X. Meng, J. Zhou, C. N. Zhao, R. Y. Gan, and H. B. Li, "Health benefits and molecular mechanisms of resveratrol: a narrative review," *Foods*, vol. 9, no. 3, p. 340, 2020.
- [46] N. Kumar, S. Sharan, A. K. Singh, A. Chakraborty, and P. Roy, "Anticancer activities of pterostilbene isothiocyanate conjugate in breast cancer cells: involvement of PPARc," *PLoS One*, vol. 9, pp. 1–7, 2014.
- [47] J. Jiang, Y. Chen, T. Dong et al., "[Corrigendum] Polydatin inhibits hepatocellular carcinoma via the AKT/STAT3-FOXO1 signaling pathway," *Oncology Letters*, vol. 17, no. 5, pp. 4505–4513, 2019.

- [48] M. Wu, X. Li, S. Wang et al., "Polydatin for treating atherosclerotic diseases: a functional and mechanistic overview," *Biomedicine & Pharmacotherapy*, vol. 128, article 110308, 2020.
- [49] D. Şöhretöğlü, M. Y. Baran, R. Arroo, and A. Kuruüzüm-Uz, "Recent advances in chemistry, therapeutic properties and sources of polydatin," *Phytochemistry Reviews*, vol. 17, no. 5, pp. 973–1005, 2018.
- [50] M. Wu, M. Liu, G. Guo, W. Zhang, and L. Liu, "Polydatin inhibits formation of macrophage-derived foam cells," *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, Article ID 729017, 8 pages, 2015.
- [51] P. Ahmad, S. S. Alvi, D. Iqbal, and M. S. Khan, "Insights into pharmacological mechanisms of polydatin in targeting risk factors-mediated atherosclerosis," *Life Sciences*, vol. 254, article 117756, 2020.
- [52] Y. Wu, L. Xue, W. Du et al., "Polydatin restores endothelium-dependent relaxation in rat aorta rings impaired by high glucose: a novel insight into the PPAR $\beta$ -NO signaling pathway," *PLoS One*, vol. 10, no. 5, article e0126249, 2015.
- [53] L. Lai Xue, K. Wub, H. Qiu et al., "Polydatin exhibits the hepatoprotective effects through PPAR- $\alpha$ /- $\beta$  signaling pathway in streptozocin-induced diabetic mice," *Journal of Functional Foods*, vol. 36, pp. 341–347, 2017.
- [54] X. J. Zhao, H. W. Yu, Y. Z. Yang et al., "Polydatin prevents fructose-induced liver inflammation and lipid deposition through increasing miR-200a to regulate Keap1/Nrf2 pathway," *Redox Biology*, vol. 18, pp. 124–137, 2018.
- [55] H. A. Jung, H. J. Jung, H. Y. Jeong, H. J. Kwon, M. Y. Ali, and J. S. Choi, "Phlorotannins isolated from the edible brown alga *Ecklonia stolonifera* exert anti-adipogenic activity on 3T3-L1 adipocytes by downregulating C/EBP  $\alpha$  and PPAR $\gamma$ ," *Fitoterapia*, vol. 92, pp. 260–269, 2014.
- [56] A. R. Ganesan, U. Tiwari, and G. Rajauria, "Seaweed nutraceuticals and their therapeutic role in disease prevention," *Food Science and Human Wellness*, vol. 8, no. 3, pp. 252–263, 2019.
- [57] P. Koirala, H. A. Jung, and J. S. Choi, "Recent advances in pharmacological research on *Ecklonia* species: a review," *Archives of Pharmacal Research*, vol. 40, no. 9, pp. 981–1005, 2017.
- [58] G. Piao and H. Yuan, "Inhibitory effects of twenty-nine compounds from *Potentilla longifolia* on lipid accumulation and their mechanisms in 3T3-L1 Cells," *Frontiers in Pharmacology*, vol. 11, p. 1719, 2020.
- [59] B. F. Negara, J. H. Sohn, J. S. Kim, and J. S. Choi, "Effects of phlorotannins on organisms: focus on the safety, toxicity, and availability of phlorotannins," *Foods*, vol. 10, no. 2, p. 452, 2021.
- [60] K. Ren, T. Jiang, and G. J. Zhao, "Quercetin induces the selective uptake of HDL-cholesterol via promoting SR-BI expression and the activation of the PPAR $\gamma$ /LXR $\alpha$  pathway," *Food & Function*, vol. 9, no. 1, pp. 624–635, 2018.
- [61] K. Ferenczyova, B. Kalocayova, and M. Bartekova, "Potential implications of quercetin and its derivatives in cardioprotection," *International Journal of Molecular Sciences*, vol. 21, no. 5, p. 1585, 2020.
- [62] Q. Deng, X. X. Li, Y. Fang, X. Chen, and J. Xue, "Therapeutic potential of quercetin as an antiatherosclerotic agent in atherosclerotic cardiovascular disease: a review," *Evidence-Based Complementary and Alternative Medicine*, vol. 2020, Article ID 5926381, 12 pages, 2020.
- [63] Q. Jia, H. Cao, D. Shen et al., "Quercetin protects against atherosclerosis by regulating the expression of PCSK9, CD36, PPAR $\gamma$ , LXR $\alpha$  and ABCA1," *International Journal of Molecular Medicine*, vol. 44, no. 3, pp. 893–902, 2019.
- [64] A. A. Oyagbemi, T. O. Omobowale, O. E. Ola-Davies et al., "Quercetin attenuates hypertension induced by sodium fluoride via reduction in oxidative stress and modulation of HSP 70/ERK/PPAR $\gamma$  signaling pathways," *Biofactors*, vol. 44, no. 5, pp. 465–479, 2018.
- [65] L. Yan, J. D. Zhang, B. Wang et al., "Quercetin inhibits left ventricular hypertrophy in spontaneously hypertensive rats and inhibits angiotensin II-induced H9C2 cells hypertrophy by enhancing PPAR- $\gamma$  expression and suppressing AP-1 activity," *PLoS One*, vol. 8, no. 9, article e72548, 2013.
- [66] X. Liu, Z. Yu, X. Huang et al., "Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) mediates the protective effect of quercetin against myocardial ischemia-reperfusion injury via suppressing the NF- $\kappa$ B pathway," *American Journal of Translational Research*, vol. 8, no. 12, pp. 5169–5186, 2016.
- [67] K. Beekmann, L. Rubió, L. H. de Haan et al., "The effect of quercetin and kaempferol aglycones and glucuronides on peroxisome proliferator-activated receptor-gamma (PPAR- $\gamma$ )," *Food & Function*, vol. 6, no. 4, pp. 1098–1107, 2015.
- [68] A. E. Peredo-Escárcega, V. Guarner-Lans, I. Pérez-Torres et al., "The combination of resveratrol and quercetin attenuates metabolic syndrome in rats by modifying the serum fatty acid composition and by upregulating SIRT 1 and SIRT 2 expression in white adipose tissue," *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, Article ID 474032, 9 pages, 2015.
- [69] H. Choi, C. S. Kim, and R. Yu, "Quercetin upregulates uncoupling protein 1 in white/brown adipose tissues through sympathetic stimulation," *Journal of Obesity & Metabolic Syndrome*, vol. 27, no. 2, pp. 102–109, 2018.
- [70] S. M. Lee, J. Moon, Y. Cho, J. H. Chung, and M. J. Shin, "Quercetin up-regulates expressions of peroxisome proliferator-activated receptor  $\gamma$ , liver X receptor  $\alpha$ , and ATP binding cassette transporter A1 genes and increases cholesterol efflux in human macrophage cell line," *Nutrition Research*, vol. 33, no. 2, pp. 136–143, 2013.
- [71] G. J. Shi, Y. Li, Q. H. Cao et al., "In vitro and in vivo evidence that quercetin protects against diabetes and its complications: a systematic review of the literature," *Biomedicine & Pharmacotherapy*, vol. 109, pp. 1085–1099, 2019.
- [72] T. Kunasegaran, M. R. Mustafa, D. D. Murugan, and F. I. Achike, "The bioflavonoid quercetin synergises with PPAR- $\gamma$  agonist pioglitazone in reducing angiotensin-II contractile effect in fructose-streptozotocin induced diabetic rats," *Biochimie*, vol. 125, pp. 131–139, 2016.
- [73] N. Arias, M. T. Macarulla, L. Aguirre, M. G. Martínez-Castaño, and M. P. Portillo, "Quercetin can reduce insulin resistance without decreasing adipose tissue and skeletal muscle fat accumulation," *Genes & Nutrition*, vol. 9, no. 1, p. 361, 2014.
- [74] D. Ortuño Sahagún, A. L. Márquez-Aguirre, S. Quintero-Fabián, R. I. López-Roa, and A. E. Rojas-Mayorquín, "Modulation of PPAR- $\gamma$  by nutraceuticals as complementary treatment for obesity-related disorders and inflammatory diseases," *PPAR Research*, vol. 2012, 17 pages, 2012.

- [75] T. Benameur, R. Soleti, and C. Porro, "The potential neuro-protective role of free and encapsulated quercetin mediated by miRNA against neurological diseases," *Nutrients*, vol. 13, no. 4, p. 1318, 2021.
- [76] U. H. Park, J. C. Jeong, J. S. Jang et al., "Negative regulation of adipogenesis by kaempferol, a component of *Rhizoma Polygonati falcatum* in 3T3-L1 cells," *Biological and Pharmaceutical Bulletin*, vol. 35, no. 9, pp. 1525–1533, 2012.
- [77] Y. Zang, L. Zhang, K. Igarashi, and C. Yu, "The anti-obesity and anti-diabetic effects of kaempferol glycosides from unripe soybean leaves in high-fat-diet mice," *Food & Function*, vol. 6, no. 3, pp. 834–841, 2015.
- [78] D. Torres-Villarreal, A. Camacho, H. Castro, R. Ortiz-Lopez, and A. L. De la Garza, "Anti-obesity effects of kaempferol by inhibiting adipogenesis and increasing lipolysis in 3T3-L1 cells," *Journal of Physiology and Biochemistry*, vol. 75, no. 1, pp. 83–88, 2019.
- [79] M. H. Hoang, Y. Jia, J. H. Lee, Y. Kim, and S. J. Lee, "Kaempferol reduces hepatic triglyceride accumulation by inhibiting Akt," *Journal of Food Biochemistry*, vol. 43, no. 11, article e13034, 2019.
- [80] G. Muni Swamy, G. Ramesh, R. Devi Prasad, and B. Meriga, "Astragaloside, (3-O-glucoside of kaempferol), isolated from *Moringa oleifera* leaves modulates leptin, adiponectin secretion and inhibits adipogenesis in 3T3-L1 adipocytes," *Archives of Physiology and Biochemistry*, pp. 1–7, 2020.
- [81] S. Gomez-Zorita, A. Lasa, N. Abendaño et al., "Phenolic compounds apigenin, hesperidin and kaempferol reduce in vitro lipid accumulation in human adipocytes," *Journal of Translational Medicine*, vol. 15, no. 1, p. 237, 2017.
- [82] K. Pallauf, N. Duckstein, M. Hasler, L. O. Klotz, and G. Rimbach, "Flavonoids as putative inducers of the transcription factors Nrf2, FoxO, and PPAR $\gamma$ ," *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 4397340, 11 pages, 2017.
- [83] Y. Cai, C. Fan, J. Yan, N. Tian, and X. Ma, "Effects of rutin on the expression of PPAR $\gamma$  in skeletal muscles of db/db mice," *Planta Medica*, vol. 78, no. 9, pp. 861–865, 2012.
- [84] C. H. Chung, "Rutin stimulates adipocyte differentiation and adiponectin secretion in 3T3-L1 adipocytes," *Journal of the Medical Association of Thailand*, vol. 98, no. 3, pp. S1–S6, 2015.
- [85] N. Chen, T. Lei, L. Xin et al., "Depot-specific effects of treadmill running and rutin on white adipose tissue function in diet-induced obese mice," *Journal of Physiology and Biochemistry*, vol. 72, no. 3, pp. 453–467, 2016.
- [86] S. Seo, M. S. Lee, E. Chang et al., "Rutin increases muscle mitochondrial biogenesis with AMPK activation in high-fat diet-induced obese rats," *Nutrients*, vol. 7, no. 9, pp. 8152–8169, 2015.
- [87] Y. H. Han, J. Y. Kee, J. Park et al., "Lipin1-mediated repression of adipogenesis by rutin," *The American Journal of Chinese Medicine*, vol. 44, no. 3, pp. 565–578, 2016.
- [88] Q. H. Hu, X. Zhang, Y. Pan, Y. C. Li, and L. D. Kong, "Allopurinol, quercetin and rutin ameliorate renal NLRP3 inflammasome activation and lipid accumulation in fructose-fed rats," *Biochemical Pharmacology*, vol. 84, no. 1, pp. 113–125, 2012.
- [89] M. M. Almutairi, W. A. Alanazi, M. A. Alshammari et al., "Neuro-protective effect of rutin against Cisplatin-induced neurotoxic rat model," *BMC Complementary and Alternative Medicine*, vol. 17, no. 1, pp. 1–9, 2017.
- [90] K. Gamo, H. Miyachi, K. Nakamura, and N. Matsuura, "Hesperetin glucuronides induce adipocyte differentiation via activation and expression of peroxisome proliferator-activated receptor- $\gamma$ ," *Bioscience, Biotechnology, and Biochemistry*, vol. 78, no. 6, pp. 1052–1059, 2014.
- [91] J. Y. Chen, C. C. Chu, S. Y. Chen, and P. Der Duh, "Inhibitory effect on lipid accumulation: comparison between two polymethoxyflavones, tangeretin and nobiletin, and one flavonoid, hesperetin, in 3T3-L1 adipocytes," *Biomedical Journal of Scientific & Technical Research*, vol. 3, no. 1, pp. 3049–3053, 2018.
- [92] X. Chen, H. W. Ding, H. D. Li et al., "Hesperetin derivative-14 alleviates inflammation by activating PPAR- $\gamma$  in mice with CCl<sub>4</sub>-induced acute liver injury and LPS-treated RAW264. 7 cells," *Toxicology Letters*, vol. 274, no. 274, pp. 51–63, 2017.
- [93] P. Bhargava, V. K. Verma, S. Malik, S. I. Khan, J. Bhatia, and D. S. Arya, "Hesperidin regresses cardiac hypertrophy by virtue of PPAR- $\gamma$  agonistic, anti-inflammatory, antiapoptotic, and antioxidant properties," *Journal of Biochemical and Molecular Toxicology*, vol. 33, no. 5, article e22283, 2019.
- [94] Y. O. Agrawal, P. K. Sharma, B. Shrivastava et al., "Hesperidin produces cardioprotective activity via PPAR- $\gamma$  pathway in ischemic heart disease model in diabetic rats," *PLoS One*, vol. 9, no. 11, article e111212, 2014.
- [95] C. Meng, Z. Guo, D. Li et al., "Preventive effect of hesperidin modulates inflammatory responses and antioxidant status following acute myocardial infarction through the expression of PPAR- $\gamma$  and Bcl-2 in model mice," *Molecular Medicine Reports*, vol. 17, no. 1, pp. 1261–1268, 2018.
- [96] A. Ghorbani, M. Nazari, M. Jeddi-Tehrani, and H. Zand, "The citrus flavonoid hesperidin induces p53 and inhibits NF- $\kappa$ B activation in order to trigger apoptosis in NALM-6 cells: involvement of PPAR $\gamma$ -dependent mechanism," *European Journal of Nutrition*, vol. 51, no. 1, pp. 39–46, 2012.
- [97] A. M. Mahmoud, "Hesperidin protects against cyclophosphamide-induced hepatotoxicity by upregulation of PPAR $\gamma$  and abrogation of oxidative stress and inflammation," *Canadian Journal of Physiology and Pharmacology*, vol. 92, no. 9, pp. 717–724, 2014.
- [98] P. Jaiswal, M. Mandal, and A. Mishra, "Effect of hesperidin on fluoride-induced neurobehavioral and biochemical changes in rats," *Journal of Biochemical and Molecular Toxicology*, vol. 34, no. 11, article e22575, 2020.
- [99] F. Hadrach and S. Sayadi, "Apigenin inhibits adipogenesis in 3T3-L1 cells by downregulating PPAR $\gamma$  and CEBP- $\alpha$ ," *Lipids in Health and Disease*, vol. 17, no. 1, pp. 1–8, 2018.
- [100] T. Su, C. Huang, C. Yang et al., "Apigenin inhibits STAT3/CD36 signaling axis and reduces visceral obesity," *Pharmacological Research*, vol. 152, article 104586, 2020.
- [101] X. Feng, D. Weng, F. Zhou et al., "Activation of PPAR $\gamma$  by a natural flavonoid modulator, apigenin ameliorates obesity-related inflammation via regulation of macrophage polarization," *EBioMedicine*, vol. 9, pp. 61–76, 2016.
- [102] J. Ji, Q. Yu, W. Dai et al., "Apigenin alleviates liver fibrosis by inhibiting hepatic stellate cell activation and autophagy via TGF- $\beta$ 1/Smad3 and p38/PPAR $\alpha$  pathways," *PPAR Research*, vol. 2021, 15 pages, 2021.
- [103] X. Feng, W. Yu, X. Li et al., "Apigenin, a modulator of PPAR $\gamma$ , attenuates HFD-induced NAFLD by regulating hepatocyte lipid metabolism and oxidative stress via Nrf2 activation," *Biochemical Pharmacology*, vol. 136, pp. 136–149, 2017.

- [104] Z. Y. Zhu, T. Gao, Y. Huang, J. Xue, and M. L. Xie, "Apigenin ameliorates hypertension-induced cardiac hypertrophy and down-regulates cardiac hypoxia inducible factor-1 $\alpha$  in rats," *Food & Function*, vol. 7, no. 4, pp. 1992–1998, 2016.
- [105] U. B. Mahajan, G. Chandrayan, C. R. Patil et al., "The protective effect of apigenin on myocardial injury in diabetic rats mediating activation of the PPAR- $\gamma$  pathway," *International Journal of Molecular Sciences*, vol. 18, no. 4, p. 756, 2017.
- [106] R. Li, X. Wang, T. Qin, R. Qu, and S. Ma, "Apigenin ameliorates chronic mild stress-induced depressive behavior by inhibiting interleukin-1 $\beta$  production and NLRP3 inflammatory activation in the rat brain," *Behavioural Brain Research*, vol. 296, pp. 318–325, 2016.
- [107] X. Zhou, T. Gao, X. G. Jiang, and M. L. Xie, "Protective effect of apigenin on bleomycin-induced pulmonary fibrosis in mice by increments of lung antioxidant ability and PPAR $\gamma$  expression," *Journal of Functional Foods*, vol. 24, no. 24, pp. 382–389, 2016.
- [108] J. Y. Ke, K. L. Kliewer, E. M. Hamad et al., "The flavonoid, naringenin, decreases adipose tissue mass and attenuates ovariectomy-associated metabolic disturbances in mice," *Nutrition & Metabolism*, vol. 12, no. 1, 2015.
- [109] J. Liang, C. Wang, J. Peng et al., "Naringin regulates cholesterol homeostasis and inhibits inflammation via modulating NF- $\kappa$ B and ERK signaling pathways in vitro," *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, vol. 71, no. 2, pp. 101–108, 2016.
- [110] K. W. Cho, Y. O. Kim, J. E. Andrade, J. R. Burgess, and Y. C. Kim, "Dietary naringenin increases hepatic peroxisome proliferators-activated receptor  $\alpha$  protein expression and decreases plasma triglyceride and adiposity in rats," *European Journal of Nutrition*, vol. 50, no. 2, pp. 81–88, 2011.
- [111] J. Goldwasser, P. Y. Cohen, E. Yang, P. Balaguer, M. L. Yarmush, and Y. Nahmias, "Transcriptional regulation of human and rat hepatic lipid metabolism by the grapefruit flavonoid naringenin: role of PPAR $\alpha$ , PPAR $\gamma$  and LXR $\alpha$ ," *PLoS One*, vol. 5, no. 8, article e12399, 2010.
- [112] J. Zhang, H. Qiu, J. Huang et al., "EETs/PPARs activation together mediates the preventive effect of naringenin in high glucose-induced cardiomyocyte hypertrophy," *Bio-medicine & Pharmacotherapy*, vol. 109, no. 109, pp. 1498–1505, 2019.
- [113] J. Cui, G. Wang, A. D. Kandhare, A. A. Mukherjee-Kandhare, and S. L. Bodhankar, "Neuroprotective effect of naringin, a flavone glycoside in quinolinic acid-induced neurotoxicity: Possible role of PPAR- $\gamma$ , Bax/Bcl-2, and caspase-3," *Food and Chemical Toxicology*, vol. 121, pp. 95–108, 2018.
- [114] X. Liu, M. Liu, Y. Mo et al., "Naringin ameliorates cognitive deficits in streptozotocin-induced diabetic rats," *Iranian Journal of Basic Medical Sciences*, vol. 19, no. 4, pp. 417–422, 2016.
- [115] H. Yoshida, R. Tshako, T. Atsumi et al., "Naringenin interferes with the anti-diabetic actions of pioglitazone via pharmacodynamic interactions," *Journal of Natural Medicines*, vol. 71, no. 2, pp. 442–448, 2017.
- [116] Z. Qi, Y. Xu, Z. Liang et al., "Naringin ameliorates cognitive deficits via oxidative stress, proinflammatory factors and the PPAR $\gamma$  signaling pathway in a type 2 diabetic rat model," *Molecular Medicine Reports*, vol. 12, no. 5, pp. 7093–7101, 2015.
- [117] A. K. Sharma, S. Bharti, S. Ojha et al., "Up-regulation of PPAR $\gamma$ , heat shock protein-27 and -72 by naringin attenuates insulin resistance,  $\beta$ -cell dysfunction, hepatic steatosis and kidney damage in a rat model of type 2 diabetes," *British Journal of Nutrition*, vol. 106, no. 11, pp. 1713–1723, 2011.
- [118] H. J. Lin, K. L. Ku, I. H. Lin, and C. C. Yeh, "Naringenin attenuates hepatitis B virus X protein-induced hepatic steatosis," *BMC Complementary and Alternative Medicine*, vol. 17, no. 1, p. 505, 2017.
- [119] S. Ding, H. Qiu, J. Huang et al., "Activation of 20-HETE/PPARs involved in reno-therapeutic effect of naringenin on diabetic nephropathy," *Chemico-Biological Interactions*, vol. 307, pp. 116–124, 2019.
- [120] F. Li, C. Gao, P. Yan et al., "EGCG reduces obesity and white adipose tissue gain partly through AMPK activation in mice," *Frontiers in Pharmacology*, vol. 9, p. 1366, 2018.
- [121] H. Kim and K. Sakamoto, "(–)-Epigallocatechin gallate suppresses adipocyte differentiation through the MEK/ERK and PI3K/Akt pathways," *Cell Biology International*, vol. 36, no. 2, pp. 147–153, 2012.
- [122] Y. Tian, C. Yang, Q. Yao et al., "Procyanidin B2 activates PPAR $\gamma$  to induce M2 polarization in mouse macrophages," *Frontiers in Immunology*, vol. 10, p. 1895, 2019.
- [123] Y. Lu, J. Chen, T. Xian et al., "Epigallocatechin-3-gallate suppresses differentiation of adipocytes via regulating the phosphorylation of FOXO1 mediated by PI3K-AKT signaling in 3T3-L1 cells," *Oncotarget*, vol. 9, no. 7, pp. 7411–7423, 2018.
- [124] A. Nur, R. Ratnawati, and D. Lyrwati, "Catechins of GMB-4 clone inhibits adipogenesis through PPAR- $\gamma$  and adiponectin in primary culture of visceral preadipocyte of Rattus Norvegicus Wistar," *Research Journal of Life Science*, vol. 5, no. 1, pp. 54–65, 2018.
- [125] J. Zhang, K. Wu, T. Xu et al., "Epigallocatechin-3-gallate enhances the osteoblastogenic differentiation of human adipose-derived stem cells," *Drug Design, Development and Therapy*, vol. 13, pp. 1311–1321, 2019.
- [126] Y. Jiang, S. Ding, F. Li et al., "Effects of (+)-catechin on the differentiation and lipid metabolism of 3T3-L1 adipocytes," *Journal of Functional Foods*, vol. 62, article 103558, 2019.
- [127] S. Zhang, X. Yang, J. Luo et al., "PPAR $\alpha$  activation sensitizes cancer cells to epigallocatechin-3-gallate (EGCG) treatment via suppressing heme oxygenase-1," *Nutrition and Cancer*, vol. 66, no. 2, pp. 315–324, 2014.
- [128] Y. Liu, B. Zhao, G. Mao et al., "Epigallocatechin-3-O-gallate, a green tea polyphenol, induces expression of pim-1 kinase via PPAR $\gamma$  in human vascular endothelial cells," *Cardiovascular Toxicology*, vol. 13, no. 4, pp. 391–395, 2013.
- [129] Z. X. Zhang, Y. B. Li, and R. P. Zhao, "Epigallocatechin gallate attenuates  $\beta$ -amyloid generation and oxidative stress involvement of PPAR $\gamma$  in N2a/APP695 cells," *Neurochemical Research*, vol. 42, no. 2, pp. 468–480, 2017.
- [130] T. Ye, J. Zhen, Y. Du et al., "Green tea polyphenol (–)-epigallocatechin-3-gallate restores Nrf2 activity and ameliorates crescentic glomerulonephritis," *PLoS One*, vol. 10, no. 3, article e0119543, 2015.
- [131] S. Y. Cao, C. N. Zhao, R. Y. Gan et al., "Effects and mechanisms of tea and its bioactive compounds for the prevention and treatment of cardiovascular diseases: an updated review," *Antioxidants*, vol. 8, no. 6, p. 166, 2019.
- [132] G. Zhou, M. Yan, G. Guo, and N. Tong, "Ameliorative effect of berberine on neonatally induced type 2 diabetic neuropathy via modulation of BDNF, IGF-1, PPAR- $\gamma$ , and AMPK expressions," *Dose-Response*, vol. 17, no. 3, 2019.

- [133] J. Zhou and S. Zhou, "Berberine regulates peroxisome proliferator-activated receptors and positive transcription elongation factor b expression in diabetic adipocytes," *European Journal of Pharmacology*, vol. 649, no. 1-3, pp. 390-397, 2010.
- [134] X. Xu, X. P. Zhu, J. Y. Bai et al., "Berberine alleviates nonalcoholic fatty liver induced by a high-fat diet in mice by activating SIRT3," *The FASEB Journal*, vol. 33, no. 6, pp. 7289-7300, 2019.
- [135] Q. Zhang, X. Xiao, K. Feng et al., "Berberine moderates glucose and lipid metabolism through multipathway mechanism," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 924851, 10 pages, 2011.
- [136] Y. L. Chow, M. Sogame, and F. Sato, "13-Methylberberine, a berberine analogue with stronger anti-adipogenic effects on mouse 3T3-L1 cells," *Scientific Reports*, vol. 6, no. 1, 2016.
- [137] H. Yu, C. Li, J. Yang, T. Zhang, and Q. Zhou, "Berberine is a potent agonist of peroxisome proliferator activated receptor alpha," *Frontiers in Bioscience*, vol. 21, no. 5, pp. 1052-1060, 2016.
- [138] W. Zhao, L. Liu, Y. Wang, T. Mao, and J. Li, "Effects of a combination of puerarin, baicalin and berberine on the expression of proliferator-activated receptor- $\gamma$  and insulin receptor in a rat model of nonalcoholic fatty liver disease," *Experimental and Therapeutic Medicine*, vol. 11, no. 1, pp. 183-190, 2016.
- [139] Y. Wu, F. Chen, X. Huang et al., "Berberine (BBR) attenuated palmitic acid (PA)-induced lipotoxicity in human HK-2 cells by promoting peroxisome proliferator-activated receptor  $\alpha$  (PPAR- $\alpha$ )," *Medical Science Monitor*, vol. 25, pp. 7702-7708, 2019.
- [140] H. Qiu, Y. Wu, Q. Wang et al., "Effect of berberine on PPAR $\alpha$ -NO signalling pathway in vascular smooth muscle cell proliferation induced by angiotensin IV," *Pharmaceutical Biology*, vol. 55, no. 1, pp. 227-232, 2017.
- [141] M. Wang, J. Wang, R. Tan et al., "Effect of Berberine on PPAR $\alpha$ /NO Activation in High Glucose- and Insulin-Induced Cardiomyocyte Hypertrophy," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 285489, 9 pages, 2013.
- [142] X. Yu, S. Wang, J. Wang, J. Gong, J. Shi, and S. Yu, "Berberine induces CYP2J2 expression in human U251 glioma cells via regulation of peroxisome proliferator-activated receptor alpha," *Pharmacology*, vol. 105, no. 5-6, pp. 360-368, 2020.
- [143] S. Chandra, A. Roy, M. Jana, and K. Pahan, "Cinnamic acid activates PPAR $\alpha$  to stimulate Lysosomal biogenesis and lower Amyloid plaque pathology in an Alzheimer's disease mouse model," *Neurobiology of Disease*, vol. 124, pp. 379-395, 2019.
- [144] Y. Wu, M. H. Wang, T. Yang et al., "Cinnamic acid ameliorates nonalcoholic fatty liver disease by suppressing hepatic lipogenesis and promoting fatty acid oxidation," vol. 2021, Article ID 9561613, 13 pages, 2021.
- [145] T. Prorok, M. Jana, D. Patel, and K. Pahan, "Cinnamic acid protects the nigrostriatum in a mouse model of Parkinson's disease via peroxisome proliferator-activated receptor $\alpha$ ," *Neurochemical Research*, vol. 44, no. 4, pp. 751-762, 2019.
- [146] J. R. Martínez-Rosas, R. Díaz-Torres, P. Ramírez-Noguera, L. D. López-Barrera, J. J. Escobar-Chavez, and E. R. Angeles, "PLGA nanoparticles of a new cinnamic acid derivative inhibits cellular proliferation on breast cancer cell line MCF-7 in a PPAR $\gamma$  dependent way," *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, vol. 75, no. 7, pp. 324-328, 2020.
- [147] X. Huo, S. Yang, X. Sun, X. Meng, and Y. Zhao, "Protective effect of glycyrrhizic acid on alcoholic liver injury in rats by modulating lipid metabolism," *Molecules*, vol. 23, no. 7, p. 1623, 2018.
- [148] C. Yoke Yin, T. So Ha, and K. K. Abdul, "Effects of Glycyrrhizic Acid on Peroxisome Proliferator-Activated Receptor Gamma (PPAR), Lipoprotein Lipase (LPL), Serum Lipid and HOMA-IR in Rats," *PPAR Research*, vol. 2010, Article ID 530265, 6 pages, 2010.
- [149] C. Z. Chang, S. C. Wu, and A. L. Kwan, "Glycyrrhizin attenuates proinflammatory cytokines through a peroxisome proliferator-activated receptor- $\gamma$ -dependent mechanism and experimental vasospasm in a rat model," *Journal of Vascular Research*, vol. 52, no. 1, pp. 12-21, 2015.
- [150] J. Sun, H. Y. Liu, C. Z. Lv, J. Qin, and Y. F. Wu, "Modification, antitumor activity, and targeted PPAR $\gamma$  study of 18 $\beta$ -glycyrrhetic acid, an important active ingredient of licorice," *Journal of Agricultural and Food Chemistry*, vol. 67, no. 34, pp. 9643-9651, 2019.
- [151] H. P. Yaw, S. H. Ton, K. A. Kadir, T. Y. Tan, Y. W. Teo, and M. Yohanes, "Effects of glycyrrhetic acid (GE) on some gluconeogenic enzymes, lipoprotein lipase and peroxisome proliferator-activated receptors alpha and gamma," *The Open Bioactive Compounds Journal*, vol. 4, no. 1, pp. 14-24, 2013.
- [152] M. Mosana, A. Ayeleso, T. Nyakudya, K. Erlwanger, and E. Mukwevho, "Potential protective effects of neonatal supplementation with oleanolic acid on peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ )-ligand dependent regulation of glucose homeostasis in high fructose-fed rats," *Natural Product Communications*, vol. 15, no. 3, 2020.
- [153] Z. Zhang, M. Jiang, X. Xie et al., "Oleanolic acid ameliorates high glucose-induced endothelial dysfunction via PPAR $\delta$  activation," *Scientific Reports*, vol. 7, no. 1, pp. 1-8, 2017.
- [154] H. Loza-Rodríguez, S. Estrada-Soto, F. J. Alarcón-Aguilar et al., "Oleanolic acid induces a dual agonist action on PPAR $\gamma/\alpha$  and GLUT4 translocation: a pentacyclic triterpene for dyslipidemia and type 2 diabetes," *European Journal of Pharmacology*, vol. 883, no. 883, article 173252, 2020.
- [155] W. Wang, K. Chen, Y. Xia et al., "The hepatoprotection by oleanolic acid preconditioning: focusing on PPAR $\alpha$  activation," *PPAR Research*, vol. 2018, 14 pages, 2018.
- [156] H. Luo, J. Liu, Q. Ouyang et al., "The effects of oleanolic acid on atherosclerosis in different animal models," *Acta biochimica et biophysica Sinica*, vol. 49, no. 4, pp. 349-354, 2017.
- [157] W. Li, X. T. Yan, Y. N. Sun, T. T. Ngan, S. H. Shim, and Y. H. Kim, "Anti-inflammatory and PPAR transactivational effects of oleanane-type triterpenoid saponins from the roots of *Pulsatilla koreana*," *Biomolecules & Therapeutics*, vol. 22, no. 4, pp. 334-340, 2014.
- [158] Y. L. Wang, Z. J. Wang, H. L. Shen, M. Yin, and K. X. Tang, "Effects of artesunate and ursolic acid on hyperlipidemia and its complications in rabbit," *European Journal of Pharmaceutical Sciences*, vol. 50, no. 3-4, pp. 366-371, 2013.
- [159] Y. Wang, Z. He, and S. Deng, "Ursolic acid reduces the metalloprotease/anti-metalloprotease imbalance in cerebral ischemia and reperfusion injury," *Drug Design, Development and Therapy*, vol. 10, p. 1663, 2016.

- [160] Y. Zhang, C. Song, H. Li, J. Hou, and D. Li, "Ursolic acid prevents augmented peripheral inflammation and inflammatory hyperalgesia in high-fat diet-induced obese rats by restoring downregulated spinal PPAR $\alpha$ ," *Molecular Medicine Reports*, vol. 13, no. 6, pp. 5309–5316, 2016.
- [161] A. Enayati, A. Salehi, M. Alilou et al., "Six new triterpenoids from the root of *Potentilla reptans* and their cardioprotective effects in silico," *Natural Product Research*, vol. 1, pp. 1–9, 2022.
- [162] X. Gao, Z. Zhang, X. Li et al., "Ursolic acid improves monocrotaline-induced right ventricular remodeling by regulating metabolism," *Journal of Cardiovascular Pharmacology*, vol. 75, no. 6, pp. 545–555, 2020.
- [163] Y. Jia, M. J. Bhuiyan, H. J. Jun et al., "Ursolic acid is a PPAR- $\alpha$  agonist that regulates hepatic lipid metabolism," *Bioorganic & Medicinal Chemistry Letters*, vol. 21, no. 19, pp. 5876–5880, 2011.
- [164] Y. Zhang, X. Li, B. Ciric et al., "A dual effect of ursolic acid to the treatment of multiple sclerosis through both immunomodulation and direct remyelination," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 117, no. 16, pp. 9082–9093, 2020.
- [165] S. H. Kim, J. H. Hong, and Y. C. Lee, "Ursolic acid, a potential PPAR $\gamma$  agonist, suppresses ovalbumin-induced airway inflammation and Penh by down-regulating IL-5, IL-13, and IL-17 in a mouse model of allergic asthma," *European Journal of Pharmacology*, vol. 701, no. 1–3, pp. 131–143, 2013.
- [166] J. J. Junco, J. Cho, A. Mancha et al., "Role of AMPK and PPAR $\alpha$  in the anti-skin cancer effects of ursolic acid," *Molecular Carcinogenesis*, vol. 57, no. 12, pp. 1698–1706, 2018.
- [167] Q. Han, Q. Yuan, X. Meng, J. Huo, Y. Bao, and G. Xie, "6-Shogaol attenuates LPS-induced inflammation in BV2 microglia cells by activating PPAR- $\gamma$ ," *Oncotarget*, vol. 8, no. 26, pp. 42001–42006, 2017.
- [168] I. Bischoff-Kont and R. Fürst, "Benefits of ginger and its constituent 6-shogaol in inhibiting inflammatory processes," *Pharmaceuticals*, vol. 14, no. 6, p. 571, 2021.
- [169] S. H. Chan, P. M. Chu, C. L. Kao, Y. H. Cheng, C. H. Hung, and K. L. Tsai, "Oleic acid activates MMPs up-regulation through SIRT1/PPAR- $\gamma$  inhibition: a probable linkage between obesity and coronary arterial disease," *The Journal of Biochemistry*, vol. 160, no. 4, pp. 217–225, 2016.
- [170] T. H. Fatoki, C. O. Akintayo, and O. Ibraheem, "Bioinformatics exploration of olive oil: molecular targets and properties of major bioactive constituents," *OCL*, vol. 28, p. 36, 2021.
- [171] H. T. Wu, W. Chen, K. C. Cheng, P. M. Ku, C. H. Yeh, and J. T. Cheng, "Oleic acid activates peroxisome proliferator-activated receptor  $\delta$  to compensate insulin resistance in *steatotic* cells," *The Journal of nutritional biochemistry*, vol. 23, no. 10, pp. 1264–1270, 2012.
- [172] M. Ebrahimi, M. A. Rajian, G. Y. Meng, A. S. Farjam, E. Oskoueian, and S. Jafari, "Diet high in  $\alpha$ -linolenic acid up-regulate PPAR- $\alpha$  gene expression in the liver of goats," *Electronic Journal of Biotechnology*, vol. 18, no. 3, pp. 210–214, 2015.
- [173] N. Riera-Heredia, E. Lutfi, J. Gutiérrez, I. Navarro, and E. Capilla, "Fatty acids from fish or vegetable oils promote the adipogenic fate of mesenchymal stem cells derived from gilthead sea bream bone potentially through different pathways," *PLoS One*, vol. 14, no. 4, article e0215926, 2019.
- [174] L. Zhang, F. Tian, X. Gao et al., "N-3 polyunsaturated fatty acids improve liver lipid oxidation-related enzyme levels and increased the peroxisome proliferator-activated receptor  $\alpha$  expression level in mice subjected to hemorrhagic shock/resuscitation," *Nutrients*, vol. 8, no. 4, p. 237, 2016.
- [175] H. Yu, Y. Liu, W. Pan, S. Shen, and U. N. Das, "Polyunsaturated fatty acids augment tumoricidal action of 5-fluorouracil on gastric cancer cells by their action on vascular endothelial growth factor, tumor necrosis factor- $\alpha$  and lipid metabolism related factors," *Archives of Medical Science*, vol. 11, no. 2, pp. 282–291, 2015.
- [176] J. Yeung, R. Adili, A. Yamaguchi et al., "Omega-6 DPA and its 12-lipoxygenase-oxidized lipids regulate platelet reactivity in a nongenomic PPAR $\alpha$ -dependent manner," *Blood Advances*, vol. 4, no. 18, pp. 4522–4537, 2020.
- [177] J. Yao, Y. Lu, M. Zhi, P. Hu, W. Wu, and X. Gao, "Dietary n-3 polyunsaturated fatty acids ameliorate Crohn's disease in rats by modulating the expression of PPAR- $\gamma$ /NFAT," *Molecular Medicine Reports*, vol. 16, no. 6, pp. 8315–8322, 2017.
- [178] S. Lin, J. Hou, F. Xiang et al., "Mammary inflammation around parturition appeared to be attenuated by consumption of fish oil rich in n-3 polyunsaturated fatty acids," *Lipids in Health and Disease*, vol. 12, no. 1, pp. 1–3, 2013.
- [179] K. G. Linghu, G. P. Wu, L. Y. Fu et al., "1, 8-Cineole ameliorates LPS-induced vascular endothelium dysfunction in mice via PPAR- $\gamma$  dependent regulation of NF- $\kappa$ B," *Frontiers in Pharmacology*, vol. 10, p. 178, 2019.
- [180] J. E. Li, K. Futawaka, H. Yamamoto et al., "Cinnamaldehyde contributes to insulin sensitivity by activating PPAR $\delta$ , PPAR $\gamma$ , and RXR," *The American Journal of Chinese Medicine*, vol. 43, no. 5, pp. 879–892, 2015.
- [181] M. Hotta, R. Nakata, M. Katsukawa, K. Hori, S. Takahashi, and H. Inoue, "Carvacrol, a component of thyme oil, activates PPAR $\alpha$  and  $\gamma$  and suppresses COX-2 expression," *Journal of Lipid Research*, vol. 51, no. 1, pp. 132–139, 2010.
- [182] J. S. Chia, A. A. Farouk, T. A. Mohamad et al., "Zerubone ameliorates neuropathic pain symptoms via cannabinoid and PPAR receptors using in vivo and in silico models," *Molecules*, vol. 26, no. 13, p. 3849, 2021.
- [183] Y. Lu, Y. Sun, J. Zhu et al., "Oridonin exerts anticancer effect on osteosarcoma by activating PPAR- $\gamma$  and inhibiting Nrf2 pathway," *Cell Death & Disease*, vol. 9, no. 1, pp. 1–6, 2018.
- [184] L. Huang, W. Ding, M. Q. Wang et al., "Tanshinone IIA ameliorates non-alcoholic fatty liver disease through targeting peroxisome proliferator-activated receptor gamma and toll-like receptor 4," *Journal of International Medical Research*, vol. 47, no. 10, pp. 5239–5255, 2019.
- [185] C. Liu, Y. J. Shen, Q. B. Tu et al., "Pedunculoside, a novel triterpene saponin extracted from *Ilex rotunda*, ameliorates high-fat diet induced hyperlipidemia in rats," *Biomedicine & Pharmacotherapy*, vol. 101, pp. 608–616, 2018.
- [186] N. Ba Ngoc, P. Lv, and W. E. Zhao, "Suppressive effects of lycopene and  $\beta$ -carotene on the viability of the human esophageal squamous carcinoma cell line EC109," *Oncology Letters*, vol. 15, no. 5, pp. 6727–6732, 2018.
- [187] G. Brusotti, R. Montanari, D. Capelli et al., "Betulinic acid is a PPAR $\gamma$  antagonist that improves glucose uptake, promotes osteogenesis and inhibits adipogenesis," *Scientific Reports*, vol. 7, no. 1, pp. 1–4, 2017.

- [188] W. Mo, C. Wang, J. Li et al., "Fucosterol protects against concanavalin A-induced acute liver injury: focus on P38 MAPK/NF- $\kappa$ B pathway activity," *Gastroenterology Research and Practice*, vol. 2018, Article ID 2824139, 13 pages, 2018.
- [189] A. M. Mahmoud, W. G. Hozayen, I. H. Hasan, E. Shaban, and M. Bin-Jumah, "Umbelliferone ameliorates CCl<sub>4</sub>-induced liver fibrosis in rats by upregulating PPAR $\gamma$  and attenuating oxidative stress, inflammation, and TGF- $\beta$ 1/Smad3 signaling," *Inflammation*, vol. 42, no. 3, pp. 1103–1116, 2019.
- [190] W. Zheng, L. Qiu, R. Wang et al., "Selective targeting of PPAR $\gamma$  by the natural product chelerythrine with a unique binding mode and improved antidiabetic potency," *Scientific Reports*, vol. 5, no. 1, pp. 1–2, 2015.
- [191] M. Jamilian, M. Samimi, N. Mirhosseini et al., "A randomized double-blinded, placebo-controlled trial investigating the effect of fish oil supplementation on gene expression related to insulin action, blood lipids, and inflammation in gestational diabetes mellitus-fish oil supplementation and gestational diabetes," *Nutrients*, vol. 10, no. 2, p. 163, 2018.
- [192] O. R. Tamtaji, M. Taghizadeh, E. Aghadavod et al., "The effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial," *Clinical Neurology and Neurosurgery*, vol. 176, pp. 116–121, 2019.
- [193] M. Jamilian, A. Shojaei, M. Samimi et al., "The effects of omega-3 and vitamin E co-supplementation on parameters of mental health and gene expression related to insulin and inflammation in subjects with polycystic ovary syndrome," *Journal of Affective Disorders*, vol. 229, pp. 41–47, 2018.
- [194] M. Jamilian, Z. Tabassi, Ž. Reiner et al., "The effects of n-3 fatty acids from flaxseed oil on genetic and metabolic profiles in patients with gestational diabetes mellitus: a randomized, double-blind, placebo-controlled trial," *British Journal of Nutrition*, vol. 123, no. 7, pp. 792–799, 2020.
- [195] C. M. Mejía-Barradas, B. E. Del-Río-Navarro, A. Domínguez-López et al., "The consumption of n-3 polyunsaturated fatty acids differentially modulates gene expression of peroxisome proliferator-activated receptor alpha and gamma and hypoxia-inducible factor 1 alpha in subcutaneous adipose tissue of obese adolescents," *Endocrine*, vol. 45, no. 1, pp. 98–105, 2014.
- [196] A. Binia, C. Vargas-Martínez, M. Ancira-Moreno et al., "Improvement of cardiometabolic markers after fish oil intervention in young Mexican adults and the role of PPAR  $\alpha$  L162V and PPAR  $\gamma$ 2 P12A," *Journal of Nutritional Biochemistry*, vol. 43, pp. 98–106, 2017.
- [197] A. AlSaleh, T. A. Sanders, and S. D. O'Dell, "Effect of interaction between PPARG, PPARGA and ADIPOQ gene variants and dietary fatty acids on plasma lipid profile and adiponectin concentration in a large intervention study," *Proceedings of the Nutrition Society*, vol. 71, no. 1, pp. 141–153, 2012.
- [198] S. Rajaram, E. L. Yip, R. Reghunathan, S. Mohan, and J. Sabaté, "Effect of altering dietary n-6:n-3 polyunsaturated fatty acid ratio with plant and marine-based supplement on biomarkers of bone turnover in healthy adults," *Nutrients*, vol. 9, no. 10, p. 1162, 2017.
- [199] K. Nasri, S. Hantoushzadeh, E. Aghadavod, M. Taghizadeh, and Z. Asemi, "The effects of omega-3 fatty acids supplementation on gene expression involved in the insulin and lipid signaling pathway in patients with polycystic ovary syndrome," *Hormone and Metabolic Research*, vol. 49, no. 6, pp. 446–451, 2017.
- [200] N. Zhao, L. Wang, and N. Guo, " $\alpha$ -Linolenic acid increases the G0/G1 switch gene 2 mRNA expression in peripheral blood mononuclear cells from obese patients: a pilot study," *Lipids in Health and Disease*, vol. 15, no. 1, pp. 1–8, 2016.
- [201] R. Shafabakhsh, Z. Asemi, Ž. Reiner, A. Soleimani, E. Aghadavod, and F. Bahmani, "The effects of nano-curcumin on metabolic status in patients with diabetes on hemodialysis, a randomized, double blind, placebo-controlled trial," *Iranian Journal of Kidney Diseases*, vol. 14, no. 4, pp. 290–299, 2020.
- [202] M. Jamilian, F. Foroozand, E. Kavossian et al., "Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial," *Clinical Nutrition ESPEN*, vol. 36, pp. 128–133, 2020.
- [203] C. Vors, C. Couillard, M. E. Paradis et al., "Supplementation with resveratrol and curcumin does not affect the inflammatory response to a high-fat meal in older adults with abdominal obesity: a randomized, placebo-controlled crossover trial," *The Journal of Nutrition*, vol. 148, no. 3, pp. 379–388, 2018.
- [204] N. Murugesan, K. Woodard, R. Ramaraju, F. L. Greenway, A. A. Coulter, and C. J. Rebello, "Naringenin increases insulin sensitivity and metabolic rate: a case study," *Journal of Medicinal Food*, vol. 23, no. 3, pp. 343–348, 2020.
- [205] S. Chatree, C. Sitticharoon, P. Maikaew et al., "Epigallocatechin gallate decreases plasma triglyceride, blood pressure, and serum kisspeptin in obese human subjects," *Experimental Biology and Medicine*, vol. 246, no. 2, pp. 163–176, 2021.
- [206] Y. Pan, D. Zhao, N. Yu et al., "Curcumin improves glycolipid metabolism through regulating peroxisome proliferator activated receptor  $\gamma$  signalling pathway in high-fat diet-induced obese mice and 3T3-L1 adipocytes," *Royal Society Open Science*, vol. 4, no. 11, article 170917, 2017.
- [207] O. A. R. AbouZaid, S. M. EL-sonbaty, and M. W. F. Afifi, "The biochemical effect of Chromium nanoparticles administration on adiponectin secretion, oxidative stress and metabolic disorders in Streptozotocin induced diabetic rats," *Benha Veterinary Medical Journal*, vol. 28, no. 1, pp. 266–275, 2015.
- [208] J. Dai, Y. Li, F. Kametani et al., "Curcumin promotes AApoAII amyloidosis and peroxisome proliferation in mice by activating the PPAR $\alpha$  signaling pathway," *Elife*, vol. 10, article e63538, 2021.
- [209] Y. Y. Li, D. Tang, Y. L. Du et al., "Fatty liver mediated by PPAR- $\alpha$  DNA methylation can be reversed by a methylation inhibitor and curcumin," *Journal of Digestive Diseases*, vol. 19, pp. 421–430, 2018.
- [210] H. Jin, N. Lian, F. Zhang et al., "Activation of PPAR  $\gamma$ /P53 signaling is required for curcumin to induce hepatic stellate cell senescence," *Cell Death & Disease*, vol. 7, no. 4, p. e2189, 2016.
- [211] S. Xu, B. Jiang, H. Wang, C. Shen, H. Chen, and L. Zeng, "Curcumin suppresses intestinal fibrosis by inhibition of PPAR $\gamma$ -mediated epithelial-mesenchymal transition," *Evidence-Based Complementary and Alternative Medicine*, vol. 2017, Article ID 7876064, 12 pages, 2017.
- [212] P. Kumar, C. C. Barua, K. Sulakhiya, and R. K. Sharma, "Curcumin ameliorates cisplatin-induced nephrotoxicity and potentiates its anticancer activity in SD rats: potential role



- of curcumin in breast cancer chemotherapy,” *Frontiers in Pharmacology*, vol. 8, p. 132, 2017.
- [213] Z. Meng, X. H. Yu, J. Chen, L. Li, and S. Li, “Curcumin attenuates cardiac rats through PPAR- $\gamma$  activation,” *Acta Pharmacologica Sinica*, vol. 35, no. 10, pp. 1247–1256, 2014.
- [214] A. A. Gbr, N. A. Baky, E. A. Mohamed, and H. S. Zaky, “Cardioprotective effect of pioglitazone and curcumin against diabetic cardiomyopathy in type 1 diabetes mellitus: impact on CaMKII/NF- $\kappa$ B/TGF- $\beta$ 1 and PPAR- $\gamma$  signaling pathway,” *Naunyn-Schmiedeberg’s Archives of Pharmacology*, vol. 394, no. 2, pp. 349–360, 2021.
- [215] Z. J. Liu, H. Q. Liu, C. Xiao et al., “Curcumin protects neurons against oxygen-glucose deprivation/reoxygenation-induced injury through activation of peroxisome proliferator-activated receptor- $\gamma$  function,” *Journal of Neuroscience Research*, vol. 92, no. 11, pp. 1549–1559, 2014.
- [216] P. Rinwa, B. Kaur, A. S. Jaggi, and N. Singh, “Involvement of PPAR-gamma in curcumin-mediated beneficial effects in experimental dementia,” *Naunyn-Schmiedeberg’s Archives of Pharmacology*, vol. 381, no. 6, pp. 529–539, 2010.
- [217] A. Bernardo, C. Plumitallo, C. De Nuccio, S. Visentin, and L. Minghetti, “Curcumin promotes oligodendrocyte differentiation and their protection against TNF- $\alpha$  through the activation of the nuclear receptor PPAR- $\gamma$ ,” *Scientific Reports*, vol. 11, no. 1, pp. 1–3, 2021.
- [218] S. Kanakasabai, E. Casalini, C. C. Walline, C. Mo, W. Chearwae, and J. J. Bright, “Differential regulation of CD4<sup>+</sup> T helper cell responses by curcumin in experimental autoimmune encephalomyelitis,” *The Journal of Nutritional Biochemistry*, vol. 23, no. 11, pp. 1498–1507, 2012.
- [219] P. N. Mimche, E. Thompson, D. Taramelli, and L. Vivas, “Curcumin enhances non-opsonic phagocytosis of *Plasmodium falciparum* through up-regulation of CD36 surface expression on monocytes/macrophages,” *Journal of Antimicrobial Chemotherapy*, vol. 67, no. 8, pp. 1895–1904, 2012.
- [220] W. San Cheang, W. T. Wong, L. Wang et al., “Resveratrol ameliorates endothelial dysfunction in diabetic and obese mice through sirtuin 1 and peroxisome proliferator-activated receptor  $\delta$ ,” *Pharmacological Research*, vol. 139, pp. 384–394, 2019.
- [221] T. R. Regnault, L. Zhao, J. S. Chiu et al., “Peroxisome Proliferator-Activated Receptor - $\beta/\delta$ , - $\gamma$  Agonists and Resveratrol Modulate Hypoxia Induced Changes in Nuclear Receptor Activators of Muscle Oxidative Metabolism,” *PPAR Research*, vol. 2010, Article ID 129173, 13 pages, 2010.
- [222] S. X. Wang, J. G. Wei, L. L. Chen, X. Hu, and W. Kong, “The role of expression imbalance between adipose synthesis and storage mediated by PPAR- $\gamma$ /FSP27 in the formation of insulin resistance in catch up growth,” *Lipids in Health and Disease*, vol. 15, no. 1, pp. 1–2, 2016.
- [223] V. Castrejón-Tellez, J. M. Rodríguez-Pérez, I. Pérez-Torres et al., “The effect of resveratrol and quercetin treatment on PPAR mediated uncoupling protein (UCP-) 1, 2, and 3 expression in visceral white adipose tissue from metabolic syndrome rats,” *International Journal of Molecular Sciences*, vol. 17, no. 7, p. 1069, 2016.
- [224] T. Tsukamoto, R. Nakata, E. Tamura et al., “A resveratrol tetramer, activates PPAR $\alpha$  and PPAR $\beta/\delta$  in vitro and in vivo,” *Nutrition & Metabolism*, vol. 7, no. 1, pp. 1–8, 2010.
- [225] J. M. Ajmo, X. Liang, C. Q. Rogers, B. Pennock, and M. You, “Resveratrol alleviates alcoholic fatty liver in mice,” *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 295, no. 4, pp. G833–G842, 2008.
- [226] Y. Huang, H. Lang, K. Chen et al., “Resveratrol protects against nonalcoholic fatty liver disease by improving lipid metabolism and redox homeostasis via the PPAR $\alpha$  pathway,” *Applied Physiology, Nutrition, and Metabolism*, vol. 45, no. 3, pp. 227–239, 2020.
- [227] V. Aires, B. Brassart, A. Carlier et al., “A role for peroxisome proliferator-activated receptor gamma in resveratrol-induced colon cancer cell apoptosis,” *Molecular Nutrition & Food Research*, vol. 58, no. 9, pp. 1785–1794, 2014.
- [228] E. L. Rossi, S. A. Khatib, S. S. Doerstling et al., “Resveratrol inhibits obesity-associated adipose tissue dysfunction and tumor growth in a mouse model of postmenopausal claudin-low breast cancer,” *Molecular Carcinogenesis*, vol. 57, no. 3, pp. 393–407, 2018.
- [229] E. N. Kim, J. H. Lim, M. Y. Kim et al., “Resveratrol, an Nrf2 activator, ameliorates aging-related progressive renal injury,” *Aging*, vol. 10, no. 1, pp. 83–99, 2018.
- [230] M. Y. Kim, J. H. Lim, H. H. Youn et al., “Resveratrol prevents renal lipotoxicity and inhibits mesangial cell glucotoxicity in a manner dependent on the AMPK–SIRT1–PGC1 $\alpha$  axis in db/db mice,” *Diabetologia*, vol. 56, no. 1, pp. 204–217, 2013.
- [231] Y. Zhou, S. Lin, L. Zhang, and Y. Li, “Resveratrol prevents renal lipotoxicity in high-fat diet-treated mouse model through regulating PPAR- $\alpha$  pathway,” *Molecular and Cellular Biochemistry*, vol. 411, no. 1–2, pp. 143–150, 2016.
- [232] C. Kalliora, I. D. Kyriazis, S. I. Oka et al., “Dual PPAR $\alpha/\gamma$  activation inhibits SIRT1–PGC1 $\alpha$  axis and causes cardiac dysfunction,” *JCI Insight*, vol. 4, no. 17, 2019.
- [233] I. Voloshyna, O. Hai, M. J. Littlefield, S. Carsons, and A. B. Reiss, “Resveratrol mediates anti-atherogenic effects on cholesterol flux in human macrophages and endothelium via PPAR $\gamma$  and adenosine,” *European Journal of Pharmacology*, vol. 698, no. 1–3, pp. 299–309, 2013.
- [234] A. Planavila, R. Iglesias, M. Giralt, and F. Villarroya, “Sirt1 acts in association with PPAR $\alpha$  to protect the heart from hypertrophy, metabolic dysregulation, and inflammation,” *Cardiovascular Research*, vol. 90, no. 2, pp. 276–284, 2011.
- [235] X. Shen, M. Wang, X. Bi et al., “Resveratrol prevents endothelial progenitor cells from senescence and reduces the oxidative reaction via PPAR- $\gamma$ /HO-1 pathways,” *Molecular Medicine Reports*, vol. 14, no. 6, pp. 5528–5534, 2016.
- [236] C. Rius, M. Abu-Taha, C. Hermenegildo et al., “Trans- but Not Cis-Resveratrol Impairs Angiotensin-II-Mediated Vascular Inflammation through Inhibition of NF- $\kappa$ B Activation and Peroxisome Proliferator-Activated Receptor- $\gamma$  Upregulation,” *The Journal of Immunology*, vol. 185, no. 6, pp. 3718–3727, 2010.
- [237] J. Pan, J. L. Jin, H. M. Ge et al., “Malibatol A regulates microglia M1/M2 polarization in experimental stroke in a PPAR $\gamma$ -dependent manner,” *Journal of Neuroinflammation*, vol. 12, no. 1, 2015.
- [238] L. Zheng, J. Wu, J. Mo, L. Guo, X. Wu, and Y. Bao, “Polydatin inhibits adipose tissue inflammation and ameliorates lipid metabolism in high-fat-fed mice,” *BioMed Research International*, vol. 2019, Article ID 7196535, 10 pages, 2019.
- [239] Z. Huang, G. Tian, S. Cheng et al., “Polydatin attenuates atherosclerosis in ApoE-/- mice through PBEF mediated reduction of cholesterol deposition,” *The American Journal of Chinese Medicine*, vol. 46, no. 8, pp. 1841–1859, 2018.

- [240] H. L. Wang, X. H. Cui, H. L. Yu, R. Wu, X. Xu, and J. P. Gao, "Synergistic effects of polydatin and vitamin C in inhibiting cardiotoxicity induced by doxorubicin in rats," *Fundamental & Clinical Pharmacology*, vol. 31, no. 3, pp. 280–291, 2017.
- [241] W. Ruan, J. Li, Y. Xu et al., "MALAT1 up-regulator polydatin protects brain microvascular integrity and ameliorates stroke through C/EBP $\beta$ /MALAT1/CREB/PGC-1 $\alpha$ /PPAR $\gamma$  pathway," *Cellular and Molecular Neurobiology*, vol. 39, no. 2, pp. 265–286, 2019.
- [242] X. Hu, J. Li, and W. Ma, "Effect of polydatin on the PPAR-r expression in mice with pulmonary fibrosis," *Advances in Integrative Medicine*, vol. 6, article S74, 2019.
- [243] X. D. Yan, Q. M. Wang, C. Tie et al., "Polydatin protects the respiratory system from PM<sub>2.5</sub> exposure," *Scientific Reports*, vol. 7, no. 1, 2017.
- [244] C. Y. Bang, J. H. Byun, H. K. Choi, J. S. Choi, and S. Y. Choung, "Protective effects of Ecklonia stolonifera extract on ethanol-induced fatty liver in rats," *Biomolecules & Therapeutics*, vol. 24, no. 6, pp. 650–658, 2016.
- [245] Y. S. Seo, O. H. Kang, S. B. Kim et al., "Quercetin prevents adipogenesis by regulation of transcriptional factors and lipases in OP9 cells," *International Journal of Molecular Medicine*, vol. 35, no. 6, pp. 1779–1785, 2015.
- [246] L. Sun, E. Li, F. Wang et al., "Quercetin increases macrophage cholesterol efflux to inhibit foam cell formation through activating PPAR $\gamma$ -ABCA1 pathway," *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 9, pp. 10854–10860, 2015.
- [247] T. Funakoshi, N. Kanzaki, Y. Otsuka, T. Izumo, H. Shibata, and S. Machida, "Quercetin inhibits adipogenesis of muscle progenitor cells *in vitro*," *Biochemistry and Biophysics Reports*, vol. 13, pp. 39–44, 2018.
- [248] M. Wang, B. Wang, S. Wang et al., "Effect of quercetin on lipids metabolism through modulating the gut microbial and AMPK/PPAR signaling pathway in broilers," *Frontiers in Cell and Developmental Biology*, vol. 9, p. 165, 2021.
- [249] L. L. Wang, Z. C. Zhang, W. Hassan, Y. Li, J. Liu, and J. Shang, "Amelioration of free fatty acid-induced fatty liver by quercetin-3-O- $\beta$ -D-glucuronide through modulation of peroxisome proliferator-activated receptor- $\alpha$ /sterol regulatory element-binding protein-1c signaling," *Hepatology Research*, vol. 46, no. 2, pp. 225–238, 2016.
- [250] Y. Pei, D. Otieno, I. Gu et al., "Effect of quercetin on nonshivering thermogenesis of brown adipose tissue in high-fat diet-induced obese mice," *The Journal of Nutritional Biochemistry*, vol. 88, article 108532, 2021.
- [251] M. Wang, F. L. Xiao, Y. J. Mao, L. L. Ying, B. Zhou, and Y. Li, "Quercetin decreases the triglyceride content through the PPAR signalling pathway in primary hepatocytes of broiler chickens," *Biotechnology & Biotechnological Equipment*, vol. 33, no. 1, pp. 1000–1010, 2019.
- [252] Y. Zhang, M. Gu, W. Cai et al., "Dietary component isorhamnetin is a PPAR $\gamma$  antagonist and ameliorates metabolic disorders induced by diet or leptin deficiency," *Scientific Reports*, vol. 6, no. 1, 2016.
- [253] S. Wein, N. Behm, R. K. Petersen, K. Kristiansen, and S. Wolfram, "Quercetin enhances adiponectin secretion by a PPAR- $\gamma$  independent mechanism," *European Journal of Pharmaceutical Sciences*, vol. 41, no. 1, pp. 16–22, 2010.
- [254] I. C. Nettore, C. Rocca, G. Mancino et al., "Quercetin and its derivative Q2 modulate chromatin dynamics in adipogenesis and Q2 prevents obesity and metabolic disorders in rats," *The Journal of Nutritional Biochemistry*, vol. 69, pp. 151–162, 2019.
- [255] R. Varshney, R. Mishra, N. Das, D. Sircar, and P. Roy, "A comparative analysis of various flavonoids in the regulation of obesity and diabetes: An *in vitro* and *in vivo* study," *Journal of Functional Foods*, vol. 59, pp. 194–205, 2019.
- [256] X. Sun, M. Yamasaki, T. Katsube, and K. Shiwaku, "Effects of quercetin derivatives from mulberry leaves: improved gene expression related hepatic lipid and glucose metabolism in short-term high-fat fed mice," *Nutrition Research and Practice*, vol. 9, no. 2, pp. 137–143, 2015.
- [257] M. J. Seo, Y. J. Lee, J. H. Hwang, K. J. Kim, and B. Y. Lee, "The inhibitory effects of quercetin on obesity and obesity-induced inflammation by regulation of MAPK signaling," *The Journal of Nutritional Biochemistry*, vol. 26, no. 11, pp. 1308–1316, 2015.
- [258] M. L. Casella, J. P. Parody, M. P. Ceballos et al., "Quercetin prevents liver carcinogenesis by inducing cell cycle arrest, decreasing cell proliferation and enhancing apoptosis," *Molecular Nutrition & Food Research*, vol. 58, no. 2, pp. 289–300, 2014.
- [259] X. Zhang, J. H. Zhang, X. Y. Chen et al., "Reactive oxygen species-induced TXNIP drives fructose-mediated hepatic inflammation and lipid accumulation through NLRP3 inflammasome activation," *Antioxidants & Redox Signaling*, vol. 22, no. 10, pp. 848–870, 2015.
- [260] Á. Rojas, P. Gallego, A. Gil-Gómez et al., "Natural Extracts Abolished Lipid Accumulation in Cells Harboring non-favourable PNPLA3 genotype," *Annals of Hepatology*, vol. 17, no. 2, pp. 242–249, 2018.
- [261] H. N. Choi, S. M. Jeong, G. H. Huh, and J. I. Kim, "Quercetin ameliorates insulin sensitivity and liver steatosis partly by increasing adiponectin expression in ob/ob mice," *Food Science and Biotechnology*, vol. 24, no. 1, pp. 273–279, 2015.
- [262] S. M. Ragab, S. K. Abd Elghaffar, T. H. El-Metwally, G. Badr, M. H. Mahmoud, and H. M. Omar, "Effect of a high fat, high sucrose diet on the promotion of non-alcoholic fatty liver disease in male rats: the ameliorative role of three natural compounds," *Lipids in Health and Disease*, vol. 14, no. 1, p. 83, 2015.
- [263] C. H. Chuang, C. L. Yeh, S. L. Yeh, E. S. Lin, L. Y. Wang, and Y. H. Wang, "Quercetin metabolites inhibit MMP-2 expression in A549 lung cancer cells by PPAR- $\gamma$  associated mechanisms," *The Journal of Nutritional Biochemistry*, vol. 33, pp. 45–53, 2016.
- [264] S. L. Yeh, C. L. Yeh, S. T. Chan, and C. H. Chuang, "Plasma rich in quercetin metabolites induces G2/M arrest by upregulating PPAR- $\gamma$  expression in human A549 lung cancer cells," *Planta Medica*, vol. 77, no. 10, pp. 992–998, 2011.
- [265] L. Ramachandran, K. A. Manu, M. K. Shanmugam et al., "Isorhamnetin Inhibits Proliferation and Invasion and Induces Apoptosis through the Modulation of Peroxisome Proliferator-activated Receptor  $\gamma$  Activation Pathway in Gastric Cancer," *Journal of Biological Chemistry*, vol. 287, no. 45, pp. 38028–38040, 2012.
- [266] J. Wang, Y. Pan, Y. Hong, Q. Y. Zhang, X. N. Wang, and L. D. Kong, "Quercetin protects against cadmium-induced renal uric acid transport system alteration and lipid metabolism

- disorder in rats,” *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 548430, 14 pages, 2012.
- [267] R. L. Castillo, E. A. Herrera, A. Gonzalez-Candia et al., “Quercetin prevents diastolic dysfunction induced by a high-cholesterol diet: role of oxidative stress and bioenergetics in hyperglycemic rats,” *Oxidative Medicine and Cellular Longevity*, vol. 2018, Article ID 7239123, 14 pages, 2018.
- [268] S. R. Shen, W. H. Hsu, C. C. Lee, W. C. Chang, and S. C. Wu, “Buckwheat extracts (*Fagopyrum tataricum*) and rutin attenuate Th2 cytokines production and cellular allergic effects in vitro and in vivo,” *Journal of Functional Foods*, vol. 4, no. 4, pp. 793–799, 2012.
- [269] H. Cao, J. Liu, P. Shen et al., “Protective effect of naringin on DSS-induced ulcerative colitis in mice,” *Journal of Agricultural and Food Chemistry*, vol. 66, no. 50, pp. 13133–13140, 2018.
- [270] C. Guan, S. Qiao, Q. Lv et al., “Orally administered berberine ameliorates bleomycin-induced pulmonary fibrosis in mice through promoting activation of PPAR- $\gamma$  and subsequent expression of HGF in colons,” *Toxicology and Applied Pharmacology*, vol. 343, pp. 1–5, 2018.
- [271] S. F. Dong, Y. Hong, M. Liu et al., “Berberine attenuates cardiac dysfunction in hyperglycemic and hypercholesterolemic rats,” *European Journal of Pharmacology*, vol. 660, no. 2-3, pp. 368–374, 2011.
- [272] H. Li, C. He, J. Wang et al., “Berberine activates peroxisome proliferator-activated receptor gamma to increase atherosclerotic plaque stability in Apoe<sup>-/-</sup> mice with hyperhomocysteinemia,” *Journal of Diabetes Investigation*, vol. 7, no. 6, pp. 824–832, 2016.
- [273] B. S. Tan, O. Kang, C. W. Mai et al., “6-Shogaol inhibits breast and colon cancer cell proliferation through activation of peroxisomal proliferator activated receptor  $\gamma$  (PPAR $\gamma$ ),” *Cancer Letters*, vol. 336, no. 1, pp. 127–139, 2013.
- [274] H. Nie, X. Xue, J. Li et al., “Nitro-oleic acid attenuates OGD/R-triggered apoptosis in renal tubular cells via inhibition of Bax mitochondrial translocation in a PPAR- $\gamma$ -dependent manner,” *Cellular Physiology and Biochemistry*, vol. 35, no. 3, pp. 1201–1218, 2015.
- [275] J. Song, Y. S. Kim, D. H. Lee et al., “Neuroprotective effects of oleic acid in rodent models of cerebral ischaemia,” *Scientific Reports*, vol. 9, no. 1, pp. 1–3, 2019.
- [276] A. Hoseini, G. Namazi, A. Farrokhian et al., “The effects of resveratrol on metabolic status in patients with type 2 diabetes mellitus and coronary heart disease,” *Food & Function*, vol. 10, no. 9, pp. 6042–6051, 2019.