Received: 16 February 2023 | Accepted: 29 April 2023

DOI: 10.1002/fft2.255

FOOD FRONTIERS Open Access

REVIEW ARTICLE

Regulation of autophagy by plant-based polyphenols: A critical review of current advances in glucolipid metabolic diseases and food industry applications

Zhenyu Wang[1,2] | Wei Quan[3] | Maomao Zeng[1,2] | Zhaojun Wang[1,2] | Qiuming Chen[1,2] | Jie Chen[1,2] | Mark Christian[4] | Zhiyong He[1,2]

[1]State Key Laboratory of Food Science and Technology, Jiangnan University, Wuxi, Jiangsu, China

[2]International Joint Laboratory on Food Safety, Jiangnan University, Wuxi, Jiangsu, China

[3]College of Food Science and Technology, Hunan Agricultural University, Changsha, Hunan, China

[4]School of Science and Technology, Nottingham Trent University, Clifton Nottingham, United Kingdom

Correspondence
Mark Christian, School of Science and Technology, Nottingham Trent University, Clifton, Nottingham, NG11 8NS, UK.
Email: mark.christian@ntu.ac.uk

Zhiyong He, State Key Laboratory of Food Science and Technology, Jiangnan University, Wuxi, Jiangsu 214122, China.
Email: zyhe@jiangnan.edu.cn

Funding information
National Key Research and Development Program of China, Grant/Award Number: 2022YFF1100204; National Natural Science Foundation of China, Grant/Award Number: 31771978; Six Talent Peaks Project in Jiangsu Province, Grant/Award Number: NY-095

Abstract

Autophagy is a complex self-degrading process, and its imbalance adversely affects local (metabolically active organs) or systemic metabolism, resulting in metabolic dysfunction correlated with obesity, fatty liver, and type 2 diabetes. Polyphenols are plant secondary metabolites and their ingestion may offer beneficial effects on biological processes, including cell proliferation, cell cycle, apoptosis and autophagy. In this review, the effects of plant-based polyphenols on autophagy and the underlying mechanisms in the regulation of glucolipid metabolic diseases (GLMDs) are examined in the context of potential health benefits. The available evidence, mainly from animal models, strongly supports that polyphenols improve the metabolic functions of different organs by acting on various molecular targets related to autophagic flux. Multiple autophagic pathways, including cAMP, AMPK, MAPK, AKT, SIRT1, PI3K, Nrf2/HO-1, PINK1/Parkin, PPARδ, and miRNAs have been implicated in the improvement of GLMDs by polyphenols. Moreover, the potential utilization of polyphenol-meditated autophagy in the food industry was discussed. The current review provides a comprehensive understanding of the prospective role and mechanisms of polyphenol-regulated autophagy in GLMDs and opens up future insights into its application to the healthcare and food industries.

KEYWORDS
autophagy, food industry, glucolipid metabolic diseases, mechanisms, polyphenols

1 | INTRODUCTION

Glucolipidosis is characterized by disorders of glucose and lipid metabolism involving multiple body organs, with hyperglycemia, dyslipidemia, fatty liver disease, overweight, hypertension, atherosclerosis, and cardiovascular disease as the main clinical manifestations (Gowd et al., 2019). Glucolipid metabolic diseases (GLMDs), particularly obesity and diabetes, have emerged as a predominant and growing public health problems worldwide. Although multiple lines of epidemiologic and laboratory research have been carried out to investigate

GLMDs, the potential causes remain unclear owing to the complexity of the syndrome. Numerous contributors involving genetic, environmental, and psychiatric factors, such as neuroendocrine dysfunction, insulin resistance, oxidative stress, inflammation, and dysbiosis of the gut bacteria are core to the pathology of GLMDs (Guo, 2017). Currently, etiological mechanisms such as oxidative stress, inflammation, apoptosis, lipotoxicity, and sympathetic overflow of catecholamines are responsible for GLMDs (Feng et al., 2017; Oda, 2012; Sciarretta et al., 2012). Importantly, abnormalities of autophagy have also been discovered as a crucial factor affecting metabolic reactions and energy homeostasis.

Classic autophagy is characterized by the production of double-membrane autophagosomes comprising cytoplasm, ribosomes, and other organelles by utilizing ubiquitin-like cascades of autophagy-associated genes (ATGs). In turn, autophagosomes eventually combine with lysosomes, where their contents are degraded (He & Klionsky, 2009). This cellular waste-eliminating process can be triggered by a wide range of factors, such as nutritional deprivation, oxidative stress, and DNA damage (Zachari & Ganley, 2017). Although baseline autophagy is required for the maintenance of cellular and whole organism homeostasis, alterations in autophagy, either increases or decreases, leads to the development of many pathological conditions, including obesity, diabetes mellitus, and cardiovascular problems (Lim et al., 2018). The lack of autophagy in the liver results in larger, more abundant lipid droplets, higher levels of triglycerides and cholesterol, as well as larger liver size. In contrast to its role in clearing lipid droplets from the liver, autophagy is responsible for the production of large lipid droplets in white adipose tissue (WAT) (Rabinowitz & White, 2010).

Some drugs that can modulate autophagy have been granted approval for human clinical applications (e.g., rapamycin, carbamazepine, cisplatin, chloroquine). The lack of specificity and organ or cellular selectivity of these compounds has led to significant limitations in their application (Lavallard et al., 2012). In view of this, natural products represent a promising therapeutic strategy in the search for effective drug candidates for controlling autophagy. Polyphenols are an important group of secondary metabolites that can be classified into four types: flavonoids, phenolic acids, stilbenes, and lignans, which are found in a variety of foods including fruits, herbs, vegetables, tea, wine, and cereals (Fu et al., 2021; Hu et al., 2020; Wang et al., 2021b). Despite their well-established antioxidative properties, current research has indicated other mechanisms through which polyphenols exhibit health benefits. The regulation of autophagy by polyphenols to benefit human health has become an important new area of research focus (Figure 1). The actions of various polyphenols in the regulation of multiple metabolic illnesses, including obesity, diabetes, and fatty liver, involve autophagy modulation (García-Aguilar et al., 2021; Liu et al., 2017). In this review, we emphasize the specific metabolic roles of polyphenols by the regulation of autophagy in metabolically active organs and highlight their interactions with signaling pathways involved in various GLMDs. The potential applications of polyphenol-regulated autophagy in the food industry are also discussed.

2 | OVERVIEW OF AUTOPHAGY AND GLMDs

Autophagy is a self-digestion process that occurs in eukaryotes and is classified into three main types; macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Menna-Barreto, 2016). Microautophagy refers to the process of direct phagocytic degradation of endosomes through lysosomes or late endosomes in three main ways: invagination, protrusion, and septation of the lysosome membrane. Macroautophagy initiation results in partial sequestration of cytoplasm into a newly formed double-membrane vesicle, known as the autophagosome. The autophagosome then fuses with the lysosome, releasing the inner vesicle into the lumen. In either case, the inner membrane of the autophagosome is degraded along with the encapsulated contents. The resulting macromolecules are released into the cytoplasm for recirculation via lysosomal membrane permease. Unlike the former two types of autophagy, CMA avoids using vesicles and is highly selective, with autophagosomes entering the lysosome as a complex facilitated by chaperone protein Hsc-70 through the lysosomal-associated membrane protein 2A (LAMP-2A) receptor (Giampieri et al., 2019). In this review, we focus on macroautophagy due to its significant contribution to human health and disease (for simplicity, the term "autophagy" refers to macroautophagy, unless otherwise stated). Approximately 30 mammalian homologs of yeast autophagy-associated proteins (Atg) have been identified, which are responsible for the initiation and expansion of the isolation membrane (Liu et al., 2017). Autophagy involves five key processes: (1) formation of autophagic vesicles (phagophore) by activating the ULK1–Atg13–FIP200 complex; (2) formation of the Atg5–Atg12–Atg16L complex and fusion with autophagic vesicles; (3) conversion of microtubule-associated protein light chain 3 (LC3) from soluble LC3-I to lipid bound LC3-II, which then binds to autophagic vesicles to form autophagosomes; (4) autophagosomes capture proteins and organelles requiring degradation or removal; (5) autophagosomes subsequently fuse with late endosomes and/or lysosomes, mature into an autolysosome, in which the endosome and contents are degraded (Figure 2). In the autophagic process, a variety of cargoes, including lipids (lipophagy), glycogen (glycophagy), peroxisomes (pexophagy), mitochondria (mitophagy), nucleus (nucleophagy), endoplasmic reticulum (reticulophagy), and microbes (xenophagy), can be eliminated, which is beneficial for the maintenance of cell homeostasis. The autophagic rate of protein degradation is estimated to be 10% of cellular protein content per day (Rabinowitz & White, 2010), and the dyshomeostasis of autophagy may have an unfavorable impact on local (metabolically active organ) or systemic metabolism, leading to metabolic dysfunction linked to obesity, insulin resistance, type 2 diabetes, atherosclerosis, and so on. Evidence suggests that autophagy deficiency can inhibit obesity, which was observed in adipose tissues, liver, and skeletal muscle (Ma et al., 2013; Menikdiwela et al., 2020; Zhang et al., 2009). In contrast, autophagy deficits may lead to metabolic dysregulation and obesogenesis, as shown in BV2 cells and microglia of the adult mouse brain, with Atg5 deletion found to be associated with inhibition of lipid droplet mobilization (Mau et al., 2022;

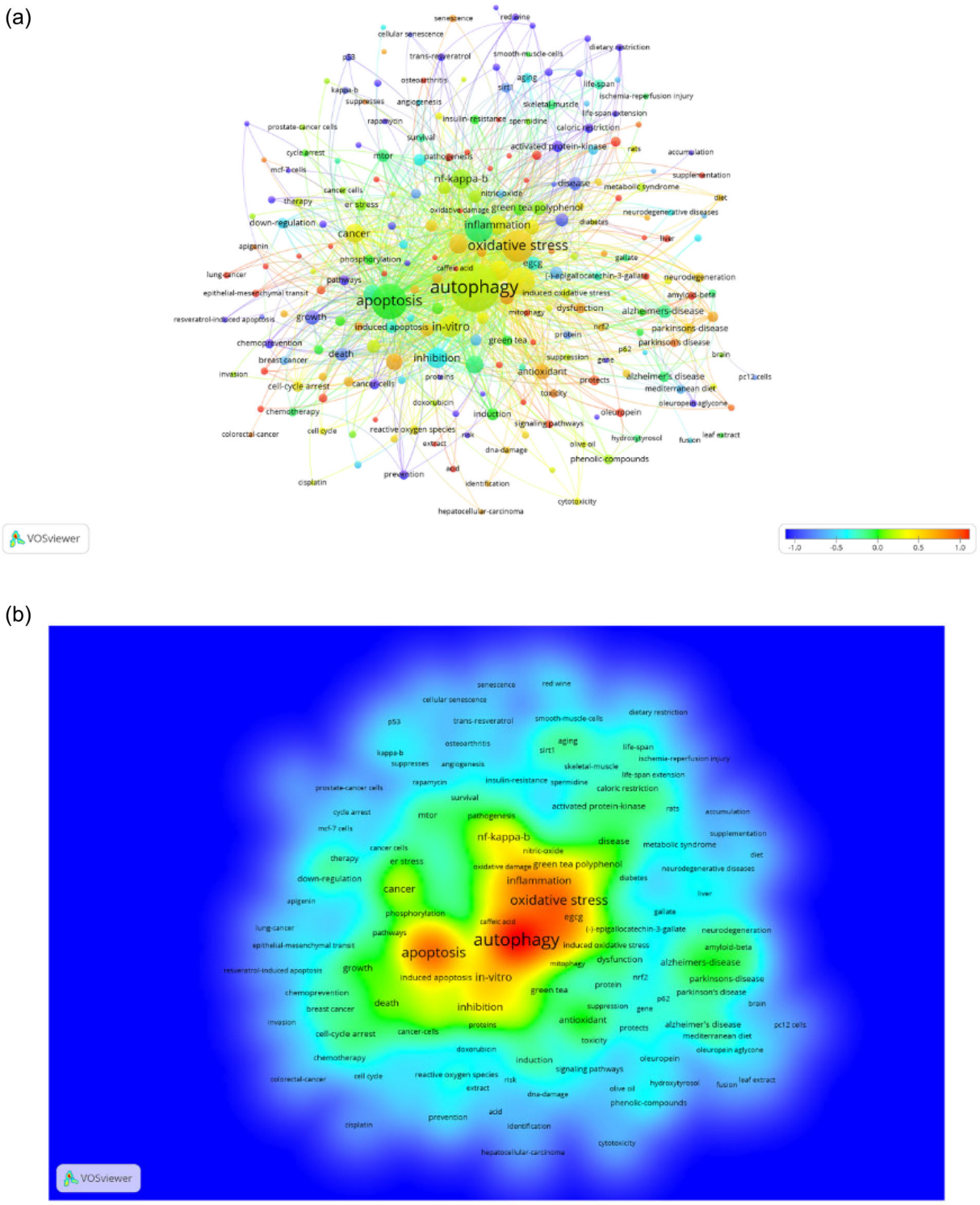


FIGURE 1 VOSviewer cooccurrence overlay visualization (A) and density visualization (B) of the most frequent keywords (minimum of five occurrences) of "polyphenol & autophagy" research (Web of Science Core Collection).

Xu et al., 2021b). It is uncertain whether autophagy is augmented or inhibited in obesity, or whether alterations in autophagy are a direct consequence of elevated lipid content or a compensatory response to reconcile lipid spillage. Moreover, autophagy serves a dual function in the cardiovascular system to maintain healthy cardiac homeostasis. The autophagy response may either inhibit or promote disease development based on the intensity and duration of the stimulus (external or internal). Activation of autophagy in the heart of diabetic mice has been implicated in diastolic dysfunction and pathology. In contrast, several preclinical surveys have shown that autophagy inhibition is an

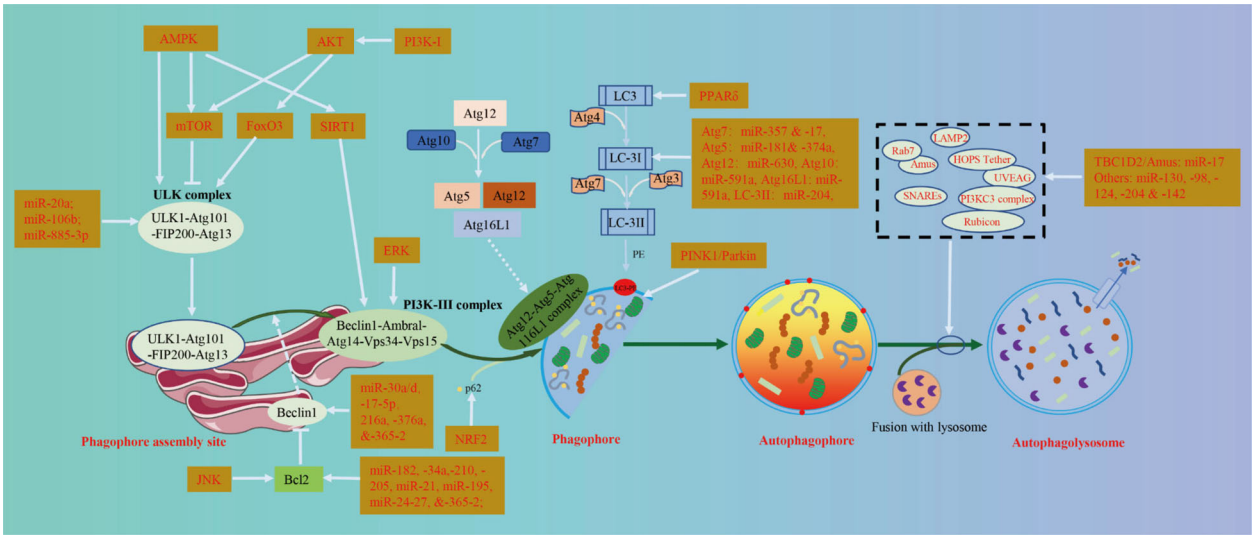


FIGURE 2 The process and regulatory mechanisms of autophagy (Li et al., 2019a; Li & Chen, 2019; Wang et al., 2019; Yang & Liang, 2015). The figure was generated using Science Slides 2006 software. Autophagy involves five steps: formation of phagophore, phagophore elongation, appearance of autophagosome, formation of autolysosome, and degradation. Under normal conditions, activity of autophagy is kept at a higher level in order to maintain cellular homeostasis via the clearance, degradation, and recycling of cytoplasmic long-lived proteins and damaged organelles. Under obese-diabetic condition, high glucose/fat causes marked changes in autophagy activity mainly through nutrient-sensing pathways, including AMPK, MAPK, AKT, PI3K-I/III, mTOR, SIRT1, PINK1/Parkin, NRF2, PPARδ, and miRNA, resulting in aberrant protein degradation and may contribute to the pathogenesis of GLMDs. AMPK, AMP-activated protein kinase; AKT, protein kinase B; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; JNK, c-JUN NH2-terminal protein kinase; MAPK, mitogen-activated protein kinase; miRNA, MicroRNA; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor erythroid 2 (NF-E2)-related factor 2; PE, phosphatidylethanolamine; PPARδ, peroxisome proliferator-activated receptor delta; PI3K, phosphatidylinositol-3-kinase; PINK1, PTEN-induced kinase 1; SIRT1, Sirtuin 1.

adaptive response that exhibits a preventive effect on diabetic cardiomyopathy (Dewanjee et al., 2021). These different observations reveal an increasing awareness of autophagy's therapeutic potential, which is critical for the management and treatment of metabolic illnesses such as diabetes, obesity, insulin resistance, and cardiovascular disease.

3 | POLYPHENOLS AND TISSUE-SPECIFIC AUTOPHAGY ALTERATIONS

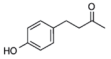
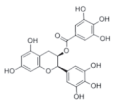
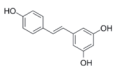
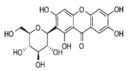
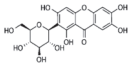
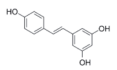
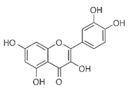
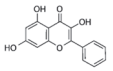
The health benefits of plant polyphenols, some of which are highlighted in the so-called Mediterranean diet, are due to epigenetic and biological modifications, including autophagy initiation or termination (Rigacci et al., 2015). Autophagy has been increasingly linked to the pathology of numerous metabolic organs, including pancreatic islets, liver, adipose tissue, and skeletal muscle, and is associated with GLMDs such as obesity, diabetes, and insulin resistance (Rocchi & He, 2015). Recent studies have highlighted the cross-talk between polyphenols and autophagy, with potential implications for obesity-related metabolic phenotypes. The changes in autophagy induced by polyphenols on metabolic organs during overnutrition and obesity are discussed in detail below (Table 1).

3.1 | Adipose

Mammals have three types of adipose tissue: WAT, brown adipose tissue (BAT), and beige adipose tissue (BeAT) (Wang et al., 2021b). WAT is mainly composed of unilocular white adipocytes containing a single, large lipid droplet. BAT features multiple smaller lipid droplets and specializes in energy burning and adaptative thermogenesis due to its high content of uncoupling protein (UCP1) in the mitochondrial inner membrane (Hu et al., 2020). BeAT is observed intermingled in WAT depots in response to cold exposure or pharmacological agents and presents with similar functions to BAT (Wang et al., 2021b).

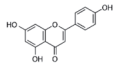
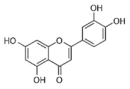
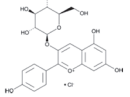
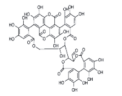
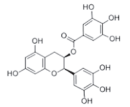
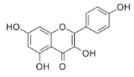
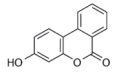
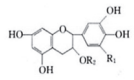
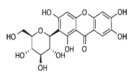
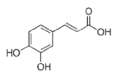
The size enlargement (hypertrophy) and/or the increase in number (hyperplasia) of white adipocytes results in excessive fat accumulation with obesity (Shin, 2020). Evidence suggests autophagy is one of the major factors involved in adipocyte differentiation. For example, genetic deletion of autophagy-related proteins (e.g., Atg5 or Atg7) markedly represses white adipocyte differentiation (Baerga et al., 2009; Zhang et al., 2009). In addition, treatment of mouse white adipocytes (3T3-L1 cells) or human wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) with carvacrol, a monoterpene phenol that occurs in various essential oils, reduces adipogenic differentiation, and this inhibitory effect is related to its ability to reduce autophagy (Spalletta et al., 2018). During the differentiation of 3T3-L1 cells, treatment

TABLE 1 Changes in autophagy regulated by polyphenols in metabolically active organs in GLMDs.

Autophagy occurs in metabolically active organs	Polyphenols	Main source	Structure	Models	Doses	Duration	Change in autophagy	Autophagy parameters	Results	References
Adipose	Carvacrol	Thyme and oregano		3T3-L1 cells	25μ M	17 days	Suppressed	LC3-II↓, and p62↑	Adipogenic differentiation↓	(Spalletta et al., 2018)
				Human WJ-MSCs			Suppressed	Autophagy bodies↓		
	Raspberry ketone	Raspberry		3T3-L1 Cells	300 μM	9 days	Suppressed	Atg12↓, LC3-II/LC-3I ratio↓, p62 (p<0.05)↑	Adipogenesis↓	(Leu et al., 2017)
				Ovx-induced obese rats	160 mg/kg	8 weeks	Suppressed	Beclin 1↓, Atg7↓, and p62 (p<0.05)↑	Fat mass↓	
				3T3-L1 preadipocyte	50 or 100 μM	2 days	Suppressed	HO-1↑, Atg12↓, and p62 (p<0.05)↑	Brown-like adipocyte formation↑	(Leu et al., 2018)
				Ovx Wistar rats	160 mg/kg	8 weeks		HO-1 ↑, Atg7 ↓, and p62 (p<0.05)↑	Inguinal adipose tissue↓	
	EGCG	Tea		C57BL/6 mice fed with HFD diet	20 mg/kg	2 weeks	Enhanced	LC3-II/LC3-I ratio, Beclin1, and Atg12 (p<0.001)↑	Gonadal WAT mass ↓	(Choi et al., 2020)
				Beclin 1 KO mouse fed with HFD diet				LC3↑		
	Resveratrol	Grape		Obese men	150 mg/day	30 days	Enhanced	PPARδ (p=0.0000634)↑; TFEB (p=0.374) ↑	Adipocyte size (d:-2.43) ↓	(Konings et al., 2014)
	EGCG+ resveratrol	Tea+Grape	—	Overweight and obese humans	282 and 80 mg/day, respectively	12 weeks	Suppressed	Lysosome (FDR q-value <0.05)↓	Adipocyte turnover↓	(Most et al., 2018)
	Mangiferin	Mango		Murine $C_3H_{10}T_{1/2}$ mesenchymal stem cells	25, 40, and 50 μM	6 days	Suppressed	PINK1 (p<0.01)↓; p62 (p<0.001)↑	Brown adipocyte phenotype↑	(Rahman and Kim, 2020)
Liver	Mangiferin	Mango		HFD-fed Kunming mice	30 or 60 mg/kg	12 weeks	Enhanced	p62 (p<0.05) ↓; LC3(p<0.05) ↑	Liver lipogenesis↓	(Wang et al., 2017)
	Resveratrol	Grapes		HFD-fed C57BL/6J mice and HFD-fed ULK1+/− mice	50 mg/kg	4 weeks	Enhanced	p65 (p< 0.05)↓; IκBα (p< 0.05)↑	NAFLD-caused hepatic injury↓	(Li et al., 2014)
	Quercetin	Edible vegetables, fruit and wine		FFA-induced HepG2 cells	25, 50, or 100μM	24h	Enhanced	Co-localization of lysosomes↑; p62 and LC3-II (p<0.05)↓	Hepatic lipid deposition↓	(Zhu et al., 2018)
				Sprague-Dawley rats fed HFD	100 mg/kg	8 weeks		Rab7↑	Liver steatosis↑	(Zeng et al., 2019)
				Ethanol-induced C57BL/6J mice	100 mg/kg	12 weeks	Enhanced	LC3-II (p<0.05) and LAMP1 (p<0.01)↑; p62 (p<0.05)↓		
	Galangin	Alpinia conchigera, Populus koreana		FFA induced HepG2 cells	100 μM	12 h	Enhanced	Becline1, LC3-II/LC3-I, and Atg3↑	Liver lipid accumulation↓	(Zhang et al., 2020b)
				HFD-fed C57BL/6J mice	100 mg/kg	8 weeks				
	Citrus flavonoids	Citrus	—	PA induced HepG2 cells	60 or 120 μg/ml	24h	Enhanced	LC3-II↑; ATG index (p<0.01) ↑		

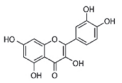
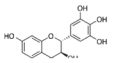
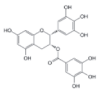
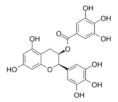
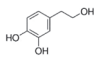
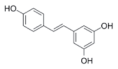
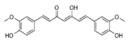
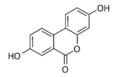
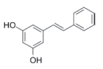
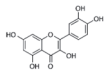
(Continues)

TABLE 1 (Continued)

				GR-LC3-HepG2 cells	120 μg/ml			LC3↑; ATG index (p<0.001) ↑		
	Apigenin	Chamomile		GR-LC3-HepG2 cells	10 or 30 μg/mL	6 h	Enhanced	LC3 (p<0.05) ↑; ATG index (p<0.001) ↑	Hepatic steatosis↓	(Lascala et al., 2018)
	Luteolin	Verbascum lychnitis, Carex fraseriana			5, 10, or 30 μg/mL	6 h	Enhanced (low dose)/Suppressed (high dose)	LC3 (5 μg/mL) (p<0.05) ↑; LC3 (30 μg/mL) (p<0.05) ↓; p62 (30 μg/mL) (p<0.05) ↑		
	Pelargonidin-3-O-glucoside	Lonicera caerulea, Ribes uva-crispa		HG+HF-induced db/db diabetic mice	150 mg/kg	8 weeks	Enhanced	TFEB (P<0.05) and LC3B↑	Improvement of glucose homeostasis and insulin sensitivity↑	(Su et al., 2020)
				HG+HF-induced HepG2 cells	2.5, 5, 10, or 20 μg/mL	24 h		TFEB (p<0.05) and LC3B (p<0.05)↑	Glucose Uptake↑	
	Punicalagin	Punica granatum		HFD-fed C57BL/6 mice	20 mg/kg	8 weeks	Enhanced	LC3-II, P62 and Beclin1 (p<0.05)↑	Insulin resistance↓	(Cao et al., 2021)
	EGCG	Tea		Ethanol-induced C57BL/6J mice	30 or 100 mg/kg	7 days	Enhanced	LC3-II and Beclin1 (p<0.01)↑; p62 (p<0.01)	Hepatic lipid accumulation↓	(Tang et al., 2016)
				HepG2 cells induced by OA and alcohol	45 μmol	48 h				
Pancreas	Kaempferol	Lotus ucrainicus, Ardisia sanguinolenta		PA-induced RIN-5F cells	10 or 50 μM	48 h	Enhanced	Atg5, Atg7, and LC3B (p<0.05)↑; Beclin1 and Ulk1(p<0.0)↑	Pancreatic β-cell dysfunction↓	(Varshney et al., 2017)
	Urolithin A	Punica granatum and Trogopterus xanthipes		Isolated rat pancreatic islets	10 μM		Enhanced	LC3-II/LC3-I (P <0.05) ↑; p62 (p<0.05) ↓	Pancreatic inflammation↓	(Tuohetaerbaike et al., 2020)
				STZ/HFD-induced C57BL/6 mice	50 mg/kg	8 weeks		LC3-II and beclin1(p<0.05)↑; p62 (p<0.05)↓		
				HGP-induced MIN6 cells	11.5 μg/ml	48 h		LC3-II/LC3-I (P<0.01)↑; p62 (p<0.01)↓		(Zhang et al., 2021b)
								LC3 (p<0.01)↑; p62 (p<0.01)↓; Pink1 and Park2 (p<0.01)↑		
Kidney	Green tea polyphenols	Tea		HFD-treated Wistar rats	200 mg/kg	18 weeks	Enhanced	LC3-II (p<0.05)↑; p62 (p<0.05)↓; cathepsin B (p<0.05) ↑; LAMP-1 (p<0.05)↓	Kidney injury↓	(Xie et al., 2017)
				PA-induced HK-2 Cells	20 or 40μM	12 h	Enhanced	Autophagic Flux↑; LC3-II (p<0.05)↑		
	Mangiferin	Mango		Sprague-Dawley rats treated with STZ	12.5, 25, or 50 mg/kg	12 weeks	Enhanced	LC3-II (p<0.001)↑; p62 (p<0.001)↓; p-ULK1 (p<0.001)↑	Diabetic nephropathy↓	(Wang et al., 2018b)
				HG-stimulated mouse podocyte cells	5, 10, or 50 μmol/L	24 h				
	Caffeic Acid	Pavetta indica, Eupatorium cannabinum		HFD/STZ-induced Wistar rat	40 mg/kg	4 weeks	Enhanced	RB1CC1 (d:7.64), ATG12 (d: 5.40), MAP1LC3B (d:4.55)↑	Diabetic nephropathy↓	(Matboli et al., 2017)

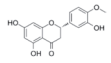
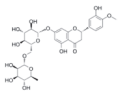
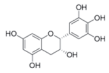
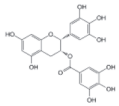
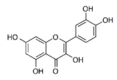
(Continues)

TABLE 1 (Continued)

Skeletal muscle	Quercetin	Edible vegetables, fruit and wine		STZ/HFD-induced rat	100 mg/mL	8 weeks	Suppressed	p62 (P<0.05)↑; Atg5 and Beclin-1 (p<0.05)↓;	Diabetic nephropathy↓	(Lai et al., 2021)
				HG-induced rat mesangial cells	50 mg/mL	72 h				
	Rutin	Buckwheat; tobacco; forsythia; hydrangea; viola, etc		C2C12 Myoblast cell	25 μM	12 h	Enhanced	Fusion/fission (i.e., Mfn1, Mfn2, OPA1, DRP1, and Fis1) (p<0.05); Mitophagy (Atg5, Atg7, Beclin, Bnip3, LC3-II, Mul1, and p62) (p<0.05)↑	Mitochondrial functions↑	(Chang et al., 2021)
	Gallic Acid	Ardisia sanguinolenta, Visnea mocanera								
	Dihydromyricetin	Vitis rotundifolia, Catha edulis		Rat skeletal muscle L6 myoblast cells	0.5 or 1 μM	2 h	Enhanced	LC3-II, Atg5, Beclin1 and the degradation of p62	Skeletal muscle insulin resistance↓	(Shi et al., 2015)
				HFD-fed Sprague-Dawley rats	10, 50 or 100 mg/kg	8 weeks		(p<0.01)↑		
Heart	EGCG	Tea		Diabetic GK rats	100 mg/kg/d	3 months	Suppressed	LC3B, Beclin1(p <0.01), and DRP1 (p<0.05)↓	Mitochondrial dysfunction↓, Glucose levels↓	(Yan et al., 2012)
	Green tea Polyphenols	Tea	–	Diabetic Sprague-Dawley	400 mg/kg	24 weeks	Suppressed	Beclin-1 and LC3-II/ LC3-I ratio (p<0.05)↓; p62 (p<0.05)↑	Diabetic cardiomyopathy↓	(Zhou et al., 2018)
	EGCG	Tea		Diabetic Goto– Kakizaki rats	100 mg/kg	12 weeks	Suppressed	Beclin1 (p<0.001), Atg7 (p<0.05), Atg12- Atg5 (p<0.01), and LC3II (p<0.001), and LC3-II/LC-3I ratio (p<0.01)↓	Myocardial mitochondrial deficiency and dysfunction↓	(Liu et al., 2014b)
	Hydroxytyrosol	Olive oil		Vascular adventitial fibroblasts stimulated with TNF-α	25, 50, and 100 μmol/L	1 h	Enhanced	LC3-II/LC3-I ratio and Beclin1 (p<0.01) ↑	Inflammatory effect in cardiovascular diseases↓	(Liu et al., 2014b)
	Resveratrol	Grapes		STZ-induced C57BL/6J mice	60 or 300 mg/kg	12 weeks	Enhanced	SIRT1(p<0.001) ↑; p62 (p<0. 05) ↓, Rab7 (p<0.001) ↑	Myocardial oxidative stress↓	(Wang et al., 2014)
				H_2O_2-induced H9C2 cells	25 μM	12 h	Enhanced	p62, cleaved caspase 3 and Ac-FOXO1↓, Rab7 (US)↑		
	Curcumin	Curcuma longa		STZ-induced C57BL/6 mice	200 mg/kg	3 months	Enhanced	p62 (p<0. 05)↓; LC3-II/LC3-I (p<0. 05)↑	Cardiac function of diabetic mice ↑	(Yao et al., 2018)
				H9c2 cells exposed to HG/PA	10 μM	24–36 h	Enhanced			
Brain	Urolithin A	Punica granatum and Trogopterus xanthipes		LPS-activated BV2 microglia	5 or 10 μM	24 h	Enhanced	LC3 HiBiT reporter activity (p<0.05)↑	Neuroinflammation↓	(Velagapudi et al., 2019)
	Pinosylvin	Alnus pendula, Calligonum leucocladum		Oxygen and glucose deprivation/reperfusion-induced PC12 cell line	10 μM	24 h	Enhanced	Beclin1 and LC3-II (p<0. 01)↑; PINK1/Parkin (p<0. 01)↓	Mitochondrial dysfunction↓	(Xu et al., 2020b)
	Quercetin	Edible vegetables, fruit and wine		6-OHDA-induced PC12 cells	10, 20,50, or 100 mg/kg	4 h	Enhanced	Parkin and PINK1 (p<0. 05)↓	Damaged mitochondria↓	(Wang et al., 2021a)

(Continues)

TABLE 1 (Continued)

	Hesperetin	Brassica oleracea var. sabauda, Dalbergia parviflora		Neuro-2A cells exposed to amyloid β1-42 and insulin	1 or 20 μM	6 h	Suppressed	LC3-I and LC3-II (p<0. 05)↓	Improvement of glucose transport↑	(Huang et al., 2012)
	Hesperidin	Ficus erecta var. beecheyana, Myrtus communis								
Aorta tissues	EGC	Tea		ox-LDL-impaired HUVECs	5 or 10 μg/mL	24 h	Enhanced	Autophagic vacuoles formation and LC3-II/LC-3I ratio (p<0. 01)↑, p62 (p<0. 01) ↓	Antiatherosclerotic activity↑	(Chen et al., 2017)
	EGCG	Tea		Bovine aortic endothelial cells	10 μM	2 h	Enhanced	LC3-II (p<0. 01)↑, autophagic flux amount (p<0. 05), p62 (p<0. 001)↓	Ectopic lipid accumulation↓	(Kim et al., 2013)
				TNFα-stimulated human endothelial cells line ISO-HAS	10 or 30μM	24 h	Suppressed	LC3A and LC3B protein (US)↓	Endothelial dysfunction↓; Atherogenesis↓	(Yamagata et al., 2015)
	Green tea polyphenols	Tea		HFD-fed ApoE-/- mice	3.2 or 6.4 g/L	15 weeks	Enhanced	LC3-II (p<0. 01), Beclin1 and p62 (p<0. 01)↑	Atherogenesis↓	(Ding et al., 2017)
Intestine	Quercetin	Edible vegetables, fruit and wine		Escherichia coli O157:H7 induced Caco-2 cells	200 μM	12 h	Enhanced	LC3B ↑	NLRP3 inflammasome↓	(Xue et al., 2017)
	Mango beverage polyphenols (475.90 mg GAE/L)	Mango	—	DSS-treated rat	—	10 weeks	Enhanced	LC3 (p<0. 05)↑, LC3A/LC3B (p<0. 05)↑	Colitis↓	(Kim et al., 2018)
				LPS-treated CCD-18 cells	5 or 10μM	48 h				

Effect sizes (*d*) were calculated using *Cohen's d* statistic by practical meta-analysis effect size calculator (compared polyphenol intervention group with model group in animal studies or human trials).
ATGs, autophagy-associated genes; DSS, dextran sulfate sodium salt; EGC, (−)-epigallocatechin; FFA, free fatty acid; HFD, high-fat diets; HG, high glucose; HUVECs, human umbilical vein endothelial cells; LAMP1, lysosomal-associated membrane protein 1; OA, oleic acid; ox-LDL, oxidized low density lipoprotein; PA, palmitic acid; STZ, streptozotocin; NLRP3, pyrin domain-containing protein 3; STZ, streptozotocin; T2DM, type 2 diabetes mellitus; TFEB, transcription factor EB; US, uncertain significance.

with raspberry ketone (300 μM) significantly inhibited autophagy as evidenced by downregulated Atg12 expression, a lower LC3-II/LC3-I ratio, and upregulated p62 (also known as SQSMT1, an indicator of autophagic clearance) protein (Leu et al., 2017). These findings reveal that polyphenols can suppress white adipocyte differentiation by inhibiting cellular autophagy. In addition to inhibiting adipocyte differentiation, polyphenols also reduce WAT mass involving the autophagic pathway. In high-fat diet (HFD)-fed mice, epigallocatechin-3-gallate (EGCG) treatment inhibited WAT hyperplasia and hypertrophy by activating Rab7/Beclin 1-dependent autophagy (Choi et al., 2020). Moreover, in obese men, supplementation with resveratrol (150 mg/day) for 30 days induced smaller adipocytes, which were accompanied by an alternate lipid breakdown mechanism mediated by autophagy upregulation (increase in transcription factor EB (TFEB) (Konings et al., 2014). However, supplementation with EGCG and resveratrol (282 and 80 mg/d, respectively) for 12 weeks suppressed gene sets associated with adipocyte turnover (adipogenesis and apoptosis/autophagy) in obese human WAT (Most et al., 2018). The reasons for the different autophagy response (enhancement or inhibition) induced by polyphenols in WAT can be as follows: (1) changes in autophagy may differ based on the duration of intervention, dose, experimental model (either in vitro or in vivo (mice/rat or humans)), and existence of complications; (2) autophagy alterations might be a direct outcome of adiposity or a compensatory defensive reaction aiming to eliminate extra lipids. This highlights the complexity of polyphenol actions in the regulation of responses in obese WAT.

Although a small amount of BAT (31–329 g) is located in the humans relative to WAT, it plays an important role in the regulation of energy metabolism (Marlatt & Ravussin, 2017). A noradrenergic-mediated inverse relationship exists between autophagy and thermogenesis capacity in BAT, implying that autophagy suppression is a mechanism by which brown adipocytes stimulate thermogenesis (Cairó et al., 2016). A study demonstrated that specific deletion of Atg7 in Myf5+ precursor cells disrupts brown adipocyte differentiation and function, suggesting the requirement of autophagy in the formation of brown adipocytes (Martinez-Lopez et al., 2013). In addition, impairment of autophagy by UCP1^{+}-adipocyte-specific deletion of Atg5 or Atg12 reduces beige adipocyte loss and maintains high-thermogenic capacity, thereby preventing diet-induced obesity and insulin resistance (Altshuler-Keylin et al., 2016). A previous report on raspberry ketone (100 μM *in* vitro and 160 mg/kg in vivo) revealed that polyphenols could induce beige adipocyte formation in 3T3-L1 adipocytes and inguinal adipose tissue of ovariectomy (Ovx)-induced obese rats, which was considered as a result of autophagy inhibition (reduction of Atg12 and increase of HO-1 and p62) (Leu et al., 2018). In agreement with this result, in both murine $C_3H_{10}T_{1/2}$ MSCs and human adipose-derived MSCs, mangiferin treatment activated brown adipocytes and maintained thermogenic ability through downregulation of PINK1/Parkin-mediated mitophagy (Rahman & Kim, 2020). However, EGCG (20 mg/kg/day) for 2 weeks significantly altered the autophagic flux in WAT but not in BAT in HFD-fed mice. There was no effect of EGCG treatment on the LC3-II/LC3-I ratio or UCP1 in BAT, suggesting that EGCG regulates autophagy by browning white fat but not activating brown fat (Choi et al., 2020b). Collectively, the role of autophagy in adipose is complex and can vary depending on the cell type, technical approach or assay conditions. It is crucial to take into account that the relationship between polyphenol-mediated autophagy and obesity is not limited to its activity on adipose tissue.

3.2 | Liver

Autophagy regulates lipid metabolism and a potential promotion of lipid depletion was observed in the liver through lipophagy (Kim & Lee, 2014). Mounting evidence supports that regular intake of polyphenols is positively associated with the promotion of liver lipophagy, thereby contributing to the alleviation of NAFLD, as in the case of mangiferin (Wang et al., 2017), resveratrol (Li et al., 2014), quercetin (Zhu et al., 2018), galangin (Zhang et al., 2020b), gallic acid (Doan et al., 2015), rosmarinic acid (Balachander et al., 2018), naringenin, and hesperitin (Parafati et al., 2015). The different amounts and positions of phenolic hydroxyl groups may be responsible for autophagic potency. A comparison of the autophagy promoting effects of citrus flavonoids (six flavanone and flavone aglycones) in GR-LC3-HepG2 cells revealed apigenin and luteolin were the most promising inducers of autophagy, followed by diosmetin, naringenin, eriodictyol, and hesperetin (Lascala et al., 2018). This finding may be explained by apigenin and luteolin having broadly similar structural properties, such as a flavone backbone with three hydroxyl groups at positions 4′, 5′, and 7, and the high number of hydroxyl groups may be important in determining their potent autophagic activity. Moreover, lipid droplets sensitized the hepatocyte autophagic machinery to the stimulation of flavonoids. LC3-II level was highly augmented in cafeteria diet-induced fatty liver following 14 weeks of bergamot polyphenol treatment, while LC3-II expression in normal liver was not significantly changed (Lascala et al., 2018). Intriguingly, a similar effect was observed in oleic acid (OA)-induced hepatic stellate cells treated with rutin (Lee et al., 2014). Thus, it is possible that lipid overloading and deficiency affect the ability of flavonoids to modulate autophagy in hepatocytes.

Glycophagy is a self-degradative mechanism that is important for maintaining hepatic glucose homeostasis in the face of nutritional excess or starvation, which functions as a regulator of glucose uptake (Zhao et al., 2018). A study by Su et al. (2020), in which high glucose (HG)- and high fat (HF)-induced HepG2 cells were treated with pelargonidin-3-O-glucoside (2.5, 5, 10, or 20 μg/mL) for 24 h, supports the positive role of anthocyanin from wild raspberry in the promotion of hepatic glucose uptake through regulating the TFEB-mediated autophagy pathway. Recent reports also found that liver insulin resistance induced by HFD is related to the suppression of autophagy. As demonstrated in HFD-fed mice, supplementation with punicalagin (20 mg/kg/day, 8 weeks) markedly upregulated liver autophagy, evidenced by elevated autophagosome number and expression of LC3-II, p62, and Beclin 1 (Cao et al., 2021), which was associated with AKT/FOXO3a signaling (Zhang et al., 2019). However, it is important to note in this study that p62 showed an increase in punicalagin-induced autophagy. The possible reason for this phenomenon is that

p62 production occurs through a transcriptional mechanism rather than degradation inhibition by autophagy deficiency. Autophagy is also a defense mechanism against alcoholic fatty liver disease (AFLD) that facilitates the removal of lipids and damaged mitochondria. Autophagy can be induced following acute alcohol exposure but may be inhibited upon chronic and/or high-dose alcohol treatment (Thomes et al., 2015; Wang et al., 2015). Accumulating evidence from in vivo studies supports that frequent consumption of polyphenols blocks chronic ethanol-induced autophagy suppression, thus alleviating alcohol hepatic steatosis (Song et al., 2015; Zhang et al., 2021d). Investigations in chronic ethanol-induced mice showed quercetin (100 mg/kg) for 12 weeks alleviated hepatic steatosis/damage by upregulating LC3-II, Parkin, p62, VDAC1, and LAMP1 expression (Yu et al., 2016; Zeng et al., 2019). The mTOR–TFEB pathway could be a significant mechanism by which quercetin rescues autophagy impairment caused by ethanol (Li et al., 2019b). In line with this study, resveratrol (30 or 100 mg/kg) administration for 8 weeks exerted a beneficial influence on alcoholic hepatic steatosis through mechanism likely involving autophagy activation (increase in LC3-II and Beclin 1 and decrease in p62) (Tang et al., 2016). Thus, the enhancement of lipolysis in chronic ethanol-induced hepatotoxicity by polyphenol intervention alleviates AFLD by activating the autophagy pathway.

3.3 | Pancreatic islets

Autophagy in islet β-cells is recognized as an essential element in the pathogenesis of obesity and diabetes, and increased autophagy may enhance β-cell function and improve metabolic profile (Lee, 2014). Deficiency of autophagy in β-cells recapitulates several features that are observed in islets during the progression of type 2 diabetes mellitus (Watada & Fujitani, 2015). For example, increased p62 accumulation has also been observed in islets of db/db mice and patients with T2DM (Abe et al., 2013). Pioneering studies using pancreatic β-cell-specific gene knockout technology revealed autophagic elimination impaired glucose tolerance and decreased serum insulin level in β-cell-specific Atg7 knockout mice (Jung et al., 2008). Analysis of the metabolic profile of $Atg7^{\Delta\beta\text{-cell}}$-ob/ob mice also showed a reduction in β-cell mass and pancreatic insulin content. Meanwhile, insulin secretion function was identified as impaired ex vivo, which may be due to organelle dysfunction associated with a lack of autophagy (Quan et al., 2012). The intervention of polyphenols may act as a positive modulator of β-cell autophagy. In palmitic acid (PA)-stimulated pancreatic β-cells, treatment with kaempferol led to the conclusion that polyphenol-induced activation of autophagy protects against lipotoxicity, ectopic lipid accumulation, ER stress, and restores β-cell function via AMPK/mTOR pathway (Varshney et al., 2017; Varshney et al., 2018). In parallel, in vivo and in vitro evidence supports the concept that urolithin A (UroA) initiates autophagy in HGP-induced MIN6 cells (mouse-derived pancreatic islet β-cell line) and the pancreas of diabetic mice upon STZ (streptozotocin)/HFD, as manifested by increased LC3 and diminished p62/SQSTM1 expression, thereby improving diabetes (Tuohetaerbaike et al., 2020; Zhang et al., 2021b; Zhang et al., 2021c). Although some studies support a relationship between islet β-cell autophagy and improved metabolic profile, sufficient evidence to reveal that polyphenol-mediated β-cell autophagy impairs diabetes is still lacking and deserves further investigation.

3.4 | Kidney

Dysregulated autophagy has been suggested to play an important pathogenic role in diabetic kidney disease (Tang et al., 2020). Several renal cell types, including podocytes, tubular epithelium cells, and mesangial cells, may participate in the vital functions of diabetic nephropathy (DN). A study by Fang et al. (2013) reported that autophagy (Beclin 1, Atg12-5, and LC3) activity was decreased in podocytes under STZ-induced diabetic conditions. Furthermore, inhibition of cellular autophagy associated with increased p62/SQSTM1 was also observed in proximal and distal renal tubular cells from diabetic animals (Ding & Choi, 2015). Evidence suggests western diet-induced autophagy suppression could be alleviated by polyphenols, as EGCG (40 μM) or astilbin (10 and 20 μM) could reverse autophagy impairment in HG/PA-induced human renal tubular epithelial HK-2 cells as indicated by increased LC3-II and decreased p62/SQSTM1 (Chen et al., 2018, Xie et al., 2017). In HG-induced mouse podocyte cell line (MPC5), mangiferin (5–50 μM) was found to upregulate LC3-II/LC3-I ratio and downregulate p62 protein levels. Furthermore, an increased number of autophagosomes was also observed by transmission electron microscopy in the podocytes of mangiferin (12.5, 25, or 50 mg/kg)-treated DN rats (Wang et al., 2018b). Bioinformatic analysis of kidney tissue from HFD/STZ rats demonstrated that caffeic acid induced autophagy by upregulating RB 1-inducible coiled coil protein (RB1CC1), microtubule-associated proteins 1A/1B light chain 3 (MAP1LC3B) and Atg12, thereby potentially alleviating DN (Matboli et al., 2017). In contrast, in renal tissues of rats with HFD/STZ-induced type 2 diabetes, the expression of the autophagy-related proteins Beclin 1 and Atg5 was significantly decreased and p62 was significantly increased, but quercetin treatment reversed this trend (Lai et al., 2021). As the regulation and function of autophagy in the kidney is likely to be cell type and context specific, characterizing how the autophagic shift in DN is modulated by polyphenols is challenging. Further study is required to understand the precise mechanisms and signaling pathways that underpin the autophagy response in DN.

3.5 | Skeletal muscle

Autophagic responses in skeletal muscle affect glucose homeostasis and metabolic profiles, which are responsible for insulin resistance. In C2C12 myotubes, rutin and gallic acid are considered to improve mitochondrial function by inducing autophagy/mitophagy (increased Atg5, Atg7, Beclin 1, LC3-II, and p62) (Chang et al., 2021). Nonetheless, when UroB was applied to C2C12 myotubes under basal or autophagy-activated conditions, the autophagy markers showed no change, but reduced protein degradation was observed (Rodriguez

et al., 2017). This phenomenon may be attributable to an impairment of the ubiquitin-proteasome pathway rather than autophagy. Dihydromyricetin, a natural flavonoid, improved skeletal muscle insulin resistance by inducing autophagy in HFD-fed rats, as confirmed by upregulated expression of LC3, Beclin 1, and Atg5, and degradation of p62 (Shi et al., 2015). However, in the skeletal muscle of diabetic rats, autophagy activity was abolished by EGCG, which contributed to impeding mitochondrial dysfunction and insulin resistance (Chang et al., 2018; Yan et al., 2012). The possible reasons for the different autophagy activities induced by polyphenols are that (1) diminished autophagy is caused by insufficient fusion between autophagosomes and lysosomes, not by the initiation of autophagy and (2) excessive fat exposure triggers aberrant autophagic flux in muscle, which leads to cellular senescence and insulin resistance. Further research needs to be conducted to investigate the molecular mechanisms by which polyphenols regulate skeletal muscle autophagy, focusing on mTORC1/ULK1-independent or Akt/FoxO3-dependent signals because these two pathways control 60% of skeletal muscle autophagy.

3.6 | Heart

Autophagy within heart tissues has been broadly described in cardiomyocytes, cardiac fibroblasts, endothelial cells, vascular smooth muscle cells, and macrophages, which are involved in cardiovascular diseases (Lavandero et al., 2015). For example, treatment of cardiovascular patient-derived macrophages with rapamycin (an autophagy inducer) successfully reduced LDL, IL-6, and TNF-α secretion by promoting autophagosome formation (Khalil et al., 2020). Evidence is growing regarding a possible effect of phenolics on diabetic cardiomyopathy via regulation of autophagy. Findings revealed that tea polyphenols (400 mg/kg/day) for 16 weeks attenuated Beclin1 and the LC3-II/LC3-I ratio, and enhanced p62 levels in diabetic cardiomyopathic rats (Zhou et al., 2018), with EGCG possibly playing a key role in this process (Liu et al., 2014a; Liu et al., 2014b; Yan et al., 2012). Furthermore, hydroxytyrosol regulates the inflammatory response in vascular adventitial fibroblasts stimulated with TNF-α through increasing the LC3-II/LC3-I ratio, Beclin1 expression, and autophagic flux, and thus is beneficial for treating cardiovascular diseases (Wang et al., 2018a). Resveratrol is also considered to be a potent cardioprotective compound and evidence suggests that resveratrol reduced NLRP3 inflammasome-derived inflammation in HFD-fed rat cardiomyocytes (Qu et al., 2019). It also ameliorated myocardial oxidative stress injury both in H_2O_2-induced H9C2 cells and STZ-induced C57BL/6J mice, associated with the regulation of autophagic flux (increases in the expression of Beclin 1 and LC-3II and decreases in the p62) (Wang et al., 2014). Furthermore, curcumin prevented diabetic cardiomyopathy by enhancing autophagy (increase in p62 expression and reduction in LC3-II/LC3-I ratio) in H9c2 cells exposed to HG/PA and heart tissues of STZ-induced diabetic mice (Yao et al., 2018). As a result, modulating autophagy could be a key mechanism for polyphenols in the treatment of diabetes-related cardiovascular disorders.

3.7 | Aorta tissues

Atherosclerosis is a chronic inflammatory disease that is characterized by lipid deposition, smooth muscle proliferation, apoptosis, necrosis, fibrosis, and local inflammation inside the intima–media layer of the artery wall, and this is commonly linked with dyslipidemia (Davies et al., 2004). The autophagic effects demonstrated for ECG against oxidized LDL-induced injury of human endothelial cells provides a new mechanism for their antiatherosclerotic activity (Chen et al., 2017). In agreement with this result, EGCG could stimulate autophagy in bovine aortic endothelial cells and HFD-fed ApoE-knockout mice to attenuate atherosclerosis and lipid accumulation (Ding et al., 2017; Kim et al., 2013). However, in TNF-α-treated human endothelial cells, EGCG was effective at suppressing the early stages of arteriosclerosis and blocking apoptosis, possibly mediated by inhibition of the autophagy mechanism (reduction in LC3A and LC3B) (Yamagata et al., 2015). The differential expression of EGCG-regulated autophagy factors likely depends on autophagy-related inflammatory and lipogenic pathways.

3.8 | Brain

Autophagy is an essential process for maintaining neuronal function, and its activation prevents excessive aggregation of NLRP3 inflammasomes and subsequent release of IL-1 family cytokines (Tang et al., 2021). The reduction in BECN1 and impairment of autophagy could result in enhanced release of cytokines IL-1β and IL-18 from microglia (Houtman et al., 2019). Simultaneously, research also found IL-1β levels in the cortex correlates positively with Beclin-1 and LC3-II and inversely with p62 (François et al., 2014). An increasing body of evidence in cell and animal models supports that autophagy responses, regulated by polyphenols, play a pivotal role neuroinflammation (Qiu et al., 2020; Yang et al., 2022). In lipopolysaccharides (LPS)-treated BV2 microglia, UroA treatment induced autophagy by increasing LC3 HiBiT reporter activity, contributing to its antineuroinflammatory activity (Velagapudi et al., 2019). The possible molecular mechanisms behind the neuroprotective effects of polyphenols may be attributed to their induction of PINK1/Parkin-mediated mitophagy (Wang et al., 2021a; Xu et al., 2020a). Furthermore, in insulin-stimulated Neuro-2A neuroblastoma cells, hesperetin and hesperidin were demonstrated to reduce beta-amyloid (Aβ)-impaired glucose consumption by blocking Aβ-induced autophagy, indicating the importance of neuronal autophagy downregulation for improving energy metabolism dysfunction that leads to neuronal damage (Huang et al., 2012). Diabetic encephalopathy (DE) includes neurophysiological, morphological, and structural changes that may cause patients to develop cognitive impairment, and one potential mechanism involves disruption of autophagy. It was found that GABA tea (similar amount of polyphenols as green tea) could ameliorate DE by downregulating the activities of Beclin1, ATG7/12, LC3-I, and LC3-II in the cerebral cortex of diabetic rats (Huang et al., 2013). Accordingly, certain polyphenols exhibit therapeutic effects for neurodegenerative disorders by targeting autophagy.

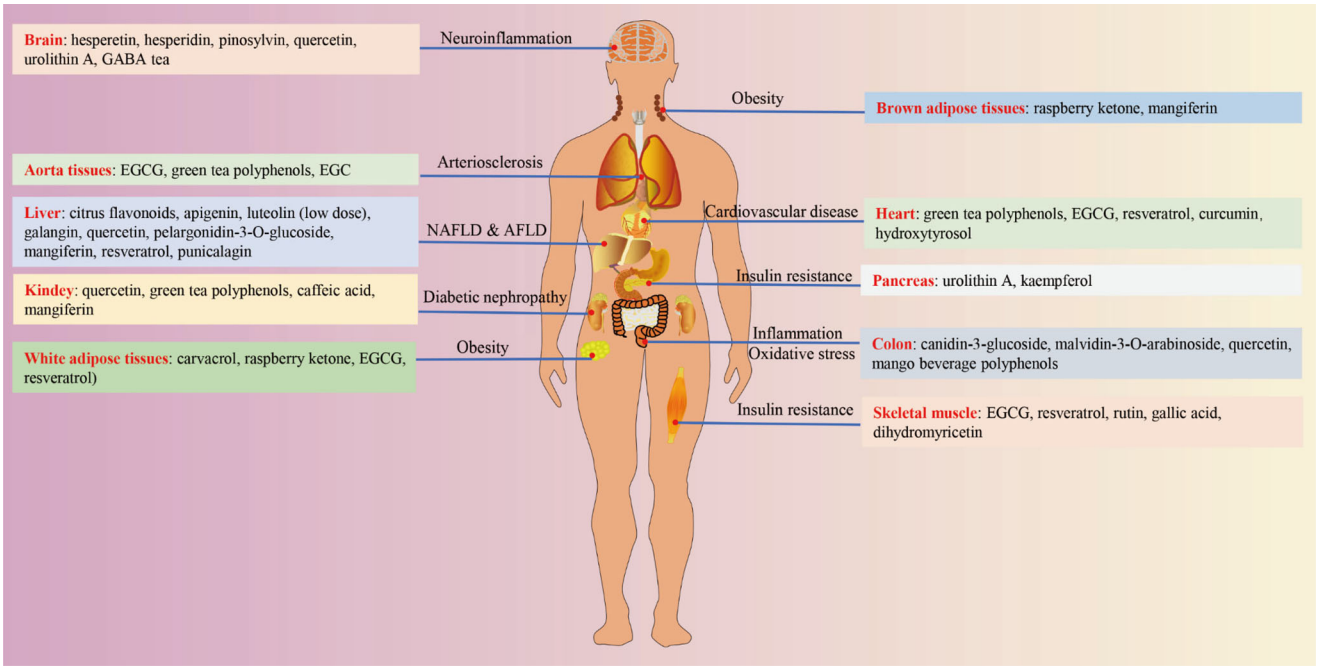


FIGURE 3 Polyphenol-mediated metabolic functions of autophagy among multiple organs in GLMDs. The figure was generated using Science Slides 2006 software.

3.9 | Intestine

Importantly, autophagy has been identified in a variety of intestinal diseases and is critical for maintaining intestinal mucosal homeostasis and regulating inflammation. A recent report on canidin-3-glucoside or malvidin-3-O-arabinoside revealed that anthocyanins could relieve gut oxidative stress by activating autophagy (Chen et al., 2021; Li et al., 2020b). In Caco-2 cells upon *E. coli* O157:H7 infection, quercetin treatment augmented autophagy (xenophagy), blocking mitochondrial ROS generation and IL-1β and IL-18 release (Xue et al., 2017). Therefore, activation of autophagy may be a way for quercetin to alleviate intestinal injury. Of note, in another study, mango polyphenol intake caused a significant increase in tannase- and butyrate-producing bacteria in DSS-induced colitis, thereby contributing to butyrate and pyrogallol production and finally inducing autophagy by regulating the histone deacetylase 1 (HDAC1)/AMPK/LC3 axis (Kim et al., 2018). These findings reveal that polyphenols maintain intestinal homeostasis and relieve intestinal inflammation by activating autophagy. Nevertheless, it is important to note that some intestinal microflora (e.g., *Lacticaseibacillus*, *Lactobacillus*, *Bifidobacterium*, *Butyrivibrio fibrisolvens*, *Megamonas*, *Roseburia*, *Desulfovibrio*, *Ruminococcus* genus, and *Fusobacterium nucleatum*) and gut metabolites (e.g., lipopolysaccharide, secondary biliary acids, cytokines, hormones) can modulate autophagy and thus stimulate extensive host molecular sensors (Lapaquette et al., 2021). Currently, whether polyphenols can modulate autophagy by modifying gut microbiota and microbiota-derived products to improve GLMDs has not been reported and therefore deserves further investigation. Collectively, the roles of polyphenol-mediated autophagy in selected tissues are summarized in Figure 3. Based on the available data in cell, animal studies, and human trials, it can be concluded that polyphenols exert autophagy-regulating effects on specific organs, resulting in the improvement of glucolipid metabolic abnormalities.

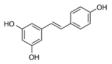
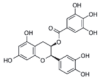
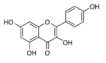
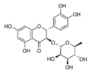
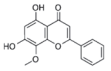
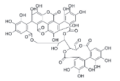
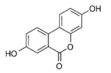
4 | POSSIBLE MECHANISMS OF POLYPHENOL-MEDITATED AUTOPHAGY IN GLMDs

Phenolics have the potential to benefit metabolic health by acting on multiple molecular targets linked with autophagic activity. The various molecular pathways of polyphenol-mediated autophagy in the regulation of GLMDs, including obesity, diabetes, fatty liver, and cardiovascular disease are discussed in detail (Table 2).

4.1 | cAMP pathway

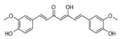
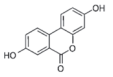
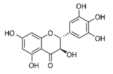
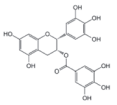
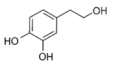
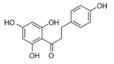
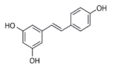
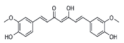
cAMP (cyclic adenosine monophosphate) is a metabolic signal modulator that controls mitochondrial homeostasis and ROS formation, and it may be involved in polyphenol-induced autophagy in response to nutritional exposure (Palmeira et al., 2019; Ugland et al., 2011). In the palmitate-induced accumulation of lipid in hepatic HepG2 cells, resveratrol markedly augmented LC3-II levels and p62 degradation. Incubation with the cAMP inhibitor KH7 (10 μM) or siRNA-mediated adenylyl cyclase knockdown attenuated resveratrol-mediated autophagy (Zhang et al., 2015). Increased cAMP levels due to resveratrol may be responsible for the decreased activation of the NLRP3 inflammasome by augmenting autophagy (Chang et al., 2015). Similarly, resveratrol attenuated endothelial inflammation in TNF-stimulated

TABLE 2 Signal pathways involving in polyphenols-regulating autophagy in GLMDs.

Mechanisms	Polyphenols	Main source	Structure	Models	Doses	Duration	Change in autophagy	Autophagy parameters	Results	References
cAMP				HFD-fed mice	0.4%	4 weeks		cAMP levels (p<0.01)↑; LC3-II and degradation of p62↑, Beclin 1 and ATG5 (US); acidic compartments and autophagosomes (p<0.01)↑	Hepatic steatosis↓	(Zhang et al., 2015)
	Resveratrol	Grapes		PA-stimulated HepG2 cells	20, 40, or 80μM	24 h	Enhanced	cAMP levels (p<0.01)↑; acidic compartments (p<0.05)↑; LC3B and degradation of p62 (US)↑	NLRP3 inflammasome↓	(Chang et al., 2015)
				LPS-induced murine macrophages	60 μM	4 or 6 h	Enhanced	cAMP levels (p<0.001)↑; MAP1LC3B2 formation and p62 degradation (p<0.01)↑	Endothelial inflammation↓	(Chen et al., 2013)
PI3K	ECG	Tea		TNF-stimulated HUVECs	10 μM	2 h	Enhanced	Class III PI3K/Beclin-1↑; PTEN/class I PI3K/Akt ↓; Autophagic vacuoles formation (p<0.01)↑; LC3-II/LC3-I ratio and p62 degradation (p<0.01)↑	Antiatherosclerotic activity↑	(Chen et al., 2017)
	Kaempferol	Lotus ucrainicus, Ardisia sanguinolenta		ox-LDL-impaired HUVECs	2 or 4 μM	24 h	Enhanced	PI3K-AKT (p<0.05)↓; LC3-II/LC3-I ratio and Beclin1↑	Antiatherosclerotic activity↑	(Che et al., 2017)
	Astilbin	Smilax corbularia, Rhododendron simsii		ox-LDL-induced HUVECs	100 μM	6 h	Enhanced	PI3K-AKT (p<0.05)↓; LC3-II/LC3-I ratio (p<0.05)↓; p62 (p<0.05) ↑	Diabetic nephropathy↓	(Chen et al., 2018)
	Wogonin	Scutellaria likiangensis, Scutellaria amoena,		STZ-induced diabetic mice	10, 20, or 40 mg/kg	16 weeks	Enhanced	p-PI3K/PI3K (p<0.05)↓; LC3II/LC3-I (p<0.05), Beclin 1 (p<0.05), and Atg7 (p<0.05)↑; p62 (p<0.001)↓	Diabetic nephropathy↓	(Lei et al., 2021)
				HG-induced HK-2 cells	2, 4, or 8μM	24 h		p-PI3K/PI3K (p<0.05)↓; LC3-II/LC3-I (p<0.05), Beclin1 (p<0.01), and Atg7 (p<0.001)↑; p62 (p<0.001)↓		
AKT	Punicalagin	Punica granatum		HG induced HepG2 cells	5, 10, or 20 μM	48 h	Enhanced	p-AKT/AKT and p-mTOR/mTOR (p<0.01)↓; LC3B (p < 0.01) ↑, p62 (p<0.05) ↓	Diabetic liver disease↓	(Zhang et al., 2019)
				STZ/HFD-fed C57BL/6J mice	20 mg/kg	4 weeks				
	Urolithin A	Punica granatum and Trogopterus xanthipes		STZ/HFD-fed C57BL/6J mice	50 mg/kg	8 weeks	Enhanced	p-AKT and p-mTOR/mTOR (p<0.05)↑; LC3-II, Atg5, and Beclin 1 (p < 0.05)↑; p62 (p<0.05)↓	Diabetic pancreas injury↓	(Tuohetaerbaike et al., 2020)

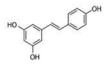
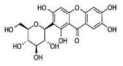
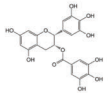
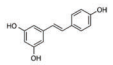
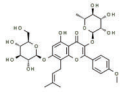
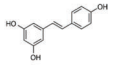
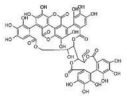
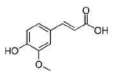
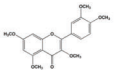
(Continues)

TABLE 2 (Continued)

	Curcumin	Curcuma longa		H_2O_2 inducted EA.hy926 cell line	5 or 20 μmol/L	4 h	Enhanced	p-AKT/AKT and p-mTOR/mTOR (p<0.05)↓; LC3-II/LC3-I ratio (p<0.05)↑	Oxidative damage↓	(Guo et al., 2016)
AMPK	Urolithin A	Punica granatum and Trogopterus xanthipe		STZ/HFD-fed C57BL/6J mice	50 mg/kg	8 weeks	Enhanced	p-AMPK (p<0.01)↑	Diabetic pancreas↓	(Zhang et al., 2021b)
				HG and PA-induced MIN6 pancreatic β cell	50 μM	48 h		p-AMPK (p<0.05)↑; LC3↑ (p<0.01); p62 (p<0.01)↓; PINK1 and Parkin (p<0.01)↑		
	Dihydromyricetin	Vitis rotundifolia, Catha edulis		PA-induced L6 myotubes	0.1, 0.5, or 1 μM	2 h	Enhanced	p-AMPK/AMPK (p<0.05)↑; LC3, Beclin 1, Atg5, degradation of p62, and number of autophagosomes (p<0.01)↑	Skeletal muscle insulin resistance↑	(Shi et al., 2015)
				HFD-fed Sprague-Dawley rats	10, 50 or 100 mg/kg	8 weeks				
	EGCG	Tea		Primary mouse hepatocytes	40 μM	24 h	Enhanced	p-AMPK/AMPK (p<0.05)↑ ; LC3-II (p<0.05) ↑; autolysosomes (p<0.01)↑; p62 (p<0.05)↓	Hepatosteatosis↓	(Zhou et al., 2014)
				HFD/western-style diet fed C57BL/6 mice	3.2 g EGCG/kg diet	17 weeks	Enhanced	p-AMPK/AMPK (US)↑ ; LC3-II (US)↑; p62 (US)↓; Number of autophagic vesicles (p<0.01)↑;		
	Hydroxytyrosol	Olea europaea		HFD-fed Blunt snout bream juveniles	100 mg/kg	10 weeks	Enhanced	p-AMPK/AMPK (p<0.05)↑; PINK1, Mul1, and Atg5 (p<0.05)↑	Hepatosteatosis↓	(Dong et al., 2020)
				OA-stimulated primary hepatocytes	10 μM	48 h				
	Phloretin	Malus doumeri, Punica granatum,		Bone marrow-derived macrophages	50 μM	20 h	Enhanced	p-AMPK/AMPK (p<0.01)↑; p62 (p<0.05) and LC3-II (p<0.01)↑	Neuroinflammation↓	(Dierckx et al., 2021)
	Resveratrol	Grapes		H9c2 cardiac myoblast cells exposed to HG combined with palmitate	25 μM	24–36 h	Enhanced	p-AMPK (p<0.05)↑; p-mTOR/mTOR (p<0.05) ↓; p62 (p<0.05) ↓; LC3-II (p<0.05)↑	Diabetic cardiomyopathy↓	(Xu et al., 2018)
MAPK	Curcumin	Curcuma longa		H9c2 cells exposed to HG/PA	10 μM	24–36 h	Enhanced	p-JNK1 (p<0.05)↑; p62 (p<0.05) ↓; LC3-II (p<0.05)↑	Diabetic cardiomyopathy↓	(Yao et al., 2018)

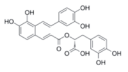
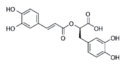
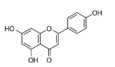
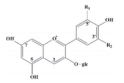
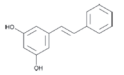
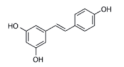
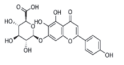
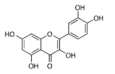
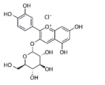
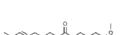
(Continues)

TABLE 2 (Continued)

SIRT1	Resveratrol	Grapes		H9c2 cells exposed to HG/PA	25 μM	24–36 h	Enhanced	p-JNK1 (p<0.05)↑; p62 (p<0.05); LC3-II (p<0.05)↑	Diabetic cardiomyopathy↓	(Xu et al., 2018)
	Mangiferin	Mango		*Staphylococcus aureus* induced RAW264.7 cells	25, 50, or 100 μM	1 h	Suppressed	p-JNK/JNK (p<0.01) ↓; LC3-II/LC3-I (100 μM) (p<0.05)↓; Beclin 1 (NS) ; p62 (p<0.001)↑	Pathological cell damage↓	(Xu et al., 2020b)
	EGCG	Tea		Type 2 diabetic Goto–Kakizaki rats	100 mg/kg/d	3 months	Suppressed	p-JNK/JNK (p < 0.05)↓; p-ERK1/ERK1 (NS))↓; LC3B, Beclin 1 (p < 0.01), and DRP1 (p<0.05)↓	Mitochondrial dysfunction↓	(Yan et al., 2011)
				OA-induced liver cell lines L02 or QSG-7701	50 μM	24 h	Enhanced	p-ERK1/2 (p<0.05)↑; p-JNK/JNK (p<0.05)↓; p-p38/p38 (p<0.05)↓; Beclin 1 and LC3 (p<0.01)↑; p62 (p<0.01)↓ Autophagic index (p<0.01)↑	Liver lipid accumulation↓	(Wu et al., 2021
				HFD-fed C57BL/6J mice	50 mg/kg/day	14 weeks				
	Resveratrol	Grapes		H_2O_2-induced H9c2 cells	20 μmol/L	–	Enhanced	p-p38 (US)↑; Beclin 1 and LC3-II (US)↑	Oxidative stress↓	(Lv and Zhou, 2012)
	Icariin	Epimedium pubescens, Epimedium grandiflorum		Oxidative Stress-Induced Endothelial Progenitor cells	30 μM	48 h	Suppressed	LC3-II and Beclin 1 (US)↓; p62 (US)↑	Endothelial dysfunction↓	(Tang et al., 2015)
	Resveratrol	Grapes		STZ-induced C57BL/6J mice	0.06% resveratrol (about 60 mg/kg/day)	12 weeks	Enhanced	SIRT1 (p<0.001)↑; acetylated FOXO1 (p<0.01)↓; Rab7 (p<0.001)↑; p62 (p<0.05)↓	Myocardial oxidative stress injury↓	(Wang et al., 2014)
	Punicalagin	Punica granatum		PA-induced HepG2 cells	10μM	24h	Enhanced	SIRT1↑, LC3-II/LC3-I↑, and p62 (US) ↓	Lipoapoptosis↓	(Zhang et al., 2020a)
	Ferulic acid	Haplophyllum griffithianum, Visnea mocanera		Lipotoxicity-induced AML12	25, 50, or 100 μM	12 h	Enhanced	SIRT1 (p<0.05)↑; Beclin 1↑, LC3-II↑, and p62 (p<0.05) ↓	Lipotoxicity↓	(Xu et al., 2021a)
	Pentamethylquercetin	Melicope subunifoliolata, Aglaia odorata		HFD-fed C57BL/6 mice	20 mg/kg	63 days	Enhanced	SIRT1 (p<0.05)↑; mTOR activity (p<0.05)↓; S6K1 (p<0.05) ↓, 4EBP1 (p<0.05)↑	Fat deposition ↓	(Ying et al., 2013)

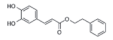
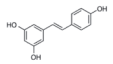
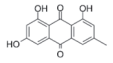
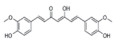
(Continues)

TABLE 2 (Continued)

	Salvianolic acid A	Salvia miltiorrhiza, Salvia flava		Ethanol-treated Sprague-Dawley rats	8 or 16 mg/kg	8 weeks	Enhanced	SIRT1↑; LC3-II/ LC3-I ratio (p<0.01)↑; p62 (p<0.01)↓; Lysosomal proteins (cathepsin B, LAMP-2, and RAB7) (p<0.01)↑	Hepatic injury and steatosis↓	(Shi et al., 2018)
Nrf2/HO-1	Rosmarinic acid	Dimetia scandens, Scrophularia scorodonia		C57BL/6 mice instilled intratracheally MRSA RAW264.7 cells were infected with MRSA	30 mg/kg 150 μM	12 h 30-120min	Enhanced	Nrf2-Keap1 activity↑, LC3-II/LC3-I ratio↑, amplitude of LC3 puncta (US)↑	Mitochondrial oxidative stress↓	(Zhang et al., 2021a)
	Apigenin	Verbascum lychnitis, Carex fraseriana		HFD/hydroquinone-fed C57BL/6 mice	40 or 60 mg/kg	9 months	Enhanced	Nrf2/HO-1 (p<0.05)↑; LC3-II (p < 0.01)↑; p62 (p<0.01)↑	Oxidative stress↓	(Zhang et al., 2020c)
	Bayberry anthocyanins	Bayberry		H_2O_2-stimulated rat pancreatic β cell line INS-1	0.5 or 1μM	2 h	Suppressed	Nrf2/HO-1↑, Beclin 1↓, LC3-II/LC3-I (US)↓	Oxidative stress↓	(Zhang et al., 2013)
PINK1-Parkin	Pinosylvin	Alnus pendula, Calligonum leucocladum		Oxygen and glucose deprivation/reperfusion-induced PC12 cells MCAO/R rats	10 μM 50 mg/kg	24 h 24 h	Enhanced	PINK1/Parkin (p<0.01)↑; LC3-II and Beclin 1 (p<0.01)↑	Oxidative stress-induced mitochondrial dysfunction↓	(Xu et al., 2020b)
	Resveratrol	Grapes		H9c2 cells induced D-galactose	25, 50, or 100 μM	48 h	Enhanced	DRP1(p < 0.05)/Parkin/Pink1 (p < 0.001)↑; LC3-II (p < 0.001)↑	Mitochondrial elongation↓	(Ren et al., 2017)
	Scutellarin	Scoparia dulcis, Sempervivum ruthenicum		HG-induced vascular endothelial cells	10 or 30 μM	48 h	Enhanced	LC3-II, Beclin 1, and Atg 5 (p<0.05)↑; p62 (p<0.05)↓	Vascular endothelial cells injury ↓	(Xi et al., 2021)
	Quercetin	Edible vegetables, fruit and wine		HFD-fed C57BL/J mice	100 mg/kg	10 weeks	Enhanced	PINK1/Parkin↑, Beclin 1↑, LC3↑, and p62 (p<0.05)↑	Hepatic Steatosis↓	(Liu et al., 2018)
	Cyanidin-3-O-glucoside	Legumes		HFD-fed mice PA-induced AML-12 cells	0.2% 100μM	17 weeks 24h	Enhanced	PINK1/Parkin↑, LC3↑, and p62 (p<0.05) ↓	Hepatic Steatosis↓	(Li et al., 2020a)
PPARδ	Capsaicin	Chili peppers		HFD-fed C57BL/6 J mice	15 mg/kg	24 weeks	Enhanced	PPARδ activation↑; LC3-II, Beclin 1, Atg5, Atg7↑ miRNA-133b (d: -4.50),	Hepatic Steatosis↓	(Li et al., 2013)

(Continues)

TABLE 2 (Continued)

miRNAs	Caffeic Acid	Pavetta indica, Eupatorium cannabinum		STZ/HFD-induced diabetic rat	40 mg/kg	4 weeks	Enhanced	miRNA-342 (d: -4.76), and miRNA-30a (d: -4.67) ↓; RB1CC1 (d:7.64), ATG12 (d: 5.40), and MAP1LC3B (d:4.55)↑	Diabetic nephropathy↓	(Matboli et al., 2017)
	Resveratrol	Grapes		Db/db mice and lean wild type db/m mice	100 mg/kg	12 weeks	Enhanced	miRNA-18a-5p (d:25.32)↑; LC3-II/ LC3-I ratio (p<0.05)↑; cleaved caspase-3 (p<0.05) ↓	Diabetic nephropathy↓	(Xu et al., 2017)
	Emodin	Rhubarb		STZ/HFD-fed mice	25 or 50 mg/kg	1 weeks	Enhanced	miR-21 (p<0.05) ↓, LC3 and ATG7 (p<0.05)↑, p62 (p<0.05)↓	Oxidative damage of diabetic nephropathy↓	(Qi et al., 2020)
				Oxidized fish oil-induced *M. amblycephala*	30 mg/kg	12 weeks	Suppressed	miR-34a (p<0.05)↑; Notch1b (p<0.01)↑; ATG3, ATG7, and Beclin 1 (p<0.01)↓	Oxidative stress↓	(Song et al., 2022)
	Curcumin	Curcuma longa		Letrozole-induced virgin Wistar rats	100 or 200 mg/kg	15 days	Suppressed	miR-223-3p (p<0.01)↑; LC3-II (p<0.0001) ↓; p62 (d_{NC-100}:-1.29, d_{NC-200}:-3.60) ↓	Oxidative stress and insulin resistance↓	(Abuelezz et al., 2021)

Effect sizes (d) were calculated using *Cohen's d* statistic by Practical Meta-Analysis Effect Size Calculator (compared polyphenol intervention group with model group in animal studies or human trials).
AMPK:AMP-activated protein kinase; ATGs: autophagy-associated genes; cAMP: cyclic adenosine monophosphate; DRP1:dynamin-related protein 1; ERK: extracellular signal-regulated kinase; FBG: fasting blood glucose; FFA: Free fatty acids; FOXO1: forkhead box O1; HFD: high-fat diets; HO-1:heme oxygenase-1; HUVECs: human umbilical vein endothelial cells; JNK: c-Jun NH 2-terminal kinase; LAMP-2: lysosomal membrane protein 2; MAP1LC3B: microtubule-associated protein light chain 3B; mTOR: mechanistic target of rapamycin; NS: no significance; Nrf2: NF-E2-related factor 2; ox-LDL: Oxidized low density lipoprotein; PI3K: phosphatidylinositol 3-kinase; PPARγ: peroxisome proliferator-activated receptor gamma; RB1CC1: RB1-inducible Coiled-Coil 1; STZ: streptozotocin; US:uncertain significance.

human umbilical vein endothelial cells (HUVECs) through the induction of autophagy. Importantly, autophagy was abolished in the presence of KH7 (10 μM), suggesting a mechanism involving activation of the cAMP signaling pathway (Chen et al., 2013). Therefore, improvement of the symptoms of hepatic steatosis and cardiovascular disease by resveratrol treatment in vitro is regulated at least partly through cAMP-modulated autophagy signaling.

4.2 | AKT pathway

As a negative regulator of autophagy, AKT (protein kinase B) signaling is involved in the onset and progression of a range of pathologies, particularly diabetic complications (Wang et al., 2012). Data from cell and murine models indicate that polyphenols modulate AKT signaling, which in turn regulates the cellular decision between apoptosis and autophagy. There is evidence that curcumin promotes LC3-II expression in H_2O_2-induced EA.hy926 cells and the suppression of AKT phosphorylation and its downstream regulator mTOR may protect cells against oxidative stress-induced damage through inducing autophagy (Guo et al., 2016). In type 2 diabetic mice, the obstructed autophagic flow could be restored in the UroA-treated pancreas of type 2 diabetic mice, partially mediated by its phosphorylation of the AKT/mTOR signaling pathway, thus remarkably decreasing apoptosis and pancreatic damage (Tuohetaerbaike et al., 2020). However, it should be noted that FoxO3a protein, another downstream kinase of Akt, regulates autophagy in various tissues/organs through multiple pathways. Whether some aspects of polyphenol-regulated autophagy by AKT signaling are mediated by phosphorylation of FoxO3a is not well understood and requires further investigation. Together, these findings support molecular mechanisms for the promotion of autophagy by polyphenols in GLMDs such as oxidative stress and diabetes through modulation of Akt/mTOR signaling.

4.3 | Phosphoinositide 3-kinase pathway

Autophagy responds to changes in phosphoinositide 3-kinase (PI3K) signaling, which is involved in glycolysis and lipogenesis. In mammals, there are three types of PI3Ks, class I, II, and III. Class I is a negative regulator of autophagy, while classes II and III act as inducers. Active class I PI3K is able to form phosphatidylinositol 3,4,5-trisphosphate (PIP3) by phosphorylating phosphatidylinositol 4,5-bisphosphate (PIP2) at the 3-OH of the inositol ring, which then activates Akt and downstream effectors, such as mTOR, to perform key actions of autophagy (Shanware et al., 2013). The activity of class III PI3K is considered to control autophagosome formation following establishing a complex with Beclin 1. To examine PI3K signaling in ECG-regulated autophagy, 3-MA (a class III PI3K inhibitor) or SF1670 (antagonist of class I PI3K) was added to ox-LDL-impaired HUVECs. The results showed that ECG reduced autophagic vacuole formation, Beclin 1 expression and the LC3-II/LC3-I ratio confirmed inhibition of autophagy by class III PI3K/Beclin 1 and PTEN/class I PI3K/Akt signaling (Chen et al., 2017). In line with this study, kaempferol potentiated the LC3-II/LC3-I ratio and Beclin 1 expression in ox-LDL-treated HUVECs. In addition, pretreatment with LY294002 (an inhibitor of PI3K) further promoted kaempferol-induced autophagy; however, insulin (an activator of PI3K) stimulation prominently repressed kaempferol-induced autophagy, indicating that autophagy enhancement was induced by kaempferol via its inhibition of PI3K signaling (Che et al., 2017). In HG-exposed HK-2 cells, astilbin increased p-Akt, reduced the LC3-II/LC3-I ratio, and enhanced p62 expression, but LY294002 reversed astilbin-induced inhibition on autophagy (Chen et al., 2018). Based on the above evidence, PI3K signaling engages in the positive effect of astilbin on the attenuation of DN. However, in HG-exposed HK-2 cells and STZ-induced diabetic mice, wogonin inhibited PI3K signaling accompanied by reduced p-Akt/Akt and increased LC3, Beclin 1, and Atg7 expression and inhibited p62 expression. Wogonin could not further suppress autophagy-related protein levels after treatment with PI3Ki (a PI3K inhibitor) suggesting PI3K-dependent mechanisms are involved in wogonin-induced autophagy (Lei et al., 2021). Overall, these research findings show that certain polyphenols mediate anti-DN and antiatherosclerosis actions in part through PI3K-regulated autophagy.

4.4 | SIRT1 pathway

When cells are subjected to nutritional stress, sirtuin1 (SIRT1) influences alternative energy pathways, resulting in changes in lipid metabolism in a variety of pathophysiological settings. In vitro studies reveal that in punicalagin- or ferulic acid-treated hepatocytes exposed to PA; silencing SIRT1 greatly reduced autophagy and increased lipoapoptosis, supporting the concept that Sirt1 plays a vital role in punicalagin- or ferulic acid-regulated autophagy in lipotoxicity (Xu et al., 2021a; Zhang et al., 2020a). In vivo studies have evaluated whether pentamethylquercetin (PMQ) exerts antiobesity activities through SIRT1-regulated autophagic signaling. A study carried out in HFD-fed mice showed that cotreatment with 400 mg/kg nicotinamide (a SIRT1-specific inhibitor) and PMQ (20 mg/kg) alleviated autophagy in WAT compared with PMQ alone, thus resulting in fat deposition (Ying et al., 2013). Importantly, in chronic ethanol-exposed rats, supplementation with salvianolic acid A (8 or 16 mg/kg) for 8 weeks dramatically restored autolysosome formation and activated autophagy. Interestingly, SIRT1 siRNA prevented salvianolic acid A-induced autophagosome–lysosome fusion. This finding suggests that salvianolic acid A, in conjunction with SIRT1/autophagy, protects against prolonged ethanol-induced liver damage (Shi et al., 2018). Notably, Sirt1 regulates the deacetylation of FoxO1, and it is hypothesized that polyphenols are capable of enhancing autophagy by activating the SIRT1–FoxO1 pathway, thereby affecting lipid metabolism. This has importance in the prevention and treatment of hyperlipidemia and hyperglycemia. In diabetic mice, activation of Sirt1 signaling by resveratrol and the resulting increased levels of deacetylated FoxO1 could bind to the Rab7 promoter to stimulate Rab7 and autophagy, thereby avoiding diabetic myocardial injury (Wang et al., 2014). Collectively, these reports evidence that SIRT1-regulated autophagy is involved in

the regulation of obesity, fatty liver, and cardiovascular diseases by polyphenols.

4.5 | AMPK pathway

AMP-activated protein kinase (AMPK) has long been recognized as an important metabolic regulator, and its activation may trigger autophagy, which in turn destroys subcellular organelles, such as lipid droplets (Ha et al., 2015). As revealed in HepG2 cells and obese mice, EGCG treatment reduced hepatic steatosis by increasing autophagy. However, following siRNA knockdown of AMPK, the formation of autophagosomes, lysosomal acidification, and autophagic flux by EGCG were significantly inhibited, suggesting an AMPK-dependent lipophagy-promoting effect of this compound (Zhou et al., 2014). In addition to lipophagy, growing evidence has indicated the importance of AMPK-mediated autophagy in glucose/glycogen metabolism and "glycophagy." As such, an AMPK inhibitor (Compound C) or AMPK siRNA abrogated dihydromyricetin-induced autophagy and formation of autophagosomes, subsequently reducing skeletal muscle insulin resistance improvement (Shi et al., 2015). Moreover, AMPK activation also mediates autophagy induction in cells with defective mitochondria (mitophagy) and thus reduces oxidative stress, apoptosis, and inflammation. In OA-stimulated primary hepatocytes and HFD-fed Blunt snout bream juveniles, mitophagy marker genes such as Pink1, Mul1, and Atg5 were upregulated in the hydroxytyrosol-treated group relative to untreated group, thus leading to the attenuation of hepatic fat accumulation. The possible mechanism is through the activation of the AMPK pathway (Dong et al., 2020). In glucolipotoxicity-induced MIN6 pancreatic β cells, treatment with Compound C reversed UroA-stimulated activation of autophagy (e.g., Pink1 and Parkin, two controllers of mitophagy signaling) and subsequently downregulated inflammatory signaling (Zhang et al., 2021b). Moreover, to investigate whether the autophagy activated by phloretin suppressed neuroinflammation in an AMPK-dependent manner, LPS-stimulated macrophages were treated with phloretin and the AMPK inhibitor BML-275. The results showed that phloretin promoted AMPK-mediated mitophagy, but BML-275 inhibited the higher expression levels of LC3-II and p62 induced by phloretin (Dierckx et al., 2021). Here, it must be noted that p62 (an autophagic clearance factor) increased in phloretin-induced autophagy. The proposed explanation is that p62 is also required for autophagosome formation, and an elevation in p62 levels in combination with an increase in LC3-II puncta might be an indication of autophagy induction.

AMPK activation by polyphenols induces autophagy through at least two different mechanisms: inhibition of mTORC1 and direct phosphorylation of ULK1 (mammalian gene homologous to Atg1) (Kim et al., 2011; Lee et al., 2015). In H9c2 cardiac myoblast cells exposed to HG/PA, Compound C not only blocked resveratrol (25 μM)-induced AMPK activation and inhibition of mTORC1 protein but also downregulated LC3-II protein levels, supporting the ability of resveratrol to promote autophagy via the AMPK/mTORC1 pathway (Xu et al., 2018). Compared with PA-induced RIN-5F cells treated with kaempferol, cotreatment with kaempferol and Compound C or AMPK siRNA resulted in dephosphorylation of AMPK with a corresponding increase in mTOR phosphorylation, subsequently inhibiting LC3-II and the progressive accumulation of p62 proteins (Varshney et al., 2017). This finding demonstrates that kaempferol-mediated AMPK/mTOR signaling is involved in autophagy activation. Nevertheless, it is important to note the diverse signaling mechanisms of mTOR complexes mTORC1 and mTORC2 in the regulation of autophagy. mTORC1 plays a critical role in the regulation of protein synthesis, cell growth and autophagy, while mTORC2 facilitates cell survival and cytoskeleton organization (Sanches-Silva et al., 2020). For example, in HG-stimulated cardiomyocytes, evidence from suppressed protein expression of autophagy markers (LC3-II, p62, and Parkin) and autophagosome formation suggests that changes associated with mangiferin treatment were driven by the suppression of the mTORC1 pathway (Hou et al., 2018). However, another study investigating the cardioprotective effects of resveratrol showed that treatment with resveratrol at lower doses (0.1 and 1 μM in H9c2 cardiac myoblast cells) under hypoxia-reoxygenation conditions induced cell survival through the induction of autophagy (increase in the protein expression of LC3-II, Atg5, and Beclin 1 and the ratio of LC3-II/LC3-I), which may, in part, depend on the activation of the mTORC2 survival pathway (Gurusamy et al., 2009). The ULK1 complex acts centrally in the initiation phase of autophagy, and it is the target of AMPK signaling pathways (Kim et al., 2011; Lee et al., 2015). This implies that polyphenols may exert their effects via this pathway. In HUVECs, under normal or hyperglycaemic conditions, treatment with ampelopsin (1 μM) significantly promoted the phosphorylation of AMPK and increased its downstream target ULK1, thereby resulting in the induction of the autophagic markers LC3-II, Beclin 1, Atg5, and p62, but exposure to the Compound C reversed these changes.(Liang et al., 2015) Taken together, polyphenols may improve GLMDs by modulating autophagy via the AMPK–mTORC1 or AMPK–ULK1 pathway.

4.6 | MAPK pathway

MAPK family members include c-JUN NH2-terminal protein kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 (Xia et al., 1995). Evidence implicates JNK signaling in Bcl-2 posttranslational remodeling and induces Beclin 1 separation from Bcl-2, controlling the crosstalk between autophagy and apoptosis. Once JNK is activated, the Bcl2 protein undergoes phosphorylation, leading to apoptosis. In contrast, when JNK cannot be activated, dephosphorylated Bcl2 interacts with Beclin 1, which is a Bcl2-interacting protein mediating the inhibition of Beclin 1-dependent autophagy (Lavallard et al., 2012). As found in STZ/HFD-fed mice or palmitate-stimulated H9c2 cardiac myoblast cells, curcumin or resveratrol relieved diabetic cardiomyopathy by modulating the transition between autophagy and apoptotic machinery, which is largely attributable to JNK-mediated dissociation of Beclin 1-Bcl2 (Xu et al., 2018; Yao et al., 2018). Similarly, mangiferin-inhibited apoptosis (e.g., upregulation of Bcl-2) and autophagy (e.g., downregulation of Beclin 1) induced by *Staphylococcus aureus* in RAW264.7 cells, which was partly dependent on the inhibition

of JNK signaling, contributing to controlling excessive inflammation and tissue damage (Xu et al., 2020b).

In addition to JNK signaling, studies have reported a potential role of the ERK pathway (two splice variants ERK1 (p44) and ERK2 (p42)), which is initiated in response to oxidative stress and insulin, in regulating autophagy. Emerging evidence reveals that EGCG could enhance autophagy in OA-stimulated liver cells and HFD-induced mice, possibly via the promotion of MAPK/ERK1/2 signaling, suggesting that polyphenols may be potential autophagy regulators useful in the treatment of NAFLD and obesity (Wu et al., 2021). However, in type 2 diabetic Goto–Kakizaki (GK) rats, EGCG improved muscle mitochondrial function by inhibiting autophagy protein LC3B, Beclin 1, and dynamin-related protein 1 (DRP1), and the molecular alterations preceding these changes were characterized by inhibition of the ERK/JNK pathway (Yan et al., 2012). This distinct phenomenon in response to EGCG is due to the fact that ERK and JNK respond to various cellular stresses (e.g. oxidative stress), and hyperglycemia-induced ROS may activate ERK and/or JNK signals, thereby triggering autophagy in skeletal muscle.

Equally important is a wealth of evidence supporting the concept that p38 MAPK is involved in autophagy. However, due to the differences in stimuli and cell types, p38 MAPK has been shown to operate as either a positive or negative regulator of this process. In H_2O_2-treated H9c2 cells, treatment with resveratrol upregulated Beclin 1 and LC3-II, but after SB202190 (a p38 inhibitor) intervention, autophagy activation was considerably suppressed, indicating that p38 MAPK signaling activation may play a central role in resveratrol-induced autophagy (Lv & Zhou, 2012). However, in oxidative stress-induced endothelial progenitor cells, isorhamnetin (30 μM) stimulation for 48 h reduced autophagy via inhibition of the p38 MAPK signaling pathway, thus protecting against endothelial dysfunction (Tang et al., 2015). Collectively, elucidating this signaling cascade in polyphenol-regulated autophagy in response to various stimuli would be highly beneficial for exploiting food plants for disease prevention and treatment.

4.7 | Nrf2/HO-1 pathway

A growing body of data suggests that the nuclear factor erythroid 2 (NF-E2)-related factor 2(Nrf2)/heme oxygenase-1 (HO-1) axis protects against oxidative stress damage through autophagy resistance, which offers a theoretical foundation for its therapeutic impact on a variety of oxidative stress-related disorders (García-Aguilar et al., 2021). Recently, there has been increased attention given to the benefits of polyphenol-induced autophagy on redox balance. It has been reported that rosmarinic acid (30 mg/kg)-mediated Nrf2 activation upregulates the autophagic (and mitophagic) pathway in a murine bacterial pneumonia model and thus mitigates mitochondrial oxidative stress and inflammation (Zhang et al., 2021a). Moreover, in wild type mice, apigenin (40 or 60 mg/kg) dose-dependently increased p62 and LC3 expression to further inhibit retinal oxidative damage but had no effect in Nrf2 KO mice, suggesting that Nrf2-dependent signaling regulates autophagy induced by apigenin (Zhang et al., 2020c). However, in H_2O_2-stimulated INS-1 cells, anthocyanin (mainly cyanidin-3-O-glucoside) (0.5 or 1 μM) treatment reduced H_2O_2-induced autophagy (downregulation of Beclin 1 and LC3-II/ LC3-I), and knockdown of HO-1 or Nrf2 diminished the inhibitory effect of anthocyanin on autophagy, indicating that Nrf2/HO-1 pathways are involved in regulating oxidative stress-mediated autophagy (Zhang et al., 2013). Nrf2 is a double-edged sword that is not always advantageous to health, depending on whether autophagy is intact; thus, adequate intake of polyphenols is essential.

4.8 | PINK1–Parkin pathway

PINK1, a serine/threonine kinase that, along with the E3-ubiquitin ligase Parkin, drives mitochondrial degradation, also regulates mitophagy, which has been considered a potential mechanism of polyphenols contributing to neuroprotection in cell and animal experiments, such as removing damaged mitochondria (Wang et al., 2021a; Xu et al., 2020a). Activation of PINK1/Pink1 may be a potential mechanism of polyphenols for treating cardiovascular complications (Ren et al., 2017). A recent study conducted on HG-induced vascular endothelial cells demonstrated that scutellarin enhanced PINK1/Parkin-mediated mitophagy by increasing autophagic flux and the expression of LC3-II, Beclin 1, and p62 degradation (Xi et al., 2021). Meanwhile, recent research has shown that PINK1/Parkin-mediated mitophagy by polyphenols plays a crucial role in the treatment of hepatic steatosis (e.g., cyanidin-3-O-glucoside and quercetin) (Li et al., 2020a; Liu et al., 2018) and activation of brown adipose (e.g., mangiferin) (Rahman & Kim, 2020). Taken together, PINK1/Parkin-dependent signaling is identified as a mechanism of action for polyphenol-mediated mitophagy in GLMDs.

4.9 | PPARδ pathway

Phosphorylation of PPARδ (peroxisome proliferator-activated receptor δ) at tyrosine-108 results in increased binding of LC3 to the LIR (LC3 interaction region) of PPARδ, and, therefore, inhibits autophagic flux (Gou et al., 2020). PPARδ-dependent signaling is found to decrease fat buildup in the liver via autophagy-mediated fatty acid oxidation (Tong et al., 2019). As shown in HepG2 cells treated with FFA, capsaicin increased the expression of PPARδ accompanied by the upregulation of autophagy-related factors (e.g., LC3-II, Beclin 1, Atg5, and Atg7). Furthermore, autophagy could be further enhanced by cotreatment with capsaicin and a PPARδ agonist (GW0742) but was inhibited by cotreatment with capsaicin and a PPARδ antagonist (GSK0660) in steatotic HepG2 cells (Li et al., 2013). Thus, chronic dietary capsaicin appears to protect against NAFLD by increasing PPARδ-dependent autophagy.

4.10 | miRNA pathways

MicroRNAs (miRNAs) are posttranscriptional modulators of gene expression which can participate in the pathophysiology of GLMDs. Evidence demonstrates cross talk between miRNAs and the autophagy

pathway; for example, ATG1 is regulated by miR-30a, ATG5 is regulated by miR-181a and miR-374a, ATG12 is regulated by miR-630, ATG4 is regulated by miR-376b, LC3 is regulated by miR-204, ATG7 is regulated by miR-375, ATG10 and ATG16 are regulated by miR-519a, ATG16 is regulated by miR-885-3p, and ATG4 is regulated by miR-101 (Frankel & Lund, 2012). As they are key regulators of autophagy, pharmacological compounds and conventional therapies targeting these miRNAs are being investigated in disease models, instigating a new wave of autophagy-targeted therapeutic strategies. Results obtained from diabetic murine models supplemented with caffeic acid, resveratrol or emodin, support the role of epigenetic regulators miRNA-133b/342/30a targeting ATG12, MAPLC3 (microtubule-associated light protein 3), and RB1CC1 (RB1 Inducible Coiled-Coil 1), miR-18a-5p targeting Caspase-3 and LC3, or miR-21 targeting p62, Atg7, and LC3 in the regulation of DN (Qi et al., 2020; Matboli et al., 2017; Xu et al., 2017). In contrast, in oxidized fish oil induced *M. amblycephala*, emodin was found to alleviate intestinal autophagy (ATG3, ATG7, and Beclin 1) induced by oxidative stress via miR-34a/Notch1b signaling (Song et al., 2022). Possible explanations for the different actions of emodin in these studies are that the relative prevalence of autophagy differs in discreet tissues (kidney and intestine) in energy metabolic processes, and exogenous factors (for example, nutritional status of foods used in the experimental model including amino acids, fatty acids, and glucose) may cause different changes in autophagy regulation. Additionally, in the rat with polycystic ovary syndrome, nanocurcumin functions to upregulate miR-223-3p in pancreatic tissues contributing to ameliorating insulin resistance by suppressing autophagy activity as confirmed by dramatic decline in LC3-II and p62 proteins (Abuelezz et al., 2021). In summary, the current data provide new mechanistic insights into possible contribution of miRNAs regulated by polyphenols involved in maintaining autophagy.

Collectively, as illustrated in Figure 4, various signaling pathways, such as cAMP, PI3K, AKT, Sirt1, AMPK, MAPK, Nrf2/HO-1, PINK1/Parkin, PPARδ, and miRNAs, have been implicated in the autophagic regulation of polyphenols and thus contribute to the treatment of GLMDs.

5 | RELEVANCE OF POLYPHENOLS-REGULATED AUTOPHAGY FOR THE FOOD INDUSTRY

5.1 | Winemaking

The traditional or Champenoise technique of producing sparkling wines entails two fermentation steps (the grape juice is initially fermented into a base wine, after which sucrose, yeast and auxiliaries are included, bottled and then fermented) followed by an ageing time in contact with yeasts, which is vital for wine quality (Cebollero et al., 2008). During the ageing period, the yeast cells die and autolyze as the sugar is consumed. Once the yeast cells undergo autolysis, nitrogenous compounds, polysaccharides, and fatty acids are released and these molecules change the wine's chemical composition, sensory properties, and foaming features. Recently, investigation shows that intracellular acetaldehyde dehydrogenase (Ald6p) is specifically targeted to the vacuole by the autophagosome (Onodera & Ohsumi, 2004). In conditions of nutrient starvation, Ald6p is quickly exhausted in yeast cells owing to the preferential degradation of Ald6p during autophagy (Cebollero & Gonzalez, 2006). In this regard, it has been reported that resveratrol and quercetin interfere with sheep cytosolic aldehyde dehydrogenase (ALDH) activity (Kitson et al., 2001). In red winemaking, polyphenols from grape skins and seeds could accumulate in the yeast cytoplasm, thus altering yeast growth and metabolism (Mekoue Nguela et al., 2019). Extracts from the yeast cells in response to resveratrol (2 mg/L) and quercetin (9 mg/L) were assayed for cytosolic ALDH activity (Orozco et al., 2012). It was found that quercetin, but not resveratrol, significantly decreased the cytosolic ALDH Ald6p (a preferred target for autophagy in yeast) activity. The same phenomenon was also argued in the mitochondrial ALDH Ald4p activity. The stronger autophagy inhibitory effect of quercetin may be due to its ability to occupy the NAD^+ pocket of ALDH, and this feature appeared to be the predominant factor leading to the inhibition of the enzyme with $NAD(P)^+$ as a cofactor. Collectively, the suppressive activity of quercetin on these enzymes may cause increased intracellular acetaldehyde, and this is probably responsible for the delayed growth.

5.2 | Food preservation

The spoilage of food and beverages is usually triggered by the combined actions of microorganisms such as yeasts, molds and bacteria, and the use of weak acid preservatives may mitigate this phenomenon (Alderees et al., 2018). In foods with high sugar, low pH, and low water activity, yeasts are usually favored while bacteria are compromised. Autophagy suppression might well be effective in preserving the survival of yeast cells that would otherwise die resulting from excessive self-digestion. Benzoic acid, a phenolic acid included in the Phenol-Explorer database (http://phenol-explorer.eu/), has been demonstrated as a membrane-perturbing agent and induces loss of mitochondrial function (mitophagy). To assay whether exposure of yeast cells (*Saccharomyces cerevisiae*) to benzoic acid impacts ability to trigger autophagy (macroautophagy) under nitrogen starvation, Hazan et al. (2004) utilized a common procedure in which the maturation of precursor amminopeptidase I (prApe1) occurs exclusively through autophagy. In yeast cells treated with 0–1 mM benzoic acid, prApe1 maturation was observed. However, it was not found at 2 mM benzoic acid, implying that this concentration had an inhibitory effect on autophagy. A possible reason for this phenomenon is that the cytoplasm-to-vacuole targeting (Cvt) pathway-independent function participates in these effects. To further validate the conclusion, a more general assay of autophagy was performed by testing yeast alkaline phosphatase (Pho8) activity because of their non-reliance on a Cvt pathway mutant background. Further results revealed that 1 mM benzoic acid reduced Pho8 activity by 50%, while 2 mM benzoic acid completely blocked the reaction. Based on the evidence, the general inhibition of autophagy by benzoic acid is indicated. In line with this study, Abeliovich and Gonzalez (2009) employed GFP-Atg8 as a marker

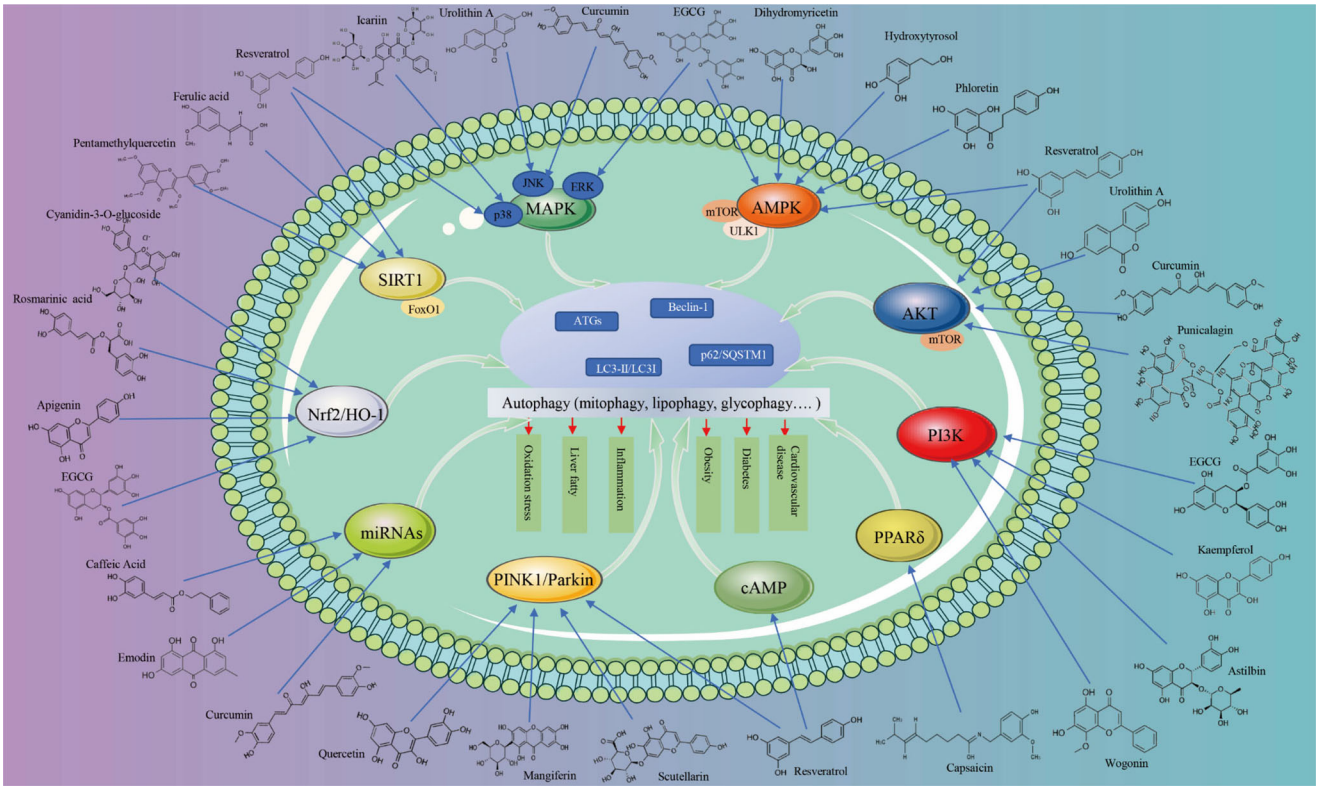


FIGURE 4 The major molecular mechanisms behind the beneficial effects of polyphenol-modulated autophagy in GLMDs. The figure was generated using Science Slides 2006 software. AMPK, AMP-activated protein kinase; AKT, protein kinase B; HO-1, heme oxygenase-1; MAPK, mitogen-activated protein kinase; miRNA, MicroRNA; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor erythroid 2 (NF-E2)-related factor 2; PI3K, phosphatidylinositol-3-kinase; PINK1, PTEN-induced kinase 1; SIRT1, Sirtuin 1.

examining autophagosome completion, it was found that 2 mM benzoic acid reduced autophagy in yeast by the observation of FM4-64 fluorescence, especially under nitrogen starvation condition. Although benzoic acid and nitrogen starvation are both cytostatic, their combination is cytocidal, as macroautophagy is crucial for survival during nitrogen starvation. While this combination is described as cytocidal in yeast, it remains uncertain if it applies for food preservation, since few foods are low enough in nitrogen to induce nitrogen starvation. For this reason, Winter et al. (2008) replaced nitrogen starvation treatment with caffeine supplementation and likewise observed a starvation response, including induction of macroautophagy, in *Zygosaccharomyces bailii* (a food spoilage yeast). Moreover, the combination of benzoic acid (2 mM) and caffeine inhibited macroautophagy and indued a cytocidal response to yeast. If we can find some polyphenols (e.g., resveratrol) similar to caffeine, and then combine with benzoic acid it will prolong improved shelf life and therefore have an economic impact.

5.3 | Healthcare foods

Health foods, also known as functional foods, are specific types of food that do not aim to treat disease but regulate the body's functions (Huang et al., 2022; Feng et al., 2020). They are mainly made from medicine and food homologous dual-use resources and are becoming increasingly popular with consumers. Evidentially, *E. ulmoides* leaves, *Morus alba* leaves, *Rhodiola crenulata* root, and *Salvia miltiorrhiza* have been widely used as key components in health products for probiotic benefits (e.g., antidiabetes, antiobesity, anti-NAFLD, and antihypertension). These species contain a large number of polyphenols and flavonoids, such as erythro-guaiacylglycerol, threo-guaiacylglycerol, 3-O-feruloylquinic acid, chlorogenic acid, and vanillic acid in *E. ulmoides* leaves (Gong et al., 2022), chlorogenic acid, rutin, isoquercitrin, and quercitrin in *M. alba* leaves (Ji et al., 2021), salidroside in *R. crenulata* root (Ren et al., 2021; Yuan et al., 2020), and salvianolic acid B in *S. miltiorrhiza* (Ko et al., 2020), which may be responsible for induction of autophagy. The prospective roles of polyphenol-regulated autophagy in health will benefit the application of polyphenol-rich herbal in healthcare products. For example, Danshen Eucommia Capsule (National Food and Drug Administration G20100571, the main ingredients are *M. alba* leaves and *S. miltiorrhiza*) contains 1.57 g salvianolic acid B per 100 g, which can be used to assist in lowering blood pressure (http://www.pharmnet.com.cn/). Therefore, the search of polyphenol-rich herbal medicine or botanicals will provide promising prospects for both the development and marketing of healthcare products.

6 | CONCLUSIONS AND PERSPECTIVES

Natural products containing phenolic compounds have been identified as a useful group of prospective agents for promoting health, as evidenced by research findings on their structure and molecular actions. Polyphenols have the potential to treat metabolic illnesses by acting on several molecular sites related to autophagic flux activation. In this review, the effects of polyphenols on various protein targets and signaling pathways in relation to autophagy have been addressed. Furthermore, we also discuss the potential applications of polyphenol-targeted autophagy in the food industry. However, several unavoidable issues must be considered when addressing the importance of autophagy control by polyphenol monomers or polyphenol-rich extracts as therapeutic strategies in metabolic illnesses.

(1) Measuring levels of early or late autophagic compartments, or autophagic fluxes, according to the standardized guidelines for autophagy research published in 2021, allows monitoring autophagy in different organisms; however, it is difficult to explain the multiple metabolic outcomes of autophagic deprivation due to the cell-specific diversity of different tissues, models, and stages. Thus, to develop dietary polyphenols as potential nutritional adjuvants for targeting GLMDs, the interplay between autophagy and diverse tissues needs to be understood. (2) From the literature, it is clear that p62 expression either increases or decreases in polyphenol-induced autophagy studies. However, p62 levels are insufficient to demonstrate autophagy fluxes because p62 is an autophagy substrate that increases even more when autophagy maturation is impaired. Thus, it is strongly advised to assess several indicators such as the LC3-II/ LC3-I (LC3 is a receptor for p62), Beclin 1, ATG, and chemical tools (chloroquine or bafilomycin), as well as molecular approaches such as knockdown, to validate the polyphenol-modulating autophagy activity. (3) Autophagy is a double-edged sword. Systemic autophagy activation might not be advantageous to nontargeted cells. On the other hand, autophagy plays a vital role in the homeostasis of cell function under stress situations, for example protecting hepatocytes from oxidative stress and inflammation. Nevertheless, overactivated or blocked autophagy can result in cellular malfunction and even induce apoptosis of normal cells. Therefore, maintaining autophagy at a healthy level is a challenging therapeutic objective. Further studies are required to assess the therapeutic potential and safety of autophagy modulation by polyphenols. It would also be intriguing to explore the beneficial autophagy-mediated mechanisms of available clinically used drugs. (4) Caution should be exercised before employing any polyphenol-rich herbal extracts and natural products targeting AMPK/mTOR as pharmaceuticals addressing obesity and diabetes via autophagy regulation because these pathways are involved in many other cellular processes. (5) The doses assayed in animal and cultured cells maybe result in different effects on autophagy, which is possibly due to disturbed balance of autophagy and apoptosis. For some treatments, low doses trigger autophagy, while high doses may induce apoptosis and in turn suppress autophagy. This is evidenced by the finding that low-dose resveratrol induced autophagy, whereas, the high dose inhibited autophagy accompanied with higher percentage of apoptosis (Gurusamy et al., 2009). (6) In comparison with research in animals and cells, substantially less is known about how GLMDs are connected with autophagy in human tissues. Clinical studies on autophagy-inducing natural products are strongly encouraged, while emphasizing dose, duration, and possible synergistic effects of different compounds. (7) A series of studies on the control of cellular autophagy by polyphenols have appeared with the majority focusing on cancer and just a few on obesity, diabetes, insulin resistance, and comorbidities. Further investigation of the metabolic effects of autophagy dysfunction within a physiologically relevant range is therefore essential to account for doubts regarding the role of polyphenol-induced autophagy in GLMDs. (8) How can the intensity and duration of autophagic flux during polyphenol stimulation be controlled and how can the autophagic regulatory activity of polyphenols be assessed and monitored in animal models or in humans? Although methods for monitoring autophagosome number and autophagic flux, such as electron microscopy, monodansylcadaverine staining, and LC3 turnover assay have been used and developed, because of the dynamic and complex processes involved in autophagy, it is always correctly analyzed. (9) Strategies to increase the autophagic-regulated effect of polyphenols provide a new perspective for their application in GLMDs. For this purpose, several methods, such as chemical and technological modification methods (e.g., solid dispersion, nanoparticles, nanostructured lipid carriers, and microcapsules), should been applied to improve bioavailability and thus increase the autophagy capacity of polyphenols. (10) There is growing experimental evidence that herbal-induced autophagy plays a crucial role in GLMDs, but most of these studies have focused only on the observation of autophagy; detailed mechanistic investigations to identify direct drug targets are rare. Further insight into directly targeting autophagy could not only facilitate medicinal food development but also provide a more effective and safe approach to pharmaceutical research.

ACKNOWLEDGMENTS

The authors acknowledge financial support from the National Key Research and Development Program of China (2022YFF1100204), the National Natural Science Foundation of China (No. 31771978), and the Six Talent Peaks Project in Jiangsu Province (No. NY-095).

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ORCID

Zhiyong He https://orcid.org/0000-0003-2965-6997

REFERENCES

Abe, H., Uchida, T., Hara, A., Mizukami, H., Komiya, K., Koike, M., Shigihara, N., Toyofuku, Y., Ogihara, T., Uchiyama, Y., Yagihashi, S., Fujitani, Y., & Watada, H. (2013). Exendin-4 improves β-Cell function in autophagy-deficient β-cells. *Endocrinology*, *154*, 4512–4524.

Abeliovich, H., & Gonzalez, R. (2009). Autophagy in food biotechnology. *Autophagy*, *5*, 925–929.

Abuelezz, N. Z., E Shabana, M., Rashed, L., & Nb Morcos, G. (2021). Nanocurcumin modulates miR-223-3p and NF-κB levels in the pancreas of rat model of polycystic ovary syndrome to attenuate autophagy flare, insulin resistance and improve ß cell mass. *Journal of Experimental Pharmacology*, *13*, 873–888.

Alderees, F., Mereddy, R., Webber, D., Nirmal, N., & Sultanbawa, Y. (2018). Mechanism of action against food spoilage yeasts and bioactivity of Tasmannia lanceolata, Backhousia citriodora and Syzygium anisatum plant solvent extracts. *Foods*, *7*(11), 179.

Altshuler-Keylin, S., Shinoda, K., Hasegawa, Y., Ikeda, K., Hong, H., Kang, Q., Yang, Y., Perera, R. M., Debnath, J., & Kajimura, S. (2016). Beige adipocyte maintenance is regulated by autophagy-induced mitochondrial clearance. *Cell Metabolism*, *24*, 402–419.

Baerga, R., Zhang, Y., Chen, P. H., Goldman, S., & Jin, S. (2009). Targeted deletion of autophagy-related 5 (atg5) impairs adipogenesis in a cellular model and in mice. *Autophagy*, *5*, 1118–1130.

Balachander, G. J., Subramanian, S., & Ilango, K. (2018). Rosmarinic acid attenuates hepatic steatosis by modulating ER stress and autophagy in oleic acid-induced HepG2 cells. *RSC Advance*, *8*, 26656–26663.

Cairó, M., Villarroya, J., Cereijo, R., Campderrós, L., Giralt, M., & Villarroya, F. (2016). Thermogenic activation represses autophagy in brown adipose tissue. *International Journal of Obesity*, *40*, 1591–1599.

Cao, Y., Ren, G., Zhang, Y., Qin, H., An, X., Long, Y., Chen, J., & Yang, L. (2021). A new way for punicalagin to alleviate insulin resistance: regulating gut microbiota and autophagy. *Food & Nutrition Research*, *65*, https://doi.org/10.29219/fnr.v65.5689

Cebollero, E., & Gonzalez, R. (2006). Induction of autophagy by second-fermentation yeasts during elaboration of sparkling wines. *Applied and Environmental Microbiology*, *72*, 4121–4127.

Cebollero, E., Rejas, M. T., & González, R. (2008). Autophagy in wine making. *Methods in Enzymology*, *451*, 163–175.

Chang, W.-T., Huang, S.-C., Cheng, H.-L., Chen, S.-C., & Hsu, C.-L. (2021). Rutin and gallic acid regulates mitochondrial functions via the SIRT1 pathway in C2C12 myotubes. *Antioxidants*, *10*, 286.

Chang, Y.-C., Liu, H.-W., Chen, Y.-T., Chen, Y.-A., Chen, Y.-J., & Chang, S.-J. (2018). Resveratrol protects muscle cells against palmitate-induced cellular senescence and insulin resistance through ameliorating autophagic flux. *Journal of Food and Drug Analysis*, *26*, 1066–1074.

Chang, Y.-P., Ka, S.-M., Hsu, W.-H., Chen, A., Chao, L. K., Lin, C.-C., Hsieh, C.-C., Chen, M.-C., Chiu, H.-W., Ho, C.-L., Chiu, Y.-C., Liu, M.-L., & Hua, K.-F. (2015). Resveratrol inhibits NLRP3 inflammasome activation by preserving mitochondrial integrity and augmenting autophagy. *Journal of Cellular Physiology*, *230*, 1567–1579.

Che, J., Liang, B., Zhang, Y., Wang, Y., Tang, J., & Shi, G. (2017). Kaempferol alleviates ox-LDL-induced apoptosis by up-regulation of autophagy via inhibiting PI3K/Akt/mTOR pathway in human endothelial cells. *Cardiovascular Pathology*, *31*, 57–62.

Chen, F., Sun, Z., Zhu, X., & Ma, Y. (2018). Astilbin inhibits high glucose-induced autophagy and apoptosis through the PI3K/Akt pathway in human proximal tubular epithelial cells. *Biomedicine & Pharmacotherapy*, *106*, 1175–1181.

Chen, J.-H., Lee, M.-S., Wang, C.-P., Hsu, C.-C., & Lin, H.-H. (2017). Autophagic effects of Hibiscus sabdariffa leaf polyphenols and epicatechin gallate (ECG) against oxidized LDL-induced injury of human endothelial cells. *European Journal of Nutrition*, *56*, 1963–1981.

Chen, M.-L., Yi, L., Jin, X., Liang, X.-Y., Zhou, Y., Zhang, T., Xie, Q., Zhou, X., Chang, H., Fu, Y.-J., Zhu, J.-D., Zhang, Q.-Y., & Mi, M.-T. (2013). Resveratrol attenuates vascular endothelial inflammation by inducing autophagy through the cAMP signaling pathway. *Autophagy*, *9*, 2033–2045.

Chen, W., Chu, Q., Ye, X., Sun, Y., Liu, Y., Jia, R., Li, Y., Tu, P., Tang, Q., Yu, T., Chen, C., & Zheng, X. (2021). Canidin-3-glucoside prevents nano-plastics induced toxicity via activating autophagy and promoting discharge. *Environmental Pollution*, *274*, 116524.

Choi, C., Song, H.-D., Son, Y., Cho, Y. K., Ahn, S.-Y., Jung, Y.-S., Yoon, Y. C., Kwon, S. W., & Lee, Y.-H. (2020). Epigallocatechin-3-gallate reduces visceral adiposity partly through the regulation of beclin1-dependent autophagy in white adipose tissues. *Nutrients*, *12*, 3072.

Davies, J. R., Rudd, J. H., & Weissberg, P. L. (2004). Molecular and metabolic imaging of atherosclerosis. *Journal of Nuclear Medicine*, *45*, 1898–1907.

Dewanjee, S., Vallamkondu, J., Kalra, R. S., John, A., Reddy, P. H., & Kandimalla, R. (2021). Autophagy in the diabetic heart: A potential pharmacotherapeutic target in diabetic cardiomyopathy. *Ageing Research Reviews*, *68*, 101338.

Dierckx, T., Haidar, M., Grajchen, E., Wouters, E., Vanherle, S., Loix, M., Boeykens, A., Bylemans, D., Hardonnière, K., Kerdine-Römer, S., Bogie, J. F. J., & Hendriks, J. J. A. (2021). Phloretin suppresses neuroinflammation by autophagy-mediated Nrf2 activation in macrophages. *Journal of Neuroinflammation*, *18*, 148.

Ding, S., Jiang, J., Yu, P., Zhang, G., Zhang, G., & Liu, X. (2017). Green tea polyphenol treatment attenuates atherosclerosis in high-fat diet-fed apolipoprotein E-knockout mice via alleviating dyslipidemia and up-regulating autophagy. *Plos One*, *12*, e0181666.

Ding, Y., & Choi, M. E. (2015). Autophagy in diabetic nephropathy. *The Journal of Endocrinology*, *224*(1), R15–30.

Doan, K. V., Ko, C. M., Kinyua, A. W., Yang, D. J., Choi, Y.-H., Oh, I. Y., Nguyen, N. M., Ko, A., Choi, J. W., Jeong, Y., Jung, M. H., Cho, W. G., Xu, S., Park, K. S., Park, W. J., Choi, S. Y., Kim, H. S., Moh, S. H., & Kim, K. W. (2015). Gallic acid regulates body weight and glucose homeostasis through AMPK activation. *Endocrinology*, *156*, 157–168.

Dong, Y.-Z., Li, L., Espe, M., Lu, K.-L., & Rahimnejad, S. (2020). Hydroxytyrosol attenuates hepatic fat accumulation via activating mitochondrial biogenesis and autophagy through the AMPK pathway. *Journal of Agricultural and Food Chemistry*, *68*, 9377–9386.

Fang, L., Zhou, Y., Cao, H., Wen, P., Jiang, L., He, W., Dai, C., & Yang, J. (2013). Autophagy attenuates diabetic glomerular damage through protection of hyperglycemia-induced podocyte injury. *PLoS One*, *8*(4), e60546.

Feng, S., Belwal, T., Li, L., Limwachiranon, J., Liu, X., & Luo, Z. (2020). Phytosterols and their derivatives: Potential health-promoting uses against lipid metabolism and associated diseases, mechanism, and safety issues. *Comprehensive Reviews in Food Science and Food Safety*, *19*, 1243–1267.

Feng, S., Dai, Z., Liu, A., Wang, H., Chen, J., Luo, Z., & Yang, C. (2017). beta-Sitosterol and stigmasterol ameliorate dextran sulfate sodium-induced colitis in mice fed a high fat Western-style diet. *Food & Function*, *8*, 4179–4186.

François, A., Terro, F., Quellard, N., Fernandez, B., Chassaing, D., Janet, T., Rioux Bilan, A., Paccalin, M., & Page, G. (2014). Impairment of autophagy in the central nervous system during lipopolysaccharide-induced inflammatory stress in mice. *Molecular Brain*, *7*, 56.

Frankel, L. B., & Lund, A. H. (2012). MicroRNA regulation of autophagy. *Carcinogenesis*, *33*, 2018–2025.

Fu, X., Wang, D., Belwal, T., Xu, Y., Li, L., & Luo, Z. (2021). Sonication-synergistic natural deep eutectic solvent as a green and efficient approach for extraction of phenolic compounds from peels of Carya cathayensis Sarg. *Food Chemistry*, *355*, 129577.

García-Aguilar, A., Palomino, O., Benito, M., & Guillén, C. (2021). Dietary polyphenols in metabolic and neurodegenerative diseases: Molecular targets in autophagy and biological effects. *Antioxidants*, *10*, 142.

Giampieri, F., Afrin, S., Forbes-Hernandez, T. Y., Gasparrini, M., Cianciosi, D., Reboredo-Rodriguez, P., Varela-Lopez, A., Quiles, J. L., Battino, M. J. A., & Signaling, R. (2019). Autophagy in human health and disease: Novel therapeutic opportunities. *Antioxid Redox Signaling*, *30*, 577–634.

Gong, M., Su, C., Fan, M., Wang, P., Cui, B., Guo, Z., Liang, S., Yang, L., Liu, X., Dai, L., & Wang, Z. (2022). Mechanism by which Eucommia ulmoides leaves Regulate nonalcoholic fatty liver disease based on system pharmacology. *Journal of Ethnopharmacology*, *282*, 114603.

Gou, Q., Jiang, Y., Zhang, R., Xu, Y., Xu, H., Zhang, W., Shi, J., & Hou, Y. J. O. (2020). PPARδ is a regulator of autophagy by its phosphorylation. *Oncogene*, *39*, 4844–4853.

Gowd, V., Karim, N., Shishir, M. R. I., Xie, L., & Chen, W. (2019). Dietary polyphenols to combat the metabolic diseases via altering gut microbiota. *Trends in Food Science Technolgy*, *93*, 81–93.

Guo, J. (2017). Research progress on prevention and treatment of glucolipid metabolic disease with integrated traditional Chinese and Western medicine. *Chinese Journal of Integrative Medicine*, *23*, 403–409.

Guo, S., Long, M., Li, X., Zhu, S., Zhang, M., & Yang, Z. (2016). Curcumin activates autophagy and attenuates oxidative damage in EA.hy926 cells via the Akt/mTOR pathway. *Molecular Medicine Reports*, *13*, 2187–2193.

Gurusamy, N., Lekli, I., Mukherjee, S., Ray, D., Ahsan, M. K., Gherghiceanu, M., Popescu, L. M., & Das, D. K. (2009). Cardioprotection by resveratrol: a novel mechanism via autophagy involving the mTORC2 pathway. *Cardiovascular Research*, *86*, 103–112.

Ha, J., Guan, K.-L., & Kim, J. (2015). AMPK and autophagy in glucose/glycogen metabolism. *Molecular Aspects of Medicine*, *46*, 46–62.

Hazan, R., Levine, A., & Abeliovich, H. (2004). Benzoic acid, a weak organic acid food preservative, exerts specific effects on intracellular membrane trafficking pathways in Saccharomyces cerevisiae. *Applied and Environmental Microbiology*, *70*, 4449–4457.

He, C., & Klionsky, D. J. (2009). Regulation mechanisms and signaling pathways of autophagy. *Annual Review of Genetics*, *43*, 67–93.

Hou, J., Zheng, D., Xiao, W., Li, D., Ma, J., & Hu, Y. (2018). Mangiferin enhanced autophagy via inhibiting mTORC1 pathway to prevent high glucose-induced cardiomyocyte injury. *Frontiers in Pharmacology*, *9*, 383.

Houtman, J., Freitag, K., Gimber, N., Schmoranzer, J., Heppner, F. L., & Jendrach, M. (2019). Beclin1-driven autophagy modulates the inflammatory response of microglia via NLRP3. *The EMBO journal*, *38*(4), e99430.

Hu, J., Wang, Z., Tan, B. K., & Christian, M. (2020). Dietary polyphenols turn fat "brown": A narrative review of the possible mechanisms. *Trends in Food Science and Technology*, *97*, 221–232.

Huang, C.-Y., Kuo, W.-W., Wang, H.-F., Lin, C.-J., Lin, Y.-M., Chen, J.-L., Kuo, C.-H., Chen, P.-K., & Lin, J.-Y. (2013). GABA tea ameliorates cerebral cortex apoptosis and autophagy in streptozotocin-induced diabetic rats. *Journal of Functional Foods*, *6*, 534–544.

Huang, H., Zhu, Y., Fu, X., Zou, Y., Li, Q., & Luo, Z. (2022). Integrated natural deep eutectic solvent and pulse-ultrasonication for efficient extraction of crocins from gardenia fruits (Gardenia jasminoides Ellis) and its bioactivities. *Food Chemistry*, *380*, 132216.

Huang, S.-M., Tsai, S.-Y., Lin, J.-A., Wu, C.-H., & Yen, G.-C. (2012). Cytoprotective effects of hesperetin and hesperidin against amyloid β-induced impairment of glucose transport through downregulation of neuronal autophagy. *Molecular Nutrition & Food Research*, *56*, 601–609.

Ji, S., Zhu, C., Gao, S., Shao, X., Chen, X., Zhang, H., & Tang, D. (2021). Morus alba leaves ethanol extract protects pancreatic islet cells against dysfunction and death by inducing autophagy in type 2 diabetes. *Phytomedicine*, *83*, 153478.

Jung, H. S., Chung, K. W., Won Kim, J., Kim, J., Komatsu, M., Tanaka, K., Nguyen, Y. H., Kang, T. M., Yoon, K.-H., Kim, J.-W., Jeong, Y. T., Han, M. S., Lee, M.-K., Kim, K.-W., Shin, J., & Lee, M.-S. (2008). Loss of autophagy diminishes pancreatic β cell mass and function with resultant hyperglycemia. *Cell Metabolism*, *8*, 318–324.

Khalil, H., Abd El Maksoud, A. I., Alian, A., El-Hamady, W. A., Daif, A. A., Awad, A. M., & Guirgis, A. A. (2020). Interruption of autophagosome formation in cardiovascular disease, an evidence for protective response of autophagy. *Immunological Investigations*, *49*, 249–263.

Kim, H., Krenek, K. A., Fang, C., Minamoto, Y., Markel, M. E., Suchodolski, J. S., Talcott, S. T., & Mertens-Talcott, S. U. (2018). Polyphenolic derivatives from mango (Mangifera Indica L.) modulate fecal microbiome, short-chain fatty acids production and the HDAC1/AMPK/LC3 axis in rats with DSS-induced colitis. *Journal of Functional Foods*, *48*, 243–251.

Kim, H. S., Montana, V., Jang, H. J., Parpura, V., & Kim, J. A. (2013). Epigallocatechin gallate (EGCG) stimulates autophagy in vascular endothelial cells: a potential role for reducing lipid accumulation. *Journal of Biological Chemistry*, *288*, 22693–22705.

Kim, J., Kundu, M., Viollet, B., & Guan, K. L. (2011). AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nature Cell Biology*, *13*, 132–141.

Kim, K. H., & Lee, M.-S. (2014). Autophagy-a key player in cellular and body metabolism. *Nature Reviews Endocrinology*, *10*, 322–337.

Kitson, T. M., Kitson, K. E., & Moore, S. A. (2001). Interaction of sheep liver cytosolic aldehyde dehydrogenase with quercetin, resveratrol and diethylstilbestrol. *Chemico-biological Interactions*, *130*, 57–69.

Ko, M., Oh, G. T., Park, J., & Kwon, H. J. (2020). Extract of high hydrostatic pressure-treated danshen (Salvia miltiorrhiza) ameliorates atherosclerosis via autophagy induction. *BMB Reports*, *53*, 652–657.

Konings, E., Timmers, S., Boekschoten, M. V., Goossens, G. H., Jocken, J. W., Afman, L. A., Müller, M., Schrauwen, P., Mariman, E. C., & Blaak, E. E. (2014). The effects of 30 days resveratrol supplementation on adipose tissue morphology and gene expression patterns in obese men. *International Journal of Obesity*, *38*, 470–473.

Lai, L.-L., Lu, H.-Q., Li, W.-N., Huang, H.-P., Zhou, H.-Y., Leng, E.-N., & Zhang, Y.-Y. (2021). Protective effects of quercetin and crocin in the kidneys and liver of obese Sprague-Dawley rats with Type 2 diabetes: Effects of quercetin and crocin on T2DM rats. *Human and Experimental Toxicology*, *40*, 661–672.

Lapaquette, P., Bizeau, J.-B., Acar, N., & Bringer, M.-A. (2021). Reciprocal interactions between gut microbiota and autophagy. *World Journal of Gastroenterology*, *27*, 8283–8301.

Lascala, A., Martino, C., Parafati, M., Salerno, R., Oliverio, M., Pellegrino, D., Mollace, V., & Janda, E. (2018). Analysis of proautophagic activities of Citrus flavonoids in liver cells reveals the superiority of a natural polyphenol mixture over pure flavones. *Journal of Nutritional Biochemistry*, *58*, 119–130.

Lavallard, V. J., Meijer, A. J., Codogno, P., & Gual, P. (2012). Autophagy, signaling and obesity. *Pharmacological Research*, *66*, 513–525.

Lavandero, S., Chiong, M., Rothermel, B. A., & Hill, J. A. (2015). Autophagy in cardiovascular biology. *Journal of Clinical Investigation*, *125*, 55–64.

Lee, J. H., Lee, S. Y., Kim, B., Seo, W. D., Jia, Y., Wu, C., Jun, H.-J., & Lee, S.-J. (2015). Barley sprout extract containing policosanols and polyphenols regulate AMPK, SREBP2 and ACAT2 activity and cholesterol and glucose metabolism in vitro and in vivo. *Food Research International*, *72*, 174–183.

Lee, K.-W., Thiyagarajan, V., Sie, H.-W., Cheng, M.-F., Tsai, M.-J., Chia, Y.-C., & Weng, C.-F. (2014). Synergistic effect of natural compounds on the fatty acid-induced autophagy of activated hepatic stellate cells. *Journal of Nutritional Biochemistry*, *25*(9), 903–913.

Lee, M.-S. (2014). Role of islet β cell autophagy in the pathogenesis of diabetes. *Trends in Endocrinology & Metabolism*, *25*, 620–627.

Lei, L., Zhao, J., Liu, X.-Q., Chen, J., Qi, X.-M., Xia, L.-L., & Wu, Y.-G. (2021). Wogonin alleviates kidney tubular epithelial injury in diabetic nephropathy by inhibiting PI3K/Akt/NF-κB signaling pathways. *Drug design, Development and Therapy*, *15*, 3131–3150.

Leu, S.-Y., Chen, Y.-C., Tsai, Y.-C., Hung, Y.-W., Hsu, C.-H., Lee, Y.-M., & Cheng, P.-Y. (2017). Raspberry ketone reduced lipid accumulation in 3T3-L1 cells and ovariectomy-induced obesity in wistar rats by regulating autophagy mechanisms. *Journal of Agricultural and Food Chemistry*, *65*, 10907–10914.

Leu, S.-Y., Tsai, Y.-C., Chen, W.-C., Hsu, C.-H., Lee, Y.-M., & Cheng, P.-Y. (2018). Raspberry ketone induces brown-like adipocyte formation through suppression of autophagy in adipocytes and adipose tissue. *Journal of Nutritional Biochemistry*, *56*, 116–125.

Li, L., Hai, J., Li, Z., Zhang, Y., Peng, H., Li, K., & Weng, X. (2014). Resveratrol modulates autophagy and NF-κB activity in a murine model for treating non-alcoholic fatty liver disease. *Food and Chemical Toxicology*, *63*, 166–173.

Li, L., Qi, J., & Li, H. (2019a). Natural products modulating autophagy pathway against the pathogenesis of diabetes mellitus. *Current Drug Targets*, *20*, 96–110.

Li, Q., Li, L., Wang, F., Chen, J., Zhao, Y., Wang, P., Nilius, B., Liu, D., & Zhu, Z. (2013). Dietary capsaicin prevents nonalcoholic fatty liver disease through transient receptor potential vanilloid 1-mediated peroxisome proliferator-activated receptor δ activation. *Pflügers Archiv - European Journal of Physiology*, *465*, 1303–1316.

Li, X., Shi, Z., Zhu, Y., Shen, T., Wang, H., Shui, G., Loor, J. J., Fang, Z., Chen, M., Wang, X., Peng, Z., Song, Y., Wang, Z., Du, X., & Liu, G. (2020a). Cyanidin-3-O-glucoside improves non-alcoholic fatty liver disease by promoting PINK1-mediated mitophagy in mice. *British Journal of Pharmacology*, *177*, 3591–3607.

Li, Y., Chen, M., Wang, J., Guo, X., Xiao, L., Liu, P., Liu, L., Tang, Y., & Yao, P. (2019b). Quercetin ameliorates autophagy in alcohol liver disease associated with lysosome through mTOR-TFEB pathway. *Journal of Functional Foods*, *52*, 177–185.

Li, Y., & Chen, Y. (2019). AMPK and autophagy. *Autophagy: Biology and Diseases: Basic Science*, 85–108.

Li, Y., Xu, Y., Xie, J., & Chen, W. (2020b). Malvidin-3-O-arabinoside ameliorates ethyl carbamate-induced oxidative damage by stimulating AMPK-mediated autophagy. *Food & Function*, *11*, 10317–10328.

Liang, X., Zhang, T., Shi, L., Kang, C., Wan, J., Zhou, Y., Zhu, J., & Mi, M. (2015). Ampelopsin protects endothelial cells from hyperglycemia-induced oxidative damage by inducing autophagy via the AMPK signaling pathway. *Biofactors*, *41*, 463–475.

Lim, H., Lim, Y.-M., Kim, K. H., Jeon, Y. E., Park, K., Kim, J., Hwang, H.-Y., Lee, D. J., Pagire, H., Kwon, H. J., Ahn, J. H., & Lee, M.-S. (2018). A novel autophagy enhancer as a therapeutic agent against metabolic syndrome and diabetes. *Nature Communications*, *9*, 1438.

Liu, C., Liao, J. Z., & Li, P. Y. (2017). Traditional Chinese herbal extracts inducing autophagy as a novel approach in therapy of nonalcoholic fatty liver disease. *World Journal of Gastroenterology*, *23*, 1964–1973.

Liu, J., Tang, Y., Feng, Z., Hou, C., Wang, H., Yan, J., Liu, J., Shen, W., Zang, W., Liu, J., & Long, J. (2014a). Acetylated FoxO1 mediates high-glucose induced autophagy in H9c2 cardiomyoblasts: Regulation by a polyphenol -(−)-epigallocatechin-3-gallate. *Metabolism*, *63*, 1314–1323.

Liu, J., Tang, Y., Feng, Z., Liu, J., Liu, J., & Long, J. (2014b). (−)-Epigallocatechin-3-gallate attenuated myocardial mitochondrial dysfunction and autophagy in diabetic Goto–Kakizaki rats. *Free Radical Research*, *48*, 898–906.

Liu, P., Lin, H., Xu, Y., Zhou, F., Wang, J., Liu, J., Zhu, X., Guo, X., Tang, Y., & Yao, P. (2018). Frataxin-mediated PINK1–Parkin-dependent mitophagy in hepatic steatosis: The Protective effects of quercetin. *Molecular Nutrition & Food Research*, *62*, 1800164.

Lv, X., & Zhou, H. (2012). Resveratrol protects H9c2 embryonic rat heart derived cells from oxidative stress by inducing autophagy: Role of p38 mitogen-activated protein kinase. *Canadian Journal of Physiology and Pharmacology*, *90*, 655–662.

Ma, D., Molusky, M. M., Song, J., Hu, C.-R., Fang, F., Rui, C., Mathew, A. V., Pennathur, S., Liu, F., Cheng, J.-X., Guan, J.-L., & Lin, J. D. (2013). Autophagy deficiency by hepatic FIP200 deletion uncouples steatosis from liver injury in NAFLD. *Molecular Endocrinology (Baltimore, Md.)*, *27*, 1643–1654.

Marlatt, K. L., & Ravussin, E. (2017). Brown adipose tissue: An update on recent findings. *Current Obesity Reports*, *6*, 389–396.

Martinez-Lopez, N., Athonvarangkul, D., Sahu, S., Coletto, L., Zong, H., Bastie, C. C., Pessin, J. E., Schwartz, G. J., & Singh, R. (2013). Autophagy in Myf5+ progenitors regulates energy and glucose homeostasis through control of brown fat and skeletal muscle development. *Embo Reports*, *14*, 795–803.

Matboli, M., Eissa, S., Ibrahim, D., Hegazy, M. G. A., Imam, S. S., & Habib, E. K. (2017). Caffeic acid attenuates diabetic kidney disease via modulation of autophagy in a high-fat diet/streptozotocin-induced diabetic rat. *Scientific Reports*, *7*, 2263.

Mau, K. H. T., Karimlou, D., Barneda, D., Brochard, V., Royer, C., Leeke, B., de Souza, R. A., Pailles, M., Percharde, M., Srinivas, S., Jouneau, A., Christian, M., & Azuara, V. (2022). Dynamic enlargement and mobilization of lipid droplets in pluripotent cells coordinate morphogenesis during mouse peri-implantation development. *Nature Communication*, *13*, 3861.

Mekoue Nguela, J., Vernhet, A., Julien-Ortiz, A., Sieczkowski, N., & Mouret, J. R. (2019). Effect of grape must polyphenols on yeast metabolism during alcoholic fermentation. *Food Research International*, *121*, 161–175.

Menikdiwela, K. R., Ramalingam, L., Rasha, F., Wang, S., Dufour, J. M., Kalupahana, N. S., Sunahara, K. K. S., Martins, J. O., & Moustaid-Moussa, N. (2020). Autophagy in metabolic syndrome: Breaking the wheel by targeting the renin-angiotensin system. *Cell Death & Disease*, *11*, 87–87.

Menna-Barreto, R. F. S. (2016). Guidelines for the use and interpretation of assays for monitoring autophagy.

Most, J., Warnke, I., Boekschoten, M. V., Jocken, J. W. E., de Groot, P., Friedel, A., Bendik, I., Goossens, G. H., & Blaak, E. E. (2018). The effects of polyphenol supplementation on adipose tissue morphology and gene expression in overweight and obese humans. *Adipocyte*, *7*, 190–196.

Oda, E. (2012). Metabolic syndrome: Its history, mechanisms, and limitations. *Acta Diabetologica*, *49*, 89–95.

Onodera, J., & Ohsumi, Y. (2004). Ald6p is a preferred target for autophagy in yeast, Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *279*, 16071–16076.

Orozco, H., Matallana, E., & Aranda, A. (2012). Two-carbon metabolites, polyphenols and vitamins influence yeast chronological life span in winemaking conditions. *Microbial Cell Factories*, *11*, 104.

Palmeira, C. M., Teodoro, J. S., Amorim, J. A., Steegborn, C., Sinclair, D. A., & Rolo, A. P. (2019). Mitohormesis and metabolic health: The interplay between ROS, cAMP and sirtuins. *Free Radical Biology and Medicine*, *141*, 483–491.

Parafati, M., Lascala, A., Morittu, V. M., Trimboli, F., Rizzuto, A., Brunelli, E., Coscarelli, F., Costa, N., Britti, D., Ehrlich, J., Isidoro, C., Mollace, V., & Janda, E. (2015). Bergamot polyphenol fraction prevents nonalcoholic fatty liver disease via stimulation of lipophagy in cafeteria diet-induced rat model of metabolic syndrome. *Journal of Nutritional Biochemistry*, *26*, 938–948.

Qi, B., Xiong, Y., Pan, Y., Xu, S., Ji, M., & Wang, J. (2020). Study on the mechanism of emodin alleviating oxidative damage of mice diabetic nephropathy by regulating miR-21-mediated autophagy (In Chinese). *Natural Product Research and Development*, *32*, 2012.

Qiu, W.-Q., Pan, R., Tang, Y., Zhou, X.-G., Wu, J.-M., Yu, L., Law, B. Y.-K., Ai, W., Yu, C.-L., Qin, D.-L., & Wu, A.-G. (2020). Lychee seed polyphenol inhibits Aβ-induced activation of NLRP3 inflammasome via the LRP1/AMPK mediated autophagy induction. *Biomedicine & Pharmacotherapy*, *130*, 110575.

Qu, X., Chen, X., Shi, Q., Wang, X., Wang, D., Yang, L. J. E., & Medicine, T. (2019). Resveratrol alleviates ischemia/reperfusion injury of diabetic myocardium via inducing autophagy. *Experimental and Therapeutic Medicine*, *18*, 2719–2725.

Quan, W., Lim, Y.-M., & Lee, M.-S. (2012). Role of autophagy in diabetes and endoplasmic reticulum stress of pancreatic β-cells. *Experimental and Therapeutic Medicine*, *44*, 81–88.

Rabinowitz, J. D., & White, E. (2010). Autophagy and metabolism. *Science*, *330*, 1344–1348.

Rahman, M. S., & Kim, Y.-S. (2020). PINK1–PRKN mitophagy suppression by mangiferin promotes a brown-fat-phenotype via PKA-p38 MAPK signalling in murine C3H10T1/2 mesenchymal stem cells. *Metabolism*, *107*, 154228.

Ren, H.-H., Niu, Z., Guo, R., Fu, M., Li, H.-R., Zhang, X.-Y., & Yao, L. (2021). Rhodiola crenulata extract decreases fatty acid oxidation and autophagy to ameliorate pulmonary arterial hypertension by targeting inhibition of acylcarnitine in rats. *Chinese Journal of Natural Medicines*, *19*, 120–133.

Ren, X., Chen, L., Xie, J., Zhang, Z., Dong, G., Liang, J., Liu, L., Zhou, H., & Luo, P. (2017). Resveratrol ameliorates mitochondrial

elongation via Drp1/Parkin/PINK1 signaling in senescent-like cardiomyocytes. *Oxidative Medicine and Cellular Longevity*, *2017*, 4175353.

Rigacci, S., Miceli, C., Nediani, C., Berti, A., Cascella, R., Pantano, D., Nardiello, P., Luccarini, I., Casamenti, F., & Stefani, M. (2015). Oleuropein aglycone induces autophagy via the AMPK/mTOR signalling pathway: A mechanistic insight. *Oncotarget*, *6*, 35344–35357.

Rocchi, A., & He, C. (2015). Emerging roles of autophagy in metabolism and metabolic disorders. *Frontiers in Biology*, *10*, 154–164.

Rodriguez, J., Pierre, N., Naslain, D., Bontemps, F., Ferreira, D., Priem, F., Deldicque, L., & Francaux, M. (2017). Urolithin B, a newly identified regulator of skeletal muscle mass. *Journal of Cachexia, Sarcopenia and Muscle*, *8*, 583–597.

Sanches-Silva, A., Testai, L., Nabavi, S. F., Battino, M., Pandima Devi, K., Tejada, S., Sureda, A., Xu, S., Yousefi, B., Majidinia, M., Russo, G. L., Efferth, T., Nabavi, S. M., & Farzaei, M. H. (2020). Therapeutic potential of polyphenols in cardiovascular diseases: Regulation of mTOR signaling pathway. *Pharmacological Research*, *152*, 104626.

Sciarretta, S., Volpe, M., & Sadoshima, J. (2012). Is reactivation of autophagy a possible therapeutic solution for obesity and metabolic syndrome? *Autophagy*, *8*, 1252–1254.

Shanware, N. P., Bray, K., & Abraham, R. T. (2013). The PI3K, metabolic, and autophagy networks: Interactive partners in cellular health and disease. *Annual Review of Pharmacology and Toxicology*, *53*, 89–106.

Shi, L., Zhang, T., Liang, X., Hu, Q., Huang, J., Zhou, Y., Chen, M., Zhang, Q., Zhu, J., & Mi, M. (2015). Dihydromyricetin improves skeletal muscle insulin resistance by inducing autophagy via the AMPK signaling pathway. *Molecular and Cellular Endocrinology*, *409*, 92–102.

Shi, X., Sun, R., Zhao, Y., Fu, R., Wang, R., Zhao, H., Wang, Z., Tang, F., Zhang, N., Tian, X., & Yao, J. (2018). Promotion of autophagosome–lysosome fusion via salvianolic acid A-mediated SIRT1 up-regulation ameliorates alcoholic liver disease. *RSC Advances*, *8*, 20411–20422.

Shin, S. (2020). Regulation of adipose tissue biology by long-chain fatty acids: Metabolic effects and molecular mechanisms. *Journal of Obesity & Metabolic Syndrome*, *31*(2), 147–160.

Song, C., Liu, B., Ge, X., Li, H., Liu, B., & Xu, P. (2022). miR-34a/Notch1b mediated autophagy and apoptosis contributes to oxidative stress amelioration by emodin in the intestine of teleost Megalobrama amblycephala. *Aquaculture*, *547*, 737441.

Song, X., Yin, S., Huo, Y., Liang, M., Fan, L., Ye, M., & Hu, H. (2015). Glycycoumarin ameliorates alcohol-induced hepatotoxicity via activation of Nrf2 and autophagy. *Free Radical Biology and Medicine*, *89*, 135–146.

Spalletta, S., Flati, V., Toniato, E., Di Gregorio, J., Marino, A., Pierdomenico, L., Marchisio, M., D'Orazi, G., Cacciatore, I., & Robuffo, I. (2018). Carvacrol reduces adipogenic differentiation by modulating autophagy and ChREBP expression. *Plos One*, *13*, e0206894.

Su, H., Xie, L., Xu, Y., Ke, H., Bao, T., Li, Y., & Chen, W. (2020). Pelargonidin-3-O-glucoside derived from wild raspberry exerts antihyperglycemic effect by inducing autophagy and modulating gut microbiota. *Journal of Agricultural and Food Chemistry*, *68*, 13025–13037.

Tang, C., Livingston, M. J., Liu, Z., & Dong, Z. (2020). Autophagy in kidney homeostasis and disease. *Nature Reviews Nephrology*, *16*, 489–508.

Tang, L., Yang, F., Fang, Z., & Hu, C. (2016). Resveratrol ameliorates alcoholic fatty liver by inducing autophagy. *American Journal of Chinese Medicine*, *44*, 1207–1220.

Tang, M., Liu, T., Jiang, P., & Dang, R. (2021). The interaction between autophagy and neuroinflammation in major depressive disorder: From pathophysiology to therapeutic implications. *Pharmacological Research*, *168*, 105586.

Tang, Y., Jacobi, A., Vater, C., Zou, L., Zou, X., & Stiehler, M. (2015). Icariin promotes angiogenic differentiation and prevents oxidative stress-induced autophagy in endothelial progenitor cells. *Stem Cells*, *33*, 1863–1877.

Thomes, P. G., Trambly, C. S., Fox, H. S., Tuma, D. J., & Donohue, T. M. Jr. (2015). Acute and chronic ethanol administration differentially modulate hepatic autophagy and transcription factor EB. *Alcoholism-clinical and Experimental Research*, *39*, 2354–2363.

Tong, L., Wang, L., Yao, S., Jin, L., Yang, J., Zhang, Y., Ning, G., & Zhang, Z. (2019). PPARδ attenuates hepatic steatosis through autophagy-mediated fatty acid oxidation. *Cell Death & Disease*, *10*, 197.

Tuohetaerbaike, B., Zhang, Y., Tian, Y., Zhang, N. N., Kang, J., Mao, X., Zhang, Y., & Li, X. (2020). Pancreas protective effects of Urolithin A on type 2 diabetic mice induced by high fat and streptozotocin via regulating autophagy and AKT/mTOR signaling pathway. *Journal of Ethnopharmacology*, *250*, 112479.

Ugland, H., Naderi, S., Brech, A., Collas, P., & Blomhoff, H. K. (2011). cAMP induces autophagy via a novel pathway involving ERK, cyclin E and Beclin 1. *Autophagy*, *7*, 1199–1211.

Varshney, R., Gupta, S., & Roy, P. (2017). Cytoprotective effect of kaempferol against palmitic acid-induced pancreatic β-cell death through modulation of autophagy via AMPK/mTOR signaling pathway. *Molecular and Cellular Endocrinology*, *448*, 1–20.

Varshney, R., Varshney, R., Mishra, R., Gupta, S., Sircar, D., & Roy, P. (2018). Kaempferol alleviates palmitic acid-induced lipid stores, endoplasmic reticulum stress and pancreatic β-cell dysfunction through AMPK/mTOR-mediated lipophagy. *Journal of Nutritional Biochemistry*, *57*, 212–227.

Velagapudi, R., Lepiarz, I., El-Bakoush, A., Katola, F. O., Bhatia, H., Fiebich, B. L., & Olajide, O. A. (2019). Induction of autophagy and activation of SIRT-1 deacetylation mechanisms mediate neuroprotection by the pomegranate metabolite urolithin A in BV2 microglia and differentiated 3D human neural progenitor cells. *Molecular Nutrition & Food Research*, *63*, 1801237.

Wang, B., Yang, Q., Sun, Y.-Y., Xing, Y.-F., Wang, Y.-B., Lu, X.-T., Bai, W.-W., Liu, X.-Q., & Zhao, Y.-X. (2014). Resveratrol-enhanced autophagic flux ameliorates myocardial oxidative stress injury in diabetic mice. *Journal of Cellular and Molecular Medicine*, *18*, 1599–1611.

Wang, H., Zhu, Y.-Y., Wang, L., Teng, T., Zhou, M., Wang, S.-G., Tian, Y.-Z., Du, L., Yin, X.-X., & Sun, Y. (2017). Mangiferin ameliorates fatty liver via modulation of autophagy and inflammation in high-fat-diet induced mice. *Biomedicine & Pharmacotherapy*, *96*, 328–335.

Wang, L., Khambu, B., Zhang, H., & Yin, X.-M. (2015). Autophagy in alcoholic liver disease, self-eating triggered by drinking. *Clinics and Research in Hepatology and Gastroenterology*, *39*(1), S2–S6.

Wang, R. C., Wei, Y., An, Z., Zou, Z., Xiao, G., Bhagat, G., White, M., Reichelt, J., & Levine, B. (2012). Akt-mediated regulation of autophagy and tumorigenesis through beclin 1 phosphorylation. *Science*, *338*, 956–959.

Wang, W.-W., Han, R., He, H.-J., Li, J., Chen, S.-Y., Gu, Y., & Xie, C. (2021a). Administration of quercetin improves mitochondria quality control and protects the neurons in 6-OHDA-lesioned Parkinson's disease models. *Aging*, *13*, 11738–11751.

Wang, W., Jing, T., Yang, X., He, Y., Wang, B., Xiao, Y., Shang, C., Zhang, J., & Lin, R. (2018a). Hydroxytyrosol regulates the autophagy of vascular adventitial fibroblasts through the SIRT1-mediated signaling pathway. *Canadian Journal of Physiology and Pharmacology*, *96*, 88–96.

Wang, X., Gao, L., Lin, H., Song, J., Wang, J., Yin, Y., Zhao, J., Xu, X., Li, Z., & Li, L. (2018b). Mangiferin prevents diabetic nephropathy progression and protects podocyte function via autophagy in diabetic rat glomeruli. *European Journal of Pharmacology*, *824*, 170–178.

Wang, Y., Zhao, H., Wang, Q., Zhou, X., Lu, X., Liu, T., Zhan, Y., & Li, P. (2019). Chinese herbal medicine in ameliorating diabetic kidney disease via activating autophagy. *Journal of Diabetes Research*, *2019*, 9030893.

Wang, Z., Zeng, M., Wang, Z., Qin, F., Wang, Y., Chen, J., Christian, M., & He, Z. (2021b). Food phenolics stimulate adipocyte browning via regulating gut microecology. *Critical Reviews in Food Science and Nutrition*, 1–27.

Watada, H., & Fujitani, Y. (2015). Minireview: Autophagy in pancreatic β-cells and its implication in diabetes. *Molecular Endocrinology*, *29*, 338–348.

Winter, G., Hazan, R., Bakalinsky, A. T., & Abeliovich, H. (2008). Caffeine induces macroautophagy and confers a cytocidal effect on food spoilage yeast in combination with benzoic acid. *Autophagy*, *4*(1), 28–36.

Wu, D., Liu, Z., Wang, Y., Zhang, Q., Li, J., Zhong, P., Xie, Z., Ji, A., & Li, Y. (2021). Epigallocatechin-3-gallate alleviates high-fat diet-induced nonalcoholic fatty liver disease via inhibition of apoptosis and promotion of autophagy through the ROS/MAPK signaling pathway. *Oxidative Medicine and Cellular Longevity*, *2021*, 5599997.

Xi, J., Rong, Y., Zhao, Z., Huang, Y., Wang, P., Luan, H., Xing, Y., Li, S., Liao, J., Dai, Y., Liang, J., & Wu, F. (2021). Scutellarin ameliorates high glucose-induced vascular endothelial cells injury by activating PINK1/Parkin-mediated mitophagy. *Journal of Ethnopharmacology*, *271*, 113855.

Xia, Z., Dickens, M., Raingeaud, J., Davis, R. J., & Greenberg, M. E. (1995). Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis. *Science*, *270*, 1326–1331.

Xie, X., Yi, W., Zhang, P., Wu, N., Yan, Q., Yang, H., Tian, C., Xiang, S., Du, M., Getachew Assefa, E., Zuo, X., & Ying, C. (2017). Green tea polyphenols, mimicking the effects of dietary restriction, ameliorate high-fat diet-induced kidney injury via regulating autophagy flux. *Nutrients*, *9*, 497.

Xu, H., Deng, R., Li, E., Shen, J., & Wang, M. (2020a). Pinosylvin provides neuroprotection against cerebral ischemia and reperfusion injury through enhancing PINK1/Parkin mediated mitophagy and Nrf2 pathway. *Journal of Functional Foods*, *71*, 104019.

Xu, J., Yao, H., Wang, S., Li, H., & Hou, X. (2020b). Mangiferin inhibits apoptosis and autophagy induced by Staphylococcus aureus in RAW264.7 cells. *Journal of Inflammation Research*, *13*, 847–857.

Xu, K., Liu, X. F., Ke, Z. Q., Yao, Q., Guo, S., & Liu, C. (2018). Resveratrol modulates apoptosis and autophagy induced by high glucose and palmitate in cardiac cells. *Cellular Physiology and Biochemistry*, *46*, 2031–2040.

Xu, T., Song, Q., Zhou, L., Yang, W., Wu, X., Qian, Q., Chai, H., Han, Q., Pan, H., Dou, X., & Li, S. (2021a). Ferulic acid alleviates lipotoxicity-induced hepatocellular death through the SIRT1-regulated autophagy pathway and independently of AMPK and Akt in AML-12 hepatocytes. *Nutrition & Metabolism*, *18*, 13.

Xu, X. H., Ding, D. F., Yong, H. J., Dong, C. L., You, N., Ye, X. L., Pan, M. L., Ma, J. H., You, Q., & Lu, Y. B. (2017). Resveratrol transcriptionally regulates miRNA-18a-5p expression ameliorating diabetic nephropathy via increasing autophagy. *European Review for Medical and Pharmacological Sciences*, *21*, 4952–4965.

Xu, Y., Propson, N. E., Du, S., Xiong, W., & Zheng, H. (2021b). Autophagy deficiency modulates microglial lipid homeostasis and aggravates tau pathology and spreading. *Proceedings of the National Academy of Sciences*, *118*, e2023418118.

Xue, Y., Du, M., & Zhu, M.-J. (2017). Quercetin suppresses NLRP3 inflammasome activation in epithelial cells triggered by Escherichia coli O157:H7. *Free Radical Biology and Medicine*, *108*, 760–769.

Yamagata, K., Xie, Y., Suzuki, S., & Tagami, M. (2015). Epigallocatechin-3-gallate inhibits VCAM-1 expression and apoptosis induction associated with LC3 expressions in TNFα-stimulated human endothelial cells. *Phytomedicine*, *22*, 431–437.

Yan, J., Feng, Z., Liu, J., Shen, W., Wang, Y., Wertz, K., Weber, P., Long, J., & Liu, J. (2012). Enhanced autophagy plays a cardinal role in mitochondrial dysfunction in type 2 diabetic Goto–Kakizaki (GK) rats: Ameliorating effects of (−)-epigallocatechin-3-gallate. *Journal of Nutritional Biochemistry*, *23*, 716–724.

Yang, C., Zhang, R., Wang, S., Tian, Y., Yang, Y., Liu, J., & Ma, Y. (2022). Astragalin Ameliorates Cognitive Dysfunction Through Inhibiting PI3K/Akt-MTOR-Mediated Autophagic Flow in Hippocampal Neurons of APP/PS1 Mice.

Yang, Y., & Liang, C. (2015). MicroRNAs: An emerging player in autophagy. *ScienceOpen Research*, *2015*, https://doi.org/10.14293/S2199-1006.1.SOR-LIFE.A181CU.v1

Yao, Q., Ke, Z.-Q., Guo, S., Yang, X.-S., Zhang, F.-X., Liu, X.-F., Chen, X., Chen, H.-G., Ke, H.-Y., & Liu, C. (2018). Curcumin protects against diabetic cardiomyopathy by promoting autophagy and alleviating apoptosis. *Journal of Molecular and Cellular Cardiology*, *124*, 26–34.

Ying, H.-Z., Zang, J.-N., Deng, L.-L., Wang, Z.-Y., & Yu, C.-H. (2013). Pentamethylquercetin reduces fat deposition via Sirt1-mediated pathways in male obese mice induced by a high fat diet. *Food and Chemical Toxicology*, *62*, 463–469.

Yu, X., Xu, Y., Zhang, S., Sun, J., Liu, P., Xiao, L., Tang, Y., Liu, L., & Yao, P. (2016). Quercetin attenuates chronic ethanol-induced hepatic mitochondrial damage through enhanced mitophagy. *Nutrients*, *8*, 27.

Yuan, C., Jin, Y., Yao, L., Liu, L., Li, J., Li, H., Lai, Y., Chen, Z., Pan, Z., Han, T., Ke, D., Li, C., Wang, S., Wang, M., Yamahara, J., & Wang, J. (2020). Rhodiola crenulata root extract ameliorates fructose-induced hepatic steatosis in rats: Association with activating autophagy. *Biomedicine & Pharmacotherapy*, *125*, 109836.

Zachari, M., Ganley, & Ian, G. (2017). The mammalian ULK1 complex and autophagy initiation. *Essays In Biochemistry*, *61*, 585–596.

Zeng, H., Guo, X., Zhou, F., Xiao, L., Liu, J., Jiang, C., Xing, M., & Yao, P. (2019). Quercetin alleviates ethanol-induced liver steatosis associated with improvement of lipophagy. *Food and Chemical Toxicology*, *125*, 21–28.

Zhang, B., Buya, M., Qin, W., Sun, C., Cai, H., Xie, Q., Xu, B., & Wu, Y. (2013). Anthocyanins from Chinese bayberry extract activate transcription factor Nrf2 in β cells and negatively regulate oxidative stress-induced autophagy. *Journal of Agricultural and Food Chemistry*, *61*, 8765–8772.

Zhang, H., Wu, H., Yin, S., Hu, H., & Zhao, C. (2020a). Punicalagin inhibits palmitate acid-induced lipoapoptosis through inhibition of ER stress, and activation of SIRT1/autophagy in HepG2 cells. *Journal of Food and Nutrition Research*, *8*, 536–542.

Zhang, W., Cheng, C., Sha, Z., Chen, C., Yu, C., Lv, N., Ji, P., Wu, X., Ma, T., Cheng, H., & Shi, L. (2021a). Rosmarinic acid prevents refractory bacterial pneumonia through regulating Keap1/Nrf2-mediated autophagic pathway and mitochondrial oxidative stress. *Free Radical Biology and Medicine*, *168*, 247–257.

Zhang, X., Deng, Y., Xiang, J., Liu, H., Zhang, J., Liao, J., Chen, K., Liu, B., Liu, J., & Pu, Y. (2020b). Galangin improved non-alcoholic fatty liver disease in mice by promoting autophagy. *Drug Design, Development and Therapy*, *14*, 3393–3405.

Zhang, Y., Aisker, G., Dong, H., Halemahebai, G., Zhang, Y., & Tian, L. (2021b). Urolithin A suppresses glucolipotoxicity-induced ER stress and TXNIP/NLRP3/IL-1β inflammation signal in pancreatic β cells by regulating AMPK and autophagy. *Phytomedicine*, *93*, 153741.

Zhang, Y., Cao, Y., Chen, J., Qin, H., & Yang, L. (2019). A New possible mechanism by which punicalagin protects against liver injury induced by type 2 diabetes mellitus: Upregulation of autophagy via the Akt/FoxO3a signaling pathway. *Journal of Agricultural and Food Chemistry*, *67*, 13948–13959.

Zhang, Y., Chen, M.-L., Zhou, Y., Yi, L., Gao, Y.-X., Ran, L., Chen, S.-H., Zhang, T., Zhou, X., Zou, D., Wu, B., Wu, Y., Chang, H., Zhu, J.-D., Zhang, Q.-Y., & Mi, M.-T. (2015). Resveratrol improves hepatic steatosis by inducing autophagy through the cAMP signaling pathway. *Molecular Nutrition & Food Research*, *59*, 1443–1457.

Zhang, Y., Goldman, S., Baerga, R., Zhao, Y., Komatsu, M., & Jin, S. (2009). Adipose-specific deletion of autophagy-related gene 7 (atg7) in mice reveals a role in adipogenesis. *Proceedings of the National Academy of Sciences*, *106*, 19860–19865.

Zhang, Y., Yang, Y., Yu, H., Li, M., Hang, L., & Xu, X. (2020c). Apigenin protects mouse retina against oxidative damage by regulating the Nrf2 pathway and autophagy. *Oxidative Medicine and Cellular Longevity*, *2020*, 9420704.

Zhang, Y., Zhang, Y., Halemahebai, G., Tian, L., Dong, H., & Aisker, G. (2021c). Urolithin A, a pomegranate metabolite, protects pancreatic β cells from

apoptosis by activating autophagy. *Journal of Ethnopharmacology*, *272*, 113628.

Zhang, Y. P., Yang, X. Q., Yu, D. K., Xiao, H. Y., & Du, J. R. (2021d). Nrf2 signalling pathway and autophagy impact on the preventive effect of green tea extract against alcohol-induced liver injury. *Journal of Pharmacy and Pharmacology*, *73*, 986–995.

Zhao, H., Tang, M., Liu, M., & Chen, L. (2018). Glycophagy: An emerging target in pathology. *Clinica Chimica Acta*, *484*, 298–303.

Zhou, H., Chen, Y., Huang, S.-W., Hu, P.-F., & Tang, L.-J. (2018). Regulation of autophagy by tea polyphenols in diabetic cardiomyopathy. *Journal of Zhejiang University. Science. B*, *19*, 333–341.

Zhou, J., Farah, B. L., Sinha, R. A., Wu, Y., Singh, B. K., Bay, B.-H., Yang, C. S., & Yen, P. M. (2014). Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, stimulates hepatic autophagy and lipid clearance. *Plos One*, *9*, e87161.

Zhu, X., Xiong, T., Liu, P., Guo, X., Xiao, L., Zhou, F., Tang, Y., & Yao, P. (2018). Quercetin ameliorates HFD-induced NAFLD by promoting hepatic VLDL assembly and lipophagy via the IRE1a/XBP1s pathway. *Food and Chemical Toxicology*, *114*, 52–60.

How to cite this article: Wang, Z., Quan, W., Zeng, M., Wang, Z., Chen, Q., Chen, J., Christian, M., & He, Z. (2023). Regulation of autophagy by plant-based polyphenols: A critical review of current advances in glucolipid metabolic diseases and food industry applications. *Food Frontiers*, 1–29. https://doi.org/10.1002/fft2.255