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REVIEW ARTICLE

Dietary Polyphenols and Obesity: A Review of Polyphenol Effects on Lipid and Glucose Metabolism, Mitochondrial Homeostasis, and Starch Digestibility and Absorption

Courage Sedem Dzah[1] · David Asante-Donyinah[1] · Emmanuel Letsyo[1] · John Dzikunoo[1] · Zeenatu Suglo Adams[1]

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Abstract

Obesity is a major global public health concern, limiting socio-economic development and human productivity. As studies focus on finding sustainable solutions to this challenge, polyphenols have shown promising results and have become a research focus. This is mainly because of associated lower risks of side effects with their use, compared to synthetic pharmaceuticals. In this study, the anti-obesity potentials of dietary polyphenols have been reviewed. Using a narrative approach, the biological activities of polyphenols and their influence on energy metabolism and mechanisms are discussed. Specifically, their roles in insulin-dependent glucose uptake, insulin sensitivity, lipid metabolism and storage in adipocytes, starch digestibility, and regulation of mitophagy and mitogenesis in muscle cells and adipocytes, were considered. After considering the major findings of many related studies, it was confirmed that polyphenols can prevent and ameliorate obesity by fighting insulin resistance (IR) induced by pro-inflammatory cytokines, scavenging reactive oxygen species (ROS) and limiting their effects, and by regulating the expression and/or activity of key enzymes along relevant pathways. More human studies are needed to reveal more about the anti-obesity effects of dietary polyphenols and their effective doses in humans.

Keywords Dietary polyphenols · Insulin resistance · Obesity · Glucose metabolism · Lipid metabolism · Adipogenesis

Abbreviations

IR	Insulin resistance
ROS	Reactive oxygen species
EGCG	Epigallocatechin-3-*O*-gallate
RSV	Resveratrol
GA	Gallic acid
CRC	Curcumin
IS	Insulin sensitivity
CR	Caloric restriction
GLUT	Glucose transporter
GSV	Glucose transporter storage vesicle
NF-kB	Nuclear factor kappa B
JNK	C-Jun N-terminal kinase
SFA	Saturated fatty acid
TNF α	Tumor necrosis factor alpha
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NOX	NADPH oxidase
IRS-1	Insulin receptor substrate 1
PI3K	Phosphatidylinositol-3-kinase
Akt	Collective name of a set of three serine/threonine-specific protein kinases
NO	Nitric oxide
eNOS	Endothelial NO synthase
mTOR	Mammalian target of rapamycin
HepG2	Human liver cells
IR-HepG2	Insulin resistant human liver cells
PEPCK	Phosphoenolpyruvate carboxykinase
G6Pase	Glucose-6-phosphatase

David Asante-Donyinah, Emmanuel Letsyo, John Dzikunoo and Zeenatu Suglo Adams contributed equally to this work.

✉ Courage Sedem Dzah
cdzah@htu.edu.gh

David Asante-Donyinah
dasantedonyinah@htu.edu.gh

Emmanuel Letsyo
eletsyo@htu.edu.gh

John Dzikunoo
jdzikunoo@htu.edu.gh

Zeenatu Suglo Adams
zadams@htu.edu.gh

[1] Department of Food Science and Technology, Faculty of Applied Sciences and Technology, Ho Technical University, P.O. Box HP217, Ho, Volta Region, Ghana

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LDL	Low density lipoprotein
HDL	High density lipoprotein
RGPD	Red grape pomace drink
AMPK	AMP-activated protein kinase
PTB1B	Protein tyrosine phosphatase 1B
LKB1	Liver kinase B1
CaMKK	Calcium/calmodulin-dependent protein kinase kinase
RA	Rosmarinic acid
IGF-1	Insulin-like growth factor 1
SREBP	Sterol regulatory-element binding proteins
PPAR	Peroxisome proliferator-activated receptors
G3P	Glyceraldehyde 3-phosphate
GPDH	Glycerol-3-phosphate dehydrogenase
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
FABP4	Fatty acid binding protein 4
LXR-α	Liver X receptor alpha
PGC-1	Peroxisome proliferator-activated receptor-gamma coactivator-1alpha
Ucpl	Uncoupling protein 1
CIDEA	Cell death-inducing DNA fragmentation factor alpha-like effector A
Tbx1	Tata-box protein 1
Cd137	Tumor necrosis factor receptor superfamily member 9
BAT	Beige adipose tissue
iWAT	Inguinal white adipose tissues
SIRT1	Sirtuin 1
SCD 1	Stearoyl-Coenzyme A desaturase 1
ATP	Adenosine triphosphate
NAD	Nicotinamide adenine dinucleotide
FOXO3	Forkhead box O3
UNC51	Autophagy-related serine/threonine kinase
ULK1	UNC-51-like kinase 1
PINK 1	PTEN induced putative kinase 1
PTEN	A tumor suppressor phosphatase and tensin homolog
ERK2	Mitogen-activated protein kinase 1 (MAPK1)
NAMPT	Nicotinamide phosphoribosyltransferase
PKD	Protein kinase D

Introduction

Obesity in humans is defined by an excessive accumulation of fats in the body that presents health risks such as cardiovascular disease, diabetes and metabolic disorders among others. Studies done from 1960—1962 through 2017—2018 showed that about 42.5% of adults were either obese or were severely obese [1]. In Europe, an annual increase in the percentage of obese people has been observed [2]. Also, an increase in the number of non-communicable diseases such as obesity, hypertension and diabetes has been observed in Africa recently [3]. In Malawi, obesity was more prevalent among urban dwellers than rural counterparts [3]. Besides the negative health implications of obesity, it contributes to economic burden on states and individual households, worsening living conditions, poverty, and productivity [4].

Medication and lifestyle changes have been recommended as ways of managing and treating obesity. Whereas the earlier may present adverse side effects, the latter also poses a challenge of discipline among others. These have led to a global preference for the use of foods or natural compounds in various forms. Recently, studies have found that, foods rich in polyphenols, such as fruits, vegetables, herbal plant materials, whole grains, and seeds, have the ability to influence the development of obesity. These polyphenols play many roles in the prevention and management of obesity [5]. For example, high dietary intake of polyphenols significantly reduced body mass index (BMI) in women in The Netherlands [6]. Another epidemiological study in Poland found that, people who consumed up to or more than three cups of tea a day had lower BMI and waist circumference [7]. Several other epidemiological and clinical studies have shown that polyphenols in tea, coffee, and wine, fight against cancer, diabetes, neurodegenerative disorders, and obesity. In a cross-sectional study, chlorogenic acid, a major polyphenol in coffee, reduced obesity and insulin resistance (IR) in humans [8]. Epigallocatechin-3-*O*-gallate (EGCG), resveratrol (RSV), gallic acid (GA), and curcumin (CRC) have shown anti-obesity potential in humans [9]. Extensive literature on the anti-obesity effects of dietary polyphenols in humans can be found in an earlier study [10].

The anti-obesity properties of dietary polyphenols discussed in this study cover some major metabolic activities that influence energy homeostasis, notably glucose and lipid metabolism, starch digestibility and absorption, and mitochondrial homeostasis in humans. Polyphenols ameliorate obesity by reducing the amount of blood glucose in circulation and glycogen synthesis in adipocytes. This is done *via* up-regulation of insulin-dependent glucose uptake and metabolism, and improved insulin sensitivity (IS) in adipocytes. In lipid metabolism, dietary polyphenols aid to convert white fat into brown fat with high thermogenic properties [11]. They limit lipid digestion and absorption from diets by complexing with lipids, and also alter hepatic cholesterol homeostasis to reduce plasma lipid levels [12]. Dietary polyphenols also downregulate adipogenesis and lipogenesis, but upregulate lipolysis. They are also able to regulate mitochondrial homeostasis by altering the redox state of cells to either upregulate mitophagy in metabolically aberrant cells, or stimulate mitogenesis through ROS control, or induction of caloric restriction (CR). Moreover, polyphenols limit carbohydrate digestion and absorption to lower blood glucose levels. Also, polyphenol-rich starches

are more resistant with lower glycemic indexes, compared to others [13]. In order to manage or prevent obesity, it is recommended to reduce carbohydrates and lipids intake and increase dietary polyphenols consumption in foods.

In this study, the anti-obesity roles of dietary polyphenols and mechanisms of action are discussed. Specific effects on glucose and lipid metabolism, mitochondrial and energy homeostasis, and starch digestion and absorption are also reviewed, and recommendations for future studies are made.

Search Strategy and Selection of Studies

Electronic searches done using Scopus, Science Direct and Web of Science databases were used to identify relevant journal publications from January 2017 to June 2021. The search terms were combinations of dietary polyphenols with either obesity, overweight, hyperlipidemia, hyperinsulinemia, steatosis, or diabetes. The search terms used were in English language. Titles and abstracts were used to screen studies for full-text review. The inclusion criteria favored studies that reported results on the effects of dietary polyphenols or polyphenols on: 1) insulin-dependent glucose uptake in cells, 2) insulin sensitivity amelioration in adipocytes, 3) mitochondrial homeostasis, 4) glucose and lipid metabolism, 5) starch digestibility and absorption, and 6) gut microflora/ microbiota. Out of 1071 initial references for all mentioned databases, 109 studies were included after duplicate removal and extensive screening.

Polyphenols and Energy Metabolism Regulatory Mechanisms

Energy metabolism and obesity are strongly linked, bringing glycolysis and lipolysis into perspective [14]. These two mechanisms produce cellular energy *via* mitochondrial respiration. Efficient energy use and prevention of excess storage in adipocytes is required to prevent obesity and attendant challenges. Thus, an imbalance in energy metabolism, where energy expenditure is less than energy production and storage (positive energy balance), increases the risk of obesity. To prevent or ameliorate obesity, dietary polyphenols have become relevant in regulating glucose and lipid metabolism, starch digestibility and absorption, and mitochondrial homeostasis in humans [15].

Influence on Cellular Glucose Uptake *via* Insulin-Dependent Pathways

Satoh has outlined various mechanisms of insulin-dependent cellular glucose uptake in skeletal muscles and adipocytes [16, 17]. The role of dietary polyphenols in insulin mediated signaling in cells, and the corresponding upregulation of glucose uptake *via* kinases activation and/or phosphorylation, among other functions, are discussed in this section. Glucose is made available through carbohydrate digestion and absorption from the gut into the blood. Glucose catabolism and oxidation is preceded by its absorption either *via* insulin-dependent or non-dependent pathways. Pancreatic beta (β) cells synthesize insulin to modulate glucose uptake *via* its ability to regulate distribution and exocytosis of glucose transporter (GLUT4) from glucose transporter storage vesicles (GSV) to the plasma membrane for active glucose transport into cells. Thus, insulin increases glucose uptake principally by increasing plasma membrane concentration of GLUT4 rather than increasing transporter activity [18]. A schematic representation of the insulin-dependent glucose uptake mechanism is shown in Fig. 1.

Insulin resistance (IR) partly occurs as a result of inflammation, *via* nuclear factor kappa B (NF-kB) and c-Jun N-terminal kinase (JNK1/2) proinflammatory cytokines activation by saturated fatty acids (SFA), or by tumor necrosis factor alpha (TNFα) (Fig. 1). Under high cellular glucose concentration and inflammation, NADPH oxidase (NOX) induces elevated ROS generation, which may damage cells and limit their functions [19]. For example, damage to pancreatic β cells may upregulate insulin synthesis (hyperinsulinemia) to sustain glucose uptake in response to insulin insensitivity. These β cells may be permanently damaged at high levels of proinflammatory cytokines and ROS, especially under chronic conditions, resulting in hypoinsulinemia and glucose intolerance. In conditions of high blood glucose concentration, insulin mediates the translocation of GLUT4 pools to the plasma membrane *via* its receptor (IRS-1) by activating the phosphatidylinositol 3-kinase (PI3K)/Akt pathway (Fig. 1). IR may also occur when ROS generated by NOX inhibits nitric oxide (NO)-mediated vascular reactivity, consequently limiting GLUT4 translocation from GSV [19]. It should also be noted that, the activation of NF-kB/JNK1/2 pro-inflammatory cytokines inhibits the PI3K/Akt pathway, resulting in hyperglycemia and glucose intolerance [17].

Meanwhile, polyphenols increase the ability of cells to take up glucose for energy production *via* insulin-dependent pathways. The antioxidant and anti-inflammatory properties of dietary polyphenols prevent ROS-mediated damage to pancreatic β cells and NO inhibition, consequentially, preventing and/or ameliorating IR, glucose intolerance and obesity [20]. Also, dietary polyphenols activate the PI3K/Akt/endothelial NO synthase (eNOS) pathway to induce NO production and GLUT4 translocation for increased glucose uptake (Fig. 1) [21]. Empirically, polyphenol-rich *Molineria latifolia* rhizome extract increased glucose uptake *via* mTOR/Akt-induced GLUT4 translocation in adipocytes. Furthermore, dietary polyphenols from Calafate (*Berberis microphylla)* increased

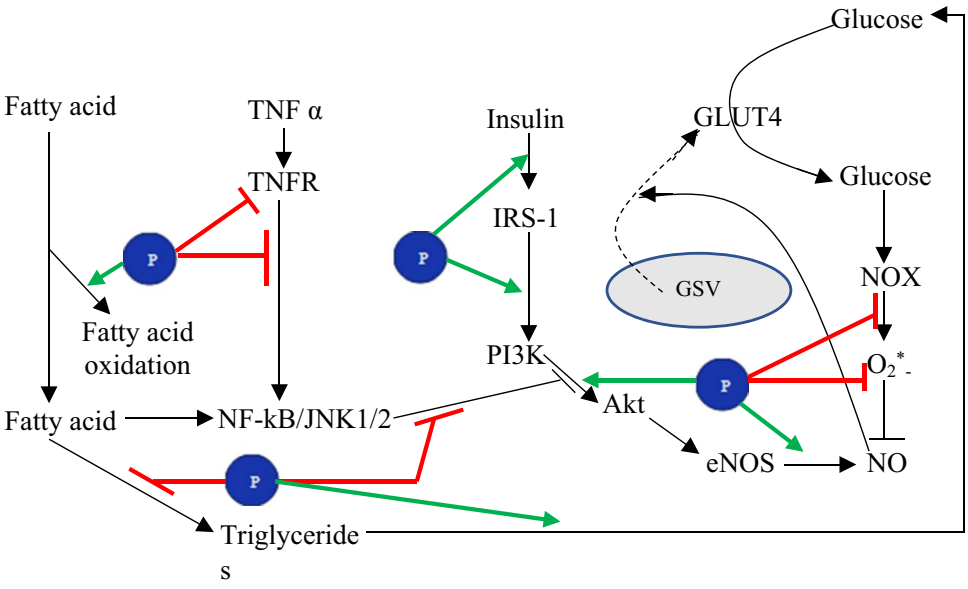

Fig. 1 Simplified mechanism of insulin-dependent glucose uptake by adipose or muscle tissue and the regulatory role of dietary polyphenols [17–20]. P = polyphenols

glucose uptake by increasing insulin sensitivity in adipocytes [22]. Xia et al. [23] also showed that polyphenol-rich vinegar extract increased glucose uptake and breakdown in high glucose-induced insulin resistant HepG2 (IR-HepG2) cells by inhibiting IRS-1 phosphorylation and activating the PI3K/Akt pathway [23]. The extract also reduced ROS generation and inhibited JNK cytokine expression in the cells [23].

Although *in vitro* observations may not be confirmed in *in vivo* experiments, some studies have reported polyphenols ability to increase insulin sensitivity and glucose uptake in humans. In a human trial, healthy men, aged between 20 and 40 years, were fed a red grape pomace drink (RGPD) after which fasting blood samples were tested for plasma glucose concentrations, insulin, triglyceride and phenolic metabolites [24]. Although no significant effects on glycemic and triglyceride responses were observed, insulin sensitivity (S_I) index increased by 36% [24]. Considering phenolic metabolites, GA levels correlated positively with insulin sensitivity, showing that the consumption of RGPD ameliorated IR in humans [24]. A summary of some other studies on the effect of dietary polyphenols on the insulin-dependent glucose uptake is given in Table 1.

Moreover, naringenin, a citrus flavonoid, stimulated glucose uptake in a dose- and time-dependent fashion. This was due to AMPK activation, which depended on the activation of liver kinase B1 (LKB1) and calmodulin-dependent protein kinases (CaMKKs), and phosphorylation [38]. Also, rosmarinic acid (RA) in rosemary polyphenol extract activated AMPK *via* phosphorylation and increased glucose uptake in rat muscle cells in a manner comparable to maximal insulin effects [25].

Influence of Dietary Polyphenols on Lipid Metabolism and Storage in Adipocytes

Lipogenesis and Lipid Storage in Adipocytes

Lipogenesis occurs when acyl-CoA is not used in the citric acid cycle to produce energy, but converted back into fatty acids for storage in adipocytes (adipogenesis). Also, when lipolysis is not favored, adipogenesis usually occurs, potentially resulting in obesity. Several pathways regulate these processes in both adipose tissues and skeletal muscles. The insulin- or insulin-like growth factor (IGF-1)- dependent pathway, involving sterol regulatory element binding protein (SREBP), PI3K, peroxisome proliferator-activated receptors (PPAR) and Akt, regulates lipid metabolism (Fig. 2) [39]. Also, the pro-inflammatory TNF-α–JNK/NF-kB elements induce IR and hyperglycemia, damage pancreatic β cells, cause hyperinsulinemia and/ or hypoinsulinemia, and reduce GLUT4 translocation. When IR is induced, new adipocytes are recruited to store excess energy by converting glucose into triglycerides through glycerol-3-phosphate (G3P) *via* the activity of aldolase and G3P dehydrogenase (GPDH), or by hepatic conversion of fatty acyl-CoA into triglycerides (Fig. 2) [9]. Inflammation also favors lipogenesis and adipogenesis by inhibiting PI3K-Akt- mediated PPAR expression/activity (Fig. 2). Free fatty acids (FFA) can also be converted into triglycerides

Table 1 A summary on the roles of dietary polyphenols on glucose metabolism

Tested biomolecule	Source	Summary of result	Reference
Rosmarinic acid	Rosemary plant	Rosmarinic acid activated AMP-activated protein kinase (AMPK) and increased skeletal muscle glucose uptake in L6 rats	[25]
Caffeic acid	Coffee beans	Caffeic acid improved insulin-independent glucose transport by increasing AMPK activity in rats	[26]
Polyphenols	Marine brown algae	Inhibited α-glucosidase and α-amylase activity, increased glucose uptake, inhibited protein tyrosine phosphatase 1B (PTP 1B) and increased insulin sensitivity in type 2 diabetic mice	[27]
Polyphenols	*Cinnamomum cassia* bark	Reduced blood sugar levels in Wistar rats	[28]
Polyphenols	Red grapes	AMPK activated by resveratrol, EGCG, berberine, and quercetin	[29]
Polyphenols	Various plants	Regulated glucose and lipid homeostasis	[30]
Polyphenols	Green tea	Increased serum insulin levels and increased glucose uptake in obese mice	[31]
Polyphenols	*Myrciaria jaboticaba* peel	Increased insulin sensitivity and reduced blood glucose concentration in humans	[32]
Polyphenols	Barley sprout	Increased AMPK activity and enhanced cholesterol and glucose metabolism *in vitro* and *in vivo*	[33]
Polyphenols	Rutgers Scarlet lettuce	Increased glucose uptake and reduced liver lipid accumulation in obese mice	[34]
Polyphenols	Red grape pomace	Increased inulin sensitivity by 36% after red grape pomace polyphenol administration in humans	[24]
Polyphenols	Apple (*Malus domestica Borkh. cv. Red Fuji)*	Promoted glycogen synthesis, inhibited gluconeogenesis, improved insulin resistance, and improved mitochondrial function	[35]
Flavonoids	*Enicostema littorale* blume	Enhanced glucose uptake in IR-HepG2 cells by activating the IRS-1/PI3K/Akt pathway	[36]
Polyphenols	*Molineria latifolia* rhizome	Improved glucose uptake *via* mTOR/Akt-activated GLUT4 translocation	[37]
Polyphenols	Calafate extract	Increased glucose tolerance in high-fat-fed mice	[22]

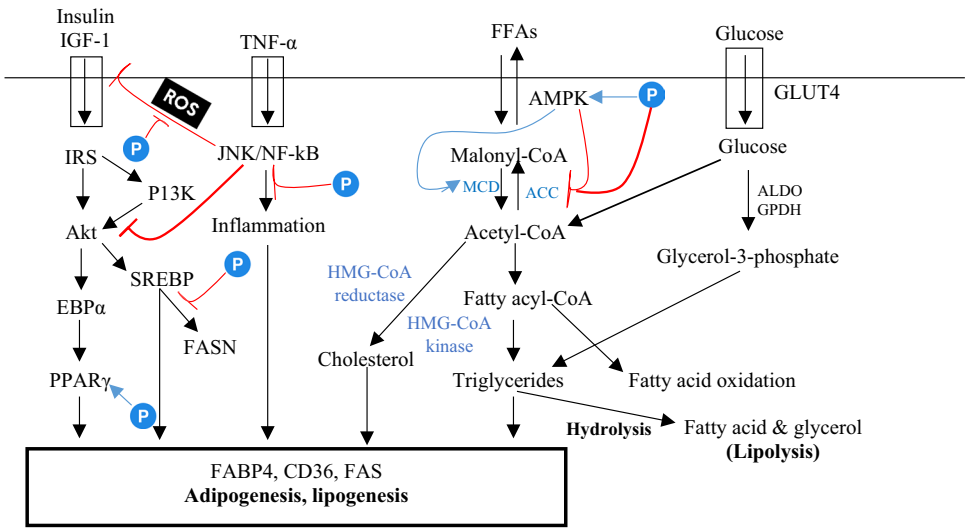

Fig. 2 Modified sketch of pathways that regulate lipid metabolism and adipogenesis, and the role of dietary polyphenols. P = polyphenol [9, 20, 40–44]

and stored in adipocytes in the presence of excess glucose. By limiting glycolysis through reduction in GLUT4 translocation as a result of PI3K-Akt pathway inhibition by JNK/NF-kB cytokines, acetyl-CoA from malonyl-CoA and glucose, is converted into cholesterol by HMG-CoA reductases and kinases and stored in adipocytes (Fig. 2) [39].

The benefits of dietary polyphenols are seen in their ability to regulate lipid metabolism and storage in adipocytes through many diverse pathways. According to Ali et al. [45], cocoa polyphenols alleviated obesity-induced liver steatosis by increasing lipolysis and inhibiting lipogenesis in obese rats [45]. Pomegranate polyphenols also reduced triglyceride accumulation and inhibited adipogenesis by reducing the expression of adipogenic genes, such as adiponectin, nuclear receptor, PPARγ, and fatty acid binding protein (FABP4) in adipocytes [40] (Fig. 2).

Studies have shown that dietary polyphenols are natural ligands of PPAR-α and LXR-α *in vitro*, which suggests that polyphenols may regulate lipolytic pathways [45]. Epigallocatechin gallate, capsaicin, curcumin, quercetin and resveratrol increased lipolysis and induced fatty acid (FA) β-oxidation by modulating PPARγ coactivator-1 (PGC-1), hormone-sensitive lipase, carnitine acyl transferase and acetyl-coA carboxylase (Fig. 2) [44]. Also, dietary polyphenols increased the levels of beige adipocytes, thereby reducing adipocyte density [46]. For example, thermogenic adaptations were induced in inguinal white adipose tissue [47] by apple polyphenols which upregulated the expression of genes selectively encoding beige adipocytes (Ucp1, CIDEA, Tbx1, Cd137) and increased the activities of mitochondrial oxidative phosphorylation enzymes [46]. Resveratrol also stimulated cellular energy expenditure and reduced the accumulation of iWAT through the formation of beige adipose tissue (BAT) [48]. Also, vanillic acid accelerated thermogenesis and the biosynthesis of mitochondria in both BAT and iWAT in high-fat-fed mice [49]. This was partly facilitated by activating interscapular BAT, shown in increased Ucp1 expression. Thus, obesity and lipid deposition in adipocytes can be reduced by dietary polyphenols through the induction of BAT. For example, immature *Citrus reticulata* water extract, rich in polyphenols, was found to markedly reduce obesity in high-fat-fed mice *via* conversion of iWAT into BAT [50]. Moreover, the role of polyphenols on gut microbiota-dependent lipid metabolism cannot be overemphasized [43]. Gut microbiota metabolize dietary polyphenols to produce small bioactive compounds and molecules, which in turn influence the manner in which these microorganisms regulate host lipid metabolism in a symbiotic relationship [43, 51]. When resveratrol-gut microbiota were transplanted into high-fat diet-fed mice, iWAT were converted into BAT and as well improved lipid metabolism [11]. Dietary polyphenols also reduced plasma lipid levels and endotoxemia. They further increased macrophage recruitment into adipose tissues and significantly reduced the buildup of cholesterol and cholesterol oxides in adipocytes in obese mice [52].

Moreover, a placebo-controlled, double-blind, randomized clinical trial showed that dietary polyphenols might reduce the risks of cardiovascular disease and atherosclerosis by reducing triglyceride levels in humans [53]. Also, diet-induced obesity in mice was prevented by flavonoids from *Scutellaria baicalensis* due to their ability to accelerate lipid oxidation [54]. The improvements observed in lipid metabolism in obese mice, and the mechanisms involved might be associated with the NAD-dependent deacetylase sirtuin-1 (SIRT1)/AMPK pathway [55].

Nonetheless, phenolic acids also reduced body weight and increased lipid oxidation in mice by regulating insulin, leptin, and adiponectin [56]. In another study, phenolic acids ameliorated obesity and related metabolic disorders through the down-regulation of fatty acid synthase (FAS), SREBP1, and stearyl coenzyme A desaturase 1 (SCD1) [43] (Fig. 2). Also, glucose and lipid homeostasis were improved by ferulic acid in high-fat diet-induced obese mice due to its ability to downregulate liver gluconeogenesis proteins (phosphoenolpyruvate carboxylase (PEPCK) and glucose-6-phosphatase

Table 2 The roles of polyphenols on lipid metabolism

Tested biomolecule	Source	Result	Reference
Polyphenol extract	*Rosa rugosa* Thunb	Improved hepatic steatosis and liver function by induction of AMPK signaling in the control of dyslipidemia	[58]
Polyphenols	Rutgers Scarlet lettuce	Lowered liver to body weight ratio and decreased total liver lipids in diet-induced obese C57BL/6 mice	[34]
Polyphenols	Annurca apple flesh	Inhibited lipase activity, enhanced low density lipoprotein (LDL) receptor binding activity and increased high density lipoprotein (HDL) levels liver cancer cell lines	[59]
Oligomeric procyanidins	Apple	May reduce hypertriacylglycerolemia by inhibiting pancreatic lipase to reduce triglyceride absorption	[60]
Polyphenols	Annurca apple	Decreased cholesterol uptake in human liver cancer cells	[61]
Polyphenols	Various plants	Polyphenols can affect lipid homeostasis through multiple mechanisms	[30]
Polyphenols	Various plants	Regulated lipid metabolism and attenuated dyslipidemia and insulin resistance	[62]
Polyphenols	Apple	Converted white adipose tissues (WAT) to beige adipose tissues (BAT)	[46]
Polyphenols	*Citrus reticulata*	Induced browning of WAT	[50]
Resveratrol	Grapes	Stimulated energy expenditure and increased BAT	[48]
Vanillic acid	Grapes	Accelerated thermogenesis and mitogenesis in both BAT and WAT in high-fat fed mice	[49]

(G6Pase)) expression [57]. Many other evidences of the effects of polyphenols on lipid metabolism are summarized in Table 2.

Polyphenols and Mitochondrial Homeostasis and Energy Metabolism

Mitochondrial Homeostasis through Mitogenesis and Mitophagy

The uptake of glucose and its subsequent use in energy generation, are closely linked to mitochondrial activity in cells. The inability of cells to produce energy from respiration implies residual glucose in blood and adipogenesis, hence obesity development. With other normal cellular functions, when mitochondria efficiently function and regulate energy metabolism and homeostasis, metabolic disorders can be prevented and/or managed.

Mitochondrial quality control and homeostasis in living things depend on autophagy of dysfunctional mitochondria and biogenesis to replace degraded ones. Malfunctioning mitochondria, through a cascade of pathway reactions, undergo mitophagy induced by either polyphenols (*i.e.*, acting as pro-oxidants) and/or ROS [63]. The tight correlation between the degradation and biogenesis of mitochondria can dysregulate due to ageing, and this is a major cause of metabolic imbalance and related disorders [64]. At the molecular level, aberrant and dysfunctional mitochondria, which are common among the aged, and also among sedentary people, are a common reason behind the development of obesity [65]. Exercise and active lifestyle have been cited to improve mitochondrial homeostasis in humans by increasing the rate of mitogenesis in muscle cells to revamp efficient respiration [66].

The Role of Polyphenols in Mitochondrial Homeostasis

The effects of dietary polyphenols on mitophagy and mitogenesis through the induction of caloric restriction (CR) in mitochondria have been given attention in recent times [67]. Dietary polyphenols have shown CR mimetic properties, which influence mitochondria homeostasis by inducing molecular mechanisms that regulate mitophagy and mitogenesis pathways (Fig. 3) [68]. The expression of mitogenesis-related genes is required for mitochondrial biogenesis. These genetic mechanisms are controlled by PGC1-α, the best-known mediator for mitogenesis, and

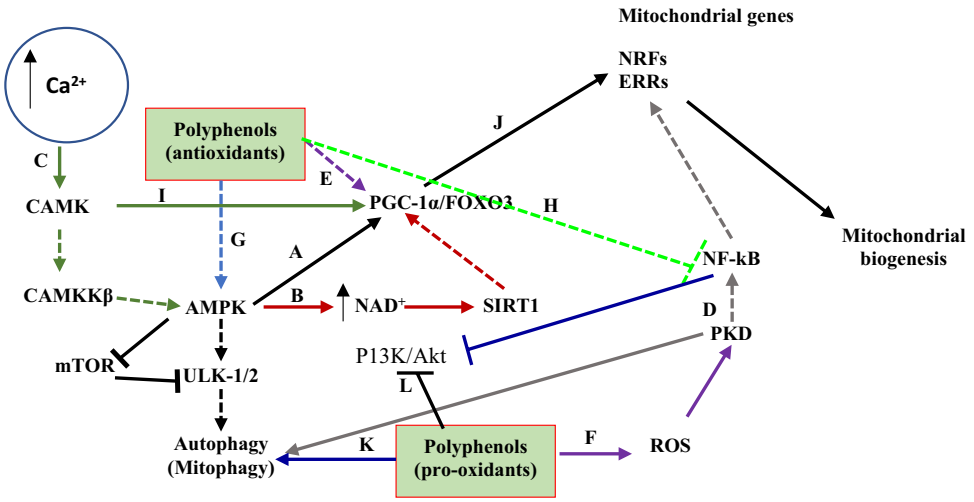

Fig. 3 Modified molecular pathways to mitogenesis and mitophagy. (**A**) AMPK mediates two responses that promote mitophagy by activating ULK-1/2 (broken black), and mitogenesis by activating PGC-1α (solid black). (**B**) AMPK increases NAD+levels and enhances SIRT1 activity (solid wine). SIRT1 deacetylates PGC-1α, inducing mitogenesis (broken wine). (**C**) Increased cytoplasmic Ca^{2+} levels activate CaMK, which phosphorylates PGC-1α (solid green) to promote mitogenesis and induce mitophagy *via* CAMKKβ/AMPK activation (broken green). (**D**) PKD is either activated to promote mitogenesis through NF-kB activation (broken ash) or autophagy in response to high ROS levels in mitochondria (solid ash). (**E**) Polyphenols which act as antioxidants activate PGC-1α to promote mitogenesis (broken purple). (**F**) Polyphenols which act as pro-oxidants induce mitophagy mediated by PKD indirectly *via* ROS generation (solid purple). (**G**) Activation of AMPK by polyphenols (broken blue). (**H**) Inhibition of mitogenesis through pro-inflammatory cytokines inhibition (broken light green) [39]. (**I**, **J**) CR induces AMPK which induces increased NAD^+ to promote mitogenesis through SIRT-1 induced PGC-1 α /FOXO3 pathway activation [42, 69]. (**K**, **L**) Pro-oxidant polyphenols can directly induce mitophagy (K) or inhibit PI3K-Akt pathway directly or indirectly through NF-kB, which also limits NO-induced GLUT4 translocation and glucose intake (L). Source: Modification of diagram from an earlier study [63] using information from other studies [39, 42, 68–72]

which can be activated by dietary polyphenol-induced CR [68]. During CR, adenosine triphosphate (ATP) depletion activates AMPK, which also increases cellular NAD^+ levels (Fig. 3) [68]. Consequentially, increased cellular NAD^+ levels activate SIRT1, a NAD^+-dependent enzyme that deacetylates PGC1-α and FOXO3, which also promotes mitogenesis [42]. Conversely, nutrient-depletion-activated AMPK promotes mitophagy in aberrant cells by inhibiting mTOR and activating UNC-51-like kinase 1 (ULK1) (Fig. 3). The canonical mitophagy mechanism in both muscle tissues and adipocytes is regulated by PTEN-induced kinase 1 (PINK1) and the cytosolic E3 ubiquitin ligase Parkin [41]. Detailed description of the pathways involved in mitophagy and mitogenesis are available in an earlier study [68].

The mitophagy-promoting properties of some polyphenols have also been studied. For example, resveratrol from red grapes has been reported to induce mitophagy in rat cardiac muscles by increasing SIRT3, FOXO3, PINK1, and Parkin activities [70]. The flavonoid, quercetin also induced mitophagy in mice liver cells by increasing FOXO3, AMPK, ERK2 and Parkin activities [71]. With keen interest, increased lipolysis has been observed to positively correlate with increased mitophagy in adipocytes, a phenomenon that may aid the fight against adipogenesis and obesity. Adipocytes are important when discussing whole-body energy homeostasis regulation, and advancement in this research area, especially regarding their autophagy, may provide new insights for the management of obesity, diabetes and other related metabolic disorders.

In addition, dietary polyphenols have been shown to activate SIRT1 directly or indirectly in a variety of models, *in vitro* and *in vivo* [72]. This has been found to essentially regulate key mechanisms such as CR, ROS generation, inflammation, mitochondrial homeostasis, adipogenesis, and many other cellular metabolic functions [72]. For example, resveratrol and quercetin activated SIRT1 indirectly *via* nicotinamide phosphoribosyltransferase (NAMPT) and AMPK activation, similar to CR-induced activation of AMPK. This may either induce mitophagy *via* ULK-1/2 activation, or mitogenesis *via* the SIRT1-PGC1-α pathway (Fig. 3) [69]. Increased oxidative stress, coupled with heightened depletion in NAD^+, limits the activation of the AMPK-SIRT1 pathway, hence the induction of mitophagy and blockage of the SIRT1-PGC1-α pathway-dependent mitogenesis (Fig. 3) [69], a phenomenon that may limit adipogenesis and enhance lipolysis.

The Effect of Dietary Polyphenols on Starch Digestion and Transport

Polyphenols have been shown to increase blood glucose uptake in skeletal muscle cells [25], but also limit the digestibility of starches by inhibiting α-amylase activity as a way of regulating blood glucose levels [73]. According to recent studies, the fraction of starches not digested by α-amylase were higher in polyphenol-rich pigmented sorghum than in the white variety [73]. This difference was attributed to the amounts of polyphenols, specifically, tannins they contained. In another study, it was found that dietary polyphenols increased the resistant starch content of starchy materials and changed their rheological properties, thereby retarding and/or inhibiting their digestion and absorption [74]. Further studies revealed that the anti-α amylase activity of polyphenols was due to their ability to bind the enzyme and prevent starch accessibility [27]. Another study showed that, co-digesting bread with berry phenolic extracts significantly ($p < 0.05$) reduced the rate and extent of starch digestion up to 61% [75]. Also, when lotus seed starch was complexed with green tea polyphenols (GTP), its physicochemical properties were influenced, such that, digestibility was reduced due to the formation of C-type crystalline structures and V-type inclusion complexes [75]. It was observed in a dynamic *in vitro* rat stomach–duodenum (DIVRSD) model that the V-type complexes on starch granule surfaces acted as a barrier against enzyme–substrate interaction, displaying a strong resistance to enzyme activity [75]. According to others, dietary polyphenols interfered with starch digestion by binding or inhibiting α-amylase- and α-glucosidase-dependent conversions of starch to maltooligosaccharides and glucose, respectively (Fig. 4) [74]. Polyphenols also induce insulin sensitivity and increase glucose uptake from blood into cells by activating PI3K/Akt-eNOS translocation of GLUT4 from GSV to the cellular plasma membrane for glucose transport [17, 19, 21].

Conclusion

Obesity is associated with energy metabolic disorder, and dietary polyphenols have shown some potential that can be further exploited. Among other biological anti-obesity activities, dietary polyphenols have been shown to stimulate glucose uptake in cells by enhancing insulin sensitivity in insulin-dependent pathways. Dietary polyphenols have also influenced lipid metabolism by limiting lipid absorption from diets. They have also mediated the conversion of iWAT to BAT to induce increased lipolysis rate, and reduce blood triglyceride levels. Concerning their role in energy homeostasis, dietary polyphenols have also played key roles in regulating mitogenesis and mitophagy in cells. By mimicking CR in cells, dietary polyphenols induce the translation of proteins that regulate mitophagy and mitogenesis pathways. They also modulate oxidative stress-related processes that enhance mitochondrial integrity and energy homeostasis in cells.

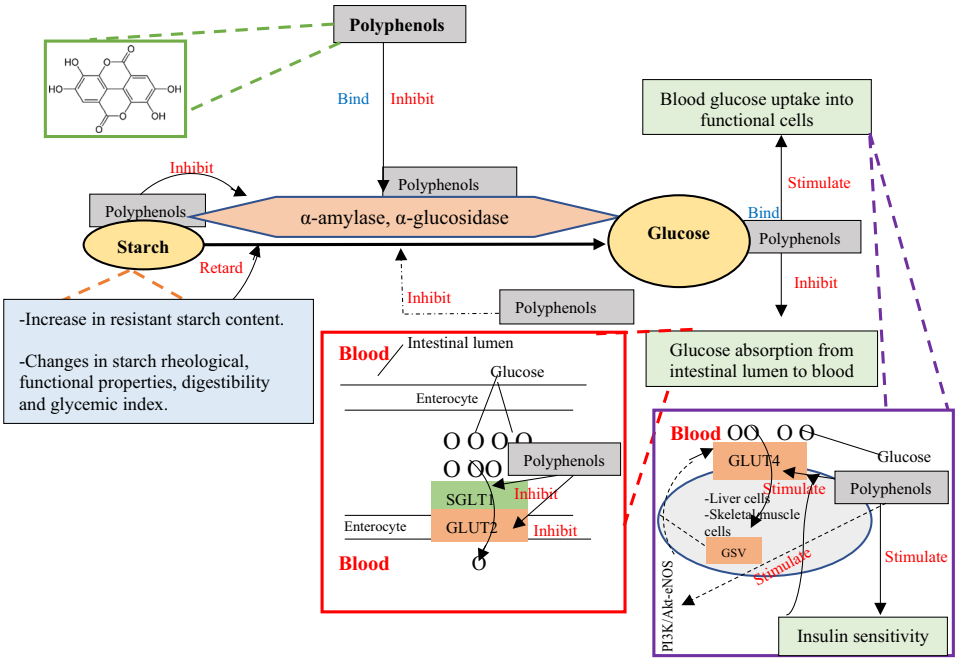

Fig. 4 Modified schematic representation of how polyphenols regulate starch digestion and absorption by binding, inhibiting or stimulating key enzymes and pathways [74]. Source: Modification of mechanism using information from other studies [19–22]

Furthermore, the co-digestion and co-ingestion of dietary polyphenols with starchy foods, and their interaction with gut-microflora, have been associated with reduced starch digestion and reduced starch glycemic index (GI), due to increased content of resistant component and α-amylase inactivation. Dietary polyphenols also limit the transport of glucose from the lumen of intestines and stimulate glucose uptake from the blood into cells. Being able to increase blood glucose uptake *via* AMPK and SIRT1 activation and other insulin-dependent pathways means reduced cellular dependence on insulin, whereas, limiting the digestibility and GI of starches culminates in lower influx of glucose after carbohydrate ingestion. These are promising findings that have the potential to offer great aid to the fight against obesity and diabetes in humans.

Future studies are needed to further identify specific factors that influence the anti-obesity properties of polyphenols *in vivo*, especially in humans, due to the limited number of studies. Particular attention on how different tissues, organs, and individual health statuses influence the anti-obesity activities of polyphenols must be considered along gender and occupational factors. Further investigation into the relationship between polyphenol structure and function is also needed to understand the mechanisms involved in the anti-obesity effects of dietary polyphenols in humans.

Authors' Contributions Courage Sedem Dzah conceptualized the study, drafted some sections, did the editing of the manuscript and finalized the paper. Emmanuel Letsyo and John Dzikunoo also drafted some sections of the paper and helped with proofreading, David Asante-Donyinah and Zeenatu Sugloh Adams contributed by drafting some sections of the paper. All authors read and approved the final version of the manuscript for submission.

Data Availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

Ethics Approval Ethics approval not applicable as no human tissues nor human subjects were used during the current study. This study only reviewed available literature.

Consent to Participate Not applicable as no human participants were used in the current study.

Consent for Publication All authors have agreed to publish this paper without any reservations whatsoever.

Conflicts of Interest Statement The authors have no competing interests to declare that are relevant to the content of this article.

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