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Review Article

Coffee, tea, and cocoa in obesity prevention: Mechanisms of action and future prospects

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ABSTRACT

Obesity, a major public health problem, causes numerous complications that threaten human health and increase the socioeconomic burden. The pathophysiology of obesity is primarily attributed to lipid metabolism disorders. Conventional anti-obesity medications have a high abuse potential and frequently deliver insufficient efficacy and have negative side-effects. Hence, functional foods are regarded as effective alternatives to address obesity. Coffee, tea, and cocoa, three widely consumed beverages, have long been considered to have the potential to prevent obesity, and several studies have focused on their intrinsic molecular mechanisms in past few years. Therefore, in this review, we discuss the mechanisms by which the bioactive ingredients in these three beverages counteract obesity from the aspects of adipogenesis, lipolysis, and energy expenditure (thermogenesis). The future prospects and challenges for coffee, tea, and cocoa as functional products for the treatment of obesity are also discussed, which can be pursued for future drug development and prevention strategies against obesity.

1. Introduction

Obesity, defined as an abnormal or excessive body fat accumulation, is a major health problem worldwide and a risk factor for several chronic disorders. Obesity usually occurs when the body's energy intake exceeds its energy expenditure, which is influenced by inherited, physiological, and/or environmental factors. Furthermore, obesity is a severe metabolic disease that can induce serious complications in all organs and is accompanied by several alterations at the hormonal, inflammatory, and endothelial levels (Seravalle and Grassi, 2017). These alterations in turn, stimulate various other mechanisms that may lead to the development of dyslipidemia, insulin resistance, type 2 diabetes mellitus, hypertension, atherosclerosis, inflammation, nonalcoholic steatohepatitis, and cancer, as well as increasing the risk of severe COVID-19 complications (Pirillo et al., 2021; Hildebrandt et al., 2023).

Pharmaceuticals that have been investigated for the treatment of obesity include mitochondrial uncouplers, sympathomimetics, serotonergic agonists, lipase inhibitors, cannabinoid receptor antagonists, and a family of gastrointestinal-derived peptides (Muller et al., 2018). Additionally, certain anti-obesity medications increase energy expenditure by inducing thermogenesis (the activation of brown and beige adipocytes to generate heat) or lipolysis (the process of breaking down stored fat into useable energy) at peripheral or central sites (Alexopoulos et al., 2020). Unfortunately, prevention and intervention strategies for obesity remain less than optimal. Protective therapies and medications have been developed against obesity, but these medications often have low efficacy and raise numerous safety concerns. Examples include amphetamines, thyroid hormones, and dinitrophenol, which were withdrawn shortly after regulatory approval owing to serious adverse effects (Muller et al., 2022). Nevertheless, a few US Food and Drug Administration (FDA)-approved medications such as orlistat is currently in the market. Orlistat acts as a lipase inhibitor to reduce the uptake of dietary fat from the gastrointestinal tract, and its side effects include liver injury and gastrointestinal symptoms. Another advanced

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therapeutic candidate are the glucagon-like peptide 1 receptor (GLP1R) agonists, such as liraglutide (Ussher and Drucker, 2023). However, gastrointestinal side effects including nausea, diarrhea, vomiting, and constipation have been found to occur in patients treated with liraglutide (1.8 mg administered subcutaneously). Thus, safe and sustainable long-term pharmacotherapy to normalize body weight remains elusive (Muller et al., 2022).

In theory, improving obesity management involves the consideration of addressing multiple pathogenic mechanisms, developing highly efficacious and safe new agents from food components, and making drastic lifestyle changes. Phytochemicals have attracted increasing attention as an alternative treatment for obesity and its related complications because of their health benefits, high safety, and low incidence of side effects (Dai et al., 2023). Coffee, tea, and cocoa are three of the most well-known plant-derived beverages globally and have been extensively researched for potential anti-obesity compounds, identifying several bioactive constituents (Gökcen and Şanlier, 2019; Pan et al., 2016). Currently a comprehensive review summarizing the anti-obesity potential of these three major beverages and their underlying molecular mechanisms is lacking. Moreover, existing publications have failed to adequately address the therapeutic capabilities of the compounds derived from cocoa in the context of obesity. Given that billions of people consume these three beverages in their daily lives, it is crucial to have a comprehensive understanding of their potential impact on anti-obesity.

Hence, in this review, the comprehensive information of this review came from electronic databases including the Web of Science (http://wokinfo.com/), ScienceDirect (www.sciencedirect.com) by using keywords: “Coffee”, “Tea”, “Cocoa”, “Obesity”, “Lipid metabolism”, “Adipocyte” and their combinations. A flow chart of the method employed is shown in Fig. 1. We aim to highlight the anti-obesity signaling pathways of bioactive ingredients from coffee, tea, and cocoa (Tables 1–3), in both *in vivo* and *in vitro* studies. It provides novel insights into the mechanisms of active components in the three popular beverages in obesity prevention, presenting a valuable contribution to the literature on diet-related remedies against obesity. It also reviews the research progress of the three major beverages from the overall level, and then objectively evaluate them, which could provide some insights into the development and treatment strategies of anti-obesity drugs.

2. Mechanisms of obesity prevention

In recent decades, there has been substantial research into the pathophysiology of obesity leading to the identification of various signal transduction pathways (Wen et al., 2022). Adipocytes are a type of cells specializing in the storage of fat and are central to metabolic regulation. White adipocytes control energy balance by storing and mobilizing triglyceride (TG) and secreting numerous lipid and protein factors (Ali et al., 2013). Excessive hyperplasia (adipogenesis) and hypertrophy of white adipocytes may lead to obesity. In contrast, brown and beige fat deficiency is associated with obesity, and the reactivation of brown and beige fat to regulate systemic energy levels provides metabolic health benefits (Chouchani and Kajimura, 2019). Adipose tissues exhibit distinctive characteristics based on their body distribution. Hence, an effective method to prevent obesity is to inhibit adipogenesis of white adipocytes and promote brown/beige adipocytes development and lipid catabolism.

2.1. Inhibiting adipogenesis in white adipocytes

Adipogenesis is a time-dependent process. For this reason, it is necessary to understand the processes that take place during the different stages of adipocyte differentiation. The adipogenesis program is accomplished through two sequential phases (Audano et al., 2022): the first includes events favoring the commitment of multipotent mesenchymal precursors to preadipocytes, whereas the second involves mechanisms that allow full adipocyte differentiation (Fig. 2A).

Adipogenesis leads to newly differentiated adipocytes, which are involved in various signaling pathways. These pathways include: the Wnt/β-catenin signaling, bone morphogenic protein (BMPs), mitogen-activated protein kinase (MAPK), hedgehog, adenosine monophosphate-activated protein kinase (AMPK), and insulin signaling pathways (Audano et al., 2022). The signaling cascade necessary for creating adipocytes encompasses a series of signaling pathways and the participation of specific cellular regulators. These regulators include important proteins like peroxisome proliferator activated receptor γ (PPARγ), CCAAT/enhancer-binding protein (C/EBPα, C/EBPβ, C/EBPδ), and sterol regulatory element binding factor 1c (SREBP1c; Mota de Sá et al., 2017). Of these, C/EBPβ and C/EBPδ are the first proteins to respond when signals initiate the formation of adipocytes. Additionally, C/EBPα, which works in conjunction with PPARγ, plays a role in the later stages of adipocyte development, helping to coordinate the final steps (Ghaben and Scherer, 2019). In contrast, SREBP1c regulates adipocyte gene expression by regulating the expression of fatty acid synthase (FAS) and lipoprotein lipase (LPL), which are involved in fatty acid metabolism. After the induction of adipogenesis, adipocyte precursors undergo several rounds of cell division, a process known as mitotic clonal expansion (Zhao et al., 2020). Decreasing the expression of these cell cycle markers has been suggested as a potential way to control the number of cells that remain proliferating or proceed to terminal differentiation (Tang et al., 2003) (Fig. 2A). Therefore, if the expression of these key transcription factors is inhibited, adipogenic

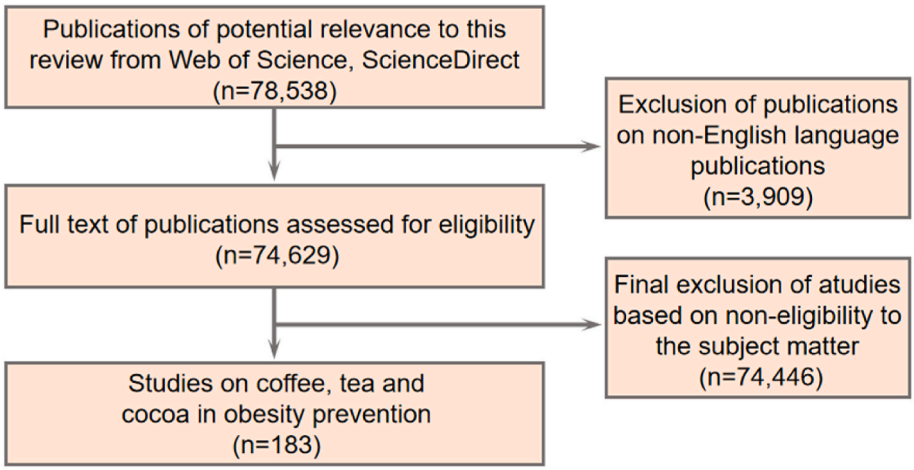

Fig. 1. A flow diagram of the strategy employed for the current review.

Table 1
Summary of mechanistic studies of coffee bioactive compounds on obesity and lipid metabolism.

Components	Models	Treatments	Effects and potential mechanisms	Reference
Caffeine	*In vivo*, yellow KK mice	60 mg/kg, s.c.	Contribute to thermogenesis in obese mice; Up-regulates the expression of UCP-1, UCP-2 and UCP-3	Kogure et al. (2002)
	In vivo, male ddy mice	0.05% and 0.1% (wt/wt), orally	Reduced serum TG level; Suppression of fat absorption	Shimoda et al. (2006)
	In vivo, 12 healthy participants	0.5, 1.5, 3.0 and 4.5 mg/kg, p.o.	Increases energy expenditure; Ingestion of 4.5 mg/kg of caffeine raised postexercise energy expenditure 15% above placebo	Fernandez-Elias et al. (2015)
	In vivo, male C57BL/6J mice	20 mg/kg, i.g.	Decreased the mass of fat tissues and lipids levels in the liver; Promoting lipid metabolism via cAMP/CREB/SIRT3/AMPK/ACC pathway	Zhang et al. (2015)
	In vivo, zebrafish larva	1, 2.5, 5, and 8% (wt/wt), orally	Reduces the body weight and hepatic lipid accumulation; Up-regulation of lipid β-oxidation gene ACO and down regulation of lipogenesis genes (SREBP1, ACC1, CD36 and UCP-2), ER stress genes (PERK, IRE1, ATF6 and BIP), the inflammatory cytokine genes (IL-1β and TNFα) and autophagy genes (ATG12 and Beclin 1)	Zheng et al. (2015)
	In vitro, 3T3-L1 cells	0.1–5 mM	Inhibits the MCE process in 3T3-L1 adipocytes through AKT/GSK3β signaling	Kim et al. (2016)
	In vivo, male C57BL/6J mice	60 mg/kg, i.g.	Reduces the body weight of dietary obesity mice; Suppression of appetite and increasing of energy expenditure; Inhibits adenosine receptor A(1)R	Wu et al. (2017)
	In vitro, 3T3-L1 cells	80, and 160 μg/mL	Decreased the content of TG; Inhibited the expression of PPARγ, C/EBPα and FAS; Increased the expression of ATGL and HSL	Zhu et al. (2017)
	In vivo, female ddy mice	0.1% (wt/wt), orally	0.1% caffeine and 0.1% EGCG were the best anti-obesity combination ratio; Suppression of fat accumulation; Increased the level of GLP-1and POMC in the hypothalamus	Liu and Sayama (2018)
	In vivo, male sprague dawley rats	20 mg/kg, i.g.	Reduced adiposity, decreased body weight, amelioration of hepatic steatosis, and improved systemic/muscle insulin resistance; Up-regulation of tissue lipogenic	Liu et al. (2018)
	In vivo, female ICR mice	0.04% (wt/wt), orally	Combination therapy of caffeine and chlorogenic acid reduce the serum LDL-c, FFA, TC, TG, IL-6, and liver TG and TC levels, and increase serum adiponectin levels; Regulate the expression of lipid-related genes and proteins through the AMPKα-LXRα/SREBP-1c signaling pathway	Xu et al. (2019)
	In vivo, male sprague dawley rats	20 mg/kg, i.g.	Combination therapy of caffeine and low-dose EGCG; Reduce body weight and improve NAFLD	Yang et al. (2019)
	In vivo, 12 healthy participants	3 mg/kg, p.o.	Increase oxidized fat; Reduce total carbohydrate oxidation and self-fatigue	Ruiz-Moreno et al. (2021)
	In vivo, male sprague dawley rats	20 mg/kg, i.g.	Show an synergistic anti-obesity effect of caffeine and EGCG; Regulate gut microbiota and bile acid metabolism	Zhu et al. (2021)
Chlorogenic acid	*In vivo*, zucker rats	5 mg/kg, i.v.	Reduced lipid content in liver; Improve glucose tolerance, decreased fasting plasma TC and TG levels and reduced liver TG levels	De Sotillo and Hadley (2002)
	In vivo, male golden hamsters	80 mg/kg, i.p.	Modify lipids and glucose metabolism; The levels of fasting serum TG, TC, FFA, LDL-c, HDL-c, and insulin were significantly lower in the GGA treatment than control, which may attributed to PPARα facilitated lipid clearance in liver and improved insulin sensitivity	Li et al. (2009)
	In vivo, 18 healthy participants	329 mg/daily, p.o.	The daily CGA consumption therefore increased postprandial fat utilization in healthy humans	Soga et al. (2013)
	In vivo, female ICR mice	0.2% (wt/wt), orally	Reduced fatty acid synthesis and fat deposition; Down regulating the gene expression of aconitase catalase, fatty acid synthetase, and PPARγ	Zheng et al. (2014)
	In vivo, male C57BL/6J mice	100 mg/kg, I.P.	Significantly blocked the development of obesity, hepatic steatosis and insulin resistance; Suppressed adipogenesis genes of PPARγ, CD36, and FABP4; Attenuated inflammation in the liver and WAT accompanied by decrease the macrophage marker genes including F4/80, CD68, CD11b, CD11c, and TNFα, MCP-1 and CCR2 encoding inflammatory proteins	Ma et al. (2015)
	In vivo, male sprague dawley rats	20, and 90 mg/kg, i.g.	Hepatic TC, TG and MDA levels were decreased; Improve lipid metabolism disorders by altering the expression of PPAR and LXR	Huang et al. (2015)
	In vivo, male sprague dawley rats	20, and 90 mg/kg, i.g.	Reduced the hepatic apoptosis and improved fat metabolism	Liu et al. (2015)
	In vivo, caenorhabditis elegans	0.53 or 2.65 mg/mL	Reduce lipogenesis related genes expression, which involved in insulin pathway	Farias-Pereira et al. (2018)
	In vivo, ICR male mice	150 mg/kg, i.g.	Reduced body weight and lipid levels; Reversed the HFD-induced gut microbiota dysbiosis	Wang et al. (2019)
	In vivo, male C57BL/6J mice	100 mg/kg, i.g.	Reduced body weight gain and food intake; Increased energy expenditure; Modified the microbiota structure	He et al. (2020)
	In vitro, 3T3-L1 cells	5, 10 and 50 μM	Activation of browning of white adipocytes and lipolysis enhancement mediated by targeting the AMPK and PPARα/γ signaling	Vasileva et al. (2020)
	In vitro, 3T3-L1 cells	100 nM	Promotes differentiation of 3T3-L1 adipocytes into brown-like adipocytes; Increase UCP1 and PGC1α expression through AMPK pathway	Sudhakar et al. (2020)
	In vitro, 3T3-L1 cells	40 μg/mL	Combination of CGA and caffeine inhibited adipocytes differentiation; Activation of AMPK pathway by regulating the fat metabolism-related enzyme	Kong et al. (2021)

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Table 1 (*continued*)

Components	Models	Treatments	Effects and potential mechanisms	Reference
Trigonelline	*In vivo*, male wistar rats	50 mg/kg, i.g.	Inhibited lipase activity in the small intestine by 56%; Significantly decrease TG and TC rates, and increase HDL-c level in serum	Hamden et al. (2013)
	In vitro, 3T3-L1 cells	75 and 100 μM	Attenuates the adipocyte differentiation and lipid accumulation; Inhibits the expression PPARγ during adipogenesis	Ilavenil et al. (2014)
	In vivo, male C57BL/6J mice; *In vitro*, HepG2 cells	50 mg/kg, i.g.; 25 and 50 μM	Prevents high TC and hepatic lipid accumulation in mice, via restoration of hepatic autophagy	Sharma et al. (2018)
	In vitro, 3T3-L1 cells	10, 25, 50 and 75 μM	Improves the lipid metabolism in adipocytes; Promotion of lipolysis and fatty acid oxidation, which induced the browning process of 3T3-L1 by activation β3-AR and inhibition PDE4 through MAPK/ATF-2 signaling	Choi et al. (2021)
Kahweol	*In vitro*, 3T3-L1 cells	5, 10 and 25 μg/mL	Inhibited lipid accumulation; The expression levels of adipogenesis gene of PPARγ, C/EBPα, FABP4, FAS were reduced by activation the AMPK pathway	Baek et al. (2017)
	In vitro, 3T3-L1 cells	40 μM	Inhibits adipogenesis in 3T3-L1 cells; Down-regulates the key adipogenic regulators of PPARγ and C/EBPα	Kim et al. (2018)
	In vivo, caenorhabditis elegans	30, 60, and 160 μM	Reduced fat accumulation in wild-type C. elegans but not in eat-2 mutant, suggesting that fat-lowering effect depends on food intake	Farias-Pereira et al. (2020)

Note: p.o.: per os; i.g.: intragastric gavage; s.c.: injected subcutaneously; i.v.: intravenous infusion; i.p.: peritoneal injection; ACC: Acetyl-CoA Carboxylase; AKT: Protein Kinase B; AMPK: AMP-Activated Protein Kinase; ATGL: Adipose Triglyceride Lipase; ATF2/6: Activating Transcription Factor 2/6; ATG12: Autophagy-Related Gene 12; BIP: Heavy-chain Binding Protein; cAMP: Cyclic Adenosine Monophosphate; CCR2: C–C Motif Chemokine Receptor 2; CREB: cAMP-Response Element Binding Protein; CD36: Platelet Glycoprotein 4; C/EBPα: CCAAT/enhancer-Binding Proteins α; EGCG: (−)-Epigallocatechin-3-Gallate; FAS: Fatty acid synthase; FABP4: Fatty Acid-Binding Protein4; FFA: Free Fat Acid; GSK3β: Glycogensynthasekinase3β; GLP-1: Glucagon-Like Peptide 1 Receptor; HDL-c: High Density Lipoprotein Cholesterol; HSL: Hormone-Sensitive Triglyceride Lipase; IRE1: Immunoglobulin-Regulated Enhancer 1; IL-1β: Interleukin-1β; IL-6: Interleukin-6; LDL-c: Low Density Lipoprotein; LXRα: Cholesterol Liver X Receptor α; MAPK: Mitogen-Activated Protein Kinase; MCE: Mitotic Clonal Expansion; MCP-1: Monocyte Chemoattractant Protein-1; NAFLD: Nonalcoholic Fatty Liver Disease; PERK: Protein kinase R-like endoplasmic reticulum kinase; PGC1α: Peroxisome Proliferator-Activated Receptor γ Coactivator 1-α; PPARγ/α: Peroxisome Proliferators-Activated Receptors γ/α; PDE4: Phosphodiesterase 4; POMC: Pro-Opio-Melano-Cortin; SIRT3: Sirtuin 3; SREBP1: Sterol Regulatory Element Binding Protein 1; TG: Triglyceride; TC: Total Cholesterol; TNFα: Tumor Necrosis Factor α; UCP-1, 2, 3: Uncoupling Protein-1, 2, 3.

differentiation may be inhibited. Characterizing and then stratifying these molecular mechanisms would allow to prioritize new possible targets to be further exploited for innovative pharmacological treatment of adipose tissue-related diseases.

2.2. Promoting brown/beige adipocytes development

Brown adipocytes possess numerous small multilocular lipid droplets and numerous mitochondria, in comparison to white adipocytes which contain large unilocular lipid droplets and few mitochondria (Fig. 2B). In addition, some adipocyte progenitors and white adipocytes residing in white adipose tissue (WAT) are capable of 'browning,' also known as beige adipocytes. Similar to white adipocyte adipogenesis, brown and beige adipocyte adipogenesis is regulated by an overlapping set of brown fat-specific transcription factors. The important transcription factors include early B cell factor 2 (EBF2), PPARγ, PR domain-containing 16 (PRDM16), peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α), BMPs and C/EBPβ (Zhang et al., 2018; Hiraike et al., 2017; Megan et al., 2016).

Activation of brown fat is associated with marked improvement in metabolic parameters. The browning pathways (Fig. 2B), include the protein kinase A (PKA), protein kinase G (PKG), MAPK, and AMPK signaling pathways. Specifically, in the classic signaling pathway noradrenaline binds to β3-AR on the membrane of brown/beige adipocytes. This binding activates the cAMP/PKA signaling pathway, which subsequently initiates a signal cascade leading to an increase of UCP1-dependent mitochondrial thermogenesis (Chouchani et al., 2016; Chouchani et al., 2019). Brown adipose tissue (BAT) thermogenesis alleviates obesity by increasing energy expenditure, which is regulated by MAPK signaling. The process involves an increased cAMP cycle, initiating a signaling cascade. In this cascade PKA phosphorylates and activates the cAMP response element building protein (CREB), and the p38/MAPK pathway. Subsequently, p38/MAPK phosphorylates and activates PGC1α, which interacts with PPARγ and PPARα to stimulate the transcription of UCP1 (Cao et al., 2004). In addition, AMPK stimulates PGC1α and UCP1 transcription, leading to WAT browning and thermogenesis (Desjardins and Steinberg, 2018). Active substances increased energy expenditure, limited weight gain, induced the development of the brown-like adipocyte phenotypes in C3H10T1/2 cells and elevated expression of PGC1α and UCP1 genes via a mechanism involving AMPK, and consequently could help to improve metabolic dysfunctions (Guo et al., 2019; Zhang et al., 2014).

Furthermore, many regulatory BAT signaling components have been identified, some of which are being tested in initial clinical trials (Pfeifer and Hoffmann, 2015). Synthetic PPARγ agonists such as thiazolidinedione drugs have been shown to induce beiging of adipose tissue by prolonging the half-life of PRDM16 (Ohno et al., 2012). Natural molecules, such as flavonoids, induce beiging by activating AMPK-PGC1α/SIRT1 and PPARγ signaling pathways (Zhang et al., 2019a). Research has advanced considerably studies during the past few years, and a multitude of potential pharmaceutical targets in BAT have been discovered. Brown fat is emerging as an interesting and promising target for therapeutic intervention in obesity. Therefore, developing active substances that promote browning of adipose tissue can be a fruitful direction to pursue in the treatment of obesity in the future. More significantly, larger, prospective controlled trials are needed to corroborate these findings and to develop effective treatment strategies.

2.3. Promoting lipid catabolism

As the primary energy reserve in mammals, WAT mainly facilitates lipolysis to furnish FFAs to other organs in instances of an energy deficit. The sequential action of three major hydrolases, namely adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL), catalyzes the neutral hydrolysis of TGs. Lipolysis (Fig. 2B) consists of ATGL initiating the process by catalyzing TGs to diacylglycerols (DGs) and mediating triglyceride hydrolysis during basal lipolysis; HSL is mainly responsible for the hydrolysis of DGs to monoacylglycerols (MGs) and MGL hydrolyzes MGs (Zechner et al., 2012; Zimmermann et al., 2004). Therefore, enhancing lipolysis enzyme activity in adipose tissue is a metabolic pathway to be investigated for pharmacological strategies against obesity. In particular, HSL harbors five serine phosphorylation sites (mouse HSL: Ser563, Ser659, and Ser660 are phosphorylated by PKA; Ser565 by AMPK; and Ser600 by ERK. For human HSL: Ser552, Ser649, and Ser650 are phosphorylated by PKA; Ser554 by AMPK; and Ser589 by ERK) that are targeted by

Table 2
Summary of mechanistic studies of tea bioactive compounds on obesity and lipid metabolism.

Components	Models	Treatments	Effects and potential mechanisms	Reference
Catechins	*In vivo*, 43 participants	582.8 mg/day, p.o.	Prevention of obesity in type 2 diabetic patients; Decrease body weight (−0.3%), visceral fat and TC level; Increased adiponectin level	Nagao et al. (2009)
	In vivo, 132 participants	625 mg/day, p.o.	Enhances exercise-induced abdominal fat loss in obese adults; Decrease TG and FFA levels	Maki et al. (2009)
	In vivo, male C57BL/6J mice	5 g/kg, i.p.	Decreased body weight and hepatic steatosis; Changed the microbiota in terms of overall structure, composition, and protein functions by regulating the metabolites, facilitating the generation of short-chain fatty acids (SCFAs)	Liu et al. (2023)
EGCG	*In vivo*, male C57BL/6J mice	0.2% (wt/wt), orally	Decreased body weight gain, and plasma and liver lipids; Increase mitochondrial DNA content and activation AMPK in BAT	Lee et al. (2017)
	In vitro, 3T3-L1 cells	5, 10 and 20 μM	Alleviates intracellular lipid accumulation of 3T3-L1 cells; Through AMPK-C/EBPα-PPARγ-SREBP-1c pathway to blocked the adipocyte differentiation	Mi et al. (2018)
	In vivo, male C57BL/6J mice	50 and 100 mg/kg, i.p.	Reduced plasma TG, TC and epididymal adipose tissue weight; Inhibited the expression of genes involved in the synthesis of *de novo* fatty acids (ACC, FAS, SCD1, C/EBPβ, PPARγ, and SREBP1) and increased the expression of genes associated with lipolysis (HSL) and lipid oxidization in WAT	Li and Gao et al. (2018)
	In vivo, male C57BL/6J mice	0.4% (wt/wt), orally	Effectively prevented obesity and NAFLD; Significantly reduction in body fat deposition and improved intestinal mucosal immunity	Huang et al. (2020)
L-Theanine	*In vivo*, female ICR mice	0.03% (wt/wt), orally	Suppress body weight increase and fat accumulation	Zheng et al. (2004)
	In vivo, male sprague dawley rats	0, 50, 200, and 400 mg/kg, i.g.	Affect the absorption of lipids by regulating the expression of intestinal fatty acid transporters	Yan et al. (2007)
	In vivo, male sprague dawley rats	100 mg/kg, i.g.	Regulate glucose, lipid, and protein metabolism via insulin and AMPK signaling pathway; Up-regulate the mRNA expression of CPT1, IR, IRS and LKB1	Lin et al. (2020)
	In vivo, male C57BL/6J mice; *In vitro*, C3H10T1/2 cells	10, 50 and 100 μM; 100 mg/kg, i.p.	Ameliorated obesity, improved glucose tolerance, insulin sensitivity, and reduced plasma TG, TC, and FFA; Activate the browning of inguinal WAT through up-regulating the expression of thermogenic genes, thus ameliorates obesity in mice	Peng et al. (2021)
	In vivo, male C57BL/6J mice	30 mg/kg, i.g.	Modulate gut microbiota composition, ameliorate adiposity and regulate the mRNA expression of genes related to lipid metabolic	He et al. (2021)
	In vivo, male C57BL/6J mice; *In vitro*, HepG2 cells	300 mg/kg, i.g.; 1, 2 and 4 mM	Ameliorates nonalcoholic hepatic steatosis by regulating hepatocyte lipid metabolic pathways via the CaMKKβ-AMPK signaling pathway	Liang et al. (2022)
	In vivo, male BALB/c mice	100 and 300 mg/kg, i.g.	The serum levels of TC and TG decreased; Regulates lipid metabolism by modulating the gut microbiota and BA metabolism via	Xu et al. (2022)

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Table 2 (*continued*)

Components	Models	Treatments	Effects and potential mechanisms	Reference
			the FXR-FGF15-CYP7A1 pathway	
Theaflavins	*In vivo*, male wistar rats; *In vitro*, HepG2 cells	50 mg/kg, orally; 50 μM	Significantly reduced lipid accumulation in HepG2 cells; Stimulating AMPK through LKB1 and reactive oxygen species pathways	Lin et al. (2007)
	In vivo, male SD rats	100 mg/kg, i.g.	Reduced leptin level, inhibited alanine transaminase and hepatic lipase activity, and increased superoxide dismutase activity	Jin et al. (2013)
	In vivo, male C57BL/6J mice	100 and 200 mg/kg, i.g.	Suppressed weight gain, reduced blood glucose level; Lowered the levels of TC, TG and LDL; Activated the SIRT6/AMPK/SREBP-1/FAS signaling pathway	Cai et al. (2021)
Thearubigins	*In vivo*, male wistar rats	50 and 100 mg/kg, i.g.	The black tea aqueous extract significantly alleviated the metabolic syndrome including hyperglycaemia, dyslipidaemia and impairment of liver functions induced by alloxan or the cholesterol-rich diet in rats	Ramadan et al. (2009)
	In vivo, male SD rats	0.2% (wt/wt), orally	Decreased liver cholesterol, increased excretion of fecal steroids	Miyata et al. (2011)
	In vivo, male SD rats	1000 mg/kg, i.g.	The black tea aqueous extract reduced lipid, glucose, urea, creatinine, AST, ALT, ALP level and increased insulin level	Imran et al. (2018)
Theabrownins	*In vivo*, male SD rats	0.135, 0.405, and 1.215 g/kg, i.g.	Regulating lipid metabolism in rats and lowering the serum levels of TC, LDL-c, and TG	Peng et al. (2013)
	In vivo, male C57BL/6J mice	225 mg/kg, i.g.	Increases the levels of ileal conjugated bile acids, inhibit the intestinal FXR-FGF15 signaling pathway, resulting in increased hepatic production and fecal excretion of bile acids, reduced hepatic cholesterol, and decreased lipogenesis	Huang et al. (2019)
	In vivo, zebrafish	1000 μg/mL	Hypolipidemic activity in high-fat-induced obese zebrafish	Xiao et al. (2020a)
	In vivo, male C57BL/6J mice	225 mg/kg, i.g.	Improved energy metabolism in white and brown adipose tissue via gut microbiota-driven bile acid alternative synthesis	Kuang et al. (2020)
	In vivo, male C57BL/6J mice	200, 400, and 800 mg/kg, i.g.	Reduced the body weight and WAT weight; Improved lipid and glucose disorders; Promote thermogenesis by stimulating the AMPK-PGC1α pathway	Wang et al. (2021)
	In vivo, male SD rats	125, 250 and 500 mg/kg, i.g.	With higher levels of theabrownin was effective in reducing serum TG, TC, LDL-c, and inflammatory cytokines (TNF-α, IL-1β, and IL-6) in rats	Deng et al. (2021)
	In vivo, male C57BL/6J mice	2300 mg/kg, i.g.	Reduced body weight gain and body fat accumulation through gut microbiota	Li et al. (2022)
	In vivo, male C57BL/6J mice	0.3% (wt/wt), orally	Reduced serum and hepatic lipid levels; Therapeutic formula for NAFLD that promoted lipid utilization and inhibited lipid synthesis and absorption	Wang et al. (2022)
	In vivo, male C57BL/6J mice	2300 mg/kg, i.g.	Reduced body weight gain, body fat rate, and hepatic TG level; improvement of fatty acid oxidation, lipolysis, and oxidative stress via the regulation of serotonin-related signaling pathways	Li et al. (2023)

Note: ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; AST: Aspartate Aminotransferase; BAT: Brown Adipose Tissue; CaMKKβ: Calmodulin-Dependent Protein Kinase Kinase-β; CPT1: Carnitine Palmitoyltransferase 1; CYP7A1: Cholesterol 7 α-Hydroxylase; DNA: DeoxyriboNucleic Acid; FGF15: Fibroblast Growth Factor 15; IR: Insulin Resistance; IRS: Insulin Receptor Substrate; LKB1: Liver Kinase B1; mRNA: messenger RNA; SCFAs: Short-Chain Fatty Acids.

Table 3
Summary of mechanistic studies of cocoa bioactive compounds on obesity and lipid metabolism.

Components	Models	Treatments	Effects and potential mechanisms	Reference
Cocoa powder	*In vivo*, male wistar rats	12.5% (wt/wt), orally	Decrease visceral adipose tissue in rats; Suppressed the expression of genes involved in fatty acid synthesis and thermogenesis in liver and WAT	Matsui et al. (2005)
	In vivo, male wistar rats	10 g/kg (0.5 and 1% polyphenol extract), orally	Lowered plasma TC concentrations, increased fecal cholesterol and total bile acids excretion	Yasuda et al. (2008)
Cocoa extract	*In vivo*, male C57BL/6N mice; *In vitro*, 3T3-L1 cells	0.04–0.2 g/kg, i.g.; 100 and 200 μg/mL	Reduction of body weight, epididymal fat and liver masses; Reduced the lipid accumulation in 3T3-L1 cells; Suppression the protein expression levels of PPARγ, C/EBPa; Suppressed the p-ERK, Akt, and their downstream signal	Min et al. (2013)
	In vivo, male wistar rats	Cocoa powder (1 g/kg), i.g.; cocoa extract (100 mg/kg), i.g.	Upregulation of the expression of genes involved in FA uptake, β-oxidation and energy expenditure in WAT; Improvement in adipose tissue function with a better capacity to store nutritional overload and to attenuate the production of inflammatory cytokines	Rabadan-Chavez et al. (2016)
	In vivo, male wistar rats	14 and 140 mg/kg, i.g.	Lower body weight gain and food efficiency; Reduced visceral (epididymal and retroperitoneal) and subcutaneous fat accumulation; Down-regulation of the genes of CEBP/α and FAS	Aranaz et al. (2019)
Quercetin	*In vivo*, male C57BL/6J mice	0.2%, 0.4% (wt/wt), orally	Combination of quercetin and resveratro lowering levels of serum TG, insulin, IL-6, and hepatic TC; Reduction of body weight and fat mass index	Zhou et al. (2012)
	In vitro, OP9 cells	5, 10 and 25 μM	Inhibited lipid accumulation in OP9 cells; Decreased the expression of C/EBPα, PPARγ and SREBP-1c; Upregulating ATGL and HSL expression and downregulating FAS, LPL and aP2	Seo et al. (2015)
	In vivo, male wistar rat	30 mg/kg, i.g.	Combination of quercetin and resveratrol led to a significant reduction in all the fat depots and body weight; Inhibited the protein expression of ACC; Increased the protein expression of ATGL	Arias et al. (2016)
	In vivo, male wistar rat	240 mg/kg, i.g.	Quercetin combined with resveratrol attenuation of systemic pro-inflammatory adipocytokine expression via the AMPKα1/SIRT1 pathway; Reduced visceral adipose tissue weights and adipocyte sizes	Zhao et al. (2017a)
	In vivo, male wistar rat	30 mg/kg, i.g.	Combination of quercetin and resveratrol reduced the body weight gain and visceral (epididymal, perirenal) adipose tissue weight; Reduced serum lipids, attenuated inflammatory markers; Modulate the gut microbiota composition	Zhao et al. (2017b)
	In vivo, female sprague dawley rats	2.5, 5, 10 mg/kg, i.g.	Inhibited pancreatic lipase activity; Reduced postprandial serum TG level in rat; Increase fat excretion in rat feces	Zhou et al. (2021)
(−)-Epicatechin	*In vivo*, male wistar rats	1 mg/kg, i.g.	Decreased the rate of weight gain, glycemia and dyslipidemia	Gutierrez-Salmean et al. (2014)
	In vivo, male C57BL/6J mice	1 mg/kg, i.g.	Reduced TG concentration in plasma and in adipose tissue; Activates the induction of a BAT phenotype, increased the protein expression levels of irisin, PRDM16 and UCP1; Promote phosphorylated levels of AMPK and ACC	Claudia Elena Varela et al. (2017)
	In vivo, male wistar rats	10, 20, 40 mg/kg, i.g.	Reduced TC, LDL-c and TG, alleviated liver fat accumulation and lipid peroxidation, increased HDL-c; Regulating Insig-1-SREBP-SCAP pathway, and lipid metabolic related genes including LXR-alpha, FAS, and SIRT1	Cheng et al. (2017)
Procyanidin B2	*In vitro*, 3T3-L1 cells	10–200 μg/mL	Significantly reduced the intracellular lipid accumulation in 3T3-L1 cells by targeting miR-483-5p as well as PPARγ	Zhang et al. (2017)
	In vivo, male new zealand white rabbits	150 mg/kg, i.g.	Reduced body weight and TG, TC, and LDL-c; Upregulation of lipogenic genes, including SREBP-1c and FAS; Alteration the gut microbiota by increasing the proportion of *Bacteroidetes* and *Akkermansia*	Xing et al. (2019)
	In vivo, male C57BL/6J mice	0.2% (wt/wt), orally	Prevents HFD-induced dyslipidemia and LPL activity; Regulates gut microbiota and twenty lipid metabolism biomarkers; Reducing the abundance of Bilophila and Proteus	Xiao et al. (2020b)
	In vitro, HepG2 cells	10, 20 μg/mL	Exerts synergistic hypolipidemic activity via the AMPKα pathway	Ji et al. (2023)
Theobromine	*In vitro*, 3T3-L1 cells	50, 100 and 150 μg/mL	Inhibits the early stage of adipogenesis through AMPK activation and suppression of the ERK and JNK signaling in 3T3-L1 cells; Induces G0/G1 phase arrest through up-regulation of p27 and p21; Inhibits the pro-inflammatory cytokine of IL-6 and TNF-α	Jang et al. (2015)
	In vivo, male ICR mice; *In vitro*, 3T3-L1 cells	100 mg/kg, i.g.; 5, 10, 25 and 50 μM	Suppresses adipose tissue weight gain in mice; Suppresses adipocyte differentiation and induced C/EBPβ degradation by increasing its sumoylation	Mitani et al. (2017)
	In vitro, SGBS cells	100 μg/mL	Reduces adipogenesis and proinflammatory cytokines; Control of macrophages infiltration in adipose tissue and inflammation	Fuggetta et al. (2019)
	In vitro, 3T3-L1 cells; HIB1B cells	10, 50, 100 and 200 μM	Inducing WAT browning and activating brown adipocytes; Increased the expression of brown-fat signature proteins (PGC-1α, PRDM16, and UCP1) and beige-specific genes (Cd137, Cidea, Cited1, Tbx1, and Tmen26);	Jang et al. (2019)

(*continued on next page*)

Table 3 (*continued*)

Components	Models	Treatments	Effects and potential mechanisms	Reference
			Elevated the expression of brown fat specific genes (Cidea, Lhx8, Ppargc1, Prdm16, Ucp1, and Zic1)	
	In vivo, male C57BL/6 mice; *In vitro*, 3T3-L1 cells	100 mg/kg, i.g.; 10, 100 and 500 μM	Browning of iWAT and activating BAT by increase expression of PRDM16 and UCP1; Regulation of lipid metabolismvia inhibition of PDE4	Jang et al. (2020)
	In vivo, male C57BL/6N mice; *In vitro*, adipose stromal cells	0.05%, 0.1% (wt/wt), orally; 0.1, 1 and 5 μM	Decreases weight gain; Inducing browning in mice and primary adipocytes; Induces UCP1 and thermogenesis and enhances PPARγ signaling	Tanaka et al. (2022)

Note: aP2: Adipocyte Protein 2; Cidea: Cell Death Inducing DFFA Like Effector a; Cited1: CBP/P-300 Interacting Transactivator 1; JNK: c-Jun N-Terminal Kinase; Lhx8: Lim Homeobox Gene 8; PRDM16: PR Domain-Containing 16; Zic1: Zic Family Member 1.

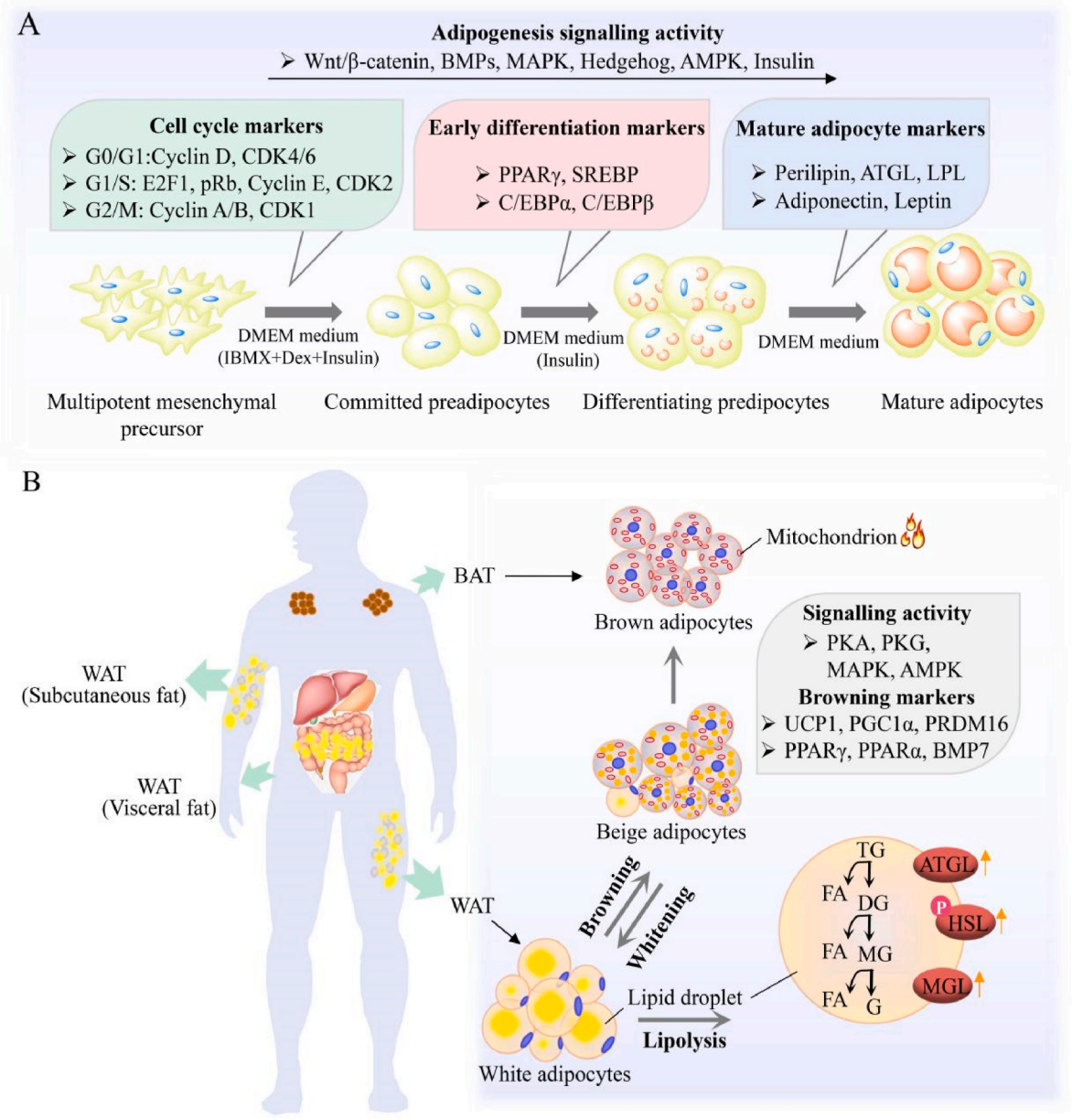

Fig. 2. The molecular regulation of adipogenesis and signaling pathways involved in obesity. (A) Diagram of the process of adipogenesis and adipogenesis markers; (B) Anti-obesity mechanism is composed of beige adipogenesis, white-to-brown adipocyte transdifferentiaiton and lipolysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

multiple protein kinases and have important regulatory functions that affect enzyme activity (Rizack, 1964; Hofer et al., 2020).

The activation pathway of lipolysis involves hormones such has catecholamines binding to β-adrenergic G-protein-coupled receptors, triggering a series of events (Pagnon et al., 2012). For instance, the α-subunit of the receptor-coupled trimeric Gs protein dissociates and

activates adenylate cyclase. This enzyme then generates cAMP, a signaling molecule. Subsequently, cAMP activates PKA, which plays a crucial role in the phosphorylation of ATGL Ser406. This has been shown to moderately increase ATGL-mediated lipolysis.

Multiple signaling may play a synergistic role in promoting lipolysis. Signaling pathways involved in lipolysis include the PKG, MAPK, and AMPK pathways discussed, as well as atrial natriuretic peptides (ANPs) via guanyl-cyclase-derived cGMP activate PKG, which phosphorylates both lipases. Additionally, HSL is phosphorylated by ERK1/2 via the MAPK pathway, and AMPK is activated under conditions of enhanced lipolysis such as exercise and fasting. Furthermore, high cellular AMP concentrations during fasting or prolonged exercise induces ATGL transcription via AMPK (Daval et al., 2006). More indirectly, the intracellular lipolysis can facilitate intracellular fatty-acid mobilization, which affects lipid-mediated signaling and metabolic regulation. Therefore, promoting the lipolysis process is beneficial to reduce the accumulation of white fat.

3. chemical components in coffee, tea, and cocoa as preventative agents against obesity

Functional foods are potential sources of bioactive agents. Bioactive components from functional foods including coffee, tea, and cocoa were able to inhibit adipogenesis, or promote brown adipogenesis, lipolysis, resulting in prevention of obesity and related metabolic diseases. Coffee, tea, and cocoa exhibit many similarities in their secondary metabolite compositions, however their contents are different in the three drinks. For example, purine alkaloids are present in all three beverages. This includes caffeine, which has an excitatory effect on the nervous system, and is one of the main reasons for the popularity of these beverages. In addition, chlorogenic acid (CGA) exists in all three plants, especially there is a high proportion of CGA in coffee (Lemarcq et al., 2020; Jiang et al., 2023). Their comparable chemical compositions enables them to have similar effects in ameliorating obesity. However, the plants also have their own characteristic chemical components, such as trigonelline and cafestol in coffee, theaflavins and thearubigins in tea, and theobromine and quercetin in cocoa (Liao et al., 2021). Table 4 presented the concentration of bioactive compounds in the three drinks. First of all, the bioactive compounds of coffee: CGA (2.7–10%), caffeine (1.2–2.4%) and trigonelline (0.7–1.0%) of the dry weight (Kusumah and De Mejia 2022; Santos and Lima, 2016; Gramza, 2014). The content of cafestol and kahweol in coffee were 0.2–0.9 mg/g, and 0.2–0.8 mg/g, respectively (Kusumah and De Mejia 2022). The highest CGAs concentration was found in coffee of the three drinks. Caffeine, CGAs, catechins, EGCG, and L-Theanine each account for 2.0–5.0%, 0.01–0.4 mg/g, 30%, 6.0–30.0%, and 1.0–4.0% in tea of the dry weight, respectively (Yang et al., 2023). In cocoa, the concentration of theobromine was 11.1–24 mg/g (Kim et al., 2014). These differences allow for potential anti-obesity effects via various molecular mechanisms. The rest of this review focuses on the characteristic chemical components present in these three beverages and the molecular mechanisms by which they exert their anti-obesity effects.

3.1. Coffee

Coffee belongs to the genus *Coffea* (family Rubiaceae), which comprises more than 90 species. Green coffee beans are primarily composed of carbohydrates, lipids, proteins, CGAs, fatty acids, caffeine, trigonelline, and diterpenes. During roasting, carbohydrates, proteins, and CGAs are reduced to produce thousands of degradation products, whereas the changes to lipids, fatty acids, caffeine, and trigonelline are minimal (Hu et al., 2019). Based on recent epidemiological and research data, long-term consumption of beverages containing coffee is associated with a lower risk of developing obesity in healthy individuals. The potential obesity prevention components in green or roasted coffee beans are mainly caffeine, CGAs, trigonelline, and diterpenoids, cafestol and kahweol (Table 1; Fig. 3).

Table 4
Comparison of the concentrations of typical coffee, tea and cocoa compositions.

Bioactive compounds	Coffee	Tea	Cocoa	Ref.
Caffeine	1.2–2.2% in green coffee; 1.3–2.4% in roasted coffee	2.0–5.0%	2.0–2.9 mg/g	Kusumah and De Mejia (2022); Gramza (2014); Kim et al. (2014)
CGA	6.5–10% in green coffee; 2.7–3.1% in roasted coffee	0.01–0.4 mg/g	3.0–20.0 μg/g in cocoa liquor	Kusumah and De Mejia (2022); Santos and Lima (2016); Zhou et al. (2008); Lemarcq et al. (2020)
Trigonelline	0.7–1.0% in green coffee; 1.0% in roasted coffee	n/a	n/a	Kusumah and De Mejia (2022)
Cafestol	0.2–0.9%	n/a	n/a	Kusumah and De Mejia (2022)
Kahweol	0.2–0.8%	n/a	n/a	Kusumah and De Mejia (2022)
Catechins	n/a	30.0%	0.05–0.10 mg/g	Kim et al. (2014)
EGCG	n/a	6.0–20.0%	n/a	Yang et al. (2023)
L-Theanine	n/a	1.0–4.0%	n/a	Yang et al. (2023)
Theaflavins	n/a	2.0–6.0% of black tea	n/a	Cheng et al. (2023)
Thearubigins	n/a	30–60% of black tea	n/a	Cheng et al. (2023)
Theabrownins	n/a	10.00–24.50% of black tea	n/a	Cheng et al. (2023)
Theobromine	n/a	2.4–4.3%	11.1–24 mg/g	Kim et al. (2014); Yang et al. (2023)
(−)-Epicatechin	n/a	1.0–4.9 mg/g	1.24–16.52 mg/g	Kim et al. (2014); Zhang et al. (2019b)

Note: n/a, not applicable.

3.1.1. Coffee extracts

Coffee extracts has been found to have beneficial effect in the management of obesity and hyperlipidemia. Evidences have shown green coffee bean extracts effectively reduce body weight and the accumulation of WAT by regulating the expressions of proteins associated with adipogenesis and lipid metabolism (Choi et al., 2016; Ilmiawati et al., 2020). Recent studies conducted by Cao et al. (2024) reported that coffee leaf extract also has the capacity to inhibit lipase activity.

3.1.2. Caffeine

Several studies have reported a correlation between caffeine intake and fat metabolism. For instance, Fernandez-Elias et al. (2015) found that an estimation of 4.5 mg/kg of caffeine raises energy expenditure 3-h post-exercise. Subsequently, a meta-analysis of randomized controlled trials showed that caffeine could also increase the body's metabolic rate and promote the decomposition of fat tissue, thus helping to reduce weight (Tabrizi et al., 2019). More recently, Ruiz-Moreno et al. (2021) found that acute caffeine ingestion (3 mg/kg) increased fat oxidation during submaximal exercise, which can enhance body fat utilization.

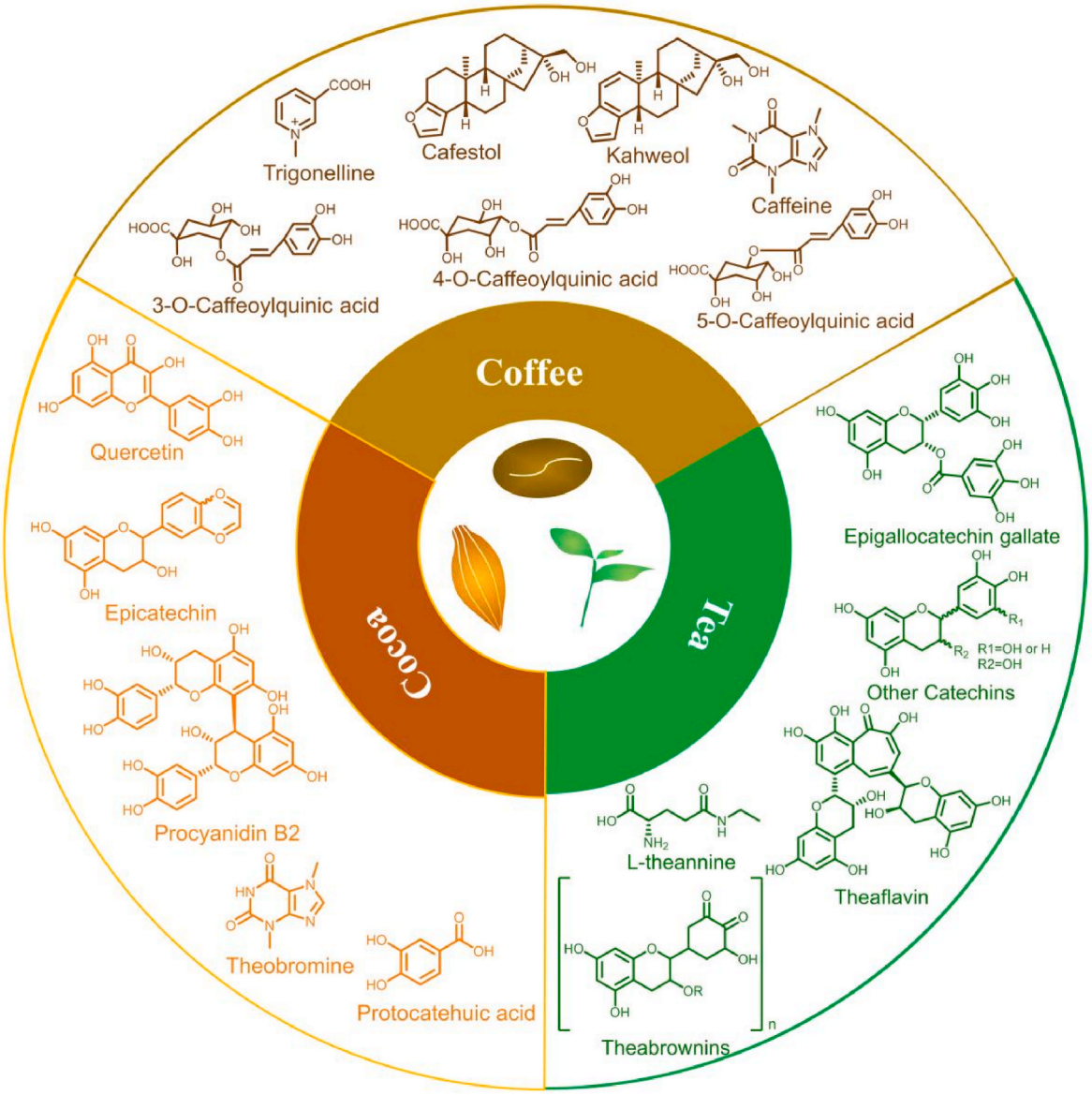

Fig. 3. The structures of the seven most classic compounds (trigonelline, cafestol, kahweol, caffeine, 3-O-caffeoylquinic acid, 4-O-caffeoylquinic acid and 5-O-caffeoylquinic acid) in coffee, five most classic compounds (epigallocatechin gallate, catechins, theaflavin and L-theannine and theabrownins) in tea and five most classic compounds (quercetin, epicatechin, procyanidin B2, theobromine and protocatehuic acid) in cocoa.

In an *in vitro* study, caffeine was found to affect the AKT/GSK3β pathway and inhibit the expression of adipogenic proteins (C/EBPα, C/EBPβ and PPARγ) during adipocyte differentiation in 3T3-L1 adipocytes (Kim et al., 2016). Furthermore, several *in vivo* studies confirmed the weight loss effect of caffeine in rats and mice (Kogure et al., 2002; Kobayashi-Hattori et al., 2005; Shimoda et al., 2006). However, researchers have provided different explanations for the underlying mechanisms. Early research conducted by Kogure et al. (2002) suggested that caffeine upregulates the expression of uncoupling proteins (UCP)-1, UCP-2, and UCP-3 to promote thermogenesis in obese mice. However, Kobayashi-Hattori et al. (2005) suggested that the weight-loss effect of caffeine may be attributed to its inhibitory effect on receptor A (1)R, which increases the secretion of catecholamines to promote lipolysis. This assumption was reiterated by Wu et al. (2017) who reported that caffeine can suppress appetite, which may be another reason for its weight-loss effect. According to Liu et al. (2018), the anti-obesity effects of caffeine may be associated with lowered inflammation levels and reduced lipogenesis. Specifically, caffeine treatment in rats suppressed inflammatory cytokines expression (TNFα, MCP-1, and IL-6), and decreased the expression of adipogenesis nuclear transcription factor (SREBP1c) and adipogenesis enzymes (FAS and ACC).

Nevertheless, the beneficial effects of caffeine on obesity makes it a promising substance for preventing nonalcoholic fatty liver disease (NAFLD). Caffeine reduced body weight and hepatic lipid accumulation in obese mice via the cAMP/CREB/SIRT3/AMPK/ACC pathway (Zhang et al., 2015), while it reduced hepatic lipid accumulation through the regulation of lipogenesis and the lipid oxidation pathway and its target genes (SREBP1, ACC1, CD36, and UCP2) in a zebrafish model (Zheng et al., 2015). Consequently, caffeine is promising as a compound for its preventive and protective effects against hepatosteatosis and NAFLD, and several studies have demonstrated that combining caffeine with other compounds usually results in prevention of obesity and lipid metabolism effects. For instance, the combination of caffeine and catechins could synergistically inhibit lipid accumulation in 3T3-L1 adipocytes by regulating the expression of enzymes (C/EBPα, FAS, and PPARγ) associated with lipid metabolism (Zhu et al., 2017). Additionally, combination therapy of caffeine and CGA can also reduce the serum lipid levels and regulate the expression of lipid-related genes and

proteins through the AMPKα-LXRα/SREBP-1c signaling pathway (Xu et al., 2019). Furthermore, the combination of 0.1% epigallocatechin-3-gallate (EGCG) and 0.1% caffeine is a good anti-obesity combination, as dietary supplementation with caffeine and EGCG in obese rats attenuates weight gain and significantly reduces WAT weight and energy intake (Liu and Sayama, 2018; Yang et al., 2019). Dietary supplementation with a combination of caffeine and EGCG exerts a synergistic anti-obesity effect by modulating the gut microbiota and bile acid (BA) metabolism (Zhu et al., 2021). According to the above results of the combination studies: caffeine or EGCG has found to be invalid in the low-dose, whereas an excessive dose of these two compounds may cause deleterious effects. Most of the safety effects of caffeine are related to exacerbation of its pharmacological effects on cardiovascular system, such as seizures, acute cardiovascular response (increase of blood pressure, cardiac arrhythmias, and tachycardia), as well as result of pharmacokinetic caffeine-drug interactions (Carrillo and Benitez, 2000). The low dose of caffeine or EGCG only showed a mild effect of anti-obesity and NAFLD amelioration. Caffeine and EGCG can exert synergistic effects when consumed together, the coadministration of them could exert a superior curative effect as well as high dose caffeine or EGCG but no anxiety regarding safety. In addition, adipose tissue browning is the focus of anti-obesity research. Based on the above research, caffeine has the potential of browning to increase the UCP1-dependent mitochondrial thermogenesis, and subsequent studies should clarify the mechanism of action in this direction.

3.1.3. Chlorogenic acid

Most CGAs are hydrolyzed to caffeic and quinic acid in the intestine through the action of special esterases and are subsequently absorbed (Miao and Xiang, 2020). In terms of lowering the amount of lipids, CGA can effectively prevent obesity. Initial reports suggested CGA improved the metabolism of lipid in male golden hamsters and explored the probable role of PPARα in these effects (Li et al., 2009). Besides, CGA can improve body weight, lipid metabolism, and obesity-related hormone levels in high fat diet (HFD) mice (Cho et al., 2010). Notably, a survey was conducted with 18 healthy male participants who consumed 185 mL of a test beverage with or without CGAs (329 mg) daily for 4 weeks. Significantly higher postprandial energy expenditure was observed after the consumption of CGA-enriched beverages, suggesting that CGA promotes human energy expenditure (Soga et al., 2013).

Zheng et al. (2014) showed that by regulating the activities of hepatic lipid metabolism-related enzymes CGA suppresses fat accumulation. In addition, evaluation of the therapeutic effects of CGA on obesity and liver steatosis revealed that CGA significantly prevented the progression of HFD-induced obesity (Ma et al., 2015). Moreover, CGA supplementation significantly reduces fat accumulation in the liver, plasma cholesterol (TC), and TG (De Sotillo and Hadley, 2002; Liu et al., 2015). Huang et al. (2015) ascertained these results by investigated the effect of 5-O-caffeyolquinic acid (5-CQA) on lipid metabolism in HFD-induced SD rats. Furthermore, using *Caenorhabditis elegans* (*C. elegans*) as a model system, 5-CQA is linked to the fat-lowering effects of green coffee bean extract (Farias-Pereira et al., 2018). Consequently, CGA has potential health benefits in the management of obesity and obesity-related lipid metabolic disorders.

Further studies have been conducted on the mechanism of action of CGA on obesity. Kumar et al. (2020) concluded that CGA primarily increased the phosphorylation of AMPK (Fig. 4), suppressed 3-hydroxy 3-methylglutaryl coenzyme-A reductase (HMGCR) and enhanced the activity of carnitine palmitoyltransferase. Furthermore, CGA-induced browning of adipocytes is mediated by the activation of AMPK (Sudhakar et al., 2020). Vasileva et al. (2020) demonstrated that CGA and caffeine synergistically activate browning in adipocytes, implicating the AMPK and PPARα/γ-mediated pathways. Additionally, CGA supplementation mitigated obesity and fat deposition in HFD-fed mice by inducing WAT browning. The underlying mechanism is that CGA activates PGC-1α/UCP-1 pathway (Zhong et al., 2020). In another study, CGA inhibited 3T3-L1 cell differentiation through the AMPK pathway by regulating the expression of PPARγ and C/EBPα to attenuate adipogenesis. It also promotes lipid metabolism by downregulating FAS and upregulating hydrolysis-related proteins (ATGL and HSL) (Kong et al., 2021). Therefore, AMPK is considered a target molecule of CGA for the treatment of obesity.

Gut microbiota bacteria regulate many important physiological functions, including homeostasis of energy and metabolism (Schachter et al., 2018). Recent studies on gut microbiota have revealed that the mechanism of CGA weight loss is also related to the regulation of the gut

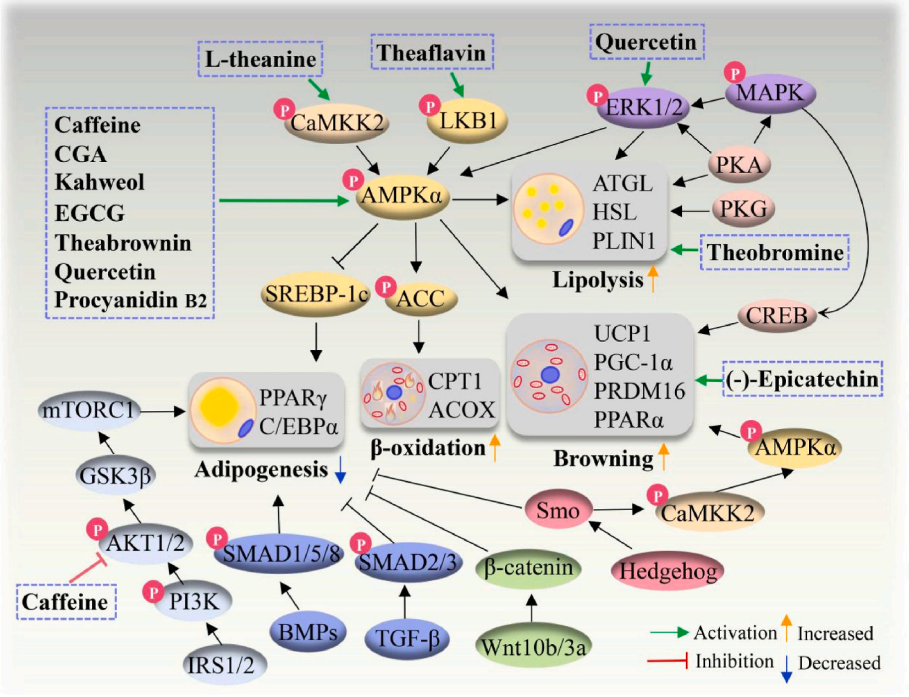

Fig. 4. Schematic representation the possible mechanisms of action of representative bioactive compounds in coffee, tea and cocoa on obesity.

microbiota. Wang et al. (2019) first demonstrated that CGA leads to weight loss, suppresses lipogenesis, and reverses HFD-induced gut microbiota dysbiosis. Subsequently, He et al. (2020) investigated the beneficial effects of CGA on energy balance and body weight. They found that CGA attenuated weight gain, increased energy expenditure, and modified the gut bacterial composition in obese mice. Furthermore, CGA significantly attenuated adipose tissue abnormalities, provided liver protection, and improved gut barrier integrity (Gao et al., 2024). Evidently, it can be concluded that the beneficial protective effect of CGA was associated with the reversal of gut microbiota dysbiosis and the improvement of gut barrier integrity. This suggests that gut microbiota is a key mechanism by which CGA improves obesity. Therefore, modulation of gut microbiota bacteria by CGA may produce optimal amounts of beneficial lipid metabolites, which is an effective strategy for promotion of lipid metabolism. Follow-up studies should using multiomics approaches identifying functional components after transformation by gut microbiota fermentation. And new research approaches based on gut microbiota-related characterization of clinically applicable functional food should be developed.

3.1.4. Trigonelline

Trigonelline is the second most abundant bioactive alkaloid found in coffee and exhibits a variety of medicinal characteristics (Ashihara et al., 2015). It also regulates obesity-related diseases and is a promising candidate for ameliorating lipid metabolism abnormalities in metabolic diseases.

Trigonelline was shown to be a potential anti-obesity agent present in coffee, which may also be linked to its lipid metabolism effects. Zhou et al. (2012) found that trigonelline exerts beneficial effects on diabetes by decreasing lipid levels, increasing the insulin sensitivity index and insulin content, upregulating antioxidant enzyme activity, and decreasing lipid peroxidation. Furthermore, trigonelline can inhibit key digestive enzymes related to starch and lipid digestion, such as lipase activity in the small intestine, for the treatment of lipid metabolic disorders, which lead to a notable decrease in serum TG and TC and an increase in high-density lipoprotein (HDL) cholesterol levels (Hamden et al., 2013). This initial study suggests that trigonelline may have a similar effect and mechanism as orlistat on obesity. Furthermore, Sharma et al. (2018) observed that trigonelline treatment reduced hepatic lipid accumulation and prevented high TC levels in HFD induced mice.

Trigonelline attenuated white adipocytes differentiation *in vitro*. This effect was partly associated with a decrease in protein levels of factors involved in adipogenesis (PPARγ and C/EBP) limiting the excessive hypertrophy of white adipocytes (Ilavenil et al., 2014). On the other hand, trigonelline enhances lipid catabolism and induces browning in white adipocytes (Choi et al., 2021). Mechanistic studies revealed that the browning effect of trigonelline is mediated by activating β3-AR and inhibiting PDE4, thereby stimulating the p38 MAPK/ATF-2 signaling pathway. Based on these findings, trigonelline could be useful for the treatment of lipid metabolism-associated diseases. However, the concentration of trigonelline (75 and 100 μM) is high in most cases (Table 1). Thus, it is speculated that the efficacy of coffee in improving obesity may also be related to long-term consumption of trigonelline. Besides, adverse effects, and bioavailability in animal or clinical studies about trigonelline should be fully carried out in future.

3.1.5. Cafestol and kahweol

Cafestol and kahweol are natural diterpenes extracted from coffee. They show similar biological activities but are not identical owing to the presence of one conjugated double bond on the furan ring of kahweol. Cafestol may be the most potent TC and TG-raising agent present in the human diet (Ren et al., 2019). Remarkably, the mechanisms underlying this effect have only been partially resolved. The most relevant mechanism involves cafestol, which increases the production rate of very low-density lipoprotein (VLDL), probably via increased assembly of VLDL1 in the liver. However, with long-term intake of coffee diterpenes, most rising serum TG levels subside (Urgert et al., 1997). In *C. elegans* model, cafestol increased fat oxidation and energy expenditure (Farias-Pereira et al., 2019a).

Kahweol is an effective inhibitor of adipogenesis (Baek et al., 2017). It activates the AMPK pathway and decreases the expression of adipogenesis-and lipid accumulation-related factors. Subsequently, Kim et al. (2018) observed that kahweol (40 μM) reduced lipid accumulation in 3T3-L1 cells by inhibiting the expression of adipogenesis and lipid accumulation-related genes including PPARγ, C/EBPα, FABP4, and FAS. However, it was suggested that the anti-obesity effect of a low concentration of kahweol (4 μM) is negligible or absent. Therefore, kahweol did not play an important role until a threshold concentration was reached. Furthermore, the fat-lowering effects of kahweol were due to reduced food intake in *C. elegans* (Farias-Pereira et al., 2020).

Our team recently conducted studies that have uncovered an intriguing finding (Wang et al., 2023): decaffarrolide B, the oxidation product of cafestol, demonstrated a significantly stronger inhibitory effect on adipogenesis in 3T3-L1 cell lines than did cafestol or kahweol. Remarkably, at a concentration of 20 μM, decaffarrolide B almost completely obstructed the accumulation of lipid droplets in the cells. Mechanistic investigations further suggested that this effect may be attributed to the inhibition of the AKT signaling pathway. These findings imply that future research should not only focus on the impact of diterpenoids, such as cafestol and kahweol, on coffee-induced weight loss activity, but also consider the potential influence of diterpenoids metabolites.

3.2. Tea

Tea is a rich source of pharmacologically active ingredients which have been identified as able to provide anti-obesity benefits. Based on the degree of fermentation, the three major forms of tea are green, black, and oolong. The active ingredients in tea include catechins, L-theanine, theaflavin, thearubigin, and theabrownin (Fig. 3). In this review, we focus on various studies highlighting the preventive effects of the active ingredients of tea (Table 2).

3.2.1. Tea extracts

Many experimental studies illustrate that tea extracts prevented the body weight gain. The feeding with tea extracts decreased the adiposity in both WAT and BAT as well as the whitening in BAT (Neyrinck et al., 2017). It also induced the browning of WAT and increasing BAT thermogenesis (Choo, 2003). In addition, tea extracts exhibited a effect on the inhibition of lipid synthesis in adipose tissue by reducing the expression of FAS, stearoyl-CoA desaturase1 (SCD1) and ACC (Li et al., 2016). Furthermore, tea extracts reduced the levels of C/EBPα and PPARγ to inhibit the adipogenesis and further alleviates the obesity in mice (Xu et al., 2020). To sum up, tea extracts exert a pronounced effect of anti-obesity could through increase energy expenditure, decrease the lipid synthesis and suppress adipogenesis.

3.2.2. Catechins

Cell cultures and animal studies have provided ample evidence that tea polyphenols, particularly catechins, exert beneficial effects against obesity. In a double-blind controlled study, Nagao et al. (2009) investigated the effects of continuous ingestion of a catechin-rich beverage in patients with type 2 diabetes who were not receiving insulin therapy. They concluded that catechins prevent obesity the patients, decrease body weight and TC levels, and increase adiponectin levels. In the same year, Maki et al. (2009), conducted a study where participants (n = 132, 107 completers) were.

randomly assigned to receive a beverage containing 625 mg catechins for 12 weeks. The research showed that catechins consumption enhance exercise-induced abdominal fat loss in overweight and obese adults. These results suggest that catechin-rich beverages may have

several therapeutic uses, including the prevention of obesity and the recovery of secretory ability.

EGCG is the most studied catechin, in animals, Wolfram et al. 2005 found EGCG supplementation prevented diet-induced increases in body weight and also decreased fed-state plasma levels of glucose, TG, and leptin. Moreover, EGCG decreased subcutaneous and epididymal adipose tissue weights. This study showed that dietary supplementation with EGCG can be a valuable natural treatment option for obesity. Subsequently, many studies have supported this finding. For instance, Klaus et al. (2005) showed that EGCG attenuated diet-induced body fat accretion and diet digestibility in mice, apparently promoting fat oxidation and leptin and stearoyl-CoA desaturase 1 (SCD1) gene expression in WAT. EGCG treatment alleviated metabolic syndrome and decreased body fat accumulation in obese mice. The beneficial effects of EGCG are associated with decreased lipid absorption and reduced levels of pro-inflammatory cytokines (Chen et al., 2011). Furthermore, EGCG reduces adipogenesis through an arrest of the cell cycle at G2/M and a blockage of adipose phenotype expression of C/EBPα and PPARγ in 3T3-L1 adipocytes (Chan et al., 2011). In addition, EGCG markedly alleviated lipid accumulation and the inhibitory effect was largely limited to the early stages of adipocyte differentiation (Mi et al., 2018). Moreover, EGCG has been reported to inhibit pancreatic lipase, salivary alpha-amylase, and starch digestion, thereby reducing metabolic parameters in obesity (Grove et al., 2012; Zhan et al., 2016; Li et al., 2018b).

Further, the connection between EGCG, the activation of BAT, and obesity has been investigated. Lee et al. (2017) demonstrated that EGCG exerts anti-obesity properties through BAT thermogenesis and mitochondrial biogenesis, which are partially associated with the regulation of genes related to mitochondrial biogenesis and the activation of AMPK in the BAT of obese mice. Consistently, Zhou et al. (2018) showed that EGCG ameliorated obesity by increasing energy expenditure through BAT thermogenesis. EGCG notably evoked the phosphorylation of AMPK and ACC and blunted key enzymes involved in lipogenesis. Moreover, EGCG increased the excretion of free fatty acids from feces (Li et al., 2018a). By measuring the mRNA expression levels of genes involved in lipid metabolism, they found that EGCG inhibited the expression of genes involved in the synthesis of *de novo* fatty acids (ACC, FAS, SCD1, C/EBPβ, PPARγ, and SREBP1) and increased lipolysis and lipid oxidization in WAT partially via activation of AMPK.

The anti-obesity benefits of catechins are strongly related to their mediating effects on the gut microbiota. Huang et al. (2020) found that EGCG reduces body fat deposition and improves intestinal mucosal immunity, which can help prevent metabolic syndrome and NAFLD. Furthermore, the dietary intake of catechins improve the gut microbiota, significantly alleviate obesity, and prevent hepatic steatosis (Liu et al., 2023). These findings indicate that catechins are capable of suppressing adipogenesis in WAT, activating of BAT and may therefore serve as a novel approach to combat obesity.

3.2.3. L-theanine

L-theanine, a non-protein amino acid first isolated from the leaves of green tea by Sakato at the end of 1940s, is one of the most fundamental substances that endows tea with its special flavor (Turkozu and Sanlier, 2017) and plays an effective role in its anti-obesity effect.

L-theanine suppresses fat accumulation in mice (Zheng et al., 2004) and affects lipid absorption by regulating the expression of intestinal fatty acid transporters in rats (Yan et al., 2007). Lin et al. (2020) discovered that L-theanine can regulate glucose, lipid, and protein metabolism via insulin and AMPK signaling. Furthermore, L-theanine enhances adaptive thermogenesis and induces browning of inguinal WAT by upregulating the expression of thermogenic genes such as UCP1 and PRDM16 (Peng et al., 2021). Moreover, L-theanine shows great potential for regulating lipid metabolism by modulating gut microbiota and BA metabolism via the FXR-FGF15-CYP7A1 pathway (Xu et al., 2022). L-theanine also ameliorated adiposity and hepatic steatosis in obese mice by regulating the expression of genes related to lipid metabolism. The underlying mechanism is that L-theanine ameliorates hepatocyte lipid metabolic pathways via the CaMKKβ-AMPK signaling pathway (He et al., 2021; Liang et al., 2022).

Based on L-theanine its positive role in WAT browning and in its improvement of the gut microbiota composition. We speculate that L-theanine could play an active role through multiple targets, and its specific targets are worth elucidation. On the other hand, L-theanine can only be used as a functional component at present, as its dose reached up to 300 mg/kg/day for mice to combat obesity (Table 2). This dose was considered too high if it is converted to human dose, so L-theanine is unlikely to be an anti-obesity drug. In addition, if the structure of L-theanine was modified by synthesis, its activity may be further improved.

3.2.4. Theaflavins

Theaflavins are benzotropolone derivatives of catechins that are formed through enzymatic oxidation during the production of black tea. Current research shows that theaflavins mainly inhibit lipid accumulation in the liver to ameliorate obesity. Theaflavins were first reported to have a hepatic lipid-lowering potential in human HepG2 cells (Lin et al., 2007). In subsequent study demonstrated that theaflavins attenuate hepatic lipid accumulation effect together with and regulate fatty acid synthesis and oxidation by stimulating AMPK through the LKB1 and reactive oxygen species pathways (Lin et al., 2007). In addition, oral administration of theaflavins may affect leptin levels to prevent fatty liver and obesity (Jin et al., 2013). Later work on the hepatic lipid-lowering effect of theaflavin-3,3′-digallate demonstrated that it relieved hepatocyte lipid deposition and directly bound and inhibited the activation of plasma kallikrein, which was further proved to stimulate AMPK and its downstream targets (Zhang et al., 2020).

In mature adipocytes, theaflavin-3,3′-digallate, attenuates TG accumulation, and stimulates lipolysis associated with the induction of UCP1 and AMPK-FoxO3A-MnSOD pathway (Ko et al., 2015). In HFD induced obese mice, the consumption of theaflavins significantly inhibited body weight gain and visceral fat accumulation (Takemoto et al., 2016). These findings were confirmed by Cai et al. (2021) who demonstrated that theaflavin consumption improves glycolipid metabolism and obesity by activating the SIRT6/AMPK/SREBP-1/FAS signaling pathway.

3.2.5. Thearubigins

Thearubigins, heterogeneous mixtures found in black teas, constitute pigments used in the food industry and contributes significantly to the biological activities of black tea (Long et al., 2023). Thearubigin can prevent or treat obesity and related metabolic disorders, such as dyslipidemia and hypercholesterolemia. Thearubigin induces liver cholesterol-lowering activity by accelerating neutral and acidic fecal steroid excretion (Miyata et al., 2011). Black tea aqueous extract (rich in thearubigins and theaflavins) significantly alleviates most signs of metabolic syndrome, including hyperglycemia, dyslipidemia, and impairment of liver function induced by alloxan or a cholesterol-rich diet in animals (Ramadan et al., 2009). Black tea extract also has beneficial effects on the risk of metabolic syndrome in rat models of human obesity. Imran et al. (2018) reported that dietary interventions based on thearubigins and theaflavins were helpful in alleviating hypercholesterolemia and hyperglycemia, and that TC, LDL, and TG levels were reduced in experimental rats, with a significant increase in HDL. Therefore, thearubigins have practical application value in the development of healthy products for the treatment of hypercholesterolemia.

3.2.6. Theabrownins

Theabrownins have been shown to prevent body weight gain. In high fat zebrafish, theabrownins exhibited hypolipidemic activity, which decreased the lipid level to 51.57% at 1000 μg/mL (Xiao et al., 2020a). Moreover, Deng et al. (2021) showed that pu-erh tea water extract,

which has high levels of theabrownins, was effective in increasing serum HDL-c levels and reducing serum TG, TC, LDL-c, and inflammatory cytokines in hyperlipidemic rats. The effects of long-term theabrownin supplementation, revealing that theabrownins can enhance BAT activity and WAT browning by activating the AMPK-PGC1α pathway and modulating short-chain fatty acids in obese mice (Wang et al., 2021). The combination of theabrownin and *Poria cocos* polysaccharides significantly reduced body weight, adipose tissue weight, and lipid levels, which promoted cholesterol synthesis of fatty acids, lipid transport, and oxidative utilization, and reduced lipid synthesis (Wang et al., 2022). Additionally, they exhibit significant preventive and therapeutic effects on NAFLD and obesity by regulating serotonin-related signaling pathways (Li et al., 2023).

Theabrownins are potential therapeutic modalities for obesity and lipid metabolic disorders that alter the composition of gut bacteria involved in BA metabolism. They enhance the conversion of cholesterol to BA in hepatocytes and the fecal excretion of cholesterol and BA in rats consuming a high-lipid diet (Peng et al., 2013). Huang et al. (2019) demonstrated that theabrownins alter the gut microbiota in mice and humans, suggesting that decreased intestinal bile salt hydrolase activity and/or decreased FXR-FGF15 signaling may be potential anti-obesity mechanisms. Additionally, 225 mg/kg/day theabrownins prevented adipogenesis in 4-week-old mice via alternative gut microbiota-driven BA synthesis (Kuang et al., 2020). Recently, Li et al. (2022) demonstrated that theabrownins significantly reduce body weight gain and body fat accumulation without affecting appetite, thereby significantly alleviating obesity via gut microbiota-related metabolic pathways. Theabrownins is one of the most abundant pigments in Pu-erh tea. Compared with the other two phenolic pigments (theaflavins and thearubigins), theabrownins are the most studied at present (Table 2). In addition, all of the three phenolic pigments can regulate lipid metabolism in liver, but the specific targets remain to be clarified.

3.3. Cocoa

Cocoa is the source seed of the popular plant-based drink worldwide after coffee and tea. It is the dried and fully fermented fatty seed of the cocoa tree (*Theobroma cacao*) fruit, used as the main ingredient in chocolate. Cocoa polyphenols consist primarily of flavanols (epicatechin, catechin, and procyanidins) and a flavonol (quercetin) and it has the highest flavanol contents of all foods (Jonfia-Essien et al., 2008). Other polyphenols, such as anthocyanins, phenolic acids, and stilbenes, have been reported to be present in small quantities (Aprotosoaie et al., 2016). More than 200 compounds, including the most-researched and abundant polyphenols, beneficial to the human body are present in cocoa (Rodríguez-Pérez et al., 2019). These compounds exhibit anti-obesity effects by certain mechanisms of action (Table 3; Fig. 3).

3.3.1. Cocoa polyphenols

Several *in vitro* and *in vivo* studies have shown that polyphenols with antioxidant and anti-obesity properties can boost energy expenditure and thermogenesis, as well as reduce oxidative stress and inflammation, while supporting weight loss management (Gouveia et al., 2022). Sustained consumption of cocoa reduces human LDL oxidation potential and increases HDL cholesterol (Mursu et al., 2004; Baba et al., 2007). The anti-obesity effects of cocoa and dark chocolate have been investigated by Golomb et al. (2012), amongst others who concluded that adults who frequently consumed chocolate had a lower BMI than those who consumed chocolate less often. The regular consumption of dark chocolate had beneficial effects on HDL cholesterol and lipoprotein ratios in women with normal-weight obesity syndrome (Di Renzo et al., 2013). Moreover, a combination of cocoa polyphenols, soy isoflavones, and myoinositol effectively reduced TG levels (D'Anna et al., 2014).

Cocoa extracts have also been found to decrease visceral adipose tissue in rats, possibly by altering the expression of genes encoding enzymes and transport molecules involved in fatty acid synthesis and thermogenesis in WAT (Matsui et al., 2005). In diabetic rats, treatment with cocoa extract for 4 weeks was associated with reduced serum glucose and LDL levels and increased HDL (Ruzaidi et al., 2005). A comparable study by Jalil et al. (2008) found that cocoa extract reduced postprandial hyperglycemia, plasma free fatty acids, and 8-isoprostane, a biomarker of oxidative stress. Human and animal studies have shown that the administration of cocoa powder has a hypocholesterolemic effect, lowering plasma TC concentrations and increasing fecal TC and total BA excretion (Kurosawa et al., 2005; Yasuda et al., 2008).

Cocoa extracts have beneficial effects on obesity, lowering body weight gain and food efficiency in rats (Aranaz et al., 2019), as well as lowering visceral adiposity and adipocyte size by downregulating key adipogenesis-related proteins (Yasuda et al., 2008). Moreover, cocoa polyphenols significant inhibited the differentiation of adipocytes and regulated the expression of genes (PPARγ, PPARα, PGC1α, SIRT1 and UCP1) involved in lipid metabolism in WAT (Min et al., 2013; Rabadan-Chavez et al., 2016). In addition, cocoa polyphenols have been reported to exert beneficial effects on obesity via molecular mechanisms involving several targets such as PPARs, liver X receptors, adiponectin genes, and uncoupling proteins. They may prevent visceral fat deposition, reduce insulin resistance, stimulate lipolysis, and increase the expression of adiponectin (Ali et al., 2014).

3.3.2. Quercetin

Quercetin from cocoa prevents adipogenesis by upregulating ATGL and HSL expression and downregulating FAS, LPL, and adipocyte fatty acid-binding protein (aP2) expression as well as the expression of transcription factors (Seo et al., 2015). Furthermore, quercetin exhibited an inhibitory effect on pancreatic lipase with IC50 value of 70 mg/mL, and pre-administration of quercetin (5 and 10 mg/kg) significantly reduced fat absorption and increased fat excretion in rats (Zhou et al., 2021).

Moreover, quercetin combined with resveratrol can improve obesity in different types of experimental mice, mainly by reducing the expression of systemic pro-inflammatory adipokines, affecting TG accumulation in WAT, and enhancing the process of glycolysis and fatty acid oxidation (Zhou et al., 2012; Arias et al., 2016; Zhao et al., 2017a). The combination of quercetin and resveratrol could also prevent the development of obesity by restoring gut microbiota dysbiosis induced by HFD (Zhao et al., 2017b).

3.3.3. (−)-Epicatechin

In rats fed a HFD for 5 weeks, (−)-epicatechin (1 mg/kg/day) improved dyslipidemia, suggesting that (−)-epicatechin could be effective in treating obesity-induced hyperlipidemia (Gutierrez-Salmean et al., 2014). Moreover, (−)-epicatechin has been found to promoted fat browning by promoting mitochondrial biogenesis, increasing fatty acid metabolism, and upregulating the expression of BAT-specific proteins in a HFD mouse model of obesity and adipocytes (Varela et al., 2017). Additionally, Cheng et al. (2017) also showed that (−)-epicatechin effectively improved the blood lipid profile and protected the liver from accumulating excessive fat. Potential molecular mechanisms were proposed to be associated with the regulation of the Insig-1-SREBP-SCAP pathway and lipid metabolism-related genes.

3.3.4. Procyanidin B2

Procyanidin B2, a naturally occurring phenolic compound in cocoa, that has a beneficial function in the prevention of obesity. For instance, Zhang et al. (2014) investigated its effects on adipogenesis in 3T3-L1 adipocytes. They found that procyanidin B2 treatment inhibited adipogenesis by targeting PPARγ. Moreover, procyanidin B2 administration leads to dramatic alterations in the intestinal microbiota and prevents the upregulation of several lipogenic genes, including SREBP-1c and FAS (Xing et al., 2019). Furthermore, procyanidin B2 reduced the levels of lipid metabolism biomarkers and increased the antioxidant abilities and lipoprotein lipase activity in HFD-induced dyslipidemic mice, which are

associated with the gut microbiota (Xiao et al., 2020b). Moreover Ji et al. (2023) revealed that a soybean protein isolate and procyanidin B2 complexes exerted synergistic hypolipidemic activity by activating AMPK, inhibiting HMGCR and FAS protein expression, and upregulating carnitine palmitoyltransferase 1 (CPT1) protein activity.

3.3.5. Theobromine

Theobromine, a bitter alkaloid found in cacao plants, can also contribute to the amelioration of obesity. *In vitro*, theobromine inhibits adipocyte differentiation during the early stages of adipogenesis by regulating the expression of PPARγ and C/EBPα through the AMPK and ERK/JNK signaling pathways in 3T3-L1 preadipocytes (Jang et al., 2015). *In vivo*, theobromine attenuated body weight gain in mice and suppressed adipocyte differentiation. Furthermore, the inhibition of adenosine receptor A1 signaling is important for theobromine-induced C/EBPβ degradation (Mitani et al., 2017). Theobromine have a therapeutic effect on obesity by controlling macrophage infiltration in adipose tissue and inflammation, which inhibits the differentiation of preadipocytes and reduces the levels of pro-inflammatory cytokines such as MCP-1 and IL-1β (Fuggetta et al., 2019).

Moreover, Jang et al. (2019) reported that theobromine improves lipid catabolic metabolism in both cultured white and brown adipocytes via the β-adrenergic and AMPK signaling pathways. Further, theobromine upregulates brown fat-specific proteins of PRDM16 and UCP1 by activating β3-AR signaling and by inhibiting PDE4D (Jang et al., 2020). Theobromine also decreased the weight gain in obese mice. The underlying mechanisms were found associated with browning in subcutaneous WAT and enhancement of PPARγ-induced UCP1 expression *in vitro* (Tanaka et al., 2022).

4. Conclusions and future prospects

In recent years, the development of anti-obesity drug candidates as functional food products have received increased attention because the targets of functional food products are usually participate regulate many signaling pathways and affect multiple tissues. Consequently, functional food products exhibit great potential for the treatment of obesity. Coffee, tea, and cocoa are rich in a wide variety of active ingredients backed by their history of use, which adds to their suitability as treatments for obesity. In this review, we describe the three main strategies for obesity prevention. The potential functions of the principal components of the three beverages, under the combined influence of the above three anti-obesity strategies, are also introduced.

The active doses of the three beverages were higher than those of commercially available anti-obesity drugs. However, the long-term effects cannot be ignored. It can be attributed to four main reasons. First, the high caffeine content in all the three beverages may be a potential anti-obesity functional substance. Second, polyphenols show the ability to regulate obesity. The third reason is the multi-target synergy of the mixtures. In addition to traditional research on the mechanism of action of the three beverages based on molecular pharmacological means, current research on gut microbiota has also become a hot topic in recent years.

The effective dose of coffee was range from 0.1 to 2.0% in diet for rodent studies (Farias-Pereira et al., 2019b). To date, a moderate intake of coffee up to 1–4 cups/day was safe and beneficial for most people. In animal level studies, the effective dose of tea was range from 150 to 1000 mg/kg or range from 0.2 to 4.0% in diet (Xu et al., 2021). The effective dose of cocoa was range from 0.5 to 3% in diet for rodent studies (Flores, 2019). The dosage of the three drinks were different, owning to there were differences in the composition of the three drinks. On the other hand, a low dose of the three drinks may have no significant effect, but a high dose of the three drinks may trigger adverse effects. In future studies, more definite information in human studies were necessary.

It's worth noting that most pharmacological studies on the anti-obesity active components in these three beverages primarily use individual compounds. However, when these compounds are consumed as functional components in food, a range of factors need to be considered, such as food processing techniques and extraction conditions, the stability of the compounds, and palatability. Processing techniques and extraction conditions significantly influence the content of active compounds in beverages. For instance, the solubility of caffeine might vary substantially due to changes in the size of coffee powder particles, water temperature, and the water-to-powder ratio. CGAs in coffee are more efficiently extracted under high temperature and pressure conditions (Lu et al., 2020). The content of theaflavins, thearubigins, and theabrownins in tea largely depends on the fermentation conditions of the tea leaves (Yang et al., 2023).

The inherent stability of the compounds is another crucial factor affecting their actual content in beverages. Active components such as caffeine, trigonelline, and theobromine generally exhibit good stability during typical food processing, but they may degrade under conditions of high temperature, light exposure, and oxygen. Moreover, polyphenolic compounds, such as CGAs and catechins, may show thermal instability during processing (Kusumah and De Mejia, 2022). Therefore, it's necessary to appropriately control pre-processing techniques to ensure the extraction rate of these.

Adipocytes play an important role in the progression of obesity. We can regulate the hypertrophy (preexisting individual adipocytes) and/or hyperplasia (adipocyte differentiation) of adipocytes to resist obesity. In these two processes, which are complicated processes accompanied by specific morphological and molecular changes. Generally, adipocyte hypertrophy is critically associated with metabolic disorders and plays a key role in the adult obesity development. Particularly, adipocyte hypertrophy existing with altered metabolism, which directly contributes to the complexities of obesity-related pathophysiology, such as inflammation, insulin resistance and type 2 diabetes. Thus, it's important to consider that bioactive compounds can have different biological effects depending on the cellular context and metabolism, which could affect their efficacy in obesity treatment. However, there is limited research cellular studies on the effects of the three beverages on adipocyte hypertrophy. Collectively, it still requires further investigations about controlling adipocyte hypertrophy without causing lipodystrophic disease.

With a deeper understanding of the pathophysiology of obesity, the cellular signaling networks involved in adipogenesis, thermogenesis, and lipolysis are being uncovered. Understanding these complex signaling pathways will enable us to move toward more precise medicine, enriching our arsenal in the fight against obesity. Constituents from functional foods (coffee, tea, and cocoa) are promising for further diversification of the available treatment options for obesity and achieving the ultimate goal of effective lipid metabolism improvement and weight management. Further studies on the structure-activity relationship would widen the research perspectives, which could be useful drug candidates for obesity. In addition, *in vitro* and animal models have been developed to investigate the effects of the active compounds and their anti-obesity effects. However, parameters such as dose requirements, efficiency, and bioavailability need to be fully clarified. Preclinical assays are necessary to generate more evidence, and special attention should be paid to dosage and duration to establish dietary recommendations. Make full use of the advanced bioinformatics analyses, the identification of the target of bioactive substances of the three beverages is possible. We believe that bioactive substances from these three functional foods will contribute greatly to human health.

CRediT authorship contribution statement

Qian Wang: Writing – original draft, Investigation, Funding acquisition. **Gui-Lin Hu:** Visualization, Methodology. **Ming-Hua Qiu:** Writing, Investigation. **Jun Cao:** Writing – review & editing, Validation, Supervision. **Wen-Yong Xiong:** Writing – review & editing, Project

administration, Methodology, Funding acquisition.

Declaration of competing interest

No potential competing interest was reported by the author(s).

Data availability

No data was used for the research described in the article.

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