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Mushroom polysaccharides regulate diet-induced obesity by targeting lipid metabolism, gut microbiota and mitochondria

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ABSTRACT: Obesity, driven by unhealthy dietary patterns, has become a global health threat. Mushroom polysaccharides (MPs) exhibits promising protective effects against obesity. This review elucidate the potential anti-obesity mechanisms of MPs, focusing on their ability to modulate lipid metabolism, cholesterol homeostasis, gut microbiota, mitochondrial function, and oxidative stress. Specifically, MPs can protect against diet-induced obesity by improving lipid and cholesterol metabolism. Additionally, MPs improve obesity by modulating gut microbiota composition, which plays a pivotal role in lipid and energy metabolism. Moreover, diet-induced mitochondrial dysfunction, endoplasmic reticulum stress, and oxidative stress disrupt metabolic homeostasis through direct lipid dysregulation and inflammation-mediated pathways. MPs mitigate these effects by enhancing mitochondrial function, alleviating ER stress, and reducing oxidative stress, thereby restoring metabolic balance. This review presents a comprehensive discussion on MPs research as functional compounds utilized in food and medicine and could be beneficial for obesity and related metabolic disorders.

Key words: Mushroom polysaccharides; Obesity; Lipid metabolism; Cholesterol metabolism; Gut microbiota; Mitochondrial dysfunction.

1. Introduction

Obesity, defined by the World Health Organization as a body mass index (BMI) ≥30 kg/m^2, results primarily from energy imbalance driven by genetic predisposition, environmental factors (e.g., high-calorie diets, sedentary lifestyles), and behavioral patterns [1]. Growing evidence suggests that the strikingly increased prevalence of obesity occurs due to the overconsumption of fat/sugar-abundant food, unhealthy lifestyle and inherited genetic disorder, making obesity an increasingly serious problem and a global public health issue. It has been estimated that the obesity rate will account for 57.8% of the global population by 2030 [2]. The most prominent feature of obesity is the excessive adipose tissue deposit, particularly subcutaneous fat. It results in systemic insulin resistance and chronic inflammation, which in turn exacerbates metabolic dysregulation. Specifically, there are four major depots in human adipose tissue: upper-body subcutaneous (UBSAT), abdominal subcutaneous (ASAT), visceral (VAT), and lower-body subcutaneous (LBSAT). UBSAT and VAT are strongly associated with metabolic dysfunction and atherosclerotic pathologies,

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whereas LBSAT exhibits a protective phenotype against diet-induced metabolic disturbances. VAT demonstrates distinct pathophysiological characteristics compared to subcutaneous depots, including higher lipolytic activity (releasing excess free fatty acids), enhanced secretion of pro-inflammatory adipokines (e.g., TNF-α, IL-6) over anti-inflammatory counterparts (e.g., adiponectin), and amplified glucocorticoid receptor responsiveness. In addition to fat deposit, obesity also manifests as abnormal lipid/cholesterol metabolism, gut microbiota (GM) dysbiosis, mitochondrial dysfunction, and chronic inflammation. Current therapeutic strategies primarily target single pathways: pharmacological agents such as GLP-1 receptor agonists (e.g., semaglutide) enhance satiety and glucose homeostasis, while lipase inhibitors (e.g., orlistat) reduce dietary fat absorption. However, long-term use of these drugs is associated with various side effects (i.e., gastrointestinal disturbances, cardiovascular issues, and psychological impacts) [3]. Bariatric surgery, though effective, is invasive and carries significant risks. Traditional interventions, such as lifestyle modifications, diet management, and physical activity, often have limited success due to poor compliance and long-term sustainability. Therefore, dietary interventions represent a promising therapeutic approach for improving diet-induced obesity.

Natural polysaccharides, complex carbohydrate molecules derived from plants, fungi, and other natural sources, have attracted increasing attention for their multiple bioactivities (i.e., hypolipidemic, hepatoprotective, antitumor, antioxidant and antibiotic activities) and toxic-free character [4]. Unlike synthetic anti-obesity drugs, natural polysaccharides are generally considered safe and well-tolerated, making them a potential alternative or complement to traditional pharmacological treatments. Since most polysaccharides cannot be digested by enzymes in the gastrointestinal tract, they are utilized primarily by the intestinal flora in the large intestine through fermentation. Therefore, there have been many reports of polysaccharides alleviating obesity by regulating the intestinal flora [5; 6]. Indeed, accumulating evidence indicates that polysaccharides can also improve obesity through multiple mechanisms such as regulating lipids metabolism and energy metabolism, reducing inflammation level, improving insulin resistance, and so on [7; 8].

Edible mushrooms, characterized by their macrofungal fruiting bodies, encompass approximately 2,000 species globally, predominantly within the Basidiomycota subphylum. Notably, 650 of these species possess documented medicinal properties [9]. Mushrooms are rich sources of bioactive compounds, notably polysaccharides, sterols, adenosine, polyphenols, and triterpenes. Numerous studies have demonstrated that these bioactive compounds exert beneficial effects on diseases such as obesity, hyperlipidemia, and cancer. Among these components, polysaccharides exhibit the broadest spectrum of functional activities, with their bioactivity intrinsically linked to structural features. Mushroom polysaccharides (MPs) primarily comprise α-glucans, β-glucans, or mixed α/β-glucans, as well as heteropolysaccharides composed of diverse monosaccharides (e.g., fructose, galactose, mannose). The most frequently reported glucan structures include (1→3)-β-D-glucans, (1→6)-β-D-glucans, and mixed (1→3)-α-D-glucans with (1→6)-β-D-glucans. Of these, β-glucans represent the most ubiquitous functional polysaccharides in mushrooms, with their structure

typically consisting of branched β-(1→3)-D-glucans [9]. The structural diversity of MPs contributes significantly to their varied pharmacological activities (i.e., hypolipidemic, anti-inflammatory, and antioxidant effects),making them a promising candidate for managing obesity [10].

Although interdisciplinary studies focusing on MPs have provided substantial knowledge regarding their functions and pharmaceutical properties, a comprehensive and systematic reviews of their anti-obesity potential and detailed mechanisms are still limited. This review aims to systematically summarize the current knowledge on the anti-obesity effects of MPs, focusing on their mechanisms related to regulating lipid metabolism, improving mitochondrial function, modulating gut microbiota, and mitigating inflammation. The manuscript also analyzes the structure-activity relationships of MPs to provide insights into how specific structural features influence their anti-obesity activities. This review highlights the potential of MPs as natural, multi-targeted agents for obesity prevention and treatment, while addressing the current insufficiency in current knowledge and proposing future perspectives. Ultimately, this review aims to provide valuable insights for the development and application of MPs in functional foods.

2. Properties of mushroom and MPs

2.1. Mushroom diversity and bioactive compounds

Mushrooms, macroscopic fungi predominantly belonging to the Basidiomycetes class with a minority classified under Ascomycetes, are widely distributed across the globe. With approximately 15,000 known species, over 2,000 of which are edible, mushrooms have been utilized as a food source for more than 2,000 years. The primary species traditionally utilized include *Ganoderma lucidum* (reishi), *Lentinus edodes* (shiitake), *Tremella fuciformis* (snow fungus), *Grifola frondosa* (maitake), *Hericium erinaceus* (lion's mane), *Agaricus blazei* (almond mushroom), *Flammulina velutipes* (enoki), *Coriolus versicolor* (turkey tail), *Inonotus obliquus* (chaga), *Pleurotus ostreatus* (oyster mushroom), *Sparassis crispa* (cauliflower mushroom), and *Poria cocos* (hoelen). These species predominantly belong to the Basidiomycetes class, with the exception of *Cordyceps militaris*, which is classified under Ascomycetes [9]. Mushrooms contain a diverse array of bioactive compounds, including polysaccharides, phenolics, glycopeptides, terpenoids, alkaloids, amino acids, peptides, sterols, sphingolipids, nucleosides, nucleotides, and organic acids. Among these, polysaccharides as one of the main bioactive components in mushrooms, are the most prevalent and extensively studied macromolecules in mushrooms. They exhibit multiple bioactive functions such as antioxidative, immunomodulatory, antitumor, anti-inflammatory, hypoglycemic, and hepatoprotective effects [11].

2.2. Structure, function, and analysis of MPs

MPs as the main component of mushroom, are composed of 10 or more single sugar molecules polymerized by glycosidic bonds in linear or branched chain. Over 130 biological properties of MPs have been reported, such as neuroprotective, antioxidant, antimicrobial, prebiotic, and gut microbiota-modulating properties, with the antitumor effects being the most extensively studied [9]. From 2018 to 2025, the potential

of MPs in obesity and metabolic diseases management has garnered significant attention. These polysaccharides exhibit diverse biological functions that depend on their unique structural and physicochemical properties, such as molecular weight (M*w*), glycosidic linkage patterns, monosaccharide composition, and solubility. MPs typically exhibit M*w* ranging from tens to several thousand kDa. Research has indicated that this characteristic is closely associated with their anti-obesity and immune-modulating activities. High M*w* MPs are known to inhibit cholesterol synthesis and possess immune-regulating properties. Specifically, the high M*w* MPs (>100 kDa) form triple helices that bind dectin-1 receptors on immune cells, suppressing SREBP-1c expression to inhibit hepatic lipogenesis [12]. Additionally, MPs are highly complex structures containing β-D-glucan group, which are primarily characterized by their glycosidic linkage patterns. The backbone of MPs typically consists of β-(1→3)-linked glucosyl residues with attached β-(1→6)-linked branches, contributing to their diverse bioactivities, particularly their potent immunostimulatory properties [9]. Noticeably, branched β-(1→3)/(1→4)-glucans have been shown to exert excellent modulation of obesity by reducing serum cholesterol levels and modulate immune responses. Beyond β-glucans, mushrooms also contain structurally diverse linear and branched α-glucans. For example, Pseudorigeran featuring (1 → 3)-α-D and amylose featuring (1→4)-α-D are the most typical linear form, while glycogen with (1→4)-α-D linear chain and (1→6)-α-D branches is the most typical branched form [9]. Notably, α-(1→3)-linked glucans demonstrate the highest cytotoxicity against breast tumor cells [13]. Monosaccharide composition and solubility are also critical factors influencing the bioactivity of MPs. Studies have reported that MPs with higher glucose and uronic acid content exhibit significantly greater antioxidant activity compared to neutral heteropolysaccharides, although the underlying mechanisms remain under investigation. One proposed mechanism involves the ability of these MPs to donate hydrogen atoms to free radicals, thereby terminating radical chain reactions and converting radicals into harmless products [14]. Generally, higher solubility MPs demonstrate superior anti-obesity effects by reducing fat accumulation and enhancing energy expenditure through modulation of key metabolic pathways, including the activation of AMPK and inhibition of adipogenesis. This can be attributed to their better absorption in the gastrointestinal tract, facilitating more efficient interactions with gut microbiota and metabolic regulators, which ultimately contribute to improved lipid metabolism and reduced fat storage [12].

In comparison with other polysaccharides, MPs differ significantly structural and functional differences from plant polysaccharides (such as cellulose and pectin) and microbial polysaccharides (such as glucans from yeast or bacteria). Structurally, MPs are characterized by highly branched β-(1→3)-glucan backbones with β-(1→6)-linked side chains, a conformation rarely observed in linear plant β-glucans (e.g., oat (1→3)(1→4)-glucan) or bacterial α-(1→6)-glucans. This unique architectural feature imparts three major functional advantages: (1) Enhanced receptor targeting through high-affinity binding to dectin-1/TLR2 [15; 16]; (2) Superior lipid sequestration capacity, where β-(1→6) branches create hydrophobic pockets binding more bile acids than cellulose, directly reducing cholesterol reabsorption [17]. While plant polysaccharides primarily function as structural components in plant cell walls and are widely studied for their ability to

regulate gut health and improve digestion. Their lipid-lowering effects are usually attributed to their ability to form gels in the digestive tract, which trap bile acids and prevent their reabsorption, thus lowering cholesterol levels. Likewise, microbial polysaccharides tend to have less complex branching and may differ in their M*w* and degree of solubility, which makes them have poor cholesterol-lowering properties compared to MPs [18]; (3) Multi-dimensional lipid regulation. MPs have been shown to improve lipid metabolism through mechanisms such as inhibiting hepatic cholesterol synthesis and promoting the excretion of cholesterol in the form of bile acids. Furthermore, the complex structure of MPs enables them to interact with various enzymes involved in lipid metabolism, thereby enhancing their efficacy in lipid-lowering. In contrast, while plant and microbial polysaccharides may also exert lipid-lowering effects, their mechanisms are generally less comprehensive, often relying on the physical properties of their fiber content to trap bile acids or promote digestion [19]. The structural and biological features of MPs isolated from different mushroom species are summarized in Table 1.

Although MPs exhibit a wide range of biological activities, they are often physically and/or chemically entangled with other biomolecules, such as proteins, polynucleotides, lipids, lignin, and certain inorganic minerals. Consequently, the study of MPs typically requires a series of processes, including defatting, extraction, concentration, precipitation, dialysis, and freeze-drying, to obtain MPs with higher purity. After obtaining pure MPs, it is essential to characterize their structural properties to better understand their biological functions and the basis for potential applications. Typically, the structural features involve molecular weight, monosaccharide composition, linkage type, configuration, and branching patterns. Molecular weight plays a crucial role in determining the polysaccharide’s functional properties, such as solubility and viscosity. Techniques like gel permeation chromatography (GPC) or multi-angle light scattering (MALS) are commonly used to determine molecular size and distribution. The monosaccharide composition, which reflects the types and proportions of sugar units present, can be analyzed using methods such as high-performance liquid chromatography (HPLC) or gas chromatography-mass spectrometry (GC-MS). The type of glycosidic linkage (e.g., α- or β-linkages) is typically elucidated by Fourier-transform infrared (FT-IR) and nuclear magnetic resonance (NMR) spectroscopy, the latter of which provides more detailed and accurate insights into the molecular connectivity and anomeric configuration. Furthermore, the branching structure, which influences the polysaccharide's conformation and solubility, can be studied using techniques like 1D and 2D NMR, along with chemical modification (i.e., acid hydrolysis and oxidation) and enzymatic hydrolysis, which are employed to release oligosaccharide fragments for further analysis [20]. Typical process in investigating the MPs from extraction to function was shown in Fig. 1. Collectively, these methods enable a comprehensive understanding of the structure-function relationships of polysaccharides, which is crucial for their applications in pharmaceuticals, food, and biomaterials.

3. MPs regulate lipid metabolism

Accumulating evidence has revealed that MPs alleviate diet-induced obesity via multiple mechanisms. Lipid metabolism, encompassing key biological processes such as lipid absorption, synthesis, decomposition,

and transportation, plays a pivotal role in maintaining energy balance, supporting cellular functions, and ensuring systemic metabolic well-being. Dysregulation of this metabolic pathway, characterized by excessive lipid accumulation and impaired catabolic activity, is a hallmark of obesity and its associated disorders. Consequently, targeting lipid metabolism has emerged as a promising therapeutic strategy for obesity prevention and treatment. Nowadays, growing evidence demonstrates that MPs modulate obesity by targeting key pathways in lipid metabolism (Fig. 2).

3.1. Inhibition of exogenous lipid absorption

Dietary fat (triacylglycerol) is hydrolyzed into triglycerides (TG) and free fatty acids (FFA) in the small intestine by the pancreatic lipase (PL), an essential enzyme secreted by the pancreas. PL breaks down 50% to 70% of TG into fatty acids and glycerol within the small intestine. Nevertheless, excessive hydrolysis by PL can contribute to obesity. Therefore, inhibition of PL activity to reduce the digestion and absorption of dietary fat represents an effective strategy for preventing and treating obesity. Notably, MPs have been shown to improve obesity induced by diet via decreasing PL activity. For instance, polysaccharides extracted from *Agaricus bisporus* have demonstrated protective effects by inhibiting lipid absorption in the mice digestive tract, primarily by decreasing the PL activity [21]. Similarly, polysaccharides from *Lentinula edodes* have been found to inhibit PL activity effectively through mechanisms such as hydrophobic forces, electrostatic forces, encapsulation and adsorption interactions, displaying their potential as additives for regulating lipid digestion [22]. Furthermore, the anti-obesity effects of MPs are influenced by their monosaccharide composition and structure. MPs containing functional groups, such as calcium ions, free carboxyl groups and sulfate groups, exhibit stronger lipase inhibitory activity, likely due to the electrostatic interactions between these anionic groups and PL. Additionally, MPs with higher rhamnogalacturonan-I content and larger branch sizes show more efficient PL inhibition. Structural features of MPs—such as the anionic groups (e.g., sulfate, carboxyl) and branched rhamnogalacturonan-I domains—enhance their PL inhibitory activity by promoting enzyme-polysaccharide binding [23] . Additionally, high-viscosity MPs impede lipid diffusion, further suppressing PL-mediated hydrolysis [24]. Notably, non-fungal sulfated polysaccharides (e.g., fucoidan from brown algae) exhibit potent PL inhibition through sulfate-mediated electrostatic interactions [25]. Since the sulfated MPs (e.g., *Tremella fuciformis*) exhibit similar anionic properties but remain understudied in obesity models, it was speculated that they may display comparable or superior efficacy [26]. Similarly, hyperbranched β-glucans from *Sparassis crispa*, structurally analogous to PL-inhibiting arabinoxylans in cereals, warrant exploration for PL inhibition effects on obesity prevention [27].

Normally, dietary cholesterol esters are difficult to be absorbed directly in the intestine. While cholesterol esterase (CE) hydrolyzes cholesterol esters into cholesterol and FFA, facilitating their absorption into the bloodstream, causing the development of hypercholesterolemia. Therefore, suppressing CE activity is regarded as a key strategy to reduce dietary cholesterol absorption and prevent obesity. In this regard, MPs have been reported to reduce cholesterol absorption by inhibiting CE. Specifically, studies indicate that polysaccharides rich in β-glucans, α-glucans, and chito-oligosaccharides exhibit significant CE inhibitory

activity and demonstrate effective cholesterol-lowering effects. Notably, β-glucan degradation products (i.e., those produced after digestion) are more bioactive in reducing cholesterol than their larger precursors [28]. However, the precise structural requirements underlying the observed cholesterol-lowering effects of fungal β-glucans remain unclear and warrant further investigation. These findings demonstrate that although MPs demonstrate excellent anti-obesity potential through PL and CE inhibition, their structural diversity provides unexplored potential for structural and functional optimization. By integrating insights from plant and algal polysaccharides, future research could focus on MPs with precisely modulated glycosidic linkages and functional groups to optimize their anti-obesity efficacy.

3.2. Regulation of lipid synthesis

Lipid synthesis in the body involves *de novo* lipogenesis, fatty acid synthesis and TG synthesis is tightly regulated by a series transcription factors and enzymes. Adipogenesis, the transformation of preadipocytes into mature adipocytes, is regulated by virous factors, including peroxisome proliferator-activated receptor-γ (PPAR-γ), adipocyte fatty acid binding protein 2 (aP2), and CCAAT/enhancer-binding protein α (C/EBPα). Among these, PPAR-γ is the pivotal adipogenic transcription factor. Studies have demonstrated that activation of PPAR-γ leads to increased body weight in mice and enhanced lipogenesis in 3T3-L1 cells [29]. aP2 plays a crucial role in the binding, storage and transport of long-chain fatty acids. Crucially, MPs concurrently target key molecules during this process to display the anti-obesity effects. It has been reported that *Pleurotus ferulae* polysaccharides can inhibit preadipocyte differentiation in 3T3-L1 cells by reducing the mRNA expression of PPAR-γ, aP2 and C/EBPα [30]. Similarly, *Pleurotus ostreatus* polysaccharides have been shown to decrease the protein expression of PPAR-γ and C/EBPα, thereby suppressing adipocyte hypertrophy and exerting lipid-lowering effects [31].

Fatty acid and TG synthesis are regulated by multiple factors. Acetyl-CoA carboxylase (ACC) catalyzes the first step in fatty acid biosynthesis. It includes two isoenzymes: ACC1 (265 kDa), predominantly expressed in the cytoplasm, and ACC2 (275 kDa), located in the mitochondria. ACC1, encoded by the ACACA gene, carboxylates the conversion of acetyl-CoA to malonyl-CoA, which is subsequently used for fatty acid mediated by fatty acid synthase (FAS) [32]. Sterol regulatory element-binding proteins (SREBPs) are membrane-bound transcription factors with three isoforms—SREBP-1a, SREBP-1c and SREBP-2-each involved in different aspects of lipid metabolism. Among them, SREBP-1c plays a crucial role in TG synthesis by promoting both fatty acid synthesis and their incorporation into TG. Overexpression of SREBP-1c leads to TG accumulation, while reduced expression of SREBP-1c results in decreased TG synthesis. This downregulation also reduces fatty acid production by suppressing the expression of ACC and FAS. Crucially, AMP-activated protein kinase (AMPK) functions as a pivotal upstream regulator integrating signals to inhibit lipogenesis. Activated (phosphorylated) AMPK exerts the regulation effects by: 1) Inhibition of mTORC1 signaling: AMPK phosphorylation attenuates the mammalian target of rapamycin complex 1 (mTORC1) pathway, thereby indirectly repressing mTORC1-dependent upregulation of PPAR-γ and SREBP1c; 2) Direct phosphorylation of lipogenic enzymes: AMPK directly phosphorylates and inactivates ACC (particularly

ACC1) and SREBP1c. This dual action blocks the rate-limiting step catalyzed by ACC (acetyl-CoA → malonyl-CoA) and disrupts SREBP1c-mediated transcriptional activation of ACC and FAS, collectively inhibiting *de novo* lipogenesis and TG synthesis [32]. Significantly, MPs demonstrate a multi-target approach to achieve multi-targeted anti-lipogenic effect by regulating AMPK-centric regulatory network. For instance, *Grifola frondosa* polysaccharide not only downregulates the expression of SREBP1c but also reduces the levels of its downstream targets ACC and FAS in HFD rats, resulting in a concerted attenuation of the adipogenesis [33]. *Pleurotus eryngii* polysaccharides upregulate AMPK activity and expression, leading to ACC inhibition and consequent reduction in serum TG levels [34]. Taken together, these findings suggest that MPs exhibit multi-targeted anti-lipogenic effects by simultaneously modulating transcriptional regulators (PPAR-γ, SREBP1c), metabolic enzymes (ACC, FAS), and energy sensors (AMPK), demonstrating an excellent ability on obesity improvement.

3.3. Regulation of lipid decomposition

Lipid decomposition includes the hydrolysis of cytoplasmic lipid droplets (LDs) and the oxidation of fatty acids. LDs are specialized organelles mainly composed of TG and cholesterol esters (CEs), which dynamically regulate lipid metabolism. The catabolism of LDs begins with the hydrolysis of TG into diacylglycerol and fatty acids by adipose triglyceride hydrolase (ATGL). Diacylglycerols are further hydrolyzed into monoacylglycerol (MAG) and FAs by hormone-sensitive lipase (HSL), and the final hydrolysis to glycerol and FAs is mediated by monoacylglycerol lipase (MGL) [35]. During this process, ATGL, as the initiatory enzyme of lipolysis, plays a crucial role in transporting hydrolyzed FAs for mitochondrial β-oxidation and intracellular signaling. . ATGL's activation of Sirtuin 1 (SIRT1) initiates peroxisome-activated receptor γ coactivator 1-α (PGC-1α)/PPARα-related autophagy in hepatocytes, further facilitating LD mobilization and fat utilization. In addition to ATGL, HSL and MGL, which are crucial enzymes in triglyceride hydrolysis, can be co-regulated by PPARγ coactivator 1α (PGC1α). The synergistic regulation of these enzymes highlights a multi-target effect, where MPs (e.g., polysaccharides from *Cordyceps militaris*, *Morchella esculenta*, and *Ganoderma lucidum*) upregulate the expression of key lipolytic enzymes such as LPL, ATGL, HSL, and p-HSL. This regulation not only promotes the breakdown of TG but also enhances the overall lipolytic process, contributing to their anti-obesity effects [36; 37; 38].

Fatty acid oxidation involves both mitochondrial and peroxisomal fatty acid oxidation. Mitochondria fatty acid β-oxidation includes dehydrogenation, hydration, dehydrogenation, and acylation process. During this process, CPT1 is the crucial rate-limiting enzyme that catalyzes the long-chain fatty acyl-CoA to acylcarnitine, which is then transported into the mitochondrial matrix by the carnitine-acylcarnitine translocase (CACT). Inside the matrix, acylcarnitine is converted back to fatty acyl-CoA by CPT1b. CPT1 can be upregulated by the transcription factors PPARα and PGC1α. Additionally, CPT1 activity can be inhibited by ACC2 on the outer mitochondrial membrane through malonyl-CoA, thereby reducing fatty acid β-oxidation [32]. Moreover, CPT1 can be regulated by activated AMPK, further promoting mitochondrial fatty acid oxidation [8]. The synergistic action of MPs on lipid metabolism is particularly evident in their

regulation of both lipolysis and fatty acid oxidation. For instance, polysaccharides from *Grifola frondosa* and *Coriolus versicolor* have been shown to enhance the mRNA and/or protein expression levels of PPAR-α and CPT-1, thereby facilitating fatty acid oxidation and exerting anti-obesity effects [39; 40]. These findings highlight the potential of MPs to modulate lipid metabolism by targeting key enzymes and regulatory pathway. Traditionally, research on MPs has predominantly focused on their immunomodulatory and antitumor properties, with lipid metabolism mechanisms—particularly mitochondrial pathways—receiving limited attention until recent years. As interest in their metabolic regulatory potential grows, future studies are expected to provide deeper insights into the multi-target, synergistic effects of MPs in regulating lipid decomposition, fatty acid oxidation, and mitochondrial function. Understanding the interrelated mechanisms involved will be crucial for exploring MPs in the development of novel anti-obesity therapies.

3.4. Regulation of lipid transportation

Lipids are hydrophobic and need to bind to lipoproteins — low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) to form water-soluble lipoprotein complexes for transportation. Apolipoprotein A (ApoA), as the major protein component of HDL-C, plays a crucial role in reverse cholesterol transport mechanism, which removes excess free cholesterol from arterial cells and fibroblasts. Conversely, apolipoprotein B (ApoB) is involved in the occurrence of atherosclerosis, particularly by mediating the accumulation of cholesterol within arterial walls, a key inducer of cardiovascular diseases. Studies have shown that certain MPs have gained attention for their potential multi-target effects in regulating lipid transport by altering the expression of these key apolipoproteins. For example, *Grifola frondosa* (maitake) polysaccharides have demonstrated significant effects in reducing blood levels of total cholesterol and LDL-C, thereby effectively alleviating diet-induced hyperlipidemia [39]. Notably, in a study involving *Morchella angusticepes* Peck polysaccharides, serum ApoB levels in treated rats were significantly lower than those in the model group, suggesting that these polysaccharides may exert cholesterol-lowering effects by reducing ApoB levels [41]. Furthermore, *Cordyceps militaris* polysaccharides have been shown to markedly reduce serum ApoB levels while significantly increasing ApoA levels, indicating that supplementation with matsutake polysaccharides can improve lipid profiles and thus reduce the risks associated with atherosclerosis and coronary heart disease [42]. These findings suggest that MPs enhance ApoA expression while suppressing ApoB expression, thereby improving overall lipid metabolism and contributing to anti-atherosclerotic effects. In summary, the discussion above suggests that the MPs can improve diet-induced lipid disorders by inhibiting exogenous lipid uptake, reducing lipid synthesis and promoting lipid transportation and decomposition.

4. MPs improve cholesterol metabolism

Diet-induced obesity is also manifested by disorders of cholesterol dynamic balance. Cholesterol metabolism involves uptake, biosynthesis, esterification, and excretion. Disorders in cholesterol metabolism manifest as abnormal levels of total cholesterol, which contribute to adipocyte hypertrophy and lead to obesity. Additionally, cholesterol accumulation triggers TLR-mediated signaling pathways, which facilitate

the formation of NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasomes and leading to deleterious inflammation. This inflammatory reaction negatively regulates white adipose tissue (WAT) browning and triggers insulin resistance and atherosclerosis. Therefore, disorders of cholesterol metabolism can also lead to obesity and related disease (i.e., hyperlipidemia, type 2 diabetes, insulin resistance and cardiovascular diseases) [8]. In contrast to the relatively limited research on plant polysaccharides in directly modulating cholesterol metabolism, MPs exhibit distinct advantages in regulating cholesterol metabolism. In addition to their direct interactions with receptor proteins, MPs predominantly exert their effects through the modulation of GM and their metabolites, thereby indirectly influencing cholesterol metabolism. The mechanisms by which MPs regulate obesity through cholesterol metabolism are illustrated in Fig. 3.

4.1. MPs regulate cholesterol uptake

Cholesterol in the body mainly consists of bile cholesterol, which is derived from bile in the liver, and cholesterol obtained from the diet. Bile cholesterol can enter cells directly and be absorbed by the small intestine, whereas dietary cholesterol is primarily esterified and can only be absorbed after being hydrolyzed by cholesterol esterase (CE) into free cholesterol. Free cholesterol is emulsified by the action of bile acid (BAs), fatty acids, and phospholipids, among factors, to form mixed micelles, which are absorbed by the Niemann-Pick C1-Like 1 (NPC1L1) receptor in the endoplasmic reticulum. It is then esterified into cholesteryl esters and incorporated into chylomicrons, which ultimately enter the bloodstream via the lymphatic system. Since CE and NPC1L1 are crucial factors in cholesterol absorption, inhibiting their expression is an effective way to reduce intestinal cholesterol absorption and reduce cholesterol levels. Several functional MPs have been reported to reduce cholesterol absorption by inhibiting CE and NPC1L1 expression. In this regard, *Cordyceps militaris* polysaccharides exhibit superior efficacy compared to other MPs in alleviating hypercholesterolemia, primarily through high-affinity direct binding and subsequent downregulation of NPC1L1 expression [42; 43]. Critically, MPs exert synergistic regulation of cholesterol uptake by modulating the gut microbiota and its metabolites. Acting as prebiotics, MPs promote beneficial bacteria that influence cholesterol metabolism through multiple mechanisms: (1) BA pool modulation: Bacterial transformation of primary to secondary BAs alters BA hydrophobicity, reducing micelle cholesterol solubility and activating host receptors (e.g., FXR receptor) to feedback-regulate hepatic BA synthesis and cholesterol homeostasis; (2) SCFA-mediated signaling: MPs fermentation generates SCFAs, which bind intestinal GPCRs (e.g., GPR41/43/109A) and signal to downregulate NPC1L1, influence cholesterol esterification, regulate bile acid synthesis/conjugation, and upregulate efflux transporters (e.g., ABCG5/G8), thereby promoting cholesterol excretion into the lumen; (3) Direct cholesterol catabolism: Some bacteria like *Bacteroides* directly compete for cholesterol, utilizing it for membrane synthesis or converting it to non-absorbable coprostanol via microbial reductases [44; 45]. These findings reveal that MPs regulate cholesterol absorption through both direct molecular targeting and indirect microbial and metabolite signaling, highlighting their potential as natural treatments for hypercholesterolemia and obesity-related metabolic disorders.

4.2. MPs regulate cholesterol biosynthesis

Cholesterol biosynthesis in the body mainly occurs in the liver through *de novo* synthesis, which involves a series of enzymatic reactions initiated from acetyl coenzyme A (acetyl-CoA). HMG-CoA reductase (HMGCR), the rate-limiting enzyme during this process, is up-regulated by the sterol-regulatory element binding protein-2 (SREBP-2) [46]. SREBP-2, a membrane-bound transcription factor, activates cholesterol biosynthesis by binding to sterol regulatory elements in the promoter regions of genes encoding enzymes involved in sterol biosynthesis. Consequently, the overexpression of HMGCR and SREBP-2 leads to cholesterol accumulation. In summary, cholesterol biosynthesis is tightly regulated by the interplay between HMGCR and SREBP-2, and dysregulation of this pathway contributes to metabolic disorders such as hypercholesterolemia and hepatic steatosis. Targeting these key regulators offers a promising therapeutic strategy for managing cholesterol-related diseases.

MPs exert their suppressive effects on cholesterol biosynthesis primarily by targeting the AMPK signaling pathway, a central metabolic regulator. AMPK activation negatively regulates both SREBP-2 and HMGCR through phosphorylation: it inhibits SREBP-2 processing/activation and directly phosphorylates/inactivates HMGCR [8]. This makes AMPK as a critical upstream node for the synergistic suppression of cholesterol synthesis. AMPK activation initiates a synergistic inhibitory cascade: concurrently suppressing the master transcriptional regulator SREBP-2 and the key enzymatic gatekeeper HMGCR, thereby inhibiting the cholesterol biosynthesis. Recent studies have revealed that *Ganoderma lucidum* polysaccharide (GLPP) can alleviate HFD induced hepatic steatosis via downregulating the mRNA expression of both HMGCR and SREBP-2 [46]. The molecular mechanism underlying this effect appears to involve the activation of AMPK, which negatively regulates both SREBP-2 and HMGCR activities [8]. Although the role of MPs in cholesterol biosynthesis regulation remains less explored compared to other metabolic pathways, accumulating evidence highlights the therapeutic potential of specific polysaccharides. Among the available reports, polysaccharides from *Ganoderma lucidum* and *Grifola frondosa* are the most frequently studied. These polysaccharides have been shown to downregulate the expression of HMGCR and SREBP-2, activate the AMPKα signaling pathway, and inhibit SREBP-2 activity, thereby suppressing cholesterol biosynthesis and improving lipid metabolism in HFD-fed mice [37; 47]. Taken together, these findings underscore the potential of MPs as natural agents for modulating cholesterol biosynthesis. Their ability to target key regulatory nodes such as HMGCR, SREBP-2, and AMPK highlights their multifaceted mechanisms of action, making MPs promising candidates for the development of functional foods or nutraceuticals aimed at managing cholesterol-related metabolic disorders.

4.3. MPs regulate cholesterol decomposition and excretion

Cholesterol homeostasis also involves synergistic regulation of liver decomposition and intestinal excretion, a process where MPs demonstrate multi-target efficacy. Cholesterol decomposition primarily occurs in the liver, where most of the cholesterol is converted into BAs, which can be divided into primary and secondary BAs. Since primary BAs are synthesized from cholesterol as the substrate, increasing primary BAs

synthesis is a key strategy to promote cholesterol decomposition. Primary BAs are synthesized via two pathways: the classical pathway (neutral pathway) and the alternative pathway (acidic pathway). The classic pathway, initiated by cholesterol 7α-hydroxylase (CYP7A1), which serves as the rate-limiting enzyme. While the alternative pathway, which occurs both in the liver and extrahepatic tissue (i.e., brain, macrophages, and adrenal glands), is mainly activated by sterol 27-hydroxylase (CYP27A1) and oxysterol 7α-hydroxylase (CYP7B1), with steroidogenic acute regulatory protein (STARD1) acting as the rate-limiting enzyme [48]. Recent investigations have revealed that *Grifola frondose*-derived polysaccharides significantly upregulate the gene expression CYP7A1 gene expression, thereby enhancing BA biosynthesis and ameliorating HFD-induced hyperlipidemia in mice [49]. Similarly, polysaccharides isolated from *Ganoderma lucidum* have been shown to upregulate the mRNA expression of both CYP7A1 and CYP7B1, facilitating the metabolic conversion of cholesterol to BAs [46]. In this regard, MPs exhibit unique regulatory effects on bile acid synthesis compared to other types of polysaccharides (i.e., plants and marine sources polysaccharides). MPs uniquely target the enzymatic pathways of bile acid synthesis. This specificity may be attributed to the structural complexity and bioactive diversity of MPs, which enable them to interact more effectively with key enzymes like CYP7A1 and CYP7B1. These findings suggest that MPs exert their cholesterol-lowering effects through coordinated regulation of bile acid biosynthesis pathways.

Meanwhile, MPs promote cholesterol excretion via structure-dependent bile acid (BA) sequestration in the intestine integrated with hepatic homeostatic signaling. In this regard, fungal β-glucans with β-(1→3)/β-(1→6) linkages exhibit superior BA-binding affinity through electrostatic capture of anionic BA surfaces and viscosity-mediated sequestration [17]. Additionally, specific monosaccharides, such as the mannose, glucose, galactose-rich compositions found in *Grifola frondosa* polysaccharides at a ratio of 25.49: 27.59: 15.02 enhance luminal excretion [39]. These mechanisms operate synergistically to create a self-amplifying homeostatic circuit. Enhanced BA synthesis depletes liver cholesterol pools, while the sequestration of BAs disrupts the enterohepatic circulation. As the BA pools become depleted, the upregulation of CYP7A1 is further promoted through FXR/LXR signaling. Simultaneously, the viscous MPs effectively trap cholesterol molecules, thereby promoting the loop of BA-mediated cholesterol excretion. These findings suggest that MPs, particularly those with specific structural features, may hold significant potential in modulating cholesterol metabolism. By coordinating these multiple pathways, MPs contribute to the dynamic regulation of cholesterol levels and exert a multifaceted role in lipid metabolism.

5. MPs regulate gut microbiota and their metabolites

Growing evidence indicates that human gut microbiota (GM) plays a crucial role in mediating the MPs regulating the lipid metabolism process. Although most MPs exhibit resistance to enzymatic digestion in the gastrointestinal system, they can be utilized by the GM via encoding various carbohydrateactive enzymes (CAZymes) (i.e., glycoside hydrolases, lyases, and esterases) in the large intestine [11]. The GM promotes the breakdown of polysaccharides, and increases the absorption of monosaccharides and SCFAs, further inducing

lipogenesis. Therefore, MPs can regulate lipid metabolism by modulating GM, with mechanisms involving the modulation of intestinal flora and regulation of gut microbial metabolites (Fig. 4).

5.1. Regulation of GM composition

The human gut microbiota, made up of around 100 trillion microorganisms, is essential for maintaining human health. Current studies predominantly focus on microbial composition at both phylum and genus levels. At the phylum level, four dominant phyla — Actinobacteria, Bacteroidetes, Proteobacteria, and Firmicutes — constitute approximately 97% of the total GM population. Notably, the Firmicutes/Bacteroidetes (F/B) ratio has emerged as a significant biomarker for obesity assessment, given the characteristic elevation of Firmicutes and reduction of Bacteroidetes in obese individuals. At the genus level, *Bacteroides* and *Bifidobacterium* represent the predominant genera, while *Staphylococcus* and *Clostridium* have been positively correlated with obesity development. Li et al. (2022) discovered that HFD significantly increases the abundance of obesity-associated genera, including *Bilophila*, *Bacteroides*, *Escherichia-Shigella*, and *Intestinimonas* [50]. Specially, *Bilophila* exhibits synergistic interactions with HFD, inducing systemic inflammation, disrupt intestinal barrier integrity, and disrupting bile acid metabolism, thereby exacerbating glucose metabolism disorders and hepatic steatosis. Furthermore, *Escherichia coli* and *Enterobacter* have been consistently associated with both obesity pathogenesis and gastrointestinal infections.

MPs demonstrate significant anti-obesity potential through modulation of gut microbiota composition and function. On one hand, MPs have been shown to modulate the F/B ratio, with Bacteroidetes utilizing polysaccharide utilization loci to degrade complex polysaccharides (i.e., glucan, inulin, xylan, mannan and pectin), while Firmicutes employ glycoside hydrolases (GHs), oligosaccharide transporters and regulatory elements for polysaccharide metabolism. This dual mechanism promotes beneficial bacterial associated with obesity while reducing harmful bacteria. Experimental evidence confirms that several MPs extracted from *Poria cocos*, *Grifola frondosa* and *Pleurotus eryngii* effectively attenuate HFD-induced fat accumulation in rats by suppressing F/B ratio elevation [33; 51]. On the other hand, MPs can improve obesity by selectively enriching beneficial bacteria (i.e., *Lactobacillus*, *Bifidobacterium*, and *Akkermansia*) while inhibiting potentially harmful bacteria (i.e., *Escherichia-Shigella*, *Pseudomonas*, and *Desulfovibrio*). HFD-induced dysbiosis typically manifests as increased pathogenic bacteria and decreased protective microbiota, leading to enhanced intestinal permeability and subsequent metabolic endotoxemia through elevated circulating endotoxin levels. Notably, *Auricularia auricula* polysaccharides have demonstrated efficacy in mitigating HFD-induced obesity by enriching the abundance of *Odoribacter, Lactobacillus, Dorea and Bifidobacterium*, while significantly reducing the abundance of *Bacteroidetes* and *Proteobacteria* [52]. Similarly, CM3-SII polysaccharide administration in male LDLR(+/-) hamsters led to significant increases in *Bifidobacterium* and *Lactobacillus* populations [43]. Collectively, MPs serve as excellent modulators of GM with unique advantages in obesity improvement. Their ability to multidimensionally target the F/B ratio, enrich beneficial bacteria, and suppress harmful genera, combined with their distinctive structural features and multi-faceted metabolic effects, establishes them as superior candidates for improving obesity.

5.2. Modulating the GM metabolites

Polysaccharides are fermented by GM to produce a series of metabolites, such as SCFAs, secondary BAs, lipopolysaccharides (LPS), oxidized trimethylamine and microbial amino acids [11]. These metabolites regulate lipid metabolism through multiple mechanisms to ameliorate obesity and related metabolic dysregulation.

5.2.1. SCFAs

SCFAs are the primary metabolites produced during the breakdown of polysaccharide. They are readily absorbed and exert diverse physiological functions. The SCFAs-producing bacteria within the human GM include *Lactobacillus*, *Sterolactobacillus*, *Lachnospiraceae*, *Alloprevotella*, *Parabacteroides*, *Firmicutes*, *Ruminococcus*, *Bacteroidetes*, and *Eubacterium*, with *Lactobacillus* and *Sterolactobacillus* representing the dominant genera [53]. These microorganisms catalyze the conversion of polysaccharides into SCFAs, primarily acetate, propionate, and butyrate. Notably, acetate and propionate are predominantly produced by Bacteroidetes, whereas butyrate production is primarily generated by Firmicutes. The type of polysaccharide influences SCFAs production profiles. For instance, β-glucan, inulin, and oligofructose are utilized by GMs to produce more butyrate, mainly by Firmicutes, whereas rhamnose-enriched polysaccharides increase propionate levels, primarily produced by Bacteroidetes. Dextran, pectin, and arabinogalactan elevate acetic acid levels in the gut [54]. The feeding of MPs from *Tremella fuciformis* has been shown to significantly inhibit weight gain in obese mice, as they are fermented by GM to produce propionic acid, which elevate postprandial PYY and GLP-1 [55]. Similarly, *Cordyceps militaris* polysaccharides enhance valeric acid concentration in HFD rats, exhibiting stronger hypoglycemic effects [56]. Furthermore, some MPs such as those from *Tremella fuciformis* and *Trametes versicolor* increase the levels of acetic acid, propionic acid, butyric acid and isovaleric acid in the obese rats, upregulating GPR41 and GPR43 expression in liver tissue, thereby improving obesity [55; 57]. High Mw of *Cordyceps militaris* polysaccharides (CMP40) have been found to alleviate obesity in HFD mice by modulating succinate-producing bacteria, further enhancing BAT thermogenesis and inducing white adipose tissue (WAT) browning [58]. Recent studies also show that MPs can activate the GPR109A expression in adipocytes by increasing butyrate levels, inhibiting adenylate cyclase activity, reducing cAMP levels, and suppressing PKA and HSL/TGL activity, ultimately decreasing free fatty acid concentrations [59; 60].

SCFAs regulate lipid metabolism through multiple mechanisms, primarily functioning as signaling molecules that act on G-protein coupled receptors (GPCRs). For example, valeric acid is the most effective ligand for GPR41, while propionic acid primarily activates GPR43. GPCR activation stimulates the secretion of glucagon-like peptide-1 (GLP-1) and peptide PYY, enhancing insulin secretion, inhibiting glucagon release and regulating glucose uptake, furtherly contributing to the improvement of obesity. Specifically, acetic acid and butyric acid exert appetite-suppressive effects independent of GPCR signaling by promoting PYY production. SCFAs can also improve obesity by promoting thermogenesis in adipose tissue. For example, succinate has been identified as a thermogenic agent that regulates brown adipose tissue (BAT) physiology,

while butyrate activates lysine-specific demethylase 1 (LSD1) in adipocytes, enhancing thermogenic capacity [61]. Recent studies have highlighted how SCFAs act synergistically with other metabolic pathways to further regulate energy balance. For instance, butyrate has been shown to interact with mitochondrial signaling pathways by promoting mitochondrial biogenesis via the activation of PGC-1α, a key regulator of mitochondrial function, thereby boosting adipocyte thermogenesis and enhancing overall energy expenditure. In obese rats treated with *Lyophyllum decastes* polysaccharide, PGC-1α expression was upregulated, and mitochondrial density in adipose tissue significantly increased, which might be attributed to enhanced butyrate production [44]. Several MPs have been reported to activate the GPR109A expression in adipocytes by increasing butyrate levels, inhibiting adenylate cyclase activity, reducing cAMP levels, and suppressing PKA and HSL/TGL activity, ultimately decreasing free fatty acid concentrations [59; 60]. These findings demonstrated that MPs exert a multi-target regulatory effect on obesity through the modulation of SCFAs.

5.2.2. BAs

Bile acids are another metabolite of polysaccharide fermentation, regulate lipid metabolism by interacting with the takeda G protein-coupled receptor 5 (TGR5) and farnesoid derivative X receptor (FXR), both of which regulate cholesterol and triglyceride metabolism upon activation [17]. Additionally, BAs can influence appetite by modulating glucagon-like peptide-1 (GLP-1) secretion and promoting adipose tissue thermogenesis via activation of the TGR5 receptor. Furthermore, BAs can inhibit obesity by upregulating the expression of horizontal ileal tight junction proteins and inhibiting the transport of lipopolysaccharides into the bloodstream, which in turn stimulates thermogenesis in beige fat. Numerous studies have demonstrated that polysaccharides can increase BAs levels and alter the GM to enhance lipid metabolism. Notably, MPs have shown excellent regulation of BAs metabolism, ameliorating HFD-induced obesity. For instance, *Lyophyllum decdeces*-derevied polysaccharides have been shown to increase BAs content and ameliorate HFD-induced obesity by upregulating the expression of TGR5, UCP1, and PGC1α in brown and white adipose tissue [44]. *Flammulina velutipes* polysaccharides also positively affect lipid metabolism by increasing PPARα and PPARγ expressions via bile acids metabolism in both obese mice and 3T3-L1 adipocytes [62]. Taken together, MPs intervention can alleviate obesity and lipid metabolism disorders through BA-mediated mechanisms.

5.2.3. Others

Accumulating evidence highlights the significant role of microbial metabolites derived from polysaccharide fermentation—including amino acids, trimethylamine (TMA), and lipopolysaccharide (LPS)—in the pathogenesis and regulation of obesity [63]. Among these metabolites, branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs) have been shown to mitigate hepatic steatosis and inflammation through multiple mechanisms, such as appetite regulation, inhibition of lipogenesis, promotion of adipocyte lipolysis, and induction of WAT browning. Trimethylamine (TMA), a metabolite produced by GM through the catabolism of fatty acylcholine, choline, and carnitine, is subsequently oxidized in the liver by flavin-dependent monooxygenase (FMO) to form trimethylamine N-oxide (TMAO). TMAO plays a pivotal

role in lipid metabolism by activating the PEPK signaling pathway, which causes hyperglycemia, and by modulating hepatic lipid synthesis through bile acid-mediated farnesoid X receptor (FXR) signaling. These mechanisms emphasize the complex interplay between microbial metabolites and host metabolic pathways in obesity development. Several studies have confirmed that MPs improve obesity by modulating the metabolic products of GM, which in turn regulate lipid metabolism. For instance, Wang et al. (2024) evaluated the anti-obesity effects of *Ganoderma atrum* polysaccharides, revealing their ability to ameliorate obesity by mediating GM-derived LPS and TMA production [64]. Both LPS and TMA can be specifically recognized by the TLR4 receptor, triggering the NF-κB signaling pathway and initiating a cytokine cascade that induces systemic inflammation, subsequently leading to obesity [65]. Furthermore, *Auricularia auricula* polysaccharides have been shown to prevent obesity and hyperlipidemia in HFD-fed mice by reducing LPS levels through the suppression of LPS-producing bacteria, such as Desulfovibrionaceae and *Bilophila*. These findings highlight the diverse mechanisms by which MPs exert anti-obesity effects, including the regulation of microbial metabolites and host inflammatory responses. Notably, the metabolites of polysaccharide fermentation are highly diverse, enabling MPs to combat obesity through multiple synergistic mechanisms. For example, polysaccharides from *Ganoderma lucidum* have been reported to exert anti-obesity effects by simultaneously modulating the production of SCFAs and BAs [47]. This multifaceted regulation underscores the potential of MPs in maintaining intestinal microbiota homeostasis and improving glycolipid metabolism, ultimately alleviating obesity and associated chronic metabolic disorders.

6. MPs regulate mitochondria and oxidative stress

HFD-induced obesity is characterized by excessive lipid accumulation in adipose tissue, leading to organelle dysfunction and the release of reactive oxygen species (ROS). These pathological changes trigger a series of inflammation responses and apoptotic signaling, ultimately exacerbating metabolic dysregulation [66]. Typically, mitochondria as the main sites for adenosine triphosphate (ATP) and ROS generation, play a central role in maintaining energy homeostasis. Studies have shown that mitochondrial homeostasis—governed by dynamic processes including mitochondrial fission, fusion, and mitophagy—critically regulates adipocyte differentiation, lipid metabolism, thermogenesis, glucose utilization, and insulin sensitivity [66]. Dysregulation of mitochondrial dynamics induces mitochondrial dysfunction, which is highly correlated with metabolic diseases such as obesity. On one hand, mitochondrial dysfunction disrupts energy metabolism, leading to lipid accumulation. Since mitochondria in adipose tissue cells are responsible for multiple anabolic and catabolic metabolisms, any damage to these mitochondria can result in reduced ATP production. This reduction leads to the accumulation of fat, ultimately contributing to obesity. Additionally, mitochondrial dysfunction disturbs immune homeostasis, promoting an inflammatory state in the body and further causing to obesity. Therefore, mitochondria have gained attention as a crucial trigger for obesity and mitochondrial health-improving pathologies. Growing evidence suggests that MPs improve obesity by targeting mitochondria through several mechanisms, including: 1) targeting UCP1 to

promote heat production; 2) regulating mitophagy; 3) alleviating mitochondrial dysfunction; and 4) inhibiting oxidative stress (OS) (Fig. 5).

6.1. Regulation of UCP1 to promote heat production

Brown adipose tissue (BAT), characterized by its high mitochondrial density, plays a crucial role in regulating energy expenditure to maintain body weight and thermoregulation. Uncoupling protein 1 (UCP1), a key mediator of thermogenesis, disrupts the mitochondrial electron transport chain, uncouples ATP synthesis, and enhances thermogenesis in response to cold exposure or other stimuli [6]. UCP1 also modulates the interaction between PR domain zinc finger protein 16 (PRDM16) — a crucial mitochondrial regulator, and several transcription factors, including PPAR-γ, PPAR-α, and peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α). This interaction upregulates thermogenic genes that characteristic of BAT. MPs have been shown to exert anti-obesity effect by activating UCP1 expression in adipose tissue, thereby promoting energy expenditure and inhibiting lipid accumulation. For example, polysaccharides extracted from *Lyophyllum decastes* have been shown to prevent fat storage by enhancing thermogenesis through upregulation of PRDM16, UCP1, and PGC-1α expression, ultimately alleviating weight gain in HFD-fed mice [44]. The regulation of thermogenesis is further influenced by AMPK and sirtuin 1 (SIRT1), both of which are critical in modulating PGC-1α activity. AMPK-mediated phosphorylation and SIRT1-mediated deacetylation of PGC-1α synergistically enhance UCP1 expression. For example, Kanagasabapathy et al. (2014) demonstrated that *Pleurotus sajor-caju* polysaccharides promote thermogenesis and energy expenditure by activating the AMPK/SIRT1/PGC-1α signaling pathway, leading to increased UCP1 expression [67]. Importantly, the modulation of these pathway is primarily attributed to gut microbiota-derived MPs' metabolisms. For instance, the SCFAs, particularly butyrate. Butyrate serves as a key metabolic signal that activates AMPK both directly (as a substrate for β-oxidation, elevating cellular AMP/ATP ratio) and indirectly (via GPR43/GPR109A signaling), while concomitantly elevating NAD^+ levels to stimulate SIRT1 deacetylase activity. Activated SIRT1 deacetylates and activates PGC-1α, which coordinately with AMPK drives mitochondrial biogenesis and UCP1-dependent thermogenesis, thus regulating the enhanced energy expenditure [44; 45]. Additionally, MPs fermentation enriches bile acid-metabolizing bacteria (e.g., *Bacteroides*, *Clostridium* cluster XIVa), leading to increased production of secondary BAs such as lithocholic acid (LCA) and deoxycholic acid (DCA). These secondary BAs act as potent agonists for the G-protein coupled bile acid receptor TGR5 (GPBAR1), predominantly expressed in brown and beige adipocytes. TGR5 activation triggers a Gsα-adenylyl cyclase cascade, elevating intracellular cAMP levels and activating Protein Kinase A (PKA). PKA then phosphorylates and activates the transcription factor CREB (cAMP Response Element-Binding protein). Activated CREB directly binds to the PGC-1α promoter, inducing its transcription. Furthermore, PKA-mediated phosphorylation enhances the activity of existing PGC-1α protein. This TGR5-PKA-CREB axis converges with the SCFA-driven AMPK/SIRT1 pathway on PGC-1α activation, synergistically amplifying mitochondrial biogenesis, oxidative capacity, and UCP1-mediated thermogenic gene expression (e.g., UCP1, Dio2, Cidea), furtherly enhancing the energy

expenditure [44; 68]. Collectively, these findings demonstrate that MPs stimulate BAT thermogenesis and induce WAT browning through two primary mechanism: 1) direct activation of UCP1 expression via AMPK phosphorylation, and 2) indirect activation of UCP1 expression through the upregulation of PRDM16 and PGC-1α, key transcription factors involved in mitochondrial biogenesis and function. These effects collectively ameliorate mitochondrial dysfunction-induced lipid metabolism disorders, highlighting the therapeutic potential of MPs in obesity management.

6.2. Regulation mitophagy

Mitophagy, a lysosome-dependent degradation pathway, is a ubiquitous cellular process essential for maintaining mitochondrial quality control in eukaryotic cells . This pathway is primarily activated under conditions of oxidative stress, nutrient deprivation, and cellular aging, which induce mitochondrial depolarization and damage. During mitophagy, dysfunctional mitochondria are selectively encapsulated by autophagosomes, which subsequently fuse with lysosomes to degrade damaged organelles, thereby preserving cellular homeostasis. Dysregulation of mitophagy impairs the clearance of damaged mitochondria, leading to their accumulation and subsequent mitochondrial dysfunction, which is closely linked to insulin resistance and metabolic disorders. Consequently, the precise regulation of mitophagy is crucial for normal cellular growth and function. Emerging evidence indicates that diet-induced obesity triggers mitochondrial disruption, characterized by disruption of mitochondrial membrane integrity, excessive mitochondrial reactive oxygen species (mtROS) production, and mitochondrial degeneration. These pathological alterations induce excessive mitophagy, significantly reducing mitochondrial content, and contributing to adipocyte hypertrophy and metabolic dysregulation. Consequently, inhibition abnormal mitophagy may represent a therapeutic strategy to prevent obesity by prolonging the retention of thermogenic adipose tissue, enhancing energy expenditure, and suppressing lipid accumulation.

Current research identifies three primary pathways regulating mitophagy: the PTEN-induced kinase 1 (PINK1)/Parkin pathway, the BNIP3/NIX (BNIP3-like protein X) pathway, and the FUNDC1 (FUN14 domain containing 1) pathway [69]. Among these, the PINK1/Parkin pathway plays a central role in mitochondrial quality control in mammals. Recent findings have indicated that several polysaccharides can inhibit PINK1/Parkin pathway to inhibit excessive mitophagy, thereby alleviating oxidative stress, hepatic inflammation, and apoptosis in liver cells, all of which are indicative of liver injury. For instance, *Dictyophora* polysaccharides have been shown to inhibit mitophagy mediated by the PINK1/Parkin pathway in L-02 cells, mitigating hepatocyte injury [70]. Interestingly, contrasting studies have revealed that diet-induced obesity and diabetic mice exhibit impaired hepatic autophagy, characterized by markedly reduced expression of autophagy-related proteins, including LC3II, Beclin1, ATG5, and ATG7 [71]. These findings imply that impairments in hepatic autophagy leads to lipid accumulation and insulin resistance, while restoration of autophagy can improve glucose metabolism and insulin sensitivity [71]. In this regard, polysaccharides derived from *Gomphidiaceae rutilus* (AGRP) have been shown to enhance hepatocytes autophagy via the AMPK signaling pathway in response to high glucose and fatty acid exposure [72]. Moreover, AGRP

upregulates LC3 II and p-AMPK expression while reducing p62 levels, facilitating autophagy and lipid degradation in the livers of obese mice [72]. Collectively, these findings indicate that various MPs can inhibit lipid accumulation by modulating mitophagy. However, current research on the role of MPs in regulating mitophagy to improve obesity remains limited. Future studies are necessary to elucidate the protective mechanisms of MPs and their therapeutic potential in obesity management.

6.3. Alleviating mitochondrial dysfunction

Extensive research has established a strong association between obesity and mitochondrial dysfunction, which refers to any disturbance in mitochondrial structure, function, and dynamics (i.e., mitochondrial biogenesis, dynamics alteration, DNA damage) [6; 73]. These disruptions compromise cellular energy metabolism and subsequently lead to various metabolic disorders. Notably, mitochondrial dysfunction in adipocytes and skeletal muscle, characterized by reduced oxidative capacity, increased lipid accumulation, and elevated ROS levels, ultimately leading to insulin resistance, a hallmark of obesity. Consequently, targeting mitochondrial dysfunction holds promise for ameliorating obesity and its associated metabolic disorders. Studies have demonstrated that HFD-induced hyperglycemia in rats is associated with reduced mitochondrial biogenesis and decreased mitochondrial DNA (mtDNA) copy number in epididymal adipose tissue, highlighting the critical role of mitochondrial biogenesis in glucose metabolism regulation [66; 74]. This process is primarily mediated by peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), a master regulator that promotes mtDNA replication and enhances mitochondrial mass to meet cellular energy demands. PGC-1α achieves this by interacting with key transcription factors, including nuclear respiratory factors (NRF1/2) and mitochondrial transcription factor A (TFAM). Additionally, PGC-1α influences estrogen-associated nuclear receptors to promote glucose uptake and ATP synthesis [8]. Several studies have indicated that MPs can regulate mitochondrial biogenesis by regulating the expression of related genes, thereby improving glucose and energy metabolism. For instance, polysaccharides derived from *Flammulina velutipes* have been reported to enhance mitochondrial biogenesis by upregulating the expression of PGC-1α, TFAM and NRF1 in the liver of HFD-fed rats [75]. Multiple studies have suggested that MPs exert a synergistic effect on mitochondrial biogenesis, glucose metabolism, and energy regulation by modulating the expression of related genes and transcription factors, exerting an synergistic anti-obesity effect. For example, polysaccharides from *Auricularia auricula-judae* and *Lyophyllum decastes* have been confirmed to enhance PGC-1α expressions, thereby improving mitochondrial function and alleviating hepatic lipid metabolism disorders. Meanwhile, these polysaccharides enhance mitochondrial ATP synthesis and glucose uptake efficiency while suppressing ROS overproduction. This multi-target effect contributes to MPs potential therapeutic action in combating obesity and related metabolic disorders, suggesting that MPs displayed a systemic manner to restore metabolic homeostasis [44; 76]. These findings collectively elucidate that MPs may ameliorate obesity by modulating mitochondrial biogenesis and mitigating mitochondrial dysfunction-induced lipid metabolism disorders. Further research is necessary to elucidate the precise

molecular mechanisms underlying the effects of MPs on obesity management through alleviating mitochondrial dysfunction.

6.4. Regulating Mitochondrial Dysfunction-Induced Stress and Inflammation

Oxidative stress (OS) and inflammation are intricately linked in the pathogenesis of obesity-related metabolic diseases. OS directly damages vascular wall cells, leading to endothelial dysfunction, impaired vasodilation, and the development of hypertension and atherosclerosis. Additionally, OS contributes to diabetes by damaging pancreatic β-cells and decreasing insulin sensitivity in peripheral tissues [77]. High-fat diets exacerbate OS by increasing fatty acid levels, which activate NADPH oxidase and elevate reactive ROS production. Concurrently, the expression and activity of antioxidant enzymes—such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPX)—are significantly reduced in the adipose tissue of obese individuals. Thus, OS, driven by lipid accumulation, serves as both an early trigger and a major contributor to obesity-related metabolic disorders, making it a promising therapeutic target. It has been reported that MPs display potential in mitigating OS by activating the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) through the PI3K/AKT and MAPK signaling pathways [59]. This activation upregulates the expression of antioxidant and detoxification enzymes. In this regard, *Sagittaria sagittifolia* polysaccharides have been reported to prevent lipid metabolic disorders associated with non-alcoholic fatty liver disease (NAFLD) through reducing the OS damage through the Nrf2/HO-1 signaling pathway [78]. *Agrocybe cylindracea* polysaccharides were confirmed to activate the Nrf2/ARE pathway, eliminate ROS accumulation, improve mitochondrial function in diet-induced obesity, and thus exhibit strong potential applications in the treatment of obesity [79].

Moreover, the endoplasmic reticulum (ER) is the primary site for lipid metabolism, as it synthesizes sterols and phospholipids, which constitute the major lipid components of biological membranes. Mitochondrial dysfunction-mediated OS disrupts protein folding homeostasis, leading to endoplasmic reticulum stress (ERS). In response to ERS, cells activate the unfolded protein reaction (UPR) to restore homeostasis. The UPR signaling involves three classical pathways: the protein kinase RNA-like ER kinase (PERK) pathway, the activating transcription factor 6 (ATF6) pathway, and the inositol-requiring enzyme (IRE1) pathway. These pathways are initiated by the ER chaperone glucose-regulated protein 78 (GRP78) [80]. Under excess RES, these transducers can activate inflammatory signaling pathways; for instance, phosphorylate IRE1 recruits TNF-α-receptor-associated factor 2 (TRAF2), activating downstream JNK and NF-κB signaling pathways. This cascade contributes to leptin resistance, energy homeostasis disruption, and lipid metabolism dysregulation. Consequently, targeting ERS may provide novel therapeutic avenues for addressing obesity-related metabolic dysregulation. Certain polysaccharides, such as *Lentinan*, *Pleurotus ostreatus* and *Ganoderma lucidum* polysaccharides, have been reported to downregulate the expression of IRE1α, ATF6, p-PERK, GRP78, and TRAF2, alleviating ER stress, showing potential to improve obesity [10; 81]. The above results indicate that MPs have shown efficacy in improving obesity by alleviating ER stress; however, the detail molecular mechanisms remain unclear. Future research should focus on strengthening the

investigation of the relationship between obesity and ER stress, particularly concerning the underlying mechanisms.

Furthermore, chronic low-level inflammation and the alterations in immune regulation are critical aspects of lipid reduction in metabolic disorder. Obesity triggers immune imbalance characterized by pro-inflammatory cytokine release (e.g., TNF-α, IL-6, and IL-1β), which exacerbates lipid accumulation. This inflammatory environment interferes with lipid metabolism, leading to further dysregulation. The suppression of pro-inflammatory cytokines and the promotion of anti-inflammatory factors, such as IL-10, can thus play a pivotal role in ameliorating lipid-related metabolic disturbances [82; 83]. This immune modulation, combined with oxidative stress reduction, contributes significantly to the alleviation of metabolic dysfunction. In this regard, certain polysaccharides, such as those from *Morchella esculenta*, have demonstrated the capacity to lower pro-inflammatory cytokines and inhibit inflammation-related enzymes like inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), leading to reduced NO and prostaglandin E2 (PGE2) production [84].

Meanwhile, regulation of the gut microbiota-immune axis critically regulates chronic inflammation and lipid metabolism. Alterations in gut microbial composition directly modulate immune responses, with pro-inflammatory exacerbation or suppression determined by the specific composition of the microbiota. Increasing the abundance of beneficial bacteria (e.g., *Firmicutes*, *Ruminococcaceae*, *Lactobacillus*) and suppressing harmful bacteria (e.g., *Proteobacteria*, *Staphylococcus*) can help restore immune balance and reduce inflammation, contributing to lipid reduction and metabolic regulation. Furthermore, activating toll-like receptor 2 (TLR2) can induce the secretion of anti-inflammatory cytokines like IL-10, thus promoting gut barrier function and reducing systemic inflammation, as shown in polysaccharides from *Hericium erinaceus* [85].

Beyond these mechanisms, immune cell regulation plays a key role in modulating inflammation through three primary mechanisms: humoral immunity potentiation via IgA/IgG antibody induction, innate immune activation through pattern recognition receptors, and lymphocyte homing inhibition via L-selectin blockade. Findings from *Agaricus bisporus* polysaccharides demonstrate enhanced IgA secretion through JAK/STAT3 signaling in plasma cells, which reinforces gut barrier integrity and reduces metabolic endotoxemia in obese mice [86]. Concurrently, *Auricularia auricula* polysaccharides activate TLR2 on macrophages via gut commensal gut commensal *Papillibacter cinnamivorans*, increasing IL-10 production and suppressing TNF-α, thereby ameliorating adipose inflammation and reducing weight gain in HFD models [87]. Collectively, MPs implement a multi-target therapeutic approach for obesity by synergistically modulating humoral immunity, innate immunity, and lymphocyte trafficking, thereby effectively modulate chronic inflammation and metabolic dysregulation. The current research status of MPs as protective modulators for obesity improvement is summarized in Table 2, which includes detailed data on experimental designs, polysaccharide characteristics, and mechanistic insights.

7. Structure–Anti-obesity Activity Relationship

The anti-obesity effects of MPs are closely related to their structural heterogeneity, wherein glycosidic linkage patterns, conformation, M*w*, monosaccharide composition, and branching degree collectively dictate target engagement and metabolic outcomes. Glycosidic bond configurations, including α/β-type linkages and their positions, are crucial in determining the three-dimensional structure of MPs, which directly influence their anti-obesity efficacy. The digestibility of MPs is influenced by the bond structure, as linear β-1,4-bonds form rigid chains that resist enzymatic breakdown, reducing caloric absorption, while branched α-1,6-bonds accelerate enzymatic hydrolysis, increasing glucose release and insulin response. Cross-linked networks create matrices that lower glycemic responses. Additionally, the conformation of MPs also regulates their anti-obesity effect, with flexible coils enhancing receptor binding through hydrophobic interactions, and rigid helices facilitating the sequestration of enterohepatic molecules. Furthermore, M*w* is another key factor in MPs that impacts their anti-obesity activity. Typically, low-M*w* MPs (5–50 kDa; e.g., *Thelephora ganbajun* derivatives) exhibit enhanced bioavailability and potent inhibition of lipogenic enzymes (FAS, ACC) and carbohydrate-digesting enzymes (α-amylase/glucosidase), directly attenuating adipogenesis and postprandial hyperlipidemia [88; 89]. Conversely, high-M*w* β-glucans (>500 kDa) from shiitake (e.g., *Lentinan*) adopt rigid helical conformations, a structural feature proven in other fungi (e.g., *Ganoderma*) to enhance bioactivity [90]. This conformation potentially facilitates bile acid sequestration, similar to viscous polysaccharides (e.g., oat β-glucan), thereby disrupting enterohepatic circulation and promoting cholesterol excretion. Meanwhile, the monosaccharide compositions of MPs also determining their anti-obesity effect. For example, *Ganoderma lucidum* polysaccharides, with a Glc/Gal ratio of approximately 8:1, enhance CYP7A1-mediated bile acid synthesis, whereas *Grifola frondosa* heteroglycans, characterized by a Glc: Man: Gal ratio of 27.6: 25.5: 15.0, are enriched in fucose and uronic acids, which in turn activate FXR-dependent bile acid efflux [39]. Crucially, β-glucan branching also plays a crucial role in modulating obesity effect, with excessive or low branching reduces the optimal anti-obesity efficacy of MPs. A study on the polysaccharides from *Grifola frondosa* polysaccharides (GFPs) reveal that moderately branched configurations (branching degree: 20%–30%) preferentially adopt flexible random coil conformations. This conformation enhances hydrophobic interactions with cell membrane receptors, such as the γ subunit of AMPK, or bile acids, thereby modulating anti-obesity effects [91]. Whereas a higher branching degree of 45.9% found in *Lyophyllum decastes* polysaccharide exhibits excellent anti-obesity effects by enhancing thermogenesis through UCP1-dependent white adipose tissue browning [44]. In summary, the anti-obesity effects of MPs are regulated by a complex interaction of structural factors, including glycosidic linkage patterns, conformation, M*w*, monosaccharide composition, and branching degree. These factors collectively modulate the digestibility, bioavailability, and metabolic activities of MPs, influencing their ability to interact biological targets and induce therapeutic responses. Therefore, future research could focus on optimizing the structural characteristics of MPs to enhance their potential as functional anti-obesity agents.

8. Challenge and perspective

MPs exhibit potential therapeutic potential for obesity management through multi-targeted mechanisms, including lipid metabolism regulation, gut microbiota modulation, oxidative stress mitigation, and mitochondrial function enhancement. Nevertheless, critical limitations constrain current evidence: Firstly, although their mechanisms of action are diverse, the structural complexity of MPs—influenced by Mw, monosaccharide composition, glycosidic linkages, and extraction methods—presents challenges in fully elucidating their structure-activity relationships. Advanced techniques and further research on the structural characterization of polysaccharides are urgently needed to provide deeper insights into polysaccharide-mediated obesity inhibition.

Additionally, although previous studies have demonstrated MPs' ability to prevent obesity in various preclinical models, including cell-based and HFD-induced obesity animal models, the translation of these results to humans is hindered by several limitations inherent in the current experimental designs. For instance, the fat content in HFD used across different studies varies significantly, from 45% to 60%, which can substantially impact the reproducibility and comparability of the findings [92]. Moreover, the actual bioavailability of MPs in humans is influenced by several factors, including molecular weight, gut microbiota composition, and dilution effects during digestion, which often lead to concentrations much lower than those used in *in vitro* studies. Therefore, the biological effects observed at elevated concentrations in laboratory settings may not accurately reflect the physiological impact of MPs when consumed by humans.

Furthermore, the immunomodulatory effects of MPs present a double-edged sword. While MPs have demonstrated potent anti-inflammatory properties by modulating oxidative stress and regulating immune responses, excessive intake may disrupt the delicate balance between pro-inflammatory and anti-inflammatory cytokines. A *in vitro* study found that β-glucan extracted from shiitake mushrooms, at concentrations >1 mg/mL, significantly increased IL-6 secretion (≈4000 pg/mL) while suppressing IL-10 production (≤500 pg/mL), thereby disordering the pro-inflammatory and anti-inflammatory balance [93]. Such findings highlight the importance of dosing in clinical applications, as excessive intake may lead to adverse effects, especially in populations with impaired immune systems.

Meanwhile, the application of MPs in specific populations warrants further attention. For instance, patients with chronic kidney disease (CKD) may benefit from low M*w* β-glucans, which have been shown to reduce markers of renal dysfunction in animal models [94]. However, further studies are needed to validate these findings in human clinical trials. Similarly, individuals with liver cirrhosis may experience altered polysaccharide metabolism, potentially exacerbating the risk of liver encephalopathy. Pregnant women must also avoid polysaccharides with strong immune-stimulating properties due to concerns about placental transfer and potential effects on fetal development.

Moreover, current purification technologies, such as membrane separation, chromatographic techniques, and novel approaches like deep eutectic solvent-ultrasound assisted extraction (DES-UAE), facilitate the isolation of high-purity MPs [95]. However, these methods are predominantly limited to laboratory-scale applications. The transition to industrial-scale processes necessitates addressing critical challenges related to

capital investment and process economics. Since MPs possess complex structural configurations that confer resistance to gastrointestinal digestion, they serve as prebiotic substrates whose degradation by gut microbiota-derived carbohydrate-active enzymes (CAZymes) mediates their beneficial effects [96]. However, the remarkable complexity of the gut microbiome presents significant challenges in deciphering polysaccharide catabolism, as bacterial consortia encode diverse and intricate arrays of carbohydrate-active enzymes (CAZymes). Nevertheless, elucidating MPs catabolism remains challenged by the gut microbiome's complexity, wherein bacterial communities express highly diverse CAZyme.

Prospectively, the development of MPs for obesity management will rely on advanced technologies for industrial-scale purification optimization, precise structural characterization, establishment of structure-activity relationships, refined experimental paradigms, and extensive clinical validation. Transitioning beyond preclinical limitations requires physiologically relevant models that recapitulate human metabolic complexity. Optimized study designs incorporating standardized dietary lipid profiles, MP structural heterogeneity, and personalized microbiome configurations will elucidate real-world efficacy. Concurrently, precision nutrition paradigms represent a pivotal frontier. Integration of genomic and metagenomic profiling could identify responder phenotypes, enabling standardized MP interventions that enhance therapeutic efficacy while minimizing the risks associated with immune dysregulation, particularly in immune deficiency individuals. Furthermore, specific population pharmacovigilance demands prioritized research. Focused studies on gravid women, CKD, and cirrhotic patients must establish population-specific safety thresholds through adaptive trial designs. Interdisciplinary collaborations across fields such as glycobiology, immunology, and regulatory science will be essential to translate the promise of MPs into clinically actionable obesity therapeutics.

9. Conclusion

Obesity as a multifactorial metabolic disorder involves dysregulated lipid metabolism, mitochondrial dysfunction, gut microbiota imbalance and chronic inflammation. Conventional single-target pharmacological interventions often fail to address the complexity of obesity, highlighting the need for safer, multi-targeted therapeutic strategies. In this context, MPs, a kind of low-toxicity, biologically active natural compounds, have emerged as promising candidates for obesity prevention and treatment due to their ability to modulate multiple pathological pathways through regulating lipid/cholesterol metabolism, gut microbiota, mitochondrial function and oxidative stress. Nevertheless, MPs as functional foods face constraints in industrial application and clinical translation due to several barriers: 1) Technical and economic challenges in purification scale-up, hindering cost-efficient production; 2) Poorly understood structure-activity relationships due to molecular heterogeneity limit target engagement and mechanistic pathways of MPs' anti-obesity effects; 3) Limited physiological relevance in preclinical models, hindering the translation of findings to human clinical application; 4) Dose-dependent immune risks, manifested as cytokine dysregulation, which may weaken therapeutic tolerability; 5) Population-specific vulnerabilities requiring personalized safety/efficacy thresholds to achieve the therapeutic application of MPs. By addressing these challenges, MPs hold great potential as multi-targeted, natural anti-obesity therapeutics, offering innovative

strategies for regulating obesity and its associated metabolic disorders. This review serves as a valuable resource for understanding the anti-obesity properties of MPs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of generative AI in scientific writing

Generative AI and AI-assisted technologies were used in the writing process to improve the readability and language of the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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