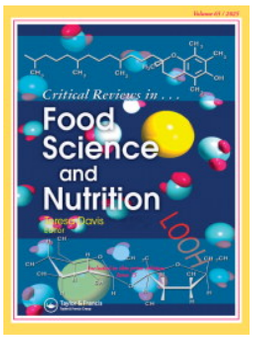

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: www.tandfonline.com/journals/bfsn20

Food-derived polysaccharides and anti-obesity effects through enhancing adipose thermogenesis: structure-activity relationships, mechanisms, and regulation of gut microecology

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To cite this article: Zhenyu Wang, Qiyu Xu, Lijuan Hou, Zhiyong He, Mark Christian & Xianjun Dai (12 May 2025): Food-derived polysaccharides and anti-obesity effects through enhancing adipose thermogenesis: structure-activity relationships, mechanisms, and regulation of gut microecology, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2025.2500675

To link to this article: https://doi.org/10.1080/10408398.2025.2500675

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2025.2500675

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REVIEW ARTICLE

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Food-derived polysaccharides and anti-obesity effects through enhancing adipose thermogenesis: structure-activity relationships, mechanisms, and regulation of gut microecology

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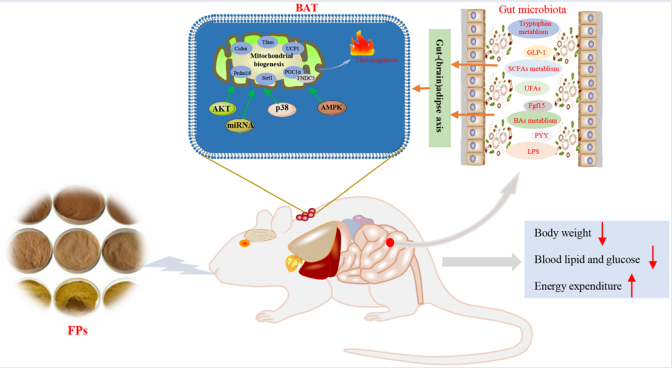
ABSTRACT

Polysaccharides represent a crucial and extensively utilized bioactive fraction in natural products, which are employed in the treatment of metabolic disorders due to their significant therapeutic potential. Recently, food-derived polysaccharides (FPs) have emerged as significant substances in obesity management, valued for their ability to activate thermogenic fat. This review discusses the correlation between the structural features of FPs and their efficacy in combating obesity. Moreover, the molecular mechanism by which FPs regulate thermogenic fat and how the intestinal microecology induces thermogenic fat activity is elucidated. The anti-obesity effects of FPs depend on their structure, including molecular weight, composition, linkages, conformation, and branching. Furthermore, FPs regulate fat thermogenesis via multiple mechanisms, including AMPK, p38, AKT, PGC-1α-FNDC5/irisin, and miRNA signaling pathways. Importantly, gut microbiota, together with its associated metabolites and gut-derived hormones, are pivotal in the regulatory control of brown fat by FPs. This work provides an in-depth examination of how adipose tissue thermogenesis contributes to the anti-obesity effects of FPs, shedding light on their potential in preventing obesity and informing the formulation of natural weight-loss remedies.

KEYWORDS

Polysaccharides; brown fat; structure-activity relationship; mechanisms; intestinal microecology

GRAPHICAL ABSTRACT



Introduction

Obesity develops when the body stores excessive fat, a condition that may result in an increased risk of cardiovascular disease, diabetes, hypertension, and cancer (B. H. Kim et al. 2024). The human body harbors three distinct types of adipose tissue: white adipose tissue (WAT), brown adipose tissue (BAT), as well as beige adipose tissue (BeAT) (Z. Zhang, Zhang, et al. 2021). They play different roles in energy metabolism and thermoregulation and have different relationships with obesity. WAT is mainly used for energy storage as fat deposits (Berry et al. 2013). BAT is rich in mitochondria and uncoupling protein 1 (UCP1), a mitochondrial inner membrane protein that uncouples oxidative phosphorylation and helps fight obesity by allowing protons to leak across the membrane and generate heat (W. Ren et al. 2024). BeAT is an intermediate type of adipose tissue with some calorie-burning capacity that can be converted to function like brown fat under certain conditions (e.g., cold exposure or certain hormones) (H. Zhou, Chen, et al. 2023). Research suggests that increasing the amount or function of BAT/BeAT could be beneficial in boosting metabolic health and lowering the likelihood of developing obesity (Dąbrowska and Dudka 2023). Therefore, research into the mechanisms

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that regulate thermogenic tissues is of significance in the search for effective obesity treatment options.

Polysaccharides are large, sugar-based macromolecules composed of chains of monosaccharides linked by glycosidic bonds, typically containing more than ten monosaccharide units (W. Yang, Zhao, et al. 2022). These carbohydrates occur in diverse structures in various food plants that are of significance for improving health (e.g., mitigating inflammation, obesity, and diabetes) and have gained the attention of researchers, especially in China, the USA, and India (Figure 1). It has been documented that food-derived polysaccharides (FPs) exhibit a wide array of biological properties, including immunomodulatory, antitumor, antioxidant, antiviral, antimicrobial, antiinflammatory, hypoglycemic, hypolipidaemic, neuroprotective, and microbiota-regulatory effects (Ramawat and Mérillon 2015). Notably, their anti-obesity effects are multifaceted, with mechanisms involving energy metabolism, fat metabolism, intestinal flora, inflammatory responses, and hormonal regulation (Y. Chen et al. 2024). Some FPs contribute to combating obesity by improving insulin sensitivity. They may enhance insulin signaling by regulating ion channels on cell membranes, such as calcium channels, thus contributing to blood sugar control (Yang et al. 2017). FPs have the capability to influence the functionality of enzymes involved in fat metabolism, including fatty acid synthase (FAS) and acetyl coenzyme A carboxylase (ACC), which consequently leads to a decrease in fat synthesis (D. Yin, Zhong, Liu, & Hu et al. 2024). Additionally, FPs can suppress preadipocyte differentiation by regulating the function of transcription factors such as peroxisome proliferator-activated receptor (PPAR)γ (X. Xu et al. 2021). Importantly, FPs, particularly those resistant to digestion, can function as prebiotics to foster the proliferation of advantageous gut bacteria, including species such as *Bacteroides* and *Anaerostipes* (Q. Song et al. 2021). These beneficial bacteria can improve the intestinal environment and influence energy metabolism and fat storage. The biological activities of FPs, including their anti-obesity effects, are dictated by their structural features, such as molecular weight, monosaccharide composition, degree of branching, type of glycosidic bonds, and their spatial conformation (Y. Chen et al. 2024). For example, FPs containing specific monosaccharides such as mannose, glucose, and galactose may be more effective in promoting fat thermogenesis and therefore provide a better anti-obesity effect (T. Wang, Han, et al. 2022). Moreover, highly branched polysaccharides may bind more readily to receptors on cells (Yi et al. 2018), activating signaling pathways that promote thermogenesis. Therefore, the different structures of FPs profoundly impact their biological activity.

Here, the structure-activity relationship of polysaccharides is discussed, and the molecular mechanism of brown fat activation by FPs and how they affect the intestinal microecology to regulate brown fat and thus exert anti-obesity effects. These findings establish a theoretical framework that supports the use of FPs as potential functional food additives or pharmaceuticals, and innovative approaches for the prophylaxis and treatment of obesity and related metabolic conditions. Future research will focus on the optimization of the conformational relationship between FPs, in-depth exploration of the mechanism of action, and the exploration of clinical applications, so that FPs can ultimately benefit human health.

Relationship between FPs structure and anti-obesity activity

The extensive structural variation of FPs spanning aspects such as molecular weight (M_w), monosaccharide content, types of glycosidic linkages, conformations, and branching extent accounts for their broad spectrum of biological functions, which includes the potential for anti-obesity effects (Table 1).

Effects of molecular weight (M_w) on FPs activity

M_w is an important physical parameter of FPs, which significantly affects their anti-obesity activity. The M_w of FPs can range from a few thousand to several million daltons, and different M_w often leads to differences in solubility, bioavailability, biodistribution, and interactions with biomolecules (Fan et al. 2023). Low M_w FPs usually have better water solubility and can be more easily dispersed in water to form stable solutions (Ji et al. 2022). This facilitates the uptake and distribution of FPs in the body, which may enhance their biological activity such as lipid-lowering effects. High M_w FPs may be difficult to dissolve in water and do not readily form a homogeneous solution, limiting their usefulness in organisms. In addition, low M_w FPs are more readily absorbed into the intestinal tract, enter the circulation, and reach their target tissue or organ due to their smaller size (X. Zhang, Hu, et al. 2020). Evidence suggests chemical modifications can alter the M_w and size of polysaccharides, thereby impacting their solubility and viscosity. These physical attributes play a significant role in how polysaccharides interact with biological systems, particularly in their anti-obesity potential. For instance, modified polysaccharides with improved solubility and viscosity can enhance satiety and reduce calorie intake, making them promising ingredients in weight management products. Furthermore, alternative extraction procedures also can potentially modify the molecular weight spectrum of FPs (Han et al. 2019; Y. Sun et al. 2022). Water extraction is usually milder and may better preserve the structure and biological activity of FPs; acid-alkali treatment alters the M_w of FPs by causing hydrolysis or degradation of their chains in response to changes in pH; enzymatic extraction can release FPs with selective structural modifications due to enzyme specificity; ultrasonic extraction uses the physical action of ultrasound, which may interrupt the polysaccharide chain and lower the M_w; microwave-assisted extraction with rapid heating may accelerate the extraction of FPs, but it may also cause structural degradation (Huang et al. 2021). Consequently, the variation in extraction methods plays a critical role in preserving the structural integrity of FPs, thereby influencing their biological activity.

Previous studies showed the antioxidant activity of FPs is usually inversely proportional to their M_w. Low M_w FPs

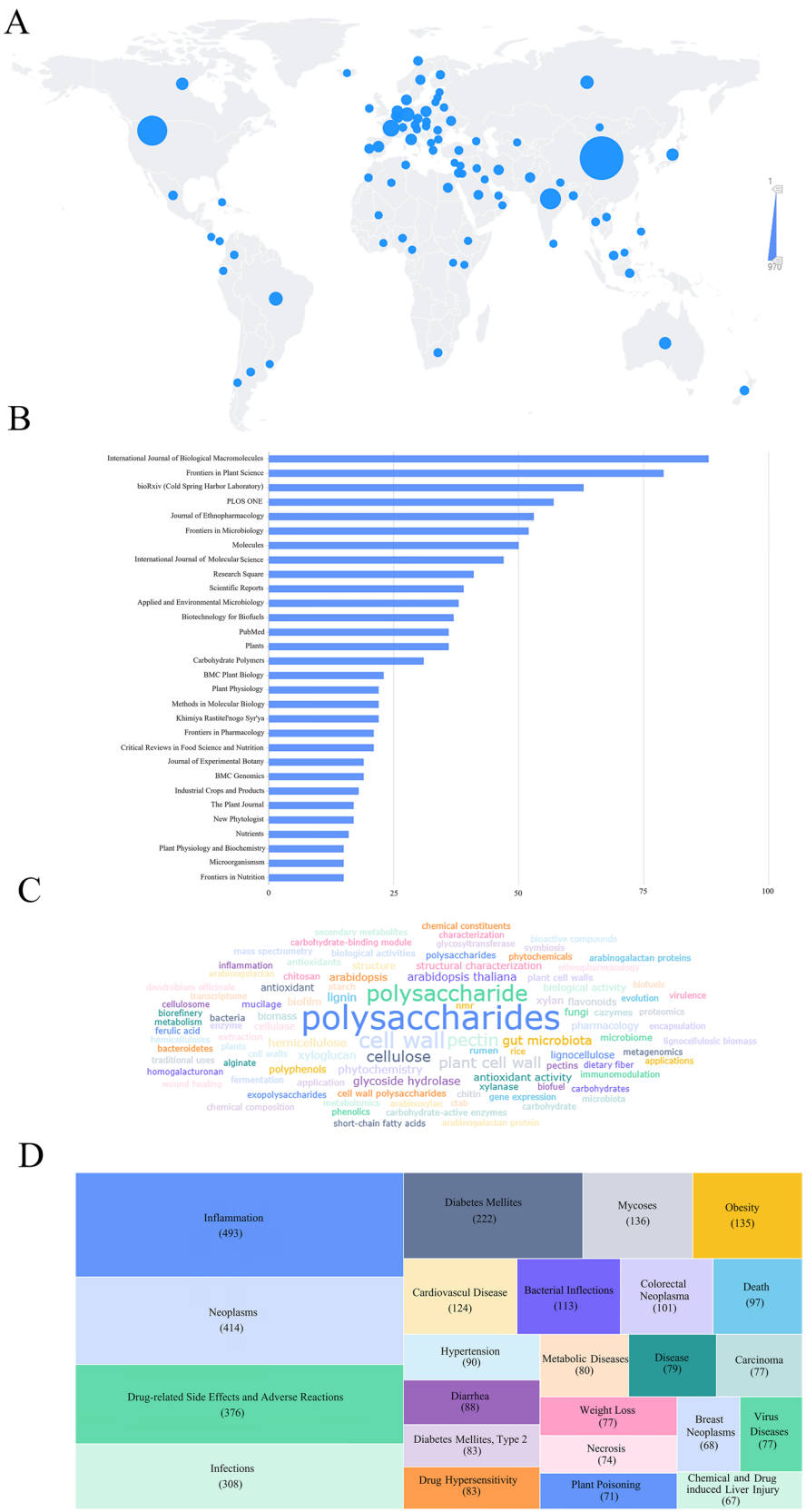

Figure 1. Bibliometric analyses of research dynamics on plant polysaccharides. (A) The top 100 countries/regions with the highest number of publications in the field of plant polysaccharides research are China (970 publications, 26.39%), USA (599 publications, 16.3%) and India (355 articles, 9.66%) (2014.01–2024.12). (B) The International Journal of Biological Macromolecules (88 articles) published the most articles among the top 30 journals in terms of number of plant polysaccharide reports. (C) The hot word frequency analysis of keywords showed that the studies mainly focused on structural features and biological activities. (D) Entity word mining and statistical cluster analysis of diseases in the abstracts of 3675 articles dealing with polysaccharides using the BioBERT biomedical speech representation model, in which the literature focuses on metabolic diseases including inflammation, diabetes, and obesity.

Table 1. FPs With anti-obesity activity of polysaccharides and their detailed structures (ND: no data).

Source	Molecular weight	Monosaccharide composition	Glycosidic bonds	Conformation	Anti-obesity activities	References
Pleurotus eryngii polysaccharides	>300,000 Da (36%); 100,000–300,000 Da (8%); 30,000–100,000 Da (5%); 10,000–30,000 Da (17%); 3000–10,000 Da (13%); <3000 Da (21%)	Glucose: 82.5%, galactose: 9.2%, and mannose: 8.3%	ND	ND	Regulation of gut microbiota	(Nakahara et al. 2020)
Lyophyllum decastes polysaccharides	LDP1-1: 39,200 Da; LDP1-2: 117,000 Da	Mannose, glucose, galactose, and fucose (1:2.38:2.58:0.73 for LDP1-1 and 1:2.33:2.51:0.78 for LDP1-2)	ND	ND	BAT thermogenic activity and sWAT browning; Regulation of gut microbiota and bile acid metabolism	(T. Wang, Han, et al. 2022)
Microalga *Spirulina platensis* polysaccharide	1.996×10^6 Da	Rhamnose, fucose, arabinose, xylose, mannose, and glucose with the molar ratio of 3.42:0.76:0.34:0.53:0.43:0.59	1→4, 1→3 and 1→6 glucoside bonds	ND	Regulation of intestinal flora	(Chen et al. 2020)
Anemarrhena asphodeloides Bunge glucomannan	5800 Da	Mannose and glucose at a molar ratio of 7.2: 2.8	1→ 4, 1→3 and 1→ 6 glucoside bonds	ND	Inhibition of glucose uptake and glycogen synthesis	(Chen et al. 2022)
Mallotus furetianus polysaccharide	ND	Mannose, galactose, arabinose, galacturonic acid and glucose with a molar ratio of 3.05:2.84:1.84:0.86:1.41	1→4 and 1→ 6 glucoside bonds	ND	Inhibitory effects on α-glucosidase activity	(J. Chen, Li, et al. 2019)
Inonotus obliquus polysaccharide	256,623 Da	Mannose, ribose, rhamnose, glucuronic acid, galacturonic acid, glucose, galactose, xylose, arabinose, and fucose =0.011:0.005:0.006:0.016 :0.002:1.000:0.008:0.003:0.004:0.001	1→4 glucoside bond	ND	Inhibitory effects on 3T3-L1 cell cycle	(B. Hu et al. 2024)
Brasenia schreberi polysaccharide	ND	ND	1→4, 1→3 and 1→6 glucoside bonds	Triple-helix conformation	Inhibition of α-amylase and α-glucosidase	(Feng et al. 2019)
Thelephora ganbajun mushroom polysaccharide	TZP1-1: 2,070,000 Da	Mannose, rhamnose, galactose, and xylose at a molar ratio of 4:1:83.9:7.55.4:1:79:8.1	ND	Triple-helix conformation	Inhibition of α-Amylase and α-glucosidase	(Gong et al. 2020)
Acidic tea polysaccharide	ND	ND	1→4 and 1→6 glucoside bond	Globular homogeneous conformation	Inhibition of α-amylase activity	(L. Yin et al. 2020)
Lycium barbarum polysaccharide	11,297 Da	Arabinose, galactose, rhamnose, glucuronic acid, mannose and galacturonic acid in molar percentages of 51.0: 25.8: 5.5: 8.4: 3.6: 5.3	1→3 and 1→6 glucoside bonds	ND	Regulation of gut microbiota; Inhibition of fat accumulation	(Y. Yang et al. 2021)
Polygonatum cyrtonema polysaccharide	5100 Da	Galactose (37.30%), mannose (19.45%), rhamnose (18.78%), galacturonic acid (15.62%), and glucose (15.09%)	ND	ND	Inhibited expression of lipid synthesis-associated genes	(Liang et al. 2021)
Mulberry fruit polysaccharide	210,120 Da (16.33%); 100,020 Da (41.37%); 62,520 Da (29.54%); 20,840 Da (12.76%)	Arabinose, galactose, glucose, rhamnose and galacturonic acid with molar ratio percentages of 28.37%, 27.51%, 17.36 %, 12.59%, and 14.07%	ND	ND	Regulation of gut microbiota	(C. Chen, You, et al. 2018)
Korean mulberry fruit Oddi polysaccharide	ND	Galactose (37.6%), arabinose (36.3%), and rhamnose (18.4 l%)	1→4, 1→3 and 1 →6 glucoside bonds	ND	Induction of apoptotic 3T3-L1 pre-adipocytes	(Choi et al. 2016)
Large yellow tea polysaccharides	28,600 Da	Rhamnose, arabinose, galactose, glucose, and galacturonic acid at the molar ratio of 8.08: 11.66:11.77:3.96:58.02	1→4 and 1→5 glucoside bonds	ND	Promotion of M2 polarization	(H. Wang, Wang, Cheng, et al. 2023)
Callerya speciosa polysaccharides	27,700 Da	Glucose (62.6%), arabinose (15.3%), galactose (13.4%), rhamnose (2.9%), and galacturonic acid (2.8%)	ND	ND	Regulation of gut microbiota and SCFA levels	(D. Li, Xu, et al. 2022)
Polysaccharide from Salviae miltiorrhizae Radix et Rhizoma	32,600 Da	Galacturonic acid (GalA), arabinose (Ara), galactose (Gal), rhamnose (Rha) and glucose (Glc), with molar ratios of 17.9:1.3:1.7:1.2:1	ND	ND	Ameliorated defects in gut structure and permeability	(L. Li, Xu, et al. 2022)

contain more terminal hydroxyl groups which are effective in scavenging free radicals and therefore usually have higher antioxidant activity (Ofoedu et al. 2021; J. Zhang et al. 2023). Importantly. FPs with lower relative M_w showed better results in terms of digestive enzyme inhibition and fermentability and had better obesity inhibition activity than polysaccharides with higher M_w. For example, Gong et al. 2020 extracted FPs with different M_w from *Thelephora ganbajun* mushroom and found that TZP2-1 (4886 Da) with lower M_w had better hypoglycemic activity the higher α-amylase and α-glucosidase inhibitory activity than TZP1-1 (2.07×10^6 Da). Furthermore, low M_w FPs may be more likely to inhibit the activities of enzymes related to fatty acid synthesis (e.g., FAS, ACC), and thus lower blood lipid levels (T. Ren et al. 2023). It was found that high-pressure preparation of a low-molecular-weight polysaccharide (125.41 kDa) from *Dendrobium officinale* could significantly downregulate lipid synthesis-associated proteins such as sterol regulatory element-binding protein (SREBP-1), FAS, and ACC, thereby mitigating lipid accumulation in *C. elegans* (Pang et al. 2024). M_w affects the structural complexity of FPs with high M_w polysaccharides typically having more complex and varied structures, which may confer a stronger anti-obesity effect (Z. Ma et al. 2022). Complex structures often contain diverse functional groups (e.g., hydroxyl, carboxyl, and sulfate groups) that can interact with biological targets, such as enzymes or receptors involved in lipid metabolism and energy homeostasis. These interactions can modulate pathways related to fat storage, energy expenditure, and appetite regulation (Zheng et al. 2024). However, this structural complexity also makes it more difficult to determine the specific mechanisms of action of FPs. Low M_w FPs are generally more readily degraded by enzymes in the body, which may affect their half-life. High M_w FPs may have longer half-lives and may also have lower toxicity because they are more difficult to absorb (T. Liu et al. 2023). Taken together, M_w is a key factor underlying the activity of FPs, which in turn affects their browning effects by influencing their physicochemical properties, biodistribution, and biomolecular interactions.

Effects of monosaccharide composition on FPs activity

Monosaccharide composition is one of the key factors determining the structure and function of FPs. The types (e.g., glucose, galactose, mannose, fucose, etc.) and proportions of monosaccharides affect the spatial structure and branching patterns of FPs and thus affect their biological activity (Andryukov et al. 2020; Lee et al. 2023). Comparison of different fractions of polysaccharides from *Dictyophora indusiata* on HFD-induced mice showed the inhibition of body weight and serum lipid levels was greater with D6P (polysaccharide fraction at 60% composed of fucose, galactose, glucose, mannose, glucuronic acid, and galacturonic acid) than with D8P (polysaccharide fraction at 80% composed of fucose, galactose, glucose, mannose, and glucuronic acid) (Yao et al. 2024). Different monosaccharide units may bring different functional groups that can interact with biomolecules (e.g., proteins, cell membrane receptors, etc.) affecting the bioactivity of FPs. The number and location of hydroxyl groups in monosaccharides affect the anti-obesity activity of FPs and monosaccharide units with more hydroxyl groups (e.g., glucose) provides greater lipid-lowering effects (Gong et al. 2020). Evaluation of the anti-obesity effect of polysaccharides extracted from the edible brown seaweed *Undaria pinnatifida* on HFD-induced mice revealed that sulfated polysaccharides (composed of mannose, rhamnose, galacturonic acid, glucose, galactose, xylose and fucose) were more effective than alginate (composed of mannuronic acid and guluronic acid) in inhibiting adipose tissue formation (P. Zhang, Jia, et al. 2022). Monosaccharide composition affects the solubility of FPs. For example, FPs containing more branched structures or hydrophilic monosaccharides generally have better solubility, which may improve their bioavailability (Singh et al. 2021). Different monosaccharide compositions may lead to different distribution throughout the body and metabolic pathway regulation by FPs, which may affect their role in specific tissues or organs (for example liver and adipose tissues) (Yao et al. 2024). Furthermore, monosaccharide composition determines the functional groups on the surface of FPs, which can interact with cell surface receptors or other biomolecules (e.g., proteins, enzymes, etc.), thus affecting the antiobesity activity of FPs (Q. Zhang, Zhang, et al. 2021). The solvents and conditions used in the extraction process may selectively solubilize different types of FPs, thus affecting the composition of the monosaccharides in the final extract (Wassie et al. 2021). In conclusion, the influence of monosaccharide composition on FPs activity is multifaceted, including but not limited to the structure of polysaccharides. Therefore, understanding and optimizing the monosaccharide composition is one of the key steps in researching and developing polysaccharides to achieve improved browning capacity.

Effects of glycosidic bonds and conformation on FPs activity

The biological activity of FPs depends not only on their monosaccharide composition but is also influenced by the type of glycosidic bond and the conformation of the FPs in solution (Dong et al. 2024). Glycosidic chemical bonds connect monosaccharide units, while conformation refers to the specific arrangement and shape of FPs molecules in space. Glycosidic bonds are either alpha or beta types, depending on the configuration of the carbon atoms connecting the monosaccharide units (Ceroni, Dell, and Haslam 2007). The presence of α-glycosidic and β-glycosidic bonds affects the physical and chemical properties of the FPs, and thus their antiobesity activity (Sułkowska-Ziaja et al. 2023). Laminaran is a β-1–3-glucan, whereas fucoidan is a sulfated polysaccharide consisting of β-(1→3) and α-(1→4) glycosidic linkages, and it was demonstrated that the browning effect of fucoidan was greater than that of Laminaran, as shown by the significant upregulation of UCP1 (Lee et al. 2022; Sharma and Baskaran 2021). The monosaccharide units can be connected by different carbon atoms, such as 1,4-glycosidic and

1,6-glycosidic bonds (Bejenaru et al. 2024). Differences in the location of the linkage lead to differences in the degree of branching and spatial structure of the polysaccharide chain, thus affecting antiobesity activity (Figueroa et al. 2022). The arrangement of glycosidic bonds (linear, branched, or cross-linked) determines the three-dimensional structure of the FPs, which affects their activity (Yaşar Yıldız and Radchenkova 2023). For example, linear polysaccharides like cellulose (β-1,4-glycosidic bond) have a straight chain structure that is indigestible by humans, contributing little to caloric intake (Saura-Martínez et al. 2024). In contrast, branched polysaccharides like amylopectin have a tree-like structure due to their glycosidic bond (α-1,6 glycosidic bond) arrangement, which allows for more accessible sites for enzyme digestion (Abubakar et al. 2017). This results in a faster release of glucose, which can lead to increased insulin secretion and potentially influence obesity. The cross-linked structure of polysaccharides like pectin, creates a complex network that can resist digestion (Manthei et al. 2023). This not only affects the texture of foods but also contributes to a lower glycemic index, which may help in managing obesity by reducing overall glucose absorption. Thus, the distinct three-dimensional structures dictated by glycosidic bond arrangements can modulate the digestibility, caloric value, and metabolic effects of FPs, playing a crucial role in their impact on obesity. External treatments during extraction may change the type of glycosidic bonds in FPs, thus affecting their efficacy. Chemical or enzymatic actions can alter glycosidic bond types by breaking and forming new bonds. For example, β-glucanase can break down β-1,3 or β-1,4 glycosidic bonds in the presence of water, leading to the formation of shorter chains or different types of linkages (Levy, Shani, and Shoseyov 2002). Enzymes like xyloglucanase can also create new glycosidic bonds by rearranging the sugar residues, thereby changing the polysaccharide's structure and properties (Zavyalov et al. 2019). Chemical methods, using acids or bases, induce hydrolysis that can randomly break glycosidic bonds, leading to a mix of new linkages or even degradation of the polysaccharide (Pan et al. 2023). These structural changes can significantly affect the polysaccharide's bioactivity, including its antiobesity properties, by modifying its interaction with biological molecules.

Additionally, the conformation of polysaccharides, which refers to the spatial arrangement of their monosaccharide units and the overall structure they adopt, can significantly affect their solubility, molecular size, and interaction with biomolecules. The conformation of FPs in solution can be straight or helical, and their flexibility affects the interaction of FPs with biomolecules (M. Xu et al. 2024). More flexible polysaccharide chains may bind more readily to receptors or other biomolecules and thus exhibit greater antiobesity activity (Tao et al. 2021). Conformation affects the effective molecular size of FPs, which in turn affects their solubility and bioavailability, and larger molecular sizes may reduce the solubility and bioavailability of FPs (Y. Yu et al. 2018). The spatial structure of polysaccharides determines whether they can bind to specific biomolecules (e.g., enzymes, receptors), which is the key to the antiobesity potential of FPs. For example, the active site of some FPs may require a specific spatial structure to bind to receptors on the surface of immune cells and thus exert immunomodulatory effects (Yuan et al. 2022). Hydroxyl groups in polysaccharide molecules can form hydrogen bonds, and these hydrogen bonds affect the conformation and aggregation state of the polysaccharide, which in turn affects its hypolipidemic activity (Y. Ren et al. 2019). Charge distribution in polysaccharide molecules is influenced by conformation and charge density, and distribution patterns affect the interaction of FPs with biomolecules (Zahariev et al. 2023). Evidence suggests chemical modifications such as acetylation or sulfation, which involve the addition of new functional groups, can alter the conformation of the polysaccharide chain (Zhang, Fu, et al. 2024). These changes in structure might significantly affect the polysaccharide's ability to bind to specific biological targets or enzymes that play a role in obesity. For instance, modified polysaccharides could modulate the activity of enzymes involved in fat metabolism or interact with receptors that regulate appetite, thereby influencing weight gain and potentially offering a therapeutic benefit in the management of obesity (Li et al. 2016). Thus, the tailored chemical modifications of polysaccharides present an innovative strategy for designing bioactive compounds used in the fight against obesity. Furthermore, the degree of sugar branching may be determined by the method of extraction (Yuliarti et al. 2015). Collectively, the type of glycosidic bond and the conformation of the FPs together determine the structure and antiobesity effects of FPs.

Effects of degree of branch on FPs activity

The branching degree of a polysaccharide refers to the number and complexity of side or branching chains in its molecular structure, a characteristic that directly affects the physiochemical properties, solubility, biocompatibility, and biological activity (Y. Yang, Zhao, et al. 2022). First, FPs with high degree of branching usually have better solubility in water because the presence of branched chains reduces intermolecular interactions (J. Lin et al. 2023). In addition, the branching degree of FPs affects its biocompatibility and biodegradability. Highly branched FPs tend to be more readily recognized and absorbed by cells *in vivo*, resulting in good biocompatibility (L. Chen, Li, et al. 2019). The bioactivity of FPs is highly dependent on the extent of their branching. If the branching is either excessively high or excessively low, the antiobesity potential of FPs will not achieve the optimal level (K. Li, Xu, et al. 2022; Jing et al. 2022). Findings from an earlier study indicate a strong correlation between the degree of branching in pectic polysaccharides and their capacity to modulate immune responses. The removal of branching segments led to a reduction in their immunomodulatory activity (Nergard et al. 2005). A comparative assessment of the therapeutic advantages of mannosiduronic acid (MA) and fucoidan sulfate (FS) in hyperlipidemia was conducted. The findings revealed that only the mice treated with FS, which comprises a significant proportion of highly branched sugar residues with a branching degree of 29%, could significantly diminish body weight

and serum cholesterol levels when fed a high-cholesterol diet (F. Fang et al. 2022). In addition, treatment of HFD-fed mice with *Lyophyllum decastes* polysaccharide (LDP1-1) (branching degree: 45.9%) significantly inhibited obesity by increasing energy expenditure, BAT thermogenic activity, and WAT browning, with effects close to those of the normal diet group (T. Wang, Han, et al. 2022). Collectively, the branching degree of FPs is fundamental to determining their biochemical properties and biological activities.

Relationship between fat thermogenesis and obesity

Thermogenic fat, mainly BAT and BeAT, differs significantly from WAT in its physiological functions (Z. Zhang, Zhang, et al. 2021). WAT's primary function is to act as an energy reservoir, whereas the main role of brown and beige fat is to facilitate thermogenesis, a mechanism that involves the conversion of fat into heat (Z. Wang, Wang, Cheng, et al. 2023). Brown adipocytes contain abundant mitochondria with high expression of UCP1, which allows them to generate heat, rather than ATP, by oxidizing fat, a process known as non-shivering thermogenesis. Due to its high metabolic rate, brown fat is integral to the maintenance of energy balance, contributing to the regulation of glycolipid metabolism and significantly increasing total energy expenditure (J. Hu et al. 2020). Research has demonstrated that there is an inverse relationship between the amount of brown fat and both body weight and body fat percentage, implying that people with higher amounts of BAT tend to have a lower propensity for obesity (Neeland, Poirier, and Després 2018). In cold environments, brown fat activity increases to produce more heat, which helps to reduce body fat storage (Nishimoto and Tamori 2017). In recent years, scientists have explored ways to activate or increase the amount of brown fat to treat obesity. Certain stimuli, including natural products, physical activity, medications, and hormones have been found to promote the development and thermogenesis in brown fat (Figure 2) (X. Liu et al. 2023; Negroiu et al. 2024). Moreover, beige fat is a type of adipose tissue with similar properties to brown fat and researchers from Harvard Medical School transplanted modified HUMBLE cells (human-like brown adipocytes) into HFD-induced mice, and the results showed that compared to mice transplanted with white adipocytes, the mice transplanted with HUMBLE cells had a significantly lower proportion of WAT in their bodies, and lower body weights, close to those transplanted with brown adipocytes directly (C.-H. Wang, Lundh, et al. 2020). Consequently, enhancing the quantity and functionality of thermogenic fat depots, such as BAT and BeAT, could offer novel approaches for preventing and managing obesity. However, the development of obesity is multifactorial, including genetics, lifestyle, and dietary habits; therefore, the role of thermogenic fat should be considered along with other factors for a comprehensive understanding of the pathological mechanisms of obesity and the development of effective therapeutic options.

Mechanism of fat thermogenesis by polysaccharides

The molecular mechanism by which FPs regulate adipose thermogenesis is a complex biological process involving multiple biomolecules and signaling pathways (Figure 3). The study of these mechanisms provides potential molecular targets for developing new anti-obesity strategies.

Molecular mechanisms

AMPK signaling

AMP-activated protein kinase (AMPK), a downstream target of the beta3-adrenergic receptor (β_3-AR), operates as a key energy sensor and is essential in the regulation of BAT function and thermogenesis (Kuryłowicz and Puzianowska-Kuźnicka 2020). It promotes fatty acid uptake and oxidation by phosphorylating multiple targets, the primary energy source for brown fat thermogenesis (Rebello et al. 2017). AMPK is capable of phosphorylating and thereby regulating the activities of various transcription factors, including PPARγ and peroxisome proliferator-activated receptor-gamma coactivator

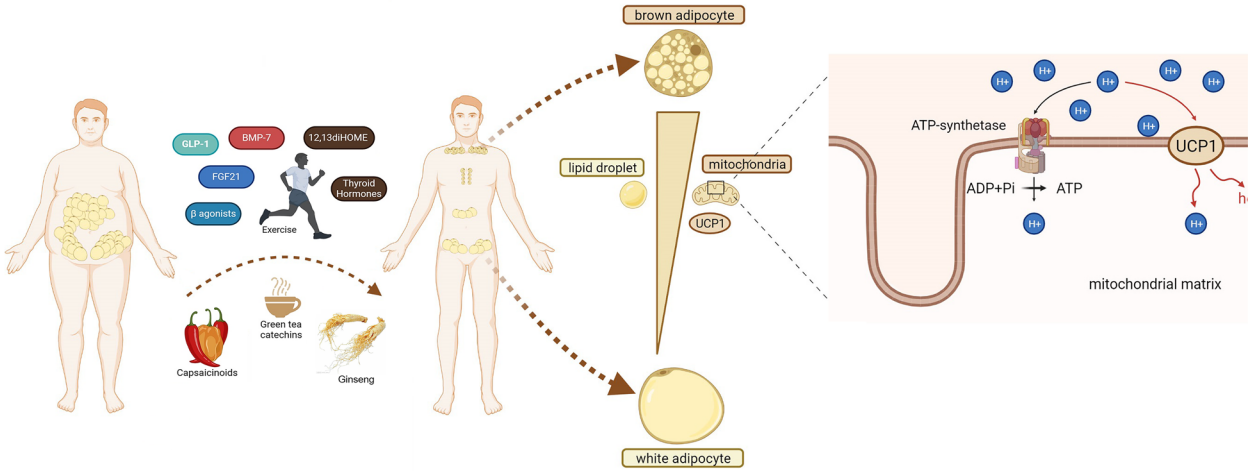

Figure 2. Multiple stimuli including natural products, hormones and exercise induce fat browning and therefore inhibit the onset of obesity. In adults, BAT is found in the back scapula and clavicle area, around the heart and kidneys, and WAT is located around the viscera and groin. Compared with white adipocytes, brown adipocytes contain a large number of mitochondria, high expression of UCP1 (dissipating proton (H+) gradient), and multiple smaller lipid droplets.

1-alpha (PGC-1α), that are crucial in the development and differentiation of brown adipocytes (J. Hu et al. 2020). Furthermore, AMPK can maintain mitochondrial mass and function by affecting mitochondrial fusion and division and promoting autophagy, which is critical for the long-term thermogenic function of brown fat (Ziqubu et al. 2023). In summary, the AMPK signaling pathway regulates the function of BAT through multiple mechanisms, including promoting fatty acid and glucose metabolism, regulating brown adipose development and differentiation, and inducing the expression of UCP1. Studies show that the polysaccharides extracted from *Anoectochilus roxburghii* (ARPs) significantly induced the expression of thermogenic genes, including UCP1, PGC-1α, PR domain-containing protein 16 (PRDM16), and Type II deiodinase (DIO2) in adipose tissue, surpassing the expression levels observed in the mice on a high-fat diet (HFD). The underlying mechanism involves the facilitation of thermogenesis by ARPs through the AMPK/silent information regulator factor 2-related enzyme 1 (SIRT1)/PGC-1α signaling pathway (Tian et al., 2022). Fucoidan is an active component derived from brown seaweed and a recent study found that the low molecular weight variant LF2 effectively induced the upregulation of UCP1. In db/db mice, this compound was observed to augment energy expenditure, an effect that is mediated through the activation of the AMPK/PGC1α pathway (Deng et al. 2022). Furthermore, it was found that mulberry leaf polysaccharides (MLP) stimulated BAT and promoted iWAT browning, evidenced by increased levels of UCP1, PGC-1α, PPARγ, SIRT1, and PRDM16, genes pivotal for energy metabolism (R. Li, Xu, et al. 2022). Induction of the browning process was *via* a mechanism involving the AMPK/PGC-1α pathway (Cheng et al. 2022). In line with previous research, the findings of Wang, Wang, Cheng, et al. (2023) demonstrated that in db/db mice, beige adipocytes exhibited a marked increase in size accompanied by a reduction in their numbers. However, these alterations were notably mitigated following treatment with FYGL, a natural hyperbranched proteoglycan derived from *Ganoderma lucidum*. Additionally, FYGL stimulated the expression of thermogenesis-related genes, specifically Cd81 and Slc25a4, and enhanced the levels of proteins involved in lipolysis, including adipose triglyceride lipase (ATGL), hormone-sensitivelipase (HSL), and lipoprotein lipase (LPL), through the activation of AMPKα signaling (Y. Wang, Wang, Cheng, et al. 2023). This activation consequently promoted lipid metabolism within mature adipocytes.

p38 MAPK signaling

The p38 mitogen-activated protein kinase (p38 MAPK) pathway is a crucial component of intracellular signaling cascades, serving a pivotal function in various biological processes such as adipocyte differentiation, lipid synthesis, fatty acid oxidative catabolism, insulin signaling, and inflammation (Wen et al. 2024). β_3-AR-mediated p38 MAPK activation triggers the phosphorylation and subsequent activation of numerous transcription factors, among which PPARγ and CCAAT/Enhancer binding protein alpha (C/EBPα) are crucial for the process of brown adipocyte differentiation (M. Leiva et al. 2020). The p38 signaling pathway may modulate the function of brown fat through its impact on the secretion of hormones such as fibroblast growth factor 21 (FGF21) (Ng et al. 2017; Y. Wang, Lundh, et al. 2020). Additionally, the p38 signaling is crucial in mediating the inflammatory

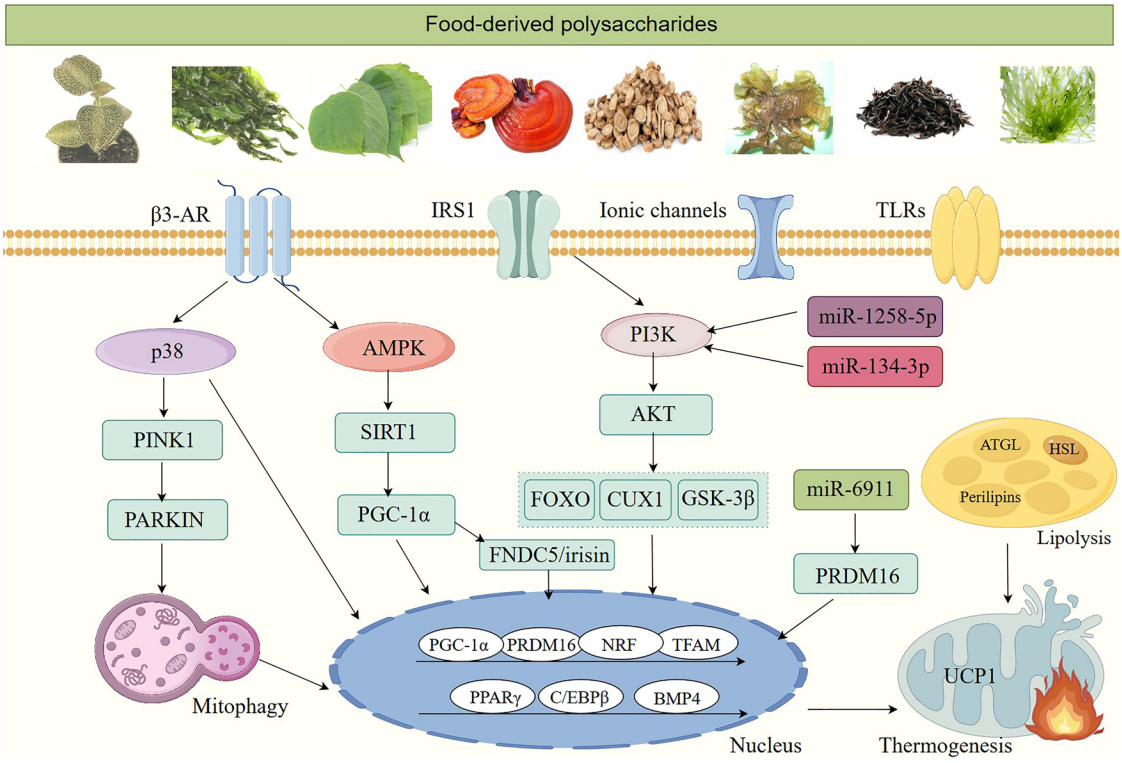

Figure 3. Food-derived polysaccharides exert anti-obesity effects and adipose tissue thermogenesis through multiple cellular mechanisms, including activation of AMPK, p38 MAPK, AKT, PGC-1α-FNDC5/irisin, and miRNA signaling.

response, with the level of inflammation, including monocyte chemoattractant protein-1 (MCP1), tumor necrosis factor (TNFα), C-X-C motif chemokine ligand-14 (CXCL14), and interleukin-6 (IL-6) exerting a substantial effect on BAT thermogenesis (M. Leiva et al. 2020). It has been reported that p38 MAPK activation inhibits PTEN-induced kinase 1 (PINK1)-Parkin RBR E3 ubiquitin protein ligase (PRKN)-mediated mitophagy, thus suppressing beige-to-white reversion (Rahman and Kim 2020). Through the above mechanisms, the p38 signaling is pivotal for the development, thermogenesis, and metabolic regulation of brown fat. It was found that in rats with heart failure (HF), *astragalus* polysaccharide (APS) treatment resulted in increased adipose tissue weight and was effective in preventing adipose atrophy and free fatty acid (FFA) release. Furthermore, the administration of APS led to the suppression of PKA-p38 MAPK signaling pathway. This inhibition was associated with a decline in thermogenic activity, as evidenced by the reduced expression in BAT of UCP1, PPARγ, and PGC-1α. Additionally, a decrease in fatty acid β-oxidation within the mitochondria of BAT was observed, indicated by lower levels of cluster of differentiation 36 (CD36), fatty acid transport protein 1 (Fatp1), and carnitine palmitoyltransferase I (Cpt1) (D. Ma et al. 2023). To conclude, FPs promote brown fat metabolism and thermogenesis through regulation of the p38 signaling pathway and may have significance in regulating energy balance and promoting health. Further studies are needed to clarify the mechanism of action of different types of FPs and their potential in the treatment of metabolic-related diseases.

AKT signaling

AKT (protein kinase B) functions as a critical intracellular signaling factor with a significant role in the regulation of brown fat and the induction of white fat browning (Jeong et al. 2017; Lu et al. 2020). AKT can promote brown adipocyte survival by inhibiting apoptosis through the phosphorylation of multiple apoptosis-associated proteins, such as Bcl-2-associated death promoter (BAD) and Caspase-9 (Ku et al. 2016). Moreover, AKT can phosphorylate and inhibit cell cycle inhibitors such as $p27^{kip1}$, which promotes the proliferation of brown adipocytes (Colon-Mesa et al. 2023). AKT can phosphorylate and activate several transcription factors, such as members of the forkhead box class O proteins (FOXOs) family, which affect the expression of brown adipose-specific genes, including UCP1 and genes related to mitochondrial biosynthesis (e.g., PGC-1α, PTP localized to mitochondrion 1 (PTPMT1)) (Ioannilli, Ciccarone, and Ciriolo 2020). By affecting mitochondrial fusion and fission proteins (e.g., OPA1 and DRP1), AKT regulates mitochondrial morphology and function (Shiau et al. 2022). The insulin signaling cascade involves AKT, which facilitates the movement of glucose transporter 4 (GLUT4) to the cell membrane, thereby enhancing glucose uptake and encouraging fatty acid oxidation. These actions are pivotal in boosting insulin sensitivity and supporting white-to-brown fat conversion (Y.-Y. Yang et al. 2024). Studies have demonstrated that the polysaccharides laminarin and fucoidan can improve obesity caused by HFD along with the accompanying complications related to oxidative stress. This improvement is attributed to their ability to induce thermogenesis by regulating AKT signaling (Sharma and Baskaran 2021). *Sargassum fusiforme* fucoidan reduced fat accumulation and augmented energy expenditure by activating BAT and beiging of iWAT by upregulating PGC-1α, PRDM16, cell death-inducing DFFA-like effector a (Cidea), cytochrome c oxidase (COXIV), and UCP1 *via* activation of AKT signaling (Zuo et al. 2022). To identify that *Taraxacum* polysaccharide (TMP) modulated brown adipogenesis through the AKT/glycogen synthase kinase 3β (GSK-3β) pathway, TMP-stimulated cells were treated with the AKT inhibitor AZD5363. The result showed that TMP-induced upregulation of p-GSK3β and brown adipogenic markers, including PRDM16, UCP1, Cidea, and PGC-1α proteins were abolished upon inhibition of AKT (Yue et al. 2024). In the classical PI3K/AKT signaling pathway, insulin binding to its receptor triggers the phosphorylation of IRS1, subsequently activating PI3K and AKT, and ultimately resulting in the translocation of GLUT4 and the uptake of glucose. Studies have revealed that *astragalus* polysaccharide (APS) enhanced the phosphorylation of insulin receptor substrate 1 (IRS1) and AKT, indicating that APS may promote insulin sensitivity in brown adipocytes. This process is proposed to occur *via* the stimulation of the insulin/AKT signaling pathway (Cao et al. 2021a). Therefore, FPs can facilitate brown fat thermogenesis and enhance their metabolism by activating the AKT signaling pathway. Future studies can further explore and identify various FPs capable of targeting AKT signaling, aiming to uncover their distinct effects on cellular metabolism and potential in treating metabolic disorders.

PGC-1α-FNDC5/irisin signaling

Irisin, a hormone derived from the proteolytic cleavage of the protein FNDC5 (fibronectin type III domain-containing protein 5), acts as a myokine regulated by PGC-1α. It contributes to the positive metabolic effects of physical activity by inducing the expression of UCP1 and facilitating the conversion of WAT into brown-like fat (Mirshafaei, Noori, and Abdi 2023; Pan et al. 2024). The Yam glycoprotein (Y-Gly), a complex consisting of polysaccharides and proteins derived from yams, was found to significantly elevate the expression of FNDC5 protein when present at moderate concentrations. The enhanced expression subsequently led to the activation of proteins involved in the browning of white fat, such as PPARγ and UCP1, thereby promoting energy expenditure (W. Li et al. 2025). Male C57BL/6 mice subjected to either a standard control diet or a high-fat diet (HFD), were supplemented with 5% *Enteromorpha prolifera* polysaccharides (EPP) for 12 wks (Xie et al. 2022). The study revealed that EPP treatment mitigated the diet-induced increase in adiposity, reduced inflammatory markers, and enhanced insulin signaling within the WAT of mice on the HFD. Additionally, it was observed that EPP augmented O_2 consumption, CO_2 output, and (body) temperature in HFD-fed mice, as evidenced by the increased expression of thermogenic genes, including PRDM16, PGC-1α, Cidea, cytochrome *c* (Cyto C),

elongation of very-long-chain fatty acids protein 3 (Elovl3), oxidase subunit VIIa polypeptide 1 (Cox7a1), and UCP1 occurring in both BAT and inguinal WAT. Simultaneously, EPP elevated serum levels of irisin and stimulated the PGC-1α/FNDC5 pathway. These findings support that the inclusion of EPP in the diet can ameliorate insulin signaling and overall energy metabolism in obese mice, potentially through inducting the PGC-1α-FNDC5/irisin pathway.

miRNA signaling

miRNAs (microRNAs) are a class of non-coding RNA molecules about 22 nucleotides in length involved in numerous biological functions through the regulation of gene expression (Iacomino and Siani 2017). In BAT, miRNAs can target and regulate key transcription factors, such as PPARγ, C/EBPα, and C/EBPβ, thereby affecting the differentiation and maturation of brown adipocytes (Y. Xu et al. 2018). Moreover, certain miRNAs (miR-328, miR-378, miR-30b/c, miR-455, miR-32) can target mitochondrial or nuclear genes related to mitochondrial activity, affecting mitochondrial biosynthesis and function, and thus regulating thermogenesis (Shamsi, Zhang, and Tseng 2017). Furthermore, miRNAs can affect energy metabolism in BAT by regulating key enzymes and proteins in metabolic pathways, such as fatty acid oxidation and glucose metabolism. Rather than acting alone, miRNAs usually exist in networks, and multiple miRNAs can synergistically regulate gene expression and function in brown fat (J. Kim et al. 2016; Lorente-Cebrián et al. 2019). Through these mechanisms, miRNAs fulfill a crucial regulatory function in the development, functional maintenance, and metabolic regulation of brown fat. Investigating how miRNAs regulate BAT will help to gain a deeper understanding of the biology of brown adipose and may provide new therapeutic strategies for the treatment of obesity and metabolic diseases. Findings from a prior study revealed that *Astragalus* polysaccharide (APS) facilitates the differentiation of brown adipocytes and enhances insulin sensitivity. This phenomenon was associated with a decrease in miR-6911 expression and a significant increase in the levels of brown adipogenic regulators such as C/EBPα/β and PPARγ, along with thermogenic proteins including UCP1, PRDM16, and PGC-1α. Of particular significance, miR-6911 was found to control brown adipocyte differentiation by targeting the Prdm16 gene. Furthermore, following the transfection of cells with miR-6911 mimics, a significant reduction in PRDM16 protein expression was observed when compared to the control group. This decrease in PRDM16 was paralleled by a concomitant reduction in PPARγ, UCP1, and PGC-1α levels, suggesting that APS modulates brown adipocyte differentiation in $C_3H_{10}T_{1/2}$ cells through downregulating miRNA-6911 (S. Zhang, Jia, et al. 2022). In parallel, the researchers discovered that APS also decreased the expression of miR-1258-5p and promoted brown adipogenic differentiation *via* the CUT-like homeobox 1 (CUX1) pathway. The use of miR-1258-5p mimics or inhibitors significantly affected the expression of CUX1 and mitigated the enhancement of key brown adipogenic markers by APS, such as UCP1, PRDM16, C/EBPβ, PGC1α, and PPARγ. These findings imply that APS could influence brown adipogenesis by regulating CUX1 expression through the action of miR-1258-5p (Cao et al. 2021). The polysaccharide from *Taraxacum mongolicum* (TMP) was observed to stimulate both the proliferation and browning of white adipocytes by upregulating PRDM16, PPARγ, C/EBPβ, and PGC1α in sheep. Furthermore, miR-134-3p was found to play a significant role in suppressing the browning process and the AKT/GSK-3β signaling. Importantly, the role of TMP in promoting the browning of white adipocytes was dependent on the action of miR-134-3p and the AKT/GSK-3β signaling pathway (Yue et al. 2024). Therefore, FPs are important in the activation of brown fat and the regulation of energy metabolism through the modulation of miRNA signaling. Research in this area provides new perspectives for understanding metabolic regulation and may offer new strategies for treating metabolic diseases.

Gut microbiota

The mutual interactions between the host and its microbiota facilitate a two-way exchange of vitamins and FPs, which are crucial in governing the host's ability to acquire and store energy, as well as shaping the composition and variety of the gut microbiota (Moreno-Navarrete and Fernandez-Real 2019). Germ-free mice experience a marked decline in energy intake, accompanied by an enlarged cecum, reduced intestinal villi, and lower inflammation (Moreno-Navarrete and Fernandez-Real 2019). Mestdagh and colleagues conducted research on the impact of a germ-free condition on the body's energy metabolism, observing an elevation in metabolites linked to BAT activity in mice without gut microbiota (Mestdagh et al. 2012). The innovative scientific investigation suggests that the gut microbiota has a significant function in the regulation of BAT activity. Confirming these findings, Li and colleagues showed that the elimination of gut microbiota, either through the use of various antibiotic mixtures (ABX) or in the context of germ-free (GF) mice, resulted in a decline in the UCP1 expression in BAT and WAT (B. Li et al. 2019).

FPs are a key factor that influences the composition and function of gut microbiota. FPs vary widely in structure and complexity, and these differences can lead to distinct interactions with the gut microbiota. One of the primary ways polysaccharides influence the gut microbiota is through their fermentability. Soluble fibers like inulin, fructooligosaccharides (FOS), and galactooligosaccharides are readily fermented by certain bacteria in the gut, such as *Bifidobacteria* and *Lactobacilli* (Altomare et al. 2021). These bacteria produce short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, which serve as important energy sources for colon cells. The type of FPs can determine the profile of SCFAs produced. For example, resistant starches are primarily fermented to butyrate, which is particularly beneficial for colon health. Different FPs can selectively promote the growth of different bacterial species, thereby affecting the diversity and composition of the gut microbiota. For instance, arabinoxylan found in whole grains can increase the abundance of Bacteroides and Firmicutes species, which

are involved in the breakdown of complex carbohydrates (Zhang, Fu, et al. 2024). Pectins and gums, on the other hand, may encourage the growth of bacteria that produce enzymes capable of degrading these polysaccharides, such as *Akkermansia muciniphila* (Zhang, Fu, et al. 2024). Certain FPs have prebiotic effects, meaning they promote the growth of beneficial bacteria. The prebiotic potential of a polysaccharide depends on its chemical structure and the ability of the gut microbiota to degrade it. For example, the degree of polymerization and branching of FOS and inulin can affect their prebiotic activity, with lower degrees of polymerization generally leading to greater fermentation by beneficial bacteria (Zhu et al. 2017). FPs can also influence the immune system through their interactions with the gut microbiota. Sulfated polysaccharides from seaweeds, such as fucoidan and laminarin, have been shown to modulate immune responses by interacting with gut bacteria to produce bioactive metabolites (Zhu et al. 2021). Understanding the effects of different types of FPs on the gut microbiota can lead to personalized nutrition strategies. For instance, individuals with certain metabolic disorders may benefit from a diet rich in specific polysaccharides that promote the growth of beneficial bacteria and support healthy metabolic homeostasis.

Evidence supports that some FPs can act as brown fat activators by remodeling the gut microflora profile. Polysaccharides derived from *Hirsutella sinensis* (HSP) enhanced thermogenesis through the stimulation of UCP1 expression within BAT and inguinal WAT. Furthermore, an analysis of gut microbiota showed that HSP selectively fostered the proliferation of *Parabacteroides goldsteinii*, a beneficial bacterium that is found in lower abundance in mice fed a HFD. *Parabacteroides goldsteinii* significantly increased UCP1 expression in BAT and iWAT, suggesting that HSP-induced thermogenesis is associated with increased *Parabacteroides goldsteinii* (T.-R. Wu et al. 2019). The polysaccharides from *Heimao* tea (HMTP) have been found to promote the browning of iWAT and to boost the thermogenic capacity of BAT through the upregulation of several thermogenic genes, including UCP1, PRDM16, and PGC-1α. Interestingly, the anti-obesity effects of HMTP are closely tied to modifications in the gut microbiota profile, with a striking increase in the populations of *Dubosiella* and *Romboutsia*. The enhanced levels of these bacteria were inversely associated with body weight and showed a positive correlation with the BAT index, suggesting a potential microbial contribution to the tea's beneficial effects against obesity (Y. Wang, Han, et al. 2022). An 8-week treatment with Fu Brick Tea polysaccharides (FBTP) was found to dose-dependently suppress the gain in body weight and the weight of epididymal, retroperitoneal, and iWAT in HFD-induced obese mice, while also promoting beige fat formation and BAT-mediated non-shivering thermogenesis. FBTP was also observed to counteract gut dysbiosis by increasing the population of beneficial bacteria such as *Lactobacillus*, *Parabacteroides*, *Akkermansia*, *Bifidobacterium*, and *Roseburia*. Furthermore, fecal microbiota transplantation (FMT) experiments corroborated that the microbial changes induced by FBTP contributed to the browning of adipose tissue and the enhancement of thermogenesis (Du et al. 2022). Furthermore, the administration of fecal microbiota from *Flammulina velutipes* polysaccharides (FVP)-treated mice counteracted the reduction in expression of UCP1, PRDM16, and PGC-1α caused by HFD (Zhao et al. 2021). This finding offers evidence that the gut microbiota has a direct involvement in the FVP-mediated process of adipose tissue browning. Therefore, regulating the intestinal microflora through the intake of specific FPs, which in turn activates brown fat, may become a new strategy for managing metabolic diseases such as obesity and diabetes.

Intestinal metabolites

The gut microbiota impacts brown fat activity and function through the production of various metabolites (Figure 4). Thus, the interaction between microbiota-derived metabolites and brown fat provides new therapeutic targets for addressing obesity and its associated metabolic conditions.

LPS

Lipopolysaccharide (LPS) is a complex molecule found in the outer membrane of Gram-negative bacteria. This molecule is recognized by the immune system as a foreign invader, leading to the activation of immune cells and the release of inflammatory cytokines. Within the gut, the demise and subsequent lysis of Gram-negative bacteria, such as *Escherichia coli*, lead to the liberation of LPS into the intestinal milieu (Molteni, Gemma, and Rossetti 2016). Once LPS accesses the systemic circulation, it can induce a wide range of diseases. This occurs through its interaction with various receptors, including LPS-binding proteins and toll-like receptors (TLRs), particularly TLR4. The engagement of LPS with these receptors activates the innate immune system, leading to the release of pro-inflammatory cytokines and other immune mediators. Importantly, some inflammatory cytokines produced by macrophages activated by LPS have been shown to inhibit the activation of the UCP1 promoter (Sakamoto et al. 2013). The stimulation of TLR4 by LPS inhibits the process of white adipocyte browning that follows β_3-adrenergic receptor stimulation, leading to an increase in ROS production and the occurrence of mitochondrial dysfunction. In contrast, the genetic elimination of TLR4 was found to defend against mitochondrial dysfunction and maintain thermogenic capabilities (Okla et al. 2018; Omran et al. 2023). Many polysaccharides, including non-starch polysaccharides (e.g., cellulose, inulin, arabinoxylans, glucomannan, β-glucans, pectin, fucoidan, and alginate) and resistant starch can inhibit LPS-producing bacteria (Ho Do, Seo, and Park 2021). The alkali-soluble polysaccharides derived from *Arctium lappa L.* demonstrated an inhibitory effect on LPS by targeting *Proteobacteria*, *Staphylococcus*, and *Bacteroidetes* (Zhang, Hu, et al. 2020). A recent investigation revealed that walnut green husk polysaccharides (WGHP) were effective in combating obesity, chronic inflammation, and the regulation of thermogenesis in BAT in HFD-fed rats. The proposed mechanism suggests that WGHP efficiently addressed the disruptions in gut microbiota caused by the HFD and effectively blocked bacterial endotoxin translocation from the intestine into the

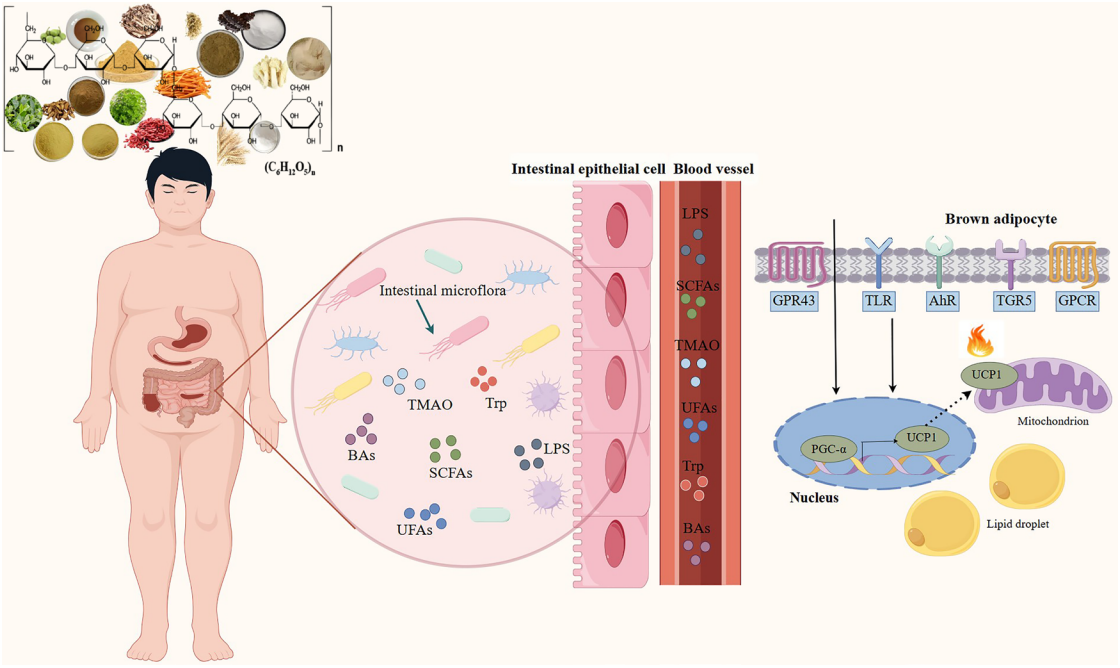

Figure 4. Food-derived polysaccharides achieve adipose tissue thermogenesis by modulating gut microecology, including specific microflora, LPS (targets adipose tissue (AT) TLR4), BAs (targets AT TGR5), SCFAs (targets AT GPR43), UFAs (possibly targets AT GPCR), TMAO (possibly directly on adipocytes) and Trp (targets AT AhR). GPCR, G protein-coupled receptor.

bloodstream. This inhibition contributed to a reduction in systemic inflammation and an increase in the activity of BAT (Wang, Yang, Wang, et al. 2021). Additionally, fucoidans from *Pearsonothuria graeffei* have been found to restore the healthy functioning of WAT in HFD-fed mice by increasing the expression of UCP1, PPARγ, and PGC-1α, achieved by elevating the expression of UCP1, PPARγ, and PGC-1α. This beneficial effect may be mediated by a mechanism that reduces inflammation, potentially by interfering with the TLR4/NF-κB signaling pathway in the colon (S. Li, Xu, et al. 2022). Therefore, FPs may counteract the microbiota disruptions caused by HFD by inhibiting LPS production, a key factor in systemic inflammation. This suppression not only reduces inflammation but also maintains BAT activity, thereby enhancing thermogenesis and potentially contributing to weight management and metabolic health improvements.

SCFAs

SCFAs, including acetic, propionic, and butyric acids, are producted through the metabolic actions of the gut microbiota. Research demonstrates that these SCFAs are instrumental in the regulation of BAT activity. SCFAs can enhance brown fat activity by activating G protein-coupled receptors such as FFAR2 (GPR43) and FFAR3 (GPR41) (Layden et al. 2013). Activation of these receptors promotes fat oxidation, contributing to increased energy metabolism. SCFAs exhibits anti-inflammatory activity, inhibiting the release of pro-inflammatory cytokines and promoting a healthy environment for BAT, thus favoring its function. SCFAs may regulate lipid storage and catabolism by affecting the metabolism of triglycerides and free fatty acids, and consequently BAT function. SCFAs may also enhance brown adipocyte differentiation and activity by regulating several transcription factors related to adipose metabolism (e.g., PPAR). Taken together, SCFAs produced by gut flora regulate brown fat activity, promote energy metabolism, and maintain metabolic health through a variety of mechanisms, which provides new perspectives for understanding the link between gut microbes and host metabolism. Recent studies have revealed that the polysaccharides in *Cordyceps militaris* consist of a structure primarily made up of (1→2)-α-D-Manp and (1→4)-α-D-Glcp linkages, along with β-D-glucan as the main backbone. Due to the inability of pancreatic digestive enzymes to break down β-glucosidic bonds, these non-digestible carbohydrates can pass through the gastrointestinal tract undigested. As a result, they undergo fermentation by the gut microbiota, yielding SCFAs that are profoundly advantageous to the host's well-being (M. Yu et al. 2021). *Artemisia sphaerocephala Krasch* polysaccharide (ASKP) augmented BAT thermogenesis and promoted iWAT browning in HFD-fed mice. This metabolic enhancement was clearly substantiated by the marked increase in the expression of key thermogenic marker genes, specifically UCP1, Cidea, and PGC1α. Notably, the use of antibiotics markedly reduced the ASKP-induced increase in fecal succinate levels, and consequently, eliminated the thermogenic effects of ASKP on adipose tissue (Zeng et al. 2022). Furthermore, Ziyang selenium-enriched green tea polysaccharide (Se-GTP) stimulated BAT thermogenesis and induced the browning of the iWAT in obese mice. This was evidenced by the increased expression of thermogenic marker proteins such as UCP1, PGC-1α, and Cidea in BAT and iWAT. Furthermore, 16S rRNA gene sequencing demonstrated that Se-GTP corrected the imbalance in the gut microbiota of obese mice, which was marked by an enhancement in the growth of probiotics including *Lactobacillus*,

Bifidobacterium, and *Akkermansia*, as well as an increase in the concentration of the thermogenesis-supporting microbial metabolite succinate in the colonic environment (D. Li et al. 2023). Evidence suggests walnut green husk polysaccharides (WGHP) modulated the composition of the gut microbiota and affected the profile of SCFAs. A strong correlation was demonstrated between thermogenic gene expression in BAT and iWAT and isobutyric and isovaleric acid levels (Wang, Yang, Wang, et al. 2021). Collectively, FPs are subject to fermentation by gut microbiota, resulting in the production of SCFAs which are subsequently absorbed by the intestinal epithelial cells, either through passive diffusion or *via* specialized transport proteins, and enter the blood circulation for subsequent action on adipose tissue.

Bile acids (BAs)

Intestinal bacterial flora can influence the conversion of cholesterol to bile acids (BAs) in the host's liver. The microbiota influences BAs production by regulating the expression of certain enzymes, such as cholesterol 7α- hydroxylase (CYP7A1), which is the rate-limiting enzyme in the BAs biosynthetic pathway (Gao et al. 2022). In addition, the gut microbiota can convert primary BAs into secondary BAs. This process includes reactions such as deconjugation (removal of glycine or taurine affixes), 7-dehydroxylation, isomerization, oxidation, desulphurization, and esterification, which increase the diversity of BAs (D. Fang et al. 2023). In addition, certain bacteria in the gut have bile salt hydrolase (BSH) activity that hydrolyzes bound BAs, producing free BAs that are less likely to be absorbed by the gut and facilitating their excretion from the body (Z. Song et al. 2019). BAs act as signaling molecules that can affect the function of brown fat by acting on Takeda G protein-coupled receptor 5 (TGR5) and farnesol X receptor (FXR) (J. Yang, Wu, et al. 2023). Isolated FPs effectively reduced obesity and related disorders in diet-induced obese mice. The administration of a crude polysaccharide derived from *Lyophyllum decastes* (LDP) over a two-month period demonstrated significant improvements in HFD-induced obesity, hyperlipidemia, and inflammatory responses. The beneficial therapeutic outcomes observed with LDP treatment have been linked to alterations in the gut microbiota composition, characterized by increased levels of *Bacteroides intestinalis* and *Lactobacillus johnsonii*, as well as a rise in secondary BAs. One proposed mechanism for the anti-obesity effects of LDP involves an enhanced energy expenditure in BAT, which is attributed to the activation of the TGR5 signaling pathway by secondary BAs (T. Wang, Han, et al. 2022). Treatment with Highland barley β-glucan (HBG) was effective in blocking fat accumulation and stimulating lipolysis in adipose tissue. The therapeutic benefits were related to an increase in energy usage and the transformation of white-into-brown fat. This metabolic regulation is believed to be mediated through the intestinal microbiota-BAs axis via FXR signaling (H. Liu, Sun, et al. 2022). Cordyceps glycosides (CGP) increased the abundance of beneficial gut microbiota, such as *Odoribacter*, *Bifidobacterium* and *Bi. pseudolongum*, which in turn regulated bile acid composition (isoallolithocholic acid, lithocholic acid-3-sulfate, taurohyocholic acid, isoallolithocholic acid and glycohyocholic acid). Stimulating TGR5 in WAT led to an increase in energy expenditure and a decrease in fat accumulation resulting from dietary intake. The findings indicate that CGP can efficiently diminish body weight gain and influence thermogenic activity, as well as altering the expression of genes associated with the browning of white fat by modulating BAs metabolism (Wang et al. 2024). The observations suggest that the positive impacts of FPs on combating obesity may result from their ability to adjust energy expenditure, a process mediated through gut microbiota-regulated BAs metabolism.

Tryptophan (Trp) derivatives

Gut flora metabolizes Trp to produce a variety of biologically active metabolites, such as indole derivatives, kynurenine, and 5-hydroxytryptophan, which can enter the circulation and affect the volume and function of brown fat (Agus, Planchais, and Sokol 2018; Gmoshinski et al. 2021). Indole derivatives can activate the aryl hydrocarbon receptor (AhR), which in turn affects gene expression such as PGC-1α, UCP1, PPARα/γ related to thermogenesis and metabolism in brown adipocytes (Pohjanvirta 2017). Supplementation with *Atractylodes macrocephala* Koidz polysaccharide (AMPs) was shown to improve diet-induced glycolipid metabolism disorders. In rats treated with AMPs, there was an observable change in the composition of the gut microbiota, marked by a higher prevalence of *Lactobacillus* and *Rothia* species. Additionally, there was a notable rise in the levels of various Trp metabolites, including indole-3-propionic acid, indole, tryptamine, and tryptophol. These metabolites are believed to enhance the activation of the intestinal AhR within nuclear compartments, thereby facilitating an improvement in lipid metabolism (He et al. 2023). In addition, treatment with *Cordyceps cicadae* polysaccharides markedly elevated the count of brown fat cells and the levels of indole derivatives, including 5-hydroxyindole-3-acetic acid, which were linked to the presence of gut microbes such as *Bacteroides, Odoribacter*, *Alloprevotella*, *Parabacteroides*, *and Mucispirillum,* in diabetic mice. The indole-based treatment notably ameliorated hyperglycemia, enhanced insulin sensitivity, and boosted the production of glucagon-like peptide-1 (GLP-1), an activator of brown fat, in diabetic mice (Y.-J. Wang, Wang, Cheng, et al. 2023). Histological examination using hematoxylin and eosin (H&E) staining showed that epididymal adipocytes and brown adipocytes in the group fed a high-fat diet (HFD) were of a larger size compared to those in the mice treated with *Dictyophora indusiata* polysaccharides (DIPs) (Yao et al. 2024). Fecal metabolomics analyses revealed that three fractions of DIPs (D4P, D6P, and D8P) all influenced the Trp metabolism pathway (increased levels of phenylpyruvic acid, L-dopa, L-phenylalanine) (Yao et al. 2024), which may be responsible for browning (Haddish and Yun 2022; Norton 2019). Arabinoxylan supplementation was found to enhance the proportion of various gut microbiota species, such as *Prevotellaceae_UCG_00*1, *Lachnospiraceae_NK4A136_group*, *Clostridia_UCG_014*, *Alistipes*, *Bacteroides*, and *Ruminococcus*.

The alteration in gut microbiota composition induced by arabinoxylan contributed to a change in the production of indolelactic acid and indoleacetic acid, which played a role in the reduction of mitochondrial biogenesis and energy metabolism (Lin et al. 2024; Wang, Yang, Wang, et al. 2021). Our study highlights the antiobesity effects of arabinoxylan through the modification of gut microbiota and the production of bioactive metabolites. Current research on how FPs regulate brown fat *via* Trp metabolites is challenging and limited. Although studies have been conducted to explore how polysaccharides affect gut microbial composition, which in turn may influence Trp metabolism and brown fat function, the exact molecular mechanisms are unclear. Future studies need to integrate analyses using multi-omics techniques to gain a comprehensive understanding of the interactions among FPs, gut microbes, Trp metabolites, and brown fat.

Unsaturated fatty acids (UFAs)

Dietary fiber (e.g., non-digestible carbohydrates from fruits, vegetables, and whole grains) is fermented by gut microflora after it reaches the large intestine. During this process, gut bacteria break down dietary fiber into SCFAs simultaneously producing a certain amount of unsaturated fatty acids (UFAs) (Su et al. 2023; H. Yang, Wu, et al. 2023) UFAs, especially long-chain UFAs (LUFAs), can help improve metabolic health by promoting the formation of brown fat and the "browning" of white fat (Beck et al. 2007). Results demonstrated that conjugated linoleic acid (CLA) significantly enhanced the expression of UCP1 by 1.6-fold in BAT and 2.4-fold in iWAT, with implications including the activation of thermogenesis in HFD-fed mice. Additionally, CLA was observed to be capable of fostering the development of both brown and beige adipocytes within differentiated stromal vascular cells that were isolated from BAT and iWAT (F. Zhang, Fu, et al. 2024). 10-oxo-12(Z)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria could upregulate brown fat-related genes (e.g., UCP1) in WAT and enhance energy expenditure by activation of TRPV1 in mice, thereby protecting mice from diet-induced obesity (M. Kim et al. 2017). Studies have shown that ginseng extract, rich in polysaccharides (over 20%), can promote the growth of *Enterococcus faecalis*, an organism capable of synthesizing the LUFA, myristoleic acid (MA). *E. faecalis*, along with its byproduct MA, has the ability to decrease body fat by stimulating BAT and promoting the development of beige fat. Moreover, the gene in *E. faecalis* responsible for encoding Acyl-CoA thioesterases (ACOTs) has been found to possess the capability for MA biosynthesis, as the suppression of the ACOT gene using CRISPR-dCas9 technology notably decreased the production of MA (Quan et al. 2020). FPs promote the beneficial bacteria capable of metabolizing UFAs by altering the composition of the gut microflora. Through bacterial-derived UFAs production, FPs indirectly promote brown fat thermogenesis and energy expenditure, contributing to improved metabolic health. Additional studies are required to confirm the definite relationships between FPs, intestinal microflora, UFAs, and brown fat.

Trimethylamine N-oxide (TMAO)

Recent findings indicate that the synthesis of trimethylamine N-oxide (TMAO), a process initiated by gut bacteria, is linked to obesity and the regulation of energy metabolism. Numerous clinical studies have noted a significant correlation between systemic levels of TMAO and the incidence of type 2 diabetes. Moreover, it has been observed that the concentration of TMAO in the bloodstream is related to obesity traits in the different inbred strains represented in the Hybrid Mouse Diversity Panel. Additionally, the deletion or knockout of the enzyme flavin-containing monooxygenase 3 (FMO3), which is responsible for TMAO production, has been shown to promote the browning of WAT (Schugar et al. 2017). Studies have demonstrated that treating HFD-fed mice with *Lycium barbarum* polysaccharide results in significant alterations to their fecal microbiota and a concomitant reduction in plasma TMAO level (Z. Zhang, Hu, et al. 2020). These observations align with previous research suggesting that FPs could lower TMAO level, and thereby serve as a promising approach for treating obesity *via* microbiome-fat axes (Guo et al. 2021). Additionally, HFD induced weight gain was reduced in rats by *Flos Lonicera* polysaccharides intervention alongside lower epididymal adipose accumulation, mainly through pathways of gut microbiota and choline metabolism (decrease in the level of TMAO) (M. Chen, You, et al. 2018). Although FPs can modulate microbiome-derived TMAO, there is no direct evidence that the browning capacity of FPs is related to fatty acids, and additional experiments need to be demonstrated.

Intestinal hormones

Gut hormones are important signaling molecules that regulate brown fat activity. They are produced primarily by gut endocrine cells and released into the circulation in response to food intake, gut flora activity, and changes in metabolic status. The following are some of the key gut hormones and the mechanisms by which they regulate brown fat.

GLP-1

Glucagon-like peptide-1 (GLP-1) is an intestinal hormone that is released following food intake primarily by intestinal L cells, which are distributed throughout the intestinal tract, particularly in the ileum and colon (Q. Wang, Wang, Cheng, et al. 2023). After release, GLP-1 enters the circulation and is transported through the bloodstream to adipose tissue, where it further binds to the GLP-1 receptor (GLP-1R) on the surface of adipocytes, leading to the inhibition of lipogenesis and thermogenesis in BAT and epididymal WAT (Chen et al. 2017). GLP-1 can activate the sympathetic nervous system, which innervates BAT. Stimulation of the sympathetic nerves leads to the release of norepinephrine, which binds to beta-adrenergic receptors on brown adipocytes (S. Wang, Wang, Cheng, et al. 2023). In addition, GLP-1

promotes the oxidation of fatty acids and glucose, which can provide the necessary energy substrates for thermogenesis (Hropot et al. 2023). By enhancing the metabolic rate, GLP-1 creates an environment that supports the energy demands of heat production. Furthermore, GLP-1's ability to inhibit lipogenesis, the process of fat storage, can also contribute to thermogenesis. By reducing the formation of new fat cells, GLP-1 may increase the availability of fatty acids that can be used as fuel for thermogenesis in BAT (Stafeev et al. 2021). *Lycium barbarum* polysaccharides were found to induce browning of iWAT, energy expenditure, and thermogenic function in a long-term (4 months) treatment. Specifically, elevated levels of *Lachnospiraceae*, *Ruminococcaceae*, and *Bacteroidaceae* (SCFAs-producing bacteria) led to increased levels of SCFAs, which subsequently triggered the release of GLP-1 which acted on iWAT, resulting in increased energy expenditure and enhanced thermogenesis (C. Sun, Su, et al. 2024). Activation of TGR5 by secondary BAs (such as DCA and LCA) triggers GLP-1 secretion and promotes adipose tissue thermogenesis, leading to the improvement of obesity (J. Wu et al. 2021). Studies have shown that the addition of arabinoxylan to the diet leads to an elevation of specific gut bacteria such as *Prevotellaceae_UCG_001*, *Lachnospiraceae_NK4A136_group*, *Alistipes*, *Bacteroides*, *Clostridia_UCG_014*, and *Ruminococcus*. This bacterial enrichment is connected to an increased activity of 7α-dehydroxylation and the synthesis of secondary BAs, including deoxycholic acid and lithocholic acid. Importantly, treatment with deoxycholic acid increases the expression of UCP1 and mitochondrial creatine kinase (CKMT)2 through the secretion of GLP-1, leading to increased thermogenesis in WAT and improved glucose metabolism (Lin et al. 2024). While the connection between FPS, GLP-1, and brown fat activity is promising, it is important to note that the effects can vary based on individual differences in gut microbiota composition, overall diet, and genetic factors. Nevertheless, incorporating foods rich in these polysaccharides into the diet could potentially offer a natural way to boost GLP-1 levels and enhance brown fat activity, which might be beneficial for metabolic health and weight regulation.

PYY

Intestinal hormone Peptide YY (PYY) is acknowledged for its role in the regulation of energy metabolism as well as the maintenance of glucose homeostasis. Additionally, it has been demonstrated that long-term treatment with PYY can lead to a decrease in body weight in models of obesity, including ob/ob mice, obese Zucker rats, and mice with diet-induced obesity (Pittner et al. 2004). Recent studies have shown that PYY, in addition to affecting appetite, can activate brown fat, which affects energy metabolism. Mice with a transgenic expression of PYY exhibited resistance to obesity induced by diet, a phenomenon linked to an elevated body temperature (a sign of enhanced thermogenesis) and a constant expression of thyrotropin-releasing hormone in the paraventricular nucleus of the hypothalamus (Boey et al. 2008). Increased plasma PYY level was observed in healthy adults following supplementation with the functional fiber PolyGlycopleX (Reimer et al. 2010). Furthermore, dietary-resistant starch decreased body fat associated with increased plasma PYY level (Shen et al. 2009), which is consistent with a previous publication (Zhou et al. 2008). Although polysaccharides can influence PYY secretion, there is currently no direct evidence available that FPs modulate BAT through PYY as a specific mechanism. To clarify the link between polysaccharides, PYY, and brown fat, future studies are to suppress PYY secretion through inhibitors or gene editing techniques and monitoring the response of FPs to brown fat after ingestion.

FGF15

Fibroblast Growth Factor 15 (FGF15) is a hormone synthesized in ileal enterocytes and released into the bloodstream, where it fulfills a crucial function in regulating biological processes such as energy metabolism, thermogenic adaptation, and lipid metabolism (Morón-Ros et al. 2021). FGF15 was identified as an intestinal FXR/TGR5-regulated hormone (Gadaleta and Moschetta 2019). Recently, it has been found that FGF15 is associated with the regulation of brown fat. The gut-specific deletion of FGF15 leads to an increased BAs pool in the body due to the decreased feedback inhibition of BA synthesis mediated by FGF15. Increased BAs in the intestine likely remodel the gut microbiota, and thus the conversion of secondary BAs from primary BAs. Increased systemic circulation of secondary BAs, such as deoxycholic acid (DCA) and aurine-conjugated deoxycholic acid (TDCA), may act as endogenous TGR5 agonists to induce the expression of thermogenesis-related genes (e.g., CD36, UCP1, adipocyte protein 2 (aP2), T-Box Transcription factor 1 (TBX1)) in BAT, which thereby improves insulin sensitivity, energy expenditure, and ultimately body weight loss (Chow et al. 2024). Evidence suggests *Lysimachia christinae* polysaccharide treatment could inhibit the expression of FXR and its downstream signaling protein FGF15 to relieve hyperlipidemia (Y.-F. Zhou, Chen, et al. 2023). Moreover, the polysaccharide from *Morinda citrifolia* fruit was observed to stimulate the intestinal expression of FXR-FGF15 and to augment both lipid oxidation and energy digestion within the body, resulting in weight reduction (Mo et al. 2023). However, no direct evidence has been shown that FPs regulate brown fat *via* FGF15. The link between FGF15, a hormone that plays an important role in metabolic regulation, and brown fat and how FPs may affect this pathway still requires further studies to elucidate. In addition, further investigation of the metabolic pathways of different types of FPs *in vivo* and how they affect the production and secretion of FGF15 is required. Furthermore, conducting experiments using brown preadipocyte cell lines to observe the effects of FPs or their metabolites as well as FGF15 on the differentiation and function of brown adipocytes will provide new strategies for the prevention and treatment of metabolic diseases by FPs.

Discussion and perspectives

With the increasing incidence of metabolic diseases worldwide, the study of brown fat activation by FPs has become a highly promising field. The role of FPs, as naturally occurring bioactive substances in food, in activating brown fat,

regulating energy metabolism, and improving metabolic health provides new strategies for metabolic disease prevention and treatment. Future research will focus on the following areas. Investigation of the bioactivity of different FPs and determining their specific effects on brown adipocytes. Currently, much remains unknown about the mechanism of action of FPs and brown fat and future studies need to delve into how different types of FPs activate brown fat by specific signaling pathways or metabolic pathways Researchers need to focus on the effects of different polysaccharides on gene expression profiles in adipose tissue using gene editing techniques (e.g., CRISPR/Cas9) to reveal their specific mechanisms. It is also important to explore the signaling pathways through which polysaccharides activate brown fat, includingthe β_3-adrenergic pathway, insulin signaling pathway, AMPK signaling pathway, etc. The study of the relationship between the structure of FPs and their bioactivities is also valuable in guiding the screening and modification of polysaccharides more effectively. In addition, it is pivotal to screen FPs with efficient brown fat activation functions from various food resources as well as to improve their bioactivity through modification of polysaccharide structure to make them more suitable for human application. FPs have become an important component of functional foods due to their good biocompatibility and diverse physiological functions. Based on the understanding of the mechanism of brown fat activation by FPs, a series of functional foods and nutraceuticals enriched with specific polysaccharides can be developed to help people control body weight, and prevent and improve metabolic diseases. However, they may also exert some side effects on the body. First, excessive intake of FPs may lead to gastrointestinal disturbances such as bloating, diarrhea, or constipation. Second, the activation of brown fat by polysaccharides may be accompanied by an increase in energy expenditure, which may lead to fatigue, hypoglycemia, or excessive weight loss if energy intake is insufficient, especially in malnourished or metabolically disturbed individuals. Finally, prolonged high intake of certain polysaccharides may also interfere with nutrient absorption, such as affecting the utilization of fat-soluble vitamins or minerals. Therefore, FPs need to be ingested with caution, avoiding excessive intake and taking into account individual differences to minimize potential side effects.

In addition to FPs, the activity of brown fat can be modulated by other nutrients. Therefore, future investigations could explore the combined use of FPs with other ingredients (e.g., polyphenols, alkaloids) to achieve better activation of brown fat. For example, the effect of combining FPs with moderate exercise, a healthy diet, or other metabolic-modulating drugs could be investigated to find the optimal intervention program. This diverse intervention strategy is expected to play a more significant role in combating obesity and related metabolic diseases. Although preliminary studies have shown that some FPs can activate brown fat, most of the studies are still at the basic research stage. Researchers need to conduct more clinical trials to validate and evaluate the safety and efficacy of FPs in activating brown fat in humans. Through rigorous clinical studies, scientists can better understand the biological effects of FPs and lay the foundation for applying these findings to clinical practice. In addition, evaluating the effects of FPs on long-term health and their interactions with genetics, lifestyle, and other factors will also be an important direction for future research. With the development of precision medicine and personalized nutrition, research on FPs will focus more on individual differences. Because the metabolic ability and response to nutrients may vary among individuals, personalized nutritional intervention programs can be developed through genomics, metabolomics, and other technologies. By analyzing the genomic and metabolic profiles of individuals, their response to FPs can be accurately assessed, leading to the development of more effective dietary regimens to activate brown fat, improve metabolic efficiency, and promote health. The field of brown fat activation by FPs holds great promise for future research and the development of functional foods alongside implementation of personalized nutrition to improve metabolic health.

Authors' contribution

Zhenyu Wang: Writing-review & editing, Conceptualization, Investigation, Funding acquisition, Resources. Qiyu Xu: Writing-original draft, Data curation, Formal analysis. Lijuan Hou: Formal analysis, Validation. Zhiyong He: Formal analysis, Validation. Mark Christian: Writing-review & editing. Xianjun Dai: Writing-review & editing, Project administration, Funding acquisition.

Disclosure statement

No potential conflicts of interest were reported by the author(s).

Funding

The authors acknowledge financial support from the Zhejiang Provincial Natural Science Foundation of China (No. LQN25C200002), the National Key Research and Development Program of China (No. 2024YFF1106203), the Science and Technology Development Project in Zhejiang, China (No. 2022C01030), and the Project of Inovation and Entrepreneurship Training for National Undergraduates (No. 202310356045).

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