

**Promotion of White Fat Browning by Food-Derived Bioactive Compounds and
Adipose Tissue-Specific Targeting Strategies**

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Abstract

Background

Obesity has become an important contributing factor to diseases such as diabetes and endocrine disorders. With the in-depth study of adipose tissue, beige adipocytes which are similar in morphology and function to brown adipocytes have attracted considerable attention. These cells can be transformed from white adipocytes in response to browning agent stimuli, offering new insights into obesity therapy.

Scope and Approach

In this review, the mechanism of food-derived bioactives to promote the formation of beige fat is briefly introduced. Furthermore, the delivery carriers of food-derived agents targeting white adipose tissue (WAT) to enhance its browning are elucidated.

Key findings and conclusions

Various food-derived bioactives have been found to induce beige adipogenesis to promote energy consumption. However, the administration of these stimulants may exhibit low bioavailability and adverse actions on non-target tissues such as the heart and the central nervous system, thus restricting their application in obesity management. Constructing a browning agent delivery system targeting WAT will improve their bioavailability and stability, as well as enhance browning ability. Collectively, the development and application of delivery systems for food bioactive targeting white fat is an important strategy to achieve appreciable weight loss with minimal side effects.

Keywords: Food-derived bioactive; Targeted delivery; Obesity; Beige fat

1. Introduction

The obesity epidemic represents a global public health challenge, with excessive energy intake and insufficient physical activity fuelling its worldwide prevalence. China has the largest number of people living with overweight and obesity (402 million) in the world. This is followed by India and the United States, with 180 million and 172 million people living with overweight and obesity, respectively (Ng et al., 2025). It is expected that by 2050, 627 million adults in China will be living with overweight and obesity (Ng et al., 2025). The occurrence of obesity increases the risk of associated metabolic diseases such as hyperglycemia, insulin resistance, type 2 diabetes, hyperlipidemia, hypertension, and cardiovascular diseases. Currently, the approved anti-obesity drugs on the market primarily achieve weight loss through four main mechanisms: 1) Acting on the intestine to inhibit fat digestion and reduce fat absorption. The representative drug is orlistat, which prevents the breakdown of triglycerides into fatty acids and their absorption in the intestine by inhibiting gastric and pancreatic lipases. However, it can cause adverse drug reactions such as diarrhea and oily stools, making long-term use difficult; 2) Acting on the central nervous system to suppress appetite and increase satiety. Representative drugs like phentermine and the controlled-release capsule Qsymia (phentermine and topiramate extended-release) induce the release of norepinephrine in the central nervous system, suppressing appetite. However, norepinephrine also has the effects of enhancing myocardial contractility and accelerating heart rate, making these drugs unsuitable for patients with cardiovascular diseases, hyperthyroidism, or anxiety disorders; 3) Promoting energy expenditure *via*

the neuron. The representative drug Contrave stimulates the pro-opiomelanocortin (POMC) neurons in the hypothalamus to reduce food intake and increase energy expenditure. However, this drug causes side effects such as nausea, headache, constipation, and dizziness (Hausenloy & Disorders, 2009). 4) Inhibiting gastrointestinal emptying. Liraglutide and semaglutide are two glucagon-like peptide-1 (GLP-1) receptor agonists with anti-obesity activity attributed to their ability to delay gastric emptying and appetite suppression. However, in addition to the gastrointestinal side effects, it increases the risk of pancreatitis and increases the heart rate (Sibuyi, et al., 2019). The adverse effects of currently available anti-obesity drugs not only limit their duration of use and applicable population but also increase the risk of developing other diseases. Therefore, there is an urgent need to develop new anti-obesity products to make treatment safer and more effective.

Adipose tissue morphology and function play a key role in the development of obesity, and it can be classified as white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue (BeAT) (Hu, Wang, Tan, & Christian, 2020). WAT mainly stores energy in the form of triglycerides, and its excessive accumulation is a major cause of obesity, while BAT consumes energy by burning fatty acids, glucose, and other substances to maintain body homeostasis. Importantly, it was found that WAT can form a type of fat called beige or brite fat under certain stimuli, which has similar activity to BAT, and has received extensive attention from researchers. Currently, although numerous agents (e.g., GLP-1 agonism, Sildenafil) that can induce the browning of WAT have been reported in the literature and investigated in clinical

81 studies (W. Zhang, Sheng, Gu, & Zhang, 2021), they not only act on adipose tissue but
82 also affect the development or function of other organs or systems, limiting their further
83 application.

84 Naturally occurring compounds hold a special interest due to their better
85 acceptability than pharmacological drugs and invasive procedures of obesity and
86 metabolic disorders. Emerging evidence suggests that some food-derived nutrients,
87 polyphenols, flavonoids, alkaloids, and terpenoids in particular, may be promising
88 candidates for adipose browning. Unfortunately, these bioactive compounds and their
89 metabolites have low bioavailability, meaning that only a small percentage of the
90 consumed compound is available to exert its effects and limiting their bioefficacy in
91 animals and humans (Y. Zu et al., 2021). For example, resveratrol, the most widely
92 studied nonflavonoid polyphenol, has shown many metabolic benefits in in vitro and in
93 vivo preclinical studies, but the low bioavailability of resveratrol and its metabolites
94 limits their applications in humans (Luca et al., 2020). Additionally, some substances,
95 when used directly, may cause off-target effects or even lead to kidney or liver toxicity,
96 limiting the use of many active substances. Capsaicin can cause side effects such as
97 gastrointestinal discomfort, heartburn, or allergic reactions in some individuals.
98 Silibinin and its effectiveness in increasing energy expenditure has been inconclusive
99 in clinical studies, and potential cardiovascular side effects limit its use (Barbagallo et
100 al., 2015).

101 To address these drawbacks, adopting an approach that directly targets delivery to
102 adipose tissue can achieve weight loss by increasing energy expenditure while reducing

damage to other tissues. Targeted therapy typically refers to designing pharmaceuticals at the cellular and molecular level that specifically target known disease-causing sites. The pharmaceuticals exert their effects by specifically binding to a particular site, effectively alleviating the disease without affecting other tissues. An increasing number of studies have focused on applying targeted delivery systems for dietary bioactive substances in precision nutrition. The manufacture of personalized precision nutrition foods based on this concept is one of the important future directions for food research. By constructing a stable targeted delivery system, bioactive substances that promote fat browning can be directly delivered and released in a controlled manner to adipose tissue, which is of great significance for improving the utilization rate of active substances. Therefore, this review summarizes the cutting-edge research on the targeted delivery of dietary bioactive substances to induce beige adipogenesis and prevent obesity, to provide a theoretical basis for their development and application.

2. BeAT

The major function of WAT is energy storage, whereas BAT generates heat by burning fat. BeAT is a distinct type of fat tissue that has gained significant attention due to its potential therapeutic implications for metabolic disorders. Research indicates that beige adipocytes may have a separate lineage from white adipocytes, originating from distinct precursors (Sidossis & Kajimura, 2015; Vargas-Castillo et al., 2024). In terms of function, beige adipocytes are particularly interesting due to their ability to utilize both UCP1-dependent and UCP1-independent thermogenesis (Wang, Sharma et al., 2024; Wang, Tsuji et al., 2024). The UCP1-dependent pathway involves the production

of heat through the action of UCP1 in the mitochondria, which is a well-documented mechanism. However, the UCP1-independent thermogenesis represents a less conventional route, which may involve other proteins or metabolic processes that contribute to heat generation. The amount and activity of BeAT can be increased by a variety of interventions such as cold exposure, exercise, or pharmacological agents (Hu, Wang, Tan, & Christian, 2020). Preclinical studies demonstrate that promoting the browning of iWAT (inguinal WAT) can lead to improved glucose homeostasis, insulin sensitivity, and lipid profiles, as well as reduced body weight and adiposity (Z. Wang, Zeng et al., 2023). However, it should be emphasized that the therapeutic potential of BeAT in humans is still under investigation, and further research is needed to fully understand its regulation, function, and long-term metabolic effects. Its ability to dissipate energy as heat and potential impact on metabolic health make it an attractive target for therapeutic interventions aimed at combating obesity and related metabolic disorders.

3. Food-derived stimulants in the regulation of BeAT formation

A variety of dietary bioactive substances have been demonstrated to possess the ability to induce beige adipogenesis, thereby increasing the overall thermogenic capacity of adipose tissue. The associated molecular mechanisms are shown in Table 1.

3.1. Polyphenols

Polyphenols are a broad category of naturally occurring organic compounds, which can be classified into several major groups, with flavonoids, phenolic acids, stilbenes, and lignans being among the most significant, playing crucial roles in human

health when consumed through diet. They have gained significant attention for their potential to induce browning of WAT. Various studies using cell culture models, animal models, and human clinical trials have demonstrated the ability of polyphenols to activate fat browning. This process involves multiple mechanisms as follows: 1) Upregulation of browning-related genes. Phenolic acids, such as caffeic acid, chlorogenic acid, and gallic acid, can upregulate the expression of key browning-related genes in white adipocytes. These genes include UCP1, PR domain-containing 16 (PRDM16), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α). Increased expression of these genes facilitates the acquisition of a brown or beige adipocyte phenotype (Hu, Wang, Tan, & Christian, 2020). 2) Activation of browning signaling pathways. Polyphenols can activate signaling pathways that promote browning, such as the β_3 -AR, PKA, AMPK (AMP-activated protein kinase), and p38 MAPK pathways (Hu et al., 2020). For example, Kim, Chung, & Song (2019) demonstrated that resveratrol leads to the activation of the β_3 -AR/p38 MAPK pathway, and thereby promotes the expression of BeAT-related proteins such as PGC-1 α and UCP1. Additionally, polyphenols can modulate the activity of transcription factors such as PPAR γ (peroxisome proliferator-activated receptor gamma), which is a master regulator of adipogenesis and browning. For example, resveratrol and quercetin treatment activated the browning program in visceral WAT through a PPAR γ -mediated pathway (Castrejón-Tellez et al., 2016). 3) Modulation of adipokine secretion. Polyphenols can modulate the secretion of adipokines, such as adiponectin and leptin, which play crucial roles in regulating energy homeostasis and metabolic processes

(Kim, Chung, & Song, 2019). By altering the adipokine profile, polyphenols may contribute to the browning of WAT and improve metabolic health. 4) Regulation of lipid metabolism. Some polyphenols can promote lipolysis and reduce lipid accumulation. This can contribute to the remodeling of white adipocytes and facilitate their conversion into beige adipocytes (Barbagallo et al., 2015). 5) Antioxidant and anti-inflammatory effects. Polyphenols promote WAT browning in association with their antioxidant and anti-inflammatory properties. Oxidative stress and inflammation can impair adipocyte function and browning, and polyphenols may counteract these effects, creating a more favorable environment for browning (Z. Wang, Zeng et al., 2023). However, it is important to note that the specific mechanisms and potency of different polyphenols may vary, and further research is needed to fully understand their therapeutic potential and translational applications for combating obesity and metabolic disorders.

3.2. Alkaloids

Alkaloids are a class of nitrogenous, alkaline organic compounds widely found in plant foods. They have a wide range of pharmacological activities, including beneficial regulatory effects on metabolism and energy balance. Recent research has shown that certain alkaloids (capsaicin, berberine, theobromine, and caffeine) can stimulate the browning of WAT, enhancing energy expenditure and potentially contributing to the management of obesity and metabolic syndrome (Table 1). Mechanisms of action include 1) Activation of the TRPV1 pathway. Specific alkaloids (e.g., capsaicin, hydroxy- α -sanshool) exert their browning effects by activating TRPV1, a key marker of thermogenic adipocyte precursor cells (Shamsi et al., 2021). 2) Modulation of the

production of irisin. Caffeine stimulates the expression of FNDC5 by upregulating the expression of PGC-1 α through the activation of calcium channels and ultimately induces irisin production, which in turn triggers WAT browning (C. Liu et al., 2023). 3) Activation of Sirt1/AMPK signaling. Bouchardatine (50 mg/kg) was found to significantly alleviate HFD-induced weight gain and dyslipidemia by enhancing the energy expenditure of adipose tissue *via* the SIRT1-LKB1-AMPK axis (Rao et al., 2017). 4) Interactions with the adrenergic system. Browning of adipose tissue is also modulated by the sympathetic nervous system through adrenergic receptors. For example, Fuziline can function as a β_3 -AR agonist, which in turn activates the downstream cAMP-PKA signaling pathway and leads to an increase in liver glycogenolysis and triglyceride hydrolysis, accompanied by enhancing mitochondrial energy metabolism (H. Gao et al., 2023). In summary, alkaloids represent a promising category of natural compounds that can stimulate the conversion of WAT into brown-like adipose tissue, offering potential therapeutic avenues for combating obesity and enhancing metabolic health. The mechanisms behind their effects involve the modulation of key signaling pathways and transcription factors involved in energy metabolism and adipocyte function. Further investigation is warranted to fully appreciate the potential of alkaloids in this context and to translate these findings into therapeutic strategies.

3.3. Terpenoids

Terpenoids are a category of compounds derived from mevalonate dihydroxy acids with a basic carbon framework mostly characterized by the structure of two or more

isoprene units (C5 units). Several terpenoids have been implicated in the regulation of beige adipogenesis. Ginsenosides (Rb1, Rg1, Rb2, and Rg3), a group of triterpenoid saponins found in ginseng, have been shown to promote beige adipogenesis by modulating various signaling pathways, including PPAR γ , AMPK, and cAMP signaling (Pu et al., 2022). These pathways play crucial roles in the regulation of beige adipocyte formation and function. For example, ursolic acid, a triterpenoid found in various food plants, has been reported to induce UCP1 expression and enhance mitochondrial biogenesis in beige adipocytes by activating the PGC-1 α -FNDC5-irisin pathway (Sun et al., 2021). Furthermore, celastrol (1 μ g/kg) injected intraperitoneally for 12 consecutive weeks promoted WAT browning in HFD-fed mice by modulating the sympathetic nervous system (SNS)-Adrb3 axis (B. Wang et al., 2021), which is involved in the regulation of energy expenditure and obesity. Collectively, triterpenoids can promote the transformation of white to brown adipocytes, thereby increasing energy expenditure, which has potential applications against obesity and related metabolic diseases. In the future, 1) The mechanism of action of triterpenoids needs to be explored in depth, including how they affect adipocyte differentiation and function at the molecular level. This will help to understand their bioactivities and drive application development. 2) Investigating the effects of additional triterpenoids on adipose tissue using animal models to provide supporting data for subsequent clinical intervention studies. 3) Identification of triterpenoid content and biological activities in different plants, screening bioactive compounds with stronger browning characteristics, and developing them into nutraceuticals or functional foods. 4) Combine triterpenoids

with other approaches that regulate fat metabolism (e.g., exercise, diet, etc.) to explore synergistic effects and improve browning. 5) Develop individualized nutritional protocols based on the genomic and metabolic profiles of individuals, using triterpenoids to target interventions in specific populations.

3.4. Polysaccharides

Polysaccharides are long chains of carbohydrate molecules found in various plant sources. These carbohydrates have been studied for their potential to influence beige adipogenesis and adipose tissue browning. For example, fucoidan and laminarin are sulfated polysaccharides extracted from brown algae, which facilitate beige adipogenesis through activation of the p38 MAPK pathway and up-regulation of the expression of browning markers, such as UCP1 and PGC-1 α , and promote mitochondrial biogenesis to increase energy expenditure (Sharma & Baskaran, 2021). Fucoidan, a storage polysaccharide extracted from *Sargassum fusiforme*, can also modulate the gut microbiota profiles, which indirectly influences non-shivering thermogenesis in WAT (Zuo et al., 2022). Important aspects of the polysaccharide regulatory process include: 1) Polysaccharides as prebiotics. Indigestible polysaccharides become an important source of nutrients for the intestinal flora as they enter the colon. These polysaccharides are fermented by specific gut bacteria to produce short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate. SCFAs can act on adipocytes by activating G protein-coupled receptors (e.g., GPR41 and GPR43), which promote UCP1 expression (Lu et al., 2016). 2) Regulation of gut microbiome composition. By providing specific nutritional support, polysaccharides can optimize

gut microecological balance and increase the population of bacteria (*Akkermansia muciniphila*, *Bacteroides* spp., *Bifidobacterium* spp., *Prevotella* spp., *Ruminococcus* spp., *Blautia hydrogenotrophic*, *Clostridium* spp., and *Streptococcus* spp.) that produce SCFAs that favor fat browning, such as some of those belonging to the Firmicutes and Bacteroidetes (Murugesan et al., 2018). 3) Activation of the gut-brain-fat axis. SCFAs and altered gut microecology may also affect the brain *via* pathways such as the vagus nerve, which in turn regulates the metabolic state of adipose tissue and promotes fat browning through hormonal and neural signaling (Li et al., 2018). In addition, SCFAs stimulate intestinal L cells to release hormones, such as GLP-1, which are important for maintaining energy balance and regulating adipose tissue function (Li et al., 2018). However, additional investigation is needed on how polysaccharides regulate the browning of WAT through cell signaling pathways, transcription factors, and metabolic pathways, including interactions with hormones (e.g. adrenaline, GLP-1, etc.) and metabolites (SCFAs, etc.). Furthermore, investigation of the effects of polysaccharides from different sources (e.g., plant polysaccharides, marine polysaccharides, etc.) is required to identify the most effective and safe candidates. Exploration of the effects of different doses and combinations of polysaccharides on the browning of white fat is required to determine the optimal regimen of use.

3.5. Organosulfur compounds

Organosulfur compounds are sulfur-containing organic molecules found in various plant sources, particularly in the *Allium* genus (e.g., garlic, onions). Some organosulfur compounds have been investigated for their potential to promote beige adipogenesis.

For example, diallyl disulfide, an organosulfur compound found in garlic, induces beige adipogenesis by activating the AMPK pathway and upregulating the expression of browning markers like UCP1 and PGC-1 α . It can also enhance mitochondrial biogenesis and increase energy expenditure in beige adipocytes (Lee, Kim, Kim, & Kim, 2011). Ranaweera et al. (2022) investigated the anti-obesity effect of sulforaphane (SFN) and glucoraphanin (GRN) in broccoli leaf extract (BLE) on 3T3-L1 adipocytes and ob/ob mice and found that SFN and GRN significantly increased the expression of beige adipose-specific markers (CD137, PRDM16, UCP1) by activating SIRT1, p38 MAPK, and β_3 -AR signaling pathways. Although these organosulfur compounds have shown promising effects in promoting beige adipogenesis in various cellular and animal models, additional investigations are required to understand their mechanism of action, potential therapeutic applications, and safety in humans.

3.6. Carotenoids

Carotenoids, a class of natural pigments found predominantly in plants, are pivotal in human health, owing to their potent antioxidant properties and role in preventing certain chronic diseases. Among the intriguing beneficial effects of carotenoids is their capacity to induce the browning of WAT. The molecular mechanisms underlying this are complex and involve various signaling pathways and regulatory factors: 1) Activation of β_3 -AR/p38/SIRT signaling. Studies have found that beta-carotene, a vitamin A agent, is a well-known carotenoid that stimulates the β_3 -AR and p38 MAPK signaling pathways and their downstream signaling molecules (SIRT1 and ATF2), thereby increasing the expression of mitochondrial biomarkers (e.g., COX4, CYT-C,

and p53) and inducing fat browning (e.g., UCP1, PRDM16, PGC-1 α) (Mukherjee & Yun, 2022). 2) Regulation of PPARs. Astaxanthin, a xanthophyll carotenoid that acts as a PPAR γ antagonist ligand, significantly upregulated the expression of UCP1 and beige adipocyte marker genes (PPAR γ and PGC-1 α) in inguinal WAT compared to the non-astaxanthin-treated group (Nawaz et al., 2021). 3) Activation of AMPK. Carotenoids have been reported to activate AMPK, thereby contributing to the browning process and improvement of insulin sensitivity (Ferreira, Jamar, Estadella, & Pisani, 2023). 4) Induction of FGF21. Evodiamine-containing microalga *Dunaliella tertiolecta* administration may stimulate FGF21 induction in BAT and thereby bolster the FGF21 autocrine/paracrine mechanism-mediated brown fat formation (Yamashita et al., 2020). 5) Retinoic acid receptor (RAR) pathway. *In vivo* assays showed that the Ucp1 mRNA expression in adipocytes was higher in the β -cryptoxanthin treatment group, an effect that disappeared upon cotreatment with an antagonist, suggesting the induction of browning *via* the RAR pathway (Hara et al., 2019). In conclusion, carotenoids demonstrate a significant potential in modulating adipose tissue function, and composition, notably through the promotion of WAT browning, which underscores their potential as natural bioactive compounds in the management of obesity and metabolic syndrome. However, human studies are needed to fully understand the efficacy and the mechanism of carotenoids in adipose tissue browning and their implications for metabolic health.

3.7. Omega-3 Fatty Acids

Omega-3 fatty acids, especially eicosapentaenoic acid (EPA), and

docosahexaenoic acid (DHA) found in high concentrations in fish oils and certain plant oils, are polyunsaturated fatty acids (PUFAs) recognized for their beneficial effects on cardiovascular health, inflammation, and metabolism (Shahidi, Ambigaipalan, & technology, 2018). Studies in cultured adipocytes, animal and human models have demonstrated that supplementation with Omega-3 fatty acids influences the differentiation of adipocytes by promoting the development of beige adipocytes within WAT (Fernández-Galilea et al., 2020; Kalupahana, Goonapienuwala, & Moustaid-Moussa, 2020). Alpha-linolenic acid-biofortified butter is considered as a novel source of n-3 PUFA, which potentiates mitochondrial biogenesis and thermogenic function (You et al. 2020). Recently, several fatty acid metabolites have been identified as novel thermogenic regulators in BAT and beige adipocytes, including PGI₂, PGE₂, PGF₂ α , 12,13-DiHOME, 9-HODE, and 13-HODE (Fernández-Galilea et al., 2020). The enrichment of cell membranes with omega-3 fatty acids changes the composition of lipid rafts, affecting membrane fluidity and the activity of membrane-bound receptors and signaling molecules (e.g., GPR120 activation, FGF21 production, AMPK-SIRT1-PGC1 α signaling activation, or inhibition of PGF₂ production) (Fernández-Galilea et al., 2020). These alterations can influence adipocyte metabolism towards increased thermogenesis and fatty acid oxidation. The above findings suggest that PUFAs and their metabolites are pleiotropic modulators of multiple pathways involved in the regulation of brown/beige adipocyte activation and could be used as a dietary strategy to combat obesity and metabolic disorders by increasing energy expenditure. However, translating these findings into human applications requires further investigation. Future

research should aim to elucidate the optimal types and doses of omega-3 fatty acids for promoting WAT browning in humans, understand individual variability in response to supplementation, and assess the long-term health outcomes of such dietary interventions.

Taken together, flavonoids, polyphenols, alkaloids, terpenoids, polysaccharides, organosulfides, and other food-derived active substances can activate SIRT1, p38 MAPK, β 3-AR, AMPK, PKA, and other signaling pathways, upregulate the expression level of browning markers and mitochondrial biosynthesis, and increase energy consumption, thereby alleviating obesity.

4. Targeted delivery vehicle for browning of WAT

The induction of WAT browning by natural products offers a promising approach to treating obesity and related metabolic diseases. However, most of the reported bioactive factors that promote the production of beige fat have the disadvantages of low bioavailability and poor water solubility, and the direct use of some substances may have off-target effects or even lead to renal or hepatic toxicity, which limits their use. For example, berberine can induce WAT browning, but in excess can damage the mucosa of the gastrointestinal tract and affect kidney function (C. Chen, Yu, Li, Fichna, & Storr, 2014). Therefore, by constructing a steady-state targeted delivery system, the active substances promoting fat browning can be directly applied to adipose tissue and with controlled release, improve efficiency and localised action (Table 2).

4.1. Passive targeting

Passive targeting refers to the preferential accumulation of drug delivery systems

in target tissues or cells due to their unique pathophysiological characteristics, without the involvement of specific targeting ligands (Amin, Seynhaeve, Sharifi, Falahati, & Ten Hagen, 2022). In the context of WAT browning, passive targeting exploits the enhanced permeability and retention (EPR) effect observed in adipose tissue during obesity. The EPR effect in adipose tissue is primarily attributed to the following factors:

- 1) Increased vascular permeability. Obesity causes chronic low-grade inflammation in adipose tissue, which induces the production of inflammatory mediators such as vascular endothelial growth factor, $\text{TNF}\alpha$, and IL-6. These factors can disrupt the endothelial barrier and increase vascular permeability, allowing nanoparticles (NPs) or macromolecular drugs to extravasate from the bloodstream into the adipose tissue more readily. Hossen et al. (2012) found that fluorescently labeled carriers with unmodified ligand peptides also showed fluorescence signals in adipose tissue vessels, and hypothesized that there is an enhanced EPR similar to that of tumor tissues that allows carriers to passively accumulate in the peripheral blood vessels of adipose tissue.
- 2) Impaired lymphatic drainage. The rapid expansion of adipose tissue during obesity can compress and impair the function of lymphatic vessels, leading to poor lymphatic drainage. This reduced clearance contributes to the retention of NPs or macromolecular drugs within the adipose tissue (J. Wang, Yang, & Kopeček, 2022).
- 3) Adipose tissue remodeling. Obesity triggers extensive remodeling of adipose tissue, including angiogenesis, adipogenesis, and extracellular matrix remodeling. These processes create a leaky vasculature and disorganized interstitial space, facilitating the accumulation and retention of NPs or macromolecular drugs (Tee et al., 2019). By

leveraging the EPR effect, various NPs-based drug delivery systems, such as liposomes, polymeric NPs, and inorganic NPs, can passively target adipose tissue. These nanocarriers can encapsulate browning agents or other therapeutic agents and preferentially accumulate in adipose tissue due to their size and physicochemical properties. Additionally, modulating the nanoparticle surface with stealth coatings, such as polyethylene glycol (PEG), can prolong their circulation time and improve their passive targeting efficiency. However, it is important to note that although passive targeting can enhance the accumulation of NPs in adipose tissue, it may not be entirely specific, as the EPR effect can also occur in other pathological tissues, such as tumors or inflamed areas. Therefore, combining passive targeting with active targeting strategies, such as incorporating adipose tissue-specific ligands on the nanoparticle surface, may further improve the specificity and efficacy of browning agent delivery.

4.2. Active Targeting

4.2.1. Targeting Adipose Vascular Niches and White Adipocytes

Vascular targeting of adipose tissue has been considered as an anti-obesity approach (Daquinag et al., 2017). Regulation of adipocyte growth, differentiation, and metabolism by affecting angiogenesis and vascular function in adipose tissue can reduce fat accumulation and combat obesity. Researchers have focused on reducing the side effects of the PPAR γ activator rosiglitazone (Rosi) and optimizing its ability to promote browning by encapsulating it within NPs that specifically bind to white adipocytes. The peptide CKGGRAKDC can specifically bind to prohibitin (PHB) predominantly expressed on the surface of vascular endothelial cells and mature white

adipocytes in WAT (Kolonin, Saha, Chan, Pasqualini, & Arap, 2004). Rosi was encapsulated in liposomes with surface-modified CKGGRAKDC and octaarginine peptide (octaarginine, R8) to target mature adipocytes (Hiradate et al., 2021). Confocal microscopy showed that the fluorescence intensity was stronger in mature adipocytes with high prohibitin (PHB) expression, suggesting that the constructed vectors had strong PHB targeting. The expression of browning genes was significantly upregulated in both cell types, and the obesity-related toxicity indicators were within the normal range. This indicates that the constructed delivery system has excellent targeting specificity for WAT and good safety. Xue et al. (2016) constructed two peptide-functionalized NPs platforms to deliver either Rosi or prostaglandin E2 analog (16,16-dimethyl PGE2) to the adipose tissue vasculature. These NPs were engineered through self-assembly of a biodegradable triblock polymer composed of end-to-end linkages between poly(lactic-co-glycolic acid)-b-poly(ethylene glycol) (PLGA-b-PEG) and an endothelial-targeted peptide. Intravenous administration of these NPs target the WAT vasculature and stimulate the angiogenesis, which is required for the efficient transformation of WAT into brown-like adipose tissue by the upregulation of angiogenesis and BAT-related markers.

4.2.2. Targeted ASCs

Adipose-derived stromal cells (ASCs) are a population of multipotent mesenchymal stem cells that can be isolated from adipose tissue with the ability to differentiate into adipocytes. Importantly, ASCs can also give rise to beige adipocytes, making them an attractive target for inducing WAT browning and combating obesity.

Nanoparticle-based delivery of browning agents like β_3 -adrenergic agonists, thyroid hormones, or natural compounds can be encapsulated in NPs functionalized with ASC-targeting ligands, such as antibodies against surface markers (CD29, CD44, CD105) or aptamers, to target ASCs for WAT browning. A study conducted by Daquinag et al. (2017) found a non-glycanated decorin isoform (ngDCN) marking mouse ASCs. They identified a specific peptide, CSWKYWFGEC, which can bind to ngDCN, suggesting its potential application as a delivery vector for therapies targeting ASCs. Furthermore, the researchers showed that NPs composed of a polymer core and coated with a lipid layer, modified with DSPE-PEG5000 linked to the peptide, were able to selectively deliver payloads to ASCs in HFD-fed rats. The successful targeting was attributed to the peptide's ability to bind specifically to the glycanation site-deficient decorin on ASCs (Y. Zu et al., 2021). Targeting ASCs for WAT browning offers several advantages over systemic delivery, including the potential for long-term effects, as ASCs can continuously replenish the adipocyte pool with beige adipocytes. However, challenges remain in achieving efficient and specific targeting of ASCs *in vivo*, as well as ensuring the long-term stability and functional integrity of the induced beige adipocytes. Ongoing research efforts are focused on optimizing targeting strategies, understanding the molecular mechanisms underlying ASCs beiging, and evaluating the therapeutic potential of ASCs-based approaches in preclinical and clinical settings.

4.3. Local delivery

4.3.1. Direct injection into iWAT

Beige formation is a complex process regulated by multiple pathways, such as

Notch signaling, which plays an important role in the regulation of beige formation and energy homeostasis. Inhibition of Notch signaling can induce the transformation of white adipocytes to beige adipocytes, and also alleviate inflammation and metabolic diseases. Furthermore, adipose-specific inactivation of Notch signaling *via* intraperitoneal drug injection (e.g., dibenzazepine (DBZ)) triggers the conversion of white-to-beige adipocytes and reduces adiposity (Bi et al., 2014). However, it is challenging to translate this finding into clinical practice due to potential off-target side effects (e.g. promotion of hepatic lipogenesis) and lack of control over the location and timeframe of beige adipocyte biogenesis. Therefore, constructing a targeted delivery inhibitor or inducer system directed to adipose tissue can avoid drug diffusion to other non-target organs. An alternative approach is using a biodegradable polymeric microsphere or NP-based drug delivery system for sustained, local release of a Notch inhibitor, DBZ. These DBZ-loaded microspheres/NPs support rapid cellular internalization and inhibit Notch signaling in adipocytes. Importantly, subcutaneous injection of these microspheres/NPs into the iWAT depots of diet-induced obese mice results in localized NP retention and browning of adipocytes, consequently improving glucose homeostasis and attenuating body-weight gain (Jiang et al., 2015). Subsequently, PLGA-PEG NPs encapsulating the Notch inhibitor DBZ were investigated and found to be rapidly internalized and inhibited Notch signaling in cultured adipocytes. Subcutaneous injection of NPs into the inguinal WAT of obese mice was able to release DBZ to inhibit Notch signaling and promote the browning of white adipose evidenced by increased expression of UCP1. The treatment also reduced

the body weight of mice and improved glucose homeostasis (Jiang et al., 2017). In conclusion, targeted delivery of Notch signaling activators/inhibitors to adipose tissue not only improves the browning effect of the active compound, but also reduces the toxicity to other organs.

4.3.2. Microneedle (MN)-based delivery into iWAT

Microneedle (MN)-based patches are a non-invasive, painless, and localized drug delivery system that reduces adverse systemic effects and does not require professional handling. It is demonstrated to be an effective way of locally inducing the browning of WAT. More importantly, the MN patch limits the browning agent locally to the area of action, which greatly reduces the potential adverse effects of the treatment on other organs. Zhang et al. (2017) prepared degradable microneedles from acid-sensitive dextran derivatives. Rosi, catalase, and glucose oxidase were encapsulated in the dextran NPs coated with alginate. These NPs were loaded into microneedle-array patches made of cross-linked hyaluronic acid (HA) matrix. The degradable MN released browning agents in the acidic environment and entered the subcutaneous area where it up-regulated the expression of brown marker genes, such as UCP1, Cidea, and PGC-1 α , and promoted the transformation of WAT to BeAT. HA, a naturally occurring biodegradable glycosaminoglycan found in the skin and connective tissues has been utilized in the production of MN arrays for the delivery of anti-obesity agents (Z. Gao, Liu, Lin, Lian, & Meng, 2024). Studies have utilized HA-based MN patches to provide rapid and targeted delivery of compounds into subcutaneous WAT. Than et al. (2017) using a mouse model of diet-induced obesity, demonstrated that a β_3 -adrenoceptor

agonist released from slowly dissolving MN could effectively induce WAT browning and inhibit body fat and weight gain, eliminating the need for daily dosing. In a subsequent study by (M. Abbasi, Fan, Dawson, & Wang, 2022), dissolvable poly(lactic-co-glycolic acid) MN was used to administer metformin into the subcutaneous WAT of obese C57BL/6J mice. The MN treatment showed enhanced anti-obesity effects compared to a control, as evidenced by reduced body weight and fat accumulation, increased energy expenditure, diminished fat pad size, and improved energy metabolism *via* WAT browning.

During microneedle insertion, the skin's elasticity can cause it to deform, leading to incomplete penetration by the MN. This impairs the efficiency of drug delivery *via* MN and constrains their use in the field of pharmaceutical delivery systems. This challenge is particularly acute for dissolvable microneedles, as they exhibit lower mechanical strength compared to their metal and monocrystalline silicon counterparts. To address the problems of skin deformation and incomplete penetration, the following approaches can be employed to improve the efficiency of microneedle drug delivery: 1) Increase the rigidity by designing a more rigid microneedle or by using a higher rigidity material. 2) Design microneedles that can comply with skin deformation, so that the microneedles can adapt to its shape change to achieve effective penetration. Application of these methods can effectively improve the penetration efficiency of microneedles into the skin, thus enhancing the overall performance of microneedle drug delivery systems.

5. Targeted delivery of food-derived bioactives

Dietary bioactive compounds, including polyphenols, alkaloids, anthraquinones, and organic sulfur compounds, exhibit a broad spectrum of specific physiological activities, including anti-oxidant, anti-inflammatory, and anti-obesity properties. In recent years, research has revealed that certain dietary bioactive substances can induce beige adipogenesis, offering a potential therapeutic approach for obesity. However, the majority of these compounds suffer from low bioavailability within the body. Consequently, the development of targeted delivery systems aims to precisely deliver bioactive agents to adipose tissue, thereby enhancing their utilization and efficacy (Table 3).

5.1. Food-derived bioactives targeting adipose tissue vasculature

The exploration of a promising therapeutic approach to induce the browning of WAT has been impeded due to the adverse effects and toxicities associated with existing methods. The directed delivery of agents that promote browning of subcutaneous WAT for the induction of beige adipocyte differentiation has the potential to surmount existing challenges and emerge as a pioneering technology for effectively addressing obesity and related disorders, with high therapeutic efficiency and reduced toxicity. To prevent systemic and hepatic side effects of quercetin and to enhance its therapeutic effectiveness and targeting precision, liposomes modified with P3(CKGGRAKDC) were developed for its encapsulation. The peptide P3(CKGGRAKDC) is known to bind to the membrane PHB in the endothelial cells (ECs) of WAT vasculature and has been employed as a critical element in the construction of targeted NPs. HPLC analysis revealed that vasculature-targeted liposomes exhibited high entrapment efficiencies for

quercetin, reaching 98.0%, with a sustained and slow release from the liposomes throughout 50 h (Tang et al., 2024). For managing obesity, oral NPs are considered superior to intravenous ones due to their convenience, which leads to higher patient compliance. Xian et al. (2023) have developed an innovative oral nano-formulation that enhances the anti-obesity effects of celastrol. This enhancement is achieved through zein-based NPs that are embellished with adipose-homing peptides (AHP) and then coated with N-trimethylated chitosan (TMC). The resulting celastrol/AHP-NPs@TMC displayed a spherical shape under transmission electron microscopy (TEM), with a narrow size range (221.76 ± 6.73 nm) and sufficient stability in the gastrointestinal tract. The celastrol/AHP-NPs@TMC leveraged delivery benefits such as enhanced cellular uptake in Caco-2 cells and improved targeting of WAT vasculature, to markedly decrease body weight, blood lipid concentrations, adipose inflammation, and WAT browning in mice with diet-induced obesity, with no adverse effects observed. In essence, the research demonstrates that TMC-based oral NPs are an effective approach of enhancing celastrol's therapeutic potential for the treatment of obesity.

Hydroxy- α -sanshool (HAS), a naturally occurring alkaloid isolated from *Zanthoxylum bungeanum* fruits, demonstrates anti-obesity potential by inducing WAT browning *via* TRPV1 receptor activation. Despite its therapeutic promise, HAS exhibits structural instability through conformational changes and oxidative vulnerability. To address this limitation, researchers utilized peptide CKGGRAKDC or an adipose-targeting sequence (ATS) that selectively interacts with PHB in WAT vasculature, enabling tissue-specific delivery. Concurrently, mesoporous silica nanoparticles (MSNs)

were employed as drug carriers due to their high surface area and tunable pore structures. Zhang et al. (2025) engineered adipose-targeting mesoporous silica nanoparticles encapsulating HAS (MSNs-ATS) to enhance therapeutic precision and stability. Experimental evaluations using diet-induced obese murine models revealed that MSNs-ATS significantly improved cellular targeting efficiency without detectable cytotoxicity. Comparative studies demonstrated superior lipid-lowering effects and enhanced WAT browning capacity in MSNs-ATS formulations compared to free HAS administration, confirming the platform's potential for obesity intervention through targeted thermogenic activation.

5.2. Food-derived bioactives targeting white adipocytes

The bcaND (baicalin-compressed aptamer nanodrug) is rationally designed for targeted obesity therapy by integrating baicalin and tailored Adipo-8 (tAdi-8), which specifically targets the adipocyte plasma membrane-associated protein (APMAP). Primers were engineered with oxyethylene glycol spacers between the tAdi-8 region at the 5'-end and the priming region at the 3'-end and following PCR amplification, double-stranded DNA amplicons are generated with single-stranded tAdi-8 domains at both bilateral 5'-ends. Through a one-pot controllable assembly process, tri-functional baicalin, tri-functional PCR amplicons, pyrophosphate (PPi), and Mg^{2+} self-assemble into an advanced multifunctional nanovehicle specifically targeting visceral white adipose tissue (Tian et al., 2023). Experimental results demonstrated that baicalin loaded in the bcaND played a three-fold role as a lipid-lowering agent, bcaND size compressor, and UCP1-inducing thermogenic activator. While allicin is known for its

weight-reducing properties, its highly unstable character can diminish its bioactivity and therapeutic efficacy. To address this issue, Chen and colleagues developed a nanoflower targeting system for allicin, utilizing the Adi-8 aptamer and isothermal rolling-circle amplification techniques to construct a dual-drug delivery system that specifically targets adipocytes for obesity treatment (Fig. 1B) (X. Chen et al., 2021). This delivery strategy is considered to have a more significant effect on promoting the beiging of adipocytes with no evident toxic reactions. However, there has been limited research on the biological impact of the nanoflower-allicin delivery system (NFA) on BAT. APMAP is not only expressed in WAT but also in BAT, which allows the Adi-8 based DNA framework to target brown fat (T. Wang et al., 2024). Compared to free allicin, NFA demonstrated significantly enhanced efficacy in upregulating gene expression associated with BAT activation, thermogenesis, and the production of batokines (e.g., NRG4, CXCL14, FGF21), which are known to induce WAT browning (T. Wang et al., 2024).

Currently, the mechanism by which organosulfide precisely targets white fat and promotes browning is not fully understood, and an in-depth investigation of their regulatory-specific molecular mechanisms as well as how to improve delivery systems to enhance their stability and bioavailability *in vivo* is a direction for future research studies. In recent times, metal nanoclusters have garnered significant interest within the biomedical fields due to their ultra-small size, superior photostability, and favorable biocompatibility (Yadav et al., 2022). In particular, a variety of novel nanosystems incorporating metal nanoclusters were designed for drug delivery, yielding promising

therapeutic outcomes. Among these, an aptamer-functionalized nanogel of gold nanoclusters (Apt-NG) has been developed as a targeted delivery vector for the browning agent docosahexaenoic acid (DHA). The Apt-NG system is characterized by several distinguishing features including nanoscale, robust autofluorescence, minimal cytotoxicity, and high specificity for white adipocytes. Subsequent to the administration of DHA-Apt-NG, a notable alteration in the morphology of lipid droplets was apparent. Concurrently, there was a significant reduction in the triglyceride content alongside an appreciable enhancement in mitochondrial activity. The therapeutic intervention with DHA-Apt-NG was found to potently up-regulate the mRNA expression of Ucp1, Pgc-1 α , Pparg, and Prdm16 genes that are critically implicated in the metabolic transformation of white adipocytes into a brown adipocyte-like phenotype (Xu et al., 2023). The findings of this investigation delineate a practical strategy for the facilitation of white adipocyte browning via targeted delivery nanosystems, thus introducing an innovative perspective in the treatment of obesity.

Furthermore, an amphiphilic conjugate, CS-PBE, is formed by the covalent bonding of chondroitin sulfate (CS) with 4-aminophenylboronic acid pinacol ester (PBE), capable of self-assembling into core-shell structures. The hydrophobic core of this conjugate can encapsulate water-insoluble substances and release drugs in a highly reactive oxygen species environment. Modulating adipose tissue macrophage polarization to attenuate inflammation represents a potential strategy for browning. In this context, a therapeutic application using celastrol (CLT) encapsulated in CS-based micelles has been developed. The researchers synthesized CLT-loaded CS micelles

modified with PBE (CS-PBE/CLT), which demonstrated an ability to target adipose tissue effectively *via* CD44-mediated mechanisms. In preliminary *in vivo* studies, the results showed that CS-PBE/CLT was more effective in reducing the body weight and promoting WAT browning of HFD-fed mice while improving their whole-body glucose homeostasis compared with the CLT group (Niu et al., 2024).

Importantly, a novel therapeutic approach for adipogenesis has been developed, utilizing the combination of aptamers and liposomes to deliver encapsulated capsaicinoids directly to adipose tissues. In this method, the Adi-8 aptamer was combined with liposomes loaded with nordihydrocapsaicin (NOR) at a 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC): cholesterol: DSPE-PEG2000 M ratio of 10:2:1 to form aptamer-liposome-NOR-encapsulated nanosystems (ALN). The results demonstrated a significant cellular uptake of the ALN, reaching up to 87.07%, which was considerably improved delivery compared to the non-encapsulated compound. Furthermore, the ALN exhibited promising effects on WAT browning and anti-obesity in mice, an outcome attributed to its ability to target adipose tissues with high precision (Fig. 1C) (Song et al., 2024). Currently, the targeted delivery of alkaloids is mainly focused on capsaicin, and the delivery of other alkaloid compounds needs to be carried out in the future.

5.3. Food-derived bioactives targeting ASCs

Resveratrol encapsulated and delivered by NPs targeting ASCs can improve its bioavailability *in vivo* and show good therapeutic effects. A study by Zu and collaborators was the first to describe the targeted delivery of trans-resveratrol (R) to

ASCs *via* NPs coated with DSPE-PEG₅₀₀₀-GSWKYWFGEGGC, which selectively attaches to glycanation site-deficient decorin receptors (Δ DCN) on ASCs. Targeted R-encapsulated NPs (R-nano) showed a substantially greater binding affinity and were more effectively taken up by Δ DCN-transduced 3T3-L1 cells compared to non-targeted R-encapsulated NPs (R-NTnano). R-nano specifically targeted subcutaneous iWAT depots resulting in a reduction in fat mass and an enhancement of glucose metabolism (Fig. 2) (Y. Zu et al., 2021). Research indicates that the ASC-targeting peptide GSWKYWFGEGGC can be successfully conjugated to R with succinyl serving as the linking agent (Mehrnaz Abbasi & Wang, 2022). The peptide-R conjugate was administered directly to the iWAT of HFD-fed mice through a combination of MN and iontophoresis (INT) transdermal delivery methods. The transdermal application of this conjugate led to a two-fold increase in the browning of subcutaneous fat, which consequently resulted in decreased body weight and reduced adiposity in obese mice, as compared to mice treated with MN alone. Additionally, a lipid formulation consisting of soy phosphatidylcholine, vitamin E acetate, Kolliphor HS15, and R, with or without the peptide ligands, was utilized to create the ASC-targeted NPs (ATnano) or non-targeted NPs (NTnano), respectively. The findings indicated that ATnano effectively targeted WAT depots. In particular, ATnano demonstrated a greater binding affinity and a superior ability to deliver R to primary stromal vascular cells compared to NTnano. This enhanced delivery may promote beige adipocyte development, thereby potentially increasing thermogenesis (Zu & Wang, 2017).

5.4. WAT injection of food-derived bioactives

Bile acids (BAs), which serve as the body's innate emulsifying agent, are among the limited noninvasive treatments approved by the FDA for double chin (submental fat) reduction. While synthetic sodium deoxycholic acid (NaDCA) is known to induce adipocyte lysis, it can lead to side effects such as inflammation, bruising, and tissue necrosis. NPs loaded with chenodeoxycholic acid (CDCA) were developed to facilitate a prolonged and targeted release. These NPs were then injected into the subcutaneous fat depot, and the changes in adipocyte size and mitochondrial activity were observed. In contrast to NaDCA, a single injection of CDCA-loaded NPs into the subcutaneous fat did not result in cytolysis. Instead, it induced a reduction in adipocyte size by stimulating fat metabolism and enhancing mitochondrial respiration, which underscores its potential as a treatment for submental fat reduction (Zhou, Lew, Choi, Kim, & Anakk, 2024). PPAR γ is a critical controller in the processes of adipocyte differentiation, glucolipid metabolism, and inflammation. In a recent study by Yu et al. (2023), the team employed virtual screening, microscale thermophoresis, and molecular verification to reveal that diosmin, a natural product with extensive clinical application, acts as a targeted modulator of PPAR γ . It was discovered that diosmin interacts with PPAR γ , inhibits its phosphorylation, and has a minimal impact on transcriptional activity. When injected locally to the inguinal WAT, diosmin was found to boost insulin sensitivity, combat obesity by stimulating WAT browning and raising energy expenditure, and reduce inflammation in both WAT and the liver as well as to lessen hepatic steatosis. Importantly, the study found no significant adverse effects following the local administration of diosmin to WAT. The research concludes that the targeted

application of diosmin to WAT in mice effectively counters diet-induced insulin resistance, obesity, and fatty liver by inhibiting PPAR γ phosphorylation while showing no major side effects, suggesting its promise as a therapeutic option for managing metabolic disorders.

5.5. Microneedle delivery of food-derived bioactives

Rutin, a phytochemical compound belonging to the class of flavonoid glycosides, is known for its significant anti-obesity properties. However, its clinical application is limited due to its low water solubility and poor oral bioavailability. To address these limitations, rutin was encapsulated within liposomes, which were formed by the self-assembly of lecithin and cholesterol. This encapsulation was found to enhance the water solubility of rutin and facilitate its uptake by adipocytes. Subsequently, these rutin-containing liposomes were integrated into a microneedle patch (MP) system composed of polyvinylpyrrolidone and poly(vinyl alcohol). The MP-liposomes demonstrated enhanced release at pH=6.5 characteristic of the adipose tissue microenvironment, enabling targeted delivery of rutin to adipocytes. In HFD-induced obese mice, the MP system improved the liposomes' ability to penetrate the adipose tissue locally, thereby enhancing the anti-obesity effects of rutin by stimulating the expression of proteins associated with beige adipogenesis, such as UCP1 and Cytochrome C (Cyt C) (Fig. 3A) (Li, Liang, Sun, Bao, & Li, 2023).

Capsaicin holds great potential as a treatment for adipogenesis. Although it possesses both anti-obesity and anti-inflammatory properties, its direct application method is limited in its ability to target adipose tissues effectively, making it unsuitable

for direct use on adipose tissue. To overcome this shortcoming, α -lactalbumin nanogel was used to fabricate MP-encapsulated capsaicin, which allowed direct delivery to WAT (Bao et al., 2021). Treatment of HFD-induced obese mice with capsaicin-loaded MP effectively promoted the expression of browning genes and mitochondrial biogenesis in WAT, leading to weight reduction and beige adipogenesis, significantly enhancing the efficacy of capsaicin (Fig. 3B). Mudhol & Peddha (2023) developed a transdermal polymeric MP by encapsulating capsaicin with clove oil, ethanol, PEG400, and sodium caseinate. In the treatment of C57BL/6 obese mice, the capsaicin in the MP exhibited higher bioavailability compared to natural capsaicin, and transdermal delivery *via* the MP effectively converted WAT into BeAT. Therefore, the targeted delivery system improved the bioavailability of capsaicin, achieving improved anti-obesity effects.

Emodin is an anthraquinone derivative extracted from plant roots and barks, but it is insoluble in water and prone to oxidative degradation *in vivo*, thereby reducing its physiological activity. Research showed emodin could improve glucose and lipid metabolism disorders in obese mice *via* activating BAT and inducing browning of WAT. Wang and colleagues have created a dissolving MP that incorporates emodin-polyvinylpyrrolidone co-precipitate (emodin-PVP). The emodin-PVP improved the solubility and compatibility of emodin within the microneedle matrix. Furthermore, the incorporation of polydopamine (PDA) into the microneedle significantly enhanced the release of emodin and facilitated fat metabolism when exposed to near-infrared light (H. Wang et al., 2024). Consequently, the dissolvable microneedle patch can potentially be utilized to deliver other water-insoluble substances for transdermal drug

administration, aiming to achieve improved localized therapeutic outcomes.

Short-chain fatty acids (SCFAs) are produced by gut microbiota fermentation of dietary fibers and polysaccharides that are abundant in various food sources (fruits, vegetables, whole grains, and legumes). Liao and colleagues reported the localized and transient transdermal administration of succinate can effectively mitigate HFD-induced obesity, primarily by enhancing energy expenditure by BAT, and not solely through the direct browning of WAT. The proposed therapeutic approach involves the use of a transdermal device to deliver succinate, a tricarboxylic acid (TCA) metabolic intermediate, as a chemical stimulant capable of accelerating the energy dissipation in BAT located under the dorsal interscapular skin. This process results in the reduction of distal WAT formation and ultimately constrains fat accumulation in organs (Liao, Yao, Chen, Wu, & Lin, 2022). The delivery strategy not only improves the bioavailability of succinate for stimulating BAT energy expenditure but also avoids possible systemic inflammation. Consequently, the straightforward concept of locally and temporarily delivering SCFAs to augment BAT energy dissipation for thermogenesis may represent a promising and effective strategy to prevent the onset of obesity.

6. Conclusion and perspectives

Tissue-specific targeting ability is conferred by the conjugation of specific ligands (such as peptides or aptamers) onto the carrier surface. These ligands facilitate targeting specific sites by recognizing and binding to corresponding receptors. Once at the target site, the encapsulated cargo is actively released through intrinsic or extrinsic stimuli,

thereby increasing the utilization efficiency of the substances and reducing their loss or off-target effects. Firstly, targeted drug delivery can reduce the effects of dietary bioactive substances on other sites, thereby decreasing toxic side effects on the body. Secondly, targeted delivery of dietary bioactive substances can improve their bioavailability and mitigate the adverse effects of poor water solubility. Thirdly, targeted delivery of signaling pathway activators/inhibitors can enable the activation or inhibition of signals at specific sites, avoiding signal disruption in other locations. Therefore, encapsulating bioactive factors with the ability to promote WAT browning for targeted delivery to adipose tissue represents a new strategy for treating obesity.

As we look to the future, several key areas of focus and potential developments stand out in the realm of leveraging food-derived components to influence adipose tissue dynamics. 1) Enhanced understanding of molecular mechanisms. Advances in molecular biology and genomics will provide deeper insights into the specific pathways through which dietary components induce WAT browning. This includes elucidating the roles of nuclear receptors, signaling proteins, transcription factors, and epigenetic modifications in mediating the effects of bioactive compounds on adipose tissue. A more comprehensive understanding of these processes will enable the design of targeted dietary strategies and functional foods to optimize fat metabolism and energy expenditure. 2) Personalized nutrition approaches. The field of nutrigenomics explores the interaction between diet and an individual's genetic makeup, revealing significant variability in how different people respond to the same dietary interventions. Personalized nutrition strategies could be developed to identify individuals most likely

to benefit from specific food-derived compounds based on their genetic predisposition, microbiome composition, and metabolic status. This tailored approach could enhance the effectiveness of dietary interventions targeting WAT browning and obesity. 3) Synergistic effects of dietary components. Research into the combined effects of various nutrients and bioactive compounds offers the potential to discover synergies that target WAT to induce browning and thermogenesis more effectively than single components. Future studies could focus on identifying optimal combinations of dietary factors that work together to modulate adipose tissue function, leading to more potent and holistic approaches to obesity management. 4) Development of functional foods and nutraceuticals. The identification of specific dietary components that target WAT browning will pave the way for the development of functional foods and nutraceuticals designed to support metabolic health. These products could provide a convenient and effective means for individuals to incorporate beneficial nutrients into their diet, potentially reducing the risk of obesity and its associated health implications. 5) Clinical trials and human studies. Although current evidence on the targeting of white fat by dietary ingredients to promote its browning mostly comes from animal models and in vitro studies, clinical trials and human studies will undoubtedly increase in the future. These investigations will be crucial for validating the efficacy of specific foods and dietary interventions in promoting WAT browning in humans, assessing their safety, and determining optimal dosages and consumption patterns. 6) Design of targeted drugs, development of delivery vehicles and investigation of release mechanisms. To develop active molecules specifically recognising WAT for targeted delivery using biomarkers

(e.g. adipocyte surface receptors). In addition, design and optimisation of delivery systems such as nanocarriers, liposomes, and polymer particles is required to improve bioactive stability and targeting. Furthermore, study of the release mechanisms of drugs in targeted tissues is necessary to ensure that they are released at appropriate times and places to maximise therapeutic efficacy. In summary, the future of targeting WAT with food-derived compounds is incredibly promising, with the potential to unlock new strategies for obesity prevention and treatment. Continued research and innovation in this area will be key to realizing this potential and translating scientific insights into practical dietary recommendations and interventions that can improve metabolic health.

Conflicts of interest

No potential conflicts of interest were reported by the authors.

Acknowledgments

This research was funded by the Zhejiang Provincial Natural Science Foundation of China (No. LQN25C200002), the Project of Innovation and Entrepreneurship Training for National Undergraduates (No. 202310356045), and the Science and Technology Development Project in Zhejiang, China (No. 2022C01030).

References

- Abbasi, M., Fan, Z., Dawson, J. A., & Wang, S. (2022). Transdermal Delivery of Metformin Using Dissolving Microneedles and Iontophoresis Patches for Browning Subcutaneous Adipose Tissue. *Pharmaceutics*, 14.
- Abbasi, M., & Wang, S. (2022). Browning Subcutaneous White Adipose Tissue Using Transdermal Delivery of ASC-Targeting Peptide and Resveratrol Conjugate. *Current Developments in Nutrition*, 6, 1042.
- Amin, M., Seynhaeve, A. L. B., Sharifi, M., Falahati, M., & Ten Hagen, T. L. M. (2022). Liposomal Drug Delivery Systems for Cancer Therapy: The Rotterdam Experience. *Pharmaceutics*, 14.
- Bao, C., Li, Z., Liang, S., Hu, Y., Wang, X., Fang, B., Wang, P., Chen, S., & Li, Y. J. A. F. M. (2021). Microneedle patch delivery of capsaicin-containing α -lactalbumin nanomicelles to adipocytes achieves potent anti-obesity effects. *Adv. Funct. Mater*, 31, 2011130.
- Barbagallo, I., Vanella, L., Cambria, M. T., Tibullo, D., Godos, J., Guarnaccia, L., Zappalà, A., Galvano, F., & Li Volti, G. (2015). Silibinin Regulates Lipid Metabolism and Differentiation in Functional Human Adipocytes. *Front Pharmacol*, 6, 309.
- Bargut, T. C. L., Martins, F. F., Santos, L. P., Aguila, M. B., & Mandarim-de-Lacerda, C. A. (2019). Administration of eicosapentaenoic and docosahexaenoic acids may improve the remodeling and browning in subcutaneous white adipose tissue and thermogenic markers in brown adipose tissue in mice. *Molecular and Cellular Endocrinology*, 482, 18-27.
- Bi, P., Shan, T., Liu, W., Yue, F., Yang, X., Liang, X.-R., Wang, J., Li, J., Carlesso, N., & Liu, X. (2014). Notch signaling regulates adipose browning and energy metabolism. *Nature medicine*, 20, 911.
- Chang, W.-T., Wu, C.-H., & Hsu, C.-L. (2015). Diallyl trisulphide inhibits adipogenesis in 3T3-L1 adipocytes through lipogenesis, fatty acid transport, and fatty acid oxidation pathways. *Journal of Functional Foods*, 16, 414-422.
- Chen, C., Yu, Z., Li, Y., Fichna, J., & Storr, M. (2014). Effects of berberine in the gastrointestinal tract - a review of actions and therapeutic implications. *American Journal of Chinese Medicine*, 42, 1053-1070.
- Chen, X., He, X., Gao, R., Lan, X., Zhu, L., Chen, K., Hu, Y., Huang, K., & Xu, W. (2021). Aptamer-functionalized binary-drug delivery system for synergetic obesity therapy. *ACS nano*, 16, 1036-1050.
- Choi, M., & Yun, J. W. (2023). β -Carotene induces UCP1-independent thermogenesis via ATP-consuming futile cycles in 3T3-L1 white adipocytes. *Archives of Biochemistry and Biophysics*, 739, 109581.
- Chu, Y., Gui, S., Zheng, Y., Zhao, J., Zhao, Y., Li, Y., & Chen, X. (2024). The natural compounds, Magnolol or Honokiol, promote adipose tissue browning and resist obesity through modulating PPAR α/γ activity. *European Journal of Pharmacology*, 969, 176438.
- Cremonini, E., Da Silva, L. M. E., Lanzi, C. R., Marino, M., Iglesias, D. E., & Oteiza,

872 P. I. (2024). Anthocyanins and their metabolites promote white adipose tissue
873 beiging by regulating mitochondria thermogenesis and dynamics. *Biochemical*
874 *Pharmacology*, 222, 116069.

875 Daquinag, A. C., Dadbin, A., Snyder, B., Wang, X., Sahin, A. A., Ueno, N. T., &
876 Kolonin, M. G. (2017). Non-glycanated Decorin Is a Drug Target on Human
877 Adipose Stromal Cells. *Molecular Therapy-Oncolytics*, 6, 1-9.

878 Fan, L., Xu, H., Yang, R., Zang, Y., Chen, J., & Qin, H. (2019). Combination of
879 Capsaicin and Capsiate Induces Browning in 3T3-L1 White Adipocytes via
880 Activation of the Peroxisome Proliferator-Activated Receptor γ/β 3-Adrenergic
881 Receptor Signaling Pathways. *Journal of Agricultural and Food Chemistry*, 67,
882 6232-6240.

883 Fang, P., He, B., Yu, M., Shi, M., Zhu, Y., Zhang, Z., & Bo, P. (2019). Treatment with
884 celastrol protects against obesity through suppression of galanin-induced fat
885 intake and activation of PGC-1 α /GLUT4 axis-mediated glucose consumption.
886 *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1865, 1341-
887 1350.

888 Fernández-Galilea, M., Félix-Soriano, E., Colón-Mesa, I., Escoté, X., Moreno-Aliaga,
889 M. (2020). Omega-3 fatty acids as regulators of brown/beige adipose tissue:
890 From mechanisms to therapeutic potential. *Journal of Physiology and*
891 *Biochemistry*, 76, 251-267.

892 Ferreira, Y. A. M., Jamar, G., Estadella, D., Pisani, L. P. (2023). Role of carotenoids in
893 adipose tissue through the AMPK-mediated pathway. *Food & Function*, 14,
894 3454-3462.

895 Gao, H., Li, Z., Cheng, C., Cui, J., Peng, J., Wang, X., Zhang, M., Hou, Y., & Bai, G. J.
896 (2023). Fuziline Ameliorates Glucose and Lipid Metabolism by Activating Beta
897 Adrenergic Receptors to Stimulate Thermogenesis. *International Journal of*
898 *Molecular Sciences*, 24, 8362.

899 Gao, Z., Liu, Y., Lin, W., Lian, H., & Meng, Z. (2024). A microneedle patch realizes
900 weight loss through photothermal induction of fat browning. *Biomaterials*
901 *Science*, 12, 1726-1737.

902 Castrejón-Tellez, V., Rodríguez-Pérez, J. M., Pérez-Torres, I., Pérez-Hernández, N.,
903 Cruz-Lagunas, A., Guarner-Lans, V., Vargas-Alarcón, G., & Rubio-Ruiz, M. E.
904 (2016). The Effect of Resveratrol and Quercetin Treatment on PPAR Mediated
905 Uncoupling Protein (UCP-) 1, 2, and 3 Expression in Visceral White Adipose
906 Tissue from Metabolic Syndrome Rats. *International Journal Of Molecular*
907 *Sciences*, 17, 1069.

908 Goodarzi, G., Tehrani, S. S., Panahi, G., Bahramzadeh, A., & Meshkani, R. (2023).
909 Combination therapy of metformin and p-coumaric acid mitigates metabolic
910 dysfunction associated with obesity and nonalcoholic fatty liver disease in high-
911 fat diet obese C57BL/6 mice. *The Journal of Nutritional Biochemistry*, 118,
912 109369.

913 Hara, H., Takahashi, H., Mohri, S., Murakami, H., Kawarasaki, S., Iwase, M.,
914 Takahashi, N., Sugiura, M., Goto, T., & Kawada, T. (2019). β -Cryptoxanthin
915 Induces UCP-1 Expression via a RAR Pathway in Adipose Tissue. *Journal of*

916 *Agricultural and Food Chemistry*, 67, 10595-10603.

917 Hausenloy, D. J. (2009). Contrave (TM)(TM): novel treatment for obesity. *Clinical*

918 *Lipidology and Metabolic Disorders*, 4, 279.

919 Hiradate, R., Khalil, I. A., Matsuda, A., Sasaki, M., Hida, K., & Harashima, H. (2021).

920 A novel dual-targeted rosiglitazone-loaded nanoparticle for the prevention of

921 diet-induced obesity via the browning of white adipose tissue. *Journal of*

922 *Controlled Release*, 329, 665-675.

923 Hossen, M. N., Kajimoto, K., Akita, H., Hyodo, M., & Harashima, H. (2012). Vascular-

924 targeted nanotherapy for obesity: Unexpected passive targeting mechanism to

925 obese fat for the enhancement of active drug delivery. *Journal of Controlled*

926 *Release*, 163, 101-110.

927 Hu, J., Wang, Z., Tan, B. K., Christian, M. (2020). Dietary polyphenols turn fat “brown”:

928 A narrative review of the possible mechanisms. *Trends in Food Science &*

929 *Technology*, 97, 221-232.

930 Jiang, C., Cano-Vega, M. A., Yue, F., Kuang, L., Narayanan, N., Uzunalli, G., Merkel,

931 M. P., Kuang, S., & Deng, M. (2017). Dibenzazepine-loaded nanoparticles

932 induce local browning of white adipose tissue to counteract obesity. *Molecular*

933 *Therapy*, 25, 1718-1729.

934 Jiang, C., Kuang, L., Merkel, M. P., Yue, F., Cano-Vega, M. A., Narayanan, N., Kuang,

935 S., & Deng, M. (2015). Biodegradable polymeric microsphere-based drug

936 delivery for inductive browning of fat. *Frontiers in endocrinology*, 6, 169.

937 Jiang, C., Zhai, M., Yan, D., Li, D., Li, C., Zhang, Y., Xiao, L., Xiong, D., Deng, Q., &

938 Sun, W. (2017). Dietary menthol-induced TRPM8 activation enhances WAT

939 "browning" and ameliorates diet-induced obesity. *Oncotarget*, 8, 75114-75126.

940 Kim, O. Y., Chung, J. Y., & Song, J. (2019). Effect of resveratrol on adipokines and

941 myokines involved in fat browning: Perspectives in healthy weight against

942 obesity. *Pharmacological Research*, 148, 104411.

943 Kolonin, M. G., Saha, P. K., Chan, L., Pasqualini, R., & Arap, W. (2004). Reversal of

944 obesity by targeted ablation of adipose tissue. *Nature medicine*, 10, 625-632.

945 La Spina, M., Galletta, E., Azzolini, M., Gomez Zorita, S., Parrasia, S., Salvalaio, M.,

946 Salmaso, A., & Biasutto, L. (2019). Browning Effects of a Chronic Pterostilbene

947 Supplementation in Mice Fed a High-Fat Diet. *International Journal of*

948 *Molecular Sciences*, 20, 5377.

949 Lee, M.-S., Kim, I.-H., Kim, C.-T., & Kim, Y. (2011). Reduction of body weight by

950 dietary garlic is associated with an increase in uncoupling protein mRNA

951 expression and activation of AMP-activated protein kinase in diet-induced

952 obese mice. *Journal of Nutrition*, 141, 1947-1953.

953 Li, Z., Liang, S., Sun, H., Bao, C., & Li, Y. (2023). Antilipogenesis Effect of Rutin-

954 Loaded Liposomes Using a Microneedle Delivery System. *ACS Applied*

955 *Materials & Interfaces*, 15, 54294-54303.

956 Li, Z., Yi, C.-X., Katiraei, S., Kooijman, S., Zhou, E., Chung, C. K., Gao, Y., van den

957 Heuvel, J. K., Meijer, O. C., & Berbée, J. (2018). Butyrate reduces appetite and

958 activates brown adipose tissue via the gut-brain neural circuit. *Gut*, 67, 1269-

959 1279.

- Li, Z., Zhang, Z., Ke, L., Sun, Y., Li, W., Feng, X., Zhu, W., & Chen, S. (2020). Resveratrol promotes white adipocytes browning and improves metabolic disorders in Sirt1-dependent manner in mice. *The FASEB Journal*, 34, 4527-4539.
- Liao, F.-H., Yao, C.-N., Chen, S.-P., Wu, T.-H., & Lin, S.-Y. (2022). Transdermal Delivery of Succinate Accelerates Energy Dissipation of Brown Adipocytes to Reduce Remote Fat Accumulation. *Molecular Pharmaceutics*, 19, 4299-4310.
- Liu, C., Li, Y., Song, G., Li, X., Chen, S., Zou, D., Li, H., Hu, C., Zhao, H., & Yan, Y. (2023). Caffeine promotes the production of Irisin in muscles and thus facilitates the browning of white adipose tissue. *Journal of Functional Foods*, 108, 105702.
- Liu, J., Li, Y., Yang, P., Wan, J., Chang, Q., Wang, T. T. Y., Lu, W., Zhang, Y., Wang, Q., & Yu, L. L. (2017). Gypenosides Reduced the Risk of Overweight and Insulin Resistance in C57BL/6J Mice through Modulating Adipose Thermogenesis and Gut Microbiota. *Journal of Agricultural and Food Chemistry*, 65, 9237-9246.
- Liu, Y., Zhong, X., Lin, S., Xu, H., Liang, X., Wang, Y., Xu, J., Wang, K., Guo, X., & Wang, J. (2022). Limosilactobacillus reuteri and caffeoylquinic acid synergistically promote adipose browning and ameliorate obesity-associated disorders. *Microbiome*, 10, 226.
- Lu, Y., Fan, C., Li, P., Lu, Y., Chang, X., & Qi, K. (2016). Short Chain Fatty Acids Prevent High-fat-diet-induced Obesity in Mice by Regulating G Protein-coupled Receptors and Gut Microbiota. *Sci Rep*, 6(1), 37589.
- Luca, S. V., Macovei, I., Bujor, A., Miron, A., Skalicka-Woźniak, K., Aprotosoiaie, A. C., & Trifan, A. (2020). Bioactivity of dietary polyphenols: The role of metabolites. *Critical Reviews in Food Science and Nutrition*, 60, 626-659.
- Ma, D., Wu, T., Qu, Y., Yang, J., Cai, L., Li, X., & Wang, Y. (2023). Astragalus polysaccharide prevents heart failure-induced cachexia by alleviating excessive adipose expenditure in white and brown adipose tissue. *Lipids in Health and Disease*, 22, 9.
- Maeda, H., Hosokawa, M., Sashima, T., Funayama, K., & Miyashita, K. (2005). Fucoxanthin from edible seaweed, Undaria pinnatifida, shows antiobesity effect through UCP1 expression in white adipose tissues. *Biochemical and Biophysical Research Communications*, 332, 392-397.
- Mudhol, S., Peddha, M. S. (2023). Development of capsaicin loaded nanoparticles based microneedle patch for transdermal drug delivery. *Journal of Drug Delivery Science and Technology*, 80, 104120.
- Mukherjee, S., & Yun, J. W. (2022). β -Carotene stimulates browning of 3T3-L1 white adipocytes by enhancing thermogenesis via the β 3-AR/p38 MAPK/SIRT signaling pathway. *Phytomedicine*, 96, 153857.
- Murugesan, S., Nirmalkar, K., Hoyo-Vadillo, C., García-Espitia, M., Ramírez-Sánchez, D., García-Mena, J. (2018). Gut microbiome production of short-chain fatty acids and obesity in children. *European Journal of Clinical Microbiology & Infectious Diseases*, 37, 621-625.
- Nawaz, A., Nishida, Y., Takikawa, A., Fujisaka, S., Kado, T., Aminuddin, A., Bilal, M.,

- Jeelani, I., Aslam, M. R., Nishimura, A., Kuwano, T., Watanabe, Y., Igarashi, Y., Okabe, K., Ahmed, S., Manzoor, A., Usui, I., Yagi, K., Nakagawa, T., & Tobe, K. (2021). Astaxanthin, a Marine Carotenoid, Maintains the Tolerance and Integrity of Adipose Tissue and Contributes to Its Healthy Functions. *Nutrients*, *13*, 4374.
- Ng, M., Gakidou, E., Lo, J., Abate, Y. H., Abbafati, C., Abbas, N., Abbasian, M., Abd ElHafeez, S., Abdel-Rahman, W. M., Abd-Elsalam, S., et al. (2025). Global, regional, and national prevalence of adult overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. *The Lancet*, *405*, 813-838.
- Niu, Y., Gao, T., Ouyang, H., Zhang, Y., Gong, T., Zhang, Z., Cao, X., & Fu, Y. J. A. A. B. M. (2024). Chondroitin Sulfate-Derived Micelles for Adipose Tissue-Targeted Delivery of Celastrol and Phenformin to Enhance Obesity Treatment. *ACS Applied Bio Materials*, *7*, 1271-1289.
- Park, S. Y., Park, K., Kang, H. M., Song, W. C., Oh, J. W., Choi, Y. W., & Park, G. (2023). Induction of Browning in White Adipocytes: Fucoidan Characterization and Gold Nanoparticle Synthesis from *Undaria pinnatifida* Sporophyll Extract. *Marine Drugs*, *21*.
- Pu, J., Akter, R., Rupa, E. J., Awais, M., Mathiyalagan, R., Han, Y., Kang, J., Yang, D. C., & Kang, S. C. (2022). Role of Ginsenosides in Browning of White Adipose Tissue to Combat Obesity: A Narrative Review on Molecular Mechanism. *Archives of Medical Research*, *53*, 231-239.
- Ranaweera, S. S., Natraj, P., Rajan, P., Dayarathne, L. A., Mihindukulasooriya, S. P., Dinh, D. T. T., Jee, Y., & Han, C.-H. (2022). Anti-obesity effect of sulforaphane in broccoli leaf extract on 3T3-L1 adipocytes and ob/ob mice. *The Journal of Nutritional Biochemistry*, *100*, 108885.
- Rao, Y., Yu, H., Gao, L., Lu, Y.-T., Xu, Z., Liu, H., Gu, L.-Q., Ye, J.-M., & Huang, Z.-S. (2017). Natural alkaloid bouchardatine ameliorates metabolic disorders in high-fat diet-fed mice by stimulating the sirtuin 1/liver kinase B-1/AMPK axis. *British Journal of Pharmacology*, *174*, 2457-2470.
- Seoane-Collazo, P., Liñares-Pose, L., Rial-Pensado, E., Romero-Picó, A., Moreno-Navarrete, J. M., Martínez-Sánchez, N., Garrido-Gil, P., Iglesias-Rey, R., Morgan, D. A., Tomasini, N., Malone, S. A., Senra, A., Folgueira, C., Medina-Gomez, G., Sobrino, T., Labandeira-García, J. L., Nogueiras, R., Domingos, A. I., Fernández-Real, J.-M., Rahmouni, K., Diéguez, C., & López, M. (2019). Central nicotine induces browning through hypothalamic κ opioid receptor. *Nature Communications*, *10*, 4037.
- Shahidi, F., & Ambigaipalan, P. (2018). Omega-3 polyunsaturated fatty acids and their health benefits. *Annual review of food science and technology*, *9*, 345-381.
- Shamsi, F., Piper, M., Ho, L.-L., Huang, T. L., Gupta, A., Streets, A., Lynes, M. D., & Tseng, Y.-H. (2021). Vascular smooth muscle-derived Trpv1+ progenitors are a source of cold-induced thermogenic adipocytes. *Nature Metabolism*, *3*, 485-495.
- Sharma, P. P., & Baskaran, V. (2021). Polysaccharide (laminaran and fucoidan), fucoxanthin and lipids as functional components from brown algae (*Padina*

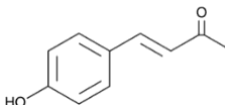
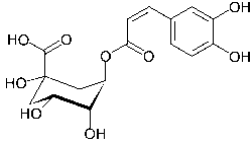
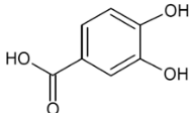
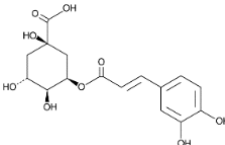
- tetrastrumatica) modulates adipogenesis and thermogenesis in diet-induced obesity in C57BL6 mice. *Algal Research*, 54, 102187.
- Sibuyi, N. R. S., Moabelo, K. L., Meyer, M., Onani, M. O., Dube, A., & Madiehe, A. M. (2019). Nanotechnology advances towards development of targeted-treatment for obesity. *Journal of Nanobiotechnology*, 17, 122.
- Sidossis, L., & Kajimura, S. (2015). Brown and beige fat in humans: thermogenic adipocytes that control energy and glucose homeostasis. *The Journal of Clinical Investigation*, 125, 478-486.
- Song, Y., Hu, Y., Gao, R., Chang, Q., He, X., Pang, G., & Xu, W. (2024). Aptamer-functionalized liposome delivery system targeting adipose for hypereffective obesity therapy. *Journal of Drug Delivery Science and Technology*, 95, 105586.
- Sudhakar, M., Sasikumar, S. J., Silambanan, S., Natarajan, D., Ramakrishnan, R., Nair, A. J., & Kiran, M. S. (2020). Chlorogenic acid promotes development of brown adipocyte-like phenotype in 3T3-L1 adipocytes. *Journal of Functional Foods*, 74, 104161.
- Sun, A., Hu, X., Chen, H., Ma, Y., Yan, X., Peng, D., Ping, J., & Yan, Y. (2021). Ursolic acid induces white adipose tissue beiging in high-fat-diet obese male mice. *Food & Function*, 12, 6490-6501.
- Tanaka, E., Mitani, T., Nakashima, M., Yonemoto, E., Fujii, H., & Ashida, H. (2022). Theobromine enhances the conversion of white adipocytes into beige adipocytes in a PPAR γ activation-dependent manner. *The Journal of Nutritional Biochemistry*, 100, 108898.
- Tang, Q., Xing, X., Huang, H., Yang, J., Li, M., Xu, X., Gao, X., Liang, C., Tian, W., & Liao, L. (2024). Eliminating senescent cells by white adipose tissue-targeted senotherapy alleviates age-related hepatic steatosis through decreasing lipolysis. *GeroScience*, 1-19.
- Tee, J. K., Yip, L. X., Tan, E. S., Santitewagun, S., Prasath, A., Ke, P. C., Ho, H. K., & Leong, D. T. (2019). Nanoparticles' interactions with vasculature in diseases. *Chemical Society Reviews*, 48(21), 5381-5407.
- Than, A., Liang, K., Xu, S., Sun, L., Duan, H., Xi, F., Xu, C., & Chen, P. (2017). Transdermal delivery of anti-obesity compounds to subcutaneous adipose tissue with polymeric microneedle patches. *Small Methods*, 1, 1700269.
- Tian, J., He, X., Lan, X., Liang, X., Zhong, Z., Zhu, L., Chen, K., Chang, Q., & Xu, W. (2023). One-Pot Controllable Assembly of a Baicalin-Condensed Aptamer Nanodrug for Synergistic Anti-Obesity. *Small*, 19, 2205933.
- Vargas-Castillo, A., Sun, Y., Smythers, A. L., Grauvogel, L., Dumesic, P. A., Emont, M. P., Tsai, L. T., Rosen, E. D., Zammit, N. W., Shaffer, S. M., Ordonez, M., Chouchani, E. T., Gygi, S. P., Wang, T., Sharma, A. K., Balaz, M., Wolfrum, C., & Spiegelman, B. M. (2024). Development of a functional beige fat cell line uncovers independent subclasses of cells expressing UCP1 and the futile creatine cycle. *Cell Metabolism*, 36, 2146-2155.e2145.
- Wang, B., Fu, X., Liang, X., Deavila, J. M., Wang, Z., Zhao, L., Tian, Q., Zhao, J., Gomez, N. A., Trombetta, S. C., Zhu, M.-J., & Du, M. (2017). Retinoic acid induces white adipose tissue browning by increasing adipose vascularity and

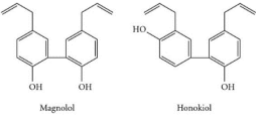
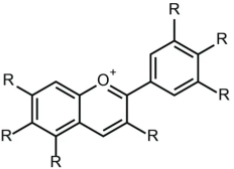
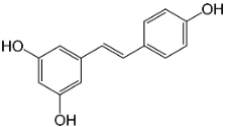
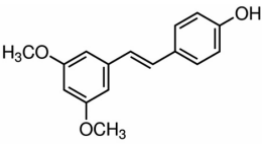
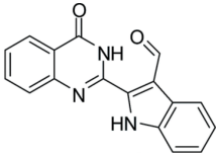
- inducing beige adipogenesis of PDGFR α ⁺ adipose progenitors. *Cell Discovery*, 3, 17036.
- Wang, T., Sharma, A. K., Wu, C., Maushart, C. I., Ghosh, A., Yang, W., Stefanicka, P., Kovanicova, Z., Ukropec, J., Zhang, J., Arnold, M., Klug, M., De Bock, K., Schneider, U., Popescu, C., Zheng, B., Ding, L., Long, F., Dewal, R. S., Moser, C., Sun, W., Dong, H., Takes, M., Suelberg, D., Mameghani, A., Nocito, A., Zech, C. J., Chirindel, A., Wild, D., Burger, I. A., Schön, M. R., Dietrich, A., Gao, M., Heine, M., Sun, Y., Vargas-Castillo, A., Søberg, S., Scheele, C., Balaz, M., Blüher, M., Betz, M. J., Spiegelman, B. M., & Wolfrum, C. (2024). Single-nucleus transcriptomics identifies separate classes of UCP1 and futile cycle adipocytes. *Cell Metabolism*, 36, 2130-2145.e2137.
- Wang, C.-H., Tsuji, T., Wu, L.-H., Yang, C.-Y., Huang, T. L., Sato, M., Shamsi, F., & Tseng, Y.-H. (2024). Endothelin 3/EDNRB signaling induces thermogenic differentiation of white adipose tissue. *Nature Communications*, 15, 7215.
- Wang, H., Wang, L., Wang, M., Niu, J., Yang, B., Wang, Y., An, M., Sun, X., Yang, Z., & Li, X. (2024). Design and development of a soluble PDA-Emodin-PVP-MN patch and its anti-obesity effect in rats. *Drug Delivery and Translational Research*, 1-15.
- Wang, J., Yang, J., & Kopeček, J. (2022). Nanomedicines in B cell-targeting therapies. *Acta biomaterialia*, 137, 1-19.
- Wang, B., Yang, X., Zhao, M., Su, Z., Hu, Z., Zhang, C., Guo, B., Liu, J., Qin, L., Zhang, W., & Zheng, R. (2021). Celastrol prevents high-fat diet-induced obesity by promoting white adipose tissue browning. *Clinical and Translational Medicine*, 11, e641.
- Wang, T., Yu, Y., Gao, R., Chen, X., Xu, W., Huang, K., & He, X. (2024). Aptamer-functionalized-nanoflower loading allicin ameliorates obesity through regulating adipose tissue energy expenditure. *Journal of Drug Delivery Science and Technology*, 92, 105367.
- Wang, Z., Zeng, M., Wang, Z., Qin, F., Wang, Y., Chen, J., Christian, M., He, Z. (2023). Food phenolics stimulate adipocyte browning via regulating gut microecology. *Critical Reviews in Food Science and Nutrition*, 4026-4052.
- Xian, J., Zhong, X., Huang, Q., Gu, H., Feng, Y., Sun, J., Wang, D., Li, J., Zhang, C., Wu, Y., & Zhang, J. (2023). N-Trimethylated chitosan coating white adipose tissue vascular-targeting oral nano-system for the enhanced anti-obesity effects of celastrol. *International Journal of Biological Macromolecules*, 236, 124023.
- Xiang, Y., Huang, R., Wang, Y., Han, S., Qin, X., Li, Z., Wang, X., Han, Y., Wang, T., Xia, B., Wu, J., & Yang, G. (2023). Protocatechuic Acid Ameliorates High Fat Diet-Induced Obesity and Insulin Resistance in Mice. *Molecular Nutrition & Food Research*, 67, 2200244.
- Xie, J., Liu, M., Liu, H., Jin, Z., Guan, F., Ge, S., Yan, J., Zheng, M., Cai, D., & Liu, J. (2021). Zeaxanthin ameliorates obesity by activating the β 3-adrenergic receptor to stimulate inguinal fat thermogenesis and modulating the gut microbiota. *Food & Function*, 12, 12734-12750.
- Xu, H., Ding, J., Du, Y., Li, L., Li, Y., Zhao, M., Su, Y., & Lin, Z. (2023). Aptamer-

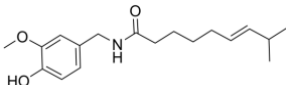
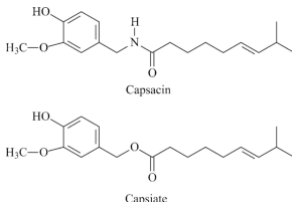
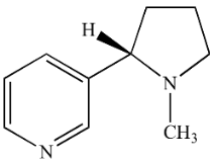
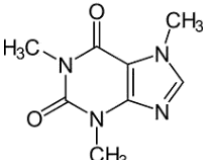
- functionalized AuNCs nanogel for targeted delivery of docosahexaenoic acid to induce browning of white adipocytes. *Journal of Materials Chemistry B*, 11, 4972-4979.
- Xue, Y., Xu, X., Zhang, X.-Q., Farokhzad, O. C., & Langer, R. (2016). Preventing diet-induced obesity in mice by adipose tissue transformation and angiogenesis using targeted nanoparticles. *Proceedings of the National Academy of Sciences*, 113, 5552-5557.
- Yadav, P., Chaturvedi, S., Biswas, S. K., Srivastava, R., Kailasam, K., Mishra, A. K., & Shanavas, A. (2022). Biodegradable Protein-Stabilized Inorganic Nanoassemblies for Photothermal Radiotherapy of Hepatoma Cells. *ACS Omega*, 7, 8928-8937.
- Yamashita, Y., Takeuchi, T., Endo, Y., Goto, A., Sakaki, S., Yamaguchi, Y., Takenaka, H., & Yamashita, H. (2020). Dietary Supplementation with Dunaliella Tertiolecta Prevents Whitening of Brown Fat and Controls Diet-Induced Obesity at Thermoneutrality in Mice. *Nutrients*, 12, 1686.
- You, M., Fan, R., Kim, J., Shin, S.-H., & Chung, S. (2020). Alpha-Linolenic Acid-Enriched Butter Promotes Fatty Acid Remodeling and Thermogenic Activation in the Brown Adipose Tissue. *Nutrients*, 12(1), 136.
- Yu, J., Hu, Y., Sheng, M., Gao, M., Guo, W., Zhang, Z., Wang, D., Wu, X., Li, J., & Chen, Y. (2023). Selective PPAR γ modulator diosmin improves insulin sensitivity and promotes browning of white fat. *Journal of Biological Chemistry*, 299(4).
- Yue, X., Zhong, L., Ye, M., Luan, Y., Zhang, Q., & Wang, Q. (2024). Taraxacum mongolicum polysaccharide promotes white adipocyte browning by regulating miR-134-3p via Akt/GSK-3 β signalling. *International Journal of Biological Macromolecules*, 257, 128296.
- Zhang, F., Ai, W., Hu, X., Meng, Y., Yuan, C., Su, H., Wang, L., Zhu, X., Gao, P., Shu, G., Jiang, Q., & Wang, S. (2018). Phytol stimulates the browning of white adipocytes through the activation of AMP-activated protein kinase (AMPK) α in mice fed high-fat diet. *Food & Function*, 9, 2043-2050.
- Zhang, F., Fu, Y., Wang, J., Li, F., Lang, L., Zhu, X., Wang, L., Gao, P., Shu, G., Zhu, C., Jiang, Q., & Wang, S. (2024). Conjugated linoleic acid (CLA) reduces HFD-induced obesity by enhancing BAT thermogenesis and iWAT browning via the CD36-AMPK pathway. *Cell Biochemistry and Function*, 42, e3937.
- Zhang, N., Wang, Q., Lin, F., Zheng, B., Huang, Y., Yang, Y., Xue, C., Xiao, M., & Ye, J. (2022). Neoagarotetraose alleviates high fat diet induced obesity via white adipocytes browning and regulation of gut microbiota. *Carbohydrate Polymers*, 296, 119903.
- Zhang, Q., He, C., Guo, J., Tang, D., Qian, D., Zheng, C., Wu, C., & Peng, W. (2025). Hydroxy- α -sanshool-loaded adipose-targeted mesoporous silica nanoparticles induce white adipose browning and reduce obesity by activating TRPV1. *Bio-Design and Manufacturing*, 8, 288-309.
- Zhang, W., Sheng, T., Gu, Z., & Zhang, Y. (2021). Strategies for browning agent delivery. *Pharmaceutical Research*, 38, 1327-1334.

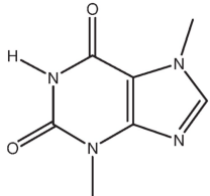
- Zhang, Y., Liu, Q., Yu, J., Yu, S., Wang, J., Qiang, L., & Gu, Z. (2017). Locally induced adipose tissue browning by microneedle patch for obesity treatment. *ACS nano*, *11*, 9223-9230.
- Zhang, Y., Luo, M., Jia, Y., Gao, T., Deng, L., Gong, T., Zhang, Z., Cao, X., & Fu, Y. (2024). Adipocyte-targeted delivery of rosiglitazone with localized photothermal therapy for the treatment of diet-induced obesity in mice. *Acta Biomaterialia*, *181*, 317-332.
- Zhou, W., Lew, B., Choi, H., Kim, K., & Anakk, S. (2024). Chenodeoxycholic Acid-Loaded Nanoparticles Are Sufficient to Decrease Adipocyte Size by Inducing Mitochondrial Function. *Nano Letters*, *24*, 1642-1649.
- Zhu, R., Wei, J., Liu, H., Liu, C., Wang, L., Chen, B., Li, L., Jia, Q., Tian, Y., Li, R., Zhao, D., Mo, F., Li, Y., Gao, S., Wang, X.-D., & Zhang, D. (2020). Lycopene attenuates body weight gain through induction of browning via regulation of peroxisome proliferator-activated receptor γ in high-fat diet-induced obese mice. *The Journal of Nutritional Biochemistry*, *78*, 108335.
- Zu, Y., & Wang, S. (2017). Targeted delivery of resveratrol to mouse white adipose tissue using adipose stromal cells (ASC) targeted nanoparticles. *The FASEB Journal*, *31*, 646.627-646.627.
- Zu, Y., Zhao, L., Hao, L., Mechref, Y., Zabet-Moghaddam, M., Keyel, P. A., Abbasi, M., Wu, D., Dawson, J. A., Zhang, R., Nie, S., Moustaid-Moussa, N., Kolonin, M. G., Daquinag, A. C., Brandi, L., Warraich, I., San Francisco, S. K., Sun, X., Fan, Z., & Wang, S. (2021). Browning white adipose tissue using adipose stromal cell-targeted resveratrol-loaded nanoparticles for combating obesity. *Journal of Controlled Release*, *333*, 339-351.
- Zuo, J., Zhang, Y., Wu, Y., Liu, J., Wu, Q., Shen, Y., Jin, L., Wu, M., Ma, Z., & Tong, H. (2022). Sargassum fusiforme fucoidan ameliorates diet-induced obesity through enhancing thermogenesis of adipose tissues and modulating gut microbiota. *International Journal of Biological Macromolecules*, *216*, 728-740.

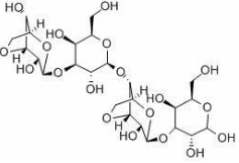
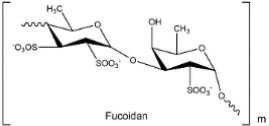
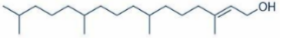
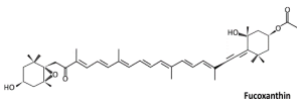
1208 **Table 1. The beneficial role of Food-derived active agents in WAT browning**

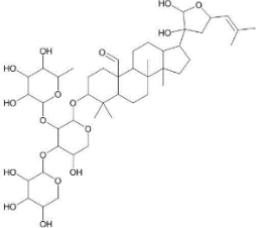
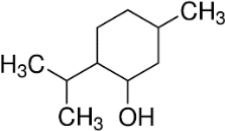
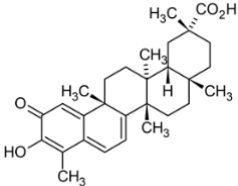
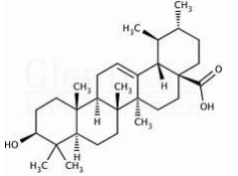
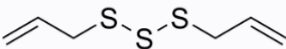
Food-derived Bioactives	Structure	Models	Dosage	Duration	Results	References
Polyphenols						
p-coumaric acid		HFD-induced C57BL6/J mice	200 mg/kg	10 weeks	Ucp1, TMEM26, and CD137 ↑	(Goodarzi et al., 2023)
Chlorogenic acid		3T3-L1 preadipocytes	100 nM	48 h	p-AMPK/AMPK, Pgc-1 α , UCP1 ↑	(Sudhakar et al., 2020)
Protocatechuic Acid		HFD-induced C57BL6/J mice	2.7 mM	4 weeks	Ucp1 and Pgc-1 α ↑	(Xiang et al., 2023)
Caffeoylquinic acid		HFD-induced C57BL6/J mice	30 mg/kg	8 weeks	Ucp1 and Pgc1 α ↑	(Y. Liu et al., 2022)
Magnolol		HFD-induced C57BL6/J mice	30 mg/kg	8 weeks	Prdm16, Pgc-1 α , Cidea,	(Chu et al.,

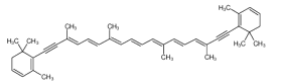
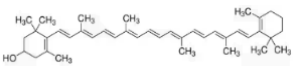
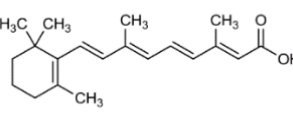
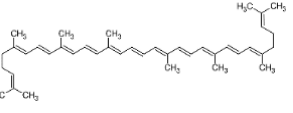
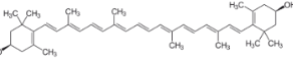
Honokiol					Dio2, and UCP1↑	2024)
Anthocyanins		HFD-induced C57BL6/J mice	40 mg/kg	14 weeks	p-PKA/PKA, p-AMPK/AMPK, Prdm16, Pgc-1 α , UCP1↑	(Cremonini et al., 2024)
Resveratrol		HFD-induced C57BL6/J mice	2 or 4 g/kg	8 weeks	FNDC5, UCP1, PRDM16, TMEM26, and CIDEA↑	(Li et al., 2020)
Pterostilbene		HFD-induced C57BL6/J mice	352 μ mol/kg	30 weeks	UCP1, Cidea, Ebf2, Pgc-1 α , PPAR γ , Sirt1, and Tbx1↑	(La Spina et al., 2019)
Alkaloids						
Bouchardatine		HFD-induced C57BL6/J mice	50 mg·kg	5 weeks	SIRT1-LKB1-AMPK, PGC-1 α , Dio2, and UCP1↑	(Rao et al., 2017)

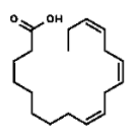
Capsaicin		HFD-induced C57BL6/J mice	0.01%	32 weeks	TRPV1, CaMKII α /AMPK α , PPAR γ - PRDM16, SIRT1, Pgc-1 α , and UCP1 $\uparrow$	(P. Baskaran et al., 2016)
Capsaicin and capsinoids		3T3-L1 White Adipocytes	25 μ M	48 h	PPAR γ , β_3 -AR, Tbx1, Tmem26, Cd40, Ucp1, Prdm16, and Pgc-1 α $\uparrow$	(Fan et al., 2019)
Nicotine		Chow-fed Sprague-Dawley rat and null κ opioid receptor mice	25 mg/kg	14 days	hypothalamic κ opioid receptor, Ppargc1a, Cidea, Prdm16, and Ucp1 $\uparrow$	(Seoane-Collazo et al., 2019)
Caffeine		HFD-induced C57BL6/J mice	2.5 and 25 mg/mL	18 weeks	Irisin, PGC-1 α , UCP1, PPAR γ , and COX2 $\uparrow$	(C. Liu et al., 2023)

Theobromine		AIN-93 M diet induced C57BL6/J mice	0.05% and 0.1%	63 days	PPAR γ , UCP1 and COXIV $\uparrow$	(Tanaka et al., 2022)
Polysaccharide						
Tea polysaccharides		HFD-induced C57BL6/J mice	100, 200, or 400 mg/kg	8 weeks	PRDM16 and UCP1 $\uparrow$	(Du et al., 2022)
Astragalus polysaccharide		Dahl salt-sensitive rats fed with HFD	200 or 800 mg/kg	6 weeks	Cd137 and Zic-1 UCP1 $\uparrow$	(Ma et al., 2023)
Taraxacum mongolicum polysaccharide		Sheep white adipocyte precursor cells	300 and 600 μ g/mL	24 h	AKT/GSK-3 β signalling Prdm16, UCP1, Cidea, PGC-1 α , and PPAR γ $\uparrow$	(Yue et al., 2024)
Mulberry leaf polysaccharides		HFD-induced C57BL6/J mice	200, 400 or 800 mg/kg	8 weeks	SIRT1, UCP-1, PGC-1 α and PRDM16 $\uparrow$	(R. Li et al., 2022)

Neogarotetraose		HFD-induced C57BL6/J mice	200, 400 or 800 mg/kg	12 weeks	SIRT1, UCP-1, PGC-1 α , Cidea, Cd137, PRDM16, and TMEM26 $\uparrow$	(N. Zhang et al., 2022)
Fucoidan		3T3-L1 White Adipocytes	200 g/mL	9 days	UCP-1, PRDM16, and PGC-1 α $\uparrow$	(Park et al., 2023)
Terpenoids						
Phytol		HFD-induced C57BL6/J mice	500 mg/kg	7 weeks	UCP-1, PRDM16, PGC-1 α , PDH, and Cyto C $\uparrow$	(F. Zhang et al., 2018)
Fucoxanthin		AIN-93 diets-fed KK-Ay mice	0.4%	4 weeks	UCP1 $\uparrow$	(Maeda et al., 2005)

Gypenoside		HFD-induced C57BL6/J mice	300 mg/kg	12 weeks	UCP-1, PGC-1 α , PRDM16, AMPK α , Cidea, Cox7 α , and Elov13 $\uparrow$	(J. Liu, et al., 2017)
Menthol		HFD-induced C57BL6/J mice	1%	12 weeks	UCP-1, PGC-1 α , PRDM16, β 3-AR, and TRPM8 $\uparrow$	(C. Jiang, et al., 2017)
Celastrol		HFD-induced C57BL6/J mice	100 μ g/kg	21 days	PRDM16, Cidea, Elov13, TMEM26, CD137, SP100, Tbx1, Scl27a1, and Hsp70 $\uparrow$	(Fang et al., 2019)
Ursolic acid		HFD-induced C57BL6/J mice	300 mg/kg	10 weeks	FNDC5, UCP1, PRDM16, PGC-1 α , CD137, TBX1 and TMEM26 $\uparrow$	(Sun et al., 2021)
Organosulfur compounds						
Diallyl trisulphide		3T3-L1 adipocytes	50 μ M	3-6 h	PGC-1 β and UCP1 $\uparrow$	(Chang, Wu, &

						Hsu, 2015)
Carotenoids (pigments)						
β -Carotene		3T3-L1 adipocytes	20 μ M	6-8 days	UCP1 $\uparrow$	(Choi & Yun, 2023)
β -Cryptoxanthin		HFD-induced C57BL6/J mice	0.05%	12 weeks	RAR, UCP1 $\uparrow$	(Hara et al., 2019)
Retinoic acid		C57BL/6 mice fed with a diet containing 15 IU g ⁻¹ Vitamin A	10 mg/kg	1 week	Prdm16, Ucp1, Elovl3 and Cox7a1 $\uparrow$	(Wang et al., 2017)
Lycopene		HFD-induced ICR mice	15 mg/kg	10 weeks	VEGFA/p38MAPK, PPAR γ , PRDM16, PGC-1 α and UCP1 $\uparrow$	(Zhu et al., 2020)
Zeaxanthin		HFD-induced C57BL/6N	20 mg/kg	22 weeks	β_3 -AR, PRDM16, PGC-1 α ,	(Xie et al.,

		mice			and UCP1↑	2021)
Omega-3 Fatty Acids						
Eicosapentaenoic acid		High-fructose-fed mice	0.847%	5 weeks	FNDC5, PPAR α , PPAR γ , NRF1, PGC1, TFAM, UCP1↑	(Bargut et al., 2019)
docosahexaenoic acid						
Linoleic acid		HFD-induced C57BL/6N mice	1.5%	13 weeks	CD36-AMPK, UCP1 ↑	(Zhang et al., 2024)

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1215 **Table 2. The Adipose Tissue-Specific Targeting Strategies**

Nanosystems	Targeted Strategies		Advantages	Limitations	References
D(KLAKLAK)2-prohibitin-targeted NPs	EPR-like passive accumulation to angiogenic regions	Passive targeting; Active targeting	Reduction in undesired entrapment in liver; Improvement of the efficient targeting to adipose vessels; Suppression of body weight	Combination of active targeting and passive accumulation enhances PTNP delivery, but have not differentiated the proportion of contribution between the two through experimentation (e.g., competitive inhibition assay or ligand-deficient control)	(Hossen et al., 2012)
DBZ-loaded PLGA NPs	Local injection in iWAT	Local delivery	Avoids off-target side effects; Browning of adipocytes	Leakage concentrations of DBZ in plasma were not detected or assessed to see if Notch activity was inhibited in organs such as the liver and intestine	(Jiang et al., 2017)
DBZ-loaded PLGA microsphere	Local injection in iWAT	Local delivery	Stimulate browning of WAT	Experiments did not demonstrate <i>in vivo</i> DBZ release profiles (e.g., cumulative release rate over 1 week, half-life)	(Jiang et al., 2015)

CKGGRAKDC peptide	Adipose tissue vasculature targeting	Active targeting	Resorption of established WAT and without detectable adverse effects	Failed to demonstrate by tissue distribution assays (e.g. immunofluorescence co-localisation) that the CKGGRAKDC peptides bind only to adipose vascular prohibitin, which may lead to systemic vascular injury (e.g., apoptosis of endothelial cells)	(Kolonin et al., 2004)
KGGRAKD-PEG liposomes	Adipose tissue vasculature targeting	Active targeting	Specifically taken up into the endothelial cells from iWAT via prohibitin-mediated endocytosis	The study only validated the targeting and uptake mechanism of the vector at the in vitro cellular level and lacked in vivo experimental data	(Hossen et al., 2010)
Rosi-R8-modified non-targeted NPs	Adipose tissue vasculature targeting	Active targeting	Minimize the off-target effects of Rosi and maximize its browning activity	Serum creatinine/urea nitrogen not assessed, may miss NPs renal clearance burden	(Hiradate et al., 2021)
PLGA-b-	Adipose tissue	Active targeting	An angiogenesis-targeted	Studies have not fully assessed the distribution and	(Xue et al., 2016)

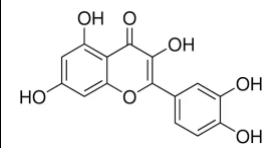
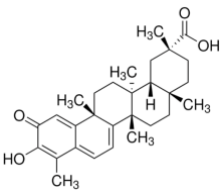
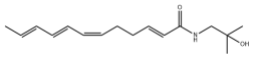
poly(ethyleneglycol) (PLGA-b-PEG)-Peptide/Rosi NPs	vasculature targeting		nanomedicine approach to deliver adipose tissue browning agents and simultaneously stimulate angiogenesis in WAT	potential toxicity of NPs in non-target tissues (e.g., liver, spleen, kidney, etc.). NPs may accumulate in these organs, leading to adverse effects; The stability of NPs in vivo (e.g., whether they are degraded or cleared) has not been fully explored and may affect their long-term effects.	
CSWKYWFGEC	ASC targeting	Active targeting	Identification of CSWKYWFGEC Peptide as a probe binding human ASCs	NS	(Daquinag et., 2017)
DSPE-PEG5000-GSWKYWFGEG GC conjugate	ASC targeting	Active targeting	Designed a new linear peptide (GSWKYWFGEGGC) bind to the delta decorin receptor on adipose stromal cells	NS	(Zu et al., 2021)

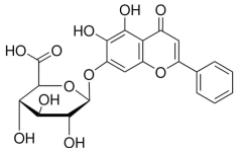
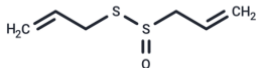
Rosi loaded NPs	Microneedles	Local delivery	Effectively deliver Rosi to the subcutaneous adipocytes; increased browning of WAT	In vitro/in vivo release curves for Rosi were not provided, and the matching of the degradation rate of microneedle materials (e.g., hyaluronic acid) to the release of the drug was not clarified	(Zhang et al., 2017)
Polydopamine (PDA) NPs	Microneedles	Local delivery	Excellent biocompatibility; Enhanced UCP1 expression	Long-term toxicologic data over 6 months are lacking	(Gao et al., 2024)
Metformin (non-nano systems)	Microneedles	Local delivery	Developed as a penetration enhancer, overcoming existing disadvantages related to hypodermic needle usage and improving patient compliance	Drug loading and release kinetics of microneedle delivery systems may affect efficacy, with insufficient local concentrations or short release times that may not sustain activation of browning. Differences in effect of different doses or delivery frequencies were not compared	(Abbasi et al., 2022)

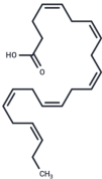
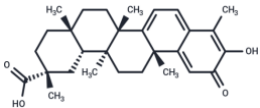
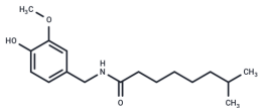
1216 DBZ: dibenzazepine; DSPE-PEG5000: N-(methylpolyoxyethylene oxycarbonyl)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine; EPR:

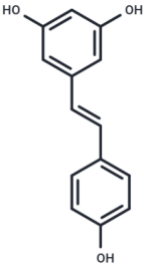
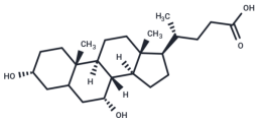
1217 enhanced permeability and retention; NPs: nanoparticles; NS, no shown; PEG: polyethylene glycol; PLGA: poly(lactide-co-glycolide); PTNP:
1218 prohibitin-targeted nanoparticles; Rosi: Rosiglitazone
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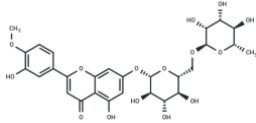
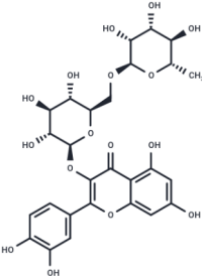
1230 **Table 3. The targeted delivery of active ingredients to promote WAT browning**

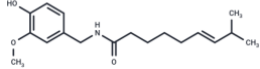
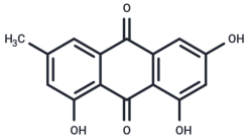
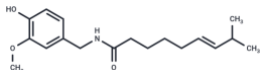
Targeting Agent	Structure	Nanosystems	Wall materials	Targeted delivery vehicle	Results	References
Quercetin		Liposomes	DSPE-PEG2000-P3 and egg yolk lecithin	WAT vasculature targeting	Decreased lipid droplet numbers; Stimulated lipolysis and FFA release	(Tang et al., 2024)
Celastrol		NPs	AHP (adipose homing peptides)-NPs@TMC(N-trimethyl chitosan)	WAT vasculature targeting	Improved internalization; Stronger effects in reducing body weight and promoting WAT browning compared with free celastrol	(Xian et al., 2023)
Hydroxy- α -sanshool		Mesoporous Silica NPs	MSN surface was modified by the short peptide ATS	WAT vasculature targeting	HAS-loaded MSNs-ATS showed effects of white adipose browning	(Zhang et al., 2025)

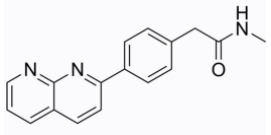
			CKGGRAKDC, and complex was loaded into the HAS (HAS@MSNs-ATS)		superior to those of HAS alone	
Baicalin		Nanoflowers	Polymerase chain reaction(PCR)-driven DNA nanoflowers	Adipocytes targeting	Assembly efficiency improvement; Payload efficacy enhancement; Increased thermogenesis and lipid- lowering effects	(Tian, Zhong et al., 2023)
Allicin		Nanoflower	Aptamer-functionalized nanoflower-allicin delivery system (NFA) constructed with the adipo-8 aptamer	Adipocytes targeting	Superior effect in activating BAT thermogenesis and promoting the beiging of WAT; Good biocompatibility with minimal side effects	(Wang et al., 2024)

Docosaheptaenoic acid		Nanogel	Aptamer-functionalized AuNCs	Adipocytes targeting	Low toxicity; Stronger browning of white adipocytes	(Xu et al., 2023)
Celastrol		Micelles	CLT-loaded 4-aminophenylboronic acid pinacol ester-modified chondroitin sulfate micelle (CS-PBE/CLT)	Adipocytes targeting	More effective in reducing the body weight and browning of WAT	(Niu et al., 2024)
Nordihydrocapsaicin		Liposomes	adipo-8 aptamer was combined with liposomes loaded with NOR at a DMPC: cholesterol: DSPE-PEG2000 M ratio of 10:2:1	Adipocytes targeting	Elevated UCP1, PPAR α and PPAR γ in WAT compared with nordihydrocapsaicin native	(Song et al., 2024)

Resveratrol		NPs	Conjugate composed of soy phosphatidylcholine (PC), alpha-tocopherol acetate (α TA), Kolliphor® HS15, and DSPE-PEG5000-GSWKYWFGEGGC	ASCs targeting	Higher suppression in body weight, body fat percentage and blood lipid; Higher upregulation of UCP1	(Zu et al., 2021)
			A lipid mixture composed of vitamin E acetate, soy phosphatidylcholine, Kolliphor HS15 with or without the CSWKYWFGE	ASCs targeting	Superior to native in enhancing beige cell formation and thermogenesis	(Zu, & Wang, 2017)
Chenodeoxycholic acid		NPs	CDCA-loaded β -CD-conjugated gelatin NPs	WAT injection	Greater efficacy than empty carriers in reducing adipocyte volume and	(Zhou et al., 2024)

					promoting brown and subcutaneous WAT thermogenesis	
Diosmin		NS	NS	WAT injection	Stronger effects in upregulating brown gene programs and UCP1 protein levels; No obvious side effects in water retention and cardiovascular systems	(Yu et al., 2023)
Rutin		Liposomes	Rutin-loaded liposomes <i>via</i> the self-assembly of lecithin and cholesterol in MN	MN	Lower body weight, WAT weight, and respiratory quotient in comparison to free rutin; Higher expression of adipose browning-associated proteins (e.g., UCP1 and Cytochrome c)	(Li, Liang, Sun, & Bao, 2023)

Capsaicin		Nanomicelles	Self-assembly process of α -lactalbumin amphiphilic peptides located in MN	MN	Higher TRPV1 expression, mitochondria biogenesis, and browning of WAT versus capsaicin native	(Bao et al., 2021)
Emodin		NS	Emodin-PVP coprecipitate located in MN patch	MN	No obvious toxicity; promotion of fat consumption, reduction of serum FFAs and WAT weight	(Wang et al., 2025)
Capsaicin		NPs	NPs formulated using clove oil, ethanol, PEG400, and sodium caseinate	MN	Dramatically prolong the local accumulation in subcutaneous adipocytes with extended circulation time in plasma	(Mudhol et al., 2023)

Succinate		NS	Succinate-encapsulated microneedle	MN	Elevated energy dissipation and browning markers in WAT compared with non-encapsulation	(Liao et al., 2022)
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1231 ATS: adipose-targeting sequence; HAS: hydroxy- α -sanshool; MN: microneedle, NPs: Nanoparticles; NS: no show; PVP: polyvinylpyrrolidone;

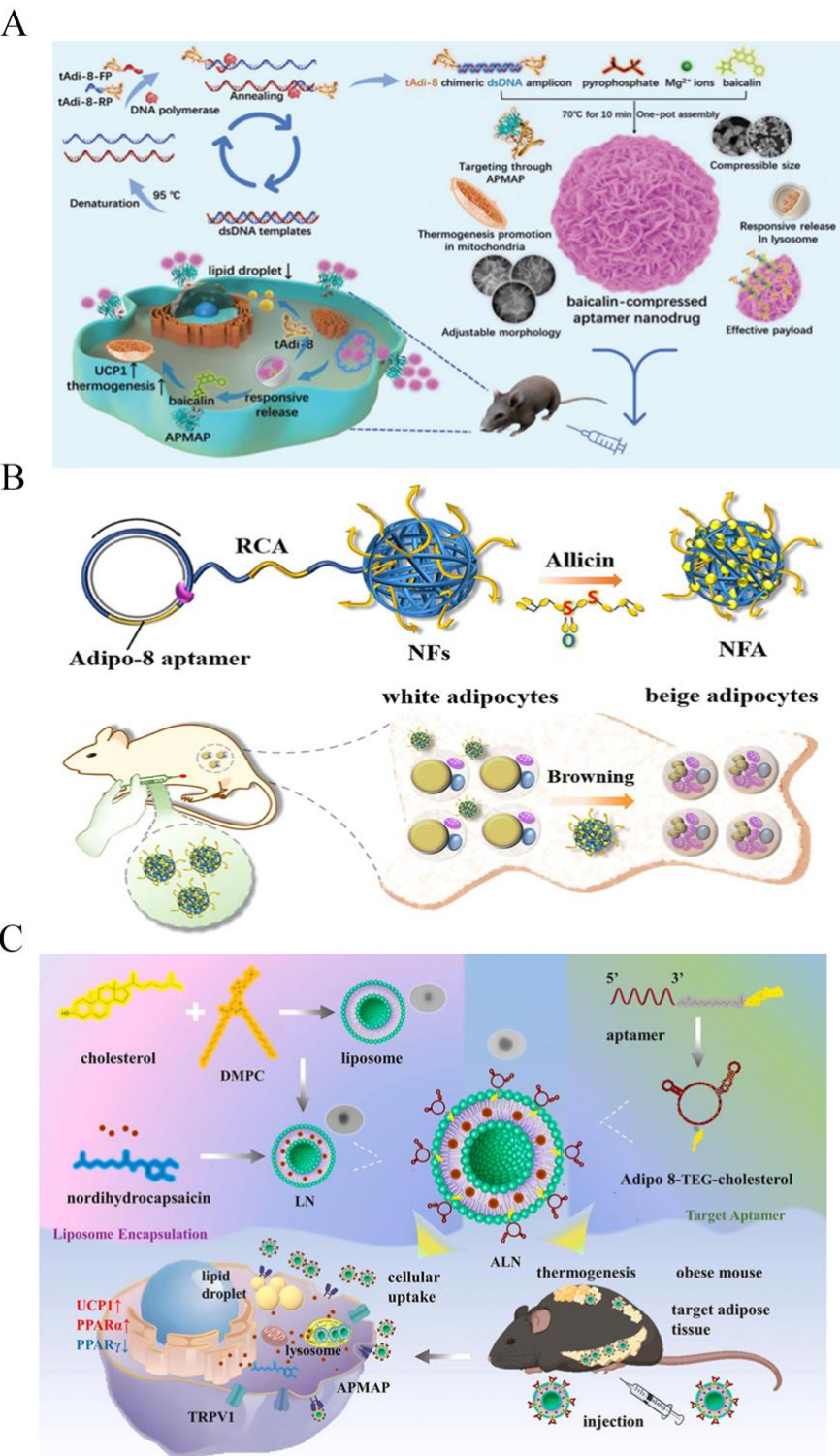
1232 WAT: white adipose tissue

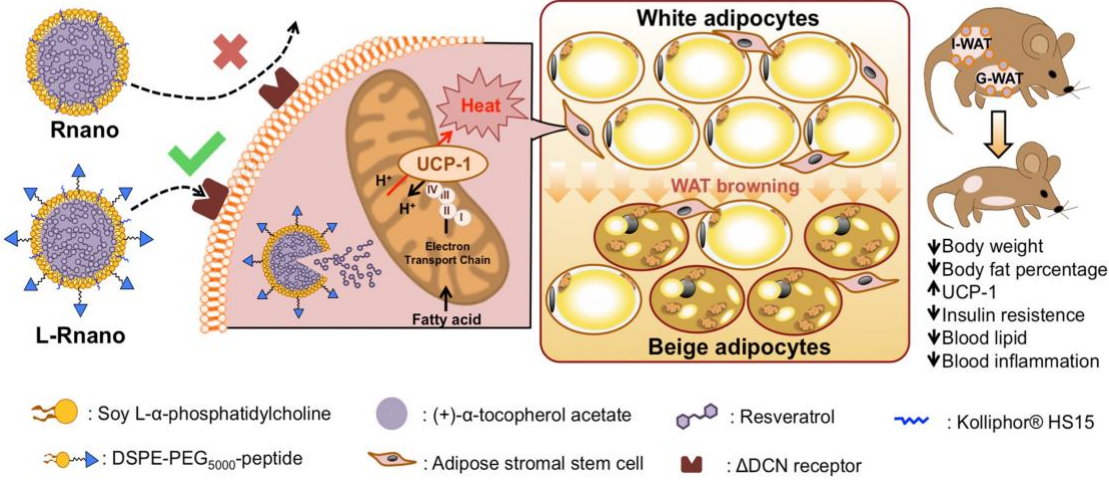
Fig. 1 Food-derived bioactives targeting white adipocytes. (A) The bcaND, constructed from baicalin and tAdi-8, is rationally designed for synergetic and targeted obesity therapy. Through the one-pot controllable assembly, the baicalin, PCR amplicons, PPI, and Mg^{2+} assemble into an advanced multifunctional nano-vehicle for targeting fat, accelerating thermogenesis, and improving assembly efficiency (License Number: 5898690164299). (B) Schematic illustration of the synthesis process of aptamer-functionalized binary-allicin delivery system. The DNA-nanoflower-allicin (NFA) binds to the target receptor in the cellular membrane and released allicin decreases the stability of **intracellular target (G454)** in the UCP1 promoter, triggering the expression of UCP1 of adipose cells, increasing systematic energy expenditure (Reproduced with permission from T. Wang (2024). Copyright 2023, American Chemical Society). (C) Aptamer-liposome-nordihydrocapsaicin (NOR)-encapsulated nanosystems (ALN) were constructed *via* film dispersion ultrasonication using liposome-anchored aptamers for obesity treatment. DMPC and cholesterol were used as the liposome bilayer materials, and the adipo-8, as the targeting part of ALN riveted onto liposomes, could enable ALN to reduce adsorption to other tissues and targeted the APMAP receptor in adipocytes, which inducing the browning of WAT (License Number: 5899130471621).

Fig. 2 The working mechanisms of resveratrol (R) targeting ASCs. R-encapsulated nanoparticles (Rnano) are equipped with DSPE-PEG₅₀₀₀-peptide GSWKYWFGEGGC that specifically targets the ASCs by binding with high affinity to the Δ DCN receptor on their surface. Upon being taken up by the ASCs within the inguinal WAT(I-WAT),

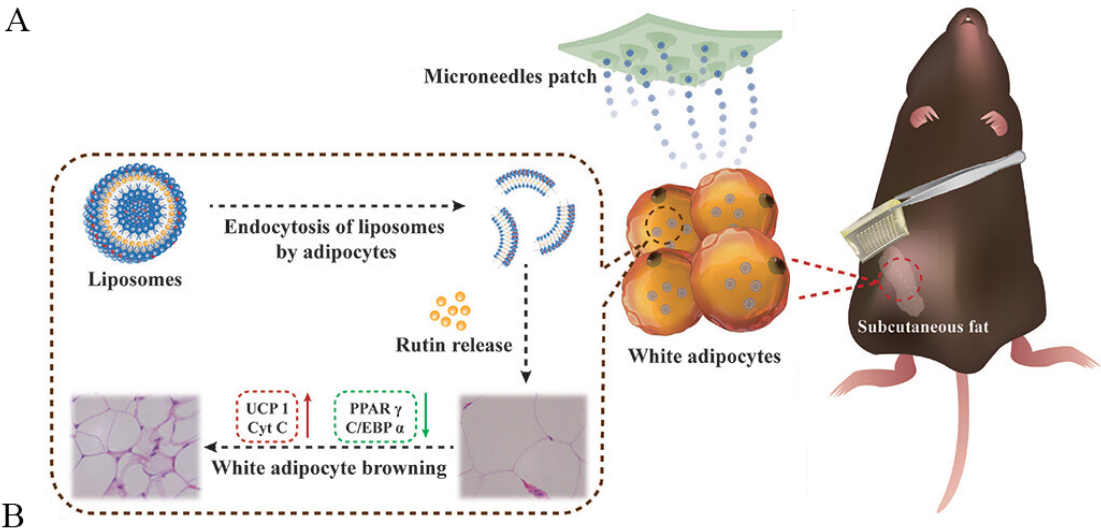
ligand-coated R-encapsulated nanoparticles (L-Rnano) releases the active compound R, which prompts the ASCs to differentiate into beige adipocytes, leading to the browning of WAT, reduction in body fat, and enhancement of metabolic health (License Number: 5898680893704).

Fig. 3 Microneedle delivery of food-derived bioactives. (A) Rutin was encapsulated in liposomes *via* the self-assembly of lecithin and cholesterol. These rutin-loaded liposomes were subsequently incorporated into a microneedle patch (MP) system composed of polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA). Upon release, rutin reduced body weight in HFD-fed mice by suppressing lipid synthesis-related proteins (PPAR γ and C/EBP α) while upregulating key markers of beige adipogenesis (UCP1 and Cyt C). (Reproduced with permission from Li, Liang, Sun, & Bao (2023). Copyright 2023, American Chemical Society). (B) Capsaicin-encapsulated micelles (M (Cap)) were fabricated through the self-assembly of α -lactalbumin-derived peptides and Cap. These M (Cap) were subsequently incorporated into a dissolving microneedle patch (MN) composed of hyaluronic acid (HA) and polyvinyl alcohol (PVA). The M (Cap)-loaded MN was applied transdermally to the subcutaneous fat of HFD-fed mice, enabling sustained release of capsaicin to induce WAT browning (License Number: 5899121253077). BLP: *Bacillus licheniformis* endoprotease.





A



B

