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REVIEW

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Keys to the switch of fat burning: stimuli that trigger the uncoupling protein 1 (UCP1) activation in adipose tissue

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Abstract

As one of the main pathogenic factors of cardiovascular and cerebrovascular diseases, the incidence of metabolic diseases such as adiposity and metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing annually. It is urgent and crucial to find more therapeutic targets to treat these diseases. Mainly expressed in brown adipocytes, mitochondrial uncoupling protein 1 (UCP1) is key to the thermogenesis of classical brown adipose tissue (BAT). Furthermore, white adipose tissue (WAT) is likely to express more UCP1 and subsequently acquire the ability to undergo thermogenesis under certain stimuli. Therefore, targeting and activating UCP1 to promote increased BAT thermogenesis and browning of WAT are helpful in treating metabolic diseases, such as adiposity and MASLD. In this case, the stimuli that activate UCP1 are emerging. Therefore, we summarize the thermogenic stimuli that have activated UCP1 in recent decades, among which cold exposure is one of the stimuli first discovered to activate BAT thermogenesis. As a convenient and efficient therapy with few side effects and good metabolic benefits, physical exercise can also activate the expression of UCP1 in adipose tissue. Notably, for the first time, we have summarized and demonstrated the stimuli of traditional Chinese medicines that can activate UCP1, such as acupuncture, Chinese herbal formulas, and Chinese medicinal herbs. Moreover, pharmacological agents, functional foods, food ingredients, and the gut microbiota are also commonly associated with regulating and activating UCP1. The identification and analysis of UCP1 stimuli can greatly facilitate our understanding of adipose tissue thermogenesis, including the browning of WAT. Thus, it is more conducive to further research and therapy for glucose and lipid metabolism disorders.

Keywords The uncoupling protein 1, Brown adipose tissue, White adipose tissue, Browning of white adipose tissue

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Introduction

With the expansion of the economy and society, diseases related to glucose and lipid metabolism disorders, such as hyperlipidemia, adiposity, and MASLD, are increasing daily and have become vital factors that are hazardous to human health [1]. Adipose tissue plays a crucial role in the occurrence of metabolic diseases and has become a new direction in seeking treatments. There are two main types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). As a main source of thermogenesis in mammals, BAT can increase energy consumption through nonshivering thermogenesis promoted by UCP1. Therefore, BAT, especially UCP1, may become a potential therapeutic target for treating diseases such as obesity and other related metabolic diseases.

Moreover, studies have shown that brown-like adipocytes can also be found in WAT depots; these so-called "beige" or "brite" adipocytes can be observed only in the WAT of animals that have experienced cold or other stimuli [2]. Beige adipocytes have a morphology similar to that of brown adipocytes, such as multilocular lipid droplets, abundant mitochondria, and UCP1 expression; these properties endow beige adipocytes with the same functions as brown adipocytes. Brown adipocytes express a relatively large quantity of UCP1 even with no stimulation, but beige adipocytes can only produce UCP1 under stimulated conditions. Brown and beige adipocytes both possess the ability to metabolize glucose and fats to generate heat. In particular, brite adipocytes can exhibit equivalent levels of UCP1 expression to brown adipocytes and engage in UCP1-dependent uncoupled respiration under full activation [3].

Essentially, stimuli such as cold, exercise, and pharmaceutical agents have the potential to trigger the activation of UCP1 within brown and white fat cells. This activation can subsequently increase heat production, improving conditions such as adiposity. The distribution and fat mass of WAT and BAT in obese and healthy individuals, the stimuli that influence the expression level of UCP1, and the structure of all adipocytes are shown in Fig. 1.

The thermogenic role of brown or brite adipocytes relies significantly on the stimulation of UCP1 [6]. When activated, UCP1 dissipates the proton gradient created by the electron transport chain [7]. UCP1 is the pivotal factor for the heat production of classical BAT and beige adipocytes. Nevertheless, owing to intrinsic inhibitory mechanisms, UCP1 remains quiescent and fails to generate heat under nonactivated situations [8]. Activating UCP1 is one of the methods used to increase the heat consumption of BAT. Moreover, inducing the production

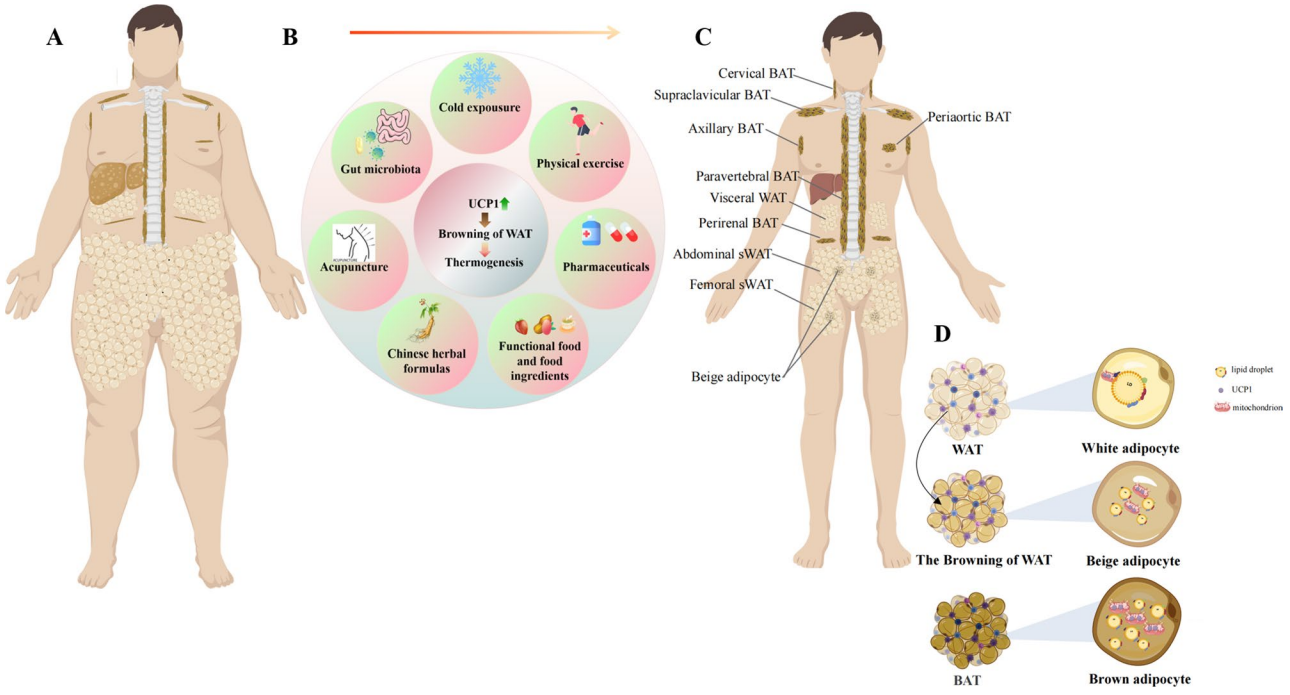


Fig. 1 Overview of adipocyte structure, adipose tissue distribution, and stimuli that activate UCP1. **A**: The distribution and fat mass of WAT and BAT in the obese human body. **B**: Stimuli that stimulate WAT browning. **C**: The distribution and fat mass of WAT and BAT in the healthy body. WAT is primarily categorized into visceral WAT and subcutaneous WAT. WAT is distributed primarily among key organs and blood vessels in the abdominal cavity as well as under the skin [4]. In contrast, BAT constitutes a small portion of all adult human fat tissue and can be found in the mediastinal, supraclavicular, abdominal, cervical, axillary, and paraspinal regions [5]. **D**: Characteristics of different fat cells. Abundant mitochondria, multilocular lipid droplets, and abundant UCP1 characterize brown adipocytes. The morphological and structural characteristics of white adipocytes are opposite those of brown adipocytes. Brite adipocytes have similar morphologies and functions as brown adipocytes

of brite adipocytes, namely, promoting the generation of UCP1 in WAT, is another way to promote thermogenesis. Researchers previously reported that there is more BAT in newborns than in adults, so BAT is critical for maintaining body temperature in infants. However, it cannot increase the heat production of adults. Owing to the development of 18 F-FDG-PET technology and other measurement techniques, emerging studies have shown that adults also have substantial depots of 18 F-FDG PET-positive adipocytes and UCP1+adipose cells, i.e., BAT [9], and when exposed to stimulus situations, these tissues can absorb glucose [10–14].

According to these studies, activating UCP1 in BAT and inducing UCP1 expression in WAT to stimulate the browning of WAT are key methods for increasing heat production. Furthermore, targeting UCP1 could offer a strategy for treating metabolic diseases. Researchers may be interested in the stimuli that activate UCP1 [15]. Therefore, this paper aims to update and summarize the experimental and clinical evidence of stimuli that can activate UCP1. Moreover, for the first time, we have summarized the stimuli of traditional Chinese medicine that can activate UCP1, such as acupuncture, Chinese herbal formulas, and Chinese medicinal herbs. We hope that this perspective can provide ideas and prospects for targeting UCP1 to treat metabolic diseases.

Characterization of UCP1

The mitochondrial inner membrane contains uncoupling proteins (UCPs), which act as metabolite transporters, facilitating controlled dissipation of the proton gradient produced by the respiratory chain [16]. These proteins typically have molecular masses ranging from 31 to 34 kDa. Additionally, five isoforms of UCPs exist, spanning from UCP1 to UCP5, which are distributed across various species and tissues, including animals, plants, fungi, and protozoa [17, 18]. For example, UCP1 is expressed mainly in brown adipocytes of mammals. UCP2 is widely distributed among most cell types. UCP3, on the other hand, is expressed only in skeletal muscle and BAT, whereas UCP4 and UCP5 are exclusively expressed in the brain [16]. Although UCP1 is pivotal for no-shivering thermogenesis and has been extensively explored by numerous researchers, UCP2 is postulated to be involved in lipid metabolism, and UCP3 could afford protection against lipid-induced oxidative damage [19]; however, the characterization and function or transport properties of UCPs, particularly UCP1, still require further examination.

The structure of UCP1

The structure of a protein determines its function. Like other UCPs, UCP1 features a structural pattern consisting of three reiterated components. Within each module, a sequence of amino acids elegantly forms a loop that traverses the membrane twice, thereby creating six transmembrane helices, labeled TM1 to TM6 [20]. Conserved proline residues create bends in odd-numbered helices, whereas conserved glycines facilitate polypeptide chain mobility. Helices 4 and 6 also contain conserved prolines, contributing to structural variations [21]. Many articles have exhaustively examined and elucidated the structural characteristics of UCP1, providing a comprehensive understanding of its unique features [16, 20–22].

As a metabolite carrier and thermogenin, UCP1 can transport fatty acids and nucleotides across the inner membrane of the mitochondrion through the coordinated movements of its helices, which control the proton-conducting activity of UCP1 [22]. Usually, the proton-conducting ability of UCP1 is inhibited by purine nucleotides, and when the concentration of free fatty acids is elevated in BAT, the inhibitory effect of purine nucleotides on UCP1 is controlled, and UCP1 can be activated for heat production [22].

The function of UCP1

UCP1, the most extensively studied isoform of UCP, is expressed predominantly in brown adipocytes and beige adipocytes of various mammalian species, including mice, rats, and humans. In addition, it has been found in the liver, kidney, and brain of certain fish species, indicating its widespread distribution and diverse physiological roles [23]. Numerous studies suggest that the core of BAT thermogenesis and overall energy balance lies in the direct control of UCP1 protein function. Upon activation, UCP1 catalyzes heat production through the dispersion of the proton gradient energy; i.e., after UCP1 facilitates proton escape, the acquired energy cannot be stored as ATP but is instead released as heat [24, 25]. Free fatty acids function as substrates that trigger the activation of UCP1 [26]. Upon activation through the binding of a fatty acid, UCP1 facilitates the transfer of protons from the membrane space into the mitochondrial matrix [27]. Furthermore, concurrent with the activation of UCP1, there is an increased utilization of glucose [26, 28]. Hence, during UCP1-mediated thermogenesis, the consumption of fatty acids and glucose also increases, contributing significantly to the improvement of adiposity and associated metabolic diseases.

In addition, to detect brite adipocytes among white adipocytes, we must identify the ectopic expression of UCP1. In other words, UCP1 is a key transcription factor that promotes WAT browning. Therefore, facilitating the elevation of UCP1 in adipose tissue is conducive to augmenting thermogenesis, thereby improving obesity or related metabolic diseases [29]. Conversely, the absence of UCP1 leads to a notable decrease in BAT heat production [30]. As an illustrative example, UCP1 knockout

neonatal mice presented lower skin temperatures surrounding the interscapular region and exhibited weight loss upon weaning. This observation underscores the crucial role of UCP1 as a bright regulatory target for maintaining body temperature during the early stages of life [31]. Moreover, the absence of UCP1 hinders BAT thermogenesis in both neonatal and mature mice, as determined through infrared imaging and indirect calorimetry, respectively [32].

In conclusion, enhancing thermogenic UCP1 and BAT activity in humans to increase energy expenditure could be highly beneficial in addressing metabolic diseases, such as adiposity and MASLD. The search for UCP1 stimuli is necessary and urgent.

Physical and environmental factors–cold stimulation

Under conditions of thermoneutrality, WAT depots primarily lack UCP1, resulting in a significant deficiency. However, when animals are chronically exposed to cold conditions, they undergo acclimation processes that involve the expansion of brown adipocytes and the upregulation of UCP1, enabling them to generate heat effectively [9]. In other words, exposure to cold conditions can stimulate the production of new thermogenic adipocytes in adipose tissues [33]. Consistent with these findings, numerous subsequent studies have corroborated these results [34]. Aleksandra et al. [35] reported an increase in UCP1 mRNA in rpWAT after exposure to cold. Walden et al. [36, 37] further demonstrated that when animals are maintained at room temperature (20℃), UCP1 levels in adipose tissue are minimal. However, when animals are placed in cold conditions (4℃), a remarkable increase in UCP1 is observed in fat tissue.

Cold exposure initiates the heat production of BAT via UCP1 activation, which in turn triggers significant modifications in the metabolism of glucose, lipids, and amino acids. Okamatsu-Ogura Y et al. [38] demonstrated that in wild-type mice, the levels of glycolytic metabolites increase significantly after exposure to cold temperatures. However, in UCP1-KO mice, the levels of these metabolites are notably decreased. These findings suggest that cold conditions trigger UCP1-stimulated thermogenesis in adipose tissue, which in turn has a profound effect on glucose utilization. Furthermore, exposure to cold primarily stimulates the metabolism of amino acids in adipose tissue, specifically enhancing glutamine utilization in a UCP1-dependent manner. This may be one of the mechanisms mediating the improvement in adiposity. However, Sepa-Kishi DM et al. [39] recently presented groundbreaking findings that, despite the marked elevation of UCP1 levels in inguinal WAT and the induction of browning in this adipose depot upon exposure to cold, adipocytes from this depot fail to exhibit an increase in glucose and lipid oxidation through UCP1-mediated mitochondrial uncoupling. These results clearly emphasize the imperative need for further investigation into the intricate mechanism by which UCP1 influences the regulation of glycolipid metabolism.

Regarding the mechanism underlying the elevation of UCP1 through cold exposure, the sympathetic nervous system (SNS)-catecholamine (CA)-UCP1 pathway plays a pivotal role [40]. When sympathetic nerves are stimulated by cold exposure, the SNS releases the CA (epinephrine and norepinephrine). Furthermore, CA activates protein kinase A (PKA) via adrenoreceptors (ARs), such as β3-AR. Subsequently, PKA significantly impacts UCP1 activity by orchestrating various cellular processes. These include AIDA, a protein containing a C2 domain known for its ability to counter obesity induced by diet, as well as the fatty acids generated through the breakdown of lipid droplets inside adipocytes [27, 41] (fatty acids, as the substrate of UCP1, can activate UCP1 directly and overcome the inhibition of purine nucleotides on UCP1 [27]). This cascade of events initiates a diverse array of alterations in adipose tissue, ultimately resulting in increased heat production. Moreover, the PGC-1α–PPARγ signaling cascade plays a pivotal role in inducing and activating UCP1 expression in WAT during cold exposure [35] (Fig. 2).

Importantly, maintaining a sustained thermogenic response and ensuring a sufficient population of brown-like adipocytes possessing thermogenic functions are crucial for the browning process of WAT. Both aspects above that induce browning are equally important and could exert a significant impact on maintaining overall energy balance and regulating body mass in the long run [35]. However, cold exposure can cause initial, dramatic, but transitory nonselective browning of most adipocytes in retroperitoneal WAT (rWAT), but few adipocytes maintain brown-like characteristics in the long term [35]. Therefore, cold stimulation may have limited significance in stimulating WAT browning and increasing heat production capacity.

In addition, its underlying mechanism for enhancing heat production remains worthy of further exploration. For example, the combination of cold exposure with other browning agents, such as pioglitazone, can significantly increase the heat production capacity of adipose tissue [42]. Alternatively, the topical use of a pharmacological cold mimic such as L-menthol, a transient receptor potential (TRPM8) cation channel subfamily M member 8 (TRPM8)) agonist, can facilitate the thermogenesis of brown fat via the activation of TRPM8 and UCP1 and the release of norepinephrine. These findings indicate that pharmacological cold mimetics, which are capable of simulating cold conditions, can achieve effects similar to those induced by actual cold exposure. The utilization of agents that mimic the natural activation

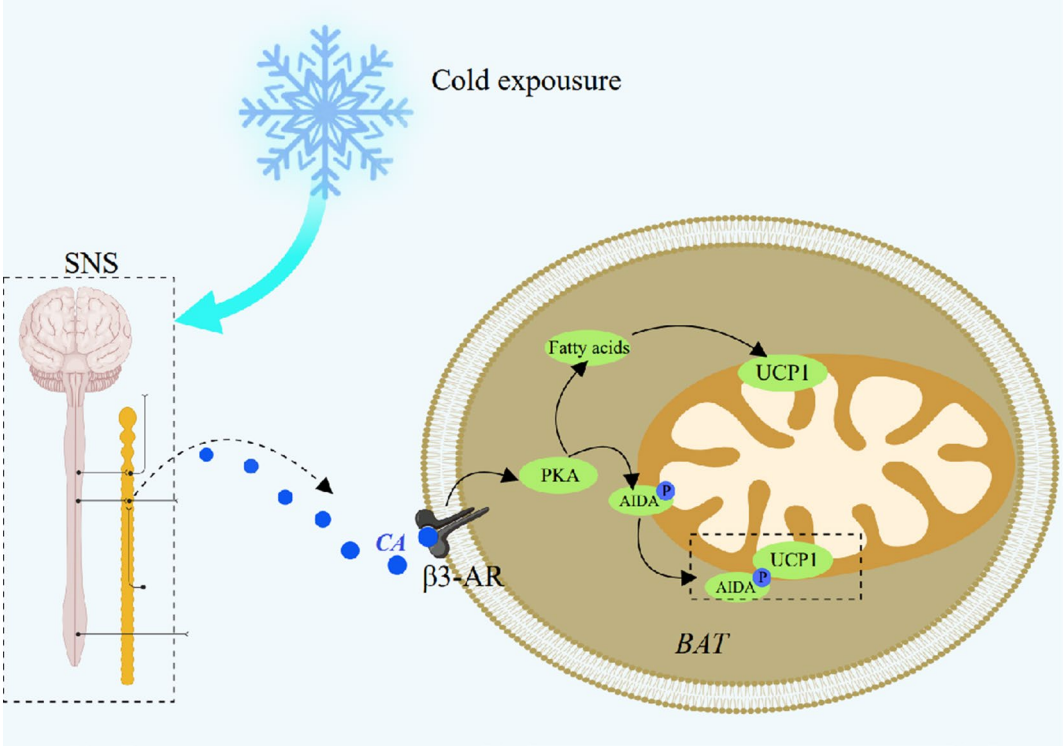


Fig. 2 The partial mechanisms by which cold exposure activates UCP1. Upon exposure to cold temperatures, both animals and humans trigger the activation of the sympathetic nervous system (SNS). This leads to the release of catecholamines (CAs) from the sympathetic nerves that innervate BAT, consequently initiating the activation of β-adrenergic receptors (β-AR) and subsequent downstream signaling pathways, such as the PKA/p-AIDA pathway, ultimately activating UCP1 activity

of BAT presents promising avenues for addressing obesity while minimizing the overall impact on the body. Furthermore, it may circumvent some of the limitations associated with traditional cold induction methods [43].

Furthermore, it is crucial to recognize that exposure to cold temperatures poses a potential risk of promoting the growth and instability of atherosclerotic plaques, a process that is facilitated by UCP1-mediated lipolysis [44]. Therefore, for individuals who already have preatherosclerotic lesions, the thermogenesis of BAT induced by cold exposure might not necessarily be beneficial for improving certain diseases. Moreover, some scholars have proposed that increasing global temperatures could diminish BAT activity [45]. At thermoneutrality, UCP1 also fails to provide protection against obesity or other metabolic diseases induced by dietary factors [32]. Therefore, establishing reliable animal models under thermoneutral conditions, which can help researchers assess diet and agent capacity for thermogenesis precisely, is urgently needed [46].

Physical and environmental factors–exercises

Engaging in physical exercise can enhance cardiometabolic health, improve pregnancy complications [47], and promote weight loss by establishing a caloric deficit [48]. Even if weight and body composition remain unchanged, engaging in physical exercise still provides beneficial metabolic effects. They are often used as a practical way to manage adiposity and other metabolic diseases. In addition, exercise can decrease BAT whitening in obese individuals [49] and is also a well-known trigger for WAT browning.

Exercise can be broadly categorized into two types: aerobic exercise training (AET) and resistance exercise training (RET). AET encompasses both constant-moderate endurance training (END) and high-intensity interval training (HIIT). Both END and HIIT are renowned for their capacity to improve overall physical fitness, including enhancing body composition, vascular function, and glucose regulation [50–52]. Although both exercise programs can confer metabolic benefits, only HIIT can increase UCP1 in adipose tissue [53, 54]. Moreover, high-intensity exercise is more likely to promote systemic adrenergic activity in the body [55] and might preferentially induce browning of WAT after HIIT over END. HIIT also increases lactate and β-hydroxybutyrate; this may be the reason for the increase in heat production (the upregulation of thermogenic factor (UCP1) in WAT) [54]. Acute swimming also has the same effect. As in Cho's study, following a session of acute swimming exercise, the UCP1 expression level in sWAT was increased [56].

Compared with AET, RET presented a lower body weight. Moreover, RET showed beneficial effects similar to those of AET, including a reduction in iWAT and rpWAT sizes, activation of UCP1, and upregulation of specific brown adipocyte phenotype genes. These interventions can effectively stimulate the browning process in WAT [57]. Researchers further revealed that HIIT can attenuate skeletal muscle loss and enhance locomotor abilities through the PGC-1α–FNDC5–UCP1 signal transduction pathways [58].

Moreover, iWAT is more sensitive to the regulatory impacts of physical exercise on UCP1 than is epididymal WAT (eWAT) [59–61]. The intensity of exercise can also influence the browning process of WAT. According to Tanimura R [62], there was a notable elevation in the protein expression levels of UCP1 in iWAT and FGF21 in skeletal muscle compared with low-intensity running.

Exercise likely triggers multiple mechanisms to facilitate the browning of WAT. First, engaging in physical exercise as a primary measure can potentially initiate the browning process by diminishing hypothalamic inflammation and enhancing gene expression in POMC neurons [63]. Furthermore, physical activity activates the SNS, resulting in the release of norepinephrine from the SNS that binds to β-AR receptors, thereby inducing adipose tissue browning and facilitating increased heat production [64]. Moreover, irisin, a myokine secreted from skeletal muscle, can also regulate the browning of WAT [65–67]. Physical exercise stimulates irisin secretion [68, 69], which affects thermogenesis, including the PPAR-α/UCP1 pathway. Moreover, PGC-1α also plays a crucial role in the stimulation of irisin secretion in skeletal muscle induced by exercise and exercise training, as does the upregulation of UCP1 in WAT [59, 70]. (The partial mechanisms by which physical exercise activates UCP1 are shown in Fig. 3.)

Interestingly, in studies of humans, researchers have reported some differences [71, 72]. After an eight-week program combining physical training, consisting of alternating 30 s strength and aerobic exercises conducted three times weekly for 60 min each session, notable improvements were observed in the resting metabolic rate, lipid oxidation, and overall physical performance. However, there was a lower expression of UCP1 mRNA in the WAT of obese women, which means that physical training cannot promote thermogenesis and WAT browning in the human body. This may be ascribed to a number of factors, which include the length of the training period, the differences between animal and human "house" conditions, the inherent differences between species, or perhaps the browning occurring in different WAT depots [73]. In addition, detection methods have many limitations [74]. Obtaining multiple biopsies from the same location, particularly from human BAT, presents challenges. Moreover, scholars have demonstrated that the enhanced thermogenic response triggered by physical activity could be a transient occurrence [64]. Consequently, the unaltered or decreased heat generation in BAT might represent a "forced choice" during exercise [75] because the thermogenesis of adipose tissue leads to an elevated core body temperature, which is detrimental to exercise. Furthermore, the process of thermogenesis is fuelled by glucose and the oxidation of fatty acids, leading to competition for energy resources with skeletal muscles during physical activity. Therefore, it is plausible that UCP1 is expressed at low levels after exercise/exercise interventions [64].

To summarize, findings from rodent studies demonstrate that engaging in physical activity can upregulate the expression level of UCP1. This, in turn, induces WAT browning, enhances the heat production of BAT, and elevates metabolic rates within the adipose tissue [76]. Physical exercise is an effective means to control metabolic diseases, such as adiposity and MASLD, even without significant weight loss.

However, the effects of improvements in physical activity on thermogenesis in the human body are controversial and need to be further studied. This may require more sophisticated clinical trials for confirmation (strictly controlled experimental conditions and perfect experimental design).

Factors related to traditional Chinese medicine

Acupuncture

Acupuncture is a traditional Chinese medicine. Under the guidance of traditional Chinese medicine theories, the doctor pricks the needle into the patient's body (the piercing point is called the human acupoint, referred to as the acupoint) through twisting, lifting, and other acupuncture techniques to stimulate the human acupoint to treat the disease. As a traditional Chinese medicine therapy, acupuncture has a history of thousands of years in China. It boasts numerous advantages, including straightforward operation, minimal adverse reactions, and the ability to regulate multiple targets. It is widely employed to alleviate various metabolic disorders, particularly adiposity, and has demonstrated exceptional therapeutic efficacy [77, 78].

The regulation of UCP1 serves as one of the underlying mechanisms of acupuncture treatment for numerous diseases, including adiposity and MASLD. Acupuncture effectively upregulates UCP1, thereby facilitating the browning of WAT, enhancing energy metabolism, and mitigating fat accumulation. A study on the treatment of obesity by electroacupuncture revealed that stimulation of acupuncture points ("Guan Yuan," bilateral "Shenshu," "Tianshu," and "Fenglong") in obese rats could increase the mitochondrial UCP1 expression level in fat tissue

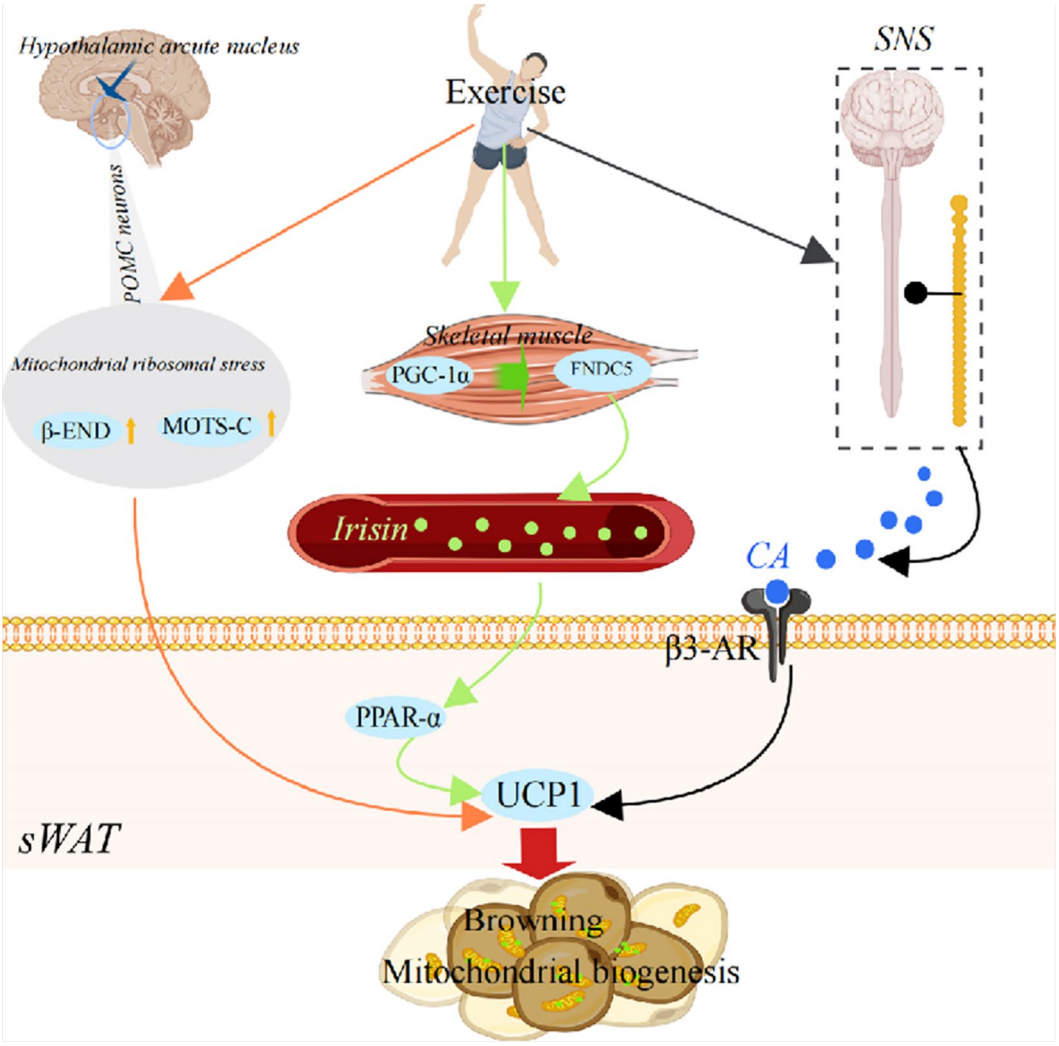


Fig. 3 The partial mechanisms by which physical exercise upregulates and activates UCP1. First, physical exercise can facilitate the upregulation of critical genes in POMC neurons, including β-endorphin (β-END) and the mitochondrial frame of the 12 S RNA-c (MOTS-c). This cascade subsequently facilitates the activation of UCP1 in adipose tissue (the yellow line). Second, engaging in physical activity results in an increase in PGC-1α within skeletal muscle. This upregulation subsequently triggers the expression of the fibronectin type III domain-containing protein 5 (FNDC5) gene, which is responsible for encoding irisin, a myokine involved in various physiological processes. Furthermore, irisin substantially affects adipose tissue by upregulating UCP1 expression (green line). Third, exercise facilitates the activation of the sympathetic nervous system (SNS) and the release of CA from the SNS, which mediates the upregulation of UCP1 (black line)

and facilitate the improvement of lipid metabolism [79]. Other studies have consistently corroborated this finding [80–84].

Furthermore, auricular acupuncture (AA) and acupoint catgut embedding (ACE), as extensions of acupuncture, can also treat obesity by regulating UCP1 [85, 86]. The stimulation of auricular points triggers a response in the corresponding ear acupoints associated with the viscera, thereby achieving the desired therapeutic effect. ACE involves the embedding of disposable, sterile, and absorbable acupoint threads into acupoints, resulting in a comprehensive and lasting effect on the acupoint and the body. ACE, with the long-acting needle feeling of a "thread instead of a needle," can improve the excitability and conductivity of acupoints. Therefore, ACE represents a significant extension and advancement of traditional acupuncture techniques. It has gained widespread application in China to manage many conditions, such as adiposity and polycystic ovary syndrome. For example, researchers treated perimenopausal obesity in female rats with acupoint embedding and discovered that acupoint embedding at the Shenshu, Pishu, and Ganshu points could increase UCP1 expression levels and promote heat production, thus strengthening energy metabolism and playing an essential role in preventing and treating perimenopausal obesity [86].

In short, acupuncture and catgut embedding can dredge meridians, regulate qi and blood, remove

dampness and eliminate turbidity, which plays an overall regulatory role in the human body. The activation of UCP1 may be only part of the mechanism by which it exerts its therapeutic effect. (The effects of acupuncture on UCP1 are shown in Table 1; acupoints are shown in Fig. 4.)

Chinese herbal formulas

Traditional Chinese medicine is a profound and extensive historical heritage of China. For thousands of years, Chinese medicine has eliminated disease and brought health to Chinese people, which has occupied a significant position in China's medical system. The Chinese herbal formula refers to a group of drugs that are meticulously mixed according to the principle of composition after the treatment method is determined on the basis of syndrome differentiation. Chinese herbal formulas, with their multicomponent and multitarget advantages, can effectively regulate numerous targets through diverse pathways. One fascinating mechanism underlying its antiobesity effects lies in the activation of UCP1 in BAT and the induction of UCP1 expression in WAT, thereby promoting WAT browning and enhancing adipose tissue thermogenesis.

Bofutsushosan, also known as Fangfengtongshengsan, was first documented in *XuanMingLunFang* by Liu WanSu in the Jin dynasty. Studies have shown that bactutosan can improve obesity [87] and MASLD [74]. Chen and colleagues demonstrated that bofutsushosan can facilitate the upregulation of UCP1 genes in BAT and primary brown adipocytes via the β3-adrenergic signaling pathway, which is associated with thermogenesis and energy consumption in BAT. As a result, bactutosan effectively improves serum biochemical indices and significantly reduces body weight in obese mice [88]. Furthermore, Akagiri's study provides further evidence supporting this mechanism of Bofutsushosan [89].

Gui Zhi Tang, a famous formula documented in the famous *Treatise on Cold Damage and Miscellaneous Diseases*, is usually used to remove exterior cold. Jiang Gui Fang, derived from Gui Zhi Tang, is also widely used to relieve cold because of its effects on heat production and the protection of vital organs in cold environments. ZU et al. [90] reported that Jiang Gui Fang can induce eWAT browning and facilitate interscapular BAT (iBAT) heat production by increasing UCP1 and PGC-1α expression. This ultimately results in an elevation of the core temperature in mice, irrespective of whether they are exposed to short-term or long-term cold conditions, thereby facilitating improved lipid and glucose metabolism. Moreover, Chinese medicinal herbs such as Ephedrae Herba, Schizonepetae Herba, Zingiberis Rhizoma, and Cinnamomi Cortex possess the properties of xin and wen and can disperse cold and warm meridians and collaterals. Moreover, the components of those prescriptions, namely, Zingiberis Rhizoma, Cinnamomi Cortex, and Cinnamomi Ramulus, also exhibit promising potential to activate thermogenesis in adipose tissue. This could explain the mechanisms underlying how these formulas enhance heat production and contribute to lipid-lowering effects. Liu's [91] study confirms this hypothesis. Treating cold-exposed mice with the Rougui-Ganjiang herb pair can increase metabolism and increase heat production in BAT, maintaining body temperature by activating the cAMP-PPARα/γ-PGC-1α-UCP1 signaling pathway.

Table 1 Acupuncture

Therapeutic method	Acupoints	Thermogenesis pathway and Adipose tissue depots	Models	References
Electroacupuncture	Guanyuan (CV4), Shenshu (BL23), Tianshu (ST25), Fenglong (ST40)	PGC-1α, PRDM16, PPARγ, Nrg4 and UCP1 (epididymis WAT, perirenal sWAT, interscapular BAT) upregulation	Obesity model of old SD mice	[79]
	Zusanli (ST36), Fenglong (ST40), Guanyuan (CV4), Zhongwan (CV12)	PGC-1α, UCP1 pathway (abdominal sWAT) upregulation	Obesity model of Wistar mice	[80]
	Tianshu (ST25)	PGC-1α, Irisin, UCP1 pathway (WAT) upregulation	Obesity model of SD mice	[81]
	Zusanli (ST36), Neiting (ST44)	PRDM16, PGC-1α, UCP1 (interscapular BAT, epididymis WAT and inguinal WAT)—upregulation	Obesity model of C57BL/6J mice	[82]
	Zusanli (ST36), Neiting (ST44)	COX4il, Nrtf1 and UCP1 (epididymis WAT) upregulation	besity model of SD mice	[83]
	Tianshu (ST25)	PGC-1α, TFAM, UCP1 pathway (inguinal WAT) upregulation	Obesity model of SD mice	[84]
Auricular acupuncture	auricular stimulation sites (Stomach, Small intestine)	NE-FNDC5-irisin-UCP1 pathway (scapular BAT) upregulation	Inflammatory obesity of C57BL/6 mice	[85]
Acupoint catgut embedding	Shenshu (BL23), Pishu (BL20), Ganshu (BL18)	PPARγ, PGC-1α, UCP1 pathway (perirenal/inguinal sWAT, interscapular BAT) upregulation	OVX mice	[86]

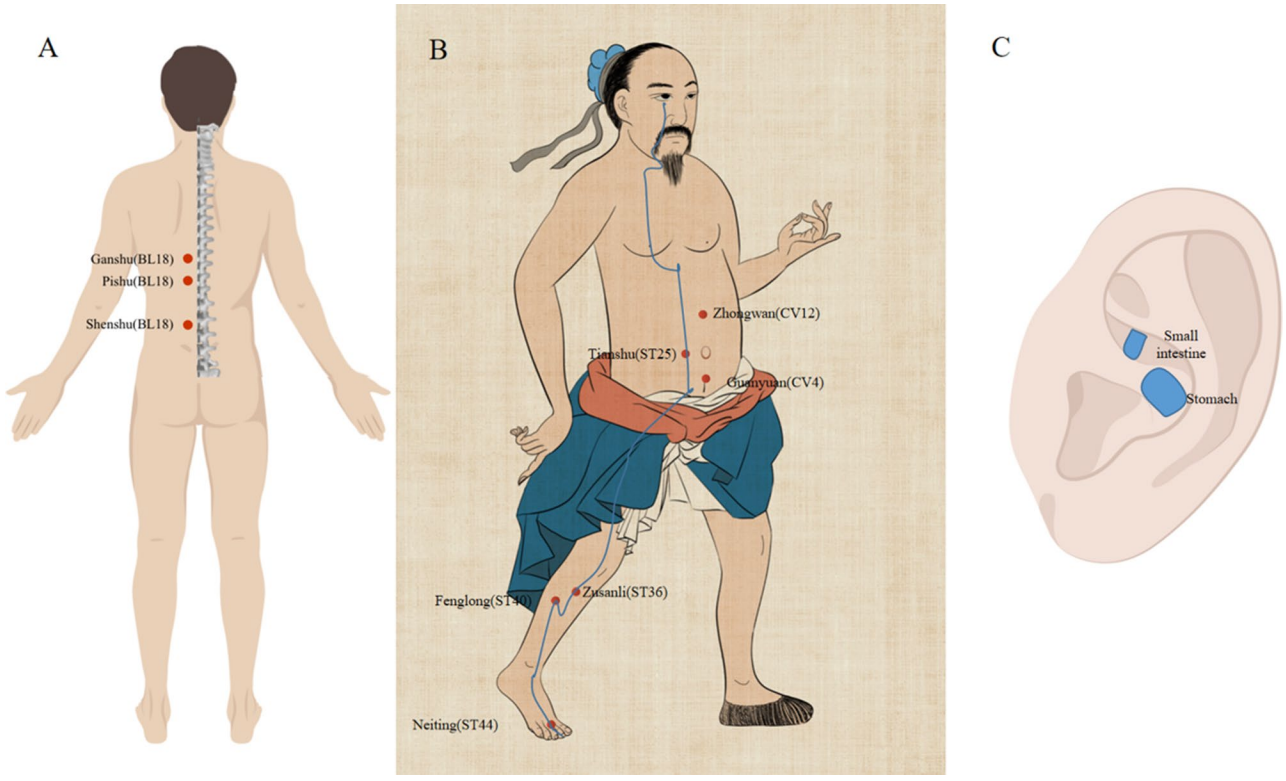


Fig. 4 Acupoints are stimuli that can promote UCP1 expression in adipose tissue. TCM defines meridians as channels that run the whole body's qi and blood and communicate with the entire body's viscera and joints. When pathological changes take place in the viscera, they may be transmitted to the body's surface through the meridian system. Similarly, we can cure diseases inside the body by stimulating acupoints, such as through acupuncture, acupoint embedding (ACE), and auricular acupuncture (AA). **A**. Shenshu (BL23), Pishu (BL20), and Ganshu (BL18) are in the gallbladder meridian; **B**. Zusanli (ST36), Fenglong (ST40), Tianshu (ST25), and Neiting (ST44) are in the stomach meridian, and Guanyuan (CV4) and Zhongwan (CV12) are in the conception vessel; **C**. Auricular stimulation sites of the stomach and small intestine.

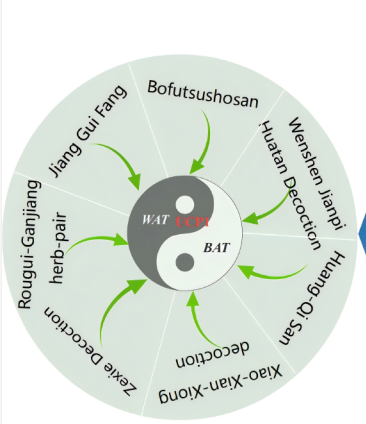
Moreover, many other formulas also activate UCP1 and thermogenesis in adipose tissue [91–96] (Fig. 5).

As stated in *Huangdi's canon of medicine*: "Only when yin is at peace and yang is compact can essence spirit be normal." Prescriptions are composed under the guidance of specific theories and principles of traditional Chinese medicine, such as the theory of Yin and Yang, and the herbs in prescriptions can interact with each other to regulate the thermogenesis gene UCP1, which exerts a balance between BAT and WAT. In other words, the formula regulates the balance of Yin and Yang in the human body through the regulation of UCP1, which achieves an overall regulatory effect on the human body.

Chinese medicinal herbs and their bioactive compounds

The effectiveness of Chinese medicinal herbs has been confirmed continuously in history, and modern research has revealed that the efficacy of Chinese medicinal herbs is based mainly on bioactive compounds of Chinese medicinal herbs—monomers of Chinese medicinal herbs. Monomers have the advantages of clear chemical structures, abundant pharmacological activities, and few side effects. Moreover, compared with synthetic compounds, monomers exhibit superior structural diversity and biological activities, which allows them to target specific biological processes with greater precision and demonstrate enhanced therapeutic efficacy. For example, artemisinin is used in Artemisia apiacea, ginsenosides are used in Ginseng Radix et Rhizoma, and so on.

Chinese medicinal herbs are often used to regulate glucose and lipid metabolism disorders; treat hyperlipidemia, obesity, and diabetes; and improve cardiovascular and cerebrovascular diseases. Among these, Cinnamomi Cortex, Ginseng Radix et Rhizoma, and Coptidis Rhizoma are commonly used in clinical practice. Moreover, studies have revealed that monomers extracted from these Chinese medicinal herbs, including berberine, not only decrease blood lipids and mitigate atherosclerosis but also exert protective effects on the cardiovascular and cerebrovascular systems. Therefore, harnessing the bioactive compounds of Chinese medicinal herbs to facilitate the upregulation of UCP1 and thermogenesis of fat tissue represents a safe and innovative approach in the fight against metabolic diseases (Fig. 6).



Prescriptions	Sourcepublication	Representative ingredients	Thermogenesis pathway and Adipose tissue depots	Models	References
Fangfengtong shengSan	*XuanMing LunFang*	Schizonepetae Herba, Rhei Radix Et Rhizoma	PGC-1α, UCP1 pathway (IBAT)	Obesity model	[90,91]
Jiang Gui Fang	*Treatise on Cold damage and Miscellaneous Diseases*	Zingiberis Rhizoma, Cinnamomi Ramulus, Glycyrrhizae Radix Et Rhizoma	PPARγ, SIRT1, PGC-1α, UCP1 pathway (iBAT, eWAT)	Cold exposure model	[92]
Rougui-Ganjiang herb-pair	\	Cinnamomi Cortex, Zingiberis Rhizoma	cAMP, PPARα/γ, PGC-1α, UCP1 pathway(BAT)	Cold exposure model	[94]
Huang-Qi San	*Sheng Ji Zong Lu*	Astragali Radix, Puerariae Lobatae Radix, Mori Cortex	PRDM16, PGC-1α, UCP1 pathway (BAT and SWAT)	Hyperlipidemia with obesity model	[96,97]
Wenshen Jianpi Huatan Decoction	\	Epimedii Folium, Cinnamomi Cortex, Citri Reticulatae Pericarpium	PRDM16, PGC-1α, UCP1 pathway (iWAT)	Obesity model	[98]
Xiao-xian-xiong Decoction	*Treatise on Cold damage and Miscellaneous Diseases*	Coptidis Rhizoma, Pinelliae Rhizoma, Trichosanthis Fructus	PkA, PGC-1α, UCP1 pathway (iWAT)	Obesity model	[99]

Fig. 5 The formula regulates the thermogenesis gene UCP1 to achieve a balance of BAT and WAT in humans. Yin and Yang summarize the attributes or two opposite aspects of interrelated things or phenomena in nature. On the basis of the properties and functions of WAT and BAT, we speculate that WAT stores energy and belongs to Yin; BAT consumes energy and produces heat, which is Yang. When the human body is in a state of adiposity, i.e., when the WAT increases, the BAT decreases, which results in dysfunction of the human fat tissue and an imbalance of Yin and Yang. The formula can increase the expression level of UCP1, thereby increasing the heat production and energy consumption of fat tissue and restoring the normal function of fat tissue and the balance of Yin and Yang in the body

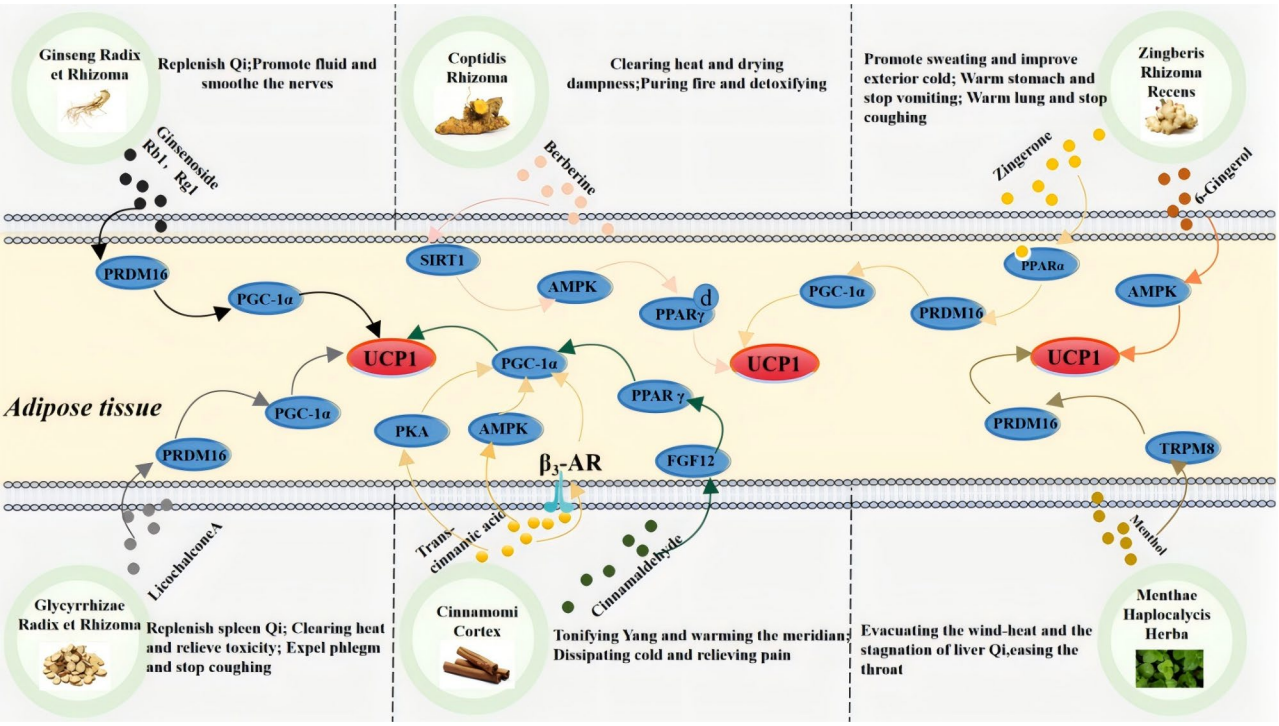


Fig. 6 Chinese medicinal herbs and their bioactive compounds are stimuli that can activate UCP1. The Ginseng Radix et Rhizoma and ginsenosides, the Coptidis Rhizoma and berberine, the Zingberis Rhizoma Recens and Zingerone and 6-Gingerol, the Glycyrrhizae Radix et Rhizoma and licochalcone A, the Cinnamomi Cortex and cinnamaldehyde, the Menthae Haplocalycis Herba and menthol, all demonstrate the capacity to activate UCP1 in adipose tissue

Ginseng radix et rhizoma

Ginseng Radix et Rhizoma, a Chinese medicinal herb in China, is highly valued for its remarkable ability to replenish Qi, promote fluid, and soothe nerves. Moreover, black ginseng (BG) exhibits numerous substantial biological activities, among which are its antiobesity and antidiabetes properties [97]; BG enhances the expression level of the critical thermogenesis protein UCP1, which may represent one of the underlying mechanisms responsible for its beneficial effects [98]. In addition,

the procedure for producing BG involves drying and steaming Ginseng Radix et Rhizoma. Interestingly, the steaming process can promote the generation of different ginsenosides, including Rb1 and Rg1 [99]. Moreover, ginsenosides Rb1 and Rg1 [100] can increase the UCP1 expression level in subcutaneous white adipocytes from C57BL/6 mice as well as 3T3-L1 cells. Consequently, they play a pivotal role in combating obesity by facilitating adipocyte browning. More importantly, the saponins found in the stems and leaves of ginseng can also facilitate the upregulation and activation of UCP1 and UCP3 within adipose tissues. This phenomenon has demonstrated remarkable efficacy in combating obesity in diet-induced obese mice [101].

Coptidis Rhizoma

Coptidis Rhizoma, renowned for its ability to clear heat, dry dampness, purge fire, and detoxify, is commonly utilized in the treatment of diarrhea, icterus, and adiposity. Berberine (BBR) is the active compound isolated from Coptidis Rhizoma. As early as two decades ago, researchers amply demonstrated that BBR is a novel antihyperlipidemic medication through animal experiments and clinical trials [102]. Numerous studies have revealed the pivotal role of BBR in enhancing glucolipid metabolism through its ability to modulate adipose tissue. Zhang et al. [103] reported that BBR can inhibit WAT accumulation and facilitate heat generation in fat tissue by increasing thermogenic gene expression. In addition, BBR can affect UCP1 promoter activity and regulate UCP1 expression levels by changing the configuration of the G-quadruplex formed by the UCP1 gene oligo fragment [104]. Wang et al. [105] have additionally shown that berberine has the ability to trigger the AMPK/SIRT1 pathway, which is responsible for energy metabolism, thereby increasing the deacetylation level of PPARγ. This process not only facilitates the restructuring of adipose tissue but also significantly enhances the expression of the thermogenic protein UCP1. The experimental findings above suggest that BBR potentially possesses therapeutic benefits and pharmacological properties in combating obesity [106] and that UCP1 is the main target of berberine in regulating the thermogenesis of adipose tissue.

Zingberis rhizoma recens

Zingiberis Rhizoma Recens is a widely utilized herb across numerous countries, including China, India, Nigeria, Australia, and Jamaica [107]. As a traditional Chinese herb, Zingberis Rhizoma Recens can promote sweating, improve exterior cold and warm stomachs, stop vomiting, warm the lungs, and stop coughing. Zingiberis Rhizoma Recens is extensively utilized to treat various ailments, including the common cold and rheumatism. Furthermore, much evidence has shown that Zingberis Rhizoma Recens possesses multiple bioactive compounds, such as zingerone and 6-gingerol [108]. These bioactive compounds all possess the potential to activate UCP1.

Derived from Zingberis Rhizoma Recens, zingerone is a bioactive ketone with various pharmacological properties. These include antioxidative, antimicrobial [108], and antiobesity effects [109, 110]. In addition, many scholars have demonstrated that zingerone can also upregulate UCP1 expression and subsequently activate thermogenesis in adipose tissue. Li et al. demonstrated that zingerone treatment could bind with PPARα. This interaction subsequently resulted in elevated levels of brown adipocyte-specific markers, including UCP1 and PGC-1α, in iWAT [111]. In addition, as a functional polyphenol of ginger, 6-gingerol can also increase the expression of the critical browning-specific marker (UCP1) through an AMPK-dependent pathway, thereby promoting mitochondrial biogenesis in 3T3-L1 adipocytes and browning [112].

Glycyrrhizae radix et rhizoma

Glycyrrhizae Radix et Rhizoma, a traditional Chinese herb, is widely used in most formulas in China. Glycyrrhizae Radix et Rhizoma possesses a range of beneficial properties, including replenishing the spleen Qi, clearing heat, relieving toxicity, expelling phlegm, and suppressing coughing. Modern experimental studies have also shown that Glycyrrhizae Radix et Rhizoma has anti-inflammatory, antioxidant, and anticancer effects. Moreover, scholars have demonstrated that extracts of Glycyrrhizae Radix et Rhizoma have the potential to significantly facilitate the upregulation of UCP1 in the BAT of obese mice [113]. In addition, licochalcone A, a unique chalcone compound extracted from Glycyrrhizae radix et rhizoma, can increase the levels of BAT indicators such as UCP1, PRDM16, and PGC-1α in inguinal WAT [114]. This discovery may provide insight into the mechanisms underlying how Glycyrrhizae Radix et Rhizoma facilitates the browning of WAT and contributes to its fundamental antiobesity effect.

Cinnamomi cortex

The Cinnamomi cortex tonifies yang, warms the meridian, dissipates cold, and relieves pain. Numerous ancient formulas in China contain this Cinnamomi Cortex, including the renowned YouGuiyin and ShenQiWan. The Cinnamomi cortex can benefit and tonify Yang, which allows it to activate thermogenesis. Li et al. reported that the extract of Cinnamomi cortex is capable of increasing the expression of thermogenic proteins, including UCP1, PGC1-α, and PRDM16, in both iBAT and iWAT through the activation of the AMPK/SIRT1 signaling pathway [115], thereby promoting the browning of iWAT and increasing nonshivering thermogenesis.

Moreover, cinnamaldehyde, a bioactive constituent of the Cinnamomi cortex, has been shown to increase UCP1 in white adipose water (WAT) and facilitate heat production [116, 117]. Neto et al. demonstrated that cinnamaldehyde can reduce BAT whitening and trigger the expression of thermogenesis markers (PPARγ, PGC1-α, and UCP1) by stimulating FGF21 expression in BAT [117]. Furthermore, trans-cinnamic acid, another bioactive constituent of the Cinnamomi cortex, can facilitate the browning of white adipocytes by stimulating the β3-AR and AMPK signaling pathways and increasing the UCP1 expression level [118].

Menthae Haplocalycis Herba

Menthae Haplocalycis Herba effectively evacuates wind heat and alleviates liver qi stagnation, providing relief for throat discomfort. Therefore, Menthae Haplocalycis Herba is extensively utilized to treat various ailments, such as rubella, headache, and the wind-heat type common cold.

Menthol, derived from the Menthae Haplocalycis Herba, acts as a cooling agent and induces a refreshing sensation upon application. Adipose tissues can absorb it through oral and topical routes, specifically via serum absorption and direct application. Studies have demonstrated that menthol can combat obesity via a glucagon-dependent mechanism controlled and mediated by TRPM8 [119], along with elevated heat production in adipose tissue [120]. Furthermore, the administration of bioavailable doses of menthol can promote the upregulation of UCP1 and other browning markers, which promote increases in energy expenditure [121]. This function of menthol is facilitated by TRPM8 in adipocytes.

Notably, however, oral menthol has little effect on humans [120]. Fortunately, topical menthol application has unexpected effects, including elevated core body temperature and improved metabolic rates [120]. This may be the direction of further research and clinical application. Mckie et al. confirmed that applying menthol to the skin could facilitate the release of norepinephrine from the SNS, which innervates BAT by activating TRPM8, ultimately enhancing UCP1-dependent thermogenesis [43].

Others

Numerous other bioactive compounds derived from Chinese medicinal herbs can induce thermogenesis by regulating the thermogenic protein UCP1. For example, Loureirin B (LB), a prominent flavonoid compound derived from Sanguis Draxonis, can increase the ratio of U3 polyunsaturated fatty acids (PUFAs) in adipose tissue. Consequently, this results in the activation of the pivotal lipid receptor GPR120, thereby triggering the browning process in WAT and stimulating BAT thermogenesis by increasing UCP1 expression [122]. Trans-anethole, a compound known for its flavor-enhancing properties, can be extracted from the essential oils of more than 20 different plant species. These include fennel, anise, and star anise [123, 124]. Kang et al. reported that trans-anethole can combat obesity induced by a HFD in a mouse model because trans-anethole can increase the brown fat-specific genes *Prdm16* and *Ucp1* [124]. Curcumin, which is extracted from the tropical plant Curcuma longa, can increase UCP1 in fat tissue and induce WAT browning [125, 126]. Baicalein, a primary bioactive flavonoid in the root of Scutellaria baicalens, has been demonstrated to promote WAT browning and activate BAT through the upregulation of UCP1 expression [127].

In conclusion, Chinese medicinal herbs and their bioactive compounds increase UCP1 expression and energy consumption, thereby serving as potential measures against metabolic diseases, such as obesity. Moreover, although the involvement of Chinese medicinal herbs in heat production has been demonstrated in small rodents, only limited information is currently available in humans, and the animal experimental design needs to be further perfected. For example, the control should be added to confirm that the perceived benefits to health conditions treated with TCM remedies are not subject to placebo effects.

Functional food and food ingredients

Functional food

Tea

Tea is classified into three primary types on the basis of its processing technique and degree of fermentation: nonfermented tea, partially fermented tea, and fully fermented tea. Tea is universally acknowledged for its diverse positive impacts on human health, including reducing fat mass and body weight and regulating glycolipid metabolism [128]. Moreover, numerous studies [129–131] have shown that tea can promote thermogenesis and suppress adiposity by increasing the UCP1 expression level in adipose tissue.

Green tea (GT), a nonfermented tea, is widely used worldwide. Considerable research has shown that green tea promotes a thermogenic phenotype by stimulating WAT browning and reducing BAT whitening [130–133]. For example, Neyrinck AM et al. reported that GT supplementation significantly elevates the expression of PGC-α, PRDM16, and UCP1, triggers WAT browning, and reduces fat storage, which improves adiposity [131]. Some researchers subsequently carried out further studies and confirmed the same results.

Various partially and fully fermented teas, including oolong tea, yellow tea, and black tea, can attenuate adiposity through mechanisms linked to the UCP1 pathway. For example, oolong tea, pu-erh tea, and black tea can

promote the phosphorylation of the critical metabolic regulator AMPK and upregulate UCP1, which results in WAT browning and improved adiposity [129]. Another study has shown that oolong tea can also decrease adipocyte size, reduce fatty acid synthase protein expression, and increase thermogenesis-related protein (PGC-1α and UCP1) expression in eWAT, which can regulate lipid metabolism and reduce weight [134]. In addition, yellow tea (fermented tea) supplementation strongly facilitates the thermogenic program in BAT and sWAT, accompanied by increased body temperature. The underlying molecular mechanism involves the enhancement of mitochondrial biogenesis and the upregulation of the thermogenic gene *Ucp1* by yellow tea [135].

Interestingly, there is a unique type of fermented dark tea, namely, Fu brick tea (FBT). Throughout the fermentation process of FBT, the predominant fungus, E. cristatum, generates the "golden flower," which blossoms atop the surface of the tea. As a probiotic, E. cristatum confers FBT with the ability to increase glucolipid metabolism, thereby serving as a crucial criterion for assessing the quality of tea. Studies have indicated that continuous consumption of E. cristatum can effectively increase heat production by increasing UCP1 expression levels in both BAT and inguinal WAT [136]. Theabrownin (TB) derived from FBT also has notable efficacy in enhancing thermogenesis through activating the AMPK-PGC-1α signaling pathway and increasing the levels of UCP1 [137]. These studies suggest that FBT has significant potential in regulating thermogenesis, enhancing glycolipid metabolism, and combating obesity.

Seeds

Seaweeds, which are widely utilized as traditional foods, are rich in numerous nutritional components, including polyphenols, fibers, and various minerals. The antiobesity effects of the abundant ingredients present in seaweed have been extensively researched. Many seaweeds, including S. lomentaria (SL) and P. telfairiae (PT), can improve adiposity by activating the thermogenesis gene UCP1. For example, Yan et al. demonstrated that SL extract can increase the expression of UCP1 in vivo and p-AMPK/AMPK and UCP1 expression in vitro, which promotes thermogenesis in adipose tissue and ameliorates obesity in mice [138]. Sargassum thunbergii (ST), a type of edible brown algae, has been found to possess the ability to enhance critical protein (UCP1) expression, as demonstrated by Kim [139]. Moreover, ST can effectively decrease the expression level of PPARγ in WAT and increase the expression level of critical genes (*Ucp1* and *Ucp3*) in BAT [140], indicating its antiobesity effects. Plocamium telfairiae (PT), another common seaweed, has been shown to effectively lower WAT weight while increasing the UCP1 expression level in BAT [141].

In summary, the activating effects of seaweed on UCP1 have been validated through rigorous experiments. There is also a need for further study to elucidate the underlying mechanisms of seaweed in humans.

Food ingredients

A diverse array of food ingredients, particularly those found in tea, fruits, vegetables, and condiments, have been shown to have the potential to increase energy expenditure, decrease fat accumulation, and activate UCP1. Therefore, food is a promising means for combating and treating diseases such as adiposity and comorbidities [142] (Fig. 7).

Resveratrol

Resveratrol is present mainly in grapes, berries, and other dietary constituents as a natural polyphenol [143]. It is a natural antioxidant that has preventive effects against hyperlipidemia, as well as cardiovascular and cerebrovascular diseases [144, 145]. Extensive research has conclusively shown that resveratrol significantly increases the heat production of BAT [146] and WAT browning [147] in rodents subjected to a high-food diet, which implies that resveratrol can combat obesity and improve various metabolic disorders. Moreover, the findings of researchers suggest that the impacts of resveratrol are likely attributable to the direct enhancement of UCP1 mRNA expression [148, 149]. For example, in Andrade JMO's study [147], it was discovered that resveratrol could improve glycemic and lipid profiles by increasing UCP1 expression levels in mouse and human subcutaneous adipose tissue. Consistent with the above research, Hui et al. [150] proved that the ability of resveratrol to increase heat production might be partially driven by the gut microbiota; i.e., resveratrol can regulate bile acid metabolism by remodeling the gut microbiota, which mediates BAT activation and WAT browning by increasing UCP1 expression, which also suggests that although polyphenolic compounds are low in bioavailability, they can affect adipose tissue through the intestinal flora, thus achieving therapeutic effects. Moreover, p38 MAPK is necessary for resveratrol to stimulate the activation of UCP1, and resveratrol can counteract the LPV (an HIV protease inhibitor)-induced loss of UCP1 [151, 152, 154]. It is feasible to achieve precise control over UCP1 induction through the administration of resveratrol and LPV, suggesting promising applications in the development of safe antiobesity therapies.

Although animal experiments confirmed the protective effects of resveratrol against many diseases, including adiposity, reports of its toxicity and adverse effects after the consumption of resveratrol by humans have been reported, which may be related to the resveratrol doses used (the conversion of the effective dose used in animal

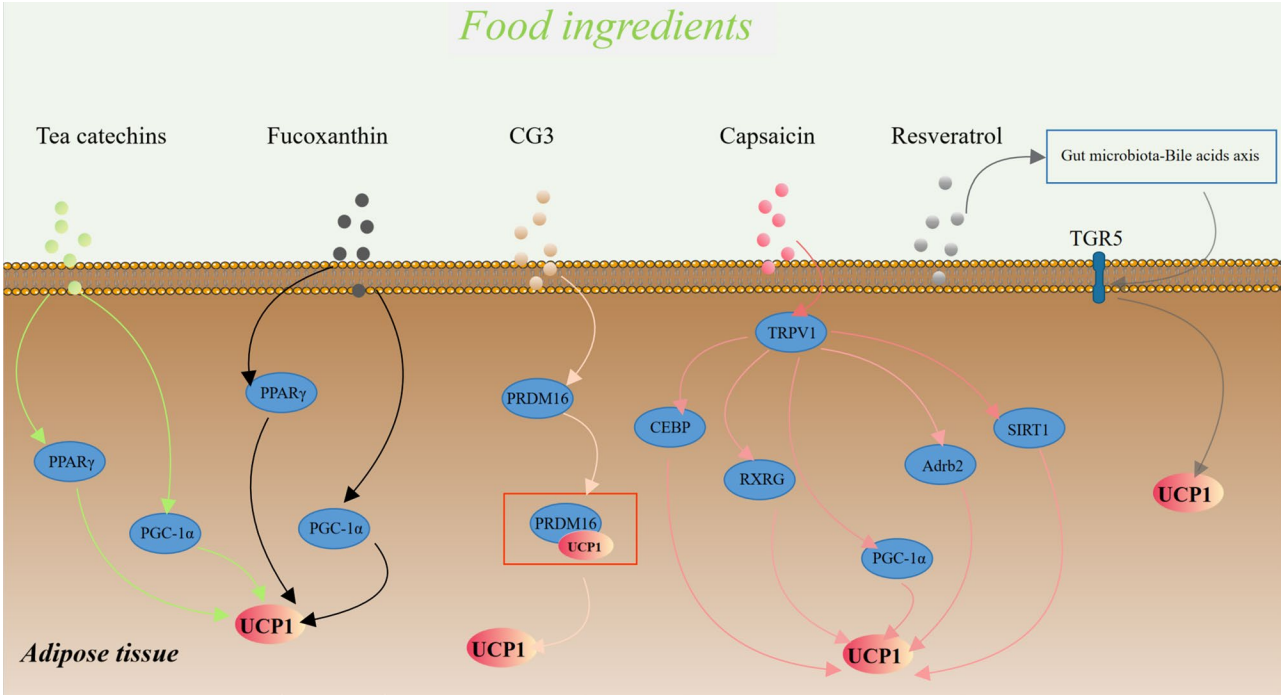


Fig. 7 Food ingredients that can activate UCP1. Resveratrol, anthocyanins, fucoxanthin, tea catechins, and capsaicin in many foods, such as fruits and vegetables, can activate UCP1 in adipose tissue

experiments to the effective dose given to humans may be toxic to humans), the duration of resveratrol supplementation and the differences in the characteristics of the enrolled patients. Moreover, resveratrol can interact with some drugs, and these interactions can decrease the activities of these drugs [152–154]. Therefore, when the ability of resveratrol to promote an increase in UCP1 is investigated in the human body, a more uniform design of clinical trials is needed to investigate the effects of resveratrol properly and define its mechanisms of disease therapy and prevention.

Anthocyanins

Anthocyanins, another polyphenolic compound, are abundantly present in fruits and vegetables with dark hues, as are pigmented grains, such as berries, cherries, grapes, and purple onions [155]. Cyanidin-3-glucoside (C3G), a member of the anthocyanin family, has promising therapeutic implications for preventing and controlling obesity [156]. This is attributed to the ability of C3G to increase mitochondrial quantity and functionality, effectively modulating UCP1 transcription in both BAT and sWAT [157, 158]. Additionally, the UCP1 expression level can be notably increased by PRDM16, which results in preadipocyte differentiation into brown adipocytes. As in Han's study [157], they reported that supplementation with C3G facilitates the upregulation of PRDM16. PRDM16 subsequently actively interacts with the promoter region of UCP1, which spans from −500 to -150 base pairs, thereby stimulating its transcription. As a result, this process serves as a pivotal factor in facilitating the programming of BAT. Moreover, cell experiments have shown that C3G can facilitate the upregulation of UCP1 during early-phase supplementation [158]. However, anthocyanins, as polyphenolic compounds, also have the disadvantage of low bioavailability, ultimately limiting their potential clinical applications. Although new approaches, such as nanotechnology, can increase the bioaccessibility and bioavailability of anthocyanins, exploring alternative options might be more appropriate and economic.

Fucoxanthin

Fucoxanthin, the most abundant carotenoid, is commonly found in brown seaweeds and diatoms. Studies have demonstrated that fucoxanthin holds promise as a potential component for the management of adiposity [159, 160]. Fucoxanthin supplementation has been shown to reduce fat weight and adipocyte size effectively [161, 162]. In addition, by facilitating the elevation of UCP1, fucoxanthin can improve fatty acid β-oxidation activity and increase heat production and energy expenditure, which mediate the potential antiobesity effect of fucoxanthin [159, 163–165]. The standardized fucoxanthin powder, derived from Phaeodactylum extract (PE), contains fucoxanthin in amounts ranging from 0.035 to 0.06 (w/w). In a study conducted by Koo, the antiobesity properties of this novel standardized fucoxanthin

powder were thoroughly evaluated in vitro and in vivo. The results indicated that PE exerts antiobesity effects by modulating lipid metabolism by suppressing PPARγ and enhancing UCP1 expression [164]. Andrea et al. [166] also researched the ability of PE to treat adiposity, and their discovery revealed that PE decreases the progression of adiposity in an animal model. This phenomenon is mediated by the accumulation of fucoxanthin metabolites in adipose tissues, facilitating the upregulation of UCP1 and heat production in iBAT and sWAT.

Furthermore, Nana et al. [167] conducted clinical trials to investigate the impact of fucoxanthin on obese Japanese adults. Although supplementation with fucoxanthin-enriched akamoku oil did not significantly affect visceral fat areas or resting energy expenditure, a noteworthy decrease in HbA1c levels was observed in the group receiving 2 mg/day fucoxanthin, particularly among individuals carrying the G/G alleles of the *Ucp1* gene. Consistent with the findings of the other studies mentioned above, this report corroborates the existence of a correlation between fucoxanthin and the *Ucp1* gene. However, further research involving a larger number of participants is necessary to establish more conclusive findings.

Unfortunately, although numerous brown seaweeds contain significant quantities of fucoxanthin, researchers have demonstrated that the bioavailability of fucoxanthin in humans is limited [168]. The combination of fucoxanthin with lipids, such as those in fish oil, may be effective. The enhanced antiobesity impact of fucoxanthin might be attributed to its solubility in fish oil, resulting in a better combination that effectively mitigates the weight of WAT by increasing UCP1 expression. Furthermore, extracting fucoxanthin at high concentrations from plants poses a significant challenge, and there are currently no economical methods available for producing fucoxanthin with a high degree of purity. This limitation restricts its further application, hence necessitating additional research efforts.

Tea catechins

Catechins are the most functional ingredients in tea. In terms of their different structures, catechins can be classified into six types: (-)- epigallocatechin gallate (EGCG), (-)-epicatechin gallate (ECG), (-)-epicatechin (EC), catechin (C), trace gallic acid (GA), and (-)- epigallocatechin (EGC). UCP1 mediates the efficacy of catechins in promoting heat production; thus, ameliorating obesity is widely acknowledged [169].

EGCG is the predominant polyphenol catechin detected in green tea. Studies have shown that EGCG has the potential to increase glucolipid metabolism in both mice and humans by suppressing adipogenesis, inducing WAT browning [170], and reducing plasma triglyceride levels [171]. Whether UCP1-related mechanisms/pathways contribute to lipid breakdown and whether EGCG exerts an effect on obesity reduction or browning of WAT in humans remain controversial. For example, Mi et al. [170] reported that EGCG can notably evoke the phosphorylation of AMPK and induce the browning of mature white adipocytes derived from iWAT preadipocytes by facilitating the upregulation of UCP1 and promoting mitochondrial biogenesis. Moreover, another study in 3T3-L1 cells revealed that EGCG supplementation promotes the upregulation of UCP1, accompanied by the downregulation of pivotal lipogenesis genes [172]. However, in another experiment, EGCG treatment did not facilitate the upregulation of UCP1 in BAT [173]. Furthermore, treatment with EGCG did not increase *Ucp1* mRNA in human white adipocytes, and the application of EGCG did not reduce obesity, lipid breakdown, or browning of WAT [171]. Unlike EGCG, EGC, another type of catechin, was also proven to increase adiponectin and UCP1 transcription in mature adipocytes [174]. Therefore, there are indeed some challenges in translating animal data to human data, and more studies need to be performed on human subjects.

Capsaicin

Capsaicin is an agonist that acts on transient receptor potential vanilloid channel 1 (TRPV1). Through activation of TRPV1, capsaicin can activate metabolic modulators, including AMPK, PPAR-α, and UCP1 [175, 176], which indicates browning and thermogenesis. A subsequent study on two murine adipocyte models also demonstrated the potential of capsaicin for WAT browning. The application of capsaicin to 3T3-L1 and X9 cells contributes to a notable increase in brown fat-specific genes such as *Ucp1*, *Prdm16*, and *Cidea* [177]. Additionally, human dermal fibroblasts can directly convert into brown-like adipocytes after treatment with capsin [178]. This partially explains the mechanisms underlying the antiobesity effects of capsaicin.

Others

There are also numerous other phytochemicals that can enhance thermogenesis by upregulating UCP1 expression, such as hyperforin in Hypericum perforatum [179], nobiletin in citrus fruit [180, 181], sesamol in sesame seeds [182–184] and quercetin in onion peel [185].

The heat production induced by the diet represents a critical element in facilitating total energy expenditure, which is beneficial for preventing obesity. However, most of these experiments were performed in rodents and cells; there have been few clinical trials in this area, so comparative evidence in humans is minimal.

Pharmaceutical agents

HMG CoA reductase inhibitors: statins

Statins, which function as inhibitors of HMG-CoA reductase, are commonly utilized for managing blood lipid levels, treating hyperlipidemia, and preventing atherosclerosis, such as simvastatin, fluvastatin, and atorvastatin.

Researchers have demonstrated that simvastatin can facilitate the upregulation of UCP1, potentially ameliorating metabolic disorders (weight gain and dyslipidemia) [186]. However, the role of other statins in upregulating UCP1, inducing the browning of white adipocytes, and facilitating BAT activation remains controversial. Mauser [187] reported that treating brown adipocytes with atorvastatin did not result in any alteration in the protein expression of UCP1. Moreover, Balaz et al. [188] reported that fluvastatin facilitates the downregulation of the *Ucp1 gene* in human BAT. In other words, the application of statins is inversely correlated with the activity of human brown fat. These findings indicate that further investigation is necessary to elucidate the effects of statins on UCP1.

β3-Adrenoceptor agonists

β3-Adrenoceptor (β3-AR) is highly expressed in rodent adipocytes, especially in prototypical brown adipocytes, and activation of β3-AR in adipocytes can promote lipidolysis, thermogenesis, and weight loss [189, 190]. One possible explanation for this may be that stimulating β3-AR in mouse adipocytes triggers the activation of UCP1, which results in increased heat generation [191, 192]. Norepinephrine (NE) binds to BAT β3-AR, triggering internal signaling pathways that result in elevated UCP1 levels and the lipolysis of triglycerides into free fatty acids, which subsequently trigger UCP1 located on the inner mitochondrial membrane.

CL316243 is an effective and selective β3-AR agonist in rodents [193]. Supplementation with CL316,243 can result in notable remodeling of WAT, which is marked by increased UCP1 expression and multilocular adipocytes. For example, Masoud Ghorbani [194] demonstrated that administering CL316,243 to both lean and obese Zucker rats resulted in significant restructuring of WAT, which possesses the characteristics mentioned above, preferentially in lean rats. However, its application in humans may be impeded by its limited efficacy, even for the cloned human β3-AR, and it has poor bioavailability, which also prevents its use in humans, possibly because human brown adipocytes lack β3-AR or have low expression levels of β3-AR. Furthermore, the use of this medication has led to notable adverse effects on the cardiovascular system, including hypertension and tachycardia [195].

Fortunately, mirabegron has numerous favorable metabolic properties in response to CL316243. It is a secure, dynamic β3-AR agonist known for its clinical application in treating overactive bladders. Recent preclinical studies [196, 197] conducted on adult humans have indicated the potential of mirabegron to increase the metabolic rate in human BAT, which suggests that mirabegron may be a favorable strategy to ameliorate metabolic disorders. Moreover, Dehvari's research [198] demonstrated that mirabegron has a direct effect on adipocytes through β3-AR, resulting in increased levels of glucose absorption, UCP1 mRNA, and OCR (oxygen consumption rate). Additionally, UCP1, an essential thermogenic protein in adipose tissues, is indispensable for the influence of mirabegron on glucose tolerance in vivo and may be one of the targets or mechanisms for its antiobesity/diabetes effects.

However, whether β3-ARs mediate thermogenesis in humans and whether mirabegrons, as β3-AR agonists, mediate thermogenesis in human adipose tissue are controversial. In Cheryl's study [199], when the expression of β3-AR was silenced, the stimulatory effects of mirabegron, a specific agonist of human β3-AR, on lipolysis and heat production were abrogated. These findings indicate that β3-ARs are necessary for maintaining lipolysis and facilitating heat generation in human adipocytes. However, Denis P et al. [195] demonstrated that the therapeutic dosage of mirabegron (50 mg) does not induce thermogenesis in human brown adipose tissue. They confirmed that β2-AR, rather than β3-AR, serves as the primary target for pharmacologically activating brown adipocytes. Human brown adipocytes lack the β3-AR receptor, thus rendering them unresponsive to mirabegron in vitro. Therefore, differences in gene expression might exist between brown adipocytes differentiated in vitro and those directly analyzed from biopsied tissue.

The PPAR agonist

Peroxisome proliferator-activated receptor (PPAR) agonists are attracting considerable interest as promising therapeutic options in MASLD and NASH research [200]. Pioglitazone and rosiglitazone, both antidiabetic drugs and PPARγ agonists, have been demonstrated to facilitate UCP1 upregulation in BAT and WAT [201]. Research by Merlin et al. [191] revealed that treating adipocytes with rosiglitazone can facilitate UCP1 upregulation and enhance mitochondrial function, particularly in brown and inguinal white adipocytes.

Moreover, studies [42, 201] have shown that pioglitazone can increase UCP1 gene expression in mouse BAT. In particular, the combined application of pioglitazone and cold acclimation exhibited a synergistic effect, resulting in a notable increase in the overall abundance of UCP1 and thermogenesis-related proteins (PGC-1α and CIDEA) in iBAT and iWAT compared with cold exposure or pioglitazone treatment alone [42]. Moreover,

pioglitazone treatment effectively enhances glucose uptake and protects iWAT from the mass reduction caused by cold.

Additionally, oleoyl ethanolamide (OEA), which serves as an agonist of PPAR-α, has garnered considerable attention recently. Compared with placebo, OEA is involved in various unique homeostatic functions, including regulating appetite and dietary intake, stimulating lipolysis, and promoting fatty acid oxidation, and scholars [202] reported that OEA supplementation can significantly facilitate the upregulation of PPAR-α and UCP1 in the peripheral blood mononuclear cells of humans with adiposity.

Finally, although PPAR agonists are effective treatments for metabolic diseases, including the potential to increase UCP1 to attenuate adiposity, we must consider the safety of the PPAR agonists. The side effects of PPAR-γ agonists are weight gain, fluid retention, and increased risk of congestive heart failure and bone fractures. Rosiglitazone increases risk of Myocardial infarction. The long-term use of pioglitazone is possibly associated with an increased risk of incident bladder cancer [203].

TRPM8 agonists—Menthol and Icilin

TRPM8 functions as the principal cold receptor within the peripheral nervous system of mice [204]. TRPM8, which is expressed in brown, brite, and white adipocytes [205, 206], is activated by chemical cooling agents, such as menthol, or when the surrounding temperature falls below approximately 26 °C, indicating its role in facilitating the recognition of cold thermal stimuli by primary sensory neurons [207]. Activation of the TRPM8 channel stimulates thermogenesis, which relies on UCP1 and acts as a protective measure against adiposity [208].

Icilin is a synthetic TRPM8 agonist. Similarly, Rossato et al. reported that treating human white adipocytes with Sicilian can significantly increase basal and insulin-induced glucose uptake and induce UCP1 expression [205]. Menthol, a natural compound derived from mint plants, serves as a TRPM8 agonist, effectively activating both TRPM8 and UCP1 in adipose tissue and subsequently promoting thermogenesis, underscoring its potential role in regulating body temperature [121].

Inhibitors of COX-2

COX-2 can facilitate lipid metabolism. Celecoxib, which serves as an inhibitor of COX-2, can lower the expression of UCP1 and COX-2 in a burn injury model and subsequently attenuate burn injury-induced hypermetabolism [209].

GSK3 inhibitor

Lithium, a widely recognized inhibitor of GSK3, is frequently prescribed for the management of bipolar disorder. Clinically, high doses of lithium supplements can increase the risk of obesity. Nevertheless, studies have shown that low doses of lithium supplements can reduce obesity and atherosclerosis [210]. For example, Fajardo et al. reported a negative correlation between trace amounts of naturally occurring lithium in water and the incidence of obesity, which is attributed, at least in part, to the inhibitory effects of lithium on GSK3 and the increase in UCP1 content in adipocytes [211, 212]. Moreover, when lithium is used at a relatively high dose (450–1500 mg) and taken for a long time, it can produce side effects, especially when combined with the administration of risperidone [213].

Other drugs

Qiu et al. [214] established a UCP1-2 A-GFP reporter mouse model, enabling the utilization of GFP intensity as a surrogate marker for the UCP1 protein. Subsequently, they embarked on a search for FDA-approved medications that possess the ability to stimulate endogenous UCP1 expression in adipocytes and discovered that Sutent could increase UCP1 levels in brown fat cells. In addition, the administration of Sutent resulted in the upregulation of various genes involved in thermogenesis or brown adipocyte differentiation, including PGC-1α and PRDM16. Consequently, weight was reduced through increased thermogenic activity and metabolism. Using this model, they reported that glyburid also has the potential to reduce UCP1 [215].

Glyburide is a medication commonly prescribed to effectively reduce blood glucose levels and manage type 2 diabetes. Qiu et al. [214] revealed that glyburide supplementation markedly facilitates the elevation of UCP1 in fat tissue. Furthermore, the direct injection of glyburide into the inguinal WAT resulted in substantial upregulation of UCP1 expression and thermogenic activity.

Notably, certain medications, such as melatonin, inhibit UCP1 expression to achieve therapeutic outcomes [216]. In other words, we should also note that in specific disease states, we need to inhibit the activity of UCP1, such as burns, sepsis, and cancer cachexia (See Table 2).

The gut microbiota

The gut microbiota has coevolved with its hosts over time, forming an integral and indispensable component of the human body's ecosystem. Known as the "microbiome," the collective genetic material encoded by these microorganisms exceeds the human genome by a staggering 150-fold [217]; it performs some essential functions of the human body. Moreover, the microbiota is often intricately linked with the treatment and management of numerous diseases, including adiposity and MASLD. The microbiota promotes thermogenesis by influencing WAT

Table 2 Pharmaceutical agents

Classification	Representative pharmaceuticals	The regulation on UCP1	References
The HMG CoA reductase inhibitors	simvastatin, atorvastatin	simvastatin(Upregulation); atorvastatin(Remain unchanged)	[186, 188]
Theβ3-adrenoceptor agonists	CL316243, Mirabegron	Remain controversial	[195, 199]
The PPAR agonist	Pioglitazone and osiglitazone	Upregulation	[42, 191]
The TRPM8 agonists	Menthol, Icilin	Upregulation	[205, 208]
The Inhibitor of COX-2	Celecoxib	Downregulation	[209]
The GSK3 inhibitor	Lithium	Upregulation	[211, 212]

browning, which may be one of the underlying mechanisms [218].

As Moreno et al. [218] demonstrated, the relative abundance of Firmicutes is positively correlated with UCP1 in sWAT. In other words, a connection exists between the gut microbiota composition and WAT browning. Moreover, Li et al. reported that diminishing the microbiota of mice with antibiotics results in a reduction in UCP1. This, in turn, suppresses the browning process of WAT and damages the heat production potential of BAT [219], which suggests that the gut microbiota directly impacts the thermogenesis of UCP1.

In addition, many other probiotics can activate UCP1 in adipose tissue. As a potential probiotic, Parabacteroides distasonis can interact with bile acids (gut microbiota-bile acid crosstalk), mediate the activation of UCP1, and promote an increase in glucose and lipid metabolism. Consequently, the administration of probiotics can control rapid postcaloric restriction (CR) weight gain [220].

Lactobacillus plantarum, a probiotic group of the human gastrointestinal tract, is widely distributed and commonly found in fermented vegetables and fruit juices. Lactobacillus plantarum has various functions, including preserving the equilibrium of the gut microbiota, enhancing the immune system, and facilitating nutrient absorption. According to the research of Gus et al. [221], Lactobacillus plantarum dy-1 (LFBE) mitigates obesity by upregulating UCP1 expression in the fat tissue of an HFD-fed animal model. Moreover, fermented barley extract with LFBE can also ameliorate HFD-induced obesity by triggering BAT activation and WAT browning. However, microbiota that damage thermogenesis genes, such as UCP1, also exist. *Porphyromonas gingivalis* (*P. gingivalis*) is a type of bacteria that can cause periodontal disease. In addition, periodontal bacteria, such as *P. gingivalis*, can migrate and settle in the gut through oral administration [222]. Thus, periodontal bacteria may result in systemic diseases, including obesity. Zheng et al. [223] reported that *P. gingivalis* can reduce UCP1 expression in the BAT of mice; these negative influences on BAT are attributed to the lipopolysaccharide (LPS) component of *P. gingivalis*, providing a plausible explanation for how periodontal disease facilitates the development of adiposity.

The gut microbiota, which serves as a metabolic "organ," can contribute to thermogenesis by generating abundant metabolites, which act as ligands to activate thermogenic pathways. Dietary bile acids (BAs) can repress HFD-induced adiposity through increased energy expenditure mediated by the thermogenesis gene UCP1 [224]. In other words, BAs, such as CDCA and LCA, can regulate UCP1 expression in adipose tissue. Han et al. demonstrated that curcumin can modulate BA metabolism by restructuring the gut microbiota, which results in increased fractions of circulating DCA and LCA, thereby increasing UCP1-dependent thermogenesis [225]. Wang et al. [220] reported that treatment with Parabacteroides distasonis primarily elevated the concentrations of unconjugated non-12OH BAs, UDCA, and LCA. These bile acids function as agonists to trigger UCP1 signaling pathways and increase energy metabolism. Moreover, in Crohn et al.'s disease, microorganisms and metabolites (succinate) can translocate to the surrounding adipose tissue due to gut barrier defects, which then promote WAT browning [226].

In summary, the gut microbiota and its metabolites can facilitate heat production through their interactions with UCP1. On the other hand, UCP1 can also reshape the gut microbiota through the adipose-liver-gut axis and contribute to decreased fat accumulation [227]. This may constitute a bidirectional regulatory system that can be exploited (Fig. 8).

The strengths and limitations of this review

The primary purpose of scientific research and theoretical exploration is to better serve clinical practice and patients. In this review, we summarize the thermogenic stimuli that have activated UCP1 in recent decades, including physical and environmental factors (cold stimulation and exercise) and factors related to traditional Chinese medicine. The summarization of these UCP1 stimuli provides clinical doctors with valuable guidance for the use of clinical drugs and helps them gain better insights into the treatment of metabolic diseases, such as adiposity and MASLD. In particular, we have summarized the nonpharmacological factors that have the potential to stimulate UCP1 activation, including physical exercise and acupuncture, which may be safer options for treating metabolic diseases. Moreover, for the first

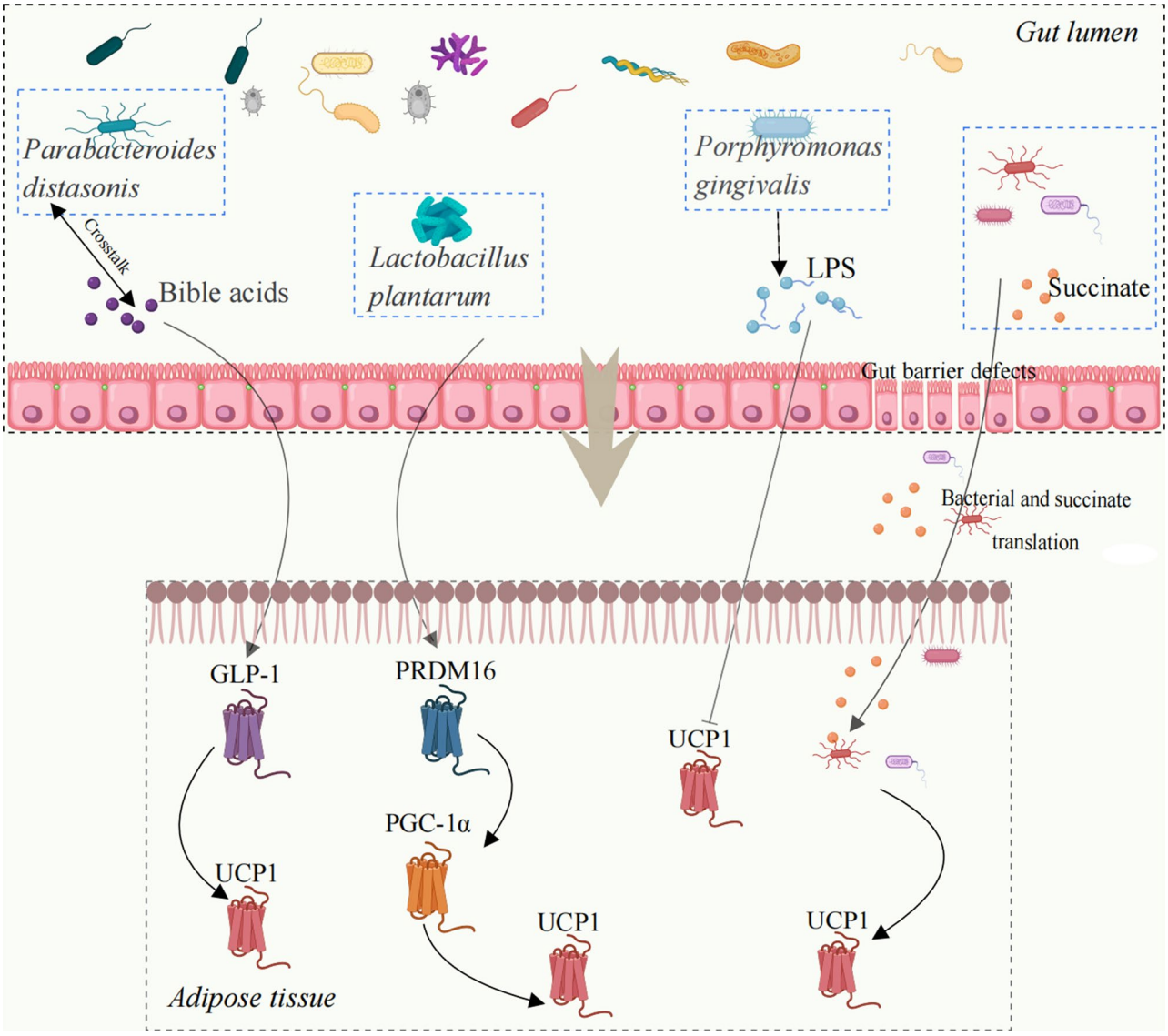


Fig. 8 The microbiota regulates the abundance of UCP1 in adipose tissue through microbiota metabolites, such as bible acids and succinate

time, we summarize the factors of traditional Chinese medicine that can stimulate UCP1 activation, providing new insights for disease treatment. Hopefully, this review will provide valuable guidance for treating clinical diseases and using clinical drugs.

Nevertheless, there are certain limitations. First, although the factors related to traditional Chinese medicine that can stimulate the activation of UCP1 have been summarized, the underlying theory of traditional Chinese medicine as to why these factors stimulate the activation of UCP1 and enhance adipose tissue thermogenesis has yet to be clarified thoroughly. Additionally, the summarization of factors that stimulate UCP1 activation is limited, and not all factors are fully understood.

Conclusion and future perspectives

Facilitating the enhancement of heat production and energy expenditure is an effective way to improve and treat numerous diseases, including adiposity and MASLD. UCP1, whose expression is restricted to brown and beige adipocytes in humans and rodents, is a critical target for facilitating heat production in adipose tissue. Cold exposure, physical exercise, acupuncture, Chinese herbal formulas, pharmacological agents, food ingredients, gut microbiota, and pharmaceutical agents are commonly associated with the activation and elevation of UCP1 in BAT and WAT.

Among the various activators that trigger thermogenesis, ambient cold exposure is the first factor discovered to activate this process. Exposure to ambient cold markedly stimulates the SNS, which subsequently triggers

β2-AR- and β3-AR-mediated nonshivering thermogenesis in humans and rodents, respectively [195, 228]. Unfortunately, cold exposure can only cause initial, strong, but short, nonselective browning of most adipocytes in rpWAT; a few adipocytes maintain brown-like characteristics in the long run [35]. In addition, exercise, as a noninvasive and tolerable physical alternative, benefits various organ systems in mammals and humans. Physical exercise is an excellent means for initiating the browning process, partly because it stimulates irisin gene expression, mitigates hypothalamic inflammation, and increases the expression of the POMC neuron gene [65]. These changes, in turn, promote the expression of the thermogenesis gene UCP1 [56, 63]. Moreover, owing to their multicomponent and multitarget advantages, traditional Chinese medicine therapies, such as acupuncture, Chinese herbal formulas, medicinal herbs, and their bioactive compounds, can also activate UCP1 and increase adipose tissue thermogenesis. With the spread and development of Chinese medicine worldwide, an increasing number of people will benefit from its prominent effects and few side effects. Furthermore, many functional foods and food ingredients have the potential to activate UCP1 and promote thermogenesis in adipose tissue, which provides more reliable ways to manage diseases and maintain health. The pharmacological activation of UCP1, such as statins, mirabegron, pioglitazone, and rosiglitazone, has gradually increased. Furthermore, there is a strong connection between the gut microbiota and the activation of UCP1. In other words, UCP1 activation can be achieved through a diverse array of methods.

From the preceding discussion, it becomes evident that UCP1 is pivotal in enhancing the heat production of adipose tissue and that activating UCP1 is an excellent way to treat obesity-related metabolic diseases, including MASLD. Most researchers are also committed to studying the agonists of UCP1. However, several crucial points deserve the utmost attention.

First, while BAT represents a minor percentage of the total adipose tissue mass, its activation can significantly increase overall oxygen consumption [229]. The powerful capacity of BAT as a target for ameliorating obesity appears encouraging. For example, Valdivia reported that although drug therapy and cold exposure can increase the UCP1 content in WAT, it only accounts for a small part (approximately 20%) of the total UCP1 content in BAT. These findings underscore the significant role of iBAT in thermogenesis compared with that of iWAT [42]. Furthermore, when the mice were fed under conditions mimicking human thermal and nutritional environments, the morphological, cellular, and molecular features of classical BAT, but not beige adipose tissue, closely resembled those of human BAT. Interestingly, only classical BAT physiologically humanized mice possess high thermogenic potential [230]. In other words, even under thermoneutrality conditions, BAT maintains its characteristic brown-like physiological properties despite being masked by a white-like morphology [33]. Therefore, when promoting the UCP1 activation in BAT, more excellent heat production will be achieved.

Second, most experimental animals are raised under standard animal housing conditions ("standard" mice). Despite the strong anatomical resemblance between brown fat deposits (for example, supraclavicular depots) in mice and humans [231], there are morphological and molecular distinctions between human and rodent BAT [230]. Importantly, if experimental animals are raised in circumstances involving human thermal and nutritional conditions ("physiologically humanized" mice), they exhibit different gene expression patterns than "standard" mice do, and their BAT phenotype is also humanized [232]. Therefore, when we evaluate the heat production capacity of fat tissue, maintaining the mice under appropriate conditions may improve the experimental conditions and increase the compatibility of the results with humans, which can better clarify the functions of the drugs. In addition, we need to conduct more clinical experiments in the future because animal experiments cannot fully explain the pathological changes in humans.

Third, much evidence proves that UCP1-independent thermogenic pathways also contribute to the body's heat production and the regulation of whole-body energy homeostasis [233, 234], such as creatine kinase b (CKB) [235], transcription factor 4 (ATF4) [236] in brown adipocytes and sarco/endoplasmic reticulum Ca2+-ATPase2b (SERCA2b)-mediated calcium cycling [237] in beige adipocytes. As the study by Rahbani JF et al. suggested, thermogenic adipocytes utilize nonparalogous protein redundancy through UCP1 and CKB to promote cold-induced energy dissipation. These mechanisms have the potential to supplement or even replace UCP1-driven thermogenesis. UCP1-independent thermogenesis enhances overall energy metabolism, which helps improve conditions such as glucose and lipid metabolism disorders, especially in specific individuals, such as aged individuals and those lacking UCP1-positive adipocytes [238]. Therefore, these mechanisms must also be treated with the utmost severity.

Fourth, we can also obtain corresponding pharmacological effects by inhibiting the activity of UCP1 in specific states of diseases, such as burns, sepsis, and cancer cachexia [239]. Specifically, the catabolism of stored nutrients can be reduced by decreasing the expression of UCP1 to slow uncontrolled metabolism in disease states. Experimental studies [240, 241] have definitively demonstrated that decreasing the expression level of UCP1 and lowering heat production are beneficial for alleviating the pathological state of cachexia. As proposed by

Cheung [242], supplementation with vitamin D could diminish the increased expression of UCP1 in beige adipose cells, thereby mitigating adipose tissue browning and consequently enhancing overall quality of life. The extracts of Arctium lappa L. Fruit (Arctii Fructus) [241], Astragalus polysaccharide [240], and the functional food SiBaoChongCao isolated from Cordyceps sinensis [243] also have the potential to attenuate the browning of WAT through UCP1. Moreover, these agents help maintain the equilibrium between whitening and browning of adipocytes and are beneficial for the development of safe therapies [151]. Therefore, exploring UCP1 inhibitors to suppress UCP1 expression and heat production may be necessary. In other words, it is equally important to research UCP1 inhibitors and UCP1 agonists.

Finally, although experimental research indicates that commonly used clinical drugs can activate UCP1 and promote heat production in adipose tissue, their primary function is not to stimulate heat production. Therefore, the use of those medications to activate UCP1 should be comprehensively considered. For example, mirabegron, a β3-adrenoceptor agonist, has been shown to upregulate UCP1, but its primary use is for overactive bladder syndrome (urgency, nocturia). The use of mirabegron is perfect and correct only when increased heat production and the treatment of overactive bladder syndrome are both required by patients. Moreover, the side effects of pharmaceuticals, such as PPAR agonists, should be considered. In addition, although animal experiments confirmed that food and food ingredients can activate UCP1, few clinical trials have investigated this topic. The conversion of the effective dose used in animal experiments to the effective dose given to humans may be toxic to humans, and how much food should we eat to reach an effective dose? These are the challenges that need to be addressed in the future.

Moreover, UCP1 activation may be a double-edged sword. The increased heat production caused by the activation of UCP1 may not be beneficial for specific diseases, such as burns, sepsis, and cancer cachexia. Therefore, clinicians should consider whether the increased heat production caused by certain medications, physical therapies, and diets could be disadvantageous factors in treating these diseases.

Abbreviations

UCP1	Uncoupling protein 1
POMC	Proopiomelanocortin
SNS	Sympathetic nervous system
ACE	Acupoint catgut embedding
MASLD	Metabolic dysfunction-associated steatotic liver disease
FNDC5	Fibronectin type III domain containing 5
AA	Auricular acupuncture
END	Constant–moderate endurance training
TRPV1	Random receptor potential vanilloid channel 1
BAT	Brown adipose tissue
GLP-1	Glucagon-like peptide 1
PGC-1α	PPAR-γ coactivator-1α
Cidea	Cell death-inducing DNA fragmentation factor A-like effector A
iBAT	Interscapular BAT
eWAT	Epididymis WAT
iWAT	Inguinal WAT
sWAT	Subcutaneous WAT
rWAT	Retroperitoneal WAT
CNS	Central nervous system
PRDM16	PR domain containing 16
β-END	β-endorphin
MOTS-c	Mitochondrial open reading frame
HFD	High-fat diet
CA	Catecholamine
WAT	White adipose tissue
PKA	Protein kinase A
AR	Adrenoreceptors
TRPM8	Transient receptor potential (TRP) cation channel subfamily M member 8
AET	Aerobic exercise training; PPARα, nuclear hormone receptor peroxisome proliferator-activated

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Data availability
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Declarations

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