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Mini Reviews

Switching on the heat: endogenous and exogenous inducers of brown adipose tissue

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The global surge in obesity presents a serious public health challenge, driving researchers to identify newer strategies for increasing energy expenditure. Among these, activating Brown Adipose Tissue (BAT), a specialized organ critical for thermogenesis, has emerged as a promising factor. While the role of sympathetic stimulation in BAT activation is well established, recent studies have unveiled a diverse array of endogenous and exogenous factors capable of modulating its thermogenic function. Understanding these pathways is crucial for developing effective anti-obesity therapies. In this review, we discuss the most common pathways that turn on BAT with a focus on recently reported thermogenic compounds and their mode of action. We reiterate the importance of evaluating the relationship between gut microbes, prebiotics and their effect on BAT function and summarize the existing literature about the prebiotic potential of thermogenic compounds. Further, we explore the Gut microflora-BAT axis asking a very relevant and less explored connection between the two important parts that control energy metabolism in the body. By exploring the relatively under-studied connection between gut microflora and BAT, this review presents a fresh perspective on how these two systems could work together to regulate energy metabolism in the body. Given the global obesity epidemic, investigating this novel connection offers valuable insights that could pave the way for targeted, interventions to improve metabolic health and combat obesity more effectively.

Keywords: Obesity, Thermogenesis, Gut microbiota, Gut-BAT axis, Prebiotics

Introduction

Over the past two decades, there has been an exponential growth in knowledge on brown adipose tissue (BAT), particularly its role as a potential therapeutic target for obesity through non-shivering thermogenesis (NST) and browning of white adipose tissue (WAT). In parallel with advances in understanding endogenous and exogenous regulators of BAT, attention has shifted from solely sympathetic activation to novel pathways, including those influenced by dietary components[1] and the gut microflora (GM). Historical use of sympathomimetic thermogenic agents such as ephedrine and caffeine illustrated the promise and pitfalls of targeting thermogenesis, as their non-specific actions led to serious adverse events and subsequent withdrawal from clinical use[2]. This experience underscores the continuing need for thermogenic strategies that can selectively activate BAT or beige adipocytes at thermoneutral conditions while minimizing systemic side effects.

Within this evolving landscape, the GM has emerged as a key endogenous modulator of energy homeostasis and a potential determinant of inter-individual variation in thermogenic capacity. Given that GM composition is highly responsive to diet, it represents an attractive, indirect target for manipulating BAT activity and whole-body energy expenditure[3]. Critical questions now include whether individuals with higher thermogenesis harbor distinct microbial signatures, whether existing prebiotics can remodel the GM towards such a thermogenic profile, and whether classical thermogenic compounds may exert part of their action via previously unrecognized prebiotic effects. Here we review the current literature on thermogenic compounds with an emphasis on their interactions with GM and evaluate emerging evidence for the thermogenic potential of prebiotic molecules as modulators of BAT function and obesity risk.

Turning on the brown adipose tissue: Where are we today?

Exposure to cold temperatures, whether through cold blown air or immersion in cold water, is recognized as one of the most effective methods for activating non-shivering thermogenesis (NST) in BAT. Research,

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including studies by Cypess *et al*[4] and Silva *et al*[5] has demonstrated that cold exposure significantly stimulates BAT, leading to increased energy expenditure. This activation mechanism has been utilized historically as a strategy to create a negative energy balance, which is essential for combating obesity. Cold exposure is widely regarded as the most reliable activator of NST in BAT, primarily because it triggers a sympathetic nervous system response that enhances metabolic activity within the tissue. Supporting this notion, research from our laboratory[6] has reiterated the role of sympathetic activation following cold exposure in stimulating BAT.

However, deliberately exposing oneself to cold can be uncomfortable and impractical for many individuals seeking to activate NST in BAT. This discomfort has sparked a surge of interest in identifying biochemical compounds that can directly or indirectly stimulate thermogenesis not only in BAT but also in beige adipocytes. Beyond the sympathetic nervous system's influence, several molecules have been identified that can modulate BAT activity. For instance, bile acids have been shown to play a role in enhancing thermogenic responses[7]. Additionally, irisin, a myokine released from muscles during exercise, has emerged as a potential thermogenic agent[8]. Other important regulators include thyroid hormones[9] and derivatives of Vitamin A, all of which influence BAT activity and contribute to thermogenesis.

The urgency to discover new activators of BAT stems from the need to achieve specific activation of this tissue and increase its overall content. The goal is to enhance the body's ability to maintain a negative energy balance effectively. Consequently, compounds with known thermogenic properties that can modulate one or more of these biochemical parameters have garnered attention as potential anti-obesity agents. Hence, while cold exposure remains the best-known method for activating NST in BAT, the exploration of various biochemical compounds presents an attractive opportunity for developing alternative strategies to stimulate thermogenesis. Below, we summarize some of the most commonly reported pathways involved in turning on thermogenesis within the body, providing insight into how these mechanisms can be leveraged for metabolic health and weight management.

Cold temperature and the involvement of sympathetic nervous system

Cold temperature is the best-known activator of NST till date. Following exposure to cold temperature, the sympathetic nervous system is activated[10] which releases norepinephrine (NOR). NOR acts through the beta 3 adrenergic receptor (β3AR) which is expressed on different tissues in the body including BAT. The presence of this receptor on numerous tissues is a primary reason for the failure of using thermogenic compounds (caffeine, ephedrine, sympathomimetics, etc) to reduce obesity as this leads to non-specific activation of many organs specially the cardiac tissue. The β3AR on BAT is a G-protein coupled receptor (GPCR) that in-turn activates the adenylate cyclase leading to an increased cAMP concentration. The net result is activation of protein kinase A (PKA) and MAP kinase pathway. This leads to an increase in the activity of hormone sensitive lipase (HSL) which results in increased free fatty acids (FFA) levels. The free fatty acids then enter the mitochondria with the help of Carnitine Palmitoyl transferase 1A (CPT 1A) and up regulate the expression of Uncoupling Protein 1 (UCP1) in BAT. FFA not only increases the expression of UCP1 but also acts as a fuel for thermogenesis in BAT[11].

Thyroid hormones and their role in NST

For more than a century now, the pivotal role that thyroid hormone plays in maintaining homeothermy has been identified. Thyroid hormone not only increases the overall metabolic rate but also enhances ATP utilization[12]. Both of these processes, especially the latter, contribute to the increased heat generation in the body. Additionally, Harper *et al*[13] identified that thyroid hormone efficiently uncoupled oxidative phosphorylation from electron transport in a highly regulated manner. This is believed to be the major mechanism through which thyroid hormone aids in maintaining the core body temperature, especially when faced with a cold challenge.

The control of type II thyroxine deiodinase in BAT by norepinephrine emphasizes the involvement of the sympathetic nervous system in controlling the thyroid gland. During cold exposure, increased circulating levels of thyroid hormone is a most expected biochemical change. As effectively summarized by F Villarroya, in his review [14], an integrated modulation of central and peripheral thyroid system is required for the physiological regulation of BAT-mediated thermogenic activation, both through intracellular mechanisms and via activation of a hypothalamic-mediated loop.

Liver to BAT connection

Bile acids secreted after meals induced BAT thermogenic activity via the induction of 5′-deiodinase is now known[15].The activated deiodinase in turn increased the intracellular T3 levels resulting in increased UCP1 expression. The involvement of Glucagon like peptide-1 (GLP1) in activating the BAT activity indirectly is reported by a few studies[16]. In addition to bile acids, another hepatic factor that is known to influence BAT activity is FGF21 or fibroblast growth factor-21. It is involved in regulating lipid and carbohydrate metabolism. More importantly increased FGF-21 levels are known to improve symptoms associated with obesity and related life style disorders[17].

Similar to thyroid hormones, they activate the uncoupling of mitochondrial respiration and enhance glucose oxidation. It is known to act through the FGF receptor present on the cell surface[18]. In 2019, Ameka *et al*[18] showed that the hepatic FGF21 can also act via the brain to increase sympathetic nerve activity in BAT. It is known that in new-borns, FGF21 released by the liver directly stimulates heat production in BAT.

TRP channels

Transient receptor potential (TRP) channels are a class of ion channels that are found in many cell types and present on the cell membrane. They are sensors for a variety of cellular and environmental signals, and are responsible for many sensory responses like heat, cold, pain, stress, vision, and taste. TRP family is divided into seven subfamilies, among which vanilloid (TRPV1) is called the capsaicin receptor[19]. Previously, many studies have highlighted the strong association between capsasinoids and NST through the TRPV1 channel. Specifically, the activation of TRPV1 leading to the prevention of adipogenesis, obesity and non-alcoholic fatty liver disease is reported[20]. In addition, it is known that the activation of TRPV1 by capsaicin leads to the promotion of lipolysis, which promotes NST. In a clinical trial conducted by Yoneshiro *et al*, the effect of capsinoids on activation of BAT in humans was evaluated. Results from this study showed a positive effect of capsinoids on BAT activation leading to an increased energy expenditure[21].

Of all the TRP channels, TRPM8 is a thermal sensor and found on BAT. Upon activation by its respective ligands, TRPM8 enhances UCP1 expression through the PKA pathway. Recently, a similar effect of TRPM8 is reported for white adipocytes as well. A recent review by Wu Z[22] effectively summarizes the list of clinical trials where thermogenic compounds are studied and their specific mode of action is discussed.

Pathways turning on the thermogenesis: cAMP-PKA Pathway

The cAMP-PKA pathway is one of the most well studied pathways that activate NST in BAT in response to cold temperatures. The process begins when catecholamines like norepinephrine bind to β-adrenergic receptors present on the surface of brown adipocytes. Binding activates the receptors leading to the stimulation of adenylate cyclase resulting in an increased intracellular cAMP level. Elevated cAMP levels activate protein kinase A. PKA is a kinase that phosphorylates various target proteins in the cell, one key target being hormone-sensitive lipase (HSL). Phosphorylation of HSL leads to the breakdown of stored triglycerides into free fatty acids and glycerol[23].

Another crucial target of PKA is the transcriptional regulation of UCP1. UCP1 is found in the inner mitochondrial membrane of brown adipocytes and is essential for non-shivering thermogenesis. PKA enhances the expression of UCP1 by influencing transcription factors such as CREB (cAMP response element-binding protein). UCP1 disrupts the proton gradient across the mitochondrial membrane generated by the electron transport chain. Instead of being used to produce ATP, the energy from this proton gradient is released as heat. This process increases the metabolic rate and generates heat, contributing to thermogenesis[24].

cGMP-AKT pathway

The cGMP-AKT pathway is another signalling mechanism involved in regulating NST in BAT, though it is less characterized compared to the cAMP-PKA pathway. The cGMP-AKT pathway starts with the production of nitric oxide (NO) or natriuretic peptides (NP) in response to various stimuli. NO is synthesized from L-arginine by nitric oxide synthase (NOS) enzymes. NO diffuses into neighbouring cells and activates soluble guanylate cyclase (sGC). Activated sGC then converts GTP (guanosine triphosphate) into cyclic GMP (cGMP), a second messenger involved in several cellular processes[25].

Elevated levels of cGMP activate protein kinase G (PKG). In some contexts, the activation of PKG by cGMP can lead to the activation of AKT (also known as protein kinase B). AKT is a key regulator of cell metabolism and survival. Its activation can influence several downstream pathways that impact BAT function. AKT affects various metabolic pathways in brown adipocytes. It can influence glucose uptake, lipid metabolism, and mitochondrial biogenesis, all of which are important for thermogenic activity[26]. By modulating UCP1 levels, AKT helps regulate the heat production process in BAT. UCP1 is crucial for uncoupling oxidative phosphorylation in mitochondria, allowing energy to be released as heat rather than being used to produce ATP. Through its effects on metabolic pathways and UCP1 expression, the cGMP-AKT pathway contributes to the activation of NST in BAT.

AMPK signalling pathway

AMPK (AMP-activated protein kinase) is a crucial regulator of energy balance and metabolism. AMPK is activated in response to cellular energy stress, such as low levels of ATP or high levels of AMP. This activation can occur due to various stimuli, including exercise, calorie restriction, or cold exposure[27]. Activation of AMPK promotes mitochondrial biogenesis in brown adipocytes by activating PGC-1α (peroxisome proliferator-activated receptor γ coactivator 1-alpha), a key regulator of mitochondrial and thermogenic gene expression[28]. Increased mitochondrial content supports enhanced thermogenesis. AMPK activation also leads to increased expression of uncoupling protein 1 (UCP1) in brown adipocytes. AMPK stimulates lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol, which are then used as substrates for thermogenesis[29]. This is partly mediated through the phosphorylation of hormone-sensitive lipase (HSL) and other lipolytic enzymes.

The latest player among BAT activators: The Gut microflora

While exploring the various means of activating NST in BAT, the influence of gut microflora is beginning to take centre stage. The influence of gut microorganisms on overall metabolism and well-being of an individual is well established over the last many decades. However, the effect of gut microflora and its metabolites on BAT and its activity is being explored only recently. We believe evaluating this less explored connection between the two important parts that control energy metabolism in the body namely Brown adipose tissue and Gut microflora could hold promising answers for activating thermogenesis. In finding answers to these questions, three important aspects that need to be addressed primarily are: Does GM has an effect on NST in BAT? Does the GM differ significantly from a lean to an obese individual? Can GM be modified by dietary compounds or prebiotics such that a favourable GM be achieved that can help activate NST in BAT and cause browning of WAT? Below we discuss answers to these three queries.

Does GM have an effect on NST in BAT?

In seeking answer to the first question, we observed that there are multiple studies that discuss the positive impact of GM in activating NST in BAT. A study by Li B *et al.*[30] shows that depletion of gut microbiota via antibiotics impairs BAT thermogenesis by reducing the expression of UCP1 and diminishes the browning of WAT. A study by Tang *et al*. reports that butyrate supplementation reverses impaired thermogenesis caused by microbiota depletion, indicating a crucial role of gut microbiota in thermogenesis[31]. Other studies also discuss the involvement of butyrate in activating thermogenesis in both BAT and WAT[32].In addition to producing butyrate, it is now known that GM may activate thermogenesis through various mechanisms, including the modulation of Gut-Brain axis, bile acid metabolism, the endocannabinoid system, activating AMPK pathway, production of fermentation products like acetate and lactate[33].

Does the GM differ significantly from a lean to an obese individual?

Following the rediscovery of metabolically active BAT in humans by three independent research groups in 2009, the difference in BAT quantity and activity between lean and obese individuals have been studied. The BAT content, activity, thermogenesis in beige cells are all found to be higher in lean individuals in comparison to people with obesity. This discussion propels one to question if the GM also varies significantly between lean and obese and hence between two individuals with high and low BAT activity respectively. A systematic review by Louise Crovesy reports the differences in profile of gut microbiota between lean and obese individuals[34]. In obese individuals, there is an increased *Firmicutes/ Bacteroidetes* ratio, *Firmicutes*, *Fusobacteria, Proteobacteria, Mollicutes, Lactobacillus* (*reuteri*), and lesser number of *Verrucomicrobia* (*Akkermansia muciniphila*), *Faecalibacterium* (*prausnitzii*), *Bacteroidetes, Methanobrevibacter smithii, Lactobacillus plantarum* and *paracasei*. Weather this specific pattern of GM seen in obese and lean individuals can be extrapolated to their impact on BAT activity should be explored more in the future.

Can GM be modified by dietary compounds to activate NST in BAT?

In the search for dietary compounds that can specifically alter the GM to facilitate activation of thermogenesis in the body, revisiting the existing thermogenic compounds, evaluating prebiotics and other compounds capable of GM modification holds promise. Many research groups are already exploring the prebiotic potential of known thermogenic compounds. In a review by Barbara *et al* they effectively summarize the ability of polyphenols from various known thermogenic compounds to alter the GM in a manner to positively impact thermogenesis in BAT. In a study by Li *et al*[35] the ability of green tea polysaccharides to activate BAT thermogenesis by modulating the GM is reported. The ability of capsaicin to prevent dysbiosis and promote the growth of specific organisms in the gut resulting in improved thermogenesis in experimental animal models is known[36].

The existing literature definitely points towards the involvement of GM in activating BAT and WAT. They influence BAT activity through multiple mechanisms some of which are mentioned here. This compels one to evaluate weather modulation of gut microbiota through dietary interventions or specific prebiotics can enhance BAT thermogenesis and promote the browning of WAT, leading to increased energy expenditure and reduced obesity. Particularly the currently existing thermogenic compounds should be re-evaluated for their prebiotic potential decoding if their mode of action is also by modulating the GM and increasing the production of useful postbiotics.

A brief on a few thermogenic compounds and their mode of action

An effective strategy for activating thermogenesis in BAT involves the use of specific thermogenic compounds. These compounds have been pivotal in advancing our understanding of BAT biology, particularly regarding the various biochemical markers that facilitate its activation. Research into these thermogenic agents has provided insights into how BAT can be stimulated to enhance energy expenditure, a key factor in combating obesity and related metabolic disorders. Studies have shown that certain thermogenic compounds can significantly influence BAT activity by promoting the expression of genes associated with thermogenesis. For instance, compounds such as berberine, and capsaicin have been identified as natural thermogenic agents that activate critical transcriptional factors involved in the thermogenic process. These compounds work by enhancing mitochondrial function and promoting the expression of UCP1, which is essential for heat production in BAT.

As we explore the thermogenic potential of various compounds, it is essential to consider their mechanisms of action. For example, as shown in (Table 1), some compounds may activate the AMP-activated protein kinase (AMPK) pathway while others may act through the cGMP-AKT pathway, all of which play a crucial role in cellular energy regulation. In summary, the exploration of specific thermogenic compounds has significantly advanced our understanding of how to activate BAT effectively. These studies not only provided insights into the underlying biology of BAT but also paved the way for developing novel therapeutic strategies aimed at enhancing energy expenditure and combating obesity. In the following section, we will discuss several promising thermogenic compounds that have been studied recently, highlighting their potential roles in activating BAT and supporting metabolic health.

Cinnamomum cassia

Cinnamomum cassia extract (CE) significantly enhances thermogenesis, especially in cold environments, by activating BAT and promoting energy metabolism. Central to its effect is the upregulation of UCP1 in BAT, which drives thermogenesis by uncoupling mitochondrial oxidative phosphorylation, leading to heat generation rather than ATP production. CE also induces lipolysis, breaking down stored triglycerides in adipose tissue, releasing fatty acids that both fuel thermogenesis and further activate UCP1. This metabolic shift increases energy expenditure, resulting in more efficient heat production. Moreover, CE activates the AMPK (AMP-activated protein kinase) and SIRT1 (sirtuin 1) pathways, which is crucial for regulating thermogenic gene expression and promoting adaptive heat generation. By leveraging these mechanisms, CE enhances non-shivering thermogenesis, enabling the body to maintain warmth in cold conditions. Thus, CE acts as a potent stimulator of thermogenesis, improving cold tolerance and providing potential protection against cold-induced stress[37]. Beyond direct BAT activation, cinnamon and its extracts have been linked to improved metabolic profiles in obesity and diabetes models, and some studies suggest interactions between cinnamon, gut microbiota, and host adiposity, though detailed microbiota-mediated thermogenesis data remain limited.

Table 1 — List of thermogenic compounds and their mode of action

Thermogenic compound	Dose effective on animal models	Mechanism of action	Reference
Cinnamomum cassia extract	Dosage for male Kunming mice - 360 mg/kg/day	1. Upregulating UCP1 in BAT 2. Induction of lipolysis and AMPK pathways	LiX, LuH,Y, JiangX,W, YangY, XingB, YaoD & ZhaoQ,C. *Cinnamomum cassia* extract promotes thermogenesis during exposure to cold *via* activation of brown adipose tissue. *J Ethnopharmacol*, 266, (2021) 113413.
Sargassum thunbergii	Dosage for Male C57BL/6 mice -100 and 300 mg/kg	1. Upregulation of UCP1 and UCP3 2. Increases mitochondrial uncoupling	KangM,C, LeeH,G, KimH,S, SongK,M, ChunY,G, LeeM,H & JeonY,J. Anti-obesity effects of *Sargassum thunbergii via* downregulation of adipogenesis gene and upregulation of thermogenic genes in high-fat diet-fed obese mice. *Nutrients*, 12, (2020) 3325.
Withaferin A	Dosage for male C57BL/6 J mice - 0.75 mg or 1.5 mg/kg	1. Upregulating thermogenic genes like UCP1, PGC1A, AND PRDM16 2. Facilitates uncoupling of mitochondrial respiration 3. Activates the AMPK, p38 and ERK MAPK pathways	LeeD,H, ParkS,H, LeeE, SeoH,D, AhnJ, JangY,J & JungC,H. Withaferin A exerts an anti-obesity effect by increasing energy expenditure through thermogenic gene expression in high-fat diet-fed obese mice. *Phytomedicine*, 82, (2021) 153457.
Piperine	Dosage for brown laying hens strain MB 402-0.2 g/kg	1. By accelerating lipid breakdown.	LekeJ,R, LaihadJ,T, TangkauL, SompieF & SiahaanR. The Quality of Chicken Eggs Fed Black Pepper (*Piper nigrum* L.) Flour. *BIO Web Conf*, 88, (2024) 00003.
Resveratrol	Dosage for Type 2 diabetic male db/db mice - 30 or 60 mg/kg/day	1. Upregulates UCP1 expression. 2. Shapes gut microbiota, influencing bile acid metabolism. 3. Alters bile acid composition, increasing LCA levels and TGR5 activation.	HuiS, LiuY, HuangL, ZhengL, ZhouM, LangH & MiM. Resveratrol enhances brown adipose tissue activity and white adipose tissue browning in part by regulating bile acid metabolism *via* gut microbiota remodeling. *Int J Obes*, 44, (2020) 1678.
Pterostilbene	Dosage for male Sprague Dawley (SD) rats -50 mg/kg body weight/day	1. Increases AMPK phosphorylation. 2. Upregulates PGC-1α expression. 3. Upregulates UCP1.	ZhengJ, LiuW & ZhuJ. Pterostilbene induces browning of white adipocytes *via* AMPK/PGC-1α pathway. *Precision Nutr*, 2, (2023) e00032. (The second reference for this entry, Wang, P., & Sang, S. (2018), is for metabolism and pharmacokinetics and is not included here as it is not present in the main reference list.)
Urolithin A (UA)	Dosage for male C57BL/6 mice – 30-50 mg/kg/day	1. Increases local T4 conversion into T3. 2. Enhances expression of thermogenic markers like UCP1. 3. Drives mitochondrial biogenesis and oxidative capacity. 4. Beneficial for brown and beige adipocytes.	XiaB, ShiX,C, XieB,C, ZhuM,Q, ChenY, ChuX,Y & WuJ,W. Urolithin A exerts antiobesity effects through enhancing adipose tissue thermogenesis in mice. *PLoS Biol*, 18, (2020) e3000688.

Sargassum thunbergii

Sargassum thunbergii is a type of edible brown seaweed found along the coasts of Korea, Japan, and China, plays a vital role in promoting thermogenesis, primarily through its influence on BAT. Its mechanism involves the upregulation of essential thermogenic genes, particularly UCP1 and UCP3, which are key regulators of energy expenditure and heat production in BAT. By increasing the expression of UCP1 and UCP3, *Sargassum thunbergii* facilitates mitochondrial uncoupling. This enhancement in energy consumption leads to increased thermogenesis, ultimately promoting heat production and reducing fat accumulation in high-fat diet (HFD)-induced obese mice.

In addition to its thermogenic effects, *Sargassum thunbergii* down regulates adipogenesis-related genes, such as PPARγ, which further inhibits fat storage in WAT. This combined effect upregulating thermogenic pathways in BAT, while down regulating adipogenic pathways in WAT suggests that *Sargassum thunbergii* effectively combats obesity by boosting energy expenditure and limiting fat deposition. This dual action of activating thermogenesis and inhibiting fat accumulation highlights *Sargassum thunbergii* as a promising natural agent for managing obesity and improving metabolic health[38]. Additionally, the polysaccharides and polyphenols from this plant is known to have prebiotic-like properties that can increase beneficial organisms and short-chain fatty acid production. However, specific data linking Sargassum-driven microbiota shifts to BAT thermogenesis are still emerging and mostly inferred from broader seaweed and algal prebiotic literature

Withaferin A

Withaferin A (WFA) is a bioactive compound extracted from *Withania somnifera*, commonly known as Ashwagandha, enhances thermogenesis and energy expenditure, contributing to its anti-obesity effects. It activates BAT and promotes the browning of subcutaneous white adipose tissue (scWAT), which increases heat production. WFA boosts thermogenesis by upregulating key genes like UCP1, PGC1α, and PRDM16, which are essential for BAT function. WFA also activates the AMP-activated protein kinase (AMPK) pathway, enhancing mitochondrial biogenesis and activity, which further supports thermogenesis. Moreover, WFA stimulates the p38 and ERK MAPK pathways, crucial for the browning of white adipocytes. These pathways lead to the expression of thermogenic genes, converting white fat into beige fat, which behaves similarly to brown fat in heat production. Direct evidence that WFA modulates gut microbiota to enhance thermogenesis is still sparse, so any microbiota contribution is at present speculative. Thus, WFA promotes thermogenesis and energy expenditure through the activation of AMPK and MAPK pathways, increasing mitochondrial activity and the expression of thermogenic genes[39].

Piperine

Piperine, is the active compound found in black pepper. It enhances thermogenesis by accelerating lipid metabolism, thereby increasing energy expenditure. By promoting the breakdown of fat, piperine facilitates the release of energy in the form of heat, contributing to fat reduction and improved weight management. The thermogenic mechanism of piperine is driven by several biochemical pathways. It improves the absorption of vital nutrients, such as selenium, vitamin B complex, beta-carotene, and curcumin, which support metabolic processes. Furthermore, piperine stimulates the production of serotonin and beta-endorphin in the brain, compounds linked to mood regulation and metabolic health, thereby augmenting the thermogenic response. Its effect on lipid metabolism is particularly significant, as it accelerates fat oxidation and energy release, intensifying thermogenesis[40].

In high-fat diet-induced obese mice, piperine is known to reduces body weight and improve lipid profile. It is reported to increasing gut microbiota diversity, enriching *Muribaculaceae* and *Ruminococcaceae* and suppressing genera associated with obesity. These compositional changes correlate strongly with improved metabolic phenotypes and suggest a microbiota-mediated component to its anti-obesity and possibly thermogenic action. In addition to its role in heat production, piperine’s thermogenic activity is also supported by its antioxidant properties, offering protection against oxidative stress. This cellular defense is critical for maintaining metabolic efficiency, further enhancing fat loss and promoting overall metabolic health[41].

Resveratrol

Resveratrol, a natural polyphenol found primarily in grapes, berries, and other dietary sources, is known to influence NST in BAT and induce the browning of WAT. Interestingly, it is also known that the additional mechanism underlying resveratrol's thermogenic effects involve the modulation of gut microbiota and bile acid metabolism. Specifically, resveratrol reshapes the gut microbiota, leading to an increase in lithocholic acid (LCA), a secondary bile acid that activates the Takeda G-protein coupled receptor 5 (TGR5). Activation of TGR5 stimulates UCP1 expression in both BAT and WAT, driving thermogenesis. This gut microbiota-bile acid-TGR5-UCP1 pathway is central to resveratrol's ability to enhance energy expenditure and improve metabolic health, making it a promising candidate for therapeutic strategies targeting obesity and related metabolic disorders[42].

Pterostilbene

Pterostilbene, is a polyphenol and analogue of resveratrol. It promotes the browning of WAT by activating AMPK/peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) pathway, which regulates mitochondrial biogenesis and thermogenic gene expression. By increasing AMPK phosphorylation and PGC-1α expression, pterostilbene upregulates thermogenic marker, UCP1. Additionally, pterostilbene enhances mitochondrial biogenesis, boosting the oxidative capacity of beige adipocytes, while reducing lipid accumulation without affecting adipogenic differentiation. This transformation of white fat into beige fat significantly contributes to increased energy expenditure and underlies the anti-obesity effects of pterostilbene[43].

As a stilbene related to resveratrol, pterostilbene shows anti-obesity and insulin-sensitizing effects in preclinical models, and resveratrol-like compounds are known to modulate gut microbial composition and increase beneficial metabolites, but direct demonstrations that pterostilbene specifically alters the gut microbiota to enhance BAT thermogenesis are still limited and mostly extrapolated from broader polyphenol–microbiota studies.

Urolithin A

Urolithin A (UA), a metabolite derived from ellagitannins found in foods like pomegranates and berries, has been shown to enhance thermogenesis. UA promotes thermogenesis through the thyroid hormone (TH) signaling pathway, increasing the local conversion of tetraiodothyronine (T4) into the active triiodothyronine (T3) in adipose tissues. This elevated T3 enhances the expression of key thermogenic markers such as UCP1, driving mitochondrial biogenesis and increasing oxidative capacity in both brown and beige adipocytes. As a result, UA-treated mice exhibit higher energy expenditure, improved cold resistance, and increased oxygen consumption. Importantly, UA's thermogenic effects are independent of β-adrenergic receptor activation, making it a promising candidate for combating obesity by promoting fat burning through a TH-dependent mechanism[44].

Notable that UA is known to improve mitochondrial function and metabolic health and is itself a product produced by some microbial communities. This implies an intimate microbiota–host interaction. However, most evidence focus on mitophagy and muscle/metabolic benefits and its capacity to reshape gut microbiota composition as an anti-obesity strategy remains an active area of investigation rather than a fully established mechanism.

Prebiotic potential of thermogenic compounds

In the process of achieving BAT specific activation with minimal side effects, newer mechanisms and pathways that activate BAT are being explored. Also, external, dietary molecules which upon consumption can activate these pathways are being researched extensively over the past two decades. One of the recently identified means of activating BAT is through the GM and its metabolites. Since GM can be modified by the use of specific prebiotics, it provides an attractive target by which BAT activity can in turn be modulated. In this perspective, revisiting the existing thermogenic compounds or identifying prebiotics which can alter GM in such a manner that it can positively influence BAT activity and cause browning of WAT holds promise for better and more importantly specific activation of thermogenesis in BAT. Below we discuss some of the most commonly reported thermogenic compounds and review if they are evaluated for their prebiotic potential. Further we looked into the literature to understand if these compounds have been evaluated to check if their prebiotic potential is involved in activating BAT activity or cause browning of white adipose tissue.

Green tea

The ability of green tea polyphenols to activate BAT through their prebiotic potential is being studied. Studies demonstrating the potential of green tea in activating BAT and promoting adipose thermogenesis, primarily through its ability to modulate gut microbiota are now coming to light. It was observed that green tea polyphenols modulate gut microbiota by increasing beneficial bacteria such as *Bifidobacterium* and *Akkermansia,* which are associated with improved metabolic health and reduced obesity[40]. Specifically, Ziyang selenium-enriched green tea polysaccharide (Se-GTP) has been shown to facilitate BAT thermogenesis and browning of inguinal white adipose tissue (iWAT) in obese mice, potentially through the enhancement of gut microbiota and microbial metabolites like succinate[41]. While animal studies show promising results, human trials with green tea polyphenols have yielded mixed outcomes, indicating that the effects may vary based on dosage, duration, and individual difference, suggesting that further research is needed to fully understand this mechanism[45].

Peppers and capsaicin

The role of pepper and its bioactive compounds, in activating BAT has been evaluated by many groups with few groups focusing on their effect on their prebiotic potential. They reported that diets supplemented with pepper can alter the gut GM composition, increasing the abundance of beneficial bacteria such as *Lactobacillaceae* and *Acetobacteraceae.* This effect is linked to the phenolic compounds and carotenoids present in peppers[46]. Capsaicin administration induces the expression of thermogenesis and mitochondrial biogenesis genes in BAT, promoting a "browning" effect in WAT and enhancing energy. However, more studies providing conclusive evidence that establishes the thermogenic ability of pepper through its ability to modulate the GM is needed.

Capsaicin shows promise in weight reduction and combating obesity, mainly by activating the Transient Receptor Potential Vanilloid 1 (TRPV1) cation channel. This activation leads to enhanced BAT activity, increased thermogenesis, lipid oxidation, and reduced WAT. It also influences the GM which plays a crucial role in its anti-obesity effects. The gut bacterium *Akkermansia muciniphila* is linked to capsaicin's anti-obesity effects. It increases beneficial gut bacteria, improves glucose tolerance, and reduces inflammation[47].

Cinnamon

Cinnamon has been evaluated for its ability to alter gut GM, which in turn can improve metabolic health and potentially activate BAT. The spice's modulation of gut microbiota, enhancement of lipid absorption, and anti-inflammatory properties collectively contribute to these beneficial effects. It is also considered a kind of hot herb because it upregulated the body temperature during cold exposure. However, direct evidence linking cinnamon to BAT activation through GM changes remains to be further explored.

Cinnamon essential oil from *Cinnamomum osmophloeum* has a notable anti-obesity potential. Studies reveal that this essential oil treatment leads to weight loss and lowered blood triglyceride levels in mice. The key component responsible for these effects is S (+) linalool. Moreover, cinnamon essential oil treatment has been shown to reduce fat accumulation and improve metabolic health, making it a promising natural remedy for obesity related issues[48]. Cinnamon oil in the form of microcapsules could significantly proliferate the abundance of beneficial bacteria such as *Bacteroides, lactobacillus, beauticians* and *Rumini clostridium*. It also significantly reduces the growth of pathogenic bacteria including *Muribaculacea, Ruminococcaceae and Gordonibacter*. This modulation in GM will enhance the BAT activity and influence energy metabolism which in turn helps combat obesity[49].

Panax notoginseng

Panax notoginseng, is a prized plant in traditional Chinese medicinal system. The bioactive compounds within this plant, collectively known as *Panax notoginseng* saponins (PNS), have shown promising effects in addressing obesity. Studies have revealed that PNS treatment can significantly alter the gut microbiota composition. Specifically, PNS is reported to increase the abundance of beneficial bacteria such as *Akkermansia muciniphila* and *Parabacteroides distansanis*[50]

Modulation of the gut microbiota by PNS has several important metabolic implications. One key outcome is the enhancement of thermogenic activity in BAT. Moreover, PNS treatment can promote the browning of WAT, leading to a more BAT-like phenotype characterized by increased thermogenic capacity and improved insulin sensitivity. The mechanism behind these beneficial effects involves the activation of the leptin-AMPK/STAT3 signalling pathway. Leptin, a hormone fat cell produces, is crucial in regulating energy balance. When PNS alters the gut microbiota, it can influence leptin signalling. This, in turn, activates AMPK (AMP-activated protein kinase) and STAT3 (signal transducer and activator of transcription 3), key players in metabolic regulation. *Panax notoginseng* and its bioactive compounds, offer a promising approach to addressing obesity. By favourably altering the gut microbiota and activating key signalling pathways, PNS can enhance energy expenditure and contribute to weight management. Further research is needed to elucidate the mechanisms involved fully and to explore the therapeutic potential of PNS in obesity treatment[51].

Nobiletin (NOB)

It is an O-methylated flavonoid, specifically a polyethoxylated flavone (PMF), which is commonly found in the peel of citrus fruits such as tangerine (*Citrus tangerina*), sweet orange (*Citrus sinensis*), and bitter orange (*Citrus aurantium*) [52]. Nobiletin has been investigated for its effects on adaptive thermogenesis in a high-fat diet (HFD)-induced obesity mouse model. Studies have found that NOB treatment significantly reduces obesity by browning of WAT and enhancing the BAT activity in HFD mice. Analysis of the GM indicated that NOB treatment altered the composition of gut microflora, which in turn changed the levels of fermentation products like acetate in the faeces and serum of the host. These findings suggest that Nobiletin may serve as a dietary therapy to combat high-fat diet-induced obesity[53]. The activation of BAT is even regulated by β-adrenergic stimulation. NOB administration was found to reduce weight gain and improve glucose tolerance in these mice, while also restoring lipid metabolic balance and down regulating genes involved in lipid metabolism. Sequencing of 16S rRNA genes from faecal samples revealed that NOB treatment altered the composition of in GM affected by HFD, especially at genus level, including shifts in the relative abundances of Bacteroidetes and Firmicutes. NOB supplementation enhanced microbiota diversity, as indicated by improved Chao1 and Simpson indices. LEfSe analysis identified significant reductions in specific bacterial taxa like *Ruminococcaceae, Ruminiclostridium, Intestinimonas, Oscillibacter*, and *Desulfovibrio* in NOB-treated mice compared to those on HFD alone[54].

Zingerone

Zingerone is a phytochemical found in ginger, known for its anti-inflammatory, antioxidant, and anti-apoptotic properties among many other therapeutic properties. It is also known to enhance the formation of beige adipocytes which makes it a potent therapeutic nutraceutical agent in obesity management. The molecular mechanism involves zingerone binding to the nuclear hormone receptor PPARα, which increases the expression of thermogenic genes (UCP1, PGC-1α, PRDM16) in both BAT and WAT[55]. Zingerone intake alters gut microbiota composition by decreasing the *Firmicutes* to *Bacteroidetes* ratio and increasing the abundance of beneficial bacteria like *Akkermansia muciniphila*. Thus, zingerone supplementation can reduce obesity and improve metabolic health by enhancing thermogenesis and modulating gut microbiota composition[56].

Quercetin

It is a plant flavonoid with antioxidant, anti-inflammatory, and anti-osteoporotic properties. It is found in many fruits, vegetables, seeds, and grains. Studies have revealed that 1% supplementation of quercetin improves obesity in HFD feed mice, by reducing overall body weight, and total plasma cholesterol, and it has also increased the expression of non-shivering thermogenesis genes in BAT, including uncoupled protein UCP1, via activation of the AMPK/PPARγ pathway and many others[57]. Quercetin fights against metabolic syndrome by enhancing energy metabolism through mice's gut microbiota-bile acids (BAs).

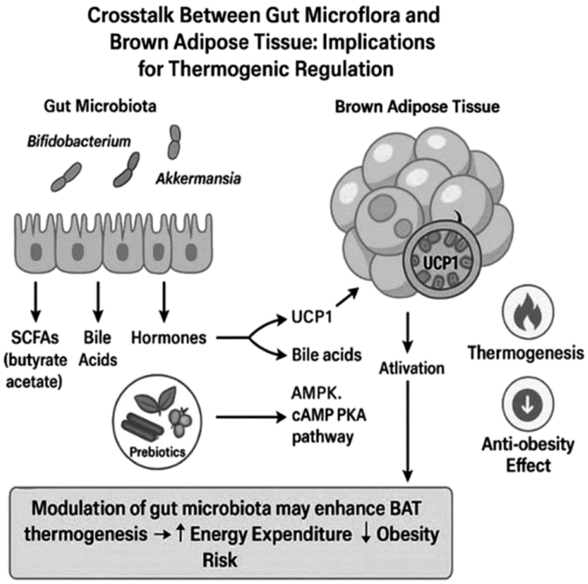

Fig. 1—Schematic representation of the gut microbiota–brown adipose tissue (BAT) axis and its role in thermogenic regulation. Gut-derived metabolites such as short-chain fatty acids (SCFAs), bile acids, and tryptophan derivatives modulate thermogenic pathways via systemic circulation and gut–brain–BAT signalling. These interactions promote UCP1 activation, mitochondrial biogenesis, and energy expenditure, contributing to improved metabolic outcomes.

Quercetin is known to improve serum antioxidant content and enzyme activity derived from intestinal bacteria, reducing intestinal flora abnormalities induced by a high-fat diet. It promotes the generation of non-12α-hydroxylated BAs (non-12OH BAs), particularly ursodeoxycholic acid (UDCA) and lithocholic acid (LCA), in serum via regulating the overall structure of gut microbiota and enriching Lactobacillus. These BAs stimulate thermogenesis via Takeda G protein coupled receptor 5(TGR5) on adipocytes. Faecal microbiota transplantation (FMT) from quercetin treated mice replicates these effects, suggesting that gut microbiota reshaping and Bas regulation drive the metabolic benefits of quercetin in combating metabolic syndrome[58]. The below picture (Fig. 1) summarises the possible interaction between the gut microflora and BAT. Identifying prebiotic potential off thermogenic compounds may prove most useful in today's times considering the fact that it can be an effective means of turning on BAT and hence combating obesity.

Conclusion

In conclusion, the current article aims to explore novel strategies for specifically activating BAT beyond the traditional sympathetic nervous system pathways, focusing on the emerging and promising role of the gut microbiota in this process. In the context of increasing obesity rates worldwide, finding effective means to enhance energy expenditure through BAT activation has become critically important. The review highlights how the gut microbiota, a modifiable ecosystem influenced by diet and environmental factors, can act as a significant endogenous regulator of thermogenesis and energy homeostasis. By dissecting the intricate interplay between gut microbial populations, dietary components such as prebiotics, and BAT function, the article has shed light on the Gut Microflora-BAT axis, an underexplored but potentially transformative connection in obesity research. Drawing on existing literature, the review emphasizes that gut microbes produce metabolites, including short-chain fatty acids, which impact thermogenic programs in BAT and facilitate the browning of white adipose tissue. This microbial influence opens avenues for intervention strategies that can alter gut microbiota composition to potentiate BAT activity and enhance metabolic health.

Furthermore, in this review we have reiterated the necessity of experimental validation to elucidate the precise mechanisms by which gut microbiota affects BAT thermogenesis in humans. We highlight gaps in current knowledge regarding how environmental stimuli, nutritional modulations, and pharmacological interventions might work synergistically with gut flora to optimize energy regulation. Ultimately, by consolidating recent findings and theorizing functional interactions between diet, microbes, and BAT, the review provides a comprehensive framework for future research focused on microbiome-based therapies to combat obesity and metabolic dysfunctions effectively. This integrative perspective is particularly relevant given the global urgency to develop safer, biologically informed anti-obesity interventions with lasting impact.

Competing Interests

Authors do not share any competing interest.

Authors contribution:

CP conceptualized the idea and contributed to all the sections. PD contributed to section 4 and referencing. GR contributed to sections 5.

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