Indexed by : DOAJ Google Crossref Dimension sinta GARUDA

J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Available online at JBTR website: https://jbtr.fk.undip.ac.id

Review Article

Sulforaphane Promotes Adipocyte Thermogenesis: Molecular Insights, Anti-Obesity Potential, and Future Perspective

Iftitan Setya Widayanti[1], Etika Ratna Noer[1], Faizah Fulyani[2*]

[1]*Department of Nutrition Science, Faculty of Medicine, Universitas Diponegoro, Indonesia*
[2]*Department of Medical Biology and Biochemistry, Faculty of Medicine, Universitas Diponegoro, Indonesia*

Article Info
History
Received: 24 Jun 2025
Accepted: 25 Sep 2025
Available: 22 Dec 2025

Abstract

Over the past five decades, the increasing incidence of obesity has sparked considerable interest in nutraceuticals as promising natural alternatives for effective weight management and metabolic health improvement. Sulforaphane (SFN), an isothiocyanate abundant in cruciferous vegetables, has gained attention for its potential in obesity management, particularly by promoting the browning of white adipose tissue (WAT) and transforming it into energy-burning fat. While its potential is significant, the underlying molecular mechanisms are complex and require a comprehensive synthesis. Therefore, this review explores sulforaphane (SFN) as a potential nutraceutical alternative by examining the scientific evidence of its anti-obesity effects, focusing on its ability to activate multiple signalling pathways, including Nuclear Factor Erythroid 2-related factor 2 (Nrf2), AMP-activated protein kinase (AMPK), and sirtuin 1 (SIRT1), as well as upregulation of uncoupling protein 1 (UCP1). These are the key pathways in mitochondrial biogenesis, lipid metabolism, and thermogenesis. Additionally, SFN can mitigate oxidative stress and modulate inflammatory responses, further contributing to improved metabolic function and energy expenditure. While much of the research on SFN has focused on its effects on mature cruciferous vegetables, current research increasingly directs attention to microgreens, which contain significantly higher concentrations of bioactive compounds, including SFN. This review highlights SFN's molecular mechanisms underlying its role in the context of obesity, specifically its effects on WAT browning, metabolic regulation, and thermogenesis. We also explored the potential of microgreen-derived SFN as a promising nutraceutical for obesity intervention and metabolic regulation, highlighting the novel bioactive chemical and biological properties of these plants.

Keywords: *Sulforaphane; Nutraceutical; Browning of White Adipose; Thermogenesis; Obesity*
Permalink/ DOI: https://doi.org/10.14710/jbtr.v11i3.28102

INTRODUCTION

Obesity results from an imbalance in energy intake and expenditure, leading to the excessive accumulation of white adipose tissue (WAT). This condition contributes to the development of other diseases, such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and particular types of cancers, all of which have a significant impact on global mortality[1] and are directly responsible for millions of deaths each year worldwide.[2] Recently, several studies have highlighted the browning of white adipose tissue (WAT) as a promising approach for managing obesity. This process transforms white fat cells into active brown-like fat cells, thereby increasing energy expenditure. As a result, it helps reduce excess fat while enhancing overall metabolic health.[3]

Natural compounds offer advantages to human health because of their bioactive properties, which demonstrate disease-modifying effects in various chronic diseases, including obesity.

*Corresponding author:
E-mail: *f.fulyani@fk.undip.ac.id*
(Faizah Fulyani)

Isothiocyanates, such as sulforaphane (SFN), are sulfur- and nitrogen-rich compounds that are abundant in cruciferous vegetables of the Brassicaceae family. The abundance of SFN in the young plants, also known as microgreens, was found to be an order of magnitude higher than that in the mature plants. Importantly, the compound has been widely acknowledged for its well-known therapeutic effects and potential applications.[4]

Recent studies have highlighted SFN's potential in managing obesity and metabolic syndrome, demonstrating its ability to promote white adipose tissue (WAT) browning and improve insulin signalling.[5] Furthermore, SFNs have demonstrated disease-modifying capabilities through various and extensive mechanisms of action, including the reduction of reactive oxygen species (ROS), activation of antioxidant enzymes, attenuation of oxidative stress, and modulation of inflammatory responses.[4] In both *in vitro* and *in vivo* models, SFN has been shown to enhance mitochondrial biogenesis, upregulate thermogenic gene expression, and improve lipid metabolism through key pathways, including Nrf2, SIRT1/PGC-1α, and AMPK.[6–10] Additionally, SFN has been found to inhibit the differentiation of preadipocytes into mature adipocytes and reduce lipid accumulation by suppressing the transcription of adipogenic factors, including PPARγ and C/EBPα. Interestingly, its effect also extends to glucose metabolism, preventing weight gain, and altering the composition of gut microbiota and inflammation. These cumulative effects further underscore the use of sulforaphane-rich nutraceuticals for managing obesity and related metabolic disorders.[11,12]

This review aims to explore the underlying molecular mechanisms of SFN as an anti-obesity nutraceutical, with a focus on its thermogenic activities. It also examines the chemical and biological characteristics, including bioavailability, biostability, and metabolism, as well as its impact on the browning of white adipose tissue (WAT). The article concludes by evaluating SFN as a promising therapeutic strategy for addressing obesity and related metabolic disorders.

MATERIALS AND METHODS

A comprehensive literature search was conducted to identify relevant studies for this review. We searched electronic databases, including PubMed, Scopus, and Google Scholar, for articles published up to June 2025. The search strategy utilised a combination of keywords related to the main topic, such as "sulforaphane," "obesity," "white adipose tissue browning," and "thermogenesis," often paired with broader mechanism-related terms like "molecular pathways" or "signaling pathways." This approach was designed to identify the full range of underlying mechanisms involved. We included preclinical studies (both *in vivo* and *in vitro*) that investigated the molecular mechanisms of sulforaphane in the context of adipocyte function and metabolic regulation. Articles were selected based on their relevance to the review's scope, and priority was given to peer-reviewed original research and review articles. No language restrictions were applied during the initial search.

DISCUSSION

Sulforaphane

Molecular Structure and stability of Sulforaphane

As a member of the isothiocyanate family, SFN possesses a molecular structure ($C_6H_{11}NOS_2$) characterised by a benzene ring (C_6H_5) attached to a short aliphatic chain (-CH_2-CH_2-) and an isothiocyanate functional group (-N=C=S). Additionally, the sulfinyl group is connected to the aliphatic chain, contributing to the compound's chemical reactivity (**Figure. 1A)**. The presence of sulfur and nitrogen atoms in SFN is particularly significant in its structure. It plays a crucial role in cellular signalling and contributes to energy production.[13] Additionally, the nitrogen atom enhances its SFN reactivity towards cellular components, such as proteins and enzymes.[14] SFN is a small molecule with a molecular weight of 177.29 g/mol, which makes it easier for the molecule to travel through cellular membranes and reduces steric hindrances during interactions with transport proteins and receptors. Furthermore, the sp3-hybridised carbon-carbon (Csp3) fraction is 0.83, indicating a predominantly aliphatic structure that enhances its ability to interact with hydrophobic regions of biological membranes and protein-binding sites, thereby contributing to its functional versatility in biological systems. These properties are essential for understanding its structural flexibility and interactions with biomolecules.[15]

SFN exhibits high conformational freedom, as evidenced by its five rotatable bonds, which feature a "pivot joint" structure, providing the molecule with flexibility. It enables various orientations and interactions with biological targets, such as enzymes and receptors, thereby enhancing their activity and binding specificity.[16] In addition, the molecule possesses two hydrogen bond acceptors and no hydrogen bond donors, which could influence its solubility and interaction with hydrophilic environments, including aqueous media and protein active sites.[17] Furthermore, the SFN's polar surface area (PSA) is calculated to be 80.73 Å² (<140 Å²), generally associated with good membrane permeability, suggesting that sulforaphane can readily cross biological membranes, including the blood-brain barrier.[18] Lastly, the molar refractivity of 48.40 further supports its lipophilic interactions and the potential to engage in van der Waals forces.[19]

The melting point of SFN is 74.6º C, indicating moderate thermal stability, which is essential for its storage and formulation in a therapeutic setting. A critical limitation of SFN regarding its delivery mechanisms is its water insolubility, which has moderate lipophilicity with a LogP of 1.93 (**Figure. 1B**). This is essential because it allows the substance to be transported through passive diffusion while maintaining solubility in aqueous fluids, such as blood plasma.[20] However, its water insolubility necessitates the development of delivery systems, such as emulsions, nanoparticles, and encapsulation systems, to enhance its solubility and bioavailability.[21]

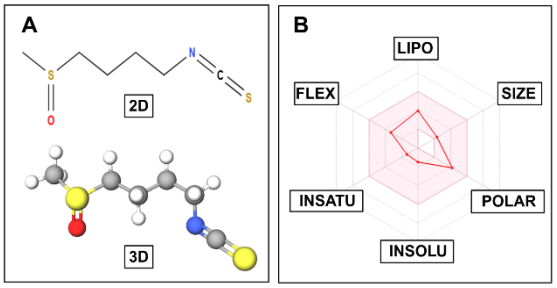

Figure 1. A. Molecular structure of sulforaphane in 2D and 3D conformations; **B.** Pharmacokinetic properties including lipophilicity (LIPO: LogP = 1.93), flexibility (FLEX: Number of rotatable bonds = 5), molecular size (SIZE: Molecular weight = 177.29 g/mol), polarity (POLAR: Polar surface area = 80.73 Å²), insaturation (INSATU: Molar refractivity = 48.40), and insolubility (INSOLU: Insoluble)

General Sources of Sulforaphane

Generally, SFN is predominantly found in cruciferous vegetables, particularly in the Brassica genus. The highest concentrations are observed in broccoli (16.6–57.7 µmol/g d.w)[22], cabbage (41.0–177.0 µg/g d.w)[23], kale (4.0–12.5 µmol/g d.w)[24], bok choy (0.3–1.4 µmol/g d.w) [25], cauliflower (3.8–9.2 µg/g d.w) [26], kohlrabi (0.78–40.25 µmol/g d.w)[27], and brussels sprouts (336–1483.76 µg/g d.w).[28] Notably, younger plants, particularly sprouts, exhibited significantly higher SFN contents than mature plants. Studies have shown that broccoli shoots contain 10 to 100 times more nutrients than mature plants.[29] Similarly, broccoli microgreens have been found to have glucoraphanin (a precursor to sulforaphane) content similar to that of broccoli shoots, making them a significant source of sulforaphane (SFN).[30] The presence of SFN in these vegetables underscores its potential health benefits, including antioxidant, anti-cancer, anti-inflammatory, and anti-obesity effects.[31]

Metabolic Digestion and Bioavailability of Sulforaphane

SFN undergoes a series of metabolic processes, from ingestion to absorption and circulation, as shown in (**Figure. 2**). Glucoraphanin (GRA) is converted to sulforaphane (SFN) by the enzyme myrosinase when plant tissue is disrupted, such as through chewing, crushing, or cooking, which allows the enzyme to come into contact with GRA. Without such disruption, myrosinase remains inactive until the oral and gut microbiota facilitate the conversion of GRA to SFN.[32] Once in the stomach, the SFN remains stable in the acidic environment and is efficiently passed through to the small intestine, where the body absorbs it through passive diffusion across the intestinal lining.[33] During this stage, SFN primarily conjugates with glutathione via the mercapturic acid pathway, forming SFN-GSH sulforaphane-glutathione conjugates (SFN-GSH). The body transports these conjugates to the liver, where they undergo phase II metabolism to form sulforaphane-cysteine (SFN-Cys) and sulforaphane-N-acetylcysteine (SFN-Nac). The latter is the predominant metabolite in the blood and urine. These substances are distributed across various organs and tissues, including the adipose tissue. Notably, SFN's presence in adipose tissue has been linked to its potential role in thermogenesis, the body's process of heat production.[34]

The bioavailability of SFN significantly influences its effectiveness and potential therapeutic benefits, with a reported bioavailability of approximately 40%. It appears in the bloodstream within 1-2 hours after consumption, with peak plasma concentrations occurring between 1 and 3 hours after ingestion. The process can differ depending on individual factors such as dietary intake, food preparation methods, and genetic differences in glutathione-S-transferase activity.[35] The bioavailability of SFN is significantly increased when GRA is administered with active myrosinase, compared to when it is absent. Moreover, gastric acidity can affect the myrosinase activity. Studies have shown that proton pump inhibitors such as omeprazole can increase the bioavailability of SFN by reducing gastric acidity, thereby protecting myrosinase from inactivation.[36] The bioavailability and stability of SFN can be improved by encapsulating it within protective molecules. For example, the microencapsulation of SFN using whey protein has been proven not only to preserve the integrity and bioavailability of the delivered substance but also to allow for its controlled release in the body, potentially increasing its absorption and effectiveness.[37] Compared to traditional forms such as dried broccoli or pea protein, microencapsulated SFN demonstrates superior resistance to harsh conditions of the gastrointestinal tract, ensuring that a higher proportion of the compound reaches its intended targets in the body. This method can protect SFN from degradation during the digestive process.[37] The enhanced stability and targeted delivery of microencapsulated SFN could pave the way for more efficient and effective nutraceutical therapeutic applications. Further research is necessary to optimise the encapsulation process and investigate the potential synergistic effects of this approach with other bioactive compounds.

Browning Reaction of White Adipose Tissue (WAT)

Adipose tissue exists in two primary forms: white adipose tissue (WAT) and brown adipose tissue (BAT), both of which play critical roles in energy homeostasis, metabolic regulation, and overall health maintenance.[38] WAT primarily serves as an energy reservoir, storing triglycerides in adipocytes for use during periods of

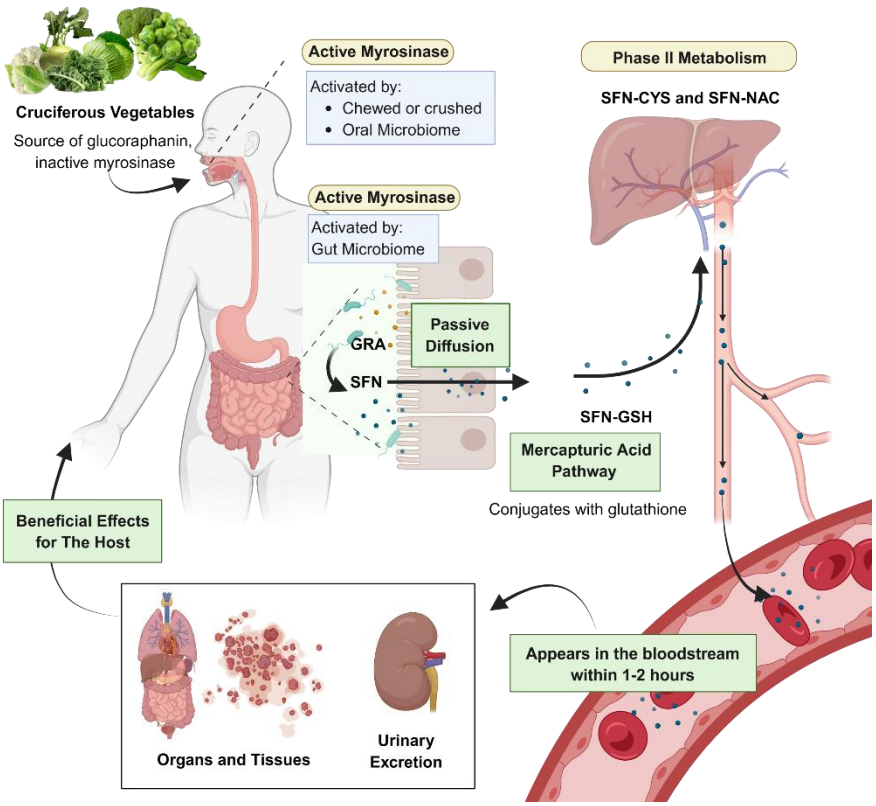

Figure 2. Schematic representation of the metabolism process of the sulforaphane compound in the human body. Cruciferous vegetables are rich in glucoraphanin with inactive myrosinase. Myrosinase is activated by chewing or through the activities of oral or gut microbiota, which enzymatically convert glucoraphanin (GRA) to sulforaphane (SFN). SFN is absorbed into the bloodstream and undergoes Phase II metabolism in the liver, producing beneficial effects on various organs and tissues before being excreted in urine

energy deficit.[39] In contrast, BAT specializes in energy expenditure and thermogenesis, which are crucial for maintaining body temperature and energy balance. It is highly vascularized and is composed of brown adipocytes rich in mitochondria, with thermogenic capacity enhanced by uncoupling protein 1 (UCP1).[40] However, WAT can undergo a phenotypic conversion known as browning, a process in which white adipocytes acquire morphological and functional characteristics similar to those of brown adipocytes. This process enhances mitochondrial biogenesis and increases UCP1 expression, facilitating proton leakage across the inner mitochondrial membrane, which ultimately leads to heat production.

Furthermore, mitochondrial biogenesis aligns with an increase in the oxidative capacity of adipocytes, promoting energy expenditure and thermogenesis similar to that of brown adipose tissue (BAT). As a result, the induction of WAT browning has been identified as a promising therapeutic strategy for obesity
and metabolic disorders, as it enhances energy dissipation and improves metabolic efficiency.[3,41] Various stimuli, including cold exposure, exercise, and specific dietary components, can stimulate thermogenesis. Cold exposure activates brown adipose tissue (BAT) via the sympathetic nervous system, increasing energy expenditure and heat production.[42] Notably, specific dietary components, such as SFN, can enhance thermogenesis by activating several molecular pathways that increase energy expenditure and stimulate WAT browning. These effects improve metabolic health and support effective obesity management.[6–12]

The Molecular Pathways of Sulforaphane (SFN) Induced White Adipose Tissue (WAT) Browning

Several studies have investigated the effect of SFN on WAT browning, primarily through *in vitro* and *in vivo* models, as shown in (**Table. 1**). This process involves a complex mechanism mediated by multiple molecular signalling pathways that enhance mitochondrial biogenesis, lipid metabolism, and energy expenditure, as illustrated in (**Figure. 3).** Despite the absence of large-scale human trials, the potential of SFN to promote brown adipose tissue (BAT) browning remains compelling. The promising data from laboratory studies establish a basis for future examinations, highlighting the necessity for more thorough studies to verify SFN's therapeutic potential in humans. These initial findings justify continued exploration and further investment in clinical trials. While the majority of studies consistently report enhanced UCP1 expression and metabolic improvements upon SFN treatment, variations in experimental models, including cell lines, animal species, dosing regimens, and treatment duration, may influence specific molecular readouts. For example, some investigations emphasise SFN's role in modulating gut microbiota and systemic endotoxemia[11], whereas others focus on intracellular

Table 1. Summary findings of in vitro and in vivo studies involving signaling the effects of sulforaphane (SFN) on White Adipose Tissue (WAT) browning and metabolic health

Model	Sulforaphane Dosage/ Duration	Key Findings	Mechanism of Action	Reference
Leptin-resistant mice	25 mg/kg, 8 weeks	Reversed leptin resistance, ↑ UCP1, ↓ inflammation, and ROS.	Nrf2-UCP1	6
3T3-L1 adipocytes (in vitro)	5 µM, 10 days	Induced lipophagy via AMPK-mTOR-ULK1 signalling; ↑ fatty acid release.	AMPK-mTOR-ULK1	7
HFD-induced obese mice	10 mg/kg, 10 weeks	↑ Browning markers (UCP1, PGC1α); improved mitochondrial biogenesis and insulin sensitivity.	AMPK- PGC1α-UCP1	8
HFD-induced obese mice	30 mg/kg/day, 12 weeks	↑ Adipose browning (UCP1, PRDM16); ↓ endotoxemia; improved systemic energy balance; changes to gut microbiome composition; ↓ plasma LPS levels.	Nrf2-UCP1 and Gut Microbiota Modulation	11
Murine 3T3-L1 adipocytes (in vitro)	10 µM, 48 hours	↑ Browning markers, enhanced mitochondrial content and respiration, ↑ and lipid oxidation.	Sirt1-PGC1α	9
HFD-induced obese mice	0.1% SFN in diet, 6 weeks	↑ AMPK activation; ↓ Adipogenesis markers (PPARγ, C/EBPα);↓ adipocyte hypertrophy; ↓ Lipogenesis	AMPK-PPARγ-C/EBPα (Adipogenesis) AMPK-ACC (Lipogenesis)	12
3T3-L1 adipocytes (in vitro)	10 µM, 24 hours	↑ Lipolysis via HSL activation; enhanced fatty acid oxidation.	AMPK-HSL	10

pathways such as AMPK-mediated lipophagy or mitochondrial biogenesis.[7] These complementary findings highlight the multifaceted effects of SFN, suggesting that its impact may vary across different physiological and experimental contexts. Therefore, a more harmonised approach in future study designs could enhance cross-study comparability and facilitate the translation of findings.

To establish a coherent framework of SFN's action, it is essential to recognise that these signalling pathways often interact in an integrated manner. The molecular pathways regulated by SFN, namely Nrf2, AMPK, and SIRT1, are not independent but are interconnected and may exert synergistic effects. For instance, AMPK activation enhances NAD+ availability, which in turn activates SIRT1 and promotes PGC-1α, a mediator of mitochondrial biogenesis. Simultaneously, SFN-induced Nrf2 activation leads to increased antioxidant defences, reduced oxidative stress, and supports mitochondrial function. This integrated response amplifies thermogenesis and promotes the browning of BAT, suggesting a concerted mechanism rather than a collection of independent effects.

Nuclear Factor Erythroid 2-Related Factor 2 (Nrf 2) pathway

Nrf2 is a key transcription factor that regulates gene expression involved in cellular defence, the production of antioxidant proteins, and the synthesis of cytoprotective enzymes. Under conditions of high oxidative stress, such as obesity, reactive oxygen species (ROS) can modify kelch-like ECH-associated protein 1 (KEAP1), leading to dysregulation of the KEAP1-Nrf2 pathway. This process can overwhelm the pathway, reducing Nrf2 availability or rendering its activation ineffective. However, this route can be restored through the use of bioactive compounds. SFN can inhibit KEAP1, thus preventing Nrf2 degradation and facilitating its migration and accumulation in the nucleus.[43]

Once SFN binds to small musculoaponeurotic fibrosarcoma (MAF) proteins, it activates antioxidant response elements (AREs) within the promoter regions of target genes, including thermogenic genes.[44] This mechanism can induce the activity of UCP1, a key mitochondrial protein responsible for thermogenesis in adipose tissue.[6,11] UCP1 dissipates the proton gradient across the inner mitochondrial membrane, generating heat instead of ATP.[45] By enhancing mitochondrial biogenesis and oxidative metabolism, SFN creates a cellular environment that favours UCP1 activation, promoting the conversion of energy-storing white adipocytes to energy-expenditure beige adipocytes.[46] This browning process increases the energy expenditure and decreases adiposity.[47]

According to studies in animal models, Nrf2 can mitigate obesity and induce the expression of UCP-1 through SFN treatment.[6,11] This induction is further supported by enhanced fat oxidation, which supplies thermogenesis with the energy substrates. Moreover, altering fatty acid synthesis reduces lipid accumulation and prompts adipocytes to shift from storing fat to utilising it for energy. Improved leptin sensitivity also stimulates thermogenic pathways and UCP1 expression, thereby contributing to browning.[6]

Consequently, the induction of UCP1 also leads to the phenomenon in which energy is released as heat instead of being converted to ATP, owing to the leakage of protons across the mitochondrial membrane.[48] Consequently, the metabolic rate increases, which is reflected in increased oxygen consumption (VO_2) and carbon dioxide production (VCO_2). These mechanisms may be beneficial for weight loss and improving metabolic health by increasing insulin sensitivity and glucose tolerance, decreasing the expression of lipogenic genes, and reducing lipid peroxidation levels and inflammation.[11]

AMP-activated protein kinase (AMPK) pathway

AMPK, or AMP-activated protein kinase, is a crucial enzyme that regulates the cellular energy balance. It becomes activated when the ratio of adenosine monophosphate to adenosine diphosphate (AMP/ADP) increases relative to adenosine triphosphate (ATP), typically during energy-deprived states. This activation promotes catabolic processes that generate ATP while inhibiting anabolic processes that utilise ATP, thus maintaining the cellular energy balance. Moreover, it also facilitates the browning of WAT, which can be further enhanced by bioactive compounds such as SFN.[49–51]

A previous study demonstrated that SFN activates adipocyte autophagy through the AMPK-mTOR-ULK1 signalling pathway [7]. This pathway is pivotal in WAT browning through lipophagy, improving mitochondrial metabolism and thermogenesis. AMPK responds to changes in energy levels and is activated in response to energy deficiency. Its activity in enhancing catabolic processes while suppressing anabolic pathways is tightly regulated by the mammalian target of rapamycin (mTOR).[49–51] Inhibiting mTOR is vital since it activates unc-51-like kinase 1 (ULK1), thereby promoting lipophagy, which breaks down lipid droplets in WAT to release free fatty acids (FFAs).[52]

The effect of SFN also increases lipolysis by activating hormone-sensitive lipase (HSL).[10] AMPK activation leads to HSL phosphorylation, which is a key enzyme involved in the lipolytic process. For instance, AMPK activation has been shown to increase the phosphorylation of HSL at specific sites, thereby enhancing its activity and promoting lipolysis in adipose tissue. This process is crucial for mobilising fatty acids that act as substrates for UCP1.[53,54] It has been shown that SFN effectively promotes the browning of WAT via the AMPK-PGC1α-UCP1 signalling pathway.[8] AMPK directly phosphorylates PGC-1α, thereby preventing its degradation and enhancing its function as a transcriptional co-activator. Once activated, PGC-1α increases the number and efficiency of mitochondria. It also enhances the expression of UCP1, which uncouples mitochondrial respiration and allows energy to be dissipated as heat. This process is crucial for enabling WAT browning, which is linked to increased energy expenditure and enhanced thermogenic function.[55]

The AMPK activation by SFN leads to a significant reduction in adipogenic markers such as peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα), both of which are key transcription factors involved in adipocyte differentiation.[12] By downregulating these markers, SFN prevents the formation of new adipocytes and limits the expansion of white adipose tissue (WAT), thereby creating a metabolic environment favourable for adipocyte browning.[56] Additionally, the activation of AMPK by SFN leads to the phosphorylation of acetyl-CoA carboxylase (ACC), a key enzyme involved in lipogenesis.[57] When ACC is inhibited, malonyl-CoA synthesis decreases, thereby reducing the inhibition of carnitine palmitoyltransferase I (CPT1) and increasing its activity. This process aids in the transport of long-chain fatty acids into the mitochondria for beta-oxidation. Consequently, the subsequent increase in fatty acid oxidation within the mitochondria enhances energy expenditure. It will then facilitate the metabolic reprogramming of white adipocytes into a beige phenotype, characterised by increased thermogenic activity.[58]

Sirtuin 1 (Sirt1) pathway

Sirtuin 1 (SIRT1) is an NAD+-dependent deacetylase that plays a vital role in cellular metabolism, mitochondrial functions, and energy regulation. It influences transcriptional regulators, including PGC1α, which is key to mitochondrial biogenesis and thermogenesis.[59] A study revealed that SFN treatment significantly promoted WAT browning via the SIRT1-PGC1α pathway in 3T3-L1 adipocytes.[9] SIRT1 deacetylates PGC1α, leading to its activation. Once activated, PGC1α upregulates citrate synthase (CS) activity, thereby increasing ATP production and mitochondrial efficiency. PGC1α also coactivates Nrf1, thereby increasing the transcription of genes essential for mitochondrial function, including UCP1.[60] This pathway also initiates lipolysis, as evidenced by the reduced lipid droplet content and increased glycerol release, while promoting fatty acid oxidation through the upregulation of carnitine palmitoyltransferase 1 (CPT1). As a result, it increases mitochondrial biogenesis and upregulates the expression of UCP1, an essential marker of thermogenic adipocytes, indicating the functional conversion of white adipocytes into a beige phenotype.[61]

Gut Microbiota Modulation

Additionally, SFN exerts anti-inflammatory and gut-modulatory effects that complement its metabolic benefits. SFN's impact on obesity was explored by supplementing HFD-fed mice with glucoraphanin, a precursor of SFN.[11] The mice in this study exhibited reduced weight gain, increased expression of UCP1 in white adipose tissue (WAT), and improved glucose tolerance. Additionally, it revealed a significant decline in pro-inflammatory markers, lower macrophage accumulation in the liver, and an altered gut microbiota composition, including decreased levels of lipopolysaccharide (LPS). The administration of broccoli seed extract (BSE), which is rich in glucoraphanin (GRP), a precursor to sulforaphane (SFN), has been shown to enhance intestinal microbiota diversity and is associated with an increased relative

abundance of Akkermansia and Lactobacillus, along with a decreased abundance of Xylanophilum.[62]

The composition of the gut microbiota significantly influences the levels of LPS, a component of the outer membrane of Gram-negative bacteria. Changes in the gut microbiota can lead to modifications in intestinal permeability, allowing LPS to pass into the bloodstream, a phenomenon known as metabolic endotoxemia. This occurrence is linked to systemic inflammation and several metabolic disorders.[63] When LPS enters the circulatory system, it binds to Toll-Like Receptor 4 (TLR4), which contributes to the metabolic derangements observed in obesity.[64] This suppression is linked to increased endoplasmic reticulum (ER) stress and reactive oxygen species (ROS) production, which leads to mitochondrial degradation and inhibits the browning of white adipose tissue (WAT), a process crucial for thermogenesis.[65]

Although SFN's effect on the gut microbiota has been highlighted in murine models, its specific mechanisms in shaping microbial populations and its long-term impact remain underexplored. Furthermore, SFN may interact with gut-derived metabolites or co-administered pharmaceuticals, potentially altering the efficacy and/or metabolism of the drugs. Despite its antioxidant and anti-inflammatory profiles, possible side effects, such as gastrointestinal disturbances or unintended microbiome shifts, should be systematically evaluated. Studies on drug interactions are also scarce, making it imperative to assess SFN's compatibility with common antidiabetic, antihypertensive, and/or lipid-lowering medications in future clinical settings.

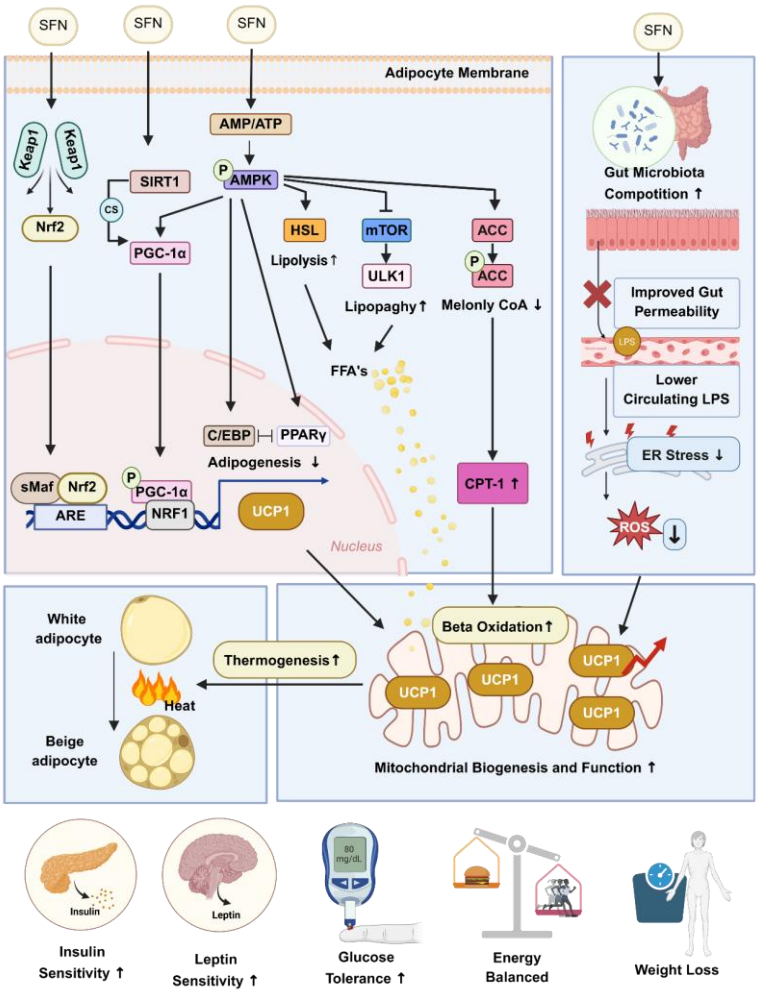

Figure 2. Schematic representation of multiple molecular signalling pathways of sulforaphane (SFN) in promoting browning reactions in white adipose tissue (WAT). The pathways involve key regulators such as Keap1 (Kelch-like ECH-associated protein 1), Nrf2 (Nuclear factor erythroid 2-related factor 2), sMaf (small Maf proteins), C/EBPα (CCAAT/enhancer-binding protein alpha), PPARγ (Peroxisome proliferator-activated receptor gamma), ACC (Acetyl-CoA carboxylase), CPT1 (Carnitine palmitoyltransferase 1), HSL (Hormone-sensitive lipase), mTOR (Mammalian target of rapamycin), ULK1 (Unc-51-like autophagy activating kinase 1), PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha), and SIRT1 (Sirtuin 1). SFN also enhances gut microbiota, improves barrier integrity, lowers LPS levels, reduces ER stress (Endoplasmic Reticulum), and decreases ROS (Reactive Oxygen Species). The process enhances mitochondrial function, biogenesis, and thermogenesis, increasing energy expenditure, insulin sensitivity, glucose tolerance, leptin sensitivity, and weight loss while balancing energy metabolism.

Future Applications and Implications

While the preclinical findings reviewed here are promising, the current clinical landscape reveals a critical research gap. Although some small-scale clinical studies have explored SFN's effects on related metabolic markers, large-scale trials confirming a direct anti-obesity effect in humans are absents. This

context is crucial as we consider future research directions. Future research should focus on clinical trials to evaluate the efficacy and safety of SFN in humans, determine the optimal dosages, and explore potential side effects. Investigating the synergistic impact of SFN with other dietary or pharmacological agents could further enhance its anti-obesity effects and expand its therapeutic applications.

Despite promising preclinical findings, the optimal dosage, form, and delivery system of SFN for practical use remains elusive. Current studies use varied concentrations and durations in animal models, and the standardized formulation has been validated for human use. Moreover, SFN's bioavailability is influenced by the food matrix, cooking methods, and individual genetic variability in enzymes, such as glutathione-S-transferase. This genetic variability directly impacts SFN metabolism and bioavailability, which likely contributes to varied efficacy in human trials and underscores the need for personalised approach. Therefore, future studies should not only explore clinical efficacy but also determine optimal dosing regimens, develop stable formulations, such as microencapsulated SFN, and evaluate the role of personalised nutrition based on genetic profiles.

CONCLUSION

The potential of sulforaphane (SFN) to induce the browning of white adipose tissue (WAT) offers a promising strategy for combating obesity and related metabolic disorders. SFN, which is naturally found in cruciferous vegetables, could be developed as a dietary supplement to support weight management and metabolic health. Its ability to enhance glucose uptake, oxidative utilisation, lipolysis, and fatty acid oxidation in adipocytes underscores its potential as a non-invasive nutritional intervention. *In vivo* studies further support SFN's therapeutic role, showing that it can significantly reduce weight gain and fat mass in high-fat diet (HFD)-induced obese mice. Additionally, SFN improves glucose metabolism and insulin sensitivity by promoting the browning of white adipose tissue (WAT), enhancing mitochondrial biogenesis, and promoting the browning of WAT, making it a valuable agent in obesity management. The molecular mechanisms underlying the SFN-induced browning of white fat also provide insights into drug development. Targeting these pathways could lead to novel pharmacological agents that mimic SFN's effects, offering more potent and targeted treatments for obesity and metabolic diseases.

ACKNOWLEDGMENTS

The figures presented in this paper were created using https://BioRender.com

REFERENCES

1. Piché ME, Tchernof A, Després JP. Obesity phenotypes, diabetes, and cardiovascular diseases. Circ Res. 2020;126(11):1477–500. doi:10.1161/CIRCRESAHA.120.316101.
2. Ahmed B, Konje JC. The epidemiology of obesity in reproduction. Best Pract Res Clin Obstet Gynaecol. 2023;89:102342. doi:10.1016/j.bpobgyn.2023.102342.
3. Alipoor E, Hosseinzadeh-Attar MJ, Rezaei M, Jazayeri S, Chapman M. White adipose tissue browning in critical illness: A review of the evidence, mechanisms and future perspectives. Obes Rev. 2020;21(12):1–8. doi:10.1111/obr.13085
4. Giles GI, Nasim MJ, Ali W, Jacob C. The reactive sulfur species concept: 15 years on. Antioxidants. 2017;6(2):1–29. doi:10.3390/antiox6020038
5. Ruhee RT, Suzuki K. The integrative role of sulforaphane in preventing inflammation, oxidative stress and fatigue: A review of a potential protective phytochemical. Antioxidants. 2020;9(6):1–13. doi:10.3390/antiox9060521
6. Çakır I, Pan PL, Hadley CK, El-Gamal A, Fadel A, Elsayegh D, et al. Sulforaphane reduces obesity by reversing leptin resistance. Elife. 2022;11:1–28. doi:10.7554/eLife.67368
7. Masuda M, Yoshida-Shimizu R, Mori Y, Ohnishi K, Adachi Y, Sakai M, et al. Sulforaphane induces lipophagy through the activation of AMPK-mTOR-ULK1 pathway signaling in adipocytes. J Nutr Biochem. 2022;106:109017. doi:10.1016/j.jnutbio.2022.109017.
8. Liu Y, Fu X, Chen Z, Luo T, Zhu C, Ji Y, et al. The protective effects of sulforaphane on high-fat diet-induced obesity in mice through browning of white fat. Front Pharmacol. 2021;12(April):1–13. doi:10.3389/fphar.2021.665894
9. Zhang HQ, Chen SY, Wang AS, Yao AJ, Fu JF, Zhao JS, et al. Sulforaphane induces adipocyte browning and promotes glucose and lipid utilization. Mol Nutr Food Res. 2016;60(10):2185–97. doi:10.1002/mnfr.201500915
10. Lee JH, Moon MH, Jeong JK, Park YG, Lee YJ, Seol JW, et al. Sulforaphane induced adipolysis via hormone sensitive lipase activation, regulated by AMPK signaling pathway. Biochem Biophys Res Commun. 2012;426(4):492–7. doi:10.1016/j.bbrc.2012.08.107
11. Nagata N, Xu L, Kohno S, Ushida Y, Aoki Y, Umeda R, et al. Glucoraphanin ameliorates obesity and insulin resistance through adipose tissue browning and reduction of metabolic endotoxemia in mice. Diabetes. 2017;66(5):1222–36. doi:10.2337/db16-0662
12. Choi KM, Lee YS, Kim W, Kim SJ, Shin KO, Yu JY, et al. Sulforaphane attenuates obesity by inhibiting adipogenesis and activating the AMPK pathway in obese mice. J Nutr Biochem. 2014;25(2):201–7. doi:10.1016/j.jnutbio.2013.10.007.
13. Hansen AW, Venkatachalam K V. Sulfur-Element containing metabolic pathways in human health and crosstalk with the microbiome. Biochem Biophys Reports. 2023;35(August):101529. doi:10.1016/j.bbrep.2023.101529.

14. Kurmi K, Haigis MC. Nitrogen metabolism in cancer and immunity. Trends Cell Biol. 2020;30(5):408–24. doi:10.1016/j.tcb.2020.02.005
15. Rai M, Singh AV, Paudel N, Kanase A, Falletta E, Kerkar P, et al. Herbal concoction Unveiled: A computational analysis of phytochemicals' pharmacokinetic and toxicological profiles using novel approach methodologies (NAMs). Curr Res Toxicol. 2023;5(August):100118. doi:10.1016/j.crtox.2023.100118.
16. Janczewski Ł. Sulforaphane and its bifunctional analogs: Synthesis and biological activity. molecules. 2022;27(5). doi:10.3390/molecules27051750
17. Mbaye MN, Hou Q, Basu S, Teheux F, Pucci F, Rooman M. A comprehensive computational study of amino acid interactions in membrane proteins. Sci Rep. 2019;9(1):1–14. doi:10.1038/s41598-019-48541-2
18. Rossi Sebastiano M, Doak BC, Backlund M, Poongavanam V, Over B, Ermondi G, et al. Impact of dynamically exposed polarity on permeability and solubility of chameleonic drugs beyond the rule of 5. J Med Chem. 2018;61(9):4189–202. doi:10.1021/acs.jmedchem.8b00347
19. Hermann J, DiStasio RA, Tkatchenko A. First-principles models for van der waals interactions in molecules and materials: Concepts, theory, and applications. Chem Rev. 2017;117(6):4714–58. doi:10.1021/acs.chemrev.6b00446
20. Datta R, Das D, Das S. Efficient lipophilicity prediction of molecules employing deep-learning models. Chemom Intell Lab Syst. 2021;213(January):104309. doi:10.1016/j.chemolab.2021.104309.
21. Mohsin K, Alamri R, Ahmad A, Raish M, Alanazi FK, Hussain MD. Development of self-nanoemulsifying drug delivery systems for the enhancement of solubility and oral bioavailability of fenofibrate, a poorly water-soluble drug. Int J Nanomedicine. 2016;11:2829–38. doi:10.2147/IJN.S104187
22. Mahn A, Pérez CE, Zambrano V, Barrientos H. Maximization of sulforaphane content in broccoli sprouts by blanching. Foods. 2022;11(13):1–9. doi:10.3390/foods11131906
23. Lekcharoenkul P, Tanongkankit Y, Chiewchan N, Devahastin S. Enhancement of sulforaphane content in cabbage outer leaves using hybrid drying technique and stepwise change of drying temperature. J Food Eng. 2014;122(1):56–61. doi:10.1016/j.jfoodeng.2013.08.037.
24. Bianchi G, Picchi V, Tava A, Doria F, Walley PG, Dever L, et al. Insights into the phytochemical composition of selected genotypes of organic kale (Brassica oleracea L. var. acephala). J Food Compos Anal. 2024 Jan 1;125:105721. doi:10.1016/J.JFCA.2023.105721
25. Kuljarachanan T, Fu N, Chiewchan N, Devahastin S, Chen XD. Evolution of important glucosinolates in three common: Brassica vegetables during their processing into vegetable powder and in vitro gastric digestion. Food Funct. 2020;11(1):211–20. doi:10.1039/c9fo00811j
26. Uher A, Mezeyova I, Hegedusova A, Slosar M. Impact of nutrition on the quality and quantity of cauliflower florets. Potravin Slovak J Sci. 2017;11(1):113–9. doi:10.5219/723
27. West LG, Meyer KA, Balch BA, Rossi FJ, Schultz MR, Haas GW. Glucoraphanin and 4-hydroxyglucobrassicin contents in seeds of 59 cultivars of broccoli, raab, kohlrabi, radish, cauliflower, brussels sprouts, kale, and cabbage. J Agric Food Chem. 2004;52(4):916–26. doi:10.1021/jf0307189
28. López-Cervantes J, Tirado-Noriega LG, Sánchez-Machado DI, Campas-Baypoli ON, Cantú-Soto EU, Núñez-Gastélum JA. Biochemical composition of broccoli seeds and sprouts at different stages of seedling development. Int J Food Sci Technol. 2013;48(11):2267–75. doi:10.1111/ijfs.12213
29. Tříska J, Balík J, Houška M, Novotná P, Magner M, Vrchotová N, et al. Factors influencing sulforaphane content in broccoli sprouts and subsequent sulforaphane extraction. Foods. 2021;10(8):1–12. doi:10.3390/foods10081927
30. Bouranis JA, Wong CP, Beaver LM, Uesugi SL, Papenhausen EM, Choi J, et al. Sulforaphane bioavailability in healthy subjects fed a single serving of fresh broccoli microgreens. Foods. 2023;12(20):1–11. doi:10.3390/foods12203784
31. Vanduchova A, Anzenbacher P, Anzenbacherova E. isothiocyanate from broccoli, sulforaphane, and its properties. J Med Food. 2019;22(2):121–6. doi:10.1089/jmf.2018.0024
32. Li X, Wang Y, Zhao G, Liu G, Wang P, Li J. Microorganisms—An effective tool to intensify the utilization of sulforaphane. Foods. 2022;11(23):1–17. doi:10.3390/foods11233775
33. Salas-Millán JÁ, Aguayo E. Bioaccessibility and unravelling of polyphenols, sulforaphane, and indoles biotransformation after in vitro gastrointestinal digestion of a novel lactofermented broccoli beverage. Food Funct. 2024;11949–60. doi:10.1039/d4fo03528c
34. Bo S, Fadda M, Fedele D, Pellegrini M, Ghigo E, Pellegrini N. A critical review on the role of food and nutrition in the energy balance. Nutrients. 2020;12(4):1–27. doi:10.3390/nu12041161
35. Bouranis J, Beaver L, Wong C, Choi J, Hamer S, Davis E, et al. Sulforaphane and sulforaphane-nitrile metabolism in humans following broccoli sprout consumption: Inter-individual variation, association with gut microbiome composition, and differential bioactivity. Mol Nutr Food Res. 2023; doi:10.1002/mnfr.202300286)

36. Fahey JW, Wade KL, Stephenson KK, Panjwani AA, Liu H, Cornblatt G, et al. Bioavailability of sulforaphane following ingestion of glucoraphanin-rich broccoli sprout and seed extracts with active myrosinase: A pilot study of the effects of proton pump inhibitor administration. Nutrients. 2019;11(7):1–16. doi:10.3390/nu11071489
37. Ali Redha A, Torquati L, Bows JR, Gidley MJ, Cozzolino D. Microencapsulation of broccoli sulforaphane using whey and pea protein: in vitro dynamic gastrointestinal digestion and intestinal absorption by Caco-2-HT29-MTX-E12 cells. Food Funct. 2024;71–86. doi:10.1039/d4fo03446e
38. Heyde I, Begemann K, Oster H. Contributions of white and brown adipose tissues to the circadian regulation of energy metabolism. Endocrinol (United States). 2021;162(3):1–14. doi:10.1210/endocr/bqab009
39. Heinonen S, Jokinen R, Rissanen A, Pietiläinen KH. White adipose tissue mitochondrial metabolism in health and in obesity. Obes Rev. 2020;21(2):1–23. doi:10.1111/obr.12958
40. Saito M, Okamatsu-Ogura Y. Thermogenic brown fat in humans: Implications in energy homeostasis, obesity and metabolic disorders. World J Mens Heal. 2023 Jul;41(3):489–507. doi:10.5534/wjmh.220224
41. Machado SA, Pasquarelli-do-Nascimento G, da Silva DS, Farias GR, de Oliveira Santos I, Baptista LB, et al. Browning of the white adipose tissue regulation: New insights into nutritional and metabolic relevance in health and diseases. Nutr Metab (Lond). 2022;19(1):61. doi:10.1186/s12986-022-00694-0.
42. Scheel AK, Espelage L, Chadt A. Many ways to Rome: Exercise, cold exposure and diet—Do they all affect BAT activation and WAT browning in the same manner? Int J Mol Sci. 2022;23(9). doi:10.3390/ijms23094759
43. Houghton CA, Fassett RG, Coombes JS. Sulforaphane and other nutrigenomic Nrf2 activators: Can the clinician's expectation be matched by the reality? Oxid Med Cell Longev. 2016;2016. doi:10.1155/2016/7857186
44. Baird L, Yamamoto M. The molecular mechanisms regulating the KEAP1-NRF2 pathway. Mol Cell Biol. 2020;40(13). doi:10.1128/mcb.00099-20
45. Schneider K, Valdez J, Nguyen J, Vawter M, Galke B, Kurtz TW, et al. Increased energy expenditure, ucp1 expression, and resistance to diet-induced obesity in mice lacking nuclear factor-erythroid-2-related transcription factor-2 (nrf2). J Biol Chem. 2016;291(14):7754–66. doi:10.1074/jbc.M115.673756.
46. Pisani DF, Barquissau V, Chambard JC, Beuzelin D, Ghandour RA, Giroud M, et al. Mitochondrial fission is associated with UCP1 activity in human brite/beige adipocytes. Mol Metab. 2018;7(November 2017):35–44. doi:10.1016/j.molmet.2017.11.007.
47. Magro BS, Dias DPM. Brown and beige adipose tissue: New therapeutic targets for metabolic disorders. Heal Sci Rev. 2024;10(December 2023):100148. doi:10.1016/j.hsr.2024.100148.
48. Esteras N, Dinkova-Kostova AT, Abramov AY. Nrf2 activation in the treatment of neurodegenerative diseases: a focus on its role in mitochondrial bioenergetics and function. Biol Chem. 2016;397(5):383–400. doi:doi:10.1515/hsz-2015-0295.
49. Hardie DG, Schaffer BE, Brunet A. AMPK: An energy-sensing pathway with multiple inputs and outputs. Trends Cell Biol. 2016;26(3):190–201. doi:10.1016/j.tcb.2015.10.013.
50. Hardie DG. AMPK: Positive and negative regulation, and its role in whole-body energy homeostasis. Curr Opin Cell Biol. 2015;33:1–7. doi:10.1016/j.ceb.2014.09.004.
51. Sukumaran A, Choi K, Dasgupta B. Insight on transcriptional regulation of the energy sensing AMPK and biosynthetic mTOR pathway genes. Front Cell Dev Biol. 2020;8(July):1–16. doi:10.3389/fcell.2020.00671
52. Wang H, Liu Y, Wang D, Xu Y, Dong R, Yang Y, et al. The upstream pathway of mtor-mediated autophagy in liver diseases. Vol. 8, Cells. 2019. 1–36 p. doi:10.3390/cells8121597
53. Kim SJ, Tang T, Abbott M, Viscarra JA, Wang Y, Sul HS. AMPK phosphorylates desnutrin/ATGL and hormone-sensitive lipase to regulate lipolysis and fatty acid oxidation within adipose tissue. Mol Cell Biol. 2016;36(14):1961–76. doi:10.1128/mcb.00244-16
54. Pollard AE, Martins L, Muckett PJ, Khadayate S, Bornot A, Clausen M, et al. AMPK activation protects against diet-induced obesity through Ucp1-independent thermogenesis in subcutaneous white adipose tissue. Nat Metab. 2019;1(3):340–9. doi:10.1038/s42255-019-0036-9
55. Zhang F, Ai W, Hu X, Meng Y, Yuan C, Su H, et al. Phytol stimulates the browning of white adipocytes through the activation of AMP-activated protein kinase (AMPK) α in mice fed high-fat diet. Food Funct. 2018;9(4):2043–50. doi:10.1039/c7fo01817g
56. Ye J, Gao C, Liang Y, Hou Z, Shi Y, Wang Y. Characteristic and fate determination of adipose precursors during adipose tissue remodeling. Cell Regen. 2023;12(1):1–19. doi:10.1186/s13619-023-00157-8.
57. Foretz M, Even PC, Viollet B. AMPK activation reduces hepatic lipid content by increasing fat oxidation in vivo. Int J Mol Sci. 2018;19(9). doi:10.3390/ijms19092826
58. Wang Y, Yu W, Li S, Guo D, He J, Wang Y. Acetyl-CoA Carboxylases and diseases. Front Oncol. 2022;12(March):1–10. doi:10.3389/fonc.2022.836058
59. Yuan Y, Cruzat VF, Newshome P, Cheng J, Chen Y, Lu Y. Regulation of SIRT1 in aging: Roles in mitochondrial function and biogenesis. Mech Ageing Dev [Internet]. 2016;155(1):10–21. doi:10.1016/j.mad.2016.02.003.

60. Jiang Y, Chen D, Gong Q, Xu Q, Pan D, Lu F, et al. Elucidation of SIRT-1/PGC-1α-associated mitochondrial dysfunction and autophagy in nonalcoholic fatty liver disease. Lipids Health Dis. 2021;20(1):1–12. doi:10.1186/s12944-021-01461-5
61. Rius-Pérez S, Torres-Cuevas I, Millán I, Ortega ÁL, Pérez S, Sandhu MA. PGC-1 α, inflammation, and oxidative stress: An integrative view in metabolism. Oxid Med Cell Longev. 2020;2020. doi:10.1155/2020/1452696
62. Mao B, Ren B, Wu J, Tang X, Zhang Q, Zhao J, et al. The protective effect of broccoli seed extract against lipopolysaccharide-induced acute liver injury via gut microbiota modulation and sulforaphane production in mice. Foods. 2023;12(14). doi:10.3390/foods12142786
63. Hersoug LG, Møller P, Loft S. Gut microbiota-derived lipopolysaccharide uptake and trafficking to adipose tissue: Implications for inflammation and obesity. Obes Rev. 2016;17(4):297–312. doi:10.1111/obr.12370
64. Boutagy NE, McMillan RP, Frisard MI, Hulver MW. Metabolic endotoxemia with obesity: Is it real and is it relevant? Biochimie. 2016;124:11–20. doi:10.1016/j.biochi.2015.06.020.
65. Okla M, Wang W, Kang I, Pashaj A, Carr T, Chung S. Activation of Toll-like receptor 4 (TLR4) attenuates adaptive thermogenesis via endoplasmic reticulum stress. J Biol Chem. 2015;290(44):26476–90. doi:10.1074/jbc.M115.677724