DIMORPHIC NATURE OF ADIPOSE TISSUE AND ROLE OF HERBAL EXTRACTS IN LIPIDS METABOLISM

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Adipose tissue, known as body fat, plays a crucial role in human health and disease. Traditionally viewed as a storage site for excess energy as body fat, advances in medical research have shown the complex and dynamic nature of adipose tissue, highlighting its critical role in the regulation of metabolism, hormone production, and immune response. Adipose tissue is subdivided into two types – lipids accumulating white adipose tissue (WAT) and brown adipose tissue (BAT), color of which is determined by the load of mitochondria; the beige adipose tissue (BeAT) is a mix of WAT and BAT cells. This review aims to explore the multifaceted aspects of WAT, focusing on key areas: the diverse cell types comprising WAT and their unique functions, the major genes expressed and secreted from adipose tissue cells, the role of adipose tissue in inflammation, and the sex-specific differences in adipose tissue transcriptomes. Understanding the intricate dynamics of adipose tissue in the context of secreted factors having systemic effects, including inflammatory response, is essential, given its central role in maintaining energy balance and metabolic homeostasis in health issues like obesity, type 2 diabetes, and cardiovascular diseases. Examining adipocyte-specific transcriptomes gives an understanding of the unique characteristics of these cells. The dimorphic nature of adipose tissue not only influences body fat distribution but also affects disease susceptibility and response to treatment. Additionally, this review will cover the increasingly recognized role and the intriguing effects of plant extracts on adipogenesis, which offer potential therapeutic avenues for treating obesity and its related disorders.

KEYWORDS: adipocytes transcriptome; dimorphic nature of adipose tissue; obesity; herbal extracts and obesity.

INTRODUCTION

Adipose tissue is a complex and dynamically undergoing changes organ composed of various cell types, each uniquely contributing to its overall function and metabolic regulation. Traditionally known for its role in energy storage, adipose tissue is recognized for its critical role in endocrine function, immune response, and metabolic homeostasis [1]. *Adipocytes*, the primary cell types of WAT, are designated for storing energy as triglycerides in the form of lipid droplets. In addition to adipocytes, many other cell types found within WAT contribute to its function and regulation. These cell types include *pre-adipocytes,* which differentiate into mature adipocytes, *mesenchymal stem cells* (MSCs) — multipotent cells that can differentiate into various cell types, including adipocytes, and contribute to tissue repair and regeneration. Other cells are *fibroblasts,* they contribute to the maintenance of the extracellular matrix within adipose tissue, surrounding blood vessels cells *pericytes* whose main function is the maintenance of blood vessels stability, and *endothelial cells* forming the inner lining of blood vessels within adipose tissue. *Lymphocytes*, a class of immune cells, such as T cells and B cells which contribute to immune surveillance and inflammation regulation are also found in white adipose tissue. *Macrophages* are another immune cells, having two distinct phenotypes - pro-inflammatory M1 and anti-inflammatory M2, play a crucial role in inflammation [2]. The presence of macrophages in adipose tissue is dictated by the inflammatory signals coming from adipocytes. The inflammation in adipose tissue activates Monocyte Chemoattractant Protein-1 (MCP-1), one of the key chemokines that regulate migration and infiltration of macrophages into adipose tissue [3]. In adipose tissue, both M1 and M2 macrophages play critical roles in maintaining tissue homeostasis and influencing metabolic health. In obesity, adipose tissue often undergoes remodeling, leading to an increase in the number of M1 pro-inflammatory macrophages secreting cytokines such as leptin, adiponectin, TNF-α, IL-6, and IL-1β, and contribute to chronic sex-specific low-grade inflammation [5]. These pro-inflammatory cytokines can interfere with insulin signaling and contribute to insulin resistance, a hallmark of obesity-related metabolic dysfunction. M2 macrophages in adipose tissue play a role in resolving inflammation and maintaining tissue homeostasis. They contribute to tissue repair and anti-inflammatory processes by secreting cytokines like IL-10 and TGF-β. M2 macrophages have been associated with improved insulin sensitivity and metabolic health. Factors like IL-4, IL-13, and other signals related to tissue repair can promote polarization of macrophages toward the M2 phenotype in adipose tissue. In healthy lean individuals, adipose tissue M2 macrophages play an anti-inflammatory role. However, in obese individuals, adipocytes expand beyond their capacity leading to hypoxia, cell death and a shift occurs towards a pro-inflammatory M1 macrophages, which trigger the expression of pro-inflammatory cytokines TNF-α, IFN-γ, IL-6, RETN, PAI-1, etc. [6]. The pro-inflammatory cytokines interfere with insulin signaling pathways, leading to decreased glucose uptake by cells and elevated blood glucose levels, which in turn contribute to the development of insulin-resistant type 2 diabetes and metabolic and cardiovascular diseases [7]. In normal physiological conditions, cytokines modulate immune responses and homeostasis. However, in conditions of excess nutrient intake and obesity, adipocytes expand beyond their healthy limits, leading

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to hypoxia and subsequent necrosis, where adipocytes and dying cells release pro-inflammatory signals.

In a study involving human subjects and mouse animal models, it was shown that the hypoxia-induced factor HIF-1α was significantly increased in the VAT of morbidly obese subjects and mice in the "feeding" group compared to the wild type. VAT HIF-1α mRNA expression is negatively correlated with ACC1, PDHB, and SIRT3 mRNA expression and positively with PPAR-γ [8]. In a comparative study of VAT and SAT from obese and lean patients, it has been demonstrated that in VAT of obese patients, hypoxia increased inflammatory TNF-α secretion and inhibited anti-inflammatory IL-10 secretion. Additionally, hypoxia upregulated the expression of a number of genes, including Vascular Endothelial Growth Factor (VEGF), which is involved in protecting cells from hypoxia-mediated cell death; Eukaryotic Translation Initiation Factor 2-Alpha Kinase 3 (PERK), which phosphorylates the alpha subunit of eukaryotic translation-initiation factor 2 (EIF2A), leading to its inactivation and thus to a rapid reduction of translational initiation and repression of global protein synthesis; and glucose transporter 1 (GLUT1) [9].

The relationship between adipose tissue and inflammation is a complex interplay between all adipose tissue cell types including various immune cells residing within the adipose tissue. Men with metabolic syndrome have been shown to produce excessive proinflammatory cytokines. In contrast, women usually have lower amounts of adiponectin, an anti-inflammatory adipokine. Understanding the distinct pathways of inflammatory dysregulation present in obese men and women support the need for sex-specific therapeutic strategies for treating metabolic and cardiovascular diseases.

ADIPOCYTE-SPECIFIC TRANSCRIPTS AND SEX-SPECIFIC ENRICHED TRANSCRIPTS

The adipocyte-specific transcriptome encompasses a unique set of genes, including non-coding and protein-coding, predominantly or exclusively expressed in adipocytes, the primary cell type in adipose tissue, play pivotal roles in pre-adipocyte differentiation, lipid metabolism, and overall adipose tissue function, setting adipocytes apart from other cell types in the body. Moreover, the adipocyte-specific transcriptome gene products are integral to the functions of adipose tissue as an endocrine organ [10]. Hormones like leptin and adiponectin, synthesized and secreted from adipocytes in response to changes in lipid metabolism, have far-reaching systemic effects on gene expression, energy balance, insulin sensitivity, and inflammatory pathways (Figure 1).

Leptin is known to regulate food intake and energy expenditure through its main receptor, the Leptin Receptor (LEPR), which activates Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway further activating inflammatory cytokines production [11]. Adiponectin activates two main signaling pathways — Adiponectin Receptor 1 (AdipoR1) and Adiponectin Receptor 2 (AdipoR2). These receptors activate AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPAR-alpha) pathways, leading to increased fatty acid oxidation and insulin sensitivity [12]**.** The pro-inflammatory cytokine Tumor Necrosis Factor-alpha (TNF-alpha) is involved in the regulation of inflammation and insulin resistance. TNF-alpha activates the TNF receptor 1 (TNFR1), leading to the activation of nuclear factor kappa B (NF-kappaB) pathway and the expression of pro-inflammatory genes impairing insulin signaling in adipocytes [13].

Dysregulation in the expression of these genes is associated with various metabolic disorders, including obesity, insulin resistance, and type 2 diabetes. The relationship between adipose tissue and inflammation is a complex interplay involving adipocytes and various immune cells residing within the adipose tissue. Adipocytes themselves are not simply lipids-storing cells but also dynamically express pro-inflammatory cytokines, just mention a few, TNF-α, IFN-γ, IL-6, IL-4, TGF-β.

Adipocyte-specific proteins not only play key roles in the basic function of adipocytes, such as lipid storage and glucose metabolism, but they are integral to the dynamic nature of adipose tissue in response to nutritional and hormonal signals. For example, PPARG and C/EBPα are central to the process of adipogenesis, where pre-adipocytes differentiate into mature adipocytes, a process critical in the expansion of adipose tissue during times of energy excess [14].

162 sex-biased differentially expressed genes mainly associated with oxidative phosphorylation and adipogenesis were identified in an analysis of a genome-wide expression data set from adult human subcutaneous adipose tissues samples of three large human cohorts across geographically and ethnically diverse populations (AAGMEx, deCODE, and GTEx). Among these genes, 45 were female-associated transcription factors (TFs), and 42 were male-associated TFs. Prominent adipogenic TFs C/EBPβ and PPARG showed elevated expression in females, and the androgen and estrogen receptors (AR and ESR1) were elevated in males, supporting the idea of sex-specific transcriptional regulation [15]

Number of studies revealed that multiple genes involved in lipid storage and adipogenesis, such as PPARG, Leptin, Resistin, and ADIPOQ, show significantly higher expression in females, suggesting a more dynamic lipid metabolism and storage capacity in female adipose tissue. In contrast, male adipose tissue often exhibits higher expression of genes associated with inflammation and fibrosis, which might contribute to the increased risk of obesity-related complications in men [16, 17]. Multiple factors such as age, hormonal changes, lifestyle, etc. have a significant impact on the adipose tissue state and physiological implications on metabolic health and disease susceptibility [18]. These differences are not just limited to the amount and distribution of adipose tissue, as commonly seen in greater subcutaneous fat (SAT) in women and more visceral fat (VAT) in men, but the difference extends to the cellular and molecular levels as well, as adipose-cell-type transcriptomes reveal [19]. In a clinical study involving over a hundred subjects in both groups, men and women, VAT and SAT were analyzed for several parameters, including deep and superficial volume, circulating cytokines, and adipokines. It has been shown that the level of circulating proteins was different not only between SAT and VAT inside the group but was different between men and women SAT and VAT as well, indicating a complex dimorphic fat tissue type and transcriptional regulation of fat deposit and inflammatory pathways. For example, in women, the expression of inflammatory proteins, including leptin, CD68, TNFα, and IL-1α, is associated only with

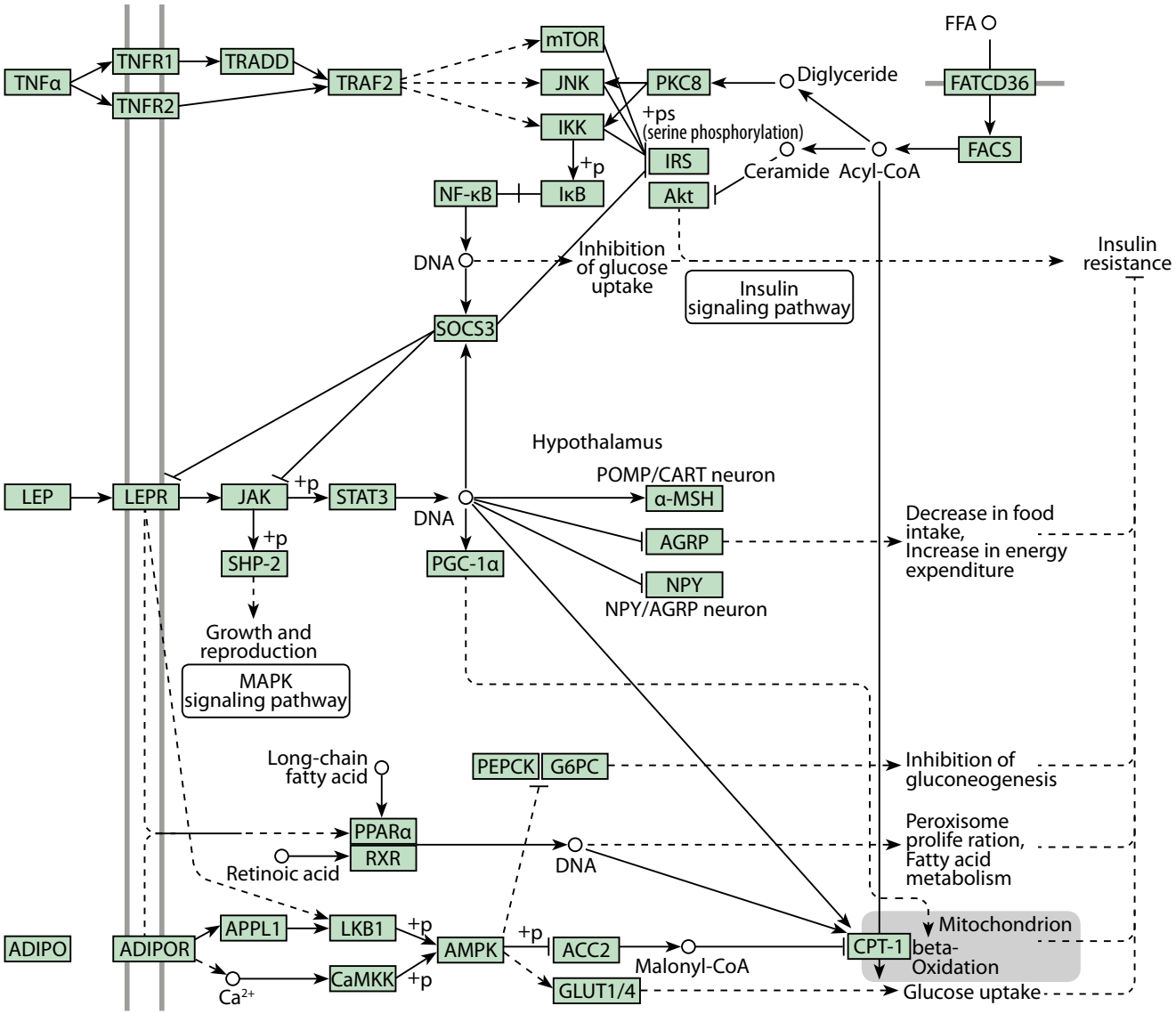

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Figure 1. Adipocytokine Signaling Pathway.
From KEGG: Kyoto Encyclopedia of Genes and Genomes

SAT, whereas in men, they are highly expressed in both VAT and SAT. The level of Fibroblast Growth Factor 21 (FGF21), a major metabolic regulator, in male VAT is three times higher compared to its own SAT (0.24 vs. 0.08) and twice higher than in female VAT (0.24 vs. 0.12). Chromatin-associated enzyme poly(ADP-Ribose) Polymerase 1 (PARP1) in women's VAT is significantly lower than in the SAT (0.09 vs. 0.16); in contrast, in the VAT of men, its level is significantly higher (0.25 vs. 0.02) than in the SAT. Interestingly enough, the expression of MCP1, a chemokine that regulates migration and infiltration of macrophages into adipose tissue, in male VAT compared to SAT is much higher (0.20 vs. 0.02), whereas in female samples its level is significantly lower (0.07 vs. -0.12, respectively) [20]

The composition of adipose tissue itself varies between sexes at the cellular level as well. In females, adipocytes in SAT tend to be smaller but more numerous, a feature associated with healthier metabolic profiles. In contrast, in male VAT dominate larger adipocytes, which are linked to insulin resistance and a higher risk of metabolic syndrome. These differences in cell size and number are partly attributed to sex hormones, with estrogen playing a protective role in adipose tissue distribution and function in females [21].

SAT and VAT vary not only compositionally and in cell size, but are metabolically different tissues as well. Moreover, dietary factors such as fatty acids have a different effect on both adipogenesis and the phenotype of mature adipocytes. For example, it has been shown in VAT-derived mesenchymal stem cells (MSC) from male patients and SAT-derived cells from female patients differentiated into adipocytes that oleic acid stimulated total lipid accumulation twice higher in SAT cells than VAT cells. Additionally, the early transcription factors PPARG and CEBPA were differentially expressed, with an increased level of PPARG and a decreased level of CEBPA in VAT-derived cells compared to SAT-derived cells [22].

Waist-to-hip (WHR) circumference ratio, adjusted for BMI (WHRadjBMI), is considered a proxy for the balance of SAT versus VAT and ectopic fat deposition. Using experimental and transcriptome-wide association studies (TWAS), multiple genes and their variants were identified that strongly correlate with obesity and a high WHRadjBMI and are gender-specific. For example, Sorting Nexin-10 (SNX10), a gene

important in adipose biology, required for human adipocyte differentiation and function, and shown to participate in diet-induced adipose expansion in female mice but not males, is the strongest female WHRadjBMI-associated gene. SNX10 expression itself is consistently higher in women [23].

It has been shown in the Genotype-Tissue Expression (GTEX) database that the expression of Adhesion G Protein-Coupled Receptor G6 (ADGRG6) is higher in the VAT of males versus females and is considered one of the major factors in adipogenesis that determines gender-specific fat distribution. Deletion of ADGRG6 in human adipocytes impairs adipogenesis due to reduced cAMP signaling. In an animal model, knockout of ADGRG6 in mouse adipocytes leads to female-type fat distribution in males and is associated with protection against high-fat diet-induced obesity and improved insulin response [24].

In a meta-analysis of the transcriptomes of human adipose tissue mesenchymal stem cells (hMSCs) from matched non-obese adults 18 years and older male and female donor subjects, several chromosomal segments and 20 differentially expressed genes in male vs female hADSCs were identified. Among the overexpressed genes in male samples was identified RNA-binding protein ZC3H7B (zinc finger CCCH-type containing 7B), a gene involved in miRNA biogenesis. ZC3H7B binds to the microRNAs mir7-1 and mir29A, highly expressed in adipocytes (GeneCards,The Human Gene Database). Other noteworthy overexpressed genes are the hypoxia-inducible factor 1 transcription factor ARNT1 (Aryl Hydrocarbon Receptor Nuclear Translocator) and the CSF1 (Colony Stimulating Factor 1) gene. The protein encoded by csf1 is a cytokine controlling the production, differentiation, and function of macrophages [25].

LONG NON-CODING (LNCRNAS) AND MICRO RNAS (MIRNAS) IN ADIPOSE TISSUE

The adipocyte-specific transcriptome encompasses a unique set of genes, including non-coding. It is well recognized the role of long non-coding RNAs (lncRNAs) to regulate chromatin remodeling with subsequent influence on transcription and post-transcriptional modifications. lncRNAs are a class of non-coding RNA molecules longer than 200 nucleotides playing regulatory roles in various biological processes, including those related to adipose tissue development, metabolism, and related disorders. The research highlighted several lncRNAs that play a role in adipose tissue function. ADINR (Adipogenic Differentiation-Induced Noncoding RNA), exclusively expressed in adipocytes, is upregulated during adipogenesis, and is involved in the regulation of adipocytes differentiation by interacting with RNA-binding proteins therefore influencing the expression of genes associated with adipogenesis [26]. HOTAIR (HOX Transcript Antisense Intergenic RNA) has been implicated in regulating adipogenesis by interacting with chromatin-modifying complexes and modulating expression of genes involved in adipose-tissue-specific pathways [27]. Circulating lncRNA-p5549, lncRNA-p21015, and lncRNA-p19461, differentially expressed in obese and non-obese individuals, regulate adipogenesis by modulating the expression of genes related to lipid metabolism and adipocytes differentiation [28]. Recently human lncRNA LYPLAL1-antisense RNA1 (LYPLAL1-AS1) was identified which expression dramatically upregulated during adipogenic differentiation of adipose-derived mesenchymal stem cells (hAMSCs) [29]. In human WAT, lncRNA ADIPINT expression is increased in obesity and linked to fat cell size, adipose tissue insulin resistance, and pyruvate carboxylase activity [30].

In the article «Identification and Characterization of Long Non-coding RNAs in Subcutaneous Adipose Tissue from Castrated and Intact Full-Sib Pair Huainan Male Pigs» Jing Wang et al. [31] explore lncRNAs in subcutaneous fat tissue from castrated and intact male pigs. They found that certain lncRNAs were associated with fat metabolism and deposition. To identify and analyze lncRNAs, in the study was used RNA sequencing. Significant differences in expression between the two groups were revealed, implicating the vital role of male hormones in gene expression regulation in adipocytes [31]. This study highlights the potential role of male sex hormones in adipose tissue regulation.

In addition to lncRNAs, numerous microRNAs (miRNAs) have been identified in human adipocytes, contributing to the gene expression regulation in various aspects of adipose tissue biology, including adipogenesis, lipid metabolism, and insulin sensitivity. Differentially expressed miRNAs in SAT and VAT were found to contribute to distinct metabolic characteristics and physiological roles of these depots. Enlarged VAT, predominantly found in males, is generally associated with higher metabolic risk due to its potential role in releasing more inflammatory cytokines and its association with insulin resistance and metabolic syndrome [32]. Understanding the specific miRNAs signatures in each adipose tissue depot can provide insights into their roles in adipogenesis, metabolism, and potential implications in metabolic disorders such as obesity, diabetes, and cardiovascular diseases.

miRNA expression patterns can vary based on factors such as age, sex, body mass index (BMI), and disease conditions. In one study were identified differentially expressed exosomal miRNAs in SAT (10 miRNAs) and VAT (58 miRNAs) between obese and lean patients. For example, hsa-miR-582-5p, hsa-miR-566, and miR-548 are predominantly VAT-specific, whereas hsa-miR-3156-5p and hsa-miR-4460 are more abundant in SAT [33]. The micro RNAs miR-221, miR-222, and mir-130 have been reported to be involved in the regulation of adipogenesis and insulin sensitivity, with differential expression observed between males and females [34,35]. Analysis of SAT biopsies from 69 female subjects ranging from lean to morbidly obese and VAT biopsies of 19 female subjects demonstrated negative correlation between ANGPTL8 (Angiopoietin-like protein 8) and miR-221-3p suggesting that miR-221-3p targets the ANGPTL8 mRNA and reduces ANGPTL8 protein expression in adipocytes [36]. In another study done by Lorente-Cebrian et al., [37] have been observed that miR-145 stimulates the expression of TNF-α in adipocytes through the activation of the nuclear transcription factor kappa-B (NF-κB) pathway [37]. The mentioned miRNAs represent just a tiny fraction of the extensive repertoire of miRNAs found in human adipocytes participating in the intricate regulatory networks controlling adipose tissue development, metabolism, inflammation, and responses to various physiological and pathological conditions, including sex-specific dimorphic backgrounds.

The sex-specific differences in adipose-cell-type-enriched transcripts have a significant impact on understand-

ing the distinct metabolic profiles in men and women. These differences highlight the importance of considering gender as a critical factor in both basic research and clinical approaches to metabolic health and disease. For instance, targeting inflammatory pathways might be more beneficial in males, while lipids accumulation and lipogenesis could be a strategy in females [38,39].

Understanding these intricate and intriguing differences in adipose tissue dimorphism is critical for the development of sex-specific strategies to treat obesity and related metabolic disorders such as insulin resistance, type 2 diabetes, and cardiovascular diseases. Given these sex-specific differences in adipose tissue and the differential expression of genes in male and female adipose tissues, therapeutic interventions need to be tailored to optimize efficiency and minimize the adverse effects of obesity-targeting drugs.

IMPACT OF PLANT EXTRACTS ON LIPIDS METABOLISM

The use of plants and their derivatives in treating obesity with chronic inflammation and related disorders has been a subject of interest for hundreds of years due to the potential health benefits they offer. Many plant-based compounds exhibit bioactive properties that can influence metabolism, appetite, fat accumulation, and inflammation, contributing to their potential in managing obesity and associated diseases, including type 2 diabetes and cardiovascular disease.

It was shown some plant-derived compounds can influence appetite and satiety. In a clinical study with enrolled overweight subjects, the consumption of 500 mg/day of mixed polyphenolic extract from ***Lippia citriodora*** and ***Hibiscus sabdarrifa*** for 60 days resulted in a significant decrease in hunger sensation with marked reduction of calorie intake during usual meal time and consequently, body weight loss. The increased satiety among the study subjects could be attributed to the changes in leptin, ghrelin, and GLP-1 expressions. The extracts from ***Lippia citriodora*** and ***Hibiscus sabdarrifa*** could modulate the activity of 5'AMP-activated protein kinase (AMPK), thereby normalizing the level of leptin typically elevated in overweight or obese people [40]. Hydroxycitric acid (HCA) from the fruit ***Garcinia cambogia*** reduces lipid accumulation in adipocytes by inhibiting the enzyme ATP citrate lyase, crucial in fat synthesis. Human subjects age from 20 to 65 years with an excess of visceral fat accumulation were enrolled and randomly assigned to placebo or HCA groups. At 16 weeks of treatment, the HCA group had significantly reduced visceral, subcutaneous, and total fat areas compared with the placebo group [41]. ***Sida rhomboidea*** Roxb leaf extract (SRLE) is being used to alleviate symptoms of diabetes and obesity. Thounaojam et al. [42] reported the effect of SRLE in vivo to modulate expression of genes responding to "high fat diet" (HFD) induced obesity and in vitro 3T3-L1 pre-adipocytes differentiation and leptin release. SRLE supplementation in mice prevented HFD-induced bodyweight increase, visceral adiposity, and adipocytes hypertrophy. Additionally, SRLE supplementation reduced food intake, and down-regulated expression of PPARγ2, SREBP1c, FAS, and LEP genes compared to obese mice. It was suggested that appetite suppression and decreased food intake could be attributed to the presence of ephedrine, a central nervous system (CNS) stimulant, and pseudo-ephedrine in the ***Sida*** plant species [42].

Human subjects were enrolled in 24-hour energy expenditure (EE), respiratory quotient (RQ), and the urinary exertion of nitrogen and catecholamines study. The study showed that treatment with green tea extract resulted in a significant increase in 24-h EE and a significant decrease in 24-h RQ without any change in urinary nitrogen. The results indicate that green tea has thermogenic and fat oxidation properties and influences metabolism potentially aiding weight management, largely by inhibiting catechol O-methyltransferase (COMT). The inhibition of COMT allows prolonged stability of catecholamine norepinephrine which regulates thermogenesis and lipids oxidation [43,44]. Green tea extract catechin epigallocatechin-3-gallate (EGCG) has been shown to inhibit adipogenesis by downregulating the expression of adipogenic transcription factors PPARG and C/EBPα, which are essential in the maturation of preadipocytes [45].

The bioactive compounds (flavonoids, flavanols, phenolic acids, etc., and their derivatives) of berries like blueberries, blackberries, strawberries, and other berries have been shown to modulate adipocyte function and insulin sensitivity, indicating potential benefits in type 2 diabetes and obesity-induced inflammation. Studies conducted on mice and rats have shown the anthocyanins of blueberry and strawberry reduced the expression of inflammatory cytokines IL-6, TNF-α, and NF-κB expression, a major transcription factor that regulates the expression of genes involved in the innate and adaptive immune responses [46]. In extensive studies involving large cohorts of men and women investigated the role of cinnamon, fenugreek, and bitter melon on the regulation of blood sugar. Mechanisms of action attributed to their antioxidant properties, anti-inflammatory effects, and effects on insulin signaling by activating insulin receptor (IR), glucose transporter (GLUT-4), and peroxisome proliferator-activated receptor gamma (PPAR-γ) expression. The extracts of these plants were found to play a role in increasing glycolysis and decreasing gluconeogenesis [47]. The anti-inflammatory effects of curcumin extracts from turmeric, have been known for a long time to possess anti-inflammatory properties. Multiple available animal studies and randomized, double-blinded clinical trials examining the effects of curcumin treatment indicate significant improvement of glucose and lipid homeostasis, reduction of oxidative stress and lipid peroxidation, and increased antioxidant enzyme activities. In addition, pro-inflammatory cytokine levels and macrophage infiltration into adipose and liver tissues were reduced. Furthermore, mitochondrial biogenesis was improved with curcumin administration [48].

A healthy gut microbiome is associated with improved metabolic health and may help to manage or prevent obesity-related complications. Number of plant-based compounds, like polyphenols found in various fruits and vegetables, positively impact gut microbiota composition. Plant-derived compounds like resveratrol from grapes and quercetin found in various fruits and vegetables have been studied for their potential role in hormone secretion and metabolic enzyme activity to produce metabolites, such as short-chain fatty acids (SCFAs). SCFAs improve gut barrier integrity, glucose and lipid metabolism, and response to inflammatory signals [49].

In a comprehensive review, Aryal D et al. [50] describe the potential benefits of selected biomolecules from fruits

and vegetables, including kaempferol (apples, broccoli, onions, tomatoes, green beans, citrus fruits, grapes, and Ginkgo biloba), catechins (green tea, cocoa), rosmarinic acid (perilla, sage, rosemary, and sweet basil), apigenin (parsley, celery, grapefruit, and chamomile), chlorogenic acid (apples, pears, carrots, tomatoes, coffees, teas, and sunflower seeds), and caffeic acid (multiple plants) affecting enzymes linked to diabetes, obesity, and inflammation. For example, certain polyphenols activate AMPK and peroxisome proliferator-activated receptor α (PPARα), leading to the inhibition of acetyl-CoA carboxylase (ACC) and fatty acid synthase.

The active compounds umbelliferone and esculetin from the plant ***Aegle marmelos*** have shown a noticeable effect on depleting the lipid content in the adipocytes and decreasing the hyperlipidemia in obese rats fed with a high-fat diet [51]. Decursin, an active compound of ***Angelica gigas***, has been investigated for its anti-obesity and antidiabetic potentials. The study focused on its ability to inhibit the differentiation of 3T3-L1 pre-adipocyte cells into adipocytes. The treatment resulted in the inhibition of adipocyte differentiation and the expression of fatty acid synthase. Further investigation of anti-obesity effects of the decursin using mice fed a normal diet, and a high-fat diet supplemented with decursin showed a drastic decrease in weight, triglyceride content, release of adipocytokines such as leptin, resistin, IL-6, and MCP-1, and improved glucose tolerance [52].

It is noteworthy to highlight the importance of the bioinformatic pipeline tools in identifying non-toxic phytocompounds as promising drug candidates to treat diabetes and obesity. For example, in an in-silico search, 22 potential compounds derived from N. sativa were identified that potentially inhibit key protein targets and signaling pathways associated with diabetes and obesity treatment. Out of these 22, only five hits associated with genes such as AKT1, IL6, SRC, and EGFR were found to be non-toxic, including Arabic and ascorbic acids, dihydrocodeine, catechin, and kaempferol [53].

The extract from ***Dioscorea oppositifolia*,** a type of yam, has been shown to downregulate adipogenic genes PPARγ, C/EBPα, SREBP-1, and FASN, while upregulating lipolytic gene CPT1. ***Dioscorea oppositifolia*** possesses a potent anti-obesity property and can be utilized to treat obesity and related disorders [54].

These examples, just a small fraction of numerous published data, suggest that plant extracts can interact with cellular pathways critical to adipogenesis and adipose tissue function and offer potential strategies for the prevention and treatment of obesity and associated metabolic disorders. However, considering that many of the studies were conducted on laboratory animal and cell models, it is advisable to approach these findings with caution, as the translation from laboratory animal research to clinical application involves multistep and complex pharmacological and physiological considerations. Moreover, herbal treatments should not be viewed as standalone solutions but rather as complementary approaches alongside lifestyle improvement, including a balanced diet and regular exercise for effective weight management and overall health improvement. Consulting a healthcare professional before incorporating herbal treatments or supplements into one's regimen is advisable, especially for individuals with existing health conditions or those who are taking medications.

As of today, six weight-loss drugs have been approved by the U.S. Food and Drug Administration (FDA) for long-term use: Orlistat (lipase inhibitor), Phentermine-topiramate (neurotransmitter-mediated appetite suppression and enhancement of satiety), Setmelanotide (melanocortin 4 (MC4) receptor agonist), Bupropion-naltrexone (bupropion opioid antagonist, naltrexone aminoketone antidepressant), Liraglutide (GLP-1 receptor agonists), and Semaglutide (GLP-1 receptor agonist). Setmelanotide has been approved for chronic weight management only for people age 6 and older with deficiency of proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) genes [55].

The drugs are involved in the regulation of either hunger, satiety, and/or energy expenditure. The limited weight-loss clinical trials that report separate data for men and women show no significant weight loss differences between men and women after long-term weight-loss drug treatment. However, certain sex-different adverse effects were observed. The most common reported adverse effects are gastrointestinal, such as nausea and vomiting, headaches, and occur at higher rates in women [56]. Liraglutide and Semaglutid, Glucagon-like Peptide 1 Receptor Agonists, are also used to control type 2 diabetes. In the treatment of type 2 diabetes, more women reported a range of adverse effects compared to men. Number of clinical studies, including over 3,800 patients, indicate a decreased level of hemoglobin A1c (HbA_{1c}) in women in response to GLP-1 RAs correlating with elevated blood glucose and increasing cardiovascular risk in women [57].

CONCLUSION

Adipose tissue is a complex and dynamically changing organ playing vital role in health and disease. We explored the multifaceted aspects of WAT, focusing on key areas, such as the diverse cell types comprising WAT and their unique functions, the major genes expressed and secreted from adipose tissue cells, the role of adipose tissue in inflammation, and the sex-specific differences in adipose tissue transcriptomes. Understanding the intricate dynamics of adipose tissue in the context of secreted factors that have a significant systemic effect, including inflammatory response, is essential. Knowledge of the adipocyte-specific, and most importantly, sex-specific differences of the transcriptomes give us an understanding of the unique characteristics of these cells. The dimorphic nature of adipose tissue not only influences body fat distribution but also affects disease susceptibility and response to treatment. Additionally, in this review we attempted to cover the increasingly recognized role and the intriguing effects of plant extracts on adipogenesis, which offer potential therapeutic avenues for treating obesity and its related disorders.

ADDITIONAL INFORMATION

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