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Perspective

Naringenin and Adipogenesis: Current Status and Perspective

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INTRODUCTION

Adipocytes are now understood to be dynamic, insulin-sensitive cells with endocrine functions that support energy homeostasis throughout the body, despite previously being believed to be passive locations of lipid storage [1]. Obesity, the main condition affecting fat cells, is a substantial risk factor for metabolic syndrome and has a crucial role in the development of cardiovascular disease, type 2 diabetes mellitus (T2DM), and some types of cancer [2,3]. In the past, limiting the growth of adipose tissue was thought to be an effective strategy for fighting obesity. Numerous studies have explored antiadipogenic substances as potential treatments for obesity, aiming to prevent or reduce weight gain by inhibiting the development of fat cells [4,5]. These substances, derived from plants, dietary compounds, or synthesized in labs, target specific pathways involved in adipogenesis (the formation of fat cells). Research suggests that these substances can help limit the formation of new fat cells and potentially reduce the size of existing ones [4,5]. Nevertheless, according to the most widely accepted theory, adipocyte differentiation disruption restricts the growth of adipose tissue, which is connected to insulin resistance and the onset of type 2 diabetes [6].

NARINGENIN

Grapefruit and other citrus fruits contain naringenin, an abundant aglycone flavanone that has recently been shown to have anti-hyperglycemic and anti-hyperlipidemic effects [7,8]. Despite these ostensibly beneficial effects on metabolism, some screening studies revealed that naringenin inhibited adipogenesis, which could have detrimental consequences on insulin sensitivity and adipose tissue growth [9,10].

Naringenin has been reported to suppress the expression of PPARγ (Peroxisome proliferator-activated receptor gamma) and C/EBPα (CCAAT/enhancer-binding protein alpha), two key transcription factors that drive adipocyte differentiation [11-13]. It reduces lipid accumulation in adipocytes by downregulating genes involved in lipogenesis (fat synthesis) and upregulating genes associated with lipolysis (fat breakdown) [14].

Naringenin activates AMP-activated protein kinase (AMPK), a key energy sensor that inhibits adipogenesis and promotes fatty acid oxidation [15,16]. It reduces inflammatory cytokine production in adipose tissue, which can indirectly affect adipogenesis since inflammation contributes to metabolic dysfunction in adipocytes [17]. Some studies suggest that naringenin may promote the browning of white adipose tissue, increasing energy expenditure [11- 20].

NARINGENIN AND ADIPOGENESIS

Some studies have demonstrated that naringenin can inhibit adipogenesis in various cell models:

- 3T3-L1 Preadipocytes: as demonstrated by lower lipid buildup and adipocyte marker protein expression, naringenin administration led to a dose-dependent suppression of adipocyte development [21]. Furthermore, mature adipocytes showed reduced expression of adiponectin and significant inhibition of insulin-stimulated glucose uptake [21].

- Human Preadipocytes (AML-I cells): increased cytoplasmic lipid droplets resulted from growth arrest and apoptosis brought on by naringenin exposure [11]. Significantly, fatty acid synthase (FAS) and peroxisome proliferator-activated receptor (PPAR)-gamma expression were increased upon naringenin therapy, indicating a complicated interaction with adipogenic pathways [11].

These findings indicate that naringenin may exert inhibitory effects on adipogenesis through multiple

mechanisms, including modulation of key adipogenic transcription factors and enzymes.

Naringenin has been demonstrated to encourage the browning of white adipocytes, a process by which white adipocytes acquire traits of brown adipocytes, such as an increased thermogenic capacity, in contrast to its inhibitory effects on white adipogenesis [11]:

- In Murine Models: by altering the composition of the gut microbiota, naringenin treatment triggered beige adipocyte browning in C57BL/6 mice fed a high-fat diet [19]. As a result, metabolic profiles improved and energy expenditure rose.
- In Cell Culture: in mouse brown pre-adipocytes, naringenin administration increased the expression of thermogenic markers including PGC1α and UCP1. PPARγ knockdown reduced these effects, suggesting that PPARγ plays a role in modulating the browning process [11,22].

CONCLUSIONS

These observations suggest that naringenin may facilitate the conversion of white adipocytes to a more metabolically active, thermogenic phenotype [Table 1].

Therefore, naringenin is a strong antiadipogenic substance obtained from plants that also inhibits the expression of the adiponectin protein in mature adipocytes. Despite being a significant component of grapefruit and other citrus fruits, naringenin does not imply that grapefruit may be detrimental to metabolism. However, by restricting preadipocyte differentiation, causing insulin resistance, and lowering adiponectin levels in adult fat cells, isolated naringenin may have an adverse effect on disorders linked to adipocytes.

In conclusion, naringenin modulates adipogenesis and adipocyte activity in a complicated way. Its capacity to induce adipocyte browning and suppress white adipocyte differentiation presents encouraging opportunities for the creation of innovative treatment approaches to combat obesity and associated metabolic diseases. To turn these discoveries into successful solutions, more research is essential, especially clinical investigations. The dual role of naringenin in inhibiting white adipogenesis and promoting adipocyte browning positions it as a potential therapeutic agent for obesity and metabolic disorders. However, several aspects require further investigation.

Table 1: Mechanisms of Naringenin in Inhibiting White Adipogenesis and Promoting Browning of Adipose Tissue

1. Inhibition of White Fat Production (Adipogenesis)	2. Promotion of Browning of White Fat
• **Naringenin → ↓ PPARγ** (Peroxisome proliferator-activated receptor gamma) • ↓ **C/EBPα** (CCAAT/enhancer-binding protein alpha) • ↓ Adipocyte differentiation and lipid accumulation • ↓ Expression of lipogenic genes (e.g., FAS)	• **Naringenin → ↑ PGC-1α** (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) • ↑ **UCP1** (Uncoupling protein 1) expression • ↑ Mitochondrial biogenesis and thermogenesis
✓ Outcome: **Reduced white adipose tissue (WAT) formation**	✓ Outcome: **WAT browning into beige adipocytes → Increased energy expenditure**

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