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Crosstalk between adipogenesis and aging: role of polyphenols in combating adipogenic-associated aging

Khalid Al-Regaiey[1*]

Abstract
In the last forty years, the number of people over 60 years of age has increased significantly owing to better nutrition and lower rates of infectious diseases in developing countries. Aging significantly impacts adipose tissue, which plays crucial role in hormone regulation and energy storage. This can lead to imbalances in glucose, and overall energy homeostasis within the body. Aging is irreversible phenomena and potentially causing lipid infiltration in other organs, leading to systemic inflammation, metabolic disorders. This review investigates various pathways contributing to aging-related defects in adipogenesis, such as changes in adipose tissue function and distribution. Polyphenols, a diverse group of natural compounds, can mitigate aging effects via free radicals, oxidative stress, inflammation, senescence, and age-related diseases. Polyphenols like resveratrol, quercetin and EGCG exhibit distinct mechanisms and regulate crucial pathways, such as the TGF-β, AMPK, Wnt, PPAR-γ, and C/EBP transcription factors, and influence epigenetic modifications, such as DNA methylation and histone modification. This review highlights the critical importance of understanding the intricate relationship between aging and adipogenesis for optimizing well-being with increasing age. These findings highlight the therapeutic potential of polyphenols like quercetin and resveratrol in enhancing adipose tissue function and promoting healthy aging.

Keywords Aging, Adipogenesis, Adipose tissue redistribution, Polyphenols, Epigenetic changes, TGF-β, AMPK, Wnt, PPAR-γ, C/EBP, Endocrine changes

Introduction

By 2050, the global population aged 60 and above is expected to nearly double, increasing from 12 to 22%. This significant shift underscores an unavoidable and irreversible biological phenomenon: aging, which leads to a gradual decline in tissue and cellular function. As aging progresses, individuals become increasingly vulnerable to age-related illnesses, including metabolic disorders. As age increases, fat cells tend to make up a greater percentage of their overall body weight [1]. Researchers found that as age increases from 20 to 50, the total body fat content doubles for both men and women. As age increases, there is a loss of lean muscle mass and an increase in fat accumulation, leading to changes in body composition. This condition, known as sarcopenia, increases the risk of metabolic diseases and disrupts metabolic balance [2]. Consequently, in old individuals, there is an excess of fat in inappropriate areas and a deficit of fat in areas where it is needed, which has significant therapeutic implications. Adipose tissue redistributes from the subcutaneous layer to the deeper abdominal cavity as part of this process. Aging also affects the development of mesenchymal stem

*Correspondence:
Khalid Al-Regaiey
kalregaiey@ksu.edu.sa
[1]Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

cells and accelerates cellular aging in subcutaneous adipose tissue [3]. These changes hinder the differentiation of adipose cells from precursor cells, restrict their ability to proliferate, and diminish their overall mass in the subcutaneous layer, thereby compromising the function of adipose cells [3, 4].

Over the years, the traditional perspective on food consumption has evolved from simply eating to survive ("eat to live") to focusing on enhancing health and preventing illness. Eating many fruits and vegetables is linked to a lower risk of obesity. These foods also contain essential micronutrients such as vitamins C and E, carotenoids, and various phytochemicals [5]. Emphasizing these dietary choices is associated with promoting longevity, preventing diseases, and fostering overall health. Plants produce polyphenols (Fig. 1) as secondary metabolites to defend against harmful radiation and pathogens. These compounds, including lignans, stilbenes, phenolic acids, and flavonoids, typically feature aromatic rings with numerous hydroxyphenyl groups [6]. Additionally, polyphenols from diverse plant sources are recognized for their additional anti-obesity benefits by enhancing plasma lipid profiles, decreasing ghrelin levels, and increasing the expression of PPAR-α and PPAR-β

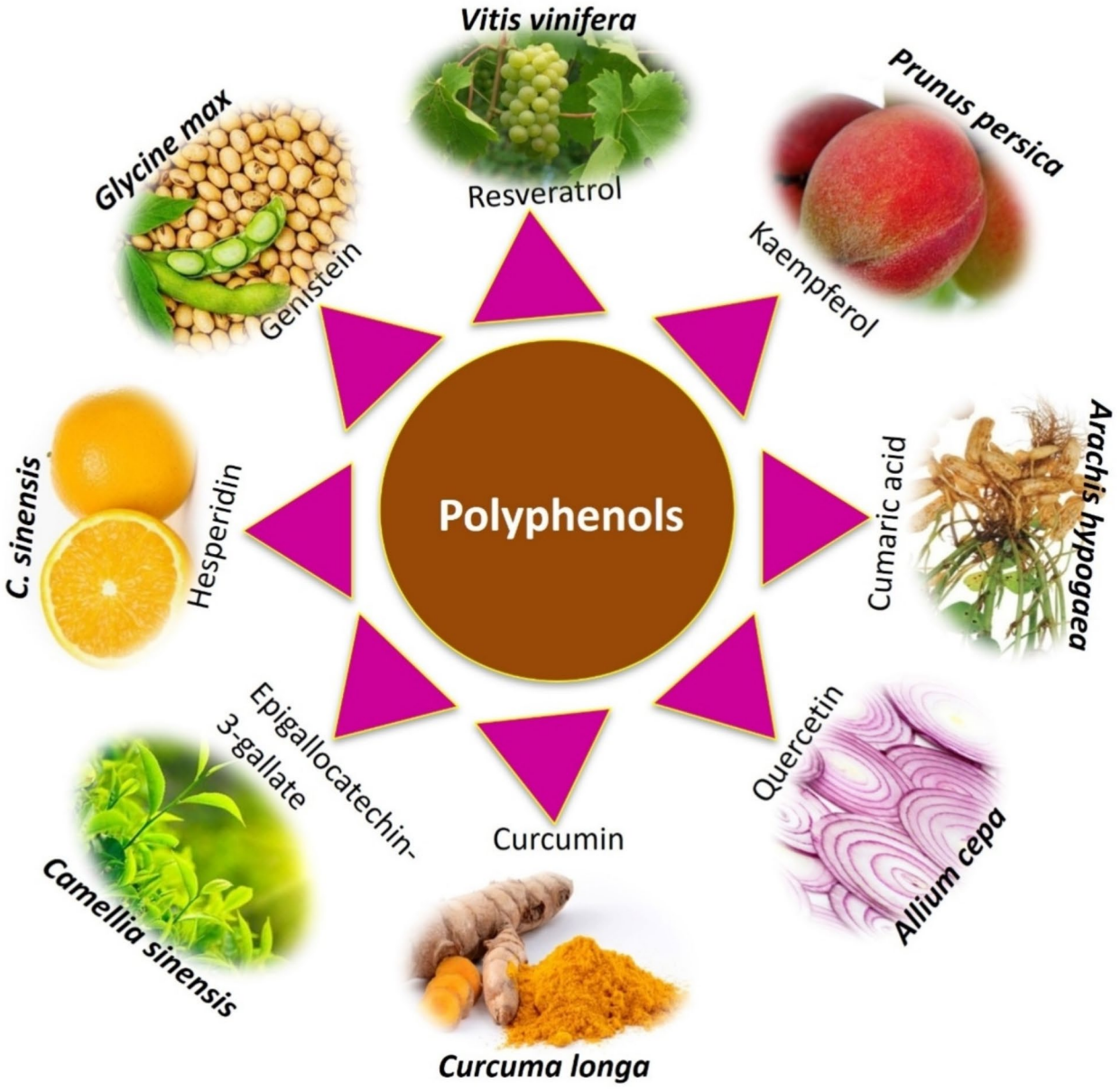

Fig. 1 Sources of polyphenols

[7]. These compounds inhibit adipocyte differentiation and adipogenesis, thereby limiting adipose tissue growth. They also lower triacylglycerol levels by either enhancing lipolysis or inhibiting lipogenesis pathways [8].

The objective of this review is to investigate the impact of dietary polyphenols on adipogenesis and aging, focusing on the underlying mechanisms and signaling pathways involved, while highlighting the potential therapeutic benefits of these compounds in promoting healthy aging and mitigating age-related metabolic disorders. It explored the roles of different dietary phenolic compounds, such as genistein, resveratrol, curcumin, epigallocatechin-gallate (EGCG), and quercetin, in several factors associated with adipogenesis and aging. These factors include proinflammatory adipokines, oxidative stress, epigenetic modifications, the accumulation of senescent cells, and anti-inflammatory adipokines. These phenolic compounds actively modulate multiple signaling pathways, either activating or inhibiting pathways such as the JNK, AMPK/MAPK, TGF-ß, and Wnt signaling pathways. This review examines how these dietary phenolic compounds can contribute to the development of innovative therapies for adipogenesis and aging.

Aging effects: transformations in Adipocyte structure and function

Aging involves a gradual decline in function across various levels, including organelles, cells, tissues, and the entire organism, leading to a decrease in overall life expectancy. Central factors contributing to biological aging include cellular senescence, oxidative stress, and disruptions in energy homeostasis. There are three primary types of adipose tissue. White adipose tissue (WAT) is distinguished by its white or yellowish color, which stems from a single, prominent lipid droplet that is responsible for fat storage [9]. WAT cells, characterized by their large, unilocular nature and fewer mitochondria, primarily function to store energy. Triglycerides, which represent surplus energy stored in WAT, can be mobilized to fuel the body during periods of energy deficit. Furthermore, WAT behaves as an endocrine organ, releasing adipokines, including resistin, adiponectin, and leptin. These adipokines influence insulin sensitivity, inflammation, metabolism, and appetite regulation [10]. Aging can disrupt adipokine production, inflammatory profiles, and adipose tissue metabolism, potentially leading to age-related metabolic disorders such as insulin resistance, diabetes, and cardiovascular ailments. Aging correlates with the presence of hypertrophic adipocytes, or enlarged adipocytes, within WAT. While hyperplastic adipocyte expansion, commonly observed in subcutaneous adipocytes, is associated with improved insulin sensitivity and metabolic regulation, hypertrophic expansion is linked to ectopic lipid accumulation, diminished triacylglycerol storage capacity, and impaired insulin sensitivity [11]. The distinct brown color of brown adipose tissue (BAT) arises from its abundant concentration of mitochondria containing iron-rich cytochromes. BAT cells, characterized by their smaller size, numerous mitochondria, and multiple small lipid droplets (multilocular), play pivotal roles in thermogenesis and heat production. A key characteristic of BAT is its ability to generate heat without shivering, a process driven by uncoupling protein 1 (UCP1) in the inner mitochondrial membrane. UCP1 disrupts the proton gradient needed for ATP synthesis, converting energy into heat instead. This thermogenic process plays a crucial role in increasing energy expenditure and burning calories, which helps in combating obesity [10]. Cold exposure and sympathetic nervous system activation stimulate BAT activity. With aging, there is a rise in body fat accompanied by a decline in BAT activity and depots, including reduced expression of UCP1. One possible reason for the decline in brown adipose tissue with age is a decrease in sympathetic nervous system activity. This reduction not only diminishes anti-inflammatory activity and increases the synthesis of inflammatory peptides but also leads to macrophage infiltration and dysfunction of adipose organs during the aging process.

Adipocytes exhibiting traits of both brown and white adipocytes are termed beige adipocytes, also known as brite adipocytes. These cells possess the unique ability to switch between a thermogenic state related to brown adipocytes and a storage state resembling white adipocytes, depending on environmental conditions [12]. Alterations in trophic factors can influence the proliferation and differentiation of beige adipocytes, which arise from progenitors within white adipose tissue, or through trans differentiation, where white adipocytes transform into brown-like cells. As age increases, white adipose cells depots diminish, and dysfunctional adipocyte-like cells emerge within WAT (Fig. 2). These cells, which are smaller than fully developed adipocytes, exhibit reduced insulin sensitivity. The aging process impedes the browning of adipocytes in older mice and humans by progressively transforming beige adipocytes into a phenotype resembling white adipocytes [13]. Moreover, aging can impair the function of adipose progenitor cells (APCs) within WAT, diminishing their capacity for adipocyte differentiation and tissue remodeling. This decline in APC function may contribute to adipose tissue dysfunction. Progenitor cells taken from older adipose tissue show diminished functionality, impaired lipid uptake, and a reduced ability to differentiate into preadipocytes. Additionally, there is an increase in senescent cells that no longer divide effectively under metabolic stress [14]. Elevated levels of PAI-1 and IL-6 signal the presence of the senescence-associated secretory phenotype, which

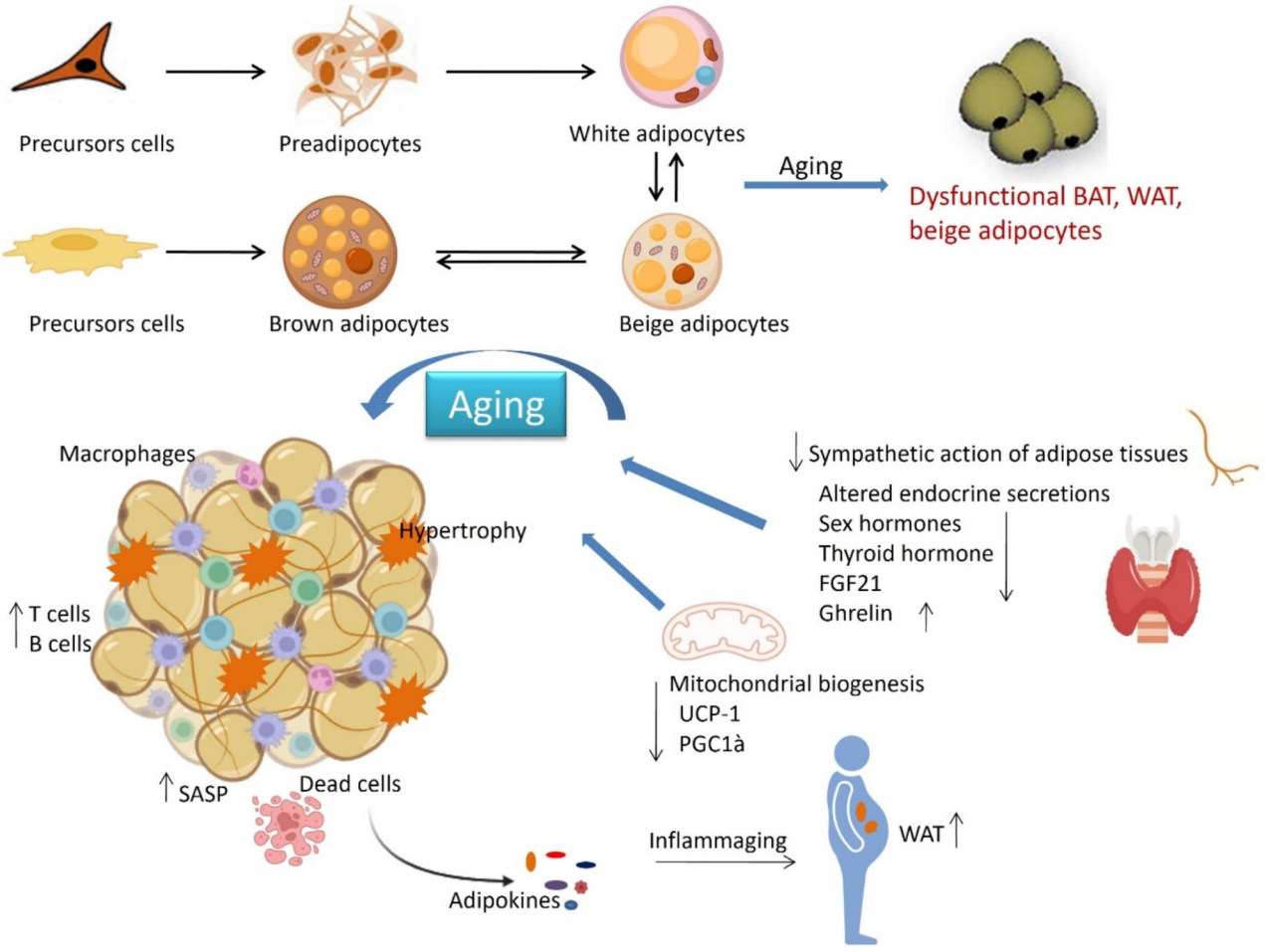

Fig. 2 Shows that aging disrupts the typical process of adipogenesis, causing dysfunction in BAT, WAT, and beige adipocytes. This disruption is characterized by disturbances in endocrine secretions, reduced mitochondrial biogenesis, and decreased sympathetic tone within adipose tissues. These factors contribute to hypertrophy and the accumulation of dead cells, increasing the release of proinflammatory adipokines and the buildup of visceral fat and inflammation

is characterized by the secretion of bioactive substances from these cells. As aging is an inevitable natural phenomenon, incorporating certain natural compounds, whether through dietary choices or medicinal interventions, becomes essential in mitigating the adverse effects of aging on adipose tissues [15].

Hormonal shifts: the endocrine evolution of adipocytes with age

Hormonal changes within adipocytes are pivotal contributors to adipose tissue dysfunction during aging. These changes encompass shifts in hormone production, secretion, and sensitivity, ultimately leading to metabolic dysregulation and related health complications. The aging process is linked to a reduction in the levels of sex hormones, including estrogen and androgens, which can affect the function and metabolism of adipocytes. This decrease in hormones can result in alterations in adipose tissue distribution and functionality. Generally, men tend to accumulate adipose tissues above the waist, especially in the visceral and subcutaneous areas of the abdomen, and they usually have lower overall body fat percentages than women do. As men age, they often experience increased adiposity, particularly around the abdomen, which is attributed to declining testosterone levels [16]. This decline, coupled with heightened levels of steroid hormone binding globulin (SHBG), diminishes the physiological availability of testosterone, potentially impairing its role in adipocyte metabolism. In premenopausal women, adipose cells are primarily stored in the gluteal-femoral subcutaneous area rather than the abdomen. This is largely due to the presence of estrogen receptor alpha (ERα) in this region, which enhances lipoprotein lipase activity and reduces the accumulation of triacylglycerols in fat cells. However, with menopause and declining estrogen levels, there is a shift toward visceral adipose tissue, leading to metabolic disturbances. Similarly, higher testosterone-to-estrogen ratios in premenopausal women

with PCOS increase abdominal visceral fat [17, 18]. With advancing age, there is a decrease in sex hormone levels alongside relatively stable glucocorticoid levels (Fig. 2). The decline in BAT activity with age may be partly due to this interaction. Triiodothyronine (T3), a key thyroid hormone, plays a significant role in regulating thermogenesis, with UCP1 levels closely related to those at T3. T3 enhances UCP1 activity by influencing cAMP levels and stimulates UCP1 production in BAT at the transcriptional level. Age-related reductions in DIO2 lead to lower serum T3 levels and less conversion of T3 to its active form, which affects UCP1 expression in both BAT and WAT [19, 20]. Ghrelin and obestatin, both derived from the preproghrelin gene, have distinct impacts on brown adipose tissues: obestatin increases UCP-1, whereas ghrelin decreases it. In older adults, higher levels of ghrelin and its receptor (GHS-R) in brown fat can aggravate problems with thermogenesis and disrupt temperature regulation [21]. Fibroblast growth factor 21 (FGF21) is a hormone released in response to diverse metabolic stressors, such as fasting, cold exposure, and physical activity. As metabolic regulators, they coordinate the body's response to these stressors, notably converting white adipocytes into beige adipocytes, which share thermogenic properties with brown adipocytes. However, the activity of FGF21 may decrease with age, potentially reducing its capacity to induce browning of WAT. Age-related hormonal changes in adipocytes can severely impair normal adipose tissue function, leading to malfunction, inflammation, and metabolic abnormalities. Comprehending these hormonal changes is critical for treating age-related metabolic diseases and developing focused treatments to maintain the health of adipose tissue in aging populations [22, 23].

Adipose tissue redistribution: changes and implications in aging

Adipose tissue redistribution involves shifts in fat distribution due to aging, hormonal fluctuations, metabolic disorders, and lifestyle choices. With age, subcutaneous fat decreases and is replaced by visceral fat. This transition significantly impacts health; a reduction in subcutaneous fat can impair insulin sensitivity, whereas an increase in visceral fat is closely linked to a heightened risk of metabolic issues such as insulin resistance, inflammation, and cardiovascular disease [11]. Visceral fat, with its heightened metabolic activity and release of proinflammatory cytokines, can induce systemic inflammation and metabolic dysfunction. The metabolic dysfunction associated with aging is, in part, attributed to the accumulation of visceral fat. In older individuals, the loss of subcutaneous fat can impact thermoregulation, metabolic control, and physical appearance. These changes in subcutaneous fat distribution may negatively affect metabolic health and contribute to age-related metabolic problems. The shift of fat storage to non-adipose tissues such as the liver, muscles, and pancreas leads to ectopic fat accumulation, which is linked to inflammation, insulin resistance, and metabolic issues. This abnormal fat deposition can disrupt key metabolic pathways, impair the function of affected organs, and contribute to the onset of metabolic syndrome and its associated health problems. Additionally, there is a progressive reduction in observable BAT with aging, which may affect thermogenic signaling and energy consumption [24]. Age-related changes in hormone levels, adipocyte function, and metabolic regulation significantly influence the redistribution of adipose tissue. Changes in hormones such as cortisol, insulin, leptin, sex hormones, and adipokines are also vital for how adipose tissue is redistributed in the body. These hormonal imbalances contribute to the shifting patterns of fat distribution observed with aging, impacting adipose tissue remodeling, fat distribution, and overall metabolic control. Moreover, "inflammaging," (chronic, low-grade inflammation) which is associated with aging, affects redistribution by altering adipocyte function and promoting changes in fat distribution (Fig. 2) [25]. Additionally, dysregulation of adipokine production, which is influenced by age-related changes, affects metabolic processes and adipose tissue function, contributing to the metabolic challenges associated with aging. Hence, controlling fat redistribution and addressing the metabolic alterations associated with aging are essential for promoting healthy aging, averting metabolic diseases, and improving general metabolic health in elderly individuals [26, 27].

Molecular pathways connecting aging and adipogenesis: the impact of polyphenols

Polyphenols as inhibitors of Proinflammatory Adipokines

Proinflammatory adipokines such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and Monocyte chemoattractant protein-1 (MCP-1) play crucial roles in aging-associated adipogenesis by promoting the expansion of adipose tissue through adipocyte hypertrophy and hyperplasia. These adipokines prevent preadipocytes from developing into fully mature adipocytes by interfering with essential transcription factors such as PPAR-γ, thus hindering the proper maturation of adipose cells. The persistent presence of these cells triggers chronic low-grade inflammation in adipose tissue, which contributes to metabolic dysfunction and insulin resistance. The increased levels of proinflammatory adipokines in aging adipose tissue further disrupts the balance between inflammatory and anti-inflammatory mediators, sustaining inflammation and worsening metabolic issues. Additionally, these adipokines contribute to cellular senescence in adipose tissue, accelerating age-related

changes in adipocyte function and metabolism through the secretion of inflammatory factors [28, 29]. Polyphenols like quercetin and resveratrol reduce inflammation by blocking NF-κB expression, which is induced by TNF-α and IL-6. As we age, polyphenols help regulate the levels of IL-10, TGF-β1, IL-6, and IL-17. Laboratory studies have shown that compounds such as p-coumaric acid, quercetin, and resveratrol can counteract TNF-α-induced increases in MCP-1, PAI-1, and ROS levels in adipose cells, emphasizing their role in reducing inflammation and oxidative stress [30].

Leptin, primarily from adipose tissue, regulates hunger and fat storage. In aging, disrupted pathways such as the JAK2-STAT3/STAT5 and PI3K/IRS/AKT pathways affect the metabolic balance of leptin, leading to inflammation and insulin resistance (Fig. 3). The proinflammatory role of leptin increases cytokine production, promoting chronic inflammation (inflammaging). Aging-related changes in the SHP2/ERK pathway further disrupt leptin signaling and metabolic regulation. These alterations contribute to adipose tissue dysfunction, which is characterized by altered adipokine secretion and impaired lipid storage, exacerbating metabolic complications in aging individuals [31]. Rutin and cumaric acid increased the protein expression of adiponectin while suppressing the expression of leptin, C/EBPα, and PPARγ (Table 1) [32]. Under conditions of metabolic stress, leptin synthesis increases in response to fat accumulation, insulin resistance, and adipocyte volume. Across all the experimental conditions, resveratrol consistently and dose-dependently decreased leptin secretion. This effect was observed independently of changes in glucose uptake and glycerol release. Moreover, resveratrol significantly reduces ATP levels in adipocytes [33]. Resistin, a 12.5 kDa protein with 108 amino acids, is a key member of the RELM family and is characterized by hormone-like functions. It promotes adipogenesis by enhancing preadipocyte differentiation, contributing to adipose tissue expansion and lipid storage during aging. Elevated resistin levels are associated with adipocyte hypertrophy, obesity, and insulin resistance in aging populations. Resistin also promotes inflammation by stimulating the secretion of cytokines (TNF-α, IL-1β, -6, -8, and −12), generating ROS, and inhibiting eNOS. Moreover, it induces MCP-1 release and activates NF-κB,

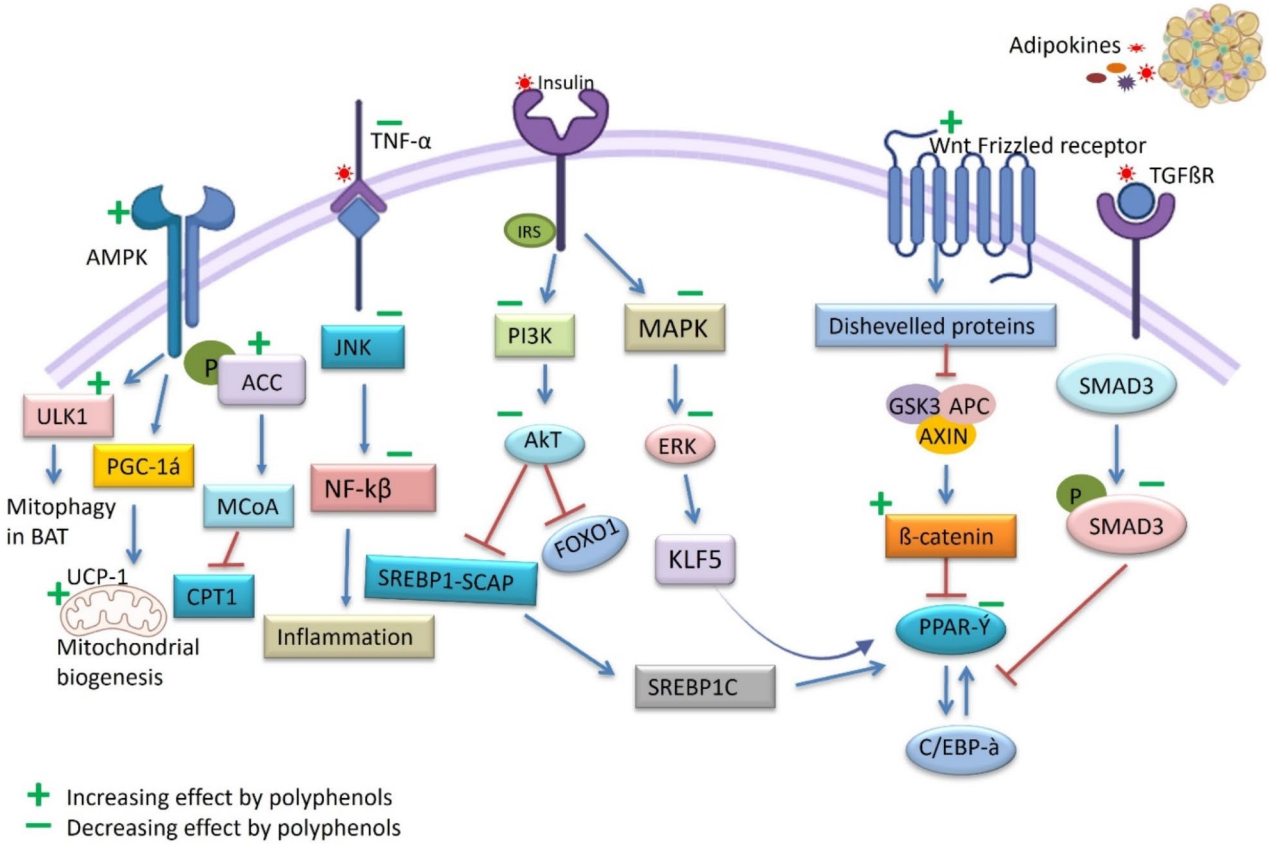

Fig. 3 Shows that, owing to aging, there is an increased release of proinflammatory adipokines that stimulate the activation of TNF, TGFBR, and insulin receptors. These factors in turn activate the PPAR and C/EBP transcription factors, leading to abnormal adipogenesis and oxidative stress. However, the negative (_) sign in green indicates that polyphenols inhibit these pathways and instead activate AMPK and the Wnt signaling pathway, as shown by the plus (+) sign. This protective action helps mitigate the effects of aging on regulated pathways

Table 1 MOA of polyphenols against aging-associated adipogenesis

Target	Natural polyphenols	Botanical source	Mode of action	Reference
Pro-Inflammatory Adipokines	*Rutin* *Cumaric acid*	*Ruta graveolens* *Malus domestica*	*Enhanced the production of adiponectin while reducing the levels of leptin, PPARγ, and C/EBPα.*	[32]
	Resveratrol	*Vitis vinifera*	*dose-dependently decreased leptin secretion, significantly reduced ATP levels in adipocytes*	[33]
	EGCG	*Camellia sinensis*	*suppresses TNF-α, IL-1β, and IL-6 expression, increases SOD activity, decreases ROS expression*	[36]
Epigenetic changes	*Resveratrol*	*Vitis vinifera*	*Mitigates aging effects by enhancing H3K9ac and H3K27ac levels.* *Modifies NRF2 pathway methylation to lower oxidative stress and fat accumulation.*	[52]
	Genistein, EGCG	*Glycine max* *Camellia sinensis*	*potentially reverse DNA hypermethylation and restore silenced genes*	[57, 160, 162]
TGF-β Signaling Pathway	*EGCG*	*Camellia sinensis*	*inhibited the activity of the TGF/SMAD pathway,* *restore autophagic activity in cells treated with TGF-β1, indicating that autophagic regulation is a key mechanism in EGCG's action against TGF-β1-induced transformation. EGCG has the potential to slow down cellular aging, and the inflammatory processes induced by senescence*	[62, 69, 163]
	Ellagic acid	*Punica granatum*	*Inhibits abnormal cell division and induce programmed cell death (apoptosis).* *Research suggests that EA may exert these effects by influencing the TGF-β/Smads signaling pathway, potentially leading to cell cycle arrest*	[71]
Senescent cell accumulation	*Resveratrol, quercetin, curcumin, epigallocatechin-3-gallate (EGCG)*	*Vitis vinifera* *Allium cepa* *Curcuma longa* *Camellia sinensis*	*Possess senolytic effects,* *mitigate oxidative stress, reduce inflammation, and inhibit telomere shortening, while simultaneously enhancing DNA repair mechanisms and selectively eliminating senescent cells*	[76, 161, 164]
	Resveratrol	*Vitis vinifera*	*induces cell senescence through the p53–p21 pathway, which is associated with both senescence and prolonged cessation of the cell cycle, alongside the p16/Rb pathway*	[79]
	Procyanidin C1, Resveratrol, Curcumin	*Cinnamomum verum* *Vitis vinifera* *Curcuma longa*	*possess anti-aging properties by modulating p53/p21cip1*	[81]
	Quercetin	*Allium cepa*	*Inhibit cellular proinflammatory pathways such as (ERK1/2)/P13K/AKT, (JNK)/P38 and MAPK*	[71, 86]
AMPK Signaling	*Genistein*	*Glycine max*	*Activates AMPK, leading to reduced expression of C/EBPα, apoptosis in mature adipocytes, inhibition of P38 MAPK phosphorylation, and prevention of adipocyte development.*	[165]
	Protocatechuic acid (PCA)	*Prunus domestica*	*increases the expression of genes linked to longevity, including sir-2.1 and daf-16*	[93, 166]
	Resveratrol	*Vitis vinifera*	*activates AMPK, thereby enhancing the effectiveness of the ROS defense mechanism.* *Reduces mitochondrial dysfunction and oxidative stress through the LKB1/AMPK signaling pathway.*	[96, 100]
	Quercetin	*Allium cepa*	*boosts UCP1 expression, suggesting heightened activity in BAT and browning of WAT*	[98]
Oxidative stress	*Quercetin*	*Allium cepa*	*Activates the Nrf2/NRF1 transcription pathway, enhancing the expression of antioxidant peroxiredoxins and providing protection against oxidative stress*	[107]
	Resveratrol	*Vitis vinifera*	*prevented DNA fragmentation and apoptosis induced by 4-HNE*	[167]
	EGCG	*Camellia sinensis*	*reduced the formation of free radical adducts, including 4-HNE adducts*	[109]

Table 1 (continued)

Target	Natural polyphenols	Botanical source	Mode of action	Reference
PPAR-γ Transcription factor	*Kaempferol*	*Pyrus malus*	*Proven effective in decreasing fat and lipid buildup linked to obesity. It works by boosting the levels of PPARα and PPARδ, along with their target genes, which helps to stimulate autophagy and improve fatty acid absorption.*	[120]
	Quercetin	*Allium cepa*	*Boosts the conversion of WAT to brown fat and stimulates BAT by activating the β3-adrenergic receptor (β3AR) and the PKA/AMPK/PPARγ/PGC1α pathways. This activation results in higher levels of uncoupling protein 1 (UCP1) and ABCA1, which enhances ATP production and reduces fat accumulation.*	[122]
	Curcumin	*Curcuma longa*	*stimulates PPARγ production, which in turn regulates insulin sensitivity and glucose homeostasis, while also reducing levels of inflammatory cytokines.*	[124]
	Hesperidin	*Citrus sinensis*	*inhibits PPARγ, CCAAT-enhancer-binding protein β (C/EBPβ), SREBP1-C, and perilipin, demonstrating antiadipogenic and delipidating effects.*	[125]
	EGCG	*Camellia sinensis*	*Inhibits the expression of genes associated with fat cell formation, such as PPARγ and C/EBPα, and blocks the development of preadipocytes into mature fat cells.*	[126]
C/EBP Transcription factor	*Genistein*	*Glycine max*	*inhibit FAS, SREBP 1, and aP2 in primary human adipocytes, promoting mitochondrial biogenesis, inducing adipocyte beigeing, and upregulating UCP1 and cellular oxygen consumption*	[130, 132]
	cis-*guggulsterone*	*Commiphora mukul*	*downregulates C/EBPβ, C/EBPα, and PPARγ2*	[168]
	EGCG	*Camellia sinensis*	*Lower body weight and plasma lipid levels, while decreasing the expression of key genes involved in fat storage like PPARγ, C/EBPα, SREBP1, aP2, LPL, and FAS. At the same time, increase the expression of genes essential for breaking down fats, β-oxidation, and generating heat, which helps to prevent the formation of fat tissue.*	[124]
	Resveratrol	*Vitis vinifera*	*Decreased lipid buildup and lowered the levels of LPL, FAS, C/EBPα, and SREBP-1c by activating AMPK*	[124]
Sirtuins	*Epicatechin*	*Camellia sinensis*	*reduces plasma triglyceride levels and increased expression of SIRT1, PGC-1α, and UCP1 in WAT*	[135]
	Resveratrol	*Vitis vinifera*	*Directly interacts with the SIRT1 isoform, boosting its protective effects by regulating antioxidant responses.*	[136, 137, 139, 141, 143]
Wnt Signaling Pathway	*Flavonoids*	*Ginkgo biloba*	*Stimulate the Wnt pathway, which could prevent adipose stem cells from turning into fat cells.*	[147]
	Resveratrol	*Vitis vinifera*	*stimulate Wnt/β-catenin signaling pathway*	[147]
	EGCG	*Camellia sinensis*	*enhancing β-catenin levels while suppressing key genes involved in adipogenesis*	[149]
	Genistein	*Glycine max*	*activate the Wnt pathway through ERK/JNK signaling and LEF/TCF4 coactivation, processes dependent on estrogen receptors.*	[150]
Anti-inflammatory adipokines	*EGCG*	*Camellia sinensis*	*provides anti-obesity benefits in humans by reducing ghrelin release and increasing adiponectin levels*	[152]
	Catechins	*Camellia sinensis*	*significantly and dose-dependently increased adiponectin secretion*	[153]
	Chlorogenic acid	*Coffea arabica*	*raise adiponectin levels in visceral adipose tissue and enhance the expression of AdipoR2 protein*	[154]
	Resveratrol	*Vitis vinifera*	*Reduced the levels of vaspin gene expression in adipose tissue*	[155]

further exacerbating age-related inflammatory processes and metabolic dysregulation [34]. EGCG uses the Erk pathway as a mechanism to decrease the expression of the adipocyte resistin gene (Table 1) [35]. Chemerin and lipocalin-2 (LCN2) play pivotal roles in inflammatory processes that are central to adipogenesis and aging-related pathophysiology. They promote chronic low-grade inflammation (inflammaging) by stimulating the production of cytokines, such as TNF-α and IL-6, in the aging population. TNF-α, IL-1β, and IL-6 expression is suppressed by EGCG (Fig. 3). Moreover, EGCG increases SOD activity, decreases ROS expression, and promotes cell proliferation. Thus, the inclusion of dietary polyphenols is recommended to reduce the effects of aging [36].

Modulatory effects of polyphenols on insulin-like growth factor 1 (IGF-1)

The IGF-1 system is a pivotal part of the endocrine system and significantly influences growth, development, and aging [37]. IGF-1 exerts its effects through the IGF-1 receptor (IGF-1R), which triggers intracellular signaling pathways such as the PI3K/AKT/mTOR pathway, regulating cell proliferation and survival. In aging, the IGF-1 system has been linked to longevity, with lower IGF-1

levels and enhanced insulin sensitivity correlating with longer life spans and reduced age-related diseases [38]. Findings from centenarians reveal unique metabolic profiles, such as lower IGF-1 levels and improved insulin sensitivity, potentially contributing to their extended lifespans [39]. Studies on animal models support the idea that downregulating the IGF-1 pathway can increase lifespan, such as metabolic adaptations induced by caloric restriction, which shifts the body's focus from cell proliferation to repair activities, reducing the number of senescent cells and promoting healthy aging [40]. Polyphenols block the activity and expression of IGF-1 and its receptor, IGF-1R, both in laboratory settings and in living organisms. Studies on GH-releasing hormone-knockout (GHRH-KO) mice, which have increased lifespans and traits such as increased insulin sensitivity, further underscore the role of IGF-1 in aging. In obese individuals, the levels of IGF-1 and IGF-1R are notably increased. In humans, IGF-1 is associated with several age-related diseases that can hinder long-term survival. Treatment with 100 μmol/L resveratrol resulted in reduced expression of insulin-like growth factor-1 [41].

Research on IGF-1 receptors (IGF1Rs) in adipose tissue has revealed several key findings. Mice lacking IGF1R exhibited an approximately 25% reduction in both WAT and BAT, indicating that IGF1R plays a moderate role in adipose tissue development and maintenance [42]. IGF1R is abundantly present in undifferentiated preadipocytes but declines as adipocytes mature, suggesting that insulin receptors (IRs) might compensate for the absence of IGF1R. Although IGF1R influences adipocyte gene expression, its role is less significant than that of IR, which is necessary for maintaining adipose tissue function [43]. Notably, the absence of IGF1R caused fewer reductions in BAT mass and had minimal impact on BAT function, with normal histology observed in the tissue. Quercetin, a dietary bioflavonoid, increases the expression of GLUT 1–4 and IGF-1 in adipose tissues [44]. Green tea aids in preventing obesity by increasing the levels of insulin-like growth factor binding protein-1 in the adipose tissue of mice fed a high-fat diet [45]. While IGF-1R plays a role in the development of adipose tissue, its importance is secondary to that of the insulin receptor, especially in regard to maintaining adipose tissue mass and function [45]. EGCG has effects similar to those of IGF-1 and insulin. It reduces Foxo1 activity, a factor that contributes to muscle loss, by causing Foxo1 to move from the nucleus to the cytoplasm in adult muscle cells. Like IGF-1 and insulin, EGCG activates the Akt enzyme, which helps relocate Foxo1 out of muscle cell nuclei. However, the effects of polyphenols on IGF-1 levels can vary with dosage, the polyphenol used, and individual health conditions [46].

Polyphenols inhibit epigenetic modifications

Age-related epigenetic changes encompass alterations in the chemical tags and structural organization of histone proteins and DNA. These modifications, which occur during aging, can significantly influence chromatin organization, genomic stability, and patterns of gene expression, ultimately contributing to the aging phenotype [47]. These epigenetic changes are vital for determining the function of adipose tissue, which comprises body fat and is essential for the process of adipogenesis or the formation of adipose cells. Adipose tissue differentiation is intricately regulated by a complex interplay of genetic factors and epigenetic mechanisms involving enzymes that modify histones, DNA methyltransferases, transcription factors (TFs), and microRNAs (miRNAs) [48]. Polyphenols play a critical role in controlling epigenetic modifications such as histone alterations, DNA methylation, and DNA demethylation. These processes are regulated by enzymes, including HDACs, HATs, and HMTs [49]. Histone acetylation is facilitated by enzymes known as histone acetyltransferases (HATs). HATs such as CBP/P300, MYST (MYST1, MYST2, TIP60), and GNAT (GCN5, PCAF, Hat1) regulate gene expression and chromatin structure. Changes in HAT levels with age influence epigenetic patterns and disease susceptibility. HATs also determine cell fate in response to environmental conditions such as cold-induced beige adipocytes adopting brown adipocyte-like H3K27ac patterns, whereas warmth induces patterns resembling white adipocytes, defining adipocyte identity [50, 51]. Age-related decreases in H3K9ac impair the browning of WAT, whereas TIP60 levels increase in aging skeletal muscle, impacting PPARγ and adipogenesis. Resveratrol mitigates the effects of aging by increasing H3K9ac and H3K27ac levels (Fig. 4) [52].

Unlike histone acetyltransferases (HATs), histone deacetyl transferases (HDACs) operate differently. HDAC1, HDAC2, and HDAC3 promote adipogenesis by facilitating the development of adipose cells, likely by suppressing genes that hinder adipocyte differentiation. The extent to which resveratrol inhibits human HDACs belonging to classes I and II depends on the dosage administered [53]. Aging is characterized by specific CpG islands experiencing increased methylation alongside general DNA hypomethylation across the genome. DNA methyltransferases (DNMTs) are enzymes that add methyl groups to the 5' cytosine residues in CpG dinucleotides, leading to the formation of 5-methylcytosine (5-mC). This methylation process typically results in gene silencing, especially when it occurs at gene promoters. In brown adipocytes, deleting Dnmt1 reduces myogenic genes and enhances fat accumulation by increasing SREBP1C expression during adipogenesis, whose activity is reduced by curcumin. Dnmt3a influences FGF21

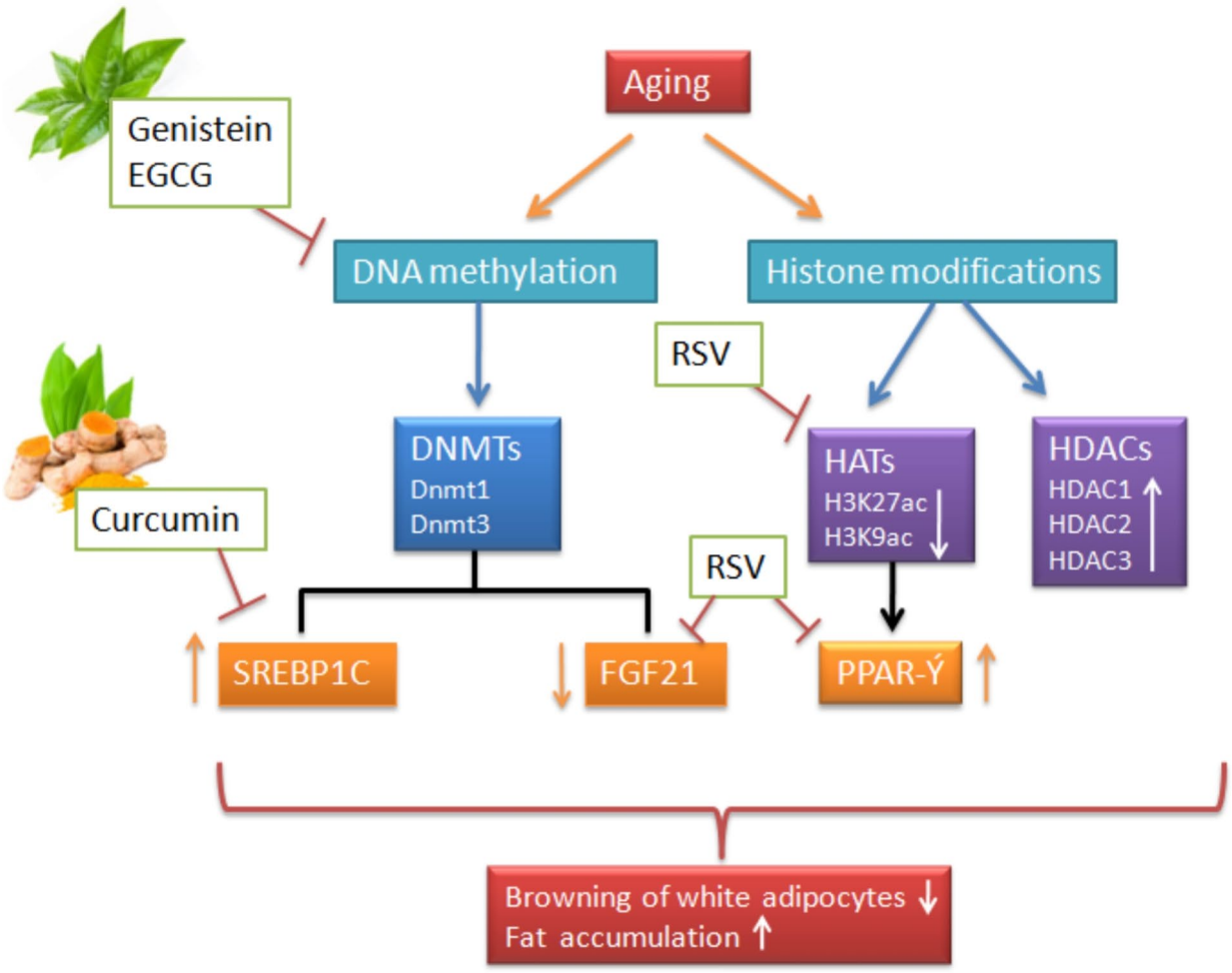

Fig. 4 Shows that aging induces epigenetic changes such as DNA hypermethylation, which can be inhibited by EGCG and genistein. Resveratrol counteracts the histone modifications caused by aging. These epigenetic alterations disrupt molecular pathways, but polyphenols have the potential to modulate these pathways and protect against fat accumulation in the body

regulation in adipocytes [54, 55]. Dnmt3a primarily acts as a gene repressor, targeting several adipocyte-specific genes, such as Fgf21. It contributes to insulin resistance, at least partially, by adding methyl groups to specific cis-regulatory regions of the Fgf21 gene, thereby inhibiting its expression [56]. Resveratrol modifies NRF2 pathway methylation to lower oxidative stress and fat accumulation. Conversely, dietary polyphenols such as genistein and EGCG potentially reverse DNA hypermethylation and restore silenced genes, necessitating further investigation for clinical application (Fig. 4) [57, 58].

Polyphenols as inhibitors of the TGF-β signaling pathway

The TGFβ superfamily consists of more than 33 members that have various functions in adipose tissue physiology. The SMAD2/3 pathway is triggered by ligands such as TGF-β, promoting the growth of adipose progenitor cells but impeding their differentiation into mature adipocytes. On the other hand, ligands such as Bone Morphogenetic Protein (BMP) encourage adipogenesis by activating the SMAD1/5/8 pathway. Myostatin, activin A, and TGFβ are examples of TGFβ-like ligands that not only prevent white adipocyte differentiation but also impede the development of brown and brite (beige) adipocytes. However, BMP7 is essential for the growth of brown adipose tissue.

Within WAT, BMP4 has been shown to stimulate the differentiation of brite adipocytes [59, 60]. Aging is a natural biological process, and recent research has established connections between TGF-β signaling and aging-related phenomena. Lin et al. reported that serum TGF-β1 levels increase with age. An increase in TGF-β signaling pathway activity with increasing age can influence the equilibrium between BAT and WAT and impact

the differentiation of MSCs derived from bone marrow and adipose stromal cells (ASCs) [61]. EGCG treatment inhibited the activity of the TGF/SMAD pathway (Fig. 3) [62]. Aging significantly enhances the activity of p38 MAPK, C-Jun terminal kinase, and ERK, which is correlated with the ROS concentration. Through its anti-MAPK action, EGCG reduces inflammation in various cell types and protects against TNF-α-induced cytotoxicity by blocking p38 MAPK1 (Table 1) [63]. Oxidative stress can activate the TGF-β signaling pathway. Elevated ROS levels lead to senescence and DNA damage. There is substantial evidence supporting the interconnection between ROS and TGF-β. TGF-β1 increases ROS production, potentially by suppressing the expression of antioxidant enzymes. Mesenchymal stem cells (MSCs) need to commit to adipogenesis for preadipocytes to mature into adipocytes, which are essential for the production of adipocytes from MSCs [64]. By activating SIRT3, resveratrol suppresses the TGF-β/Smad3 pathway. Reduced oxidative stress and ROS generation are achieved by the downregulation of TGF-β1 and Smad3 expression by quercetin and EGCG [65–67].

TGF-β plays an important role in both initiating and perpetuating the senescent state, actively participating in Senescence-Associated Secretory Phenotype (SASP) secretion; proinflammatory factors secreted by senescent cells [67]. EGCG can restore autophagic activity in cells treated with TGF-β1, indicating that autophagic regulation is a key mechanism by which EGCG affects TGF-β1-induced transformation. EGCG has the potential to slow cellular aging and the inflammatory processes induced by senescence (Table 1) [68].Studies consistently demonstrate that older individuals have significantly higher levels of active TGF-β1 in their plasma than their younger counterparts do. TGF-β signaling effectively regulates cellular senescence by activating pathways such as p21, p15, and p27 while concurrently suppressing critical proliferation factors such as c-Myc [69]. Ellagic acid (EA), which is abundant in pomegranates, muscadine grapes, walnuts, and strawberries, is a polyphenol flavonoid that inhibits abnormal cell division and induces programmed cell death (apoptosis). Research suggests that EA may exert these effects by influencing the TGF-β/Smad signaling pathway, potentially leading to cell cycle arrest in laboratory settings [70, 71]. Understanding how aging affects TGF-β signaling in adipogenesis is crucial for uncovering the mechanisms involved in age-related metabolic disorders and for exploring potential therapeutic strategies.

Polyphenols inhibit senescent cell accumulation

The buildup of senescent cells is a major factor driving inflammation and dysfunction in adipose tissue with increasing age. Cellular senescence, a critical mechanism of aging, induces persistent inflammation and dysfunction within adipose tissue. Various internal and external factors, such as DNA damage, shortened telomeres, oncogenic mutations (such as Ras, B-Raf, and Myc), and environmental stressors (such as unfolded proteins and protein aggregation), can contribute to the buildup of senescent cells [72]. Resveratrol, curcumin, quercetin, and EGCG are polyphenols known for their senolytic effects, as evidenced by several studies [73, 74] (Table 1). They mitigate oxidative stress, reduce inflammation, and inhibit telomere shortening while simultaneously enhancing DNA repair mechanisms and selectively eliminating senescent cells [75, 76]. As adipose-derived stem cells (ADSCs) age, they exhibit reduced expression of CD105. The primary regulator driving the buildup of senescent cells is p53. Inhibiting p53 via compounds such as polyphenols encouraged senescent cells to re-enter the cell cycle [77]. Resveratrol induces cell senescence through the p53–p21 pathway, which is associated with both senescence and prolonged cessation of the cell cycle, alongside the p16/Rb pathway [78]. DNA damage triggers the upregulation of ATM/p53/p21 signaling. ADSCs progressively lose their replicative capacity before reaching cellular senescence, characterized by increased expression of senescence markers such as p16INK4a, p21Waf1, and caveolin-1. The activation of p16INK4a via p38 MAPK signaling potentially contributes to cellular senescence. Additionally, upon activation, p53 MAPK is implicated in age-related functional changes in ADSCs, which compromise mitochondrial function [79]. Several polyphenols, such as procyanidin C1, resveratrol, and curcumin, possess antiaging properties by modulating the p53/p21cip1 and p16INK4A/Rb tumor suppressor pathways [80]. Cellular senescence in preadipocytes results in significant functional changes, including reduced adipogenesis, decreased proliferation, and increased release of proinflammatory cytokines and enzymes that modify the extracellular matrix. Progenitor cells are also adversely affected by senescent preadipocytes, leading to their own senescence. Persistent elevation of proinflammatory molecules such as IL-6, TNF-α, IL-1β, COX-2, and iNOS characterizes chronic inflammation, contributing to the onset of cellular senescence and perpetuating a cycle of proinflammatory activity. Senescent cells in adipose tissue release SASP factors, which include proinflammatory molecules such as chemokines and cytokines. As age increases, the ability to clear senescent cells diminishes, leading to increased inflammation in tissues [81]. Polyphenols such as naringenin, quercetin, EGCG, fisetin, hesperidin, hesperetin, rutin, kaempferol, apigenin, luteolin, and procyanidin C1 have demonstrated antiaging properties by potentially modulating SASP factors or their effects, operating at various stages either upstream or downstream. These effects have been consistently

observed in numerous in vitro and in vivo studies [82, 83].

Various molecular mechanisms that influence the regulation of the SASP have been discovered, indicating possible therapeutic targets for addressing age-related diseases. Senescent cells activate C/EBPβ and NF-κB, leading to increased mRNA expression of SASP components. The JAK/STAT pathway, which is crucial for adipose tissue development, function, and SASP regulation, can partially inhibit SASP secretion when it is blocked [84]. The ability of quercetin to directly inhibit proinflammatory pathways such as the 1/2 (ERK1/2)/(JNK)/P38 (MAPK) and P13K/AKT/glycogen synthase kinase 3 pathways enhances its potential in addressing aging-related conditions (Table 1). It also targets key regulators such as NF-κB and inducible nitric oxide synthase, leading to a reduction in cytokine levels. This regulatory effect helps mitigate the self-amplifying inflammatory cascade commonly associated with degenerative and chronic conditions triggered by the SASP [85]. Future research should focus on accurately delineating the detrimental effects of the SASP and cellular senescence, given their complex roles in aging [74].

Polyphenols enhance AMPK Signaling

AMPK signaling critically regulates cellular homeostasis, the stress response, cell survival, proliferation, apoptosis, and autophagy. Studies have consistently shown that activating AMPK can mitigate aging and increase longevity in diverse organisms. AMPK plays crucial roles in the fundamental metabolic processes associated with aging. AMPK inhibits the NF-κB, mTOR, and CRTC-1 signaling pathways. As sensitivity to AMPK activation diminishes with age, it can lead to decreased cellular autophagy, heightened cellular stress, and increased inflammation [86]. Moreover, this decrease may disturb the equilibrium of energy metabolism and accelerate the onset of metabolic diseases related to aging [87]. A decrease in AMPKα activity in adipocytes has been shown to impair adaptive thermogenesis and the response to cold exposure. Specifically, reduced AMPKα activity in adipocytes selectively decreases the synthesis of thermogenic proteins induced by cold in iWAT. This reduction in thermogenic protein production results in decreased energy expenditure and increased adipocyte size, underscoring the critical role of adipocyte AMPKα in promoting browning of iWAT [88]. Genistein activates AMPK, leading to reduced expression of C/EBPα, apoptosis in mature adipocytes, inhibition of P38 MAPK phosphorylation, and prevention of adipocyte development. Polyphenols activate the AMPK signaling pathway, thereby blocking the AMPK–Gfi1–OPN axis pathway and subsequently preventing adipogenesis [89, 90]. Aging leads to reduced AMPK responsiveness, and enhanced oxidative damage, decreased cellular stress resilience, and impaired autophagic clearance mediated by mTOR, potentially due to the downregulation of pathways such as p53 and DAF-16/FoxO [91]. The Nrf2/SKN-1, FoxO/DAF-16, and SIRT1 signaling pathways are stimulated when AMPK is activated, which increases cellular stress resistance. Lychee seeds activate the AMPK/mTOR/ULK1 pathway, which in turn triggers autophagy. Protocatechuic acid (PCA) increases the expression of genes linked to longevity, including sir-2.1 and daf-16 [92, 93]. Resveratrol activates AMPK, thereby enhancing the effectiveness of the ROS defense mechanism [94] (Table 1). In vitro research has shown that AMPK phosphorylates human FoxO1 at Thr649, leading to the upregulation of catalase and manganese superoxide dismutase transcription by FoxO1 [95]. The increased expression of UCP1 suggested that the activation of AMPK and PGC-1α promoted differentiation into the brown-fat lineage (Fig. 3). Flavonoids likely participate in this process by enhancing AMPK activation [96]. By activating the AMPK/PPARγ pathway, quercetin increases UCP1 expression, suggesting increased activity in BAT and browning of WAT [97].

Reducing or eliminating the activity of the AMPK β1 and β2 subunits specifically in adipose tissue worsens insulin resistance, affecting the function of both WAT and BAT. On the other hand, genetically removing both the AMPK α1 and α2 subunits from adipose tissue decreased fat accumulation by increasing lipolysis and fatty acid oxidation within the tissue. Specifically, reduced AMPKα activity in adipocytes significantly affected mitochondrial function and biogenesis in both BAT and iWAT but not in eWAT. This resulted in an increase in adipocyte size in BAT and iWAT, whereas the size remained unchanged in eWAT [98]. Resveratrol activates AMPK through LKB1 to promote mitochondrial biogenesis (Fig. 3). In aged rats experiencing muscle atrophy due to a high-fat diet, resveratrol alleviates mitochondrial dysfunction and oxidative stress through the LKB1/AMPK pathway. These findings indicate that AMPK signaling is essential for maintaining the overall health of adipose tissues as aging progresses [99].

Polyphenols inhibit oxidative stress

An imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract them with internal antioxidants leads to oxidative stress [100]. Aging is a multifaceted biological process characterized by a gradual decline in physical function and increased susceptibility to chronic diseases. This process is also associated with cellular and tissue damage. As we age, our antioxidant defenses weaken, ROS production increases, and ATP production decreases [101]. Elevated ROS levels result in oxidative stress, which significantly damages proteins, lipids, DNA, organelle membranes,

and cells, thereby contributing to the overall aging process [102]. In adipose tissue, oxidative stress can lead to impaired adipocyte function, altered secretion of adipokines, and increased insulin resistance [103, 104]. Oxidative stress can cause damage to tissues and trigger inflammation. The antioxidant effectiveness of polyphenols is influenced by their structure. Hydroxyl groups are essential for their antioxidant actions, such as binding metal ions and neutralizing free radicals [105]. Quercetin activates the Nrf2 pathway, increasing the expression of antioxidant peroxiredoxins and providing protection against oxidative stress (Table 1) [106]. The accumulation of ROS impedes adipose tissue growth, contributing to increased fat deposition and a heightened risk of IR. Oxidative stress in adipose tissue triggers lipid peroxidation, resulting in the accumulation of reactive aldehydes such as 4-hydroxynonenal (4-HNE), a bioactive byproduct of lipid peroxidation. Elevated levels of 4-HNE induce structural and functional cellular damage by forming stable adducts with DNA, phospholipids, and proteins [107]. Resveratrol treatment prevented DNA fragmentation and apoptosis induced by 4-HNE. EGCG reduced the formation of free radical adducts, including 4-HNE adducts [108]. Oxidative stress in adipose tissue promotes secretion of pro-inflammatory adipokines and exacerbates insulin resistance in adipocytes by disrupting intracellular signaling [109, 110]. It also reduces adiponectin synthesis while increasing the production and release of MCP-1, IL-6, leptin, and TNF-α by adipocytes. Polyphenols such as EGCG, quercetin, and resveratrol effectively inhibit MCP-1, TNF-α, and IL-6 by inhibiting the MAPK and NF-κB signaling pathways (Table 1) [111–113].

Obesity arises from a long-term imbalance between energy consumption and expenditure, leading to the excessive expansion of WAT depots. WAT serves as the primary organ for fat storage, making adipocyte macromolecules vulnerable to carbonylation and other oxidative modifications. Prolonged oxidative stress adversely affects the homeostatic and endocrine functions of WAT [114]. This includes disruptions in hormone secretion, elevated blood cholesterol levels, inadequate cellular antioxidant defenses, and compromised mitochondrial function. BAT, which is crucial for non-shivering thermogenesis due to its high energy expenditure, is considered vital for systemic metabolism. However, with increasing age, both the mass and activity of BAT decline progressively. Oxidative stress induces functional and molecular changes in BAT. However, the consumption of resveratrol may stimulate the activation of BAT and browning of WAT [114]. Oxidative stress-induced reductions in adipogenesis can cause the enlargement of mature adipocytes and the subsequent release of free fatty acids, a phenomenon known as lipotoxicity. Additionally, adipocyte hypertrophy is associated with a shortened lifespan. Exploring strategies to mitigate naturally occurring low-level oxidative stress with age is essential for promoting adipogenesis and preventing the accumulation of harmful hypertrophic adipocytes while favoring beneficial adipocyte hyperplasia [115, 116].

Polyphenols reduce PPAR-γ transcription factor activity

PPARγ is widely recognized as the primary regulator of adipogenesis. Its essential role is evident, as other factors cannot initiate adipogenesis without its presence, making ectopic expression of PPARγ in fibroblasts sufficient to start the process. PPARγ significantly influences adipocyte biology and lipid metabolism, impacting differentiation, lipid storage, and the conversion of white fat to brown fat. To combat obesity associated with increasing age, natural compounds such as kaempferol regulate the expression of PPARγ [117]. Kaempferol, a polyphenol, has demonstrated efficacy in reducing lipid accumulation associated with obesity. This occurs through increased expression of PPARδ, PPARα, and their target genes, which promotes autophagy and increases fatty acid uptake. Furthermore, kaempferol influences key signaling pathways related to obesity and metabolic disorders, resulting in lower levels of PPARγ and SREBP-1c [118]. PPARγ agonists stabilize the PRDM16 protein, promoting the transformation of WAT into brown-like adipocytes. This mechanism supports the thermogenic capacity of beige adipocytes by enhancing the interaction within the PPARγ/PRDM16 complex. Compared with those in BAT, the PRDM16 levels in iWAT, the origin of beige fat cells, decrease with age. Specifically, reduced PPARγ expression in the subcutaneous fat of 12-month-old aging mice contributes to increased body weight and insulin resistance. This is attributed to disrupted energy balance and accelerated loss of the browning effect in white fat [119]. Quercetin enhances browning of WAT and activates BAT by stimulating the β3-adrenergic receptor (β3AR), as well as the PKA/AMPK/PPARγ/PGC1α pathways (Table 1). This leads to increased expression of UCP1 and ABCA1, promoting ATP synthesis and inhibiting fat accumulation [120]. With increasing age, the phosphorylation of PPARγ at Ser273 increases, potentially altering its interaction with cofactors and directing its metabolic pathways toward genes associated with brown fat characteristics. Additionally, a decrease in SRC-1 expression is observed with age in both human and rodent adipose tissues, which could disrupt the function of the PPARγ/SRC-1 complex in regulating adipogenic activity and insulin sensitivity [121]. Curcumin stimulates PPARγ production, which in turn regulates insulin sensitivity and glucose homeostasis while also reducing the levels of inflammatory cytokines. SREBP1 enhances adipogenesis by increasing

PPARγ activity and regulating the expression of LPL and FAS. CREB stimulates lipid accumulation by upregulating PPARγ and FABP [122]. Hesperidin inhibits PPARγ, SREBP1-C, and perilipin, demonstrating antiadipogenic and delipidating effects (Fig. 3). These components are critical for lipolysis and lipogenesis [123]. By suppressing adipogenesis-related genes, including PPARγ and C/EBPα, EGCG prevents preadipocyte maturation (Fig. 3) [124].It is crucial to investigate how PPARγ and its cofactors behave during aging and their impact on the loss of adipose tissue function, given the metabolic changes that occur in adipose tissues with age and the critical role that PPARγ plays in adipocyte function.

Polyphenols decreases C/EBP transcription factors activity

As age increases, the capacity of preadipocytes to mature into fully functional adipocytes decreases due to reduced levels of adipogenic transcription factors such as PPARγ, C/EBPδ, and C/EBPα and increased levels of antiadipogenic factors such as CHOP and C/EBPβ-LIP, which are elevated by stress factors, including metabolic dysfunction, cytokines, and DNA damage [125]. Increased levels and activity of CUGBP1 in aged preadipocytes cause impaired differentiation and diminished adipose tissue function. As a result, reduced adipogenesis leads to dysfunction in fat cells, a smaller fat depot, and the redistribution of fat to nonadipose tissues. The possible opposing effects of polyphenols on these molecular pathways are not yet fully understood [126]. Abdominal obesity, which is often associated with aging, significantly contributes to insulin resistance and metabolic syndrome. It is a major risk factor for the development of T2D and insulin resistance. By reducing early adipogenic transcription signals, the ensuing transcriptional cascade can be disrupted, thereby limiting terminal adipogenic differentiation [127].Consequently, inhibiting C/EBPβ has emerged as a promising strategy for treating or preventing obesity. Genistein has been shown to inhibit FAS, SREBP 1, and aP2 in primary human adipocytes, whereas cis-guggulsterone downregulates C/EBPβ, C/EBPα, and PPARγ2 [128, 129]. Recent studies suggest that guggulsterone enhances its antiobesity effects by stimulating mitochondrial biogenesis, encouraging the formation of beige adipocytes, and increasing UCP1 expression and cellular oxygen consumption [130]. In white adipose tissue (WAT), EGCG has been found to lower plasma lipid levels and body weight; decrease the expression of C/EBPα, PPARγ, SREBP1, LPL, and FAS; and increase the levels of genes important for β-oxidation, lipolysis, and thermogenesis. On the other hand, resveratrol significantly reduces fat accumulation and decreases the expression of LPL, FAS, C/EBPα, and SREBP-1c by activating AMPK (Fig. 3). Research suggests that aging diminishes the ability of preadipocytes to proliferate, replicate, and resist apoptosis. However, practical applications for potential medications are lacking, necessitating further in vivo studies [122].

Polyphenols enhance Sirtuins' activity

Sirtuins are class III histone deacetylases (HDACs) characterized by their reliance on NAD + for catalytic activity. Studies have demonstrated that SIRT1 levels decrease with age, probably because of lower NAD + availability. A shortage of SIRT1 results in increased expression of genes related to aging [131]. SIRT1 is essential for managing adipose tissue through multiple pathways. It promotes lipolysis by activating AMPK, suppressing PPARγ, and encouraging FOXO1 to produce ATGL. Additionally, it hinders adipogenesis by facilitating the binding of CACUL1 to the PPARγ-responsive region, which in turn regulates PPARγ. In aged AT-MSCs, a lack of SIRT1 encourages the formation of beige adipocytes through the p53/p21 pathway. Additionally, SIRT1 decreases the number of lipid droplets by inhibiting the proper expression of PPARγ2 and C/EBPα in stem cells derived from visceral adipose tissue [132]. In experiments using epicatechin, mice presented reduced plasma triglyceride levels and increased expression of SIRT1, PGC-1α, and UCP1 in WAT [133]. Resveratrol directly engages with the SIRT1 isoform, boosting protective effects by influencing antioxidant responses (Table 1) [134]. Additionally, polyphenols like resveratrol, and quercetin have been found to induce processes such as browning in WAT through a mechanism dependent on SIRT1 [135]. SIRT2 plays a crucial role in regulating adipose tissue metabolism. By deacetylating FOXO1, SIRT2 facilitates its binding to PPARγ, thereby halting the differentiation process and reducing adipogenesis. Additionally, SIRT2 promotes lipolysis by deacetylating PGC-1α, an essential protein for lipid breakdown [136]. Resveratrol reduces the expression of PPARγ, FAS, and Bcl-2 at both the mRNA and protein levels. Moreover, it enhances the expression of SIRT1, AMPKα, FOXO1, HSL, LPL, caspase-3, and Bax [137]. SIRT3 plays a pivotal role in promoting the differentiation of brown adipocytes by increasing the levels of PGC-1α, a crucial protein for the growth of brown fat cells. Additionally, SIRT3 suppresses the AMPK-ULK1 pathway, which in turn reduces both the size and concentration of lipid droplets. SIRT3 inhibits the dampening of inflammatory responses by NLRP3. Furthermore, a deficiency in SIRT3 diminishes FOXO3a, which facilitates the development of adipocytes [138]. Resveratrol activates SIRT3 (Table 1). Resveratrol treatment facilitates the phosphorylation of FOXO3, thereby maintaining its localization in the cytoplasm [139]. SIRT4 interacts with transcription factors such as HOXA5, E2F-1, and C/EBPβ to promote adipocyte development. By deacetylating MCD and thereby inhibiting FAO, SIRT4

enhances lipogenesis [140]. Resveratrol has been shown to increase SIRT4 levels, demonstrating antiaging and antiapoptotic effects. Conversely, SIRT5 inhibits MAPK and activates AMPK, leading to decreased adipocyte differentiation, lipid synthesis, and deposition. A deficiency in SIRT5 reduces the browning of adipose tissue and increases lipolysis [141]. SIRT6 enhances lipolysis by reducing PPARγ signaling, suppresses inflammation by inhibiting the NF-κB pathway, and limits adipocyte development through AMPKα activation. A deficiency in SIRT6 diminishes the browning of adipose tissue, impairs adipogenesis, and inhibits lipolysis by affecting FOXO1 regulation [142]. Resveratrol has significant therapeutic potential as an activator of both SIRT5 and SIRT6.Polyphenols may increase the activity of sirtuins and promote longevity by altering their pathways throughout aging [135].

Polyphenols activate wnt signaling pathway

Wnt signaling inhibits the expression of PPARγ and C/EBPα, thereby preventing preadipocytes from undergoing differentiation. In 3T3-L1 preadipocytes, Wnt signaling disrupts adipogenesis by reducing the levels of C/EBPα and PPARγ and influencing the cell cycle. Conversely, adipogenic differentiation is facilitated by the suppression of Wnt signaling. GSK3β directs the breakdown of β-catenin during adipogenesis, which inhibits Wnt signaling [143]. Wnt signaling promotes the nuclear translocation and stabilization of β-catenin, which subsequently inhibits PPARγ and C/EBPα, crucial steps that halt the adipogenic process. The aging process in organisms, particularly mammals, is characterized by the deterioration of multiple organ systems and a reduced capacity for regeneration. In aged mice, muscle regeneration, which is typically poor, was improved by blocking canonical Wnt signaling. These findings suggest that aging may be connected to a decline in tissue stem cell function and diminished tissue regeneration, potentially due to factors in the serum of older organisms that activate Wnt signaling in a manner similar to that of Wnt itself [144]. The Wnt pathway plays an important role in mitigating age-related changes, which is beneficial for maintaining health as age increases. Resveratrol, through its action mediated by Sirt1, activates the Wnt/β-catenin signaling pathway (Table 1) [145]. Wnt signaling regulates preadipocytes by maintaining them in an undifferentiated state, thus preventing adipogenesis through the modulation of C/EBPα and PPARγ. Wnt signaling achieves this by inhibiting the induction of C/EBPα and PPARγ, which are crucial regulators of adipogenesis. Conversely, disruption of Wnt signaling either through internal mechanisms (such as constitutive Axin expression) or external factors (such as recombinant sFRP1/2) causes preadipocytes to spontaneously differentiate into adipocytes. In addition to its role in adipogenesis, Wnt signaling is pivotal in determining the fate of mesenchymal stem cells (MSCs). The activation of Wnt signaling suppresses adipogenesis while promoting myogenesis, which involves the formation of muscle tissue [146]. EGCG increased β-catenin levels while suppressing key genes involved in adipogenesis (Fig. 3). This pathway is crucial for the ability of EGCG to prevent fat accumulation. EGCG reduces triglyceride buildup, suppresses C/EBPα and PPARγ expression, promotes AMPK phosphorylation, increases the expression of Wnt signaling genes, and stimulates thermogenesis and energy expenditure [147]. Genistein also inhibits adipogenesis by activating the Wnt pathway through ERK/JNK signaling and LEF/TCF4 coactivation, processes dependent on estrogen receptors (Table 1). Polyphenols like EGCG, quercetin, resveratrol are known to activate Wnt signaling pathways in older individuals, helping to regulate adipogenesis and maintain a healthy balance of fat tissue, thereby preventing excessive fat accumulation associated with aging [148].

Polyphenols increases anti-inflammatory adipokines

Human serum contains a significant amount of adiponectin, a crucial anti-inflammatory adipokine. Adiponectin plays a vital role in promoting adipogenesis and expanding adipose tissue through hyperplasia, which enlarges fat pads, reduces inflammation, and maintains glucose balance. PPARγ agonists enhance adiponectin synthesis and inhibit the production of inflammatory cytokines, such as IL-18, IL-6, and TNF-α, by blocking NF-κB activation [149]. While adiponectin levels typically increase with age, age-related obesity can decrease its secretion, contributing to insulin resistance and T2D. Adiponectin has beneficial effects on diabetes and atherosclerosis through its receptors, AdipoR1 and AdipoR2. EGCG provides antiobesity benefits in humans by reducing ghrelin release and increasing adiponectin levels (Table 1) [150]. Supplementation of rats with catechins increased protein expression and elevated plasma levels of adiponectin and other anti-inflammatory adipokines in adipose tissue. In a study using 3T3-L1 cells, TNFα administration decreased adiponectin secretion, whereas treatment with catechins significantly and dose-dependently increased adiponectin secretion. Catechin supplementation has also been shown to improve insulin sensitivity-related metabolic factors and reduce inflammation [151]. Additionally, chlorogenic acid has been demonstrated to increase adiponectin levels in visceral fat and increase the protein expression of AdipoR2 [152]. Vaspin, a newly identified adipokine from visceral fat, is strongly linked to insulin resistance and obesity. It plays a critical role in regulating lipid and carbohydrate metabolism, improving insulin sensitivity, and reducing inflammation. Vaspin also enhances lipid accumulation within cells and

upregulates the expression of key differentiation factors, such as FABP4, C/EBPα, and PPARγ. Obesity associated with aging decreases vaspin levels in the serum. Vaspin promotes 3T3-L1 preadipocyte differentiation. In diabetic rats, treatment with RVS (an intervention or treatment method) decreased the expression of vaspin genes in adipose tissue (Table 1) [153].

Complications related to aging-associated adipogenesis

Aging is the primary risk factor for diabetes, cancer, heart disease, stroke, and many chronic illnesses. As age increases, fat shifts from subcutaneous areas to abdominal and ectopic sites such as the liver and muscles, with an increase in adipose tissue during middle age followed by a decline later. This redistribution, particularly the accumulation of fat beyond the subcutaneous layer, is strongly associated with dyslipidemia and insulin resistance, and obesity significantly increases the risk of NAFLD [154]. When subcutaneous adipose tissue reaches its expansion limit, there is increased mobilization of FFAs, leading to fat accumulation at visceral and ectopic sites. One such ectopic site is muscle, where elevated FFA levels promote insulin resistance (IR) by impairing insulin-mediated glucose uptake [155].

Insulin resistance in adipose tissue promotes lipolysis, which increases the flow of free fatty acids (FFAs) to the liver, leading to hepatic insulin resistance and the production of glucose, new lipids, and very low-density lipoproteins (VLDLs), as well as contributing to atherogenic dyslipidemia. The twin cycle hypothesis suggests that FFAs cause β-cell failure in the pancreas through lipotoxicity, resulting in hyperglycemia and diabetes. Elevated liver fat also causes hepatic glucagon resistance, affecting amino acid metabolism and leading to hyper aminoacidemia, whereas reactive oxygen species (ROS) in adipose tissue, produced by mitochondrial oxidative phosphorylation, xanthine oxidase, and NADPH oxidase, contribute to inflammation, protein carbonylation, and disrupted adipokine secretion, particularly in elderly and obese individuals (Fig. 5) [155].

Adipose tissue influences vascular health by releasing bioactive substances, particularly through PVAT. In aging-related obesity, oxidative stress in PVAT disrupts the balance between relaxing and contracting factors, leading to increased vasoconstriction and vascular dysfunction [156]. The interaction between the heart and epicardial adipose tissue (EpAT) is governed by intricate bidirectional mechanisms. Adipokines released from EpAT affect heart function, while the heart influences EpAT through reverse paracrine signaling. Elevated oxidative stress in EpAT can contribute to cardiac issues, and adipokines also alter the electrophysiological properties of the atria, such as action potential duration and the activity of sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) in atrial cardiomyocytes, impacting the risk of arrhythmias (Fig. 5) [157].

Age is the primary risk factor for osteoarthritis (OA), and adipokines such as adiponectin, resistin, visfatin, and chimerin, along with inflammatory cytokines, play a role in OA development and progression, suggesting that exploring the interaction between adipose tissue and cartilage could offer new treatment options for OA and related metabolic disorders (Fig. 5) [158]. Additionally, the risk of osteoporosis increases with age. Adipokines are produced by both WAT and the CNS, which house receptors for these molecules. Adipokines are generated in peripheral tissues that can cross the BBB or influence its physiology by interacting with the cells that compose the BBB. Adipokines are essential for modulating neuroinflammation and oxidative stress, two critical processes linked to neurodegeneration and chronic neurodegenerative diseases [159]. To reduce the risk of age-related metabolic illnesses, maintaining healthy adipogenesis and proper adipose tissue function is crucial. These complications highlight the intricate effects of aging on adipose tissue.

Conclusion and outlook

This review highlights the intricate relationships among aging, body composition, and metabolic health. Age-related changes in fat distribution, muscle mass, and adipose tissue function play significant roles in the development of metabolic disorders in older adults. Disruptions in adipogenesis increase the risk of metabolic diseases. Modifying one's lifestyle can significantly delay age-related diseases. One effective strategy is incorporating polyphenol-rich fruits and vegetables into diet. Polyphenols, owing to their varied effects on inflammation, oxidative stress, mitochondrial function, and signaling pathways, hold promise for addressing sarcopenia. However there are some limitations in current research. Like long-term studies on the safety and efficacy of polyphenols are necessary so that polyphenols can be evaluated for effective anti-aging intervention. Further research is needed to clarify their mechanisms and determine the best dosages for managing adipogenesis in aging populations. The dosage and bioavailability of polyphenols are critical factors in achieving therapeutic effects. Future research should focus on determining optimal dosages and enhancing bioavailability to ensure that polyphenols can effectively exert their beneficial impacts on aging and metabolic health. Addressing these factors will be crucial for translating research findings into practical dietary recommendations and therapeutic applications.

Investigating specific signaling pathways, epigenetic factors, and cellular aging in adipose tissue could provide insights for targeted treatments. Additionally, exploring

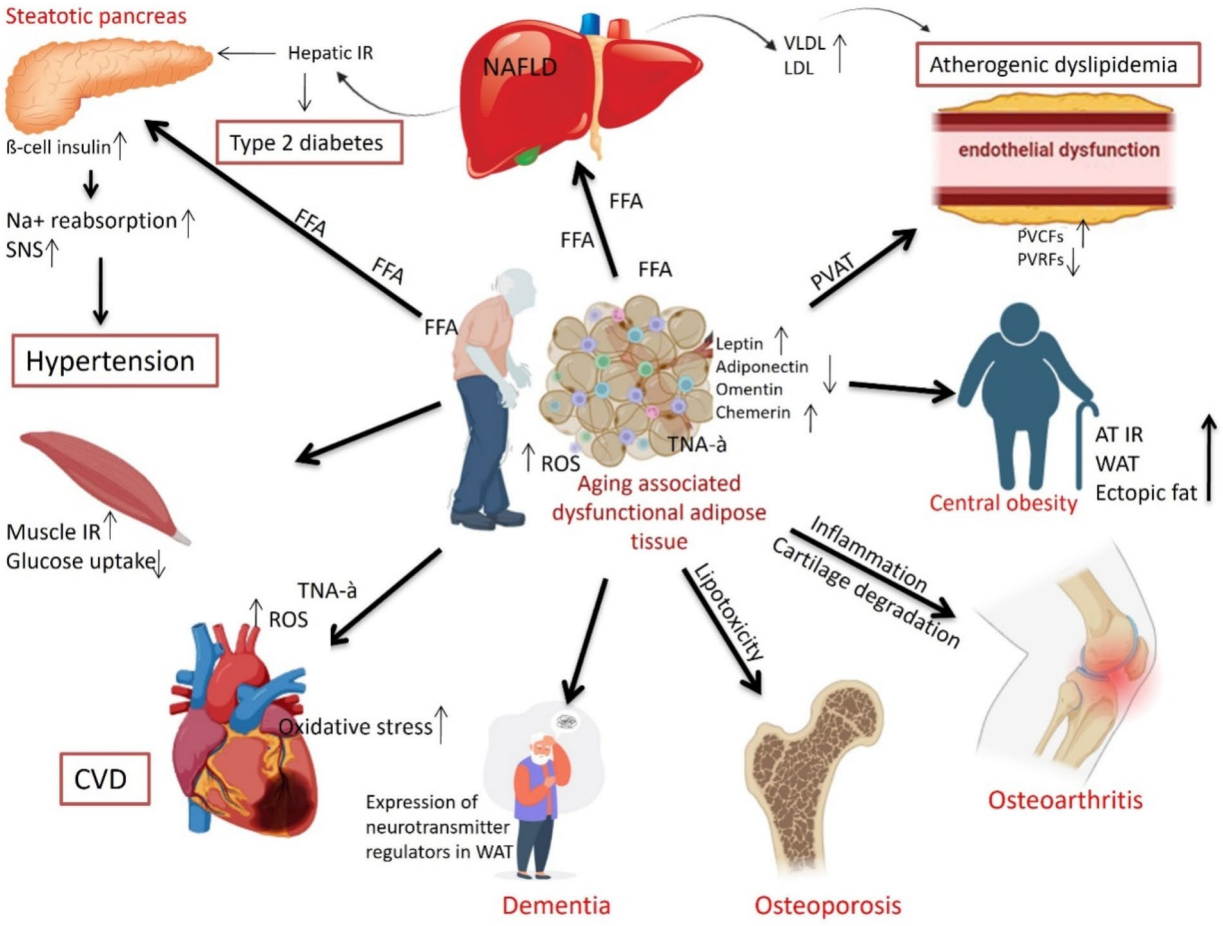

Fig. 5 Shows that aging-related dysfunction in adipose tissues contributes to metabolic issues by increasing the levels of proinflammatory adipokines and FFAs. These FFAs lead to NAFLD and contribute to hepatic and muscle insulin resistance. Additionally, they promote B-cell proliferation, increase Na + reabsorption, and contribute to hypertension. Endothelial dysfunction also occurs due to inflammatory adipokines, while increased ROS production damages cardiovascular health and cartilage and contributes to conditions such as osteoarthritis and osteoporosis. Furthermore, aging disrupts neurotransmitter balance in WAT, potentially contributing to dementia

new compounds such as senolytics and AMPK modulators may reveal innovative approaches for mitigating age-related metabolic disorders. Understanding how these compounds interact with adipose tissue, muscle mass, and metabolic processes could lead to effective strategies for promoting healthy aging and preventing metabolic diseases in older adults. Future research will advance our knowledge of age-related metabolic changes and help develop personalized interventions to improve health outcomes for elderly individuals.

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Declarations

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