Review

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Review

Cognitive-Enhancing Effects of Bioactive Compounds and Traditional Herbal Medicines in Elderly Patients with Metabolic Syndrome

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Abstract

Aging is a multifactorial process that leads to progressive physiological changes characterized by senescence, cellular loss, and organ decline, which accelerate the development of metabolic syndrome (MetS) in elderly individuals. MetS, in turn, not only significantly increases the risk of developing cardiovascular disease (CVD) but also contributes to decreased functional and cognitive capacity due to the inability of elderly patients to adopt with metabolic stress. While genetic predisposition has a substantial influence on the risk of developing MetS, other intrinsic factors, including chronic inflammation, insulin resistance (InsR), and altered neurohormonal activation, also play crucial roles. Targeted therapies, lifestyle interventions, and pharmacotherapy can decelerate the progression of CVD, increasing the likelihood of survival with good neurologic and functional outcomes among elderly individuals with MetS. However, drug adverse reactions and the lack of adequate interventions for cognitive decline have led to the emergence of self-medications with nonprescription medicines. The anti-inflammatory, antioxidant, anti-channelopathy, antiaging, and neuroprotective properties of flavonoids, alkaloids, polysaccharides, and polyphenols found in key traditional medicines showed promising data in the treatment of MetS-induced cognitive decline. Thus, the objective is to provide a comprehensive review of bioactive compounds and herbal medicine that show promising cognitive benefits for elderly patients with MetS.

Keywords: insulin resistance; oxidative stress; cellular senescence; vascular complications; vascular dementia; channelopathies; adipose tissue dysfunction; inflammatory pathways; hepatic steatosis; skeletal muscle insulin resistance

1. Introduction

The older population has been growing globally from 1960 to 2024, although at varying levels, according to recent reports published by the United Nations (UN) Population Division [1] and the United States Census Bureau [2]. The global number of people aged 65 years and older is projected to double within the next thirty years.

Older adults are at increased risk of developing multiple chronic metabolic diseases, which are strongly associated with cognitive decline [3,4]. Poorly controlled metabolic diseases and longer disease duration significantly elevate illness risk and are major drivers of vascular cognitive impairment [5]. These conditions disrupt the structural and functional integrity of the cerebral microcirculation [6], promoting microvascular rarefaction [7] and contributing to both micro- and macro-vascular dysfunction, as well as impaired neurovascular coupling [8]. Together, these alterations lead to dysregulated cerebral blood flow and nutrient delivery, resulting in neuronal injury and accelerated cognitive decline. Chronic metabolic diseases also compromise blood–brain barrier integrity, triggering neuroinflammation [9], a key contributor to cognitive deterioration.

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Cognitive impairment in individuals with metabolic diseases is a multifaceted phenomenon and a well-recognized contributor to poor health outcomes among the global elderly population, influencing how the body utilizes essential metabolites and transitions from a healthy, well-functioning state to a chronic and debilitating disease.

This review critically delves into the pathophysiology and clinical significance of metabolic disease–induced comorbidities and emphasizes their role in cognitive decline, with the aim of consolidating current understanding of how these conditions are linked to the most common cause of cognitive impairment. It explores the significant role of metabolic diseases in the context of fading cognitive function, highlighting current knowledge on how metabolic disorders affect cognitive function and the associated challenges. We intend to offer a roadmap for identifying research gaps and outlines opportunities for potential clinical translation.

In this study, PubMed, Scopus, Google, and Google Scholar were searched in tandem to identify core mechanisms involved in MetS and herbal medicines used to improve their functionality. Google was included because of its broad search capabilities for locating various document types, such as conference papers, patents, government reports and statistics. The major keywords used to perform the search were as follows: herbs or supplements for improving lipid distribution and metabolism; alleviating InsR and boosting insulin sensitivity; lessening oxidative stress damage; suppressing hepatic inflammation; ectopic fat deposition; fibrosis; improving mitochondrial dysfunction; strengthening blood vessels and improving circulation problems; aging; cognitive decline; and dysregulated intestinal flora.

This review also summarizes a thorough grasp of the current treatment landscape of traditional medicines for metabolic disease–mediated cognitive decline, evaluates their emerging global roles, and highlights their evidence-based integration approaches, including potential molecules derived from traditional medicines that are currently undergoing clinical trials. The review specifically aims to provide a comparative analysis of representative traditional medicines from different regions that show promise in treating metabolic disease–mediated cognitive deterioration.

2. An Overview of Insulin Function and Its Role in Metabolism

Metabolism is primarily regulated by hormones of the autonomic nervous system and other contributing factors, highlighting the highly interconnected nature of physiological systems. Insulin, a key metabolic hormone, orchestrates glucose distribution, lipid metabolism, and protein synthesis through complex interactions involving multiple positive and negative feedback mechanisms (Figure 1). These tightly regulated processes are essential for maintaining the functional integrity of various tissues and organs.

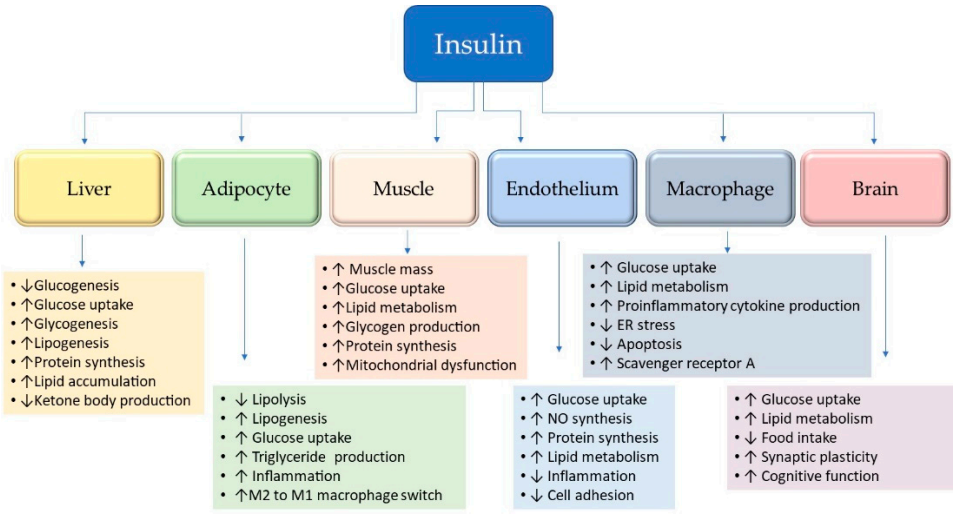

Figure 1. schematic presentation of insulin action on multiple tissues.

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Insulin exerts its effects through interactions with insulin receptors (IRs), which can be nuclear-associated [10,11] or act through classical phosphorylation-dependent signaling pathways [11]. IRs exist in two main isoforms, A and B, which have similar affinities for insulin but differ in their affinities for insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2) [12,13]. Upon insulin binding, IRs undergo conformational changes that promote the formation of stable dimers and subsequent signal transduction [14].

Insulin functions not only as a vasodilator but also as an anti-inflammatory agent. These effects are mediated in part by nitric oxide (NO) release and inhibition of the transcription factor nuclear factor-κB (NF-κB). Impaired insulin signaling alters cellular responses through dysregulation of phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, both of which depend on tyrosine phosphorylation of insulin receptor substrates 1 and 2 (IRS-1 and IRS-2). Among insulin's metabolic actions (Figure 1), the PI3K-dependent pathway mediates vasodilatory and anti-inflammatory effects via activation of NO synthase, whereas the MAPK pathway promotes mitogenic effects, leading to cell growth and proliferation. In InsR, activation of the PI3K pathway is impaired while the MAPK pathway is enhanced, shifting the balance toward the pro-atherogenic actions of insulin and contributing to metabolic disorders.

Glucose, the primary metabolic substrate, is utilized by most human cells to varying extents. Its uptake is largely insulin-dependent, underscoring the critical role of insulin signaling across multiple tissues. Disruption of this signaling impairs glucose influx into cells. In addition, insulin can rapidly modulate metabolism through receptor-mediated interactions with several intracellular signaling molecules, including forkhead box O (FOXO) proteins to regulate glucose production [15]; tuberous sclerosis complex 2 (TSC2), which forms a complex with TSC1 (negative regulators of insulin signaling [16]) to initiate lipid and protein synthesis [17]; glycogen synthase kinase 3 beta (GSK3β) to promote glycogen synthesis [18,19]; and TBC1 domain family member 4 (TBC1D4) to enhance glucose uptake [20,21]. Through these pathways, insulin-mediated IR activation plays a central role in metabolism, growth, and cellular proliferation [4]. Importantly, because IRs exert tissue-specific effects, the functional integrity of local IR tissue is critical in determining the overall physiological outcome of insulin action in a given tissue (Figure 1).

Although the precise underlying mechanisms of InsR remain incompletely understood, several major contributing factors have been identified. These include reduced expression or functional impairment of both IR isoforms, leading to decreased insulin sensitivity; impaired insulin secretion [22]; disruption of intracellular signaling pathways [23]; oxidative stress [24]; chronic inflammation [25]; and mitochondrial dysfunction characterized by a reduced ATP production-to-oxygen consumption ratio [26], mitochondrial DNA damage, and altered mitochondrial biogenesis and dynamics [27]. Endoplasmic reticulum stress has also been implicated [22]. InsR may develop physiologically with aging [28,29] but can also be exacerbated or induced by pathological conditions. For a comprehensive review of insulin signaling mechanisms, insulin-induced IR-mediated actions, and their physiological roles, readers are referred to the following publications [10,11,17,30].

3. Cognitive Deterioration in the Context of Metabolic Diseases

MetS, also known as InsR syndrome, has evolved from a Western phenomenon into a pressing global healthcare problem, affecting 12.5% to 31.4% of adults worldwide [31]. While the global burden of MetS remains a dilemma, it is thought to arise from bidirectional causal associations between abnormal remodeling of specific adipose tissue depots (e.g., visceral adipose tissue accumulation), disruptions in skeletal muscle and hepatic tissues, and endothelial dysfunction (Figure 2). InsR and the biochemical responses of of insulin-target organs play a significant role in the pathogenesis and clinical course of MetS [32,33].

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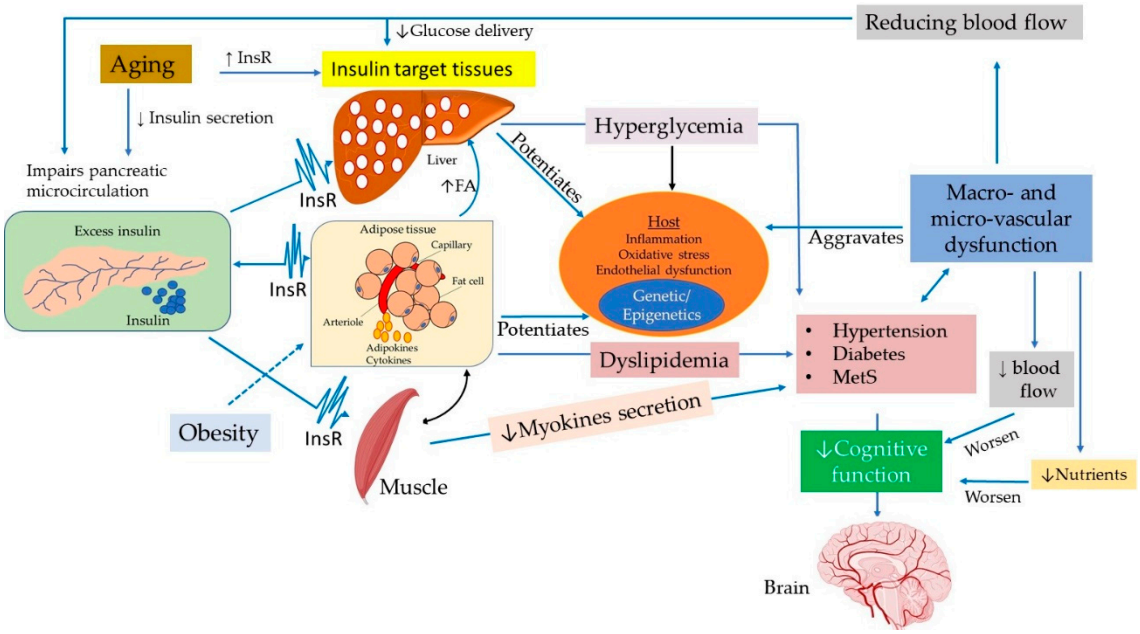

Figure 2. Schematic presentation of the pathophysiological mechanisms linking MetS (MetS) to cognitive decline. As InsR develops in major insulin-target tissues due to intrinsic and modifiable factors, multiple pathological processes are triggered. These include inflammation, oxidative stress, impairment of endothelial functional integrity, epigenetic alterations, hyperglycemia and dyslipidemia, and reduced myokine secretion. These processes collectively contribute to the development of hypertension, diabetes, and MetS, which predispose individuals to cognitive decline and promote the progression of endothelial-related diseases, including macro- and microvascular dysfunction. Vascular dysfunction further exacerbates hypertension, diabetes, and MetS, accelerates cognitive decline, and aggravates dysfunction of insulin-target tissues and the pancreas, establishing a vicious cycle. While aging reduces insulin secretion from pancreas and increases InsR due to fat accumulation, obesity is also associated with the development of InsR and impaired cognitive function. Muscle and brain images were created using BioRender. Akhlaghi, S. 2026. https://app.biorender.com/illustrations/6969c48d00f26499747783a7.

It is well established that obesity is an unusually heterogeneous medical condition [34]. Although obesity is associated with several life-threatening comorbidities [35], not all obese individuals develop these conditions. Genetic variants, as well as environmental and psychosocial factors, have been proposed to markedly influence the prevalence of overweight and obesity [36]. The combined effects of body fat distribution and abnormal remodeling of adipose tissue depots are major correlates of perturbed physiological pathways, leading to imbalances in inflammatory and anti-inflammatory processes, adipokines, and key regulators of metabolism, inflammation, and cardiac and skeletal muscle function and growth, all of which significantly influence health and disease.

The release of fatty acids from adipocytes is hormonally regulated: glucagon stimulates, whereas insulin inhibits, fatty acid release from adipose tissue. In the presence of InsR, dysfunctional adipocytes persistently allow the release of a non-optimal supply of fatty acids into the circulation. Once in the bloodstream, fatty acids are delivered to skeletal muscle (a major insulin target tissue) [37], cardiac muscle, and the liver. Elevated mobilization of fatty acids contributes to obesity-associated metabolic complications and excess lipid deposition as lipid droplets within hepatocytes, which can promote the development of chronic liver diseases such as metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD) (Figure 2). Elevated InsR is associated with chronic liver disease, a pathophysiological hallmark of hepatogenous diabetes [38].

Both hepatic and adipocyte InsR potentiate oxidative stress, inflammation, and endothelial dysfunction in the host [39,40], while perpetuating dyslipidemia and hyperglycemia (Figure 2). A

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decline in muscle mass due to InsR impairs glycogen production and reduces the secretion of myokines, an insulin sensitizing effects [41], thereby further exacerbating InsR [42–44]. Most importantly, myokines have anti-inflammatory, a role in maintaining the homeostasis of the brain microenvironment and blood-brain barrier integrity [45], anti-atrophic role [46,47], and cardiovascular protective effects, which can potentially help counteract the complications of metabolic diseases. Consequently, dysfunctional responses in insulin-target organs can not only trigger failure in downstream organs in a domino-like effect, but also reflect and exacerbate systemic conditions that predispose individuals to hypertension, diabetes, and MetS, a phenomenon that becomes more pronounced with aging [48]. Notably, both diabetes [49] and hypertension increase incidence of cognitive impairment and dementia. In parallel, they promote the progression of endothelial-related diseases, including macro- and microvascular dysfunction. Vascular dysfunction further exacerbates hypertension, diabetes, and MetS, accelerates cognitive decline, and aggravates dysfunction of insulin-target tissues and the pancreas, establishing a vicious cycle.

There are undoubtedly additional pathophysiological features of insulin-resistant tissues beyond those described above. Insulin signaling involves intricate interactions with diverse cellular functions, and numerous signaling pathways have been identified as impaired under insulin-resistant conditions.

4. The Complex Interplay Between the Individual Components of the Metabolic Syndrome

MetS is an umbrella term encompassing a diverse yet interconnected set of metabolic dysregulations that exhibit spatial and temporal variability and progress silently across multiple organ systems. The severity of MetS is influenced by numerous intrinsic and modifiable factors.

MetS is commonly observed not only in individuals with central obesity and reduced high-density lipoprotein (HDL) levels, but also in those presenting with any two of the following metabolic abnormalities: hypertriglyceridemia, hyperglycemia, and high blood-angiotensin II (Ang II). This highlights the significant roles of triglycerides [50], insulin [51], and angiotensin-related molecules [52] in their respective target tissues. Each of these components, and the potential role of ion channels in the development of InsR, impaired insulin signaling and inflammation are discussed in the following sections. A schematic representation of the topics along with their respective potential biomarkers covered in the following two sections is shown in Figure 3.

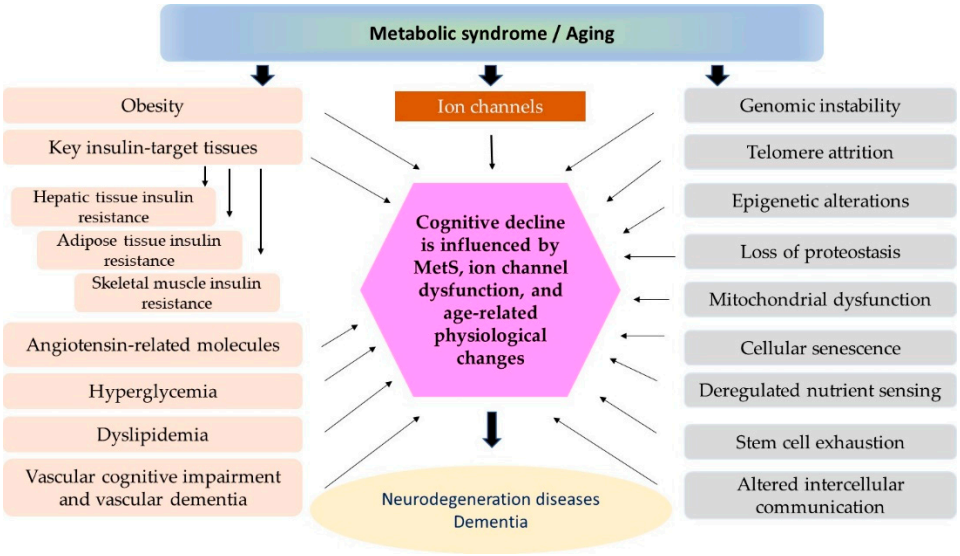

Figure 3. A schematic representation of factors contributing to MetS-induced cognitive decline.

4.1. Obesity and Metabolic Syndrome

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Obesity is commonly defined by body mass index (BMI), which is considered as a proxy parameter of adiposity. Elevated BMI is associated with an increased risk of CVD [53]. However, individuals with identical BMI values may display substantial variability in body fat distribution. Susceptibility to preferential fat accumulation in subcutaneous versus visceral depots is influenced, in part, by genetic predisposition [54,55]. Individuals with increased visceral adipose tissue exhibit a range of metabolic abnormalities, including atherogenic dyslipidemia, hyperinsulinemia, and glucose intolerance [56].

Excess visceral adiposity may form from adipose tissue dysfunction, genetic factors, or hormonal imbalances, such as elevated estrogen levels [57] combined with reduced testosterone levels [58,59] in both women and men. Notably, obesity is a risk factor for, but not an absolute requirement in, the diagnosis of MetS. A subset of individuals classified as obese are metabolically healthy, exhibiting normal blood pressure, lipid profiles, insulin sensitivity, and cardiovascular risk [60–62]. These individuals typically present with lower levels of visceral adipose tissue and ectopic fat deposition [63]. Furthermore, evidence suggests that overweight and obese individuals with established chronic disease may experience a more favorable prognosis than their normal-weight counterparts, a phenomenon often designated as the “obesity paradox” [64].

BMI is not included as a variable in cardiovascular risk prediction models such as the Framingham Risk Score or the Pooled Cohort Equation [65], underscoring the limitations of BMI as a standard measure of cardiometabolic risk. Although obesity prevalence varies among populations, age does not appear to be a major determinant in the development of obesity [66]. The relative distribution of subcutaneous and visceral adipose tissue varies considerably between individuals [67]. While most cases of obesity are polygenic in nature, rare monogenic disorders directly lead to obesity, including Bardet–Biedl syndrome and Prader–Willi syndrome.

A strong association exists between increased waist circumference (a surrogate marker of intra-abdominal or visceral adiposity) and cardiometabolic as well as CVD risk, even among individuals with normal-weight obesity [68]. At the molecular level, obesity-associated InsR is driven in part by reduced insulin receptor availability and impaired insulin signaling pathways.

4.2. Key Insulin-Target Tissues

4.2.1. Hepatic Tissue InsR

In the liver, ongoing wound healing and InsR can lead to the progression of MASLD, which is a major cause of liver-related morbidity, including hepatic steatosis, previously known as fatty liver infiltration [69] (Figure 2). The liver is capable of repair and regeneration.

Hepatic macrophages are heterogeneous [70], with unique dynamics and functions [71]. A subpopulation of hepatic macrophages promotes fibrosis through the recruitment of proinflammatory immune cells [72]. Hepatic macrophages also play a significant role in resolving fibrosis through extracellular matrix degradation, as well as through the production of anti-inflammatory mediators and growth factors [73].

If unresolved, this condition leads to hepatic inflammation and fibrosis, progressing to cirrhosis [74], a phenomenon known as the transition from MASLD to metabolic dysfunction–associated steatohepatitis (MASH), the advanced stage of MASLD. MASH is mainly mediated by inflammation, oxidative stress, and dysbiosis [74]. Moreover, factors such as obesity and dyslipidemia are associated with the progression of MASLD to MASH [75].

MASH is a complication of type 2 diabetes mellitus (T2DM) [76] and occurs in approximately 37% of the global T2DM population [77]. MASH is considered a progressive form of fatty liver disease [78] with a bidirectional association with metabolic dysfunction [79]. MASH results from impaired glucose metabolism, hypertension, and atherogenic dyslipidemia [75]. It has been speculated that insulin InsR may be associated with the development and progression of MASLD [80]. Dyslipidemia-induced InsR appears to promote the development of MASLD.

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Fetuin-A, a hepatokine, is implicated in obesity, InsR, T2DM, MetS, and MASLD [81,82]. It is considered a risk factor for diabetes and fatty liver disease in individuals with normoglycemia or prediabetes [82]. Elevated levels of fetuin-A disrupt insulin signaling not only by inducing injury to pancreatic β cells but also, more significantly, by impairing the translocation of GLUT4 in insulin target tissues [79]. In contrast, reduced fetuin-A levels diminish FFA availability, promote triglyceride uptake in adipose tissues, and highlight the importance of fetuin-A's role in protecting against the development of InsR. It is reasonable to suggest that the reduction in fetuin-A levels may prevent the accumulation of visceral adipose tissue by modulating macrophage polarization[83], which has a pro-inflammatory action.

4.2.2. Adipose Tissue InsR

Insulin is involved in metabolic regulation, cellular communication, cellular aging theories, and neuroendocrine signaling. It influences processes governing lipid metabolism via insulin–related mechanisms and is deeply involved in nutrient partitioning and satiety–associated signaling within the organism.

Adipose tissue regulates systemic energy metabolism through not only adipokine production (Figure 2) but also energy storage, which is fundamental for ensuring the energy supply to other organs such as skeletal muscle and liver during the fasted state. Its dysfunction contributes to a plethora of metabolic disorders, influencing several systems in parallel. Because of this, the relationship between adipocytes and insulin–mediated receptor activation remains important [30], where it is frequently examined for its molecular interactions and physiological consequences within the organism in the absence of InsR.

InsR contributes to the development of hypertension, dyslipidemia, macro- and microvascular complications, and metabolic dysfunction–associated alterations in the size and function of adipose tissue (Figure 4). Evidence indicates that altered adipose tissue reduces insulin's effects, leading to adipose tissue remodeling due to immune cell infiltration and inflammation. Macrophage play important roles in the maintenance of tissue homeostasis [84]. During immune cell infiltration and inflammation, even though adipose tissue macrophages are heterogeneous [85], a population of adipose tissue macrophages switches from an M2 (rely on both tricarboxylic acid and oxidative phosphorylation), insulin-sensitive phenotype to an M1 (relay on glycolysis), an InsR phenotype [86,87]. This condition can result in cardiovascular and metabolic pathologies, including obesity. The loss of the insulin-sensitive phenotype results in the secretion of pro-inflammatory cytokines, including TNF–α, IL–1β, and IL–6. While the mechanism by which inflammation initiates in adipose tissue remains debated, inflammation-induced InsR is generally well recognized.

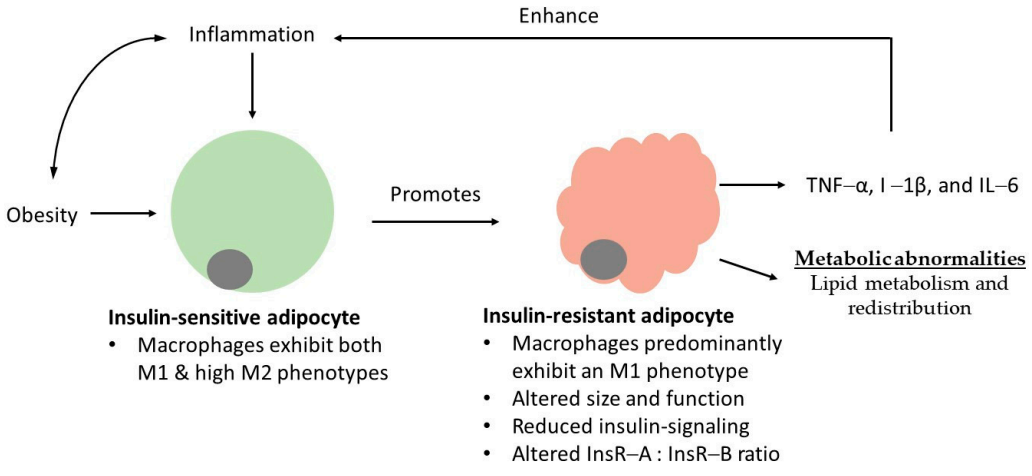

Figure 4. A schematic representation of the events occurring in an insulin resistant adipocyte.

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The link between obesity and InsR has been shown [88]. Moreover, obesity appears to alter the size and function of adipose tissue [89]. Because of the bidirectional relationship between obesity and InsR, the causal direction between them is difficult to establish. An observational study suggests that obesity is a strong determinant of InsR [90]. Insulin plays fundamental roles in the normal physiology of adipose tissue via insulin receptors, namely InsR–A and InsR–B. Alterations in the InsR–A:InsR–B ratio appear to be responsible for metabolic abnormalities (e.g., lipid metabolism and redistribution) during the onset of InsR [91]. Similar to waist circumference, visceral fat mass is a predictor of cardiometabolic risk among hypertensive men over the age of 40 [92]. Contrary to these findings, African Americans have lower visceral fat compared with their White counterparts [93,94], yet appear to exhibit greater InsR [95,96]. Interestingly, studies repeatedly show that adults with InsR can be non-obese and exhibit neither increased intra-abdominal fat nor elevated circulating markers of inflammation [97–99]. Thus, it is feasible to suggest that InsR may precede obesity.

In conclusion, chronic inflammation in adipose tissue and reduced insulin–related mechanisms resulting from adipose tissue remodeling appear to contribute to the development of InsR and to influence each other. The molecules described in the following paragraphs can potentially be used as biomarkers to evaluate the effectiveness of biomolecules derived from tradition herbal medicines in mitigating MetS complications.

Visfatin

While visfatin, an adipocytokine, is expressed in hepatocytes, adipose tissue, kidney, and heart, it is predominantly released from macrophages in response to inflammatory signals [100]. Visfatin, also known as an extracellular form of nicotinamide phosphoribosyitransferase (eNampt) or pre-B cell colony-enhancing factor (PBEF, a cytokine), catalyzes the synthesis nicotinamide mononucleotide (NMN) from nicotinamide in a mammalian nicotinamide adenine dinucleotide (NAD) biosynthetic pathway [101]. Heterozygous Nampt females exhibit reduced eNampt and NMN levels [102]. The author suggests that Nampt-mediated systemic NAD biosynthesis is a key of beta cell function. Evidence further indicates that the heterozygous visfatin gene phenotype is associated with glucose intolerance due to impaired insulin secretion, which can be corrected by administration of NMN, a precursor in NAD biosynthesis. Moreover, NMN has been reported to protect against diabetes, endothelial dysfunction, and inflammation [103]. NMN is present in numerous foods, including mushrooms, and may represent a potential dietary source.

Visfatin has insulin-mimetic activity and proinflammatory effects, which can not only influence glucose metabolism but also increase inflammation [104]. Increased serum visfatin levels are associated with endothelial dysfunction [105,106] and beta-cell function impairment [107]. Visfatin appears to play a key role in regulating insulin sensitivity in the liver [108]. Its reduction in MASH patients is associated with steatohepatitis [109]. It is elevated in individuals with obesity [110] and T2DM [111]. Polymorphisms of visfatin are linked to an increased risk of MetS [112]. Recently, it has been proposed that visfatin could serve as a potential biomarker for chronic kidney disease [113]. Collectively, there is sufficient evidence supporting a causal effect of obesity, diabetes, and MetS on circulating visfatin concentrations.

Fetuin-A

Fetuin-A, a multifunctional negatively charged glycoprotein, circulates in the blood as well as in extracellular fluid and is capable of inhibiting insulin signaling both in vivo and in vitro [114,115]. There is a direct relationship between plasma fetuin-A levels and T2DM. Fetuin-A, a cysteine protease inhibitor, is produced in numerous cell types, including adipocytes and monocytes/macrophages [83]. However, it is predominantly synthesized in the adult liver [116] and secreted into the bloodstream. Fetuin-A undergoes phosphorylation in the circulation [117]. Phosphorylated plasma fetuin-A appears to counteract both the insulin signaling pathway and ectopic calcification [118,119].

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Fatty pancreas and fatty liver, along with adipocytes, cause elevation of fetuin-A, leading to inflammation through several biological mechanisms and subsequent reduction in insulin secretion [120,121]. Fetuin-A also aggravates IR by inducing its secretion from the pancreas, promoting macrophage migration [122] and transformation into the M1 phenotype [123], thereby creating a vicious cycle. Fetuin-A, serves as a chemoattractant, also appears to transform anti-inflammatory (M2) macrophages into the inflammatory (M1) phenotype [124]. This cysteine protease inhibitor is considered to have both anti-inflammatory and pro-inflammatory features and is important in the metabolic dysfunction of MASLD [125,126]. Fetuin-A contributes to the pathogenesis of components of MetS, including IR, T2DM, CVDs, MAFLD, and ischemic stroke [127,128].

Since evidence supporting a direct link between fetuin-A and the components of MetS is strong, the levels of this hepatic protein could be used as clinical predictor of MetS and to evaluate the effectiveness of bioactive compounds derived from traditional herbal medicines.

Vaspin

Vaspin, a serine protease inhibitor, is ubiquitously expressed in various tissues, including visceral adipose tissue [129], liver, and pancreas [130], and skeletal muscle [131]. It inhibits serine proteases and is found at higher levels in obese individuals with T2DM. Underweight children appear to have markedly lower vaspin levels compared with controls [132]. Individuals carrying the vaspin rs617574459 or rs77060950 polymorphisms exhibit either deficient circulating vaspin levels [133] or markedly increased serum levels, respectively [134].

Vaspin is actively involved in improving glucose intolerance and enhancing insulin sensitivity in aged skeletal muscle [131], as well as reducing the synthesis of pro-inflammatory cytokines. Studies indicate that vaspin plays a crucial role in endothelial cell function by protecting these cells from fatty acid–induced apoptosis through the PI3K/Akt (also known as protein kinase B)/endothelial nitric oxide (eNOS) signaling pathway. It also contributes to maintaining cellular homeostasis by attenuating inflammation and oxidative stress associated with metabolic disorders, partly through inhibition of tissue kallikrein–induced kinin generation. In addition, vaspin suppresses vascular cell proliferation and migration by downregulating the c-Jun N-terminal kinase (JNK) and extracellular signal-related kinases 1 and 2 (ERK1/2) pathways, while promoting collagen synthesis via activation of the PI3K/Akt pathway. Taken together, vaspin, as a potential biomarker, reduces the synthesis of proinflammatory cytokines, improves glucose intolerance and insulin sensitivity and protects the vascular tissues from fatty acid-induced apoptosis. For a detailed overview of the roles and mechanisms by which vaspin protects the vascular tissues from fatty acid-induced apoptosis, readers are referred to previous reviews [135,136].

Skeletal muscle InsR

Skeletal muscle plays a key role in whole-body glycemic control, a process that depends on insulin signaling and the presence of functional glucose transporters within muscle tissue [137]. Recent studies have greatly advanced our understanding of these mechanisms, as summarized in a previous review [138]. In this section, we summarize current evidence regarding skeletal muscle InsR, with particular focus on its contribution to MetS.

Following contraction, skeletal muscle becomes more sensitive to subsequent insulin stimulation, which elicits distinct and highly regulated effects mediated by complex signaling cascades. Evidence indicates that activation of the *SIRT2* and *FBXW5* genes in muscle, which are involved in lipid metabolism, autophagy, and the mechanistic target of rapamycin (mTOR) signaling, is correlated with insulin sensitivity [139]. Briefly, insulin-mediated insulin receptor tyrosine kinase signaling induces the activation of endothelial insulin receptor substrate 2 (IRS2) triggers downstream signaling pathways that lead to the production of NO. The formed NO promotes relaxation of arterial smooth muscle, causing vasodilation, increased blood flow, and enhanced capillary perfusion. Endothelial cell-specific IRS2 knockout mice exhibit impaired signaling pathways in pancreas, including glucose-, arginine-, and glucagon-induced insulin secretion, due to

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reduction in islet blood flow [140]. During insulin stimulation, this increase in muscle capillary perfusion enhances the delivery of both insulin and glucose to skeletal muscle [141], thus maintaining interstitial glucose concentrations and supporting overall glucose uptake. For a detailed overview of the mechanisms by which insulin promotes glucose uptake and the molecular mechanisms of InsR in skeletal muscle, readers are referred to previous reviews [138,142].

Pancreatic desensitization results in decreased insulin secretion following prolonged exposure to nutrients such as glucose and free fatty acid, or to pharmacological stimuli that interfere with insulin release or calcium influx [143]. Desensitization of muscle tissue to chronic increased blood glucose levels contributes to InsR and exacerbate skeletal muscle atrophy and dysfunction [144]. Evidence indicates that skeletal muscle InsR develops prior to the onset of β-cell failure and the development of symptomatic T2DM [37]. Insulin-stimulated glucose uptake in skeletal muscle InsR is reduced. Importantly, skeletal muscle InsR is a reversible condition. Skeletal muscle InsR and InsR signatures have been reported in both normoglycemic individuals and those with T2DM [145,146], supporting the concept that InsR is an initiating factor in the pathogenesis of T2DM. As skeletal muscle is the primary site of insulin-stimulated glucose uptake in humans, it is considered a major contributor to systemic InsR [146]. Reductions in skeletal muscle mass have been identified as a predictor of InsR progression in older adults [147]. Hyperinsulinemic–euglycemic clamp studies demonstrate delays not only in insulin action but also in glucose uptake in both normoglycemic individuals and patients with T2DM [148].

While skeletal muscle is a target for insulin, it is increasingly recognized as an endocrine organ that produces myokines and bioactive peptides with autocrine, paracrine, and endocrine effects [44]. Dysfunctional skeletal muscle contributes to the development and progression of MetS such as obesity, T2DM, and sarcopenia through impairment of these endocrine function.

Here, we focus on myokines that are intimately relevant to the progression of MetS, including irisin, myonectin, and IL-6 (myokine IL-6) (Figure 2) [149]. For a detailed overview of the history, functions, and mechanisms by which myokines may respond to energy deficit and help preserve muscle mass during MetS, readers are referred to previous reviews [149,150].

Irisin

While irisin reduces inflammation, it also converts white tissue adipose (WAT) into brown or beige adipose tissue [151–153], thus enhancing energy expenditure and contributing to weight loss [136]. Irisin-induced adipocyte browning suppresses adipogenesis [154], reduces cholesterol synthesis, and optimizes lipid oxidation. Importantly, irisin appears to enhance insulin signaling [155], not only by increasing insulin sensitivity and promoting the translocation of glucose transporters to the plasma membrane in insulin-dependent tissues, but also by improving components of MetS. Study supports the idea that irisin can serve as an indicator of metabolic stress and could be used to enhance early detection of cardiometabolic risk in dysglycemic populations [156].

Myonectin

Myonectin, a myokine predominantly expressed in skeletal muscle, contributes to the regulation of fatty acid uptake by stimulating adipose tissue and the liver, while also modulating hepatic gluconeogenesis. Muscle and liver are closely interconnected metabolic systems. Evidence indicates that IRS-2 is primarily involved in body growth, whereas IRS-1 is implicated in normal growth and the glucose-lowering effects of insulin [157]. Significant improvements in lipid profiles occur after bariatric surgery in severely obese individuals [158]. It has therefore been inferred that myonectin may regulate lipid metabolism [159] and muscle mass following bariatric surgery [160], which does not compromise muscle strength in humans [161]. Moreover, myonectin improves insulin sensitivity in the liver via IR–mediated IRS-2 activation and potentially in muscle through IR-mediated activation of both IRS-1 and IRS-2. Deletion of IRS-1 leads to InsR and impaired IR signaling in both muscle and liver [157]. Taken together, these studies suggest that myonectin may serve as an early biomarker of T2DM and MetS.

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Myokine IL-6

Among many IL-6 (myokine IL-6)-targeted tissues, adipose tissues, liver, and skeletal muscle are responsive during energy deficit, as they are the three major sites of energy distribution and metabolism [162]. Elevated myokine IL-6 levels released by skeletal muscles appear to induce insulin release through the glucagone-1-like peptide mediated effect [163]. Moreover, myokine IL-6 exerts anti-inflammatory effects [164] through transmembrane signaling capability mediated by the IL-6 receptor [165]. Myokine IL-6 promotes energy availability not only by stimulating lipolysis [166] and fatty acid oxidation, but also by enhancing gluconeogenesis [150], improving glucose uptake in multiple tissues including myocytes and white adipose tissues [136], and modulating inflammatory responses. Although redundant signaling pathways exist in IL-6-targeted tissues to respond to energy deficit, chronic elevated levels of myokine IL-6, as a regulator of energy metabolism, can adversely affect the skeletal muscle mass, exert proinflammatory effects, and subsequently promote muscle InsR. IL-6, as a biomarker, may be useful for assessing the effectiveness of herbs while monitoring the disease activity during MetS.

4.3. The Roles of Angiotensin-Related Molecules

Ang II, a circulating hormone, is the final metabolite of the renin–angiotensin–system (RAS). The RAS regulates a wide range of biological functions, including maintenance of blood pressure, electrolyte homeostasis, and fluid balance, thus ensuring adequate blood flow to organs and tissues. The RAS exists in two forms: a circulating RAS and a tissue–specific RAS, which is expressed in organs such as adipose tissue, the brain, and T cells (Figure 5). Dysregulation of tissue RAS expression or elevation of systemic Ang II contributes to multiple pathological conditions, including cardiovascular disease, T2DM, and renal fibrosis [167].

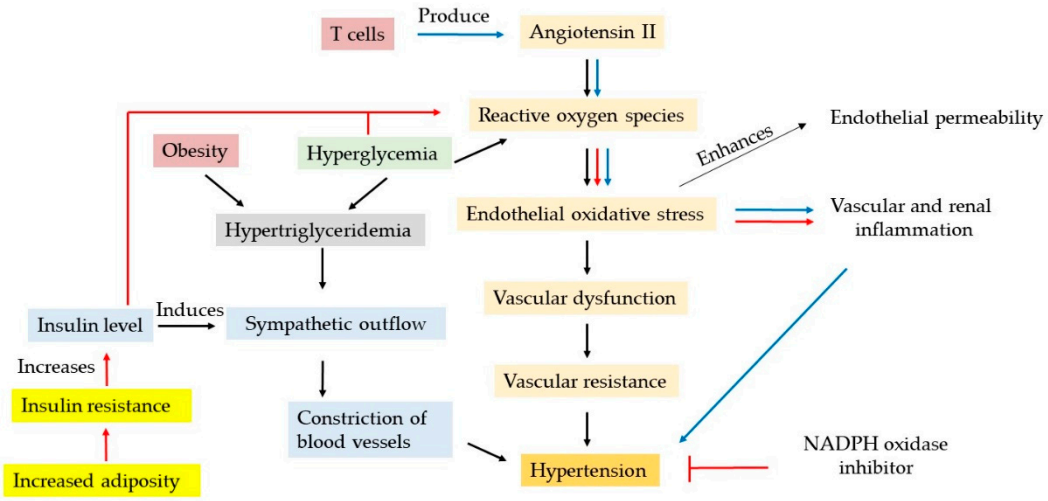

Figure 5. A schematic representation of the interrelationship among components of MetS leading to endothelial oxidative stress, increased endothelial permeability, vascular resistance, and vascular and renal inflammation.

Elevated circulating Ang II levels, T cell–derived Ang II, or hyperglycemia each enhance the production of reactive oxygen species (ROS), leading to cytosolic oxidative stress in endothelial cells through reduced NO bioavailability [168]. Oxidative stress not only causes vascular dysfunction but also increases endothelial permeability. Vascular remodeling, driven by persistent elevation of Ang II–induced oxidative stress [169], contributes to the onset and progression of increased vascular resistance and promotes hypertension, a key component of cardiometabolic syndrome. Other components of MetS, such as hyperglycemia– and obesity–induced hypertriglyceridemia further increase sympathetic outflow, resulting in vasoconstriction and hypertension. In addition, increased adiposity–associated InsR promotes compensatory insulin secretion, leading to hyperinsulinemia. Elevated insulin levels can induce hypertension via sympathetic activation and further exacerbate

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ROS production [170]. Taken together, hyperglycemia and dyslipidemia play integral roles in the development of vascular dysfunction and hypertension.

Although insulin is widely recognized for its anti-inflammatory effects, including suppression of proinflammatory proteins and inflammatory mediators [171], Ang II through both local and systemic actions can induce inflammation in critically ill patients regardless of age. Ang II promotes oxidative stress and activates immune cells upon binding to Ang II–responsive tissues [172,173], contributing to vascular and renal inflammation (Figure 5).

Ang II signaling via the angiotensin II type 1 receptor (AT1R), a key regulator of cellular function, activates multiple intracellular signaling pathways, including MAPK, ERK, and JAK/STAT, which also mediate the actions of several cytokines and insulin. For a detailed overview of the history, structure, and function of the RAS, readers are referred to previous reviews [173,174].

Furthermore, evidence indicates that upregulation of AT1R expression in the liver leads to dysregulated glucose and lipid metabolism and increased hepatic lipid accumulation [175]. Polymorphisms in genes encoding components of the RAS have been associated with increased susceptibility to MetS [176]. Consistently, hypertensive transgenic mice expressing the human AT1R haplotype are prone to developing MetS [177]. Notably, endothelial cells exhibit sexually dimorphic responses to Ang II exposure [178], which may contribute to the increased risk of CVD in women. Collectively, hyperglycemia and dyslipidemia appear to interact with elevated Ang II-induced hypertension leading to vascular injury that may further aggravate hypertension.

4.4. Vascular Cognitive Impairment and Vascular Dementia

While vascular cognitive impairment and vascular dementia can occur following a stroke, they may also result from damaged blood vessels and reduced circulation [179]. Endothelial-related diseases, macro- and microvascular dysfunction, are characterized by reduced distensibility of the arterial wall, vascular calcification, and increased arterial wall thickness. This abnormal functional and structural damage, when amplified by a cluster of metabolic disorders including hyperglycemia, prolonged elevation of angiotensin II which can contribute to a sustained increase in blood pressure, reduced circulating myokines, and dyslipidemia can disrupt vascular homeostasis. As a result, there is a significantly higher risk of vascular injury in the elderly population, which may manifest as heart disease, atrial fibrillation, venous thromboembolism, stroke, and organ damage, as well as cognitive decline involving progressive losses in memory, reasoning, and attention. This type of vascular cognitive impairment, known as subcortical ischemic vascular dementia, results from damage to the small blood vessels and nerve fibers within the brain's white matter.

Endothelial dysfunction has emerged as a significant contributor to the etiology of MetS, affecting various signaling pathways critical for physiological processes such as blood flow, inflammation, cell adhesion, and coagulation. It also plays an important role in the pathogenesis and progression of both diabetes [180,181] and hypertension [182]. Diabetes [183], hypertension [184,185], and potentially MetS [186] are major drivers of both microvascular and macrovascular complications, which share common risk factors and exhibit a bidirectional relationship (Figure 1).

Crosstalk between dysfunctional microvascular and macrovascular systems [187], along with subsequent structural vascular damage, reduces blood flow and nutrient delivery, including impaired pancreatic microcirculation and diminished glucose delivery to target organs. Elderly individuals with a combination of these conditions are at a significantly higher risk of cognitive decline.

5. Ion Channels Play an Important Role in the Development and Progression of MetS

5.1. Potassium Channels

Potassium ion (K^+) channels serve not only as key regulators of vascular smooth muscle cell membrane potential, but also help maintain cardiac rhythm stability. They are therefore important determinants of vascular smooth muscle contractility, vascular tone, and myocardial electrical

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activity. Both vascular endothelial cells and vascular smooth muscle cells express several types of K^+ channels [188], which contribute to vascular homeostasis through different mechanisms (Figure 6).

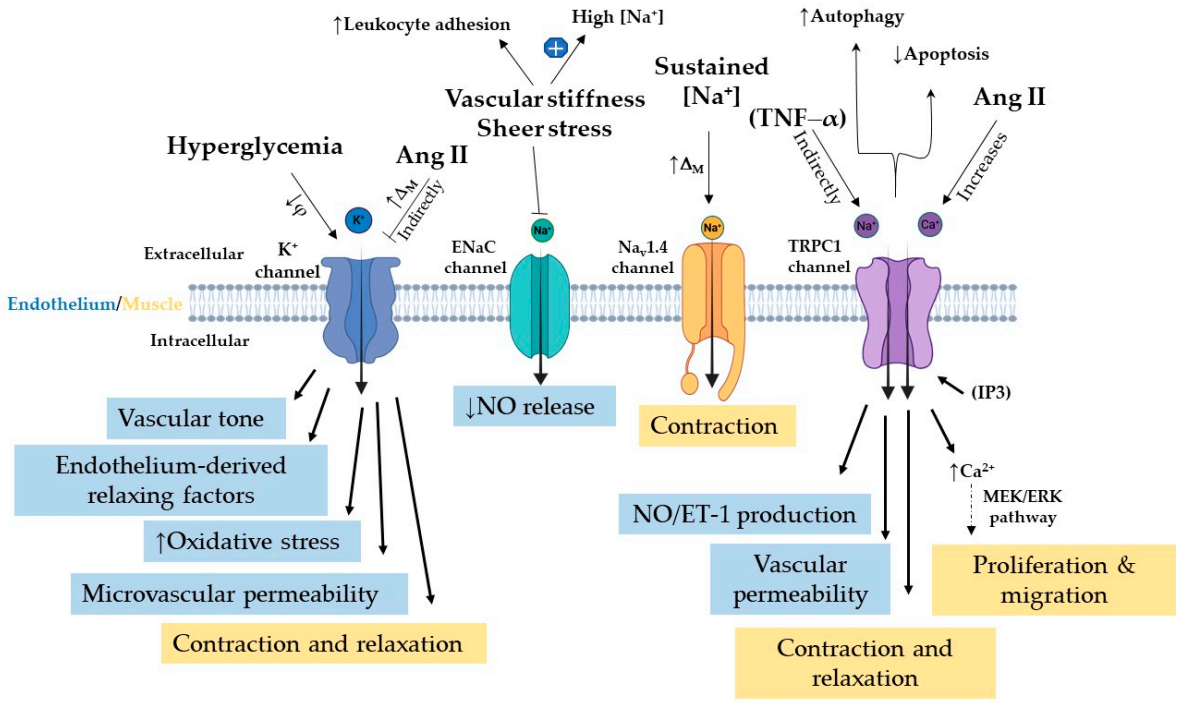

Figure 6. This figure depicts how different vascular cation channel network contribute to vascular homeostasis through different mechanisms. Channel images were created using BioRender. Akhlaghi, S. 2026. https://app.biorender.com/illustrations/6969c48d00f26499747783a7.

Arterial tension is closely linked to membrane potential and the activity of ion channels within the vascular wall. In vascular smooth muscle cells, K^+ channels play a key role in regulating contractility and vasoconstriction/vasodilation by controlling membrane potential and directly influencing intracellular calcium levels [189]. In contrast, endothelial K^+ channels regulate vascular tone indirectly by modulating the release of endothelium-derived relaxing factors and contributing to the regulation of microvascular permeability. Activation of K^+ channels in endothelial cells supports the maintenance of vascular tone and blood flow [190], while in vascular smooth muscle cells these channels govern both contraction and relaxation. Dysfunction of the vascular K^+ channel network can therefore significantly alter arterial tone.

Ang II induces smooth muscle contraction in blood vessels, leading to increased vascular resistance and elevated blood pressure [191]. Notably, Ang II modulates vascular tone by influencing multiple ion channels, including K^+ channels [192]. Inhibition of K^+ channel activity by Ang II leads to membrane depolarization (Δ_M), which promotes contraction and reduces blood flow (Figure 6). Hyperglycemia also affects K^+ channel function through oxidative stress–mediated mechanisms [193,194]. Hypertension and diabetes, the two components of MetS, impair K^+ channel activity, leading to reduced vasodilatory capacity (φ) (Figure 6) [195,196]. Dysfunction of these channels contributes to vascular disease and hypertension by disrupting the regulation of basal vascular tone, ultimately impairing blood flow and increasing cardiovascular risk. For a detailed overview of the roles of K+ channels, readers are referred to previous review [197], including their interactions with perivascular adipose tissue as well as their involvement in diabetes mellitus and its complications [198].

5.2. Sodium Channels

Vascular endothelial cells play a significant role in sodium homeostasis. The epithelial sodium channel (ENaC) is expressed in vascular tissue (Figure 6) [199,200] and skeletal muscle [201]. Skeletal

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muscle expresses $Na_v1.4$; a voltage-gated sodium channel that triggers muscle contraction by initiating and propagating action potential (Figure 6) [202]. This condition is caused by sustained sodium conductance, which is associated with hyperkalemia. Mutations of $Na_v1.4$ appear to cause muscles stiffness, known as myotonia [202]. ENaC and $Na_v1.4$ play important roles in endothelial and skeletal muscle function, and their dysfunction can contribute to metabolic disease.

In cultured endothelial cells, ENaC acts as a negative modulator of endothelial eNOS and NO production in resistance arteries [203]. Evidence indicates that the vasodilatory response to shear stress is enhanced by ENaC blockade [203]. The study shows that ENaC activation reduces NO release, whereas its inhibition results in elevated NO release and vasodilation. Further investigations are needed to confirm this paradigm. Deletion of ENaC prevents stiffening of the endothelial cells both in vitro and in vivo [204]. Genetic deletion of endothelial ENaC alters the vascular response to fluid shear [205]. Arterial stiffness is an independent risk factor for CVDs [206]. ENaC contributes to diabetes, hypertension, and aging, leading to impaired IR signaling, a key factor in MetS.

Patients with diabetes [207], hypertension [208], or chronic kidney disease [209,210] exhibit damage to the endothelial surface layer. Vascular stiffening is an age–related phenomenon that is accelerated by InsR, particularly in the context of diabetes. A key downstream mediator of IR activation is the endothelial Na^+ channel, which plays an important role in endothelial dysfunction, cardiovascular fibrosis, and vascular stiffening [211]. Incubation of endothelial cells with high sodium concentrations leads not only to increased stiffness of the endothelial surface layer but also to a significant decrease in endothelial surface layer heparan sulfates (a key component of the endothelial glycocalyx), resulting in reduced sodium buffering capacity (↓φ) (Figure 6) [212]. The endothelial glycocalyx binds sodium through its negatively charged surface, thereby protecting endothelial cell function and regulating vascular permeability via its buffering effect [213].

These alterations impair barrier function, facilitating sodium entry into endothelial cells, either directly or through increased activity of endothelial sodium channels [214]. Sodium–induced increases in endothelial stiffness and reduced buffering capacity enhance leukocyte adhesion via both vascular cell adhesion molecule 1 (VCAM-1)–dependent and intracellular adhesion molecule 1 (ICAM-1)–dependent mechanisms [215]. These processes play a significant role in regulating homeostasis and in pathologic states, including T2DM [216], Ang II-induced arterial hypertension and vascular dysfunction [217], and in cognitive impairment pathogenesis [218]. Additionally, these changes reduce shear stress–mediated NO production [219] and increase ROS levels, leading to vascular remodeling that drives impaired vascular homeostasis and subsequent dysregulation of blood pressure [220].

Non–voltage–dependent Na^+ channels, such as the Na^+ leak channel (NALCN), are predominantly expressed in neurons [221] but also appear to contribute to the resting membrane potential of arterial smooth muscle cells, where they help limit excessive depolarization. Mutations in NALCN are associated with cognitive delay [222]. NALCN-mediated Na^+ influx influences membrane excitability [223] and interacts with sodium-activated potassium (K^+) channels [224].

It has been proposed that sodium-activated potassium currents help lower blood pressure [225], particularly during heightened sympathetic nervous system activity [226], which increases heart rate and blood pressure to enhance blood flow. Mutant animals lacking normal NALCN function are more vulnerable to vasoconstrictive agents, resulting in a paroxysmal hypertensive phenotype. However, evidence also suggests that sodium-activated potassium currents oppose arterial smooth muscle depolarization independently of a specific relationship with the sympathetic nervous system [224]. Taken together, these studies suggest that endothelial/muscle sodium transporters are able to alter vascular signaling.

5.3. Transient Receptor Potential (TRP) Isoforms in Metabolic Syndrome

Endothelial cells express several TRP channel isoforms, each exhibiting different functions and expression profiles (Figure 6) [227]. TRP channels, cation-permeable channels, play essential roles in numerous tissues [228]. Among TRP channels, transient receptor potential canonical 1 (TRPC1)

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channels, contribute to endothelial–dependent vasodilation [229] and vascular permeability, as demonstrated in TRPC1/TRPC4 double knockout mice [230]. Evidence indicates that TRPC channels assemble as either homo– or heterotetramers and play a crucial role in regulating intracellular calcium [231]. Study provides evidence that TRPC1 may serve as a negative regulator for TRPC4 and TRPC5, thus protecting neurons from cell death via reducing calcium influx [232]. TRPC1, a nonselective cation channel, is expressed in vascular endothelial cells [233], the cerebellar hemisphere [232], skeletal muscle [232], as well as in adipocytes, where it appears to promote increased autophagy and reduced apoptosis (Figure 6) [234]. Further experiment has demonstrated that TRPC1 knockout mice display reduced adipocyte content in both subcutaneous and visceral adipose tissues, underscoring the importance of TRPC1 in adipocyte regulation [234].

TRPC1 channels are activated in a diacylglycerol (DAG)–, inositol trisphosphate (IP3)–, or phospholipase C (PLC)–independent manner; however, TRPC channels primarily support calcium and sodium influx in response to agonists of G protein–coupled receptors (GPCRs) [235]. TRPC1 has also been implicated in the regulation of endothelial repair capacity [236]. Notably, TRPC1 expression is increased under high–glucose milieu compared with other TRPC isoforms, highlighting its key role in vascular homeostasis [237]. Enhanced TRPC1–dependent calcium entry has been proposed as a key driver of cellular dysfunction in this context [237,238]. Surprisingly, TRPC1 knockout mice exhibit normal vasculature, indicating that targeted TRPC1 silencing may be well tolerated. Therefore, targeted inhibition of TRPC1 in vascular endothelial cells may represent a viable therapeutic strategy to alleviate hyperglycemia–induced endothelial dysfunction.

However, genetic ablation of TRPC1 in endothelial cells promotes the formation of heteromeric TRPV4–TRPP2 channels [235], which has been associated with reduced cardiac hypertrophy [239]. Moreover, a non-synonymous single nucleotide polymorphism (rs7638459) in the TRPC1 (TRPC1-rs7638459) gene has been identified as an independent risk factor for T2DM in the Han Chinese population [240]. Thus, it is reasonable to suggest that TRPC1 plays a protective role. TRPC1 regulates the production of both nitic oxide (NO) and endothelin–1 (ET-1) (Figure 6) [241]. Recently, evidence strongly indicates that the loss of endothelial TRCP1 triggers aortic hypercontractility and induces hypertension [241]. Notably, the study further demonstrates that knock–in of endothelial TRPC1 can ameliorate enhanced endothelial-dependent contraction and hypertension in obese mice. TRPC1 expression levels are elevated in Ang II -treated vascular smooth muscle cells (VSMCs) [242]. TRPC1 deficiency in VSMCs attenuates AngII – induced vasoconstriction, hypertension, and cardiac hypertrophy (Figure 7) [243]. The study shows that Ang II-Ca^{2+} influx and activation of mitogen-activate protein kinase/extracellular signal-regulated kinase (MEK-ERK) promote VSMC proliferation and migration, contributing to hypertension and cardiovascular remodeling. Taken together, these findings highlight that TRPC1 aberrant expression and function are associated with vascular dysfunction, thus contributing to MetS.

Activation of TRPC1 by tumor necrosis factor–α (TNF–α) increases vascular permeability [244]. Similarly, TRPV4 contributes to vascular permeability [245], endothelial-dependent vasodilation [246], and regulation of vascular tone [247]. TRPC3 channels are involved in both vascular smooth muscle contraction and endothelial NO release [248]. Evidence further supports the existence of TRPV4–TRPC1 heterodimeric channels that mediate flow shear stress–mediated calcium influx in endothelial cells [246,249].

Activation of TRPA1 by oxidative stress induces sodium and calcium influx in vascular endothelial cells, highlighting its role in ROS signaling. Moreover, TRPA1 activation at myoendothelial junctions in cerebral arteries promotes endothelial–dependent smooth muscle relaxation via activation of calcium–activated potassium channels (KCa3.1), resulting in myocyte relaxation [250]. Taken together, these studies underscore the significant involvement of TRPA1 and TRPV4 channels, particularly TRPC1, TRPC4 and TRPC5 channels, in MetS–associated pathological processes, including endothelial dysfunction, inflammation, oxidative stress, T2DM, and neurodegenerative disease.

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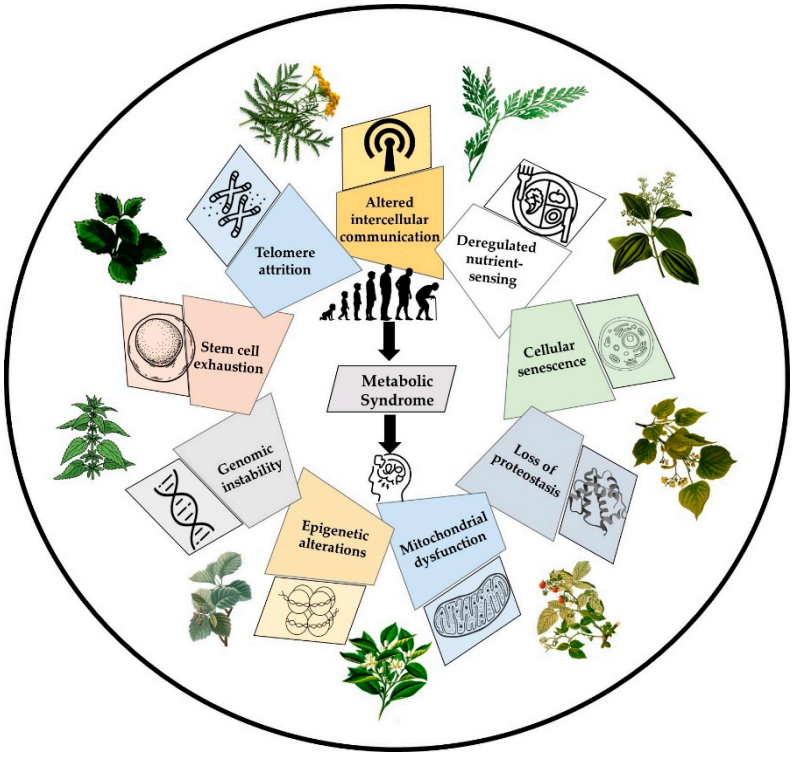

Figure 7. Herbal medicines influence aging at the molecular level.

6. Age-Dependent Changes in Cell Remodeling and Herbs That Influence These Changes at the Molecular Level

While MetS and aging share common risk factors, including unhealthy diet, increased central adiposity, and sarcopenia [251], both are major contributors to the development of chronic diseases such as diabetes and cardio- and cerebrovascular disorders. MetS affects approximately 40% of older adults in Ireland [252], yet nearly 60% remain unaffected. This disparity raises important questions about why certain individuals demonstrate resilience despite exposure to well-established risk factors, including central adiposity and advancing age.

Several mechanisms have been proposed to explain the high prevalence of MetS in older populations; however, these explanations have not been clearly associated with causation. Emerging evidence delineates that MetS–associated chronic subclinical inflammation accelerates epigenetic aging in older adults [253]. In parallel, adipose progenitor cells isolated from older individuals exhibit reduced lipid incorporation alongside increased oxidative stress [254,255].

The progression of aging is not uniform among individuals, either within or between ethnic communities. Aging should therefore be considered a syndrome, an array of traits rather than a singular process. Understanding the variability in traits that predispose certain individuals to a more rapid aging trajectory is central to unlocking the complexities of human aging. MetS, a constellation of interconnected physiological dysfunctions, is not universally prevalent among older adults in the Irish population, underscoring the presence of protective or resilience-associated traits that may shield against accelerated aging.

The relationship between MetS and aging is complex and non-linear, shaped by interactions among modifiable lifestyle factors, intrinsic biological processes, and genetic influences. Both of them are increasingly recognized as gradual and irreversible pathological processes.

Aging is delineated in the context of MetS based on the “hallmarks” of aging originally proposed by López-Otín and colleagues [256]. These hallmarks reflect harmful dysfunctions that correspond to specific aging traits. Aging in relation to multiple aging-related diseases in humans has recently been eloquently reviewed [256–258]. Here, we focus on nine hallmarks that describe the biological

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processes of aging and their important roles in the context of MetS, an aging-related disease in humans (Figure 7). This section also provides insights into the roles of bioactive compounds and herbal medicines in each hallmark of aging, which may, in turn, provide beneficial effects on cognitive decline.

6.1. Genomic Instability

Genomic instability refers to the gradual alterations in the function and structure of DNA stemming from chemical modifications over time, which ultimately lead to impaired genome integrity [259]. Genomic instability, as a fundamental process contributing to aging [260].

Micronutrient deficiencies can lead to cognitive decline through damaging DNA stability, including zinc, selenium, copper, and iron deficiencies [261]. In addition to trace elements, a growing body of evidence has addressed the link between natural products and herbal medicines and genomic instability. Ginseng (Panax ginseng C.A. Meyer), a long-lived perennial herb belonging to the family of Panax (Araliaceae), is one of the most commonly used herbal nutritional products promoting vitality, longevity, diminishing stress, mental and physical health, fatigue, and weakness [262]. Recent evidence demonstrated that ginseng callus cells subcultured for 12 consecutive years retained chromosomal stability and totipotency, with minimal decline over time [263]. In an 8-week double–blind randomized controlled trial on 57 subjects, Korean red ginseng significantly attenuated lymphocyte DNA damage, particularly at least via upregulating the activity of antioxidant enzymes, including plasma superoxide dismutase (SOD), glutathione peroxidase and catalase [264]. In another study on 14 healthy subjects, 1 cup of American ginseng tea substantially attenuated cellular DNA damage through decreasing oxidative stress [265]. Human clinical trials found that Panax notoginseng [266] and rosemary (Rosmarinus officinalis) significantly decreased the H_2O_2-induced DNA damage in human lymphocytes via protecting DNA against oxidative damage [267]. An 8-week randomized controlled trial (RCT) on 91 healthy subjects revealed the beneficial effects of Aronia melanocarpa supplement on attenuating H_2O_2-induced DNA strand breaks ex vivo [268]. A randomized crossover study found that supplementation with blueberries can significantly reduce H_2O_2-induced DNA damage within 1 hour after blueberry consumed [269].

6.2. Telomere Attrition

Telomeres are made up of complex structures encompassing RNA, proteins, and a tandemly repetitive DNA sequence of TTAGGG, which protects the ends of chromosomes from degradation caused by oxidative stress and cell division, as well as end-to-end fusion [270–273]. Three pivotal factors indicate the average length of leukocyte telomeres at a given age, including chronic oxidative stress (the main factor), inherited telomere length, and the rate of immune cell proliferation. Telomere shortening is strongly linked to elevated risk of developing numerous age-associated conditions comprising CVDs [274,275], T2DM [276], and liver diseases [277]. Contrary to the generally accepted view, cross-sectional analyses have also revealed a paradoxical increase in leukocyte telomere length among patients with T2DM and MASLD [277].

Compelling research has indicated a link between telomere attrition and cognitive decline [278–281], while some studies did not find a relationship between telomere shortening and neurodegenerative disorders such as Alzheimer's disease [282]. Furthermore, a longitudinal study on 880 subjects demonstrated that short telomere, but not telomere attrition rates, might be a predictive indicator for aging–induced memory decline [283]. The reverse of telomere attrition can occur via the activity of telomerase, an enzyme that is active in several tissues, including lymphocytes, stem cells, and, in general, in high–proliferating cells [284,285]. Therefore, any natural or synthetic compound that exhibits telomerase activator effects may have promising anti-aging effects.

Resveratrol, a polyphenol found primarily in certain berries, grains, roots, seeds, tea [286], the Japanese knotweed, grapes, and red wine, have been shown to demonstrate anti-aging effects via telomere maintenance [287]. Resveratrol is capable of upregulating telomerase reverse transcriptase (hTERT), as well as stimulating the SIRT1 (silent information regular 1)/Nrf2 (nuclear factor erythroid

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2–related factor 2) signaling pathways in human HepG2 hepatocellular carcinoma cells [288]. In a study conducted on older adults with chronic kidney disease, resveratrol substantially mitigated telomere shortening [289]. In a 12-week randomized controlled trial on older adults, pomegranate extract demonstrated beneficial effects on the blood levels of IGF-1, with no changes in telomere length [290]. IGF-1 has been shown to have potentially protective effects on vascular aging by mitigating oxidative stress and inhibiting signaling pathways leading to inflammation and apoptosis [291–293].

Astragalus, a plant commonly utilized in traditional Chinese medicine, was shown to exhibit anti-aging effects through activating telomerase and induce telomere length extension [294]. In addition, several studies, including animal and in vitro experiments, have demonstrated the potential effects of astragalus active compound such as astragalosides IV and cycloastragenol, on the activation of telomerase [295–297]. In a randomized controlled trial on 40 middle-aged healthy individuals, an astragalus-based supplement for 6 months significantly demonstrated longer median and shorter telomere length compared to the control group, where no changes in telomere length were exhibited [294]. Cantella asiatica (L.) Urban, also known as gotu kola, a herb widely grown in tropical and subtropical regions belonging to the Apiaceae family [298–300], has also been shown to have anti-aging effects via upregulating the activity of telomerase in human peripheral blood mononuclear cells (PBMCs) [301]. In an 8-week randomized controlled trial on 32 middle-aged Thai adults, Mylife/Mylife100® dietary supplement significantly increased the average telomere length between the baseline and the 8-week time point, possibly through the antioxidant properties of its ingredients [302]. This dietary supplement consists of soy protein, guava fruit, mangosteen aril, black sesame seed, and pennywort leaves. In another study, fortified mangosteen extract exhibited anti-aging properties via slowing telomere shortening [303]. Scarlet beebalm (Monarda didyma L.), a perennial plant predominantly grown in Canada and the US and belonging to the Lamiaceae family, is rich in essential oil and phenolic compounds [304]. M. didyma L. contains didymin, which is a flavonoid glycoside giving the plant anti-aging, antioxidant, and anti-inflammatory properties (M. Didyma [305]. A randomized controlled trial found that daily supplementation with M. didyma meaningfully stabilized DNA methylation age and improved telomere length [306].

It should be noted that not all natural products have promising effects on telomere maintenance. For instance, curcumin, a polyphenolic compound found primarily in the turmeric root [287], has been found to promote telomere attrition via inhibiting telomerase activity in tumor cells [307–309]. In addition, epigallocatechin gallate (EGCG), a catechin derived from green tea [310], exhibits telomere shortening features via genotoxicity [311]. However, further research is needed to establish the exact mechanisms of action of various natural products on telomere maintenance/attrition and their potential adverse effects.

6.3. Epigenetic Alterations

Epigenetic is defined as “an epigenetic trait is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence” [312]. Both genetic and epigenetic alterations can lead to a wide spectrum of human diseases, such as aging, cardiovascular, and neurological diseases [313]. Epigenetic alterations include remodeling of chromatin, changes in DNA methylation pattern, and histone modification, and non-coding RNAs [314]. Epigenetic alterations do not alter the DNA sequence, yet they affect gene expression and architecture of chromosome [315].

A growing body of literature has examined the potential impacts of natural products and plant-derived compounds on epigenetic alterations, which impact the epigenetic pathways [315]. One of these natural products is curcumin, which is a polyphenolic compound derived from Curcuma longa plant [316]. Curcumin has been shown to affect DNA methylation by inhibiting DNA methyltransferase 1 (DNMT1) to modulate histone modification via inhibition of histone acetyltransferases [315]. On the other hand, in a study conducted in human leukemia cells, the authors found that curcumin and its derivates can alter histone methylation and the activity of

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histone methylation/demethylation enzymes, highly depending on context and cell types [317]. Sulforaphane, an isothiocyanate abundantly found in broccoli and other cruciferous vegetables, has been shown to affect DNA methylation [318]. Naringenin, a flavanone predominantly found in citrus fruits, has been shown to exhibit promising effects on epigenetic alterations [319].

Several studies have examined the effects of EGCG on the epigenetic alterations. It has been shown that EGCG can suppress DNMT, ultimately leading to an alteration in the DNA methylation status [320]. In addition, EGCG can affect epigenetic alterations though elevating histone 3 and 4, and decreasing histone deacetylase (HDAC) activity via modulating the gene expression of HDAC2 and histone methyltransferase (G9a), and HDAC1, respectively [321]. Emodin, an anthraquinone primarily found in knotweed, rhubarb, buckthorn, and Da Huang, can also target HDAC activity, at least in part, through chelating zinc ions within HDAC catalytic domains, resulting in histone acetylation [322]. Resveratrol is capable of inhibiting the activity of HDAC and histone acetyltransferase [323], as well as aiming for histone H3K9 gene expression through inducing the activity of SIRT1 [324].

6.4. Loss of Proteostasis

Loss of proteostasis is one of the primary hallmarks of aging, leading to cellular aging [325]. Proteostasis or protein homeostasis refers to quality control mechanisms conducted by all cells in order to maintain the functionality and stability of proteomes [314]. The quality control mechanisms involve protein synthesis, stabilizing and accurately folding proteins, and degradation of proteins primarily by two pathways, namely proteasome system and the autophagy–lysosomal pathways [326]. Loss of proteostasis can result in the accumulation of damaged and misfolded proteins and increased protein aggregation overwhelming chaperone, proteasome, and autophagy systems [314,327].

American ginseng (Panax quinquefolius) maintained proteostasis through enhancing the activity of cathepsin B, a lysosomal protease in the autophagy–lysosomal pathway, leading to removing of damaged proteins, as well as enhanced autophagic flux [328].

Spermine and spermidine, polyamines, have been shown to have neuroprotective effects via stimulating autophagy [329], which subsequently resulting in reducing the aggregation of Tau and αS in neurons and microglia [330]. A cross-sectional study of 2674 older adults demonstrated a significant association between dietary intake of spermine and better cognitive function [331]. Icariside II, a metabolite of Icariin in the intestines, can diminish the levels of Aβ, leading to protective effects against Alzheimer's Disease in animal models [332]. Myricetin, a flavonoid falling under flavanols, has been shown to favorably affect proteostasis status via various pathways, namely alleviating misfolded proteins related to neurodegenerative diseases, stabilizing ubiquitin ligase E6-AP, and regulating the levels of endogenous Hsp70 chaperone [333].

6.5. Mitochondrial Dysfunction

Mitochondrial dysfunction is one of the hallmarks of aging [314], which refers to diminished ATP generation capacity and elevated electron leakage owning to attenuated efficacy of the respiratory chain [334]. Mitochondrial dysfunction plays a pivotal role across a spectrum of physiological and pathological diseases, including T2DM [335] and cardiometabolic diseases [336]. The relationship between mitochondrial dysfunction and cognitive decline can be mediated through alterations in mitochondria morphology, disruptions in energy metabolism, oxidative stress, damages to mitochondrial DNA and RNA, disruptions in calcium homeostasis, neuroinflammation, alterations in mitochondrial biogenesis and dynamics, and apoptosis pathways [337]. It should be noted that any natural products and their active compounds, which target the aforementioned pathways, is capable of reversing and preventing mitochondrial dysfunction, which subsequently hinder the progress of cognitive decline.

Recent evidence has examined the effects of numerous natural products on mitochondrial dysfunction. Resveratrol has been shown to boost the production of energy, trigger mitochondrial biogenesis, and stabilize mitochondrial fission-fusion dynamics via activation of SIRT1/ SIRT3-FoxO

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pathway [338]. Baicalin is an active ingredient predominately found in *Scutellaria baicalensis*, a Chinese herbal medicine, exerts anticancer, antifibrotic, anti-inflammatory, antioxidant, and antimicrobial properties [339–341]. In Parkinson's disease rat models, baicalein exhibited neuroprotective effects via recovering mitochondrial dysfunction and activating mitochondrial autophagy through the SIRT1/AMPK/mTOR and miR-30b-5p pathways [342]. Baicalin also delineated protective effects against heart failure via improving mitochondrial dysfunction, as evidenced by reduced ROS production, apoptosis, and cardiac fibrosis in both in vivo and in vitro [343]. Furthermore, baicalin has been shown to inhibit hypoxia-inducible factor-1α, thus, reversing mitochondrial dysfunction and improving aerobic glycolysis [344].

Thymoquinone is an active ingredient primarily found in the Nigella sativa seeds [345]. Thymoquinone exhibits protective effects against neuro-related disorders via ameliorating Aβ-induced neurotoxicity and depolarization of mitochondrial membrane mediated through the inhibition of ROS formation and diminishing oxidative stress, as well as preventing apoptosis via changing mitochondrial function and reducing Cytochrome–C and Caspase-3 [345]. Similarly, in a study on rats, thymoquinone ameliorated inflammation, apoptosis, and oxidative stress, as well as preserving the mitochondrial DNA content in cardio cells [346]. Syringin, a phenylpropanoid glucoside found predominantly in the medicinal plant *Acanthopanax senticosus*, antioxidant and anti-inflammatory activities [347]. Syringin has been demonstrated to stimulate autophagy through, at least in part, modulating the axis of miR-34a/SIRT1/Beclin-1 and inhibit apoptosis induced by 6-hydroxydopamine in Caenorhabditis elegans models [348]. SIRT1 plays a crucial role in mitophagy and mitochondrial biogenesis [349,350]. Astragaloside IV exhibits a promising capacity to attenuate mitochondrial dysfunction in podocytes through SIRT1/PGC1α/Nrf1 pathway, as well as diminishing oxidative stress [351]. Furthermore, Fangji Huangqi Decoction, a traditional Chinese medicine, demonstrated a significant elevation in mitophagy in podocytes in rat models via increasing BNIP3 expression [352].

6.6. Cellular Senescence

Cellular senescence is a biological process entails an irreversible and permanent arrest of the cell cycle occurring in response to numerous endogenous and exogenous cellular stressors, including oxidative stress, telomere shortening, oncogene activation, and DNA damage with the aim of halting the proliferation of damaged cells [353–355]. The accumulation of senescent cells due to aging can stimulate the production of pro–inflammatory proteins, also known as pro–inflammatory senescence-associated secretory phenotype (SASP), leading to chronic inflammation, which ultimately results in metabolic diseases [356], including MetS, osteoporosis, metabolic CVD, and diabetes [357]. Cellular senescence ultimately activates cytokine–dependent kinase inhibitors namely $p16^{INK4a}$, p21, ad p53 [353]. Therefore, natural products with the potential to attenuate and delay cellular senescence can play pivotal roles in alleviating metabolic diseases.

Although cellular senescence is one of the major drivers for metabolic diseases, there is a dearth of human studies in older adults with MetS addressing the potential role of natural products in cellular senescence. An randomized controlled trial (RCT) of quercetin, a natural flavonoid, in male patients with coronary artery diseases found a significant decrease in vascular senescence and inflammaging signatures indicating the potential sex-specific effects of quercetin on regulating senescence-associated biology in humans [358]. Of particular interest, a short–term clinical trial in patients with idiopathic pulmonary fibrosis demonstrated that the combination of dasatinib and quercetin significantly diminished cellular senescence via decreasing the expression of $p16^{INK4a}$, $p21^{CIP1}$, and attenuating circulating SASP markers, such as IL–1α, IL–6, and matrix metalloproteinases (MMPs)–9 and –12, as well as cells with senescence–associated β–galactosidase activity [359].

6.7. Deregulated Nutrient Sensing

Nutrient–sensing pathways entail both extracellular ligands, and intracellular signaling cascades, including sirtuins (SIRT), insulin and IGF-1, AMP-activated protein kinase (AMPK), and

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mTOR, all of which play a vital role in the aging process [256]. A growing body of literature has explored the association between deregulated nutrient sensing and metabolic diseases, including but not limited to MetS. For instance, recent evidence delineated a close link between dysregulation of AMPK and InsR [360,361]. It has been shown that dysregulated nutrient sensing is associated with T2DM in older adults [362,363]. Natural products targeting the aforementioned signaling pathways can mitigate deregulated nutrient sensing, resulting in substantial improvements in MetS and InsR.

It is worth mentioning that various natural products have been evaluated in older adults with outcomes that map onto nutrient–sensing signaling pathways, such as SIRT, mTOR, and AMPK, as well as NAD^+–dependent pathways. In an RCT, resveratrol has been found to efficiently increase the blood levels of SIRT1 in older adults with T2DM [364]. A 6–month RCT on older adults with T2DM demonstrated that resveratrol activated nutrient sensing namely mTOR, SIRTs, and AMPK [365]. In a study on older adults with mild cognitive impairment, nicotinamide riboside, a vitamin B3 derivative, significantly increased blood levels of NAD^+ indicating the potential role of this product in nutrient sensing network [366].

Salidroside, a phenylpropanoid glycoside derived from the plant *Rhodiola rosea L.*, is capable of increasing the expression of SIRT1 and inducing autophagy via AMPK-SIRT1 pathway [367], mTOR [368], and reduce the expression levels of IGF-1 and regulate insulin/IGF-1 signaling pathway [369]. Thus, salidroside can mitigate MetS and improve InsR via diminishing the deregulated nutrient sensing. Of particular interest, honokial, an active ingredient belonging to neolignane biphenols stemmed from traditional Chinese herb magnolia [370], has been shown to alleviate InsR through the activation of AMPK [371]. Theaflavins, functional phytochemicals found primarily in black and dark tea, have beneficial effects on MetS [372]. Theaflavins act on multiple signaling pathways targeting dyslipidemia, obesity, and hyperglycemia. For instance, theaflavin TF3 activates AMPK signaling pathway leading to meaningful diminished hepatocyte lipid deposition [373].

6.8. Stem Cell Exhaustion

One of the repercussions of aging is stem cell exhaustion leading to a substantial functional loss of tissues and diminished regenerative potential of the tissues at steady state [374]. With aging, stem cell exhaustion occurs in multiple tissues, including, but not limited to satellite cells in muscles, intestinal epithelial stem cells, mesenchymal, and neurol, as well as hematopoietic [375]. Of particular interest, stem cell exhaustion can arise from DNA damage, telomere attrition, mitochondrial dysfunction, cellular senescence and epigenetic alterations [314]. Ultimately, stem cell exhaustion can lead to various age–related diseases, namely muscle atrophy, neurodegeneration, immune system malfunctioning [374], frailty, osteoporosis, and diminished physical performance [376].

Recently, the potential therapeutic effects of stem cells in various metabolic disorders, including MetS have attracted the attention of researchers globally. In an animal study on high-fat diet-induced obese mice, the researchers found that mesenchymal stem/stromal cells significantly decreased body weight and improved dyslipidemia, mainly through activation of AMPK signaling pathway in adipose tissue [377]. Other studies showed the same promising effects of mesenchymal stem cells on glucose homeostasis, energy metabolism, and insulin sensitivity [378,379]. In a T2DM mouse model, mesenchymal stem cells improved insulin sensitivity and reduced lipid accumulation in hepatocytes via activating of the P13K-AKT signaling pathway, as well as suppressed senescence and apoptosis of β–cells in pancreas [380]. Furthermore, In human studies, mesenchymal stem cells therapy has been shown to improve insulin sensitivity through various mechanisms, including anti-inflammatory effects, improving insulin sensitivity, oxidative stress, and β–cell functions in pancreas [381]. In a human trial on individuals with T2DM, the combination of bone marrow mesenchymal stem cells and mononuclear cells revealed promising effects on the complications of T2DM over an 8–year follow-up, including a substantial decline in the incidence of diabetic peripheral neuropathy, as well as macrovascular complications [382]. All of these studies highlight the presence of a tight link between stem cell exhaustion and the different components of MetS, particularly InsR.

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There is a growing body of evidence linking natural products to stem cell exhaustion in mechanistic stem/progenitor cells. Hence, human intervention trials are rare regarding quantifying stem cell exhaustion directly, highlighting a gap in the literature. Since stem cell exhaustion is an attuned consequence of other hallmarks of aging, including mitochondrial dysfunction, telomere attrition, DNA damage, and epigenetic alterations, natural products targeting the above-mentioned hallmarks may also play a critical role in alleviating stem cell exhaustion. In this regard, several nutraceutical agents seem to converge on senescence program regulation and mitochondrial quality control. Lower doses of quercetin treatment in human exfoliated deciduous teeth stem cells exhibited promising effects on the energy metabolism of stem cells and enhanced SIRT expression [383]. Spermidine has been shown to effectively protect mesenchymal stromal cells against oxidative stress and exhibit antisenescence effects, at least in part, through SIRT3 [384]. Fisetin is a naturally occurring flavone with senolytic activity via upregulating anti-apoptotic pathways [385]. Fisetin has been shown to target various canonical indicators of cellular senescence in adipose–derived stem cells, including ROS, senescence-associated β–galactosidase, as well as senescence–associated heterochromatin foci [386].

Since there is a dearth of direct human clinical trials, further research is needed to address the effects of different natural products on stem cell exhaustion.

6.9. Altered Intercellular Communication

Aging is accompanied with altered intercellular communication, which in turn compromises the maintaining of hormesis and homeostasis [256]. Intercellular communication occurs via the release of soluble factors influencing the function of neighbor and distant cells [387]. Among intercellular communication mediators, extracellular vesicles (EVs)[388], and senescence-associated secretory phenotype (SASP) [389] are of great importance. Exosomes are small extracellular vesicles, releasing by all cell types, serving a crucial role as an important mediators of intercellular communication [390]. Notably, aging and numerous pathological diseases can downregulate the communication between mitochondria and the host cells [391]. Given the pivotal role of mitochondria in both intra- and intercellular communication pathways, age-related deregulation of mitochondria communications affects all tissues [391]. Various age-related diseases are associated with altered intercellular communication, including MetS [392,393] and atherosclerosis [394]. Various studies have delineated that EVs can undergo significant changes in metabolic–related diseases, including obesity and MetS [395–399]. Targeting SASP has been demonstrated to reverse the complications of diabetes, including InsR and glucose homeostasis [400].

Numerous herbal medicines and natural products have been shown to positively alter intercellular communications, which in turn can help with the development of MetS and InsR. Bazi Bushen is a traditional Chinese medicine has been shown to activate SASP, leading to a significant alteration in impeding inflammation–related pathways, including arachidonic–linoleic acid metabolism and TNF– and IL-17–induced inflammatory pathways [401]. In contrast to Bazi Bushen, procyanidin C1, a polyphenolic component of grape seed extract, can inhibit SASP at lower concentrations and selectively destroys senescent cells at higher concentrations [402].

It has been shown that baicalin is capable of preventing atherosclerosis via regulating the SIRT1/NF-κB signaling pathway mediated by exosomes stemming from the treatment of mesenchymal stem cells by baicalin [403].

Salidroside is a phenolic compound found primarily in plants of *Rhodiola rosea L* exhibits anti–inflammation, anticancer, and antioxidation activities [404–406], with a potential capacity to improve insulin sensitivity through down–regulating miR-21 [407]. Moreover, salidroside has been shown to exhibit protective effects against liver fibrosis via triggering miR-146a-5p, a major component of human liver stem cell exosomes [408], which ultimately inhibits hepatic stellate cell activation [409].

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7. Traditional Anti-Aging Medicines with the Potential to Be Translated into Effective Treatments for MetS-Induced Cognitive Decline

T2DM, hypertension, and obesity are common chronic conditions among older adults across ethnic groups. Multiple studies have demonstrated that these disorders are well-established risk factors for the development of vascular dysfunction -induced InsR, as described earlier (Figure 8).

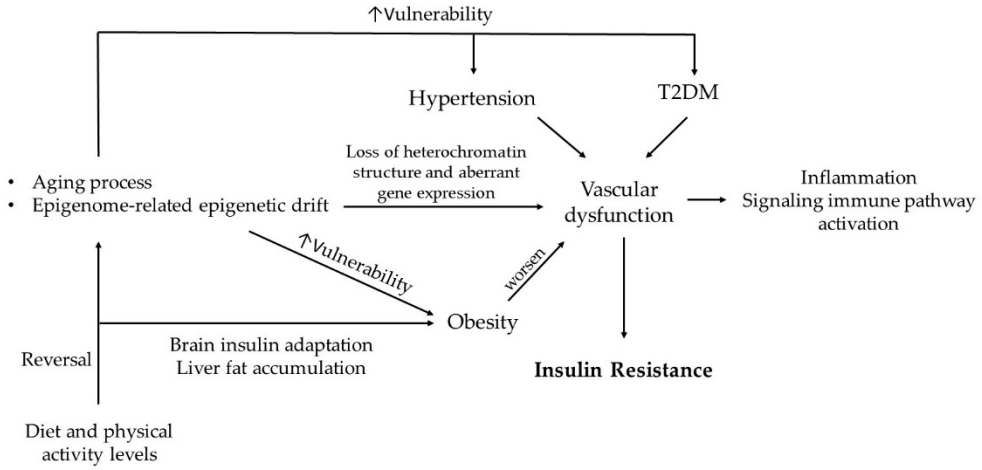

Figure 8. Reduced physiological and functional capacity due to aging, along with poor diet, contribute to the development of vascular dysfunction–induced cognitive decline.

These conditions adversely affect cellular metabolism and aging-related processes, including senescence and apoptosis, metabolic distribution, as well as the metabolic effects of carbohydrates and Ang II, thus promoting the development of MetS complications (Figure 8). In addition, meta-analyses have shown that antihypertensive therapy in individuals with hypertension can lead to modest improvements in glycemic control. Equally, several newer antidiabetic agents are associated not only with improved glycemic management but also with better blood pressure control and multiple anti-atherosclerotic effects, conferring cardiovascular benefits. This suggests that relationships among these conditions are bidirectional. A balanced diet, adjuvant therapy with traditional herbal medicine, regular moderate exercise, and appropriate weight management improve glycemic control, may modulate the rate of cellular aging, and provide cardiovascular benefits beyond weight reduction alone.

Even in the absence of common risk factors, aging itself can make metabolic and cardiovascular systems more susceptible to the chronic disorders that comprise MetS, as described earlier (Figure 8). Although aging cannot be prevented, accumulating evidence suggests that aging and epigenome-related epigenetic drift are possible to slow their progression. In various traditional medical systems, medicinal herbs are regarded as potential anti-aging phytotherapeutic agents.

In summary, risk factors for elevated DNA fragmentation include advanced age, chronic conditions such as diabetes and cardiovascular disease, oxidative stress, obesity, and poor dietary habits. Increased blood pressure, hyperglycemia, and dysregulated lipid metabolism commonly arise from age-related alterations in both the vascular system and the neurovascular network. These changes disrupt inflammatory responses, coagulation pathways, interactions between extracellular cytokine pathways and intracellular signaling molecules, and immune homeostasis.

Such disturbances subsequently affect the molecular mechanisms governing the apoptosis–proliferation balance, which involves a complex interplay of signaling pathways, regulatory proteins, and cellular processes. Ultimately, this shift tilts the balance from health toward disease, characterized by impaired apoptosis, increased senescence-associated accumulation of damaged

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cells, heightened inflammation and oxidative stress, and consequent disruption of tissue homeostasis.

Herbal medicines possess considerable therapeutic potential to slow aging processes associated with MetS and to prevent MetS-induced cognitive decline. In this section, we summarize in vitro and in vivo studies published within the past five years that investigate nonspecific bioactive compounds and herbal medicines with anti-aging properties and focusing on their roles in modulating inflammation and oxidative stress, two key contributing factors in MetS-induced cognitive decline. Accumulating evidence indicates that many of these agents exert anti-aging effects across multiple organs and physiological systems, promote tissue homeostasis, and may thereby serve as a nutraceutical and therapeutic agent to mitigate MetS-related cognitive impairment (Table 1).

Table 1. Summary of experimental studies on bioactive molecules and herbal medicines that offer therapeutic benefits in managing MetS, promoting antiaging effects, and improving clinical outcomes.

Herb	Main Bioactive compound	Host	Mechanism of action	Pharmacological effects	Ref.
Lycium barbarum L.	Diverse compounds	Rat, aortic endothelial cells	SIRT3/CypD pathway, AKT/eNOS signaling pathway, SOD activity, Bcl-2 expression, Bax levels, reduced lncRNA sONE expression	Immunomodulatory, antioxidant, neuroprotective, blood pressure regulation, antiaging, hypoglycemic, immunomodulator	[410–414]
Atractylodis Rhizoma	ND	AD rats, HT22 cells	cAMP-dependent pathway, PI3K/Akt/NF-κB signaling pathway	Neuroinflammation, reduce inflammatory response, enhance immune function, potentially delay aging	[415–417]
Psoralea corylifolia and *Rubus chingii Hu* complex	Bakuchiol, isopentenyl flavonoids, Psoralen	Mice	Wnt/β-catenin, PI3K/Akt, PPAR-γ/Wnt, NF-κB and RANKL/RANK/MAPK signaling pathways, p38 MAPK and ERK pathways	Antiosteoporosis effects, anti-inflammatory properties, neuroprotective, inhibits oxidative stress, induces apoptosis	[418,419]
Monochoria angustifolia	Diverse compounds	In silico and in vitro, mice	Hydrogen atom transfer mechanisms	Antioxidative, prevents neuroinflammation or neurotoxic accumulation	[420–422]
Astragalus membranaceus	Diverse compounds	In vitro, in vivo	Increases SOD activity, reduce malondialdehyde (MDA) levels, senescence (AMPK/mTOR), miR-124–regulated ATF-6	Immunomodulatory, antihyperglycemic, antioxidant, anti-aging, anti-inflammatory	[423,424]
Jingfang Granule	Diverse compounds	Rat	AKT1, EGFR, MAPK3, MAPK1, IL6, and TNF and the PI3K-AKT and MAPK signaling pathways	Antioxidant, anti-inflammatory, proangiogenic, promotes wound healing in diabetic rat	[425–427]

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Si Jun Zi Tang	glycyrrhizin, ginsenoside Rg5, ginsenoside Rh2, liquiritin, polyporenic acid C, atractylenolide II	In vitro, in vivo	PI3K-AKT and p38 MAPK, reduces p53, p-p53, and p21, modulates cellular senescence signaling	anti-aging, antioxidant, immunomodulator, antiapoptotic	[428–430]
Wuzi Yanzong Pill	Diverse compounds	In vitro, in vivo	PI3K/AKT signaling, TP53, TNF-α, AKT1, NF-κB, and IκBα, increase superoxide dismutase	Antiapoptotic, neuroprotective, anti-inflammatory increases secretion of neurotrophic factors, restores metabolic imbalance	[431–434]
Astragali radix	Diverse chemical constituents	In vitro, in vivo	MyD88-independent pathway, NF-κB/Rel, elevation of the expression of IL-17F, IL-17A, IFN-γ, IL-22, increases superoxide dismutase, inhibits the MAPK and NF-κB pathways, Wnt signaling pathway, AMPK/SIRT1 and PI3K/AKT	Gut microbial modulation, reduces Mash, anti-inflammatory, reduces oxidative stress, antiaging	[435–439]
P-coumaric acid	4-hydroxycinnamic acid derivative	In vitro, in vivo	Inhibits NF-κB activation, MAPK, facilitates GLP-1 secretion, increases glucose-regulated protein 78 kDa (GRP78) expression	Anti-inflammatory, antioxidant, improves MASLD, boosts mitochondrial biogenesis	[440–442]
Flavonoids	Diverse chemical constituents	In vitro, in vivo	Reduces JAK/STAT3, Nox4/ROS-NF-κB, and MAPK, PI3K/AKT/eNOS	Antioxidant, anti-inflammatory, and anti-aging, proliferative effect	[443–445]

Lycium barbarum L. (*L. barbarum*), commonly known as wolfberry or goji berry, is widely used in traditional Chinese medicine. Among multitude of its therapeutic effects, various strains of *L. barbarum* contain bioactive compounds that target 90 aging-related genes, providing evidence that they may represent a molecular source for anti-aging, and age-delaying properties [415]. Evidence indicates that this herb possesses antioxidant, immunomodulatory, and glycemic-regulating properties, making it a promising candidate for addressing metabolic and obesity-related health challenges [411].

Atractylodis macrocephalae rhizoma (Atractylodes macrocephala Koidz.), a herb approved for use as a supplement in China, has demonstrated notable neuroprotective potential in preclinical studies. Evidence indicates that its medicinal properties include gastrointestinal support, anti-aging and antioxidant effects, and promote blood circulation [415]. Study indicates that Atractylodis

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macrocephalae rhizome alleviate neuroinflammation in AD through enhancing the cAMP signaling pathway [416]. It counteracts cyclophosphamide-induced immunosuppression in mice and restores normal immune function [417]. Evidence also indicates that Atractylodis macrocephalae rhizoma may enhance lymphocyte proliferation by inhibiting the PI3K/Akt/NF-κB signaling pathway, reducing IL-6, IFN-γ, and TNF-α levels, correcting immune cell imbalances, attenuating inflammatory responses, and improving immune function in aging rats. This herb may potentially delay aging due to its ability to reduce inflammation and enhance immune function [415].

The fructus of *Psoralea corylifolia* (L.), the fructus of *Rubus chingii Hu*, and tuber onion seed are Chinese herbs that significantly enhance limb grip strength and reduce the level of T cell receptor excision circles, an indicator of thymic emigrants, in the spleen following rapamycin-induced thymic atrophy in mice [419]. Notably, tuber onion seed appears to restore thymic function and tissue structure more effectively than the other tested herbs. Further investigation confirmed its effectiveness in reducing p21 and p53 expression in rapamycin-induced thymic atrophy in mice. The authors proposed that tuber onion seed can accelerate the regeneration process of the mouse thymus.

Monochoria angustifolia, or Siam violet pearl, is the newest species of the genus Monochoria C. Presl, found in Thailand, and has long been consumed as food and in herbal medicine. It has been shown to produce apigenin-7-O-glucoside, an abundant antioxidant phytochemical [421]. Recent in silico and in vitro studies indicate that apigenin-7-O-glucoside is a potential anti-aging agent due to its ability to inhibit collagenase and elastase [422]. The authors also provide evidence that the compound is safe based on its pharmacokinetic properties.

Astragalus membranaceus (A. membranaceus) has high medicinal and edible value, including immunomodulatory, antihyperglycemic, antioxidant, anti-aging, anti-inflammatory, antiviral, antitumor, cardioprotective, and antidiabetic effects, with minimal side effects. Astragalus polysaccharide (APS), a bioactive molecule derived from Astragalus membranaceus, has been shown to significantly reduce malondialdehyde (MDA) levels and increase SOD activity in response to d-galactose-induced senescence [446]. At a dose of 100 μM, it attenuates hepatocyte senescence both in vitro and in vivo in an H_2O_2-induced hepatocyte senescence model through AMPK/mTOR–induced reduction of ROS [447]. A previous study indicates that APS prolongs the lifespan of Caenorhabditis elegans via ATF-6–induced RNAi knockdown, demonstrating that it may modulate miR-124–regulated ATF-6, thereby contributing to lifespan extension [423]. Moreover, the active components of APS exert beneficial effects on metabolic disorders by reducing ROS [424], alleviating inflammation, and regulating lipid metabolism. Importantly, APS improves InsR while protecting pancreatic beta-cell function.

Jingfang Granule, a traditional Chinese medicine, is often used for the treatment of infectious diseases. *Jingfang Granule* is a blend of 11 herbs. A recent study shows that Jingfang Granule not only significantly increases the median lifespan of C. elegans by 31.2% at a dosage of 10 mg/mL, but also enhances oxidative stress resistance by reducing ROS levels [427]. Jingfang Granule also delays reproductive senescence in C. elegans. The authors propose that Jingfang Granule protects C. elegans from oxidative stress, thereby extending their lifespan. *Jingfang Granule* effectively promotes wound healing in diabetic rats [426]. It exerts anti-inflammatory, and proangiogenic effects in vitro.

Si Jun Zi Tang (SJZT) is composed of four herbal medicines: Ginseng Radix et Rhizoma, Atractylodis macrocephalae Rhizoma, Poria, and Glycyrrhizae Radix et Rhizoma. SJZT is a classic traditional Chinese medicine prescription used to treat aging-related diseases, including skin disease. One study identified 131 bioactive compounds that met absorption, distribution, metabolism, and excretion (ADME) parameters, along with 235 target genes associated with aging [429]. According to the Kyoto Encyclopedia of Genes and Genomes (KEGG), the anti-aging mechanism of SJZT appears to be mediated through inhibition of the PI3K-AKT and p38 MAPK signaling pathways [429]. Thus, SJZT is a potential anti-aging herbal medicine.

Another study indicated that SJZT reduces ROS generation and oxidative stress, increases mitochondrial membrane potential, and upregulates the expression of stem cell markers in vitro [430]. SJZT was also found to suppress the expression of p53, p-p53, and p21, and to downregulate

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p38 phosphorylation. Importantly, the anti-cellular senescence effect of SJZT in eliminating epidermal stem cells (EpiSCs) harboring genomic lesions disappeared after treatment with the p38 inhibitor adesmapimod. This study also identified the top active components, glycyrrhizin, ginsenoside Rg5, ginsenoside Rh2, liquiritin, polyporenic acid C, and atractylenolide II, which exhibited strong affinity for key proteins involved in cellular senescence signaling. Interestingly, SJZT modulates intestinal flora composition, which plays an immunomodulatory role [428].

Wuzi Yanzong Pill (WYP) is a traditional herbal prescription widely used in the treatment of male infertility. It consists of several herbs, including Gouqizi (Fructus Lycii), Tusizi (Semen Cuscutae), Wuweizi (Fructus Schisandrae Chinensis), Fupenzi (Fructus Rubi Chingii), and Cheqianzi (Semen Plantaginis). WYP exhibits neuroprotective and anti-inflammatory properties [432]. Although its precise molecular mechanisms remain unclear, evidence suggests that WYP exerts protective effects on nerve cells. Studies indicate that WYP appears to inhibit apoptosis and enhance the secretion of neurotrophic factors through activation of the PI3K/AKT signaling pathway [433].

In addition, WYP has been shown to reduce apoptosis in testicular tissue and modulate the expression of TP53, TNF-α, AKT1, NF-κB, and IκBα, as well as apoptosis-related proteins including Bcl-XL, Bcl-2, Bax, caspase-3, and caspase-9 [434]. Importantly, clinical studies have demonstrated that WYP can decrease semen elevated DNA fragmentation index (DFI) and reactive oxygen species (ROS) levels, increase SOD activity, and improve sperm DNA integrity [448]. The study also indicates that Wuzi Yanzong inhibits liver injury, lowers blood sugar and blood lipid levels, and appears to exert anti-aging and immunomodulatory effects.

Astragali radix is a widely used herb that exerts immunomodulatory[437], anti-hyperglycemic, anti-oxidant [449], anti-aging, anti-inflammatory[438], cardioprotective [450], antiaging [451], and anti-diabetic effects [439], with minimum side effects [435,449]. Astragali radix contains diverse chemical constituents [452].

p-Coumaric acid is a 4-hydroxycinnamic acid derivative that is abundant in Chinese herbal medicines. It plays a role in oxidative stress–related diseases [453], including inflammation [440], cardiovascular diseases [454], diabetes, MASLD [455], and nervous system disorders, according to recent reviews [451,456]. One study further indicates that the combination of metformin and p-coumaric acid improves MASLD by decreasing lipid accumulation and inhibiting inflammation [457]. p-Coumaric acid also increases outer and plasma membrane permeability in bacteria [458], which may potentially affect endothelial structure and function.

Flavonoids, common constituents of fruits and Chinese herbal medicines, have been shown to protect vascular homeostasis through their antioxidant, anti-inflammatory, and antiaging effects in both in vitro and in vivo studies [445]. One study demonstrated that luteolin, a flavonoid, activates eNOS and increases NO production, resulting in concentration-dependent relaxation of vascular tension in rat aortic rings. Another study reported that luteolin-7-O-glucoside exerts antiproliferative and significant antioxidant effects by inhibiting the signal transduction and activator of transcription 3 (STAT3) pathway [443].

Baicalin, a flavonoid, exhibits antioxidant and antiapoptotic effects and has shown protective effects against Ang II–induced endothelial cell injury. These effects are mediated through inhibition of Bax, Bcl-2, and cleaved caspase-3 expression, subsequent activation of the ACE2/Ang-(1–7)/Mas axis, and upregulation of the PI3K/AKT/eNOS pathway [444].

In summary, while some of these herbal medicines demonstrate clinical benefits, the majority exhibit their antiaging effects primarily in preclinical studies, largely through modulation of inflammation and oxidative stress, two key contributing factors in MetS-induced cognitive decline. These herbs can be categorized as “biologically based practices,” and may be regulated as drugs, dietary supplements, or foods, according to the National Center for Complementary and Alternative Medicine (NCCAM) guidelines [459]. Multiple herbal medicine options for antiaging treatment are increasingly becoming available in various countries, but there is often a lack of evidence from head-to-head preclinical studies to determine whether one of herb is more efficacious than another or than other existing, reported herbs. Moreover, robust and well-designed clinical studies are required to

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support the integration of many of these herbal medicines into standard treatment regimens for the antiaging indications reviewed here. Nonetheless, their long-standing use among diverse ethnic population may help pave the way for them into future therapeutic applications and support their potential role as drugs or dietary supplements.

8. Conclusions

Over the past three decades of research in the glucose metabolism field, it has become clear that insulin and its signaling machinery play numerous critical physiological and pathophysiological roles in MetS. Mutations in the InsR gene reduce receptor number or function, leading to hyperinsulinemia, marked glycemic instability (alternating hypoglycemia and hyperglycemia), and severe InsR, as observed in individuals with Donohue syndrome. Clinically, this syndrome is characterized by multiple abnormalities, most notably a paucity of subcutaneous adipose tissue and marked muscle atrophy.

The image shown in Figure 9 illustrates the interactions among the insulin secretory machinery, IRs, insulin, IGFs, aging, ion channels, and angiotensin-related signaling pathways which are discussed in this review along with their potential roles in MetS-induced cognitive decline.

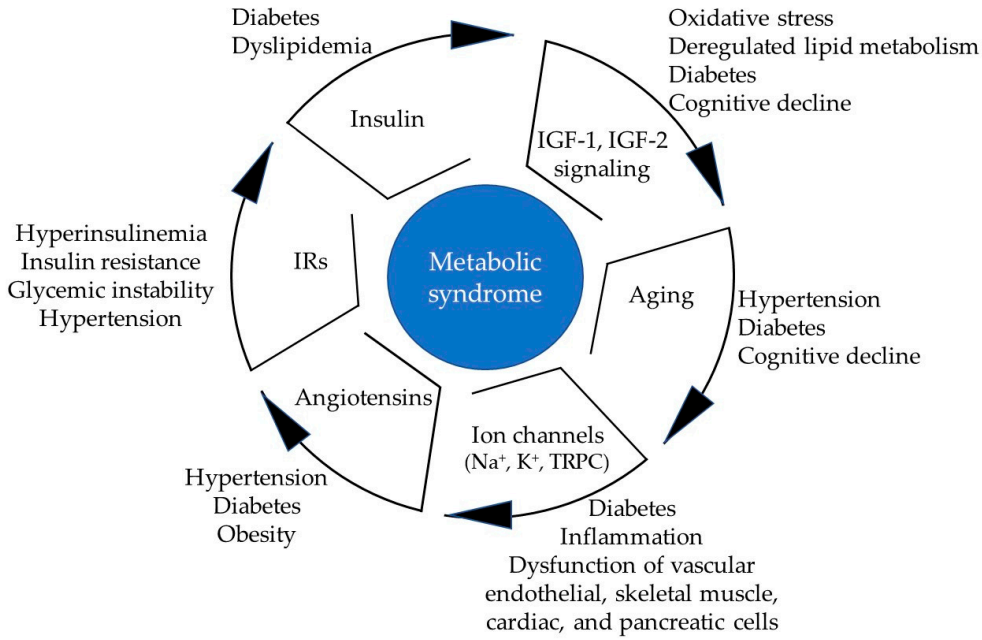

Figure 9. Risk factors contributing to the development and progression of cognitive decline associated with MetS. Insulin and IGF-1 signaling are closely interrelated, and modulation of vascular IGF-1 signaling can lessen the adverse vascular effects of InsR. Reduced IGF-2 receptor expression, a critical regulator of insulin secretion, cell proliferation, and autophagy, has been reported in islets from individuals with T2DM. Angiotensin-dependent AT1 and AT2 receptors also interact with insulin-signaling pathways, regulating insulin's microvascular and metabolic actions in muscle. Clinical observations indicate that the balance between AT1R and AT2R activity is markedly altered in hypertension, obesity, and diabetes, the three major components of MetS. Disruption of ion channel function impairs the physiology of cardiac, vascular endothelial, skeletal muscle, and pancreatic cells, leading to defective glucose-induced insulin secretion. Consequently, structural and functional alterations in any key regulator of electrolyte and fluid balance, glucose metabolism, or insulin secretion can compromise the normal function of the others.

IRs are widely distributed across major tissues and mediate cellular glucose uptake while also participating in IGF-1– and IGF-2–dependent signaling pathways that stimulate protein synthesis in muscle and regulate glucose metabolism. Through these mechanisms, IRs play a central role in

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maintaining glucose homeostasis, a critical physiological process in human body. When homeostatic regulation is impaired or overwhelmed, dysglycemia and diabetes can ensue, highlighting the importance of the agonist–IR axis in metabolic control.

Ion channels, including sodium, potassium, and members of the TRPC subfamily, play critical roles in numerous physiological and pathological processes by regulating cytosolic cation concentrations and membrane potential; their dysfunction has been implicated in the development of diabetes mellitus and its associated complications.

MetS significantly increases the risk of developing diabetes, cardiovascular and kidney disease, and cognitive decline. It is therefore not surprising that structural and functional abnormalities in ion channels can disrupt the physiology of the heart and pancreas, as well as vascular endothelial and smooth muscle cells. Such disturbances may impair cardiac performance, promote inflammation, alter vasomotor function, and contribute to abnormal cellular growth. Collectively, these abnormalities in turn can intensify vascular risk and accelerate tissue and organ dysfunction in individuals with MetS.

The use of pharmacological tools has been instrumental in slowing or preventing the progression of MetS components. However, factors such as drug specificity, potential ion channel gene polymorphisms, and alterations in the expression of genes involved in glucose and lipid metabolism, as well as the RAS, must be carefully considered on an individual basis. In recent years, advances in the identification of new therapeutics, bioactive molecules, and the roles of herbal medicines, along with modifiable extrinsic factors, have significantly improved the management of hypertension, diabetes, and dyslipidemia.

Despite tremendous progress over the last two decades, our understanding of the mechanisms by which traditional herbal medicines influence human health and disease remains incomplete. Although obesity prevalence is low in African nations such as Benin and The Gambia, countries that also report some of the lowest prevalence of diabetes according to the IDF Diabetes Atlas, their traditional diets warrant detailed molecular analysis to identify bioactive compounds, either alone or in combination, that modulate gut microbial composition and function, enhance insulin sensitivity, and reduce chronic inflammation and hypertension, and importantly, promote tissue resilience against cytotoxic stress, thereby contributing to the prevention of cognitive decline. Thus, while we celebrate the discovery of potent antihypertensive, antidiabetic, anti-inflammatory, and lipid lowering drugs, as well as traditional medicines, new research is still needed to address the myriad unanswered questions that remain. Nonetheless, the use of traditional herbal medicine to modulate these risk factors and enhance tissue resilience against cytotoxic stress may offer the potential for mitigating cognitive decline.

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Abbreviations

The following abbreviations are used in this manuscript:

ADA	American Diabetes Association
AMPK	AMP-activated protein kinase
AngII	Angiotensin II

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AT1R	Angiotensin II type 1 receptor
BMI	Body mass index
CVD	**Cardiovascular disease**
CNS	**Central nervous system**
DAG	diacylglycerol
DFI	DNA fragmentation index
DNMT	DNA methyltransferase
EGCG	Epigallocatechin gallate
EVs	Extracellular vesicles
FOXO	Forkhead box O
GPCRs	G protein–coupled receptors
GSK3β	Glycogen synthase kinase 3 beta
HDAC	Histone deacetylase
HDL	High-density lipoprotein
IGF-1	Insulin-like growth factor 1
IGF-2	Insulin-like growth factor 2
IP3	Inositol trisphosphate
IRS-1	Insulin receptor substrates 1
IRS-2	Insulin receptor substrates 2
InsR	Insulin resistance
IRs	Insulin receptors
MAPK	Mitogen-activated protein kinase
MASH	Metabolic dysfunction–associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MetS	Metabolic syndrome
MMPs	Matrix metalloproteinases
mTOR	Mammalian target of rapamycin
NO	Nitic oxide
PBMCs	Peripheral blood mononuclear cells
PLC	Phospholipase C
PI3K	Phosphatidylinositol 3-kinase
RAS	Renin–angiotensin–system
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SASP	Senescence-associated secretory phenotype
SIRT	Sirtuin
SOD	Superoxide dismutase
TBC1D4	TBC1 domain family member 4
NF-κB	Transcription factor nuclear factor-κB
TRP	Transient receptor potential
TSC1	Tuberous sclerosis complex 1
TSC2	Tuberous sclerosis complex 2
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor–α
UKPDS	United Kingdom Prospective Diabetes Study
UN	**United Nation**

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