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Nutritional interventions in prevention of chronic diseases - phytochemicals as sirtuin activators and their role in the regulation of metabolic processes

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Abstract

Introduction: Diet plays a crucial role in preserving health and enhancing overall wellness. Dietary phytochemicals are naturally occurring substances found in foods that may be beneficial in preventing chronic conditions. Sirtuins (SIRTs) are part of a group known as class III NAD-dependent histone deacetylases, which are important in key cellular functions. They participate in multiple processes, such as the balance between oxidants and antioxidants, controlling inflammation, insulin sensitivity, fatty acid metabolism, and aging. The involvement of sirtuin activation through the action of phytochemicals contained in natural products has been described as potentially beneficial in many chronic diseases such as obesity, type 2 diabetes and cardiovascular diseases. In this review, we discussed how selected phytochemicals influence the activation of sirtuins and the impact of their intake on the development and progression of chronic illnesses.

Materials and Methods: A comprehensive literature analysis was conducted using information found in the PubMed database. The research concerned the relationships between phytochemicals, the activation of sirtuins, and the onset of chronic diseases.

Conclusions: Studies show that activation of sirtuins may have a beneficial effect on the development of chronic diseases and should be the subject of further research. Nutritional interventions based on the use of natural products remain the subject of research, and developments in this field have the potential to bring new solutions in the prevention or treatment of chronic diseases.

Keywords: phytochemicals; sirtuin; chronic diseases; nutrition.

Introduction

A well-balanced diet that includes the right amounts of nutrients, microelements, macroelements, vitamins, and minerals is essential for the proper functioning of the body and is crucial for numerous metabolic processes. Diet serves as a vital tool for maintaining health, preventing disease, and supporting overall well-being. It also has an influence on genes expression, production and activation of molecules participating in regulation of various functions in body [1]. In recent decades, researchers have conducted numerous studies

focusing on the supplementation of sirtuin activators and their role in maintaining homeostasis. Dietary phytochemicals are a group of compounds that occur naturally in plants and have properties that can potentially be used in creating strategies to prevent the development of chronic diseases. Phytochemicals are found in many natural foods such as grapes, blueberries, cranberries, cucumbers, apples, raisins, onions, peanuts, olive oil, strawberries, herbs and green tea [2]. In recent years, scientists have been intensively studying effects of their use in human cells. Phytochemicals influence many metabolic pathways and present antioxidant, anti-cancer, anti-aging and anti-inflammatory properties [3, 4, 5]. They have also been described as sirtuin activators [6].

Sirtuins (SIRTs) belong to a family of class III NAD-dependent histone deacetylases that mediate in essential cellular pathways and are present in the cells of a wide range of species. They are involved in various functions, including regulating of processes such as inflammation, insulin sensitivity, the oxidant-antioxidant balance, fatty acid oxidation, aging, and DNA repair, among others [7]. SIRTs are found in various tissues and subcellular compartments, each playing a distinct role in diverse cellular pathways. SIRT1 and SIRT2 are found in both the nucleus and the cytoplasm [8]. Among all the sirtuins, SIRT1 is the most extensively studied and well-characterized. SIRT1 promotes the deacetylation of histones H3, H4, H1, as well as various other proteins [9]. SIRT1 is essential for providing protection against oxidative stress, as it influences the transcription of genes linked to inflammatory factors such as tumor necrosis factor, interleukins, and various other factors [6]. SIRT2 primarily functions through deacetylation and plays a crucial role in regulating the cell cycle as well as maintaining the balance between oxidants and antioxidants [10]. SIRT3, SIRT4, and SIRT5 are located in the mitochondria [7]. Among the mitochondrial sirtuins, SIRT3 is the most extensively studied enzyme. It primarily resides in the mitochondrial matrix and exhibits both deacetylase and decrontonylase activities. SIRT4, primarily found in the mitochondrial matrix, possesses both deacetylase and ADP-ribosyl transferase activities. SIRT5 resides in the mitochondrial matrix and exhibits demalonylase, desuccinylase, and deacetylase activities. This enzyme plays a crucial role in various cellular processes, including ketone body formation, apoptosis, fatty acid oxidation, and the urea cycle [11, 12]. SIRT6 and SIRT7 are primarily located in the nucleus and nucleoli. SIRT6 with ADP-ribosyl-transferase and deacetylase activities, is found in the nucleus, where it plays a crucial role in DNA repair [6]. SIRT7 is primarily found in the nucleus, particularly within the nucleoli. It functions as a deacetylase and plays a key role in several biological processes, including ribosomal DNA

transcription, chromatin remodeling, lipid metabolism, and the regulation of protein production [13, 14].

Resveratrol is a polyphenol classified within the stilbenes family, commonly found in dark grapes, raisins, and peanuts. This compound is thought to offer several health benefits, acting as a protective agent against glycation, oxidative stress, inflammation, neurodegeneration, aging, and various types of cancer [15]. Resveratrol is an active compound with anti-oxidative, anti-inflammatory, anti-obesity properties, potentially able to decrease serum lipids and modulate glucose level [16]. These effects are related, among others, to the activation of sirtuins [16, 17]. Xia et al. described the beneficial effects of resveratrol on improving endothelial function. Some of them were attributed to increased endothelial nitric oxide (NO) synthase derived NO levels due to stimulating its synthesis and preventing superoxide-mediated NO breakdown by resveratrol. This polyphenol activates SIRT1 which stimulates endothelial nitric oxide synthase activity by deacetylation [18]. Curcumin is an active ingredient found in the herbal medicine and dietary spice isolated from the root of the Curcuma longa [6]. Curcumin, through the activation of AMP activated protein kinase (AMPK) and the upregulation of SIRT1, has the potential to work against a diabetes, cardiac fibrosis, ischemia/reperfusion injury and lipid metabolism abnormalities [19]. Curcumin exhibits anti-inflammatory properties by modulating the JAK/STAT inflammatory pathway [20]. Curcumin enhances lipid metabolism in adipocytes through AMPK phosphorylation and SIRT1 activation, suggesting its potential role in preventing obesity [21]. Quercetin is a natural polyphenol found in a variety of foods, including apples, berries, grapes, brassica vegetables, onions, shallots, tomatoes, capers, and tea [22]. Additionally, it is known to be one of the natural activators of SIRT1 [23]. It presents anti-oxidative, anti-inflammatory, immuno-modulating, anti-cancerogenic and cardioprotective properties [23, 24]. Quercetin, a potent reactive oxygen species (ROS) scavenger, reduces the impact of free radicals associated with various pathologies, including diabetes, atherosclerosis, hypertension, neurodegenerative diseases, inflammation, and cancer [25]. Hung et al. demonstrated that quercetin alleviates oxidative damage to endothelial cells caused by oxidized LDL. This protective effect is achieved through the activation of SIRT1 and the modulation of the AMPK/NADPH oxidase/AKT/endothelial nitric oxide synthase signaling pathway [26]. In rat groups experiencing myocardial ischemia-reperfusion injury, the expressions of SIRT1 and PGC-1α were notably reduced. However, following treatment with quercetin, their levels showed a significant increase [27]. Fisetin is a bioactive flavonol molecule of fruits and vegetables such as strawberries, apples, persimmons, lotus root, onions, grapes, kiwi, peach

and cucumber. This compound is known for its potential cardiovascular benefits and anti-inflammatory properties [6]. Its neuroprotective effects have been demonstrated in several models of Huntington's disease [28]. Fisetin effectively alleviates oxidative stress and modulates the immune response by engaging the AMPK/SIRT1 and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways [6]. Singh et al. demonstrated that fisetin exerts protective effects against aging in the rat brain by activating SIRT1, which enhances the deacetylation of NF-κB and promotes the inhibition of pro-inflammatory gene expression [29].

Phytochemicals, through the activation of sirtuins, affect a number of metabolic processes, often important in the pathogenesis of chronic diseases. The growing number of chronic diseases in recent decades, increasing life expectancy of society and high treatment costs burdening healthcare systems require the scientific community to search for new strategies to prevent their development [30, 31]. The beneficial effects of phytochemicals found in natural products, along with nutritional interventions, present an interesting area for further exploration and research. This review aims to summarize current knowledge regarding the potential benefits of consuming naturally occurring sirtuin activators.

Materials and Methods

A comprehensive literature search was performed across several databases, including PubMed and Google Scholar. To identify relevant studies, keywords and their combinations were used, including terms like "phytochemicals", "sirtuins", "nutrition", and "chronic diseases". The analysis incorporated findings from clinical trials, reviews, and meta-analyses that explored the connections between sirtuin activation, diet rich in phytochemicals, and the development of chronic diseases. To ensure that no relevant research was overlooked in the initial search, we gathered additional data from the reference lists of the selected studies.

Phytochemicals and cardiovascular diseases

In last decades cardiovascular diseases (CVDs) remain leading cause of deaths and a serious global problem, especially among elderly population [32]. Diet is well-known modifiable cardiovascular risk factor [33]. The consumption and supplementation of products rich in sirtuin activators appear to be a promising strategy for prevention and a novel therapeutic option. Research proves that decreased level of sirtuins may lead to increased morbidity and progression of CVDs. By deacetylation of the peroxisome proliferator-activated receptor gamma co-activator 1α (PGC-1α), SIRT1 stimulates transcription factors participating in energy metabolism. Lower expression of PGC-1α has been found in cardiac

tissue of patients with heart failure and reduced ejection fraction [34]. Deficit of SIRT3 in cells derived from cardiac tissue causes increased susceptibility to ischemia-reperfusion injury. These cells, compared to the wild-type cardiac tissue, present greater infarct and worse recovery [35]. The deacetylation of the transcription factor GATA4 by activated SIRT7 appears to play a vital role in preventing cardiac hypertrophy in myocardial tissue that is subjected to the combined effects of hypertension and aging. Decreased level of SIRT7 leads to pressure overload and cardiac hypertrophy [36]. However, overexpression of SIRT1 might be harmful for cardiac cells and result in worse cardiac function. Constitutive overexpression of SIRT1 causes impairments of mitochondrial functions and leads to dilated cardiomyopathy in transgenic mice [37, 38]. Sirtuins are known to modify lipids metabolism and protect blood vessels against atherogenesis [39]. These properties might be used in the primary and secondary prevention of cardiovascular events. In mice model, a decrease in sirtuin 1 levels due to a high-fat diet led to DNA damage and cellular senescence in vascular smooth muscle cells. These results suggest that SIRT1 plays crucial role in protection against atherosclerosis in inflamed endothelium [40]. Decreased level of SIRT6 caused increased expression of NKG2D ligand involved in atherogenesis process in macrophages and endothelial cells of mice model. That resulted in activation of natural killer (NK) cells and increased production of inflammatory cytokines. Examined mice had less stable atherosclerotic plaques and more severe atherosclerosis [41].

Efficacy of sirtuins activators consumption and supplementation has been proven in many clinical trials. For instance, a double-blind, randomized, placebo-controlled trial was conducted on group of 56 patients with type 2 diabetes mellitus and coronary heart disease. All participants were divided randomly into 2 groups. 28 study participants consumed 500 mg of resveratrol daily for 4 weeks, another 28 patients received placebo for the same duration. Real-time PCR analysis showed upregulated SIRT1 in peripheral blood mononuclear cells of participants supplementing resveratrol. Researchers observed increased total antioxidant capacity (TAC), HDL-cholesterol level and beneficial effect on total-/HDL-cholesterol ratio in resveratrol group. Authors of the study assumed, that elevated level of SIRT1 activated by resveratrol consumption was partially responsible for all these effects [42]. Another double-blind randomized placebo-controlled trial examined effects of omega 3 fatty acids and vitamin E co-supplementation on expression of SIRT1 gene in patients with coronary artery disease (CAD). Sixty male participants with CAD had at least 50% stenosis in coronary artery. Patients were randomly divided into three groups receiving 4g/day of omega 3 and 400 IU of vitamin E (group 1), 4g/day omega 3 and vitamin E placebo (group 2), omega 3 placebo and

vitamin E placebo (group 3). The analysis showed statistically different SIRT1 gene expression between group 1 and group 3. Authors conclude that supplementation of omega 3 and vitamin E results in increased activation of SIRT1 in CAD patients and can cause beneficial effects such as modulation of endothelial nitric oxide synthase (eNOS) and decrease of CRP, important in relieving inflammation of coronary arteries [43]. However, it needs to be noted that beneficial effects presented in both studies were caused not exclusively by sirtuins activation, but also by other pathways associated with resveratrol or omega 3 and vitamin E intake. Further research describing exact role of sirtuins activation in cardiovascular diseases are required.

Phytochemicals in obesity

Obesity ranks among the most significant public health challenges due to its strong links to increased morbidity and mortality. The rising prevalence of obesity in the coming decades will be driven by lifestyle factors such as sedentary jobs, advancements in technology, and the consumption of unhealthy foods [44]. Research on SIRTs has highlighted their crucial role in maintaining metabolic homeostasis, regulating insulin secretion and sensitivity, and facilitating the mobilization and oxidation of stored fat. This is achieved through their interaction with transcription factors and adipokines [45]. Research on subcutaneous adipose tissue in individuals with normal weight, overweight, and obesity has revealed notable differences in the mRNA expression levels of SIRT1, SIRT2, SIRT3, and SIRT6 [46]. In overweight and obese patients, the expression of SIRTs in subcutaneous adipose tissue was found to be lower compared to individuals of normal weight. The expression levels of sirtuin genes and their target genes (PPAR- α, PGC1- α, NRF1, DGAT1, PPAR-γ and FOXO3α) was measured by qPCR. In obesity, several factors contribute to the persistent activation of JNK1 (c-Jun N-terminal kinase 1), which leads to the degradation of SIRT1. JNK1 phosphorylates SIRT1 and induces protein degradation [47]. Research has demonstrated that AMPK/Sirt1 activators possess weight loss properties [48]. Resveratrol supplementation has been shown to significantly reduce body weight, BMI, fat mass, and wrist circumference, while also increasing lean mass. Notably, these changes occur without impacting leptin and adiponectin levels [49]. A study by Fischer-Posovszky et al. suggested that resveratrol impacts adipose tissue mass and function in ways that could potentially disrupt the development of obesity-related comorbidities. Resveratrol SIRT1-dependently inhibits preadipocyte proliferation and adipogenic differentiation [50]. Resveratrol is known to decrease lipid accumulation in mature adipocytes by repressing PPARγ activity through a SIRT1-dependent mechanism [51]. In a

randomized, double-blind, 30-day crossover study involving obese men, participants received either 150 mg per day of resveratrol or a placebo. Those in the resveratrol group exhibited enhanced activation of AMPK, along with increased levels of SIRT1 and PGC-1α proteins. Additionally, there was a notable rise in citrate synthase activity and an improvement in muscle mitochondrial respiration on a fatty acid-derived substrate [52]. In another study, a daily dosage of 3 grams of resveratrol taken for 12 weeks significantly elevated the expression of skeletal muscle SIRT1 and AMPK in patients with type 2 diabetes mellitus. This increase was associated with a noticeable rise in resting metabolic rate, suggesting potential exercise-mimicking benefits of the treatment [53]. Numerous studies have demonstrated that AMPK, SIRT1, and PGC-1α play a crucial role in inhibiting the differentiation of preadipocytes, reducing adipocyte proliferation, inducing adipocyte apoptosis, decreasing lipogenesis, and promoting both lipolysis and fatty acid β-oxidation, particularly in conjunction with resveratrol [54].

Phytochemicals in diabetes

Glucose homeostasis is maintained through the coordinated interactions among various organs and tissues. When there are disruptions in insulin secretion or sensitivity, it can lead to metabolic disorders [55]. The mammalian sirtuin family, which is distributed across various cellular compartments, plays a crucial role in regulating numerous biological functions and is associated with a wide range of diseases, including diabetes. Sirtuins continue to be a focus of research, demonstrating their significant role in regulating glucose and lipid homeostasis [56]. SIRT1 is involved in a range of metabolic processes, including gluconeogenesis, pancreatic insulin secretion, hepatic lipid metabolism, the accumulation and maturation of fat cells and the daily regulation of metabolism [57]. The regulation of systemic metabolism, particularly through glucose control and lipid homeostasis, is influenced by SIRT1, which exerts its effects through its deacetylating ability. SIRT1 promotes production of adiponectin by acting on white adipose tissue [58].

Pancreatic β-cells play an important role in glucose homeostasis. SIRT1 enhances insulin secretion from pancreatic β-cells by reducing the transcription of Ucp2 (uncoupling protein 2). Ucp2 is responsible for uncoupling ATP synthesis in mitochondria and reducing inulin secretion. SIRT1 suppresses the NF-κB pathway and protects β-cells from cytokine-mediated damage [59]. Mice with the missense mutation L107P in the SIRT1 gene showed

greater destruction of islets and experienced early hyperglycemia following treatment with streptozotocin, in contrast to wild-type mice without the SIRT1 knockout [60]. SIRT1 is emerging as a promising target for novel therapies aimed at type 2 diabetes mellitus. This is largely due to its ability to modulate insulin secretion and enhance insulin resistance through regulatory effects on post-insulin receptor signaling, inflammation, mitochondrial function, and circadian rhythms [61]. SIRT4 is also involved in the regulation of insulin secretion. Zaganjor et al. demonstrated that SIRT4 knockout mice showed increased insulin secretion and developed insulin resistance after a period of seven months. Chronic hyperinsulinemia is thought to lead to insulin resistance [62]. In different study it was observed that SIRT4-knockout mice exhibited uncontrolled elevated insulin secretion, resulting in persistently high levels of insulin. This condition ultimately led the mice to develop insulin resistance [63].

Clinical trials examining the supplementation of sirtuins activators in patients with diabetes mellitus show promising results. In randomized placebo-controlled, double blind trial researchers examined effects of green cardamom (Elettaria cardamomum) consumption in patients with type 2 diabetes mellitus. Cardamom is a spice rich in polyphenols (such as quercetin) that are able to activate sirtuins. Eighty-three overweight or obese participants diagnosed with type 2 diabetes mellitus were randomly assigned to two groups. The intervention group received 3 grams of green cardamom each day for a duration of 10 weeks, while the placebo group was given rusk powder during the same period. Analysis revealed a reduction in insulin, triglycerides, and serum HbA1C levels in the cardamom group when compared to the placebo group. Statistically significant increase of SIRT1 was observed in the intervention group. Authors notice that improved glycemic indices were probably the result of cellular pathways associated with polyphenols and sirtuins [64]. A different double-blind, randomized, placebo-controlled clinical trial conducted on the group of 75 adult patients with type 2 diabetes mellitus, examined effects of daily consumption of vitamin D and calcium on serum SIRT1, SIRT6 and adiponectin. Participants were randomly divided into three groups consuming D-fortified-yogurt drink with 1000 IU of vitamin D and 300 mg of calcium, Ca+D-fortified-yogurt drink with 1000 IU of vitamin D and 500 mg of calcium or plain yogurt drink with no vitamin D and 300 mg of calcium, respectively. All interventions were conducted over a period of 12 weeks. SIRT1 and SIRT6 levels were notably higher in the group that consumed a drink containing 1000 IU of vitamin D and 500 mg of calcium. The researchers note that a higher level of sirtuin 6 may help enhance glycemic control by influencing essential pathways involved in the development of type 2 diabetes, including gluconeogenesis, insulin secretion or lipogenesis [65].

Discussion

In this article we present many potential advantages of daily consumption of SITRs activators and their significant role in homeostasis. According to research, sirtuins are regulators of pathways associated with pathogenesis of many disorders, including type 2 diabetes mellitus, obesity and cardiovascular diseases, which remain growing problem of worldwide healthcare. Statistics of American Heart Association and NHANES (National Health and Nutrition Examination Survey) present data concerning prevalence of CVD, such as coronary heart disease, heart failure, hypertension or stroke. According to that data, prevalence in adults aged 20 years or more is 49,25% and expands with age [66]. Analysis from 2017 indicate that constantly growing problem of overweight and obesity affects about 2 billion people, which consists about 30% of the population [67]. In last two decades number of adult patients suffering from type 2 diabetes mellitus increased from 151 million to 463 million worldwide [68]. Such a high prevalence of these diseases results in significant financial burden of healthcare around the world. Diet enriched in activators of SIRTs might be a promising strategy of prevention and new treatment opportunity in diseases that remain a serious global problem. Except SIRTs activation, dietary compounds such as resveratrol and quercetin, participate in sirtuin-independent pathways providing beneficial effects on discussed diseases. This property of presented method might be considered as its advantage and disadvantage at the same time. It should be determined to what extent the benefits observed in studies are the result of sirtuin-dependent mechanisms, and what part is the result of other properties, provided by SIRTs activators. Although research clearly indicates the direct beneficial effect of sirtuins, the results of analysis still remain inconsistent. Some authors conclude there is no association between increased serum concentrations of sirtuins and desirable metabolic changes. No correlation between improvement of metabolic markers and higher SIRT1 activity were found [69]. Future randomized research is required to explain that matter.

Despite many promising results of research performed on mammals, current knowledge regarding role of sirtuins in human metabolism is not complete. So far, the data obtained in last decades mainly concern SIRT1-mediated cellular pathways. To use sirtuins as the new prevention strategy or therapeutic option, further analysis explaining more mechanisms of all SIRTs are needed. More randomized double-blinded clinical trials with consumption of products rich in SIRTs activators or their daily supplementation are crucial to obtain the best results and determine all cellular mechanisms mediated by sirtuins activated by

different foods and supplements. It can be problematic to determine the amounts of consumed products necessary to achieve adequate activation of sirtuins and what products should be recommended to patients with specific diseases. It also needs to be determined whether the level of sirtuin activation induced by food supplementation should be monitored by laboratory testing.

Author's contribution

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