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Sirtuins as multifunctional regulators: Role in the pathogenesis of metabolic, inflammatory and neurodegenerative diseases and the effect of physical activity on their activity

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Abstract

Sirtuins, a family of NAD+-dependent deacetylases and ADP-ribosyltransferases, regulate cellular homeostasis and adaptive responses to environmental changes. Comprising seven isoforms (SIRT1–SIRT7), these enzymes have diverse functions, including gene expression regulation, mitochondrial function, oxidative stress response, and cellular aging. Dysregulated sirtuin activity is implicated in metabolic, inflammatory, and neurodegenerative diseases such as obesity, type 2 diabetes, cardiovascular disease, Alzheimer's, and Parkinson's. Sirtuins modulate metabolic pathways by influencing glucose and lipid metabolism, enhancing insulin sensitivity, and promoting mitochondrial biogenesis. Their role in reducing inflammation and oxidative stress positions them as potential therapeutic targets for chronic conditions and age-related disorders. Compounds like resveratrol and lifestyle factors such as physical activity are potent sirtuin activators, highlighting their therapeutic potential.

Physical activity, a cornerstone of non-pharmacological health interventions, increases NAD+ availability, upregulating sirtuin activity. This effect underscores exercise as a modulator of sirtuin pathways, with protective effects against chronic diseases. Studies show that regular physical activity can enhance sirtuin function, improving metabolic health, reducing oxidative damage, and providing neuroprotection. This review offers an overview of sirtuin biology, their role in disease pathogenesis, and the molecular mechanisms underlying the beneficial effects of exercise on sirtuin activity.

Keywords

Exercise and sirtuins, Sirtuins, Multifunctional regulators, Physical activity, Oxidative stress, Mitochondrial function, Gene regulation, Neurodegenerative diseases, Metabolic diseases, Inflammatory diseases, Sport, NAD+ metabolism

Sirtuins

Sirtuins are a family of NAD+-dependent enzymes that play a crucial role in cellular regulation, influencing processes such as metabolism, inflammation, and stress responses. These enzymes were initially identified in yeast, where they were linked to lifespan extension, and subsequent research has revealed their critical involvement in mammalian physiology. In humans, seven sirtuin isoforms (SIRT1–SIRT7) have been identified, each with distinct functions and intracellular localization. Nuclear sirtuins, such as SIRT1, SIRT6, and SIRT7, are involved in chromatin remodeling, gene expression, and DNA repair. In contrast, SIRT2 is predominantly cytoplasmic and regulates cell cycle progression, while mitochondrial sirtuins (SIRT3, SIRT4, and SIRT5) are key modulators of energy metabolism and oxidative stress resistance (1). The primary mechanism through which sirtuins exert their regulatory functions is deacetylation, a process that involves the removal of acetyl groups from lysine residues in target proteins. This reaction is dependent on NAD+, linking sirtuin activity to cellular energy status. Under conditions of metabolic stress, such as caloric restriction or exercise, increased NAD+ levels enhance sirtuin function, promoting adaptive cellular responses (2). Beyond their metabolic roles, sirtuins have been implicated in cellular defense mechanisms, particularly in oxidative stress and inflammation. SIRT3 plays a protective role in mitochondria by activating antioxidant enzymes, such as superoxide dismutase 2 (SOD2), which neutralizes reactive oxygen species and prevents mitochondrial dysfunction (3). Similarly, SIRT1 has been shown to inhibit nuclear factor kappa B (NF-κB) signaling, thereby reducing pro-inflammatory cytokine expression and contributing to the resolution of chronic inflammation. This anti-inflammatory function of SIRT1 is particularly relevant in metabolic disorders, where excessive inflammation contributes to insulin resistance and cardiovascular complications (4).

Despite significant advances in understanding sirtuin biology, several unanswered questions remain regarding their precise mechanisms of action and the potential side effects of long-term pharmacological modulation. Future research should focus on elucidating the context-dependent roles of sirtuins, particularly in the interplay between metabolic and neurodegenerative diseases. By further exploring their regulatory networks, sirtuins may

provide novel insights into aging-related disorders and open new avenues for targeted therapeutic strategies.

Importance of sirtuins in psoriasis

Psoriasis is a chronic inflammatory skin disease of complex etiology, affecting 2-3% of the population worldwide (5). Its clinical manifestations include well-demarcated, erythematous, oval plaques covered with silvery scales. The characteristic features of this disease are excessive proliferation and abnormal differentiation of keratinocytes, as well as infiltration of numerous inflammatory cells (6). The immune system plays a key role in the development of psoriasis, although there is still a lack of conclusive evidence supporting its autoimmune nature. To date, the specific autoantigen responsible for initiating the disease process has not been identified. In addition, psoriasis can be triggered by a variety of intrinsic and extrinsic factors, such as skin trauma, sunburn, infection, use of certain medications and chronic stress (7). Sirtuins, thanks to their ability to modulate the immune response through deacetylation mechanisms, affect cytokine production and immune cell differentiation, suggesting their important involvement in the pathogenesis of inflammatory diseases, including psoriasis (8). Studies have shown that SIRT1 plays an important role in the differentiation of human keratinocytes, while inhibiting their excessive proliferation (9). SIRT1 limits the expression of TNF-α through a deacetylation mechanism, leading to reduced production of pro-inflammatory cytokines (10). Overexpression of SIRT1 has been correlated with a decrease in TNF-α, IL-1β and IL-8 levels, indicating its potential anti-inflammatory effects (11). In contrast, NAD+-mediated SIRT6 activity may lead to increased TNF-α synthesis. The balance between SIRT1 and SIRT6 may be important for controlling inflammation in psoriasis (12). Fan et al. (13). found that in psoriasis patients, not only is the expression of SIRT1 reduced, but also SIRT2, SIRT3, SIRT4 and SIRT5, while the levels of SIRT6 and SIRT7 are increased. A study by D'Amico et al. (14) showed that in healthy skin, almost all cell nuclei in the epithelial layer show intense staining indicative of SIRT1. In contrast, in samples from psoriasis patients, the level of this protein was significantly reduced, and its presence was rarely detectable and of low intensity. These results suggest that sirtuins, especially SIRT1, may have a key function in regulating immune mechanisms within the epidermis, and their abnormal expression may have a significant impact on the development of psoriasis.The experimental use of the activator SIRT1 (SRT2104) in the treatment of moderate to severe psoriasis has provided promising results. The compound significantly reduced the expression of genes associated with the response to IL-17 and TNF-α, as well as genes involved in the

process of keratinocyte differentiation. In addition, SRT2104 showed a good safety profile, suggesting that pharmacological modulation of sirtuin activity may be a potential therapeutic direction for the treatment of psoriasis (15).

Importance of sirtuins in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic disease of autoimmune origin. The disease has an unknown etiology and is more common in women, mainly in the elderly (16). RA leads to joint inflammation and subsequent joint damage, but it also involves other organs, such as heart, lungs, and kidneys. Typical symptoms of the disease are pain, swelling and joint stiffness, most commonly in the hands and feet, but it can also involve larger joints, such as the knee joint. The lesions usually occur symmetrically (17). The presence of morning stiffness lasting more than one hour is also characteristic. The onset of the disease is sometimes insidious and may manifest as a subfebrile state, fatigue, or weight loss (18). Rheumatoid arthritis is a progressive disease and can lead to numerous serious complications, including disability and even premature death, so it is important to implement appropriate treatment as soon as possible and achieve clinical remission (16). A properly functioning joint is formed by a synovial membrane and synovial fluid that enable its free mobility. The synovial membrane is composed mainly of connective tissue cells, but also of specialized cells: macrophage-like synovial cells (type A) and fibroblast-like synovocytes (type B) (19). In the course of rheumatoid arthritis, there is excessive stimulation of the synovial membrane in the affected joints, proliferation of fibroblast-like synovocytes (FLS) and their release of pro-inflammatory cytokines along with proteases that destroy cartilage and bone tissue. Therefore, it seems that an effective method to slow the development of the inflammatory process in RA is to inhibit the proliferation and promote apoptosis of FLS (20). In view of the research conducted on SIRT proteins and the demonstration of their broad effects on cellular processes, their involvement in the pathogenesis of rheumatoid arthritis has begun to be investigated (21). The proteins, influencing the cells of the immune system, can modulate the course of the inflammatory disease, and their action regulating the processes of maturation, differentiation, and apoptosis of chondrocytes, osteoblasts, and osteoclasts has a protective effect on the cartilage and bone tissue of the joint (20). Among the entire family of sirtuins, SIRT1 is the most well-understood when it comes to its role in the development of autoimmune diseases (20). This protein affects many cells involved in the progression of rheumatoid arthritis and plays a key role in regulating the inflammatory process. SIRT1

inhibits the proliferation and induces apoptosis of fibroblast-like synovocytes, leading to a decrease in synovial membrane hypertrophy and inhibition of inflammatory processes (22). In addition, overexpression of SIRT1 contributes to the reduction of pro-inflammatory cytokines release (TNF-α, IL-1β, IL-6) and osteoblast apoptosis through proper regulation of NF-κB and p53 signaling (23). SIRT1 also affects macrophages, participating in their adhesion and migration during the inflammatory process by interacting with intercellular adhesion molecule 1 (ICAM-1) (24). The role of other sirtuins in the pathogenesis of rheumatoid arthritis is still poorly understood, and previous research results often show inconsistencies (17). Continued research on SIRT1 and clarification of its effects on specific molecular pathways occurring in cells should bring new therapeutic options and a chance to reduce the negative effects of the disease (22).

Sirtuins in neurodegenerative diseases – Parkinson's disease and Alzheimer's disease

Sirtuins are common proteins present in the human brain. There are different types of them with different activities depending on the type of brain cell, age or brain area. Using MRM mass spectrometry methods, 7 mammalian sirtuins were identified, of which the most common in the human brain turned out to be SIRT-2 with strong expression in oligodendrocytes and SIRT-1 in neurons. (25). SIRT-2 has been shown to not only affect the differentiation of oligodendritic cells (26), but also by being present in microglia cells, inhibit their activation, thereby showing anti-inflammatory effects within the brain tissue. (27). In addition, both SIRT-2 and SIRT-1 play a role in the cell's response to exposure to oxidative stress and nutrient depletion. While SIRT-2 activity in cells increases under exposure to oxidative stress and nutrient depletion, promoting cell death (28), SIRT-1 plays a role in mechanisms of immunity and cell longevity (29). Alzheimer's disease is a neurodegenerative disease that progresses with age, is a serious modern health problem and typically manifests as progressive cognitive decline. (29). Underlying the pathogenesis of the disease is the deposition in various regions of the brain of deposits made up of abnormal hyperphosphorylated tau forming proteins known as NFTs and beta- amyloid. Their accumulation causes local chronic inflammation, and thus leads to impaired nerve transmission and nerve cell death (29). The activity of individual sirtuins has been shown to change over the course of Alzheimer's disease. That is how the expression of the neuroprotective and longevity-promoting SIRT-1 as well as SIRT-3 decreases with the progression of Alzheimer's disease, while the amount of SIRT-5 present in activated microglia

cells increases (30). This creates a potential therapeutic target for creating factors that penetrate the brain across the blood-brain barrier, promoting SIRT-1 activity and thus neuroprotective processes (31). In addition, sirtuins are thought to help reduce the pathological intracellular accumulation of NFTs by affecting the inhibition of tau protein phosphorylation (32), while SIRT1 by promoting the degredation of their hyperphosphorylated deposits (33). Furthermore, SIRT-1 contributes to reducing the formation of toxic Aβ deposits in nerve cells by affecting a cascade of reactions leading to inhibition of the activity of AβPP-cleaving enzyme 1 (BACE1), which is responsible for their formation (34). Additionally, SIRT-1 may exhibit anti-inflammatory effects, if only by inhibiting the activity of the NF-κB dependent pro-inflammatory signaling pathway in microglia cells (35). Another neurodegenerative disease influenced by sirtuins is Parkinson's disease, which is characterized by a progressive deterioration of dopaminergic transmission, thereby impairing motor function (36). Resveratrol, which enhances SIRT-1 activity, has been shown to have protective effects against dopaminergic neuron-damaging cytotoxic agents such as MPP+, sodium azide and thrombin (37) and through SIRT-1-mediated activation of Peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) may exhibit neuroprotective effects in Parkinson's disease by not only combating oxidative stress, but also increasing nerve cell viability (38). In contrast, the role of SIRT-2 in Parkinson's disease remains ambiguous. On the one hand, most reports indicate that inhibition of SIRT-2 activity contributes to the reduction of dopaminergic cell death, showing a neuroprotective effect. On the other hand, some point to a protective role of SIRT-2 against oxidative stress and its increased susceptibility to death under inhibition of SIRT-2 activity (39).

Huntington's disease is an autosomal dominant disorder characterized by impairment of the brain's motor and cognitive functions due to the accumulation of the abnormal huntingtin protein in nerve cells (40). Although there is now considerable evidence on the neuroprotective effects of SIRT-1 activation and SIRT-2 inhibition in Huntington's disease, the role of sirtuins in Huntington's disease remains inconclusive and requires further study (41).

It has also been shown that an increase in SIRT-1 activity stimulated by resveratrol, for example, exhibits neuroprotective effects against nerve cells in prion disease by inhibiting the deposition of abnormal prion isoforms (42).

It is due to the aforementioned properties that sirtuins are believed to play a very important role in the proper homeostasis of the entire central nervous system during the aging process and are seen as a promising therapeutic target in the search for new treatments for neurodegenerative diseases (43).

Insulin resistance and its relationship to mitochondrial function and SIRT1

Insulin resistance is a state of reduced tissue sensitivity to insulin that affects carbohydrate, lipid and protein metabolism and increases the risk of type 2 diabetes (T2D), cardiovascular (44). Impaired insulin signaling plays a key role in its development, especially in skeletal muscle, which accounts for about 80% of insulin-dependent glucose uptake (45). The most significant disorder leading to the development of insulin resistance in muscle is impaired insulin signaling, resulting in impaired translocation of GLUT4 to the cell membrane, which leads to reduced glucose transport into the muscle cells, and consequently reduced glucose metabolism inside the cell (46). Free fatty acids, whose blood levels are elevated in obesity and related diseases, also play a role in impaired insulin action and impaired glucose transport into muscle cells (47). Obesity is a chronic disease affecting the entire body, in which there is an excessive accumulation of adipose tissue that causes changes in the functioning of tissues and organs (48). Adipose tissue plays an important endocrine role, secreting adipokines, including adiponectin, which increases tissue sensitivity to insulin by inhibiting gluconeogenesis in the liver and enhancing glucose uptake and fatty acid oxidation in muscle (49). In obese individuals, especially those with excess visceral fat, adiponectin levels are reduced, which promotes the development of insulin resistance (50). Free fatty acids are the second primary energy substrate used by skeletal muscle, and a decrease in the oxidation of VFAs results in excessive accumulation of toxic forms of lipids in the form of ceramides and diacylglycerols in muscle, resulting in post-receptor impairment of insulin signaling (51). Obesity leads to chronic inflammation, in which adipocytes and macrophages secrete inflammatory mediators (CCIs, ROS, cytokines) that activate the NFκB and JNK pathways. NFκB regulates the transcription of pro-inflammatory genes, while JNK phosphorylates IRS-1, inhibiting insulin (52). Further factors that are associated with the development of insulin resistance include mitochondrial dysfunction in skeletal muscle, caused by abnormal structure, reduced oxidative capacity or impaired biogenesis. The coactivator PGC1α, which affects glucose and lipid metabolism, plays an important role in regulating mitochondrial biogenesis (53). Its reduced expression in muscle is observed in animal models of diabetes (54). Studies have shown that PGC1α overexpression increases the activity of fatty acid transport and oxidation proteins, and improves insulin-dependent glucose transport (55). Despite intensive research, the molecular mechanisms of insulin resistance are not fully understood, and as a result of this problem, new factors that regulate insulin sensitivity are constantly being sought.

New reports also suggest a role for SIRT1 in regulating glucose and lipid metabolism (56). Sirtuin 1 (SIRT1) is an NAD+-dependent enzyme that affects gene expression by deacetylating histones and other proteins (57). Sirtuins are activated by increasing NAD+/NADH ratio. In a state of caloric surplus, NAD+ is consumed by intense glycolysis, in contrast to the starvation period, when respiratory chain activity increases and there is an increasing NAD+/NADH ratio and consequent activation of sirtuins (58). Activation of SIRT1 under caloric restriction can improve insulin sensitivity and increase glucose uptake in skeletal muscle (59). SIRT1 can also be activated by polyphenols, such as resveratrol, which mimics the state of starvation. Studies on mice fed a high-fat diet showed that resveratrol improved insulin sensitivity and had a slight effect on weight loss (60). In contrast, studies using resveratrol in obese humans showed a reduction in plasma glucose and insulin values, which resulted in a lower HOMA index, indicating an increase in insulin sensitivity. A reduction in triacylglycerols and inflammatory markers such as IL-6 and TNF-α was also observed, while free fatty acid levels were not reduced (61). SIRT1 is one of the factors responsible for normal white adipose tissue insulin sensitivity (60). SIRT1 expression in human subcutaneous adipose tissue is negatively correlated with macrophage count. Silencing of SIRT1 in adipose tissue leads to increased release of pro-inflammatory cytokines and macrophage infiltration (62). SIRT1 reduces insulin resistance by inhibiting NFκB activity and affecting IRS-1 phosphorylation, which reduces glucose uptake (63). The importance of sirtuins in controlling glucose and fat metabolism, as well as in the development of insulin resistance in the liver, adipose tissue and skeletal muscle, underscores their role in regulating metabolic diseases such as type 2 diabetes and its diabetic complications (64).

Key factors influencing sirtuin activity

Dietary

The earliest reports on caloric restriction and its beneficial effects on the body emerged in the 20th century, highlighting the importance of reducing calorie intake without causing malnutrition (65). Recent studies suggest that reducing calorie intake may help slow down aging and prevent age-related diseases (66). Maldonado et al. (2021) identified it as the most effective strategy for delaying the development of various age-related diseases. In mice, a short-term reduction in calorie intake following a shift from a standard diet leads to an increased expression of all seven sirtuin proteins (67). A higher expression of SIRT1 was also detected in mice placed on a diet with a 20% calorie reduction following a period of

overfeeding. Caloric restriction alleviated hepatic steatosis, lowered superoxide anion levels, and enhanced the expression of catalase and superoxide dismutase proteins (68). Aditionally, caloric restriction helps mitigate the negative effects of excessive fat accumulation. Opstad et al. identified a strong link between sirtuins, obesity, and caloric restriction. Their study focused on obese patients who underwent bariatric surgery, revealing that gastric bypass surgery led to a significant reduction in plasma SIRT1 levels. Triglycerides and CRP (C-reactive protein) were identified as independent variables influencing SIRT1 levels. As patients lost weight, SIRT1 concentrations declined, suggesting a notable decrease in inflammation and oxidative stress (69). Overall, caloric restriction regulates the activity and interactions of sirtuins, promoting anti-aging and disease-preventing effects at the cellular and physiological levels (70). The expression of SIRT1 and SIRT2 also rises when the intake of simple sugars in the diet is reduced. However, their levels are lower in individuals with type 1 and type 2 diabetes (71). Adiotionally, a diet rich in fructose leads to an accumulation of glycation products, which suppress SIRT1 expression and negatively affect muscle function in mice (72).

Physical activity

Multiple studies have investigated the effects of exercise on sirtuin expression by assessing mRNA levels, protein content, and enzymatic activity. Although direct comparisons between these studies can be challenging, several key findings stand out (73). Physical activity induces metabolic stress at the cellular level, influencing sirtuin activity (74). Exercise promotes the expression of SIRT1 and SIRT3 in skeletal muscles by modulating oxidative metabolism, supporting mitochondrial biogenesis, and increasing ATP production (75). Dali-Youcef et al. (2007) further emphasized that physical activity enhances sirtuin activity and/or expression, leading to improved oxidative metabolism efficiency, increased biogenesis and mitochondrial function, and better maintenance of the antioxidant system (76). In 2009, Palacios et al. found that SIRT3 in mouse skeletal muscle adapts dynamically to six weeks of voluntary exercise, playing a role in regulating downstream molecular responses. Their study demonstrated that physical activity elevates SIRT3 protein levels, enhances the phosphorylation of cAMP response element-binding (CREB), increases the expression of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), and boosts citrate synthase activity (74). Lanza et al. (2008) were among the first to investigate the relationship between exercise, aging, and sirtuin expression. They conducted a cross-sectional study involving both young and older healthy individuals, categorized as either sedentary or

trained (engaging in at least 1 hour of exercise six days per week for over four years). Their findings indicated that regular endurance exercise helps mitigate age-related mitochondrial dysfunction. Regardless of age, consistent training led to increased citrate synthase activity and elevated expression of proteins associated with mitochondrial biogenesis, including PGC-1α, nuclear respiratory factor 1 (NRF1), mitochondrial transcription factor A (TFAM), and SIRT3 (75). These results were later confirmed by Villanova et al. (2013), who reported that sirtuin deacetylase activity declines after the age of 40 but remains upregulated in athletes (77). Sellitto et al. (2022) identified exercise training as a natural stimulator of SIRT1 in humans. Middle-distance runners exhibited higher levels of SIRT1 mRNA compared to individuals with a sedentary lifestyle. Interestingly, the use of dietary supplements like vitamin C, vitamin E, and mineral salts during training impeded the activation of SIRT1 induced by physical activity (78).

Moreover, physical activity exerts a cardioprotective effect. Continuous moderate exercise has been shown to activate the SIRT1 pathway, especially in the early phases of myocardial infarction. SIRT1 activation leads to the deacetylation of p53, which in turn decreases the expression of apoptosis-related proteins such as Bax and caspase-3, thereby reducing cell apoptosis (79). This protective effect is particularly notable in the border zone following myocardial infarction (80). Additionally, moderate exercise lowers the release of pro-apoptotic molecules, significantly decreasing myocardial cell apoptosis and safeguarding the heart before ischemic injury. SIRT1's ability to shuttle between the nucleus and cytoplasm further enhances its role in protecting cardiac cells by improving nuclear target deacetylation (81). SIRT1 plays a crucial role in the development of various cardiovascular diseases by modulating multiple cellular processes (79). Also, the upregulation of SIRT3 through exercise helps protect myocardial cells from oxidative stress (82). Regular physical training significantly enhances SIRT3 expression, influencing various cellular pathways (83).

Resveratrol

Research on sirtuin activators primarily examines resveratrol, a flavonoid naturally present in various foods and beverages (84). In 2003, resveratrol was discovered through a high-throughput screening of small molecules acting as allosteric activators of yeast SIRT1, aiming to identify a caloric restriction mimetic. This screening also identified other compounds, including stilbenes (e.g., resveratrol), chalcones (e.g., butein), and flavones (e.g., quercetin). These molecules enhanced SIRT1 enzymatic activity by reducing its binding affinity for the substrate. In this pioneering study, resveratrol emerged as the most effective

SIRT1 activator, replicating the effects of caloric restriction in yeast. It was shown to enhance SIRT1 activity, promote DNA stability, and extend the lifespan of yeast by 70%. Resveratrol has been recognized as the first known sirtuin activator (85). However, its effects on SIRT1 can vary, as it has been shown to inhibit SIRT1 depending on the specific substrate involved (86). Similarly, resveratrol can also inhibit SIRT3 and SIRT5, with its influence being substrate-dependent (87). In an extensive 2015 study, Clémence D. Coté's research team explored the molecular and cellular mechanisms underlying resveratrol's anti-diabetic effects. Their findings revealed a notable rise in NAD+ levels and an increased NAD+/NADH ratio in the duodenal mucosa after resveratrol administration compared to saline treatment (88). Furthermore, by analyzing the acetylation state of liver kinase B1 (Lkb1) in HEK293 cells following resveratrol exposure, they confirmed a significant enhancement of SIRT1 activity (89). In 2017, Pan et al. found that resveratrol enhances the lysine deacetylation activity of Sirtuins, thereby activating SIRT2 (90). This activation leads to the deacetylation of Prx1-27AcK, significantly boosting its ability to reduce H_2O_2. Since cancer cells typically exhibit elevated H_2O_2 levels, which contribute to malignant transformation, increasing the activity of H_2O_2-detoxifying enzymes can suppress cancer cell proliferation and inhibit metastasis (91). Thus, resveratrol's ability to activate SIRT2 helps regulate the intracellular redox balance, ultimately slowing tumor progression and limiting cancer spread (92). Liang et al. (2023) demonstrated that resveratrol, by influencing SIRT2 activity, enhances insulin sensitivity, restores glycolysis, and may help mitigate ovarian damage in rats with polycystic ovary syndrome (PCOS) (93). Resveratrol stands out as a key activator of sirtuins with broad biological activity, attracting significant scientific interest. Extensive research has highlighted its potential therapeutic applications, particularly in slowing aging processes and managing diseases linked to oxidative stress (70). Resveratrol also exhibits anti-inflammatory, anticancer, and neuroprotective properties (94). Its diverse effects across various health-related areas emphasize its role as a multifunctional therapeutic compound, highlighting its potential as a target for future therapeutic research and drug development (70).

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