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Journal of Physical Medicine and Rehabilitation | Review Article

Role of Exercise and Natural Protective Substances on Sirtuin Activation

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Received date: June 08, 2021, **Accepted date:** July 22, 2021

Abstract

Chronic diseases are the leading drivers of the nation's $3.8 trillion in annual health care costs. International laboratories are increasingly focused on fitness and preventive strategies because prolonging healthy survival is not only desirable, but also represents a moral goal of any modern and responsible society. In fact, in addition to preventing human suffering, extension of healthy lifespan could save over $7 trillion in the United States alone. Sirtuins (SIRTs) are seven nicotinamide adenine dinucleotide (NAD+) dependent protein deacetylases enzymes that play an important role in maintaining cellular homeostasis. Among those, the most studied are nuclear SIRT (SIRT1) and

mitochondrial SIRT (SIRT3), which significantly impact humans' lifespan by modulating metabolic cellular processes. These proteins begin to decrease after 35 years of age, and after 60 years of age they are minimally produced by the human body. The progressive decrease of SIRTs leads to a series of overall inefficiencies in the human body, contributing to the loss of personal autonomy, with deterioration and shortening of healthy lifespan and overall longevity. SIRTs can be activated by caloric restriction, resulting in a doubling of lifespan in preclinical model systems; however, they can also be activated by exercise and plant-derived natural compounds.

Exercise is certainly still beneficial in older individuals to maintain fitness and overall wellness but may become insufficient for SIRTs activation. Nevertheless, older individuals could still benefit from selected protective factors needed to restore SIRTs and their capacity to correct altered methylation patterns, to improve the function and prevent dedifferentiation of specialized tissues like the Central Nervous System. Those SIRTs activating substances are contained in common foods but can be taken also in the form of supplements that could help decrease the extra calories associated with the intake of an effective amount of fruit and vegetables containing natural SIRTs activators. This review outlines the potential synergistic and complementary role of exercise and supplementation with selected protective substances in SIRTs activation and wellness, to prevent or delay progression of age-related chronic diseases.

Keywords: Sirtuins, SIRT, Exercise, Sirtuin Activators, Polyphenols, Healthspan, Aging

Introduction

The advancement of chronological age is characterized by the progression of symptoms of chronic degenerative diseases that are triggered or accelerated in their progression by unhealthy lifestyles, decreased fitness and inadequate nutrition with decreased consumption of natural protective substances. Recent scientific evidence indicates that it could be possible to prevent, or at least delay age-related chronic diseases to extend the period of healthy longevity, by strategies that could minimize the duration of the decline phase. In the United States, over 90% of the population over 65 has at least one degenerative disease, and over 75% of them have 2 co-morbidities [1]. It was once thought that modern medicine could continue to improve the survival, albeit unhealthy, of the humanity. A first alarm bell came from the USA, where life expectancy has decreased in the last 3 years, and for the first time, children born today could live for fewer years than their parents [2]. During the COVID-19 Pandemic, it painfully emerged that chronic diseases together with older age, represent formidable risk factors for the development of serious complications of COVID-19. It is now projected that COVID-19 will reduce US life expectancy even more in 2020, by 1.13 years [3]. Estimated reductions for the Black and Latino populations are 3 to 4 times that for Whites. The median estimate indicates a reduction in US life expectancy at birth of 1.13 years to 77.48 years, lower than any year since 2003 [3]. International laboratories are increasingly focused on fitness and preventive strategies because prolonging healthy survival is not only desirable, but also represents a moral goal of any modern and responsible society, given that in addition to avoiding preventable suffering, improving healthy lifespan would save $7 trillion in the United States alone. Chronic diseases are in fact the leading drivers of the nation's $3.8 trillion in annual health care costs [4]. The potential economic benefits of delayed aging are therefore enormous, and realizing the promise of the current extension of healthy aging strategies might net society trillions in yearly net benefits [5].

It has to be considered that only a percentage of our life expectancy is determined by our DNA, our healthy lifespan largely depends on our epigenome, which determines our ability to correctly read this information, selecting which genes to activate and deactivate, what to read and when. A group of protein deacetylases enzymes called Sirtuins (SIRTs) are essential for maintaining youth and the differentiation of our more specialized tissues, contributing significantly to our healthy life expectancy. It is precisely through the optimization of our epigenome that we could slow down the aging clock, or even make it go back in time [6]. Nature dedicated the cover of the December 3, 2020 edition to the first demonstration of the possibility of "Turning Back Time" by David Sinclair group [6]. Aging is paralleled by a progressive decline in the differentiation and function of tissues because of epigenetic changes and inefficiencies in maintaining normal metabolic and differentiation pathways. Inefficiencies in the epigenome are emerging as significant elements responsible for altered gene expression, tissue dysfunction and progressive exhaustion of regenerative and repair processes [7,8,9]. SIRTs are seven nicotinamide adenine dinucleotide (NAD+) dependent protein deacetylases enzymes that play an important role in maintaining cellular homeostasis. The research on SIRTs began in 1991 with Leonard Guarente at MIT (Massachusetts Institute of Technology). More recently, David Sinclair began to study SIRTs as possible new molecules with anti-aging effects. These proteins begin to decrease after 35 years of age, and after 60 years of age they are minimally produced by the human body. The progressive decrease of SIRTs leads to a series of overall inefficiencies in the human body, contributing to the loss of personal autonomy, with deterioration and shortening of healthy lifespan, and overall longevity. SIRTs can be activated by caloric restriction, resulting in a doubling of lifespan in preclinical model systems.

However, SIRTs can also be activated by exercise and natural compounds extracted from plants that can mainly be found in Asia, such as Pterostilbene, Polydatin and Honokiol. These natural plant-based compounds can be taken in the form of supplements that could help decrease the extra calories associated with the intake of an effective amount of fruit and vegetables containing natural SIRTs activators.

The exponential progress of genomics and biological marker platforms allows us to identify disease risk factors, follow the progress of personalized strategies to improve the biological age of an individual, and evaluate the effectiveness of fitness and preventive strategies adopted to rejuvenate, or at least slow down aging. Altered DNA methylation patterns are associated with the progression of the aging clocks [10], and recently, a DNA methylation clock was proposed to estimate the biological age of individuals [11]. A lifestyle behavior beneficial in older individuals to maintain fitness and overall wellness is constituted by exercise; however, with the advancing of age it may become insufficient for SIRTs activation. Older individuals could therefore benefit from a diet rich in selected protective factors that could be of assistance to restore SIRTs and their capacity to correct altered methylation patterns, to improve the function, and prevent dedifferentiation of specialized tissues, like endocrine and nervous tissues.

An international initiative named 'A one health approach to food' sought to define diets that could specifically prevent chronic diseases, while ensuring environmental sustainability while having the least environmental impact. To the surprise of many, it was realized that the same nutrition and lifestyle recommendations were similar for preventing diabetes, cardiovascular disease, neurodegenerative disease, autoimmune disease, or cancer, to name a few [12]. At the same time, the less recommended food classes also had the greatest environmental impact, generating what it became known as the Double Pyramid. Good recommendations are associated with lower levels of inflammation. In addition, diet-induced chronic subliminal inflammation (which causes no pain or discomfort, so no one notices) has emerged as a significant risk factor that can influence the incidence and progression of the pandemic of degenerative diseases, including obesity, diabetes, cardiovascular, osteo-articular, neurodegenerative diseases, just to name a few [13].

This review will outline the role of exercise on SIRTs activation and wellness. In addition, it will be discussed how exercise, fitness, lifestyle, healthy nutrition, and supplementation with selective protective substances could help us to successfully prevent or delay age-related chronic diseases. From healthy nutrition and fitness strategies to polyphenols, SIRTs activators, Omega 3, Vitamin D, and fisetin, to name a few, these are natural weapons that can help us prolong healthy lifespan.

Exercise and SIRTs

In the past two decades, the clinical importance of physical activity and exercise has become extremely relevant, both in the general public as well as in the aging population. The two terms 'physical activity' and 'exercise' denote two different concepts, and that was highlighted since the first important document on public health [14].

'Physical activity' refers to any bodily movement produced by skeletal muscles that results in energy expenditure and includes a broad range of occupational, leisure, and daily activities.

'Exercise' refers to planned or structured physical activity to improve or maintain one or more of the components of physical fitness: aerobic capacity (or endurance capacity), muscular strength, muscular endurance, flexibility, and body composition [14]. Nevertheless, the two terms are often used interchangeably, and, in this section, we will refer to studies on both physical activity and exercise. Considering a broader perspective, exercise helps to manage and improve cardiovascular health [15], to reduce the occurrence of cognitive decline [16,17] and the risk of developing breast and colon cancer [18]. Overall, it improves health and reduces all-cause mortality risk [19]. In the context of metabolic health, the effects of exercise have been studied extensively and its effects considered so relevant, that for decades exercise has been considered a cornerstone of diabetes management, along with diet and medication [20]. A mechanism that could mediate the exercise benefits is the reduction of the inflammatory state, due to several exercise-induced modifications as the reduction of oxidative stress and the increase in energy generation efficiency [21]. Another mechanism that could explain the general benefits of exercise is its related expression and/or activity of SIRTs. As previously mentioned, SIRTs are seven nicotinamide adenine dinucleotide (NAD+) dependent protein deacetylases enzymes that play an important role in maintaining cellular homeostasis. Among those, the most studied are a nuclear SIRT (SIRT1) and a mitochondrial SIRT (SIRT3), which significantly impact humans' lifespan by modulating metabolic cellular processes. Much of the literature on the role of SIRTs as regulators of the benefits of exercise is based on those two SIRTs.

In the last years the interest on the role of SIRTs was largely investigated in the scientific community and was initially based on knowledge accumulated on *in vitro* and animal models, and to a lesser extent in healthy humans.

Skeletal Muscle, Exercise and SIRTs

It is well known that skeletal muscle is an active tissue that acts as an endocrine organ secreting cytokine, myokines, and transcription factors into the bloodstream. Skeletal muscle plays a fundamental role in lipid metabolism [22,23], in the insulin stimulated and insulin independent glucose uptake [24]. Moreover, it plays a central role in maintaining a proper metabolic flexibility which is the capacity for the organism to adapt fuel oxidation to fuel availability [25]. The roles of SIRTs have been widely investigated in skeletal muscle in various aspects such as lipid metabolism, glucose uptake, insulin sensitivity, and mitochondrial biogenesis [26].

In Table 1 and 2 a summary of the most relevant studies executed on animal models, cellular cultures and on humans can be found. The tables summarize the most relevant research evidence on the role of physical exercise, and more specifically aerobic exercise, on Sirtuin activation by increasing NAD+ levels and the NAD+/NADH ratio.

Summary on the Effects of Exercise on Skeletal Muscle and SIRTs Activation

It is well accepted that SIRTs activation can be considered one of the mechanisms that underlie the positive benefits of exercise in the treatment of chronic conditions like metabolic syndrome, obesity, insulin resistance, and type 2 diabetes, as well as improved longevity and successful aging.

The most important effects of SIRTs activation induced by exercise can be considered the reduction of oxidative stress and, more generally, an increase in mitochondrial health. The metabolic pathways that activate SIRTs expression through exercise are multiple, and the available evidence probably have explored only some of the mechanisms with experiments executed on animal models and humans. The effects on SIRT1 and SIRT3 in human skeletal muscle are related to both exercise modality and intensity. Only aerobic exercise seems to consistently increase the expression of SIRT1 and SIRT3 and the intensity ranges from moderate to the high intensities with most of the evidence based mainly on SIRT1.

Table 1: Studies on animal models and cellular cultures.

Author	SIRTs studied	Relevant findings on the role of different exercise modalities on SIRTS activation on animal models and cellular cultures
Palacio et al. 2009 [27]	SIRT1, SIRT3	**Aerobic Exercise increases**: - SIRT3 protein content - PGC-1 and CS activity - SIRT3 is more expressed in type I muscle fiber.= - AMPK activity
Hokari et al. 2010 [28]	SIRT3	- **Aerobic Exercise increases SIRT3 content** - Immobilization reduces SIRT3 content - Contractile activity plays an important role in maintaining a high level of SIRT3 protein expression in postural muscle
White & Schenk. 2012 [29]	SIRT1-SIRT3	**Exercise (general)** - Increase in the NAD+ level and NAD+/NADH ratio provides increased substrate for SIRT1 and SIRT3, and electron transport chain. - SIRT3 acutely reduces mitochondrial protein synthesis - SIRT1 contributes to mitochondrial biogenesis through PGC1α-dependent and independent mechanisms
Bayod et al. 2012 [30]	SIRT1	**Aerobic exercise:** - Increases SIRT1protein content - Increases PGC-1 - Improvement in antioxidant defenses
Gurd et al. 2012 [31]	SIRT3	**Acute Aerobic Exercise** SIRT3 may play an acute regulatory role in oxidative metabolism in skeletal muscle *in vivo*
Huang et al. 2016 [32]	SIRT1	**Aerobic training** - Swimming can regulate the SIRT1/PGC-1α, AMPK and FOXO3a proteins expression
Shi et al. 2018 [33]	SIRT3	**Aerobic interval training** - Attenuates neuronal apoptosis and improve cognitive function through the positive regulation of SIRT3, and the reduction of oxidative stress levels
Bianchi et al. 2021 [34]	SIRT1	**Moderate Aerobic Exercise** Increased SIRT activity and enhance deacetylation of key transcriptional regulators of inflammation and metabolism

PGC-1: Proliferator-activated receptor Gamma Coactivator-1; CS: Citrate Synthase; AMPK: AMP-activated protein Kinase; FOXO1A: Forkhead box O1

Table 2: Studies on humans.

Author	SIRTs studied	Relevant findings on the role of different exercise modalities on SIRTs activation in humans
Dumke et al. 2009 [35]	SIRT1	**Chronic Aerobic training on cycle ergometer** Acute increases of SIRT1 and chronic increase in mitochondrial biogenesis and oxidative enzyme capacity
Guerra et al. 2010 [36]	SIRT1	**Sprint exercise** Two hours after the sprint SIRT1 (its upstream deacetylase) increased
Gurd et al. 2010 [37]	SIRT1	**High-intensity interval training** Increases SIRT1 activity in human skeletal muscle Exercise-induced mitochondrial biogenesis is accompanied by elevated SIRT1 activity in human skeletal muscle.
Villanova et al. 2013 [38]	SIRT3	**Aerobic activity** Upregulates the deacetylase activity of SIRTs in athletes
Johnson et al. 2015 [39]	SIRT3	**Endurance training** Increase in skeletal muscle content of the mitochondrial deacetylase SIRT3 in both young and elderly subjects
Koltai et al. 2018 [40]	SIRT1 SIRT3	**In master athletes** Greater expression of SIRT1; SIRT3 protein compared with sedentary participants
Vargas Ortiz et al. 2018 [41]	SIRT3	**Aerobic and resistance training** Only aerobic training increased SIRT3. Resistance training increased muscle mass without improving SIRT3.
Lanza et al. 2008 [42]	SIRT3	**Endurance training** Lower SIRT3 expression with age in sedentary but equally elevated regardless of age in endurance-trained individuals.

Regarding the role of resistance training on SIRTs activation there is less literature if compared with that of endurance training, even if it is generally agreed that SIRTs plays an important role in the physiology of skeletal muscle determining various metabolic benefits. SIRTs activation during resistance training induced hypertrophy may result in downregulation of catabolic and up-regulation of anabolic pathways, through different mechanisms that in turn improve longevity and overall health [43]. At present there is no evidence to our knowledge, on the effects of different resistance training intensities as well as on different strength training protocols (e.g. linear Vs. periodized load) on SIRTs activation. However, it has been reported that endurance training seems to be superior to resistance training, to improve telomerase activity and telomer length which are factors affecting cellular senescence, regenerative capacity, and thus, healthy aging [44].

In the last decade, significant knowledge on the role of exercise in SIRTs activation has been accumulated and their positive effects on health have been established. However, there is still much to be learned, both in terms of the mechanism underlying SIRTs induced effects as well as on the most effective exercise regimes.

The Role of Natural Protective Substances in Promoting SIRTs Activation

As we have previously seen, the effects of exercise on SIRTs activation were well investigated by Zarzuelo [45] who showed that appropriate long-term exercise training can be associated with a cardioprotective effect through SIRT1 activation and reduction of ROS [46]. It has been reported that the SIRT3 and PGC-1α increase in white blood cells activate an antioxidant response after intense swimming. In addition, SIRT3 and PGC-1α in human skeletal muscle decreased with age and correlated with a sedentary proteomic profile in subjects with decreased metabolic output [42]. With exercise, it was observed that the effect is reversed and a positive association between Exercise Training and SIRT1 was reported in young (3 months old), and middle-aged (12 months old) rats, even if no significant increase in SIRT1 was observed in older rats (18 months old) [27]. Aerobic exercises were shown to lengthen telomeres and stimulate the production of SIRTs, especially SIRT1 and SIRT3. However, strength sports, which more generally do not involve aerobic activity, did not seem to stimulate the production of SIRTs, or lengthen telomeres. Furthermore, in older mice specimens, SIRTs production induced by aerobic activity was not substantial. The results of the experiments therefore suggest that with the advancement of aging, natural SIRTs activating substances could be considered to supplement a healthy nutrition.

SIRTs activating substances are certainly contained in many common foods like blueberries or black currant, to maximize the beneficial effects of exercise on the body. In Table 3, the studies on the most powerful SIRTs activators

Table 3: Natural protective substances and SIRTs activation.

Substance	**Type of SIRTs activated**	**Relevant Findings**
Honokiol	SIRT3	Mitochondrial SIRT3 has been shown to protect against doxorubicin-induced cardiotoxicity [47]. Honokiol have been recently identified as an activator of SIRT3, which protects from developing pressure-overload cardiac hypertrophy [48].
Ellagic Acid	SIRT1-SIRT3- SIRT6	Ellagic acid improves muscle dysfunction in cuprizone-induced demyelinated mice via mitochondrial SIRT3 regulation [49]. The potent antioxidant and antiapoptotic effects of Ellagic Acid were indicated by the significant overexpression of SIRT1 in renal tissue, leading to a significant decrease in renal MDA content [50]. Ellagic acid increased SIRT6 activity and decreased the expression of SIRT6 associated proteins involved in cancer development [51]
Niacin	SIRT1	Correction of niacin deficiency and SIRT1 modulators may prolong the life span of patients with diabetes [52].
Polydatin	SIRT1, SIRT3	Polydatin protects against lipopolysaccharide-induced endothelial barrier disruption via SIRT3 activation [53]. Polydatin attenuated cardiac dysfunction, increased autophagy flux and improved mitochondrial bioenergetics by up-regulating SIRT3 [54] SIRT1 Activation by Polydatin Alleviates Oxidative Damage and Elevates Mitochondrial Biogenesis in Experimental Diabetic Neuropathy [55].
Zinc	SIRT1, SIRT3	SIRT1 and SIRT3 are physiological modulators of metabolism [56].
Selenium	SIRT1	Selenium causes a significant decrease in the inflammatory response due to the overexpression of the SIRT1 gene [57].
Pterostilbene	SIRT1	SIRT1 activation by pterostilbene attenuates the skeletal muscle oxidative stress injury and mitochondrial dysfunction induced by ischemia reperfusion injury [58]. Restoration of SIRT1 function by pterostilbene attenuates hypoxia-reoxygenation injury in cardiomyocytes [59].

and their relative main findings are reported. The substances shown in the Table 3 are able to stimulate SIRTs even individually, however there are patented compounds as SIRT500 Plus (A5+) that exploit the synergistic effect of the compounds to maximize SIRTs activation:

Supplementation with SIRTs activating substances could be of assistance in the following cases: with the advancing of age [32], even when performing regular aerobic activity; when practicing strength enhancing physical activity and sports, or anaerobic activity. The beneficial effects may be also related in part to SIRTs role in inflammation. Diet-induced chronic inflammation is emerging as a significant factor that can affect the incidence and progression of many degenerative conditions, including obesity, diabetes, cardiovascular, osteo-articular, neurodegenerative, autoimmune disease conditions and cancer, to name a few. Randomized controlled trials (RCT) are in progress in several disease conditions including Type 1 Diabetes, to determine also the effects of other substances, as for example high dose Omega 3 and Vitamin D on disease progression in both pediatric and adult subjects, in early and late onset T1D. It is important to rely on high quality research because this supplementation could be considered a viable solution to assimilate a sufficient amount of the protective substances above suggested, a goal would be difficult to be achieved just with natural food. Table 4 indicates what would be the volume of selected fish, fruit and vegetables you would have to consume every day to assimilate a sufficient amount of the protective substances above suggested and the calories assumed by the consumption of these foods [60].

Summary on the Effects of Protective Substances on SIRTs Activation

Proper nutrition offers a solution since SIRTs activating substances are certainly contained in many common foods, and the most effective SIRTS activators are represented by Honokiol, Ellagic acid, Polydatin, Zinc, Selenium, and Pterostilbene. Those substances can be effective individually but also in the form of compounds that exploit their synergistic effect to maximize SIRTs activation. Those natural plant-based compounds taken in the form of supplements could also help decrease the extra calories associated with the intake of an effective

Table 4: Theoretical volume of protective substances to consume every day to assimilate enough selected protective substances.

Protective substance	Daily consumption of alternative products	Calories that these alternative products will introduce
40 mg Resveratrol	10-12 Liters of red wine	6.000 – 7,800
	27 Liters of white wine	17,550
	33-60 Kg of black grapes	21,650 – 39,000
	22 Kg of peanuts	1,24,740
	13 Kg of cocoa	2,964
60 mg Pterostilbene	10 Kg of blueberries	5,700
	16 Kg of black currants	10,800
200 mg Polydatin	200 grams of Sophora Japonica	Difficult to find and to digest
5 g Omega3 (EPA + DHA)	6 Kg of lobsters	8,580
	2 Kg of tuna	2,588
	600 g of salmon	1,236
1 g Vitamin C	2.25 Kg of oranges	1,012
	0.750 Kg fresh red peppers	300
7,000 UI Vitamin D3	159 eggs	11,448

amount of fruit and vegetables containing natural SIRTs activators. With the advancement of aging, natural SIRTs activating substances could be considered to supplement a healthy nutrition and exercise.

Nevertheless, an increasing number of subjects are considering selected protective substances, while waiting for the long-term results, also because emerging diseases could pose an immediate threat (e.g., COVID-19) to our health. In fact, recent data indicate how appropriate nutrition [61] and selected protective substances could be of assistance to prepare our body to better resist viral infections such as COVID-19, and in case of infection how to decrease the risk of severe disease progression.

Conclusions

SIRTs activation can be considered one of the mechanisms that underlie the positive benefits of exercise on the treatment of chronic conditions like the metabolic syndrome, obesity, insulin resistance and type 2 diabetes, as well on improved longevity and successful aging [62-64]. The most important effects of SIRTs activation induced by exercise can be considered the reduction of oxidative stress and, more generally, an improved mitochondrial health. Aerobic exercises have been shown to lengthen telomeres and stimulate the production of SIRTs, especially SIRT1 and SIRT3. However, strength sports, which more generally, do not involve aerobic activity, do not seem to stimulate the production of SIRTs or lengthen telomeres. In addition, aerobic activity did not significantly improve SIRTs production in older mice. Exercise is still undoubtedly beneficial in older individuals to maintain fitness and overall wellness but may become insufficient for SIRTs activation. For that reason, older individuals could still benefit from selected protective factors needed to restore SIRTs production and their capacity to correct altered methylation patterns, to improve the function, and prevent dedifferentiation of specialized tissues, like the Central Nervous System. Those SIRTs activating substances are contained in common foods but can be taken also in the form of supplements that could help decrease the extra calories associated with the intake of an effective amount of fruit and vegetables containing natural SIRTs activators. The natural weapon that can help us prolong healthy lifespan is constituted by a combination of exercise and the intake of protective substances deriving from healthy nutrition or specific supplements.

References

1. Dorronsoro A, Santiago FE, Grassi D, Zhang T, Lai RC, McGowan SJ, et al. Mesenchymal stem cell-derived extracellular vesicles reduce senescence and extend health span in mouse models of aging. Aging Cell. 2021 Apr 20(4):e13337.

2. Woolf SH, Schoomaker H. Life Expectancy and Mortality Rates in the United States, 1959-2017. JAMA. 2019 Nov 26;322(20):1996-2016.

3. Andrasfay T, Goldman N. Reductions in 2020 US life expectancy due to COVID-19 and the disproportionate impact on the Black and Latino populations. Proc Natl Acad Sci U S A. 2021 Feb 2;118(5):e2014746118.

4. https://www.cdc.gov/chronicdisease/resources/infographic/chronicdiseases.htm.

5. Goldman D. The Economic Promise of Delayed Aging. Cold Spring Harb Perspect Med. 2015 Dec 18;6(2):a025072.

6. Lu Y, Brommer B, Tian X, Krishnan A, Meer M, Wang C, et al. Reprogramming to recover youthful epigenetic information and restore vision. Nature. 2020 Dec;588(7836):124-129.

7. Sinclair DA, Mills K, Guarente L. Accelerated aging and nucleolar fragmentation in yeast sgs1 mutants. Science. 1997 Aug 29;277(5330):1313-6.

8. Imai S and Kitano H. Heterochromatin islands and their dynamic reorganization: a hypothesis for three distinctive features of cellular aging. Exp Gerontol. 1998 Sep;33(6):555-70.

9. Oberdoerffer P, Michan S, McVay M, Mostoslavsky R, Vann J, Park SK, et al. SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. Cell. 2008 Nov 28;135(5):907-18.

10. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14(10):R115.

11. Wang M and Lemos B. Ribosomal DNA harbors an evolutionarily conserved clock of biological aging. Genome Res. 2019 Mar;29(3):325-333.

12. www.indiaenvironmentportal.org.in/files/file/one%20health%20approach%20to%20food.pdf

13. Ricordi C, Garcia-Contreras M, Farnetti S. Diet and Inflammation: Possible Effects on Immunity, Chronic Diseases, and Life Span. J Am Coll Nutr. 2015;34 Suppl 1:10-3.

14. U.S. Department of Health and Human Services (ed.). Physical Activity and Health: A Report of the Surgeon General (1996). Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic disease Prevention and Health Promotion.

15. Shiroma EJ and I-Min Lee. Physical Activity and Cardiovascular Health. Circulation. 2010 Aug 17;122 (7):743–52.

16. Barros L, Eichwald T, Solano AF, da Luz Scheffer D, da Silva RA, Gaspar JM, et al. Epigenetic modifications induced by exercise: drug-free intervention to improve cognitive deficits associated with obesity. Physiol. Behav. 2019 May 15;204:309–23.

17. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC et al. Exercise-linked FNDC5/ irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat. Med. 2019 Jan; 25 (1):165–75.

18. Oruç Z and Kaplan MA. Effect of exercise on colorectal cancer prevention and treatment. World J. Gastrointest. Oncol. 2019 May 15;11(5):348–66.

19. Kelly P, Kahlmeier S, Götschi T, Orsini N, Richards J, Roberts N, et al. Systematic review and meta-analysis of reduction in all cause mortality from walking and cycling and shape of dose response relationship. Int J Behav Nutr Phys Act. 2014 Oct; 24:1–15.

20. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care, 2010 Dec;33(12):e147-67.

21. da Luz Scheffer D, Latini A. Exercise-induced immune system response: Anti-inflammatory status on peripheral and central organs. Biochim Biophys Acta Mol Basis Dis. 2020 Oct 1;1866(10):165823.

22 Gemmink A, Schrauwen P, Hesselink MKC. Exercising your fat (metabolism) into shape: a muscle-centred view. Diabetologia. 2020 Aug; 63(8):1453–63.

23. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001 Dec 13;414(6865):799–06.

24. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med.1998;49:2 35–61.

25. Goodpaster BH, Sparks LM. Metabolic Flexibility in Health and Disease. Cell Metab. 2017 May;225(5):1027–36.

26. Jing E, O'Neill BT, Rardin MJ, Kleinridders A, Ilkeyeva OR, Ussar S, et al. Sirt3 regulates metabolic flexibility of skeletal muscle through reversible enzymatic deacetylation. Diabetes. 2013 Oct;62 (10):3404–17.

27. Palacios OM, Carmona JJ, Michan S, Chen KY, Manabe Y, Ward JL et al. Diet and exercise signals regulate sirt3 and activate ampk and pgc-1alpha in skeletal muscle. Aging. 2009 Aug 15; (9):771–83.

28. Hokari F, Kawasaki E, Sakai A, Koshinaka K, Sakuma K, Kawanaka K. Muscle contractile activity regulates sirt3 protein expression in rat skeletal muscles. J. Appl. Physiol. 2010 Aug;109:332–40.

29. White AT, Schenk S. Nad(+)/nadh and skeletal muscle mitochondrial adaptations to exercise. Am J. Physiol. Endocrinol. Metab. 2012 Aug 1;303:E308–21.

30. Bayod S, DelValle J, Lalanza JF, Sanchez-Roige S, de Luxan-Delgado B, Coto-Montes, et al. Long-term physical exercise induces changes in sirtuin 1 pathwayand oxidative parameters in adult rat tissues. Exp Gerontol. 2012 Dec;47(12): 925–35.

31. Gurd BJ, Holloway GP, Yoshida Y, Bonen A. In mammalian muscle, SIRT3 is present in mitochondria and not in the nucleus; and SIRT3 is upregulated by chronic muscle contraction in an adenosine monophosphate-activated protein kinase-independent manner. Metabolism. 2012 May;61(5):733-41.

32. Huang CC, Wang , Tung YT, Lin WT. Effect of Exercise Training on Skeletal Muscle SIRT1 and PGC-1alpha Expression Levels in Rats of Different Age. Int J Med Sci. 2016;13, 260–270.

33. Shi Z, Li C, Yin Y, Yang Z, Xue H, Mu N, et al. Aerobic interval training regulated sirt3 attenuates high-fat-diet-associated cognitive dysfunction. Biomed Res Int. 2018 Mar 22; 2018:2708491.

34. Bianchi A, Marchetti L, Hall Z, Lemos H, Vacca M, Paish H, et al. Moderate Exercise Inhibits Age-Related Inflammation, Liver Steatosis, Senescence, and Tumorigenesis. J Immunol. 2021 Feb 15;206(4): 904–16.

35. Dumke CL, Mark Davis J, Angela Murphy E, Nieman DC, Carmichael MD, Quindry JC, et al. Successive bouts of cycling stimulates genes associated with mitochondrial biogenesis. Eur J Appl. Physiol. 2009 Nov;107(4):419–27.

36. Guerra B, Guadalupe-Grau A, Fuentes T, Ponce-Gonzalez JG, Morales-Alamo D, Olmedillas H, et al. Sirt1, amp-activated protein kinase phosphorylation and downstream kinases in response to a single bout of sprint exercise: Influence of glucose ingestion. Eur J Appl Physiol. 2010 Jul;109(4):731–43.

37. Gurd BJ, Perry CG, Heigenhauser GJ, Spriet LL, Bonen A. High-intensity interval training increases sirt1 activity in human skeletal muscle. Appl Physiol Nutr Metab. 2010 Jun;35(3):350–57.

38. Villanova L, Vernucci E, Pucci B, Pellegrini L, Nebbioso M, Mauri C, et al. Influence of age and physical exercise on sirtuin activity in humans. J Biol Regul Homeost. Agents. 2013 Apr-Jun; 27(2):497–07.

39. Johnson ML, Irving BA, Lanza IR, Vendelbo MH, Konopka AR, Robinson MM, et al. Differential Effect of Endurance Training on Mitochondrial Protein Damage, Degradation, and Acetylation in the Context of Aging. J. Gerontol. A Biol Sci Med Sci. 2015 Nov;70(11):1386–93.

40. Koltai E, Bori Z, Osvath P, Ihasz F, Peter S, Toth G, et al. Master athletes have higher mir-7, sirt3 and sod2 expression in skeletal muscle than age-matched sedentary controls. Redox Biol. 2018 Oct;19:46–51.

41. Vargas-Ortiz K, Perez-Vazquez V, Figueroa A, Diaz FJ, Montano-Ascencio PG, Macias-Cervantes MH. Aerobic training but no resistance training increases sirt3 in skeletal muscle of sedentary obese male adolescents. Eur J Sport Sci. 2018 Mar;18(2):226–34.

42. Lanza IR, Short DK, Short KR, Raghavakaimal S, Basu R, Joyner MJ, et al. Endurance exercise as a countermeasure for aging. Diabetes. 2008 Nov;57(11):2933–42.

43. Radak Z, Suzuki K, Posa A, Petrovszky Z, Koltai E, et al. The systemic role of SIRT1 in exercise mediated adaptation. Redox Biol. 2020 Aug;35:10146.

44. Werner CM, Hecksteden A, Morsch A, Zundler J, Wegmann M, Kratzsch J, et al. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. Eur Heart J. 2019 Jan 1;40(1):34-46.

45. Zarzuelo MJ, López-Sepúlveda R, Sánchez M, Romero M, Gómez-Guzmán M, Ungvary Z, et al. SIRT1 inhibits NADPH oxidase activation and protects endothelial function in the rat aorta: implications for vascular aging. Biochem Pharmacol. 2013 May 1;85(9):1288-96.

46. Ferrer MD, Tauler P, Sureda A, Tur JA, Pons A. Antioxidant regulatory mechanisms in neutrophils and lymphocytes after intense exercise. J Sports Sci. 2009 Jan 1;27(1):49-58.

47. Pillai VB, Kanwal A, Fang JH, Sharp WW, Samant S, Arbiser J, et al. Honokiol, an activator of Sirtuin-3 (SIRT3) preserves mitochondria and protects the heart from doxorubicin-induced cardiomyopathy in mice. Oncotarget. 2017 May 23;8(21): 34082–98.

48. Pillai VB, Samant S, Sundaresan NR, Raghuraman H, Kim G, Bonner MJ, et al. Honokiol blocks and reverses cardiac hypertrophy in mice by activating mitochondrial Sirt3. Nature Communications. 2015;6:6656.

49. Khodaei F, Rashedinia M, Heidari R, Rezaei M, Khoshnoud MJ. Ellagic acid improves muscle dysfunction in cuprizone-induced demyelinated mice via mitochondrial Sirt3 regulation. Life Sci. 2019 Nov 15; 237:116954.

50. Mohammed, Hashem KS, Abdelazem AZ, Foda F. Prospective Protective Effect of Ellagic Acid as a SIRT1 Activator in Iron Oxide Nanoparticle-Induced Renal Damage in Rats. Biol Trace Elem Res. 2020 Nov; 198(1):177-88.

51. Rahnasto-Rilla M, Järvenpää J, Huovinena M, Schroderus AM, Ihantola E, Küblbeck J, et al. Effects of galloflavin and ellagic acid on sirtuin 6 and its anti-tumorigenic activities. Science Direct. 2020 Nov; 131:110701.

52. Zillikens MC, van Meurs JB, Sijbrands E, Rivadeneira F, Dehghan A, van Leeuwen J et la. SIRT1 genetic variation and mortality in type 2 diabetes: interaction with smoking and dietary niacin. Free Radic Biol Med. 2009 Mar 15;46(6):836-41.

53. Wu J, Deng Z, Sun M, Zhang W, Yang Y, Zeng Z, et al. Polydatin protects against lipopolysaccharide-induced endothelial barrier disruption via SIRT3 activation. Laboratory Investigation. 2019 Oct;100:643–656.

54. Zhang M, Wang S, Cheng Z, Xiong Z, Jianjun Lv, Yang Z, et al. Polydatin ameliorates diabetic cardiomyopathy via Sirt3 activation. Biochem Biophys Res Commun. 2017 Nov 25;493(3):1280-87.

55. Bheereddy P, Yerra VG, Kalvala AK. SIRT1 Activation by Polydatin Alleviates Oxidative Damage and Elevates Mitochondrial Biogenesis in Experimental Diabetic Neuropathy. Cell Mol Neurobiol. 2020 Jul 18.

56. Nogueiras R, Habegger KM, Chaudhary N, Finan B, Banks AS, Dietrich MO, et al. Sirtuin 1 and sirtuin 3: physiological modulators of metabolism. Physiological Reviews. 2012;92(3):1479–14.

57. Khazdouz M, Daryani NE, Alborzi F, Jazayeri MH, Farsi F, Hasani M, et al. Effect of Selenium Supplementation on Expression of SIRT1 and PGC-1α Genes in Ulcerative Colitis Patients: a Double Blind Randomized Clinical Trial. Clin Nutr Res. 2020 Oct 26;9(4):284-95.

58. Cheng Y, Di S, Fan C, Cai L, Gao C, Jiang P, et al. SIRT1 activation by pterostilbene attenuates the skeletal muscle oxidative stress injury and mitochondrial dysfunction induced by ischemia reperfusion injury. Apoptosis. 2016 Aug;21(8):905-16.

59.Guo Y, Zhang L, Li F, Hu CP, Zhang Z. Restoration of sirt1 function by pterostilbene attenuates hypoxia-reoxygenation injury in cardiomyocytes. Eur J Pharmacol. 2016 Apr 5;776:26-33.

60. https://fit4pandemic.com/ricordi-protocol/

61. Natalucci V, Marini C, Flori M, Pietropaolo F, Lucertini F, et al. Effects of a Home-Based Lifestyle intervention Program on Cardiometabolic Health in Breast Cancer Survivors during the COVID-19 Lockdown. J Clin Med. 2021;10:2678.

62. Ricordi C, Pacifici F, Lanzoni G, Palamara AT, Garaci E, Della-Morte D. Dietary and Protective Factors to Halt or Mitigate Progression of Autoimmunity, COVID-19 and Its Associated Metabolic Diseases. International Journal of Molecular Sciences. 2021;22(6):3134.

63. Pacifici F, Rovella V, Pastore D, Bellia A, Abete P, Donadel G, et al. Polyphenols and Ischemic Stroke: Insight into One of the Best Strategies for Prevention and Treatment. Nutrients. 2021;13(6):1967.

64. Pacifici F, Di Cola D, Pastore D, Abete P, Guadagni F, et al. Proposed Tandem Effect of Physical Activity and Sirtuin 1 and 3 Activation in Regulating Glucose Homeostasis. Int J Mol Sci. 2019;20(19):4748.