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**Review Article**

# Myonectin: The Muscle's Signal to Metabolic Harmony

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## ABSTRACT

Myonectin is a skeletal muscle-secreting cytokine with a molecular size ranging from 55-77 kDa. It was first discovered by Seldin and his coworkers in 2011. This myokine is secreted predominantly by the skeletal muscle in response to nutrient availability and physical activity. Myonectin is known to have a significant role in somatic metabolism, lipid metabolism, modulation of skeletal mass and function, cardio protectivity, etc. Physical activity being a major stimulator of this myokine production, plays substantial role in the prevention as well as the progression of metabolic diseases and skeletal muscle degeneration. From its initial discovery in 2012, still its biological, pathophysiological, physiological, and pharmacological functions with special emphasis on the amelioration of serious ailments are yet to be delved into deeply. Myonectin is involved in micronutrient metabolism and attenuation of metabolic disorders. Many research papers do not seem to investigate the correlation of myonectin in attenuating various disease conditions. Also, many research papers have delineated the significance of myonectin and its correlation with metabolic syndromes. As a science pursuer, it is important to broadcast the science of myonectin to future biology researchers which will contribute to the knowledge of researchers, teachers, and health professionals. In this review, we have attempted to have a fundamental knowledge about myonectin which will induct the researchers to expedite the studies involving myonectin for the benefit of human health.

## INTRODUCTION

**Key Messages:**

In modern medicine (allopathy), there are about 4,000 drugs available. As per DSM 11, there are more than 55,000 different disease conditions of human. Furthermore, adding up of new drugs for every disease is challenging and also imposes high financial requirements. Almost every biological system possesses an endogenous protective and curative pathways to make a system survive for long and control disease progression. The metabolic syndrome is a multiple array of

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disorders arising from overeating, a sedentary lifestyle, insulin resistance, diabetes,hypertension etc. This review focus on *myonectin*, a muscle secreting cytokine which is known from 2012 and imparting tremendous role in controlling metabolic syndromes through various means of biological actions. The readers are encouraged to pursue further knowledge and research ideas to make use of it.

Skeletal muscle is the most abundant organ of the human body in terms of weight. In addition to being a major storage site for glucose, lipids, and amino acids, muscle is also a regulator of whole-body energy metabolism[1]. Myokines are secreted in retaliation to skeletal muscle contractions. In response to physical activity or nutrients, skeletal muscles secrete myokines which exert their effect in autocrine, paracrine, or endocrine manner[1]. Myonectin is one novel myokine that shows positive implications for human health such as regulation of metabolic homeostasis, cardioprotective action, lipid metabolism, cell signaling, muscle mass modulation, stress erythropoiesis, etc. Physical activity produces a significant increase in the expression and circulating levels of myonectin. Most lifestyle disorders such as obesity can be controlled by physical activity and myonectin may play an important role in it. Our goal of the review is to provide insights into the understanding of myonectin and how it is influenced by physical activity and nutrient uptake, through which a comprehensive method for prevention and treatment of various disorders can be derived[2].

**A brief history of Myonectin- From Initial Discovery to Recent Developments**

In 2011, Seldan et al. identified myonectin as a novel myokine predominantly expressed in skeletal muscle. It was concluded that myonectin is a potent nutrient-responsive metabolic regulator secreted by the skeletal muscle[2]. In 2014, Seldin M delved deeper into how myonectin acts as a skeletal muscle nutrient sensor influencing glucose and fat metabolism. It was demonstrated that myonectin as a skeletal muscle protein is secreted as a reflection of tissue-specific nutrient availability. Also of note, myonectin was found to regulate hepatic autophagy, further underscoring its integral role in energy regulation[3]. Moving forward to 2018, Kejia et al., conducted a study involving 128 healthy subjects, demonstrating that myonectin levels were elevated in individuals with impaired glucose tolerance (IGT) and non-type 2 diabetes (nT2DM). This highlighted myonectin as a potential predictor for the development of type 2 diabetes[4]. In 2018 Naoya et al. found that myonectin protects the heart from ischemia-reperfusion injury by reducing apoptosis and inflammation which suggested therapeutic applications in ischemic heart disease[5]. In 2020, Altajar et al. studied the intricate association between skeletal muscle dysfunction and the liver in various stages of non-alcoholic fatty liver disease (NAFLD). Their study provided valuable insights into the role of myonectin levels in the pathophysiology of NAFLD, contributing to prognostication and identification of potential therapeutic targets[6]. Moreover, recent research in 2023 by Jorge et al. revealed that adults with metabolic syndrome had lower serum myonectin levels and that they had a negative correlation with android fat mass[7].


**Figure No 1: Brief history of myonectin studies**

## Chemistry of Myonectin

Myonectin is structurally analogous to adiponectin, consisting of an N-terminal signal peptide, a short variable region, a collagen domain containing collagen triples (Gly-X-Y), and a C-terminal globular complement factor C1q (Complement 1q) domain[8]. The C1q domain is homologous to the complement protein and is structurally similar to TNFα (Tissue Necrosis Factor α), thus the name of the protein family (C1q/TNF-related protein)[9]. Myonectin forms trimers as its basic structural unit, which further assembles as hexamers and high-molecular-weight (HMW) oligomers. Protein glycosylation is essential for proper folding and secretion from the cells. Myonectin possesses four cysteine residues (Cys-142, Cys-194, Cys-273, and Cys-278), of which Cys-142 and Cys-194 are vital for secretion and assembling of HMW oligomers and hexamers by mediating intermolecular disulfide bond formation. Proline hydroxylation and lysine glycosylation are vital for the stability of the triple-helical structure of the collagen domain. Myonectin also contains nine proline residues that can be hydroxylated[10].

## Biological Significance of Myonectin

### Somatic Metabolism

Myonectin plays an important role in somatic metabolism. Myonectin has been linked to metabolic syndrome, a cluster of conditions that increase the risk of heart disease, stroke, and type 2 diabetes[7]. Research has shown that myonectin levels are lower in individuals with metabolic syndrome, suggesting a potential role in its pathogenesis. Furthermore, studies have demonstrated that myonectin can improve insulin sensitivity and reduce inflammation, both of which are key components of metabolic syndrome[2]. These findings highlight the potential of myonectin as a therapeutic target for metabolic syndrome and also establish a clear link between myonectin and body metabolism. Myonectin affects iron and fatty acid metabolism, the differentiation of osteoblasts and osteoclasts, and adipogenesis[11,12].

### Lipid Metabolism

Myonectin decreases plasma-free fatty acid levels through the enhancement of their uptake in the adipose tissue and liver. This is mediated by an increase in the expression of scavenger and transporter proteins, such as the fatty acid transporter protein- (FATP-) 1, and fatty acid binding protein- (FABP-) 4 [13,14]. Myonectin, however, has no effects on adipocyte lipolysis. Peroxisome proliferator-activated receptor γ (PPARγ) is a regulator of adipogenesis and adipocyte differentiation. It also regulates the expression of enzymes that promote lipid accumulation within adipocytes along with Enhancer Binding Protein α (C/EBPα). The mRNA expression levels of PPARγ, C/EBPα, and Adiponectin (adipokine secreted from mature adipocytes) decrease in myonectin-treated cells. Thus, myonectin inhibits adipogenesis by regulating the expression of transcription factors involved in adipocyte differentiation. Myonectin

suppresses the early stage of adipogenesis. The MAPK pathway, a key regulator of cell cycle and proliferation, is involved in adipogenesis. Myonectin increases p38 MAPK activity which prevents differentiation of 3T3-L1 preadipocytes by activating the C/EBP homologous protein (CHOP), which acts as a dominant-negative regulator of C/EBPs and PPAR [11].

**Cardioprotective Function**

Myonectin exhibits cardioprotective function by attenuating the inflammatory response in macrophages. It reduces the expression of pro-inflammatory cytokines such as TNF-α, Interleukin- 6 (IL-6), and MCP-1 (Monocyte chemoattractant protein-1), in macrophages stimulated with lipopolysaccharide (LPS). Myonectin also inhibits the phosphorylation of NF-κB, a key mediator of inflammation, in response to LPS. These anti-inflammatory effects of myonectin are mediated through the activation of the cAMP/Akt signaling pathway. Myonectin attenuates myocyte apoptosis through its ability to promote the cAMP/Akt signaling pathway, via the Sphingosine 1-phosphate (S1P) dependent pathway. It can be inferred that myonectin functions as an exercise-induced myokine that prevents acute ischemic injury in the heart by its ability to reduce cardiomyocyte apoptosis and macrophage inflammation through the S1P/cAMP/Akt. Myonectin hence, is a cardioprotective myokine, which mediates the cardiovascular benefits of endurance exercise [5].

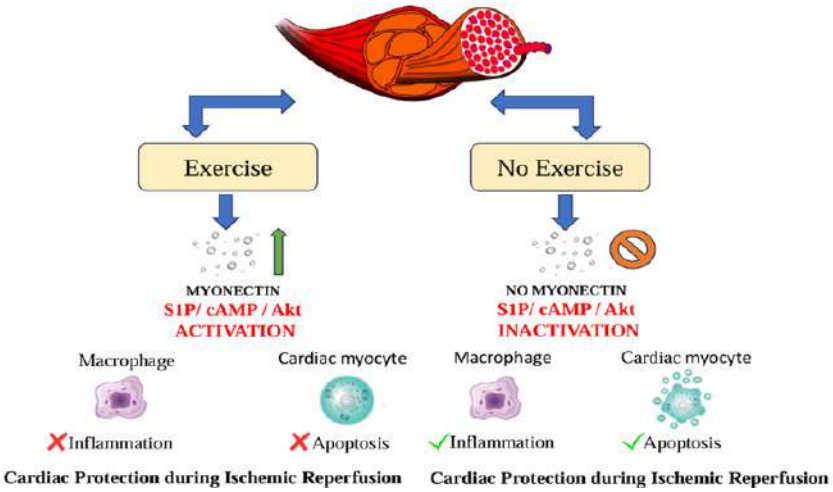


**Figure No 2: Cardioprotective function of Myonectin**

**Modulation of Skeletal Muscle Mass and Function**

Myonectin acts as a protective factor against skeletal muscle dysfunction. Peroxisome proliferator-activated receptor-γ coactivator (PGC1α) is a transcriptional coregulator induced by exercise training and controls mitochondrial energy metabolism. Exercise-induced myonectin levels were found to improve mitochondrial biogenesis and function stimulated by PGC1α, which benefits the treatment of various conditions like muscle dysfunction and sarcopenia. Endurance exercise increases circulating levels of myonectin, and this myonectin positively regulates AMPK/PGC1α signals in skeletal muscle. Myonectin improves muscle atrophy induced by disuse or steroid use through the upregulation of PGC1α expression. Myonectin also aids in PGC1α stimulated mitochondrial biogenesis which therapeutically could be used in the prevention or amelioration of Duchenne muscle dystrophy (DMD), an early progressive and life-threatening disease. Patients with DMD suffer from symptoms of muscle weakening, finally leading to loss of

ambulation from the ages of 8 to 12. Myonectin serves as a protective factor for skeletal muscle dysfunction caused by various pathophysiology conditions, such as age-associated, disuse-induced, or steroid-induced muscle atrophy. Thus, myonectin restores and maintains muscle mass and function which is essential for healthy aging [15].

**Liver Autophagy**

Myonectin has been described as a nutrient-responsive regulator of liver autophagy. Prolonged periods of food deprivation turn on autophagy, by inducing the expression of autophagy-related-genes. This intracellular degradative pathway is highly regulated and sensitive to metabolic alterations. Skeletal muscle-derived myonectin, induced by food intake or the availability of nutrients (e.g., glucose and free fatty acids), mediated a hormonal signal to inhibit autophagy in hepatocytes through mTOR (mechanistic Target of Rapamycin) activation, which is also evidence of a novel skeletal muscle liver axis in modulating tissue homeostasis. Hence direct endocrine communication between skeletal muscle and liver exists and it highlights the importance of inter-tissue crosstalk in mediating the physiological functioning of the body. Hormone-mediated tissue cross-talk under different metabolic states, such as food deprivation and exercise, is a potential therapeutic possibility for metabolic disorders like obesity and type 2 diabetes[16].

**Inter-Tissue Crosstalk**

Myonectin acts as a potential post-prandial nutrient-sensing signal derived from skeletal muscle which integrates metabolic processes like glucose and lipid metabolism[13]. Myonectin levels increase on exercise which further regulates metabolic processes in the body[2]. Thus, Myonectin is likely a significant mediator in inter-tissue crosstalk[13]. Myonectin in an endocrine manner, activates mTOR signaling pathways and suppresses liver autophagy genes thereby establishing a liver-skeletal inter-signaling pathway[15]. Myonectin also activates AMPK/PGC1α signaling pathways and PGC1α stimulated mitochondrial biogenesis, which plays a significant role in the modulation of skeletal mass and function. This shows that myonectin acts in an autocrine manner establishing an inter skeletal tissue crosstalk[15]. Also, myonectin is involved in various anti-inflammatory pathways and apoptotic mechanisms[5,17].

**Anti-Inflammatory Response**

Myonectin attenuates the inflammatory response in macrophages. It reduces the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1 in macrophages stimulated with lipopolysaccharide (LPS). Myonectin also inhibits the phosphorylation of NF-κB, a key mediator of inflammation, in response to LPS. These anti-inflammatory effects of myonectin are mediated through the activation of the cAMP/Akt signaling pathway[5]. The upregulation of myonectin by vitamin B6 also indicates its potential role in the antioxidant system[18]. Increased circulatory inflammatory mediators like tumor necrosis factor, C-reactive protein (CRP) in Obstructive Sleep Apnoea Syndrome (OSAS), and decreased levels of serum myonectin levels in OSAS further suggest the correlation of myonectin with its anti-inflammatory action[17]. Thus, it can be inferred that myonectin might exhibit anti-inflammatory responses.

**Iron Metabolism**

Myonectin is coded by the gene *Erfe*. The gene product myonectin, can also be referred to as erythroferrone (ERFE). ERFE is a mediator of the response to erythropoietic stress, by suppressing hepcidin to promote the mobilization of stored iron and the absorption of dietary iron so that the increased iron demands of developing erythrocytes can be met. In response to anemia, pathophysiological conditions leading to blood loss, inflammation, etc., increased EPO production by the kidney stimulates erythroblasts to increase

the production of ERFE, both because EPO increases the number of erythroblasts and because EPO increases the synthesis of ERFE by each erythroblast. Circulating ERFE acts directly on hepatocytes to suppress hepcidin production. Low levels of hepcidin allow the efflux of stored iron, primarily from macrophages and hepatocytes, as well as increased dietary iron absorption so that more iron is loaded onto transferrin. Increased flows of plasma holotransferrin then deliver iron to erythroblasts for augmented heme and hemoglobin synthesis. Thus, myonectin/ERFE plays an important role in facilitating iron availability during stress erythropoiesis[19].

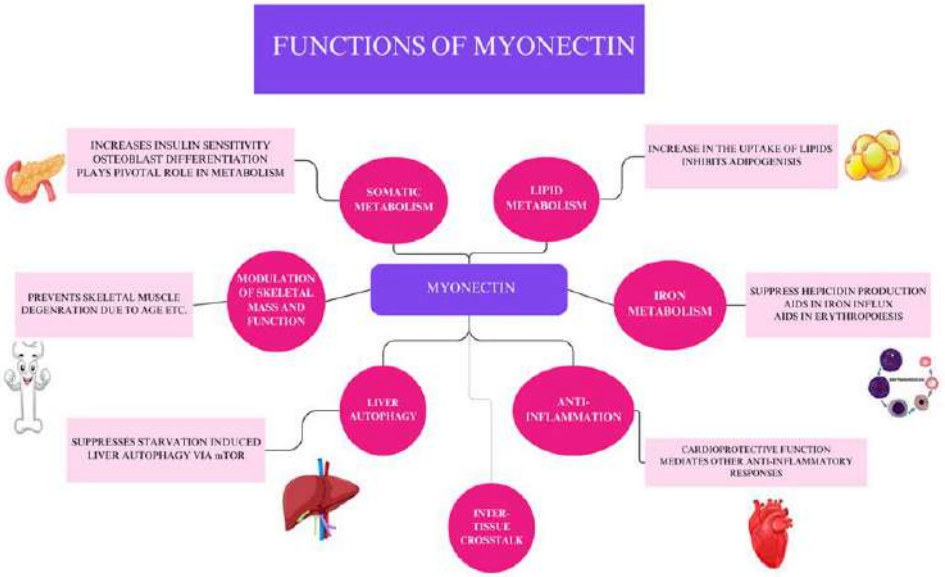


**Figure No 3: An overview of myonectin functions**

**Myonectin as a Biomarker of Various Disorders:**

**Diabetes**

In 2018, Kejia Li et al., carried out some experiments aiming to investigate the relationship between myonectin and type 2 diabetes mellitus (T2DM). Circulating myonectin was found to be higher in Type 2 Diabetes Mellitus (T2DM) patients than in prediabetic Impaired glucose tolerance (IGT) subjects, indicating a progressive increase of myonectin levels from a prediabetic to a diabetic state. Also, circulating myonectin levels were significantly increased in obese subjects. This proposed that myonectin might act as a circulating biomarker of adiposity and obesity-related metabolic diseases. Circulating myonectin levels were not affected by an oral glucose challenge, EHC (a euglycemic-hyperinsulinemic state), or a 45-minute bout of exercise[4]. In 2020, Jie Zhang et al., carried out a study to find the association between serum myonectin concentrations with Diabetic Nephropathy. Serum myonectin is negatively correlated with body mass index (BMI), total cholesterol, low-density lipoprotein cholesterol, blood urea nitrogen, creatinine, uric acid, and ACR, and positively correlated with glomerular filtration rate and insulin treatment. Serum myonectin is decreased in DN patients and correlated with renal function[20]. Obese nondiabetic controls had significantly lower serum myonectin levels compared with lean nondiabetic controls. Serum myonectin levels were correlated with metabolic markers of T2DM[21].

**Liver Steatosis**

In 2019, Hannah C. Little et al., carried out studies using a genetic mouse model including myonectin knock-out and wild-type mice. Studies revealed

that fat distribution between adipose and liver was altered in myonectin-deficient male mice. Liver histology revealed a marked reduction in steatosis in myonectin knock-out mice compared to the wild type. This is due to a significant reduction in Triglyceride (TG) accumulation. Quantification of lipids also revealed significantly reduced hepatic TG content and lower cholesterol levels. Histologic analysis of visceral epididymal and subcutaneous white adipose tissue (WAT) indicated significantly larger adipocytes in myonectin-knock-out animals. The enhanced size of adipose tissue was associated with increased postprandial lipoprotein lipase activity in adipose tissue. The data from studies suggest that myonectin plays a significant role in lipid partitioning between tissues and its deficiency enhances lipid storage in adipose tissue and reduces lipid accumulation in the liver[22].

**PCOD**

Jiajia Zhang et al., in 2021 conducted studies to investigate the relationship between myonectin levels and metabolic and hormonal disorders in patients with polycystic ovary syndrome (PCOS). A comparison of myonectin levels and other metabolic parameters was carried out between the control group (100) and PCOS subjects. There was no significant difference in age, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Compared with the control group, the levels of myostatin and HDL-C in the PCOS group were significantly decreased. Fasting Blood Glucose, Homeostasis Model Assessment- Insulin Resistance (HOMA-IR), and TG levels were significantly increased. Also, when compared with the control group, the luteinizing hormone (LH) level of the PCOS group was significantly higher, and the Sex Hormone-Binding Globulin (SHBG) level was significantly lower. There was no significant difference in follicle-stimulating hormone (FSH), estradiol (E2), testosterone, or progesterone between the two groups. The results suggest that myonectin may be an effective index to predict metabolic and hormone disorders in PCOS patients[23].

**Endogenous Factors Upregulating the Expression of Myonectin**

**1. High Intensity Interval Training**

High-intensity interval swimming program comprised of 30-second high-speed swimming repetitions with 2-minute active rest intervals. Studies found that HIIT and moderate-intensity continuous training (MICT) programs increased muscle FNDC5, myonectin, and GLUT4 gene expression in diabetic rats. The study suggests that physical activity may alter myonectin through its effect on GLUT. The positive relationship between all variables suggests that exercise training can also be beneficial in managing diabetes conditions. MICT induced a greater increase in myonectin and GLUT4 compared to HIIT[24,25]. High-intensity interval swimming training effectively elevated plasma myonectin levels while also improving the lipid profile and weight.

**2. Progressive Resistance Training (PRT)**

The study showcases PRT efficacy in elevating serum myonectin levels, curbing weight gain, enhancing muscle mass, and reducing fat accumulation induced by a high-fat diet combined with sucrose solution intake. The study focused on PRT highlighted the potential of PRT as a strategy to enhance myonectin levels, consequently aiding in managing metabolic disorders associated with obesity. PRT elevated serum myonectin levels and increased muscle weight while reducing retroperitoneal fat weight. The research highlighted that high-intensity progressive resistance training (HIPRT) might be more effective in elevating myonectin levels compared to low or moderate-intensity aerobic exercises due to its potential impact on cellular cAMP and calcium levels, factors known to up-regulate myonectin[26].

**3. Aerobic Exercise**

A significant elevation in serum myonectin levels among participants engaged in the exercise regimen was observed. Concurrently, a reduction in insulin resistance was observed within the exercise group, suggesting a potential association between heightened myonectin levels and improved metabolic outcomes following structured aerobic exercise. Exercise increases the amount of glut-4 in trained muscle which thereby improves the action of insulin. Shreds of evidence suggested that aerobic exercise significantly increased myonectin levels and decreased insulin resistance after eight weeks. The rise in myonectin levels with exercise is attributed to reduced BMI, whereas obesity decreases circulating myonectin by limiting free fatty acids and their tissue absorption. This connection paves the way for better strategies to tackle the health problems linked to obesity.

The study also demonstrated a significant reduction in myonectin levels and insulin resistance in older and younger patients after 10 weeks of moderate-intensity training while earlier pieces of evidence observed increased myonectin expression in muscle and circulation after two weeks of aerobic exercises[27].

**4. Fasting Followed by Nutrient Supplementation**

Myonectin expression and circulating levels are highly induced by refeeding following an overnight 12-hour fasting[13]. Myonectin curbed starvation-induced autophagy in both mouse liver and cultured hepatocytes by suppressing autophagosome formation and altering gene expression related to this process. Myonectin expression is repressed by starvation but robustly induced by nutrient availability[16]. Myonectin levels equally spiked when fasted mice were administered a glucose or lipid bolus, showing its responsiveness to acute metabolic shifts post-nutrient intake in skeletal muscle. This nutrient-responsive myokine exhibited heightened expression in cultured mouse myotubes upon glucose or free fatty acid addition, further linking its secretion to nutrient flux in muscle tissue[13].

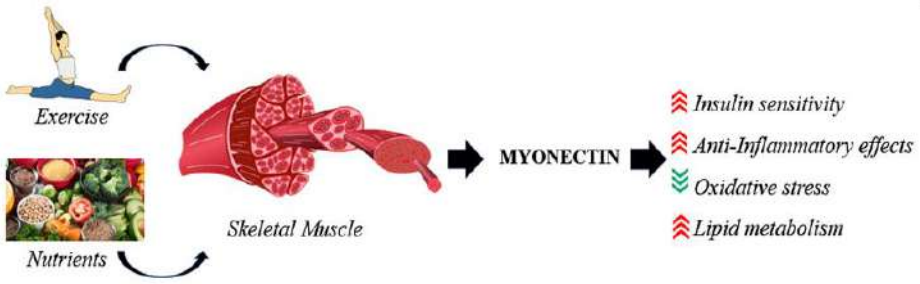


**Figure No 4: Upregulation of myonectin expression and its effects**

**Exogenous Factors Stimulating Myonectin Expression**

The possible exogenous dietary factors that upregulate myonectin expression as evidenced by ethnopharmacological experiments and studies have been elucidated below:

**a. Dietary vitamin B6:** It elevates the expression of exercise-induced genes. Myokines, including myonectin, are released during exercise and may be partly responsible for the beneficial effects of exercise[2]. Dietary vitamin B6 upregulates myonectin expression. It also upregulates the expression of myogenin, which is significantly correlated with the expression of other myokines, including myonectin[18].

**b. Curcumin:** The Curcumin group ameliorates exercise fatigue through specific improvements, including a reduced AMP/ATP ratio and lactic

acid content, along with increased glycogen synthase and myonectin levels. Curcumin's anti-fatigue effects may be attributed to its regulation of energy metabolism through the modulation of proteins in the PI3K/Akt/AMPK/mTOR pathway[28]. It is also evidently established that myonectin regulates liver autophagy via the mTOR signaling pathway[16]. Thus, curcumin may upregulate myonectin expression and this perhaps explains one of the reasons for its anti-fatigue effect.

**c. Culinary herbs and spices:** Extracts of various plants, such as caraway, chili pepper, nutmeg, licorice, black and white pepper, paprika, coriander, saffron, and stevia tea, activates PPARα, thereby lowering lipid levels in the body. Compounds like resveratrol (found in grapes and bilberries) and apigenin (found in various herbs and spices) showed weaker activation of PPARα. Chalcones, found in various plants, are strong activators of PPARα. PPARα is a regulator of adipogenesis and adipocyte differentiation and also, regulates the expression of factors that enhance lipid accumulation[29]. This highlights the potential of certain plants as sources of compounds that can lower lipids. Myonectin inhibits adipogenesis by regulating the expression of transcription factors involved in adipocyte differentiation[11]. It can be speculated that myonectin expression and PPARα activating food items have some correlation.

**d. Olive oil and other oils:** Several myokines, mainly IL-6 and myonectin, myokines with anti-inflammatory properties, are seen to be significantly regulated in high-fat diets including lard oil, olive oil, and crude palm oil. The gene expression of myonectin is dependent on both the level and the type of fat. When comparing only fat diets to each other, a significant increase in myonectin gene expression level was observed with the refined Palm Oil and Olive oil diets compared to the crude palm oil inclusive diet. The level of IL-10 or myonectin gene expression with the lard-rich diet was seen to be intermediate between that of crude Palm Oil and refined palm oil or olive oil[30,31]. Thus, these diets upregulated myonectin expression, but significantly less than what exercise can induce.

## Conclusion

Myonectin is a novel myokine that has the potential to regulate homeostasis and major metabolic regulations in the body. As it is evident that the skeletal muscle secretes myonectin in response to physical activity or nutrient availability, it becomes apparent that nutrient uptake and exercise can be leveraged to avail the benefits of myonectin. It can also be concluded that Myonectin-mediated effects could prevent the incidence and progression of metabolic disorders. Myonectin expression could be employed as an alternative to drug-therapeutic intervention in major lifestyle disorders and also in the adaptation of skeletal muscle mass especially during old age. This review of Myonectin will provide major insights into further studies in exploiting the substantial potential of myonectin and aid in establishing an alternative to drugs. In conclusion, Myonectin is a novel myokine that harmonizes body metabolism, modulates skeletal health, ameliorates cardiac ischemic injuries, and probably many more functions that are yet to be unveiled.

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