# Polyphenols in Modulating Mitochondrial Bioenergetics

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## Definition

Polyphenols are naturally derived compounds that are increasingly being explored for their various health benefits. In fact, foods that are rich in polyphenols have become an attractive source of nutrition and a potential therapeutic strategy to alleviate the untoward effects of metabolic disorders. The last decade has seen a rapid increase in studies reporting on the bioactive properties of polyphenols against metabolic complications, especially in preclinical models.

## 1. Overview

Polyphenols are naturally derived compounds that are increasingly being explored for their various health benefits. In fact, foods that are rich in polyphenols have become an attractive source of nutrition and a potential therapeutic strategy to alleviate the untoward effects of metabolic disorders. The last decade has seen a rapid increase in studies reporting on the bioactive properties of polyphenols against metabolic complications, especially in preclinical models. Various experimental models involving cell cultures exposed to lipid overload and rodents on high fat diet have been used to investigate the ameliorative effects of various polyphenols against metabolic anomalies. Here, we systematically searched and included literature reporting on the impact of polyphenols against metabolic function, particularly through the modulation of mitochondrial bioenergetics within the skeletal muscle. This is of interest since the skeletal muscle is rich in mitochondria and remains one of the main sites of energy homeostasis. Notably, increased substrate availability is consistent with impaired mitochondrial function and enhanced oxidative stress in preclinical models of metabolic disease. This explains the general interest in exploring the antioxidant properties of polyphenols and their ability to improve mitochondrial function. The current review aimed at understanding how these compounds modulate mitochondrial bioenergetics to improve metabolic function in preclinical models on metabolic disease.

## 2. Background

Polyphenols are naturally derived compounds that are widely studied for their health benefits [1]. In fact, polyphenols can be grouped into four major categories, which include flavonoids, phenolic acids, stilbenes, and lignans. Flavonoids, one of the larger classes of polyphenols, can be further grouped into flavones, flavonols, flavanols, flavanones, isoflavones, proanthocyanidins, and anthocyanins [2]. Chemically, flavonoids have the universal structure of a 15-carbon skeleton, containing two phenyl rings and a heterocyclic ring. This carbon structure can be abbreviated as C6-C3-C6 [2]. Consumed food or beverage sources such as tea, fruits, and vegetables are known to contain high levels of polyphenols which include aspalathin, catechin, hesperetin, cyanidin, proanthocyanidins, quercetin, and rutin [3]. There is a significant interest in understanding the bioactivities of these compounds, with the PubMed search showing that over 4599 relevant records can be accessed to date, and a considerable growth in publications has been seen in the last decade [4]. In addition, many plants that are rich in polyphenols such as Aspalathus linearis “rooibos tea plant” [5] and Camellia sinensis “tea plant” [6] are widely investigated for their health benefits such as improving cardiovascular function and combating cancer [7][8]. In fact, our group has been actively involved in understanding the therapeutic effects of rooibos, including assessing its ameliorative effects against diverse metabolic complications [9][10]. Accumulatively, we have shown that polyphenolic compounds such as aspalathin, isoorientin, and rutin can activate various physiological pathways such as protein kinase B (AKT) and AMP-activated protein kinase (AMPK) to improve insulin signaling and regulate energy metabolism [11][12]. Likewise, polyphenolic compounds such as gallic acid and catechins can reduce body weight and attenuate metabolic abnormalities, especially scavenging free radical species through their abundant antioxidant properties

[13].

Indeed, the bioactivity of polyphenols has been mainly attributed to their abundant antioxidant properties, which have been linked with improved metabolism, reduced inflammation, and ameliorating oxidative stress [14]. Notably, inflammation and oxidative stress are some of the key destructive components that are implicated in the development of metabolic anomalies and deteriorated metabolic health. Inflammation is characterized by abnormally enhanced pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [15]. On the other hand, oxidative stress arises because of overproduction of reactive oxygen species (ROS) that trigger suppression of intracellular antioxidants such as glutathione, superoxide dismutase, catalase, and thioredoxins [16]. Recently, impaired mitochondrial dysfunction has been reported to play an important role in the generation of oxidative stress through the altered actions of the electron transport chain [17]. For example, enhanced substrate delivery including free fatty acids (FFAs), especially under the conditions of metabolic syndrome, can impede the actions of the mitochondrial electron transport chain, resulting in the leakage of electrons and the overproduction of ROS. In fact, a few studies have correlated impaired mitochondrial bioenergetics with the generation of oxidative stress and reduced metabolic function [18]. As a result, many studies have targeted the main energy regulating tissues with abundant mitochondria, such as the skeletal muscle, to understand how increased substrate availability reduces or affects metabolic function [19][20]. Similarly, several studies have been published focusing on understanding how polyphenols affects mitochondrial bioenergetics in conditions of metabolic stress [21][22]. Currently, there is limited reviews on this topic or those targeting the modulation effect of polyphenols on skeletal muscle physiology. Thus, the current study aims to systematically extract and discuss relevant literature on the impact of polyphenols and plants rich in these compounds on their ameliorative effects against metabolic complications by targeting mitochondrial bioenergetics within the skeletal muscle.

## 3. Future Perspectives

It is now widely accepted that a healthy diet is essential to defend the human body against certain types of diseases, especially non-communicable diseases such as obesity, type 2 diabetes, and cardiovascular diseases [23]. Certainly, food sources such as fruits and vegetables have become an attractive source of nutrients and health benefits. In fact, these food sources are known to contain various biological compounds, including polyphenols, that present with enhanced potential beneficial effects in improving metabolic function. Accumulative preclinical evidence suggests that polyphenols can improve metabolic function by effectively regulating energy metabolism, as well as enhancing glucose uptake and mitochondrial function. Here, it was apparent that polyphenolic compounds such as gingerol, icariin, and resveratrol can target the skeletal muscle to regulate energy metabolism and improve mitochondrial function in preclinical models of metabolic syndrome. This is important to establish since it is already known that the pathogenesis of metabolic diseases like diabetes is consistent with skeletal muscle mitochondria deficiency, leading to impaired cellular functions [24][25][26]. Apparently, in addition to the effective modulation of cellular mechanisms such as insulin signaling and energy regulating pathways through PI3K/AKT and AMPK, these polyphenols seem to target PGC1α and other mitochondrial functional genes such as TFAM, mfn2, and drp1 to improve mitochondrial bioenergetics. These findings also highlight the potential impact naturally derived compounds and micronutrients can have on improving human health by targeting major organ tissues such as the skeletal muscle, as previously discussed [27]. In fact, the summarized data remain essential in developing precise therapeutic targets to be further tested in human subjects and to protect against the rapid rise of metabolic diseases. Although the current study informs on essential preclinical mechanisms that may be involved in the amelioration of metabolic complications, additional experiments and elucidations are still necessary to better understand the therapeutic potential of polyphenols, especially the relevance of their metabolism and bioavailability in the human body.

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**Keywords**

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