Chapter 10

Skeletal Muscle as a Therapeutic Target for Natural Products to Reverse Metabolic Syndrome

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Abstract

Natural compounds, especially polyphenols have become a popular area of research mainly due to their apparent health benefits. Increasing the phenolic content of a diet, apart from its antioxidant benefit, has a beneficial effect on signaling molecules involved in carbohydrate and lipid metabolism. These effects could potentially protect against metabolic syndrome, a cluster of metabolic complications such as obesity, insulin resistance and type 2 diabetes that is characterized by a dysregulated carbohydrate, and lipid metabolism. Research continues to investigate various natural compounds for their amelioration of impaired signaling mechanisms that may lead to dysregulated metabolism to find means to improve the life expectancy of patients with metabolic syndrome. In this chapter, a systematic search through major databases such as MEDLINE/PubMed, EMBASE, and Google Scholar of literature reporting on the ameliorative potential of commonly investigated natural products that target skeletal muscle to ameliorate metabolic syndrome associated complications was conducted. The selected natural products that are discussed include apigenin, aspalathin, berberine, curcumin, epigallocatechin gallate, hesperidin, luteolin, naringenin, quercetin, resveratrol, rutin, and sulforaphane.

Keywords: skeletal muscle, metabolic syndrome, insulin resistance, type 2 diabetes, natural products

1. Introduction

A considerable amount of interest has been placed on the discovery of novel naturally occurring plant-derived compounds for the treatment and prevention of various diseases. Bioactive

compounds of plant origin have long been shown to possess strong ameliorative properties against various communicable and noncommunicable diseases [1, 2]. For example, since its traditional use during the 1950s, artemisinin, an antimalarial *qinghao* derived lactone, has been the leading therapy for the treatment of *Plasmodium falciparum* malaria worldwide [3]. Similarly, the traditional use of galegine, an alkaloid isolated from *Galega officinalis*, led to the discovery of biguanide class of antidiabetic medications such as metformin [4]. Agents such as metformin are effective at lowering blood glucose levels and combating complications associated with insulin resistance (IR), the major characteristic of the metabolic syndrome [5]. However, the continued rise in the mortality of diabetic patients warrants an investigation into alternative therapies to reduce the burden of noncommunicable diseases. Naturally derived compounds such as polyphenols are increasingly explored for their therapeutic potential to reverse IR and thus decrease the risk of developing the metabolic syndrome. This may eventually lead to an increased life expectancy of diabetic individuals [6]. Thus, due to its modulatory effect of glucose and lipid metabolism, skeletal muscle has been a target to a growing number of therapeutic interventions in an effort to reverse IR and improve the management of metabolic syndrome [7, 8]. Here, we systematically assessed the available literature on the ameliorative potential of some of the prominent natural products against IR associated complications. A systematic search was conducted on all major databases such as MEDLINE/PubMed, EMBASE, and Google Scholar, for available literature reporting on the ameliorative properties of some of the prominent natural compounds including apigenin, aspalathin, berberine, curcumin, epigallocatechin gallate, hesperidin, luteolin, naringenin, quercetin, resveratrol, rutin, and sulforaphane against IR related to the development of metabolic syndrome. The search was conducted from inception until the end of January 2018, gray literature such as abstract proceedings and pre-prints were also included. There were no language restrictions implemented while review articles were screened for primary findings.

2. Apigenin

Apigenin (PubChem CID: 5280443) is a natural flavone (4′,5,7-trihydroxyflavone) with the molecular formula $C_{15}H_{10}O_5$ (MW 270.24 g/mol) that is abundantly present in fruits and vegetables, including parsley, chamomile, and celery (**Figure 1**) [9]. Apigenin was identified as the main yellow dye compound in the flowers of *Delphinium Zalil* as early as the 1890s [10], and its bioavailability and metabolism profile has been studied as far back as the 1970s [11].

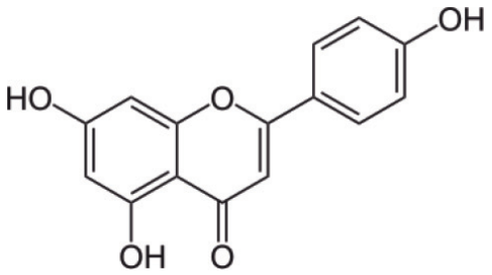

Figure 1. The chemical structure of apigenin (4′,5,7-trihydroxyflavone).

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Although pharmacokinetic studies show that apigenin has low bioavailability [12, 13], this compound has been detected in rat plasma after intravenous bolus administration [14], and it was demonstrated that human intestinal microbiota might contribute to its metabolism [15]. The known metabolites of apigenin detected in the urine of rats consist of p-hydroxyphenylpropionic acid, p-hydroxycinnamic acid, and p-hydroxybenzoic acid metabolites [11] while it is known glucosides include apiin, apigenin, vitexin, isovitexin, and rhoifolin.

In relation to its biological activities, increasing studies have demonstrated that apigenin displays a broad spectrum of anticarcinogenic properties as reviewed by Sung et al. [16]. Some of the well-studied mechanisms associated with the chemo-preventative capabilities of apigenin include its anti-inflammatory activity, its ability to suppress cell proliferation and oxidative stress, as well as its modulatory effect of autophagy and apoptosis [16, 17]. Interestingly, similar mechanisms have also been implicated in the development and aggravation of IR and its related complications. In a recent study, Jung et al. [18] showed that in addition to reducing circulating free fatty acids (FFAs), total cholesterol, and apolipoprotein B levels, apigenin modulated transcriptional factors linked with the development of obesity and related metabolic disturbances in high fat diet (HFD)-induced mice. This study showed that apigenin upregulated the expression of genes responsible for the regulation of beta-oxidation, oxidative phosphorylation, as well as electron transport chain and cholesterol homeostasis, which are all essential target sites for the control of substrate usage in cells. Although limited studies are reporting on its effect on skeletal muscle, two recent studies have shown that apigenin can regulate skeletal muscle function. For instance, Choi et al. [19] showed that this flavone improved mitochondrial function and exercise capacity by reducing the expression of atrophic genes such as RING-finger protein-1 and Atrogin 1 in mice fed HFD. Jang et al. [20] demonstrated that in C2C12 cells and skeletal muscle of C57BL/6 mice, this flavone promoted hypertrophy and myogenic differentiation by regulating protein arginine methyltransferase 7 (Prmt7)-peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)-G protein-coupled receptor 56 (GPR56) pathway, as well as the Prmt7-p38-myoD pathway. Although additional studies are required to further assess the impact of apigenin in the modulation of metabolic disease-related complications through the regulation of skeletal muscle function, the two aforementioned studies suggest that this flavone has a potential to protect against skeletal muscle weakness associated with metabolic complications.

3. Aspalathin

Aspalathin (PubChem CID: 11282394) is a natural *C*-glucosyl dihydrochalcone (3′-β-D-glucopyranosyl-2′,3,4,4′,6′- pentahydroxydihydrochalcone) with the molecular formula $C_{21}H_{24}O_{11}$ (MW 452.412 g/mol) (**Figure 2**) [21]. Although aspalathin was known to be uniquely found in rooibos [22], recent evidence has shown that this *C*-linked dihydrochalcone glucoside can be detected in trace amounts in two other species of *Acacia pendula* [23]. Aspalathin is considered to have a poor bioavailability profile in different experimental settings as reviewed by Muller et al. [24] and Johnson et al. [25]. While Stalmach et al. [26], using high-performance liquid chromatography-mass spectrometry method, showed that *O*-methyl-aspalathin-*O*-glucuronide

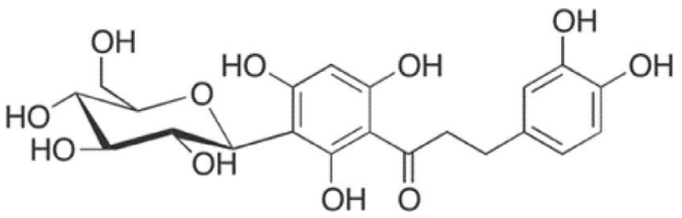

Figure 2. The chemical structure of aspalathin (3′-β-D-glucopyranosyl-2′,3,4,4′,6′- pentahydroxydihydrochalcone).

and eriodictyol-*O*-sulfate were the main metabolites excreted following ingestion of rooibos extract containing 10-fold higher levels of aspalathin in human subjects. In addition, a recent study by Bowles et al. [27] showed that aspalathin can be absorbed and metabolized to mostly sulfate conjugates detected in the urine of mice. However, additional evidence is required to establish the pharmacokinetic profile of aspalathin.

Relevant to its biological activity, the initial evidence demonstrated that aspalathin possess strong antioxidant properties by scavenging 2,2-diphenyl-β-picrylhydrazyl (DPPH) radical in vitro [28]. This effect was important since experimental and clinical studies support the notion that drug compounds that enhance intracellular antioxidant properties can further exhibit a wide range of beneficial effects against the development of metabolic syndrome [29]. In addition to its robust antioxidant activity [28, 30–34], aspalathin can ameliorate inflammation [35–39], protect cardiac cells exposed to high glucose concentrations [40–44], and also display glucose lowering properties [45–50]. In addition to work by our group [46, 48], studies conducted by Kawano et al. [51] and Son et al. [50] have reported on the effect of pure aspalathin or an aspalathin rich green rooibos extract on the signaling mechanisms that regulate glucose and lipid metabolism in skeletal muscle. Activation of 5' AMP-activated protein kinase (AMPK), an important kinase in the regulation of energy production, as well as increasing the expression and translocation of glucose transporter (GLUT) 4 have been the key molecular targets by aspalathin in the skeletal muscle. Thus, although additional evidence such as assessing the therapeutic effect of this dihydrochalcone on skeletal muscle biopsies of insulin-resistant human subjects is still necessary, its aforementioned potential to target AMPK, and improve glucose uptake is of major importance for future therapeutic development.

4. Berberine

Berberine (PubChem CID: 2353) is a quaternary alkaloid (5,6-Dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium) with the molecular formula $C_{20}H_{18}NO_4^+$ (MW 336.37 g/mol) that is present in several plants including *Hydrastis canadensis*, *Xanthorhiza simplicissima*, *Phellodendron amurense*, and *Berberis aristata* (**Figure 3**) [52]. Berberrubine, thalifendine, demethyleneberberine, and jatrorrhizine are some of the major metabolites detected in plasma following the administration of berberine in rats, with the liver and intestinal bacteria identified to participate in the metabolism, and disposition of this compound in vivo [53]. Although a number of factors, including it being hydrophilic in nature and its containment of quaternary ammonium groups contribute to the low bioavailability of berberine [54]. Interestingly, the absorption of berberine in the small intestine can be enhanced by d-α-tocopheryl polyethylene glycol 1000 succinate [55].

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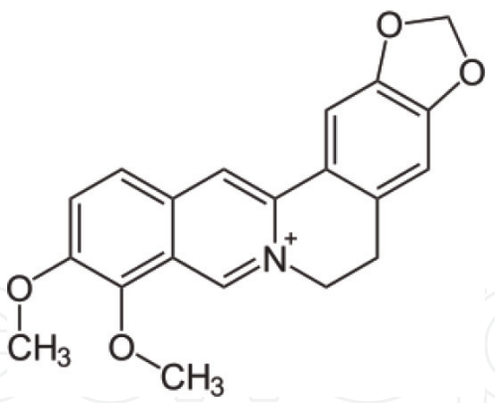

Figure 3. The chemical structure of berberine (5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium).

Therefore, further research is required to better understand and inform on mechanisms that can add to our current knowledge on the bioavailability of berberine, which is crucial in improving its efficacy in vivo.

Berberine has a long history of medicinal use in traditional Chinese and Native American medicine [56] and has demonstrated a number of beneficial effects against metabolic complications, including amelioration of IR. Berberine demonstrated an enhanced effect to reduce body weight and raise plasma triglyceride levels while improving glucose tolerance and insulin action in both type 2 diabetic (*db*/*db*) mice and in FHD fed rats [57]. Interestingly, similar to aspalathin, an increase of glucose uptake through activation of AMPK as well as enhanced translocation of GLUT4 in skeletal muscle remains important in the ameliorative potential of berberine against IR [58–62]. However, it has been reported that berberine can alter muscle metabolism by altering mitochondrial function, resulting in the development of muscle atrophy in normal, and diabetic (*db*/*db*) mice [63]. Although the results were not in human subjects, these findings remain relevant since loss of muscle mass is an important feature that occurs in type 2 diabetic patients, especially in older individuals [64]. These results suggest that precaution should be taken when using these quaternary alkaloids, especially considering the toxicity of high doses [65]. In addition to acting by targeting the mitochondria [65], another mechanism by which berberine can reverse IR include downregulating toll-like receptor 4 (TLR4)/inhibitor of nuclear factor kappa-B kinase subunit beta (IKKbeta)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inflammation signaling pathway, leading to reduced inflammation [66].

5. Curcumin

Curcumin, also known as diferuloylmethane (PubChem CID: 969516; (1E,6E)-1,7-Bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione), is a major polyphenolic derivative of turmeric (*Curcuma longa*) with the molecular formula $C_{21}H_{20}O_6$ (MW 368.39 g/mol) (**Figure 4**) [67]. A single oral dose administration of curcumin can lead to the detection of its metabolites, glucuronide, and sulfate conjugates in plasma of human subjects [68]. Although is considered to have a safety profile, curcumin displays poor bioavailability profile that is coupled with quick metabolism and systemic removal [69]. However, recent developments such as blocking of metabolic pathways by

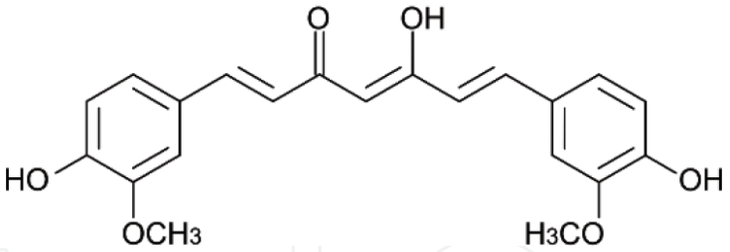

Figure 4. The chemical structure of curcumin ((1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione).

concomitant administration with other agents, conjugation, and modification of structure, as well as modulation of route and medium of administration are some of the explored approaches to improve the bioavailability of curcumin as reviewed by Prasad et al. [70]. Indeed, increasing research over the past 30 years has focused on exploring the pharmacokinetics, safety profile, and efficacy of this natural product in order to enhance its therapeutic profile in humans [71].

An increasing number of reviews has been published to keep track of the cumulative literature informing on the therapeutic potential of curcumin, including anticancer, antioxidant, anti-inflammatory, and antibacterial activities [70–72]. Relevant to its effect on skeletal muscle function. A study published in 2005 by Farid et al. [73] showed that curcumin failed to inhibit NF-κB activity, leading to its inability to ameliorate loss of muscle mass in the soleus. However, in a follow-up study published in 2008, curcumin presented enhanced effect in blocking sepsis-induced muscle proteolysis, at least in part by inhibiting NF-κB, and p38 activities in rats [74]. In L6 or C2C12 myotubes exposed to high palmitate concentrations as a model of IR, curcumin reversed IR by increasing glucose and FFA oxidation, at least in part by mediating LKB1-AMPK pathways, as well as suppressing insulin receptor substrate 1 (IRS-1) Ser^{307} and protein kinase B (AKT) phosphorylation [75–77]. Although similar evidence has been supported by in vivo experiments on skeletal muscle tissue of either diabetic or nondiabetic rodents [75, 77], curcumin displays an enhanced capacity to protect against oxidative stress associated complications by improving mitochondrial biogenesis, and other antioxidant mechanisms [78–81]. This involves activation of the nuclear factor (erythroid-derived 2)-like 2 (NRF2) [82], an essential intracellular antioxidant response element that is a target of various natural products aiming to reduce metabolic disease-associated complications.

6. Epigallocatechin gallate

Epigallocatechin gallate (PubChem CID: 65064) is an ester of epigallocatechin and gallic acid ([(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl] 3,4,5-trihydroxybenzoate, with the molecular formula $C_{22}H_{18}O_{11}$ (MW 458.375 g/mol), that is abundantly found in tea (**Figure 5**) [83]. Due to the popularity of green tea and as one of its major components, epigallocatechin gallate remains one of the highly consumed polyphenolic compounds [84]. Although it is detectable in its original form in human plasma after oral administration [85], epigallocatechin gallate is considered to have very low oral bioavailability profile as reviewed by Mereles and colleagues [86]. Although additional evidence is required to improve its

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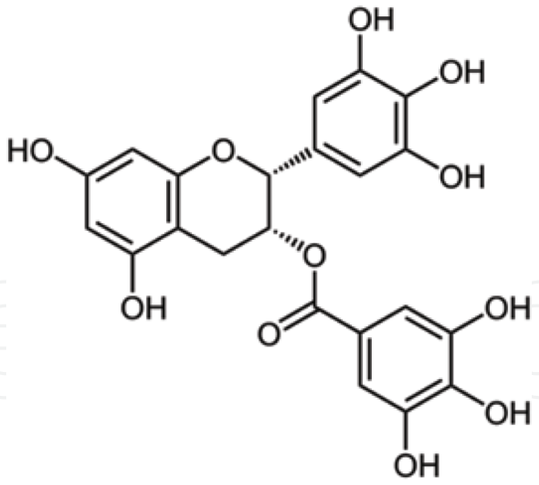

Figure 5. The chemical structure of epigallocatechin gallate ([(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl] 3,4,5-trihydroxybenzoate).

bioavailability, there has been an extensive exploration of this polyphenolic compound for its chemopreventive properties. Among the 10 polyphenols present in green tea, epigallocatechin gallate was found to exhibit the most antiproliferative and antiapoptotic effects [87].

It has already been established that epigallocatechin gallate can ameliorate complications linked with the development of the metabolic syndrome, by improving insulin sensitivity in both obese rodents and patients [88–90]. The enhanced therapeutic effect of this catechin has been associated with the modulation of various signaling pathways, including targeting of genes involved in cell survival, FFA regulation, mitochondrial energetics, intracellular antioxidant response, and others as reviewed by Singh and colleagues [91]. A number of studies have demonstrated several mechanisms associated with the ameliorative effect of epigallocatechin gallate on IR and associated complications in skeletal muscle. In addition to strengthening muscle integrity [92–94], accumulative data has been presented that this catechin can improve insulin sensitivity by enhancing glucose uptake, reduce lactate concentrations, enhancing mitochondrial capacity and stimulating beta-oxidation in cultured cells, or rodents as well as obese human subjects [95–100]. Inhibition of oxidative stress, activation of AMPK, increased expression of PGC-1α, NAD-dependent protein deacetylase sirtuin-1 (SIRT1), nuclear respiratory factor 1, medium chain acyl coA decarboxylase, uncoupling protein 3 (UCP3), AKT, and peroxisome proliferator-activated receptor alpha (PPARα) are some of the mechanisms targeted by epigallocatechin to enhance skeletal muscle function in a diseased state [101–104].

7. Hesperidin

Hesperidin (PubChem CID: 10621) is a flavanone glycoside ((2S)-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxy-2,3-dihydrochromen-4-one) with the molecular formula $C_{28}H_{34}O_{15}$ (MW 610.565 g/mol) that is present in high amounts in citrus fruits (**Figure 6**)

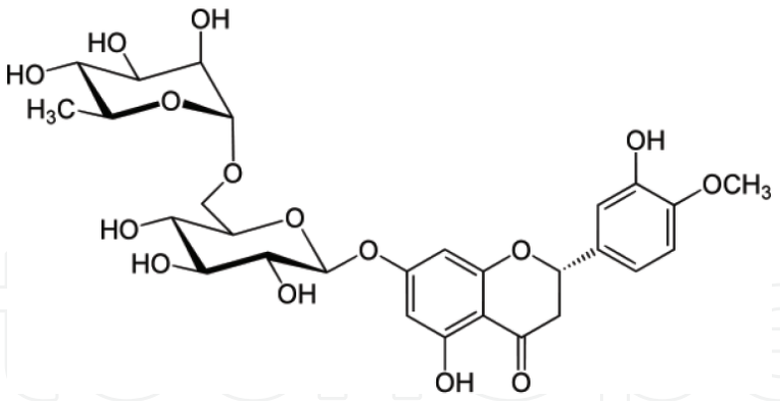

Figure 6. The chemical structure of hesperidin ((2S)-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxy-2,3-dihydrochromen-4-one).

[105]. Although it has a low bioavailability due to the rutinoside moiety attached to the flavonoid [106], hesperidin can be converted to glucuronides and sulfoglucuronides, which have been shown to be excreted in urine nearly 24 hours after the orange juice ingestion [107]. In a randomized controlled trial, Nielsen et al. [108] demonstrated that removal of the rhamnose group to yield hesperetin-7-glucoside improved the bioavailability of the aglycone hesperetin. Suggesting that additional interventions are required to improve the bioavailability of citrus flavonoids such as hesperidin.

Increasing data has supported the notion that hesperidin possesses increased potential to lower raised blood glucose and lipid levels in various models of type 2 diabetes [109–111]. When administered in rats subjected to swimming exercise, this citrus flavonoid improved the biochemical and antioxidant profile of the animals [112]. This compound may induce its therapeutic effect through the regulation of genes implicated in insulin signaling such as insulin receptor substrate 1, GLUT2/4, and those linked with lipid metabolism, including sterol regulatory element–binding protein 1c (SREBP-1c), fatty acid synthase (FAS) and acetyl-CoA carboxylase [113]. Although data on its effect on skeletal muscle is currently limited, it can reverse IR by reducing muscle glycogen content and ischemia–reperfusion injury while promoting myogenic differentiation through the activation of MyoD-mediated myogenin expression in cultured cells and animals [109, 114, 115].

8. Luteolin

Luteolin (PubChem CID: 5280445) is a flavone glycoside (2-(3,4-Dihydroxyphenyl)- 5,7-dihydroxy-4-chromenone) with the molecular formula $C_{15}H_{10}O_6$ (MW 286.239 g/mol) that is rich in various dietary sources such as fruits, vegetables, and teas (**Figure 7**) [116]. As with most flavonoids, during its metabolism luteolin is broken down to its glucuronides, which can eventually pass through intestinal mucosa as shown by Yasuda and colleagues [117]. Although studies reporting on the pharmacokinetic profile of luteolin in human subjects are limited, this flavone is quickly absorbed in rats and can be detected in urine and feces while showing a slow elimination rate [118]. Furthermore, luteolin from peanut hull extract can be easily absorbed compared to the pure compound, with its absorption more efficient in the

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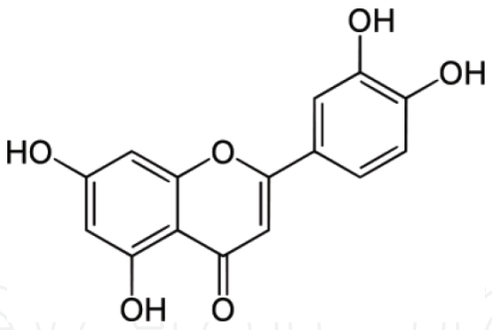

Figure 7. The chemical structure of luteolin (2-(3,4-dihydroxyphenyl)- 5,7-dihydroxy-4-chromenone).

jejunum and duodenum than in the colon and ileum [119]. Alternatively, luteolin-loaded solid lipid nanoparticles prepared by hot microemulsion ultrasonic technique can also improve the solubility and increase the compound concentration in plasma of rats [120].

In addition to its strong antioxidant effects [121], in vitro experiments have provided evidence that luteolin possesses chemopreventive and anti-inflammatory properties [122, 123]. Hydroxyl groups and 2–3 double bond remain key structural features of luteolin that are linked to its enhanced therapeutic effect [124]. Recent studies show that this flavone attenuates hepatic steatosis and IR by upregulating PPARγ protein expression and activating AMPKα1 signaling, which may be linked to the improvement in circulating FFA levels in diet-induced obese mice [125, 126]. However, only a few studies have reported on the effect of luteolin on the skeletal muscle. Available literature has reported on its effect in preventing lipopolysaccharide-induced muscle atrophy, oxidative stress-induced tissue injury and inflammation, partly through regulation of atrogin-1/MAFbx expression, and c-Jun N-terminal kinases (JNK) phosphorylation reported on [127–129].

9. Naringenin

Naringenin (PubChem CID: 932) is a flavanone (5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one) with the molecular formula $C_{15}H_{12}O_5$ (MW 272.256 g/mol) that is also predominantly found in citrus fruits (**Figure 8**) [130]. The chemical structure of naringenin comprises three hydroxy groups at the 4′, 5, and 7 carbons while its glycoside, naringin contains an additional disaccharide neohesperidose that is linked via its carbon end. Although naringenin can be

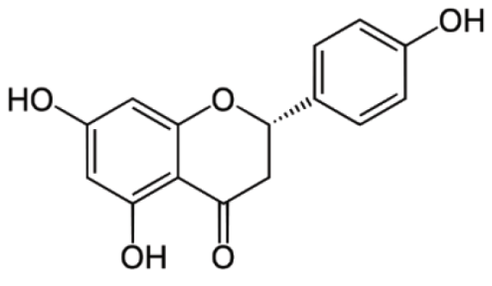

Figure 8. The chemical structure of naringenin (5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one).

detected as monoglucuronides in plasma and urine after ingestion of orange fruit juice in human subjects [131], the bioavailability of naringenin can be influenced by its glycosidic moiety. Felgines et al. [132] demonstrated that kinetics of absorption of naringenin and naringenin-7-glucoside was similar. In addition, naringenin-7-rhamnoglucoside exhibited a delay in its intestinal absorption, resulting in decreased bioavailability after ingestion in rats. On the other hand, complexation of naringenin with hydroxypropoyl-β-cyclodextrin has been another viable alternative to improve the bioavailability of naringenin, which is important to enhance its therapeutic potential [133].

Naringenin is among the well-studied citrus flavonoids shown to prevent complications associated with IR and the metabolic syndrome. Its role in preventing the deterioration in skeletal muscle mass and protecting against metabolic associated complication is summarized. In low-density lipoprotein (LDL) receptor–null ($Ldlr^{-/-}$) mice fed HFD, this flavanone reduced fasting hyperinsulinemia, improved glucose utilization and increased insulin sensitivity through regulation of SREBP-1c–mediated lipogenesis [134]. It stimulated glucose uptake but failed to have a significant effect on basal or insulin-stimulated AKT phosphorylation while significantly increasing AMPK phosphorylation/activation in cultured L6 myotubes [135]. Bhattacharya and colleagues showed that naringenin stimulates glucose uptake, indicating a dependence on GLUT4 activity as well as phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and/or p38MAPK activity [136]. Maintenance of muscle mass by reducing muscle diacylglycerol content, improving hyperinsulinemia, promoting phosphorylation of p38/MAPK via estrogen receptor beta (ERβ), lowering reactive oxygen species (ROS) production, and enhancing tyrosine phosphorylation are other mechanisms associated with protective effect of naringenin in either cultured cells or in vivo animal models [137–140].

10. Quercetin

Quercetin (PubChem CID: 5280343) is classified as a flavonol (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) with the molecular formula $C_{15}H_{10}O_7$ (MW 302.238 g/mol) that is abundantly found in various fruits and vegetables (**Figure 9**) [141]. Quercetin is one of the most abundant dietary flavonoids that is rapidly metabolized to glucuronides and sulfates that can be detected in plasma and urine [142]. Although oral bioavailability of quercetin remains

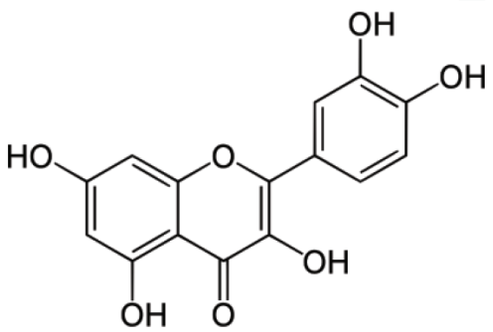

Figure 9. The chemical structure of quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one).

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low, the type of sugar moiety attached to its structure may affect its absorption. This has been as demonstrated with quercetin glycosides from onion which have a higher absorption rate compared to apple-derived quercetin [143, 144]. Quercetin-4′-*O*-glucoside and quercetin-3-*O*-rutinoside (rutin) are one the accomplished glycosides of quercetin, and their absorption rate and extent can be influenced by plant matrix as demonstrated by Graefe and colleagues [145]. However, it is clear that further investigations into improvement strategies for pure quercetin aglycone are required to improve the therapeutic potential of this flavonol.

Quercetin exhibits a wide range of biological functions. Although Stewart et al. [146] failed to show any beneficial effect of quercetin against IR in diet induced-obese mice, other researchers have shown that this flavonol plays a major role in modulating several signaling pathways to reverse metabolic syndrome and improve skeletal muscle function, either in vitro on cultured cells or in vivo in animals and samples from human subjects [148–168]. In L6 myotubes and skeletal muscle of genetical modified (*ob*/*ob*) mice, quercetin improved insulin sensitivity by increasing GLUT4 expression [147]. Several studies using different experimental models have also demonstrated the positive effect of quercetin in improving skeletal muscle insulin sensitivity through enhanced uptake of glucose, and reducing oxidative stress or inflammation-induced damage, with modulation of tumor necrosis alpha (TNF-α), AKT, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and AMPK as prime pathways involved in the process [148–158]. The therapeutic potential of quercetin extends to its preventative effect against ischemia–reperfusion injury, as well as strengthening muscle fibers through the modulation of calcium homeostasis, and enhancing intracellular antioxidants [159–168].

11. Resveratrol

Resveratrol (PubChem CID: 445154) is a phytoalexin stilbenoid (3,5,4′-trihydroxy-trans-stilbene) with the molecular formula $C_{14}H_{12}O_3$ (MW 228.247 g/mol) that is present in abundant amounts in various food sources such as grapes, blueberries, and red wine (**Figure 10**) [169]. Upon ingestion, resveratrol can be metabolized to form conjugated sulfates and glucuronides, namely resveratrol monosulfate, monosulfate dihydroresveratrol, and monoglucuronide dihydroresveratrol, as reviewed by Gambini and colleagues [170]. Although the bioavailability of resveratrol is considered low, it can vary depending on the method of administration and type of dietary source ingested [171]. The dimethyl ether analog of resveratrol, pterostilbene,

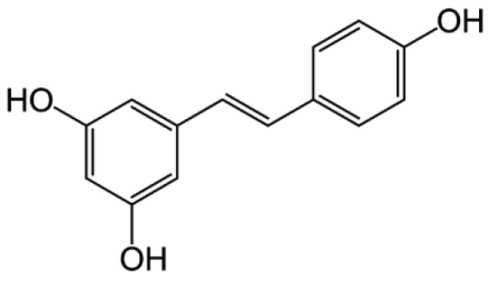

Figure 10. The chemical structure of resveratrol (3,5,4′-trihydroxy-trans-stilbene).

has been shown to exhibit a higher bioavailability, in terms of total plasma levels of both the parent compound and metabolites than does resveratrol [172]. However, Li et al. [173] showed that intravenous and oral pharmacokinetic characteristics of trans-resveratrol can be improved through encapsulating with PP123 self-assembling lecithin-based mixed polymeric micelles. Suggesting that alternative methods to improve the bioavailability of resveratrol are required, which may translate to enhanced therapeutic potential in vivo.

Resveratrol has displayed a variety of antidiabetic effects in rodent models. In addition, resveratrol attenuates thermal hyperalgesia, cold allodynia, as well as raised serum lipid levels [174–176]. In diabetic individuals, resveratrol administration is associated with significantly improved glucose and insulin control [177]. The systematic search of evidence linking resveratrol and IR in skeletal muscle revealed up to 18 studies published between 2007 and 2017, with 9 papers produced between 2016 and 2017, suggesting that this phytoalexin stilbenoid is increasingly explored for therapeutic effect against metabolic associated complications. Although Williams and colleagues showed no effect on insulin signaling pathways [178], stimulation of glucose uptake by resveratrol in cultured C2C12 cells or skeletal muscle has been linked with activation of extracellular signal-related kinase/p38/PI3K [179]. Its effect in promoting glucose uptake and improving insulin sensitivity was also associated with increased NAD-dependent protein deacetylase sirtuin-1 (SIRT1) expression, activation of AMPK while abolishing phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2), JNK, and IκB kinase α/β (IKKα/IKKβ) [180–190]. Other documented beneficial effect of resveratrol includes inhibiting ischemia–reperfusion injury through its potent antioxidant properties [191], reducing cell proliferation through upregulating PGC-1α [192], promoting muscle regeneration and attenuating the impact of ROS [193], and elevated forearm skeletal muscle mitochondrial capacity [194].

12. Rutin

Rutin (PubChem CID: 5280805) is a glycoside combining the flavonol quercetin and the disaccharide rutinose (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[α-L-rhamnopyranosyl-(1→6)-β- D-glucopyranosyloxy]-4H-chromen-4-one) with the molecular formula $C_{27}H_{30}O_{16}$ (MW 610.521 g/mol) that is found in many plants and fruits, as well as tea infusions (**Figure 11**) [195]. Upon oral administration, rutin can be metabolized into sulfates and glucuronides of quercetin that are detected in blood, whereas unchanged forms of rutin and quercetin were not detected [142, 196]. Although quercetin glycosides from onions demonstrate an enhanced absorptive capacity than pure aglycones [143, 144], some studies have showed that rutin has a lower oral absorption rate than quercetin [142, 197]. However, as with the use of natural deep eutectic solvents [198], alternative methods to improve the absorptive capacity of rutin is tested to improve therapeutic effect in vivo.

Like quercetin, rutin exhibits a wide variety of biological properties, mostly attributed to its strong antioxidant properties [199, 200]. It is accomplished that rutin displays enhanced potential

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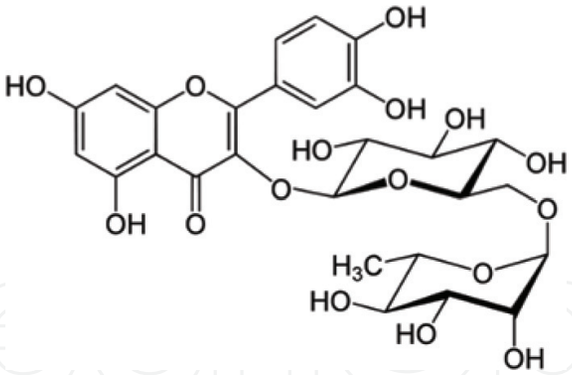

Figure 11. The chemical structure of rutin (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyloxy]-4H-chromen-4-one).

to improve insulin sensitivity by regulating genes involved in glucose and lipid metabolism such as GLUT4, PPARγ, and tyrosine phosphatase 1B in cultured cells or skeletal muscle of rodents [201–204]. However, from the study by Zyma et al. [205], that demonstrated that rutin induces conformational changes in the myosin structure of skeletal muscle of rabbits accompanied by an increase in ATPase activity, accumulative evidence has supported muscle strengthening capacity of this polyphenol. For example, Su et al. [206] presented data showing that rutin promoted skeletal muscle endurance capacity by modulating markers of mitochondrial biogenesis such as PGC-1α and SIRT1 expression in ICR mice subjected to a weight-loaded forced swim test. These findings were further supported by data showing that rutin increased the mitochondrial size and mitochondrial DNA content as well as gene expression related to mitochondrial biogenesis, such as PGC1-α, NRF-1, transcription factor A, and SIRT1 [207, 208].

13. Sulforaphane

Sulforaphane (PubChem CID: 5350) is an isothiocyanate (1-isothiocyanato-4-methylsulfinylbutane) with the molecular formula $C_6H_{11}NOS_2$ (MW 177.28 g/mol) that is found in cruciferous vegetables such as cabbages, broccoli, and brussels sprouts (**Figure 12**) [209]. Although sulforaphane displays a dose-dependent pharmacokinetic behavior, as higher doses show reduced absorptive potential, lower doses of the compound can be rapidly absorbed in rats following intravenous administration, with the absolute bioavailability being able to reach 82% [210]. In human subjects consuming fresh broccoli sprouts or the broccoli sprout extract, with each estimated to provide 200 μmol sulforaphane daily, the

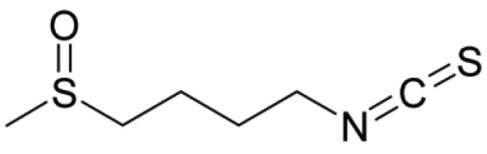

Figure 12. The chemical structure of sulforaphane (1-isothiocyanato-4-methylsulfinylbutane).

compound metabolites were found to be three times higher in plasma and urine of sprout consumers, suggesting enhanced sulforaphane absorption from sprouts [211]. Therefore, dietary form and dosing schedule of sulforaphane may influence impact absorption and therapeutic potential in human subjects.

Sulforaphane has received a considerable interest due to its ability to simultaneously control multiple cellular targets involved in various metabolic complications. For instance, in rats fed HFD, this isothiocyanate has displayed an enhanced hypoglycemic potential as well as the elevation of GLUT3 expression in the cerebral cortex and hypothalamus, leading to improved glucose tolerance [212]. Other studies [213, 214] have supported the beneficial effect of sulforaphane or its stable precursor glucoraphanin, to reverse IR, mostly through its robust antioxidant properties. In skeletal muscle, sulforaphane has exhaustive exercise-induced muscle damage, reducing muscle glycogen content, and enhanced exercise endurance capacity through inhibition of pro-inflammatory response and enhancing antioxidant response by upregulating NRF2 expression [215–220].

14. Conclusions

Natural compounds have gained popularity for their potential beneficial effect to fight metabolic diseases due to their less adverse effect compared to synthetic drugs. Furthermore, natural compounds serve as a valuable source for the discovery of new drugs. Currently, knowledge shows that natural compounds can ameliorate IR, however, the gap in scientific evidence of plant-derived therapeutic benefits still exist due to the slow rate of translation of animal studies findings into human clinical trials. In this chapter, evidently reported the great potential and the future promise of natural compounds for the management and treatment of metabolic disorders, specifically IR, obesity, and T2D. Therefore, further research is required to assess the use of natural compounds alone or in combination with well know antidiabetic drugs might result in synergistic and enhanced effects in combating metabolic diseases.

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Abbreviations

AKT	protein kinase B
AMPK	5' AMP-activated protein kinase
ATP	adenosine triphosphate
CD36	cluster of differentiation 36
DPPH	2,2-diphenyl-β-picrylhydrazyl
ERβ	estrogen receptor beta
FAS	fatty acid synthase
FFA	free fatty acid
GLUT	glucose transporter
HFD	high fat diet
IR	insulin resistance
IRS-1	suppressing insulin receptor substrate 1
JNK	c-Jun N-terminal kinases
LDL	low density lipoprotein
LKB1	serine/threonine kinase 11
MAPK	mitogen-activated protein kinase
MW	molecular weight
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NRF2	nuclear factor (erythroid-derived 2)-like 2
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PPAR	peroxisome proliferator-activated receptor
Prmt7	protein arginine methyltransferase 7
SIRT1	NAD-dependent protein deacetylase sirtuin-1
SREBP-1c	sterol regulatory element–binding protein 1c
T2D	type 2 diabetes mellitus
UCP	uncoupling protein

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