Due to the complexity of chronic conditions like the metabolic syndrome (MetS), tailored dietary approaches beyond macronutrient ratio modification may be necessary to effectively address metabolic measures. Mounting data on whole foods-based, phytochemical-abundant dietary patterns, such as the Mediterranean diet, reveal that they contain constituents, such as phytochemicals, that may be beneficial for treating MetS. The role of food-based phytochemicals on underlying mechanisms of MetS, specifically as they impact insulin signaling, has yet to be investigated thoroughly. This review discusses various dietary approaches for MetS, with a focus on certain foods and dietary phytochemicals known to impact insulin signaling.

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INTRODUCTION

The metabolic syndrome (MetS) has been defined as a constellation of abnormal cardiometabolic factors that increase risk of cardiovascular disease (CVD) and type 2 diabetes. Traditionally, these measurements have included increases in waist circumference, blood pressure, triacylglycerols (TG), and fasting glucose, as well as decreased HDL-cholesterol (Figure 1). In past years, the definition of MetS has expanded to include indicators of thrombosis and inflammation.

A rather complex disorder, providing a gateway to a host of chronic diseases, MetS appears to be precipitated by a number of underlying risk factors relating to genetics and lifestyle, and as proposed by Sullivan,1 a mismatched, incongruent combination of both those aspects. MetS is the subject of a plethora of scientific publications, with over 10,000 publications listed in the National Library Medicine Database (accessed 14 April 2008), yet there is continued debate over its definition and whether it is clinically relevant. Regardless of the terminology or the precise definition, MetS provides an intersection of markers that leads to a spectrum of chronic diseases.

Currently, prevention and treatment of MetS are often handled according to the presence and degree of the individual risk factors. Fitch et al.2 assessed that individuals with MetS most commonly exhibit abdominal obesity and dyslipidemia, providing support for the use of lifestyle modification as a major cornerstone of MetS therapy. In fact, lifestyle therapies have been specifically recommended for reducing several cardiometabolic risk factors beyond obesity and atherogenic dyslipidemia, including elevated blood pressure and glucose, and treating a pro-inflammatory state.3,4 The Scientific Statement proposed by the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI)3 states: “In the long run, the greatest benefit for those with metabolic syndrome will be derived from effective lifestyle intervention.” Indeed, lifestyle intervention has been demonstrated to be more effective than metformin for reducing the incidence of MetS and type 2 diabetes5,6 in high-risk populations. In 3234 nondiabetic subjects with elevated fasting glucose, a lifestyle-modification program composed of a low-calorie, low-fat diet plus physical activity, reduced the incidence of type 2 diabetes by 58%, and metformin by 31%, compared with placebo.4 The authors concluded, “... the lifestyle intervention was significantly more effective than metformin”. Similarly, the same lifestyle-modification program was able to reduce the incidence of MetS in 1711 subjects by 41% (metformin by 17%) compared with placebo.5 Considering that side effects may be experienced while taking...
HIGHS AND LOWS

In addition to physical activity, one of the aspects of lifestyle modification for MetS is diet; however, researchers have agreed that a uniform consensus is lacking as to which dietary approach is most efficacious. Since the primary endpoint for treatment of MetS is to reduce the risk of CVD, traditional dietary recommendations such as those proposed by the National Cholesterol Education Panel (NCEP)-Adult Treatment Panel (ATP) III and the AHA have primarily emphasized the macronutrient content of the diet with their recommendations to keep carbohydrate energy intake to 50–60%, protein to ~15%, and fat to 25–35%, with saturated fat at <7%, along with an avoidance of trans fat and restriction on daily cholesterol intake (300 mg/d). In addition to a low-fat, high-carbohydrate diet, NCEP-ATP III promotes the inclusion of fruits, vegetables, and whole grains. In a joint scientific statement on MetS, the AHA and NHLBI advocated “modification of an atherogenic diet” for MetS, defined as reducing intakes of total fat (25–35 en%), saturated fat (<7 en%), trans fat, and cholesterol (<200 mg/d). Additional guidance was provided as follows: “most dietary fat should be unsaturated, simple sugars should be limited.”

Hence, the overarching recommendation for MetS from pivotal opinion leading organizations is essentially to follow a low-fat diet. However, it could be argued that focusing solely on dietary macronutrient quantity and their individual contributions to total calories, such as with a low-fat diet, may not be the sole approach to a complicated, chronic disease precursor like MetS. It is reasonable that the low-fat diet may serve as an adequate foundation upon which other dietary additions could be made.

Certainly, some studies have demonstrated that low-fat diets are somewhat effective for lowering certain CVD risk markers such as LDL-cholesterol. On the other hand, Knopp et al. commented that in combined hyperlipidemia, which is common in MetS, LDL-cholesterol levels are only one-third as responsive to dietary fat and cholesterol as simple hypercholesterolemia. Ordovas et al. speculated that the response of total and LDL-cholesterol to a low-fat diet could present a high degree of inter-individual variability due, in part, to genetic factors.

Aside from LDL-cholesterol levels, a low-fat diet may not completely address the full array of cardiometabolic risk factors that comprise MetS in all individuals. For example, TG and inflammation are two other MetS markers that have been shown to respond differentially to a low-fat diet. Lukaczer et al. reported that postmenopausal, hyperlipidemic women with MetS on a low-fat diet for 12 weeks had a substantial decrease in TG (23.5%), but this change was not statistically significant from baseline. Forsythe et al. compared low-fat and very-low-carbohydrate diets in a population of overweight men and women with atherogenic dyslipidemia and found that the low-carbohydrate diet was more effective at reducing markers of inflammation than the low-fat regimen.
In a recent study by Muzio et al., two diets with altered macronutrient compositions (high-carbohydrate vs. low-carbohydrate, high-protein and monounsaturated fat) were tested for their ability to impact CVD risk factors over 5 months in 100 obese patients with MetS. Interestingly, all the components of the MetS decreased significantly in both groups with no significant difference in the net resolution of MetS on either dietary regimen. Of note is that although no differences were found between the groups, each of the diets impacted measures of MetS uniquely: for example, the low-carbohydrate diet resulted in better reductions in systolic blood pressure and heart rate compared with the high-carbohydrate diet, and the latter led to greater lowering of LDL cholesterol.

A complete review of the effects of various macronutrient permutations on MetS has been extensively investigated by Feldeisen and Tucker and will not be repeated within this text. Generally, it is becoming increasingly recognized that operating within the macronutrient nutritional paradigm may not adequately prevent and treat chronic disease.

Ultimately, recommending exceedingly high and low quantities of macronutrients can result in an unbalanced diet. A diet low in fat usually implies a higher refined carbohydrate intake, which has been shown to result in elevated TG and reduced HDL-cholesterol, two important markers of cardiometabolic risk. Similarly, low-carbohydrate, high-protein diets, which have gained popularity in the past decade, tend to be higher in saturated fats and low in fruits, vegetables, and whole grains. Also, the increased levels of protein in this diet may present a greater renal burden in individuals with compromised kidney function. Moreover, low-carbohydrate, low-protein diets, even with substitution of monounsaturated fats for carbohydrate, have inconsistently been reported to increase insulin sensitivity and blood pressure. Finally, the amount of saturated fat may be greater in low-carbohydrate diets. A recent study suggests that higher intake of saturated fat results in increased carotid artery intimal medial thickness. The authors from the GOCADAN study conclude that “high consumption of saturated FAs [fatty acids] . . . may have an adverse effect on MS [metabolic syndrome]” as they found saturated fat consumption to increase TG levels and blood pressure.

**Carbohydrate and glycemic index**

Some recent studies have been instrumental in demonstrating the concept that macronutrients in the form of carbohydrate have different impacts on insulin signaling and action. For example, Kallio et al. tested the effect of feeding two types of dietary carbohydrate, rye and oat-wheat-potato, in the form of breads and baked products, to subjects with MetS for 12 weeks, on gene expression of their subcutaneous adipose tissue. Findings revealed that the rye-fed individuals displayed downregulation of 71 genes, including those responsible for insulin signaling such as insulin-like-growth-factor binding protein-5 and the insulin receptor (IR). Feeding oat-wheat-potato led to different results than those of the rye-pasta diet. Specifically, there was an upregulation in 62 genes related to stress-like serum glucocorticoid-regulated kinase, and mitogen-activated protein kinase. Activation of these stress-related kinases may contribute to the underlying pathology of MetS. Pathways triggering oxidative stress, interleukins, and inflammation were also expressed with this diet, providing more support for the role of certain dietary carbohydrate in the inflammatory processes that compose MetS. Furthermore, insulin action, as measured by the insulinogenic index, improved in individuals on the rye diet but not on the oat-wheat-potato diet (P = 0.004). Interestingly, these effects occurred in the absence of overall body weight change.

In response to the Kallio et al. study, Salsberg and Ludwig commented: “Traditionally, food is thought to influence human health through its nutrient content, whereas drugs are recognized to act through molecular pathways. However, consumption of a meal stimulates the release of numerous hormones that can powerfully affect signal transduction and gene function.” In addition, the studies by Kallio et al. may point to some other key concepts: 1) significant metabolic changes and gene expression can occur in the absence of weight loss, 2) carbohydrate as a macronutrient responds differently based on its constituents. One might suggest that these effects were anticipated due to the differences in the glycemic indices of the carbohydrates used in the study. Glycemic index is a well-recognized marker of how a carbohydrate is processed postprandially. Several excellent reviews have been written on this topic as it relates to the health outcomes and, thus, will not be repeated in this text. Although it is useful, it is a relatively gross measurement and does not provide details of how the released glucose and insulin trigger intracellular pathways relevant to MetS. Since various dietary carbohydrates contain different compositions, it may be worthwhile to investigate how the phytochemical signature of a carbohydrate can further impact glycemic index and specific genes related to glucose and insulin dynamics.

Available data indicate that rather than identifying levels of particular nutrients as a percentage of calories, it may be worthwhile to broaden the nutritional approach to chronic clinical conditions like MetS into one that takes into consideration the global dietary pattern of food intake.
**DIETARY PATTERNS RICH IN PHYTOCHEMICALS**

An increasing number of studies indicates that dietary patterns high in whole, unprocessed plant foods and, as a result, abundant in phytochemicals, may have benefit for MetS. Myriad epidemiological studies have consistently demonstrated the benefits of a phytochemical-rich diet for decreasing the development of or treating chronic disease. Increased fruit and vegetable consumption has been associated with reduced incidence of MetS, type 2 diabetes, and CVD. In a cross-sectional study of 486 female teachers aged 40–60 years, higher intakes of fruit and vegetables were found to correlate with a lower risk of MetS. In support of these data, lower vegetable and fiber intake have been associated with a greater incidence of MetS. Using results from three large epidemiological studies, Baxter et al. noted that certain dietary patterns are associated with the development of MetS: diets high in meat and refined grains were associated with high incidence of MetS while diets high in fruits, vegetables, and minimally processed grains were found to be inversely associated with MetS. The overall conclusion from this review was that “no individual dietary component could be considered wholly responsible for the association of diet with MetS”. In the authors’ opinion, the quality of the diet conferred the most protection against MetS compared with these individual foods. After examining food patterns within a population of 1514 men and 1528 women, Papanikolaou et al. similarly demonstrated that consumption of fish, cereals, legumes, vegetables, and fruits was inversely associated with the following MetS markers: waist circumference, systolic blood pressure, TG, and positively associated with HDL-cholesterol levels, whereas meat and alcohol intake showed the opposite results.

One of the common denominators in these studies is the role of fruits and vegetables. An observation to note is that the rise of obesity and MetS has appeared to parallel the staggering low consumption of fruits and vegetables in the United States population. Despite the nationwide campaign to increase consumption of fruits and vegetables, the average American continues to eat only about 1½ servings of vegetables and less than one serving of fruit per day. Blanck et al. recently assessed the consumption of fruits and vegetables of 1,227,969 adults in the United States and found that the number of men and women eating these foods five or more times daily between 1994 through 2005 was essentially unchanged (men: 20.6% vs. 20.3%; women: 28.4% vs. 29.6%, respectively).

**Mediterranean-style diets**

An example of a high phytochemical dietary pattern that has been studied extensively for MetS in the past 5 years, and has been shown to favorably impact markers of MetS, is the well-recognized “Mediterranean diet”. In a noteworthy study by Knoops et al., the Mediterranean diet was found to be associated with a more than 50% lower rate of all-cause and cause-specific mortality in elderly European adults aged 70–90 years, suggesting it has the ability to significantly impact overall health.

Despite the fact that it is widely referred to as such, the “Mediterranean diet” is not well defined since it reflects the eating characteristics of more than 15 countries in the Mediterranean Basin. However, there is general consensus that it includes 1) copious quantities of minimally processed, fresh, plant-based foods such as fruits, vegetables, whole grains, seeds, and nuts; 2) olive oil as the principal source of dietary fat; 3) minimal consumption of red meat and dairy products; and 4) wine in low to moderate amounts with meals. Individual foods that compose the Mediterranean diet may be uniquely responsible for addressing specific MetS criteria. For example, in one study, fruit intake was shown to be protective for TG levels and in another, olive oil, vegetables, and fruit were inversely associated with systolic and diastolic blood pressure. A general distillation of the Mediterranean dietary pattern into some general beneficial constituents for MetS could include the following: 1) high monounsaturated fat and polyphenol (tyrosol and hydroxytyrosol) content found in extra virgin olive oil; 2) high fiber, complex carbohydrates, vitamins C and E, minerals, polyphenols, and thousands of phytonutrients from cereals, legumes, vegetables and fruits.

Some researchers contend that olive oil is the major component of the Mediterranean diet and that it provides the most therapeutic benefit. In fact, the monounsaturated fat (i.e., oleic acid) content of olive oil fueled the preliminary interest in the Mediterranean way of eating, and has been purported to be one of the most relevant foods in the Mediterranean diet for individuals with MetS as it appears to improve insulin sensitivity. However, the advantages of olive oil consumption may extend beyond its monounsaturated fat content. Virgin olive oil is particularly high in a plethora of phytochemicals that encompass phenolic compounds that belong in a variety of classes: phenolic acids, phenyl ethyl alcohols, hydroxyl-isochromans, flavonoids, lignans, and secoiridoids. Three phenolics have been given increased attention for their potent antioxidant activity: hydroxytyrosol, tyrosol, and oleuropein. Covas et al. studied the effect of olive oils varying in phenolic content on heart disease risk factors in 200 healthy male volunteers. MetS marker, HDL-cholesterol, increased linearly for low-, medium-, and high-polyphenol olive oil. TG levels reduced to the same extent for all three oils. It would be valuable to repeat this study in individuals with MetS.
Since fatty acids can affect lipid membrane composition, one of the pivotal ways that olive oil can impact signal transduction would be through modification of signaling proteins embedded in the plasma membrane. Perona et al.73 fed virgin olive oil to elderly individuals who were healthy or who had type 2 diabetes. Consumption of olive oil increased the monounsaturated fatty acid content of erythrocyte membranes in both groups. Perhaps more importantly, levels of G proteins and protein kinase Cα were decreased in both groups to varying degrees (reductions: 46–59% in control group; 17–72% in diabetics). Along similar lines, Ficková et al.74 found that feeding rats mono- and polyunsaturated oils like olive oil resulted in alteration of insulin tyrosine kinase.

Additionally, another means by which olive oil may work mechanistically in MetS via signal transduction is through reduction of nuclear factor-kappa beta (NF-κB). An insulin-resistant, hyperglycemic state leads to the deacetylases.83–85 Fröjdö et al.81 elegantly demonstrated walnut consumption resulted in improved survival middle-aged mice on a high-calorie diet showed that resveratrol has been studied the most extensively and found to have antioxidant, vascular, protective actions, and even anti-inflammatory effects.80 Of all the polyphenols, resveratrol (28.6% and 30.9%, respectively).86 report that flavonoids such as quercetin and myricetin (a metabolite derived from quercetin) interact directly with the glucose transporter GLUT4 to inhibit its uptake of glucose into the cell. Quercetin and myricetin also work on multiple targets within the insulin signaling pathway directly by inhibiting PI3K at relatively low concentrations87–89 and modulating activity of Akt/protein kinase B (PKB) and PKC.90–92

Plant food diets rich in soy, fiber, and phytosterols

Phytochemical-rich foods with recognized health benefits have been explored for their application to MetS parameters. Jenkins et al.93 studied a dietary portfolio of cholesterol-lowering foods versus a statin (Lovastatin) on lipid levels in healthy, hyperlipidemic adults (n = 46). The diet was high in particular foods known to be beneficial for CVD prevention: plant sterols (1g/1000 kcal), soy protein (21.4g/1000 kcal), viscous fibers (9.8g/1000 kcal), and almonds (14g/1000 kcal). These foods are in alignment with the dietary recommendations from the NCEP-ATP III of 2 g/d plant sterols and 10–25 g/d viscous fibers. The US Food and Drug Administration’s regulations claims on viscous fibers, soy protein, plant sterols, and nuts indicate that substantial research of these foods supports their ability to lower serum lipids and, as a result, reduce the risk of heart disease. Impressively, results from this study indicated that subjects on the dietary portfolio had significant reductions in LDL-cholesterol similar to results achieved through treatment with a statin (28.6% and 30.9%, respectively).

Similarly, Lukaczer et al.14 demonstrated that a beverage consisting of 30 g soy protein and 4 g phytosterols added to a Mediterranean-style, low-glycemic-index diet led to better improvements in MetS lipid markers, such as TG, in hyperlipidemic, postmenopausal, overweight women than a low-fat diet without these key phytochemical-rich foods. At baseline, both groups had Framingham risk scores for coronary heart disease that were not statistically different; however, after the intervention, subjects in the group provided with soy protein and phytosterols had a much lower CVD risk compared with the group on the low-fat diet (median 6.0, 95% CI 4.4–7.6 and 9.0, 95% CI 7.9–10.1, respectively).

Soy foods

Soy is becoming increasingly recognized as a food that is beneficial for MetS, particularly for its effects on serum
lipids and inflammatory cytokines. An extensive body of literature indicates that soy food consumption leads to significant decreases in total cholesterol (10–19%), LDL cholesterol (14–20%), and TG (8–14%). Despite these key findings in the hyperlipidemic population, very few clinical studies have examined the effect of soy food consumption in subjects with MetS. In a crossover study with 42 postmenopausal women with MetS, Azad-bakht et al.95 implemented three dietary treatments: a control diet (Dietary Approaches to Stop Hypertension, DASH), a soy-protein diet, and a soy-nut diet, each for a total of 8 weeks. Consumption of soy nuts resulted in the most favorable impact on MetS markers relative to the other dietary therapies, including decreasing the homeostasis model of assessment-insulin resistance score, fasting plasma glucose, LDL-cholesterol, and serum C-peptide concentrations. Markers of endothelial function and inflammation also improved more significantly with the soy-nut diet than with the DASH diet or the soy protein diet. These results allude to the importance of the contribution of the entire food matrix (soy nuts vs. soy protein) in addressing the complexity of MetS markers.

In further support of the application of food matrices and complexity, Noriega-López et al.97 demonstrated that the effects of soy isoflavones in rats were determined by their interaction with a pattern of amino acids. When amino acids were added to pancreatic islets that paralleled the appearance of amino acids in the plasma of animals fed either a soy or casein diet, different responses were obtained. Interestingly, the soy protein group stimulated insulin secretion to a lesser extent, and reduced GLUT-2 expression compared to when the isoflavones accompanied the casein amino acid profile.

Finally, soy isoflavones may help combat inflammatory processes that are active in MetS by inhibiting pro-inflammatory cytokines, cell adhesion proteins, and inducible nitric oxide production.98

**THE PROOF IS IN THE PIGMENT**

A closer examination of dietary patterns that influence MetS, such as the Mediterranean diet or vegetarian-style diets that are high in soy, phytosterols, and fiber, reveals a generous palette of whole foods of plant origin. One might propose that phytochemicals, or non-nutritive substances in plants that possess health effects, are an essential component of a diet for MetS. Certainly, fruit and vegetable consumption has declined slightly between 1994 and 2005; in parallel, there has been a rise in the incidence of chronic diseases such as MetS. Although eating more fruits and vegetables may not be the simple answer to a complex issue like MetS, one could question whether consumption of the Western-style, oft-called “standard American diet”, has created a state of “phytochemical deficiency” as it contains an array of processed foods devoid of the colors embodied by naturally occurring phytochemicals.

A body of literature attests to how food-derived pigments provide color, enhance the enjoyment of eating, and, most importantly, protect organisms from disease. Decker99 has identified almost 2000 known plant pigments in food, including over 800 flavonoids, 450 carotenoids, and 150 anthocyanidins. More recent numbers from Walsh et al.100 indicate there are 5000–10,000 phytochemicals present in human food, and a large percentage most likely remains unknown.101 On average, an individual receives about 1.5 g of phytochemicals in their diet.102 Although the quantity may seem negligible relative to the several hundred grams of macronutrients typically ingested, the immense diversity and potential interaction of these compounds occurring in the food supply could conceivably result in a significant number of cellular reactions within the body after ingestion. Certainly, the literature is headed towards supporting the concept that food is more than simply energy and that phytochemicals may play a larger role than originally assumed, especially for MetS. As a case in point, a recent report by Walsh et al.100 demonstrated that dietary phytochemicals significantly impact human urinary metabolic profiles within a couple of days.

Taking phytochemicals into account together with macronutrients more accurately reflects how individuals eat, i.e., foods containing a plethora of phytochemicals along with a base of macronutrients, all in a certain proportion. Accordingly, extending the dietary focus for MetS (and other chronic conditions) beyond macronutrients seems warranted. Macronutrients obtained through diet may have limited effects on their own without any accompanying phytochemicals. Furthermore, the resulting physiological effects of complex cell-signaling patterns could be dramatically altered by the presence or absence of the multitude of phytochemicals occurring in their usual proportions. An example of this concept has been illustrated in the study by Esposito et al.103 in which 25 healthy subjects were given three meals randomly for 1 week intervals: a high-fat meal, an isocaloric high-carbohydrate meal, and the same high-fat meal plus 100 g tomatoes, 200 g carrots, and 100 g peppers. Postprandial endothelial function was shown to be impaired in subjects fed the high-fat diet; however, most interestingly, the addition of vegetables to the diet partially prevented this dysfunction.

Some researchers104 have suggested a return to the concept of food synergy and the value of the food matrix as a pivotal cornerstone of nutrition. As Lila105 states: “…what many people don’t fully appreciate is that it is
not a single component in these plant-derived foods, but rather complex mixtures of interacting natural chemicals, that produce such powerful health-protective effects.”

**EFFECTS OF PHYTOCHEMICALS ON INSULIN SIGNALING**

The previous descriptions of dietary patterns briefly discussed some of the food-based phytochemicals that may potentially impact, in a variety of ways, cell-signaling pathways related to MetS. Despite the fact that intakes of fruits, vegetables, and whole grains appear to be important for reducing the incidence of chronic diseases, the mechanisms related to their action(s) remain, for the most part, unclear. The effect of specific food-based phytochemicals on the underlying pathology of MetS has not been adequately explored. Current evidence suggests that markers of MetS appear to be unified by dysfunctional insulin action,\(^{19}\) which may, in part, arise due to heightenened inflammatory processes\(^{106–109}\) and overspill of lipid from adipose tissue leading to chronic lipotoxicity (Figure 2).

In MetS, adipocytes are infiltrated by macrophages to produce pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-\(\alpha\)), resistin, leptin, and interleukin-6 (IL-6), that can crosstalk with skeletal muscle, significantly altering insulin signaling.\(^{106–109}\) Adding to the pathophysiology induced via the influence of adipokines on muscle, chronic, excessive caloric intake results in a surplus of glucose and lipid that overflows from adipose to non-adipose tissue (e.g., skeletal muscle and liver). The overabundance of energy engages non-oxidative pathways, producing reactive lipid species and, ultimately, a state of intramyocellular lipid accumulation and chronic lipotoxicity.\(^{111}\) Lipotoxicity exacerbates dysfunctional protein kinase activity related to controlling inflammatory pathways. Through negative feedback, hyperactive PI3K, PKC, and glycogen synthase kinase (GSK)-3 terminate insulin signaling,\(^{110}\) causing insulin resistance.\(^{112–114}\)

Thus, in MetS, there is increased resistance of target tissues to the effects of insulin,\(^{115}\) which is the reflection of cumulative changes in the activity of cell membrane-bound IRS docking proteins. When IRS-1 is phosphorylated upon serine 307 via cellular stressors such as TNF-\(\alpha\), insulin signal transduction is negatively regulated through inhibition of IRS-1-associated stimulation of

![Figure 2](image-url)  
**General diagrammatic representation of the insulin-signaling cascade.** Insulin is the central substrate that leads to a cascade of cellular reactions responsible for glucose and lipid metabolism. Insulin stimulates the insulin receptor (IR) tyrosine kinase, leading to the tyrosine phosphorylation of the insulin receptor substrate (IRS) family of proteins. Activated IRS then displays binding sites for numerous signaling partners such as phosphatidylinositol-3 kinase (PI3K), a key player in insulin function through the activation of the Akt/protein kinase B (PKB). When stimulated, Akt/PKB promotes glycoen synthesis via upregulation of the glycogen synthase enzyme, which occurs with inhibition of glycogen synthase kinase (GSK)-3. Additionally, insulin activates glucose uptake via a family of glucose transporters (GLUT). Through negative feedback, PI3K, Akt/PKB, and GSK-3 can result in serine phosphorylation of IRS, and subsequent inactivation. Activation of G-protein receptors can lead to activation of protein kinase C (PKC). Excessive stress through inflammatory mediators, such as tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), or through metabolic overflow of lipid from adipose tissue could also impact the insulin signaling cascade. Schematic adapted from Frame and Zheleva (2006),\(^{182}\) Schinner et al. (2005),\(^{115}\) and Kido et al. (2001).\(^{183}\)
PI3K. Kinases such as PI3K are essential for transducing intracellular communication signals that eventually culminate in an overall cellular action. If PI3K is inhibited, other kinases such as Akt/PKB and GSK-3 will also be impacted, resulting in the cell not being able to transport glucose or synthesize glycogen. These findings are supported by clinical observation: individuals with type 2 diabetes have ~50% and ~70% reduction in PI3K activity in skeletal muscle and adipose tissue, respectively. More notably, even those who are normoglycemic but have a genetic predisposition for type 2 diabetes, as defined by two first-degree relatives with the disease, also have impaired insulin-stimulated PI3K activity, as measured in their adipocytes.

Whereas some agents may inhibit kinases directly, leading to complete cessation of activity and causing undesirable side effects, it would be worthwhile from a safety point of view to identify less potent food-derived actives which selectively modulate (rather than completely block) activity of certain kinases. The concept of identifying and leveraging phytochemicals to impact kinase activity specifically for MetS has not been researched thoroughly. However, there are some traditional foods that have been researched for their molecular effects on processes related to defective insulin signaling that may prove to be worthwhile from a therapeutic standpoint, including the following: cinnamon, green tea, bitter melon, berberine, ginseng, and hops.

**Cinnamon**

Clinical trials suggest that modest amounts (1–6 g) of cinnamon can favorably impact glucose and/or lipid levels in healthy subjects and individuals with conditions related to insulin dysregulation. Conversely, some reports have also concluded that cinnamon had no effect on reducing these measurements. This discrepancy may be due to the varied population of subjects, or even the different types of cinnamon that are used, which may contain a different panel of actives.

The insulin-signaling mechanisms behind cinnamon’s long-recognized insulin sensitizing properties, have been elucidated in several in vitro studies. Specifically, cinnamon bioactives affect protein phosphorylation-dephosphorylation reactions in the adipocyte and may impact activity of PI3K through its upstream effects. In rats fed 300 mg/kg bw cinnamon extract, IRβ and IRS-1 tyrosine phosphorylation levels in the skeletal muscle were 18% and 33%, respectively, greater than those of controls, indicating that insulin action and glucose uptake might be improved in these rats. Further, in a later study, Qin et al. detected that a cinnamon extract fed to rats on a high-fructose diet was effective in improving IRβ stimulation by insulin, IRS-1 tyrosine phosphorylation, and PI3K activation in skeletal muscle relative to control rats.

The different fractions of cinnamon have been studied for their effects on insulin signal transduction. HPLC-purified cinnamon polyphenols and a water-soluble cinnamon extract were tested in mouse 3T3-L1 adipocytes for their effects on mRNA levels of IR and GLUT4. At relatively high concentrations, the extract decreased IRβ protein and IR mRNA. GLUT4 mRNA levels were also modified by addition of the extract. In the same 3T3-L1 adipocyte model, Jarvill-Taylor et al. demonstrated that treatment with a hydroxychalcone from cinnamon triggered insulin transduction via activating glycogen synthase and IR, and inhibiting GSK-3β. Interestingly, when insulin was added together with the cinnamon-derived hydroxychalcone, a synergistic response was obtained. Similarly, research by Kim et al. demonstrated that of a series of cinnamon-derived, phytochemical synthetic derivatives, a naphthalenemethyl ester of 3,4-dihydroxyhydrocinnamic acid displayed a significant impact on glucose transport in epididymal adipocytes through its effects on IRβ phosphorylation and subsequent activation of PI3K and Akt/PKB.

**Green tea (Camellia sinensis)**

Green tea, a common staple of the Asian dietary pattern, has a well-documented reputation as a health-promoting beverage, particularly for chronic diseases such as cancer and type 2 diabetes. Consistent consumption of 5–6 or more cups daily or 200–300 mg of epigallocatechin gallate (EGCG), the primary polyphenol in green tea, has demonstrated benefit for cardiovascular and metabolic health. In an eloquent review by Wolfram et al., it was discussed that in cell culture and animal models of obesity, green tea constituents have the ability to reduce adipocyte proliferation and differentiation, as well as important markers of MetS, like plasma levels of TG, cholesterol, glucose, and insulin.

In a retrospective cohort study consisting of 17,413 Japanese adults, Iso et al. obtained data on intake of coffee and black, green, and oolong teas and assessed whether consumption of any of these beverages was associated with type-2 diabetes occurrence after a 5-year follow-up. Results showed that green tea (and coffee) was inversely associated with risk for diabetes. Hill et al. evaluated the effect of EGCG supplementation on abdominal fat in overweight or obese postmenopausal women in conjunction with regular aerobic exercise. Waist circumference (one of the MetS criteria) and adipose tissue were reduced in the control and EGCG groups; however, those subjects on EGCG experienced a decrease in plasma glucose if glucose intolerance was present. Prospective studies have yielded mixed results for the effect of...
The mechanisms of green tea are diverse. EGCG has been studied extensively for its chemopreventive activity via regulating multiple signaling pathways (e.g., VEGF, IGF-1, EGFR). In conjunction with its effect on cell growth cycles, EGCG indirectly influences inflammation processes and insulin activity via inhibiting NF-κB, PI3K, and Akt/PKB, to name a few.146 In a review of mechanisms of EGCG by Moon et al.,146 it was reported that EGCG impacts a number of kinases. They concluded: “...dietary supplementation with EGCG could potentially contribute to nutritional strategies for the prevention and treatment of type 2 diabetes mellitus”.

More specific to direct influence on insulin signaling, published studies indicate a wide range of effects by EGCG. It has been suggested that EGCG mimics insulin action by activating similar signaling pathways, although to a lesser degree, in that it increases tyrosine phosphorylation (thus activation) of the IRβ and IRS-1 in H4IIE rat hepatoma cells.147 Additionally, it increases PI3K and Akt/PKB in this cell line, ultimately impacting genes that regulate gluconeogenic enzymes.147 Animal studies have demonstrated that oral administration of a green tea extract (80 mg/kg/d) for 12 weeks to obese dogs resulted in a 60% higher insulin sensitivity index and 50% lower extract (80mg/kg/d) for 12 weeks to obese dogs resulted in a 60% higher insulin sensitivity index and 50% lower extract (80mg/kg/d) for 12 weeks to obese dogs demonstrated that oral administration of a green tea extract rather than the beverage preparation.140,141,143,144

Of note, some of these studies used green tea extract rather than the beverage preparation.140,141,143,144

The targets of berberine relative to MetS and insulin signaling have been reasonably well explored. Zhou et al.162 commented that berberine’s effects on cellular glucose metabolism may be more indirect in that it may activate glucose transport in 3T3-L1 adipocytes by increasing the activity of GLUT1, with no appreciable effect on Akt/PKB or GLUT4 or response to PI3K inhibition. In support of these findings, Kim et al.163 reported that incubation of 3T3-L1 adipocytes with berberine led to an 8.5-fold increase in insulin-independent glucose uptake and a 1.3-fold increase in insulin-activated glucose uptake. As expected, berberine increased the levels of GLUT1 (responsible for basal, insulin-independent glucose uptake) but had no effect on GLUT4 (insulin-stimulated glucose uptake) in this study. Consistent with Zhou et al.’s findings, no effect of berberine was observed on upstream insulin signaling involving IR activation or IRS-1 phosphorylation. In contrast to these two studies, Ko et al.164 noted that berberine at 5 or 50 μM plus insulin increased tyrosine phosphorylation of IRS1 to levels comparable to that produced with 10 nM insulin in 3T3-L1 adipocytes. Akt/PKB phosphorylation was stimulated in the presence of berberine despite no change in Akt/PKB

Bitter melon (Momordica charantia L.)

Bitter melon, a common vegetable grown in tropical cultures, is widely eaten and used in traditional medicine for its anti-diabetic properties.130 Hence, it has commonly been referred to as “vegetable insulin”.131 Bitter melon contains a number of constituents such as charantin, vicine, and polypeptide-p that cause it to impact glucose metabolism, as shown in cell, animal, and human studies.132,133 Two recent animal studies134,135 indicate that bitter melon may have some pronounced effects on the insulin signaling cascade. Sridhar et al.134 reported that high-fat feeding of male Wistar rats for 10 weeks reduced IRS-1 tyrosine phosphorylation in muscle compared with control rats, while bitter melon supplementation was able to improve IRS-1 activation after 2 weeks. In a similar fashion, Nerurkar et al.155 documented bitter melon’s ability to modulate IR phosphorylation and downstream signaling in female C57BL/6 mice fed a high-fat diet. Specifically, mice treated with bitter melon juice experienced a significant increase of 55% in IRS-2 phosphorylation in liver over that of control. Moreover, bitter melon juice supplementation in addition to the high-fat diet alone resulted in an increase in interaction between IRS-1 and PI3K of 280%. Conversely, no effect was seen in Akt/PKB expression and its phosphorylation.

Berberine (Coptis chinesis)

Berberine, a naturally occurring alkaloid phytochemical from the Chinese botanical Coptis chinesis, is well-known in traditional medicine for its glucose-lowering effects. In addition to its therapeutic effects of enhancing insulin sensitivity in animal studies,156,157 numerous clinical studies from China have documented significant plasma glucose reductions when administering berberine (1.0–1.5 g daily dose divided throughout the day) to subjects with type 2 diabetes.158–161 Most recent is the clinical study by Zhang et al.,161 which indicated noteworthy reductions in fasting and postprandial plasma glucose, hemoglobin A1c, and relevant lipid biomarkers due to berberine supplementation of 1.0 g daily for 3 months compared with placebo.

The targets of berberine relative to MetS and insulin signaling have been reasonably well explored. Zhou et al.162 commented that berberine’s effects on cellular glucose metabolism may be more indirect in that it may activate glucose transport in 3T3-L1 adipocytes by increasing the activity of GLUT1, with no appreciable effect on Akt/PKB or GLUT4 or response to PI3K inhibition. In support of these findings, Kim et al.163 reported that incubation of 3T3-L1 adipocytes with berberine led to an 8.5-fold increase in insulin-independent glucose uptake and a 1.3-fold increase in insulin-activated glucose uptake. As expected, berberine increased the levels of GLUT1 (responsible for basal, insulin-independent glucose uptake) but had no effect on GLUT4 (insulin-stimulated glucose uptake) in this study. Consistent with Zhou et al.’s findings, no effect of berberine was observed on upstream insulin signaling involving IR activation or IRS-1 phosphorylation. In contrast to these two studies, Ko et al.164 noted that berberine at 5 or 50 μM plus insulin increased tyrosine phosphorylation of IRS1 to levels comparable to that produced with 10 nM insulin in 3T3-L1 adipocytes. Akt/PKB phosphorylation was stimulated in the presence of berberine despite no change in Akt/PKB
protein content. Overall, glucose uptake was enhanced with berberine plus 0.2 nM insulin through activation of the IRS1-PI3K-Akt/PKB-GLUT4 sequence.

Finally of note are two studies\textsuperscript{165,166} that showed berberine is effective at improving free fatty acid-induced insulin resistance in \textit{3T3-L1} adipocytes through downstream signaling by inhibiting \(\operatorname{IκB}\) kinase \(\beta\) and NF-\(\kappa\)B.

**Ginseng (\textit{Panax ginseng})**

Like berberine, ginseng has been used as part of traditional Chinese medicine for thousands of years, particularly as a restorative tonic to increase blood flow and decrease fatigue. Vuksan et al.\textsuperscript{167} reported improvements in the postprandial plasma glucose measurements (decrease of 8–11\%) and fasting and postprandial insulin (33–38\%) with 6 g per day \textit{Panax ginseng} in 19 individuals with controlled type 2 diabetes. Administration of \textit{Panax ginseng} extract to older rats (1.5 years) resulted in an increased number of insulin receptors in bone marrow cells (407 \(\pm\) 46 vs. 1038 \(\pm\) 84, for control and ginseng-supplemented rats, respectively, \(P < 0.01\)).\textsuperscript{168}

One of the active anti-diabetic phytochemicals is thought to be ginsenosides.\textsuperscript{169–171} For example, when ginsenoside Rh2 was intravenously injected into fasting Wistar rats for 60 min, plasma glucose decreased and insulin increased, indicating that the compound stimulated insulin secretion.\textsuperscript{172} The mechanisms behind the action of ginsenosides have been investigated to a limited extent. Based on animal work, Lai et al.\textsuperscript{173} reported increased gene expression in mRNA and protein levels of GLUT4 in soleus muscle of streptozotocin-induced diabetic rats when treated with ginsenoside Rh2 intravenously. Zhang et al.\textsuperscript{174} documented that ginsenoside Re administration to \textit{3T3-L1} cells leads to the activation of IR-1, with effects cascading downstream through PI3K.

Additionally, more current research suggests that ginsenoside Rg3 may lower blood glucose and stimulate insulin secretion through its activation of AMP-activated protein kinase (AMPK).\textsuperscript{175}

One of the intestinal metabolites of ginsenosides, known as compound K, was shown to be effective in combination with metformin in improving plasma glucose and insulin levels in diabetic \(db/db\) mice.\textsuperscript{176}

**Hops (\textit{Humulus lupulus})**

Hops is a climbing perennial vine that has grown wild since ancient times in Europe, Asia and North America, and is primarily used in the manufacture of beer.\textsuperscript{177} Emerging research suggests that hops-based phytochemicals may impact insulin sensitivity. When diabetic KK-Ay mice were treated with either isohumulone and isocohumulone from hops, or pioglitazone, similar reductions in plasma glucose, TG, and free fatty acids were obtained.\textsuperscript{178} Furthermore, select hop-based constituents have been found to impact MetS markers through specific cellular insulin-targeted pathways. Cell-free assays conducted by Tripp et al.\textsuperscript{179} identified one of the bittering agents of hops, \(\rho\) isoh-\(\alpha\)-alpha acids, as modulators of a number of protein kinases implicated in insulin signaling, such as PI3K-\(\gamma\), \(\beta\), \(\delta\), GSK-3\(\alpha\), GSK-3\(\beta\), and PKC-\(\beta\)\textsubscript{11}.

**CONCLUSION**

MetS is a complex condition that may be best treated by an array of dietary interventions. While a unified dietary recommendation for MetS has yet to be determined, a survey of emerging literature indicates it may ultimately involve a diet high in phytochemicals that favorably target kinases involved in cellular insulin signaling (Table 1). From the aspect of prevention, chronic consumption of

<table>
<thead>
<tr>
<th>Phytochemical</th>
<th>Insulin pathway targets*</th>
<th>IR</th>
<th>IRS</th>
<th>PI3K</th>
<th>Akt/PKB</th>
<th>PKC</th>
<th>GSK</th>
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</table>

* Various phytochemicals have been shown to influence select targets in the insulin signaling cascade.
\textsuperscript{t} In presence of insulin.\textsuperscript{164}

\textit{Abbreviations}: Akt/PKB, Akt/protein kinase B; GLUT, cellular glucose transporters; GS, glycogen synthase; GSK, glycogen synthase kinase; IR, insulin receptor; IRS, insulin receptor substrate; PKC, protein kinase C; PI3K, phosphatidylinositol-3 kinase.
phytochemicals, whether through a whole-food diet rich in fruits and vegetables or from specific extracts, may provide consistent healthy insulin-signaling patterns to ensure protection against MetS, although stronger scientific support for this premise is needed. For an individual with MetS and a lifetime of accumulated unhealthy insulin signaling via dietary intake, it may take more than switching from a low-phytochemical diet to one that is rich in "phyto-signaling" potential (Figure 3). In this case, although it has not been demonstrated, it may theoretically be clinically necessary to ingest targeted phytochemicals known to affect insulin signaling positively in addition to maintaining a healthy dietary baseline. Further clinical studies are required to support this concept.

Acknowledgments

The authors would like to thank Drs. Matthew Tripp, Amy Hall, Brian Carroll and Veera Konda for their contributions to the manuscript. Thanks to Christie Clark and Jim Planet for their assistance with the graphics.

Declaration of interest. Both authors are employees of MetaProteomics, LLC, a wholly owned subsidiary of Metagenics, Inc. Dr. Bland is a shareholder of Metagenics, Inc. Metagenics is a life sciences company and the premier manufacturer and distributor of science-based medical foods and nutraceuticals marketed to healthcare professionals.

REFERENCES


