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Natural supplements for improving insulin sensitivity and glucose uptake in skeletal muscle

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1. ABSTRACT

Type 2 diabetes is a common metabolic disorder characterized by resistance to the actions of insulin to stimulate skeletal muscle glucose disposal. In light of the staggering financial/human cost of type 2 diabetes, there is considerable need for safe and effective agents that can be used to prevent and/or adjunctively treat the disease. Available evidence suggests that a number of natural supplements, including cinnamon, biotin, fenugreek, ginseng, banaba, and alpha-lipoic acid, have the potential to reduce the risk for type 2 diabetes in the large at-risk population. The evidence also suggests that, when used adjunctively, these natural products are likely to help clinicians achieve optimal glycemic control, improve long-term prognosis, and/or minimize the need for insulin therapy in type 2 diabetics. More research, particularly well-designed, long-term human clinical trials, is certainly needed to accurately define the value and place of these supplements in diabetes prevention and management.

2. INTRODUCTION

Type 2 diabetes mellitus, a progressive and complex disorder that is difficult to treat effectively in the long term, is rapidly emerging as one of the greatest global health challenges of the 21st century (1). It is a chronic metabolic disorder that affects nearly every organ in the body, kills more people annually than the acquired immunodeficiency syndrome (AIDS) and breast cancer combined, and is associated with staggering social, health, and economic consequences (2). Basic pathophysiological mechanisms of type 2 diabetes involve insulin resistance, excessive hepatic glucose production, impaired insulin secretion, and abnormal fat metabolism (3-4). Insulin resistance, closely linked to obesity and physical inactivity, refers to a reduction in the ability of insulin to act effectively on target cells, especially skeletal muscle cells, hepatocytes and adipocytes (5). Declined insulin efficacy impairs glucose utilization and increases hepatic glucose output, both contributing to hyperglycemia. Precise underlying mechanisms for the development of insulin resistance are still unknown. However, increasing evidence has suggested that multiple defects in intracellular insulin signaling and glucose uptake in skeletal muscle and adipose tissues, as well as inflammation, play a major role in the manifestation of insulin resistance (6-9). Management of asymptomatic or mildly symptomatic patients with newly diagnosed type 2 diabetes focuses initially on non-pharmacological approaches including diet modification, regular exercise, and patient education (10-11). The objective is always to improve metabolic control and insulin sensitivity through lifestyle modification and reductions in bodyweight (the majority of type 2 diabetic patients

are overweight or obese at diagnosis). However, even if these lifestyle modifications are successfully implemented, the majority of patients will be unable to achieve or sustain near normoglycemia without prescription antidiabetic drugs (e.g., insulin sensitizers, insulin secretagogues, alpha-glucosidase inhibitors, etc) (12-13). Some type 2 diabetic patients will eventually require insulin therapy to maintain long-term glycemic control, either as monotherapy or in combination with other antidiabetic drugs. The frequent need for escalating therapy is attributed to the progressive loss of islet beta-cell function, usually in the presence of obesity-related insulin resistance (14-15).

Patients with type 2 diabetes are prone to both short-term and long-term complications and premature death (2). The impact of the disease on quality of life, the possibility of severe complications, and the undesirable adverse effects that are associated with long-term use of prescription antidiabetic drugs are all factors that motivate patients to seek out and use botanical products and nutraceuticals as complementary/alternative therapies (16). Natural products have long been used in traditional systems of medicine in many cultures around the world for managing and/or preventing type 2 diabetes and its complications with relatively low incidence of adverse effects (17-20). Numerous studies, both preclinical and clinical, have demonstrated the ability of many of these natural supplements to exert beneficial effects on insulin sensitivity, insulin secretion, glucose uptake, glucose tolerance, glycemic control, and lipid profiles by targeting different molecular mechanisms and pathways (17-20). Studies have also shown evidence for the ability of some of these natural products to prevent diabetic complications via anti-inflammatory activities. Today, a significant number of type 2 diabetics in the United States are using botanical and/or nutritional dietary supplements, in conjunction with or as a substitute for conventional antidiabetic drugs, for managing their illness (20). In addition, an increasing number of non-diabetic individuals who are at-risk for type 2 diabetes are also seeking out botanicals and other natural supplements in an effort to prevent or postpone the onset of the disease. In this review, we highlight a number of molecular strategies that are aimed at improving insulin sensitivity and glucose uptake in skeletal muscle and provide an overview of the mechanism(s) of action, safety and efficacy of some of the most promising and commonly used natural supplements that are known to exert an insulin sensitizing effect in skeletal muscle cells. The reviewed natural products include alpha-lipoic acid, cinnamon, biotin, fenugreek, ginseng, and banaba.

3. MOLECULAR TARGETS FOR IMPROVING INSULIN SENSITIVITY AND GLUCOSE UPTAKE IN SKELETAL MUSCLE

Skeletal muscle is the primary source for blood glucose disposal in the body, accounting for removal of 80-90% during the postprandial state (21). Thus, skeletal muscle plays a central role in blood glucose homeostasis. Insulin resistance in skeletal muscle has been shown to be the precipitating factor in the development of type 2 diabetes (21). It is believed that accumulation of lipids, such as diacylglycerol (DAG) and ceramides, in skeletal myocytes promotes impaired insulin signaling and, thereby, reduces insulin-stimulated glucose transport and glycogen synthesis (21).

Stimulation of the insulin receptor (IR) leads to the recruitment and phosphorylation of insulin responsive substrate-1 (IRS-1). Phosphorylation of IRS-1 promotes the recruitment and activation of phosphatidylinositol 3-kinase (PI3-kinase) which, in turn, phosphorylates Akt2. Akt2, via AS160 and Rab-GTPase, stimulates translocation of GLUT4 glucose transporter storage vesicles (GSV) to the plasma membrane enabling glucose transport and glycogen synthesis (22). Figure 1 illustrates the insulin signaling pathway.

Insulin resistance in skeletal muscle is typically not associated with reduced expression of GLUT4, but rather defects in the insulin signaling pathway resulting in suppressed translocation of GSV (23). Specifically, impairment in the activation of the IR, IRS-1, PI3-kinase and Akt2 have all been shown to occur in skeletal muscle from obese and/or type 2 diabetic patients (22-23). Possible mechanisms of insulin signaling impairment may involve protein kinase C (PKC) theta, PKC zeta, serine/threonine protein phosphatase 2A (PP2A), and/or c-Jun N-terminal kinase 1 (JNK1) (22-23). Activation of these signaling molecules via DAG, ceramides or cytokines lead to impaired insulin signaling via inactivation of the IR, IRS-1 and/or Akt2 (22-23).

Various modalities have been shown to improve glucose uptake in skeletal muscle. For example, weight loss has long been known to improve insulin resistance in skeletal muscle and

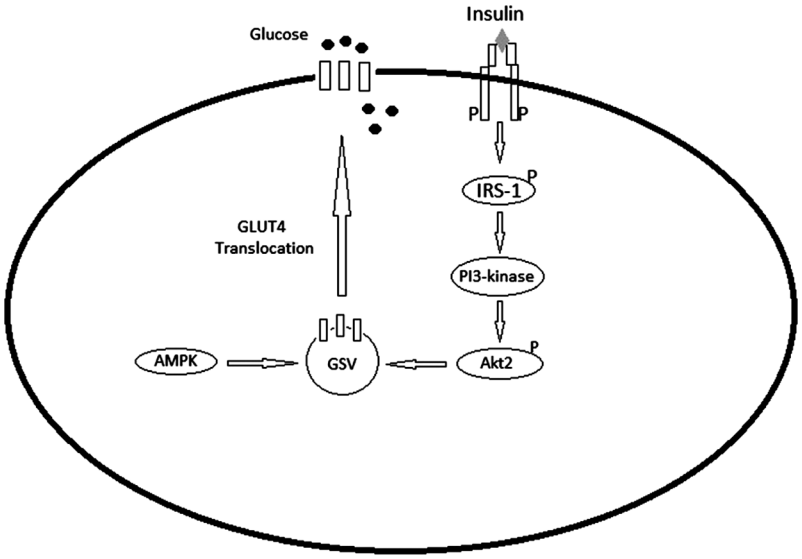

Figure 1. Simplified scheme of insulin signaling in skeletal muscle. Insulin-stimulated tyrosine phosphorylation of the IR leads to phosphorylation of IRS-1. IRS-1 activation stimulates PI3-kinase which, in turn, phosphorylates Akt2. Activation of Akt2, via AS160 and Rab-GTPase (not shown), promotes translocation of GSV to the plasma membrane and insertion of GLUT4. Activation of AMPK can stimulate translocation of GSV in an insulin-independent manner.

has been shown to increase IR expression, insulin-stimulated IR and IRS-1 tyrosine phosphorylation, and PI3-kinase activity (23). Thiazolidinediones (TZD) have also been shown to improve insulin-stimulated IRS-1, PI3-kinase and Akt activity (23). Exercise training and metformin are also well known modalities to improve glucose disposal, however, the mechanisms are not clear. As shown by weight loss and TZD treatment, a logical therapeutic target to improve insulin resistance and glucose transport in skeletal muscle is reversal of impairment of insulin signaling. However, an alternative approach to improve glucose disposal and glucose transport into skeletal muscle is targeting of insulin-independent activation of AMP kinase (AMPK). AMPK is activated by increases in cellular AMP (23-24). AMPK-induced GSV translocation plays an important role in glucose uptake during exercise, for example. Thus, potential therapeutic targets for improving insulin sensitivity and glucose transport in skeletal muscle include the insulin and/or AMPK signaling pathways.

4. BANABA

Banaba is the common name in the Philippines for *Lagerstroemia speciosa*. Other common names for banaba include Queen's Flower, Queen Crape Myrtle, and Pride of India. Banaba is a small to medium-sized deciduous tree with white to pink or purple flowers native to Southeast Asia, India, China, and the Philippines (25). The leaves of the banaba tree are primarily used in Southeast Asia (26) and the Philippines (27) as an antidiabetic agent. There are multiple active constituents in banaba that have been cited to contribute to the hypoglycemic effects observed with the herb. Available literature reports corosolic acid (27-28) and components of tannins (29) as active chemical constituents for lowering blood glucose levels.

Corosolic acid is the active component that is used to standardize banaba extracts for many banaba supplements (26). Corosolic acid has been reported to increase glucose transport by inducing GLUT4 translocation from low density microsomal membrane to the plasma membrane in hindlimb muscles of diabetic mice (28). The exact antidiabetic mechanism of action for corosolic acid in specific skeletal muscles has yet to be thoroughly investigated. Shi *et al*. examined the cellular effects of corosolic acid and how it contributes to lowering glucose levels in L6 myoblast cells. Their study reported that corosolic acid might enhance glucose uptake and GLUT4 translocation through insulin receptor beta phosphorylation by inhibiting a class of protein tyrosine phosphatases (PTP1B, TCPTP, SHP1 and SHP2) in the insulin signaling pathway. The researchers also reported that corosolic acid did

not affect the AMPK phosphorylation pathway that is responsible for increasing muscle cell glucose uptake by contraction or exercise (30).

Corosolic acid in banaba reduces hyperglycemia by other means in addition to inducing GLUT4 translocation and increasing glucose transport. Corosolic acid has been reported to reduce gluconeogenesis and contribute to the antidiabetic effects of banaba. Yamada *et al*. investigated the mechanism of action of corosolic acid in rat liver and reported that corosolic acid enhanced fructose-2,6-bisphosphate production by lowering cyclic AMP levels and inhibiting protein kinase A during lactate-stimulating gluconeogenesis. This resulted in increased glucokinase activity without affecting glucose-6-phosphatase activity, suggesting that glycolysis increases leading to a reduction in gluconeogenesis (31). Other studies have also reported that corosolic acid inhibits alpha-glucosidase, which is responsible for hydrolyzing carbohydrates in the diet that is later absorbed in the small intestine, contributing to the glucose lowering effects of banaba (32).

Other antidiabetic constituents in banaba include components of tannins that have been shown to work in adipocytes. There are two major groups of tannins or tannic acids called gallotannins and ellagitannins (29). Liu *et al*. reported that the glucose lowering effects observed with banaba is actually due to the mechanism induced by tannic acids. The researchers found that tannic acids may induce glucose transport by activating insulin receptors in 3T3-L1 adipocytes and may affect adipocyte differentiation (29, 26).

Several studies have investigated the effects of banaba in human subjects. Available human clinical studies of banaba have a small sample size and are short-term. A one year open label study with 15 human subjects reported a 16.6% decrease in fasting blood glucose and no hypoglycemia (33). Another study utilized banaba extract that was standardized to a 1% corosolic acid and found a 30% decrease in blood glucose after 2 weeks (34). To date, no adverse effects have been reported in animal studies or human clinical trials. In addition, there have been no animal studies investigating the toxicities or lethal doses of corosolic acid or any other banaba constituents. There is only one single report that suggested that corosolic acid may have caused enhanced nephrotoxicity and lactic acidosis in a diabetic patient with kidney impairment who was also taking diclofenac. The role of corosolic acid in this particular report is not clear since diclofenac is a non-steroidal anti-inflammatory agent known to cause renal damage and failure (26). Future long-term studies evaluating the efficacy and safety of banaba in humans are warranted.

5. FENUGREEK

The fenugreek plant (*Trigonella foenum-graecum*) is part of the Fabacceae family. Fenugreek seeds are commonly used as a spice in many dishes from India. The most used parts of the plant are the seeds and the leaves. The therapeutic effects seen with fenugreek are thought to be due to components of saponins, 4-hydroxyisoleucine, trigonelline, and high-fiber content (35).

The antihyperglycemic effect of fenugreek is related to the 4-hydroxyisoleucine component present in the fenugreek seeds (35-36). The 4-hydroxyisoleucine acts by enhancing insulin sensitivity that affects glucose uptake in peripheral tissues (37-38). Jaiswal *et al*. demonstrated that fenugreek enhanced intracellular translocation of GLUT4 receptors to the plasma membrane by stimulating the phosphatidylinositol 3-kinase/Akt-dependent pathway in skeletal muscles (37). The PI3-kinase/Akt (PI3K/Akt) pathway plays a critical role in insulin-stimulated GLUT4 translocation. Normally, once PI3K/Akt is activated, the active Akt phosphorylates multiple downstream effectors that promote diverse biological responses, including the stimulation of glucose transport and regulation of gene expression. Jaiswal *et al*. suggested that 4-hydroxyisoleucine increases Akt (Ser-473) phosphorylation, leading to increased glucose uptake and GLUT4 translocation.

There are other suggested mechanisms for the antidiabetic effects of fenugreek. Fenugreek has been shown to increase beta cell activity by increasing beta cell mass, contributing to a decrease in blood glucose (35). Fenugreek has also been reported to decrease blood glucose by limiting the hydrolysis and absorption of food containing polysaccharides through inhibition of intestinal digestive enzymes, such as alpha-amylase and sucrase (39). Additionally, a study by Vijayakumar *et al*. reported that fenugreek seed extract decreases glucose levels by stimulating the PI3K/PKC pathway in adipose and liver cells and enhancing GLUT4 translocation (40).

Several studies have documented the efficacy of fenugreek in human patients. A review by Haber *et al*. reported a number of clinical studies showing fenugreek to significantly lower glucose levels in type 2 diabetic patients (41). In one trial from 1988, 21 type 2 diabetic patients were fasted overnight and underwent two meal tolerance tests, one with and one without administration of fenugreek. The results of the study showed 17 of the 21 study patients reported significantly lower postprandial blood glucose after fenugreek consumption (42). Another study in 2001 investigated the effects of hydro-alcoholic extracts of fenugreek seeds on glycemic control in type 2 diabetic patients (43). This study was performed as a double-blind, placebo-controlled trial with 25 participants who were randomly assigned to receive 1 g of hydro-alcoholic extracts of fenugreek or placebo. In addition, 10 patients in each group were receiving a sulfonylurea with or without a biguanide (43). After 2 months of therapy, the mean glycosylated hemoglobin (HbA1c) value was decreased significantly in the fenugreek group (from 8.25% to 7.54%); the decrease in HbA1c in the control group was not statistically significant (from 8.25% to 8.14%) (43).

No clinically significant adverse effects have been reported with fenugreek use (44). However, fenugreek can cause mild gastrointestinal adverse effects such as diarrhea, dyspepsia, abdominal distension, and flatulence (41, 44). Fenugreek can also cause hypoglycemia and has been associated with decreased potassium levels, dizziness, hunger, increased frequency of urination, and a body or urine odor of maple syrup in newborns or infants. The long-term effects with fenugreek are still uncertain (41). Patients known to be allergic to chickpeas (44), peanuts, and coriander should avoid fenugreek due to a possible cross-reactivity (41). Inhalation of the fenugreek powder is known to cause numbness of the head and facial angioedema (41). In addition, fenugreek is known to contain curry powder, an allergen that can stimulate severe bronchospasm, wheezing, and diarrhea (44, 41).

6. GINSENG

Ginseng is a perennial plant that belongs to the *Panax* family and grows mainly in North America and Eastern Asia. The North American ginseng is called *Panax quinquefolius* and the Asian or Korean ginseng is known as *Panax ginseng*. The active ingredients in ginseng are a combination of triterpene saponins known as 'ginsenosides' (45). The roots are the part of the plant mainly used for its medicinal properties.

Studies have shown that the active components, ginsenosides, have direct effect on modulation of skeletal muscle pathways to lower glucose levels. A study of Korean red ginseng in diabetic-prone fatty rats found that long term administration of ginseng prevented hyperglycemia. When HbA1c was measured, it was found to be higher in the control group than in the treatment group (46). This same study also investigated the antidiabetic mechanism of action of ginseng. The researchers suggested that Korean red ginseng induced activation of the AMP-activated protein kinase (AMPK) pathway, which led to the phosphorylation of acetyl-CoA carboxylase (ACC) and an increase in beta oxidation in skeletal muscles. Activation of the AMPK pathway also enhances insulin sensitivity and glucose uptake via GLUT4 translocation and enhanced myocyte enhancer factor-2 (MEF-2) (46). The mechanism of ginsenosides was also confirmed in a study investigating ginsenoside Rg1 in C2C12 muscle cells. The study showed that ginsenoside Rg1 activated the AMPK insulin signaling pathway and directly stimulated GLUT4 translocation; however, the PI3K insulin signaling pathway was not affected (47).

Other proposed mechanisms of action for the antidiabetic effects of ginseng have been documented. Ginseng can stimulate the AMPK pathway and inactivate ACC which leads to an increase in fatty acid oxidation, an increase in PGC-1 expression and mitochondrial biogenesis, and preserving the insulin secretory function of beta cells, all contributing to an increase in insulin sensitivity and a decrease in blood glucose levels (46). Stimulation of the AMPK pathway by ginseng has also been shown to promote GLUT4 translocation from the intracellular space to the plasma membrane in adipose cells and increase glucose transport (48). One study demonstrated that Korean red ginseng up-regulated the expression of GLUT4 and down-regulated PTP-1B expression in adipose tissues of rats. PTP-1B negatively inactivates the insulin-stimulated translocation of GLUT4 in the adipose tissue (48). Other antidiabetic mechanisms of ginseng include modulation of gastrointestinal absorption and regulation of insulin secretion and/or sensitivity (49). A study found ginseng to cause an increase in C-peptide levels, insulin secretion, and beta-cell proliferative effects, suggesting that an increase in cell mass is one explanation for ginseng's antidiabetic effects (49).

Several studies have found ginseng to be effective for glucose management in individuals with type 2 diabetes. A systematic review by Shergis *et al*. found 6 randomized and controlled studies investigating the effects of *P. ginseng* on glucose metabolism (45). Four of the studies from the systematic review reported significant results from ginseng therapy, while 2 of the studies did not find any statistical significance (45). One of these studies reported that a 3 g dose of *P. ginseng* significantly lowered the area under the glucose curve with a reduction of 27% (50), and indicated a significant reduction in postprandial glucose at 45, 60, 90, and 120 minutes in type 2 diabetic patients (50). Another systematic review evaluated 11 randomized and controlled studies that were selected based on a Jadad score of 3 or more (51). Of the 11 trials, 8 reported significant results and 2 trials yielded no significance (51). One of the significant studies looked at ginseng efficacy in 19 patients with type 2 diabetes and found a decrease in plasma glucose levels by 8-11% following a 75 g oral glucose tolerance test (52). The researchers also found an increase in insulin sensitivity index by 33% when compared with placebo (52).

Ginseng has a good safety profile based on systematic reviews (45). However, some studies have reported minor adverse effects. *P. ginseng* has been associated with gastrointestinal problems ranging from stomach discomfort to nausea, vomiting and diarrhea, and has also been associated with hypoglycemia. *P. quinquefolius*, on the other hand, has been shown to cause insomnia, headache, chest discomfort and diarrhea (51).

7. CINNAMON

There are hundreds of species of plants within the genus *Cinnamomum* (53). Four of these species are typically used to produce the spice commonly used around the world, of which *C. aromaticum*, *C. cassia* and *C. zeylanicum* are the most common (53-54). Similarly, these species are also the most widely used and extensively studied in the management of hyperglycemia. Looking broadly at the genus, dozens of compounds including cinnamaldehydes, flavonoids, volatile oils, and coumarins have been identified in a number of the plants and multiple explanations for the proposed glycemic effects of the cinnamon supplements have been hypothesized (54).

In skeletal muscle, cinnamon is thought to improve glucose control through a number of mechanisms (53-54). Nearly all of these proposed mechanisms stem from data obtained from animal or *in vitro* studies. Human studies with cinnamon have focused largely on clinical outcomes. Looking specifically at improvements in insulin sensitivity, two recent studies have demonstrated the effectiveness of cinnamon through improved glucose uptake (55-56). Absalan and colleagues demonstrated improved glucose uptake secondary to enhanced GLUT4 translocation in myoblastic cell lines using hydro-alcoholic cinnamon extract (55). Similarly, Anand *et al*. administered cinnamaldehyde from *C. zeylanicum* orally to diabetic rats and demonstrated improved glucose uptake in skeletal muscle via increased GLUT4 translocation to the cell membrane (56). It is not clear from these trials whether exposure to cinnamon improves GLUT4 translocation through amplification of insulin signaling or if another effect on transcription of GLUT4 proteins is the reason for the improvement (55-56).

Other proposed mechanisms for the effect of cinnamon on hyperglycemia include suppression of gluconeogenesis through reduction of liver and kidney phosphoenolpyruvate carboxykinase (PEPCK) (56). Restoration of normal glycolysis via increased pyruvate kinase in the liver and kidney and increased phosphofructokinase-1 in the liver and intestine have also been demonstrated (56-57). In addition, cinnamon exposure resulted in reduced absorption of glucose through inhibitory effects on intestinal alpha-glucosidase and pancreatic alpha-amylase (58). Similar to the results described above for skeletal muscle, data showing improvements in glucose uptake and translocation of GLUT4 in adipose tissue have also been published (59-60). Finally, cinnamon is proposed to stimulate insulin release and improve insulin signaling through phosphorylation of the insulin receptor (56, 61).

In terms of the therapeutic application of cinnamon, human studies are limited, small and generally of too short a duration to demonstrate any meaningful effect on clinical outcomes. However, meta-analyses do show promise for a positive impact on fasting glucose, weight, multiple lipid parameters and hemoglobin A1c (HbA1c) while being well tolerated and free from complaints of adverse effects (53, 62).

8. BIOTIN

Biotin, also referred to as Vitamin H or B7, is a water-soluble vitamin that must be taken

in through the diet or supplementation and is most readily available in organ meats and green leafy vegetables (63). Biotin is a cofactor for carboxylases that play an essential role in gluconeogenesis, amino acid catabolism, and fatty acid synthesis (64). In addition, biotin is thought to modify gene expression that results in increased insulin receptor expression and hepatic glucokinase and decreased hepatic PEPCK, all playing a significant role in glucose homeostasis (65).

The role of biotin in improving skeletal muscle insulin sensitivity is not as well established. The majority of pre-clinical studies evaluating the mechanisms of biotin action with regard to lowering glucose have studied its effects on blood glucose, hepatocytes, and pancreatic beta cells (66-71). However, hypotheses do exist that advocate for the role of biotin as a means to improve glucose uptake in skeletal muscle. In both the acute and chronic setting of exercise, cyclic guanosine monophosphate (cGMP) is at least partially responsible for provoking translocation of and transcription factors for GLUT4 (72). This process is normally brought about by increased nitric oxide that stimulates cGMP production (73). Similarly, biotin, when given in supraphysiologic doses, can have a direct effect on guanylate cyclase that results in increased cGMP. A biotin-induced increase in muscle cGMP may result in improved sensitivity and glucose uptake (73-74).

Human trials evaluating biotin supplementation in patients with diabetes are few in number and generally have small sample sizes. While devoid of reports of any significant adverse effects or toxicities, most trials evaluated biotin in combination with chromium picolinate and demonstrated only a modest effect on hemoglobin A1c (75-76). Thus, the therapeutic utility of biotin for improving glucose control remains a question despite the apparent pharmacological effects described above.

9. ALPHA-LIPOIC ACID

Alpha-lipoic Acid (LA) is an endogenous compound produced by the mitochondrion and serves as a cofactor for cellular energy production and natural antioxidant. LA may also be supplemented in the diet via organ meats, certain vegetables and brewer's yeast, although absorption of dietary LA is generally considered poor (77).

In skeletal muscle, LA is proposed to influence glucose transport via a number of direct and indirect mechanisms. Lipoic acid may bind directly to and stimulate the beta subunit of the insulin receptor (78). It has also been proposed to prevent the inhibitory effect of dephosphorylation by protein tyrosine phosphatase B1 (79). Additionally, LA promotes insulin responsive substrate-1 (IRS-1) expression which facilitates signaling between the insulin receptor and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway that promotes GLUT4 translocation (80). Indirectly, LA provokes a number of these same responses through activation of AMP-activated protein kinase (AMPK). Specifically, a LA-induced increase in AMPK is thought to induce phosphorylation of IRS-1 which facilitates signaling down the PI3K/Akt pathway as well as directly promote GLUT4 translocation by mimicking the effect of Akt on GLUT4 vesicles (81-83). While LA is thought to provide a number of other physiologic benefits, these are the primary effects proposed for treatment of hyperglycemia.

Supplementation with LA has been evaluated clinically. Most of the data from human trials focuses on treatment of neuropathies related to diabetes (84-85). As with other natural product studies, the size and duration of the trials is a significant limitation to recommending regular therapeutic use, although the therapy seems to be well tolerated with no significant toxicities. Doses of LA typically ranged from 600 mg to 1800 mg in divided doses and, when statistically significant, only produced a modest reduction in glucose (86-88).

10. PERSPECTIVES

The global prevalence of type 2 diabetes is increasing exponentially. Unless major preventive measures are implemented, it is estimated that the number of individuals suffering from this disorder will rise to 438 million worldwide in 2030 (1). In light of the tremendous cost of type 2 diabetes, both in terms of monetary resources and of human suffering, there is considerable need for safe and effective agents that can reduce the risk for this disease in the large at-risk population even when diet and exercise habits remain suboptimal (89-90). A number of self-selected natural products, including the supplements discussed herein, have the potential to offer strategies for preventing or postponing the onset of type 2 diabetes that are both attractive and practical from cost-effectiveness, convenience, and safety standpoints. In addition, these products are likely to have a favorable impact on vascular risk in non-diabetics; this is important because non-diabetic

insulin resistance is associated with a significant increase in vascular risk (91-92). However, more research, particularly large-scale, long-term clinical studies, is certainly needed to establish/confirm the efficacy and safety profiles of these products in diabetes prevention.

In treating type 2 diabetes, the majority of patients need prescription antidiabetic drugs to achieve tight glycemic control, especially in the absence of substantial lifestyle changes. None of the natural products with antidiabetic potential, including the supplements that we discussed in this review, has demonstrated benefit comparable to prescription antidiabetic agents and/or insulin therapy. At best, these products should be considered as adjunctive therapies in type 2 diabetes management, except in patients who are near goal and are most likely using the supplements in conjunction with a lifestyle overhaul. More rigorous, well-designed human trials are required to accurately define the value and place of these supplements in diabetes treatment. It is important to note that regardless of whether or not health care providers choose to recommend any of these natural supplements, they (the supplements) will still be marketed directly to type 2 diabetics by lay healers and supplement manufacturers or recommended to them by family and friends. Therefore, clinicians need to take a complete history of natural product use and enter the information into the patient's medication profile along with prescription and nonprescription drug history (including antidiabetic drug history). These histories are critical because hypoglycemia and interactions between natural products and other drugs are of great concern (93-94). Moreover, health care providers and patients should always keep in mind that available natural supplements may have other health effects, both beneficial and harmful, may be contaminated with other substances, or may simply not be present in the brand purchased.

In summary, the self-selected natural supplements that we discussed in this review have the potential to adjunctively treat and possibly prevent type 2 diabetes. None of them should be recommended for use in pregnant and lactating women or in children. Patients and consumers who elect to use these supplements, as monotherapy or in combination with prescription antidiabetic drugs, should be counseled on their contraindications/precautions, interactions, and adverse effects. These individuals should also be counseled on how to self-monitor therapy outcomes in order to avoid hypoglycemia.

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Abbreviations: ACC: acetyl-CoA carboxylase; AIDS: acquired immunodeficiency syndrome; Akt: protein kinase B; AMP: adenosine monophosphate; AMPK: adenosine monophosphate-activated protein kinase; AS160: Akt substrate of 160 kDa; cGMP: cyclic guanosine monophosphate; DAG:

diacylglycerol; GLUT4: glucose transporter type 4; GSV: GLUT4 glucose transporter storage vesicles; HbA1c: glycosylated hemoglobin or hemoglobin A1c; IR: insulin receptor; IRS-1: insulin responsive substrate-1; JNK1: c-Jun N-terminal kinase 1; LA: alpha-lipoic acid; MEF-2: myocyte enhancer factor-2; PEPCK: phosphoenolpyruvate carboxykinase; PGC-1: peroxisome proliferator coactivator-1; PI3K or PI3-kinase: phosphatidylinositol 3-kinase; PI3K/Akt pathway: phosphatidylinositol 3-kinase/Akt-dependent pathway; PI3K/PKC: phosphatidylinositol 3-kinase/protein kinase C; PKC: protein kinase C; PP2A: serine/threonine protein phosphatase 2A; PTP-1B: protein tyrosine phosphatase 1B; Ser-473: phosphor-Akt antibody; SHP1: protein-tyrosine phosphatase SHP1; SHP2: protein-tyrosine phosphatase SHP2; TCPTP: T-cell protein tyrosine phosphatase; 3T3-L1: mouse cell line 3T3; TZD: thiazolidinediones.

Key Words: Type 2 diabetes mellitus, Natural products, Dietary supplements, Skeletal muscle, Insulin resistance, Review

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