



## Anti-diabetic effects of excipients: possibility of formulation of an anti-diabetic dosage form using pharmaceutical excipients or their constituents, or food additives.

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### ABSTRACT

The ability of pharmaceutical excipients to exhibit significant bioactivity independent of the active pharmaceutical ingredient is beginning to be recognized. Certain types of diets or foods have been demonstrated to alleviate diabetic symptoms. Because most excipients are derivatives of food products, it is not unreasonable to assume that these molecules are responsible at least in part for the diabetes ameliorative properties of such foods or food products. Indeed, evidence has accumulated that such excipients act on well defined pharmacologic pathways and targets in order to exercise their beneficial effects. If excipients that act on multiple diabetogenic pharmacologic targets or pathways are combined together in concentrations that are at or above their recommended dietary allowances, the possibility exists that such a formulation may provide “stand alone” control of type II diabetes. The formulation could be as simple as a mixture of these solid powders presented in a ‘sachet’ or pack to be mixed with water and taken once or twice a day.

**KEY WORDS:** Excipient, diabetes, food additive, promiscuous, bioactive, dietary supplement

### INTRODUCTION

There has been increasing evidence in recent years that pharmaceutical excipients may not be innocuous, “inert” components of a dosage form, but may possess either “stand alone” biological activity or may act to change the biological activity of the active pharmaceutical ingredient (API). Excipients may inhibit drug metabolizing, cytochrome P-450 enzymes, modify drug pharmacokinetics, alter the efflux of drug from cells or enhance gene transfection efficiency and nuclear localization.

Because most excipients have historically originated from food or food products, they have been assigned - and in most cases; experimentally proven to have - generalized pharmacological bioactivity profiles based on the ingestion of those particular food products. For example, oils, green leafy vegetables and nuts have antioxidant and cardioprotective properties. Fish oil (containing docosahexaenoic acid [DHA]) has anti-inflammatory properties. Whole grains, fruits and vegetables contain fiber (e.g. guar gum) that decreases the incidences of non-infective diseases of the bowel and promotes cardiovascular health. Coconut oil contains medium chain triglycerides (MCTs) and has

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**Table 1** GNC Preventative Nutrition Diabetic Nutrition Plan Dietary Supplement Packs (as presented in www.GNC.com)

<b>Glucose Support Formula™ Serving Size: Three Dark Brown Softgels</b>	<b>Amount Per Serving</b>	<b>% Daily Value</b>
Vitamin E (as d-alpha tocopherol)	30 IU	100%
Vitamin B-6 (as pyridoxine hydrochloride)	1 mg	50%
Folic Acid	200 mcg	50%
Vitamin B-12 (as cyanocobalamin)	3 mg	50%
Biotin	125 mg	42%
Selenium (as sodium selenate)	70 mcg	100%
Manganese (as manganese gluconate)	2.5 mg	125%
Chromium (as chromium picolinate)	200 mcg	167%
alpha-Lipoic Acid	600 mg	*
Fenugreek Seed Powder (Trigonella foenum-graecum)	500 mg	*

\* Daily Value not established

**Other Ingredients:** Soybean Oil, Gelatin, Glycerin, Soy Lecithin, Caramel Color, Titanium Dioxide (natural mineral whitener)

been historically used as a “functional food” to cure a multitude of ailments (1). The advent of detailed knowledge of mechanisms of action of these ingredients has prompted their distillation into individual “nutritional supplements” in order to alleviate specific deficiencies of individual diets. Tables 1 and 2 list the ingredients of two commonly used dietary supplements designed to have antidiabetic properties.

## HYPOTHESIS AND DEVELOPMENT OF THE CONCEPT

The purpose of the manuscript is to propose a formulation consisting entirely of excipients or food chemicals that may demonstrate clinical efficacy in controlling the symptoms of type II diabetes. It requires but one more step to realize that a combination of such excipients, food chemicals or food additives may provide protection against diabetes or insulin resistance; that may be comparable to the effects of single

API's; due to their effects on multiple pathways and targets. Some potential molecules that may prove worthy of consideration for such a formulation are discussed below:

**Table 2:** Glucocil™ antidiabetic supplement ingredients (as presented at [www.glucocil.com](http://www.glucocil.com))

<b>Supplement Facts</b>	
Serving Size 2 Capsules Servings Per Container 60	
<b>Amount Per Serving</b>	<b>% Daily Value</b>
Vitamin B <sub>1</sub> (as Thiamine Hydrochloride) 4mg	<b>266%</b>
Vitamin B <sub>6</sub> (as Pyridoxine Hydrochloride) 4mg	<b>200%</b>
Folic Acid 400mcg	<b>100%</b>
Vitamin B <sub>12</sub> (as Cyanocobalamin) 15mcg	<b>251%</b>
Chromium (as Chromium Polynicotinate) 200mcg	<b>167%</b>
<b>Glucocil Blood Glucose Management Blend 1005mg †</b>	
Proprietary Mulberry Leaf Extract	†
Insulina (Cissus Sicyoides) Leaf Extract	†
Alpha Lipoic Acid	†
Cissus Quadrangularis (stems) (alcohol extract)	†
Banaba Leaf Extract (18% Corosolic Acid)	†
† Daily Value not established	

**OTHER INGREDIENTS:** MICROCRYSTALLINE CELLULOSE, MAGNESIUM STEARATE, GELATIN, TITANIUM DIOXIDE, FD&C BLUE #1, FD&C YELLOW #5,

## L-Arginine

It was demonstrated that L-Arginine significantly improved peripheral and hepatic insulin sensitivity in type 2 diabetic patients (2). L-Arginine, a precursor for the synthesis of nitric oxide (NO), caused an increase in the depressed cGMP (the second messenger of NO) levels of diabetic subjects thereby attenuating insulin resistance partly by normalizing the vasodilatory response (3) and partly by increasing glucose transport (4).

L-Arginine is an excipient in the tissue plasminogen activator formulation, Activase<sup>®</sup>.

## Niacin (Nicotinic acid)

Incomplete suppression of lipolysis by insulin in the fed state in insulin-resistant subjects leads to increased lipolysis in adipose tissue with elevated circulating free fatty acids (FFA) and in the eventual development of the atherogenic dys-lipidaemic phenotype. It has been demonstrated that FFA cause hepatic and skeletal muscle insulin resistance by inhibiting insulin suppression of glycogenolysis (5) and by increasing the flux of fructose-6-phosphate into the hexosamine pathway (6) respectively. FFA also induce insulin resistance in muscle cells by interfering with phosphatidylinositol 3-kinase (PI3K) activity which in turn causes reduced translocation of GLUT4 (the transport protein that facilitates glucose diffusion into cells) to the cell surface (7). Niacin suppresses lipolysis in adipose tissue, thereby leading to a decreased flux of FFA to the liver with reduced very low density lipoprotein (VLDL) production. The anti-atherogenic effects of niacin on the lipid profile hence may mitigate hepatic insulin resistance as well as attenuate a major source of cardiovascular risk in insulin-resistant populations (8). Niacin is present as an excipient to discourage addictive narcotic opioid dosing in Acurox<sup>™</sup> tablets (9).

## Magnesium

Oral supplementation with MgCl<sub>2</sub> solution has been shown to restore serum magnesium levels,

improve insulin sensitivity and metabolic control in type 2 patients that exhibit decreased serum magnesium levels (10). The mechanism of action has been suggested to be a restoration of the defective tyrosine kinase activity of insulin receptors that is observed in hypomagnesemia (11). Magnesium stearate is used as a glidant in the manufacture of tablets, magnesium carbonate is used as an excipient in Tenormin<sup>™</sup>.

## Guar gum

Guar gum and other fiber analogs increase the gastric emptying time, reduce the rate of glucose formation (by inhibition of disaccharidases) (12) and reduce the rate of glucose absorption from the small intestine (13). The increased viscosity seems to be the cornerstone of their efficacy. Highly viscous or gel forming fibers also increase satiety, thereby mimicking calorie restriction, which has the effect of upregulation of Sirtuin 1 (SIRT1). SIRT1 upregulation stimulates glucose-dependent insulin secretion from pancreatic  $\beta$  cells and attenuates insulin resistance through its modulation of adiponectin secretion, gluconeogenesis, inflammatory responses and levels of reactive oxygen species (14). Plasminogen activator inhibitor-1 activity, which correlates strongly with the degree of insulin resistance, is also lowered by guar gum. Guar gum is used as a binder in the manufacture of tablets, as a viscosity modifier in suspensions or syrups.

## D-chiro-Inositol

D-chiro-inositol may act to bypass a defective normal in-vivo epimerization of myo-inositol to D-chiro-inositol associated with insulin resistance and act to partially restore insulin sensitivity and glucose disposal (15). Myo-inositol is an excipient used in dry powder inhalable vaccines in the preclinical stage (16). Because D-Chiro-inositol is a stereoisomer of myo-inositol, it is expected that the latter can be used without any significant safety issues in humans as well.

## Vitamin E

It has been demonstrated that reactive oxygen species play a causal role in multiple forms of insulin resistance (17). Albeit transient, vitamin E has been shown to improve insulin resistance in human subjects (18). FFA induced activation of Nuclear factor-kappaB (NF-kB) has been shown to be associated with the development of insulin resistance via the serine phosphorylation of Insulin receptor substrate-1 (IRS-1) and subsequent downstream interference with Phosphoinositide 3 kinase (PI3K) association (19). The FFA induced NFkB activation can be prevented by Vitamin E (20). Vitamin E is sometimes added as an antioxidant to vegetable oils.

## Docosahexaenoic acid (DHA)

Omega-3 fatty acids elicit hypotriglyceridemic effects by coordinately suppressing hepatic lipogenesis, upregulating fatty oxidation in the liver and skeletal muscle through peroxisome proliferator activated receptor (PPAR) activation, and enhancing flux of glucose to glycogen through downregulation of hepatocyte nuclear factor (HNF-4 $\alpha$ ). The net result is the repartitioning of metabolic fuel from triglyceride storage toward oxidation, thereby reducing the substrate available for VLDL synthesis (21). DHA is used as a food additive in dairy items such as milk and yogurt.

## Acetic acid

The addition of vinegar to high glycemic load meals has been shown to result in significantly reduced postprandial glycemia. This effect has been attributed in part to a suppression of intestinal disaccharidase activity by acetic acid (22, 23) and is independent of gastric emptying time (24). Acetic acid is a constituent of vinegar.

## Lecithin

Impairment of Stat-3 activation and reduction of PPAR $\alpha$  activity contributes in part to leptin

resistance and consequently, obesity (25). Obesity, in turn, contributes to the modulation of multiple signaling pathways and effectors such as Leptin, NF-kB, FFA, SIRT1, that – in concert – contribute to insulin resistance. PPAR agonists partly restore the liver's capacity to oxidize fatty acids and attenuate insulin resistance. It has been demonstrated that 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine, a component of lecithin, is an endogenous ligand for PPAR $\alpha$  in the liver (26). This substance is a component of lecithin, which has long been used in food additives and in intravenous fat emulsions primarily for its emulsification properties.

## Alpha-Lipoic acid

Copious anecdotal evidence exists regarding the efficacy of alpha-lipoic acid in restoring insulin sensitivity in type 2 diabetes. Alpha lipoic acid has been demonstrated to inhibit mammalian pyruvate dehydrogenase kinase, thereby providing a possible mechanism for a glucose (and lactate) lowering effect in diabetic subjects (27).

## Caprylic/capric triglyceride

Adenosine receptor agonists have been demonstrated to prevent diabetes development in murine models, in part due to the suppression of pro-inflammatory cytokine expression (28). Miglyol<sup>®</sup>, a medium chain triglyceride (MCT) of caprylic and capric acids, has been shown to upregulate adenosine receptors, A3 and A2A (29). MCT administration has been shown to increase insulin mediated glucose disposal (30) and to decrease insulin resistance (31). Miglyol is a solubilizer that is widely used in various approved drug products.

## DISCUSSION

Almost every molecule has at least *some* measurable affinity toward a target receptor. Such affinity may neither necessarily be very specific nor very high, so that therapeutic

modulation of the target receptor and/or signaling pathway may not be enabled. Many of the “bioactive excipients” listed in table 3 have been reported to possess non-specific affinities toward a myriad of target receptors because:

1. Many of them act by mechanisms of action that are generic to the activation of multiple targets, one of them being redox and/or free radical manipulation.
2. Many of them function as cofactors of enzymes.
3. Many are (or activate) precursors of second messengers that propagate signal transduction.

Such non-specificity exhibited by these individual “bioactive excipients” may tend to attenuate their (individual) actions on the desired target specific biochemical signaling pathway, necessitating either the administration of much larger doses of individual excipients in order to achieve therapeutic effects, or administering most or all of these “bioactive excipients” concurrently. The latter concept is based on the proposition that an ideal drug may be one whose efficacy is based not on the modulation of a single target, but rather on the rebalancing of the several proteins, or events, that contribute to the etiology, pathogenesis, and progression of diseases, i.e., in effect a promiscuous drug (32). For example, in some instances, herbal extracts with anti-diabetic properties have been demonstrated to be “bio-equivalent” to FDA approved drugs based on efficacy in animal models.

When combined with bioenhancers/solubilizers, the hypoglycemic activity of an extract of *Artemisia dracuncululus* L. containing at least 6 bioactive compounds was shown to be comparable to the activity of the anti-diabetic drug metformin (33). This lends credence to the observation that the multicomponent and multimechanistic advantage of botanical preparations compared to single chemical

entities derives in part due to their promiscuity in targeting multiple pharmacologic targets (34, 35) and there seems to be no reason; a priori; why these advantages should not also translate to a mixture of ‘bioactive’ pharmaceutical excipients. Co-administering these excipients/excipient constituents /food additives provides this advantage that is especially relevant for a disease such as non-insulin dependent diabetes whose etiology is multifactorial in nature and whose predisposing factors – such as obesity – are associated with a state of generalized chronic low level inflammation (36).

Table 3 compares the recommended dietary allowances of the excipients demonstrating pharmacological bioactivity toward attenuating type II diabetic symptoms versus their use in clinical studies obtained from the literature. A proposed amount of each ingredient to be included in the formulation is also presented per the criteria described below.

Column 3 in table 3 indicates the amounts of these bioactive excipients (per day) that have been used as supplements in human clinical studies. Vitamin E supplementation reduced glucose AUC, increased glucose disappearance, increased total glucose disposal and increased non oxidative glucose metabolism (37). Niacin-treated subjects experienced significantly reduced total cholesterol and triglyceride levels (38). Oral supplementation with MgCl<sub>2</sub> solution restored serum magnesium levels, improving insulin sensitivity and metabolic control in type 2 diabetic patients with decreased serum magnesium levels (39). Guar gum supplementation participants that had the highest mean fasting blood glucose and HbA1c levels, showed a significant reduction in their fasting glycemic levels as well as a significant reduction in total cholesterol levels (40).

Arginine, in an amount likely to be ingested in a high-protein meal, did not stimulate insulin secretion but attenuated the increase in glucose when given with glucose (41).

**Table 3** Excipients or food chemicals used in human clinical studies that demonstrate a beneficial effect in biomarkers of type-2 diabetes.

<b>Ingredient</b>	<b>RDA<sup>1</sup> (per day)</b>	<b>Supplementation amounts used in clinical studies (per day)</b>	<b>Amount used in proposed formulation<sup>3</sup></b>
Vitamin E	15 mg	900 mg	900 mg
Niacin	20 mg	500 mg	500 mg
Magnesium	400 mg	1 g	400 mg
Inositol	~ 30 mg	100 mg	30 mg
Guar gum	25 g <sup>2</sup>	10 g	10 g
L-Arginine	3.5 – 5.0 g	10.6 g	3.5 g
Docosahexaenoic acid	500 mg	1.5 g	500 mg
Lecithin	Not established	3.6 g	3.6 g
Caprylic/Capric acid	Not established	5 g	5 g
Alpha lipoic acid	Not established	600 mg	600 mg
Sodium acetate/Acetic acid (acetate buffer)	Not applicable	Not applicable	Buffering agent

1. Recommended dietary allowance.

2. As dietary fiber.

3. Calculated as described below. Total weight is 25.3 g packaged in two, 15 g sachets, to be taken twice a day each with a glassful of water.

Supplementation of DHA in men and women with below-average HDL cholesterol concentrations raised the LDL cholesterol level, but had favorable effects on triglycerides, the triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles (42). Orally administered alpha lipoic acid increased insulin stimulated glucose disposal in significantly more subjects when compared to placebo (43). MCT administration as part of daily food intake showed a reduction in body weight, cholesterol and a reduction in homeostasis model assessment of insulin resistance (31).

## PROPOSED FORMULATION

Because most of the ingredients in Table 3 are found in foods; either as minor constituents or as additives, it should theoretically be possible

to make dietary adjustments so that these ingredients are ingested in sufficient amounts. However, in practice, dietary habits are not easily modified and ingestion of significantly large amounts of food substances would be required at least for those ingredients that are present as food additives.

Because of the (postulated) synergistic effects of the combined ingredients due to the principle of promiscuity (see above), it should be possible to decrease the supplementation amount for each ingredient without sacrificing biological efficacy for the mixed ingredients. As a crude first approximation, if the amount used for a particular ingredient in clinical studies is more than an order of magnitude greater than the RDA, then the proposed formulation will utilize the former. If the amount used for a

particular ingredient in clinical studies is less than the RDA, then the RDA amount will be utilized in the formulation. Where the RDA is not specified, the amount used in clinical trials will be used in the proposed formulation (Column 4 of Table 3). The total weight of ingredients in the proposed formulation is calculated to be 25.3 g.

The dosage form could hence be presented as two ~ 15 g “sachets” or packs containing the solid ingredients. Each sachet would be taken (for example) with a glass of water. Two sachets per day would constitute a long term management therapy for diabetes. The formulation would presumably also need to include; at a minimum; glidant(s) and flavors to improve the manufacturability and palatability of the dosage form.

## LIMITATIONS

1. Although each ingredient alone has been demonstrated to act via well studied and validated signaling pathways, the modulation of which results in the amelioration of the symptoms and/or the aetiology of diabetes; there can be no assurance that the combination of all these ingredients will act additively or synergistically. They may, in fact, act entirely out of concert with each other that negate their individual or combined beneficial effects.
2. Most of the signaling pathways or mechanisms of action have not been studied in humans. Furthermore, quite a few have been studied in vitro. The results of these experiments cannot be extrapolated to their actions in vivo in humans. Well controlled clinical studies using such a combination of excipients are necessary in humans before any justification for efficacy can be claimed.
3. The paradigm of administering “bioactive excipients” is possible for diseases that are chronic in nature and for whom gradual and lasting beneficial effects may be observed from the modulation of signaling pathways that lead to incremental but discernible improvements in the quality of life. Such “bioactive excipients” may not be effective for acute diseases for which drastic interventions are required such as pathogenic infections, cancer, or organ or tissue (neuromuscular, cognitive) deterioration which can irreversibly affect the capacity to function normally.
4. The calculation for the amount of each ingredient to be used in the proposed formulation assumes a “one size fits all” paradigm and discounts the differing predominance of one (or more) etiological factors for different patients. For example, the relative contributions of dyslipidemia, hypomagnesimias, oxidative stress, inflammation, obesity and mitochondrial function (etc.) toward disease progression may be different for different individuals. Individual patients would be better treated with a dosage form containing relative concentrations of individual ingredients that “match” their etiological contribution profile. This can, in practice, be achieved by prior examination of (for example) key biomarkers in the blood or expression of genes in a microarray; and extemporaneously preparing the mixture of ingredients that “match” the profile. However, it can be readily appreciated that conventional therapy using single API's does not follow this paradigm. The necessity of such “tailor made” extemporaneous preparations using a combination of excipients actually assumes lesser significance because such a combination of excipients meets the criteria of promiscuity in targeting multiple pharmacologic targets.

It should be readily apparent that; should such a formulation of ostensibly “non active” substances as outlined in this manuscript demonstrate a significant improvement in biomarkers in patients with type 2 diabetes in a controlled clinical study; future formulations

containing “active” pharmacological drugs that are formulated with one or more of these “bioactive excipients” must unequivocally demonstrate that the clinical effect demonstrated by the “active” is not dependent on the inclusion of such “bioactive excipients” in the formulation. For this purpose, the placebo must contain the “bioactive excipients”.

## NOTE

The content of the manuscript is the subject of Indian Patent Application number 66/MUM/2010 dated 1/7/2010 entitled “Anti-Diabetic formulation” by the Author.

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