



Combination therapy: A new strategy to manage diabetes and its complications



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ABSTRACT

Diabetes mellitus is the most common metabolic disorder. The major cause of mortality and morbidity here is due to the complications caused by increased glucose concentrations. All the available commercial antidiabetic drugs are associated with side effects. The combination therapy could be a new and highly effective therapeutic strategy to manage hyperglycemia. Combination of commercial drugs with phytochemicals may reduce the side effects caused by these synthetic drugs. Herbal products have been thought to be inherently safe, because of their natural origin and traditional use rather than based on systemic studies. New formulation and cocrystallisation strategies need to be adopted to match the bioavailability of the drug and the phytochemical. This review describes in detail, the observed synergy and mechanism of action between phytochemicals and synthetic drugs in effectively combating. The mode of action of combination differs significantly than that of the drugs alone; hence isolating a single component may lose its importance thereby simplifying the task of pharma industries.

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Introduction

Diabetes mellitus (DM) is a metabolic endocrine disorder. It is mainly characterized by hyperglycemia and is associated with the imbalance in carbohydrate, protein and lipid metabolisms (Lin and Sun 2010). It is a chronic disease that arises when the pancreas does not produce enough insulin (insufficient), or when the body cannot effectively use the insulin it produces (Das and Elbein 2006). The International Diabetes Federation estimates that there are over 300 million people around the world with diabetes. This total is expected to reach close to 500 million within 20 years (King et al. 1998; Lin and Sun 2010). Each year another 7 million people develop diabetes. The reasons for this global rise in diabetics are increase in the aging population and increasing trends toward obesity, unhealthy diet and sedentary lifestyle or combination of these (Harris et al. 1998).

There are two main forms of diabetes namely type 1 diabetes (arise due to the diminished production of insulin) and type 2 diabetes (T2DM) (due to impaired response to insulin and β -cell dysfunction) (Kahn 1997). In the case of the former, little or no insulin is being produced. People with T2DM do have sufficient insulin production but the body is not able to use it

effectively (Prabhakar and Doble 2008a). Both these types lead to hyperglycemia, excessive urine production, compensatory thirst, increased fluid intake, blurred vision, weight loss, lethargy and changes in energy metabolism. About 20% of the population over the age of 65 have T2DM (Zimmet 2000). In many countries about 5–10% of the total health care budget is used for treating this problem.

Hyperglycemia can cause serious damage to the nerves and blood vessels, the latter leading to macro- and microvascular complications. Three key factors during the onset of hyperglycemia in T2DM are increased hepatic glucose production, diminished insulin secretion, and impaired insulin action (DeFronzo et al. 1992; Lin and Sun 2010; Stumvoll et al. 2005). Insulin resistance refers to suppressed or delayed responses to insulin. It is a problem with the cells that respond to insulin rather than a problem with insulin production itself. Other rare causes of diabetes include pregnancy, due to certain medications, or diseases such as maturity onset diabetes in the young (MODY) (Blanc et al. 2001).

Five classes of oral antidiabetic drugs (OHDs) that are available which work via four different mechanisms are namely those that (i) enhance secretion of insulin in pancreas (sulfonylurea & non-sulfonylurea); (ii) decrease glucose release from the liver (biguanides); (iii) reduce gastrointestinal absorption of carbohydrates (α -glucosidase inhibitor); and (iv) improve peripheral glucose disposal (biguanides and thiazolidinediones) (Cheng and Fantus 2005). All the drugs are associated with side effects.

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Though it is important that glycaemic control should be achieved as rapidly as possible to minimize the impact of glucose toxicity, it is also necessary to provide therapy to control other related risk factors, including oxidative stress, dyslipidaemia, mitochondrial dysfunction, vascular complications, etc. (Duckworth 2001; Jain and Saraf 2010). Hence, a combination therapy becomes necessary to combat the multiple risk factors in diabetics.

World ethnobotanical information reports that about 800 medicinal plants can be used in the control of diabetes mellitus. There are around 450 experimentally proven medicinal plants having antidiabetic properties but complete mechanism of action is available only for about 109 of them (Prabhakar and Doble 2008a,b).

Also, it is equally important to provide sustained glycemic control in the long term to prevent the development of complications (Andersson and Svärdsudd 1995). Hence, a judicious selection of suitable agents for combination therapy which can provide most metabolic benefits to the patient with type 2 diabetes should be considered. Thus, a synergistic combination therapy (having more than two pharmacodynamic agents), to treat T2D conditions is necessary. Such a strategy can help to:

- (1) Attain rapid and long term glycemic control
- (2) Combat other risk factors which arise as a consequence of the T2D
- (3) Treat the multiple risk factors that are responsible for the onset and development of T2D
- (4) Provide a mild anti-inflammatory effect – since inflammation is both the cause and consequence of T2D condition.

The traditional medicinal plants with various active principles and properties have been used since ancient times by physicians and laymen to treat a variety of human diseases including diabetes, coronary heart disease, and cancer (Alarcon-Aguilara et al. 1998). India has a long history of use of medicinal plants for the management of diabetes. Charaka and Shushruta described in their Charaka samhita and Shushruta samhita the phytopharmacology aspects of diabetes and its complications (Grover and Vats 2001). Medicinal plants have beneficial multiple activities including manipulating the carbohydrate metabolism by various mechanisms, preventing and restoring integrity and functioning of β -cells, controlling insulin release, improving glucose uptake and utilization, and antioxidant properties (Prabhakar and Doble 2008b). Herbal products have been thought to be inherently safe, because of their natural origin and traditional use rather than based on systemic studies (Wood and De Smet 2002). Adverse effects from herbal remedies are reported, but their frequency and severity are unknown. To overcome these drawbacks scientific study of herbal remedies and their potential to cause interactions when used in combination with conventional medicines need to be thoroughly understood and systematically studied (Inamdar et al. 2007).

Nutraceuticals are used as food components (such as vitamins, polyphenols, flavonoids, etc.) and are claimed to have a beneficial effect on health or medical conditions (Kalra 2003). Several of these nutraceuticals have shown to have a beneficial effect on a variety of pathological conditions, including, dyslipidemia, oxidative stress, mitochondrial dysfunction, etc. There is an increasing evidence that in certain pathologic states, the increased production and/or ineffective scavenging of reactive oxygen species (ROS) may play a critical role in many diseases (Robertson 2004). It has been suggested that enhanced production of free radicals and oxidative stress are the main causes for the development of diabetic complications. Nutraceuticals are potent antioxidants and anti-inflammatory agents. An overview of the possible targets of the nutraceuticals that could be used in the treatment of T2D and their related complications is given in Table 1.

Table 1

Nutraceuticals in the treatment of T2D (Kelsey et al. 2010; Mazzio et al. 2011; Omar et al. 2010; Schemmel et al. 2010).

Nutraceuticals with similar activities	Target/function	Rationale
α -Lipoic acid	CNS insulin	Potent inhibitor of glucose production
Phytosterols, PUFA	CNS leptin	Reduces food intake Increases gluconeogenesis
Bioactive proteins	CNS GLP1	Reduces hepatic glucose production
Resveratrol, Quercetin, chlorogenic acid	AMPK	Reduces hepatic glucose production
Quercetin, Vitamins B6, B12, Folic acid, EPA, α -lipoic acid, L-carnitine, 4-Hydroxy isoleucine (Fenugreek)	Dopamine	Improves insulin sensitivity
EGCG, caffeic acid	Serotonin	Improves glucose tolerance, increases glucose uptake into cells
EPA, curcumin	Inflammation	Since inflammation and glucose impairment are related
Bioflavonoids, Ellagic acid, EGCG, Cinnamic acid derivatives, Carotenoids, α -lipoic acid, vitamin C&E	Oxidative stress	Since ROS are implicated in most of the metabolic disorders
Garlic constituents, Guggul constituents	Blood lipid	Since lipid profile and glucose impairment are related
Kaempferol, leucocyanidin, hesperidin, Apin	Aldose reductase	Inhibition of polyol pathway

Long term treatment of type 2 diabetes and its complications requires alternation of conventional monotherapy with oral antidiabetic drugs (Jovanovic et al. 2004). Several oral drugs have been studied in combination and have been shown to improve glycemic control when compared to monotherapy. This review discusses the use of drug–drug and drug–phytochemical combinations for the treatment of diabetics. Understanding the effects of one on the other could pave the way for finding effective strategy for treatment of diabetics with less side effects and reduced toxicity.

Combination therapy

Historically, drug combinations have been used for treating diseases and reduce suffering. Attempts have been made to quantitatively measure the dose–effect relationships of each drug alone and in combinations and determine the type of effect of the combination (Bijnsdorp et al. 2011). The choice of the second agent should be based on individual characteristics. Reasonable combinations of drugs include a sulfonylurea plus metformin, a sulfonylurea plus an α -glucosidase inhibitor, a sulfonylurea plus a thiazolidinedione, metformin plus repaglinide, biguanide plus α -glucosidase inhibitor, and metformin plus a thiazolidinedione (Lin and Sun 2010).

Many of the phytomedicines in the drug market are whole extracts of plants because it is known that various components of individual or mixtures of herbs act in synergy and hence are a vital part of their therapeutic efficacy (Lin and Sun 2010). Medicatrix naturae – the power of self-preservation or adjustment has been the motto of traditional medicine and it always prescribes combination therapy (Tiware and Rao 2002).

Two drugs that produce almost similar effect when used together may sometimes produce enhanced, same or diminished effect. In this interaction there might be three different types of behaviors namely synergy, antagonistic and additive/indifferent. Different types of synergism in combination therapy are possible and they include (Wagner and Ulrich-Merzenich 2009):

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