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A novel management of diabetes by means of strong antioxidants' combination

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Abstract Despite the current existence and availability of synthetic drugs for the treatment of diabetes mellitus (DM), these medications are neither cheap nor completely effective. Furthermore, the long-term consumption of synthetic drugs may cause adverse effects, while those medications provided from natural sources are more affordable and have shown lesser adverse effects. The current belief is that oxidative stress plays a substantial role in the pathogenesis of diabetes and its complications. The characteristics of DM as a multifactorial disease are related to a deficit in the β-cells of the pancreas that results in defective production and release of insulin. Antioxidant therapy can protect β-cells from apoptosis and preserve their function. Therefore, the higher the antioxidant effects a compound might have, the higher the positive effects in diabetes anticipated. Our idea is that a combination of strong antioxidants might positively work in control of hyperglycemia by activating the production and release of insulin to the blood. In this scenario, if the strongest multi-herbal antioxidant complex called Setarud (IMOD™) is combined with curcumin and quercetin, then much stronger antioxidant activity with positive effects in the control of diabetes would be produced. To prove the idea, this combination has to be pharmaceutically prepared and then its safety and efficacy must be examined in preclinical and clinical studies.

Introduction

Diabetes mellitus (DM) is the most common health problem of the world in the current century. Nowadays more than 366 million people suffer from DM and 552 million are expected to be affected by diabetes by 2030 [1]. At the moment there is no doubt that DM and its related complications are associated with increased oxidative stress resulting from the imbalance in the production of free radicals such as reactive oxygen species (ROS) and the body's antioxidant defence sys-

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tem [2]. The ROSs have an important role in the aetiology of diabetes and its complications [3]. The characteristics of DM as a multifactorial disease are related to deficit in β-cell mass that leads to defects in production and release of insulin or even improper action of insulin in various organs [4]. The antioxidant therapy can preserve β-cell function by suppression of β-cell apoptosis [3].

Even though, currently, many drugs have been used for treatment of DM, many problems including the adverse effects are associated with their continuous use. Moreover, the high cost of these drugs is another issue in both developed and developing countries [5,6] for patients who must use them for a long time. Therefore, it seems very logical to think of alternative approaches in the management of diabetes. In the recent years, a number of studies have been conducted on the use of herbal/natural products in diabetes. Although most of these studies reported better antidiabetic effects with less side effects and lower cost than synthetic drugs, most of them have remained virgin [7,8]. Our team's studies in the last decade have shown that most antidiabetic herbs have high antioxidant power and can improve β-cell function and increase secretion of insulin from Langerhans islets [6,8–10]. On the other hand, a tight link between oxidative stress, triggering of an inflammatory cascade and pathogenesis of many chronic illnesses, particularly DM [11], has been proved in the recent years. Thus, any compound with good antioxidant and anti-inflammatory powers is fundamentally anticipated to show a good antidiabetic effect if used properly [8]. Our recent studies and systematic reviews brought up the idea that a combination of two or three or more strong antioxidants can have an additive antidiabetic effect [8]. In the present hypothesis, three natural compounds including Setarud (IMOD™), curcumin and quercetin are proposed for combination to result in a much better antioxidant and antidiabetic drug.

Setarud is a patented multi-herbal complex composed of *Rosa canina*, *Tanacetum vulgare*, *Urtica dioica*, containing selenium and urea treated by pulsed high frequency of an electromagnetic field [12]. Its effective antidiabetic activity has been shown in autoimmune experimental diabetes and also on the viability and function of islets based on *in vitro* studies [13,14]. Curcumin as diferuloylmethane or 1,6-heptadiene-3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl) is the active ingredient of the dietary spice turmeric, from the plant *Curcuma longa* that has a long history of use as a traditional medicine in China and India [15]. The chemical structure of curcumin is shown in Fig. 1. Curcumin was first introduced for its antibacterial activity, but later other characteristics including hypolipidaemic, antidiabetic, anti-inflammatory, antioxidant and anticancer activities were discovered [16]. Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a polyphenol classified as a bioflavonoid, and it is widely distributed in various plants, fruits and vegetables [17]. Its chemical structure is shown in Fig. 1. Beneficial effects of polyphenol-rich food on reduction of the risk of cardiovascular diseases and cancer have been shown in numerous prospective observational studies [18,19]. The antidiabetic effect of quercetin with reduction of blood glucose, promotion of Langerhans islets' regeneration and increasing insulin release have been demonstrated both *in vitro* and *in vivo* [20–23].

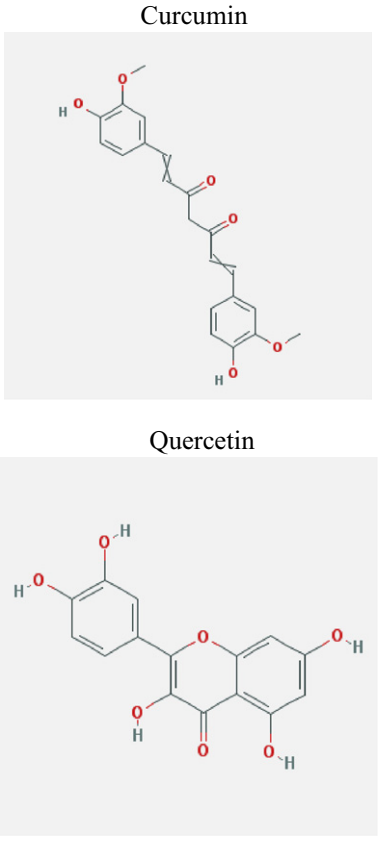

Figure 1 The chemical structure of curcumin and quercetin. Adapted from free PubChem database provided by National Center for Biotechnology Information, US National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894, USA.

Hypothesis

As mentioned above in addressing the current status in the treatment of DM and the need for development of 'new antidiabetic drugs' with lower price and higher safety and efficacy, we aimed to hypothesise a 'novel treatment of diabetes by means of combined antioxidant compounds'. Although the induction of possible additive or synergistic effects of phytochemicals is not a new idea in general [24], specifically, no idea has been raised on the combination of Setarud, curcumin and quercetin in a specific disease such as diabetes. Using these substances, one can assume that the new, generated compound could be appropriate not only for ameliorating DM but also for other diseases in which oxidative stress plays a role. Our idea is to combine Setarud with curcumin and quercetin in the best possible formulation to provide a lyophilised form with sufficient solubility. If lyophilised, there will be no or little problem with the absorption of the combination form and hopefully a better antidiabetic effect will be produced [16,25]. We also assumed that this compound can protect Langerhans islets from free radical damage and improve islets' function in terms of better performance in the production and release of insulin to control hyperglycemia.

Evaluation of the hypothesis

First, work should be carried out on this combination to prepare a mixture with the best appearance, solubility and bioavailability. Then, the antioxidant power of the combination must be compared to each compound alone and to a standard.

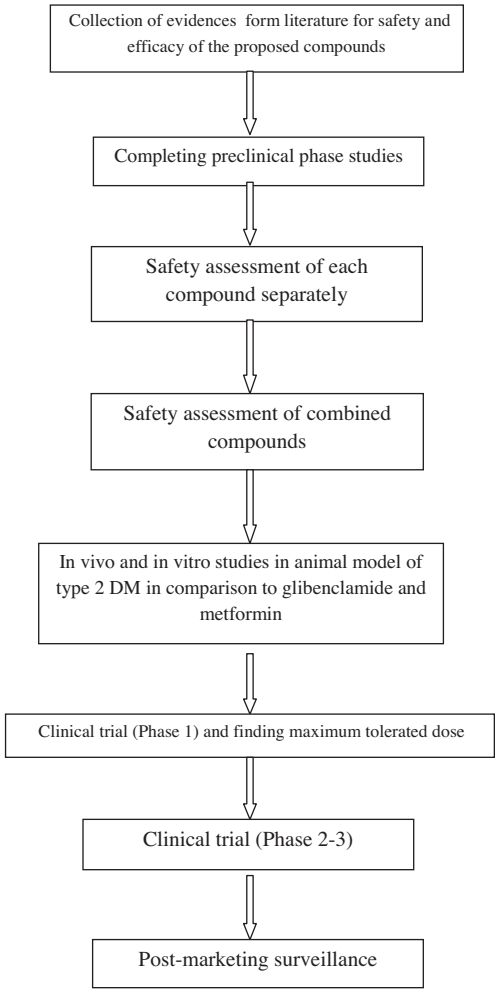

Figure 2 Flowchart of practicing the hypothesis.

After that, an animal model of type 2 DM should be induced by use of streptozocin (STZ) or alloxan and the compound must be tested in these models in order to assess the potential of the mixture in comparison to each compound alone and to positive standards such as an oral hypoglycaemic agent (glibenclamide or metformin). The preference is to use both standards as they work by different mechanisms. A pilot study is needed to reach the optimal dose of the combination compound that has the highest efficacy and safety. If preclinical studies were successful and revealed worthwhile effects, then clinical studies would be designed to start the clinical trial phases of I–IV. The above-mentioned processes are shown as a flowchart in Fig. 2.

Discussion

In fact, Setarud has been already known for its direct and indirect antioxidative effects through reduction of free radicals and inhibition of inflammatory mediators [26–29]. The immunomodulatory effect of Setarud results in attenuation of tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), myeloperoxidase and lipid peroxidation in many inflammatory conditions including colitis, immune model of DM, islet cell transplantation and polycystic ovary syndrome [14,26,27,29,30]. Its anti-inflammatory effects are also shown in patients with oral Lichen planus, severe sepsis and acquired immunodeficiency syndrome (AIDS) [28,31,32]. The beneficial anti-free-radical activity and usefulness for treatment of oxidant-related diseases are shown in the herbal constituents of Setarud [6]. In addition, several studies have shown the separate antioxidative activity of the main components of Setarud and other strong antioxidants with the same components such as *U. dioica*, *Teucrium* and selenium [33–36]. Fortunately, the safety of Setarud has been proved in preclinical and clinical studies [37,38]. Administration of 400 mg day^{-1} Setarud for 3 months showed an anti-inflammatory effect in patients with oral Lichen planus [28]. The maximum tolerated dose in intravenous (IV) infusion of Setarud in HIV-infected patients was found to be 10 ml day^{-1} [38].

Curcumin has direct and indirect molecular targets which are shown in Table 1 [16,39], though the major targets are key survival pathways regulated by nuclear factor κB (NF-κB) and protein kinase B, as well as cytoprotective pathways dependent on nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Nrf2, also known as NFE2L2, is a transcription factor that in humans is encoded by the NFE2L2 gene [39]. The pro-inflammatory transcription factors NF-κB and signal transducer and activator of transcription 3 (STAT3) are major mediatory effectors in inflammatory responses acting through modulation of pro-inflammatory cytokines [16]. The inhibitory effect of curcumin on pro-inflammatory cytokines and lipid peroxidation has been already demonstrated [16]. Furthermore, its antioxidative and free-radical-scavenger activities have been shown in rats [16]. Animal studies have shown its beneficial effects on various diseases including obesity, cancer (especially colon cancer), wound healing, arthritis, psychiatric disorders such as depression and Alzheimer's, neurological,

Table 1 Direct and indirect molecular targets of curcumin.

Indirect molecular targets
–Transcription factors (16, 41)
–Enzymes (16, 41)
–Growth factors (16, 41)
–Receptors (16, 41)
–Cell-cycle regulatory proteins (16)
–Inflammatory molecules or mediators (16, 41)
–Protein kinases (16, 41)
–Drug resistance proteins (16)
–Adhesion molecules (16, 41)
–Cell survival proteins (16, 41)
–Chemokines and chemokine receptor (16)
–Invasion and angiogenesis biomarkers (16)
–Heat shock protein 70 (16, 41, 42)
–Metal ions, particularly iron and copper (42)
–Protein reductase (41)
Direct molecular targets
–Inflammatory molecules (16, 41)
–Cell survival proteins (16)
–Protein kinases (16, 41, 42)
–Protein reductases (16)
–Enzymes: histone deacetylase, glyoxalase I, xanthine oxidase, proteasomes, HIV1 integrase, HIV1 protease, sacro/endoplasmic reticulum Ca^{2+}-ATPase, DNA methyltransferase 1 (16, 42)
–FtsZ protofilaments (16)
–Carrier proteins (16)
–Metal ions (16)

pulmonary and cardiovascular diseases [16,40,41]. Nearly 50 clinical trials have been conducted for assessing the potential effects of curcumin in human diseases such as cancer, skin and eye disorders and inflammatory conditions [16]. There are strong evidences from animal studies regarding the positive effects of curcumin in diabetic nephropathy, diabetic retinopathy and insulin sensitivity [16,42]. All the evidences are in support of the idea that curcumin in adjuvant therapy of type 2 DM might be helpful through its antiangiogenic and antitoxic activities [16,42]. The main problem of both Setarud and curcumin is their low bioavailability, which calls for use of some rather new techniques including employment of nanoparticles, liposome encapsulation, micelles, phospholipid complexes, structural analogues, etc. [16,43]. Combination of curcumin with some antineoplastic drugs or with certain diet-derived polyphenols such as epigallocatechin-3-gallate, piperine and genistein has already demonstrated synergistic effects [44]. No animal or human studies have reported any toxic effect even at very high doses of curcumin [45,46]. In healthy human volunteers, no dose-limiting toxicities by a single dose of curcumin ranging from 500 to 1200 mg day^{-1} was observed [46]. In another study, as little as 150 mg twice a day oral administration of curcumin in humans showed anti-inflammatory effects [47].

On the other hand, anti-free-radical activity and inhibitory effects of quercetin on oxidation of bio-molecules have been fairly shown *in vitro* and *in vivo* [48,49]. Exposure of isolated islets of rat to certain flavonoids, particularly quercetin, enhances insulin secretion by 44–70% [50]. Its effect on controlling the fasting and postprandial blood glucose is shown in animal models of DM [51]. Other potential effects of quercetin are iron chelation, preservation of nitric oxide, inhibition of secretion of secretory phospholipase A2 (SPLA2) as stimulator of tumour formation in colorectal, breast and prostate cancers, anti-inflammatory effects, reduction of activity of transcription factors and NF-κB, cardiac, hepatic and renal protection, protection of β-cells against oxidative damage, anti-lipid peroxidation and antiproliferative effects, protection of red blood cell membrane against haemolysis and acting as a chemopreventive agent. Further, improvement of several diseases such as metabolic syndrome, upper respiratory infection and rheumatoid arthritis by quercetin has been reported [17,24,25,52]. In one study, combination of curcumin and quercetin successfully restored liver function and architecture, normalised kidney functions and inhibited oxidative injury induced by paracetamol [51]. Within the flavonoid family, quercetin has the strongest antioxidant and anti-inflammatory activities [52,53]. Depending on the type of glycoside in food source, the bioavailability

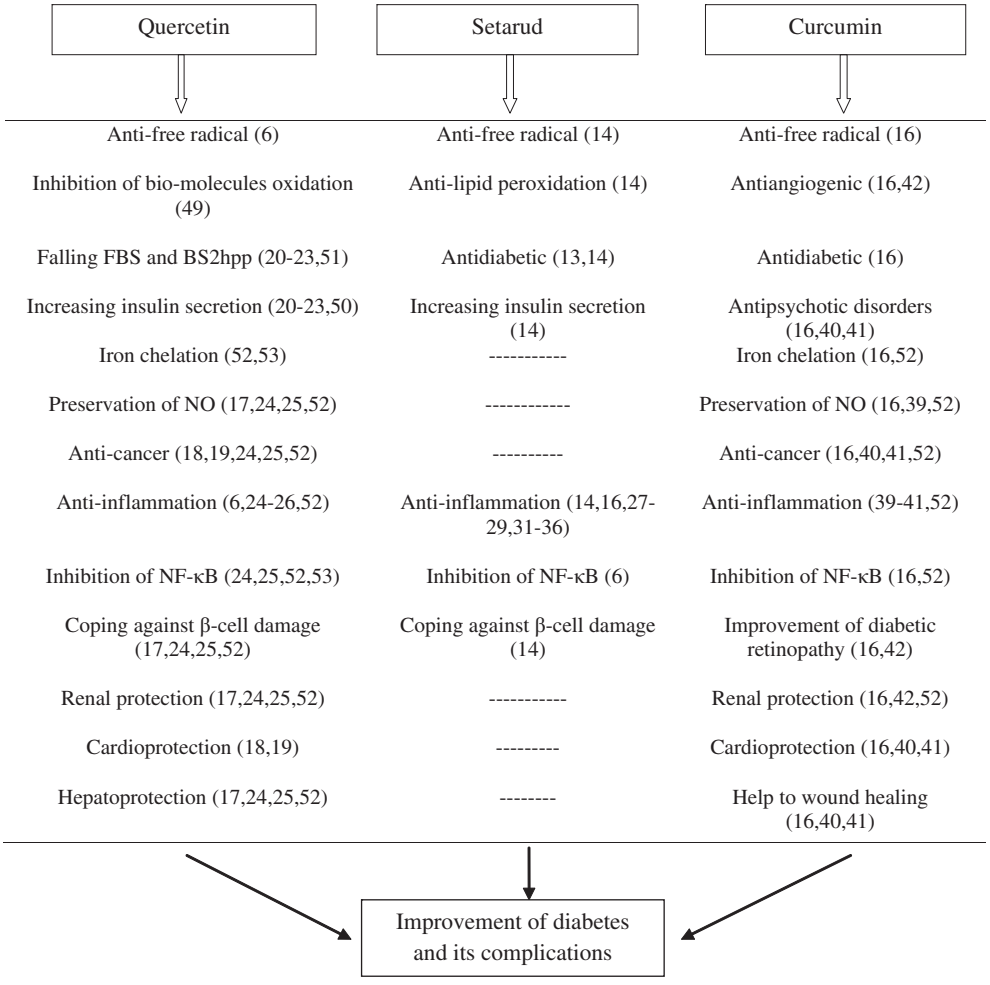

Figure 3 Schematic probable synergistic effects of combination Setarud, curcumin and quercetin in management of oxidative stress as main etiology of diabetes and its complications.

of quercetin differs among fruits and vegetables [54]. Further, its half-life can increase by repeating intakes from 11 to 28 h. However, contrary to Setarud and curcumin, quercetin has a very good bioavailability, even better than other polyphenols. Its safety has been already confirmed in humans [25]. Quercetin was trialed in doses that ranged from 150 mg daily in subjects with metabolic syndrome to 2000 mg day^{-1} in sarcoidosis patients [25]. A schematic suggestion of the synergistic effects of the proposed combination on oxidative stress as the main aetiology of diabetes and its complications is shown in Fig. 3.

Conclusion

Through an alternative pharmacological approach for the control of diabetes, a combination of Setarud with curcumin and quercetin might be an appropriate treatment.

Overview Box

First question: What do we already know about the subject?

Diabetes is one of the most common health problems of the world. Most current antidiabetic drugs have side effects and are costly. Oxidative stress plays a major role in the physiopathology of diabetes and results in damage to Langerhans islets and decrease of insulin secretion. Any compound with higher antioxidative activity could be an effective antidiabetic drug.

Second question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

Our hypothesis introduces a novel natural mixture that might improve function of pancreatic Langerhans islets ending up with better management of diabetes mellitus.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

First, the *in vitro* and *in vivo* studies in animal models of type 2 diabetes should be tested to assess the efficacy, bioavailability, the optimal dose and the safety of the mixture. Then, further trials should be continued in clinic to complete phases 1–4 of drug approval.

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