Literature Review on Effects of Ingredients of Churu-5, a Bhutanese Traditional Concoction on Diabetes Mellitus.

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Abstract

This study reports a literature review aimed to assess studies related to the efficacy of various herbs in diabetes mellitus used in Bhutan. The incidence of Diabetes Mellitus is rising and many of the diabetics frequently use herbal treatments along with modern medical treatment for glycaemic control and improve their well-being. An electronic database (Pub med) was searched for 2002-2014 period and 31 related articles were assessed. Many studies-mostly animal trials- have been conducted in this field. Among the herbs, we searched for *Phyllantus emblica* Linn., *Curcuma longa* Linn., *Berberies aristata* Berberidaceae, *Tribulus terristries* Linn., and *Thlaspi arvense* Linn. Their chemical compositions, ethno medical uses and anti diabetic activities were summarized.

Introduction

Herbal medicine is one of the methods of traditional therapy that plays a key role in the treatment of various diseases specifically in diabetes mellitus, hyperlipidemia and obesity that are growing rapidly in the world (Ranjbar et al., 2013). Diabetes mellitus is an endocrinological disorder arising from insulin deficiency or due to ineffectiveness of the insulin produced by the body. This results in high blood glucose and with time, to neurological, cardiovascular, retinal and renal complications. It is a debilitating disease and affects the population of every country of the world. Around 200 million people of the world suffer from this disease and this figure is projected to rise to 300 million in the coming years. The disease cannot be cured with allopathic medicine as the drugs used do not restore normal glucose homeostasis and moreover have side-effects (Rahmatullah et al., 2012). This review is carried out in order to assess the efficacy of traditional herbs namely *Phyllantus emblica* Linn. (*P. emblica*), *Curcuma longa* Linn. (*C. longa*), *Berberies aristata* Berberidaceae (*B. aristata*), *Tribulus terristries* Linn. (*T. terristries*) and *Thlaspi arvense* Linn. which are being used as the ingredients in the Bhutanese traditional medicine concoction, named churu-5.

Method

We searched the Pub Med, from 2002 to March 2013.
The terms used were as follows: ‘phyllantus emblica and diabetes mellitus’, ‘curcum longa and diabetes mellitus’, ‘Berberies aristata and diabetes mellitus’, ‘tribulus terristries and diabetes mellitus’, and ‘thlaspi arvense and diabetes’.

Results

In the search using the keywords ‘phyllantus emblica and diabetes mellitus’’ 19 articles were found. Likewise 48 articles were found with the keyword ‘curcuma longa and diabetes mellitus’ but only 45 articles were of within 2002. 2 articles were found with the keywords

'berberies aristata and diabetes mellitus' and 4 articles with 'tribulus terristries and diabetes mellitus'. As for the 'thlaspi arvense and diabetes mellitus' no articles were available.

P. emblica (*Emblica officinalis,* amla, gooseberry*)*

*P.*emblica extract demonstrated significant antiplatelet activity (Fatima et al., 2013). *P.* emblica are the plants widely used in Ayurveda for their anti-hyperglycemic activity. Additionally their anti-oxidant properties have been scientifically validated in various experimental *in vitro* and *in vivo* models. *P.* emblica extract significantly inhibited malondialdehyde release from rat inculinoma cells indicating protective effect against streptzotocin-induced oxidative damage. They also exhibited a dose dependent anti-apoptotic effect (Kalekar et al., 2013). *P.emblica* is known for its antioxidant and antihyperlipidemic activity. *P.emblica* significantly improved endothelial function and reduced biomarkers of oxidative stress and systemic inflammation in patients with type 2 diabetes mellitus, without any significant changes in laboratory safety parameters (Usharani et al., 2013). In traditional Indian medicine, all parts of *Emblica officinalis* Gaertn. (*E. officinalis*) plant including the fruit, seed, leaves, root, bark and flowers are used in various herbal preparations for the treatment of diabetes mellitus, chronic diarrhea, anti-inflammatory and antipyretic. The hydro methanolic extract of leaves of *E. officinalis* was seen to effectively normalize the impaired antioxidant status in streptozotocin-induced diabetes at dose dependent manner compared to the glibenclamide-treated groups. The extract exerted rapid protective effects against lipid peroxidation by scavenging of free radicals and reducing the risk of diabetic complications (Nain et al., 2012). *P. emblica* is also one of the herb which have been shown to possess widespread pharmacological application against multitude of diseases namely cancer, diabetes, liver disorders, and oxidative stress. The study demonstrated that these extract have potential hepatoprotective activity which is mainly attributed to the antioxidant potential, which might occur by reduction of lipid peroxidation and cellular damage (Hiraganahalli et al., 2012). The plant *E. officinalis* has been used for thousands of years as a traditional Indian Ayurvedic preparation for the treatment of diabetes in humans. Extracts from this plant have been shown to be efficacious against the progression of cataract in a diabetic rat model (Puppala et al., 2012). Fenugreek and composite supplements containing *E. officinalis* showed the most consistency in lowering fasting blood sugar or glycated hemoglobin levels in diabetic patients in a study done by Deng (2012). *P. emblica* is one of the twelve herbs used by Marakh sect of the Garos residing in Mymensingh district of Bangladesh for treatment of diabetes for it possess antidiabetic and/or antioxidant properties (Rahmatullah et al., 2012). Study found that oral administration of a 1:1 mixture of epigallocatechin gallate and amla extract for 3 months significantly improved antioxidant defense as well as diabetic and atherogenic indices in uremic patients with diabetes (Chen et al., 2011). *E. officinalis* fruit in normal and diabetic human volunteers indicated a significant decrease ($p<0.05$) in fasting and 2-h post-prandial blood glucose levels. Both normal and diabetic volunteers receiving 2 or 3 g *E. officinalis* powder significantly ($p<0.05$) improved high-density lipoprotein-cholesterol and lowered low-density lipoprotein-cholesterol levels (Akhtar et al., 2011). Combination of insulin with *E. officinalis* extract not only attenuated the diabetic condition but also reversed neuropathic pain through modulation of oxidative-nitrosative stress in diabetic rats (Tiwari et al., 2011). Methanol extract of *T. bellerica* and *E. officinalis* fruits exhibited maximum scavenging activity against diphenylpicrylhydrazyl, superoxide, hydroxyl and nitric oxide radicals. Liquid chromatography-mass spectroscopy analysis revealed that methanol extract of *E.officinalis* contains ascorbic acid as the major compound (Nampoothiri et al., 2011). Treatment with *E. officinalis* extract and quercetin in diabetic rats showed significant increase in tail flick latency in hot immersion test and pain threshold level

in hot plate test compared to control rats. The changes in lipid peroxidation status and anti-oxidant enzymes (superoxide dismutase and catalase) levels observed in diabetic rats were significantly restored by *E. officinalis* extract and quercetin treatment. Both, *E. officinalis* extract and quercetin attenuated diabetic induced axonal degeneration. The study provides experimental evidence of the preventive and curative effect of *E. officinalis* on nerve function and oxidative stress in animal model of diabetic neuropathy. Since, *E. officinalis* fruit is already in clinical use for diabetic patients it may be evaluated for preventive therapy in diabetic patients at risk of developing neuropathy (Kumar et al., 2009). *P. emblica* is one of the Thai medicinal plants, traditionally used as alternative treatments in diabetes and seen to have strong antioxidant which have free radical scavenging activity and might be used for reducing oxidative stress in diabetes (Kusirisin et al., 2009). It was reported that the aqueous extract of *E.officinalis* and its constituent tannoids inhibit aldose reductase in vitro and prevent hyperglycemia-induced lens opacification in organ culture. The study suggest that Emblica and its tannoids supplementation inhibited aldose reductase activity as well as sorbitol formation in the lens. The results also point out that Emblica and its tannoids might counter the polyol pathway-induced oxidative stress as there was a reversal of changes with respect to lipid peroxidation, protein carbonyl content, and activities of antioxidant enzymes. Emblica also prevented aggregation and insolubilization of lens proteins caused by hyperglycemia (Suryanarayana et al., 2007).

Amla extracts showed strong free radical scavenging activity. Amla also showed strong inhibition of the production of advanced glycosylated end products. The oral administration of amla extracts to the diabetic rats slightly improved body weight gain and also significantly alleviated various oxidative stress indices of the serum of the diabetic rats. The elevated serum levels of 5-hydroxymethylfurfural, which is a glycosylated protein that is an indicator of oxidative stress, were significantly reduced dose-dependently in the diabetic rats fed amla. Similarly, the serum level of creatinine, yet another oxidative stress parameter, was also reduced. Furthermore, thiobarbituric acid-reactive substances levels were significantly reduced with amla, indicating a reduction in lipid peroxidation. In addition, the decreased albumin levels in the diabetic rats were significantly improved with amla. Amla also significantly improved the serum adiponectin levels. These results forms the scientific basis supporting the efficacy of amla for relieving the oxidative stress and improving glucose metabolism in diabetes (Rao et al., 2005).

Methanolic extract (75%) of *Terminalia chebula*, *Terminalia belerica*, *E.officinalis* and their combination named 'Triphala' (equal proportion of above three plant extracts) are being used extensively in Indian system of medicine. They were found to inhibit lipid peroxide formation and to scavenge hydroxyl and superoxide radicals in vitro. Oral administration of the extracts (100 mg/kg body weight) reduced the blood sugar level in normal and in alloxan (120 mg/kg) diabetic rats significantly within 4 h. Continued, daily administration of the drug produced a sustained effect (Sabu & Kuttan, 2002).

C. longa (*turmeric*)

Curcumin as a natural flavonoid from C. longa has considerable effects on nervous system such as, antidepressant, antinociceptive and neuroprotective effects. Curcumin can be considered as a new therapeutic potential for the treatment of diabetic neuropathic pain and the activation of opioid system may be involved in the antinociceptive effect of curcumin (Banafshe et al, 2013).

C. longa commonly known as turmeric has been recently discovered to have renoprotective effects on diabetic nephropathy (Huang et al., 2013). Curcumin acts on adipocytes to suppress the lipolysis response to tumor necrosis factor-α and catecholamines. The antilipolytic effect could be a cellular basis for curcumin decreasing plasma free fatty acids levels and improving insulin sensitivity (Xie et al., 2012). Turmeric volatile oils inhibited glucosidase enzymes more effectively than the reference standard drug acarbose (Lekshmi et al., 2012). The Ayurvedic medicine "Rajanyamalakadi" containing C. longa, *E. officinalis* and *Salacia oblonga* has showed significant antidiabetic, hypolipidemic and antioxidant effects. In addition to that significant ameliorating effects on the elevated serum *aspartate aminotransferase* and *alanine aminotransferase* activities were also demonstrated by the treatment. The nutraceuticals present in the drug like terpenoids, polyphenols, curcumin etc are responsible for the medicinal effects (Faizal et al., 2009). Turmeric and curcumin appear to be beneficial in preventing diabetes-induced oxidative stress in rats despite unaltered hyperglycemic status (Suryanarayana et al., 2007). Chronic treatment with curcumin significantly attenuated both renal dysfunction and oxidative stress in diabetic rats (Sharma et al., 2006). Turmeric and curcumin are effective against the development of diabetic cataract in rats (Suryanarayana et al., 2005). The chemistry of *C. longa* includes curcuminoids and sesquiterpenoids as components, which are known to have anti-oxidative, anticarcinogenic, and anti-inflammatory activities (Nishiyama et al., 2005).

B. aristata

Berberine, an isoquinoline alkaloid isolated from medicinal plants such as B. aristata, *Coptis chinesis*, *Coptis japonica*, *Coscinium fenestatun*, and *Hydrastis canadensis*, is widely used in Asian countries for the treatment of diabetes, hypertension, and hypercholesterolemia. *In vivo*, berberine showed the same hypoglycemic activity as metformin, an established hypoglycemic drug. Berberine has the potential to modify the expression of cytochrome P450 enzymes (CYPs) by either suppression or enhancement of CYPs' levels. Consumption of berberine as an anti-hyperglycemic compound by diabetic patients might provide an extra benefit due to its potential to restore the expression of Cyp2e1, Cyp3a, and Cyp4a to normal levels (Chatuphonprasert et al., 2009). B. aristata DC root is used in traditional medicine for a number of ailments including metabolic disorders. The extract of B. aristata (root) has strong potential to regulate glucose homeostasis through decreased gluconeogenesis and oxidative stress (Singh & Kakkar, 2009).

T. terristries

The extract of the *T. terristries* showed moderate cytotoxicity against HeLa cell line and considerable antioxidant potential (Gacche & Dhole, 2011). The extracts of *T.* terrestris significantly decrease fasting glucose level in diabetic rats. The extracts also caused a significant decrease in the levels of glycosylated hemoglobin, total cholesterol, triglycerides and low density lipoprotein cholesterol (Tantawy & Hassanin, 2007).

T. terrestris is used in the Arabic folk medicine to treat various diseases. The tested *T. terrestris* extract significantly decreased the levels of alanine aminotransferase and creatinine in the serum ($p<0.05$) in diabetic groups and lowered the malondialdehyde level in liver ($p < 0.05$) in diabetic and ($p < 0.01$) non diabetic groups. On the other hand, levels of reduced glutathione in liver were significantly increased ($p<0.01$) in diabetic rats treated with *T. terrestris*. Histopathological examination revealed significant recovery of liver in herb-treated

rats. This investigation suggests that the protective effect of *T. terrestris* for streptzotocin-induced diabetic rats may be mediated by inhibiting oxidative stress (Amin et al., 2006).

The level of serum glucose could be significantly reduced by saponin from T. terrestris, which was the rate of 26.25% and 40.67% in normal mice and diabetic mice in respectively. The level of serum triglyceride could be reduced 23.35%. Serum superoxide dismutase activity of the mice was increased by the saponin (Li et al., 2002).

Thlaspi arvense to our best knowledge has not been shown to have any antidiabetic properties yet.

Conclusion

These plants are found to be with a high citation values which has given some leads for the further pharmacological research. More importantly, healthcare professionals caring for diabetic patients need to be aware of phytotherapy to incorporate phytomedicine into their practices and should undertake more responsibility in relation to these kinds of therapies that are commonly-used throughout the world (Parildar et al., 2011).

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