

**TOXICOLOGY OF COMPLEMENTARY AND ALTERNATIVE MEDICINES
(CAM) IN DIABETES PATIENTS – A REVIEW**

Akanksha Rathi* and Saurabh Sharma

Baba Saheb Ambedkar Medical College and Hospital, Delhi, India

ABSTRACT

Diabetes is a modern epidemic affecting both developed and developing economies. Diabetes is a high inertia and low emergency disease and patients often struggle to maintain good glycemic control. They often resort to complementary and alternative therapies in hope of improved disease outcome and no side effects. The trend for the use of CAM has been upward in most of the world prevalence ranging between 30%-57%. In India, the use of CAM is as high as 67%. The commonly used herbs like cinnamon, bitter gourd and fenugreek. However, few studies have shown that various CAM agents are not completely free from side effects. They can lead to drug interactions, hypoglycemic episodes, toxicity, and other side effects. Thus, there is a need to improve awareness about CAM amongst both patients and healthcare providers. This review article has been written to throw light on the toxicity profile of various CAM agents.

Keywords: CAM, Diabetes, Fenugreek, Bitter Gourd, Cinnamon.

INTRODUCTION

India is progressing towards being the diabetic capital of the world with 62 million diabetic patients, and the figure is expected to increase to 79.4 million by 2030 (Rathi *et al.*, 2017). There have been massive strides taken in diabetes care and management but it continues to be a public health concern as it causes substantial morbidity and mortality and long-term complications (Yeh *et al.*, 2002). The grave concern we are faced with is that diabetes is an important risk factor for the development of cardiovascular disease (CVD) and cases of CVD are also expected to increase with increasing rates of both childhood and adult diabetes (Yeh *et al.*, 2002). Good glycemic control is imperative to keep diabetic complications at bay (Rathi *et al.*, 2017). However, patients do not get good control many a times with conventional therapies. The available conventional treatment has its own limitation in the form of efficacy and safety and thus this has led to the emergence of alternative therapy for more safety and efficiency (Mirhoseini *et al.*, 2013). There is an ever-growing interest in complementary and alternative medicine (Yeh *et al.*, 2002). The National Centre for Complementary and Alternative Medicine of the United States defines CAM as “a group of medical and health care systems, practices and products that are not presently considered to be part of conventional medicine” (Medagama *et al.*, 2014). The interest in CAM is obvious not just amongst the patients or public but also among intellectual groups of researchers, care providers and health educators (Payne, 2001 and Berman *et al.*, 1999). It is interesting to know that the mainstay of treatment of diabetes, the drug metformin, was first obtained from French lilac, which is an herb (Oubre *et al.*, 1997). This emerging trend seen in the use of CAM is majorly an attempt of patients to improve their diabetic outcomes, quality of life, and general well-being. In addition it has been stated that, “CAMs have gained academic, industrial and economic interest due to its high prevalence of use” (Medagama *et al.*, 2014).

CAM USE – PREVALENCE

The main cause of CAM use is that it is a general perception that CAM agents will have a lower risk profile for adverse events than conventional medicines (Medagama *et al.*, 2014). Not just developing nations, but the interest is also growing among the developed ones like USA, where there has been a 380% increase in use of herbal remedies (Vuksan *et al.*, 2000). Looking at the worldwide trend for the use of the same, the prevalence has increased by 30-57% in last few years (Bell *et al.*, 2006). India, the country that is said to be the origin of Ayurveda (ancient science about herb medication), recorded a high use of CAM (67%) among diabetic patients (Kumar *et al.*, 2006). The most commonly used CAM therapy being naturopathy of herbalism is used by over 97% of CAM users (Kumar *et al.*, 2006). Also, it is seen that due to the nature of disease, side effects of conventional medicines, poor diabetic outcomes – diabetic patients are 1.6 times more likely to use CAM (Gawwow *et al.*, 2006).

CAM USE – POSSIBLE TOXICITIES

The various CAM therapies being used are Ayurveda, homeopathy, acupuncture, spiritual prayers, yoga, massages, hypnosis and aromatherapy (Yeh *et al.*, 2002). However, the most widely studied are the toxic effects of some herbal remedies. There are 3 herbs that re widely used in India to treat or control diabetes – Cinnamon, Bitter Gourd and Fenugreek.

Cinnamon is known to have anti-diabetic, anti-oxidant properties, anti-inflammatory and anti-bacterial properties (Brahmachari *et al.*, 2009 and Aggarwal *et al.*, 2010). Few trials have shown that it can lead to reduction in fasting blood glucose and lipids. Few safety trials in animals show that it has no toxic effects on liver but as far as kidney is concerned, the findings are obscure (Medagama *et al.*, 2014).

Bitter gourd is another herb that has high use among diabetics as a CAM therapy.

It has been evaluated that just like cinnamon, bitter gourd (whole plant including fruit) also has multiple properties like anti-diabetic, anti-viral, anti-bacterial and anticancer properties (Grover *et al.*, 2004). Though no studies have found any serious adverse events with it's use, few studies show that the plant possesses hypoglycemic effects including an isolated report of hypoglycemic coma in a child consuming bitter gourd (Medagama *et al.*, 2014). Dans *et al.* reported minor side effects like abdominal pain and diarrhea in patients consuming it (Dans *et al.*, 2007).

The third herb frequently used is Fenugreek, whose leaves, chemical extracts and shoots have shown anti-oxidant, anti-diabetic and hypocholesterolaemic properties (Haber *et al.* 2013). Like bitter melon, fenugreek taken orally can cause mild gastrointestinal disturbances like diarrhea, dyspepsia, abdominal bloating and flatulence and hypoglycaemia (Medagama *et al.*, 2014 and Madar *et al.*, 1988). Few reports have also revealed episodes of hypokaleamia, dizziness and increased frequency of urination (Haber *et al.* 2013).

Table 1: The possible toxicities of other CAM agents are summarized.

CAM Agent	Possible Toxicity
Opuntia streptacantha (prickly pear cactus, nopal)	<ul style="list-style-type: none"> Abdominal disturbances like loose stools, nausea and fullness (Birdee <i>et al.</i>, 2010). Additive effects when used with conventional therapy (Geil <i>et al.</i>, 2008).
Panax ginseng, P.quiquefolius (ginseng)	<ul style="list-style-type: none"> Can react with anti-coagulation and anti-platelet medication (Birdee <i>et al.</i>, 2010) Can have estrogenic effects leading to breast tenderness, excessive bleeding or amenorrhea, impotence, high BP and insomnia (Birdee <i>et al.</i>, 2010). Additive effects when used with secretagogues (Geil <i>et al.</i>, 2008).

Alpha-lipoic acid	<ul style="list-style-type: none"> • Can cause allergic reactions like rashes, itching etc. (Smith <i>et al.</i>, 2014). • Thyroid function needs to be monitored while using alpha-lipoic acid in thyroid patients (Birdee <i>et al.</i>, 2010).
Omega-3 fatty acids	<ul style="list-style-type: none"> • Risk of hypoglycemia increases when used with conventional medicines like metformin, sulphonylureas and insulin (http://umm.edu/health/medical/altmed/supplement/omega3-fattyacids). • Intake needs to be restricted to less than 3 grams as excessive use can increase risk of bleeding and LDL (Birdee <i>et al.</i>, 2010 and Riediger <i>et al.</i>, 2009). • One should be aware that excessive use also carries the risk of methyl-mercury contamination as omega-3 fatty acids are derived from fishes (Birdee <i>et al.</i>, 2010 and Riediger <i>et al.</i>, 2009).

CAM USE – CONCERNS

Since some studies have reported toxicity involving CAM therapies in individuals with diabetes, there indiscriminate use raises several concerns. One of the major concerns is that in diabetic patients the quality of life was not found to improve with CAM therapy. On the contrary, more use of CAM was associated with more deteriorated quality of life (Spinks *et al.*, 2014). This can be due to that patients have to take multiple medicines that interact with each other (Spinks *et al.*, 2014).

Other important concerns related to CAM use are:

- Patients using CAM might skip or cease to take medicines (Alfian *et al.*, 2016).
- Often patients stop insulin injections to start the CAM therapy, which leads to poor outcomes (Yeh *et al.*, 2002).
- If taking CAM with conventional medicines, they are at risk of hypoglycemia (Birdee *et al.*, 2010).
- Although CAM therapy is being used for various diseases or general well being since times immemorial, their use is not completely devoid of side effects (Kesavadev *et al.*, 2017).
- Patients have minimal knowledge about CAM and its toxicity and are heavily dependent on family and friends for suggestions.
- Patients tend to hide the use from their practicing physicians in fear of criticism.
- Safety profile of CAM is not completely known and sporadic and only heterogeneous studies are available.
- Widespread misconception exists that CAM is absolutely free from side effects.
- Conventional therapies are often unaffordable (Kesavadev *et al.*, 2017).
- Use of CAM may delay the use of effective modern conventional treatments.
- Adverse effects on health can arise due to interaction of CAM & conventional medicines, adulteration of CAM agents with heavy metals or other harmful reagents, or due to presence of excessive amounts of active ingredients in the product Guthrie *et al.*, 2008, Marchetti *et al.*, 2007 and Rehman *et al.*, 2015).

- There is a major scarcity of good quality and strictly controlled, efficacy and safety trials and no consideration has been given to see their safety in vulnerable population groups like pregnant females, children, or seriously ill patients (Kesavadev *et al.*, 2017).
- Government endorsement of CAM products lacking adequate safety trials.

CONCLUSIONS AND RECOMMENDATIONS

Due to such high prevalence of use and rising concerns over safety and efficacy of CAM therapy, there is an urgent need of conducting well-designed, long-term and good quality clinical trails (Medagama *et al.*, 2014). The current findings do not provide a strong basis for use of CAM in diabetes and hence it is important that the healthcare provider be also aware about the increasing use of the same (Kesavadev *et al.*, 2017). There is also increased need of improved awareness about CAM amongst the healthcare providers. They should keep in view that almost 50% of diabetic patients might be taking CAM and so they should improve communication with the patients. They should listen empathetically and keep in mind the finances, while prescribing conventional medicines. New and recently developed conventional medicines are most costly and should be spared for affording patients. Also, patients with diabetes should be made aware that some therapies are not doing any good rather might even be harmful if taken for a long time. If the patient is adamant on using CAM therapy then such patients should be closely monitored for side effects of the CAM components and should be alerted about possible contraindications. They should also be made aware about the possible interactions between CAM and conventional drug therapy. The government funded organizations should conduct extensive safety trials in humans before endorsing CAM products as people often, have a high trust quotient when the government endorsement is involved. Thus, their trust should not be played with and a true picture should be kept in front of them. Awareness programs on judicious use of CAM therapy will be advantageous for diabetic patients and they will be encouraged to share the information of CAM use with their healthcare provider. This is important to monitor their health outcomes and identify any adverse effects. When strictly controlled clinical trials will be done then various CAM practices and products will be reevaluated and the useful CAM therapies can be incorporated with conventional therapies to improve treatment outcomes, patient compliance and patient satisfaction. Fortunately, many agencies such as the National Center for Complementary and Alternative Medicine have recognized the need for further investigation, and research on CAM therapies that have potential benefits for diabetes is beginning to emerge (Payne, 2001, Vuksan *et al.*, 2000 and Shane-McWhorter L, 2001).

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Correspondence Author:

Akanksha Rathi *

Baba Saheb Ambedkar Medical College & Hospital, Delhi, India

E-mail: akanksharathi.dr@gmail.com

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