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# RECENT PATENT TECHNOLOGIES OF *TINOSPORA CORDIFOLIA* FOR ANTI-DIABETIC POTENTIAL : A REVIEW

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## Abstract

Diabetes Mellitus has been considered an epidemic with great threat of other illness and death by the World Health Organization. The treatment of this pathology consists of glycemic control, which can be done by oral hypoglycemic agents, insulin therapy, dietary guidance, regular physical activity, and psychosocial support. In addition, other adjuvant treatments are employed, such as phototherapy, and one of the most used plants is *Tinospora cordifolia*. In the current review, patents using *Tinospora cordifolia* for the Diabetes Mellitus treatment have been analyzed and discussed. Although there are some phytotherapy products containing this medicinal plant which has hypoglycemic effect, here is still a need for the development of more products based on natural resources, for the treatment of this pathology, without side effects and with other benefits, to assist in the control of glycemic level in patients with diabetes mellitus, and to improve their quality of life.

***Keywords*:** Diabetes, antidiabetic, patent, formulation, herbal drug

## Introduction

According to the WHO, Diabetes mellitus (DM) defined as a disorder which affect a metabolism of living being characterized by chronic high glycemic level with disturbances in metabolism of fat, carbohydrate, and protein resulting from deficiencies in secretion or action of insulin or both" (WHO, 1999). DM is the most common endocrine disorder which leads to disturbance in functioning of vital systems of the body such as renal, nervous, cardio vascular and digestive system (Haller *et al*., 1996). It is known that more than 400 million people have diabetes and the worldwide occurrence of diabetes is predicted to rise over 640 million by 2040 (King *et al*., 1998). Two major categories of DM are insulin dependent diabetes mellitus (Type-1 or IDDM) and non-insulin dependent diabetes mellitus (Type-2 or NIDDM). Diabetes is still not cured successfully even with the improvement in synthetic antidiabetic drugs. Due to the various side effects of existing antidiabetic drugs treatment of diabetes is complicated. On the other hand, medicinal plants perform a substantial role in the treatment of various life-threatening illnesses due to their less adverse effects, lower cost as compared to synthetic drugs and long-term effect. A lot of medicinal plants containing different phytoconstituents like alkaloids, glycosides, steroids etc. are used in the treatment of diabetes. Approximately 800 plants are available which have remarkable antidiabetic potential acc. to the ethnobotanical survey (Alarcon *et al*., 1998). Despite remarkable antidiabetic potential of herbal drugs 75% of type-2 diabetic patients rely on synthetic drugs while type-1 diabetic patients (10%) use herbal drugs along with their insulin treatment (Eddouks *et al*., 2002). Despite single antidiabetic herb, herbal formulations are preferred for the treatment (Mallick *et al*., 2007). Ayurvedic literature discloses that since the time of Charak and Sushrut different oral formulations containing antidiabetic herbs have been recommended in Madhumeha (DM) and confident claims of cure are on record (Ayurvedic Pharmacopoeia of India, 2001). Present review given an update on patents of *Tinospora cordifolia* for the Diabetes Mellitus treatment during the last twenty years.

### Types of Diabetes

As per WHO classification in 1998, diabetes is broadly classified into three subcategories (Alberti and Zimmet, 1998).

- Type-1 Diabetes Mellitus (T1DM)
- Type-2 Diabetes Mellitus (T2DM)
- Gestational Diabetes Mellitus (GDM)

### Type-1 Diabetes Mellitus (T1DM)

It is an autoimmune disorder occurs when our own immune system permanently destroys pancreatic β cells which are functioning as a insulin hormone producer (Fig.1) Due to permanent damage of beta cells sugar level increase in the blood which leads to lack of energy, drowsiness, bigger appetite and weight loss. Type-1 diabetes mostly occurs in childhood but it can occur in adults (10%) also. These patients require a daily dose of insulin either in form of an injection or in form of inhalation (Atkinsen *et al*., 1984, Atkinsen and Maclaren, 1994).

Type-1 diabetes further categorized into two i.e. Immune-mediated and idiopathic. In immune-mediated type-1 diabetes pancreatic β cells destroying because of the presence of anti-glutamic acid decarboxylase antibodies. In this type ketoacidosis is the first manifestation which occurs in children and adolescents followed by modest hyperglycemia to severe hyperglycemia. On the other hand, idiopathic diabetes is type-1 diabetes with complete deficiency of insulin, a genetic factor and no indication of auto-immunity (Kaufman *et al*., 1992).

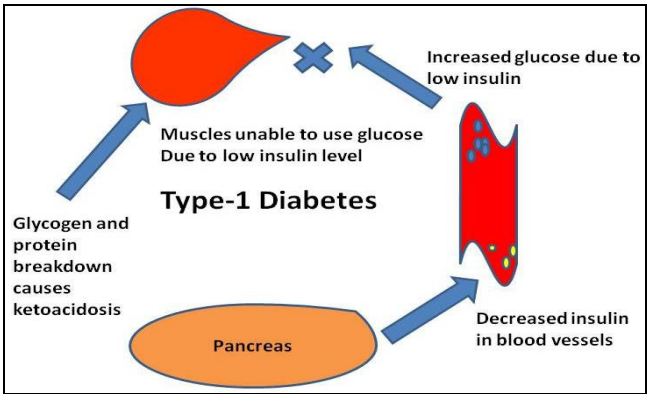


**Fig. 1 :** Overview of Type -1 Diabetes Mellitus

**Type-2 Diabetes Mellitus (T2DM)**

It is the most common type of diabetes which occurs in almost 90% population having age more than 30 years, family history of diabetes, overweight or obese and exhibit signs of insulin resistance (Mayfield, 1998). T2DM occurs when body can't appropriately use the released insulin or does not able to produce enough insulin. As a consequence, sugar builds up in the blood instead of being used as energy (Fig. 2). Type 2 diabetes identified by some common symptoms like increased thirst, fatigue, weight loss, frequent urination, blurred vision etc. These patients generally do not require insulin therapy.

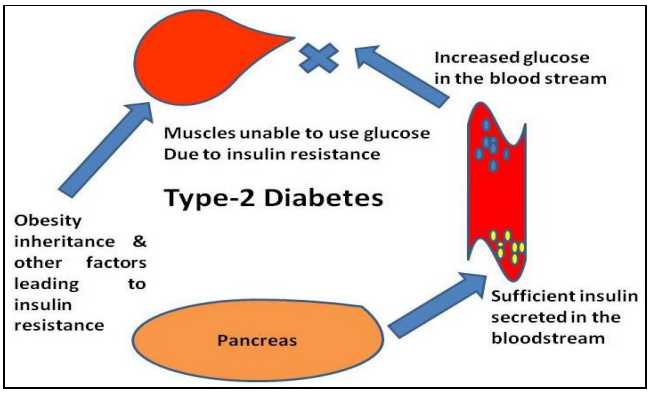


**Fig. 2 :** Overview of Type 2 Diabetes Mellitus

**Gestation Diabetes Mellitus (GDM)**

In GDM glucose intolerance occurs in pregnant (3-20%) women due to some hormonal change and generally goes away when the baby is born. Women having diabetes prior to pregnancy are not included in this category. About 60% of women with gestational DM will develop T2DM in the ensuing 5 to 10 years and all remain at an increased risk for the development of T2DM later in life (Lemos Costa *et al*., 2011, Alina *et al*., 2011).

***Tinospora cordifolia***

*Tinospora cordifolia* (*guduchi)* is a climbing shrub of the medium size found in Burma, Ceylon, and China. Due to its property of curing various diseases, it is also called as a magical herb (Wealth of India, 2003, Srivastava, 2011). In Ayurvedic system of medicine, the plant is referred to as a most important traditional remedy for diabetes. Various dosage form of *guduchi* in combination with other herbal drugs have been mentioned in the Ayurvedic text as shown in Table 1. It contains a variety of phytoconstituents like alkaloids, cardiac glycosides, tannins flavonoids etc. which present in different parts of the plant (Khosa and Prasad, 1971). These reported phytoconstituents found to have different pharmacological properties like antioxidant (Prince *et al.,* 2004), antidiabetic (Stanely *et al*., 2000), hepatoprotective (Bishayi *et al*., 2002), anti-inflammatory (Badar *et al*., 2005), anticancer (Jagetia and Rao, 2006), antipyretic (Vedavathy and Rao, 1991) etc.

The drug shows antiperiodic and antispasmodic properties due to the presence of bitter principles which is useful in treatment of swine flu. In addition, it also acts as an immune-modulator in immune-suppression of certain illnesses such as hepatic fibrosis, obstructive jaundice, sepsis and peritonitis (Maanjrekar *et al*., 2000, Satija *et al*., 2015). It has also reported as a promoting liver regeneration against hepatic toxicity induced by $CCl_4$. This is also useful in metabolic disorders such as diabetes.

**Table 1 :** Marketed formulation of *Tinospora Cordifolia*

| S. No. | Name of product | Company | Dosage form | Uses |
|---|---|---|---|---|
| 1. | Guduchyadi churna | Kerala Ayurveda Pharmacy Ltd | Liquid | Diabtes, fever |
| 2. | Guduchi taila | Vhca Ayurveda | Liquid | Liver infection, diabetes |
| 3. | Sanjivani vati | Patanjali Ayurveda | Tablet | Gastro-enteritis, chronic fever |
| 4. | Guduchi sattva | Dabur India Ltd. | Powder | Burning sensation, liver disease |
| 5. | Guduchi ghrita | Vyas Panchatikta | Tablet | Treatment of Gout |
| 6. | Amritaguggulu | Himalaya pvt. Ltd | Tablet | Gout, arthritis |
| 7. | Punchnimba churana | Vyas pharamaceuticals | Powder | Diabetes, poisons, ascites, arthritis. |

**Patent instances on recently explored studies on *Tinospora Cordifolia***

Several patents have been published during last twenty years regarding their preparation, biological properties etc. A brief description of the patents and findings are presented here (Table 2). In 1997 Dhaliwal gave a method to prepare a medical composition which consists of *Tinospora cordifolia, Trigonella foenum graceum, Azardichta indica, Cinnamomum tamala, Syzygium cumini, and Ficus racemosa.* According to the invention this composition should also contain a significant quantity of epicatechin along with gymnemic acid. This composition shows a substantial decrease in level of blood glucose due to pancreatic β cells regeneration (Dhaliwal, 1997). In another study, inventor disclose the preparation of herbal extract containing Tinospora along with jamun, methi, neem, amla, senna, and kalmegh. The administration of this extract showed a significant change in diabetic patients (Jain, 2008,

Ramchandra, 2009). In 2010 Mazeed *et al*. formulated a nutritional supplement using *Tinospora cordifolia* which is capable of improving person's well being. It reduces the risk of diabetes, cardiovascular disease, and Alzheimer's disease (Mazaed *et al*., 2010). Another study in 2011 discloses the methods to screen plant metabolites which are helpful in the treatment of diabetes. These separated constituents have been used to prepare dietary supplements or nutritional supplements. The therapeutic compositions can be derived from plants such as *Momordica charantia, Emblica officinalis, Tinospora cardifolia, Morinda citrifolia, Phyllanthus emblica, Azadiractha indica, Terminalia chebula, Mucunapuriens, Curcuma longa, Phyllanthus niruri and Ficus glomerata* (Patel, 2011). Recently one study discloses the use of borapetoside E present in Tinospora for treatment of diabetes mellitus and hyperlipidemia. The research discovers that a compound borapetoside E is capable of obviously reducing the level of blood sugar and blood lipid of HFD (High Fat Diet) induced mice and improving insulin sensitivity of the HFD induced mice. The hypoglycemic and anti-hyperlipidemic effects of 40mg/kg of the compound borapetoside E are superior to those of 200mg/kg of metformin. In addition, the duration time of the hypoglycemic effect is longer than that of 200mg/kg of the metformin (Liu *et al.,* 2017).

**Studies on formulations of *Tinospora cordifolia***

The antidiabetic potential of *Tinospora cordifolia* extract as well as various dosage forms of *Guduchi* mentioned in traditional system of medicine has been proven experimentally and clinically in numerous journals (Satija *et al*., 2015). Tinospora not only helpful for diabetic peoples but also beneficial in other diseased conditions. An Indian patent was filed in 2003 by National Institute of Immunology that Tinospora formulation enhances the vaccine efficacy for the treatment of infections and diseases. The study provides the process for preparing a formulation containing enriched protein fraction obtained from Tinospora along with additives such as alum, lipids and immunomodulators. This invention shows that *Tinospora cordifoiia* enhances the efficacy of vaccine against infections and tumours by inducing antigen specific cell medicated and Th-1 type antibody response (Upadhyay *et al*., 2007)

'Ilogen-Excel' an Ayurvedic polyherbal formulation having *T. cordifolia* as one of the constituents showed substantial reduction in serum glucose and growth in insulin, total hemoglobin and hepatic glycogen after administration at the dose of 50 and 100 mg/kg for 60 d. The plant root extract dropped the glycosylated hemoglobin levels, ceruloplasmin, hydroperoxides and plasma thiobarbituric acid reactive substances in diabetic rat model (Umamaheswari and Prince, 2007). Babu *et al*., in 2004 studied the antidiabetic and antioxidant effect of an Ayurvedic herbomineral formulation i.e. Hyponidd in STZ-induced diabetic rat model. Formulation consists of extracts of ten medicinal herbs which cause substantial drop in level of blood glucose at a dose of 200 mg/Kg (Babu and Prince, 2004).

Antidiabetic property of polyherbal formulation 'Trasina' is reported due to the antioxidant enzyme i.e. superoxide dismutase (SOD) activity of islet cells of pancreases in the rats. Trasina brings a dose dependent reduction in high glycemic level and increases SOD activity of islet cells (Bhattacharya *et al.,* 1997). Another polyherbal Ayurvedic formulation, 'Dihar', presented potential antihyperlipidemic, antihyperglycemic, and antioxidant effects in experimental animals. There was a substantial reduction in reduced glutathione (GSH), SOD, catalase (CAT) levels and increase in thiobarbituiric acid reactive species levels in the liver (Patel *et al*., 2009).

**Table 2 :** Patent instances on recently explored studies on *Tinospora cordifolia*

| S. No | Summary of Invention | Patent No. | Inventor | Reference |
|---|---|---|---|---|
| 1. | Use of parts of *Tinospora cordifolia* in the treatment of cancer | WO1991008750A1 | Kruger C | Kruger, 1991 |
| 2. | An ayurvedic formulation reported for hepatoprotective activity and also as a protective drug therapy for flu, TB and AIDS. | US5529778A | Rohtangi S | Rohtangi, 1996 |
| 3. | A formulation containing *Tinospora cordifolia* for alleviating symptoms associated with arthritis | US5683698A | Sambasiva R et al. | Sambasiva *et al*., 1997 |
| 4. | Polyherbal composition for the treatment of hepatitis B. | US6136316A | Mehrotra R et al. | Mehrotra *et al*., 2000 |
| 5. | Process for increasing a number of hematopoietic cells with the help of the Tinospora extract. | US6251383B1 | Upadhyay SN et al. | Upadhyay *et al*., 2001 |
| 6. | Use of Tinospora extract in the treatment of immune system-modulated disorders | WO2002053166A1 | John De SN et al. | John *et al.,* 2002 |
| 7. | Method of α-amylase preparation from *Tinospora cordifolia* benefecial for saccharification of starch | US6379721B1 | Sengupta S et al. | Sengupta *et al*., 2002 |
| 8. | Noval beverage formulation containing a decoction of plant extracts including *Tinospora cordifolia, Vitis vinifera, Boerhaavia diffusa and Withania somnifera.* | WO2004056382A1 | Palpup et al. | Palpup *et al*., 2004 |
| 9. | Herbal pediatric tonic formulation consisting of various plant extracts including withania tinospora and picrorhiza. | WO2005077392A1 | Singh R et al. | Singh *et al*., 2005 |
| 10. | Herbal formulation for AIDS treatment | WO2005030232A2 | Ayare S | Ayare, 2006 |
| 11. | The discovery offers a method for consuming the nasty tasting herbs in a herbal formulation for treatment of liver related diseases. | WO2007093897A2 | Chauhan SK et al. | Chauhan *et al*., 2007 |

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| 12. | D-glucan polysaccharide isolated from *Tinospora cordifolia* exhibits immune system stimulating properties | US20060009501A1 | Nair PK | Nair, 2008 |
| 13. | A herbal formulation for inflammatory disorders comprising a blend of an extract of *Tinospora cordifolia*, *Zingiber officinale, Commiphora wightii, Boswellia serrata* and *Curcuma longa* | WO2011080579A2 | Paramesh R et al. | Paramesh *et al*., 2011 |
| 14. | The invention provides a formulation for the prevention and treatment of bacterial infections | US8445033B2 | Vaidya SP | Vaidya, 2013 |
| 15. | Herbal cattle feed supplement compositions using Tinospora for enhancing the productivity and quality of milk | US20120263697A1 | Patil PN | Patil, 2014 |
| 16. | A preparation containing *Gymnema sylvestre* extracts together with extracts of one or more of *Boswellia serrata, Tinosporacordifolia,* and *Commiphora mukul* provide effective weight loss management when administered to a patient | US8936817B2 | Chatterji AK | Chatterji, 2015 |
| 17. | Prepared herbal composition derivatives of artemisinin, berberine, capsaicin and *Tinospora Cordifolia* for treatment and prevention of zika virus | US9675582B2 | Rosen BD | Rosen, 2017 |

**Perspectives and future directions**

Current review summarizes various antidiabetic studies of plant which indicated that it has significant, blood glucose lowering effect. It helps in improving certain prolonged symptoms and difficulties due to diabetes used either in form of extract or dosage form. Additionally if it is used in combination with other drug treatments, it also lower doses and/or reduced regularity of allopathic drugs administration which declines the adverse effects usually perceived. It improves the pathological status of diabetes via several mechanisms. By discovering the opportunity of particular synergistic or additive effects of *Tinospora* with other constituents and the pharmacology of such mixtures will benefit to establish basis behind combination *Tinospora* formulations. It can also give a support to other synthetic or semi synthetic drug to increase their pharmacological activity or reduce their possible side effects. So far no any adverse effect of the plant has been reported. Hence it can be further use as an alternative option for managing diabetes. Studies on molecular level to find an exact mechanism of the plant need to be established.

Future trials should be encouraged with similar antidiabetic herbs. A combined approach towards identification of the possible mechanistic features of the herb is absent. Without reported mechanism of action (MOA), it will be tough for current medicine system to admit herbal formulations in conventional therapeutics. Further studies are required in the field of tissue culture to raise the success rate, molecular analysis of any genetic changes if comes through indirect regeneration process, exploration of a variety of fungal endophytes to reveal the exact pathway of natural product synthesis in the plant cells, and in the field of nano biotechnology to solve the emerging problems of various incurable diseases through drug delivery system

## Conclusion

The therapeutic potential of *Tinospora cordifolia* mentioned in Ayurvedic texts has been validated by various researchers suggesting that this plant has enormous potential in current pharmacotherapeutics. On the basis of reported literature and patent it has been determined that DM treatment by *Tinospora cordifolia* is great option. This leads to the expansion of different herbal formulations being promoted nationally and internationally. This review report undertakes the effort for providing efficient info on the type of DM and various patented Tinospora herbal formulations which will increase the existing information of the investigators.

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