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# HYPOGLYCEMIC AND ANTIOXIDANT ACTIVITY OF *TINOSPORA CORDIFOLIA*: A REVIEW

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***ABSTRACT***

*Tinospora cordifolia popularly known as Neem Giloe is an evergreen perenninal climber. This deciduous and dioeciously plants belongs to the family Menispermaceae. This review gives an idea on the basis of recent discovery of active components and biological function of T. cordifolia in diabetes control. The diabetes is a group of many different diseases and long-term complications affecting the eyes, kidneys, heart, skin particularly the blood vessels and nerves. The study summarized information about the plant along with role of alkaloids, glycosides, steroids, aliphatic compound and other miscellaneous compound in antioxidant and hypoglycemic activities. The future scope of the review remains in exploiting the therapeutic use of this herb in biopharmaceutical industries as excellent sources to create medicines.*

**Key words:** *Tinospora cordifolia, Diabetes mellitus, Antioxidant, Hypoglycemic, plant Constitutes.*

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## INTRODUCTION

Diabetes mellitus (DM) is one of the most common non-communicable diseases (NCDs) globally. Diabetes is a group of metabolic disease characterized by hyperglycemia resulting from defects insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [1].

## INCIDENCE OF DIABETES AROUND THE WORLD:

Diabetes is undoubtedly one of the most challenging health problems in the 21st century. It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many economically developing and newly industrialized countries. The number of studies describing the possible causes and distribution of diabetes over the last 20 years has been extraordinary. Diabetes affects 347

million people and this number is projected to reach 438 million by the year 2030 [2].

According to the World Health Organization (WHO), diabetes caused 1.3 million deaths worldwide in 2008 [3]. Diabetes increases the risk of both heart disease and stroke. The risk of death for people with diabetes is about twice as high as that for people without diabetes [4]. The cost of diabetes ranges from 0.4% to 2.3% of GDP in some countries in the world [5]. Asia has the largest population with diabetes in the world accounting for 60% of people with the disease [6]. India has the largest number of people with diabetes, followed by china [7].

**DIABETES COMPLICATIONS:**

People with diabetes have an increased risk of developing a number of serious health problems. Consistently high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys, and nerves (Fig 1). In addition, people with diabetes also have a higher risk of developing infections. In almost all high-income countries, diabetes is a leading cause of cardiovascular disease, blindness, kidney failure, and lower limb amputation. Maintaining blood glucose levels, blood pressure, and cholesterol close to normal can help delay or prevent diabetes complications. Peoples with diabetes need to regular monitoring for the complications [2].

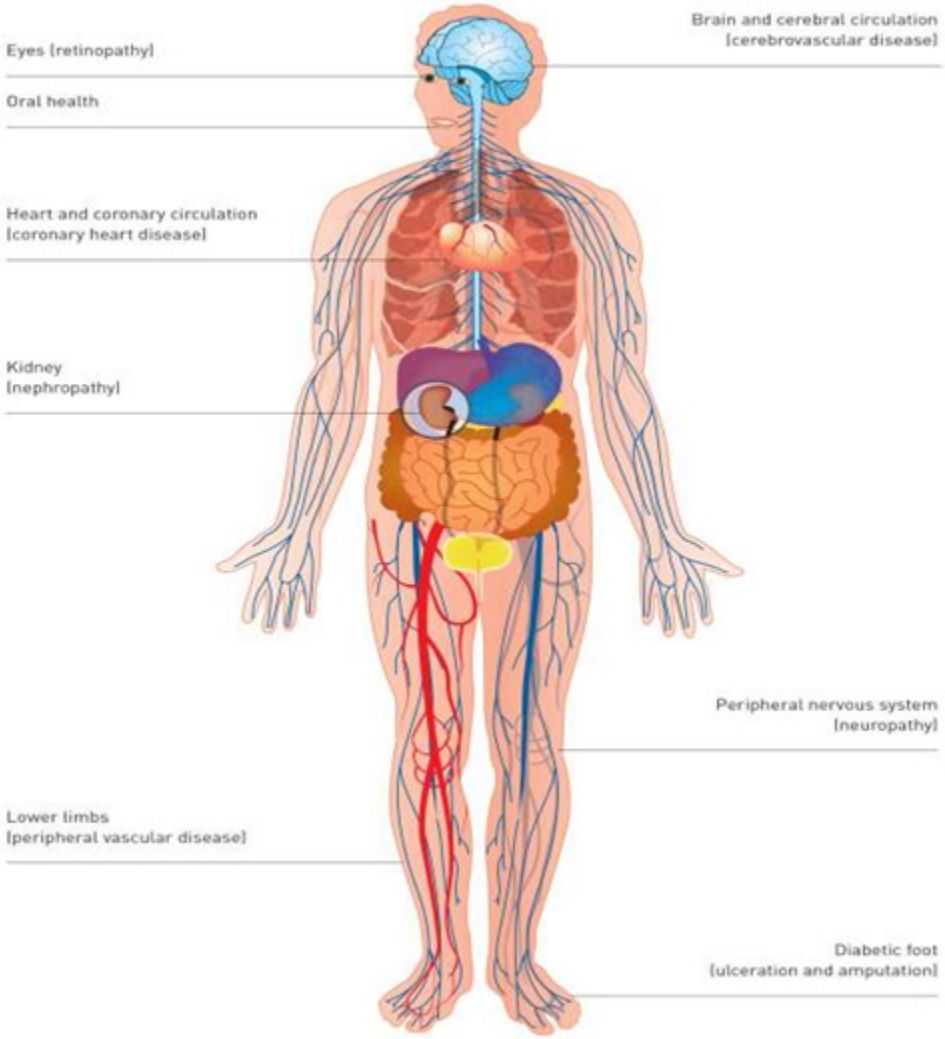


**Figure1: Diabetes Complication (adapted from www.idf.com)**

**CONVENTIONAL TREATMENT OF DIABETES:**

Diabetes is a multidimensional disorder and its management needs firm adherence to the prescribed treatment plan. The contemporary treatment of diabetes is focused on suppressing and controlling blood glucose to a normal level.

Anti-diabetic drug therapy includes insulin injections and oral hypoglycemic drugs. These drugs act by various mechanisms to control the blood glucose level [8]. On a cellular level, it defines the inadequate strength of insulin signaling from the insulin receptor downstream to the final substrates of insulin action involved in multiple metabolic and mitogenic aspects of cellular function [9]. The pathogenesis of type 2 diabetes involves abnormalities in both insulin action and secretion [10]. This review deals with the mechanisms related to type 2 diabetes. Below, we describe the basic knowledge of the molecular mechanisms involved in insulin secretion and insulin action in normal conditions. The following process occurs: insulin action and insulin secretion on the cell.

1. Insulin secretion :

Insulin secretion in response to glucose is a complex, multistep process that requires transport and oxidation of glucose, electro physiological changes and fusion of insulin-containing secretory granules with the beta-cell plasma membrane (Fig.2) [11]. The β cell through Glucose transporter 2 (GLUT-2) vesicle of the glucose inactively diffuses. Contained by the β cell, Glucose gets rehabilitated to Glucose-6-Phosphate during Glucokinase and Glucose -6- Phosphate is subsequently oxidized to from ATP. In this procedure inhibits the ATP sensitive K+ ions channels of the cell causing the K+ ions channels to close and not to work anymore. The depolarization of the cell membrane causes by the closure of Potassium channels. Causing the cell membrane to get longer which causes the voltage-gated Calcium channel on the membrane to unwrap causing an entrance of Ca2+ ions. This influx then excites fusion of the insulin vesicles to the cell membrane and assembly of insulin in the extracellular fluid exterior the β cell [12].

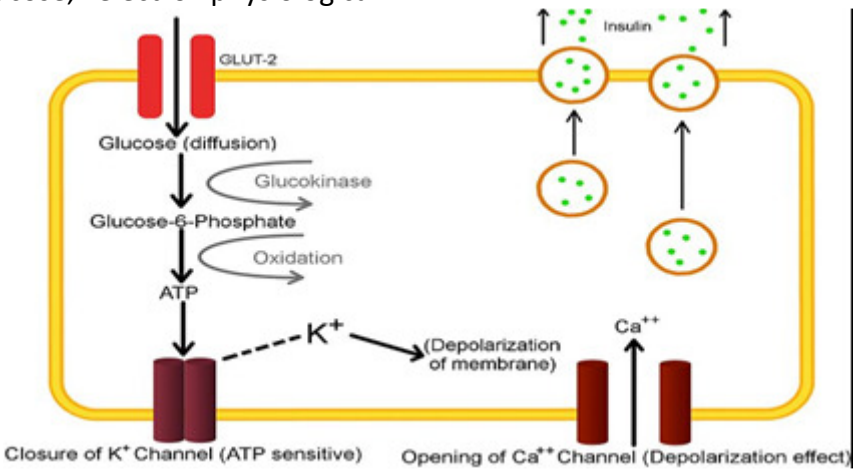


**Figure 2: Insulin secretion in response to glucose (adapted from Wikipedia)**

2. Mechanism of Action :

Insulin receptors consist of 2 extra cellular α and transmembrane β subunit linked by disulphide bond. α subunit contains insulin binding site and β have tyrosine protein kinase activity. Binding of insulin to α subunit induces aggregation and internalization of the receptor along with bound insulin molecule. This activates tyrosine protein kinase activity of β subunit. Tyrosine residue of β subunit gets auto phospholyrated. Hence the activity of this subunit to phosphorylate tyrosine residue of insulin receptor substrate protein (IRS1, IRS2) is increased. In a cascade of phosphorylation and dephosphorylation reaction is set into motion resulting in stimulation or inhibition of enzyme involved in rapid metabolic function of insulin [13].

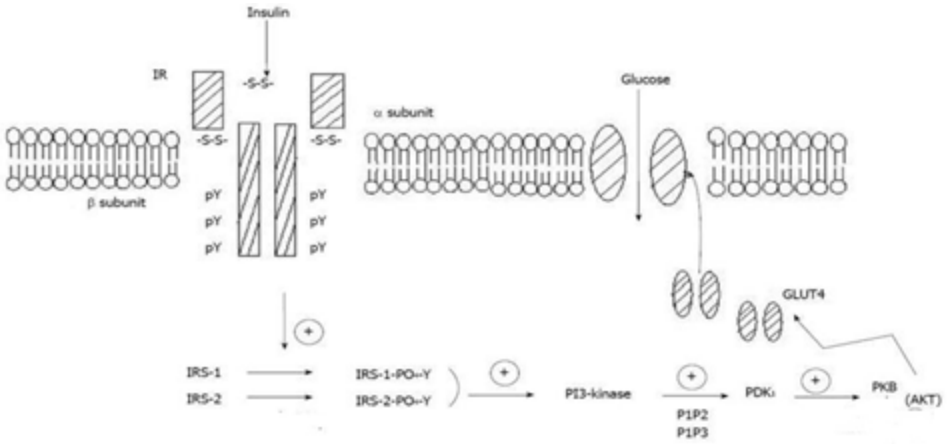


**Figure3: Insulin signaling pathway**

**HERBAL DRUG:**

Medicinal plants serve as essential remedial agents as well as valuable raw materials for developed various traditional and modern medicines. In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. They offer alternative remedies with tremendous opportunities to generate income, employment and foreign exchange for developing countries [14]. Many traditional healing herbs and their parts have been shown to have medicinal value and can be used to prevent, alleviate or cure several human diseases [15]. It is estimated that 80% of people worldwide rely chiefly on traditional, largely herbal medicine to meet their primary healthcare needs [16]. Many of the pharmacists are interested in providing counseling to all their customers (patients) regarding herbal products [17].

Herbal medicines can be relevant today only if they are applied and tested within the framework of modern sciences and subjected to the rigorous criteria for quality, safety and efficacy. Herbal medicines are ended, labeled therapeutic products that include as underground part, dynamic ingredients and aerial part of plant materials or combination thereof, whether in the crude state or as plant preparations. Medicines containing plant materials combined with chemically defined active substances, including chemically defined isolated constituents of plants are not considered to be herbal medicines [18]. A number of medicinal plants, used for over 1000 years named rasayana are present in herbal preparations of Indian traditional health care systems [19].

According of World Health Organization (WHO) has considered 21,000 plants, which are used for healing purpose around the world. Surrounded by these varieties are in India, out of which 150 species are used commercially on a moderately large scale. India is the leading producer of therapeutic drugs and is known as botanical garden of world.

**ANTIDIABETIC AND ANTIOXIDANT ACTIVITY:**

As per earliest literature, more than 800 plants are reported to have antidiabetic properties [20]. Ethno pharmacological surveys are a sign of that than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity [21]. The use of herbal medicines for the treatment of diabetes mellitus has gained importance throughout the world. The W.H.O. also suggested and encouraged this practice especially in countries where access to the conventional treatment of diabetes is not sufficient. Hundreds of plants have been tested for their anti-diabetic potential and for most of them based on the ethno botanical claims [22].

In traditional medicine, diabetes mellitus is treated with diet, physical exercise and medicinal plants and more than 1200 plants are used around the world in the empirical control of diabetes mellitus, most of them have not been pharmacologically and chemically investigated [23].

The use of herbs in the management of diabetes mellitus has been prevalent in Indian society from a long time and there are several medicinal plants have reported to possess potential hypoglycemic activity in Indian system of medicines [24]. More than 100 medicinal plants are mentioned in the Indian system of medicines including folk medicines for the management of diabetes, which are effective either separately or in combinations [25]. There are 400 various cultural and other traditional groups in India. Each domestic group has its endemic folk language, way of life. Folklore and knowledge about use of usual resources as remedy [26].

*T. cordifolia* finds a particular declares for its exploit in cultural or folk medicines in different parts of country. There are various herbal anti-diabetic remedies used in various traditional systems of medicine prevailing around the world, although only some of them have been scientifically assessed for their efficacy [8]. Many of them are used to treat highly prevalent disorder diabetes mellitus [27]. The present review highlights the phytochemistry and pharmacology of one of popular antioxidant and hypoglycemic plant *Tinospora cordifolia.*

*Tinospora cordifolia* (fig.no.3) is an Ayurvedic plant. It is distributed throughout tropical Indian subcontinent, Srilanka and China, ascending to an altitude of 300 meter [28]. In Sanskrit plant named is amrita, guduchi. In Hindi, the plant is commonly known as Giloe [29]. *T.cordifolia* belongs to the family Menispermaceae [30, 31, 32] which consist of about 70 genera and 450 species that are found in tropical lowland regions. This family is a rich source of alkaloids and terpenes [33].


**Figure 3: *T. cordifolia*. (a) Heart shape leaves; (b) Young stems; (c) Aerial roots (d) Plant bearing fruit of *T. cordifolia***

*Tinospora cordifolia* is a glabrous, deciduous, large, mountaineering shrub. The stem structure is fibrous and the transverse section exhibits a yellowish wood with radially arranged wedge shaped wood bundles, containing large vessels, separated by narrow medullary rays. The bark of *T.cordifolia* is deeply left spirally, creamy white to grey and stem contains rosette like lenticels [34]. The leaves are membranous and heart shaped with circular petiole and mid-rid [35, 36]. The plant blooms is spring to tiny, unisexual, small and creamy-greenish flowers (figure 2). Male and female flowers are formed on different branches [37]. Flowers are in axillary position, 2-9 cm long raceme on leaflet branches, yellow in color, unisexual and small. Female flowers are usually solitary and Male flowers are clustered. Fruits are single coat seeded and freshly. The seeds are curved. Fruits grow during the winter season and Flowers during the summer season [34].

Ayurvedic pharamacology is based on biophysical, experimental, inferential and intuitional mechanisms. All these mechanisms related to drug action are biophysical in nature. Giloy is the action that involves the activity or performance. It is the final effect of the drug [38.] The properties of action (phytochemical) and antioxidant and antidiabetic effect of *T.cordifolia* are given Table 1 and Table 2. *T.cordifolia* is claimed to be useful in treating fever, jaundice,

chronic diarrhea, diabetes and dysentery. Juice or decoction of leaves is administered orally with honey in fever [37, 39, 40.] The powdered root or stem is used along with milk for treatment of cancer [41]. Oral administration of decoction of stem is used for treatment of various skin diseases while the decoction with cold or hot water in morning on empty stomach is used as a tonic in general debility [42]. Paste and juice of leaves is applied locally for relieve of burning sensation. Juice of stem with honey is used orally for treatment of asthma [37].

**PHYTOCHEMICAL CHARACTERIZATION:**

Various chemical constituents have been isolated from different part of *Tinospora cordifolia*. They belong to different classes such as flavanoids, saponin, glycosides, steroids, alkaloids, sesquiterpenoid, polysaccharides, diterpenoids lactones, phenolis and aliphatic compounds. Leaves of this plant are rich in protein (11.2%), calcium and phosphorus [43]. Three major groups of compounds; protoberberine alkaloids, terpenoids and polysaccharides are considered as putative active constituents of *T.cordifolia* [44, 45]. These chemical constitutions of *T.cordifolia* are given in Table 1.

**Table 1: Chemical constituents characterized in different parts of *Tinospora cordifolia*.**

| S.No. | Types | Active principle | Part which in present | References |
|---|---|---|---|---|
| 1. | Alkaloids | Berberine, Tembetarine<br>Choline, Tinosporin, Isocolumbin, Tetrahydropalmatine, Jatrorrhizine<br>Palmatine, Magnoflorine | Stem<br>Root<br><br>Stem & Root | 46, 47 |
| 2. | Glycosides | 18-norclerodane glucoside, furanoid diterpene glucoside, tinocordiside, tinocordifolioside, cordioside, cordifolioside A, cordifolioside B, syringing- apiosylglycoside, Palmatosides P1, cordifolioside C, cordifolioside D, cordifolioside E | Stem | 46,48-52 |
| 3. | Diterpenoid lactones | Clerodane derivatives, tinosporon, tinosporides, jateirine, columbin | Whole plant | 46, 51, 53-55 |
| 4. | Sesquiterpenoids | Tinocordifolin | Stem | 56 |
| 5. | Steroids | β- sitosterol, δ- sitosterol, 20β-hydroxy-ecdysone<br>Ecdysterone, Makisterone A, Giloinsterol | Aerial part | 46 |
| 6. | Aliphatic compounds | Octacosanol, heptacosanol, nonacosan-15-one | Whole plant | 46, 57 |
| 7. | Miscellaneous compounds | Tinosporidine, cordifol, cordifelone, N-trans-feruloyl tyramine as diacetate, Giloin, Gilonin, Tinosporic acid<br>Gilonin, tinosporic acid, 3-(α, 4-dihydroxy-3-methoxy-benzyl)-4-(4-hydroxy-3-methoxy-benzyl)-tetrahydrofuran | Root<br><br>Whole plant | 58, 59 |

**ANTIOXIDANT AND ANTIDIABETIC ACTIVITY:**

Antidiabetic plant Ayurveda and other Indian literature advocate the use of medicinal plant in treatment of various human diseases. India has about 45,000 plant species and among them, several thousands have been claimed to possess medicinal properties. Researchers conducted in the last few decades on plants, mentioned in ancient literature or used traditionally for diabetes, have shown antidiabetic property [60]. Diabetes mellitus is a clinical syndrome characterized by inappropriate hyperglycemia caused by a relative or absolute deficiency of insulin or by a resistance to the action of insulin at the cellular level.

Plant materials which are being used as traditional medicine for the management of diabetes are well thought-out one of the excellent sources for an innovative remedy or escort to create a novel medicine. Plant extract or different folk plant preparations are being prescribed by the traditional practioners and also accepted by the users for diabetes like for any other diseases in many countries [61]. Table 2 clears that this plant is in detail studied for its antioxidant and hypoglycemic activity with different animal model. Indigenous people use various parts of the plant to get relief from diabetes mellitus [62]. In present times, the various extracts / fraction (mainly aqueous and alcoholic) even chemical constitutes of *T.cordifolia* have been subjected for numerous pharmacological, pre-clinical and clinical investigation [63]. Many clinical trial studied has also proven effectiveness and safety of this plant parts and derived formulations for anti-diabetic effect.

**TABLE 2: Anti-diabetic and Antioxidant activities the herbal plant of *Tinospora cordifolia* and related beneficial properties.**

| S.No. | Activity | Model | Plant part | Extract dose | Remark | References |
|---|---|---|---|---|---|---|
| 1. | Antidiabetic activity | Alloxan diabetic rabbits | Alcoholic, Aqueous & Chloroform leaves extract | 50, 100, 150, 200 mg/kg | Significantly reduce blood glucose level | 64 |
| 2. | Anti-hyperglycemic activity | Streptozotocin diabetic rats | Ethanolic stem extract | 100 mg/kg | Found be active | 55 |
| 3. | Antioxidant activity | Diabetic mice | Plant extract | 25mg/kg | To reduce the toxic side effects of cyclophosphamide and also reducing the chemo toxicity induced by free radical forming chemicals. | 65 |
| 4. | Anti-hyperglycemic effect | Diabetic animals | Aqueous & Alcoholic extract | 400 mg/kg | Reduced the blood glucose level | 66 |
| 5. | Hypoglycemic activity | Alloxan diabetic rats | Aqueous root extract | 100 mg/kg | Significant reduction in blood glucose and brain lipids. | 67 |
| 6. | Antidiabetic activity | Streptozotocin diabetic mice | Plant extract | 400 mg/kg | To reduce the plasma glucose concentration in diabetic mice. | 68 |

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| 7. | Antioxidant activity | Alloxan diabetic rats | Aqueous extract | 2.5gm/kg & 5.0 gm/kg | Reduction in thiobarbituric acid reactive substances (TBARS) and increasein reduced glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD) in alloxan diabetic rats. | 69 |
| 8. | Hypoglycemic & hypolipidaemic activity | Alloxan diabetic rats | Alcoholic root extract | | Significant reduction in blood & urine glucose and lipid in serum, also decrease in body weight. | 70 |
| 9. | Antioxidant effect | Alloxan Diabetic Rats | Alcoholic root extract | 100 mg/kg | Significant increase in the concentration of thiobarbituric acid reactive substances (TBARS) in liver and kidney was observed in diabetic rats. | 71 |
| 10. | Hyperlipidemia activity | Streptozotocin diabetic rats | Aqueous and alcoholic stem extract | 200 & 400 mg/kg | Significantly reduced in all lipid profile. | 72 |
| 11. | Anti-hyperglycemic-anti-hyperlipidemic and antioxidant activity | Streptozotocin diabetic rats | Plant extract | 100 mg/kg | Significantly decrease in serum creatinine, urea level, reduced glutathione, superoxide dismutase, catalase level, increase in thiobarbituiric acid and also significantly reduced the levels of lipid paroxidation and increased the activities of antioxidant enzymes. | 73 |
| 12 | Antidiabetic effect | Streptozotocin Diabetic rats | Hexane, ethyl acetate & methanol Stem extract | 250 mg/kg | Reduced the blood glucose level and moreover significantly decreased the glycosylated hemoglobin level, reduced glucokinase and increased glucose -6-phosphatage activity. | 74 |
| 13. | Antidiabetic activity | High fructose diet wistar rats | Aqueous stem extract | 100 mg/kg | Improvement of glucose and lipid metabolism in high-fructose fed rats by treatment with *Tinospora cordifolia*. | 75 |

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|---|---|---|---|---|---|---|
| 14. | Hypoglycemic activity | Diabetic rats | Leaf extract | 20-80 mg/kg | Found be active | 76 |
| 15. | Antioxidant effect | Streptozotocin diabetic rats | Aqueous stem extract | 500 mg/kg | Significantly increase level in lipid peroxidation and increase antioxidant properties. | 77 |
| 16. | Antidiabetic activity | Streptozotocin diabetic albino rats | Aqueous and alcoholic stem extract | 200 & 400 mg/kg | Increase in serum insulin levels or regeneration of pancreatic β cells and also increased hepatic glycogen synthase and decreased glycogen phosphorylase activity. | 78 |
| 17. | Antioxidant activity | | Hexane, Chloroform, Methanol, Ethanol and Aqueous leaves extract | | Justifies the ethno medical use of this plant. | 79 |
| 18. | Anti-hyperglycemic effect | Alloxan and streptozotocin diabetic rats | Methanolic stem extract | 150 mg/kg | Significantly reduced blood glucose level. | 80 |
| 19. | Hypoglycemic activity | Alloxan Diabetic rabbit | Stem extract | 50 mg/kg | Significant decrease blood glucose level. | 81 |
| 20. | Anti-hyperglycemic activity | Streptozotocin diabetic rats | Aqueous & Alcoholic root and stem extract | 100 & 200 mg/kg | Reduced blood glucose level in liver | 82 |
| 21. | Hypoglycemic activity | Diabetic rats | Alcoholic leaf extract | 0.5 mg/kg | Significant decrease blood glucose level. | 83 |
| 22. | Hypoglycemic and antioxidant activity | Alloxan diabetic rats | Methanolic stem extract | 500 mg/kg | Significantly decrease in blood glucose, glycosylated hemoglobin, cholesterol and increase in body weight and protein level. | 84 |

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| 23 | Hyperglycemia | Streptozotocin diabetic rats | Plant extract | 22.5 mg/kg | Significantly reduced blood glucose level and also reduced body weight | 85 |
| 24. | Antidiabetic and anti-hyperlipidemic activity | Streptozotocin diabetic rats | Aqueous stem extract | 1000 mg/kg | Significantly reduced blood glucose level. | 86 |
| 25. | Anti -hyperlipidemic activity | Streptozotocin albino wistar diabetic rats | Aqueous stem extract | 100 & 200 mg/kg | Significantly reduced blood glucose level and also reduced body weight. | 87 |
| 26. | Antidiabetic and anti-hyperlipidemic activity | Streptozotocin diabetic rats | Alcoholic stem extract | 100 & 200 mg/kg | Significant hypoglycemic effect | 88 |

**CONCLUSION:**

The herbal drugs *T. cordifolia* discussed in the review express significant clinical and pharmacological activity. The potency of herbal drugs *T.cordifolia* is significant and they have negligible side effect than the synthetic diabetic drugs. In this review article an attempt has been made to focus on hypoglycemic and antioxidant activity of plant and may be useful to the health professional, scientists in the field of pharmacology and therapeutics to develop evidence based alternative medicine to cure different kinds of diabetes in animal models. Isolation and identification of active constituents from this plant, preparation of standardized dose and dosage treatment can play a significant role in improving the antioxidant and hypoglycemic activity.

**Conflict of Interest:** There is no conflict of interest.

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