Review Article

# Exploring the Anti-Diabetic Potential: A Comparative Review of Phytoconstituents from *Costus igneus* and *Gymnema sylvestre* with Structure-Activity Correlation Analysis

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**ABSTRACT**

Diabetes is a major global health problem. Herbal formulations are preferred to control diabetes due to their less side effects. A study in Tamil Nadu, India found that *Costus igneus* and *Gymnema sylvestre* are potential natural alternatives to chemical means of blood sugar regulations. This study emphasizes the need for further research on structure-activity correlation of the chemical constituents present in *Costus igneus* and *Gymnema sylvestre* plants for controlling diabetes and clinical efficacy of herbal medicines generated from the phytoconstituents. Aim of this review is to combat diabetes through investigation of antioxidant and antidiabetic activities of the phytoconstiuents, the secondary metabolites like flavonoids (quercetin and catechin), β-sitosterol, corosolic acid, diosgenin and gymnemic acids of *Costus igneus* and *Gymnema sylvestre* plants and also that of some chemically modified quercetin compounds (derivatives), some transition metal ion quercetin complexes. Structure-activity relationship of these phytoconstituents will also be discussed to find the causes of antioxidant and anti-diabetic activities. Medicinal compounds from plants might have side effects. By altering their structures including functionalities, useful drugs may be developed with improved activities and less side effects. Structure elucidation of phytoconstituents is important to know stereochemical configuration since the orientation of functional groups and the ring conformations are basic points to understand the mechanism of biological activities like anti-diabetic and anti-tumor etc. An attempt has been made to compare the antidiabetic potentials of *Costus igneus* and *Gymnema sylvestre* based on pharmacological activities of their chemical constituents.

**Keywords:** *Costus igneus*, *Gymnema sylvestre*, Structures, Quercetin, Gymnemic acids, Antioxidants, Anti-diabetics

## INTRODUCTION

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose in human body causing damage in heart, kidney and eyes. About 422 million people worldwide have diabetes, and about 1.5 million deaths occurred due to diabetes each year. The prevalence of diabetes has been steadily increasing over the past few decades –as stated in WHO reports[1]. Over the past five decades, lifestyle changes and globalization have significantly impacted societies, political systems, the environment, and human behavior. Diabetes has significantly increased in both developed and developing countries[2,3]. Diabetes is a growing challenge in India with estimated 8.8 % diabetic population in the age group of 20 and 70 years[4]. Diabetes is of two types. In Type 1 diabetes our body pancreas doesn't make insulin or makes very little insulin. Once it was called insulin-dependent or juvenile diabetes. It can develop at any age[5]. In Type 2 diabetes, our body does not make enough insulin or doesn't use insulin properly. So, glucose stored in our body and not enough to reach cells. Type 2 diabetes is the most common type of diabetes[6].

There are number of treatments available to control or to cure diabetes. Insulin and some allopathic drugs like Metformin hydrochloride are advised by doctors to the diabetic people[7]. Allopathic medicines have various side effects. Natural products are the excellent sources of new anti-diabetic drugs. Traditionally medicinal plants extract having fewer side effects have been used since long to control diabetes[8]. They play an important role as alternative medicine due to less side effects and low cost. The active principles present in medicinal plants have been reported to possess pancreatic beta cells re-generating, insulin releasing and fighting the problem of insulin resistance[9]. Medicinal plants with bioactive constituents having antioxidant and related pharmacological activities have been reported in the literature[10-13]. There are evidences of various medicinal plants with anti-diabetic ingredients[14-15], thus it has been suggested that plants are a rich, untapped source of perhaps helpful antidiabetic medications.

This prompted us to choose the *Costus igneus* and *Gymnema sylvestre* as an antidiabetic plant for our review as these are grown widely throughout the world[16]. Because *Costus igneus*, commonly known as the 'Insulin Plant', is noted for its hypoglycemic characteristics. Extracts of *Costus igneus* leaves enhance insulin secretion and sensitivity in cells[17]. *Gymnema sylvestre* plant's leaf extracts are employed in homoeopathic and Ayurvedic treatments for diabetes mellitus, gastrointestinal disorders, and diuretics[18-19]. Given that the two chosen plants are well-known for having therapeutic qualities, a screening was conducted to see whether any recognized phytochemicals were present. Various studies of *Costus igneus* and *Gymnema sylvestre* have been reported[20]. This

review is an attempt to show the potential chemical constituents, their structures and bioactivities. Causes of antioxidant and anti-diabetic activities have been explained through the structure activity correlation studies of the phytoconstituents and their derivatives (that is through chemical modification) of the said plants to combat diabetes. An attempt has also been made to compare the antidiabetic effects of both the plants based on the pharmacological activities of the chemical constituents which have not yet been reported.

## MATERIALS AND METHODS

***Costus igneus*-** Scientific name: *Costus igneus*, Botanical name: *Costus igneus* N.E.Br, Family: Costaceae, Plant type: Pernnial. Herbarium specimen is located in different herbaria of Botanical Survey of India.

**Sources**- *Costus igneus* commonly known as Insulin plant, is native to South and Central America. This is a recent introduction to India from America as an herbal cure for diabetes and hence commonly called as 'insulin plant[21]. It is widely grown in gardens as ornamental plant in South India[22]. It is used in India to control diabetes, and it is known that diabetic people eat one leaf daily to keep their blood glucose low. Leaves of *Costus igneus* were one among the plants known to be effectively used for treating diabetes by the tribal people of Kolli hills of Namakkal district, Tamilnadu[23]. The family Costaceae consists of four genera and approximately 200 species. The genus Costus is the largest in the family with about 150 species that are mainly tropical in distribution[17]

***Gymnema sylvestre*-** Common name: Gurmar, Botanical name: *Gymnema sylvestre* R.Br. Family: Apocynaceae. Plant type: perennial, woody climber. Herbarium specimen is located in different herbaria of Botanical Survey of India.

**Source-** The plant is found in tropical and subtropical regions, well distributed in parts of central and southern India and in the southern part of China, tropical Africa, Malaysia, and Sri Lanka [25]. The genus is classified into 40 species, some of which like G. sylvestre, G. montanum, G. yunnanense, and G. inodorum[25]. *Gymnema sylvestre*, a plant native to tropical forests of India that is effective in type 1DM and type 2DM[24] (DM-Diabetes Mellitus).

Reported results of phytochemical screening of both the plants, anti-diabetic, antioxidant activities, other pharmacological activities in vitro, in vivo studies, structure of the phytoconstituents of the plants are collected by consulting scientific databases including PubMed, Scopus, Google Scholars, Science Direct activities and scientific journals.

**Table 1:** Reported Biological Activities of Different Parts of the plant

| Plant Part | Reported biological activities | Result |
|---|---|---|
| Leaf | antidiabetic | By decreasing blood glucose levels, increasing insulin sensitivity, and blocking critical enzymes involved in carbohydrate metabolism[34] |
| | antioxidant | *via* decreasing oxidative stress, scavenging free radicals, and increasing the activity of natural antioxidant enzymes[35] |
| | antimicrobial | by preventing a variety of harmful bacteria and fungus from growing, indicating its potential use as a natural antibacterial agent[36] |
| | anti-inflammatory | by decreasing pro-inflammatory cytokines, suppressing inflammatory mediators, and reducing inflammatory cell infiltration, indicating its potential therapeutic utility in inflammatory diseases[37] |
| Stem | antioxidant | attributed to its ability to protect against cellular damage, highlighting its potential therapeutic relevance in fighting oxidative illnesses[38] |
| | antimicrobial | blocking the growth of several harmful bacteria and fungi[39] |
| | anti-inflammatory | *via* lowering inflammatory cell infiltration, blocking inflammatory mediators, and regulating pro-inflammatory cytokines[40] |
| Root | antimicrobial | preventing the development of harmful fungus and bacteria[41] |
| | antibacterial | efficiently identifying and preventing the spread of different harmful bacterial strains[39] |
| Rhiozome | Anti-inflammatory | *via* suppressing pro-inflammatory cytokines, decreasing inflammatory mediators and attenuating inflammatory responses[42] |
| | Anti-diabetic | *via* regulating the metabolism of glucose, improving insulin sensitivity and reducing blood glucose levels[43] |

## RESULTS AND DISCUSSION

### *Costus igneus*— Phyconstituents and their structures

Phytochemical screening of the plant grown in around of Kannada district, Karnataka, South India using different non aqueous solvents shows the presence of the following chemical constituents in different parts of the plants-

a) Leaves: methanolic extract of the leaves of the *Costus igneus* plant showed the presence of maximum number chemicals (secondary metabolites) like steroids, phenols, triterpenoids, alkaloids, tannins, flavonoids, glycosides, saponins, carbohydrates, and proteins[26-27]compare to other solvents[28].The sequential antioxidant screening for phytochemicals of Costus leaves showed that it is rich in protein, iron, and components such as ascorbic acid, α tocopherol, β carotene, terpenoids, steroids, flavonoids and diosgenin[29]

b) Stem: showed the presence of a terpenoid compound lupeol and a steroid compound stigmasterol[30]

c) Rhizome: contains mainly quercetin, diosgenin, a steroidal sapogenin[31,32]

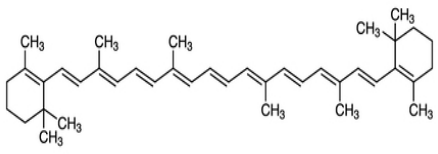
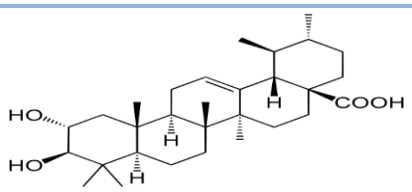
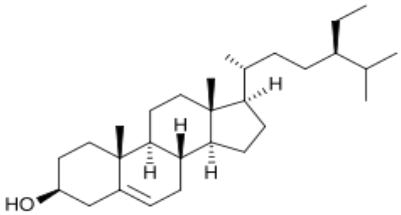
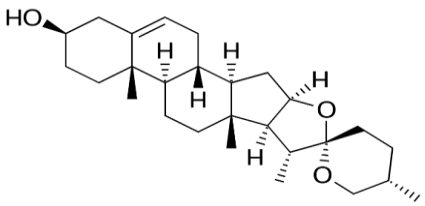
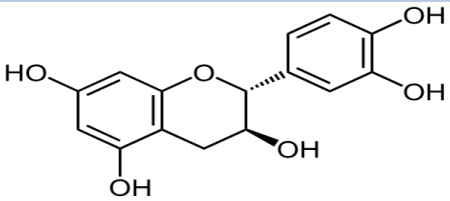
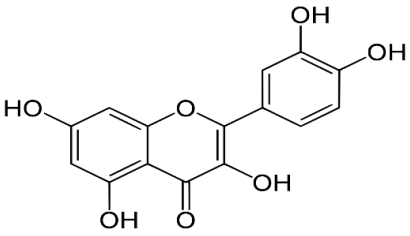
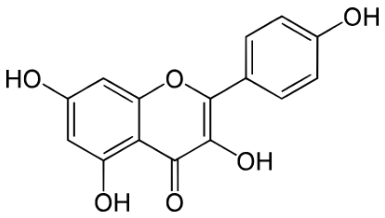
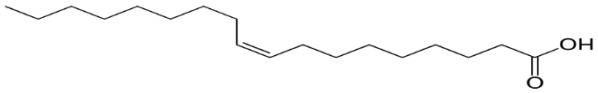
d) Root: Terpenoid, alkaloids, Tannins, etc.[33]

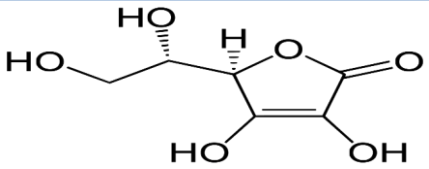
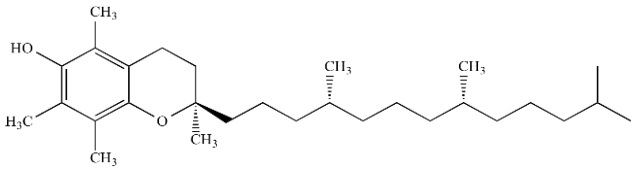
The biological activities of different parts of plant are described in Table 1.

**Structure of the potential bioactive constituents –**

Beside this, the structure is important to understand potential bioactivity. All the structures (Table 2) are represented below -

**Table 2:** Structure of some bio-active constituents of *Costus igneus* having antioxidants and anti-diabetic activities

| Plant Part | Class of Compound | Chemical structure | | References |
|---|---|---|---|---|
| Root | Tri-terpenoids |  beta-Carotene |  Corosolic acid | (Shinde S, et. al. 2022)[44] |
| Rhizome, Leaves | Steroids |  beta-Sitosterol |  Diosgenin | (Shinde S, et. al. 2022)[44] |
| | Phenols |  Catechin | | (Shinde S, et.al. 2022)[44] |
| Leaves | Flavonoids |  Quercetin |  Kaempferol | (Reddy PJ,et.al.2018)[45] |
| | Fatty acids |  Oleic acid | | (Shinde S, et. al. 2022)[44] |

| | | | |
|---|---|---|---|
| | Vitamin C |  Ascorbic acid | (Prabhu A,et.al. 2015)[46] |
| | Vitamin E |  alpha-Tocopherol | (Sivastava S,et.al. 2012)[47] |

**Antioxidant and anti-diabetic effects of potential phytoconstituents**

**Antioxidant and Anti-Diabetic Effects of diosgenin**--Leaves of *Costus igneus* containing steroids and flavonoids (secondary metabolites) produce significant anti-diabetic activities.

Antioxidants play a key role in the treatment of diabetes. Free radicals react with proteins, nucleic acids and lipids and produce reactive oxygen species (ROS). The generation of ROS in cellular membrane, mitochondria, nucleus and cytoplasm is associated with hyperglycemia[48]. Antioxidants resist the oxidation of other molecules. Clinical tests suggested the efficacy of antioxidants in preventing diabetes[49].

It is also reported that the role of oxidative stress in the pathogenesis of both Type 1 and Type 2 diabetes and increased insulin resistance due to oxidative stress caused by formation of different free radicals. So, antioxidants can scavenge free radicals and resist the formation of oxidative stress thereby control diabetes[50].

**Diosgenin—Antioxidant and anti-diabetic effect—structure-activity correlation**

Diosgenin has been found to be effective in improving diabetic condition in both Type 1 and Type 2 diabetes[51]. Diosgenin a steroidal saponin, increases plasma insulin level and decreases serum glucose—supporting studies are discussed here. Diosgenin, a natural steroid function as antioxidant mainly due to their redox properties[52].It is reported that diosgenin (Table 2) and its novel derivatives[53] substituted at C3 position of diosgenin with various organic acids: cinnamic, nicotinic and 4-aminobenzoic acids act as potent antioxidants tested *in vitro* model[54]. Diosgenin was considered a good target for scavenging free radicals due to the lack of toxic side effects and its therapeutic importance. Recently anti-diabetic effect of diosgenin has been confirmed through different in vitro and in vivo studies[54]. Due to poor water solubility of diosgenin it has low oral bio availability in animals[55]. Structural modification of diosgenin will also increase its bio availability.

Based on the antioxidant effects and pharmacological effects diosgenin has a good effect against diabetes and its complications through multiple targets and multiple pathways cited as:

**(a)** ***Reduce intestinal glucose absorption*** -Diosgenin through different enzymes and carriers block the absorption of carbohydrates in the small intestine and reduce the level of blood sugar[56-57].

**(b)** ***Affect the metabolism of glucose in tissues and organs***-Diosgenin significantly elevated serum and muscular DHEA (dehydroepiandrosterone) levels, decreased blood glucose level and increased skeletal muscle GLUT4 (glucose transporter) translocation level. Experiments were performed on mice that developed spontaneous thymic lymphomas and PKCζ/ λ (a typical protein kinase C)to affect glucose uptake and utilization in skeletal muscle, thereby improving diabetes[58]. Research has shown that the administration of diosgenin increased hepatocyte absorption of glucose and decrease blood glucose[59].

**(c)** ***Improve Insulin resistance*** - Diosgenin was administered to diabetic rats to find an improve in the levels body weight, glucose, insulin, insulin resistance, free fatty acids, phospholipids and low-density lipoprotein in blood and it was observed that it altered insulin resistance by alleviating metabolic dysregulation of lipid profile in both plasma and tissues[60].

**(d)** ***Promotion of Insulin secretion***- In vivo studies show that in STZ (streptozotocin-induced diabetic rats, diosgenin can stimulate the renewal of β-cells in the pancreas or may permit the recovery of partially destroyed β-cells and stimulates pancreatic insulin secretion, which leads to significant increase in the plasma insulin levels and control the blood glucose[61].

**Anti-Diabetic Effects of Flavonoids: Structure-Activity Correlation of Quercetin**

Phytochemicals may have side effects. Some modification in the structure of the chemical constituents from plants through structure orientations, position of the functional groups and introducing proper functional group through substitution to make new potent lead compound which will act as a drug to be therapeutically useful.

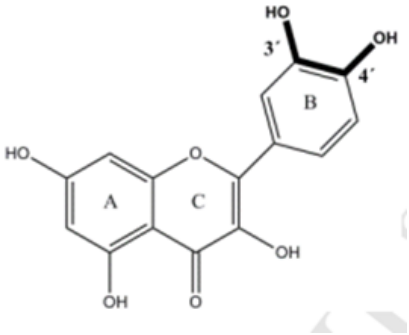
To serve this purpose structure-activity relationship (SAR) study for each potent chemical from the plant source is important. Flavonoids, a group of hydroxylated phenolic substances, a potent free radical scavenger i.e. a potent antioxidant which plays an important role in the alleviation of diabetes mellitus[62]. Flavonoids are benzo-$\gamma$-pyrone derivatives and synthesized by plants to protect from microbial infection. The pharmacological properties of flavonoids mostly structure dependent, degree of hydroxylation, methylation, other substitutions and conjugations, and degree of polymerization[62]. Antioxidant potential was evaluated through different studies[62].

Presence of C-2-C-3 double bond and C-4 ketonic group are two essential structural features of flavonoids especially for antidiabetic property—as shown below. This molecular rearrangement (having five -OH groups at 3,3′,4′,5,7) is optimum for scavenging free radicals -responsible for antioxidant effect.

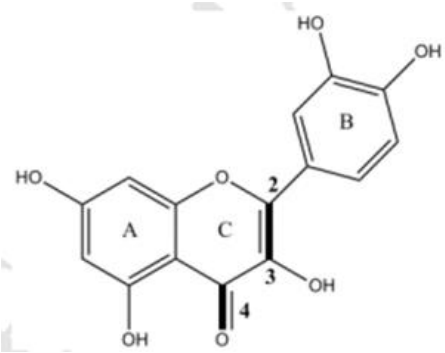
Quercetin (3,5,7,3′,4′-pentahydroxyflavone) a flavonoid present in the plant is known to exhibit antidiabetic activity in Type 2 Diabetes Mellitus due to its antioxidant property.

Quercetin has a common flavone nucleus, composed of two benzene rings linked through a heterocyclic pyrone ring. The main structural features of quercetin required for efficient radical scavenging are as follows[63-64] responsible for antioxidant properties.

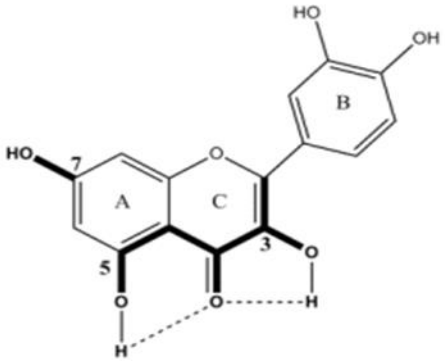
i) an ortho-dihydroxy (catechol) structure in the B ring of quercetin, for electron delocalization, as shown below:




ii) 2,3-double bond in conjugation with a 4-oxo function in the C ring of quercetin provides electron delocalization from the B ring, as shown below:




iii) hydroxyl groups at position 3,5and 7 in combination with 4-oxo group of quercetin for better antioxidant properties as shown below:




The antioxidant capacity has been suggested to be proportional to the number of -OH groups present in the flavonoid (quercetin) molecule. The absence of C-4 of ring carbon double bond and ketonic group at C-3 reduced alpha-glucosidase and DPP-4(Dipeptidyl peptidase-4) inhibitory activities which is used to manage type-2 diabetes mellitus[44]

Low solubility and poor bioavailability of quercetin have limited its applications; therefore, the researchers have tried to synthesize many new derivatives of quercetin through different strategies to modify quercetin restrictions and improve its biological activities viz antioxidant activities.

Quercetin and its derivatives are important metabolites that belong to the flavanol class of flavonoids. Quercetin and some of the conjugates have been approved by the FDA for human use. They are widely distributed among plants and have various biological activities, such as antioxidant. Hence, the biosynthesis of novel derivatives is an important field of research.

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one), a major class of flavonoids, contains five hydroxyl groups at 3,5,7,3’ and 4’ of the basic skeleton of flavonoid. This unique structure of quercetin and the functional groups of quercetin are accountable for the stability and antioxidant activity; these are 3- and 5-OH groups, in conjugation with the 4-oxo group and the ortho dihydroxy group.[65]Some of these hydroxyl groups are glycosylated to various quercetin glycosides and constitute the major quercetin derivatives.

Some O-substituted quercetin derivatives were isolated with the aim to optimize bioavailability and redox properties of quercetin. These compounds have multiple health beneficial effects including diabetes[66].

Thus, the novel synthetic derivatives of quercetin (Figure 1): 3′O-(3-Chloropivaloyl) quercetin (CPQ) or Monochloropivaloylquercetin, Monoacetylferuloylquercetin (MAFQ) and chloronaphthoquinonequercetin (CHNQ) are better antioxidants compared to quercetin (QC) confirmed through experiments in vitro studies in cellular biological systems[66]. Structural modifications of quercetin at position 4′ resulted the active derivatives CHNQ and MAFQ.

These derivatives may scavenge stable free radicals of DPPH(2,2-Diphenyl-1-picrylhydrazyl)more efficiently compare to that of quercetin[66]. In the recent study[67], the three novel derivatives of quercetin CPQ, CHNQ and MAFQ were synthesized for their ability to inhibit α-glucosidase activity, using quercetin and acarbose as references. The IC50 values showed that CPQ, the 3′ substituted derivative of quercetin, as the most efficient inhibitor of α-glucosidase, exceeding the inhibition activity of unsubstituted quercetin (Table 3). Monoacetylferuloylquercetin (MAFQ) and chloronaphthoquinonequercetin (CHNQ) (Figure 1) are good antioxidants and exhibited a prominent inhibitory effect on the key enzymes involved in diabetic complications, aldose reductase and α-glucosidase, suggesting their promising therapeutic application[68]

**Table 3:** Inhibition of α-glucosidase

| Compound | $IC_{50}$/μM# | Ref |
|---|---|---|
| CPQ | 14.86 ± 4.35 | (Soltesova PM,et.al.2016)[67] |
| CHNQ | 49.28 ± 4.86 | |
| MAFQ | 74.83 ± 12.79 | |
| QC | 39.78 ± 2.46 | |
| Acrabose | 303.30 ± 5.22 | |

#Experimental results are mean value ± SD from at least three experiments

So, the novel O-substituted quercetins: CPQ, CHNQ and MAFQ (Figure 1) may represent promising agents for prevention and treatment of diabetes, a chronic age-related disease[66].

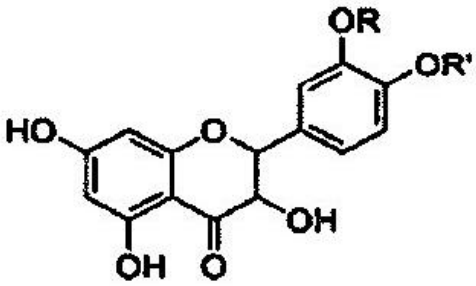



**Figure 1:** Structures of QC, CPQ, CHNQ and MAFQ[67]

| Compound | R | R/ | Reference |
|---|---|---|---|
| QC | H | H | (Soltesova PM et.al.2016)[67] |
| CPQ | 3-Chloropivaloyl | H | |
| CHNQ | H | 2-Chloro-1,4-naphtoquinone-3-yl | |
| MAFQ | H | 4-O-acetyl-feruloyl | |

**Bioactivities of other potential phytoconstituents and their Structure-activity correlation**

**a) Phenol (Catechin)**

Catechins (Table 2) are potent antioxidants. Antioxidant effects are related to: i) their chemical structure (Table 2) and the total number of hydroxyl groups, ii) double bond between C-10 and C-9 decreases the inhibitory activity for both the alpha-glucosidase and DPP-4 antidiabetic effects[44].

Catechin shows its antioxidant effect due to hydrogen atom transfer from phenolic OH group. This is confirmed in-vivo and in-vitro studies[69].Catechin regulates diabetes by inhibiting the sucrose of blood glucose and alleviating oxidative stress.

**b) Steroid (β-sitosterol)**

Structure of beta-Sitosterol (Table 2) is equipped with a C24-ethyl group. It is stigmast-5-ene substituted by a beta-hydroxy group at position 3. Its antioxidant potential is due to the presence of OH group. This is confirmed in vivo studies. β-sitosterol improves glycemic control through activation of IR and GLUT4 receptors in the adipose tissue of high fat and sucrose induced type-2 diabetic rats. In-silico analysis also coincides with in-vivo results. So, β-sitosterol can act as an antidiabetic agent.[70]

**c) Tri-terpenoids (Corosolic acid)**

Corosolic acid is composed of a complex structure consisting of five fused rings. The chemical formula of Corosilic acid is $C_{30}H_{48}O_4$.]. It contains hydroxyl (-OH) and carboxylic acid (-COOH) groups which are responsible for its antioxidant activity (Table 2). It has been shown to scavenge free radicals, reduce oxidative damage, and protect cells from damage induced by oxidative stress[71]. Corosilic acid acts as insulin on glucose metabolism; hence it also called plant insulin in treating diabetes mellitus.

Corosolic acid has been proven to inhibit α-glucosidase and increase cellular uptake of glucose to reduce blood sugar and help to overcome insulin resistance[72]. These mechanisms are responsible for improved glycemic control

and helpful in management of diabetes mellitus. Corosolic acid is suggested to be a promising lead compound for curing diabetes.

**Pharmacokinetic studies of Corosolic acid in support of its antidiabetic activity**

Corosolic acid has been reported to decrease blood sugar levels within 60 min in human subjects[72]. The effects of corosolic acid with respect to various aspects of glucose metabolism involve in mechanisms: i) including enhanced cellular uptake of glucose, ii) impaired hydrolysis of sucrose and starches, iii) decreased gluconeogenesis. Several studies in genetically diabetic (KK-AY) mice to which corosolic acid was administered. At a single dose of 10 mg/kg, corosolic acid significantly reduced blood sugar levels. In a subsequent study, they showed that a single dose of 2 mg/kg corosolic acid reduced blood sugar levels for up to two weeks which supports that corosolic acid improves glucose metabolism by reducing insulin resistance.[73]

**Some metal ion complexes of quercetin as antioxidant and anti-diabetic agents**

Antioxidant and Antidiabetic activity of some metal - flavonoid, quercetin complexes are reported in the literature[74]. Some studies of metal-quercetin complexes have indicated that Complexation of this polyphenolic phytochemical with metal ions may modify its antioxidant ability.[75] Metal ions such as Cr, Cu, Fe, Co, Cd, Mg, Ga, Ru and some rare earth elements when complexed with quercetin improve its antioxidant activity compared to quercetin. Co (II) and V(IV) – Quercetin complexes have promising anti-diabetic effect confirmed through in vitro and in vivo studies with low toxicity.

**i) Co(II)-Quercetin Complex : antidiabetic effect**

Recently antidiabetic effect of Co(II)-Quercetin Complex(CQC) in solution has been reported through pharmacological studies[16]. Diabetes was prompted in male rats via one injection of streptozotocin (STZ, 50 mg/kg). Daily, diabetic animals were treated with either a dose of CQC or insulin for 15 days[76]. CQC treatment effectively reversed all the studied diabetes-induced changes on the applied rat *via* its strong antioxidant properties. Antidiabetic effects of CQC and insulin to diabetic rats were comparable--results show that CQC to some extent was better.

**ii) $[VO]^{2+}$-Quercetin Complex: anti-diabetic effect**

It is reported that synthetic bis(quercetinato)oxovanadium (IV) conjugate (BQOV) complex has potent insulin enhancing activity in an animal model in vivo and also in vitro studies and this complex could be a valuable therapeutic agent for the treatment of treat type 1 and 2 diabetes.[77]

**Anti-diabetic activities of *Costus igneus* (aqueous extract of leaf) based on α-amylase and α-glucosidase inhibition activity and its comparison with allopathic drug in vitro studies**

A recent study was reported to compare the α-amylase and α-glucosidase inhibition activity of aqueous extract of the plant with that of allopathic drug metformin in vitro-studies.

Different concentrations of the aqueous extract of the leaf from the plant *Costus igneus*, the solution of drug metformin (100-500 µl), standard drug (Acarbose) and alpha-amylase in buffer, alpha-glucosidase and phenyl alpha- D-glycosidase were taken and assessed for the antidiabetic activity based on their α-amylase and α-glucosidase inhibition[78].

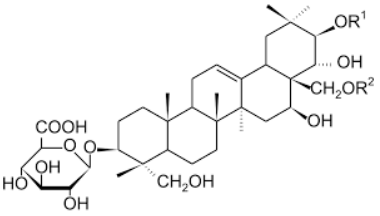
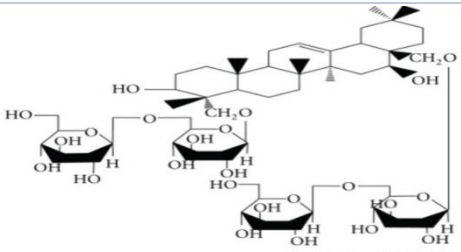
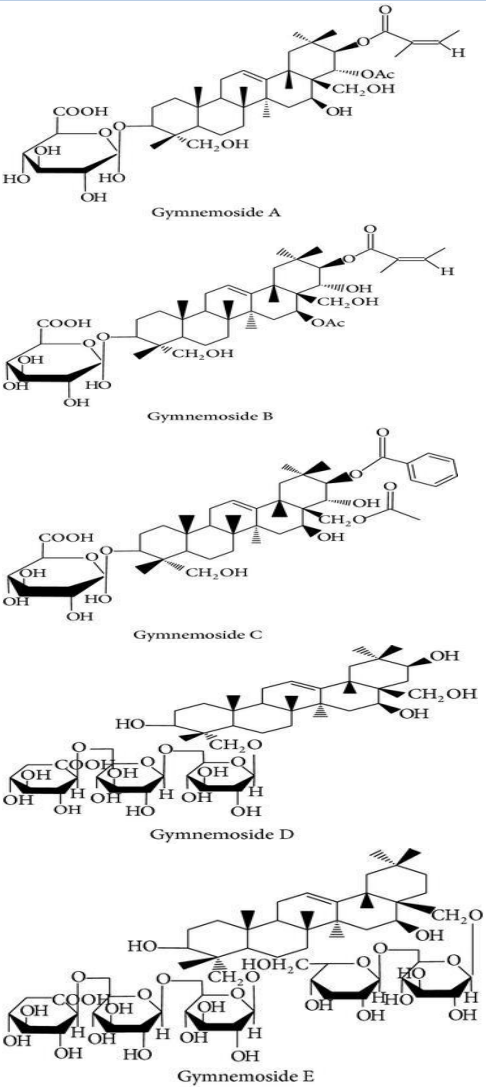
The alpha-amylase inhibition action of *Costus igneus* was 89% of that of metformin at a concentration of 500 µg. The alpha-glucosidase inhibition action of *Costus igneus* was 66.6% of that of metformin at a concentration of 500 µg. This result indicates a strong basis for the support of antidiabetic properties of *Costus igneus*. The aqueous extract of the leaves of *Costus igneus* could serve as an alternative to the commonly used allopathic antidiabetic (type 2) drug metformin as inhibition of alpha-amylase and alpha-glucosidase can significantly reduce post prandial increase of blood glucose. Clinical studies need to be performed for confirming the use of the aqueous extract of the plant leaves[79].

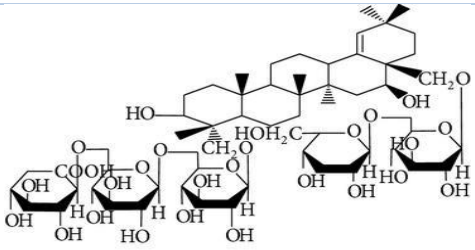
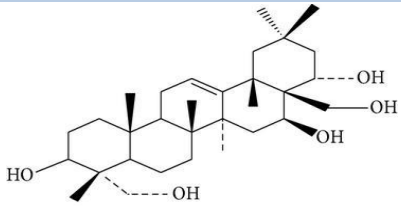
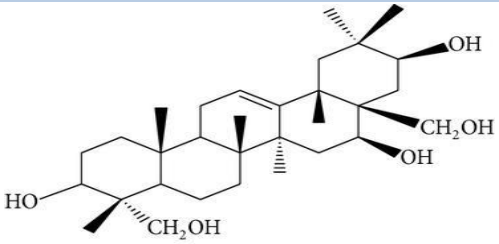
***Gymnema sylvestre***

**Phytoconstituents**

Phytochemical screening of the plant grown in the forests of Tamil Nadu and Karnataka show that aqueous extract of the leaves contains triterpene saponins which are of oleanane and dammarane classes. Gymnemic acids and gymnema saponins are major constituents which are members of oleanane type of saponins (Table 4). Other major constituent gymnemasides are member of dammarane saponin. Besides these other constituents are anthraquinone, flavones, hentriacontane, pentatriacontane, phytin, resins, tartaric acid, formic acid, butyric acid, lupeol, *β*-amyrin related glycosides, stigmasterol, calcium oxalate and gurmarin, a polypeptide[80]. Plant extract also contain some alkaloids. Most of the bioactive constituents are secondary metabolites and present in the leaves.

**Table 4:** Molecular structures and Bio activities of major constituents of *Gymnema sylvestre* (***Plant Parts-leaves***)

| Phytoconstituents | Classification | Molecular Structure | Bio-activity | References |
|---|---|---|---|---|
| **Triterpene Saponins** | Gymnemic acids-Acylated(triglolyl, Methylbutyroyl) derivatives of de acylgymnemic acid |  Gymnemic Acid I- $R^1$- Trigloyl; $R^2$- Ac<br>Gymnemic Acid II- $R^1$- 2-Methyl butyroyl; $R^2$- Ac<br>Gymnemic Acid III – $R^1$-2-Methyl butyroyl; $R^2$- H<br>Gynemic Acid IV- $R^1$- Trigloyl ; $R^2$- H | Antioxidant and anti-diabetic | (Liu HM et.al. 1992)[81] |
| **Oleanane Saponins** | Gymnemic acids and gymnemasaponins |  Gymnemasaponins V | Antioxidant and anti-diabetic | (Yoshikawa M et.al. 1997)[82] |
| **Dammarane Saponins** | Gymnemosides-A,B,C,D,E and F |  Gymnemoside A<br>Gymnemoside B<br>Gymnemoside C<br>Gymnemoside D<br>Gymnemoside E | Antioxidant and anti-diabetic | (Yoshikawa M et.al. 1997)[82] |

| | | | | |
|---|---|---|---|---|
| | |  Gymnemoside F | | |
| **Gurmarin** | A polypeptide with 35-amino acids | <[1]Glu- Gln- Cys- Val- [5]Lys- Lys- Asp- Glu- Leu- [13]Cys- Ile- Pro-Tyr- Tyr- [17]Leu- Asp- Cys- Cys- Glu- [23]Pro- Leu- Glu- Cys- Lys-[29]Lys- Val- Asn- Trp- Trp- [35]Asp- His- Lys- Cys- Ile- [42]Gly>. (Glu = pyroglutamic-acid residue) | Sugar suppression activity | (Imoto T, et.al. 1991)[83] |
| **Gymnemanol (aglycone)** | 3,β-16,β-22,α-23-28 Pentahydroxyolean-12-ene |  | Anti-oxidant and antidiabetic | (Sahu NP, et.al. 1996)[84] |
| **Gymmestrogenin** | Pentahydroxytriterpene |  | Anti-oxidant and antidiabetic | (Yoshikawa M ,et.al. 1997)[82] |

**Antioxidant and anti-diabetic effects of potential phytoconstituents**

**Antioxidant property**: Antioxidant activity of Gymnema leaf extract is the sole cause of its antidiabetic activity. Phytoconstituents flavones, phenols and saponins present in the ethanolic leaf extract of the plant are the potential source of free radical scavenger which supports the antioxidant potential of *Gymnema sylvestre*[85]. Antioxidant activity of the plant has been confirmed by several clinical trials, ex vivo studies and in vitro studies[86] with the ethanolic extract of the plant.

**Anti-diabetic activities - *Gymnema sylvestre*: Structure - Activity relationship**: The prime constituents like gymnemic acids (I-IV) and gymnema saponins are members of oleanane type of saponins while gymnemasides are dammarane saponins[87]. Other structural varieties are also there. The major secondary metabolites in Gymnema includes a group of nine closely related acidic glycosides, (a type of triterpene saponin compounds) the main are gymnemic acid I-IV (for its antidiabetic activity) and found in all parts of the plant as shown in Table 4[88]. Actually, Gymnemic acids comprise of several members designated as gymnemic acids I–VII (I-IV shown in Table 4), gymnemosides A–F (Table 4) and gymnemasaponins,[25] a triterpenoids saponins[Gymnemasins A = 3-O [*β*-D-glucopyranosyl (1-3)-*β*-D-glucopyranosyl]-22-O-tiglyol gymnemanol, Gymnemasins B = 3-O-[*β*-D-glucopyranosyl-(1-3)-*β*-D-glucuro-nopyranosyl]-gymnemanol, Gymnemasins C = 3-O-*β*-D-glucuronopyranosyl-22-O-tigloyl gymnemanol, Gymnemasins D = 3-O-*β*-D-glucopyranosyl-gymnemanol]84 isolated from *Gymnema sylvestre* leaves extract.

The aglycone, gymnemanol, which is a new compound, was characterized as 3β,16β,22α,23,28-pentahydroxyolean-12-ene. In addition to gymnemic acids, gymnemosides called gymnema saponins, a new category of antisweat agents has been separated from *Gymnema sylvestre* extract and studied chemically. Five constituents (gymnemosides A-F) (Table 4) were isolated and their structures were established as novel d-glucosides of 3b, 16b, 23, 28-tetrahydroxyolean-12-ene on the basis of spectroscopic analysis[89].

Gymnema saponins are good antioxidants and the role of antioxidants was confirmed in diabetic rats performed by Kang et.al.[90] using ethanolic extracts of *Gymnema sylvestre*.

Gymnemic acids I-IV structures show the presence of -OH, COOH and glycosyl groups confirmed by IR and UV studies.[91] Presence of -OH (hydroxyl) group indicates antioxidant activity[92]. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules and it blocks the receptor site for sugar in the intestines, preventing the absorption of sugar which reduces blood sugar level. Structure-activity relationship of gymnemic acids has not yet been reported so far.

Gurmarin, a polypeptide consists of 35 amino acids having a molecular weight of 4209, was isolated from methanolic leaf extracts of *Gymnema sylvestre*[83]. It has sugar

suppression activity which was determined electro physiologically on the taste responses of rat.[93]

**Pharmacological studies in support of its antidiabetic activity**

The universally known effect of *Gymnema sylvestre* is its anti-diabetic activity. Ethanol extract of this plant is reported to reduce glucose level by 46% where the water extracts reduced glucose level by 26%. Gymnemic acid II extracted from the leaves consumed orally by the animals found to be useful in restoring the altered levels of total protein-bound polysaccharide components and glycosaminoglycans in serum and tissues of experimental animals during short-term alloxan-induced hyperglycemia[94].

Other gymnemic acid categories like II, III, IV, V and VII are also found to have inhibitory effects on the absorption of glucose from rat small intestinal fragments and this effect is found to be absent with gymnemic acid I[95].

Also, gymnemic acid IV increased plasma insulin levels[25] in STZ-diabetic mice when administered at a concentration of 13.4 mg/kg. In a study, oral administration of small concentrations (0.2 g/kg) of this plant produced a reduction in the elevated levels of blood sugar[96] induced by sucrose. After ingestion of Gymnemic acid, the pancrease tissue increases the secretion of insulin which promotes the regeneration of Islet cells of Langerhans and enhances the utilization of glucose, the phosphorylase activity also intensifies for utilization of glucose by insulin dependent pathway[91]. This molecule also inhibits the absorption of glucose from the intestine by binding with the receptors of intestine and prevents the glucose molecule to bond with the receptors, thus glucose absorption does not occur in the intestine

From the alpha amylase alpha glucosidase inhibitory effect of gymnemic acids and its comparison with metformin drug[97] and antidiabetic activity of gymnemic acid in streptozotocin induced diabetic rats it can be concluded that metformin is having multiple side effects but if given with gymnemic acid the dose can be decreased and side effects also can be reduced. So, this is an advantageous effect of gymnemic acid for antidiabetic activity

**Mechanism of Action of *Gymnema sylvestre* for Antidiabetic Activity**

Several mechanisms have been proposed to explain the anti-diabetic activity of *Gymnema sylvestre*. Gymnemic acids can prevent absorption of sugar molecules by the intestine, which leads to a reduction in blood sugar levels [98].

In a study, methanol extract of this plant showed increased effect on β-cell regeneration and was extrapolated that this plant might be able to completely recover pancreatic-cells function and thus treating type I diabetes[99].

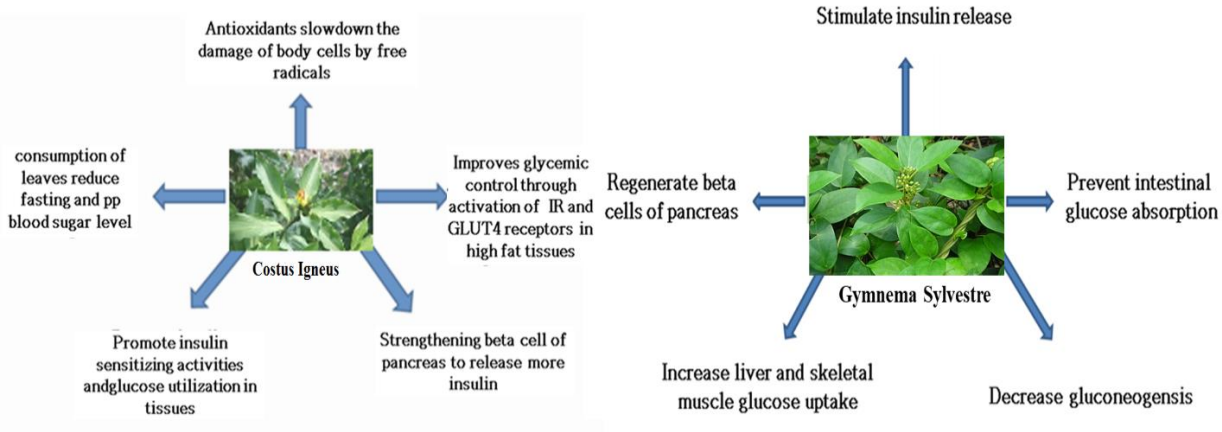



**Figure 2:** Mechanism of antidiabetic activities of *Costus igneus* and *Gymnema sylvestre*

**Comparison of anti-diabetic potential of *Costus igneus* and *Gymnema sylvestre***

The mechanism of antidiabetic activities of *Costus igneus* and *Gymnema sylvestre* as mentioned is summarized in Figure 2. *Costus igneus* is known as the insulin plant because it may lower glucose levels for some people (population based) with diabetes[100] due to its chemical constituents such as flavonoids, steroids and alkaloids. Various clinical researches have reported the therapeutic efficacy of *Costus igneus* leaves extract against Type 2 DM[101]. Dried leaf powder was administered to some diabetic patients with insulin and hypoglycaemic drugs treatment and to some diabetic patients without any allopathic therapies. After 15 days blood sugar was under control to both types of patients with or without allopathic oral drugs treatment[100] as flavonoids may enhance insulin secretion *via* pancreatic β-cell regeneration.

*Gymnema sylvestre* is effective in T1DM and T2DM. It enhances production or activity of insulin and promotes regeneration of pancreas beta cells confirmed by clinical report[102] in T1DM, leaf extract reduces insulin requirements and fasting glucose and improves glycemic control. It improves glycemic control in T2DM, reducing hypoglycemic drug needs.

Gymnemic acids, active constituents isolated form *Gymnema sylvestre* which are having prominent influence on blood sugar level[89]. Given orally even at small concentrations (0.2 g/kg), they produced a reduction in the elevated levels of blood sugar induced by sucrose[103]. Overnight fasted experimental animals treated with gymnemic acid and sucrose showed a reduction of fasting blood glucose level to 53 and 68% at 15- and 30-minutes intervals when compared to that of control group. Gymnemic acid given 1-2 hour before sucrose treatment and even with sucrose simultaneously resulted in 58 and 60% reduction after 15 and 30 min in concurrent to single gymenmic acid administration[89]. Gymnemic acids were reported to inhibit the conversion of glycogen in live to glucose molecules in blood[98].

Moreover, *Gymnema sylvestre*, a storehouse of antioxidants, combats detrimental toxins from oxidising healthy cells and prevents oxidative stress in the body. *Gymnema sylvestre* has great antioxidant potentiality[104] compared to that of *Costus igneus*.

Considering above it may be concluded that *Gymnema sylvestre* has more anti diabetic potential than *Costus igneus* (Table 5).

**Table 5:** Comparison between *Gymnema sylvestre* and *Costus igneus*

| ***Gymnema sylvestre*** | ***Costus igneus*** | **References** |
|---|---|---|
| 1.Anti-diabeticconstituents--Triterpenesaponins-gymnemic acids, gymnemasaponins, gurmarin and flavonol, glycosides. | 1.Anti-diabetic constituents----Flavonoids, Steroids and Alkaloids | (Shankarappa L, et.al, 2011)[26] (Irimpan MT, et.al,2011)[85] |
| 2.Antioxidants—Phenolic compounds-Alkaloids, Flavonoids, Phenols and Tannins | 2. Antioxidants---Ascorbic acid, α-tocophenol, β-carotene, Terpinoids, Steroids and Flavonoids | (Shankarappa L et.al, 2011)[26] (Irimpan MT et.al,2011)[85] |
| 3.It is effective in both Type-1 and Type 2 diabetes- Enhance production of insulin and promotes regeneration of pancreas β cells confirmed through clinical reports | 3. It is effective in Type-2 diabetes-- Corosolic acid in leaves of the plant helps to generate insulin, thereby treat diabetes. Research needs to cure Type 1 diabetes. | (Hedge PK, et.al. 2014)[17] |
| 4.For people with high HbA1C, *Gymnema sylvestre* can help reducing fasting, post meal and long term blood sugar level. There is no report of reducing blood sugar of certain people with diabetes | 4. Research show that it can help lower blood glucose level of certain people with diabetes. (population based). It can help reduce fasting and post meal blood sugar level. | (Goodson A et. al,2023)[105] (Shetty AJ, et.al. 2010)[100] |
| 5.*Costus igneus* leaves extract can significantly reduce post prandial blood glucose (type 2 diabetes) through inhibition of enzymes alpha amylase and alpha glucosidase confirmed in vitro studies and is comparable with that of metformin drug, the α-amylase and α glucosidase inhibitor. Epigallocatechin gallate (EGCG), a component of catechin and triterpenoids are responsible for α amylase and α glucosidase inhibition | 5. *Gymnema sylvestre* leaves Extract (methanolic) can also reduce post prandial blood glucose (type 2 diabetes) through inhibition alpha amylase and alpha glucosidase and is more potent with that of acarbose drug, the α amylase and α glucosidase inhibitor—confirmed through *in vitro* studies. Five new pregnane glycosides, gymsylosides (bioactive compounds) isolated from *Gymnema sylvestre* and four new arylated gymnemic acids are responsible for α-amylase and αglucosidase inhibitory activities. | (Laha S, et.al,2019)[106] (Imbrahim A, et.al.2017)[107] (Kiem PV et.al, 2020 )[108] (Alkefai NHet.al, 2018)[109] |

## CONCLUSION

In spite of various records of pharmacological and biological activities of the chemical constituents of *Costus igneus* and *Gymnema sylvestre*, the comparative study of anti-diabetic potential of these plants has not been reported. Structure activity relationship of gymnemic acid a chemical constituent of *Gymnema sylvestre* has not been reported so far.

This review will help –

i) future researchers to design/develop more potent 'lead' compounds through chemical synthesis having key

functional groups with proper position as new antidiabetic drugs from the parent natural phytoconstituents of *Costus igneus* and *Gymnema sylvestre*.

ii) further research is needed to compare antidiabetic activities of the phytochemical constituents of the Costus Ignues and *Gymnema sylvestre* through their structure-activity studies and through their chemical modification.

iii) generating conditions /doses of the drugs derived from Phyto constituents viz Flavonoids, Diosgenin and Gymnemic acids to find accurate efficacy for therapeutic applications through clinical studies. Besides these, this review will help the researchers to develop and design new herbal drugs. These clinically approved herbal drugs will cure diabetes as the constituent components are plant chemicals which have promising antioxidant and antidiabetic effects.

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