Review Article

# A Review on Secondary Metabolism in Anti-Diabetic Plants of Braj Region

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**ABSTRACT**

Plants produced different chemical substances which are biologically active with therapeutic applications in humans. Secondary metabolites are the chemical compound that includes alkaloids, flavonoids, phenols, glycosides, terpenoids and tannins etc. These play a major role in the world population which depends on herbal drugs for anti-diabetic treatments. Diabetes mellitus is a serious health issue with continuously increasing rates of incidence and mortality. The plants selected in the present review belongs to the families Malvaceae, Lamiaceae, Anacardiaceae, Combretaceae, Moraceae, Apocynaceae, Menispermaceae, Myrtaceae, Meliaceae, Asphodelaceae and Cucurbitaceae which shows hypoglycemic effects. The reviewed literature provides ample information on secondary metabolites with anti-diabetic properties in medicinal plants of Braj region. The Braj region plants and their parts are miraculous to the treatment of diabetes all over the World.

**Keywords:** Secondary metabolites, anti-diabetic properties, braj region plants, Diabetes mellitus, herbal drugs.

## INTRODUCTION

Plant metabolites are chemical substances which are produced in plants during their metabolic activities. Phytochemicals are produced by plants as the primary or secondary in origin[1].

Primary metabolites are direct product of metabolism while secondary metabolites are derived from primary metabolites. The concept of secondary metabolite can be liable to Kossel (1891) who was first to define these metabolites. Secondary metabolites do not participate directly in plant metabolism hence non-vital for plant[2].

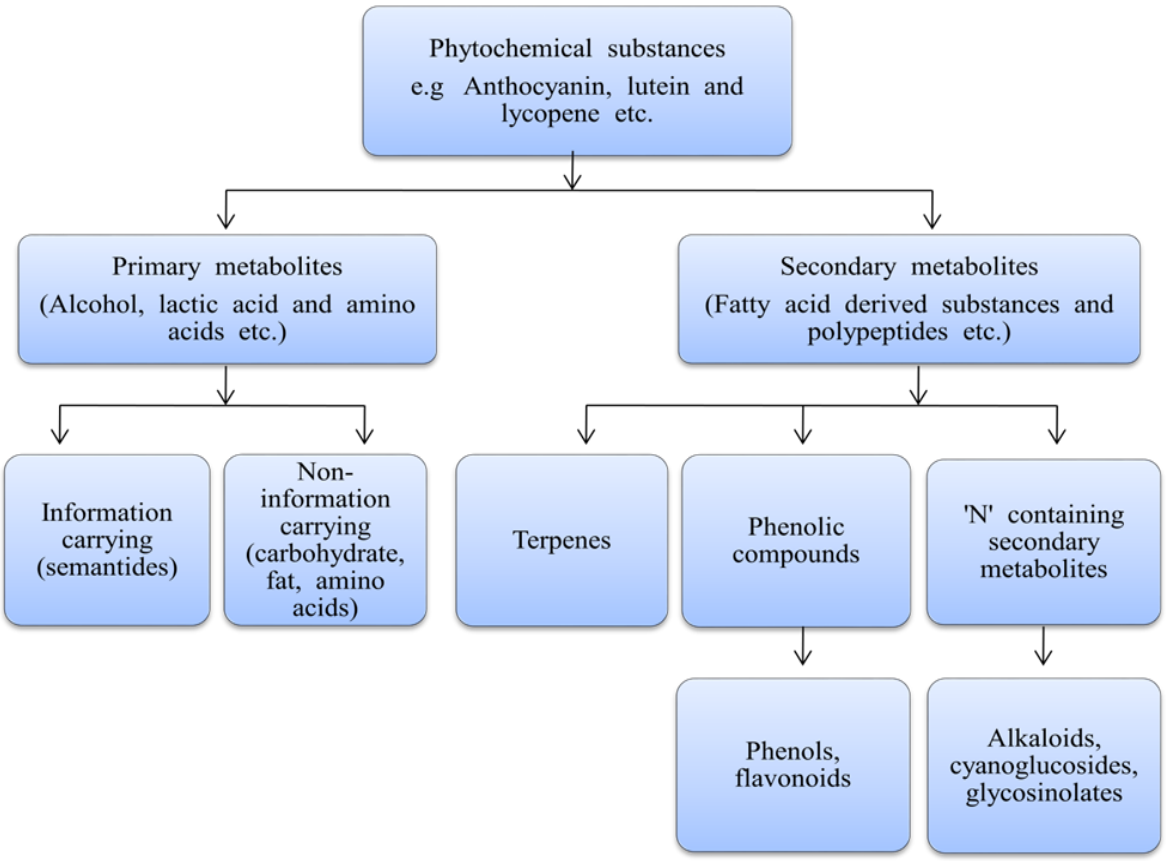



**Figure 1:** Classification of primary metabolites and secondary metabolites on the basis of origin

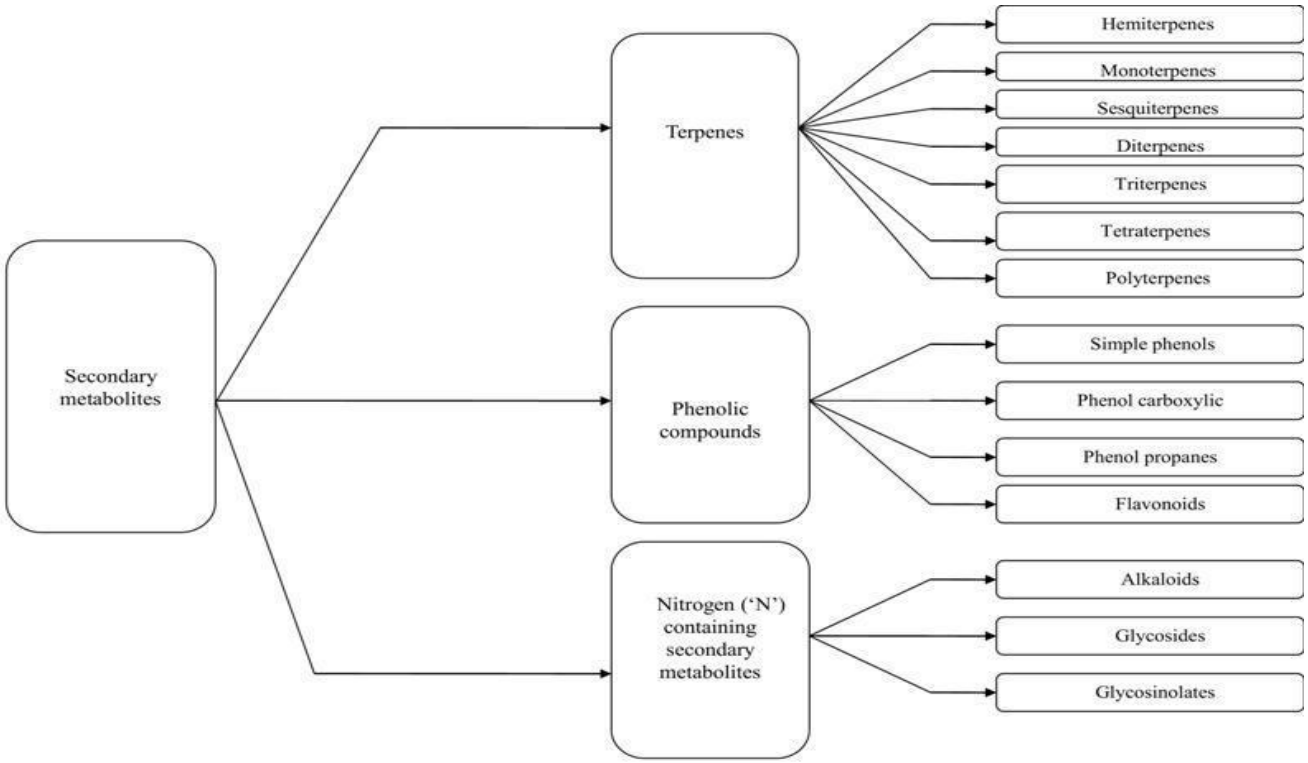
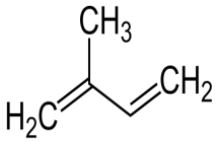
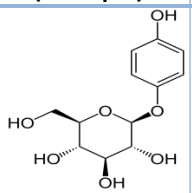
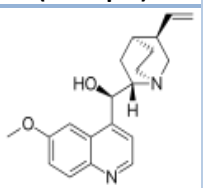
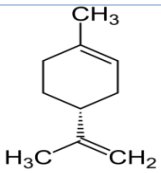
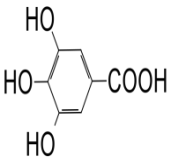
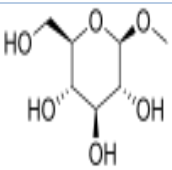
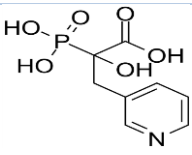
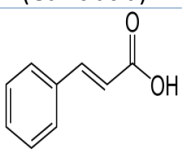
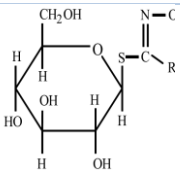
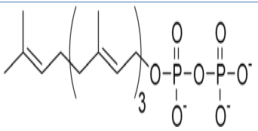
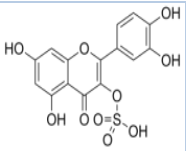
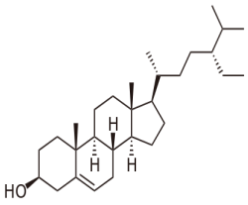
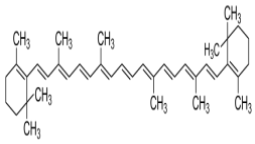
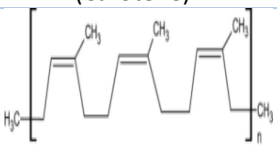



**Figure 2:** Classification of secondary metabolites on the basis of chemical nature

Classification of secondary metabolites are consists terpenes, nitrogen containing compounds (alkaloids, glycosides and glycosinolates), phenolic compounds (flavonoids, phenols and its derivatives) which are the part of them according to their specific structure.

**Table 1:** Secondary metabolites with structure and example[1,3,4]

| Terpene name | Chemical structure (example) | Phenolic compound | Chemical structure (example) | 'N' containg secondary metabolite | Chemical structure (example) |
|---|---|---|---|---|---|
| **Hemiterpenes** Single 5 carbon Unit (5C) |  (Isoprene) | **Simple phenol** One or more hydroxyl group and aromatic ring |  (Arbutin) | **Alkaloids** Crystalline non-volatile solid, bitter in taste and colourless |  (Quinin) |
| **Monoterpenes** Two 5 carbon unit (10C) |  (Limonene) | **Phenol carboxylic acids** Simple phenol bearing a carboxylic group |  (Gallic acid) | **Glycosides** Conjugated sugar (Non sugar and sugar) |  (Methyl glucoside) |
| **Sesquiterpenes** Three 5 carbon unit (15C) |  (Farnesyl Pyrophosphate) | **Phenol propanes** Phenyl and propane having side chain of 3C |  (Cinnamic acid) | **Glycosinolates** Natural component glycosides |  General glycosinolate |

| | | | | | |
|---|---|---|---|---|---|
| **Diterpenes** Four 5 carbon unit (20C) |  (Geranylgeranyl pyrophosphate) | **Flavonoids** Flavan skeleton with two aromatic ring |  (Quercetin) | - | - |
| **Triterpenes** Six 5 carbon unit (30C) |  (Sitosterol) | - | - | - | - |
| **Tetraterpenes** Eight 5 carbon unit (40C) |  (Carotene) | - | - | - | - |
| **Polyterpenes** Polymer of terpene unit |  (Natural rubber) | - | - | - | - |

Secondary metabolites are organic compounds produced by plants, fungi or bacteria and are not directly involved in the normal growth and development of the organism. Secondary metabolites often play an important role in plant protection against herbivore and other inter-species preservation[5]. Secondary metabolites play major role in the survival of the plant in their environment such as, attraction to pollinators, protection against predators and diseases[6,7]. Secondary metabolites are non essential to plant growth, hence are produced in small quantity[8].

Medicinal plants are the chief source of life saving drugs since ancient time. There has been keen attraction to evolve substitute to the whole plant for the production of secondary metabolites. However, several workers have extracted different secondary metabolites from many plants of Braj region which have anti-diabetic properties.

**Table 2:** Production of secondary metabolites from anti-diabetic plants of Braj region

| Plant | Family | Plant Part | Secondary metabolite | Reference |
|---|---|---|---|---|
| *Hibiscus rosa-sinensis* | Malvaceae | Flower and leaves | Alkaloids, phenols and glycosides | 9, 10, 11, 12 |
| *Ocimum sanctum* | Lamiaceae | Leaves | Phenols | 13 |
| *Mangifera indica* | Anacardiaceae | Leaves, stem, bark and fruit | Phenolics and flavonoids | 14 |
| *Terminalia chebula* | Combretaceae | Seed and fruit | Phenols and steroids | 15 |
| *Ficus benghalensis* | Moraceae | Bark | Terpenes | 16 |
| *Catharanthus roseus* | Apocynaceae | Whole plant | Alkaloids | 13 |
| *Tinospora cordifolia* | Menispermaceae | Stem | Glycosides and glucosinolates | 17 |
| *Eucalyptus globulus* | Myrtaceae | Leaves | Glycosides | 18 |
| *Azadirachta indica* | Meliaceae | Leaves and seeds | Terpenes | 19 |
| *Aloe vera* | Asphodelaceae | Leaves | Phenols | 20, 13 |
| *Momordica charantia* | Cucurbitaceae | Whole plant | Steroids and glycosides | 21, 22 |
| *Adansonia digitata* | Malvaceae | Stem and bark | Glycosides, tannins and alkaloids | 18 |

Bioactive constituents are defined as components of food and drugs that have an effect on physiological or cellular and metabolic activities in the human or animals that consume such compounds[23]. Plant products have laid out the formula for finding new drugs[24].

**Diabetes mellitus**

Diabetes mellitus in Ayurveda is known as 'Madhumeha' which is lifelong fatal condition due to insulin deficiency and affects 10 % of the population of the world. Diabetes is a group of metabolic diseases represented by high blood glucose levels that result from insulin overload. Insulin is a hormone which converts sugar, starches and other food into energy needed for daily needs. This disease is characterized by abnormally high plasma glucose levels, leading to major complications, like as insulin resistance, hypertension and obesity[25,26].

**A. Causes of Diabetes**

Generally, main causes of the diabetes are genetic makeup, family history, ethnicity, health, lazy life style, environmental factors and temporary pregnancy[27].

**B. Consequences of Diabetes**

Diabetes may result in the polyuria, polydipsia, polyphagia, fatigue, causing problems in the eyes, kidneys, feet and nerves, macrovascular and microvascular complications[28,29]. Many new bioactive drugs isolated from plants having hypoglycemic effects showed anti-diabetic activity equivalent to these plant and their parts or plant extract and sometimes even more potent than known synthetic oral hypoglycemic agents. There are different artificial medicines developed for patients, but it is the fact that it has never been reported that someone had recovered totally from diabetes[30]. Diabetes is causing many health issues to millions people worldwide and has become a powerful disorder in different countries[31,32,33]. The number of diabetic patients is expected to boost from present survey of 150 million to 230 million in 2025[34].

**C. Types of Diabetes**

These are mainly of two types:

Type I Diabetes or Insulin-dependent diabetes, juvenile diabetes or early-onset diabetes which there is usually total failure to secrete insulin which is known as ketoacidosis causing of autoimmune destruction of insulin secreting cells in the islets of Langerhans[35,36].

Type II Diabetes or Non insulin-dependent diabetes which occurs an inadequate amount of insulin secretion[37,38,39]. It is the result of a combined defect in insulin resistance, β-cell dysfunction, increased hepatic glucose dysfunction and reduced glucagon levels[40].

Gestational Diabetes is other type of diabetes which is effects females during pregnancy[41,42].

*Hibiscus rosa-sinensis, Ocimum sanctum, Mangifera indica, Terminalia chebula, Ficus benghalensis, Catharanthus roseus, Tinospora cordifolia, Eucalyptus globulus, Azadirachta indica, Aloe vera, Momordica charantia* and *Adansonia digitata* have consisted of large number of bioactive phytochemicals such as flavonoids, alkaloids, phenols, tannins, glycosides, saponins and steroids etc possess hypoglycemic effect used for remedial purposes[43]. Anti-diabetic plants of Braj region and their bioactive compounds sources and pharmaceutical attributes are summarized below.

**Table 3:** Anti-diabetic plants of Braj region and their biocactive compounds

| Plant | Parts | Bioactive compound | Solvent employed in various studies for extraction | Pharmaceutical activity attributed | Reported experimental validation | References |
|---|---|---|---|---|---|---|
| *Hibiscus rosa-sinensis* | Whole plant, leaf powder | Cyanidins, Quercetin, and Hentriaconta-ne | Aqueous methanol | Anticomplimentary, Antidiarrhetic, Antimicrobial, Antioxidant and Antidiabetic | Oral dose of 100 and 200 mg/kg body weight to non-obese diabetic mice shows significant reduction in blood glucose level | 44 |
| *Ocimum sanctum* | Leaf | Eugenol (1-hydroxy-2-methoxy-4- allyl benzene) | - | Antidiabetic | - | 13 |
| *Mangifera indica* | Leaf, stem and bark | Tannins, Saponins, Glycosides, and Phenols | Methanol, hexane and ethyl acetate | Antioxidant, Radioprotective, Immuno modulatory, Antiallergic, Antiinflammatory, Anti-tumor, Lipolytic, Antiviral, Antibacterial and Antifungal | Oral admin istration of aqueous leaf extract 1 g/kg in streptozotocin induced diabetic rats reduced blood glucose level | 45, 46 |
| *Terminalia chebula* | Seed and fruit | Shikimic, Gallic, Triacontan oic, Palmitic acid, β- | Aqueous chloroform | Hypoglycemic | Oral administration dose 200 mg/kg in streptozotocin induced | 47 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | sitosterol and Daucosterol | | | diabetic rats reduced blood glucose level | |
| *Ficus benghalensis* | Root and bark | Leucopelargonidin | - | Antidiabetic | - | 48 |
| *Catharanthus roseus* | Whole plant | Tannins, Triterpenes, Alkaloids, Flavonoids and Saponins | Aqueous ethanol, acetone and methanol | Hypotensive, Antibacterial, Antifungal, Antiviral and Anticancer | Dry leaf powder at dose 3 mg/kg shows significant antidiabetic effect in streptozotocin induced diabetic rats | 49, 50, 51 |
| *Tinospora cordifolia* | Stem | Alkaloids, Glycoside, Terpenoids, Lactones and Steroids | Aqueous alcohol | Hypolipidemic, Hypoglycemic, Cardioprotective, Hepatoprotective, Antioxidant and Antiinflammatory | Oral administration of the aqueous root extract led to a decrease in blood and urine glucose and lipids level in alloxanized rats | 52 |
| *Eucalyptus globulus* | Leaf | Calytoside | - | Antidiabetic | - | 53 |
| *Azadirachta indica* | Leaf, bark, fruit and seed oil | Isopreinoids, Azadirone, Azadirachtin, Polyphenolic, Flavonoids, Glycoside, Terpenoids, Caumarin and Tannin | Aqueous methanol, Chloroform | Antiinflammatory, Antiarthritic, Anti-pyretic, Hypoglycemic, Antigastric ulcer, Spermicidal, Antifungal, Antibacterial, Diuretic, Immunomodulatory, Antimalarial, Hepatoprotective and Antioxidant in serum total, LDL and HDL cholesterol and triacylglycerol which increased in diabetic rats | Aqueous leaves extract at a dose of 250 mg/kg body weight for 16 weeks resulted significant fall in blood glucose and improvement | 54 |
| *Aloe vera* | Leaf | Pentosidesbarbaloin, Isobarbaloin, Betabarbaloin, Anthraquinones, Saponins, Lignin, and Salicylic acid | Aqueous | Cardioprotective, Antitumor, Antioxidant, Anti-inflammatory, Hepatoprotective, Immunomodulatory and Antifungal | *Aloe vera* extract was orally administered at 0.5 ml/100 gm body weight showed antihyprerglyc-emic effect | 20, 55 |
| *Momordica charantia* | Whole plant | Charantin, Polypeptide, Polypeptidep, Vicine and Momo rdicine | Aqueous methanol | Antidiabetic, Hypoglycemic, Hepatoprotective, Antibacterial, Antiviral and Antitumor | The treatment of streptozotocin induced diabetic rats with *M. charantia* fruit extract over a 10 week period returned the levels of blood glucose and lipid profile close to normal | 56, 57 |
| *Adansonia digitata* | Stem and bark | Glycosides, Tannins, Alkaloids, Lupeol and Semigossypal | Methanol | Hypoglycemic | The dose of 400 mg/kg also showed a significant decrease of blood glucose after 5 and 7 hours. It possesses anti-diabetic effect on streptozotocin induced diabetic Wistar rats | 58 |

**Exploration of Braj region plants to show anti-diabetic activity**

1. ***Hibiscus rosa-sinensis***

It is a flowering small tree which is found throughout India and the leaves and commonly known as 'Gurhal' flowers of this plant are having potential as anti-diabetic action. Its leaves and flowers adopted to treat as anti-diabetic, anti-hypertensive, anti-oxidants, anti-inflammatory, cardiovascular and anti-fertility activity etc.

**2. *Ocimum sanctum***

It is commonly known as 'Tulsi' which is used traditionally as home remedies for various types of diseases. *Ocimum sanctum* leaves in water on an empty stomach upon rising which caused a significant decrease in both fasting and postprandial blood glucose levels[59]. The leaves of *Ocimum sanctum* have been reported to reduce blood glucose when administered to rats and humans.

**3. *Mangifera indica***

It is popularly known as 'Mango' belongs to family Anacardiaceae which is a large fruit-tree and capable of growing to a height and crown width of about 30 m and trunk circumference of more than 3.7 m. The leaves of this plant have potential to treatment of diabetes. Aqueous extract of *Mangifera indica* leaves possess hypoglycemic activity which is responsible to an intestinal reduction of the absorption of glucose[60].

**4. *Terminalia chebula***

It has been widely used in diabetes in Ayurveda and widely distributed in India. Herbal constituents are containing with *Terminalia chebula* which is commonly known as 'Triphala' used for the treatment of diabetes.

**5. *Ficus benghalensis***

It is commonly known as the 'Banyan tree', a very large tree with spreading branches which belongs to the family Moraceae. Bark of this plant is used for the treatment of diabetes. The stem and bark of *Ficus benghalensis* are contains ß-sitosterol, α-D-glucose and meso-inositol. Anti-diabetic activity of the various parts of the plant used glibenclamide as a standard drug[61].

**6. *Catharanthus roseus***

It is commonly known as 'Rose periwinkle' or 'Sadabahar' which belongs to the family Apocynaceae. The medicinal preparations of this plant have been formulated and developed to the treatment of diabetes.

**7. *Tinospora cordifolia***

It is a huge, glabrous, deciduous climbing shrub, belonging to the family Menispermaceae which is widely distributed throughout India and commonly known as 'Guduchi' or 'Giloy'. Oral administration of the extract of roots for 6 weeks resulted in a significant reduction in blood and urine glucose in alloxan diabetic rats[62]. Alcoholic and aqueous extract of *Tinospora cordifolia* decreases the blood glucose level and increases glucose tolerance capacity.

**8. *Eucalyptus globulus***

It is popularly known as 'Safeda'. Its rapid growth and adaptability to a range of conditions is responsible for its popularity. The leaves of this plant used as a traditional treatment for diabetes.

**9. *Azadirachta indica***

It is commonly known as 'Neem' and a tree in the mahogany family Meliaceae. Products made from neem have been used in India for their medicinal properties such as anti-fungal, anti-diabetic, anti-bacterial, anti-viral, contraceptive and sedative. 'Nimbin' is the bitter compound which have isolated from its seeds and bitter taste of this compound due to the presence of terpenes. The most important bioactive compound is azadirachtin which is an insect repellent. Leaves and seeds extracts of *Azadirachta indica* may actually help to repair or regenerate the pancreas's beta cells which play a crucial role in the production and secretion of insulin[59].

**10. *Aloe vera***

It is one of the most popular house grown plant have a long history as a multipurpose folk remedy. The plant can be divided into two basic products: gel and latex. *Aloe vera* gel is the leaf pulp. Latex of *Aloe vera* all time referred to as "aloe juice". It is bitter yellow exudates from the pericyclic tubules just around outer skin of the leaves. Its bitter principle is through stimulation of synthesis of insulin from pancreatic beta cells[63]. Extraction of aloe gum increases glucose tolerance and decrease blood sugar level.

**11. *Momordica charantia***

It is a member of family Cucurbitaceae which is commonly known as 'Kugua', 'Karela', 'Bitter gourd' or 'Bitter melon'. It is popular herbal resource and is often used to treat diabetes. *Momordica charantia* increases the revival of parietal cells in the pancreas or may permit the recovery of partially destroyed cells[64] and stimulates secretion of pancreatic insulin. Polypeptide p, isolated from fruit, seeds and tissues of this plant which showed important hypoglycemic effect[65].

**12. *Adansonia digitata***

*Adansonia digitata* commonly known as 'Baobab' is the most widespread tree and native to the African continent. It has been traditionally valued as sources of food, health remedies or places of shelter and is steeped in legend and superstition. Stem, bark and entire plant of Baobab are used to the treatment of diabetes.

Active secondary metabolite product currently to pull out from above plants which are used as food additives, dyes, fragrances, flavors, pharmaceuticals, pesticides, cosmetics and fine chemicals[66]. Secondary metabolites are used as medicines, narcotic, flavorings and pigments. Some secondary metabolites are also produced in response to different stress[67].

**Table 4:** Anti-diabetic plants of Braj region's containing bioactive compound with their action[68]

| Plant | Local name | Part used | Mechanism of action | Bioactive compound |
|---|---|---|---|---|
| *Hibiscus rosa-sinensis* | Gurhal | Entire plant | Stimulate insulin secretion from beta cell | Vitamin 'B' and 'C,' cyanidin, quercetin, and hentiacontane |
| *Ocimum sanctum* | Tulsi | Leaves | Lowering blood sugar level | Volatile oil, phenol, aldehyde, fixed oil, alkaloid, tannin and ascorbic acid |
| *Mangifera indica* | Mango | Leaves | Reduction of intestinal absorption of glucose | Mangiferin |
| *Terminalia chebula* | Haran | Seed and fruit | Decrease blood sugar level | Polyhydroxytri terpenoid and ellagic acid |
| *Ficus benghalensis* | Bargad | Bark | Rising serum insulin | Tannin |
| *Catharanthus roseus* | Sadabahar | Leaves | Beta cell rejuvenation, regeneration and stimulation | Vincristine and vinblastine |
| *Tinospora cordifolia* | Giloy | Stem and root | Stimulates insulin release from islets or decrease brain lipid | Berberin and starch |
| *Eucalyptus globulus* | Safeda | Leaves | Increase insulin secretion from clonal pancreatic beta line | Essential oil and Cinol |
| *Azadirachta indica* | Neem | Leaves | Glycogenolytic effect due to epinephrine action was blocked | Nimbidin, Nimbin, Nimbidol and Nimbosterol |
| *Aloe vera* | Gheequar | Entire plant | Stimulating synthesis or release insulin | Aloin glycoside |
| *Momordica charantia* | Karela | Fruit | Reduce blood glucose level | Momordicine alkaloid, ascorbic acid |
| *Adansonia digitata* | Baobab | Seed, fruit and bark | Decrease blood sugar level | Kaempferol glucoside and chlorogenic acid |

**Herbal drug**

Herbal medicine or phytomedicines are refers to the use of any plant's part viz; seeds, fruits, roots, leaves, bark or flowers, etc in pharmacy. Whole herbs contain many phyto-ingredients which is likely that they work together to produce the desired medicinal effect. Herbal extracts are reported to treatment of Diabetes mellitus which are classified the drugs according to their mode of action as[69].

**A.** Herbal extracts act as α-glucisidase or α-amylase inhibitor which are able to reduce the blood glucose level by inhibiting the gastric enzymes which is obligatory for the break polysaccharides into the simple sugar. There are large numbers of plants which have the capability to inhibit the *α*-glucosidase and *α*-amylase activity and may be used as treatment of diabetes (Type I and Type II).

**B.** Herbal extracts act as increases insulin secretion or *β*-cell regeneration which is directly concern with the Type I diabetes to secrete the less or few amount of insulin.

**C.** Herbal extracts performed as the hypoglycemic, anti-hyperglycemic effect to reduce the blood glucose level directly which are used to the treatment of Type I and Type II diabetes.

**Action of herbal drug as anti-diabetics**

The anti-diabetic activity of herbal drugs depends upon various mechanisms of action as[70]:

1. Adrenomimeticism, pancreatic beta cell potassium channel blocking, cAMP (2nd messenger) stimulation.
2. Inhibition in renal glucose reabsorption.
3. Stimulation of insulin secretion from beta cells of islets or inhibition of insulin degradative processes.
4. Reduction in insulin resistance.
5. Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta cells.
6. Regenerating or repairing pancreatic beta cells.
7. Increasing the size and number of cells in the islets of langerhans.
8. Stimulation of insulin secretion.
9. Stimulation of glycogenesis and hepatic glycolysis.
10. Protective effect on the destruction of the beta cells.

11. Improvement in digestion along with reduction in blood sugar and urea.
12. Prevention of pathological conversion of starch to glucose.
13. Inhibition of β-galactocidase and α-glucocidase.
14. Cortisol lowering activities.
15. Inhibition of alpha-amylase.

## CONCLUSION

Plants have been a source of medicinal bioactive compounds since ancient times and used to treat diabetes. The study of secondary metabolism in anti-diabetic plants is an important source for the finding of bioactive compounds with diverse applications. Secondary metabolites are frequently produced at highest level during active growth to stationary phase. Diabetes mellitus is a universal health disorder that causes a leading risk of vascular diseases, decline in the quality of life and enhanced mortality rate. Recently, researches have revealed that a number of medicinal plants belonging to families like Malvaceae, Lamiaceae, Anacardiaceae, Combretaceae, Moraceae, Apocynaceae, Menispermaceae, Myrtaceae, Meliaceae, Asphodelaceae and Cucurbitaceae have shown anti-diabetic and hypoglycemic activities attributed to their unique secondary metabolites such as flavonoids, terpenes, phenols, alkaloids and glycosides etc. Many complications of diabetes have raised the demand to produce bioactive phytochemicals with anti-diabetic activity increases and their constituents to prepare a strong area of efficient and secure drugs for management and prohibition of diabetes. The present review will be an aid to add the information of the anti–diabetic compound containing plants found in the Braj region (Agra, U. P.; India) and other surrounding vegetations. Commercial value of phytoconstituents may generate considerable interest in drug companies for the manufacture of new drugs for diabetes.

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## DECLARATION OF INTEREST STATEMENT

The author declares that they have no competing interests.

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