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COSTUS IGNEUS – A THERAPEUTIC ANTI-DIABETIC HERB WITH ACTIVE PHYTOCONSTITUTENTS

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ABSTRACT: Objective: Diabetes mellitus is an interminable metabolic disorder that has highly affected human health and quality of life. Conventional agents are being applied to control this disorder along with lifestyle management. But they are not totally effective and nobody has ever been diagnosed with full recovery of diabetes. Medicinal plants have been used for greater extent for control of diabetes mellitus in various traditional system of medicine worldwide as they are of natural origin and many of them are known to be effective against diabetes. *Costus igneus* is known as a blazing *Costus*, step stepping stool or Spiral banner. In India, it is popularly known as insulin plant due to the consumption of leaves of *Costus igneus* helps to prevent diabetes mellitus by decreasing the blood glucose level. A comprehensive review was conducted to collect data about medicinal herbs used for the treatment of diabetes mellitus. This review deals with the study of chemical structures of plant constituents and their mechanism of action. **Materials and Methods:** Review is mainly focused on *Costus igneus* especially on its anti-diabetic activity. **Result:** Reviews suggest that *Costus igneus* has anti-diabetic potential especially on diabetes mellitus. **Conclusion:** Considering the ability of the valuable things present in *Costus igneus*, this review is aimed to summarize the information of the biochemical constituents, their chemical structures, and mode of action. Due to the high therapeutic potential, these bio-compounds deserve special attention.

INTRODUCTION: Nowadays people are very conscious about their health due to the prevalence of fatal diseases, due to their food habits, workloads, hypertension, a time gap of having foods and various other daily activities. Diabetes mellitus is such a chronic metabolic disorder related to above-said activities. It is defined as a disorder in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood.

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It is of two types, *i.e*. Type 1 and Type 2. Type 1 diabetes is also called as insulin-dependent diabetes or juvenile-onset diabetes due to its appearance in childhood. But in the present situation Type 2 is mostly concerned due to its deleterious effects. Statistical reports are available on death rates of diabetic patients like in 2012 diabetes caused 1.5 million deaths around worldwide. Many of these deaths (43%) occur under age of 70. [1] This number may be increased up to 592 million people by 2030, *i.e.*, 9% of the country's population is likely to be affected from diabetes [2].

Hence, it is important to control diabetes. The management of diabetes is still major demand for research on natural products with anti-diabetic properties [3]. In India, the herb *Costus igneus* is popularly known as insulin plant. Due to consumption of one leaf of *Costus* a day keeps diabetes away [4].

India has great variation in various factors like geographical, topographical, climatic and edaphic conditions that leads to a great diversity in biological wealth, variations in agronomic conditions like plant species, cultivar, developmental stage, plant organ, plant competition, fertilization, pH, season, climatic factors, water availability, light intensity, quality, and duration and CO_2 *etc.* These factors are known to significantly affect the phytochemical profile of the plant. In the Indian scenario, WHO estimates about 70% to 80% of Indians depend on the Indian system of medicine like Unani, Siddha and Ayurveda [5]. Traditional use of herbal medicine is usually an integral part of the culture around the world, which has been used in medical practice for thousands of years and has made a great contribution for maintaining human health before the spread of modern science [6]. Herbal drugs are playing major role in the world because of their safety, efficacy and cost-effectiveness.

India has come into view as the diabetic capital of the world. Scientists are desperately trying to tackle this disorder. Evaluation of plant products for the treatment of diabetes mellitus is of growing eagerness as they contain many bio-active compounds with action potentials. In recent years several authors evaluated and identified the anti-diabetic potential of traditionally used Indian medicinal plants using experimental animals. *Costus igneus* is known as insulin plant [7]. It is widely grown in gardens as an ornamental plant in south India [8]. The anti-oxidant, anti-diabetic, anti-inflammatory and hypolipidemic potential of *Costus igneus* leave been evidenced by research [9]. People have been consuming raw leaves of *Costus igneus* to control blood glucose level for its anti-diabetic activity.

Various important bio components are present in aqueous and methanolic extracts of *Costus igneus* [10]. These components are flavonoids, tannins, saponins, alkaloids, glycosides, lignins, and phytosterol *etc*. Besides these components, another important triterpenoid component is corosolic acid. Having a natural concentration of corosolic acid, insulin plant can have a positive effect on blood sugar levels [11]. Corosolic acid works on lipid metabolism and regulation of glucose like insulin into cells and out of the bloodstream. This can be effective for anyone who has a problem with diabetes. In this review, we critically discuss the potential utility of several anti-diabetic biocomponents from *Costus igneus* with their possible mode of action for treatment of Type 2 diabetes.

Diabetes Mellitus and Folk Medicine: Diabetes mellitus is a debilitating human disease. It is known to man since time immemorial [12]. Diabetes is a major cause of morbidity and mortality, though these outcomes are not due to the immediate effects of the disorder. It is a disorder of carbohydrate metabolism characterized by the impaired ability of the body to produce or respond to insulin which is known as insulin resistance. In such a situation, beta cells of the pancreas cannot meet its demand [13].

Blood vessels and blood are the routes that transport sugar from where it is taken in (the stomach) or manufactured (in the liver) to the cells where it is used (muscles) or where it is stored (fat). Sugar cannot move into the cells but the helper or key agent, insulin produced from β cells of pancreas helps to move it into the cells for use as energy. When sugar leaves the bloodstream and takes entry into the cells, the blood sugar level is lowered. Without insulin, sugar cannot get into the body's cells for use as energy. This causes sugar to rise. Too much sugar level in the blood causes "hyperglycemia" or diabetes.

Two main types of diabetes are found *i.e.* Type 1 and Type 2.

Type 1 is a chronic illness manifested by the body's incapability of producing insulin due to the autoimmune destruction of the beta cells in the pancreas. Various symptoms like polyuria, polydipsia, polyphagia, and unexpected weight loss *etc*. are found. It is the most common form of diabetes in people who are under age 30, but it can occur at any age. 10% of people are diagnosed with Type 1 diabetes.

In Type 2 diabetes, insulin resistance occurs. Nine out of ten people with diabetes have Type 2. It is more common in young adults, teens and children and accounts for roughly 90% of the population. It is found most often in people who are over 40 years old and overweight.

It is of greater concern because in Type 2 diabetes the keyhole is rusty means the body makes insulin, but the body's cells are resistant to it. As a result, we have keys, but they have trouble opening the cells. Various symptoms like increased thirst, increased hunger, dry mouth, frequent urination, unexplained weight loss, weak, tired feeling, blurred vision, numbness, slow-healing sores, dry and itching skin, frequent yeast infection *etc*. are common. Serious long term complications include cardiovascular disease, chronic renal failure, retinal damage, nerve damage and microvascular damage which may cause erecting dysfunction and poor healing [14]. Type 2 diabetes is now a common and serious global health problem which, for most countries has evolved in association with rapid cultural and social changes, aging populations, increasing urbanization, dietary changes, reduced physical activity, and other unhealthy lifestyle and behavioral patterns (IDF, 2006). Herbal products or plant products are rich in phenolic compounds, flavonoids, terpenoids, coumarins and other constituents which show a reduction in blood glucose levels [15, 16].

Several species of herbal drugs have been described in the scientific and popular literature as having anti-diabetic activity [17]. Several investigators reported anti-diabetic properties of various herbs not only in rats but also in human [18, 19, 20]. Some of these showed the mechanisms by which medical plants produce anti-diabetic effects include recovery of beta cells inhibition of glucose absorption, stimulation of insulin release, increased glucose tolerance and lipid-lowering properties [21, 22, 23, 24]. Many treatments are available to treat Type 2 diabetes control like the use of synthetic drugs (Metformin, statin, insulin therapy, *etc*.), surgeries, joining of weight loss programme, etc are not at all permanent procurement. Permanent cure with low or no side effects of any compounds is essential. So, herbal medicine with bioactive components may be an important missile. Folk medicine is such a type of medicine that use herbs with low or no side effects and cost-effective. WHO defines traditional medicine is "the total of the knowledge, skills, and practices based on theories, beliefs and experiences indigenous to different cultures, whether explicable or not, prevention, diagnosis, improvement and treatment of physical and mental illness."

The proportion of use of plants in the different Indian system of medicine is Ayurveda 2000, Siddha 1300, Unani 1000, Homeopathy 800, Tibetian 500, Modern 200, and folk 4500. In India, around 25,000 active plant-based formulations are used in traditional and folk medicine. Plant derivatives with hypoglycemic properties have been used in folk medicine and traditional healing system around the world from ancient time [25]. Despite, the introduction of hypoglycemic agents from natural and synthetic resources, diabetes and its secondary complications continue to be a major medical problem to people [26]. In traditional medicine, diabetes mellitus is treated with diet, physical exercise, and medicinal plants. Even though more than 1200 plants were used in the control of diabetes mellitus, approximately 30% of the anti-diabetic plants were pharmacologically and chemically investigated [27].

In the Indian System of Medicines, more than hundred medicinal plants were mentioned including folk medicines for the management of diabetes, which is effective either separately or in combinations. *Costus igneus* is such a type of herb that can be used as an alternative therapeutic agent with its availability, low or no side effects, and cost-effectiveness.

METHODOLOGY: Folk medicine or traditional medicine conveys medical aspects of traditional knowledge that developed over generations within various societies before the start-up of modern medicine. In some Asian and African countries, up to 80% of the population relies on traditional medicine for their primary healthcare needs. In India, about 70% of the rural population depends on the traditional Ayurvedic system of medicine. Most of the traditional system user makes their formulation by their recipes and dispense to the patients. The WHO notes, however, that "further research is needed to ascertain the efficacy and safety" of several of the practices and medicinal plants used by traditional medicine systems. Alternative medicines are becoming more popular day by day because of their cost-effectiveness, conventional treatments, wide availability and pure in preparation.

Plants can contain sugars, minerals, proteins and other chemicals that interact with the active

compounds in a variety of ways *viz.* they may concentrate or intensify its effect, they may take it easier to digest or absorb, or they may lessen its harsh or toxic side effects [28]. Leaves of *Costus igneus* were among the plants known to be effectively used for treating diabetes by the tribes of Kolli hills of Namakkal district of Tamil Nadu [29]. Innumerable biologically active compounds that are present in plants occupy anti-diabetic properties.

Medicinal plants used to treat hypoglycemic and hyperglycemic events are of thirst area to ethnobotanical community as the plants contain valuable bioactive medical properties in its various parts. *Costus igneus* leaves (Costaceae family), the leaves of the so-called INSULIN plant, have been claimed to have anti-diabetic effects in the Ayurvedic system of medicine, as a treatment for diabetes. The main objective of the study is to assess the effects of the insulin plant on the blood sugar levels of diabetic Type 2 patients.

According to the data, collected from various sources like Research Gate, PubMed, Science Direct, *etc*. for evaluating on the biological and pharmacological activities of *Costus igneus*, there are many herbal remedies suggested for diabetes and diabetic complications. Medicinal plants form the main ingredients of these formulations.

It is important to know the active components and their molecular interaction, which will help to analyze the therapeutic efficacy of the product and also to standardize the product. Efforts are now being made to investigate the mechanism of action of active bio-components of *Costus igneus*.

Different literature and review articles were searched on *Costus igneus* about its phytochemical constituents, parts used, a method of use, color, taste, duration of use, *etc*. The list of references for all relevant articles was also studied to include all reports and reviews related to the matter.

Occurrence: It is native to eastern Brazil (states of Bahia and Espirito Santo) and South America. It is also found in Tropical Africa, Asia, Australia, and North America also. It is introduced to India from America as an herbal cure for diabetes. In India, *costus* is mainly found in the regions of Kashmir and South India [30].

Morphology: It is an upright, perennial shrub and is about two feet tall. Long branches are falling over the ground. Leaves are simple, alternate, oblong, twenty to twenty-five cm in length with several parallel thick veins. Soft, cylindrical, fleshy, pale brown rhizome is present. Strong tap root is also present which is wider at the top, sub-cylindrical in shape with light brown to pale, dark brown color. At the top of the branches, orange flowers are present. Fruits are very small, green in color.

Growth and Propagation: It grows under full sun or partial shade. It needs fertile soil with heavy moisture and is often planted near water. Propagation occurs by the division of the clumps, cuttings, or by separating the offsets that form below the flower heads. It is cultivated in the coastal area, Uttar Kannada district of Karnataka and Tamil Nadu.

Bio-Active Compounds (Anti-Diabetic): *Costus igneus* contains various phytochemicals like flavonoids, alkaloids, terpenoids and it was traditionally used in India to control diabetes and in experimental diabetic rats [31, 32, 33, 34, 35, 36]. Chemical structures of various anti-diabetic components are mentioned in **Fig. 1**. Such bio-components are present in various plant parts like in leaves, stems, rhizomes, *etc*.

In Leaves: Carbohydrates, triterpenoids, proteins, alkaloids, tannins, saponins, and flavonoids, *etc*. are present in leaves [37]. Besides these, steroids and carbohydrate like roseoside, fatty acids like hexadecanoic acid, 9, 12- octadecanoic acid, tetradecanoic acid, ethyl oleate, oleic acid, squalene are also present in leaves.

In Stem: Terpenoid compound lupeol and steroid compound stigmasterol are present in the stem.

In Rhizome: Quercetin, diosgenin, a steroidal sapogenin *etc*. are available in rhizome [38].

In Root: Terpenoid, alkaloids, Tannins, *etc*. are available in root portion [39].

Chemical Nature:

Tri-terpenoids: Triterpenoids are class of three terpene units or six isoprene units, *e.g*. β-carotene, corosolic acid / glucosol, glycyrrhetinic acid, lupeol, β-amyrin.

Steroids: Steroids are biologically active organic compounds with four rings arranged in a specific molecular configuration, *e.g*. stigmasterol, β-sitosterol, diosgenin.

Alkaloids: Alkaloids are nitrogen-containing natural compounds containing heterocyclic and non-heterocyclic chemical structure. But in *Costus igneus*, no remarkable alkaloids are present.

Phenols: Phenols are chemical compounds consisting of a hydroxyl group bonded directly to an aromatic hydrocarbon group, *e.g.* catechin, stricnin, isostricnin, christinin-A.

Flavonoids: Flavonoids are a group of hydroxylated polyphenolic compounds that are known to be potent free radical scavengers, have attracted tremendous interest as possible therapeutics against free radical-mediated diseases, particularly diabetes mellitus. They are benzo-gama = pyrone derivatives, *e.g*. epigallocatechin gallate, cinchona in ib, quercetin, epicatechin.

Proteins: Proteins are large bio-molecules or macromolecules consisting of one or more large chains of amino acid residues, *e.g.* Insulin-like protein.

Fatty Acid: Fatty acid is a carboxylic acid with a long aliphatic chain which is either saturated or unsaturated, *e.g.* hexa decanoid acid, 9, 12 octa-decanoic acids, tetradecanoic acid, ethyl oleate, oleic acid.

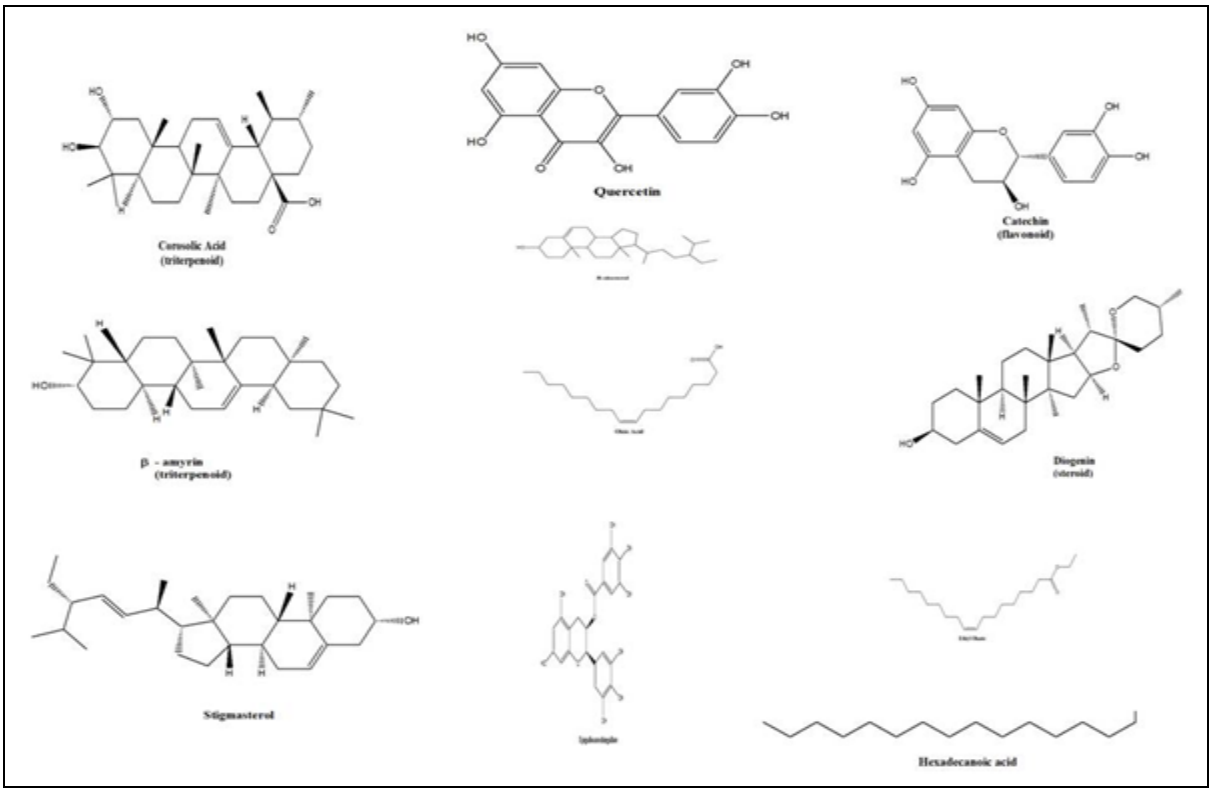

FIG. 1: CHEMICAL STRUCTURE OF THE IMPORTANT BIO-ACTIVE COMPOUNDS FROM *COSTUS IGNEUS*

Mode of Action:

Tri-terpenoids: Tri-terpenoids acts mainly by inhibiting alpha-glucosidase and alpha-amylase activity that delay the absorbance of carbohydrates in intestine leading to a decrease in the postprandial insulin level [40]. It causes insulin resistance, normalization of plasma glucose and insulin level and glucose metabolism. The known triterpenes, oleanolic and ursolic acid show activity against diabetic complications might be due to its effect on expression of aldose reductase and SDH. The suppression is caused by aldose reductase, and SDH decreases endogenous AGE generation and carbonyl stress involved in the progression of diabetic complications. Ursolic acid reduces expression of DGAT in protein which might also be involved in the hepatic triglyceride deposition and also helps in enhancing insulin receptor [41]. Corosolic acid helps in glucose uptake [42]. But the amount of corosolic acid present in *Costus igneus* is very less, obtained from different literature.

Steroids: Steroids like diosgenin decreases the activities of diabetes associated enzymes (such as ATP-cytrate lyase, pyruvate kinase and glucose -6-phosphate dehydrogenase) in the liver of diabetic rats [43]. Diosgenin is effective against reducing plasma glucose levels in diabetic rats. It can be useful in the treatment of diabetes by promoting adipocyte differentiation and by inhibiting inflammation in adipose tissues. Therefore, it may be useful to improve the patients' condition in the glucose metabolic disorder associated with obesity. In this context, in another experimental model, it was observed that diosgenin led to a reduction of plasma and hepatic triglyceride in obese diabetic mice and may be useful for the management of diabetes-related hepatic dyslipidemias. In diosgenin treated diabetic rats, a reduction of hyperglycemia, hypercholesterolemia, and hyperglyceridemia was observed. In another report, it was demonstrated that after administration of diosgenin to diabetic rats, the activity of glucokinase decreased, while the activities of glucose-6-phosphatase and fructose-1, 6-biphosphatase in the liver have increased.

In another study, among other positive changes in several parameters linked with diabetes, the supplementation with diosgenin decreased blood glucose levels in diabetic rats when compared to the group of rats fed with normal diet. It stimulates the renewal of β-cells in the pancreas or helps in recovery of partially destroyed β-cells and helps in pancreatic insulin secretion as a result plasma insulin level increased and blood glucose is controlled. All of these reports stating that diosgenin has hypoglycemic properties. It is highly present in *Costus igneus* [44]. Another steroid, stigmasterol increases cholesterol efflux and decreases LDL-induced pro-inflammatory cytokine secretion and to prevent beta-cell dysfunction induced by glucolipotoxicity. Glucolipotoxicity reduces insulin secretion by inducing cholesterol accumulation because excess cholesterol is a possible contributing factor to beta cell failure.

The direct effect of stigmasterol on beta cells is not clearly known. Stigmasterol protects pancreatic beta cells from glucolipids-toxicity by preventing accumulation of free cholesterol and ROS improving insulin secretion, increasing insulin context. Stigmasterol is present in *Costus igneus* [45]. But the mode of action is not obtained from various literature. Beta-sitosterol, another antidiabetic component is obtained from *Costus igneus* [46]. It increases the fasting plasma insulin levels. It improves the oral glucose tolerance test with an increase in glucose-induced insulin secretion. It also increases glucose uptake in adipocytes and stimulates adipogenesis in differentiating preadipocytes. Like insulin it down regulates GLUT4 but no clinical study has yet progressed.

Alkaloids: No remarkable anti-diabetic alkaloids are found in *Costus igneus*.

Flavonoid: Flavonoid like quercetin increases the activity of glycogen synthesis, the rate-limiting enzyme of glycogen synthesis [47]. It also increases anti-oxidant enzymes like SOD, GPX, CAT, *etc*. and reduces intestinal glucose absorption by inhibiting GLUT 2. By blocking tyrosine kinase, quercetin is reported to have effects against diabetes [48]. Some other functions of flavonoids are enhancing insulin secretion via pancreatic β-cell regeneration, enhancement of insulin-mediated glucose uptake by target cells, inhibition of aldose reductase, calcium uptake increase etc. it is highly present in *Costus igneus* [49].

Catechin, epicatechin showed strong radical scavenging activity due to the presence of hydroxyl group [50]. They are alpha-glucosidase inhibitors because they act to decelerate the breakdown of complex sugars into glucose resulting in a delay in glucose absorption which lowers the postprandial blood sugar level. Epigallocatechin gallate (EGCG), a component of catechin reduce the blood glucose level by alpha-glucosidase inhibition and retard the postprandial rise in blood glucose with sucrose loading but not glucose loading.

Proteins: Insulin-like protein present in *Costus igneus* acts to lower the blood glucose [51].

Fatty Acid: Hexadecanoic acid, 9, 12 octadecanoic acid, tetradecanoic acid, and oleic acid can enhance insulin production in INS-1. [52] TNF-alpha inhibits insulin production but pre-treatment with oleic acid reverses the inhibitory activity. Thus glucose level is decreased. Various bio-components from *Costus igneus* showing anti-diabetic activities are also mentioned in **Table 1**. [53-60]

TABLE 1: MAJOR COMPOUNDS ISOLATED FROM *COSTUS IGNEUS* SHOWING ANTI-DIABETIC ACTIVITY

Name of the Compounds	Activities	Reference
Triterpenoid (Corosolic acid)	Glucose uptake activity	53
Steroid (Diosgenin)	Hypoglycemic property	54
Steroid (β- sitosterol)	Increases plasma insulin level and also increases glucose uptake activity	55
Flavonoid (Quercetin)	Increases insulin mediated glucose uptaking and activity of antioxidant enymes	56
Phenol (catechin)	Inhibit α- glucosidase activity and antioxidant activity	57
Insulin like protein	Hypoglycemic activity	58, 59
Fatty acid (Oleic acid)	Hypoglycemic activity	60

RESULT AND DISCUSSION: Diabetes mellitus is possibly the world's fastest-growing metabolic disorder. Appropriate therapies are required to prevent it. Traditional plant medicines are used throughout the world for the management of diabetes due to its easy availability and cheap rate. Folk medicine consists of the healing practices and ideas of body physiology and health preservation known to some in a culture, transmitted verbally as general knowledge, and practiced or applied by anyone in the culture. The scientific validation of several plant species has proved the efficacy of the botanicals in the management of diabetes acting through various methods.

Various herbal remedies used today, have not undergone careful scientific assessment and few of them have the potential to cause serious poisonous effects. There is an immense need to search and develop new herbal formulations and nutraceuticals for natural sources especially with pure bioactive compounds for the treatment of diabetes with its deleterious side effects. Mode of action of these particular bio components is essential for its anti-diabetic effects. In this review, some bio-components like corosolic acid, alkaloids, quercetin, stigmasterol, β-sitosterol, catechin, *etc*. are reported in *Costus igneus*, but their actual mode of action is still unknown.

SUMMARY:

1. Presence of triterpenoids (like β-amyrene, corosolic acid, squalene), flavonoids (like catechin, quercetin), steroids (like stigmasterol, β-sitosterol, diosgenin), fatty acids (oleic acid, tetradecanoic acid), *etc*. are responsible for antidiabetic action of *Costus igneus*.
2. Availability, no side effects and cost-effective nature of *Costus igneus* increases its value in herbal medication

CONCLUSION: The actual anti-diabetic prospective associated with active bio-compounds like triterpenoids, steroids, alkaloids, flavonoids, proteins, fatty acids, carbohydrates, *etc*. are usually large as a result of their modulatory effects on blood sugar level by increasing insulin secretion and promoting proliferation of pancreatic cells and by reducing insulin resistance. The molecular mechanism underlying the glucose metabolism in diabetes would provide require insights in the field of drug development, future inventions may one day yield therapeutic benefit.

In this review, an attempt has been made to conclude the biological activities, chemical constituents with their chemical nature and occurrence of *Costus igneus.* Actual potential activities of anti-diabetic compounds of this species will open a door for future research on herbal medicine in an efficient way.

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