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COSTUS IGNUS: INSULIN PLANT AND IT'S PREPARATIONS AS REMEDIAL APPROACH FOR DIABETES MELLITUS

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Keywords:

Insulin plant, Diabetes Mellitus, Plant leaves, Phytoconstituents, Pharmacological activities, Marketed products.

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ABSTRACT: *Costus igneus*, commonly known as insulin plant, has been traditionally reported for its anti-diabetic, anti-oxidant, anti-inflammatory, anti-proliferative, anti-urolithiasis, hypolipidemic, neuroprotective and anti-microbial activity. This review is all about anatomical and morphological investigations of *Costus igneus*, including its medicinal use. Secondary metabolites of this plant such as b-sitostirol, corosolic acid, diosgenin, quercetin, catechine, oleic acid show mainly anti-diabetic activity. At present finding, *Costus igneus* have characteristic morphological, anatomical, and proximate features that could be used to differentiate it from other members of the *Costaceae* family. This review article collected information using the following searching engines such as Pub Med, Science Direct and Google Scholar, *etc*., and mainly focused on English written documents. The present review article attempts to explore various medicinal properties of *Costus igneus* (insulin plant) and mode of action of all major phytoconstituents as anti-diabetic activity for advanced research purposes and its suitable formulations development in the future for the welfare of mankind.

INTRODUCTION: *Costus igneus* is a medicinal herb belongs to family *Costaceae* and commonly known as Insulin plant as its leaves help to generate insulin in the human body. Nowadays, the Insulin plant is one such ayurvedic plant that is globally demanding and is now vigorously used as an ayurvedic medicinal herb. Eating leaves of this plant is believed to lower blood glucose levels, and diabetic people who consumed the leaves of this plant has experienced to have a fall in their blood glucose levels. The insulin plant is native to Southeast Asia, specifically on the Greater Sunda Islands in Indonesia. It is relatively a new plant to India from south Central America, and it has been used as an ornamental plant in Kerala. In herbal treatment, diabetes is traditionally treated by chewing the plant leaves for at least a period of one month to get a controlled blood glucose level.

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Fig. 1 is a picture of the insulin plant and its leaves part [1]. There is another plant which is also known as insulin plant scientifically named as "*Costus Pictus*" this also has an antidiabetic effect but the constant use of *C. pictus* leaves for diabetic treatment may cause cardiac diseases, so it's not recommended for the treatment [2].

FIG. 1: PICTURE OF INSULIN PLANT AND ITS LEAVES PART

Morphology of the Plant: *Costus igneus* is a perennial, straight, tropical plant from the family *Costaceae*. It has evergreen leaves, which are simple, alternate, entire, and oblong in shape, having 4-8 inches length with a parallel venation system. The large, dark green and soft leaves possess light purple undersides and are spirally bound around the stems of the tree, forming attractive, arching clumps arising from underground rootstocks.

Maximum it has 60 cm in height with the tallest stems falling over and lying on the ground. Beautiful orange flowers produced on hot days having a 2.5-12.5 cm diameter appear on cone-like heads at the end of branches. Insulin plant propagation is by stem cutting. Common names are *Fiery Costus*, *Spiral flag*, *Insulin plant*, Step ladder, and *spiral ginger* [2, 3, 4].

Binomial Name:

- *Chamaecostus cuspidatus* Synonyms:
- *Costus cuspidatus* (Nees & Mart.)
- *Costusigneus* N.E.Br
- Globba cuspidate Neet & Mar

Taxonomic Position:

Botanical name	:	*Costusigneus*
Domain	:	Eukaryota
Kingdom	:	Plantae
Subkingdom	:	Viridaeplantae
Phylum	:	Tracheophyta
Subphylum	:	Euphylophitina
Infra-phylum	:	Radiotopses
Class	:	Liliopsida
Subclass	:	Commelinidae
Superorder	:	Zingiberane
Order	:	Zingiberales
Family	:	Costaceae
Subfamily	:	Asteroideae
Tribe	:	Coriopsidae
Genus	:	Costus
Specific epithet	:	Igneus[5]

Active Compounds (Anti-Diabetic): Several phytochemicals like flavonoids, alkaloids, and terpenoids are present in these plant parts. In India, traditionally, people were using this plant to control diabetes and in experimental diabetic rats. Bio-components are present in various plant parts like in leaves, stems, and rhizomes and roots [6, 11] such as in leaves carbohydrates, triterpenoids, proteins, alkaloids, tannins, saponins, and flavonoids. Also, leaves contain carbohydrates like rose oxide, fatty acids like hexadecanoic acid, 9, 12- octadecanoic acid, tetradecanoic acid, ethyl oleate, oleic acid, squalene in leaves of this plant [12]. In stems, terpenoids like lupeol and steroids like stigmasterol are present. Quercetin, diosgenin, a steroidal sapogenin *etc.* are present in rhizome [13]. Terpenoids, alkaloids, Tannins, etc., are available in root portion [14].

Chemical Nature:

Triterpenoids: These contain three terpene units or six isoprene units, *e.g.*, β-carotene, corosolic acid / glucosyl, lupeol, glycyrrhetinic acid.

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

Alkaloids: These are nitrogen-containing phytocon stituents containing heterocyclic and non-heterocyclic chemical structures. But in *Costus igneus*, no remarkable alkaloids are present.

Phenols: Phenols are chemical compounds consisting of a hydroxyl group attached directly to an aromatic hydrocarbon group, *e.g.*, catechin, strychnine, is strychnine.

Flavonoids: Flavonoids are a type of hydroxyl poly phenolic phytoconstituents that are known as potent free radical scavengers, have attracted

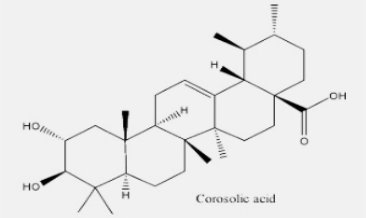
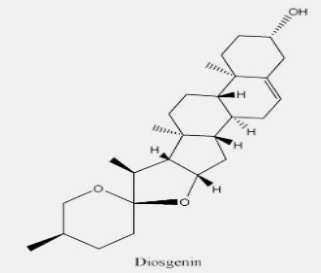
tremendous interest as possible therapeutics against free radical-mediated diseases, particularly diabetes mellitus. They are benzogamapyrone derivatives, *e.g.* epigallocatechin gallate, cinchona, quercetin, epicatechin.

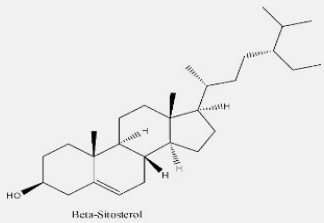
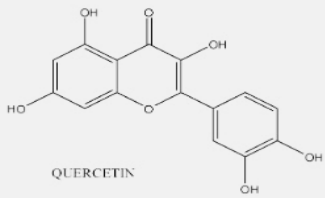
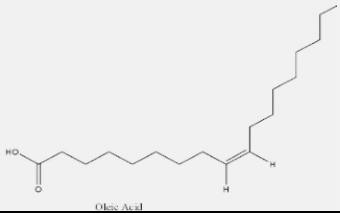
Proteins: Proteins are large biomolecules consisting of large chains of amino acid residues, *e.g.,* Insulin-like protein.

Fatty Acid: Fatty acid is a long aliphatic chain that is either saturated or unsaturated, *e.g.*, hexadecanoic acid, 9, 12 octadecanoic acids, tetradecanoic acid, ethyl oleate, oleic acid.

The list of all phytoconstituents present in leaves of the Insulin plant and their structure-activity relationship is shown in **Table 1** as follows.

TABLE 1: CHEMICAL STRUCTURE OF THE IMPORTANT BIOACTIVE COMPOUNDS FROM *COSTUS IGNEUS*

Name And Structure of The Compound	Structure-Activity Relationship	Mechanism of Action
Tri-terpenoids (Corosolic acid)  	1. Carboxylic group is important for inhibitory activity. 2. Methyl hydroxy or carboxyl will reduce the activity. 3. OH and carboxylic groups increase the glucose uptake activity.	1. Corosolic acid may improve insulin resistance conditions. The function of insulin is controlled by tyrosine phosphorylation and initiated by insulin binding to the insulin receptor.[15] 2. Corosolic acid may act as an insulin sensitizer, increasing insulin receptor B phosphorylation indirectly by blocking certain nonreceptor protein tyrosine phosphatases.[16,17] 3. Corosolic acid may also stimulate the GLUT4 glucose transporter course of glucose taking up into muscle cells[6]. 4. Another study reported that corosolic acid inhibited gluconeogenesis by increasing the production of the gluconeogenic intermediate fructose-2,6-bisphosphate in isolated hepatocytes, which can be corosolic acid may promote glycolysis [18,19]
Steroids (Diosgenin)  	1. The aliphatic esters and aromatic esters of diosgenin without F ring have no anti-tumor activity in vitro. The triazole bromides of diosgenin work against tumor activity *in-vitro*, and those with a larger hydrophobic group have the better activity. Due to the stronger hydrogen bonding interaction and dipole-dipole interaction of the heterocyclic of diosgenin and diosgenin without F ring and the acid ester of diosgenin without F ring gives the better activity. 2. Electron withdrawing substituents (-NO2 and -CN) at meta position in R moieties and analogs bearing bromo substituted R moieties seem to have a beneficial impact on antifungal activity. 3. Electron withdrawing substituents (-NO2 and -CN) at ortho/para position in R moieties were inactive towards both the tested fungal strength. 4. The SAR studies of diosgenin revealed an interesting finding that these steroidal triazolyl	Mechanisms of action are like this diosgenin in ameliorating experimentally induced diabetes include restoration of pancreatic β-cells, downregulation of enzymes involved in hepatic gluconeogenesis and glucose export, upregulation of hepatic glucokinase, and increases the quantity of hepatoprotective and antioxidant enzymes.[20]

	analogs will have no effect on bacterial pathogens but have the potential to be called an antifungal agent.	
Steroid (b-sitosterol) 	1. Sitosterol is equipped with a C24-ethyl group. Stigmasterol is the C22 desaturation product of sitosterol.	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. Hence we can say that β-sitosterol can act as an antidiabetic agent [21]
Flavonoid (Quercetin) 	1. Introduction of long alkyl chains such as propyl group at the C-3 OH position or short alkyl chain such as group at the C-4' OH position, increasing the inhibitory activities against cancer cell. 2. Replacement of C-3 and C-4 OH' group with OMe moiety enhances the activity. 3. Replacement of C-7 OH group with the OMe moiety to enhances the activity. 4. Hydroxyl groups the total number of hydroxyl configurations, playing an important role in regulating the bioactivity of flavonoids. 5. The absence of C-4 of ring c double bond and ketonic group at C-3 reduced the xanthine oxidase, alpha-glucosidase, and DPP-4 inhibitory activities.	The mode of action of quercetin is pleiotropic. It involves inhibiting intestinal glucose absorption, insulin secretory and insulin-sensitizing activities, and improved glucose utilization in peripheral tissues.[22]
Phenol (Catechine) 	1. Double bond between C-10 and C-9 decreases the inhibitory activity for both the alpha-glucosidase and DPP-4 antidiabetic effects. 2. A ring and B ring of the catechin B ring, a decrease in the number of OH groups led to decreased potency. 3. Introduction of a hydrophobic benzyl group into the 8th position did not significantly affect the inhibitory potency	Catechin shows its antioxidant effect through hydrogen-donating tendency and a scavenger of free radicals in vivo and *in-vitro*. Catechin controls oxygen radical generation because that there is increased hyperglycemia, hyperlipidemia, and oxidative stress in STZ-diabetic rats
Insulin like protein		Insulin-like protein acts via insulin signalling pathway and can be therapeutic use as oral insulin mimetic
Fatty acid (Oleic acid) 	1. It is a long chain of carboxylic acid that contains one double bond between C-9 and C-10 with cis configuration. 2. If any of the bonds is double or triple, the acid is unsaturated and is more reactive	Oleic acid can enhance insulin production in INS-1. TNF-alpha inhibits insulin production, but pre-treatment with oleic acid reverses the inhibitory activity, so glucose level is decreased [23]

Pharmacological Activities: After various studies, it is concluded that the insulin plant has many therapeutic activities. Among them, some are yet to be investigated. The varied plant parts like leaf, stem, root, rhizome and whole plant show such therapeutic activities. Leaves contribute to essential hypoglycemic potential. The stem part of this plant is mainly reported with anti-urolithiatic activity. Both stem and root are shown significant antioxidant activity [24].

Anti-diabetic Effects: Traditionally, this insulin plant was used as an ornamental plant in south Indian gardens. Leaves of the insulin plant are that

the major part that produces significant antidiabetic activity. It decreases fasting furthermore as postprandial blood sugar levels in the blood. Actually, the precise mechanism of action behind the antidiabetic activity of those major phytoconstituents is not known yet. This plant shows other therapeutic activities like reducing diabetic-associated complications, bringing renal and hepatic parameters to a controlled level, decreasing the number of glycosylated hemoglobin, increasing weight and insulin level, and showing significant improvement within the histopathological examination of diabetic patients.

Anti-proliferative Potential: S. Dhanasekaran *et al.,* (2014) examined the anti-proliferative as well as apoptotic action of methanolic extract of *Costus igneus* powdered leaves (MECiL) on in vitro MCF 7 (Michigan Cancer Foundation-7) breast cancer cell line. The extract (MECiL) was able to reduce the tumor size without affecting the conventional cells. Also evaluated the Cytotoxicity and Cell Viability for given extract (15- 2000 µg/ml) on L6 Rat skeletal muscle cell line using MTT (3- (4, 5-dimethyl thiazol-2-yl)-2, 5-diphenyl tetrazolium bromide assay test. This study showed IC- 50 value of 2000 µg/ml extract of insulin plant leaves. The extract showed cytotoxicity aligned with the conventional cell lines only at very high concentrations, but it wasn't apoptotic to the conventional cell lines. At the utmost dose of 2000 µg/ml the extract showed potent anticancer activity, that is 97.46 ± 0.74 percentage Cytotoxicity. The extract of the plant also has the property of dose-dependent cytotoxicity against the MCF-7 cell line [24].

Antimicrobial Activity: Arun Nagarajan *et al.,* (2011) worked and studied the antimicrobial activity of *Costusigneus* using its 100mg of root powder. Gram-negative bacterial cultures like *Pseudomonas aeruginosa* , *Klebsiella pneumonia*, *Salmonella sp*, *Proteus vulgaris* were employed in the study to work out the antibacterial activity (in vitro raised root extracts of *Costusigneus*). Around 10 grams of the Indole 3-acetic acid that's IBA and Indole butyric acid that's IAA derived root materials accustomed Soxhlet extraction using 5ml of acetone, chloroform, and methanol. Within the study, two growth regulators IAA and IBA in combinations, were added to MS (Murashige and Skoog) medium for direct root induction. *Klebsiella pneumonia* was found to be most liable to both above regulators derived from insulin plant roots using acetone as solvent. Its zone of inhibition was found to be 25 mm area which was almost the same as of antibiotic Gentamycin [25].

Antiurolithiatic Property: Kesavan Manjula *et al.,* (2017) studied the antiurolithiatic property of insulin plant using its aqueous extract of stem and rhizome and through the work revealed that the plant extract was ready to initiate the formation of hydroxyapatite (HAP) crystals and reduces the nucleation rate of CHPD crystals, a significant component of urinary calcium stone. The expansion of Calcium hydrogen phosphate dihydrate (CHPD) crystals has been done because of the only diffusion gel growth technique, and also the repressive effect of aqueous extracts of leaves, stems, and rhizome of *Costus igneus* on the expansion of CHPD crystals has been studied.

To evaluate the effect of the aqueous extract of leaves, stems, and rhizomes of *Costus igneus* plant on the expansion of CHPD crystals, a series of 5 different concentrations of 0.15, 0.25, 0.50, 0.75, and 1.00% of those plant extracts were selected. The plant extract exhibited a repressive effect compared to manage (pure calcium chloride), and a minimum length of growing crystals. Because the concentration of aqueous extracts of *Costus igneus* increased from 0.15% to 1.00% (w/v), the load of the formed crystals gradually reduced from 2.03 g to 0.06 g (leaves), 0.05 g (rhizome), 0.030 g (stem), respectively. The inhibitory activity of plant extract is thanks to the presence of natural substances like protein (18%), iron (40 mg), and antioxidant components like water-soluble vitamin, β-carotene, α Tocopherol, glutathione, phenols, flavonoids (diosgenin, quercetin), steroids, alkaloids,

Anti-Inflammatory Potential: Kripa Krishnan (2014) studied the anti-inflammatory potential of β-amyrin extracted from the leaves of *Costusigneus* using carrageen, an induced rat model together with LPS-induced human peripheral blood mononuclear cells (hPBMCs) *in-vitro* model. The differential fractionation methanolic extract (MEC) of *Costusigneus* leaves indicated a maximum percentage inhibition of paw edema at a given dose of 100 mg/kg weight. The fractionation of MEC

had been dispensed using various solutions like chloroform, hexane, ester, and butanol. The most useful effect was shown by chloroform extract (CEC) of MEC at a dose of fifty mg/kg weight. Treatment of carrageenan-induced rats with CEC drastically decreased cyclooxygenase (COX), lipoxygenase (LOX), myeloperoxidase (MPO), and gas synthase (NOS) activities in comparison to carrageenan-induced rats. β-amyrin isolated from it shown a dose-dependent decrease in paw edema, and at a dose of 100 µg it produced a 97 and reduced in carrageenan-induced paw edema in rats [25].

Effect on Learning and Memory: Shalini Adiga *et al.,* (2014) have assessed the effect of *Costusigneus* on learning and memory in normal and diabetic-induced rats using a passive avoidance test at doses of 250 and 500 mg/kg ethanolic extract. For the induction of diabetes, one dose of streptozotocin was injected (35 mg/kg) intraperitoneally. After a study period of 30 days, blood sugar level was measured, and rats were subjected to a passive avoidance test. The treatment with *Costusigneus* significantly reduced the blood sugar level in an exceedingly dose-dependent manner (75.70% reduction for 500 mg) in diabetic treated groups in comparison to the diabetic control group. But no significant effect was obtained with non-diabetic rats, and it had been such as the normal control values. Rats were subjected to a few acquisition trials. *Costusigneus* treated diabetic rats showed a decrease within the time taken to enter the dark constituents, suggesting that they maintained their innate behavior and showed improvement in learning tendency. Non-treated diabetic rats showed impairment within the passive avoidance test. During their post-shock retention testing at 24 and 48 h, treatment with insulin plant extract showed a major increase within the entrance latency and reduced within the time spent within the darkroom. As summarizing, the ethanolic extract of *Costusigneus* was able to produce a big effect on learning and memory in diabetic rats when treated with at a dose of 500 mg.

Antioxidant activity: Ramya SK *et. al.,* (2015) studied the effect of Methanol extract on antioxidant activity against *Klebsiella Oxytoca*, *Pseudomonas Fragi*, *Enterobacter aerogens* using various concentrations starting from 100 µg/mL - 500 µg /mL. The antioxidant and radical scavenging activities of *Costusigneus* were evaluated in both stem extract and Root extract. Root extract showed a high inhibition rate than stem extract. And among the stem and root extracts of this plant, the overall phenolic contents were found to be greater in root extract. Root extract also contains a high amount of antioxidant. Flavonoids with a particular structure and hydroxyl position within the molecule can act as proton donating and show radical scavenging activity. It was evident from the study that the polyphenols and antioxidants scavenge off the atoms and inhibit the generation of the free radical [26].

Neuroprotective Role: Gupta D, Rai S, Hajam YA *et al.,* (2018) investigated the neuroprotective role of exogenous melatonin and insulin plant (*Costusigneus* nak) extract on the brain in streptozotocin-induced female diabetic rats. The extract showed a major decrease of lipid peroxidation (TBARS) in brain tissue compared to the control group of rats.

Additionally, plant extract and melatonin produced a significant decrease in antioxidative enzyme *viz.* SOD (SOD), catalase (CAT), reduced glutathione (GSH) of the brain. Melatonin, further as plant extract, showed significant recovery to revive the brain complication induced by a hyperglycemic effect caused by the diabetic condition and rescued the brain tissue by restoring the number of astrocytes and glial cells [26].

Hypolipidemic Activity: Pazhanichamy Kalailingam *et al.,* (2011) investigated the antihyperglycemic, and hypolipidemic activities of methanol extract of *Costusigneus* rhizome (MECiR) in streptozotocin (STZ) induced diabetic albino rats. MECiR has been given at doses of 100, 200 mg/kg orally as one dose per day to diabetes-induced rats for a period of 30 days.

The results indicated that fasting glucose, total serum cholesterol(TC), triglycerides(TG), low-density lipoprotein(LDL), very-low-density lipoprotein(VLDL), levels were significantly ($p<0.05$) decreased, whereas serum high-density lipoprotein (HDL level significantly ($p<0.05$) increased within the diabetic rats. The better result obtained with 200 mg/kg. The antidiabetic and

hypolipidemic effects in STZ induced diabetic albino rats were reminiscent of standard reference drug glibenclamide (5 mg/kg/b.w) [16].

Toxicity Study: Administration of ethanolic extract of *C. Igneus* leaves from 50 mg/kg b.w up to the dose of 5000 mg/kg b.w didn't show significant toxicity signs during the primary four hours and followed by daily observations for 14 days and no death rate was also observed; the drug was found to be safe at the tested dose regimen of 5000 mg/kg b.wt.

However, in an exceedingly study allotted on the methanolic extract of *C. Igneus*, findings indicated toxicity at 250 mg/kg weight [27].

TABLE 2: LIST OF FEW MARKETED PRODUCTS OF *COSTUSIGNEUS* ALONG WITH ITS RECOMMENDED DOSES AND MANUFACTURER'S NAME

Product Name	Category	Dose	Manufacturer
Insulin Plant Leaf powder 180g	Dietary supplement	For 1st 60 days, consume 3gm (1 scoop) of powder every day in the morning & evening before meal. After 60 days, take 1 scoop within the morning before breakfast. Boil for a few min in water, strain & drink. Or consume as directed by physician/pharmacist	The Insulin Plant.com, USA [24]
Kostam Keerai (Costusigneus) Capsule 500mg		Agroline Mori tantraa [25]	Four capsules twice daily Or as directed
Glucobeet plus Capsule 500mg	Blood glucose supportive supplement	As directed	Orange organic pharma [27]
Daun Insulin	20 Herbal tea bags	Simply make a decoction by pounding one leaf & boiling it in water till it reduces in half. Consume this water daily in the morning & night	Tigadaun [28]

Precautions: Consumption of insulin plant leaves or crude drugs without knowing the right dosage may adversely affect your health. One should take advice from a medical supervisor before consuming it. Pregnant & lactating mothers should avoid consuming this plant or any part of the plant.

CONCLUSION: The papers reviewed provide ideas on how the insulin plant can be used to develop pharmaceutical products or as a dietary combination to current therapies in the future. Since oral hypoglycemic drugs show several side effects, there is a growing demand for herbal products to treat diabetes mellitus.

Several plant preparations are used in the traditional system of medicine to control diabetes mellitus. Research on new oral hypoglycemic products from medicinal plants will set a milestone for developing herbal or semi-synthetic pharmaceutical products. Based on the various chemical constituents present, the insulin plant has a wide therapeutic range and pharmacological, biopharmaceutical, and chemical properties. The structure-activity relationship and mechanism of actions of every phytoconstituent have been summarized along with their structures in **Table 1.** With the help of this review, various more effective formulations of insulin plant extract can be developed for different ailments where it shows good results as an anti-diabetic for diabetes mellitus treatment as well as anti-inflammatory, antioxidant, anti-proliferative, anti-urolithiasis, hypolipidemic, neuroprotective.

Insulin plant leaves and their phytochemical constituents show the promising effect of the in-silico method of study and not to forget that there is a need to investigate further their actions towards Diabetes mellitus treatment as a dietary supplement or conjugating with synthetic anti-diabetic drugs for better therapeutic action and less side effects. Future research is suggested for the advances in the novel formulation of insulin plants using each isolated compound and improving bioavailability, therapeutic effect, and delivery of the drug.

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