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Analysis of hypoglycemic effect of an aqueous extract of *Costus spicatus* on *F1* mice subjected to hyperglycemic diet.

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Abstract

Costus speciosus (Koen ex. Retz.) Sm. (crepe ginger, family Costaceae) is an ornamental plant used in traditional medicine for the treatment of inflammation, rheumatism, bronchitis, fever, headache, asthma, flatulence, constipation, helminthiasis, leprosy, skin diseases, hiccough, anemia, as well as burning sensation on urination. Plant-derived extracts have been used as folk remedies for Type 2 diabetes mellitus for many centuries, and offer the potential of cheap and readily available alternatives to conventional pharmaceuticals in developing countries. Extracts of *Costus*, a plant belonging to the Costaceae family, are reported to have antidiabetic activity *in vivo*. Hyperglycemia, abnormal lipid and antioxidant profiles are the most usual complications in diabetes mellitus. This study aimed to evaluate the possible hypoglycemic effect of an aqueous extract of *Costus spicatus* in animals subjected to a hyperglycemic diet. *F1* mice used were male, aged 8 weeks were initially separated into two groups (treated with hyperglycemic diet and treated with hyperglycemic diet and aqueous extract of *Costus spicatus*). They were initially undergo hyperglycemia diet for 8 days and from the ninth day, the group treated with the plant extract also spent undergoing treatment with aqueous extract of *Costus spicatus*. The aqueous extract *Costus spicatus* was administered daily orally (1 mL) with the aid of a gavage needle for 16 days. The group treated with aqueous extract of *Costus spicatus* showed a steady rise in their fasting glucose (29.25% growth). Compared to the group received the same diet but had been treated with the extract, this group observed a reduction in their fasting blood sugar (down 20.59%). From the results obtained, it can be speculated that the aqueous extract of *Costus spicatus* has a hypoglycemic effect possibly related to the phytochemical compounds of *Costus spicatus* plant leaves include glycosides, tannins, saponins, terpenoids, phenolics, flavonoids, alkaloids as well as eremanthin which can optimize sugar uptake in the liver. These feats could induce insulin secretion and release from cells, as well as stimulates the tissue's insulin sensitivity leading to an increase of the tissues' glucose uptake, storage, and oxidation.

Keywords: *Costus spicatus*, aqueous extract, hypoglycemic effect, phytochemicals compounds, diabetes.

Introduction

The pharmacological potential of medicinal plants may be output to a more economic treatment of various diseases including chronic diseases. In developing countries, about 80% of deaths are caused by chronic diseases (OPS, 2005). Among these Diabetes mellitus, has drawn attention to its growth in the number of occurrences. The World Health Organization estimates that annually occur 3 million deaths caused by diabetes. There are also consequences as 1 million amputations, 500 000 cases of kidney disease, 300 000 blindness, 285 million people worldwide with diabetes, and by 2030 will be 435 million diabetics mostly in developing countries (IDF, 2009). There is an estimate that these problems related to that disease generate annual spending of $ 150 billion (IDF, 2009).

Diabetes mellitus dysfunction is recognized as a heterogeneous group of disorders with the common elements of hyperglycemia and glucose intolerance and is caused by a deficiency of production and / or action of insulin, which leads to acute symptoms and chronic complications characteristics. This disorder involving the metabolism of glucose, fats and proteins, and has serious consequences both when arises as when rapidly settles slowly. Nowadays it constitutes a public health problem by the number of people who have the disease. Diabetes mellitus is classified based on clinical presentation of the disease etiology and in three types; Type I diabetes, Type II diabetes, and gestational diabetes (Guyton, 2011).

The genus belongs to *Costus* family. They are perennial tropical plants. They are often distinguished from plants of the genus Zingiber the spiraling growth of their stems. Besides the *Costus spictus* we can mention the *Costus pulverulents* and *Costus speciosus* who already have some properties of pharmacological interest described. *Costus pulverulentus* (Costaceae), a species endemic to Mexico, is used for the empirical treatment of cancer, pain, and inflammation (Alonso-Castro et. al., 2016).

Costus speciosus (crepe ginger, family Costaceae) is an ornamental plant used in traditional medicine for the treatment of inflammation, rheumatism, bronchitis, fever, headache, asthma, flatulence, constipation, helminthiasis, leprosy, skin diseases, hiccough, anemia, as well as burning sensation on urination (Al-Attas et. Al., 2015).

Selim and Jaouni (2015) related that *Costus speciosus* is an important medicinal plant widely used in several indigenous medicinal formulations. They may suggested that diosgenin isolated from *Costus speciosus* possess anticancer, apoptotic and inhibitory effects on cell proliferation. Biologic based therapies are frequently used as complementary medicines in diabetes. (Medagama and Senadhira, 2015).

Since 2006 the World Health Organization (WHO) has encouraged the Ministries of Health (MOH) of the governments of developing countries to support research of herbal medicines (OMS, 2007). Such plants that were used in natura (by choice or because it is the only alternative available). There are cultures in their system of medicine employing medicinal plants processed into formulations such as Chinese and Ayurvedic medicine (traditional Indian). In addition, herbal medicines are officially recognized by the WHO as a therapeutic resource since 1978 and are widely consumed worldwide. It is estimated that global trade in herbal turnover figures of 22 billion dollars annually. This framework has been called "the revolution of herbal medicines" (OMS, 2007).

The aim of this study is to evaluate the possible hypoglycaemic effect of an aqueous extract of *Costus spicatus* in animals subjected to a hyperglycemic diet.

Materials and Methods

Sample Plant and Collection

We used the leaves of *Costus spicatus* collected during flowering (December-January) on the site My Dream, the municipality of Itacuruça, RJ, Brazil. The choice of the time of collection was based on data from the literature indicate that concentrations of flavonoid substances, tend to increase during this time. This is due to the action of flavonoids as attractors of pollinators and as co-pigments of anthocyanidins (Dourado & Ladeira 2008). A voucher specimen of the species shall be deposited in the Herbarium of the UFRJ National Museum for botanical certification by an expert.

Preparation of extract:

Costus spicatus The sheets were dried in an oven with circulating air at 40°C, manually crushed and stored in amber glass vial. The crude aqueous extract was obtained by infusion of the barks of the powder using

distilled water as liquid extractor. The extract was lyophilized and stored in amber glass bottle refrigerated minimum temperature of - 20 °C.

Characterization of sample:
Organoleptic characterization.

Characteristics were observed related to the color, odor, flavor and texture and pH of the aqueous extracts of leaves of *Costus spicatus* (Farmacopéia Brasileira, 1988).

Experimental animal:

The animals used in the study were *F1* mice, with about two months old, male, kept to food (food and water *ad libitum*) except during the experimental phase, temperature (22 ± 25 ° C) and cycles of 12 hours light / dark in the Vivarium the State University Center of the West Zone (UEZO).

F1 mice used were male, aged 8 weeks. The animals were separated into two groups (treated only with hyperglycaemic diet and treated with hyperglycaemic diet and the aqueous extract of *Costus spicatus*),the animals were subjected to high-carbohydrate diet for 8 days and on the ninth day, the group treated with the plant extract, also happened to be subjected to treatment with the aqueous extract of *Costus spicatus*. The diet was comprised of feed involved in maize glucose and refined sugar {100 g feed / 30mL corn syrup (food Yoki glucose basis) / 30 g sugar (Guarani) Refined} serum by water replacement 5% dextrose plus refined sugar (500 mL of dextrose / 100 g of sugar) and daily oral administration of 1 mL of corn syrup diluted in glucose solution (1mL / 1mL).

The aqueous extract of *Costus spicatus* was administered daily orally (1 mL) with the aid of a gavage needle for *F1* male mice for 16 days. The animals were divided into two groups:

(A) Diet Group untreated hyperglycaemic: five animals previously subjected to a hyperglycemic diet and continued with the same for another 16 days. After checking the increase in blood glucose were given oral administration of 1 ml of 0.9% NaCl.

(B) Group Before subjected to hyperglycemic diet and kept the same for over 16 days: With five animals treated with oral administration of 1 mL of lyophilized aqueous extract of *Costus spicatus* (10 mg / mL).

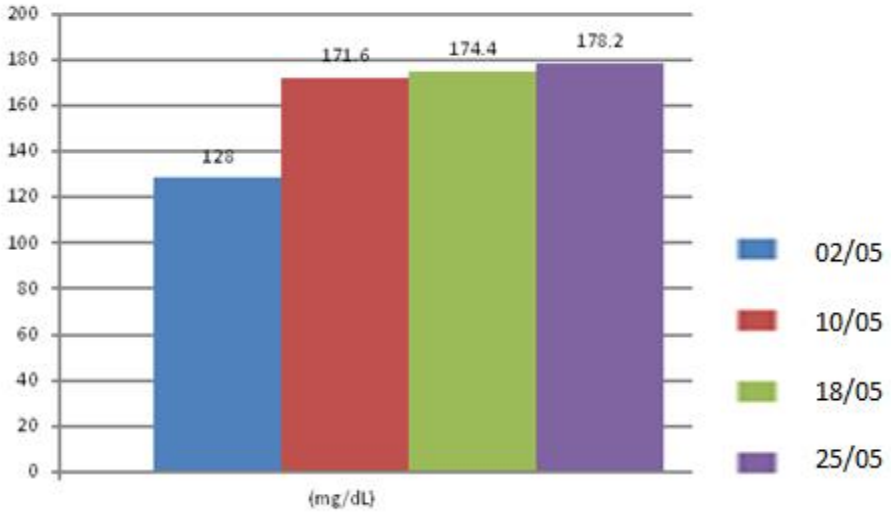
Dosage of Plasma Levels of Glucose and Weight Monitoring:

During the rising phase of the blood glucose, fasting blood glucose 6 hours and weight was observed (semi-analytical balance class II Bel Mark 220 - 220 g) of each animal prior to initiation of the diet, and after 8 days of special food.

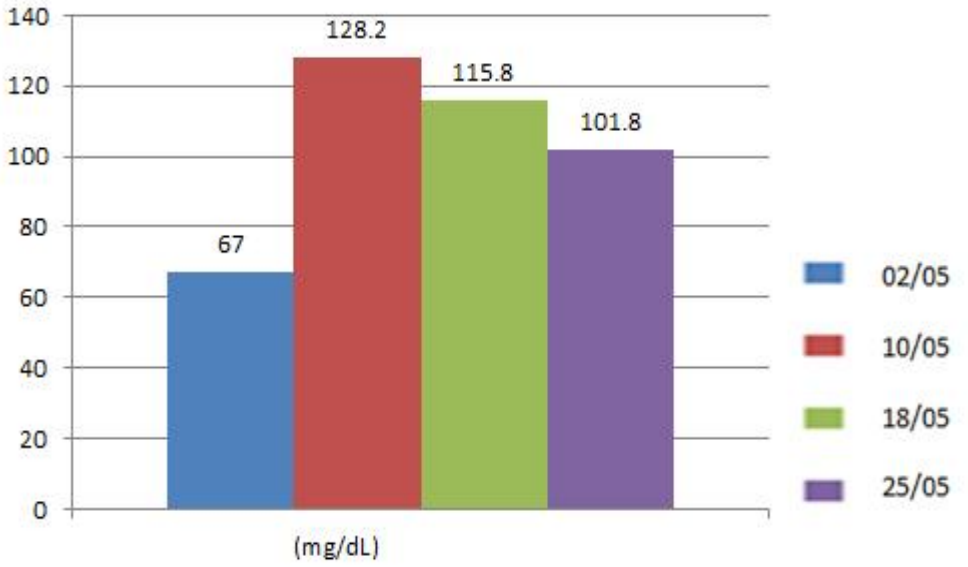
The next step was checked for fasting glucose 6 hours and weight (semi-analytical balance class II Bel Mark 220-220 g) after the 8th day of treatment and on the 16th day of treatment.

Results

Graph 1- Evolution of average fasting glucose *F1* mice of Group A not treated with the freeze-dried aqueous extract of *Costus spicatus*. Continued hyperglycaemic diet.

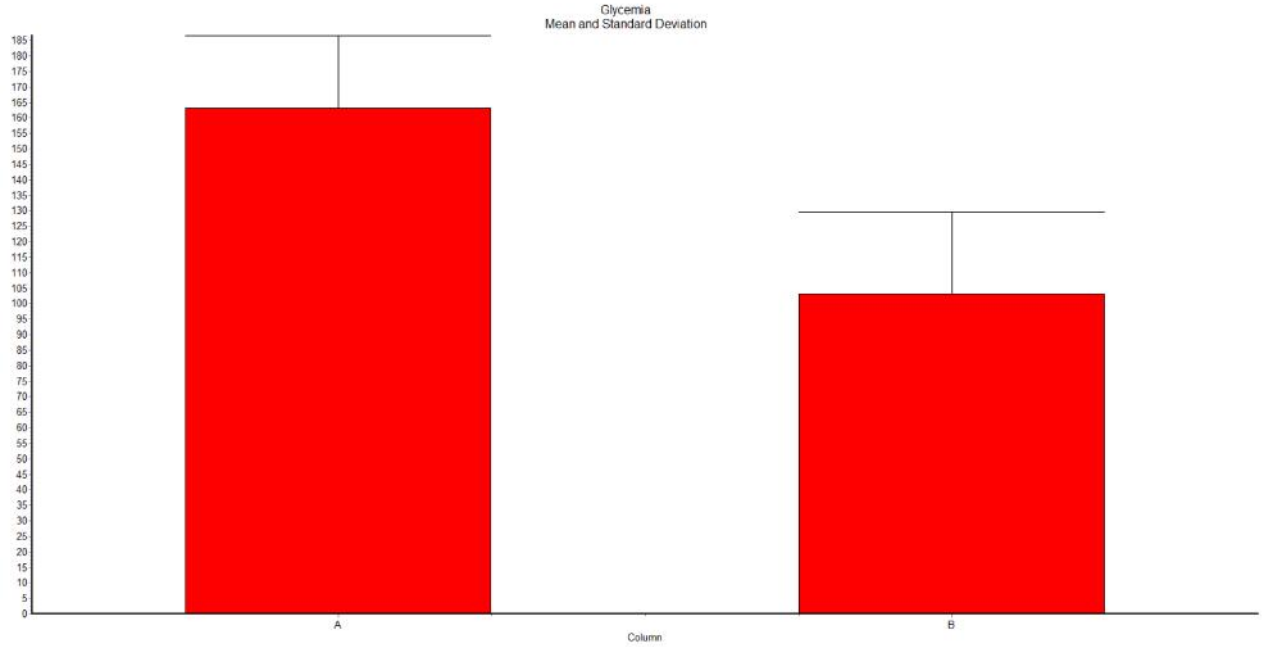


Graph 2- Evolution of average fasting glucose *F1* mice in Group B treated with freeze-dried aqueous extract of *Costus spicatus*. Continued hyperglycaemic diet.



The graph 1 shows the average blood glucose levels related to the group in which animals were treated with the hyperglycemic diet throughout the 16 days of treatment. In graph 2 shows the average blood glucose levels related to group animals were treated with the hyperglycemic diet over the first eight days of treatment and with the hyperglycemic diet together with the aqueous extract of *Costus spicatus* the last eight days of treatment.

Graph 3- Comparative statistical analysis between the groups (treated only with hyperglycaemic diet) and B (treated with hyperglycaemic diet and the aqueous extract of *Costus spicatus*).



Glycemia

Unpaired t test with Welch correction

Do the means of untreated and treated differ significantly?

P value

The two-tailed P value is 0.0196, considered significant.
Welch correction applied. This test does not assume equal variances.

Welch's approximate t = 3.383 with 5 degrees of freedom.

95% confidence interval

Mean difference = -59.850 (Mean of treated minus mean of untreated)
The 95% confidence interval of the difference: -105.34 to -14.364

Assumption test: Are the data sampled from Gaussian distributions?

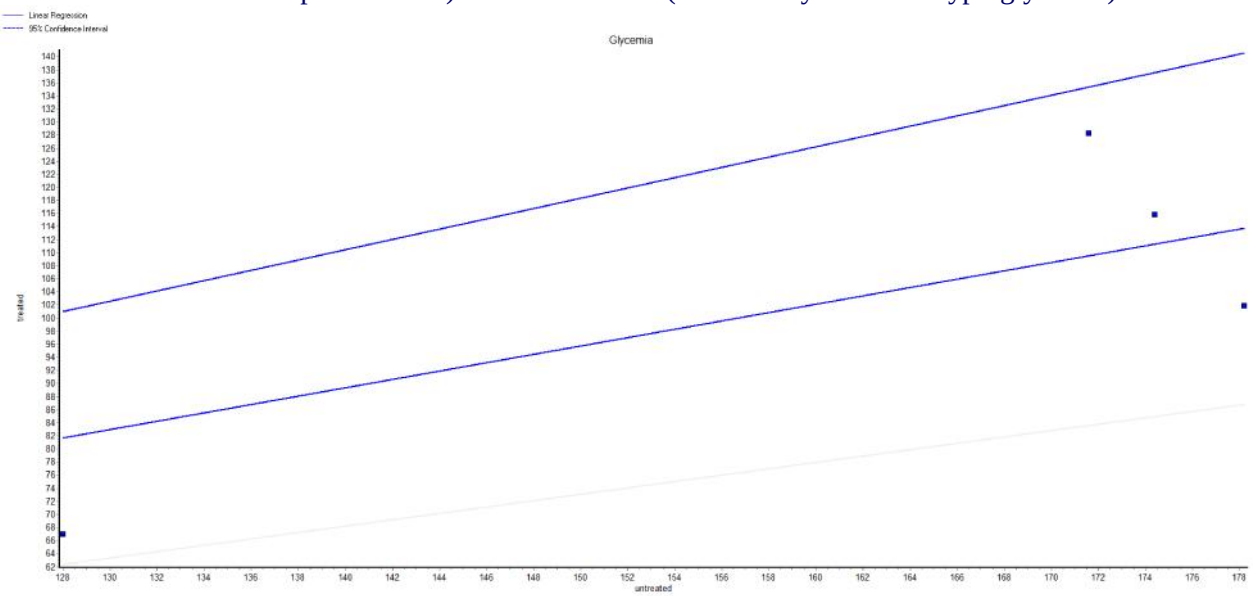
The t test assumes that the data are sampled from populations that follow Gaussian distributions. This assumption is tested using the method Kolmogorov and Smirnov:

Group	KS	P Value	Passed normality test?
untreated	Too few values to test.		
treated	Too few values to test.		

Summary of Data

Parameter:	untreated	treated
Mean:	163.05	103.20
# of points:	4	4
Std deviation:	23.523	26.433
Std error:	11.761	13.217
Minimum:	128.00	67.000
Maximum:	178.20	128.20
Median:	173.00	108.80
Lower 95% CI:	125.63	61.145
Upper 95% CI:	200.47	145.26

Graph 4- Linear regression analysis comparing the A-treated group (treated with hyperglycemic diet and treated with the plant extract) and untreated B- (treated only with diet hyperglycemic).



Linear Regression

Number of points = 4

Parameter	Best-fit Value	Standard Error	95% confidence interval from	to
Slope	0.6381	0.04738	0.4873	0.7888
Y intercept	0.000			
X intercept	0.000			

The line was forced through the point:
X=0.000 Y=0.000

Standard deviation of residuals from line (Sy.x) = 15.571

Test: Is the slope significantly different from zero?

The P value is 0.0009, considered extremely significant.
The slope is significantly different from zero.

t = 13.466 with 3 degrees of freedom.

From the analysis of the results we can see that there was a highly significant difference ($p < 0.05$) between the group treated with hyperglycemic diet and who also received the plant extract compared with the group that was treated only with hyperglycemic diet.

Discussion

The freeze-dried aqueous extract of *Costus spicatus* was administered orally in F1 mice with blood glucose levels in increased fasting. The hypoglycemic effect can be examined associated with the presence of flavonoids (Antoniolli, 2007). As can be seen in Chart 1, Group A that was kept at hyperglycemic food and did not receive the freeze-dried aqueous extract of *Costus spicatus* showed a steady rise in their fasting glucose (29.25% growth).Compared to the B group that received the same diet, but had been treated with the extract, observed in this group a reduction of their fasting glucose (20.59% reduction). The hypoglycemic effect of *Costus spicatus* extract could be related to the increase in glucose uptake by hepatocytes as suggested by Chen and Yen (2007) when analyzing the hypoglycaemic effect of an aqueous extract of *Psidium guajava* L.

It is interesting to handsome que *Costus pulverulents* exerts moderate cytotoxic effects in human cancer cells, anti-inflammatory and moderate antinociceptive effects. *Costus pulverulentus* induces antinociceptive effects without inducing sedation. (Alonso-Castroet. Al., 2016), it could be speculated that the effects related to the plant extract can be linked to hypoglycemic inducing action of that phyto extract.

It is important to consider the good anti-inflammatory activities exhibited of the isolated compounds from *Costus speciosus* corroborate the usefulness of this plant in the traditional treatment of inflammation and related symptoms. (Al-Attaset. Al., 2015). According to the referred authors, the n-hexane-$CHCl_3$ soluble fraction afforded a new eudesmane acid, specioic acid (8), along with seven known compounds, 22,23-dihydrospinasterone (1), dehydrodihydrocostus lactone (mokko lactone) (2), dehydrocostus lactone (3), stigmasterol (4), arbusculin A (5), santamarine (douglanin) (6), and reynosin (7). Compounds 1, 4, and 5-7 were isolated for the first time *C. speciosus*. Compounds 1-4 displayed potent anti-inflammatory activity, while 7 and 8 showed moderate activity. Compounds 1-8 exhibited a concentration-related decrease in the levels of IL-1β, IL-6, TNF-α, PGE2, lipoxgenase-5, and COX-2. Compounds 5 and 6 did not significantly decrease levels of different cytokines, PGE2, lipoxgenase-5, and COX-2 from PHA treatment at 1µM. However, all tested compounds significantly decreased cytokines, PGE2, lipoxgenase-5, and COX-2 levels at concentration 100µM. It is noteworthy that compounds 1-4 had the highest activity, where it lowered levels of cytokines, PGE2, lipoxgenase-5, and COX-2 to the extent that was no statistical difference from the control group.

Thus, they decreased proinflammatory cytokines (IL-1β, IL-6, and TNF-α) with decreased level of the target enzymes (COX-2 and lipoxgenase-5) and subsequent reduction of its inflammatory product (PGE2). These findings could complement those observed by Nascimento et al., (2014) where it was observed that interestingly, the anti-hemolytic action related to an aqueous extract *of Costus spicatus* would be possibly related to the presence of phenolic molecules in the extract, which would have its most obvious action spectrum in more dilute salt concentrations while saponins molecules exhibit its effect at lower concentrations saline, with its more free hydroxyl groups in this way, these hydroxyl groups may join possible towards oxidative reactions such as the Fenton reaction in the presence of heme plus interact with membrane proteins such as transport proteins band 3 and pump Na+ /K+ATPase, besides interacting with the membrane lipid peroxidation promoting actions that could possibly contribute to achieve osmotic fragility of erythrocyte membrane and consequent hemolysis.

The practice of using household ingredients as complementary medicines is common in Sri Lanka. Few herbal remedies and their methods of preparation have limited evidence for efficacy. In view of the frequent use by diabetic patients each needs to be documented for reference and scientifically explored about their hypoglycemic potential. (Medagama and Senadhira, 2015), based on this report becomes interesting disclosure of results from our study of the hypoglycemic effect of an aqueous extract of *Costus spicatus.*

Hyperglycaemia is a salient feature of poorly controlled diabetes mellitus. Rate of protein glycation is increased with hyperglycaemia leading to long term complications of diabetes. One approach of controlling blood glucose in diabetes targets at reducing the postprandial spikes of blood glucose. The objectives of this study were to assess the in vitro inhibitory effects of *Costus speciosus* leaves on α-amylase and α-glucosidase activities, fructosamine formation, protein glycation and glycation-induced protein cross-linking. Related to Pereraet. al., (2016), we could speculate that the extracts of the leaves of *Costus spicatus* would demonstrate an inhibitory activities on α-glucosidase, fructosamine formation, glycation and glycation induced protein cross-linking. These findings would provide scientific evidence to support the use of *Costus spicatus* extract for hypoglycemic effects with an added advantage in slowing down protein glycation.

According to the the study by Cógáin et al., (2015) an aqueous extract of *Costus arabicus* L. may disrupt calculogenesis by interacting with calcium oxalate (CaOx) crystal surfaces. Activity was present in the aqueous extract; therefore, this agent may be bioavailable when administered orally. Fractionation results suggest that the active agent might be a polar polysaccharide. In our study the animals were treated with an aqueous extract of *Costus spicatus* and it could be observed the antihyperglycemic related to the extract. It might be suggested that this antihyperglycaemic effect related to the *Costus spicatus* extract could collaborate so that there was a lower level of adhesion on epithelial surface in view of the possible lower expression of glycosylated proteins as well as to the lower expression of free hydroxyls groups. In the study by Cógáin et al., (2015), the aqueous extracts of *C. arabicus* decreased crystal growth in a concentration dependent manner. They reported that an aqueous extract of *C. arabicus* can disrupt calculogenesis interacting with crystal surfaces CaOx. Precoating crystals with *C. arabicus* extract prevented their adhesion to kidney cells, while pretreating cells did not show any effect. The activity was present in the aqueous extract and we may suggest based on our study that the referred activity related to the aqueous extract of *Costus spicatus* would have its effect mediated by hydroxyls groups which may be common to polar polysaccharides.

Considering the antihyperglycemic and antioxidant activity of herbs, in a study evaluated the morphological changes, the hypoglycemic effect and the comparative effects of a *Costus spicatus* leaf extract with antidiabetic drug glibenclamide in pancreatic injury induced aloxano. According to Ejiofor et al. (2015), the phytochemicals of *Costus spicatus* plant leaves include glycosides, tannins, saponins, terpenoids, phenolics, flavonoids and alkaloids. The *Costus* extract expressed a significant hypoglycemic effect ($p < 0.05$) and reversed the effect of histopathological damage of the pancreas in diabetic rats induced by alloxan comparable to those of glibenclamide, similar results were found in our experiment since observed a hypoglycemic effect in animals subjected to hyperglycemic diet for 16 days and treated simultaneously with an aqueous extract of *Costus spicatus*.

The increasing prevalence of diabetes mellitus worldwide is an issue of major socio-economic concern. Diabetes mellitus is a complex and a multifarious group of disorders that disturbs the metabolism of carbohydrates, fat and protein.

Medicinal plants play an important role in the management of diabetes mellitus especially in developing countries. *Costus speciosus* is widely used in Indian medicine to treat various diseases. Eliza et. al., (2009) reported that eremanthin, molecule found in the composition of *Costus spicatus* was responsible for a Significantly Decreased glycosylated hemoglobin (HbA (1c)), serum Total cholesterol, triglyceride, LDL-cholesterol and at the same markedly team Increased plasma insulin, glycogen tissue, HDL-cholesterol and serum protein. Eremanthin also restored the altered plasma enzyme (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase and acid phosphatase) levels to near ordinary. Results of this experimental study Indicated que eremanthin possessed hypoglycemic and hypolipidemic activities and hence it could be used as a drug for treating diabetes. According to the findings in our studies, we could speculate that eremanthin molecule would be related to the hypoglycemic effect of the aqueous extract.

Conclusion

From the results obtained, it can be speculated that the aqueous extract of *Costus spicatus* has a hypoglycemic effect possibly related to the phytochemical compounds of *Costus spicatus* plant leaves include glycosides, tannins, saponins, terpenoids, phenolics, flavonoids, alkaloids as well as eremanthin which can optimize sugar uptake in the liver. These feats could induce insulin secretion and release from cells, as well as stimulates the tissue's insulin sensitivity leading to an increase of the tissues' glucose uptake, storage, and oxidation.

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