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EVALUATION OF ANTIDIABETIC POTENTIAL OF *KANDELIA CANDEL* AND *RHIZOPHORA APICULATA*- AN *IN VITRO* APPROACH

Arun Kashivishwanath Shettar and Ankala Basappa Vedamurthy *

PG Department of Studies in Biotechnology and Microbiology, Karnatak University, Dharwad - 580003, Karnataka, India.

Keywords:

Kandelia candel, *Rhizophora apiculata*, Alpha-amylase assay, Glucose uptake assay, *In vitro* Antidiabetic activity

Correspondence to Author:
Dr. A. B. Vedamurthy

Professor and Chairman
PG Department of Studies in Biotechnology and Microbiology
Karnatak University, Dharwad - 580003, Karnataka, India.

E-mail: vedamurthybt@gmail.com

ABSTRACT: Objective of the present work was to evaluating the antidiabetic property of *Kandelia candel* and *Rhizophora apiculata* extracts by using *in vitro* assays. The serial exhaustive extraction was carried out with a series of solvents: chloroform, ethyl acetate, methanol, ethanol and water with increasing polarity using Soxhlet apparatus. The concentrated and dried extracts were evaluated for antidiabetic activity by employing standard *in vitro* techniques (Alpha-amylase and glucose uptake assay using yeast model). *In vitro* antidiabetic studies show that in case of *Kandelia candel* methanol extract showed higher antidiabetic activity where as incase of *Rhizophora apiculata* aqueous extract exhibited significant activity when compared to other solvent extracts. Results confirm that aqueous extract of *Rhizophora apiculata* exhibited highest antidiabetic activity among all extracts. This study provides scientific evidence that the leaves of *Kandelia candel* and *Rhizophora apiculata* have anti-diabetic efficacy. However further comprehensive chemical and pharmacological investigation should be carried out to isolate the active compounds and appropriate elucidation of its mechanism of action and it helps in the development of new pharmaceuticals to treat Diabetes mellitus.

INTRODUCTION: Diabetes mellitus (DM) is a non-communicable disease often genetic in nature but can be developed due to life style and habits [1, 2]. DM is a set of metabolic disorder with a common feature of high blood glucose level. It is characterized by increased blood glucose, triglyceride and hypo insulinemia that may lead to decrease in both insulin action and secretion [3, 4]. Diabetes mellitus ranks highly with the top ten disorders which cause mortality throughout the world and is affecting approximately 30% of the worldwide population [5-7].

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Uncontrolled Diabetes mellitus is often associated with many complications which include development of micro and macro vascular complications such as neuropathy, nephropathy, retinopathy and cardiovascular diseases [8, 9]. Normally blood glucose levels are controlled by insulin produced by pancreas [10]. Treatment of diabetes mainly focuses on reducing rise in blood sugar and subsequent complications. Inhibitors of α-amylase are currently used as oral hypoglycemic agents for treatment and management Diabetes.

Currently available anti-diabetic drugs possess severe side effects such as risk of hypoglycemia, anemia, and cholestatic jaundice [11]. Since from immemorial time traditional medicines have been used to treat Diabetes mellitus [12]. Many natural medicines have been reported to show anti-diabetic activity through different mechanisms.

Plants have been reported to reduce the absorption of glucose by retarding the digestive enzymes *i.e*. α-amylase and α-glucosidase from pancreas and gut which in turn helps preventing the high rise of glucose in blood [13-16]. Several works demonstrated that many medicinal plants can be used to treat and management of diabetes and already many medicinal plants have been reported for potent antidiabetic activity [17-23].

In the present study *Kandelia candel and Rhizophora apiculata* plants were selected for screening antidiabetic property. *Kandelia candel* is the mangrove tree belonging to Rhizophoraceae family which is distributed along the western region of India. *K.candel* whole plant is reported to have antidiabetic activity [24, 25]. In fact Rhizophoraceae species are known to have pharmacological activities. Methanolic extract of *K.candel* is used as antihyperglycemic agent in India [26] and bark, flowers and leaves were reported to have antiviral and antimicrobial properties [27, 28]. *Rhizophora apiculata* is the tree species of mangrove tree belonging to rhizophoraceae family.

In Malaysia, the leaves of *R. apiculata* are assayed as antibreast cancer [29]. Studies on HPLC investigation of *R. apiculata* have shown the presence of catechin monomer, an antioxidant flavonoid [30]. This plant is reported to possess anti-inflammatory and anti tumor properties and is also used to regulate the antioxidant enzymes in biological system [31]. Presence of tannins is reported in the bark of *R. apiculata*, which is known to possess antibacterial and antiviral properties [32-34]. Bark of *R. apiculata* is used as a traditional medicine in the treatment of diarrhoea and wounds [35, 36]. In Malaysia, pyroligneous acid from *R. apiculata* species have been used as sterilizing agent, deodorizer, fertilizer, antimicrobial agent and growth promoting agent [37].

Alkaline extract from leaf of *R. apiculata* reported to inhibit the HIV replication and HIV induced cytopathic effects. Some other studies have confirmed the antiviral property of *R. apiculata* extracts, which may be due to presence of antipolysaccharide in the extracts that acts as an antiviral agent [38]. With this background, the present study was undertaken to evaluate antidiabetic properties of *Kandelia candel* and *Rhizophora apiculata* plants collected from Mangrove region of Karnataka, India by using *in-vitro* assays.

MATERIALS AND METHODS:

Plant collection: Leaves of *Kandelia candel* and *Rhizophora apiculata* were collected from Mangrove region, Sadashivghad, Karwar, Uttar Kannada District, Karnataka, India during the period of May, 2015. The leaves were identified and authenticated by Dr. Kotresha K, Dept of Botany, Karnatak Science College, Dharwad; Karnataka by referring to the voucher specimen deposited in the Dept of Botany, Karnatak Science College, Dharwad, Karnataka (Voucher specimen No 003 and 004). Fresh plant leaves material was collected and washed under running tap water, shade dried and then homogenized to coarsely powder. The powder was stored in airtight containers at -20°C for further use for crude solvent extraction.

Crude Extraction: Coarsely powdered dried leaves of *Kandelia candel* and *Rhizophora apiculata* [100g each] were subjected to successive solvent extraction using soxhlet apparatus separately. The extraction of each plant leaves material was done with different solvents in their increasing order of polarity which includes chloroform, ethyl acetate, methanol, ethanol and distilled water. Each time the plant material was dried and later extracted with next high polar solvents (following the strategy of extraction in series of increasing the solvent polarity). All extracts were concentrated in Buchi rotary evaporator, followed by removal of traces of solvent by using desiccator.

Evaluation of Antidiabetic activity by using *in vitro* assays:

Alpha -amylase inhibitory assay: The Alpha-amylase inhibitory assay for different solvent extracts of *Kandelia candel* and *Rhizophora apiculata* were evaluated according to a previously described method by Malik and Singh *et al*., (1980) with slight modification [39]. In brief, 0.5 ml of extract was mixed with 0.5 ml of α-amylase solution (0.5 mg/ml) with 0.02 M sodium phosphate buffer (pH 6.9 with 0.006 M NaCl).

The mixture was incubated at room temperature for 10 min and 0.5 ml of starch solution (1%) in 0.02 M sodium phosphate buffer (pH 6.9 with 0.006 M NaCl) was added. The resulting mixture was incubated at room temperature for 10 min, and the reaction was terminated using 1mL of dinitrosalicylic acid color reagent. At this time, the test tubes were placed in a water bath (100 ^{0}C and 5 min) and cooled until room temperature was reached. The mixture was then diluted with 10 ml of deionized water, and absorbance was determined at 540 nm. The absorbance of blank (buffer instead of extract and amylase solution) and control (buffer instead of extract) samples were also determined. Acarbose was used as standard drug. The inhibition of α-amylase was calculated using the following equation:

% inhibition of α-Amylase = (Abs $_{control}$ − Abs $_{sample}$) / (Abs $_{control}$) × 100

Where Abs $_{control}$ corresponds to the absorbance of the solution without extract (buffer instead of extract) and with α -amylase solution and Abs $_{sample}$ corresponds to the solution with extract and α -amylase solution.

Glucose uptake in Yeast cells: Glucose uptake assay by using yeast cells was performed according to the method of Cirillo *et al*., (1963) [40]. The commercial baker's yeast in distilled water was subjected to repeated centrifugation (3,000×g, 5 min) until clear supernatant fluids were obtained and 10% (v/v) of the suspension was prepared in distilled water. Various concentrations of solvents extract of *Kandelia candel* and *Rhizophora apiculata* (50 to 250 µg/mL) were added to 1mL of glucose solution (5 mM) and incubated together for 10 min at 37 ^{0}C. Reaction was started by adding 100 µL of yeast suspension followed by vortexing and further incubation at 37 ^{0}C for 60 min. After 60 min, the tubes were centrifuged (2,500 × g, 5 min) and amount of glucose was estimated in the supernatant. Metronidazole was used as standard drug. The percentage increase in glucose uptake by yeast cells was calculated using the following formula:

$$\text{Increase in glucose uptake (\%)} = \frac{\text{Abs sample} - \text{Abs control X 100}}{\text{Abs sample}}$$

Where, Abs sample is the absorbance of test sample and Abs control is the absorbance of control reaction (containing all reagents except the test sample). All the experiments were carried out in triplicates.

Statistical analysis: All experiments were performed in triplicates (n=3) and the data are presented as the mean ± standard error. Differences between the means of the individual groups were analyzed using the analysis of variance procedure of SPSS software 20 Version (IBM). The significance of differences was defined at the $P < 0.05$ and $P < 0.01$ level.

RESULTS AND DISCUSSION: Diabetes mellitus is one of the three known major killers that cause deterioration in human health after cancer and cardio-cerebral vascular diseases and it is rising over the years [41]. The increasing prevalence of diabetes mellitus puts a large burden on the public health sector presenting an emerging health problem in the world [42]. One of the therapeutic strategies to control hyperglycemia in diabetics is to avoid the hydrolysis of carbohydrates by the inhibition of α-amylase enzyme in order to slow down the intestinal absorption of glucose [43]. Alpha-amylase is the type of enzyme involved in the metabolism of carbohydrates *i.e*. hydrolysis of starch and disaccharides to glucose. In humans α-amylase expressed as two isoforms, secreted from Salivary glands and Pancreas respectively. These enzymes play an important role in digestion of polysaccharides like starch which is the main source of glucose in the human diet [44-46]. Human Salivary α-amylase (HSA) initiates the hydrolysis of α-(1, 4) glycosidic bonds in the dietary starch in to smaller oligosaccharides [47]. Further digestion of carbohydrates takes place in the gut under control of human pancreatic α-amylase (HPA) [48].

Hence, hydrolysis of polymeric starch by HAS and HPA produces maltose, maltotriose and other oligomers, which are then degraded into glucose by α-glucosidase [49]. Inhibition of α-amylase results in delayed carbohydrate digestion and glucose absorption with attenuation of post prandial hyperglycemia [50]. The inhibitors of these enzymes are considered as the potential targets in the management of diabetes mellitus. Some synthetic antidiabetic drugs are available such as Acarbose, Miglitol and Voglibose but they are associated with gastrointestinal side effects such as adnominal pain, meteorism and diarrhea [51, 52].

These side effects arise as a consequence of maltose fermentation which accumulates due to α-amylase inhibition. Therefore a non-carbohydrate based α-amylase inhibitor is expected to be better agent to restrain post prandial hyperglycemia since it would not lead to abdominal accumulation of maltose [53]. Many herbal products including several metals and minerals have been described for the case of diabetes mellitus. Plant products are frequently considered to be less toxic and significantly free from side effects than synthetic ones [54]. Inhibition of carbohydrate hydrolyzing enzymes by medicinal plants might be attributed to several possible factors such as encapsulation of starch by the fibers present in sample thus reduce the availability of starch to the enzymes or direct absorption of the enzyme on fibers that decrease enzyme activity [55]. Recently inhibition of α-amylase enzyme method became very good tool to estimate the antidiabetic potential of plant extracts [56].

In the present study the concentrated and dried extracts *Kandelia candel* and *Rhizophora apiculata* were evaluated for antidiabetic activity by employing standard *in vitro* techniques (Alpha-amylase and glucose uptake assay using yeast model). In the Alpha-amylase inhibitory assay the known concentration (100µg) of different solvent extracts of *Kandelia candel* and *Rhizophora apiculata* were subjected to α-amylase inhibitory assay along with Acarbose as a standard. In case of *Kandelia candel* among five solvent extracts methanol extract showed very good antidiabetic activity on comparison with other tested extracts with Alpha-amylase inhibitory percentage 50.1907±0.33250 with IC_{50} value 99.62µg/ml other remaining extracts *i.e.* chloroform extract, ethyl acetate extract, ethanol extract and aqueous extract showed percentage of inhibition 8.8481±0.46397, 13.3486±0.40362, 43.5545±0.80724 and 28.0701± 1.05970 respectively (**Table 1**).

TABLE 1: α -AMYLASE INHIBITORY ACTIVITIES AND IC_{50} VALUES BY *KANDELIA CANDEL* EXTRACTS

Samples	Concentration	Inhibition (I %)	IC_{50} (µg/ml)
Chloroform extract	100µg/ml	8.8481±0.46397	565.09 µg
Ethyl acetate extract	100µg/ml	13.3486±0.40362**	374.57 µg
Methanol extract	100µg/ml	50.1907±0.33250**	99.62 µg
Ethanol extract	100µg/ml	43.5545±0.80724**	114.79 µg
Aqueous extract	100µg/ml	28.0701±1.05970*	178.12 µg
Standard (Acarbose)	100µg/ml	71.0907±0.67796**	70.33 µg

Results are expressed as Mean±SE (n=3); **significant at the P < 0.01

**Correlation is significant at the 0.01 level (2-tailed) **, *Correlation is significant at the 0.05 level (2-tailed)*

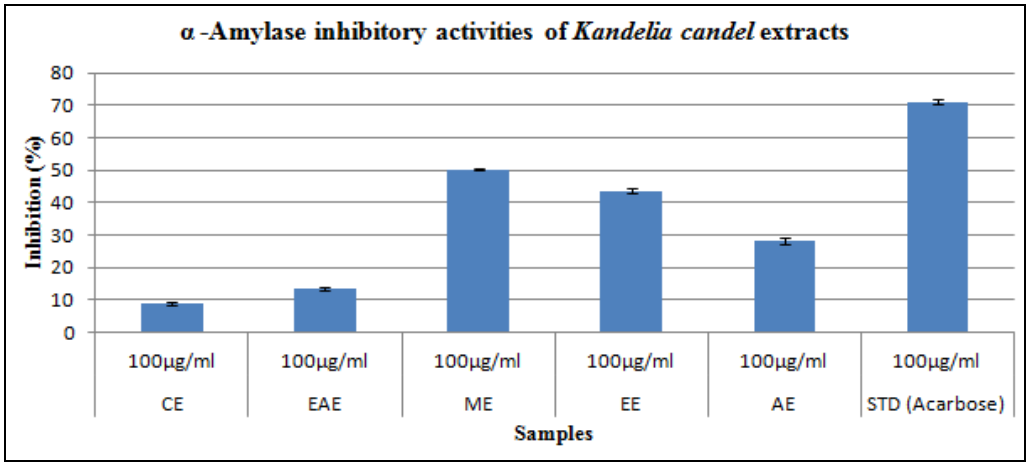

FIG. 1: α -AMYLASE INHIBITORY ACTIVITIES OF KANDELIA CANDEL EXTRACTS

CE: Chloroform extract; EAE: Ethyl acetate extract; ME: Methanol extract; EE: Ethanol extract; AE: Aqueous extract; STD: Standard (Acarbose)

In case of *Rhizophora apiculata* the aqueous extract showed higher activity among all other extracts as well as methanol extract of *Kandelia candel* with percentage of inhibition 52.7078±0.66497 and IC_{50} value observed to be 94.86µg /ml **(Table 2)**. On comparison with

standard acarbose methanol extract of *Kandelia candel* and aqueous extract of *Rhizophora apiculata* shown less activity *i.e* standard showed highest percentage of Inhibition 71.0907±0.67796 with IC_{50} value 70.33 µg/ml **(Table 2).** In Glucose uptake in Yeast cells model the different solvent extracts of *Kandelia candel* and *Rhizophora apiculata* leaves at different concentrations (50µg-250 µg) are subjected to *in vitro* glucose uptake assay using yeast as model. The percentage of glucose uptake in yeast cells by the extract was compared with Metronidazole standard drug. In Glucose uptake assay both *Kandelia candel* and *Rhizophora apiculata* extracts and standard showed dose dependant manner of activity *i.e.* as the concentration of sample increased even the percentage of inhibition also increases. In case of *Kandelia candel* methanol extract shown higher activity than the remaining extracts with the percentage of inhibition 60.3143±0.56826 at 250µg concentration and it was less as compared to activity of standard.

TABLE 2: α-AMYLASE INHIBITORY ACTIVITIES AND IC_{50} VALUES BY *RHIZOPHORA APICULATA* EXTRACTS

Samples	Concentration	Inhibition (I %)	IC_{50} (µg/ml)
Chloroform extract	100µg/ml	34.4775±0.67799*	145.02 µg
Ethyl acetate extract	100µg/ml	20.6712±0.80722	241.89 µg
Methanol extract	100µg/ml	41.2662±1.00038*	121.16 µg
Ethanol extract	100µg/ml	35.2402±0.57589*	141.88 µg
Aqueous extract	100µg/ml	52.7078±0.66497**	94.86 µg
Standard (Acarbose)	100µg/ml	71.0907±0.67796**	70.33 µg

Results are expressed as Mean±SE (n=3); **significant at the P < 0.01.

Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed)*

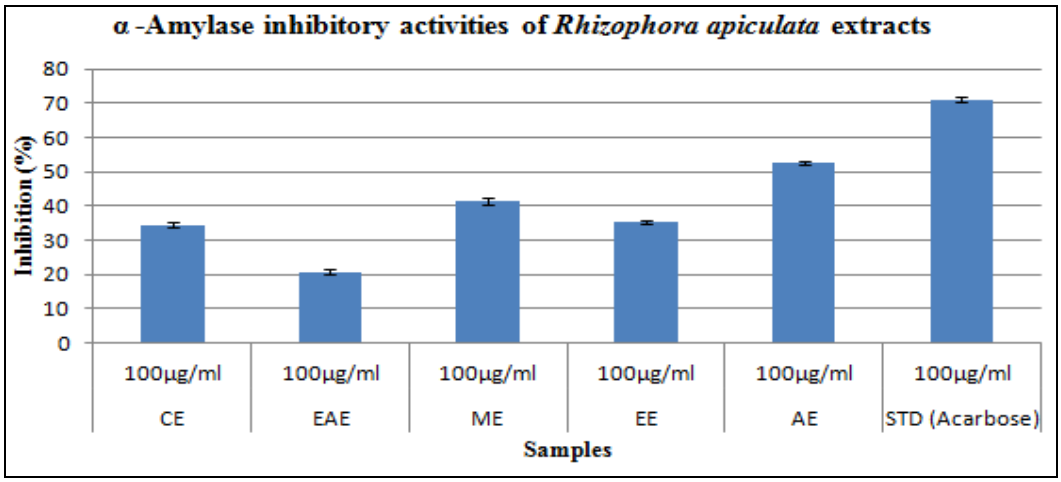

FIG. 2: α -AMYLASE INHIBITORY ACTIVITIES OF *RHIZOPHORA APICULATA* EXTRACTS

CE: Chloroform extract; EAE: Ethyl acetate extract; ME: Methanol extract; EE: Ethanol extract; AE: Aqueous extract; STD: Standard (Acarbose)

In case of *Rhizophora apiculata* aqueous extract exhibited significant activity over all remaining tested extracts with percentage of inhibition 61.3667±0.73106 at 250µg concentration. Both plant extracts exhibited lesser activity on comparison with Metronidazole standard drug; results are shown in **Table 3 and Table 4**. The results indicate that methanol extract of *Kandelia candel* and aqueous extract of *Rhizophora apiculata* shown appreciable antidiabetic activity in performed *in-vitro* assays where as other tested extracts showed the least antidiabetic activity.

Plants are provided with secondary metabolites such as alkaloids, flavonoids, tannins, phenols and saponins which are also known as bioactive compounds and these bioactive compounds possess different biological activities which include antibacterial, antioxidant, anti-inflammatory, anticancer and antidiabetic and especially flavonoids already reported to treat type 2 diabetes [57-60]. In the recent years medicinal plants and their products have been investigated for potential benefits in the management of type 2 diabetes [61, 62].

TABLE 3: PERCENTAGE OF GLUCOSE UPTAKE IN YEAST CELLS TREATED WITH *KANDELIA CANDEL* EXTRACTS

Samples	Concentration(µg/ml)	Inhibition (%)	IC_{50}(µg/ml)
Standard	50µg	51.4728±1.00666**	48.56 µg
	100 µg	58.2081±1.05007**	
	150 µg	62.4862±0.50774**	
	200 µg	65.7095±0.28285**	
	250 µg	69.7436±0.25643**	
Chloroform extract	50µg	28.2821±1.66743**	263.68 µg
	100 µg	32.6267±1.68956**	
	150 µg	35.6433±1.50203**	
	200 µg	43.0174±1.36312**	
	250 µg	47.4055±1.02680**	
Ethyl acetate extract	50µg	19.9406±1.54161**	312.76 µg
	100 µg	22.9640±1.08193**	
	150 µg	27.2281±1.27374**	
	200 µg	33.8680±1.58547**	
	250 µg	39.9660±0.85895**	
Methanol extract	50µg	40.6864±1.26919**	206.89 µg
	100 µg	41.5685±1.99040**	
	150 µg	47.4187±0.83227**	
	200 µg	48.3345±1.17442**	
	250 µg	60.3143±0.56826**	
Ethanol extract	50µg	32.6267±1.68956*	267.95 µg
	100 µg	30.0059±1.77459*	
	150 µg	38.6814±1.13079*	
	200 µg	40.6864±1.26919*	
	250 µg	46.6490±0.68465*	
Aqueous extract	50µg	23.1713±3.03673**	283.02 µg
	100 µg	28.1289±2.90468**	
	150 µg	35.8993±1.81378**	
	200 µg	41.6871±0.62110**	
	250 µg	44.1659±0.74987**	

Results are expressed as Mean±SE (n=3); * significant at the P < 0.01.
Correlation is significant at the 0.01 level (2-tailed)**, Correlation is significant at the 0.05 level (2-tailed)*

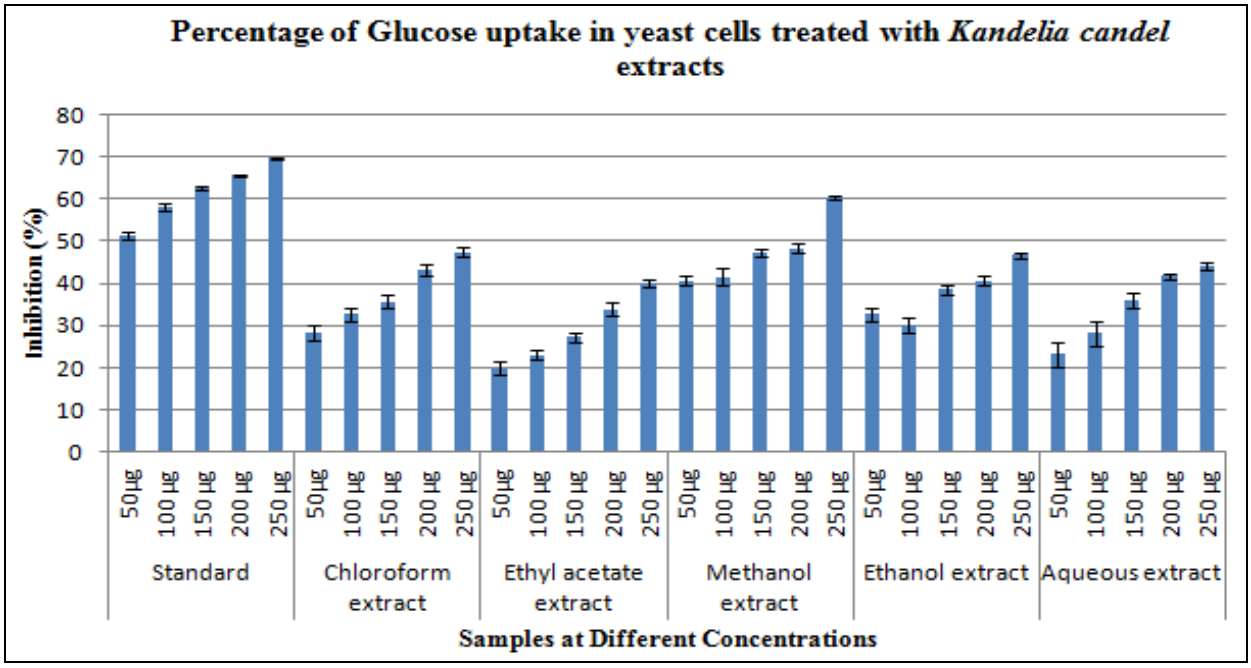

FIG. 3: PERCENTAGE OF GLUCOSE UPTAKE IN YEAST CELLS TREATED WITH *KANDELIA CANDEL* EXTRACTS

TABLE 4: PERCENTAGE OF GLUCOSE UPTAKE IN YEAST CELLS TREATED WITH *RHIZOPHORA APICULATA* EXTRACTS

Samples	Concentration(µg/ml)	Inhibition (%)	IC_{50}(µg/ml)
Standard	50µg	51.4728±1.00666**	48.56 µg
	100 µg	58.2081±1.05007**	
	150 µg	62.4862±0.50774**	
	200 µg	65.7095±0.28285**	
	250 µg	69.7436±0.25643**	
Chloroform extract	50µg	34.3361±2.64282**	271.86 µg
	100 µg	33.7635±2.41615**	
	150 µg	38.9199±3.13700**	
	200 µg	42.5529±1.46574**	
	250 µg	45.9786±1.56950**	
Ethyl acetate extract	50µg	22.1038±1.49677**	350.69 µg
	100 µg	24.4071±2.73330**	
	150 µg	28.6134±1.89819**	
	200 µg	31.7131±1.18220**	
	250 µg	35.6433±1.50203**	
Methanol extract	50µg	28.4437±3.14001**	291.81 µg
	100 µg	31.9918±1.67603**	
	150 µg	36.4030±2.23033**	
	200 µg	40.2346±0.65233**	
	250 µg	42.8355±0.78602**	
Ethanol extract	50µg	24.9511±1.35471*	305.41 µg
	100 µg	31.3912±1.13222*	
	150 µg	32.3328±1.43023*	
	200 µg	31.7322±0.85042*	
	250 µg	40.9273±1.29690*	
Aqueous extract	50µg	47.2144±1.00523**	102.20 µg
	100 µg	48.9207±0.62763**	
	150 µg	55.5453±0.47539**	
	200 µg	58.3183±1.14551**	
	250 µg	61.3667±0.73106**	

Results are expressed as Mean±SE (n=3); * significant at the P < 0.01.
Correlation is significant at the 0.01 level (2-tailed)**, Correlation is significant at the 0.05 level (2-tailed)*

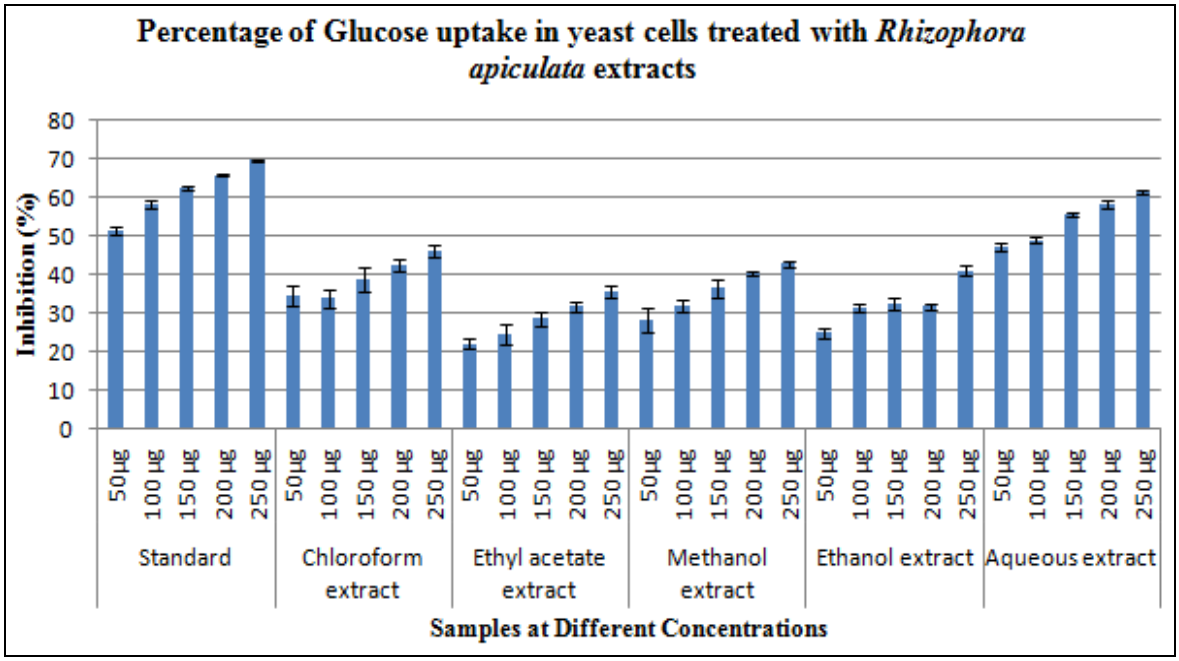

FIG. 4: PERCENTAGE OF GLUCOSE UPTAKE IN YEAST CELLS TREATED WITH *RHIZOPHORA APICULATA* EXTRACT

CONCLUSION: In the present study in both *in-vitro* methods *Kandelia candel* and *Rhizophora apiculata* plant extracts showed antidiabetic activities but among tested extracts methanol extract of *Kandelia candel* and aqueous extract of *Rhizophora apiculata* exhibited higher antidiabetic activity over all extracts with good percentage of inhibition. Based on the present study results it can be used for the development of new pharmaceutical drugs for treatment and curing of diabetes and also this study shows that these extracts offer a safe method or supplement treatment strategy to control diabetes through its alpha amylase inhibition. However further comprehensive chemical and pharmacological investigation should be carried out to isolate the active compounds and appropriate elucidation of its mechanism of action and it helps in the development of new pharmaceuticals to treat diabetes mellitus.

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CONFLICT OF INTEREST: We wish to confirm that there are no known conflicts of interest associated with this publication

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