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In Vitro Evaluation of Antidiabetic Potential of Methanolic Extract of Carica Papaya Stem

Mrs. Bhavya Sivadas*, Associate professor, Alert Joseph Chacko[1], Arjun P[2], Asna Shirin N[3], Jwala George[4], Rameesa Jabin[5],Snigdha P[6]
[1,2,3,4,5,6] *Students of KMCT College of Pharmaceutical Science Kallanthode, NIT, P.O Kozhikode-673601*
Corresponding Author: Jwala George

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ABSTRACT: The study aimed to investigate the anti-diabetic properties of Carica papaya flesh part of stemand evaluating the quantitative determination of saponin, and in-vitro anti-diabetic activityof the extract. The methanolic extract was obtained using the Soxhlet apparatus, was used for the Antidiabetic study. Phytochemical screening was conducted to access the qualitativechemical composition of the crude extract to identify the major natural chemical groups and secondarymetabolites present in the plants. The study provides valuable insights into thepotential anti-diabetic properties of Carica papaya flesh part of stem and its potential as anatural anti-diabetic agent.
KEYWORDS: Anti-diabetic activity; methanolic extract of Carica papaya; Saponin

I. INTRODUCTION

Diabetes mellitus, more simply called diabetes, is a chronic condition that occurs when there are raised levels of glucose in the blood because the body cannot produce any or enough of the hormone insulin or use insulin effectively. It is a metabolic disorder of multiple etiologies distinguished by a failure of glucose homeostasis with disturbances of carbohydrate, fat and protein metabolism as a result of defects in insulin secretion and/or insulin action.

TYPES OF DIABETES MELLITUS

•**Type1diabetes:** Due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency.

•**Type 2 diabetes:** Due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance.

•**Gestational Diabetes Mellitus (GDM):** Diabetes diagnosed in the second third trimester pregnancy.

SCREENING MODELS OF ANTIDIABETICS

1.IN VIVO MODELS

FOR INSULIN DEPENDENT DIABETES MELLITUS

1.Alloxan induced DM
2.Streptozocin induced DM
3.Virus induced DM
4.Hormone induced DM
5.Insulin deficiency due to insulin antibodies
6.Genetic models
-Non obese diabetic mouse
-Bio breeding rat

2.IN VITRO MODELS

•Effect on liver
•Effect on muscle cell
•Enzyme inhibition assay for anti-diabetic activity.
-Alpha-amylase inhibition assay
-Alpha-glucosidase inhibition assay

IN VITRO MODELS

1.Effect on liver

Isolated hepatocyte

 Purpose & rationale : Isolated hepatocytes can be used to study the effect of drug on hepatic gluconeogenesis and other hepatic metabolic reactions such as ketone bodies formation and tricarboxylic formation.

 Animals: Male Wister rat (200 - 250 g) anesthetized with hexobarbital (150 ml/kg)

 Procedure :

•Male Wister rat taken- hepatocytes isolated by collagenase method .
•Cell suspension is preincubated – substrates are added -test drug added
•Glucose is evaluated by glucose oxidase method and pyruvate, lactate and acetoacetate are evaluvated by enzymatic method

 Evaluation:

The sample for analysis is withdrawn by catheter and are evaluated for net glucose production

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2.Effect on muscle cell

Use of isolated diaphragm from mice and rat:

 Isolated diaphragm from rat and divide it in equal part. Incubated with kreb-henselit buffer with 5Mm glucose, insulin or compound to be separate.

 After 30 min hemi diphragm are blotted on the tissue and frozen in liquid nitrogen. **Powered** tissue is dissoveld in 30% KOH. After freezing sample are centrifused

 Glycogen pallets are wash with 70% ethanol and labeled C14 glycogen is determined after hydrolysis to glucose.

 The total concentration dependence of glucose uptake and conversion into glycogen by insulin is determined.

 Evaluation:

•Body weight
•Lipid profile
•Serum insulin level
•Histopathology of pancreas and liver

3.Enzyme inhibiton assay for antidiabetic activity

 INVITRO amylase inhibitons can be studied by allowing the test sample to react with alpha – amylase followed by incubation.Starch solution is added to analyze the amylase activity.

 After incubation dinitro salicylic acid reagent was added to both control and test

 Maltose released from starch is measured by the reduction of 3,5-dintro salicylic acid (pale yellow to orange red colour)

 Keep this mixture in boiling water bath for few mins.Theabsorbance was taken at 540nm using spectrophotometer and the percentage inhibition of alpha- amylase enzyme was calculated.

Inhibition of alpha-glucosidase activity

 The alpha- glucosidase enzyme inhibition activity was analysed by incubating alpha- glucosidase enzyme solution with phosphate buffer containing test samples for different concentrations at 37 ℃ for 1 hr in maltose solution

 The reaction mixture is kept in boiling water for few mins and cooled

 Glucose reagent is added and its absorbance was measured at 540nm to estimate the amount of liberated glucose from maltose by the action of alpha- glucosidase enzyme

 Percentage inhibition and IC50 is calculated

II. MATERIALS AND METHODS

EXTRACTION

Sufficient amount of plant material was collected and brought to the laboratory andwashed thoroughly with tap water. After that, it was air dried completely under shadearea at room temperature and then grounded with electric machine grinder separately.The resultant powder was sieved, weighed and stored in clean stoppered bottle and keptin dry place until the extraction processes were started. Methanolic extraction was performed by Soxhlet extraction method. The Powdered dry plant material (40.08 g) wasextracted with 100 ml methanol for 24 h and thus, it is named as MECP. The extract wasfiltered and concentrated under vacuum-sounding apparatus for 30 min and then stored at40°c.

TEST FOR ALKALOIDS.

1.Mayer's test: Small quantities of the extracts were treated with few drops Mayer's reagent (mercuric chloride and potassium iodide).Formation of yellowish buff color precipitate indicates the presence of alkaloids.

2.Dragendroff's test: To 2-3 ml of extracts, few drops of the Dragendorff's reagent (Sodium iodide, basic bismuth carbonate, glacial acetic acid and ethyl acetate were added. Development oforange brown precipitate indicates the presence of alkaloids

3. Wagner's test: Small quantities of the extracts were treated with Wagner's reagent (solution of iodine in potassium iodide) and reddish-brown precipitates indicate the presence of alkaloids**.**

4.Hager's test:

Small quantities of extracts were treated with Hager's reagent and development of reddish brown precipitate indicates the presence of alkaloids.

TEST FOR FLAVONOID

1.Ferric chloride test: To a small quantity of extracts few drops of neutral ferric chloride solution wereadded.Formation of blackish red color indicates presence of flavonoids**.**

2.Alkaline reagent test: To the extracts, increasing concentration of NaOH were added. Formation of anintense yellow color, which turns to colorless on addition of few drops of dilutehydrochloric acid, indicates the presence of flavonoids.

TEST FOR PHYTOSTEROLS AND TRITERPENOIDS

1. Libermann - Burchard test: Small quantities of extracts were treated with few drops of acetic anhydride, followedby a few drops of concentrated

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sulphuric acid. A brown ring was formed at thejunction of two layers and the upper layer turns green color, infers the presence ofphytosterols and formation of deep red color indicates the presence of triterpenoids.

2. Salkowski test: A small quantity of the extracts was treated with chloroform and few drops of concentrated sulphuric acid and allowed to stand for few minutes. Yellow color at thelower layer indicates the presence of triterpenoids.

TEST FOR REDUCING SUGARS

1. Benedict's test: To the test samples, the equal volume of Benedict's reagent (alkaline solutioncontaining cupric citrate complex) was mixed in a test tube and heated for fewminutes. Formation of Brick red Precipitate confirmed the presence of sugars.

2. Fehling's test: Equal volume of Fehling's- A [copper sulphate in distilled water] and Fehling's- B [potassium tartarate and sodium hydroxide in distilled water] reagents were mixed ina test tube and boiled for one minute. To this 1 ml of sample was added and heatedfor few minutes. Formation of brick red precipitate confirmed the presence of sugars.

3. Barfoed's test: To a few ml of the test samples, 5 ml of Barfoed's reagent was added and boiled.Formation of red precipitate of copper oxide indicates the presence ofmonosaccharides.

TEST FOR TANNINS

1.Lead acetate test: Mixed 1ml of test samples with 10% aqueous lead acetate solution. Development Ofyellow color precipitate indicates the presence of tannins.

 Treated I ml of test sample with I mL of ferric chloride solution. Dark blue orgreenish black was produced, which indicated the presence of tannins.

TEST FOR GLYCOSIDES

1.Keller killiani test: Extracts (2ml) were dissolved in acetic acid containing trace of ferric chloride andtransferred to the surface of concentrated sulphuric acid. At the junction of two liquids, a reddish-brown color formed, which gradually became blue color due to thepresence of glycosides.

2.Legal's test: Dissolved 2ml of extracts in pyridine; sodium nitroprusside solution was added to itand made alkaline. Pink red color was formed which indicates the presence ofglycosides.

3.Baljet test: Extracts(2ml) was added with sodium picrate solution. Formation of yellow toorange color indicating the presence of glycosides.

4.Borntrager's test: Added 1 ml of diluted sulphuric acid was added to 2 ml of extracts. The mixture wasboiled, filtered and the filtrate was extracted with ether or chloroform. Then organic layer was separated to which ammonia was added, pink, red or violet color wasproduced in organic layer, which indicates the presence of glycosides.

TEST FOR PROTEINS AND AMINO ACIDS

1. Biuret test: To 1 mi of test sample, I ml of biuret reagent was added. Formation of violet colorindicates the presence of proteins.

2. Ninhydrin test: To 1 ml of test sample, 2 drops of freshly prepared 0.2% ninhydrin reagent was addedand heated, Development of blue color indicates the presence of proteins, peptides or amino acids.

TEST FOR SAPONINS

1. Foam test: About 1 ml of test sample is diluted separately with distilled water to 20 ml and shaken in a graduated cylinder for 3 minutes. Foam of 1 cm after 10 minutes indicates the presence of saponins.

2. Froth test:

To 5 ml of the test sample, a drop of sodium bicarbonate was added. The mixture was formed which shows the presence of saponins

TEST FOR PHENOLS

1. Ferric chloride test :

To 1 ml of the extracts, 2 ml of distilled water followed by few drops of 10% ferricchloride was added. Formation of blue or green color indicatesthe presence ofphenols.

2. Lead acetate test

The extracts were diluted with 5 ml of distilledwater and to these few drops of 1%aqueous solution of lead acetate was added. A yellow color precipitate was formed which indicates the presence of phenols.

QUANTITATIVE DETERMINATION OF SAPONIN

The TLC plate was prepared by using silica gel and activated. The methanolic extract was prepared by soxhlet extraction method. The small quantity of the prepared extract is taken for preparation of TLC. Use capillary tube or micropipette to apply the sample solution to the spots. Allow the spots to dry completely. Pour the mobile phase, Acetone:Hexane (4 : 10) into the TLC chamber. Place the plate in the chamber with the sample line facing the mobile phase.Close the

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chamber with a lid. Wait for the spot to develop. The developed chromatograms were air dried. Detected by using iodine chamber and the Rf value was calculated.

Rf = Distance travelled by solute / Distance travelled by solvent front.

INVITRO ANTI-DIABETIC ACTIVITY
ALPHA- AMYLASE INHIBITORY ASSAY
SAMPLE PREPARATION

The sample stock was prepared by mixing 10 mg of sample in 1 ml methanol to form 10mg/ml stock solution. The samples are taken at different concentration (T1-T4) such as 100, 200, 400 and 800 µg/ml. These stock solutions were then utilized for inhibition of Alpha- amylase enzyme. The α-amylase inhibition assay was conducted using the chromogenic DNSA method. The assay mixture consisted of 100 µl of α-amylase solution (0.5 mg/ml) in sodium Phosphate buffer (0.02 M) and 100 µl of plant extract at concentrations ranging from 100 to 800 µg/ml (T1-T4). The mixture was incubated at 37°C for 10 minutes. Subsequently, 100 µl of 1% (v/v) starch solution, prepared in the same buffer, was added to each tube and incubated again at 37°C for 15 minutes. The reaction was stopped by adding 200 µl of DNSA reagent, followed by heating the tubes in a boiling water bath for 5 minutes. After cooling to room temperature, the absorbance was measured at 540 nm. Acarbose (100µg/ml) was used as the standard, while control Samples, were prepared under identical conditions without the addition of plant extracts.

Percentage inhibition = (Abs Control−Abs sample) × 100/Abs control

III. RESULT AND DISCUSSION

EXTRACTION OF PLANT MATERIAL:

The methanolic extract of Carica papaya stem was carried out by using soxhlet apparatus. The resultant methanolic extract was brownish green in colour and semisolid in nature. The percentage yield was found to be 64.3%. The resultant extract was named as MECP and it was stored under vacuum desiccator

METHANOLIC EXTRACTION OFCARICA PAPAYA STEM

PERCENTAGE YIELD AND CONSISTENCY OF EXTRACT

EXTRACT	Methanolic
COLOUR	Brownish green
CONSISTENCY	Semi-solid

METHANOLIC EXTRACT OF CARICA PAPAYA STEM

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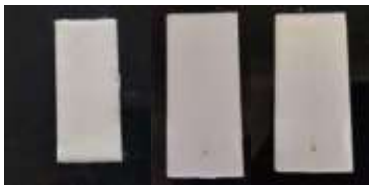
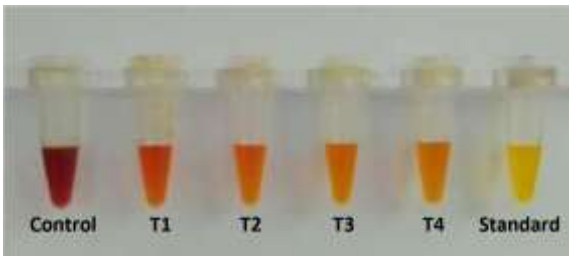
QUANTITATIVE DETERMINATION OF SAPONINS

The TLC plate was prepared by using silica gel and activated. The small quantity of the prepared extract is taken for preparation of TLC using capillary tube or micropipette to apply the sample solution to the spots. Allow the spots to dry completely. Pour the mobile phase into the TLC chamber. Place the plate in the chamber with the sample line facing the mobile phase. Close the chamber with a lid. Wait for the spot to develop. The developed chromatograms were air dried. The Rf value of the MECP was found to be 53 and this indicates the presence of diosgenin(55)



QUANTITATIVE DETERMINATIONOF SAPONIN

ALPHA-AMYLASE INHIBITORY ASSAY OF MECP

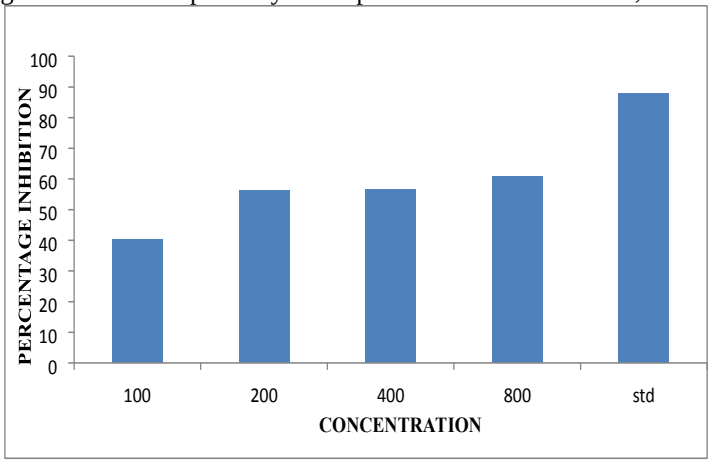


ALPHA AMYLASE INHIBITORY ASSAY OF SAMPLE WITH CONTROL AND STANDARD

PERCENTAGE INHIBITION OF SAMPLE MECP

Concentration (µg/ml)	Absorbance	% of Inhibition
100	0.298	40.293±0.23
200	0.218	56.301±0.14
400	0.208	58.425±0.31
800	0.195	60.930±0.12
Standard	0.061	87.778±0.38
Control	0.499	

Each value of percentage inhibition of alpha-amylase is presented as mean ± SEM, n = 3



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INVITRO ANTI-DIABETIC ACTIVITY OF MECP

The alpha-amylase inhibitory activity in methanol extract is most likely to be due to polar compounds and is worth investigating further and isolating pure active compounds. In this study the results indicated that MECP exhibited a significant dose dependent inhibitory effect on Alpha-amylase assay. At the highest concentration investigated the extract displayed appreciable effect by 60.930±0.12%.

IV. SUMMARY AND CONCLUSION

Diabetes mellitus is a metabolic disorder with increasing incidence out the world. Insulinis a key player in the control of glucose homeostasis. Lack of insulin affects carbohydrates, fats and protein metabolism. Management of diabetes without side effect is still challenge to the medical community. It was proposed that inhibition of the activity such as, alpha-amylase and alpha-glucosidase would delay the degradation of carbohydrate, which would in turn cause a decrease in the absorption of glucose, as a result the reduction of postprandial blood glucose level elution. In the present study, research has been carried out to evaluate the preliminary phytochemical investigation and the potential of the methanol extract of Carica papaya inhibiting alpha-amylase. The present finding of phytochemical screening of the plant extract confirm to the presence of several bioactive components like alkaloids, flavonoids, tannins, glycosides, proteins, phenols, saponin which would be responsible for the versatile medicinal properties of this plant. The present finding reveals that Carica papaya efficiently inhibits the alpha-amylase enzyme in IN VITRO in a dose dependent manner. The methanolic extract from flesh part of Carica papaya stem shows a dose dependent inhibitory effect on alpha-amylase activity. The anti-diabetic action of Carica papaya can also be attributed to the intestinal alpha-amylase inhibitory activity. Further studies are required to elucidate whether the Carica papaya have anti-diabetic potential by in-vitro for validating the traditional claim of the plant. In this present study we evaluated IN VITRO alpha-amylase activity of crude methanolic extract of Carica papaya stem. The plant showed the significant inhibition activity, so further the compound isolation, purification and characterization which is responsible for the inhibiting activity, has to be done for the usage of anti-diabetic agent.

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