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Phytochemical Screening and Evaluation of Anti Diabetic Activity of Carica Papaya Fruit Extract

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ABSTRACT:
The present study was conducted to evaluate the influence of Carica papaya alcoholic extract (CPAE) and Carica papaya Hydro alcoholic extract (CPHAE) on anti-diabetic activity of glibenclamide Carica papaya belongs to the family of Caricaceae and several species of Caricaceae have been used as remedy against a variety of diseases. Hydro Alcoholic and alcohlic extracts of C.Papaya were prepared and were subjected to phyto chemical evaluation and acute toxity studies following OECD guidelines. Acute toxicity studies indicated that upto 1000mg/kg in mice and upto 2000mg/kg in rats. No toxicity was observed. To study the influence of C.papaya an antidiabetic activity of Glybenclamide albino rats weighing 135 to 190gms were randomly distributed into 8 groups each group containing 6 rats. Diabetic was induced in all rats with Alloxan 150mg/kg interpretonially. Group I served as diabetic control. Group II was given Glibenclamide 10mg/kg body weight; Group III, IV and V were given Carica papaya Hydro alcoholic extract (CPHAE) 200mg, 300mg and 400mg/kg. Group VI, VII and VIII were given CPAE 200mg, 300mg and 400mg/kg respectively. All the drugs were gven orally and blood samples were collected before and after drug administration at 0,1,2,4 and 6 hour from Rats tail vein and blood glucose levels at each time interval was estimated by glucometer. C.Papaya was shown mild anti diabetic activity when it was given with Glibenclamide it enhanced the anti diabetic activity of glibenclimide.

Key words: Carica papaya, Fruit extract, Alloxan, Glibenclamide, Diabetes.

I. INTRODUCTION

In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter. A number of medicinal plants, traditionally used for over 1000 years named rasayana are present in herbal preparations of Indian traditional health care systems. In Indian systems of medicine most practitioners formulate and dispense their own recipes. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as botanical garden of the world. As the present study is concerned about anti diabetic activity brief review about pathophysiology of antibiotic mechanism of drugs were given.

Diabetes mellitus

Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. WHO has predicted that the major burden will occur in developing countries. Studies conducted in India in the last decade have highlighted that not only is the prevalence of diabetes high but also that it is increasing rapidly in the urban population [4]. It is estimated that there are approximately 33 million adults with diabetes in India. This number is likely

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to increase to 57.2 million by the year 2025.Diabetes mellitus, or simply diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia[1-2] (increased hunger).

There are three main types of diabetes mellitus (DM).

- Type 1 DM results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".
- Type 2 DM results from insulin resistance[3-4], a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as non insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".
- The third main form, gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. It may precede development of type 2 DM.

Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which beta cell loss is a T-cell-mediated autoimmune attack[5].

Type 2 diabetes

Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion[6-8]. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type.

II. AIM AND OBJECTIVES:

Since there are reports that papaya decrease the nitrite – nitrate in the body, decreased nitrite – nitrate and increased potassium levels in diabetes mellitus increases the effect of insulin on control of blood sugar. Hence, the present study was conducted.

- To study the influence of Alcoholic Extract of C.Papaya (CPAE) on the anti diabetic activity of Glibenclamide in Alloxan induced diabetic rats.
- To study the influence of Hydro Alcoholic Extract of C.Papaya (CPHAE) on the anti diabetic activity of Glibenclamide in Alloxan induced diabetic rats.
- Influence of c.papaya extract on anti diabetic activity of glibenclamide.

III. MATERIALS AND METHODS:

Alcoholic and Hydro Alcoholic extracts of C.Papaya were prepared and subjected to

1. Phyto chemical evaluation
2. Acute toxicity studies in rats
3. To Study the influence of Alcoholic extract of C.Papaya (CPAE)
4. To Study the influence of Hydro Alcoholic extract of C.Papaya (CPHAE)

Phytochemical evaluation: phytochemical evaluation is conducted for Carica papaya following standard chemical tests.

Phyto chemical studies:

Qualitative phytochemical screening:

The different qualitative tests were performed for establishing profile of the given extract for its chemical composition. The following tests were performed on extracts to detect various phyto constituents present in them.

Detection of Alkaloids: Solvent free extracts of 50mg was stirred with few ml. of dilute Hydrochloric acid and filtered. The Filtrate was tested carefully with various alkaloidal reagents as follows:

To a few ml of filtrate, a drop or two of Mayer's / Wagner / Hagers / Dragendroff's reagent were added by the side of the test tube.

Mayers reagent

Mercuric chloride (1.358 g) was dissolved in 60ml. of water and potassium iodide (5.0g0 was dissolved in 10ml. of water the two solutions were mixed and made up to 100ml. with water.

Legal Tests

Fifty mg of the extract was dissolved in pyridine sodium nitroprusside solution was added and made alkaline using 10% sodium hydroxide. Presence of glucose was indicated by pink color.

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Detection of proteins and Amino acids:
The extract (100mg) were dissolved in 10ml of distilled water and filtered through Whatmann No. 1 filter paper and the filtrates were subjected to tests for proteins and amino acids.

Millions Test:
To 2 ml. of filtrate, few days of millions reagent was added. A White precipitate indicated the presence of proteins

Biuret Test:
An aliquot of 2ml. of the filtrate was treated with one drop of 2% copper sulphate solution. To this, 1 ml of ethanol (95%) was added, followed by excess of potassium hydroxide pellets. Pink color in the ethanolic layer indicated the presence of proteins.

Ninhydrin test:
Two drops of ninhydrin solution (10mg of ninhydrin in 200ml. of acetone were added to 2ml. of aqueous filtrate. A characteristic purple color indicates the presence of Amino acids.

Detection of phytosterols:
The extract of the formulation (50mg) were dissolved in 2 ml. acetic anhydride. To this, one or two drops of cone. Sulphuric acid was added slowly along the sides of the test tube. An array of color changes showed the presence of phytosterols

Detection of phenolic compounds and tannins:
Ferric chloride test:
The Extract (50mg) was dissolved in 5ml. of distilled water. To this, few drops of neutral 5% ferric chloride were added. A dark green color indicated the presence of phenolic compounds.

Lead acetate test:
The extract (50mg) was dissolved in distilled water and to this, 3ml of 10% lead acetate solution was added. A bulky white paper precipitate indicated the presence of phenolic compounds.

Alkaline reagent test:
An aqueous solution of the extract was treated with 10% ammonium hydroxide solution. Yellow fluorescence indicated the presence of flavorides[9-15].

Acute toxicity studies:
The acute toxicity studies were carried out by following the standard guidelines (OECD-423 guidelines). With Alcoholic and Hydro Alcoholic extract of C.Papaya in mice and rats.
Hydroalcoholic extract of C.Papaya did not produce any toxic symptoms or mortality up to the dose level of 1000 mg/kg body weight in mice, 2000mg/kg body weight in rats and hence the extract was considerd to be safe and non-toxic for further pharmacological screening[16-18].

Influence of cpae and cphae on the anti diabetic actvity of glibenclamide
Experimental animals:
Male Albino rats weigh about 135 – 190 grams were selected for the study and maintained under standard conditions of temperature and humidity.The use of animals in these experiments were authorized by IAEC (Instutional Animal Ethical Committee).Throughout the experiment, experimental rats were processed in accordance with the CPCSEA guidelines.
Various drugs used in the study:
1. Glibenclamide: Natco pharmaceuticals (Hyderabad).
2. Alloxan: Natco pharmaceuticals (Hyderabad).
3. Carica Papaya Alcoholic and Hydro Alcoholic extract.
4. 0.25% Sodium CMC

IV. METHODLOGY

PREPARATION OF CARICA PAPAYA EXTRACT:

Papaya fresh fruit was taken and dried in the shade for few days then dried fruit was powdered finely ,the fine powder was macerated for 72 hours with the composition of 70% water and 30% alcohol (hydro alcoholic extract) was made then it was evaporated to dryness and was kept in the dessicator for 24 hours for the prevention of growth of micro-organisms . That adduct was weighed and used for the experiment
Actual powder : 2500gms
Dry powder :1325 gms

For the preparation of Alcoholic extract Papaya fresh fruit was taken and dried in the shade for few days then dried fruit was powdered finely ,the fine powder was macerated for 72 hours with Absolute Alcohol and was evaporated to dryness was kept in the dessicator for 24 hours for the prevention of growth of micro-organisms . That adduct was weighed and used for the experiment
Actual powder : 1200gms
Dry powder : 850 gms

In this study diabetics was induced in rats by given 150mg per kg of Alloxan. To prevent the

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death of animal due to hypoglycaemia every 6 hours 10% of glucose solution was given intra peritonially upto 24 hours Blood glucose level is estimated periodically and the rats showing blood glucose level above 250mg per100 ml were considered as diabetic about 48 diabetic rats were selected and randomly distributed in to 8 groups each containing 6 animals[19-22].

All drugs were given orally and treat schedule is as follows:-

Group 1:Diabetic Control (0.25% Sodium Carboxy Methyl Cellulose)
Group 2:Glibeclamide 10mg/kg.
Group 3:CPHAE 200mg+Glibencamide 10mg /kg.
Group 4:CPHAE 300mg+ Glibencamide 10mg /kg.
Group 5:CPHAE 400mg+ Glibencamide 10mg /kg.
Group 6:CPAE 200mg+ Glibencamide 10mg /kg.
Group 7:CPAE 300mg+ Glibencamide 10mg /kg.
Group 8:CPAE 400mg+ Glibencamide 10mg /kg.

All Drugs were given orally and blood samples (0.5ml) were collected from tail and vein of 0,1,2,4 and 6 hours. Glucose was estimated in all blood samples using Glucometer and percentage blood glucose reduction was calculated at each Time Interval –'t' is calculated by using the formulae

t=A-B/A X 100

A is Blood Glucose concentration at time 0
B is Blood Glucose concentration at time t

And results were expressed as Mean ± SEM
And were represented in tables (Table Number) and were graphically represented in figure (Image number)

Method for oral administration of drug:

An 18-gauge needle was suitably covered with flexible polythene tubing, where the edge was made blunt; the needle was fixed to 1ml tuberculin syringe the rat was held firmly in left hand, the tubing was moistened with glycerin and inserted right into the esophagus and gently pressing plunger for drug administration, and this was followed by 0.2ml of distilled water to ensure administration of correct dose of the drug.

Table:1

Diabetic Control							
Hours	R1	R2	R3	R4	R5	Mean±SEM	%reduction in blood glucose
0 Hour	335	338	337	340	345	339	0%
1 Hour	337	339	340	342	343	340.2	-0.29
2 Hour	336	338	339	340	342	339	0%
4 Hour	340	342	344	345	346	343.4	-1.30
6 Hour	342	343	346	349	360	348	-2.65

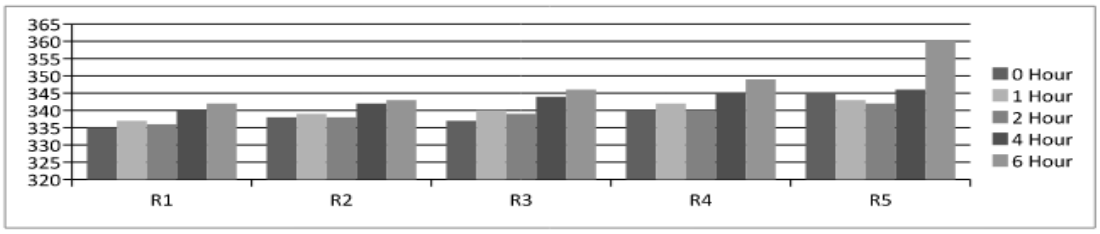

Fig: 1

Table:2

Glibenclamide 10mg/kg							
Hours	R1	R2	R3	R4	R5	Mean±SEM	% reduction in blood glucose
0 Hour	320	335	339	340	340	334.8	0.00
1 Hour	329	320	321	330	305	321	4.12
2 Hour	295	280	280	290	290	287	14.28
4 Hour	230	254	258	245	240	245.4	26.70

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6 Hour	206	208	210	214	226	212.8	36.44

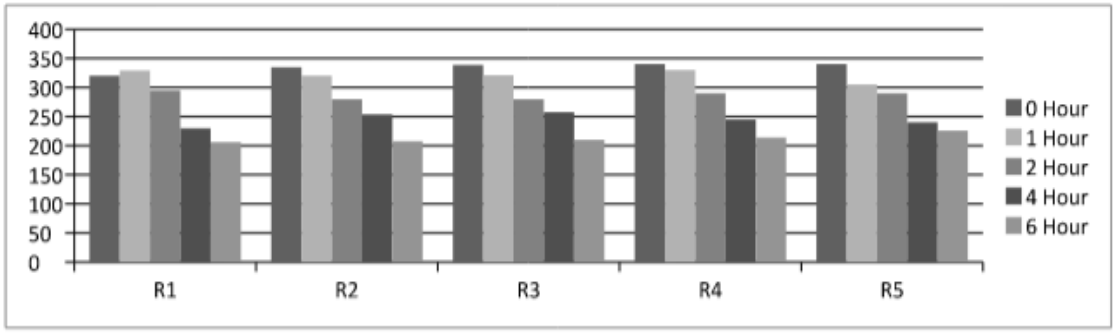

Fig:2

Table:3

CPHAE 200 mg+ Glibenclamide 10mg/kg							
Hours	R1	R2	R3	R4	R5	Mean±SEM	% reduction in blood glucose
0 Hour	328	330	331	338	345	334.4	0.00
1 Hour	310	312	312	310	300	308.8	7.66
2 Hour	290	285	275	269	272	278.2	16.81
4 Hour	240	235	240	249	235	239.8	28.29
6 Hour	215	210	185	196	190	199.2	40.43

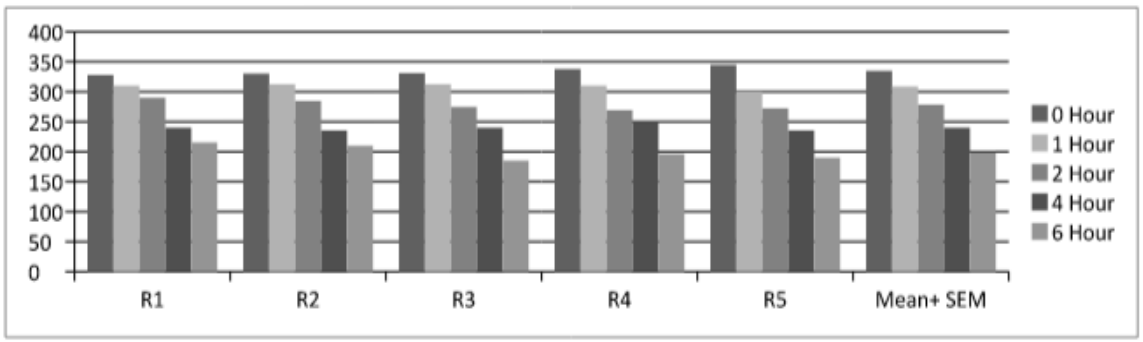

Fig:3

Table:4

CPHAE 300 mg+ Glibenclamide 10mg/kg							
Hours	R1	R2	R3	R4	R5	Mean±SEM	% reduction in blood glucose
0 Hour	320	319	318	317	319	318.6	0.00
1 Hour	295	298	290	287	280	290	8.98
2 Hour	270	275	272	269	220	261.2	18.02
4 Hour	202	212	205	200	201	204	35.97
6 Hour	180	173	164	152	120	157.8	50.47

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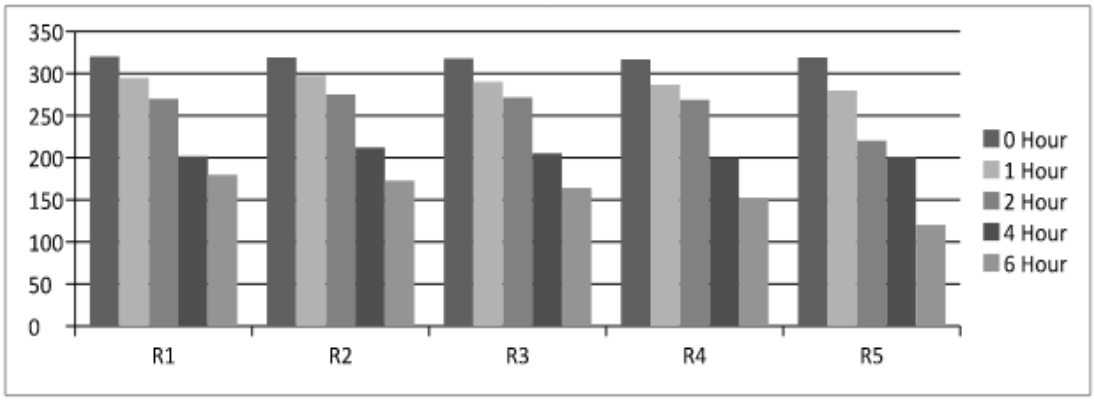

Fig:4

Table:5

CPHAE 400 mg+ Glibenclamide 10mg/kg							
Hours	R1	R2	R3	R4	R5	Mean±SEM	% reduction in blood glucose
0 Hour	345	349	335	350	350	345.8	0.00
1 Hour	310	305	310	309	320	310.8	10.12
2 Hour	290	292	280	270	255	277.4	19.78
4 Hour	203	202	195	195	180	195	43.61
6 Hour	168	160	165	150	130	154.6	55.29

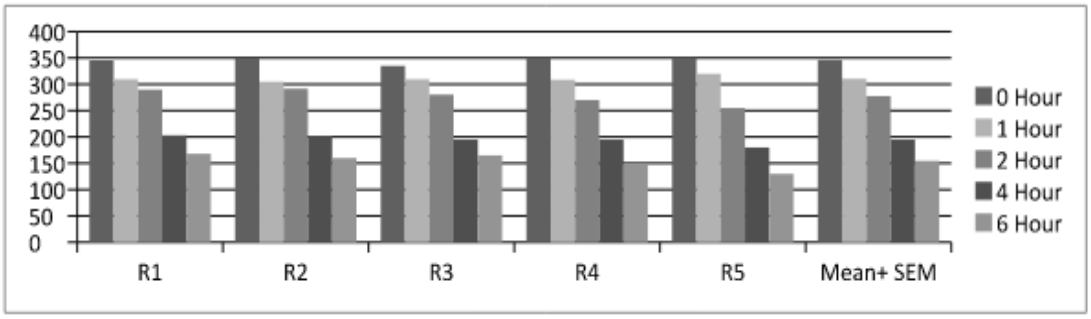

Fig:5

Table:6

CPAE 200 mg+ Glibenclamide 10mg/kg							
Hours	R1	R2	R3	R4	R5	Mean±SEM	% reduction in blood glucose
0 Hour	340	334	337	338	338	337.4	0.00
1 Hour	330	330	332	338	338	333.6	1.13
2 Hour	320	309	315	308	300	310.4	8.00
4 Hour	285	280	275	280	270	278	17.61
6 Hour	224	222	223	222	221	222.4	34.08

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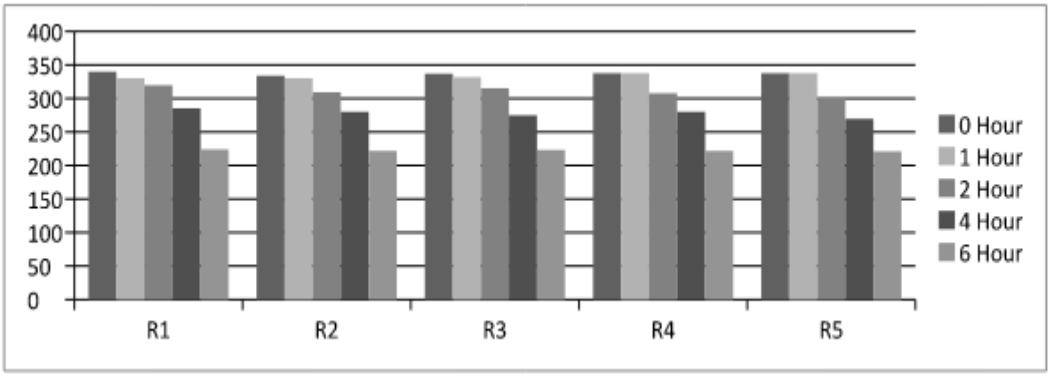

Fig:6

Table:7

CPAE 300 mg+ Glibenclamide 10mg/kg							
Hours	R1	R2	R3	R4	R5	Mean±SEM	% reduction in blood glucose
0 Hour	345	333	335	340	345	339.6	0.00
1 Hour	340	338	330	332	335	335	1.35
2 Hour	315	312	311	311	312	312.2	8.07
4 Hour	250	249	248	247	249	248.6	26.80
6 Hour	220	221	215	216	219	218.2	35.75

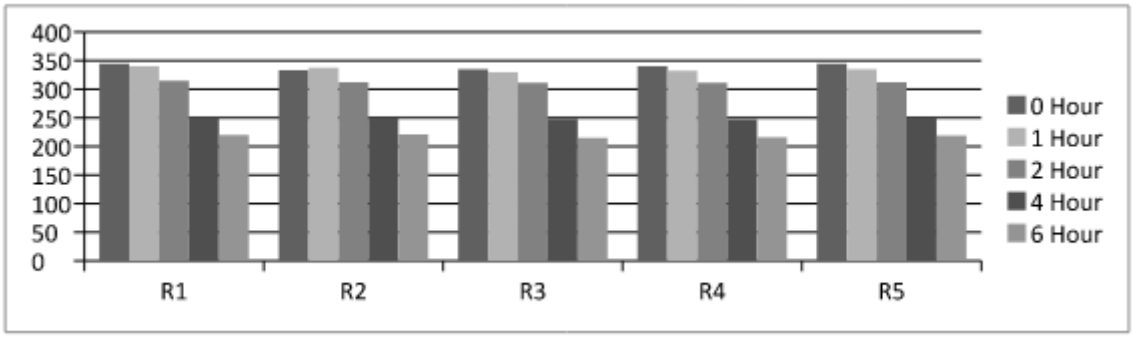

Fig:7

Table:8

CPAE 400 mg+ Glibenclamide 10mg/kg							
Hours	R1	R2	R3	R4	R5	Mean±SEM	% reduction in blood glucose
0 Hour	330	337	339	333	345	336.8	0.00
1 Hour	322	332	332	330	330	329.2	0.23
2 Hour	279	278	275	278	278	277.6	17.58
4 Hour	198	196	199	198	195	197.2	41.45
6 Hour	160	150	153	151	150	152.8	54.63

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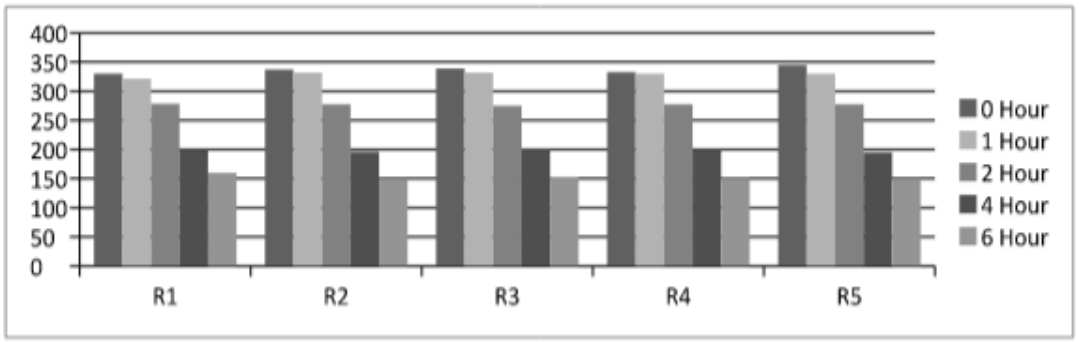

Fig:8

Method for collection of blood sample:

The rat was placed into the rat holder; the tail was pulled out and was depilated for collection of blood sample. Tail vein was dilated by focus in galow voltage electric lamp. A small prick was made using a small needle and a drop of blood was collected through capillary action of glucometer test strips. Later dry cotton was applied for few minutes to stop the blood flow and the tail is sterilized by spirit. Estimate the blood glucose level[23-24].

V. DISCUSSION

The high cost and poor availability of current therapies to many of the rural population in India necessitates the need for the development of indigenous, inexpensive herbal remedies used as anti diabetic drugs. Herbal medicines are being used by 80% of the world population for primary health care. The natural products shall be considered as the best in the primary health care because of better cultural acceptability, safety, and efficacy, potent, inexpensive and lesser side effects. Several herbal medicines and supplements have been studies as potential therapeutic agents in the management of diabetes and its related complications. Scientific investigation of traditional herbal remedies many result in the availability of valuable leads for the development of the drugs and therapeutic strategies. Even the discovery widely used hypoglycemic drug, metformin came from the traditional approach of using Galega Officinali. Cost efficient, potent and lesser side effect of drugs and plant origin have been achieved through compound formulations either in their natural or semi processed forms. The herbal remedies can act as good adjuvant drug to reduce the requirement of insulin/suplonylurea derivatives[25-26.]

VI. CONCLUSION

Serum blood glucose was measured in all groups and %blood glucose reduction was estimated.Glibenclamide 10mg/kg showed 37%blood glucose level reduction at 6th hour. When glibenclamide 10mg/kg was given with CPHAE 200mg, 300mg, 400mg/kg the blood glucose reduction was enhanced to 40%, 50%, 55% respectively.CPHAE is shown have more effect than CPAE.In presence of study as per the literature C.Papaya was shown to have mild anti diabetic activity. As it is a fruit there is possible for taking along with antidiabetic drugs such as insulin, sulfonylureas etc.

In present study results indicate that CPHAE and CPAE enhanced antidiabetic activity of Glibenclamide in dose dependent manner. These results suggest that concomitant administration of Glibenclamide and papaya is safe in diabetes at lower dose and with higher dose hypoglycemia is more due to enhancement of antidiabetic activity of Glibenclamide. The patient should be conscious while taking papaya the dose of Glibenclamide can be adjusted accordingly. These results indicate that papaya might be influencing the absorption of Glibenclamide as shown by the enhancement of peak effect induced by Glibenclamide. So it can be concluded that papaya appears to interfere with the insulin resistance in pancreases their by further enhancing the reduction of blood glucose shown Glibenclamide.

C.papaya higher dose interfering with pharmacodynamics of Glibenclamide.All results were statistically significant at **P<0.05 **P<0.01.When Glibenclamide 10mg/kg was given with CPAE 200mg, 300mg, 400mg/kg the blood glucose reduction was enhanced to 38, 43,51 respectively. This indicated C.Papaya extracts is shown to influence the antidiabetic activity.

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