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AN INVESTIGATION OF THE HYPOGLYCEMIC EFFECT OF THE AQUEOUS EXTRACT OF THE FRUITS OF *PSIDIUM GUAJAVA*, AVERRHOA BILIMBI AND THE PEEL OF TAMARINDUS INDICA IN NORMOGLYCEMIC GUINEA PIGS

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ABSTRACT

Diabetes is a common endocrine disorder worldwide. Selected plants are a potential complementary source of hypoglycemic drugs to combat diabetes, in addition to the use of synthetic drugs: insulin, metformin etc. This research focused on the hypoglycemic effect of the aqueous extract of the fruits of *Psidium guajava*, *Averrhoa bilimbi* and the peel of *Tamarindus indica* on normoglycemic guinea pigs. The guinea pigs were divided into three groups of three: control group, aqueous fruit extract treatment group at a dose of 6 ml/kg) and *glibenclamide* treatment group (with the dose 2.5 mg/kg). Guinea pigs received treatment twice daily for 12 days for each fruit and peel. Blood glucose and body weight were measured before treatment and between three days interval. Additionally, each plant extract at the dose of 6ml/kg was orally administered for glucose tolerance test during 120 minutes study in comparison to *glibenclamide* at the dose of 2.5 mg/kg. Administration of extracts of *Psidium guajava*, *Tamarindus indica* and *Averrhoa bilimbi* resulted in a marked hypoglycemic (reduction) activity in blood glucose levels when compared to the control and *Glibenclamide* treated group on the 12th day: *Psidium guajava* (90 ± 3.0 to 75.7 ± 3.5 mg/dL), *Tamarindus indica* (89.0 ± 5.6 to 70.7 ± 2.1 mg/dL) and *Averrhoa bilimbi* (110.0 ± 9.2 to 86.7 ± 10.0 mg/dL). *Glibenclamide* also resulted in a reduction (88.0 ± 2.0 to 67.3 ± 3.5 mg/dL) as

compared to the control. This research marked the continuation of the use of plant extracts in Guyana as a possible herbal treatment for diabetes *mellitus*.

KEYWORDS: Diabetes mellitus, Psidium guajava, Tamarindus indica, Averrhoa bilimbi, blood glucose, hypoglycemic activity, *glibenclamide*, guinea pigs.

INTRODUCTION

Diabetes mellitus is a chronic health problem with long term consequences that are potentially preventable. It is a heterogeneous group of disease, characterized by high blood glucose levels resulting from impaired insulin secretion, impaired insulin action, or both.[1-4] In a hyperglycemic state, the body tries to remove excess glucose by excreting in the urine. This increases urine output, causing glycosuria and result in frequent thirst. In addition, the body is deprived of glucose energy and seeks alternative energy sources such as fats and muscle tissues, leading to weight loss.[5] A diminishing growth effect and increased predisposition to certain infections, may also be present with chronic hyperglycemia.[4] These combinations along with polyuria, polydipsia, polyphagia, and blurry vision produces the common symptoms of diabetes.[6] As this disease progresses, vascular damage ensues leading to severe diabetic microvascular and macrovascular complications[7] (Cade, 2008). Therefore, diabetes covers a wide range of diseases which are the major causes of chronic morbidity and death in diabetic subjects.[8]

Being described as the “the perfect epidemic” this condition affects an estimated 387 million people worldwide. According to the WHO[9], the incidence of diabetes has risen dramatically over the past years with a current prevalence of 9% and it is expected to affect more than 500 million adults by 2030. North America and the Caribbean are the regions with a higher prevalence of 11%, having 37 million people affected. In 2012, an estimated 1.5 million deaths were directly caused by diabetes, with 80% deaths occurring in low and middle-income countries.[9] A national survey revealed the total number of diagnosed diabetic cases in Guyana as 49,800, with an estimated number of 1025 deaths; a substantially high value for a population as small as that of Guyana’s.[10]

Although, antidiabetic agents such as insulin, biguanides, thiazolidinediones and α glucosidase inhibitors are available in Guyana to treat diabetes, a safe and effective treatment paradigm is yet to be achieved (Cheng, 2005). This is due to that fact that these drugs fail to significantly reduce the course of diabetic complications and have limited use

because of their undesirable pathological conditions and high secondary failure rates. Therefore, it is essential to discover more effective antidiabetic agents with few adverse effects, low costs and ease of accessibility.[12]

In recent years, there has been a resurgence of interest in medicinal plants for the treatment of diseases.[12] A World Health Organization (WHO) study shows that 80% of the world's population solely relies on medicinal plants for their primary health care needs.[13] Medicinal plant extracts, having antidiabetic properties can be a useful source for the development of oral hypoglycemic agents in both animal models and human subjects[14] Over 350 plants are used in the treatment of diabetes *mellitus*, but only a small number of these plants had gained scientific and medical evaluation to assess their effectiveness and efficacy. For the management of diabetes, the World Health Organization[15] (WHO) has recommended the evaluation of traditional plant treatments as they are effective, non-toxic, with little or no side effects and are considered to be excellent candidates for oral therapy.[16]

The significance of this study is that synthetic drugs currently in use for diabetic treatment have undesirable side effects including weight gain, hypoglycemia, nausea and diarrhea. These contributes a great deal to non-compliance in patients which can lead to further deleterious progression of their condition and result inevitably, in the increased mortality rate of the disease. For this reason, natural hypoglycemic compounds found in plant extracts present an attractive alternative to synthetic drugs or as reinforcements for currently used treatments.

This research paper aims to explore the hypoglycemic activity of the aqueous extracts of the fruits of Psidium guajava, Averrhoa bilimbi and the peel of Tamarindus indica in guinea pigs with normal blood glucose in comparison to standard synthetic treatment of *glibenclamide* used in Guyana. To the best of our knowledge, no study was conducted to assess the effectiveness of local fruits to lower blood glucose levels. Therefore, the objective of this study was to determine the hypoglycemic effects of the aqueous extracts of selected fruits in guinea pigs, to explore to what extent these extracts reduce blood glucose level in guinea pigs with normal blood glucose, to compare the hypoglycemic activity of the selected extracts with a standard anti-diabetic drug (*glibenclamide*), to examine the body weight of the guinea pigs before and after administering each fruit extracts. To increase public awareness of local and easily accessible fruits that can be incorporated into the diet to lower blood glucose levels

and manage diabetes and to determine the time it takes for each plant extract to exhibit minimum blood glucose level after the administration of glucose.

It is assumed that the guinea pigs are healthy, free from disease and infections. Also, the syringes used for injection are aseptic and sterilized and the aqueous solvent of the fruits does not hinder experimental results.

Literature review revealed that the anti-diabetic activity of *Psidium guajava* have been reported.[17-20] For example, a study to evaluate the hypoglycemic potential of the aqueous extract of *Psidium guajava* unripe fruit peel on blood glucose level (BGL) of normal and streptozotocin induced mild and severely diabetic rats has been undertaken. This study revealed that the fruit peel of *P. guajava* had marked hypoglycemic effect.[17]

A study to test for the hypoglycemic potential of the ethanolic extract of *Psidium guajava* leaves on normal and alloxan induced diabetic rats have been reported.[19] After 21 days of administering the ethanolic leaf extracts, blood glucose was found to attain normal levels in the plasma of the *Psidium guajava* treated rats However, in this study, adequate results were not obtained to indicate sufficient evidence of anti-hyperglycemic activity of *Psidium guajava.* Nevertheless, the study confirmed that *P. guajava* has some form of hypoglycemic action, as is evident in prior research carried out on the species.[19]

The antidiabetic activity of *T. indica* extract (100mg/kg and 200mg/kg) and standard compound *glibenclamide* were investigated.[20] A significant decrease of blood glucose level in treated diabetic rats compared to untreated diabetic rats (227.10 mg/dL), $p < 0.01$ was observed.. The *glibenclamide* produced a reduction in blood glucose to 127.32 mg/dL which was lower than the 100mg/kg dose, resulting in a decrease in blood glucose to 133.27 mg/dL[20]

The hypoglycemic and hypolipidemic activities of an ethanolic extract of *Averrhoa bilimbi* Linn. leaves (Oxalidaceae, in streptozotocin (STZ)-diabetic rats have been reported[21]. The beneficial effects of the ethyl acetate fraction of A. bilimbi fruit (ABAEE) on the antioxidant/oxidant status in diabetes mellitus rats have also been reported.[22]

Research Methodology

Research design

A cross sectional experimental design was conducted in this study. This experiment sought to investigate the hypoglycemic effect of three fruit extracts (*Psidium guajava, Tamarindus indica, Averrhoa bilimbi*) in animal models. The researchers also sought to compare the hypoglycemic effect of the fruit extracts with the standard drug *glibenclamide*. The independent variables were the three fruit extracts; *Psidium guajava, Tamarindus indica, Averrhoa bilimbi* and the drug *glibenclamide*. The dependent variables were the blood glucose concentration of the guinea pigs and the body weight of the guinea pigs.

Population

The targeted population were guinea pigs found in West Bank Demerara, Georgetown. The guinea pigs were healthy, consisting of only males and had a body weight mass ranging from 300-600 g. A total of nine guinea pigs were chosen randomly from a single farm in West Bank Demerara.

Plant collection and extraction

The fruit of *Psidium guajava* were picked from trees in Grove, Guyana in the month of March, while *Tamarindus indica* and *Averrhoa bilimbi* were purchased at the Stabroek Market in the month of April. Authentication of each fruit was done by supervisor Professor Raymond Jagessar.

Psidium guajava and Averrhoa bilimbi

The fruits were washed thoroughly in warm distilled water to remove bacterial/fungal growth and residual pesticides from the surface. The fruits were weighed to attain a mass of 800 g and were chopped into tiny pieces to introduce into an electric blender. 1100 ml of distilled water were added to the blender and the mixture was blended for approximately five minutes. The mixture was filtered using a kitchen strainer and the Whatman filter paper #. The filtrate was kept into large glass bottles, labeled appropriately and stored in the refrigerator at a temperature range between 2-8^{o}C.

Tamarindus indica

The fruit was washed thoroughly to eliminate foreign particles that may adhere on the surface. The pulp was removed from the shell and the seeds of the fruit. The pulp was weighed to acquire a mass of 800 g. The pulp and 1100 ml of distilled water were poured into

the electric blender. The mixture was pureed for five minutes, after which it was filtered using a kitchen strainer and Whatman filter paper #. The filtrate was kept in large glass bottles, labeled appropriately and stored in the refrigerator.[23] (B.S. Nayak et al, 2011).

Animals and diet

The Principles of Laboratory Animal Care (NIH, 1985) were followed throughout the duration of the experiment. Nine guinea pigs, weighing between 300- 600g were selected for this experiment. The animals were kept for one week as an acclimatization period, before starting the experiment.[24] The guinea pigs were housed in colony cages (three per cage), made of wood with slotted floors (24.5x30.5x48.28 cm) and mesh in an average temperature of 23-28^{o}C, with twelve hours light and twelve hours dark and received a normal basal diet consisting of green fodder, wheat grain, pellets and tap water ad libitum. The cage pans were cleaned three times per week and the cage racks were cleaned weekly.[19]

3.7 Experimental design

The guinea pigs were divided into three groups:

Group I (Control group)

Three guinea pigs were subjected to administration of wheat grain, green fodder, pellets and water only for 12 days by oral route.

Group II (Aqueous (1:1) extracts, co-administered (6ml/kg)

Three guinea pigs were subjected to oral administration of the aqueous extract at the dose of 6ml/kg twice daily (every twelve hours) for 12 days.

Group III (*Glibenclamide* co-treated (2.5 mg/kg) group)

Three guinea pigs received *glibenclamide* at a dose of 2.5 mg/kg twice daily (every twelve hours) for 12 days. Before the supplements were administered, the basal blood glucose were taken for all the guinea pigs. The supplements were administered at 8 am, 8 pm and food was given at 10 am each day.

Oral Glucose Tolerance Test, OGGT

The oral glucose tolerance test was carried out, following the method described by Badole *et al*[25] with minor modifications.

The guinea pigs were divided into five groups containing three each:

Group I (Control group)

Three guinea pigs were given glucose solution by oral route.

Group II (Aqueous (1:1) extracts co-administered (6ml/kg))

Three guinea pigs were subjected to oral administration of glucose followed by *Psidium guajava* at the dose of 6ml/kg.

Group III (Aqueous (1:1) extracts co-administered (6ml/kg))

Three guinea pigs were subjected to oral administration of glucose followed by *Tamarindus indica* at the dose of 6ml/kg.

Group IV (Aqueous (1:1) extracts co-administered (6ml/kg))

Three guinea pigs were subjected to oral administration of glucose followed by *Averrhoa bilimbi* at the dose of 6ml/kg.

Group V (*Glibenclamide* co-treated (2.5 mg/kg) group)

Three guinea pigs received glucose solution followed by *glibenclamide* at a dose of 2.5 mg/kg.

The guinea pigs were fasted for eight hours, and their blood glucose level before glucose load was recorded as BGL at 0 min. Without delay, glucose solution (2 gm/kg body weight) was administered to all the groups orally. After 30 mins, *glibenclamide* (2.5 mg/kg body weight) and fruit extracts (6ml/kg body weight) were administered orally to the respective groups. The blood glucose was measured at 30 mins, 60 mins and 120 mins after glucose administration.

Validity

The method used in this experiment was guided from similar research, with minor modifications made. This contributed to the validity of the study.

Reliability

When conducting the experiment, three guinea pigs were placed in each group to ensure consistency of the results.

Blood collection and analysis

After overnight fasting (guinea pigs were deprived of food for eight hours, but allowed free access to water), blood samples were collected on the 0th 3rd, 6th, 9th and 12th day, from the lateral vein in 10 ml tubes. Glucose concentrations were determined using the On Call Plus Glucometer. The results were expressed in terms of milligram per deciliter of blood (mg/dL). Body weight of each guinea pig were measured on the 0th 3rd, 6th, 9th and 12th day using a top loading scale.

RESULTS

Table 1.0. Fasting blood glucose level for *P. guajava* treated group.

Blood Glucose (mg/dL)					
Group	**0 day**	**3 days**	**6 days**	**9 days**	**12 days**
Control					
A	88	82	83	88	86
B	86	79	82	86	82
C	84	83	87	85	81
Mean	86.0 ± 2.0	81.3 ± 2.1	84.0 ± 2.6	86.3 ± 1.5	83.0 ± 2.6
Confidence Interval (95%)	2.3	2.4	3.0	1.7	3.0
Psidium guajava					
A	87	80	79	80	72
B	93	72	81	83	79
C	90	84	75	79	76
Mean	90.0 ± 3.0	78.7 ± 6.1	78.3 ± 3.1	80.7 ± 2.1*	75.7 ± 3.5*
Confidence Interval (95%)	3.4	6.9	3.5	2.4	4.0
Drug (*Glibenclamide*)					
A	88	81	75	66	71
B	86	68	72	75	64
C	90	77	80	72	67
Mean (x ± SD)	88.0 ± 2.0	75.3 ± 6.7	75.7 ± 4.0*	71.0 ± 4.6**	67.3 ± 3.5**
Confidence Interval (95%)	2.3	7.5	4.6	5.2	4.0

Table 2.0. Baseline body weight (BW) of the Guinea Pig over 12 days.

Body Weight (g)					
Group	**0 day**	**3 days**	**6 days**	**9 days**	**12 days**
Control					
A	440	440	440	440	460
B	440	440	430	430	430
C	480	500	500	500	500
Mean	453.3 ± 23.1	460.0 ± 34.6	456.7 ± 37.9	456.7 ± 37.9	463.3 ± 35.1
Confidence Interval (95%)	26.1	39.2	42.8	42.8	39.7

P. guajava					
A	560	560	560	540	540
B	480	480	480	460	460
C	440	440	430	430	430
Mean	493.3 ± 61.1	493.3 ± 61.1	490.0 ± 65.6	476.7 ± 56.9	476.7 ± 56.9
Confidence Interval (95%)	69.1	69.1	74.2	64.3	64.3
Drug (*Glibenclamide*)					
A	360	360	360	360	370
B	340	340	340	340	340
C	450	450	450	460	460
Mean	383.3 ± 58.6	383.3 ± 58.6	383.3 ± 58.6	386.7 ± 64.3	390.0 ± 62.4
Confidence Interval (95%)	66.3	66.3	66.3	72.8	70.7

Table 3.0. Fasting blood glucose for *Tamarindus indica* treated group.

Blood Glucose (mg/dL)					
Group	**0 day**	**3 days**	**6 days**	**9 days**	**12 days**
Control					
A	97	100	90	99	99
B	93	92	89	92	96
C	94	96	95	101	102
Mean	94.7 ± 2.1	96.0 ± 4.0	91.3 ± 3.2	97.3 ± 4.7	99.0 ± 3.0
Confidence Interval	2.4	4.5	3.6	5.3	3.4
Tamarindus indica					
A	90	65	96	90	78
B	75	78	99	88	85
C	106	88	94	98	60
Mean	90.3 ± 15.3	77.0 ± 11.5	96.3 ± 2.5	92.0 ± 5.3	74.3 ± 12.9*
Confidence Interval	17.5	13.1	2.8	6.0	14.6
Drug (*Glibenclamide*)					
A	88	92	75	73	70
B	84	107	77	70	69
C	95	74	71	70	73
Mean	89.0 ± 5.6	91.0 ± 16.5	74.3 ± 3.1**	71.0 ± 1.7***	70.7 ± 2.1***
Confidence Interval	6.3	18.7	3.5	2.0	2.4

Table 4.0. Body weight for *Tamarindus indica* treated group.

Body Weight (g)					
Group	**0 day**	**3 days**	**6 days**	**9 days**	**12 days**
Control					
A	440	440	440	430	460
B	460	490	520	500	520
C	480	490	520	520	500
Mean	460.0 ± 20.0	473.3 ± 28.9	493.3 ± 46.2	483.3 ± 47.3	493.3 ± 30.6
Confidence Interval (95%)	22.6	32.7	52.3	53.5	34.6
Tamarindus indica					
A	500	480	440	460	460
B	400	480	480	500	510
C	370	440	440	460	460
Mean	423.3 ± 68.1	466.7 ± 23.1	453.3 ± 23.1	473.3 ± 23.1	476.7 ± 28.9
Confidence Interval (95%)	77.0	26.1	26.1	26.1	32.7
Drug (*Glibenclamide*)					
A	420	440	460	480	490
B	600	610	600	600	610
C	470	460	440	470	480
Mean	496.7 ± 92.9	503.3 ± 92.9	500.0 ± 87.2	516.7 ± 72.3	526.7 ± 72.3
Confidence Interval (95%)	105.1	105.1	98.6	81.9	81.9

Table 5.0. Fasting blood glucose for *Averrhoa bilimbi* treated group.

Blood Glucose (mg/dL)					
Group	**0 day**	**3 days**	**6 days**	**9 days**	**12 days**
Control					
A	112	110	113	112	112
B	115	115	100	112	112
C	108	100	100	105	115
Mean	111.7 ± 3.5	108.3 ± 7.6	104.3 ± 7.5	109.7 ± 4.0	113.0 ± 1.7
Confidence Interval (95%)	4.0	8.6	8.5	4.6	2.0
Averrhoa. bilimbi					
A	108	112	99	94	91
B	119	112	96	88	93
C	102	97	96	91	96
Mean	109.7 ± 8.6	107.0 ± 8.7	97.0 ± 1.7	91.0 ± 3.0**	93.3 ± 2.5***
Confidence Interval (95%)	9.8	9.8	2.0	3.4	2.8
Drug (*Glibenclamide*)					
A	112	103	84	80	98
B	118	105	64	59	83
C	100	89	82	76	79
Mean	110.0 ± 9.2	99.0 ± 8.7	76.7 ± 11.0*	71.7 ± 11.2**	86.7 ± 10.0*
Confidence Interval	10.4	9.9	12.5	12.6	11.3

Table 6.0.Body weight for *Averrhoa bilimbi* treated group.

Body Weight (g)					
Group	**0 day**	**3 days**	**6 days**	**9 days**	**12 days**
Control					
A	440	440	440	440	460
B	440	440	430	430	430
C	480	500	500	500	500
Mean	453.3 ± 23.1	460.0 ± 34.6	456.7 ± 37.9	456.7 ± 37.9	463.3 ± 35.1
Confidence Interval (95%)	26.1	39.2	42.8	42.8	39.7
Extract (*A.bilimbi*)					
A	600	600	590	580	520
B	480	480	440	480	440
C	460	440	440	420	440
Mean	513.3 ± 75.7	506.7 ± 83.3	490.0 ± 86.6	493.3 ± 80.8	466.7 ± 46.2
Confidence Interval (95%)	85.7	94.2	98.0	91.5	52.3
Drug (*Glibenclamide*)					
A	450	400	440	400	420
B	360	390	400	360	390
C	440	440	500	500	480
Mean	416.7 ± 49.3	410.0 ± 26.5	446.7 ± 50.3	420.0 ± 72.1	430.0 ± 45.8
Confidence Interval (95%)	55.8	29.9	57.0	81.6	51.9

Table 7.0. Oral Glucose Tolerance Test, OGTT.

	0 mins (mg/dL)	**30mins (mg/dL)**	**60mins (mg/dL)**	**120mins (mg/dL)**
Control				
A	147	218	170	159
B	104	119	101	123
C	116	141	163	176
Mean ($\bar{x}$ ± SD)	122.3 ± 22.2	159.3 ± 52.0	144.7 ± 38.0	152.7 ± 27.1
Confidence Interval (95%)	25.1	58.8	43.0	30.6
Drug (*Glibenclamide*)				
A	116	167	160	120
B	107	162	101	93
C	100	114	109	102
Mean ($\bar{x}$ ± SD)	107.7 ± 8.0	147.7 ± 29.3	123.3 ± 32.0	105.0 ± 13.7
Confidence Interval (95%)	9.1	33.1	36.2	15.6
Tamarindus indica				
A	117	130	210	139
B	104	180	104	120
C	109	160	184	123
Mean ($\bar{x}$ ± SD)	110.0 ± 6.6	156.7 ± 25.2	166.0 ± 55.2	127.3 ± 10.2
Confidence Interval (95%)	7.4	28.5	62.5	11.6
Psidium guajava				

A	112	173	188	130
B	106	125	158	113
C	119	173	161	115
Mean ($\bar{x}$ ± SD)	112.3 ± 6.5	157.0 ± 27.7	169.0 ± 16.5	119.3 ± 9.3
Confidence Interval (95%)	7.4	31.4	18.7	10.5
Averrhoa bilimbi				
A	118	190	149	121
B	107	151	144	129
C	124	167	137	95
Mean ($\bar{x}$ ± SD)	116.3 ± 8.6	169.3 ± 19.6	143.3 ± 6.0	115.0 ± 17.8
Confidence Interval (95%)	9.8	22.2	6.8	20.1

Table 8.0. Oral glucose tolerance test (OGTT) for the fruits of *Psidium guajava*, *Averrhoa bilimbi* and peel of *Tamarindus indica*.

Group	0 mins	30 mins	60 mins	120 mins
Control	122.3 ± 22.2	159.3 ± 52.0	144.7 ± 38.0	152.7 ± 27.1
Psidium guajava	112.3 ± 6.5	157.0 ± 27.7	169.0 ± 16.5	119.3 ± 9.3
Tamarindus indica	110.0 ± 6.6	156.7 ± 25.2	166.0 ± 55.2	127.3 ± 10.2
Averrhoa bilimbi	116.3 ± 8.6	169.3 ± 19.6	143.3 ± 6.0	115.0 ± 17.8
Glibenclamide	107.7 ± 8.0	147.7 ± 29.3	123.3 ± 32.0	105.0 ± 13.7

Blood glucose (mg/dL)

Data are expressed as mean ± S.D.; n = 3 guinea pigs in each group. ANOVA testing was done. Values are statistically significant at: *p<0.05 **p<0.01 ***p<0.001. Non-asterisk bars do not differ significantly from one another (P > 0.05) within the same duration of treatment. Statistical significance was compared within the groups as follows: *Averrhoa bilimbi* treated guinea pigs were compared with control guinea pigs; *glibenclamide* treated guinea pigs were compared with control group.

Statistical analysis

The results were reported as mean with standard deviation, SD. All data analysis were done with 1-way analysis of variance (ANOVA). A P value of < 0.05, p < 0.01 or p < 0.001 will be considered significant.

Table 9.0. Fasting blood glucose for Control vs *Psidium guajava* treated group.

Days		F value	P value
0	Between groups	3.692	.127
3	Between groups	0.512	0.514
6	Between groups	5.898	0.072
9	Between groups	14,450	0.019
12	Between groups	8.345	0.045

Table 10.0. Fasting blood glucose for Control vs. *Glibenclamide* treated groups.

Days		F value	P value
0	Between groups	1.5	0.288
3	Between groups	2.219	0.211
6	Between groups	8.929	0.040
9	Between groups	30,229	0.05
12	Between groups	38,086	0.004

Table 11.0. Body weight for Control vs *Psidium guajava* treated group, ANOVA.

Days		F	P values
0	Between Groups	1.125	0.349
3	Between Groups	0.676	0.457
6	Between Groups	0.581	0.488
9	Between Groups	0.257	0.639
12	Between Groups	0.119	0.747

Table 12.0. Body weight for Control vs *Glibenclamide* treated group, Anova.

Days		F	P values
0	Between Groups	3.706	0.127
3	Bewteen Groups	3.806	0.123
6	Between Groups	3.315	0.143
9	Between Groups	2.641	0.179
12	Between Groups	3.143	0.151

Table 13.0. Fasting blood glucose for Control vs *T. indica* treated group, Anova.

Days		F	P values
0	Between Groups	0.230	0.656
3	Between Groups	7.268	0.054
6	Between Groups	4.5	0.101
9	Between Groups	1.695	0.263
12	Between Groups	10.411	0.032

Table 14.0. Fasting blood glucose for Control vs *Glibenclamide* treated group, Anova.

Days		F	P values
0	Between groups	2.73	0.174
3	Between groups	0.260	0.637
6	Between groups	44.085	0.003
9	Between groups	82.118	0.001
12	Between groups	180.625	0.000

Table 15.0. Body weight for Control vs *Tamarindus indica* treated group, Anova.

Days		F	Significant
0	Between groups	0.801	0.421
3	Between groups	0.098	0.770
6	Between groups	1.800	0.251
9	Between groups	0.108	0.758
12	Between groups	0.472	0.530

Table 16.0. Body weight for Control vs *Glibenclamide* treated group, Annova.

Days		F	P-values
0	Between groups	0.446	0.541
3	Between groups	0.285	0.622
6	Between groups	0.014	0.912
9	Between groups	0.446	0.541
12	Between groups	0.541	0.503

Table 17.0. Fasting blood glucose for Control vs *Averrhoa bilimbi* treated group.

Days		F	P-values
0	Between groups	0.138	0.729
3	Between groups	0.040	0.851
6	Between groups	2.719	0.174
9	Between groups	41.263	0.003
12	Between groups	124.321	0.000

Table 18.0. Fasting blood glucose for Control vs *Glibenclamide* treated group Anova.

Days		F	P-values
0	Between groups	0.087	0.783
3	Between groups	1.945	0.236
6	Between groups	12.925	0.023
9	Between groups	30.796	0.005
12	Between groups	20.132	0.011

Table 19.0. Body weight for Control vs *Averrhoa bilimbi* treated group, anova.

Days		F	P values
0	Between groups	1.723	0.260
3	Between groups	0.803	0.421
6	Between groups	0.373	0.574
9	Between groups	0.506	0.516
12	Between groups	0.010	0.926

Table 20.0. Body weight for Control vs *Glibenclamide* treated group, Anova.

Days		F	P-values
0.0	Between groups	1.36	0.308
3	Between groups	3.947	0.118
6	Between groups	0.076	0.797
9	Between groups	0.608	0.479

Table 21.0. OGTT: Control vs *Glibenclamide* treated group, Annova.

Minutes		F	P-values
0.0	Between groups	1.159	0.342
30.0	Between groups	0.115	0.752
60.0	Between groups	0.554	0.498
120	Between groups	7.398	0.053

Table 22.0. Oral glucose tolerance test (OGT) for the fruits of Psidium guajava, Averrhoa bilimbi and peel of Tamarindus indica.

Group	0 mins	30 mins	60 mins	120 mins
Control	122.3 ± 22.2	159.3 ± 52.0	144.7 ± 38.0	152.7 ± 27.1
Psidium guajava	112.3 ± 6.5	157.0 ± 27.7	169.0 ± 16.5	119.3 ± 9.3
Tamarindus indica	110.0 ± 6.6	156.7 ± 25.2	166.0 ± 55.2	127.3 ± 10.2
Averrhoa bilimbi	116.3 ± 8.6	169.3 ± 19.6	143.3 ± 6.0	115.0 ± 17.8
Glibenclamide	107.7 ± 8.0	147.7 ± 29.3	123.3 ± 32.0	105.0 ± 13.7

Blood glucose (mg/dL)

Data are expressed as mean ± S.D.; n = 3 guinea pigs in each group. ANOVA testing was done. Values are statistically significant at: *p<0.05 **p<0.01 ***p<0.001. Non-asterisk bars do not differ significantly from one another (P > 0.05) within the same duration of treatment. Statistical significance was compared within the groups as follows: *Averrhoa bilimbi* treated guinea pigs were compared with control guinea pigs; *glibenclamide* treated guinea pigs were compared with control group.

Graphs

Acute toxicity test

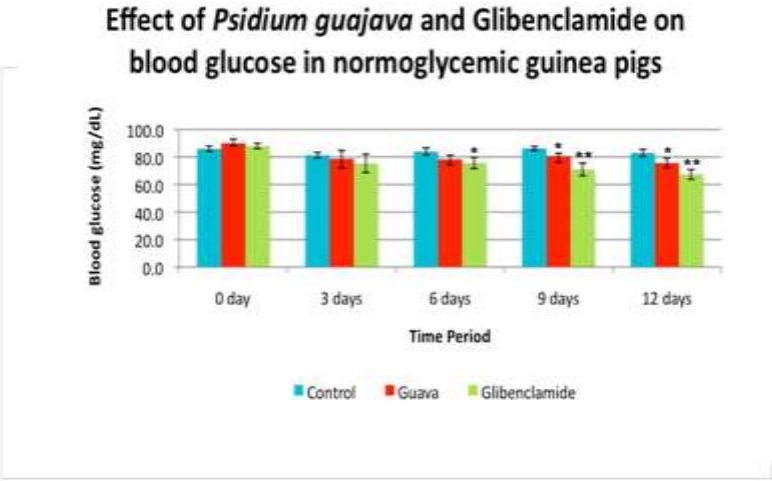

Fig.1. The Effect of Aqueous Extract of *Psidium guajava* Fruit on Blood Glucose Levels in Normoglycemic Guinea Pigs.

Data are expressed as mean ± S.D.; n = 3 guinea pigs in each group. ANOVA testing was done. Values are statistically significant at: *p<0.05 **p<0.01 ***p<0.001 Non-asterisk bars do not differ significantly from one another (P > 0.05) within the same duration of treatment. Statistical significance was compared within the groups as follows: *Psidium guajava* treated

guinea pigs were compared with control guinea pigs; *glibenclamide* treated guinea pigs were compared with control group.

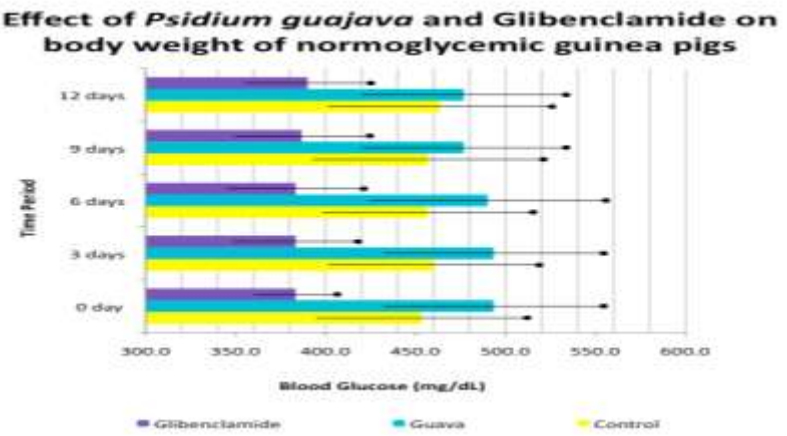

Fig. 2. The Effect of Aqueous Extract of *Psidium guajava* Fruit on Changes in Body Weight of Control and Experimental Guinea Pigs.

Data are expressed as mean ± S.D.; n = 3 guinea pigs in each group. ANOVA testing was done. Values are statistically significant at: *p<0.05 **p<0.01 ***p<0.001 Non-asterisk bars do not differ significantly from one another (P > 0.05) within the same duration of treatment. Statistical significance was compared within the groups as follows: *Psidium guajava* treated guinea pigs were compared with control guinea pigs; *glibenclamide* treated guinea pigs were compared with control group.

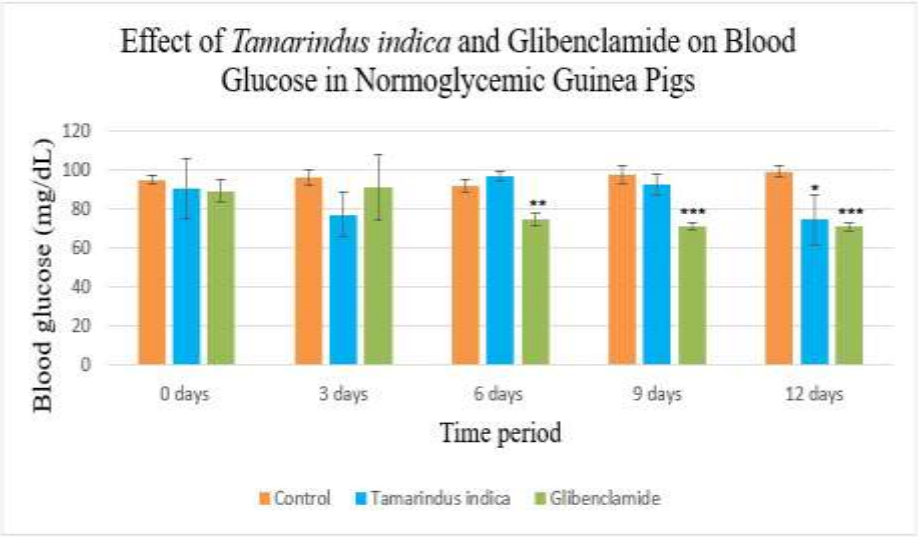

Fig.3. The Effect of Aqueous Extract of *Tamarindus indica* Fruit on Blood Glucose Levels in Normoglycemic Guinea Pigs.

Data are expressed as mean ± S.D.; n = 3 guinea pigs in each group. ANOVA testing was done. Values are statistically significant at: *p<0.05 **p<0.01 ***p<0.001. Non-asterisk bars do not differ significantly from one another (P > 0.05) within the same duration of treatment. Statistical significance was compared within the groups as follows: *Tamarindus indica* treated guinea pigs were compared with control guinea pigs; *glibenclamide* treated guinea pigs were compared with control group.

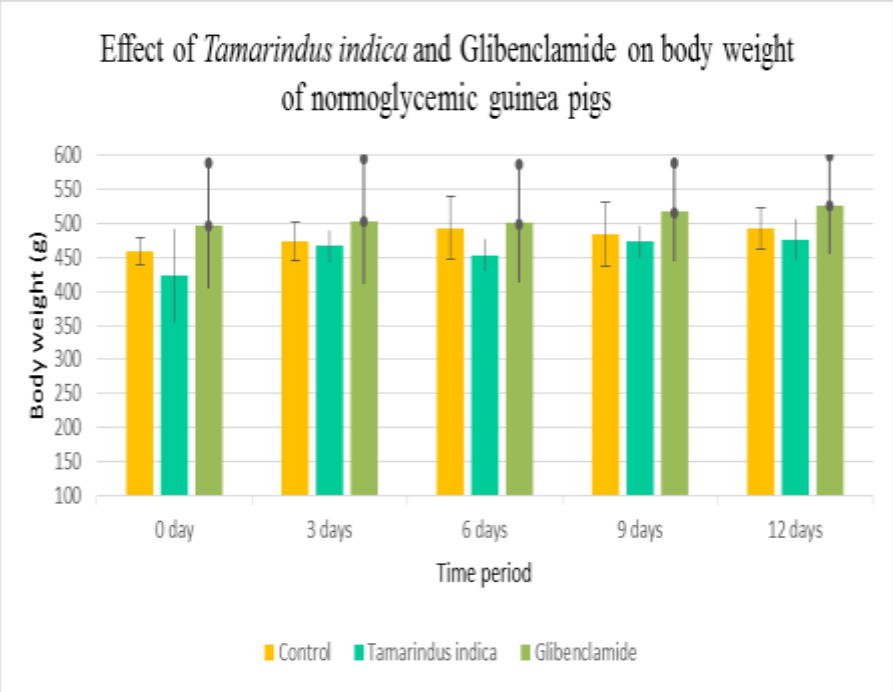

Fig. 4. The Effect of Aqueous Extract of *Tamarindus indica* Fruit on Changes in Body Weight of Control and Experimental Guinea Pigs.

Data are expressed as mean ± S.D.; n = 3 guinea pigs in each group. ANOVA testing was done. Values are statistically significant at: *p<0.05 **p<0.01 ***p<0.001. Non-asterisk bars do not differ significantly from one another (P > 0.05) within the same duration of treatment. Statistical significance was compared within the groups as follows: *Tamarindus indica* treated guinea pigs were compared with control guinea pigs; *glibenclamide* treated guinea pigs were compared with control group.

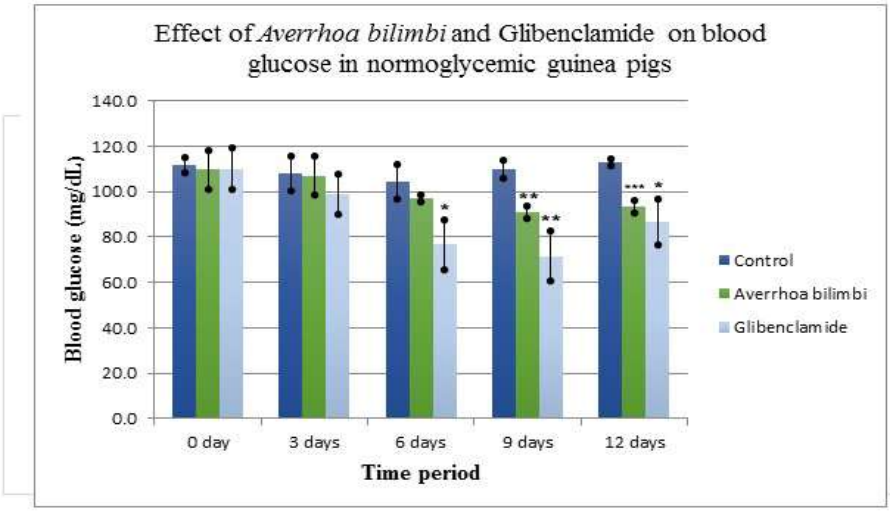

Fig.5. The Effect of Aqueous Extract of *Averrhoa bilimbi* Fruit on Blood Glucose Levels in Normoglycemic Guinea Pigs.

Data are expressed as mean ± S.D.; n = 3 guinea pigs in each group. ANOVA testing was done. Values are statistically significant at: *p<0.05 **p<0.01 ***p<0.001. Non-asterisk bars do not differ significantly from one another (P > 0.05) within the same duration of treatment. Statistical significance was compared within the groups as follows: *Averrhoa bilimbi* treated guinea pigs were compared with control guinea pigs; *glibenclamide* treated guinea pigs were compared with control group.

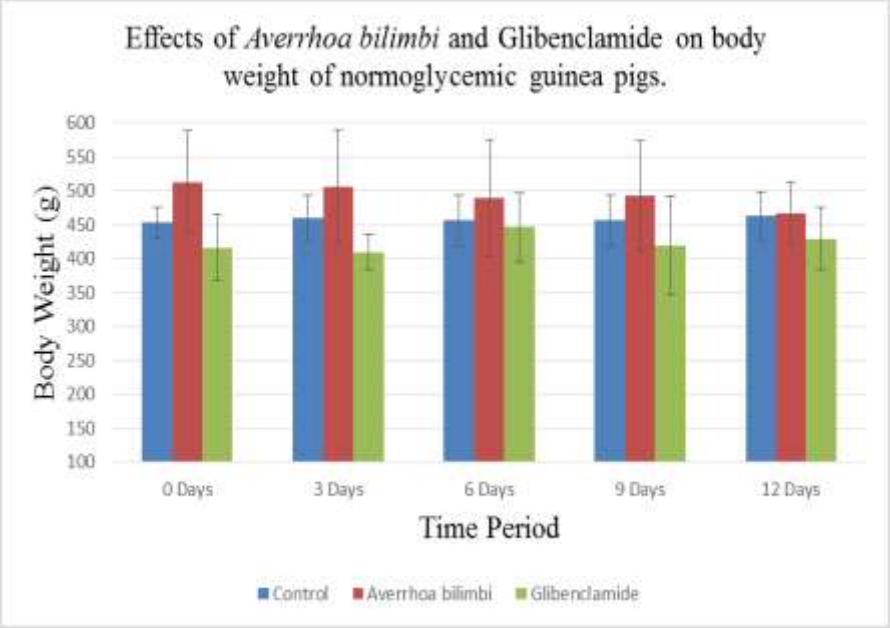

Fig. 6. The Effect of Aqueous Extract of *Averrhoa bilimbi* Fruit on Changes in Body Weight of Control and Experimental Guinea Pigs.

Data are expressed as mean ± S.D.; n = 3 guinea pigs in each group. ANOVA testing was done. Values are statistically significant at: *p<0.05 **p<0.01 ***p<0.001. Non-asterisk bars do not differ significantly from one another (P > 0.05) within the same duration of treatment. Statistical significance was compared within the groups as follows: *Averrhoa bilimbi* treated guinea pigs were compared with control guinea pigs; *glibenclamide* treated guinea pigs were compared with control group.

DISCUSSION

Fasting Blood Glucose of the guinea pigs, Baseline Body Weight (BW) and Oral Glucose Tolerance Tests (OGTT) were tested. During the experiments, there were no signs of intoxication observed, including restraint of animals, chills, hesitation, rustling hair, anuria and finally death.

The hypoglycemic potential of *Psidium guajava* was tested over a 12-days period, alongside reference drug *glibenclamide* to determine whether the blood glucose lowering effect was comparable to that *glibenclamide*. Results were recorded at 3-day intervals, after first establishing fasting blood glucose (FBG) baseline values for each group.

On the third day of treatment, there was a notable decrease (12.56%) in the mean baseline FBG values for both the *Psidium guajava* group (from 90.0 ± 3.0 mg/dL to 78.7 ± 6.1 mg/dL) and the *glibenclamide* group, 14.43 % (from 88.0 ± 2.0 mg/dL to 75.3±6.7 mg/dL). During the 9^{th} and 12^{th} day of treatment with the aqueous extract of *P.guajava*, FBG decreased by 10.3% (80.7 ± 2.1 mg/dL) and 11.9% (75.7 ± 3.5 mg/dL respectively) when compared to the control. These values were considered highly significant when compared to the control ($p < 0.05$). The maximum reduction was seen on the final day of treatment.

A consecutive reduction in FBG was noted for the *glibenclamide* treated group. On the 6^{th} day of treatment, blood glucose was reduced by 13.98% (From 88.0 ± 2.0 to 75.7± 4.0 mg/dL), indicating a p value < 0.05. On the 9^{th} and 12^{th} day of treatment, blood glucose had reduced by 19.3% (From 88.0 ± 2.0 to 71.0±4.6 mg/dL) and 23.5% (67.3 ± 3.5 mg/dL) correspondingly ($p < 0.01$).

When compared to the control group, both the extract and drug groups evidently display hypoglycemic activity, however, the reduction was more evident in the *glibenclamide* group.

In our study, *Psidium guajava* fruit extract administration to the guinea pigs resulted in a significant reduction in blood glucose level ($p < 0.05$) when compared to the control on the 9th and 12th days of treatment, with maximum reduction on the latter day. The blood glucose was reduced to 15.9% from 10.3% (from 90.0 ± 3.0 mg/dL to 80.7 ± mg/dL) and 90.0 ±3.0 mg/dL to 75.7±3.5 mg/dL respectively. However, treatment with *glibenclamide* for the 12 days interval resulted in a greater reduction in blood glucose of 23.5 % (From 88.0 ± 2.0 to 67.3±3.5 mg/dL) when compared to the control group ($p<0.01$).

At baseline, the fasting blood glucose of the control, *glibenclamide* and aqueous extract of *Tamarindus indica* treated groups were similar. After the administration of *Tamarindus indica* extract and *glibenclamide*, a reduction in blood glucose was achieved, Table 3.0.

On the 3rd day, a decrease in blood glucose of 14.7% was shown for the *Tamarindus indica* extract group (from 90.3 ± 15.3 mg/dL to 77.0 ± 11.5 mg/dL, $p = 0.054$) approaching a significant p value = 0.05. During days 6th and 9th day of treatment with the aqueous extract, there was an upsurge in blood glucose by 6.98% (From 90.3 ± 15.3 mg/dL to 96.3 ± 2.5 mg/dL) and 1.88% (From 90.3 ± 15.3 mg/dL to 92.0 ± 5.3 mg/dL) respectively. The greatest reduction of 17.7% in blood glucose was seen on the final day of treatment (From 90.3 ± 5.3mg/dL to 74.3 ± 12.9 mg/dL), with a p value < 0.05.

During the 6th day of the *glibenclamide* treated group, blood glucose had decreased by 16.5% (From 89.0 ± 5.6 to 74.3 ± 3.1 mg/dL) which was highly significant ($p < 0.01$) when compared to the control group. Administration of the extract on the 9th and 12th day resulted in the diminution to 20.2% (From 89.0 ± 5.6 to 71.0 ± 1.7 mg/dL), $p = 0.001$ and 20.6% (From 89.0 ± 5.6 to 70.7 ± 2.1 mg/dL), $p < 0.001$ respectively. Therefore, both *glibenclamide* and *Tamarindus indica* aqueous extracts are shown to have possess anti- hyperglycemic activity, however the effect was more pronounced in the *glibenclamide* group throughout the study.

For the aqueous extract of *Averrhoa bilimbi*, on the 9th day of treatment, blood glucose was reduced by 17.05% (from 109.7 ± 8.6 mg/dL to 91.0 ± 3.0 mg/dL), indicating a p value < 0.01 when compared to the control, Table 5.0. It had increased slightly, 17.1% (from 91.0 ± 3.0 mg/dL) to 14.9% (93.3 ± 2.5 mg/dL) on the 9th and 12 day respectively. However there was still a 17.1% reduction in blood glucose. This result was highly significant ($p < 0.001$) when compared to the control, Table 5.0. From the graph, a gradual reduction in blood

glucose was seen over the 6 day period for the aqueous extract group (from 109.7 □ 8.6 mg/dL to 97.0 □□1.7 mg/dL).

In the drug group, *Glibenclamide*, a slight reduction in fasting blood glucose was seen on the 3rd day, 10% (from 110.0 ± 9.2 mg/dL to 99.0 ± 8.7 mg/dL), while a significant decrease was shown on the 6th day, 30.3% (From from 110.0 ± 9.2 mg/dL to 76.7± 11.0 mg/dL ($p < 0.05$). The greatest diminution was seen on the 9th day, (71.7 ± 11.2 mg/dL) in which the blood glucose was reduced by 34.8% ($p < 0.01$). However, there was an upsurge in the blood glucose on the 12th day (From 71.7 ± 11.2 mg/dL to 86.7 ± 10.0 mg/dL) in which FBG had increased by 20.9%, however this figure was still highly significant when compared to the control group ($p < 0.05$), Table 5.0. Overall, both the extract of *Averrhoa bilimbi* and *glibenclamide* have proven to exhibit hypoglycemic activity, however *Averrhoa bilimbi* is considered to have a more potent hypoglycemic effect.

For the baseline body weight (BW) of the guinea pigs, an important difference was recorded for each group. The BW of the control group were kept constant within the 12 days period. This was adopted as the standard values for the comparison between the aqueous extract and drug group. Over the 6 days period, there was a gradual reduction in body weight for the group treated with *Psidium guajava*, 0.7% (from 493.3 ± 61.1g to 490.0 ± 65.6g). This was followed by a sharp decrease in body weight on the 9th, 3.37% (476.7 ± 56.9) and 12th day, 3.37% (476.7 ± 56.9g). However, for the *glibenclamide* treated group, a consistent body weight was achieved throughout the 6th day of treatment (From 383.3 ± 58.6 to 383.3 ± 58.6g). While during the 9th and 12th day of treatment, an increase in BW was notable, 0.89% (386.7 ± 64.3 g and 1.75% (390.0 ± 62.4 g) respectively. *Psidium guajava* produced the opposite effect of *glibenclamide* and is therefore not comparable in this regard.

Before the administration of *Tamarindus indica* extract and *glibenclamide*, there was a significant difference of baseline body weight of the guinea pigs, when compared to the control.

The guinea pigs that were treated with *Tamarindus indica* extract did show a significant increase in body weight on the 12th day of treatment, 11.2%, (476.7 ± 28.9g), when compared to the initial BW of the guinea pigs (423.3 ± 68.1g). A prominent increase in BW was also seen for the *glibenclamide* treated groups on the 9th, 4%, (516.7 ± 72.3g) and 12th day, 6.0%, (526.7 ± 72.3g) when compared to the initial BW, 6.04% (496.7 ± 92.9mg/dL) of the guinea

pigs. However this value was not considered to be highly significant. Overall the aqueous extract group of *Tamarindus indica* had the greatest elevation in BW.

After the administration of the *Averrhoa bilimbi* extract, there was a decrease in body weight on the 3rd day when compared to the initial day, 1.3% (from 513.3 ± 75.7g to 506.7 ± 83.3g). A continuation in the decrease of the BW was noticeable on the 6th and 9th day, 4.54 % (490.0 ± 86.6g) and, 3.89% (493.3 ± 80.8g) respectively. On the final day of treatment, the greatest reduction in BW, 9.0% (466.7 ± 46.2g) was seen. When compared to the control group there was a decrease in BW. In the *glibenclamide* treated group, a decrease in the BW of 1.61% was seen on the third day (from 416.7 ± 49.3g to 410.0 ± 26.5g). However, on the 6th and 9th days there was an elevation of 7.19% (446.7 ± 50.3g) and 0.79% and 0.79% (420.0 ± 72.1g) respectively in the BW of guinea pigs. While on the 12th day, the greatest increase in BW was seen (430.0 ± 45.8 g).

Finally, from the graph, there was a diminution in the BW of the aqueous extract of *Averrhoa bilimbi* treated group when compared to the control group, while there was a rise in the body weight of the *glibenclamide* treated groups. These variances in BW were analyzed and were not significant ($p > 0.05$).

An oral glucose tolerance (OGTT) test was carried out for the three fruit extracts; *Averrhoa bilimbi, Tamarindus indica and Psidium guajava* along with the reference drug, *glibenclamide* over a two hours period. Initial blood glucose levels for each group had a slight difference before glucose overload, However, the blood glucose level of all groups spiked at the 30 minutes and were considered to be hyperglycemic. The blood glucose level of the control group fluctuated across the remaining time intervals but still maintained higher when compared to the treatment groups. The results for the *glibenclamide* treated group showed a gradual decrease in blood glucose level from the 60 minutes interval (123.3 ± 32.0 mg/dL) to the 120 minutes interval (105.0 ±13.7 mg/dL). However, this decrease was not significant when compared to the control Group.

In analyzing the results for the *Tamarindus indica* group it can be seen that the blood glucose level of the group further increased even to the 60 minutes interval to 166.±55.2 mg/dL compared to 110.0 ± 6.6 mg/dL). However there was a sharp decrease in blood glucose level at the 120 minute interval to 127.3 ± 10.2 mg/dL. Although, the reduction in blood glucose was higher that the control group, a postprandial hypoglycemic effect was still seen.

The *Psidium guajava* treated group showed a similar trend to the *Tamarindus indica* treated group, following the sharp increase to 169.0±16.5 mg/dL over the first two intervals, compared to the initial value of 112.3 ± 6.5 mg/dL and then a sharp decrease to 119.3 ± 9.3 mg/dL at the final interval of 120 minutes. However in this group, the reduction in the blood glucose level was lower than that of the control group, indicating a hypoglycemic effect.

The *Averrhoa bilimbi* group however followed a similar trend to that of the *glibenclamide* group, i.e. sharply increasing to 169.3 ± 19.6 mg/dL at the 30 minute interval compared to the initial value of 116.3 ± 8.6 mg/dL) and gradually decreasing over the remaining intervals to 115.0 ±17.8 mg/dL at 120 minutes.

This provides evidence that *Tamarindus indica* and *Psidium guajava* may have a greater rate of reduction in blood glucose level but the *Averrhoa bilimbi* may have a faster onset of action. Although with further analysis these results proved to be non-significant in this experiment, it can be assumed that with further research and prolong time interval up to 240 minutes the results can be significant in reducing blood glucose.

An oral glucose tolerance test was done to access the ability of each extract to reduce and control postprandial hyperglycemia. The postprandial elevation of blood glucose constantly fuels chronic hyperglycemia, which is a risk factor for the development of life threatening complications of diabetes (Mosaddik, A., Nahar, L., Nasrin, F., Zahan, R., Haque, A., & Haque, E., 2014).

The results of the glucose tolerance test indicated that each extract suppressed the rise in blood glucose level after a heavy glucose meal, with maximum suppression at 120 minutes. In relative assessment, *A.bilimbi* had the greatest hypoglycemic effect, followed by *P.guajava* and *Tamarindus indica* after the 120 minutes interval. Therefore a reduction and control of postprandial hyperglycemia was exhibited. The underlying mechanism may be due to enhancement of gluconeogenesis, which is characteristically activated at fasting state in hyperglycemic animals or enhanced disposal of glucose by increased insulin sensitivity. Similarly anti-hyperglycemic effect just after a glucose load may be due to delayed absorption of glucose by inhibitory activities on α-glucosidase and α-amylase in the gut responsible for digestion of carbohydrates (Mosaddik, A. et al, 2014).

CONCLUSION

In conclusion, the administration of *A. bilimbi*, *P.guajava* and *T. indica* fruit extract to normoglycemic guinea pigs resulted in the lowering of blood glucose level. In comparative evaluation, hypoglycemic activity, was exhibited by each extract, however *A. bilimbi* produced the greatest reduction in blood glucose, followed by *T. indica* and lastly *P.guajava.* These findings suggest that these extracts have the complimentary potency to develop as anti-hyperglycemic agents for the treatment of diabetes. However, further studies are needed to establish safety profiles and evaluate the potential of each extract and its active constituents for the management of diabetes and associated complications in the clinical trials.

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