

6. SUMMARY AND CONCLUSIONS

Diabetes mellitus (DM) or simply diabetes is a group of metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. The more prevalent form of diabetes is type 2 diabetes which accounts for more than 90% of cases. The pathogenesis of type 2 diabetes is complex and involving progressive development of insulin resistance and a relative deficiency in insulin secretion. The burden of this disorder is enormous, owing to its rapidly increasing global prevalence, the devastating damage it can do to many organs of the body, and the direct and indirect costs. The estimated worldwide prevalence of diabetes among adults was 285 million (6.4%) in 2010, and this value is predicted to rise to around 439 million (7.7%) by 2030. The pandemic of type 2 diabetes, along with its high human and economic costs, is showing no signs of abatement and, therefore, new approaches are urgently needed to prevent, slow the progression, and limit the consequences of this disease.

The treatments of diabetes include diet, exercise, use of oral hypoglycemic agents and insulin is the primary forms of treatment for diabetes. Currently available synthetic anti-diabetic agents besides being expensive produce serious side effects. Apart from currently available therapeutic options, traditional medicines or complementary and alternative medicines are a fruitful source of future drugs to counteract insulin resistance. A major advantage of traditional medicine is that they have been used to treat human diseases for many years and so there is considerable knowledge concerning in vivo efficacy and safety, two of the confounding problems facing other new chemical entities. However, in most cases there is little rigorous scientific evidence proving their efficacy and the mode of action is generally not known. It has been estimated that up to one-third of patients with diabetes mellitus use some form of complementary and alternative medicine.

Bitter melon (*Momordica charantia*) is a popular fruit used for the treatment of diabetes and related conditions amongst the indigenous populations of Asia, South America, India and East Africa. Abundant pre-clinical studies have documented the anti-diabetic and hypoglycemic effects of Bitter melon however the precise mode of action is still unclear. This thesis aimed to evaluate the hypoglycemic activity and the probable underlying mechanisms of action of Bitter melon extract in diabetic rats by studying the changes in insulin signaling pathway in different peripheral tissues.

To achieve this aim we use rat model of type 2 diabetes mellitus which generated by injecting Wistar rats on the 5th day of their birth (n5=birth) intra-peritoneally with 100 mg/kg of STZ. All rats were followed up for 8-12 weeks to establish diabetes which was confirmed by fasting blood glucose level more than 200 mg/dl. The male diabetic rats will be divided into four groups: Group 1: the diabetic control group which received no treatment. Group 2: Bitter melon treated group. This group was divided into 4 subgroups (10 rats each) each group was treated daily with different oral doses of Bitter melon ethanolic extract (100 mg/kg, 200 mg/kg, 400 mg/kg and 600 mg/kg) for 30 days. Group 3: Glibenclamide treated group that was treated with glibenclamide 0.1 mg/kg (n=10) for 30 days. Also the study included a 10 healthy control rats (Group 4).

The results indicated that, the n-STZ diabetic rat model showed the typical manifestations of type 2 diabetes mellitus (T2DM) including increased weight gain, hyperglycemia, decreased insulin level and elevated HOMA-insulin resistance index compared to control rats. Also in the diabetic rats, the impaired glucose homeostasis is associated with disturbed lipid metabolism as indicated by elevated triglycerides, total cholesterol and LDL-cholesterol and decline in HDL-cholesterol.

The treatment of the diabetic rats with serial doses of ethanolic extract of bitter melon showed a dose dependent decrease in body weight and increase in fasting insulin level while the fasting blood sugar and HOMA-insulin resistance index showed dose-dependent decline with the doses from 100 to 400 mg/kg with the best results obtained with 400 mg/kg dose, the highest dose (600 mg/kg) showed significant elevated values compared to untreated diabetic rats. When comparing the efficacy of bitter melon with conventional drugs like sulfonylurea (glibenclamide) we found that bitter melon extract at dose of 400 mg/kg showed comparable improvements in glucose homeostasis parameters with glibenclamide.

The insulin resistance in diabetic rats was associated with impaired insulin signaling in liver and muscles as indicated by lowered phosphor-insulin receptor (Phospho-IR), IRS-1, PKC and Glut4. The treatment of diabetic rats with bitter melon showed a dose-dependent increase of several components of insulin signaling in liver (P-IR and IRS-1) and muscle (P-IR, IRS-1, PKC and Glut4) with the doses from 100 to 400 mg/kg while the highest dose (600mg/kg) showed less efficient effect than the lower doses. This induction effect on the expression of these components of insulin signaling at the protein level may indicate that the constituents of bitter melon may act as a positive regulators at the transcriptional, post-transcriptional and/or translational level of gene expression, however the specific constituents responsible for these induction effect need further studies.

The treatment with bitter melon show triglycerides lowering effect at low doses (100 and 200 mg/kg) while the higher doses have no significant effect. Total cholesterol showed very mild correction with bitter melon treatment. While HDL-cholesterol showed dose-dependent increase, the LDL-cholesterol showed a dose-dependent decline with bitter melon extract at doses from 100 to 400 mg/kg while highest dose showed lesser effect. Also, glibenclamide showed partial correction of lipid profile.

From the results of the present study and other related studies we can conclude that:

- 1- Bitter melon extract is a powerful glucose -lowering factor that play important role as anti-diabetic treatment.
- 2- Bitter melon produces its effect through multiple pathways:
 - a- Acting as insulin secretagogue, which induce insulin secretion from β -cell
 - b- Mimicking insulin action, through its constituents like p-insulin (polypeptide P) which induce insulin like action in peripheral tissue
 - c- Induce peripheral tissues expression of the insulin signaling components and act as insulin sensitizer.

- 3- The bitter melon extract at low doses produce anti-diabetic effects equivalent to classical sulfonylurea (glibenclamide) however, high dose is less efficient and may worsen the diabetic situation.
- 4- Bitter melon extract have a lipid-lowering effect which partially correct dyslipidemia observed in the diabetic rats
- 5- Bitter melon is recommended as food supplement or pharmacological extract to treat type 2 diabetes mellitus.

7. REFERENCE

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Table: Weight (gm) in healthy control and diabetic groups with and without treatments.

Weight (gm)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	180.0	191.0	232.0	210.0	198.0	205.0	209.0
2	235.0	240.0	180.0	214.0	263.0	260.0	231.0
3	250.0	290.0	206.0	228.0	286.0	180.0	202.0
4	190.0	215.5	193.0	250.0	243.0	221.0	214.0
5	217.0	265.0	202.8	288.0	213.0	269.0	208.3
6	177.0	252.7	197.9	235.0	173.0	227.0	208.1
7	206.0	240.2	200.3	235.0	268.0	248.0	208.1
8	207.9	260.0	199.1	245.0	234.9	237.5	209.6
9	206.9	190.0	199.7	244.0	251.4	242.8	208.5
10	207.4	291.0	199.4	230.0	243.1	240.1	208.6
Mean ± SD	207.7±22.7	243.5±36.0	201.0±13.0	237.9±21.8	237.3±34.2	233.0±26.2	210.7±7.7

Table: The levels of FBS (mg/dl) in healthy control and diabetic groups with and without treatments.

FBS (mg/dl)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	85.0	223.0	112.0	149.0	169.6	123.0	160.5
2	106.0	197.0	110.0	139.0	118.5	117.0	195.5
3	93.0	257.0	122.0	136.0	109.6	98.0	171.5
4	89.0	210.0	126.5	141.3	89.6	163.0	167.0
5	95.0	227.0	105.0	138.8	103.2	112.0	173.6
6	93.0	233.5	126.0	138.7	223.0	78.4	176.9
7	100.0	230.5	104.0	139.6	139.0	81.0	172.3
8	94.4	230.0	124.0	139.0	177.0	110.3	172.4
9	97.0	197.0	139.0	140.2	121.0	95.7	173.8
10	96.0	255.0	115.0	139.6	138.9	103.0	173.9
Mean ± SD	94.8± 5.7	226.0± 20.7	118.4 ± 11.1	140.1± 3.4	138.9±40.5	108.1± 24.1	173.7± 8.9

Table: The levels of Insulin (ug/mg protein) in healthy control and diabetic groups with and without treatments.

Insulin (ug/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	0.4	0.3	0.6	0.3	0.3	0.3	0.4
2	0.3	0.3	0.4	0.2	0.2	0.3	0.7
3	0.7	0.2	0.4	0.2	0.2	0.4	0.6
4	0.2	0.2	0.5	0.4	0.4	0.9	0.5
5	0.5	0.3	0.4	0.6	0.6	0.4	0.7
6	0.4	0.3	0.6	0.3	0.3	0.5	0.4
7	0.5	0.3	0.4	0.5	0.5	0.4	0.8
8	0.3	0.3	0.6	0.4	0.4	0.4	0.5
9	0.4	0.2	0.4	0.4	0.4	0.4	0.5
10	0.3	0.3	0.6	0.4	0.4	0.4	0.4
Mean ± SD	0.40±0.13	0.25 ± 0.02	0.46 ± 0.10	0.32 ± 0.09	0.38 ± 0.11	0.44 ± 0.17	0.56 ± 0.16

Table: The levels of HOMA-IR in healthy control and diabetic groups with and without treatments.

HOMA-IR	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	2.0	3.7	3.6	2.4	2.6	2.1	3.7
2	2.1	2.9	2.3	2.3	1.6	2.0	8.5
3	3.8	3.7	2.6	1.4	1.5	2.4	6.5
4	1.3	2.7	3.8	4.4	2.3	8.6	4.9
5	2.9	3.5	2.4	2.8	3.5	2.4	7.6
6	1.9	3.7	4.1	2.6	4.6	2.1	4.2
7	2.8	3.4	2.3	2.7	3.8	2.0	8.6
8	1.7	3.7	4.1	2.7	4.2	2.8	5.1
9	2.2	2.4	3.0	2.7	3.1	2.4	5.1
10	2.0	4.2	3.8	2.7	3.4	2.6	4.1
Mean ± SD	2.27± 0.72	3.40 ± 0.54	3.23 ± 0.77	2.68 ± 0.72	3.07 ± 1.05	2.94 ± 2.01	5.84 ± 1.85

Table: The Levels of Triglycerides (mg/dl) in healthy control and diabetic groups without and with Treatments.

T.G (mg/dl.)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	43.6	112.0	59.4	75.3	133.0	105.4	115.0
2	29.8	143.0	87.0	88.1	74.1	105.9	83.0
3	35.5	122.0	73.2	159.5	158.1	82.3	135.0
4	28.3	127.0	80.1	81.0	23.3	84.0	118.0
5	29.1	116.0	76.7	66.0	42.4	92.0	90.3
6	29.8	131.0	78.4	57.0	108.0	66.1	99.1
7	49.0	98.0	77.5	68.1	95.0	108.7	103.1
8	35.0	88.0	77.9	48.3	59.5	132.1	95.1
9	42.0	112.0	77.7	80.4	47.9	120.4	96.9
10	38.5	131.0	77.8	64.4	53.7	126.2	98.5
Mean ± SD	36.1±7.1	118.0±16.5	76.6±7.0	78.8±30.8	79.5 ± 43.1	102.3±21.1	103.4±15.2

Table: The Levels of Total Cholesterol (mg/dl) in healthy control and diabetic groups without and with Treatments.

Total Cholesterol (mg/dl.)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	158.0	173.0	142.3	200.0	191.0	195.5	138.0
2	135.5	180.0	164.3	202.0	226.0	212.0	191.0
3	147.0	159.0	153.0	192.0	127.0	201.0	141.0
4	145.5	189.0	159.0	144.2	149.0	159.0	157.0
5	138.0	194.0	156.5	175.0	188.0	156.0	156.0
6	150.0	188.0	155.0	141.0	193.0	144.5	161.0
7	115.0	197.0	155.0	185.0	170.5	174.0	154.0
8	135.0	185.0	160.0	153.0	165.0	177.0	157.0
9	149.0	187.0	156.0	174.0	166.0	176.0	157.0
10	148.0	205.0	156.0	164.0	184.0	177.0	158.0
Mean ± SD	142.1±11.9	185.7±12.9	155.7±5.7	173.0±22.1	176.0±27.1	177.2±21.0	157.0±14.1

Table: The Levels of LDL- Cholesterol (mg/dl) in healthy control and diabetic groups without and with Treatments.

LDL- Cholesterol (mg/dl.)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	100.3	126.0	113.2	132.6	109.4	111.4	78.2
2	88.2	121.3	95.4	139.4	157.6	109.8	135.1
3	101.9	107.4	104.0	120.8	27.9	130.4	76.7
4	88.8	136.3	100.1	92.2	101.2	111.8	91.6
5	93.2	142.6	102.5	122.0	120.0	90.3	99.2
6	103.4	134.2	98.5	98.5	108.4	95.5	101.9
7	60.2	149.3	99.8	150.7	127.0	102.6	94.1
8	84.0	139.6	104.2	115.0	134.3	99.0	98.2
9	91.6	136.7	100.5	121.4	132.8	101.3	98.3
10	96.3	150.8	100.3	118.7	152.1	100.6	98.7
Mean ± SD	90.8±12.5	134.4 ±13.2	101.9±4.8	121.1±17.4	117.1±36.3	105.3±11.3	97.2±15.9

Table: The Levels of HDL- Cholesterol (mg/dl) in healthy control and diabetic groups without and with Treatments.

HDL- Cholesterol (mg/dl)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	49.0	24.6	17.2	52.3	55.0	63.0	36.8
2	41.3	30.1	51.5	45.0	53.6	81.0	39.3
3	38.0	27.2	34.4	39.3	67.5	54.1	37.3
4	51.0	27.3	42.9	35.8	43.1	30.4	41.8
5	39.0	28.2	38.6	39.8	59.5	47.3	38.8
6	40.6	27.6	40.8	31.1	63.0	35.8	39.3
7	45.0	28.1	39.7	20.7	24.5	49.7	39.3
8	44.0	27.8	40.2	28.3	18.8	51.6	39.8
9	49.0	27.9	40.0	36.5	23.6	50.7	39.3
10	44.0	28.0	40.1	32.4	21.2	51.1	39.6
Mean ± SD	44.1±4.5	27.7 ± 1.3	38.5±8.7	36.1±8.8	43.0±19.2	51.5±13.8	39.1±1.4

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Table: The Levels of Liver P-IR (pg/mg protein) in healthy control and diabetic groups without and with treatments.

P-IR (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	8.3	3.9	5.00	5.0	4.1	4.3	4.6
2	5.6	5.9	4.50	5.3	4.1	5.8	4.7
3	4.9	3.8	5.20	4.1	5.6	5.8	4.0
4	8.4	4.0	5.80	4.0	4.6	5.3	4.4
5	6.8	4.4	4.60	4.1	4.8	5.6	4.4
6	6.4	4.6	5.10	5.0	5.0	5.6	4.3
7	6.6	4.2	4.80	5.1	4.8	5.5	4.4
8	7.1	4.3	5.20	4.7	4.9	5.6	4.3
9	6.7	4.4	5.10	4.1	4.9	5.5	4.3
10	6.7	4.4	5.03	4.0	4.8	5.5	4.3
Mean ± SD	6.77±1.06	4.39±0.59	5.03±0.36	4.53± 0.53	4.77±0.43	5.45± 0.43	4.37±0.18

Table: The Levels of Liver IRS-1 (pg/mg protein) in healthy control and diabetic groups without and with treatments.

IRS-1 (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	2.4	1.1	1.6	1.4	1.5	1.7	1.3
2	1.5	1.7	1.4	1.4	1.4	1.5	1.5
3	1.8	1.4	1.5	1.6	1.6	1.8	1.4
4	1.9	1.6	1.4	1.5	1.5	1.7	1.3
5	1.7	1.5	1.5	1.6	1.5	1.7	1.4
6	1.8	1.5	1.5	1.5	1.5	1.7	1.4
7	1.8	1.5	1.5	1.6	1.5	1.7	1.4
8	1.8	1.5	1.5	1.5	1.5	1.7	1.4
9	1.8	1.5	1.5	1.6	1.5	1.7	1.4
10	1.8	1.5	1.5	1.5	1.5	1.7	1.4
Mean ± SD	1.82±0.25	1.48±0.15	1.47± 0.05	1.53±0.06	1.51±0.05	1.66±0.05	1.38± 0.07

Table: The Levels of Liver PKC (pg/mg protein) in healthy control and diabetic groups without and with Treatments.

PKC (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	65.9	15.1	4.3	60.3	38.0	79.9	11.1
2	29.1	37.6	72.6	60.2	34.1	54.8	41.1
3	63.2	26.3	38.5	50.0	57.8	18.4	57.3
4	52.8	32.0	55.5	56.8	43.3	39.4	51.6
5	48.4	29.2	47.0	55.7	45.1	48.1	40.3
6	54.8	30.6	51.3	54.2	48.7	40.2	47.6
7	52.0	29.9	49.1	55.5	45.7	36.5	49.2
8	51.7	30.2	50.2	54.9	46.5	41.1	47.2
9	52.8	30.0	49.7	54.9	47.0	41.5	46.0
10	52.2	30.1	49.9	55.1	46.4	39.8	47.5
Mean ± SD	52.3±9.8	29.1±5.7	46.8±17.2	55.7±3.0	45.2± 6.3	44±15.6	43.9±12.5

Table: The Levels of Muscle P-IR (pg/mg protein) in healthy control and diabetic groups without and with Treatments

P-IR (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	4.3	4.8	4.3	5.5	4.3	4.2	5.2
2	7.6	3.6	4.0	4.7	5.0	4.1	4.1
3	7.1	4.0	4.1	4.1	4.7	4.8	3.9
4	5.1	3.8	4.1	4.8	4.8	4.3	4.4
5	6.0	3.9	4.1	4.8	4.7	4.4	4.1
6	6.4	3.9	4.1	4.6	4.8	4.4	4.2
7	6.2	3.9	4.1	4.7	4.8	4.5	4.2
8	5.9	3.9	4.1	4.7	4.8	4.4	4.2
9	6.0	3.9	4.1	4.7	4.8	4.4	4.2
10	6.0	3.9	4.1	4.7	4.8	4.4	4.2
Mean ± SD	6.06 ±0.92	3.95±0.33	4.12±0.08	4.72±0.33	4.74±0.17	4.38±0.18	4.27±0.35

Table: The Levels of Muscle IRS-1 (pg/mg protein) in healthy control and diabetic groups without and with Treatments.

IRS-1 (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	1.3	1.6	1.4	1.5	1.6	1.4	2.0
2	1.6	1.5	1.7	1.3	1.3	1.5	1.4
3	2.0	1.6	1.6	1.6	1.5	1.5	1.0
4	1.6	1.5	1.7	1.4	1.5	1.4	1.8
5	1.7	1.6	1.6	1.4	1.4	1.5	1.5
6	1.8	1.5	1.6	1.4	1.5	1.5	1.4
7	1.7	1.5	1.6	1.4	1.5	1.5	1.4
8	1.7	1.5	1.6	1.4	1.5	1.4	1.5
9	1.7	1.5	1.6	1.4	1.5	1.5	1.5
10	1.7	1.5	1.6	1.4	1.5	1.5	1.5
Mean ± SD	1.69±0.18	1.55±0.04	1.62 ±0.08	1.44±0.06	1.46±0.09	1.46±0.03	1.5± 0.25

Table: The Levels of Muscle PKC (pg/mg protein) in healthy control and diabetic groups without and with Treatments.

PKC (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	47.4	55.0	41.9	52.7	32.6	54.3	49.4
2	86.5	23.7	52.1	41.0	40.0	39.5	35.0
3	36.5	39.4	47.0	38.0	52.1	44.0	27.5
4	56.8	31.6	49.5	43.9	41.6	50.0	44.0
5	59.9	35.5	48.3	41.0	44.6	45.9	39.0
6	51.0	33.5	47.8	41.0	46.1	47.0	36.4
7	55.9	34.5	48.9	41.9	44.1	47.6	39.8
8	55.6	34.0	48.6	41.3	44.9	46.9	38.4
9	54.2	34.2	48.4	41.6	45.0	47.2	38.2
10	54.2	34.1	48.4	41.5	44.7	47.2	38.8
Mean ± SD	55.97±12.61	35.55±7.89	48.10±2.56	42.38±3.9	43.55±4.99	46.97±3.79	38.64±5.65

Table: The Levels of Muscle Glut-4 (pg/mg protein) in healthy control and diabetic groups without and with Treatments.

Glut-4 (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	213.079	38.0	44.1	75.0	58.6	60.0	70.0
2	43.458	50.8	65.0	50.5	43.1	60.0	64.0
3	89.082	44.4	54.6	50.0	49.0	62.4	50.0
4	95.297	47.6	59.8	83.1	31.4	60.0	72.0
5	125.633	46.0	59.8	66.9	41.6	48.0	64.0
6	66.928	46.0	56.6	76.5	164.0	100.0	68.0
7	106.724	47.0	58.2	29.6	69.5	54.0	66.0
8	105.743	46.5	57.4	61.7	50.8	63.5	67.0
9	106.233	46.7	57.8	45.6	34.1	58.7	66.5
10	96.407	46.6	57.6	53.6	60.2	61.1	66.7
Mean ± SD	104±44.4	46.0±3.2	57.1±5.3	59.2±16.5	60.2±38.3	62.8±13.8	65.4±5.9

الملخص العربي

الداء السكري أو مرض السكري هو مجموعة من اضطرابات التمثيل الغذائي نتيجة لأسباب متعددة مما يؤدي الى ارتفاع السكر في الدم مصاحباً باضطرابات في التمثيل الغذائي لأيض الدهون والكربوهيدرات والبروتين وذلك ناتج عن خلل في إفراز أو عمل الأنسولين، أو كليهما. وقد وجد أن آثار وأضرار مرض السكري يظهر على المدى الطويل، ويمتد آثاره إلى حدوث خلل وفشل في وظائف أعضاء الجسم.

المرض السكري من النوع الثاني والذي يمثل 90% من المرضى ويعد أكثر الأنواع انتشاراً وأكثر تعقيداً نتيجة للتطوير التدريجي لمقاومة الأنسولين ونقص نسبي في إفراز الأنسولين .

يشمل العلاج لمرض السكري وضع نظام غذائي، وممارسة الرياضة، واستخدام أدوية علاج السكر لخفض مستوى السكر في الدم عن طريق الفم أو الأنسولين ويعتبر ذلك أشكالاً أولية من العلاج لمرض السكري. يوجد العديد من الخيارات العلاجية المتاحة حالياً وتتضمن الأدوية المخلفة أو المصنعة والتي تعتبر بجانب إنها مكلفة لها آثار جانبية خطيرة. الأدوية التكميلية أو البديلة هي مصدر مثير للأدوية في المستقبل لمواجهة مقاومة الأنسولين. والميزة الرئيسية للطب البديل هو أنها استخدمت لعلاج الأمراض التي تصيب الإنسان لسنوات عديدة ويعتبر من الخيارات العلاجية الآمنة وغير مكلفة وتشير التقديرات إلى أن ما يصل إلى ثلث المرضى الذين يعانون من مرض السكري تم استخدامهم لبعض أشكال الطب البديل أو التكميلي .

قرع المر هو ثمرة شعبية تستخدم لعلاج مرض السكري وهي منتشرة بين السكان الأصليين من آسيا وأمريكا الجنوبية والهند وشرق أفريقيا. وقد وثقت الدراسات الوفيرة لقرع المر في علاج المرض السكري ولكن الوضع الدقيق للعمل لا يزال غير واضح. كان الهدف من هذه الدراسة هو تقييم نشاط مستخلص قرع المر في خفض مستوى السكر في الدم والآليات الكامنة و المحتملة لعمله في الفئران المصابة بداء مرض السكري وذلك من خلال دراسة التغيرات في مسار إشارات الأنسولين في الأنسجة الطرفية المختلفة.

لتحقيق هذا الهدف تم حث مرض السكري كيميائياً في ذكور الفئران البالغة من العمر 5 أيام عن طريق الحقن بالستربتوزوتوسين (100 مجم /كجم) وتم متابعة جميع الفئران التي تم حقنها لمدة تصل من 8- 12 أسبوعاً لحدوث المرض السكري وهو ما أكدته مستوى السكر الصائم في الدم أكثر من (200 مجم / ديسيليتزر). تم تقسيم الفئران المصابة بالمرض السكري إلى خمس مجموعات:

1. المجموعة الضابطة المصابة بالمرض السكري والتي لم تتلقى أي علاج.
2. المجموعة المصابة بالمرض السكري التي تم علاجها بالمستخلص الايثانولي لقرع المر وقد تم تقسيم هذه المجموعة إلى أربع مجموعات فرعية كل مجموعة تم علاجها يومياً بجرعات مختلفة من مستخلص قرع المر (100مجم /كجم، 200 ، مجم / كجم، 400 مجم / كجم، 600 مجم/كجم) وذلك لمدة 30 يوماً .
3. المجموعة التي عولجت بجلايبيكلاميد 0.1 مجم / كجم لمدة 30 يوماً .
4. المجموعة الضابطة (الفئران الأصحاء).

وبعد 30 يوم من العلاج تم جمع الدم وتشريح جميع المجموعات للحصول على أنسجة الكبد والعضلات لتعيين دلالات إشارات الأنسولين.

وقد أشارت النتائج إلى أن الفئران التي تم حقنها بالستربتوزوتوسين قد أظهرت مظاهر نموذجية للمرض السكري من النوع الثاني. بما في ذلك زيادة في الوزن، ارتفاع مستوى السكر في الدم، وانخفاض مستوى الأنسولين وارتفاع مؤشر مقاومة الأنسولين (HOMA) وأيضا هذا الخلل في توازن الجلوكوز مرتبط بحدوث خلل في أيض الدهون حيث ظهرت في زيادة الدهون الثلاثية والكوليسترول الكلي والكوليسترول الضار، وانخفاض في الكوليسترول النافع.

وقد أظهرت نتائج العلاج بالمستخلص الايثانولي لقرع المر معتمدا على جرعة العلاج حدوث انخفاض في وزن الجسم وزيادة في مستوى الأنسولين بينما أظهرت نسبة السكر الصائم في الدم ومؤشر مقاومة الأنسولين انخفاض في المستوى وذلك في الجرعات (100-400 مجم/كجم) وقد وجد أن جرعة العلاج 400 مجم/كجم هي أفضل النتائج، و عندما تم مقارنة فاعلية قرع المر مع الأدوية المخلفة مثل السلفونيل يوريا (جليبنكلاميد) وجد أن مستخلص قرع المر في جرعة 400 مجم/كجم أظهرت تحسينات مماثلة للجليبنكلاميد في دلالات توازن الجلوكوز.

وقد ارتبطت مقاومة الأنسولين في الفئران المصابة بالمرض السكري بخلل في مسار إشارات الأنسولين في الكبد والعضلات والذي ظهر من خلال انخفاض مستقبلات الأنسولين (Glut-4, PKC, IRS-1, P-IR) وقد أظهر العلاج بقرع المر زيادة في العديد من مكونات مسار إشارات الأنسولين في الكبد والعضلات معتمداً على الجرعة وذلك من 100-400 مجم / كجم في حين أظهرت أعلى جرعة (600مجم/كجم) تأثير أقل كفاءة من جرعات أقل. هذا التأثير المحث على التعبير عن هذه المكونات من إشارات الأنسولين على المستوى البيروتيقي لهم ويشير إلى أن مكونات قرع المر قد يكون بمثابة منظم إيجابي في التعبير الجيني.

وقد تبين أيضا أن العلاج بقرع المر له تأثيره في خفض الدهون الثلاثية في الجرعات المنخفضة (100 و 200 مجم / كجم) في حين أن الجرعات العالية ليس لها تأثير كبير. بينما أظهر الكوليسترول تصحيح معتدل مع العلاج بقرع المر. في حين أظهر العلاج بمستخلص قرع المر زيادة الكوليسترول النافع و انخفاض الكوليسترول الضار معتمدا على الجرعة بجرعات 100-400 مجم / كجم في حين أظهرت أعلى جرعة تأثير أقل كما أظهر أيضا جليبنكلاميد تصحيح جزئي لدلالات الدهون .

من نتائج هذه الدراسة وغيرها من الدراسات ذات الصلة يمكن أن نستنتج ما يلي:

- 1- مستخلص قرع المر هو عامل قوي لتخفيض مستوى السكر والذي يلعب دورا هاما لعلاج المرض السكري.
- 2- قرع المر له تأثيره من خلال مسارات متعددة:
 - أ- له تأثير مثل تأثير إفراز الأنسولين، مما يحفز على إفراز الأنسولين من خلايا بيتا .
 - ب- يحاكي عمل الأنسولين، من خلال مكوناته مثل الأنسولين بي (بولي ببتيد بي) (p-insulin / polypeptide P) مما يحفز على عمل مماثل للأنسولين في الأنسجة الطرفية.
 - ج- يحث الأنسجة الطرفية علي التعبير أو إظهار إشارات الأنسولين مما يعمل بمثابة الأنسولين المحفز أو المحسن.
- 3- مستخلص نبات قرع المر في الجرعات المنخفضة يظهر تأثير مماثل للجليبنكلاميد (السلفونيل يوريا) بينما الجرعة العالية هي أقل كفاءة وربما يؤدي إلى تفاقم المرض السكري .
- 4- مستخلص قرع المر يكون له تأثير في خفض الدهون مما يصحح جزئيا مرض (dyslipidemia) في الفئران المصابة بالمرض السكري.
- 5- ينصح بقرع المر كمكمل غذائي لعلاج النوع الثاني من مرض السكري

لجنة الإشراف

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أستاذ بقسم الكيمياء الحيوية

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تقييم تأثير قرع المر على مسار إشارة الأنسولين فى الفئران المصابة بمرض السكر من النوع الثانى

مقدمة من

هالة محمد عبد البارى حسن الحاج

للحصول على درجة

الدكتوراه

فى

الكيمياء الحيوية

التوقيع

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رسالة مقدمة إلى
معهد البحوث الطبية - جامعة الإسكندرية
إيفاء جزئياً للحصول على درجة

الدكتوراه في الكيمياء الحيوية

من

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