

CINNAMON: POTENTIAL ROLE IN THE REDUCTION OF OVERWEIGHT, BLOOD GLUCOSE AND HYPERLIPIDEMIA AMONG TYPE 2 DIABETIC PATIENTS THROUGH NEUROHORMONAL REGULATION FROM HYPOTHALAMUS

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The purpose of this study is to systemize a neuro-physiological modification scopes that is related to regulate the obesity and food intake among diabetics type2. the plant cinnamon was examined in order to understand its influence upon beta pancreatic cells to secret insulin as well as to comprehend its effects upon leptin (which is secreted from adipose tissue) and on neuropeptide Y(a potent food intake) which participate in obesity.

Keywords: *cinnamon, leptin, neuropeptide Y, obesity, neural regulation.*

ROLUL POTENȚIAL AL SCORȚIȘOAREI ÎN REDUCEREA EXCESULUI DE GREUTATE, GLICEMIEI ȘI HIPERLIPIDEMIEI PRINTRE PACIENȚII CU DIABET ZAHARAT TIP 2, PRIN REGLAREA NEUROHORMONALĂ DE CĂTRE HIPOTALAMUS

Scopul acestui studiu este de a sistematiza domeniile modificării neurofiziologice care este asociată cu regularea obezității și aportul alimentar printre diabeticii tip 2. Planta „scorțișoara” a fost studiată pentru a înțelege influența acesteia asupra capacității celulelor β pancreatice de a secreta insulină, precum și pentru a înțelege efectele ei asupra leptinei (care este secretată din țesutul adipos) și asupra neuropeptidei Y (un aport crescut de alimente), care participă în mecanismul obezității.

Cuvinte-cheie: *scorțișoară, leptină, neuropeptida Y, obezitate, reglare neurală.*

Introduction

Carrying extra body weight and body fat go firmly with the development of type 2 diabetes. People who are overweight are at much greater risk of developing type 2 diabetes than normal weight individuals. Being overweight puts added pressure on the body's ability to properly control blood sugar using insulin and therefore makes it much more likely for you to develop diabetes. Almost 90% of people with type 2 diabetes are overweight [18].

Over twenty three million Americans (7.8 % of the population) have diabetes. Almost 5.7 million Americans are unaware they have the disease. Type 2 diabetes is linked to obesity and physical inactivity. In this form of diabetes your body makes insulin but can't use its insulin properly. At first, the body overproduces insulin to keep blood sugar normal, but over time this causes the body to lose its ability to produce enough insulin to keep blood sugar levels in the normal healthy range. The result is sugar rises in the blood to high levels. Over a long period of time, high blood sugar levels and diabetes can cause heart disease, stroke, blindness, kidney failure, leg and foot amputations, and pregnancy complications [2].

Obesity is also no longer a condition that just affects older people, although the likelihood does increase with age, and increasing numbers of young people have been diagnosed with obesity. For type 2 diabetes, this includes being overweight or obese (having a body mass index - BMI - of 30 or greater). In fact, obesity is believed to account for 80-85% of the risk of developing type 2 diabetes, while recent research suggests that obese people are up to 80 times more likely to develop type 2 diabetes than those with a BMI of less than 22 [7].

Studies suggest that abdominal fat causes fat cells to releases 'pro-inflammatory' chemicals, which can make the body less sensitive to the insulin it produces by disrupting the function of insulin responsive cells and their ability to respond to insulin. This is known as insulin resistance - a major trigger for type 2 diabetes. Having excess abdominal fat (i.e. a large waistline) is known as central or abdominal obesity, a particularly high-risk form of obesity [11].

Obesity is also thought to trigger changes to the body's metabolism. These changes cause fat tissue (adipose tissue) to release fat molecules into the blood, which can affect insulin responsive cells and lead to reduced insulin sensitivity. Another theory put forward by scientists into how obesity could lead to type 2 diabetes is that obesity causes prediabetes, a metabolic condition that almost always develops into type 2 diabetes [8].

Hypothalamic neurohormonal regulation upon obesity: when the diabetic patient gets overweight, he increases the number of adipocytes (fat cells) due to both mitotic division of the adipocytes and the conversion of preadipocytes (derived from fibroblasts) into new adipocytes. In addition to storing fat (triglyceride, or triacylglycerol), adipocytes produce and secrete regulatory molecules like leptin, a hormone that signals the hypothalamus to indicate the level of fat storage. This hormone is involved in long-term regulation of eating and metabolism [19].

The type 2 obese patients display hyperphagia (they eat too much) and decreased energy consumption and respectively they develop "insulin resistance" which means more insulin is required to maintain normal blood glucose concentrations. People with excessive amounts of large adipocytes (overweight) require more insulin to maintain normal blood glucose levels than do thinner people, who have smaller adipocytes which makes the B cells of pancreas to produce more insulin, however, after a while the pancreas gets "pancreatic insufficiency" and less insulin is secreted [20].

When the insulin secretion is decreased, it lowers the stimulation of adipose cells to secrete leptin which leads to increase the amount of neuropeptide Y (a potent stimulator of appetite) in the hypothalamus [10,12,17]. It functions as a neurotransmitter of axons that extend within the hypothalamus from the arcuate nucleus to the paraventricular nucleus, two regions implicated in the control of eating behavior. When weight is gained, an increased secretion of leptin from the adipocytes may result in decreased production of neuropeptide Y, which then inhibits hunger and food intake and increased expenditure of energy [1, 5].

In summary, leptin is believed to target the arcuate nucleus of the hypothalamus, where it affects two populations of neurons. One population produces neuropeptide Y; these neurons are inhibited by leptin. The other population produces MSH and is stimulated by leptin. As a result, in obese diabetics, low leptin levels (due to low secretion from adipocytes by decreased insulin levels) should boost appetite, which leads to obesity [3,10].

During the last decades, it has been established many researches of plants upon diabetes mellitus type 2 and obesity so as to understand better physiological and pathological manifestations in order to cure diabetic patients. One of these plants is cinnamon which is a spice obtained from the inner bark of several trees from the genus *Cinnamomum* that is used in both sweet and savory foods. While *Cinnamomum verum* is sometimes considered to be "true cinnamon", most cinnamon in international commerce is derived from related species, which are also referred to as "cassia" to distinguish them from "true cinnamon" [4].

OBJECTIVE – The objective of this study was to determine whether cinnamon reduces obesity (body mass index) and improves blood glucose, insulin secretion, leptin, neuropeptide Y, lipids levels among type 2 diabetics.

Research design and methods

This study was conducted in the Department of Biology, University of the state of Moldova (USM), Chisinau, Moldova. The study included 128 male mice of 125-250 grams and they were 8–13 weeks old which housed individually under standard conditions with a light/dark cycle of 12 h and the ambient temperature for mice was 23°C-26°C, which were divided into 8 groups:

1. Mice were injected with leptin 1 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day of the research), Alloxan 15 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day), Cinnamon was given to be consumed orally 1 mg (powder form)/ 30 ml of water.

2. Mice were injected with leptin 1 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day of the research), Alloxan 15 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day).

3. Mice were injected with Neuropeptide Y (NPY) 0,5 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day of the research), Alloxan 15 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day), Cinnamon was given to be consumed orally 1 mg/ 30 ml of water.

4. Mice were injected with Neuropeptide Y (NPY) 0,5 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day of the research), Alloxan 15 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day).

5. Alloxan 15 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day), Cinnamon was given to be consumed orally 1 mg/ 30 ml of water.

6. Cinnamon was given to be consumed orally 1 mg/ 30 ml of water.

7. Alloxan 15 mg/1 ml NaCl 0,9% intraperitoneally (in 1,3,6,9 day).

8. Control group which was given 1 ml NaCl 0,9% intraperitoneally.

Cinnamon (an extract of cinnamomum cassia) certified and purchased from Migal Institute from israel, while alloxan was obtained from Moldova in a form of 5% (200 mg/kg). Leptin and Neuropeptide Y were purchased from Eurogentec company- Belgium and were kept in minus 20 celsius.

For measurement of the body weight of the mice, it was used an electronically body weight calculator ISK, it was measured at the first, third, sixth and at the ninth day of the experiment. however for urine glucose, protein, ketone bodies it was used special standard indicator Combi 3A, Combi 5S also at the first, third, sixth and at the ninth day of the experiment.

For insulin and thyroid hormones T₃ (triiodothyronine), T₄ (thyroxine) it was used the ELISA (enzyme-linked immunosorbent assay) method at the faculty of biology USM university – Moldova. The blood sugar levels were measured by Glucometer device "Accu-Chec" (Germany). The levels of leptin and neuropeptide Y were measured by ELISA method at Synevo laboratory at Chisinau- Moldova at the first and the last day of the experiment.

Results

The consumption of 1 g of cinnamon by the mice of sixth group, led to significant decreases in serum glucose levels after 10 days till 4,61±0,11 mmol/l in comparison with group 7 which had 9,82±0,18 mmol/l (P<0,05). Administration of neuropeptide Y increases blood glucose till 8,98±0,74 mmol/l (with cinnamon) in comparison with neuropeptide Y 10,73±0,25 (without cinnamon).

Table 1

Influences of cinnamon, alloxan, leptin and neuropeptidul Y upon blood glucose levels in diabetes mellitus type 2

Indication	Leptin		Neuropeptide Y		Control	Alloxan	Cinnamon	Cinnamon +Alloxan
	Whith cinnamon	Whithout cinnamon	Whith cinnamon	Whithout cinnamon				
Number(n)	12	12	12	12	20	20	20	20
Glucose (mmol/l)	2,08 ±0,85	2,58 ±0,74	8,98 ±0,18	10,73 ±0,25	4,43 ±0,08	9,82 ±0,06	4,61 ±0,11	6,83 ±1,13
	P<0,05	P<0,05	P<0,05	P<0,05		P<0,05	P>0,05	P<0,05

However, in group 1 – the leptin with cinnamon administration, the blood glucose was 2,08±0,18 mmol/l (P<0,05). While in group 2- the leptin without cinnamon giving, the blood glucose was 2,58±0,74 mmol/l (P<0,05). The control mice had 4,43±0, mmol/l.

The reduction of body weight (10,2%) was notably noticed in group1 of leptin with cinnamon in the ninth day 176,86±0,12 gr since it was 196,92±0,78 gr in the first day of experiment (P<0,05). While in group 2 of leptin administration without cinnamon, the body weight loss was 4,3% when the body weight at the ninth day 186,45±0,80 gr since it was 194,86±0,65 gr in the first day (P<0,05).

In group 6, with administration of cinnamon, the body weight loss was observed markedly of (5,79%) when the body weight has reduced from 182,33±0,16 gr (in the first day) till 171,78±0,89 gr (in the ninth day) in comparison with group 7 with alloxan administration while it registered 186,06±0,14 gr in the first day, while 178,67±0,86 gr in the ninth day of experiment (reduction of 3,97%) (P<0,05).

Since there is relationship between the insulin secretion and the stimulation of adipose tissue to secret leptin into the blood to reach arcuate nucleus of the hypothalamus (central nervous system), in our research it was manifested obviously the levels of insulin in the plasma among the researched groups of mice.

The insulin levels were measured by ELISA method (enzyme-linked immunosorbent assay). In group 3, with administration of neuropeptide Y injections with cinnamon consumption, the insulin level has got 1,96±0,85 pmol/l (P<0,05), while in group 4 with neuropeptide Y injections without cinnamon consumption 1,85±0,75 pmol/l (P<0,05) in comparison with control group 8, that had 1,29±0,05 pmol/l.

Table 2

**Influences of cinnamon, alloxan, leptin and neuropeptidul Y
upon blood insulin levels in diabetes mellitus type 2**

Indication	leptin		Neuropeptide Y		Control	Alloxan	Cinnamon	Cinnamon+ Alloxan
	With cinnamon	Without cinnamon	With cinnamon	Without cinnamon				
Number(n)	12	12	12	12	20	20	20	20
Insulin (pmol/l)	1,41 ±0,28	1,12 ±0,48	1,96 ±0,85	1,85 ±0,75	1,29 ±0,05	0,58 ±0,07	1,36 ±0,03	0,81 ±0,04
	P>0,05	P>0,05	P<0,05	P<0,05		P<0,05	P>0,05	P<0,05

In group 6 with cinnamon consumption, the plasma insulin was $1,36 \pm 0,03$ pmol/l ($P > 0,05$), while in group 5, with alloxan injections and cinnamon consumption, the insulin level got $0,81 \pm 0,04$ pmol/l ($P < 0,05$) in comparison with control group.

In group 1, with leptin injections and cinnamon consumption, the insulin level in the plasma was $1,41 \pm 0,28$ pmol/l, in comparison with group 2, with leptin but no cinnamon consumption, the insulin level was $1,12 \pm 0,48$ pmol/l ($P > 0,05$).

It is possible to observe that cinnamon has a significant effect role upon insulin secretion from pancreatic β cells as well as upon adipose tissues to secrete leptin. The difference of insulin levels between group 1 and 2 is based mainly on the cinnamon effect upon adipose tissues.

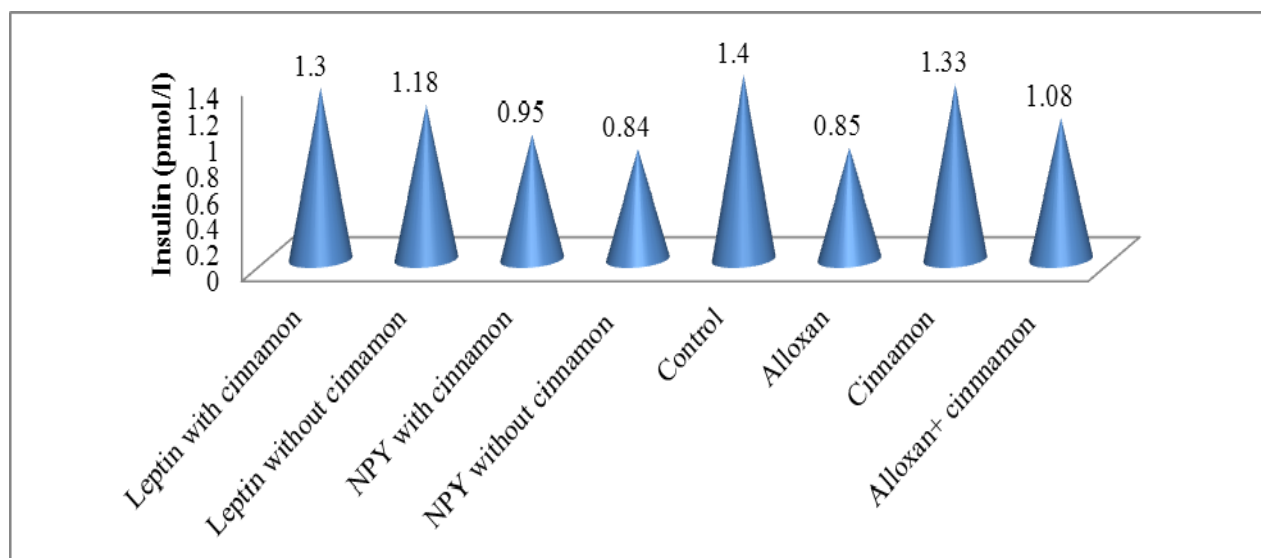


Fig.1. Influences of cinnamon, alloxan, leptin and neuropeptidul Y upon blood insulin levels in diabetes mellitus type 2.

One of the substantial targets of our study was converged on the obesity of the diabetic mice so as to explore the relationship between obesity and pancreatic insulin secretion. As far as it is known, when the body weight is increased, it boosts the adipose tissue and it will increase the lipids profile more in the blood (like total cholesterol, LDL, triglycerides) and decreased HDL.

The total cholesterol level in group 1 (with leptin injections and cinnamon consumption) had the lowest level among all the groups. It's level was $1,93 \pm 0,68$ mmol/l ($P < 0,05$) while in group 2 (with leptin injections only) had $2,3 \pm 0,15$ mmol/l ($P < 0,05$) in comparison with control group that had $5,17 \pm 0,36$ mmol/l.

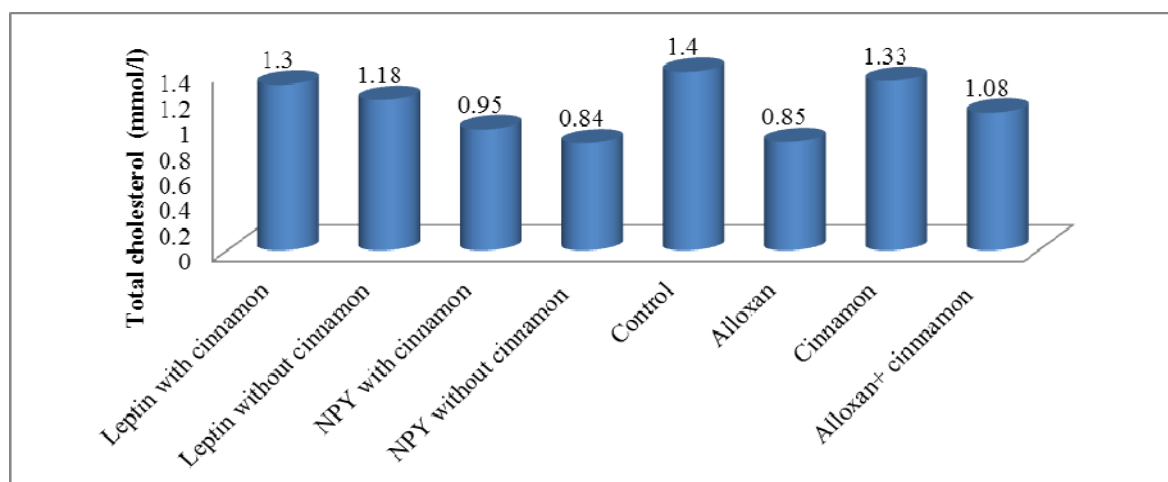


Fig.2. Influences of cinnamon, alloxan, leptin and neuropeptidul Y upon total cholesterol levels in diabetes mellitus type 2.

The highest level of total cholesterol was registered in group 7 (with alloxan injections) - $10,36 \pm 0,72$ mmol/l ($P < 0,05$) while in group 5 (with alloxan injections and cinnamon consumption), the total cholesterol had level of $7,75 \pm 0,86$ mmol/l ($P < 0,05$) in comparison with control group that had $5,17 \pm 0,36$ mmol/l.

Table 3

Influences of cinnamon, alloxan, leptin and neuropeptidul Y upon blood triglycerides levels in diabetes mellitus type 2

Indication	Leptin		Neuropeptide Y		Control	Alloxan	Cinnamon	Cinnamon+ Alloxan
	With cinnamon	Without cinnamon	With cinnamon	Without cinnamon				
Number (n)	12	12	12	12	20	20	20	20
Triglycerides (mMol/l)	1,3 $\pm 0,72$	1,6 $\pm 0,84$	2,32 $\pm 0,23$	3,4 $\pm 0,65$	1,7 $\pm 0,28$	2,04 $\pm 0,13$	1,08 $\pm 0,56$	1,55 $\pm 0,84$
	$P < 0,05$	$P < 0,05$	$P < 0,05$	$P < 0,05$		$P < 0,05$	$P > 0,05$	$P > 0,05$

The mice of group 4 (neuropeptide Y injections without cinnamon consumption) have developed blood triglycerides of $3,4 \pm 0,65$ mmol/l ($P < 0,05$), while group 3 (neuropeptide Y injections with cinnamon consumption) had $2,32 \pm 0,23$ mmol/l ($P < 0,05$) in comparison with control group that had $1,7 \pm 0,28$ mmol/l. In group 1 (with leptin injections and cinnamon consumption) the triglycerides level was $1,3 \pm 0,72$ mmol/l ($P < 0,05$) while in group 2 (with leptin injections only) had $1,6 \pm 0,84$ mmol/l ($P > 0,05$) in comparison with control group that had $1,7 \pm 0,28$ mmol/l.

In our study it has been so paramount to check how does cinnamon affect the level of leptin and neuropeptide Y secretions. For this scope, we have measured the levels of the leptin and neuropeptide Y in the first and the last day of the experiment in order to compare their levels under the effect of cinnamon consumption. In the following table, we will show the influence of cinnamon upon the leptin secretion levels.

Table 4

Influences of cinnamon upon leptin plasma levels

Indication	With cinnamon (days)		Without cinnamon (days)		Control	
	first day	10 th -day	first day	10 th -day	first day	10 th -day
Leptin (ng/ml)	32,16	46,12	15,33	22,35	10,64	11,23
P	$> 0,05$	$< 0,05$	$> 0,05$	$< 0,05$		

In the first day of experiment the level of leptin in the plasma was 32,16 ng/ml ($P>0,05$) in group 1 (with cinnamon consumption), while it was 46,12 ng/ml ($P<0,05$) in the tenth day of the same group. However, in group 2 (without cinnamon consumption), the leptin level in the first day was 15,33 ng/ml ($P>0,05$), while its level in the tenth day was 22,35 ng/ml ($P<0,05$).

Table 5

Influences of cinnamon upon leptin plasma levels

Indication	With cinnamon (days)		Without cinnamon (days)		Control	
	first day	10 th -day	first day	10 th -day	first day	10 th -day
Neuropeptide Y (ng/ml)	52,18	41,45	50,58	72,73	46,64	48,23
P	<0,05	<0,05	<0,05	<0,05		

In the first day of experiment the level of neuropeptide Y in the plasma was 52,18 ng/ml ($P<0,05$) in group 3 (with cinnamon consumption), while it was 41,45 ng/ml ($P<0,05$) in the tenth day of the same group. However, in group 4 (without cinnamon consumption), the neuropeptide Y level in the first day was 50,58 ng/ml ($P<0,05$), while its level in the tenth day was 72,73 ng/ml ($P<0,05$), all in comparison with control group mice, the neuropeptide Y in the first day was 46,64 ng/ml ($P<0,05$), while in the tenth day, it was 48,23 ng/ml ($P<0,05$).

Conclusions

This study demonstrates effects of low levels (1 gr per day) of cinnamon on the reduction of glucose, triglyceride, LDL cholesterol, and total cholesterol levels in subjects with type 2 diabetes [6]. The study design serves to replicate the results because there were similar effects at the three doses tested. It is not clear whether even less than 1 gr of cinnamon per day would also be beneficial. The mechanism of the effects of cinnamon on glucose and blood lipids must be determined. Symptoms of reduced insulin secretion include decreased stimulation of muscle glycogen synthesis as well as defects in glycogen synthase activity and glucose uptake. In addition, altered enzymatic activities, such as an increased phosphatase activity and/or seryl phosphorylation of the insulin receptor substrate by glycogen synthase kinase-3 (GSK-3), have also been shown to be involved in some cases of type 2 diabetes [13].

Dephosphorylation of the receptor β -subunit is associated with the deactivation of its kinase activity and, therefore, is associated with insulin signal downregulation. Maximal phosphorylation of the insulin receptor is associated with increased insulin sensitivity, which is associated with improved glucose and lipid levels. Extracts of cinnamon activated glycogen synthase, increased glucose uptake, and inhibited glycogen synthase kinase-3 β [9].

Extracts of cinnamon also activated insulin receptor kinase and inhibited dephosphorylation of the insulin receptor, leading to maximal phosphorylation of the insulin receptor. All of these effects would lead to increased insulin sensitivity. We have shown that extracts of cinnamon also function as potent antioxidants, which would lead to additional health benefits of this substance.

The active component in cinnamon responsible for its insulin-like activity is a water-soluble chemical compound called methylhydroxychalcone polymer (MHCP) which is highly effective, providing essentially the same biological activity as insulin itself. It is effective not only in increasing the uptake of glucose (blood sugar) by cells, but also of stimulating the synthesis of glycogen, a polymeric form of glucose that is stored primarily in the liver and muscle tissues for use at times of peak energy demand [22].

In type 2 diabetes, high blood sugar levels occur when glucose is prevented, to a significant degree, from entering cells of the body, notably liver, muscle, and fat cells. This is caused by a "short circuit" in the insulin signaling pathway, a cascade of highly specific chemical reactions that allow insulin to fulfill its role as the facilitator of glucose transport through the cell walls. Insulin is produced by the pancreas in response to elevated blood glucose levels; once it enters the blood, it signals the body's cells to take up the excess glucose until normal levels are restored [14].

When insulin molecules bind to the insulin receptors on cell walls, tiny molecular "gates" open up and allow glucose molecules to pass through. If this system is impaired, the gates don't respond adequately to the

insulin signal, thus preventing the glucose from entering the cell. This condition, which is a common consequence of obesity, is called insulin resistance, and it's both a harbinger and a symptom of diabetes. With insulin resistance, glucose levels in the blood remain high, a very dangerous condition in the long run. The pancreas tries to compensate by making more insulin, but this works only for so long. Eventually, the pancreas becomes overburdened and starts making less insulin. That's when things go from bad to worse. MHCP makes cells more responsive to insulin, it increases insulin sensitivity, the opposite of insulin resistance [15].

Researchers in Japan found recently that when an aqueous extract of cinnamon (containing MHCP) was given orally to laboratory rats, the insulin receptors on their skeletal muscle cells became more responsive. Enhanced insulin sensitivity means more glucose going into the cells, so the blood glucose levels fall, and biochemical order is restored [16].

In conclusion, cinnamon reduced serum glucose, triglyceride, total cholesterol, LDL, VLDL cholesterol levels in people with type 2 diabetes and increased HDL cholesterol levels. So, cinnamon may be beneficial for the remainder of the population to prevent and control elevated glucose and blood lipid levels and may benefit from the regular inclusion of cinnamon in their daily diet and finally the body weight will decrease [17].

Cinnamon increases the β cells of pancreas to secrete more insulin. Once the insulin secretion is high in the plasma, it will stimulate the adipose tissue to secrete more leptin [5], henceforward, leptin will penetrate the brain blood barrier to reach the arcuate nucleus where it decreases the secretion of neuropeptide Y and the later will less stimulates the secondary hypohalamic nuclei which leads to decrease the appetite sensation that dampens the food intake with lowers the obesity of diabetic patients [8,20].

When the obese diabetic patients get to loss some of their overweight state, it will alleviate upon the β cells of the pancreas to secrete insulin. Conclusively, cinnamon decreases the overweight state among diabetics which improves the pancreas to secrete ample insulin to the body cells.

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