

## The glycemic effect of thaumatin and its mixture with sucrose in type 2 diabetes patients

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### Abstract:

A randomized, prospective, single-blind, and parallel group study was conducted to investigate the effect of several sweeteners on blood glucose level (BGL). It included 29 healthy subjects and 22 with T2D. Three phases were included; a screening phase, a test phase, and a follow-up evaluation. Sweeteners included sucrose (S), thaumatin (T), and their mixture (M), which their amounts in 150 ml of water were: 24.05 g, 9.62 mg, 9.41 g and 5.85 mg, respectively. S group has promoted a significant elevating in BGL after 30 min, whether in healthy or T2D groups ( $p < 0.01$ ). On the other hand, there was no peak in T solution which has reduced BGL especially in those with T2D, ( $p < 0.01$ ). Whereas M solution has shown an intermediate state. Despite its low peak that it induced in BGL, it proved safety since its similarity to relevant BGL of T group at all intervals ( $p > 0.05$ ) whether for healthy or T2D groups. Ingestion of thaumatin by T2D ones worked for their benefit; it can indirectly decrease BGL. The studied mixture can be consumed safely by mild to moderate T2D who reducing both body weight and blood glucose for them would be enough for glycemic control.

**Keywords:** Binary mixture, Blood glucose, Sucrose, Thaumatin, Type 2 diabetes

### 1. Introduction

The prevalence of obesity and type 2 diabetes (T2D) is increasing globally and preventive strategies are urgently needed. It is estimated that in 2015, number of deaths due to diabetes reached 5 million while prevalence of diabetes worldwide was 8.8 % and it will continue rising to 10.4 % in 2040 [1,2]. Diabetes mellitus is a chronic disease caused by inherited or acquired deficiency in production of insulin by the pancreas or by ineffectiveness of the insulin produced [2,3]. The difficulty of managing hyperglycemia in diabetes is the most important factor in reducing the risks associated with diabetes and its complications, and is the third highest risk factor for premature mortality globally according to World Health Organization (WHO) [2,4].

Therefore, there is a great need for sugar substitutes, which can help reduce caloric intake, in order to maintaining blood glucose levels in individuals with diabetes [5]. Artificial sweeteners like saccharin, aspartame, and acesulfame K are widely used as low calorie sweeteners because they are sweeter than sucrose several hundred times on a weight basis. But on the other side, they have side effects such as undesirable weight gain, psychological problems, mental disorders, bladder cancer, heart failure, and brain tumors [3]. Moreover, some researchers have linked between artificial sweeteners consumption found in diet beverages and food products, and increasing the risk and/or development of some conditions including: metabolic syndrome, obesity, and T2D in genetically susceptible hosts. One of the hypotheses is by impacting the host physiology and metabolism and decreasing beneficial bacterial species [6,7].

Thaumatococcoside is a sweet tasting protein obtained from the fruit of the tropical plant *Thaumatococcus daniellii* (Benth.) that grows in West Africa [8]. It is 2000-3000 times sweeter than sugar on a weight basis [9]. Although a large number of studies have studied many bulk and intense sweeteners for their effects on several blood parameters in healthy and diabetic individuals, thaumatococcoside was not incorporated in anyone of them [5, 10-14].

In our previous study on Wistar rats [15], thaumatococcoside among other sweeteners were administered for 2 months. In the mentioned study, thaumatococcoside did not increase blood glucose level (BGL) significantly. The present study was designed to test our hypothesis that short-term and long-term BGL would still unaffected when thaumatococcoside would be consumed by humans; at least in healthy volunteers.

Since thaumatococcoside has no acceptable daily intake (ADI) limit, it can be assumed that humans can consume it as much as they want without any harmful or serious effects. It is authorized as a food additive in the European Union (EU) since 1984, and metabolized in body like other proteins [9,16]. Beside that thaumatococcoside alone is an intense sweetener and cannot be used in large amounts unlike sucrose, sucrose the most common bulk sweetener has other functions other than sweetening that thaumatococcoside cannot replace it for i.e. filling, viscosity-increasing [17]. Hence, this study has been designed to investigate the effect of the binary mixture of thaumatococcoside and sucrose as a useful potential combination in different dietary products for diet regimes needed by T2D individuals.

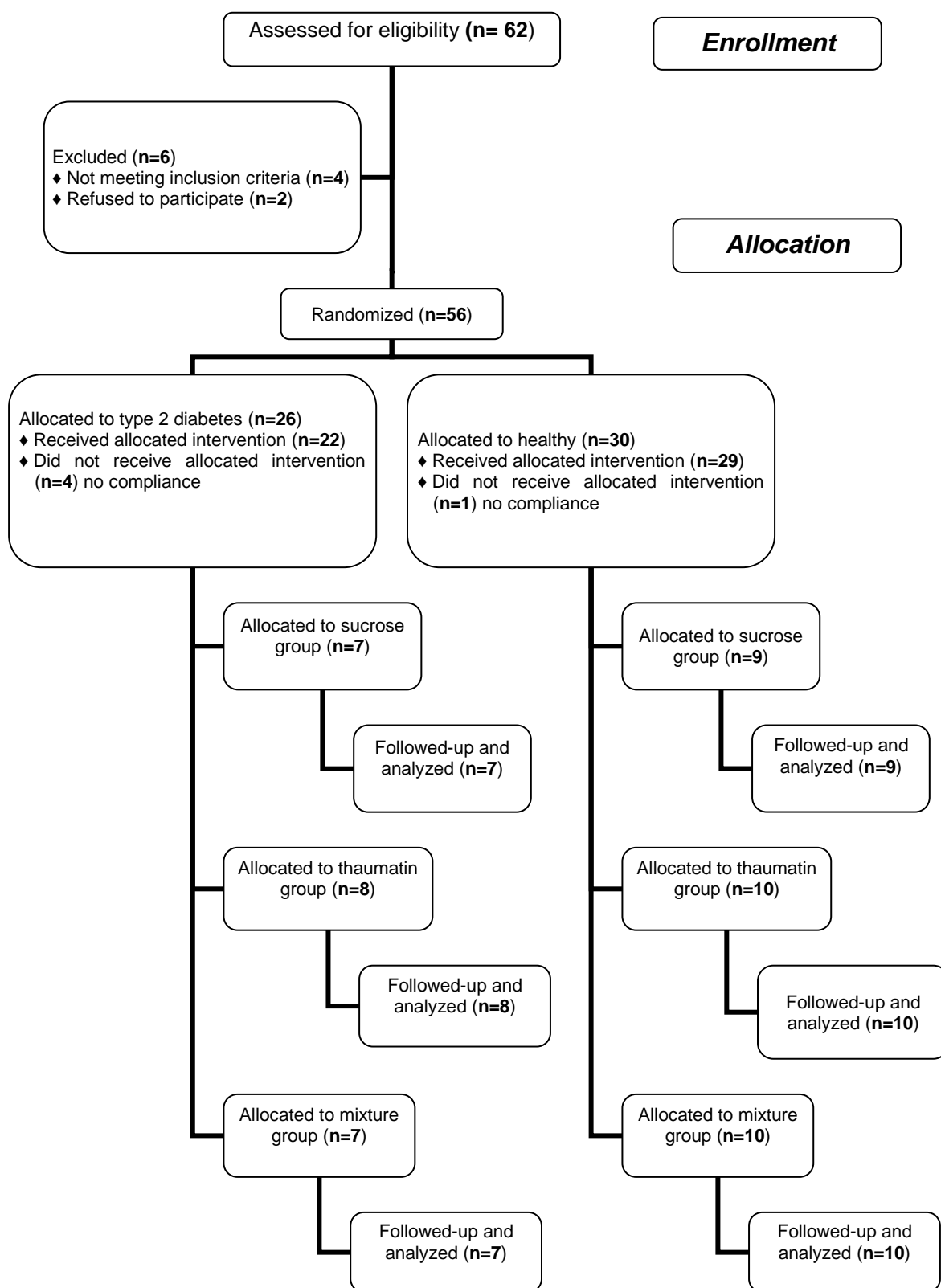
## **2. Materials and methods**

### **2.1 Materials**

Thaumatococcoside (T) was purchased from Naturex (England), Sucrose (S) was obtained from Scharlau Chemie S.A. (Spain). Sweeteners were freshly prepared in potable water.

### **2.2 Subjects**

Participants were enrolled from Aleppo city habitants (Aleppo University Residence). This study included 29 normal healthy and 22 T2D men and women volunteers between the ages of 30 and 70 years. Diagnosis of diabetes had been established by an evident medical history of diabetes at least for 3 months before the study had begun ( $8.5 \pm 1.8$  years). T2D subjects were on an oral antidiabetic agent (a biguanide i.e. *Metformin* and/or a 2nd generation sulfonylurea i.e. *Gliclazide*) where their dose was stable for at least 1 month before the study. None of the subjects had been treated with insulin. A total of 62 subjects have been evaluated for this trial, and several of them have been dropped out for different reasons, see Fig.1 for the complete phases of subjects' participating.



**Fig. 1** Flow diagram of the progress through the phases of the parallel randomized trial

Only 51 subjects have continued for the whole period of the study. Participants were excluded if they had undergone any major surgical procedure in the previous 3 months, if they were pregnant or lactating. All subjects

provided their signed informed consent for publication of their clinical information and were aware of the possibility of withdrawing from the study at any time they desired or would be necessary. The study was approved by the University of Aleppo Review Board (reference number 5573/2014). Baseline descriptive data on these participants are shown in Table 1.

**Table 1. Participant characteristics**

<b>Parameter</b>	<b>Healthy subjects (n=29)</b>	<b>Type 2 diabetes subjects (n=22)</b>
<b>Age (y)</b>	46.9 ± 2.0	53.2 ± 1.8
<b>Gender</b>	7 men, 22 women	10 men, 12 women
<b>Height (cm)</b>	158.4 ± 2.0	157.0 ± 2.1
<b>BMI (kg/m<sup>2</sup>)</b>	31.4 ± 1.5	36.8 ± 2.1
<b>Initial PG (mg/dl)</b>	69.6 ± 2.4	149.8 ± 13.2

Data are presented as mean ± S.E.M. BMI: Body mass index, PG: Plasma glucose.

### 2.3 Experimental design

This study was conducted between September and December 2015. It was an 8 week, randomized, prospective, single-blind, and parallel group study comparing the effects of 3 different equivalently sweetened solutions on BGL. Subjects were blinded as to the type of sweetener.

Three phases were included in the protocol of this human trial; a 2-3 week screening phase, a 4 week test phase, and a follow-up evaluation. Firstly, a baseline analysis session was done after completion of screening phase. Then subjects started drinking the solutions (day 0) for 4 subsequent weeks, and a 2 hour test of monitoring BGL was scheduled after 7 days of drinking commencement. Approximately 1 month after finishing the drinking phase, subjects returned for a follow-up evaluation which involved the last analysis session.

Participants of both healthy and T2D groups were randomly assigned (using "RANDBETWEEN" function in Microsoft® Excel® 2013 software) to 1 of 3 subgroups consumed sucrose (S), thaumatin (T), or their mixture (M), respectively and sweeteners were presented as aqueous solutions in 250 ml bottles.

Doses have been selected from a previous statistic study [18] that estimated the average daily intake of sucrose in 2010. Since bottles will be introduced once a day and it is not possible to consume this whole daily intake at once, half this amount has been applied in our study. Another reason for that dose reducing, is to alleviate potential side effects especially for those with T2D. Concentration of thaumatin in the solution was slightly higher than its usually level used in food industry (50 mg/kg) as stated by EU regulations [19].

While for M solution, sucrose quantity was calculated to the minimum amount approximately expected to promote insulin release in humans [20] in order to not demand that much insulin from beta cells of the pancreas, and in the same time benefit from this amount for its different functions other than sweetening. The rest of the sweetness has been complemented with thaumatin.

Every subject was provided every day in the morning with a 250 ml sequentially numbered transparent bottle containing 150 ml of fresh sweetened solution, according to the group he/she was assigned to. Subjects were asked to make up missed or forgotten bottles with the next meal, or as soon as they remembered. Logs of daily consumption of

bottles for every subject were recorded. Questions were asked regarding possible adverse reactions as well as intercurrent illnesses.

Subjects fasted overnight before coming for the initial or final blood drawing, and venous blood samples were collected in heparinized tubes for obtaining plasma which has been analyzed for glucose level by glucose oxidase/oxidase method using glucose kit (BioSystems S.A., Spain).

### **2.3.1 Preparations of sweeteners' solutions**

All sweeteners' amounts were calculated and solutions were prepared freshly every day with potable water where their sweetness was equivalent. Quantities of sweeteners in 150 ml of solution were as follows: 24.05 g of sucrose (it was applied much higher than this amount in several previous studies [10], 9.62 mg of thaumatin, and the mixture solution contained sucrose and thaumatin about 9.41 g and 5.85 mg (99.94% of S and 0.06% of T), respectively. After preparation of these solutions, they have been distributed in dry and clean 250 ml bottles.

### **2.3.2 Monitoring of blood glucose level (BGL)**

Subjects fasted overnight before the day of the blood drawing and asked not to take any drug before the test. At morning of day 8, fasting samples were taken before the bottles were presented (time 0), then subjects were asked to drink the solutions within 5 minutes after which postprandial capillary samples were taken at following intervals: 30, 60, 90, and 120 minutes as shown in Table 2. At all intervals, capillary blood samples were taken for determination of BGL using an Accu-Chek ® Active glucometer (Roche, Mannheim, Germany). At the end of test, subjects were allowed to eat and drink water, and take their medications if any.

### **2.4 Statistical analysis**

Data were expressed as mean  $\pm$  standard error of mean (S.E.M). Analysis of data was performed with IBM® SPSS® statistics software v.20 using a 2-way analysis of variance (ANOVA) with repeated measures (6 groups  $\times$  5 time points) or only 2-way ANOVA as appropriate, each followed by Tukey's test for multiple comparisons.

These tests were used to determine whether there were significant differences in blood glucose concentration or percentage of its change between sweeteners, and to study changes over time compared to baseline value. Differences were considered statistically significant at  $p < 0.05$ .

## **3. Results and discussion**

Compared to corresponding sucrose group (i.e. healthy T with healthy S), two hour test BGL values at all time points were not significantly different in both T and M groups of healthy cohort. The only exception was at the 30 min peak, when a slightly increase in BGL occurred for M ( $p < 0.05$ ) whereas it declined for T group ( $p < 0.001$ ). These results were as expected, since the mixture M contained sucrose but in much less amount than S solution it caused a slightly increase in BGL ( $p < 0.05$ ). Whereas for T solution which is a protein, did not present glucose so the body began to consume its own blood glucose and subsequently BGL declined ( $p < 0.001$ ). BGL for T and M groups in T2D cohort had maintained the same trends but at lower significance level.

**Table 2. BGL during the two hour test after 7 days of drinking sweeteners' solutions**

Group	Blood glucose (mg/dl)				
	0 min	30 min	60 min	90 min	120 min

	<b>S(9)<sup>3</sup></b>	98.7 ± 7.0	130.2 ± 8.0 <sup>††</sup>	100.2 ± 5.3	93.3 ± 3.0	90.4 ± 2.9
<b>Healthy</b>	<b>T(10)</b>	95.7 ± 3.6	92.6 ± 3.0 <sup>***</sup>	90.7 ± 2.2	92.0 ± 2.1	89.9 ± 2.5 <sup>†</sup>
	<b>M<sup>2</sup>(10)</b>	99.4 ± 5.2	109.5 ± 3.8 <sup>*</sup>	95.5 ± 3.6	93.6 ± 3.5	91.8 ± 2.4
	<b>S(7)</b>	179.0 ± 19.9	220.3 ± 19.0 <sup>†</sup>	197.3 ± 23.7 <sup>††</sup>	195.7 ± 24.9	180.6 ± 20.7
<b>T2D<sup>1</sup></b>	<b>T(8)</b>	164.3 ± 19.7	154.6 ± 17.5 <sup>*†</sup>	150.5 ± 18.4 <sup>††</sup>	144.1 ± 17.9 <sup>††</sup>	142.8 ± 17.0 <sup>††</sup>
	<b>M<sup>2</sup>(7)</b>	163.6 ± 14.9	178.4 ± 15.0 <sup>†</sup>	170.6 ± 17.9	155.0 ± 15.4	146.0 ± 15.3

Data are expressed as mean ± S.E.M. S: sucrose 24.05 g, T: thaumatin 9.62 mg, M: mixture of the previous two 9.41 g and 5.85 mg, respectively in 150 ml of solution. T2D: Type 2 diabetes. <sup>1</sup>BGL values in T2D groups were always significantly higher than corresponding ones in healthy groups;  $p < 0.001$  in both S and M groups, and  $p < 0.01$  in T groups. <sup>2</sup>At all time points, BGL values of M groups were not significantly different from corresponding T ones;  $p > 0.05$ . <sup>3</sup>number of subjects.

\* $p < 0.05$  vs. corresponding S group. \*\*\* $p < 0.001$  vs. corresponding S group.

<sup>†</sup> $p < 0.05$  vs. corresponding baseline value. <sup>††</sup> $p < 0.01$  vs. corresponding baseline value.

Over the 2 hour test, a significant elevating in BGL occurred after 30 min of S solution drinking (peak time), whether in healthy or T2D groups as shown in Table 2, due mainly to the glucose component arising after sucrose digestion. However, it had still high significantly in T2D group even after 60 min ( $p < 0.01$ ); because of the impaired tissue glucose uptake. So, the declining phase of BGL was slower in T2D than healthy individuals.

On the other hand for healthy group, T solution resulted in small decreasing in BGL insignificantly until 120 min when it was significant ( $p < 0.05$ ), whereas in those with T2D, decreasing was significant from 30 min and continued like that till the end of test ( $p < 0.01$ ). There was not a peak because thaumatin is a protein, neither a sugar converted to glucose to raise BGL, nor a direct energy source to maintain it. In addition, it is high probably that an insulin secretion had happened indirectly since amino acids can promote it [21]. Eventually as a result of all these events, the trend of T solution was decreasing in BGL values as demonstrated in Table 2.

Finally for M solution, a low peak at 30 min has occurred in both healthy and T2D cohorts. Then, BGL declined gradually to become lower than the baseline value; this was more clearly although not significant in T2D. According to that, the little sucrose content in M solution could be uptake easily (as glucose) by the low insulin secreted by remained effective beta cells in the pancreas and it did not overload it.

The blood sugar response to M solution, investigated in this human trial has shown an intermediate state between that of S and T solutions. It was similar to S response in causing a peak (lower than sucrose's peak and did not last to 60 min), and resembled T solution in that BGL values were always not significantly different from corresponding T ones ( $p > 0.05$ ) whether in healthy or T2D cohorts which was true for all time points.

Fig. 2 supported previous observations where percentage of blood glucose changes from 0 to 30 min have been calculated and plotted against time. There were no significant differences in change percentage between healthy and T2D cohorts for all sweeteners ( $p > 0.05$ ). In other words, sweeteners' response had maintained the same trends in the case of diabetic patients.

Although the differences were not significant, we have noticed clearly that percentage of BGL rising in T2D was lower than healthy cohort in S groups (-14%) and was less lower in M groups (-7%), this can be due to slow gastric emptying that may develop as a result of peripheral neuropathy in this condition [2].

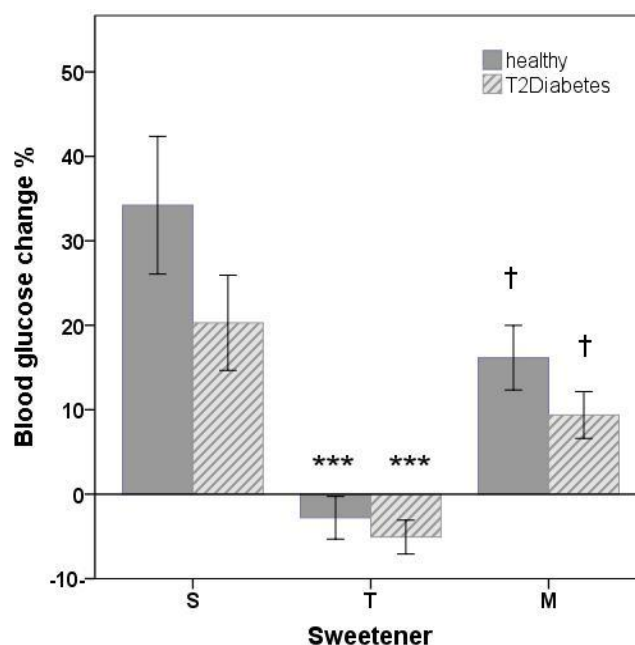


Fig.2 Percentage of blood glucose changes (0-30 min) after 7 days of drinking sweeteners' solutions

Data are expressed as mean  $\pm$  S.E.M. S: sucrose 24.05 g, T: thaumatin 9.62 mg, M: mixture of the previous two 9.41 g and 5.85 mg, respectively in 150 ml of solution. \*\*\*  $p < 0.001$  vs. corresponding S group. †  $p < 0.05$  vs. corresponding T group.

Furthermore, some antidiabetic drugs (i.e. metformin) reduces intestinal glucose absorption [22]. However, the case was different for T solution where BGL decreasing in percent was comparable between healthy and T2D cohorts (the difference was just 2.3%) as shown in Fig.2. Although slow gastric emptying is still active, there were no glucose molecules to elevate BGL only amino acids, that promote insulin release with a different pathway almost not altered with T2D disease [23].

The change in BGL during the first 30 minutes in T groups in the two cohorts was significantly lower ( $p < 0.001$ ) than corresponding S group (-37 and -25 % for healthy and T2D, respectively). While in M groups, BGL change was like that of S (lower without significance (-18 and -11 % for healthy and T2D, respectively), but higher than corresponding T group ( $p < 0.05$ ); 19 and 14%, respectively). These findings confirmed the middle state of M solution mentioned before, since it can be noticed that BGL change percentage for M solution is both less of that of S by -18% and more than correspondent T almost to the same extent by about +19% for healthy cohort and -11, +14% for T2D, respectively.

However, thaumatin has a delayed-onset taste profile and licorice-like aftertaste that is not favorable by some peoples [17]. The studied mixture has proved its safety in terms of BGL where it induced a small peak that declined immediately and did not last like sucrose. Moreover, by reducing amount of sucrose about 60% and completing the sweetness level with thaumatin, the calorie intake would fall intensely if that mixture will be used by consumers in

future. It will be a very important and useful replacement to diabetic people helping them reducing their body weight and blood glucose. It is expected that the mixture would have a more pleasant taste than thaumatin alone, since the thaumatin quantity will be less in the mixture solution which means that liquorice-like aftertaste will diminish. Additionally, sweetness will quickly be tasted due to sucrose and last for a longer time due to thaumatin.

As related to final BGL values obtained at the follow-up session, they were not different significantly from initial ones ( $p > 0.05$ ); (initial:  $69.6 \pm 2.4$ , final:  $91.2 \pm 3.4$  and  $149.8 \pm 13.2$ ,  $182.3 \pm 23.9$  mg/dl, for both healthy and T2D cohorts respectively), which demonstrate that there were no long-term adverse effect on the level of blood sugar for any of sweeteners investigated. This finding agreed with the fact that thaumatin is metabolized in body like other proteins [9].

## Conclusion

This study has demonstrated that ingestion of thaumatin for consecutive 4 weeks by humans at the dose level used (half the average of daily intake of sugar), had no significant effect either on short-term or long-term glycemic response for healthy individuals. Moreover, for T2D patients it worked for their benefit; where it indirectly decreased blood glucose significantly. Hence, thaumatin can serve as a safe natural sweetener for human in general and T2D patients in particular capable of imparting extreme sweetness to food while decreasing blood sugar rather than maintaining or rising it as well as helping in limiting calorie intake.

However as we mentioned above, because of the delayed-onset taste profile and licorice-like aftertaste of thaumatin the studied mixture containing thaumatin and sucrose will be an effecting and more pleasant sweetener replacement useful for some food products need a little amount of sucrose while keeping the healthy effects refer to thaumatin. Therefore, in future, this mixture can be used in food industry for low-energy food by obese people who want to lose their weight or subjects with mild to moderate T2D disease who a little limiting in their sugar intake would be enough for them.

More studies are required to investigate thaumatin effect on other physiological and biochemical aspects and their results would be more effective and confirmed if they will be conducted on a wider population and for longer time. We also suggest evaluating sensory and physiochemical properties of the mixture studied and other different mixtures in composition and quantity through other research works.

## 5. Conflicts of interest

The authors declare no conflicts of interest.

## 6. Acknowledgements

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