

# Effect of bee propolis as a hypoglycemic agent and diabetes control

## Summary

Propolis is a natural product derived from plant resins collected by honey bees. This natural product has been used in folk medicine for centuries. The main chemical classes present in propolis are phenols, flavonoids are well-known plant compounds with biological activity properties, including anti glyceemic effect. This study tested the impact of Colombian propolis as a regulating agent of glucose concerning metabolic activity on 45 healthy young people of two sexes aged between 17 and 24 years and five men as volunteers with a medical declaration of hyperglycemia was considered. The metabolic conditions for glucose were evaluated in pre-and postprandial conditions besides the blood group and the arterial pressure. The work was carried out in three different stages that included the characterization of total equivalent flavonoids present in an ethanolic fraction of propolis, in a second phase, the glycemia curves in a group of volunteers that were evaluated, and in the final phase, a regulatory effect of EEP on blood glucose. Equivalent total flavonoids in propolis samples were evaluated, and samples from Cucaita were used as an antihyperglycemic test. Fasting glucose levels in the studied population was of  $82,3 \pm 7,10$  mg dL<sup>-1</sup>, which conform to a normal distribution and which evolves to  $127,1 \pm 9,65$  mg dL<sup>-1</sup> after ingestion of glucose solution and subsequently at  $83,3 \pm 11,7$  and  $72,4 \pm 12,3$  mg / dL at 60 and 90 min. When comparing these values with the glucose and EPP treatments given in the test, the regulatory effect of the propolis components is observed. Normally, the absorption of glucose in the body occurs rapidly, and blood glucose levels rise within 30 to 60 min. of fluid intake. *Diabetes* is a metabolic disorder in which there is an inability to oxidize carbohydrates generated by disturbances in insulin function. Propolis may have acted indirectly by increasing  $\beta$  cell insulin secretion and improving insulin sensitivity.

**Keywords:** diabetes, glucose, metabolic regulation, propolis

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## Introduction

*Propolis* is a resin collected by bees from different plant sources and used to protect the hive. It is a resinous mixture of honeybees' materials from tree buds, sap flows, or other botanical sources. This complex substance with resinous, gummy, and balsamic characteristics results from compounds collected by bees from regional plants.<sup>1-3</sup> The complex composition of propolis varies according to the resinous plant sources; in addition to the geographic region where the bees collect them, many variabilities in components have been identified worldwide since they are of different color, smell, and taste. It was used as a sealant for unwanted spaces in the beehive. Its composition is based on resins, balsams, pollen, polyphenols, flavonoids, phenolic acids and esters, terpenoids, steroids, and other constituents, including amino acids, minerals, and vitamins.<sup>4</sup>

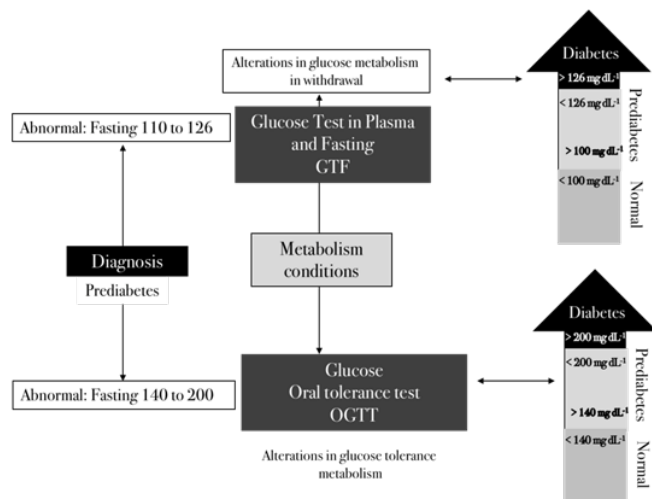
In ancient times, the Greeks, Romans, and Egyptians used and knew the healing properties of propolis and used it extensively to heal. Recently, the pharmaceutical industries have been extensively marketed as alternative medicine and health food in various parts of the world.<sup>5</sup> Nevertheless, the chemical composition of propolis, with provides a wide range of functional properties, including antioxidant, antibacterial, anti-inflammatory, and anticancer, is highly variable depending upon the season, the species of bee, and the flora around the hive. Furthermore, some studies have highlighted a correlation between chemical composition and specific biological activity of propolis.<sup>6-9</sup>

*Diabetes* is a disease that causes disorders in the body, using glucose, a sugar that fuels the body. People with type I and II diabetes require regular insulin injections or use an insulin pump. In type I diabetes,

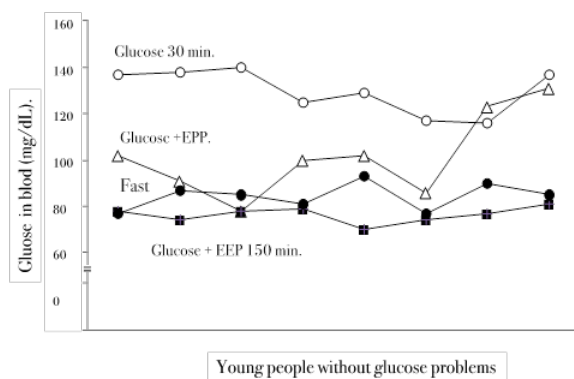
the body does not make insulin, which triggers cells throughout the body to take up glucose from the blood. In type II diabetes—the most common type—the body does not make or use insulin well, both types can lead to heart, nerve, kidney, and eye diseases over time.<sup>10-13</sup> Research has suggested that propolis may act as a regulating agent in controlling blood glucose and modulating glucose and blood lipid.<sup>14</sup> Propolis has shown an antihypertensive effect in rats.<sup>15</sup> In Diabetic rats, administration of bee propolis extracts led to decreased levels of blood glucose (FBG), fructosamine (FRU), malonaldehyde (MDA), nitric oxide (NO), nitric oxide synthetase (NOS), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) in serum of fasting rats.

In the Hispanic and African-American population, it is more frequent for women than men to have diseases after 35.<sup>16</sup> Different investigations in animals have suggested using propolis ethanol solutions as a normalizing agent of basal metabolism, leaving the possibility of investigating its effect on lipid regulation and carbohydrates. One of the problems that affect the human population resides in the disorder of the diet and the deficiencies in its metabolic regulation. The glycemic index (GI) has been suggested as a representative measure of the glycemia produced after food intake and its subsequent relationship to blood glucose levels. The restricted secretion of insulin causes the elevation of blood glucose associated with diabetes in the pancreas. All forms of diabetes are characterized by chronic hyperglycemia and the development of diabetes-specific microvascular pathology in the retina, renal glomerulus, and peripheral nerve. As a consequence of its microvascular pathology, diabetes is a leading cause of blindness, end-stage renal disease, and

various debilitating neuropathies. When islet  $\beta$ -cell function is impaired, insulin secretion is inadequate, leading to overproduction of glucose by the liver and under-utilization of glucose in peripheral tissue Figure 1.<sup>17</sup> The study's general objective was to identify the role of propolis and its effect as a hypoglycemic agent and diabetes control among selected and volunteers young people at the Universidad del Tolima, Colombia.



**Figure 1** Relationship of glucose tolerance tests under preconditions and postprandial conditions.<sup>10</sup>



**Figure 2** Blood glucose profile in young people free from glucose metabolic disorders.

## Materials and methods

In this work, the effect of an ethanolic extract of propolis (EEP), collected in the lower montane dry forest area (*bs-MB*) in the department of Boyacá (Colombia) and its effect as a regulator of the levels of glucose in the blood, in healthy young people of two sexes aged between 17 and 24 years. The metabolic conditions for glucose were evaluated in pre- and postprandial conditions besides the blood group and the arterial pressure (Table 1). The work was carried out in three different stages that included the characterization of total equivalent flavonoids present in an ethanolic fraction of propolis, in a second phase, the glycemia curves in a group of volunteers that were evaluated, and in the final phase, a regulatory effect of EEP on blood glucose. The participation of five men as volunteers with a medical declaration of hyperglycemia was considered. After the first fasting blood draw, the person is asked to drink a liquid, contains glucose. The blood test is done two hours after drinking the solution, usually

done with a glucometer and test strips. Informed consent protocols were applied to the test participants. The study was conducted in Universidad del Tolima, and the site where it was developed was appropriate for the researcher in terms of time and distance.

## Propolis extracts

In work, an ethanolic extract of propolis (EEP) collected in the biogeographic zone of the lower montane dry forest (*bs-MB*), of Cucaita (05°32'45" N and 73°27'26" E; 2650 ovsl; 14.2 °C; 760 mm/year), Boyacá (Colombia). Crude samples of propolis were extracted with 96% ethanol.<sup>18</sup> The samples were conditioned in sterile and hermetic amber glass containers, kept individually in a refrigerator at 5 °C until the moment of use.

## Glycemic curves

The hypoglycemic effect of propolis was evaluated in healthy young people of two sexes aged between 17 to 24 years. A previous pilot study was carried out determining blood glucose levels in 45 young volunteers who remained in fasting conditions for 11 h. before the test. With an interval of 15 days, the glycemia curves were made supplying 300 mL of glucose solution (0.25 g mL<sup>-1</sup>) and record with intervals of 30 minutes for 2,5 h. In another subsequent test and with the same conditions, 300 mL of solution (0.25 g mL<sup>-1</sup> of glucose in 300 mL of water and a fraction of the EPP, identified as the highest carrier of total flavonoids) supplied. Blood glucose profiles with intervals of 30 min for 2,5 hours. The amount of propolis as an active base supplied in each dose contained 6.1 mg of (flavones + flavonols) and 119 mg of total flavanones.

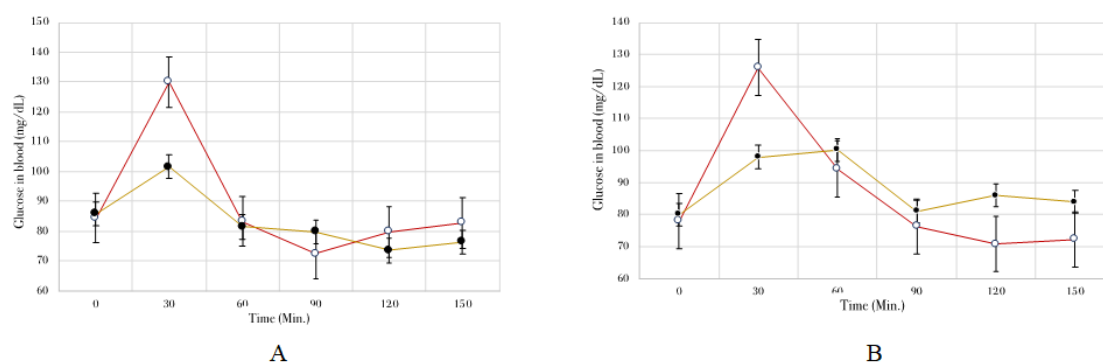
## Results

**Equivalent total flavonoids:** The content of flavones and flavonols (such as quercetin) in the analyzed samples is of the order of 0,52±0,03% (Santa Rosa de Viterbo) and 3,26±0,26% (Cucaita); 12,3±0,25% Total flavonoids (Table 2).

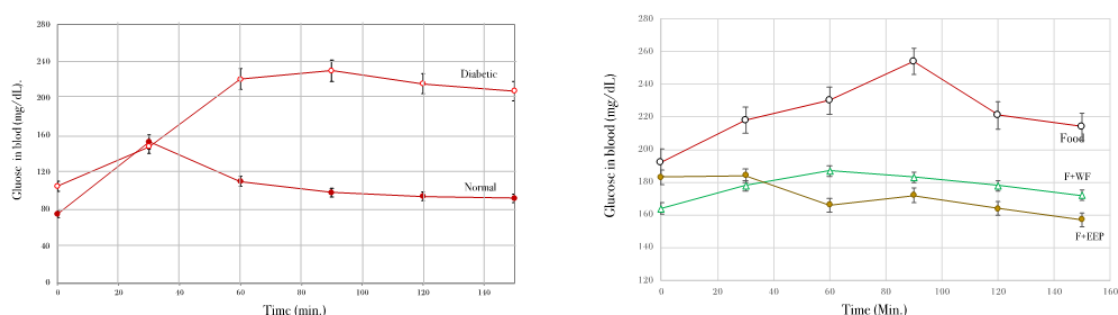
## Glucose regulation

Fasting glucose levels in the studied population is of the order of 82,3±7,10 mg dL<sup>-1</sup>, which conform to a normal distribution (Pv 0.85) and which evolves to 127,1±9,65 mg dL<sup>-1</sup> after ingestion of glucose solution and subsequently at 83,3±11,7 and 72,4±12,3 mg/dL at 60 and 90 min. When comparing these values with the glucose and EPP treatments given to in the test, the regulatory effect of the propolis components is observed; the regulation ranges from 127 ± 9,65 to 99,8±21,9 mg dL<sup>-1</sup> of glucose, that is, a reduction of up to 21% for the maximum observed in men, while in women the reduction at 30 min. occurs from 121,5±7,90 to 117,3±0,50 mg dL<sup>-1</sup> (Table 3). The difference between the mean values of 27,3 mg dL<sup>-1</sup> (Figure 2), with a significance level of 5% (Pv 0,001). The trend in time after the consumption of PPE is that of regulation; when glucose levels decrease, then the components of EEP contribute to the maintenance of basal levels.

In diabetic adults, averages of 115 to 205 mg dL<sup>-1</sup> were observed for pre and postprandial conditions. In the phases after evaluating the glycemic curves for each of the observation groups, administration of a standard dose of solution (EEP) demonstrated a substantial effect on blood glucose levels. This condition suggests that the solutions (EEP) can contribute to the control and modulation of the metabolic rate of blood glucose in humans, with possible modulations on the lipid profiles of patients with diabetes problems (Figure 4).



**Figure 3** Typical profile for blood glucose levels in young male (A) and female (B) populations. (-Glucose) and (-Glucose+EEP).



**Figure 4** Typical case blood glucose profile in Normal and diabetic patient (A). Food-Normal curve. Fasting conditions without food F+WF and food with a dose of propolis F+EEP. (B)

**Table 1** Characteristics of the population women and men considered in the study

Age	Women				Men			
	Post	Pre	Weight kg	Height cm	Post	Pre	Weight kg	Height cm
17	113	84	54	159	82,7	88,3	60,0	170,3
18	87	83	43	159	84,0	86,5	55,5	175,0
19	97	93	53	170	83,5	86,5	55,5	169,5
20	-	-	-	-	84,0	86,0	54,0	168,5
21	114	86	44	160	87,0	88,0	79,0	177,0
24	93	77	40	149	-	-	-	-
Total	102,8	84,5	48	159,5	83,8	87,1	58,9	171,4

**Table 2** Typical composition of flavonoids insamples of Colombian propolis from the high Andean zone of Boyacá

Sample Origin	AICI3 Flavones and flavanols (% Quercetin)	2,4D Flavanones (% Naringenin)	Total Flavonoids (%)
Combita	0,63 ± 0,04	11,7 ± 0,20	12,3 ± 0,25
Ceranza	0,79 ± 0,12	6,70 ± 0,50	7,50 ± 0,48
Santa Rosa	0,52 ± 0,03	4,83 ± 0,50	5,30 ± 0,51
Cucaita	3,26 ± 0,26	19,0 ± 5,40	22,3 ± 5,41
Belén	0,90 ± 0,30	5,30 ± 0,20	6,20 ± 0,38

**Table 3** Mean blood glucose values observed in male and female volunteers before and after fasting glucose quantification and after glucose tolerance test with and without EEP

Time (Min)	Men (mg/dL)		Woman (mg/dL)	
	Glucose	Glucose+EEP	Glucose	Glucose+EEP
0	84,4 ± 5,80	85,8 ± 6,60	78,0 ± 8,50	80,0±2.20
30	130 ± 9,70	101,6 ±17,9	126 ±7,90	117.3±0.50
60	83,3 ± 11,7	81,5 ±18,0	94,3 ±19,7	100.3±9.70
90	72,4 ± 12,3	79,8 ± 6,00	76,3 ±11,0	75.0±3.70
120	79,8 ± 4,80	73,5 ± 6,10	70,8 ± 6,24	58.7±0.90
150	82,8 ± 5,00	76,4 ± 3,50	72,3 ± 5,30	64.7±2.10

## Discussion

Diabetes is considered a metabolic disorder that occurs as an inability to oxidize carbohydrates generated by alterations in insulin production. This pathology is associated with elevated plasma glucose levels and episodic ketoacidosis, including excessive thirst, glycosuria, polyuria, lipemia, and hunger. If left untreated, the disease leads to fatal ketoacidosis. The clinical criteria associated with diabetes affectations consider fasting plasma glucose levels higher than 126 mg dL<sup>-1</sup> (7 mmol L<sup>-1</sup>) as a suspect; normal levels are lower than 100 mg dL<sup>-1</sup> (5.6 mmol L<sup>-1</sup>) of glucose. The (IG) has been used in clinical diagnosis of insufficiency in the metabolism of the hepatic system and the regulatory activity of insulin generated in some cases by disconnection of cells in later phases of infections-cytotropic virus infections (choriomeningitis, hepatitis, or parotitis, among others) or by the immunopathological destruction of cells within pictures of lymphocytic insulinitis. In general, diabetes is more frequent in women than in men. Affected people tend to be older than 35 years of age. The diagnostic test is as shown in Figure 1, in the fasting situation and after the fast.

Under normal conditions, glucose is absorbed and metabolized in the body, resulting in a rapid increase in glucose levels 30 to 60 minutes after fluid intake. The elevation of blood glucose associated with diabetes is caused by the restricted secretion of insulin in the pancreas. Diabetes is a metabolic disorder in which there is an inability to oxidize carbohydrates generated by disturbances in insulin function. This pathology is associated with elevated plasma glucose levels and episodic ketoacidosis, which also includes excessive thirst, glycosuria, polyuria, lipemia, and hunger. If left untreated, the disease leads to fatal ketoacidosis. How do you know the main function of insulin is to counteract the concerted action of hyperglycemia and the generation of hormones to maintain low blood glucose levels, the control of which is necessary to prevent loss of life. Also, considerations about diabetic retinopathy (DR) is in type I and II *Diabetes mellitus*, a microvascular complication occurs that is capable of causing visual impairment, and blindness can be considered.<sup>19</sup>

The metabolic alterations that generate diabetes can also be caused during the reduced formation of proinsulin, in the erroneous synthesis of insulin, during the alteration of the conversion of proinsulin to insulin, or by inactivation of insulin or simply by intracellular blockage before secretion. Defective uncoupling of glucose receptors can occur in cells, as occurs in diabetes mellitus in adults. Alterations in insulin transport are also deficient contributions to insulin requirements or degradation at the level of liver, kidney, and adipose tissue.<sup>19-22</sup> The glucose-insulin stimulates lipogenesis, reduces lipolysis, and increases the transport of amino acids in cells, modulates transcription, growth. Insulin secretion from  $\beta$  cells is regulated primarily by plasma glucose levels.<sup>8</sup>

The increase in glucose uptake by pancreatic  $\beta$  cells leads to a disorder in metabolism. This condition generates an increase in the ATP/ADP ratio and inhibits ATP in the potassium channel. This work systematically addresses the application of propolis extracts as a regulator of blood glucose in regular hypoglycemic and diabetic patients. The production of reactive oxygen species (EROS) induces hyperglycemia-activated electron-transport chain in mitochondria, linking oxidative stress and pancreatic  $\beta$  cells dysfunctions. Propolis may have acted indirectly by increasing  $\beta$  cell insulin secretion and improving insulin sensitivity. Studies have shown that propolis improves glycemic indices and increases plasma insulin levels and other factors related to glycemic control.

In diabetes, the antioxidant defense system is altered, and the body's inability to scavenging free radicals may play a significant role in tissue damage. Previous research has shown that supplementing with propolis can improve glycemic indexes in people with diabetes. The glycemic controls referenced by the American Diabetes Association<sup>23</sup> in fasting plasma glucose are (80-130 mg dL<sup>-1</sup>), glycosylated hemoglobin (<7.0%), and casual plasma glycemia (<180 mg dL<sup>-1</sup>). Hyperglycemia increases the risk of pathogenicity and mortality when there are complications of diabetes. Currently, it has known that glycosylated hemoglobin correlates with hyperglycemia in the long term, and blood glucose is an important marker that helps predict possible disease; improving these factors can be very effective in their additional control with support in a healthy and balanced diet.

## Conclusion

Propolis is one of the few therapeutic efficacy natural products that has remained popular since ancient times. The secondary metabolites present in propolis are active molecules with enjoyable biological activity, including as a modulator of blood pressure and an anti glycemic agent, as evidenced in this work. Propolis is beneficial in inflammatory conditions, oxidative stress, and glycemic control in people with chronic diseases due to its various antioxidant and polyphenolic compounds. The advantage in the consumption of propolis resides in the supply of various metabolites with a differentiated synergistic action that makes it possible that there are no significant side effects, its availability has a significant role in the different types of cells and the glycemic control in the pancreatic cells as well as in the treatment of some of the chronic diseases. The results of this study about the composition and properties of propolis ethanolic extract confirm that its content of bioactive compounds can vary significantly depending on the region in which propolis is collected. Besides, the study shows the potential use of propolis as an adjunct in blood glucose control and regulatory capacity. It suggests the control of glycemic disorders and types of diabetes. Because of the increased prevalence of chronic diseases like diabetes, therapeutic strategies for preventing and treating these diseases may help reduce the societal burden of these problems.

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## Conflicts of Interest

None.

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