Review Article

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Apitherapy for diabetes mellitus: mechanisms and clinical implications

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Abstract

Introduction: Diabetes mellitus is a complex disease in terms of its causes and pathophysiological processes, it produces a significant impact on health and leads to complications that are difficult to manage.
Content: This review summarizes and analyzes recent advances in the understanding of the mechanisms of diabetes mellitus and how apitherapy affects them. Also present the available clinical evidence on its application.
Summary: Apitherapy (complementary-integral use of beehive products) is a potentially useful therapeutic system with a significant level of evidence. This review shows and analyzes the preclinical and clinical evidence on the use of apitherapy in diabetes mellitus.
Outlook: Apitherapy shows significant effects on epigenetics, chronic inflammation, oxidative stress, metabolic control, dysbiosis, premature cell death and tissue remodeling. Clinical evidence shows an impact on these mechanisms. Apitherapy is a very useful complementary medicine in the treatment of diabetes mellitus.

Keywords: diabetes mellitus; apitherapy; bee venoms; propolis; royal jelly

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Introduction

Diabetes mellitus (DM) is a complex and chronic diseases group that produces relevant and severe complications. More than 10 % of the population will suffer from DM [1] and more than 13 % of the population is at risk of developing [2]. DM is a disease that produces direct and indirect costs on patients, their families and society [3].

There is no curative treatment for DM, its control requires the use of different drugs and adherence to their use is not optimal [4]. Complementary medicine (CAM) is considered by many people to be a suitable and additional treatment option and there is growing scientific evidence demonstrating its effectiveness in the management of many chronic diseases [5, 6]. The use of CAM for DM and its complications is an active field of research and the available scientific evidence on its efficacy is increasing [7].

Apitherapy is a therapeutic system based on the use of hive products (bee venom–BV, propolis, honey, bee pollen-BP, royal jelly-RJ, bee bread-BB) to treat different diseases, including DM. Interest in research and use of new therapeutic alternatives has increased and for this reason apitherapy is an attractive option. Apitherapy has proven to be effective and there are several potential mechanisms of action in various diseases [8–10]. In this review, we analyze the existing scientific evidence on beehive products usage for treating DM, its mechanisms of action and clinical implications.

Pathophysiological aspects

DM is a group of metabolic disorders marked by chronic hyperglycemia due to insulin resistance, production failure, increased glucose production, or a combination of these factors, leading to nerve, kidney, eye, heart, and artery damage [11]. DM is classified into type 1 (autoimmune beta cell loss), type 2 (non-autoimmune beta cell loss), DM from other causes (monogenic, exocrine pancreatic disease, or drug-induced), and gestational DM [12]. Multifactorial causes include genetic, environmental, and socio-cultural factors, such as HLA alterations, pro-inflammatory environment, beta cell changes, epigenetics, viral infections, and diet [13].

Despite different origins, DM shares similar pathophysiological mechanisms, including insulin resistance, chronic inflammation, mitochondrial dysfunction, oxidative stress, dysbiosis, cell death, and tissue remodeling [14].

Epigenetics

Epigenetic modifications explain both lifelong acquired risks and the transmission of metabolic risk across generations. Fetal exposure to a diabetogenic environment (poor diet, stress, malnutrition) increases the risk of DM through epigenetic effects on beta cells, liver, muscle, and hypothalamic networks [15]. DNA methylation, histone modification, and non-coding RNA are key mechanisms in DM. Animal studies show that reduced food availability during pregnancy raises obesity and DM risk in two generations, likely as an adaptive response [16]. Fathers with low-protein, high-fat diets increase their children's risk of obesity and T2DM via small non-coding RNA [17]. Fat-rich, IR-inducing environments trigger epigenetic changes [18]. Methylation of metabolic genes in T2DM adolescents links epigenetic changes to metabolic dysfunction, IR, OE, and cell death [19]. Gestational DM accelerates aging in affected women through epigenetic alterations [20], which also contribute to DM complications [21].

Insulin resistance

IR is an inappropriate response to this hormone in cells that depend on its signal. IR appears as a consequence of alterations at the mitochondrial level and involves different cell lines [22]. IR is related to OE, dyslipidemia, and chronic inflammation [23], common factors involved in the development of DM. IR is a primary mechanism in the development of DM and its complications.

Chronic inflammation

Activated nuclear factor kappa B (NF-κB) family of transcription factors trigger critical cellular processes, including cell survival, but are also involved in chronic inflammation [24]. Its alteration is associated with various diseases where inflammation is beyond its homeostatic range, such as DM [25]. They are inducible and respond to diverse stimuli, like OE [26]. The development of DM is related to chronic inflammation, and obesity is one of its main triggering factors [27].

IR results in high levels of proinflammatory cytokines, activating the mitogen-activated protein kinase (MAPK) c-Jun N-terminal kinase (JNK), resulting in the activation of NF-κB, AP-1 transcriptional complex and inactivation of IRS1/2 [28, 29], or Janus Kinase (JAK)-Signal and Activator of Transcription (STAT) pathway, which upregulates inflammatory genes [30].

Mitochondrial dysfunction

MD is a key process in the development of chronic inflammation, OE, IR, and cell death. MD leads to disruption of the ability of natural processes in skeletal muscle [31]. MD produces a chronic inflammation, OE and cell death [32].

Genes and environmental factors modify mitochondrial function. Genes and environmental factors modify mitochondrial function. Evidence shows diet significantly impacts mitochondrial functioning [33]. Inadequate diets cause mitochondrial stress, leading to mitochondrial loss or reduced capacity, contributing to metabolic pathophysiological processes [34]. MD also partly explains the development of complications of DM [35].

Oxidative stress

OE causes premature aging and is linked to degenerative diseases, leading to hyperglycemia and pancreatic beta cell death by disrupting function [36]. Excess free radicals impair beta cell formation, reduce GLUT receptor expression, and alter protein expression via NF-kB [37]. OE is associated with DM complications, including nephropathy, neuropathy, dementia, and cardiovascular disease [38]. It worsens glycemic control and DM complications, contributing to DM progression through MD, cell death, and systemic inflammation [39].

Dysbiosis

Dysbiosis, an imbalance in microbial communities, is linked to adverse host reactions [40] and may accelerate type 1 and 2 DM development [41]. Diet, especially high fat intake and low fiber consumption, is a key factor in dysbiosis, increasing inflammatory markers. This imbalance affects microbiota metabolites, some tied to T2DM development [42], and alters intestinal epithelium integrity and metabolism [43].

Cell death and tissue remodeling

Insulin secretion is regulated by various factors affecting pancreatic beta cells. Pathophysiological processes, along with genetic susceptibilities, lead to beta cell death [44]. Beta

cell stress triggers increased NF-κB activity, establishing a pro-inflammatory microenvironment [45]. This is evidenced by pancreatic fibrosis and amyloidosis in DM patients [46]. NF-κB overactivation may promote DM by causing beta cell dysfunction and death [47].

Beehive products mechanism

The products of the hive favorably modify several of the pathophysiological mechanisms of DM. In this section, the review and analysis of the scientific evidence on its use will be carried out.

Epigenetic modifications

It is a growing field of research, several of the products of the hive show to have effects on epigenetic aspects. BV has been shown to have effects on the modification of epigenetic alterations present in cancer cell cultures [48]. Propolis also shows activities on epigenetic mechanisms in cancer research [49]. RJ also has properties in the modification of epigenetic processes [50]. Specific studies are needed on the effects of the use of bee products.

Insulin resistance

Some hive products show direct favorable results in terms of IR modification. Honey via IRS-serine phosphorylation, inhibiting insulin receptor substrate-serine phosphorylation could improve IR [51], honey consumption could improve IR. Some results suggest that propolis is useful in the control of IR, even without fully understanding the mechanisms that explain its effect. It is possible that the effects of propolis result from control of inflammation and related transcription factors [52]. RJ consumption shows reduction of IR, modification of receptors in hepatocytes could explain the effects of RJ on IR [53].

Chronic inflammation

Beehive products have been found to produce significant effects in the control of DM, honey being one of those products. The diversity in the composition of each honey provides it with different therapeutic characteristics, although most have physicochemical similarities resulting in immunomodulatory, anti-oxidant and anti-inflammatory effects [54]. These effects are in part explained by the flavonoids and phenolic acids contained in it, animal models shows down-regulation of proinflammatory cytokines such (IL-1β, IL-6 and TNF-α) together with the production of anti-inflammatory cytokines (IL-10, TGF-β), preventing the over-activation of NF-kB, MAPKs and JAK-STAT pathways [54].

Propolis composition varies depending on the region and type of source used for its preparation by bees and its anti-inflammatory properties *in vivo*, *in vitro* and in clinical trials have been studied [55]. An abundant polyphenol in propolis is CAPE. It has been shown (*in vitro* and mouse models) to reduce IL-6, TNF-α, MCP-1, NF-kB, COX-2 and activate insulin receptor and AKT. Brazilian red propolis also show an anti-inflammatory effect by decreasing the levels of IL-1β, IL-4, IL-6, TNF-α and IFN-γ and decrease in the activation of MAPK ERK1/2 and NF-kB [56]. Propolis ethanol extract, RJ and BP inhibits NF-kB, proinflammatory cytokines and caspases, also increases IL-10 and PPAR-α [57]. In a randomized double-blind clinical trial, it was found that in patients with T2DM, the administration of propolis significantly decreased the serum levels of TNF-α [58]. In a diabetic mouse model induced with streptozotocin, BP polysaccharides were administered, a restoration of retinal function and structure was evidenced, as well as a dose-dependent decrease in serum IL-6 and TNF-α [59]. Administration of RJ shows NF-kb and chronic inflammation modulatory properties [60].

Mitochondrial dysfunction

Some effects of hive products have been described on MD. BV decreases cell mortality of hepatocytes by regulating mitochondrial activity [61]. In hepatocyte cell cultures, RJ (particularly because of its major royal jelly protein) reduces intracellular fat accumulation, restores superoxide dismutase levels, and restores mitochondrial membrane potential [62]. Effects of RJ on mitochondrial function in skeletal muscle have also been described, producing an increase in mitochondrial biogenesis and optimizing its functioning [63]. Propolis and BB by increasing the availability of antioxidants and induction of key enzymes in the OE control process favor mitochondrial function and prevent premature cell death [64].

Oxidative stress

OE is a relevant pathophysiological process in DM and several bee products are useful for its control. Propolis shows significant effects explained by the OE control, a systematic review of experimental models has shown that the effects of the use of propolis positively affects different MD indicators and these effects are partly due to the OE control [65]. Propolis reduces OE

by modifying at least two mechanisms: Nrf2 (Nuclear factor erythroid 2-related factor 2) and nuclear factor kappa beta (NF-KB), transcription factors activated by OE [66]. BV shows promising results in terms of the modification of effects produced in the organism as part of the response to EO [67].

The different components of the RJ show control the OE in DM models. RJ consumption could decrease hepatotoxicity by modulating the expression of Bcl-2, GSK3 and NF-κB [57] and shows significant effects in controlling damage caused by OE [68]. The complexities of these molecular pathways suggest that they are likely to impact not only on short-term outcomes such as glycemic control, but possibly that these effects will be more important on future outcomes such as damage to the central nervous system, kidneys, arteries, and heart. BP extracts show favorable effects on fat accumulation in hepatocytes. These effects derive from the protective action on the OE [69]. The combination of beehive products in the management of OE is probably useful, the sum of effects seems to be key in its therapeutic effect.

Dysbiosis

Propolis shows properties on the regulation of the composition of the intestinal flora [70]. Evidence derived from animal models has shown that propolis improves parameters of the lipid profile, glycemia and body weight in models of DM [71]. One of the mechanisms through which these effects could occur is through the modulation of the gut microbiota. It has been described how the modification of the gut microbiota after the use of propolis extract leads to changes in the composition of adipose tissue and, these changes are related to effects on lipid and carbohydrate metabolism [72]. Propolis shows significant effects on muscle mass and sarcopenic obesity through modulation of muscle inflammation and regulation of gut microbiota [73]. Similar beehive products like BB may have similar effects.

Honey has also shown interesting properties on the regulation of intestinal bacterial flora, decreases bacterial populations that induce metabolic alterations and intestinal permeability, and favors a healthy gut microbiota [74]. Honey consumption decreases disease-causing bacterial populations and increases normal bacterial flora, with increased species of lactobacilli and bifidobacteria through local regulation of pro-inflammatory cytokine production, local antioxidant effects, and regulated selection of bacterial populations [75].

Cell death and tissue remodeling

There are several effects of the beehive products on this pathophysiological process. In an experimental model of liver fibrosis, honey administration upregulated Nrf2, inhibited NF-kB, and prevented excess deposition of collagen and α-SMA [76]. *In vitro* assay in RAW264.7 LPS-stimulated macrophages treated with Manuka honey, a recovery of mitochondrial function and cell viability and proliferation was demonstrated, in addition to a reduction in apoptosis given a downregulation in the expression of effector caspase three and ERK1/2 [77].

Administration of propolis in a diabetic mouse model induced with streptozotocin-nicotinamide demonstrated a recovery of normal pancreatic histological patterns [78]. Administration of Malaysian propolis with Metformin demonstrated favorable changes in pancreatic histology and morphometry as well as a decrease in proinflammatory markers (IL-1β, TNF-A and NF-kB) [79]. Malaysian propolis has been shown to produce an increase in the proliferative activity of the pancreas [80].

In a diabetic-streptozotocin-nicotinamide mouse model, BV was shown to have protective effects against biochemical and histopathological degenerative changes in the diabetic pancreas, liver and kidney [81].

In a streptozotocin-induced diabetic mouse model, intragastric administration of BP extract, was shown to alleviate intrahepatic lesions seen in T2DM mice by downregulating IL-6, TNF-α, and TGF-β in the pancreas [82]. BP stimulates insulin production and proliferation, demonstrated by increased Ins2, Pdx1, and Maf2 and increased Ki-67 [83].

In a mouse model of liver damage, it was shown that the administration of RJ has a protective effect through anti-inflammatory and anti-apoptotic means, by decreasing TNF-α and caspase 3 [84]. Administration of RJ results in decrease in TNF-α, caspase 3, increased Bcl2 expression, along with an improvement of histological patterns in renal tissue [85].

Table 1 shows a summary of mechanisms of beehive products in DM.

Clinical implications of the scientific evidence

DM is a complex disease that requires a comprehensive approach for its effective control. Patients with DM with or without complications prefer the use of CAM as part of their treatment [86]. CAM use makes it necessary for both physicians in regular health care and health professionals who use CAM to have shared knowledge about the best possible treatments and patient preferences. The use of apitherapy as a complementary treatment in DM requires health professionals duly trained in it. Although apitherapy has been used as a treatment for more than 10 centuries for different

Table 1: Mechanisms of apitherapy in DM.

Pathophysiological mechanism	Beehive product	Effect
Epigenetics, chronic inflammation	Bee venom Propolis Honey	Modification of acetylation and methylation NF-kB modification mitochondrial effect
Oxidative stress	Propolis Bee venom	OE control Methylation Modification Mitochondrial effect
Metabolic alteration	Honey Propolis Bee venom	OE control Induction of antioxidant enzymes IR modulation Regulation of cholesterol metabolism
Dysbiosis	Bee pollen	OE control Microbiota modulation Regulation of chronic inflammation
Mitochondrial dysfunction	Bee bread Bee venom Royal jelly Propolis	Mitochondrial biogenesis Regulation of mitochondrial membrane potential
Premature cell death and tissue remodeling	Royal jelly Bee venom Propolis Honey Bee bread	OE control Survival signal Induction stem cells

IR, insulin resistance; NF-kB, nuclear factor kappa beta; OE, oxidative stress.

diseases, it has not been adequately regulated and the knowledge of the people who practice it is not standardized. It is necessary that this knowledge is appropriated and applied by health professionals according to the health regulations of each country. Apitherapy should be understood as a specialty within CAM that must be applied by health professionals.

Apitherapy shows modulatory effects over DM. It is an old therapeutic tool, but it has a recent in contemporary medicine. The main scientific support of his practice is based on preclinical studies and high-quality clinical trials are required to show the therapeutic effects in people with DM. In the opinion of the authors, considering the safety profile of bee products, there is no evidence to indicate that their use should be avoided in the context of integrative care.

One of the most questioned aspects about the use of apitherapy in DM derives from the possible increase in blood glucose, particularly with the use of honey and its potential effects on body weight and blood glucose [87]. Sociocultural aspects derived from its sweet taste as well as the high prevalence of falsification of honey throughout the world [88] cause fear about its use in DM, it is evident that adulterated honeys will not produce any of the favorable therapeutic effects. Clinical trials have evaluated the impact of honey consumption in patients with DM (see Table 2).

Table 2: Clinical trials on the consumption of honey in DM.

DM	Groups, n	Outcome	Resultado	Ref.
2	H 30 g (n=39) H 75 g (n=28) G 75 g (n=30)	BG (mg/dL) % Of patients with blood glucose levels >200 mg/dL	75 g H=261.8 30 g H=222.4 75 g G=358.3 75 g H=2.5 % 30 g H=0 % 75 g G=13.3	[89]
1	H 75 g (n=20) S 75 g (n=20) G75 g (n=20)	BG (mg/dL) C-peptide in blood at 2 h (ng/mL)	G=297.90 ± 106.86 S=310.15 ± 92.63 H=236.75 ± 76.80 G=0.29 ± 0.53 S=0.32 ± 0.53 H=0.47 ± 1.09	[90]
1	H 0.5 mL/kg (n=10) NI (n=10)	BG-12 weeks (mg/dL) HBA1C-12 weeks (%) C-peptide/12 weeks (ng/mL) TC-12 weeks (mg/dL) HDL-C 12 weeks (mg/dL)	H=133.0 ± 24.2 NI=138.1 ± 21.6 H=7.1 ± 1.1 NI=6.9 ± 1.2 H=0.8 ± 0.1 NI=0.6 ± 0.1 H=192.5 ± 15.9 NI=212.0–20.8 H=50.5 ± 12.2 NI=45.6 ± 6.8	[91]
1	H 0.5 mL/kg (n=10) NI (n=10) H 75 g (n=50) S 75 g (n=50) G 75 g (n=50)	BG (mg/dL) C-Peptide/12 h	H=203.66 ± 59.75 S=318.70 ± 76.75 G=273.84 ± 85.92 H=0.60 ± 0.41 S=0.36 ± 0.20 G=0.33 ± 0.18	[92]
2	H 2.5 g/kg day (n=25) NI (n=23)	BG-8 weeks (mg/dL) HBA1C 8 weeks TC-8 weeks HDL-C 8 weeks LDL-C 8 weeks TG-8 weeks Body weight-8 weeks	H=124.3 ± 37.5 NI=131.9 ± 45.5 H=7.7 ± 1.5 NI=7.3 ± 1.6 H=177.4 ± 36, NI=198.0 ± 38.3 H=66.1 ± 15.1 NI=65.1 ± 14.1 H=107.6 ± 20.9 NI=115.2 ± 24.0 H=148.0 ± 80.4 NI=154.1 ± 71.8 H=69.5 ± 11.9 NI=70.3 ± 8.0	[93]
2	H 50 g/day (n=18) NI (n=24)	BG-8 Weeks HBA1C-8 weeks	H=142.65 ± 40.45 NI=134.59 ± 34.01 H=7.04 ± 1.67 NI=6.83 ± 1.65	[94]

Table 2: (continued)

DM	Groups, n	Outcome	Resultado	Ref.
		Weight difference (kg)	H= −0.83 (IC95 %- −1.20 −0.42) NI= −0.41 (IC95 %- −0.84–0.03)	

Ref, Reference; DM, diabetes mellitus; HBA1C, % Glycosilated HEmoglobin A1C; TC, total cholesterol; HDL, HDL-cholesterol; LDL-C, LDL cholesterol; BG, blood glucose at 2 h (mg/dl); G, glucose; NI, no intervention; H, honey; S, sucrose.

The consumption of honey does not produce significant negative effects on important parameters in the glycemic control of patients with DM, it is possible that its use improves important outcomes such as HBA1C, total cholesterol, HDL cholesterol and LDL cholesterol. Future studies will be able to determine the effects of its consumption in a long-term follow-up.

Integrative clinical approach is especially useful in all populations, not only because of the potential benefits due to its molecular effects, but also because of cultural and social closeness, human care, and comprehensive management. The benefits of the use of apitherapy are not only due to its pharmacological effects, but also due to a comprehensive vision. These effects have also been described in other complementary medicine alternatives [95]. Obviously, for this type of alternative, an evaluation based on evidence is required in such a way that the most favorable intervention is always made for each patient. The addition of beehive products to the diet by themselves could contribute to improving the state of health in people with DM or at risk of developing it and, probably, in the entire general population and the complications derived from these diseases. Beehive products (propolis, honey, BP, and BB) have varying effects based on the flora they come from. These features are an active research field, and future ecological studies and RCTs will provide a better comprehension of their effects and the suitability of their use on metabolic health.

Conclusions

The use of complementary medicine is common in people with DM, apitherapy is one of them. The different beehive products (apitherapy) produce significant effects on the pathophysiological processes of DM and its complications. Modulation of epigenetic effects, OE, dysbiosis, mitochondrial function, chronic inflammation, metabolic control, cell death, and tissue remodeling are relevant mechanisms that explain its effects. The clinical perspective shows that the use of apitherapy could be useful in the management of DM. More clinical studies are required to determine the impact of the mechanisms of beehive products on clinical outcomes. Potentially, apitherapy shows to be useful in the treatment of DM due to its effects on different pathophysiological mechanisms involved in the development and complications derived from the disease.

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