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Honey and Type 2 Diabetes Mellitus: Reconstruction of Problematic Field Using the Lakatosian Method

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Abstract: *The paradigm of the medical use of honey transits to model of regulation of the internal medium in the patient with type 2 diabetes mellitus (T2DM); for this reason, this study was carried out with the purpose of reconstructing the problematic field of research related to honey and T2DM by means of the lakatosian method. It included three stages: construction of the thematic field defining categories of analysis (pharmacology, properties and antidiabetic effect of honey); identification of the firm core, protective belt and heuristic; and development of the problematic field. The general theories of the firm nucleus derive from the carbohydrate content of honey, its antioxidant and anti-inflammatory properties, and the oxidative stress associated with T2DM. Protective belt hypotheses configure the architecture of the antidiabetic effect of honey through the content of fructose and the antioxidant activity of honey. Methodological approaches focused on randomized clinical trials give meaning to the heuristic. The problematic field includes: honey as probiotic, glucose absorption, oxidative stress; establishing problematic networks with the pharmacological treatment of T2DM. It is concluded that the scientific trend is oriented to the study of microbiota, probiotics and the reconstruction of the conceptual model of T2DM.*

Keywords: *honey, diabetes mellitus, antidiabetic, hypoglycemic, antioxidant.*

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I. Introduction

Contemporary medicine in the context of postmodernity is configured from the horizon of incessant change, attention to multicultural diversity, acceptance of alternative and complementary medicine, as well as traditional medicine, but there are also significant advances of a technological nature and computerized in the emergence of robotic medicine, telemedicine and nanomedicine [1]. Its distinctive element is the rupture between the scientific discourse in its aspiration to legitimize medical practice [2] and the meta-narratives that provide the foundations and coherence to scientific theories from the neoliberal field with the aim of increasing the usefulness of scientific production [3,4].

The technological society of postmodernity, makes scientific research its instrument to determine the health/disease/care relationship [5-8] at times when diseases such as diabetes mellitus are manifested as global pandemics associated with the development of lifestyles harmful to health [9].

The understanding of the natural history of infectious and chronic-degenerative diseases, the development of preventive measures and specific protection, pharmacological research for the development of new drugs, biotechnological advances in the nutritional field, have fostered a scientific explosion that deepens, day to day, the gap between basic biomedical research and patient medical care [10,11]. In this meaning, highlights the study conducted by Siahpush [12] in which he explored the postmodern conception of health by finding that the population was approaching a holistic view of health, with beliefs in individual responsibility to maintain health, reject medical authority, they prefer natural products, they consider that drugs have side effects and not all diseases require medical prescription, and although they show anti-technological feelings they have faith in science.

The foregoing exposes the need to incorporate complex and non-linear explanatory models, the generation of knowledge through the scientific method. This task requires the use of methodologies derived

from the philosophy of science to assess and systematize scientific and technological advances in the general theories of the disease; propitiating with it a syncretism between contemporary medicine, complementary and alternative medicine and traditional medicine.

In this sense, the use of honey beyond a simple nutritional product stands out, since it has been attributed healing properties of medical application. Honey is a sweet, natural substance, produced by honey bees from the nectar of plants. It was used in medical treatments in Sumeria (2000 BC), described in the papyri of Smith (1700 BC) and Ebers (1550 BC), in the compendium of Chinese medicine of Shen Nang, in Ayurvedic medicine in India, in the Greek medicine, included in the Roman pharmacopoeia and used in Mayan medicine. It was also appreciated in the ancient testament of the bible, as well as in the Koran [13,14]. The composition of honey contains around 181 constituents [15] and varies if the honey bees collected the nectar of the plant, the secretion of the plant or the excretions of the insects that suck plants; besides the floral source, environmental and seasonal factors [16]; so that about 320 varieties of honey have been identified [17,18]. However, the main constituents of honey are: carbohydrates, organic acids, amino acids, enzymes, minerals, vitamins, volatile compounds, polyphenols and flavonoids [19].

Carbohydrates comprise between 95% and 97% [20]. Fructose and glucose are the main monosaccharides present in honey; it also contains disaccharides, trisaccharides and oligosaccharides [21]. Among the organic acids, gluconic acid stands out, although the presence of formic acid, acetic acid, citric acid, lactic acid, malic acid, oxalic acid, pyroglutamic acid and succinic acid has also been identified [19-21]. The presence of all essential and non-essential amino acids is reported, except glutamine and asparagine; although proline, aspartate and glutamate predominate [21]. The enzymes present in honey are: diastase, invertase, glucose oxidase and catalase derived from plants. It also contains all the vitamins soluble in water, with vitamin C predominating; and 31 minerals have been identified, among which predominate are: calcium, phosphorus, potassium, sulfur, sodium, chlorine and magnesium [19-22]. These compounds contribute to the antioxidant [23,24], antimicrobial [25,26], anti-inflammatory [27], antiproliferative, anticancer and antimetastatic effects associated with honey [21,28-30].

The usefulness of honey in the history of mankind is recognized for its industrial, cosmetic, nutritional, therapeutic and spiritual value [13,14,31]. The use of honey has been made by oral ingestion or topical application. Oral ingestion is used for respiratory, gastrointestinal, hepatic (hepatitis), cardiovascular (hypertension, dyslipidemias), neurological (insomnia), metabolic (osteoporosis, diabetes mellitus), neoplastic, infectious diseases and for the treatment of nonspecific symptoms. At the respiratory level, it is indicated for the treatment of laryngitis, bronchial asthma and tuberculosis; in the gastrointestinal tract is used for the treatment of intestinal and gastric ulcers, constipation and infestation by worms [32-34]. It is also used in the treatment of cough, anorexia, thirst, hiccups, fatigue and dizziness [21,28,32,34]. Applied topically it is used for the treatment of athlete's foot, eczema, labial ulcers, eye diseases, throat infections, hemorrhoids, ulcers, wounds and abscesses [21,28,32,34].

The relationship of the consumption of honey with type 2 diabetes mellitus type 2 (DM2) is an example that makes it possible to analyze the dynamics of the model of the natural history of the disease to incorporate scientific advances into medical practice in the prevention, diagnosis, treatment and control of DM2, moving from a mechanistic perspective towards understanding from a biopsychosocial and spiritual approach in the welfare state, sustaining a permanent process of adaptation to the environment to maintain the homeostatic balance of the internal environment in the patient with DM2 [35].

In this conception, the consumption of honey acquires importance in two fundamental levels: nutritional [15] and medical [32]. At a medical level, the consumption of honey is important in prevention and as a therapeutic tool. The explanatory scheme to support preventive, diagnostic and therapeutic interventions is based on the properties of bee honey as an antioxidant and anti-inflammatory. However, scientific advances in the understanding of the pathophysiology of DM2 or in the understanding of biological variability in the course of the disease and response to pharmacological and nutritional treatments go beyond the mechanistic explanatory model of molecular biology [35,36].

The adherence to treatment and healthy lifestyles, access to health services, exposure to social risk factors and determinants of health, patterns of food consumption, nutritional habits, attention to the spiritual sphere of the patient, experience and coexistence in an environment that generates emotional stress (not only biological), social isolation, are material conditions of life that need to be linked causally with the balance of the internal environment during the patient's transit in the natural history of T2DM.

Currently the antioxidant and anti-inflammatory property of honey is accepted in the scientific community [24,27,37], however, there is not enough scientific evidence to assess the capacity of honey as a natural product with hypoglycemic activity, so that it is followed debating the physiological effects involved in the control of glycemia in patients with T2DM [35,38]. Studies in laboratory animals and humans that try to explain the effects of honey on the treatment and control of T2DM, are based on the metabolic effects of honey [38,39]. These mechanisms are explained according to molecular mechanisms to highlight the participation of

honey in processes of adaptation to the changing environment; but they also show the need to articulate horizons of understanding that derive in complex and non-linear explanatory models, circumscribed to homeostasis to maintain the health of the individual.

The generation of knowledge in the field of apitherapy applied to T2DM promotes a change of view of the physiological properties associated with the medical use of honey that is transiting from a complementary tool to the pharmacological and nutritional treatment of T2DM, towards a model of internal regulation of the state of health and disease in humans. Given this paradigm shift, the study was conducted with the purpose of reconstructing the problematic field of research related to honey and T2DM using the lakatosian method.

II. Method

Even though the investigation of the consumption of honey related to the effect on glycemia in patients with DM2 is relatively recent, it is based on a logic of scientific research that has led to its rapid development, based on the dialectic of the construction and rational reconstruction of the thematic field of this discipline. In this sense, the epistemological approach of the study focuses on the lakatosian perspective of the Methodology of the Scientific Research Programmes (MSRP) that makes it possible to identify rival research programs as well as progressive and stagnant problems [40]; reason for which the development of the study was divided into three stages. The first delimited the bibliohemerographic content to construct the thematic field diachronically and synchronously from categories of analysis and identify the internal and external history of honey. In the second, the components of the research program were determined: firm nucleus, protective belt and heuristic (positive and negative). In the third, a problematic field was developed.

2.1 First stage: construction of the thematic field

The thematic field represents the analytical-conceptual delimitation of the object of study [41,42], in this case, of honey and its relationship with T2DM. The construction of the thematic field corresponds to the reconstruction of the internal historical development from the objective knowledge derived from the logic of scientific discovery, to give way to external history [40,43], that is, to the social conditions in which the logical processes of the investigation of the antidiabetic properties of honey.

In this stage, the following categories of analysis were determined: honey pharmacology, properties of honey, antidiabetic effect of honey. These were used as Medical Subject Heading (MeSH) terms to retrieve articles from the databases of medical journals included in PubMed, MEDLINE, EMBASE, AMED, CINAHL, The Cochrane library, Google scholar and Google [44]; in addition, the relevant publications were retrieved through the secondary search system (Pearling). The review was conducted between January and September 2017. The scientific literature published in English was included.

2.2 Second stage: identification of MSRP elements

Lakatos describes the MSRP as the descriptive unit of the scientific advances in which sequentially scientific theories are integrated with space-time continuity, so that it is configured in the epistemological analysis unit [40,45]. Following the approach of Lakatos, after having made the first approach to the object of study by theoretical cut considering the categories of analysis, we proceeded to identify the elements of the MSRP: firm core, protective belt and heuristic; representing with it the scientific reconstruction of the logic of the investigation and deriving the problematic field in the following stage.

The firm nucleus is the structure that characterizes the MSRP and is integrated with general hypotheses, theories or universal statements that provide stability and support the entire MSRP. The firm core includes the scientific knowledge that has been conventionally accepted by the scientific community and is considered irrefutable [40,46].

The protective belt is composed of explicit auxiliary hypotheses, observational statements and assumptions underlying the description of the initial conditions. It is located in the periphery of the firm nucleus protecting it but also allows the dynamism of the MSRP adapting it gradually [40,46].

The heuristic refers to the methodological rules that have enabled the development of research processes by organizing the MSRP conceptually, methodologically and empirically. Those methods that must be avoided configure the negative heuristic and imply the impossibility of modifying the firm nucleus. The suggestions that make possible changes to the firm nucleus constitute the positive heuristic, in a way that defines methods and problems to make sense to the protective belt from the construction of auxiliary hypotheses [40,46].

2.3 Third stage: development of the problematic field.

The problematic field is the articulation of a set of research problems that derive from the demarcation of the thematic field and is constructed from processes of clipping of reality sustained in problematization processes [41,42]. The problematization as a cognitive tool to develop the problematic field is generated by the

dialectic of question and answer. The questions arise from the questioning that is made to reality and the answer is inscribed in the firm nucleus. When identifying unanswered questions, it is incorporated into the problematic field and will result in the outline of auxiliary hypotheses that will give meaning to the research processes. The problematic fields are contained in the thematic field and establish relationships with each other, configuring themselves in networks of problems.

III. Results

The search and retrieval of available scientific information was analyzed to place it in one of the following disciplinary fields: pharmacology of honey; antioxidant and anti-inflammatory property of honey; hypoglycemic effect of honey. The reconstruction of the explanatory model of the oxidative and anti-inflammatory processes associated with the physiopathology of T2DM shows the complexity and transdisciplinary of the research processes in the field of apitherapy. Considering the scientific value of the evidence, it is noted that there are two ways to understand the properties of medical utility of honey: an indirect way in which it is argued from physiopathological mechanisms described in the scientific literature, assuming possibilities of participation of honey without having scientific evidence; and the direct route, in which the scientific evidence directly related to the effect of the honey described is shown.

In this sense, the scientific field of Endocrinology, as well as Immunology, provide universal theories and general hypotheses to the firm nucleus of the antidiabetic properties of honey, so it is necessary to demarcate points of disciplinary intersection through evidence that provide the scientific facts. The demarcation of thematic fields was carried out through the selection of scientific evidence that explores the relationship of the properties of honey with T2DM.

This relationship is represented in the logic of scientific research in two moments: diachronic and synchronic. In the diachronic moment, the analysis goes through the history of honey from its first reports of use in the daily life of the human [31] being to the different uses of today [47]; differentiating between nutritional [15,20] and medical use [32]. This implies that the medicinal use of honey transits in its own way and arises from purely empirical evidence, based on the experience provided by trial and error, generating a knowledge derived from experience. Finally, we arrive at the integration of scientific evidence to traditional knowledge. These evidences are incorporated as scientific facts obtained through *in vivo* and *in vitro* studies in which the scientific method is strictly used. Derived from the diachronic analysis it is understood that through the use of honey for the treatment of wounds it was possible to identify the antibacterial, anti-inflammatory and antioxidant activity [26,27]. The epistemological model adopted for the analysis carried out in the construction of the thematic field was the natural history of the disease, where the diachronic explanation provides generalizations that contribute to integrate the hard core of the Lakatosian MSRP, making it possible to integrate a horizon of understanding of the relationship between the properties of honey and T2DM.

In the synchronic moment, the historical analysis is located at a specific point of time and space. This implies placing in the model of the natural history of the disease, the medical use of honey in each of its applications. That is, a synchronous moment is the use of honey for the treatment of bronchial asthma; another synchronous moment will be its use as antitussive; and another use as an antidiabetic. To approach the synchronic explanation in the model of the natural history of the disease, scientific evidences were identified that derive from the advance of other disciplines. For example, to identify the antioxidant activity of honey it was necessary to describe the oxidative stress as well as to have characterized the composition of phenolic compounds in honey to associate these with the consequences of oxidative stress in T2DM.

In this sense, considering the synchronic explanation of the hypoglycemic effect [37-39,49], the relationship of oxidative stress with T2DM is highlighted, focusing the discussion on two levels: as a causal factor for the development of the disease, or as a factor associated with the natural evolution of the disease towards the appearance of complications: diabetic retinopathy [50], diabetic nephropathy [51] and diabetic neuropathy [52]. The alteration of the balance between reactive oxygen species (ROS) and antioxidants is related to the pathogenesis of insulin resistance [53]. On the other hand, it is important to identify positive feedback mechanisms of the oxidation mechanisms that have been described associated with hyperglycemia, such as the activation of the polyol pathway, which induces damage at the crystalline level and neuronal dysfunction [54], so that the level of metabolic control is associated with the degree of severity of oxidative stress in the pathophysiology of vascular damage induced by hyperglycemia [55].

Another example of the synchronic explanation is the analysis of the variability of the effects attributed to honey, which are explained in terms of the different varieties of honey. This diversity is determined by the honeybee species, area of geographic origin [22,56]. Reports have been made with different types of honey from Argentina [57], United States [58], Peru [59], Cuba [60], Venezuela [61], Ecuador [62], Mexico [63], Spain [64], Portugal [65], Poland [66], Croatia [67], Turkey [68], Saudi Arabia [69], Lebanon [70], Egypt [71], Ethiopia [72], Tunisia [73], Malaysia [74] and Australia [75].

3.1 Firm core: antidiabetic properties of honey

The knowledge of scientifically supported honey has been oriented, at first, to determine the physical and chemical properties [76]. The physical parameters of honey of biomedical and clinical interest are color, pH, humidity and enzymatic activity. The color varies from light yellow to dark. The pH has been reported in a range of 2.4 to 4.7 [73,77]. Moisture is linked to the solidity of honey and has been reported in a range of 13% to 20% [56,70,78]. The bioactive components of biomedical and clinical interest include carbohydrates, water, proteins and amino acids, phenols, pigments, vitamins and minerals. The enzymatic activity is determined by the presence of the following enzymes: glucose oxidase that produces hydrogen peroxides and glucose gluconic acid, invertase that converts sucrose into fructose and glucose; diastase (amylase) that breaks down starch or glycogen into monosaccharides; and catalase, which produces oxygen and water from hydrogen peroxide [21].

By linking the physical properties and bioactive components of honey, they give meaning to the model that explains the effect of honey consumption on the glycemia of patients with DM2. This model is integrated by structures that give coherence and consistency to the scientific reconstruction of the firm nucleus. These structures are: carbohydrate content, antioxidant and anti-inflammatory property of honey, oxidative stress in DM2.

3.1.1. Carbohydrate content in honey

Honey contains 17.1% of water, considered a saturated carbohydrate solution representing 95% to 99% of dry honey matter. Monosaccharides, disaccharides, trisaccharides and oligosaccharides have been detected.

Fructose is the predominant monosaccharide representing 38.5%, followed by glucose with 31%, representing 85% to 95% of total carbohydrates [22]. A fructose/glucose ratio of 1.23 has been reported; this relationship acquires importance when recognizing that the presence of glucose promotes a homogenous absorption of fructose. The disaccharides identified in honey are: maltose, sucrose, trehalose, isomaltose, nigerose, turanosa, kojibiosa, maltulosa, gentibiosa and laminarribiosa [28]. Some 25 different oligosaccharides have been detected in small concentrations, among which are: erlosa, teanderosa, panose, maltotriose, 1-ketose, isopanosa, isomaltosiltetraose, teanderosa, centosa, isomaltosil glucose, ismaltosiltriosa, isomaltosiltaosa.

Honey is recognized as a natural source of fructose, a sweetener recognized by the Food and Drug Administration (FDA). The sweetening power of fructose is 173 while for glucose it is 73 [79-81]. The fructose provides 4 kcal/g; so that a spoonful of honey provides 64 calories [21]. The fructose and glucose found in honey are the stereoisomers D-fructose and D-glucose [82] so they are ready for intestinal absorption. Glucose is absorbed through the Na^+ dependent SGLT transporter. Fructose is absorbed in the duodenum and jejunum by means of GLUT5 and CLUT2 transporters not dependent on Na^+. In tissues, glucose enters the interior of the cell through the GLUT4 insulin-dependent transporter; and fructose by means of the GLUT5 transporter and does not require the participation of insulin [80,83-86]. It has been reported that in fasting, 66% of fructose is converted to glucose, 2% is released as a lactate and 8% can form glycogen [87].

The Erejuwa work team has provided scientific evidence of the hypoglycemic or antidiabetic effect through fructose [88] and oligosaccharides such as palatinose, turanosa, raffinose, trachalosa and isomaltose [89]. This is correlated with studies that report the effects of fructose linked to the reduction of blood glucose levels, limited insulin production, lower glycemic response, delayed gastric emptying, reduced food intake and body weight [90].

An important parameter in the nutritional control of T2DM is the use of the glycemic index, which shows the effect of carbohydrate sources on blood glucose levels. The glycemic index reported for honey varies between 32 and 87, depending on the variety of honey, with an average of 11 varieties of honey of 55, corresponding to an average glycemic index. However, considering its geographical origin, a low glycemic index has been reported for honey from Romania (Locus honey) and Australia; other varieties of honey from Australia have a medium glycemic index; and honey from Canada (Honey, NS) has a high glycemic index [91].

3.1.2. Antioxidant property of honey

Oxidative stress consists of the homeostatic failure to regulate the balance between the production of oxidants and the protective antioxidant activity in cells, tissues, organs and compartments; leading to oxidative damage of biological structures of the human body altering homeostasis regulated by physiological functions. In the biomedical explanatory model, oxidative stress is associated with the natural history of T2DM, at two fundamental moments: in the development of insulin resistance and in the evolution of the disease towards its complications.

It is currently recognized that honey contains enzymatic and non-enzymatic antioxidants [64,92], among which are catalase, ascorbic acid, phenolic compounds, flavonoids and alkaloids; that contribute to modulate the production of free radicals and reactive oxygen species (ROS) that are generated during metabolism [37,93]. These compounds support the antioxidant activity of honey in both *in vivo* and *in vitro*

studies, either by delaying, preventing or eliminating oxidative damage [37]. The antioxidant capacity of honey is color dependent, so dark honey is related to a high content of antioxidants [34].

Among the compounds that participate in the antioxidant property of honey, phenolic compounds (benzoic acid, cinnamic acid and flavonoids) have a greater participation in the sequestration of free radicals, nitric oxide, ferric cations, metal chelating ions [24,94,95], contributing to the control of oxidative stress. Also inhibiting lipid peroxidation and the bleaching of beta-carotene [96,97]. In vivo studies show that it stimulates the antioxidant defense system in pancreas, serum, kidney and liver of mice and rats, through stimulating the activity of cellular antioxidant enzymes such as superoxide dismutase, CAT, glutathione peroxidase, glutathione S-transferase and increasing reduced glutathione levels [21,23,37].

3.1.3. Anti-inflammatory property of honey

Honey reduces the inflammatory response in animal models [98], cell cultures [99] and clinical trials [100]; identifying two actions [101]: as immunostimulant and anti-inflammatory; which implies a paradoxical effect of the use of honey, mainly in the treatment of infected wounds.

The capacity of honey as immunostimulant (inflammatory action) represents a positive event to improve the evolution of wounds, a process that is produced by stimulating the production of immunological mediators among which are the following pro-inflammatory factors: tumor necrosis factor alpha (TNF-α) [102,103], interleukin-1β (IL-1β) and interleukin 6 (IL-6) [104,105]. In healthy subjects, the consumption of pure honey decreases the blood concentration of prostaglandin E2, prostaglandin F2α and thromboxane B2, possibly by the regulation of cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) [30,106,107].

The anti-inflammatory activity of honey is attributed to the phenolic and flavonoid compounds that act by inhibiting, attenuating, reducing or regulating the pro-inflammatory activity of immunological and cytotoxic mediators. Among the pro-inflammatory factors inhibited by honey are: cyclooxygenase-2 (COX-2), TNF-α, inducible nitric oxide synthase (iNOS), production of matrix metalloproteinases (MMPs) [27,30,105,108-110]. The inhibited cytotoxic factors are: reactive oxygen intermediates. Honey attenuates the activation of the nuclear factor κB (NF-κB) and reduces the production of nitric oxide (NO) [111-113]; in that it regulates the activity of ornithine decarboxylase and tyrosine kinase [30].

In relation to the cellular immune response, bee honey induces the increase of T and B lymphocytes [114], eosinophils [115], neutrophils [116], monocytes [102], and natural killer cells [30,117]. On the other hand, the ability of honey to induce the production of short chain fatty acids (SCFA) by fermentable agents in a way that induces the immune response through fermentable sugars has been described; as is the case of the nigerooligosaccharides [30,118].

3.1.4. Oxidative stress in T2DM

T2DM is a metabolic disease linked to the increase of ROS and decreased antioxidant capacity [119]; among the mechanisms involved in the increase of oxidative stress are: autoxidation of glucose, glycation of protein, activation of the pathway of polyols and decrease of antioxidant defenses [54,120-122]; in addition, lipid peroxidation and protein oxidation have been described [123,124]. Glucose is capable of autooxidation to enediols, in addition to the end products of advanced glycation promotes the production of free radicals and decreases intracellular levels of antioxidants [122,125]. Thus, glyoxal generates cytotoxicity by increasing ROS and decreasing intracellular reduced glutathione [126]. Glycation of antioxidant proteins decreases their activity and glycated hemoglobin can donate reactive oxygen to the vascular wall in diabetic patients [119,125,127]. The hyperglycemia favors the production of mitochondrial superoxide radical, producing the activation of the polyol pathway with a decrease in NADPH, leading to a decrease in the activity of the enzymes that generate reduced glutathione [128]; as well as an increase in the free radical peroxynitrite, a lipid and protein oxidant and the activity of protein kinase C [129-131]. Among the antioxidant mechanisms that decrease during diabetes mellitus are: reduced glutathione, enzymatic activity and antioxidant vitamins.

In lipid peroxidation, unsaturated fatty acids react with molecular oxygen to form hydroperoxides, which are degraded to conjugated dienes, alkanes, aldehydes and isoprostanes; affecting both the lipids of the cell membrane and plasma lipoproteins. It is important to note that the oxidation of low density lipoproteins increases the atherogenic capacity [125,132]. Protein oxidation increases its lysosomal degradation by increasing hydrophobicity. Of special importance is the oxidation of insulin causing chemical and structural changes that induce the loss of its biological function, while the carbonyl stress affects the insulin receptor and the intracellular cascade [53,133].

3.2 Protective belt: honey as an anti-diabetic substance

Advances in understanding the properties of honey and its effect on T2DM have strengthened the firm nucleus but have also generated the production of auxiliary hypotheses that are located in the protective belt. The most significant advances correspond to the characterization of the antioxidant effect of honey, the analysis

of the variability of the effect between the different varieties, characterization of the anti-inflammatory effect, and are aimed at exploring the effect and mechanism of action in the control and treatment of T2DM [38,39,134].

The development of research processes in the generation of knowledge in relation to the anti-diabetic and hypoglemic activity of honey has an exponential behavior, since studies are being carried out at the level of the immunological architecture, identifying the effect of phenolic flavonoids in components inflammatory and cytotoxic related to the complications of T2DM at the level of retina, kidney and nerve fibers [15,135].

Erejuwa, Sulaiman and Wahab [38] have carried out the analysis of several experimental and clinical evidences at the level of the gastrointestinal tract, intestinal microbiota, liver and pancreas; In addition, they have described a hypoglycemic and antidiabetic effect, since the decrease in blood glucose concentrations was demonstrated both in diabetic rats [49,136,137] and in patients with type 1 diabetes mellitus [138]. However, an increase in the glycosylated hemoglobin value has been reported in patients with T2DM [139], evidence that contrasts with the effect of honey on blood glucose levels [140,141]. This effect is associated with the low glycemic index of fructose compared to sucrose and glucose [143-145].

The mechanism of action by which honey is considered to lower blood glucose concentrations is still under discussion. Based on the experimental evidence obtained in *in vitro* and *in vivo* studies, the participation of fructose [88] and oligosaccharides [89] in the hypoglycemic effect of honey consumption is being analyzed [135,146,147]. Still there is no scientific evidence to show the regulation that could be made by honey in the modulation of the absorption of glucose, micro or macronutrients, as well as different drugs administered orally. Another of the proposed mechanisms involved in the regulation of glycemia in T2DM is the antioxidant action of honey at the pancreatic [49,148-151], renal [136], and hepatic levels [152].

The dose of honey administered orally to reduce hyperglycemia is 1-2.4 g/kg of weight, with 1 g/kg of weight being considered as the optimal dose. Doses less than 1 g/kg of weight have no effect on the blood glucose level and doses greater than 3 g/kg can increase blood glucose with the consequent increase in the value of glycosylated hemoglobin [141,153]. The establishment of the dose-dependent hypoglycemic effect of honey made it possible to explore the effect of honey consumption in patients with T2DM with pharmacological treatment of glibenclamide and/or metformin. In this sense, experimental and clinical evidence allow us to consider the use of honey as a coadjuvant in the treatment with glibenclamide and metformin to improve the control of glycemia in patients with T2DM [150,154-156].

3.3 Heuristics: Research logic of the relationship between consumption of honey and T2DM

The methodological approaches identified from the analyzed literature are linked to the type of research that is carried out, whether basic or clinical biomedical; even when the research reports are circumscribed to the contemporary scientific discourse. On the other hand, the review articles that have been published have the merit of systematizing the scientific findings of the use of honey, providing also the scientific basis to support the antioxidant, anti-inflammatory, anti-diabetic and hypoglycemic activity. In this context, the research logic underlying the scientific study of the use of honey in the prevention, treatment and control of T2DM is based on the physiopathological model of the disease, which is reductionist in nature, which favors the description of multiple biological effects that add to the properties of honey.

By opening the epistemological horizon, we can see the contradiction between two fundamental tendencies: understanding and explanation [157]. Undoubtedly, the experimental models contribute to provide scientific explanations of the anti-diabetic effects of honey, but by incorporating the cultural traditions on which traditional medicine is based as well as alternative and complementary medicine, the impossibility to offer conceptual schemes of understanding in the use of honey in the context of the experience the patient has with his disease [158].

When recovering the natural history of T2DM as the diachronic epistemological model to understand the evolution of the disease, and incorporate the different scientific advances in a synchronic way, it can be verified that those studies carried out in conditions of an optimal state of health, they contribute to decrease the risk of presenting insulin resistance; preventing the patient from developing biochemical, metabolic and physiological alterations that alter the homeostatic conditions of regulation of blood glucose concentration. Other synchronic moments that can be incorporated into the natural history of T2DM is the antioxidant, anti-inflammatory and anti-diabetic activity making it possible to generate comprehension schemes where the consumption of honey contributes to control both the hyperglycemia and the metabolic damage that the own complications of T2DM. Finally, the association of honey with the pharmacological treatment adds benefits to the patient.

In this context, the positive heuristic, that is, the definition of methodological approaches that help to establish research problems that give meaning to the hypotheses includes physicochemical methods to determine the composition of honey [159], as well as animal models of diabetes mellitus, whether induced by streptozotocin or by alloxan [160]. An important advance in positive heuristics is the use of Manuka honey as a

gold standard to evaluate the antioxidant capacity of other types of honey [161]. In addition, the use of clinical trials has increased; and it remains to carry out clinical studies that assess the honey-microbiota-diabetes mellitus triad, which will make it possible to deepen the conception of honey as a probiotic [162]; as well as the participation of the microbiota in the evolution of T2DM [163] and the relationship between honey and melatonin by sharing antioxidant properties and modulating effects in glucose homeostasis [164,165].

The epistemological and empirical limitations of the physiopathological model of a biomedical nature to analyze a natural product with potential for medical use, such as honey [4,166], makes it possible to comply with the criteria of the negative heuristic, since it is unable to resolve the contradictions between the components of the firm nucleus propitiating the stagnation of the auxiliary hypotheses of the protective belt. In this context, the absence of global standard scales that make it possible to group the 320 varieties of honey by the level of antioxidant, anti-inflammatory, antidiabetic and hypoglycemic activity; as well as to assess the biomedical and clinical effects during prolonged consumption of honey by patients with T2DM2. The review carried out by Erejuwa and collaborators [38,39,134] of the Department of Pharmacology of the School of Medical Sciences at Universiti Sains Malaysia, exposes the analysis of the scientific evidence obtained from experimental or clinical studies, concluding with the need to carry out methodologically appropriate clinical studies, clinical trials randomized studies and studies that analyze the effects of short and long-term honey supplementation.

3.4 Problem field: honey as a modulator of the internal environment

In the last decade, interest in the medical use of honey has increased [167-169]. The studies were oriented to explore the composition of honey characterizing the antimicrobial, antioxidant and anti-inflammatory activity, both *in vivo* and *in vitro*. The diversity of studies implies the use of multiple methodological approaches that have generated an increase in controversies when analyzing the biological effect of honey in experimental models and clinical trials of T2DM [18].

In addition to the concern for the control of the T2DM pandemic, the research groups that influence the consumption of honey have directed their efforts to the following approaches: physical-chemical properties [19,22]; characterization of medical use [32], identifying other effects such as gastroprotective, renoprotective, hepatoprotective [16], neuroprotective [16] and antitumor effects [30]; characterization of biological effects [27,29]; biological mechanisms of therapeutic properties [21,28]; consumption patterns among the population [39].

The research logic focused on the relationship honey-diabetes mellitus requires defining a specific problem area. By understanding the problematic field as the space of reality in which a set of previously delimited problems interact, which need to be analyzed critically from epistemic approaches [170]. The analysis from the critical epistemology allows specifying problematic knots in which problematic axes are integrated from which derive research projects that contribute to develop intervention processes by articulating the knowledge obtained in each of the problematic knots. As Zemelman [170] points out: "the problematic fields sketched challenge to construct instruments of reasoning capable of accounting for the context", which corresponds to the external and internal history of the MSRP mentioned by Lakatos. The problematic field is explained by the concurrence of multiple and diverse problems that are articulated in the causal structure of the investigated phenomenon. The problematic knot is the articulating point where problems are grouped into causal paths that are presented as relevant and fundamental. The problematic axis is the causal path from which reality is interpreted; so that it is constituted in the starting point of the knowledge that will be obtained when developing the research project.

In this context, the scientific reconstruction of the MSRP using the lakatosian methodology to understand the scientific development of the relationship between honey and T2DM demarcates a problematic field that expresses a field of observation of the phenomena that underlie the natural history of T2DM. This field of concrete possibilities for scientific research is limited to the theoretical content to understand honey as a homeostatic modulator of the internal environment of the patient with T2DM. Thus defined the problematic field integrates the following problematic nodes: honey as probiotic, glucose absorption, oxidative stress; in which questions related to the source and origin of honey are inserted, as well as the mechanism by which the blood glucose concentration is regulated in patients with T2DM.

Another problematic knot derived from the development of research processes linked to patient care enables the application of scientific knowledge to technological development in the field of medical sciences. In this line of reflection, highlights the development of nanotechnological applications aimed at the study and understanding of the effects of honey, for example the development of platinum nanoparticles [171,172].

In order to define the problematic axes as causal trajectories that allow us to interpret, understand and apply the knowledge in specific interventions, it is important to keep in mind the following questions elaborated by Erejuwa [39]: “Are there studies that reported the beneficial effect of long-term honey administration in diabetes? Are the observed effects of honey exclusive to a particular honey (such as Tualang honey)? Could these findings be generalized to other honey samples that originates from other parts of the globe? Are the

observed beneficial effects of honey in combination with these drugs exclusive to this particular honey (Tualang honey)? Could similar data be reproduced if anti-diabetic drugs are co-administered with other potent antioxidants such as vitamin C or E?" These questions emphasize the effects depending on the type of honey, the treatment of T2DM, and the antioxidant property of honey; and contribute to understand the modulating role of honey in the constancy of the internal environment in the homeostasis of glucose in the patient.

Placing the relationship honey-diabetes mellitus in the phenomenological context of glucose homeostasis makes it possible to specify the logic of research at levels of understanding that require the rehabilitation of basic concepts as conceptual instruments, in addition to validating the conceptual frameworks that are integrated into the natural history of T2DM. Exploring the effects of honey in the treatment of T2DM integrated into a basic model of homeostasis will contribute to direct efficient therapeutic interventions.

In this line of reflection, problematic knots establish networks with the following axes of problems: coadjuvants in the pharmacological treatment of T2DM, participation of the microbiota in the immune response of the intestinal mucosa, sweeteners and probiotics in the management of T2DM, which will help to reconfigure the conceptual model of the natural history of T2DM.

IV. Conclusion

The development of the study was oriented to the scientific reconstruction of the problematic field of honey and T2DM. The presented results expose, in general lines, the application of the MRSP methodology, constituting an approximation from the philosophy of science to a thematic field relevant for the development of the health of the human being in the postmodern society.

The results show a tendency towards the analysis of the influence of fructose, the antioxidant and anti-inflammatory property of honey in the regulation of the internal environment in the patient with T2DM, which makes it possible to reconstruct a comprehension horizon to analyze the interaction of honey with intestinal microbiota, sweeteners and probiotics. The development of these areas will establish networks of scientific work with the biotechnological area of food, in addition to the concern to transfer the results of basic biomedical research to treatment strategies for patients with obesity, metabolic syndrome and diabetes mellitus. It is also concluded that there are elements to modify the comprehensive model of T2DM.

The development and evolution in the understanding of the mechanism of action of honey in general, and its antidiabetic and hypoglycemic effect, presents a variability that needs to be explored through the use of avant-garde methodological and technological approaches to delve into the different levels of the natural history of T2DM. On the other hand, the study opens paths to epistemological research as well as to the field of philosophy of science to understand the logic of scientific research in the field of traditional medicine and complementary and alternative medicine.

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