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EDITORIAL

Alternative therapies in diabetes☆

Terapias alternativas en diabetes

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Alternative and/or complementary therapies constitute a management approach which is not integrated into a scientifically based medical practice, and include traditional medicine based on the use of natural products (NPs). It is difficult to estimate the proportion of the population that resorts to such therapies, since practices of this kind are spread through non-conventional channels (with the internet as a catalyzing element). Nevertheless, they are assumed to be increasing considerably in both developing countries and in the industrialized world. In its strategy on traditional medicine for the period 2014–2023,[1] the World Health Organization (WHO) estimates that 100 million people use such therapies in Europe, and in the United States alone the sales of NPs totalled approximately 14,800 million USD in 2012. In Spain, an estimated 45% of the population is estimated to use herbal remedies.[2] The WHO indicates that such therapies are not without risks, and can have direct and indirect side effects. Likewise, it is emphasized that the information supplied with them is often unreliable if not simply misleading. The WHO also alerts to the poor quality, adulteration or falsification of products. Nevertheless, the WHO emphasizes that its strategy is to facilitate the integration of such practices within national health systems, in order to make access to medical care easier for certain populations.

A number of questions must be considered for improved understanding of this subject: When and why do people resort to alternative therapies? What benefits do they provide? How and by who are they accredited? In developing countries, the traditional use of herbal remedies or extracts in medical practice is often the most likely cause. However, in the western world, the use of such products is possibly explained in some cases by the lack of efficacy of scientifically based medicine, as well as by patient fear of the adverse effects of drugs, or the mythification of ''natural'' as meaning healthy, in contrast to all that is industrial or synthetic.[3,4]

The treatment of diabetes mellitus is no exception to the growing use of NPs, given the current pandemic and the expectations for the future. In this respect, there is growing scientific interest in the use of natural products with glucose homeostatic activity (NPGHs). Moreover, the DIRECT study, as the culminating reflection of Taylor's hypothesis, shows that a decrease in body fat through the implementation of a demanding food plan, is able to revert diabetes and normalize carbohydrate homeostasis.[5] However, most people find a restrictive food plan, characterized by intermittent fasting or hypocaloric intake, difficult to maintain, since it involves a significant change in lifestyle and comes into conflict with the hedonic component of food. Searches for the active ingredients of foods possessing this potential have been made with the purpose of favoring the benefits of these food plans, while limiting their associated adherence problems.

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In this line, attention has focused on supplementing food with so-called ''caloric restriction mimetics'' (CRMs) or ''fasting-mimicking diets'' (FMDs), with the aim of reaching the targets regarding lowered body fat.[6]

Using the ''natural products for diabetes'' search criterion in PubMed, we identified 18 reviews published in 1995, 92 in 2010, and 172 in 2017. In addition to the clinical possibilities, scientific interest has also focused on the search for new active ingredients with blood glucose-lowering activity. It should be borne in mind that metformin comes from the guanidine contained in *Galega officinalis*, and that the sodium and glucose cotransporter inhibitors (iSGLT) are derived from phlorizin present in the bark and leaves of the apple tree, as well as in the bark of the pear tree, in rose hip and strawberries. Even concentrated immature apple extracts possess iSGLT1 activity.[7]

Over 200 plant compounds, largely polyphenols, exert an influence upon glucose homeostasis both *in vivo* and *in vitro*, though in most cases their precise mechanisms of action are not known. On the basis of these studies, effects have been demonstrated upon insulin-resistance/glucose-transport in the liver, muscle and adipose tissue, as well as in terms of decreased intestinal glucose absorption, increased insulin secretion, and the preservation of beta-cell mass. Furthermore, interactions with the microbiota have been described, as well as modulating effects upon the inflammatory phenomena associated with type 2 diabetes. According to the comparator used in the *in vitro* studies, the different NPGHs can be grouped into products related to sulfonylureas, biguanides, alpha-glucosidase inhibitors, insulin or thiazolidinediones.[8]

The possibly associated metabolic mechanisms or targets are related to adenosine monophosphate-activated protein kinase (AMPK), glucose transporters 4 and 2, tyrosine phosphate 1B protein, peroxisome proliferator-activated receptor gamma (PPAR), α-glucosidase, the iSGLTs, COX-2, NF-kB and TNF-α, among others.[8–12]

Although *in vitro* research has been carried out in mice, and there have been some observational studies and small clinical trials, most NPs used as dietetic supplements are not supported by sufficient scientific evidence to justify their use in the treatment of diabetes or its associated metabolic alterations. Their pharmacokinetic characteristics are, moreover, not known, and there have been no supporting toxicological studies.[10] In sum, the efficacy and safety of such NPs remain unknown. It should be also taken into account that there may be synergic actions among different products that can cancel or enhance their effects. Furthermore, in some cases the active ingredient is present in such low concentrations in the plant of origin that consumption of the raw product might not produce effects, while in other cases the extract preparation methods may inactivate the active ingredient. In sum, the precise amount of the active ingredient actually contained in the commercial formulation is not known.

Curcumin, a polyphenol, may be an example of this. When supplied at different concentrations in the diet in animal models, curcumin reduces fasting glycemia, improves insulin resistance and reduces liver gluconeogenesis. It appears to increase insulin production through GLP-1 and interacts with PPARγ. However, these results have not been reproduced in humans, or the results obtained have been controversial. Such discrepancies can be due to different causes, but its form of administration is not adequate (curcumin is insoluble in water), and its resulting bioavailability is low. Different nanoparticle, micronization, micellization or liposome inclusion techniques are being developed with the purpose of improving bioavailability, though doubts remain regarding what the toxicity impact will be.[13]

The toxicological information on these NPs with clinical activity is scarce. The medicinal plants produced in the European Union are registered, though not so the products coming from other countries, particularly from Asia. This means that products of this kind can be marketed under less strict regulations as cosmetics or foods, but cannot be promoted in terms of the therapeutic indications of scientific medicine. Nevertheless, even these regulations are often not complied with, as any examination of websites offering such products will soon demonstrate.[2] With regard to safety, oriental herbal remedies in many cases contain ingredients that are pharmacologically active and potentially hazardous, either alone or as a consequence of interactions, particularly in polymedicated populations. However, in the European Union there is no legal imperative to supply information on the safety of consumption of these products.[2] The main toxicity data recorded by the Spanish Agency for Medicinal Products and Medical Devices (AEMPS) are not related to the intrinsic properties of the plants, but to their contamination or adulteration by other substances, such as sibutramine or sildenafil.[2]

In Europe, attempts are being made to adopt uniform legislation regarding NPs, in order to assist professionals regarding their knowledge of and their prescription of those products in their clinical activity.[14] Such legislation seeks to protect user health, ensuring the safety and high quality of all medicinal products. Since the market for these products is currently international, and NPs are usually manufactured in a country different from the country where they are sold, it may prove difficult to guarantee their safety and high quality.

A strong effort is required to improve scientific knowledge (both the basic science and routine clinical practice) regarding NPs, and it should be made clear that NPGHs can interact with currently used prescription drugs, causing unexpected side effects. Moreover, since in most cases the distribution chains are not of a physical nature, patients must be made aware that these products might not be safe—even if they are supposedly ''natural''—and that they may be adulterated, not to mention being of highly variable efficacy, depending on the commercial formulation involved. Furthermore, the manufacturers of raw plants or extracts should submit to standardization controls, and commercial formulations of this kind should be subjected to randomized clinical trials in order to guarantee the bioactivity and safety of their use in the diabetic population.[9,10]

It is not our aim to take a stand either for or against the use of natural products or extracts derived from plants. However, we do wish to draw attention to the uncertainties that exist in relation to their production, preparation, distribution, efficacy and safety. Likewise, emphasis has been placed on the risk of interactions with other medications which diabetic patients may be using.

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