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The Role of Flavonoids in the Effort to Prevent Obesity: Nutrition 4.0

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Nowadays, obesity is a world-class nutritional problem, reporting that around 1.9 billion adults (18 and older) were overweight, of which 600 million were obese, according to World Health Organization statistics in 2014. The scientific evidence describes obesity as a chronic disease, influenced by many factors including physiological and molecular mechanisms, environment and genetic susceptibility.

Thus, one of the main strategies in the prevention and treatment of obesity is the achievement of a negative energy balance, based on changes in lifestyle (including diet and physical activity). Unfortunately, dietary interventions are not usually long-term lasting and sometimes another treatment appears necessary as a coadjuvant in the integral management of obesity. In this context, recently, it has been growing interest on biocompounds such as flavonoids that can exert biological properties including antiobesity effects.[1]

Flavonoids are defined as non-nutritive components derived from plants or parts of plants (leaves, stems, flowers, roots, tubers or fruit) used for the treatment of some diseases. Based on the variation in the type of heterocycle involved, more than 5,000 different flavonoids have been identified and categorized into six subclasses: flavones, flavonols, flavanones, flavanols, isoflavones and anthocyanins.[1] Flavones,

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flavanols and their glycosides are the most abundant compounds in plants, and on the other hand, proanthocyanidins are the most complex structures. Results obtained from *in vitro* and *in vivo* studies, using isolated compounds, natural extracts and functional foods, have shown biological and pharmacological properties of flavonoids.

Most flavonoids are found naturally as glycosides (conjugated with one or more glucose residues). When they are ingested, some of them can be absorbed in the small intestine or partially metabolized in the colon by the gut microbiota. If they are absorbed, most of them lose the glucoside and are modified in different metabolites that can be found in body fluids or tissues. These metabolites may have different biological activities than the initial compounds. Finally, flavonoids are metabolized in the liver as a process that allows to detoxify and facilitate the elimination by urine. The circulating flavonoids in blood can be transported to different tissues and metabolized to exert biological functions.

On the other hand, in addition to factors related to the host such as the physiological processes and others related to age, pathology, genetics and different physiological conditions, studies of bioavailability should consider different factors that can directly affect the quality and quantity of the flavonoids present in food. Some of these factors are the environment (UV radiation), the processing of food (thermal effect, cooking and different culinary methods), and the synergistic or antagonistic effect between different compounds such as fat and fiber. For example, regarding bioaccesibility, catechins, flavanones and quercetin glycosides are the flavonoids that are most easily absorbed due to their chemical structure.

Thus, there is scientific evidence underlying the antiobesity effects of flavonoids through different mechanisms such as regulation of food intake and energy homeostasis[2], the inhibition of fat digestion decreasing fat absorption[3], and the regulation of metabolic turnover of substrates and thermogenesis.[4] In addition, flavonoids are widely recognized for their antioxidant and anti-inflammatory properties.[5,6]

Furthermore, recently the understanding of the mechanisms and metabolic processes involved in the biological properties of flavonoids has been increasing through emerging technologies and with the "omics" sciences. Flavonoids can have an effect at the molecular level through the regulation of gene expression involved in metabolic pathways such as adipogenesis, lipolysis, novo lipogenesis, and therefore influencing the prevention of diseases such as obesity. In addition, epigenetics has recently emerged as a new tool in the study of antiobesity effect of flavonoids. In general, the most common epigenetic modifications involve acetylation and methylation of histone residues. The hiperacetylation induces an upregulation, while the hipoacetylation generally downregulate the gene expression.[7] On the other hand, DNA methylation is associated with downregulated genes. Finally, recently it has been proven that flavonoids can affect the expression profile or function of miRNAs.[8]

Moreover, one of the new mechanisms studied to prevent and control obesity is the modulation of the intestinal microbiota through the flavonoids. The human microbiome consists of more than 10^{23} bacterial cells throughout the digestive tract, finding around 160 different species per person and identifying more than 1500 different species. The intestinal microbiota is metabolically adaptable and in this sense, scientific evidence has demonstrated the positive influence of flavonoids on bacterial growth and metabolism, thus representing a relevant mechanisms in the treatment of obesity.[9]

Summarizing all these data, different studies suggest that flavonoids are associated with a preventive role against the development of obesity. Therefore, the omics sciences become an attractive strategy in the understanding mechanisms of the most common dietary flavonoids and their influence on biological properties associated with obesity intervention.

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