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Research trends in flavonoids and health

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ABSTRACT

Herein we describe, based on some bibliometric data, how the field of research on flavonoids has evolved over the last 25 years. The number of papers on flavonoids has risen in an exponential manner over these years, much faster than other fields on food constituents. This increase appears to be related to the contemporary explosion of interest in healthy foods, supplements and nutraceuticals. It was also probably triggered by large epidemiological studies on fruits and vegetables, and particularly on flavonoids, consumption and incidence of cancer, stroke and coronary heart disease. The widely distributed flavonols constitute the flavonoid subgroup upon which the greatest interest has been focused, followed by flavanols and more recently by anthocyanidins and other related polyphenols such as resveratrol. Research on isoflavones rapidly emerged in the 1990s but plateaued in the 2000s. In the 1990s flavonoids were mainly considered as the active components of medicinal plants, while from 2000 onward, they switched to be mainly regarded as bioactive food ingredients. We envision a continuation in the growth of research for the coming decade focused on clearly demonstrating the importance of flavonoids for human health.

1. Introduction

Interest in flavonoids has bloomed in the last decades. Fueled by the recognized importance of consuming fruits and vegetables to achieve better health, researchers became interested in knowing how these compounds synthesized by plants can alter animal biology and whether they can truly make the human body function better. In this paper, by analyzing publication trends, we will try to explain how research in flavonoids developed into an area of global interest with unusual impact on our knowledge of biology. Our analysis will be based on Web of Science-Science Citation Index Expanded (Clarivite Analytics, Philadelphia, US) including the available data up to 2016.

2. Early research on flavonoids

2.1. Discovery of flavonoids and their biological activity (1800s-1940s)

The existence of pigments in plants, which were later identified as flavonoids, has been known since ancient times but their chemical structure was not identified until the end of the 19th century. In the early years of the 20th century, flavonoids and related substances were chemically characterized in multiple plants and synthetized in the laboratory. Most interest was centered on their role as pigments and research was mainly focused on the flavonoid family of anthocyanins. It was not until the late 1930s that Albert Szent-Györgyi focused his attention on the effects of certain flavonoids on human health. In his Nobel lecture in 1937 [1], he advanced the potential health-promoting activity of flavonoids: "*… I investigated with my friend St. Rusznyák and his collaborators Armentano and Bentsáth the effect of the other link in the chain, the flavones. Certain members of this group of substances, the flavanone hesperidin and the formerly unknown eriodictyolglycoside, a mixture of which we had isolated from lemons and named citrin, now had the same therapeutic effect as paprika itself. It is still too early on in our experience for us to make any definitive statements. But it does seem that these substances possess great biological activity*." He and his coworkers had found that citrin stabilized the biological activity of ascorbic acid, pointing out that scurvy resulted from a combined deficit of vitamin C and flavonoids and coined the term "Permeabilitäts-Vitamin" or "vitamin P" for a mixture of citrus flavonoids. Although synergistic effects with ascorbic acid were later widely reproduced and found to be much more

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impressive for flavonols, anthocyanins and catechins, his enthusiastic claim that flavonoids are equivalent to vitamins for human health has never been fully substantiated, and the term “vitamin P” was discontinued in the 1950s [2].

2.2. The dark ages (1950s-80s)

Research with flavonoids from the 1950s to the 1980s was relatively limited. Some chemists continued isolating multiple chemical structures from plants and biochemists analyzed their biological effects, especially on several mammalian enzymatic activities. The scarce investigations of the effects of flavonoids on human health were mostly concentrated on the compounds present in medicinal plants. Pharmaceutical companies had developed certain flavonoids or flavonoid-rich extracts and clinicians analyzed their potential value for chronic venous insufficiency; however, little attention was paid to the nutritional value of flavonoids, especially those present in foods. Despite that their biological activity was recognized, at least *in vitro*, doubts about absorbability of pharmaceutical flavonoid preparations administered orally led to the rejection from official registration by the US FDA [3].

3. Trends in flavonoid research from the 1990s

Research has experienced impressive growth in all fields of science in recent years. The number of scientific publications has risen continuously from the 1980s until the present. The field of flavonoid research, however, has experienced a remarkable progression.

Over the years, the work on flavonoids has developed from very basic chemistry to clinical studies in humans. In this manner, very basic chemistry was employed to isolate and characterize flavonoids present in plants and to synthetize flavonoid derivatives including actual and potential products of flavonoid metabolism. The main bulk of the research was studies that included cells and animal tissue preparations (subcellular fractions) in culture. Unfortunately, only a fraction of these studies was performed under conditions that allowed for useful conclusions, e.g. using relevant cells or tissues, appropriate flavonoid amounts, and measuring parameters that could have physiological relevance. Flavonoid research also allowed for an interesting number of clinical interventions in humans, most of them of short duration. These studies were often based on epidemiological data, the latter of which have also been successful in demonstrating casual associations between the consumption of certain flavonoids and markers of diseases [4].

We have analyzed the number of documents indexed in the Web of Science as articles or reviews in the field of flavonoids from 1991 to 2016 (Figs. 1–4). We think that the numbers shown indicate the interest in the field by the scientific community, and quite accurately reflect the trends in the research on flavonoids. This analysis does not intend to be exhaustive and has several limitations including the following: i) keywords used may not encompass all possible flavonoid subtypes and individual compounds; ii) the analysis does not consider the total number of papers published by research subject or country; and iii) publications from the different regions of the world only include the top productive countries. In addition, it should be noted that numbers do not reflect the quality of the research.

The number of papers published per year on flavonoids has risen from 740 in 1991 to more than 9000 in 2015, overall reaching nearly 90,000 (Fig. 1A). For comparative purposes, Fig. 1A shows the evolution of the publications on other food constituents. While that research has also grown continuously, it has done so at a much slower rate. In contrast to the exponential growth rate of publications on flavonoids, the research on vitamin C, carotenoids or selenium, for example, has increased linearly. Publications on vitamin E also rose in the 1990s but the interest seems to have stabilized from 2000 onward. In 2016, the number of papers on flavonoids has surpassed those on vitamin C and the sum of papers on vitamin E, selenium and carotenoids.

We think that the main stimulus for the development of the research on flavonoids was the general belief in the population that diets rich in fruits and vegetables are healthier than those based on meat and dairy products. This triggered initially solid epidemiological research on the health effects of fruits and vegetables and their components. Thus, pivotal for the development of flavonoid research was the publication in the 1990s of several epidemiological studies showing inverse associations between dietary flavonoid intake and the three major causes of death in Western countries: coronary heart disease, stroke and cancer [5–7]. These early studies showed a significant risk reduction when comparing mortality due to heart disease or stroke or incidence of lung cancer in the highest quartile or tertile of flavonoid intake vs those in the lowest quartile or tertile. Research with flavonoids has also been stimulated by public research programs, as occurred for example in the United States, European Community, Korea and Japan, and by global food and beverage and supplement companies.

The progress of the field is clearly diverse in the different world regions. Fig. 1B shows the regional distribution of number of papers per year on flavonoids together with papers on vitamin C (discontinuous line), which may be taken as a reference. Today, China is the leader in the number of papers published on flavonoid research. In the US and Canada, flavonoid research has grown at a slower rate. In Europe, the growth in flavonoid research was delayed compared to that of vitamin C, and while the latter seems to be plateauing, flavonoid research seems to be still growing. Notably, China, India and Latin-American countries had a relatively weak research record in the 1990s but have experienced important developments since 2000, probably associated in part with research interest in folklore medicine. By contrast, the research in Japan grew until 2000 for the two fields but plateaued thereafter. Fig. 1C shows the number of citations per article in 2015 and indicates that the research from the US, Canada and European countries seems to have a higher impact.

The most active areas of research on flavonoids according to the Web of Science are Chemistry, Pharmacology and Pharmacy, Food Science and Technology, Biochemistry and Molecular Biology, and Plant Sciences, the latter two of which experienced a relatively lower growth from 2000 (Fig. 2A). Among the studies directly related to the health effects of flavonoids, Oncology is the leading research area followed by Endocrinology, Neuroscience, and Cardiology (Fig. 2B). All these areas follow a similar temporal trend.

Fig. 2C shows the papers selected from the top flavonoid publishing journals and compares those papers published in journals devoted to food science or nutrition vs those in the area of Pharmacology, mostly journals dedicated to natural products and phytotherapy. Interestingly, the latter had a continuous growth but it was clearly slower than the former. Accordingly, in the 1990s flavonoids were mainly considered as the active components of medicinal plants. From 2000, however, they switched to be mainly regarded as active food constituents.

4. Evolution of research in flavonoid subgroups and flavonoid-rich foods

As shown in Fig. 3A, research in all subgroups of flavonoids and the related polyphenols has grown steadily. The number of papers on flavonoids related to specific foodstuffs is shown in Fig. 3B. Most of the research was associated with tea, grapes and wine, and berries. Other fruits and vegetables, e.g. citrus and apples, follow in importance, and, to our surprise, cocoa and chocolate generated less than 100 papers per year.

4.1. Flavonols lead

In absolute numbers, investigations on flavonols have accumulated the largest number of papers and shown the highest growth rate since 2000 (Fig. 3A). This trend parallels the general trend of whole flavonoids and may simply reflect that flavonols are among the most abundant and widely distributed flavonoids. In fact, publications on