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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

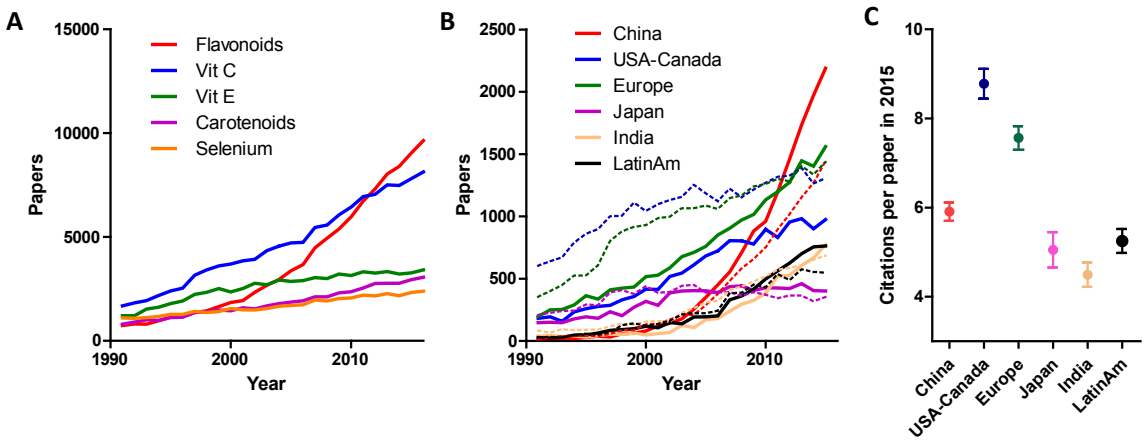

Fig. 1. Trends in research (1991–2016) in the field of flavonoids. **A.** Flavonoid research compared to research on other related food constituents. Whole flavonoids were identified using the queries "flavonoid* or flavonol* or flavanol* or anthocyan*"; vitamin C using "vitamin C or ascorb*"; vitamin E using "vitamin E or tocopher*"; carotenoids using "caroten*". **B.** Flavonoid research by world region. Europe identifies the sum of the most productive European countries (Italy, Spain, Germany, France and England), LatinAm the sum of the most productive Latin-American (Brazil, Mexico, Argentina and Chile). The continuous line represents the research in flavonoids using the query "flavonoid* or flavonol* or flavanol* or anthocyan*". The dashed line represents the research in vitamin C using the terms "vitamin C or ascorb*" for comparative purposes. Data are annual number of papers (articles and reviews) indexed in the Web of Science (Science Citation Index Expanded). **C.** Citations (as of Jan 2018) per paper published in 2015. Data are only for articles.

flavonols comprised more than one third of the total of those on total flavonoids. Among the individual flavonols, quercetin was by far the one that attracted the most attention within the scientific community because it is the most widely distributed in foods and it exerts a wide range of effects with relatively high potency [8]. For instance, 2262 papers published in 2015 mentioned quercetin or its glycosides quercitrin and rutin in the abstract or keywords.

4.2. Flavanols, tea, wine and chocolate

Flavanols are a family of flavonoids whose main representatives are catechins and epicatechins. Interestingly, flavanols are present in high amounts in plants that are of widespread consumption, i.e. tea (*Camellia sinensis*), grapes and wine, and cocoa and chocolate. The chemical structure of flavanols is not the same in all these plants. Thus, in tea they are present mostly as galloylated compounds and their oligomers, in grapes as monomers or in the formation of tannins, and in cocoa as monomers and oligomers of epicatechin (proanthocyanins). Research on flavanols, as well as that on flavanol-rich foods, has followed a trend similar to that of other flavonoids (Fig. 3A). Notably, tea is the leading flavonoid-rich food attracting the interest of the scientific community, but some caution should be exercised because "tea" is also often used to identify infusion or decoction of herbs different from *Camellia sinensis*. Tea, cocoa and wine have been consumed and used as medicines for thousands of years. The evidence achieved on the effect of flavanols on decreased risk of cardiovascular disease and associated risk factors is strong [9]. Importantly this evidence is not only based on clinical and preclinical experiments and epidemiological data, but it is also supported by well-established biochemical mechanisms involving nitric oxide and oxidant entities, such as superoxide anion [10,11]. All of this provides a rationale for advising an increased consumption of flavanol-containing foodstuffs. However, caution should be taken when considering the consumption of wine (see below) and chocolate since they deliver substances (fat, sugars and alcohol) with negative impacts on human health and behavior.

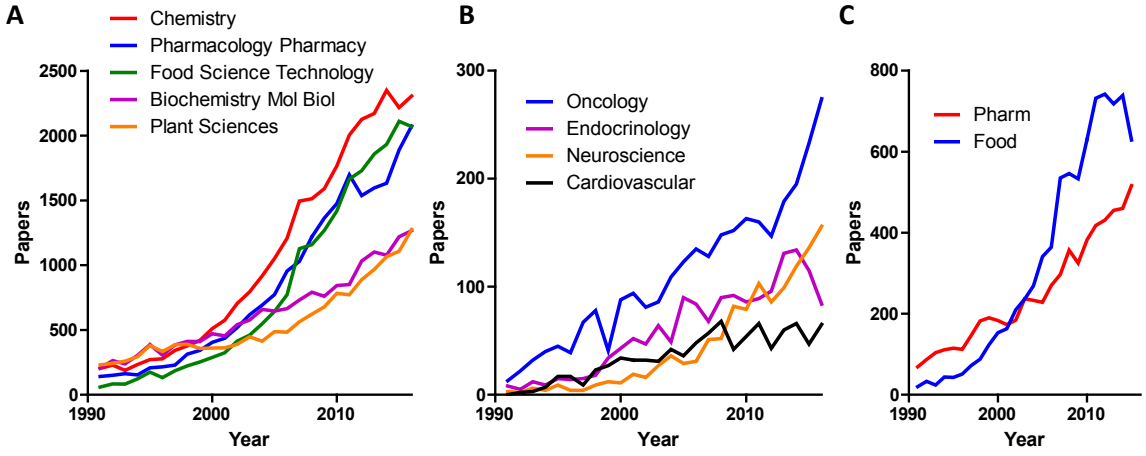

Fig. 2. Trends in research (1991–2016) in the fields of flavonoids by areas. **A.** Research areas as classified in the Web of Science. Flavonoids were identified as in Fig. 1. **B.** Medical specialties as extracted from the Web of Science categories. Data are annual number of papers (articles and reviews) indexed in the Web of Science (Science Citation Index Expanded). **C.** Documents (articles and reviews) selected from the top flavonoid publishing journals and classified into journals devoted to food science or nutrition (Food) vs those in the area of Pharmacology (Pharm), mostly journals dedicated to natural products and phytotherapy. Data are annual number of papers (articles and reviews) indexed in the Web of Science (Science Citation Index Expanded).

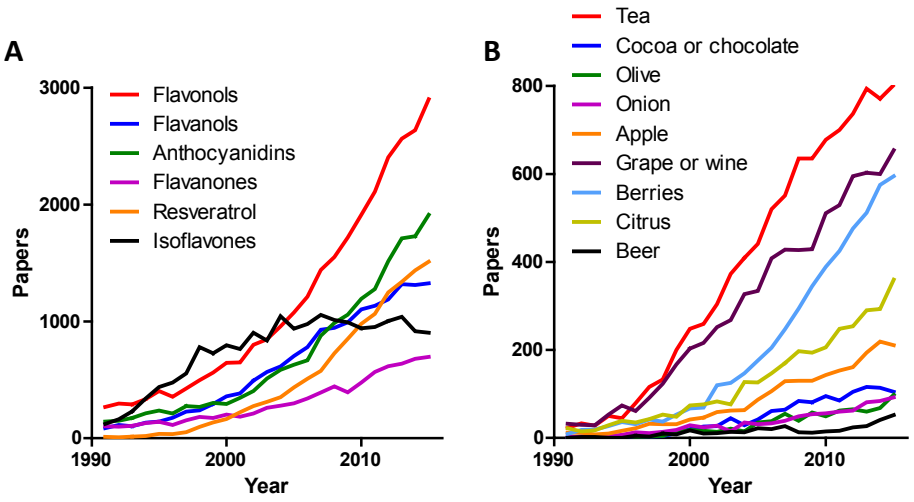

Fig. 3. Trends in research (1991–2016) in the fields of the different flavonoid classes and related polyphenols (isoflavonoids and resveratrol) and flavonoid rich foods. **A.** Flavonols were identified by the search "flavonol* or quercetin or kaempferol or isorhamnetin or myricetin or morin or fisetin or quercitrin or rutin", flavanols by "flavanol* or flavan-3-ol* or catechin or epicatechin or epigallocatechin", anthocyans by "anthocyan* or cyanidin* or delphinidin or malvidin or pelargonidin or peonidin or petunidin", isoflavonoids by "isoflavon* or genistein or daizdein", flavanones by "flavanon* or eriodictyol or hesperetin or hesperidin or naringenin or naringin", resveratrol by "resveratrol". Data are annual number of papers (articles and reviews) indexed in the Web of Science (Science Citation Index Expanded). **B.** Research on flavonoid-rich foods. Identified documents for whole flavonoids as in Fig. 1 were combined with the queries "tea", "Cocoa or Chocolate", "Olive*", "berries or strawberr* or raspberr* or blueberr* or redcurrant* or blackcurrant*", "citrus or orange* or lemon* or grapefruit", "beer*", "grape* or wine*", "apple* or cider*", "onion*". Data are annual number of papers (articles and reviews) indexed in the Web of Science (Science Citation Index Expanded). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4.3. Anthocyanidins and berries: a touch of color and health

The research on anthocyanidins and their glycosides anthocyanins deserves special consideration. Traditionally, these compounds have been studied as natural colorants, and there is great interest in the wine industry because they are responsible for the colors of red wine. As anthocyanidins are positively charged, and hence highly hydrophilic, their ability to cross membrane barriers was thought to be especially limited. However, multiple studies have shown that they have clear biological activity *in vivo* that correlates with either their ability to cross membranes using active transporters or their metabolism into more lipophilic and readily-absorbable compounds. Therefore, the interest in these compounds has shifted from their color to their potential health-promoting properties [12]. Accordingly, research on berries including raspberry, blackberry and blackcurrant, whose main active components are anthocyanidins, has also risen impressively in recent years (Fig. 3A and B).

4.4. Rise and fall of isoflavones

The evolution of the research on isoflavones shows a strikingly different profile compared with the research on other flavonoids (Fig. 3A). In the 1990s, the use of hormone replacement therapy (HRT) for menopausal women was at its peak. Early observational data on HRT showed many health benefits. Isoflavones as the main phytoestrogens were very fashionable alternatives to estrogens. In fact, the lower prevalence of osteoporotic fractures, breast cancer, and cardiovascular disease in women in Asia had been attributed to their soy-based diet, rich in isoflavones. Thus, this area developed much earlier than that of the other flavonoids. Later randomized trials with HRT showed no such benefit and, indeed, an increased risk of coronary heart disease, which led to an abrupt decrease in the use of HRT. Research in this area declined after 2002, as can be seen by the decreasing trend in the number of published papers identified with the query "hormone replacement therapy" (not shown). This was probably the main reason why research on isoflavones plateaued at the beginning of this century. More recent re-analysis of data and newer randomized trials consistently show reductions in coronary heart disease and mortality when

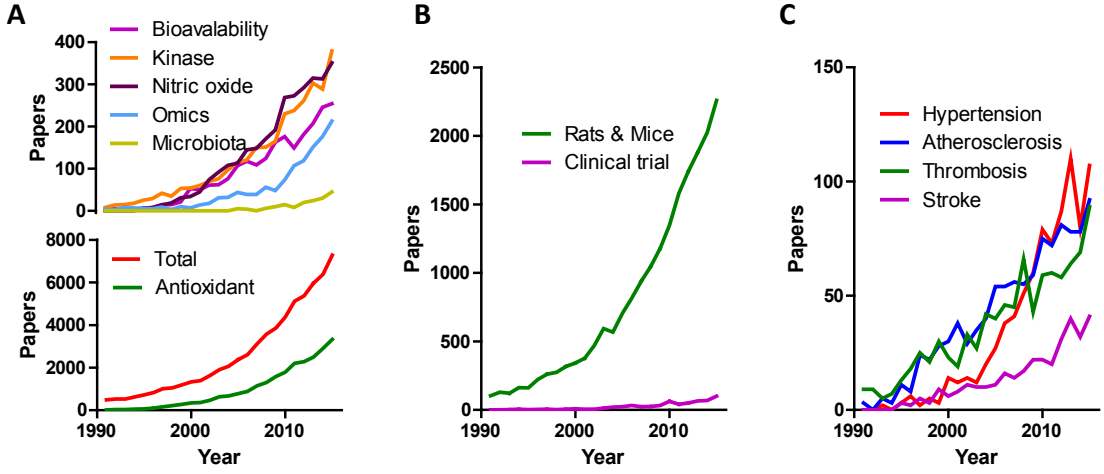

Fig. 4. Trends in research (1991–2016) on flavonoids by topic. **A.** Research on flavonoids identified as in Fig. 1 combined with some keywords. Omics included "proteomic*", "genomic*" "transcriptomic*" or "metabolomic*". **B.** Research on flavonoids identified as in Fig. 1 combined with "rat*" or "mouse" or "mice" or with clinical trial identified as such by WOS. C. **B.** Research on flavonoids identified as in Fig. 1 combined with some cardiovascular specific subareas. All data are annual number of papers (articles and reviews) indexed in the Web of Science (Science Citation Index Expanded).

HRT is initiated soon after menopause [13]. However, the effect of isoflavones against bone loss or menopausal symptoms is still controversial and published data only support a weak protective effect [14], and their impact on coronary heart disease has not been tested in large randomized controlled trials.

4.5. Long life to resveratrol?

The first published documents on resveratrol date back to the late 1970s. The research on this stilbene started much later than that on flavonoids (Fig. 3A). A few papers characterized its antioxidant, antiatherogenic and antiplatelet effects in the 1990s and attributed to it part of the beneficial effects of red wine. However, the spark triggering the expansion of resveratrol research was the publication of its activator effect on sirtuins and the extension of lifespan, initially in yeast and then in higher organisms including mammals. Because resveratrol is found mainly in grapes and red wine, this has also likely contributed to the continuous rise in the research on the effects of wine on human health. However, results in recent years failed in confirming positive health effects and that seems to be reflected in the lower growth of papers published in the last years observed in Fig. 3A.

4.6. Wine. Alcohol versus polyphenols. To drink or not to drink? How much? How good?

One of the early suggestions that moderate wine consumption could be good for cardiovascular health was based on the so called “French Paradox”. This phenomenon was reported in the early 1990s [15] and describes the paradoxical situation in the French population, which, having a high intake of saturated fat, display a low mortality from coronary heart disease. This low mortality was attributed in part to high wine consumption. This has led to a general consensus that light or moderate intake of wine or alcoholic beverages is cardioprotective. However, this is not been without controversy. One controversy is regarding whether the beneficial effects are due to the alcoholic content, the polyphenolic content or both [16]. Several reports indicate that alcohol itself may have some beneficial effects on plasma lipids and the fibrinolytic system. On the other hand, wine, and particularly red wine, is very rich in flavonoids (flavonols, flavanols and anthocyanins) and other polyphenols such as resveratrol, and evidence for the positive effects on cardiovascular health of these compounds is abundant. No doubt, this controversy has stimulated the very robust research on wine and grapes as shown by the growing number of papers on grapes and wine shown in Fig. 3B. Another controversy relates to public statements on drinking recommendations [16]. There is no doubt that excessive consumption of alcohol is clearly detrimental to human health and, in fact, alcohol drinking is one of the main causes of mortality, morbidity and social dysfunction worldwide. Given the potential addictive effect of alcoholic drinks, and hence the difficulty of keeping consumption moderate in some individuals, there is by no means consensus on whether moderate wine drinking should be recommended or not. Currently, the American Heart Association guidelines recommend that if you drink do so in moderation, i.e. $\leq$ 1 drinks for women and $\leq$2 drinks for men.

5. Research on flavonoid targets

5.1. Are flavonoids still antioxidants? Something else?

Flavonoid research was largely supported by the potential antioxidant capacities of these compounds and the assumed relevance of free radical mediated deterioration of the biological systems and its association with diseases. Although these antioxidant actions were based on the chemical structures of flavonoids, they were not accompanied by flavonoid bioavailability. In the last years such potentiality has fallen from a universal dogma, to a possibility circumscribed to special situations. In the last decade, there is an emerging opinion that flavonoids mostly do not act as conventional antioxidants but may exert antioxidant actions at enzymatic targets involved in multiple signaling pathways such as those involving protein kinases and redox sensitive cysteines, among other oxidant-prone moieties [17–20]. Thus, the research with flavonoids in the field of protein kinases has experienced an important growth (Fig. 4A). In any case, the association between flavonoid research and antioxidant actions remains significant since almost half of the publications on flavonoids mention “antioxidant effects” (Fig. 4A). In Fig. 1, we compared the evolution of polyphenol research with antioxidant vitamins (C, E and carotenoids) and selenium research. Especially for vitamin C and vitamin E, flavonoid research followed a similar trend until the 2000s when the flavonoid research started growing exponentially. This dissociation could be due to the failure of large prospective randomized clinical trials in the late 1990s and early 2000s to demonstrate that vitamin C, vitamin E and carotenoids have health benefits [21]. In a certain manner it is possible to infer that research in traditional antioxidants (vitamin E, vitamin C, selenium) moved to promising new promoters of health, e.g. flavonoids and other polyphenols.

While research in animal models with flavonoids has grown considerably, clinical trials are still scarce (Fig. 4B). Unfortunately, large and long term randomized trials on cardiovascular risk factors and mortality with flavonoids have not been performed. The ongoing project Cocoa Supplement and Multivitamin Outcomes Study (COSMOS) designed to test the effects of food bioactives and nutrient supplements on cancer and cardiovascular disease (CVD) prevention will be the first large-scale randomized trial to include a vast population (22,000 participants) over a long period (5 years).

Fig. 4A shows that besides studies on protein kinases, research on other determinants of flavonoid biological actions also have grown, e.g. flavonoid bioavailability and interaction with nitric oxide [22]. The field of omics technologies has emerged rapidly since 2010 and more recently, several papers focused on the role of microbiota, yet the impact in the whole field of flavonoids is still limited. When considering the health effects of flavonoids, and cardiovascular disease being a major target of flavonoid research, it can be observed that interest in thrombosis and atherosclerosis started in the 1990s while research in hypertension was initiated later, but it is now catching up.

6. Birth, evolution and role of the International Conference on Polyphenols and Health (ICPH)

The presented data on the exponential evolution of the research on flavonoids is also reflected in the number of different conferences that are organized around the world to discuss the subject. We have been involved in the development of the ICPHs, a series of scientific meetings dedicated to present and discuss the relevance of flavonoids and other polyphenols on human health.

Started In 2003, when Augustin Scalbert organized the 1st ICPH with the intention of generating a space in which investigators in polyphenols, including flavonoids could benefit from the growing space of “health”. The meeting was a success with more than 600 attendants, almost 300 poster presentations and more than 50 speakers and chairpersons. The second conference took place in 2005 at the University of California Davis, and was led by Cesar Fraga, Andy Waterhouse, and Alison Mitchell. The success of both of these ICPH was the confirmation of the existence of a niche for considering flavonoids as health promoters and resulted in the instauration of ICPH as a biennial meeting rotating among Europe, the Americas, and Asia. Thus, the following ICPH were 2007 in Kyoto organized by Junji Terao; 2009 in Harrogate organized by Gary Williamson and Andrea Day; 2011 in Sitges organized by Cristina Andres Lacueva and Paco Tomás-Barberan; 2013 in Buenos Aires organized by Cesar Fraga and Patricia Oteiza; 2015 in Tours organized by Christine Morand; and 2017 in Quebec organized by Yves Desjardins and Andre Marette. The series is expected

to continue in 2019 in Kobe organized by Hitoshi Ashida and Kayoko Shimoi, and in 2021 in a major university-town in the U.K. headed by Jeremy Spencer.

In brief, it is possible to say that the ICPH provides the appropriate environment for presentations and discussions on the role of flavonoids and other polyphenols in health and disease. Interestingly, while an academic-based conference, it has been able to maintain the interest of major global companies that have actively participated in all the ICPH. We are proud that the most relevant scientists in this area of research recognize and support the ICPH as premiere global scientific meetings.

7. Future adventures

We envision a continued growth in flavonoid research, and consequently of publications, for the coming decade(s). However, to reach a real maturity, this increase should be accompanied by research of quality that allow demonstrating the importance of flavonoids to human health. Thus, future endeavors should not just provide phenomenological and casual relationships, as much of the flavonoid research has done up to this moment, but solid data that can be extrapolated to human conditions.

Some actions that should be considered to accomplish in future research in flavonoids, which are extensive to other bioactives, are:

a) running experiments to corroborate a hypothesis as primary (or secondary) endpoints (not “fishing expeditions”).
b) performing more randomized controlled clinical trials, of long duration, that involve clinically important endpoints.
c) considering thoroughly the limitations of *in vitro*, animal and human studies when making conclusions.
d) using state of the art laboratory techniques to corroborate presence and quantify flavonoids in the foodstuff, supplement, etc., to be used.
e) establishing mechanisms of action; we need to surpass the empirical observations and treat flavonoids as chemical compounds no matter they are consumed as dietary components.
f) using computing assisted methodologies to improve routines that allow to obtain stronger epidemiological and food composition data.

Conflicts of interest

The authors have no competing interest to declare.

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