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Review

Antioxidant polyphenols in cancer treatment: Friend, foe or foil?

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ABSTRACT

Cancer prevention can be probably obtained with easier, faster and less financial strains by pursuing educational programs aimed to induce changes in lifestyle, starting from dietary habits. In the past decades, observational and case-control studies tried to establish a functional relationship between cancer mortality and morbidity and diet. The field becomes even more intricate when scientists investigated which dietary components are responsible for the putative, protective effects of fruits and vegetables against cancer. A relevant part of the literature focused on the positive role of "antioxidant" compounds in foods, including polyphenols. The present review critically evaluate clinical and pre-clinical studies based on polyphenol administration, which contributed to support the concept, deeply rooted in the general population, that antioxidant polyphenols can fight cancer. The controversial and contradictory issues related to the pros and cons on the use of polyphenols against cancer reflect the confounding assumption that cancer treatment and cancer prevention may overlap. We conclude that a clear cut must be done between these two concepts and that the experimental approaches to investigate one or the other should be significantly different, starting from adequate and specifically selected cellular models.

1. Introduction and scope

In accordance with the recent report from the World Health Organization (WHO), the average number of new diagnosed cases of cancer in the World overcomes 14 million per year and, among these, more than 60% result in dead (8.8 million in 2015) [1]. In this scenario, cancer early detection and prevention should represent one of the priority for governments, health agencies, international organizations in all countries, especially those with low and middle incomes. Multiple strategies can be effective to improve early diagnosis of cancer, depending upon specific cancer types, availability of adequate medical structures and, overall, important financial investments from the governments involved. However, cancer prevention can be probably obtained with easier, faster and less financial strains by means of educational programs aimed to induce changes in lifestyle, starting from dietary habits.

Early in 1992, the analysis of 156 case-control studies revealed in 128 of them a significant inverse relationship between fruit and vegetable consumption and the occurrence of cancer [2]. This observation was one of the key element that initiated the well-known campaign "5 a day" (the suggestion to consume at least 5 daily servings of fruits and vegetables) in United States, followed shortly by many other countries. No much later, the conclusions of the 1997 World Cancer Research Fund (WCRF) report [3] estimated that adequate consumption of fruit and vegetables could reduce by 23% the incidence of all cancer types, classifying as "convincing" the level of available scientific evidence. However, the second WCRF report, published ten years later [4,5], lowered this level from "convincing" to "likely", based on the evidence emerging from the publication of new cohort studies. The inverse relationship between a diet rich in fruit and vegetable and cancer incidence further weakened when the consumption of alcohol and tobacco was also considered, leading the authors to suggest caution regarding the positive and measurable effects of fruit and vegetable consumption on cancer rates, at least in well-nourished populations [6]. The divergences emerged on this topic have been further complicated by two recent reviews which expressed more favorable opinions on the inverse association between consumption of vegetables and fruit and cancer incidence. In one case, the intake of vegetables and fruits and lower cancer risk was defined "probable" [7]. Similarly, the 2015 report of the Diet & Cancer European Code Against Cancer concluded that a diet characterized by high intake of plant foods (fruits, vegetables, legumes and whole grains), low consumption of red meat and sausages, low intake of sugars simple, low salt intake could reduce the overall risk of cancer (the decrease was additive and resulted of about 5% for each of the previous recommendations). The most noticeable benefits were observed for cancers of the stomach, endometrium, esophagus, colon

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and rectum, mouth, pharynx and larynx (risk reduction of 12–16%) [8]. A very recent systematic review and dose-response *meta*-analysis concluded that, for total cancer, the lowest risk is observed at an intake of 600 g/day of fruit and vegetable [9].

From the above analysis, it appears evident the complexity to establish a functional relationship between cancer mortality and morbidity and diet based on observational and case-control studies. The field became even more intricate when scientists tried to identify which dietary components are responsible for the putative, protective effects of fruit and vegetable against cancer. A relevant part of the literature in the last two decades focused on the positive role of "antioxidants" in foods. The so-called "antioxidant hypothesis" or "free radical theory" for degenerative diseases originated back in the late 1980s – middle 1990s, after the publication of a series of important papers by influential groups who suggested that increasing plasma concentrations of vitamin E, vitamin C, and β-carotene with the diet would contribute to prevent cardiovascular diseases and cancer ([10,11] and references therein). To make an example, in his pivotal article published in 1994, Dr. Barry Halliwell declared that "our endogenous antioxidant defenses are inadequate to prevent oxidative damage completely. Hence, sources of dietary antioxidants may be especially important to us" [12], a sentence clearly going in the direction of a beneficial role of dietary antioxidants against degenerative diseases. However, since then, he raised the problem of the "optimal intake" and warned about the possibility that several of these compounds, e.g. carotenoids, "…can be made to exert antioxidant effects *in vitro*, but there is no evidence as yet that this mechanism produces any beneficial action in humans" [12]. He recently critically reviewed his original position concluding that "plants are full of antioxidants, but we cannot just pull out one or two individual 'antioxidant' molecules and expect pills containing high doses of them to protect us" [11]. In fact, the unexpected negative results of large intervention studies with clinical endpoints belong now to the history of science: in the ATBC trial in Finland (29,133 male smokers receiving daily 20 mg β-carotene, 50 mg α-tocopherol, or both), β-carotene significantly increased risk of lung cancer (RR: 1.16, CL: 1.02–1.33) [13]. In the CARET study in the USA (daily administered of 30 mg β-carotene and 25,000 IU retinyl palmitate to 18,318 smokers and asbestos-exposed subjects for 10 years with a follow-up of 11 years), a significant increase in lung cancer (RR:1.28; CL: 1.04–1.57) and prostate cancer was detected (RR: 1.52; CL:1.03–2.24) [14,15]. It is not the purpose of this article to review the extensive and qualified literature on this topic. In the following paragraphs, we will concentrate our analysis on clinical and pre-clinical studies based on polyphenol administration, which contributed to support the concept, deeply rooted in the general population, that antioxidant polyphenols can fight cancer.

We (authors and readers) all know that this field is incredible fertile to be concentrated in a single, comprehensive review. Therefore, we selected those works that, in our opinion, may help to better clarify our point of view; thus, we apologize in advance for the many omissions, hoping that this review may help to predict future developments in the field.

2. Clinical study investigating the anticancer effect of polyphenols

We approached the analysis of the functional relationship between polyphenols administration/consumption and cancer prevention starting from the results of clinical studies already published or ongoing. Searching PubMed (http://www.ncbi.nlm. nih.gov/pubmed/) for meta-analyses on polyphenols and cancer, we retrieved only four studies [16–19], all leading to inconclusive and partial results. The authors' conclusions go in the same direction, since in all meta-analyses published they encourage to design new case-control and prospective epidemiological studies with larger cohorts, longer duration of follow-up, new methods to evaluate exposure to polyphenols (i.e. metabolism and excretion), before taking final conclusions on the health benefits of polyphenols in cancer. Among these meta-analyses, one regarded the association between coffee consumption and glioma in adults in 6 studies (four cohort and two case–control for a total of about 2100 cases) [18]; a second study ended up with no significant association between tea consumption and risk for pancreatic cancer (six cohort and eight case–control), even at high doses [16]. In this case, it is worthwhile to note that subgroup analyses failed to identify any difference between tea types, e.g., green versus black tea, although in a different meta-analysis green tea (three cohort and one case–control), but not black tea (five cohort and eight case–control) consumption was associated with a decreased risk of breast cancer [19]. The most comprehensive meta-analysis has been very recently published and includes 143 studies [17]. Here, in female cancers, medium/high evidence of decreased risk associated with isoflavones was only measured for lung and gastric cancers (low evidence for quercetin and kaempferol in lung cancer and anthocyanins for gastric cancer). However, low evidence of increased risk was associated with flavanones in breast cancer and matairesinol in endometrial cancer. In male, only for prostate cancer a low evidence of decreased risk was associated with genistein and daidzein, while a low increased risk was associated with flavonols. The authors concluded that the results, although promising, remain uncertain [17].

Table 1 reports a selection of observational and interventional studies published in the last 10 years where polyphenols, as single compounds or in mixtures, have been tested against different types of cancers. It appears clear that the large part of them show uncertain, null or even negative results. Examples of positive outcomes are represented by standardized formulations of green tea in the treatment of human papilloma virus (HPV) and chronic lymphocytic leukemia (CLL) [20,21]. However, in the case of HPV treatment, a more recent case-control study on a larger number of women suggested that Polyphenon E intervention did not promote the clearance of persistent high-risk HPV [22]. It is also interesting the chemopreventive effect of a flavonoid mixture made of apigenin and epigallocathechin-gallate to prevent recurrence in patients with resected colorectal cancer [23].

The uncertainty of the clinical studies proving anticancer effects of polyphenols is confirmed by data summarized in Table 2. Here, we interrogated the ClinicalTrials.gov database, a service of the U.S. National Institutes of Health, for "antioxidant" and "cancer" and retrieved only 65 studies "with results". Among these, surprisingly, only five were based on the administration of polyphenols. Some general criticisms emerge from data in Table 2: (i) in many cases, they refer to phase II clinical trials; in other words, these studies gathered to obtain preliminary data on polyphenol effectiveness; (ii) four out of five of them are testing green tea extracts, probably because Polyphenon E represents a standardized formulation, ideal for pharmacological administration; (iii) the results described appear ambiguous, preliminary and of limited clinical significance.

3. Pre-clinical models to approach the anticancer effect of polyphenols

Despite the uncertain results deriving from clinical studies, the efficacy of polyphenols against cancer strongly emerges considering their usage in pre-clinical investigations. Table 3 reports examples of studies on the anticancer effects of selected polyphenols in animals (mice or rats) genetically programmed to develop cancer, or in models where tumours were experimentally induced by means of chemical carcinogens or radiations. Not surprisingly, the large majority of these studies ended with positive results, both in terms of cancer therapy or prevention (examples are given in Table 3). Some critical issues can be easily evidenced analysing these works all together: (i) independently from the preventive or therapeutic treatment considered, the dosage is very often in the order of hundreds mg/kg, which means grams in humans; these quantities exclude any consequential cause-effect rela-