Review Article

High quality, good health: The case for olive oil

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The healthful properties of olives and their main derivatives are being actively investigated. In this review, we briefly appraise and descriptively review the most recent evidence on the purported correlations between olive oil consumption and health, and we provide some bibliometric analyses that show how fast the field of "olive components and health" is indeed moving. Based on accumulated findings, we expect olive oil (and related products) research to further grow in the next few years, when more olive-derived nutraceuticals and functional foods will enter the market and when targeted basic mechanism research will further clarify the manifold mechanisms of action of olive (poly)phenols.

Practical applications: Our findings underscore the need to produce and consume high quality olive oil, whose "minor components" are endowed with heathful properties.

Keywords: Bibliometry / Cardiovascular disease / Hydroxytyrosol / Mediterranean diet / Nutraceuticals / Olive oil

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1 Introduction

The attempt to find causal links between food intake and disease prevention has considerable traction in the scientific community and also enjoys wide coverage in the lay press. One notable case among macronutrients is that of fatty acids: dietary recommendations are shifting from discouraging the consumption of saturated fatty acids to more balanced views in which saturates from, e.g., dairy products are allowed within the frame of a balanced diet [1]. (Poly)phenol-rich foodstuffs also receive extensive press coverage and many of them are exploited to formulate nutraceuticals [2]. Examples are cocoa, tea, coffee, wine, and—in general—fruits and vegetables, and functional foods [3]. One food item for which research is most advanced is extra-virgin olive oil [4]. Indeed, hydroxytyrosol (HT; olive's foremost phenolic component) is the only (poly)phenol that has been granted a European Food Safety Authority health claim [5].

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Abbreviations: CVD, cardiovascular disease; **HT,** hydroxytyrosol; **LDL,** low density lipoprotein

The healthful properties of olives and their main derivatives, i.e., olive oil and olive mill waste water (OMWW) are being actively researched and have been reviewed in other publications [4, 6, 7]. Here, we want to briefly appraise and descriptively review the most recent evidence on the purported correlations between olive oil consumption and health and we want to provide some bibliometric analyses that show how fast the field of "olive components and health" is indeed moving. Of note, we provide an extensive and relevant bibliography for readers to peruse.

2 The oleic acid argument

As reviewed elsewhere [1, 4, 8], the contribution of oleic acid to the healthful actions of olive oil is scientifically feeble. Several reasons concur to the formulation of this statement. In brief: (i) oleic acid (18:1n-6) is not an essential fatty acid: the body can synthesize it and no clinical signs of deficiency have been described [9]; and (ii) the overall amount of oleic acid in the diet is not much different between olive oil consuming countries (namely those facing the Mediterranean basin) and other countries such as the USA and the UK that consume oleic acid through, e.g., pork and chicken [10]. If we look at human evidence, namely at clinical trials and at blood fatty acid composition as related to disease incidence, accumulated, albeit probably insufficient evidence clearly indicates that high plasma or phospholipid concentrations of 18:1 are associated with higher cardiovascular disease (CVD) risk. In an elegant recent study, Würtz, et al. [11] showed—by a metabolomics approach—that higher serum monounsaturated fatty acid concentrations are associated with increased CVD risk (in contrast to polyunsaturated fatty acids). These data confirm those of Marangoni et al. [12] and of Block et al. [13], who reported higher monounsaturated fatty acid concentrations in myocardial infarction patients as compared with controls. In synthesis, the available evidence for cardiometabolic benefits of total monounsaturated fat (largely oleic acid) is quite weak. It must be underscored that: (i) plasma levels of monounsaturates do not accurately reflect intakes, precisely because these fatty acids are not essential, i.e., they can be synthesized in vivo; and (ii) there might be considerable health differences depending on the source of oleic acids, i.e., vegetables and olive oil versus animal products [8]. Therefore, even though some authors, e.g., [14, 15] indeed point to the fact that the substitution of saturated fatty acids with oleic acid reduces total and LDL-cholesterol and replacement of carbohydrates with oleic acid lowers triacylglycerols and LDL-cholesterol (all effects that reduce cardiovascular risk), accumulated evidence strongly suggests that 18:1 is not the olive component chiefly responsible for their biological actions and we would like to adduce the reader to the pivotal biological roles of (poly)phenols.

3 Recent evidence on olive oil minor components and human health

3.1 Molecular studies

As mentioned above (and in other publications, e.g., [4, 6]), if extra virgin olive oil consumption indeed affords better cardiovascular prognosis and is chemopreventive this is most likely not due to its fatty acid profile. Olives and their products contain very peculiar molecules (most of which phenolic in nature such as oleuropein, oleocanthal, and hydroxytyrosol) that are being very actively investigated worldwide (vide infra). In addition, it should be underlined that an additional class of potentially healthful compounds, i.e., triterpenes such as oleanolic and maslinic acids, uvaol, and erythrodiol are emerging as potential contributors to the extra virgin olive oil-associated heath effects, as elegantly reviewed by Sánchez–Quesada et al. [16].

Indeed, even though other vegetable oils such as argan oil also contain potentially healthful minor components [17, 18], those of extra virgin olive oil enjoy abundant literature, spanning from in vitro mechanistic studies to animal and human intervention trials.

The primary activities of olive (poly)phenols concern CVD. Even though over the past few years most attention has been paid to the antioxidant properties of olive (poly) phenols, the recent 5 or 6 years witnessed a shift toward a wider range of cardioprotective activities. In this regard, Giordano et al. [19] showed that HT and—interestingly—its foremost metabolites, i.e., 3-O-hydroxytyrosol glucuronide and 4-O-hydroxytyrosol glucuronide [20] are able to inhibit endoplasmic reticulum (ER) stress in human hepatic cells, at physiological concentrations. This might be very relevant to CVD prevention, because misfolded proteins and, therefore, dysfunctional lipoproteins are likely to be atherogenic via uptake by the macrophage scavenger receptor [21]. In fact, this action (to be confirmed in humans) is likely more relevant to CVD prognosis than the prevention of low density lipoprotein (LDL) oxidation observed after the administration of high-(poly)phenol olive oil [22]. Also of relevance to CVD prevention, even if unrelated to anti-oxidation, are the findings that HT is able to inhibit cannabinoid CB1 gene expression [23] and to stimulate lipolysis in pre-adipocytes [24] might bear import consequences in the adjunct treatment of the metabolic syndrome and related pathologies, namely obesity.

Endothelial dysfunction is a common attribute of atherosclerotic CVD and its onset, and modulation are profoundly influenced by inflammation and redox status [25, 26]. Therefore, provision of anti-inflammatory and/or "antioxidant" molecules (regardless of their true mechanism of action) should, actually, provide benefits, and improve prognosis. Indeed, a couple of recent papers [27, 28] investigated—at the molecular level—the effects of HT in two different cellular models of endothelial dysfunction. The Catalán et al. [28] paper is particularly important in that the authors also tested the effects of HT's metabolites, which are the ones that, purportedly, exert the biological effects and are most often ignored by the scientific community. In this respect, the use of sera from subjects who were given extra virgin olive oil provides an interesting and physiologically relevant model to investigate the actions of olive (poly) phenols on cultured endothelial cells [29]. It should also be reiterated that HT per se, i.e., in the absence of stimuli, does not increase nitric oxide production by endothelial cells [30] and thus, we still need extensive investigation and human trials to ascertain its role in endothelial function [31]. Finally, we would like to remind readers that results obtained with cultured endothelial cells need to be interpreted with extreme caution because cultured media do not contain antioxidants and, therefore, such cells are prone to oxidative damage [32].

The chemopreventive potential of olive oil phenolics are still debated and have never been demonstrated in vivo [33]. However, several in vitro studies [33] indeed indicate that HT and related compounds might indeed prevent the onset and development of some cancers, especially those in the colo-rectal tract, via several mechanisms such as down-regulation of epidermal growth factor receptor expression [34] or limitation of oxidized cholesterol-induced parietal damage [35]. It is important to note that the gastrointestinal tract is exposed to higher concentrations of (poly) phenols, including those ingested with extra virgin olive oil and might, therefore, be the most relevant target of chemoprevention. Also, even though antioxidant actions do not entirely explain the healthful actions of olive (poly) phenols, limitation of oxidized lipid- and oxidized cholesterol-induced damage might greatly contribute to prognosis, as suggested by, e.g., the IMPROVE-IT trial [36].

3.2 Animal studies

As repeatedly highlighted, the vast majority of studies on olive (poly)phenols concern their cardioprotective activities. However, in recent years, many other biologically relevant properties have been investigated. Of course, ethical and practical limitations hamper human trials and, therefore, the totality of available data currently come from in vitro and animal studies.

In terms of neuroprotection, after the initial studies of Schaffer et al. [37], some evidence is emerging that points to neuroprotective actions of olive phenolics such as reduced damage following brain ischemia [38]. Of note, HT does accumulate in the brain of rats administered HT with olive oil [39] yet decreases the amount of brain-derived neurotrophic factor in the hippocampus [40], which should be seen as a noxious, yet unconfirmed [41] activity. Also of note, extra virgin olive oil improves memory and learning in mice, possibly via modulation of the antioxidant network [42, 43].

Another active area of research is that of muscular-skeletal diseases such as bone loss (menopausal- or drug therapy-induced) or arthritis/arthrosis. Indeed, considerable evidence is accumulating and indicates that olive phenolics can indeed find a place beside the current medical armamentaria [44–47].

3.3 Human studies

The most important trials (from a pharma-nutritional viewpoint) are the ones performed in humans. In this regard, Crespo et al. [48] tested the "nrf2 hypothesis" that posits that (poly)phenols do not act as direct antioxidants, but, rather, as para-hormetic inducers of Phase II enzymes [49]. Albeit interesting and supported by extensive in vitro and animal literature, this hypothesis has never been confirmed in humans (neither for HT nor for any other (poly)phenol). Indeed, the authors were unable to observe any modification of Phase II enzyme expression in human volunteers who were given 5 or 25 mg/d of bioavailable [50] HT (vs. placebo) for 1 wk. In synthesis, the current popular proposition that (poly) phenols activate the stress response pathways via nrf2 induction awaits unequivocal proof-of-concept in humans.

One of the most important nutrition trials of the past few years is PREDIMED [51]. The main conclusions of that study is that diets that incorporate extra virgin olive oil or nuts (which are rich in both phenolic compounds and omega 6 fatty acids [52]) significantly lower CVD recurrence in cardiovascular patients. Recently, the authors sought to ascertain which components of the two cardioprotective diets were responsible for the observed effects. Martinez–Gonzalez and other authors recently reported that, indeed, the (poly) phenols ingested via extra virgin olive oil by PREDIMED patients were significantly associated with the health effects observed for the experimental diets [53–56].

3.4 Toxicology

Given the considerable interest in the commercial exploitation of olive (poly)phenols, toxicological studies are accumulating [57–60]. Even though more studies are needed, accrued evidence underscores the safety profile of individual molecules, i.e., HT and raw extracts [61, 62]. Indeed, HT is Generally Recognized as Safe (GRAS) in the USA and its current NOAEL is 500 mg/kg/day [2].

4 The scientific impact of olive (poly)phenols: A bibliometric analysis

4.1 Methods and results

4.1.1 Scopus search

Searches in the data base Scopus have been performed (on January 21, 2016) by using the following strings (timeframe up to 2015): TITLE-ABS-KEY(hydroxytyrosol)AND(EXCLUDE(PUBYEAR,2016)) = 1335 records; TITLE-ABS-KEY(oleuropein)AND(EXCLUDE(PUBYEAR,2016)) = 1209 records; TITLE-ABS-KEY(oleocanthal)AND(EXCLUDE (PUBYEAR,2016)) = 87 records.

Through the combination of such search strings, we noticed that the documents shared by hydroxytyrosol and oleuropein, oleuropein and olecanthal, hydroxytyrosol and olecanthal are 485, 23, and 18, respectively (see strings).

(TITLE-ABS-KEY(hydroxytyrosol))AND(TITLE-ABS-KEY(oleuropein))AND(EXCLUDE(PUBYEAR,2016)) = 485 records; (TITLE-ABS-KEY(oleuropein))AND(TITLE-ABS-KEY(oleocanthal))AND(EXCLUDE(PUBYEAR,2016)) =

23 records; (TITLE-ABS-KEY(hyd roxytyrosol))AND (TITLE-ABS-KEY(oleocanthal))AND(EXCLUDE(PUBYEAR,2016)) = 18 records.

In total, the three search strings led to 2117 de-duplicated documents

(TITLE-ABS-KEY(hydroxytyrosol))OR(TITLE-ABS-KEY(oleuropein))OR(TITLE-ABS-KEY(oleocanthal)) AND(EXCLUDE(PUBYEAR,2016)) = 2117 records.

The results were analyzed by using the "Analyze search results" function, available in the database for each set of

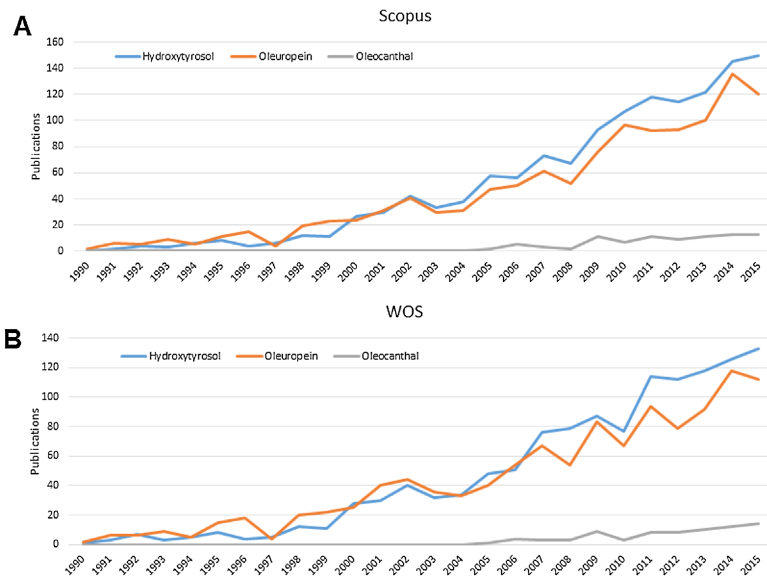

Figure 1. Number of publications on HT, oleuropein, and oleocanthal plotted against year of publication according to Scopus (A) or WOS (B). Search details are given in the main text and data start from 1990.

Figure 2. Journals in which publications on HT, oleuropein, and oleocanthal appear, according to Scopus (A) or WOS (B). Search details are given in the main text and the top ten journals are shown.

results and by extracting in a cvs format all data concerning Year (publication year), Source (source titles), Affiliation and Country/territory. Data were then imported into Excel to create the graphs.

4.1.2 WOS search

Searches in the Web of Science Core Collection database (Timespan 1985–2016) were performed (on January 21, 2016) by using the following strings, excluding publications later than 2015: TOPIC: (hydroxytyrosol); Refined by: (excluding) PUBLICATION YEARS:(2016); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years = 1245 records; TOPIC: (oleuropein); Refined by: (excluding) PUBLICATION YEARS: (2016); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years = 1150 records; TOPIC: (oleocanthal); Refined by: (excluding) PUBLICATION YEARS: (2016); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years = 75 records.

Through the combination of such strings, we noticed that the documents shared by hydroxytyrosol and oleuropein, oleuropein and olecanthal, hydroxytyrosol and olecanthal were 463, 11, and 14, respectively (see strings).

TS = (hydroxytyrosol AND oleuropein); Refined by: (excluding) PUBLICATION YEARS:(2016); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years = 463 records;

TS = (hydroxytyrosol AND oleocanthal); Refined by: (excluding) PUBLICATION YEARS:(2016); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years = 11 records;

TS = (oleuropein AND oleocanthal); Refined by: (excluding) PUBLICATION YEARS:(2016); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years = 14 records.

In total, the three search strings led to 2015 de-duplicated documents

TS = (hydroxytyrosol OR oleuropein OR oleocanthal); Refined by: (excluding) PUBLICATION YEARS:(2016); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years = 2015 records.

The results were then analyzed by using the “Analyze results” function, available in the database for each set of results, extracted in a txt format via “Save analysis data to file” as Publication Year, Source titles, Organizations and Countries/Territories. Data were then imported into Excel and elaborated to create graphs.

The number of publications on olive (poly)phenols is rapidly and steadily increasing (Fig. 1). Of note, HT is a more

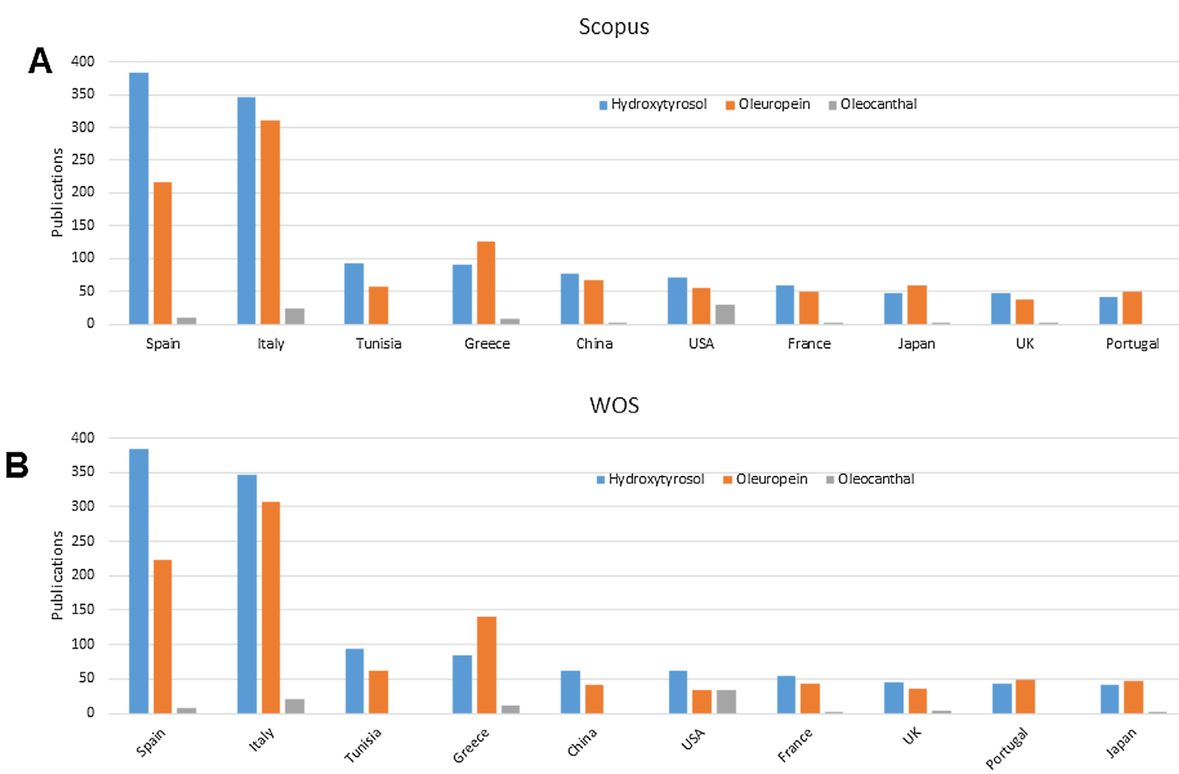

Figure 3. Geographical origin of publications on HT, oleuropein, and oleocanthal according to Scopus (A) or WOS (B). Search details are given in the main text.

coveted molecule than the other (poly)phenolic molecules such as oleuropein and oleocanthal. This might be due to its use in nutraceutical and functional food preparations.

As expected, the great majority of papers are published in agricultural and food journals (Fig. 2), but nutrition journals are also popular means of dissemination. It is conceivable that future, biomedical research will increasingly be published also in medical or biomedical journals.

Most olive (poly)phenol research is performed in Mediterranean countries, namely Spain, Italy, Tunisia, and Greece (Figs. 3 and 4). Of note, geographical distribution is calculated differently by the two databases we used (Fig. 3, Panels A and B). Also noteworthy is the fact that both China and the USA, i.e., countries where olive oil production and consumption is not part of agricultural and gastronomic practice, are publishing a considerable proportion of papers, indicating the (current or future) pharma-nutritional use of these molecules.

One remarkable of our bibliometric analysis is the disparity we found between Scopus and WOS (see the Figs. 1–4). Therefore, we recommend the use of more than one database for bibliometric and scientometric analyses as well as for paper redaction. It should also be underscored that some papers have been retracted yet are still being cited (e.g., 15 to >20 times since retraction) and add up to the final score. Thus, we strongly encourage researchers to carefully read the literature they cite to sort the most appropriate literature.

5 Conclusions

In this narrative update of the recent literature on olive's biologically attractive by-products, i.e., extra virgin olive oil, olive mill waste water, and supplements derived from this pipeline, we wanted to bring forward how rapidly the field is evolving and the large amount of information we have. In this respect, the "olive field" is more advanced than those of, e.g., wine, tea, or other (poly)phenol-rich foods and beverages. Together with abundant in vitro mechanistic studies, there is copious in vivo, including human, literature that is rapidly accumulating. Of course, several important pieces of information are still missing and warrant further research. Possibly, the primary missing piece of the complex puzzle is that of having sufficient randomized trials with adequate

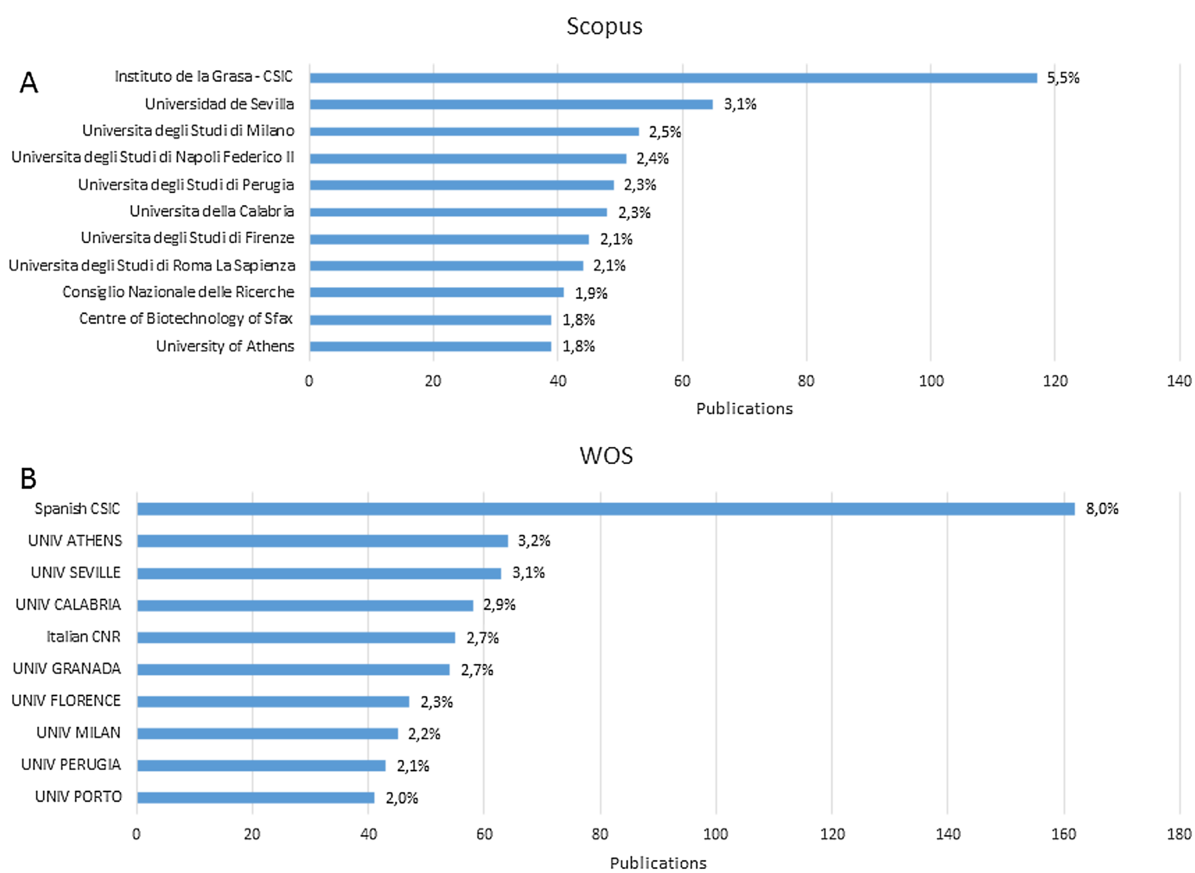

Figure 4. Affiliations of authors publishing on HT, oleuropein, and oleocanthal according to Scopus (A) or WOS (B). Search details are given in the main text.

endpoints to establish the in vivo actions of olive (poly) phenols beyond doubt. While most investigators focus on the redox code [63] (which attracts considerable yet scientifically unjustified attention by the lay press), several other—often more important—activities might explain the reduced cardiovascular mortality of extra virgin olive oil consumers. One example is that of hormesis and associated nrf2 activation [64]. Even though this hypothesis has not been confirmed in humans, it is conceivable that such activity be site-specific and chiefly takes place in the liver. Validation of this theory would require liver biopsies and is of difficult execution in humans. Inflammation is also a potential and likely target of olive (poly)phenols. However, it is currently quite difficult to accurately quantify inflammation in humans (beyond measuring CRP) and, consequently, ad-hoc trials are problematic to implement.

In summary, we expect olive oil (and related products) research to further grow in the next few years, when more olive-derived nutraceuticals and functional foods will enter the market, and when targeted basic mechanism research will further clarify the manifold mechanisms of action of olive (poly)phenols. With these data in hand, the scientific community should then also be better equipped to identify health indications responsive to the prophylactic and therapeutic intervention with olive-derived food products.

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