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Apple polyphenols in human and animal health*

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Apples contain substantial amounts of polyphenols, and diverse phenolics – mainly flavonoids and phenolic acids, have been identified in their flesh and skins. This work aimed to analyze the overall landscape of the research literature published to date on apple phenolic compounds in the context of human and animal health. The Web of Science Core Collection electronic database was queried with (apple* polyphenol*) AND (health* OR illness* OR disease* OR medic* OR pharma*) to identify relevant papers covering these words and their derivatives in the titles, abstracts, and keywords. The resulted 890 papers were bibliometrically analyzed. The VOSviewer software was utilized to produce term maps that illustrate how the frequent phrases fared in terms of publication

and citation data. The apple polyphenol papers received global contributions, particularly from China, Italy, the United States, Spain, and Germany. Examples of frequently mentioned chemicals/ chemical classes are quercetin, anthocyanin, catechin, epicatechin, and flavonol, while examples of frequently mentioned medical conditions are cardiovascular disease, atherosclerosis, diabetes, Alzheimer's disease, and obesity. The potential health benefits of apple polyphenols on humans and animals are diverse and warrant further study.

KEY WORDS: apple polyphenol / quercetin / anthocyanin / cardiovascular disease / atherosclerosis / diabetes / Alzheimer's disease / obesity / Web of Science / VOSviewer

Apples, the fruits of the apple tree (*Malus domestica* (Suckow) Borkh., Family: Rosaceae), are among the most broadly distributed and consumed fruits in the world. According to recent data by the United States Department of Agriculture in 2017, apples were the most consumed per capita fruit in the United States (accounting for the total intake of both fresh and processed apples), followed by oranges (second place) and bananas (third place) [USDA 2019]. While a major part of the produced apples is marketed as fresh fruits, a significant amount is also processed into apple juice, cider, and diverse other processed, frozen, and dried products. While processing apples for the gain of liquid products (e.g., juice, cider, or wine), apple pomace is obtained as a by-product that can be used for further applications, for example, for the extraction of pectin or other valuable bioactive molecules or as a functional ingredient in other food products [Bhushan *et al.* 2008, Grassino *et al.* 2018, Antonic *et al.* 2020, Lyu *et al.* 2020].

The health benefits of human diets enriched with fruits and vegetables are multiple and well-reviewed elsewhere [Slavin and Lloyd 2012, Huminiecki *et al.* 2017, 2020, Huminiecki, Horbańczuk 2018, Mozos *et al.* 2018, Pogorzelska *et al.* 2018, Wang *et al.* 2018, Horbańczuk *et al*. 2019, del Río-Celestino and Font 2020, Estruch *et al.* 2020, Pieczyńska *et al.* 2020, Wang *et al.* 2020, Yeung *et al*. 2020c, Li *et al*. 2021]. Due to the above-discussed prevalence of apple consumption in the population, this fruit represents a significant contributor to total fruit consumption and there are multiple documented health benefits associated with apple intake in particular. Thus, apple consumption was documented to be associated with a decreased risk of all-cause mortality [Hodgson *et al.* 2016], as well as with reduced risk of specific diseases such as stroke [Larsson *et al.* 2013] and cancer death [Hodgson *et al.* 2016, Tu *et al.* 2017]. In the face of these documented benefits, it is of great interest to characterize which bioactive ingredients contained in apples are major contributors to such effects. Along with other nutrients, apples are rich in fiber and polyphenols. Phenolic compounds present in apples, which have well-documented health-promoting effects, likely contribute, at least in part, to such health benefits [Mink *et al.* 2007, Auclair *et al.* 2008, Williamson 2017, Durazzo *et al.* 2019]. Apples contain considerable amounts of polyphenols, and diverse phenolics present in apple flesh and skins have been described, belonging mainly to the compound groups of flavonoids (e.g., quercetin, (−)-epicatechin, phloridzin, procyanidins, and anthocyanins) and phenolic acids (e.g., caffeic acid and chlorogenic acid) [Bondonno *et al.* 2020]. Moreover, many diverse apple varieties exist and there are significant differences in their polyphenolic contents [Bondonno *et al.* 2020, Zhang *et al.* 2020]. Importantly, the content of compounds of nutritional and nutraceutical character in apples and products thereof are well documented in databases such as FoodData Central of U.S. Department of Agriculture, FoodExplorer, PhenolExplorer, and eBASIS [Neveu *et al.* 2010, Rothwell *et al.* 2012, Rothwell *et al.* 2013, Finglas *et al.* 2014, Scalbert 2015, Plumb *et al.* 2017, Haytowitz *et al.* 2018a, Haytowitz *et al.* 2018b, EuroFIR AISBL 2020, U.S. Department of Agriculture 2020].

Aside from human health benefits, apple products enriched with polyphenols, as well as isolated polyphenolic compounds, have been extensively studied for their potential for promoting animal health. Thus, many studies used different animal species as models to study different diseases, and apple products or isolates were for example documented in rodents to alleviate high-fat-diet-induced hepatic steatosis [Li *et al.* 2019], protect against gastric mucosal damage [Paturi *et al.* 2014], and relieve hypoxia-induced pulmonary arterial hypertension [Hua *et al.* 2018]. Moreover, apple polyphenols are studied as feed supplements aimed at the promotion of the health of farm animals or enhancement of the quality of animal-derived food products. Thus, it was demonstrated that dietary supplementation with apple polyphenols improves lipid metabolism in weaned piglets [Xu *et al.* 2019c], while in finishing pigs supplementation with apple polyphenols led to a decrease in hepatic fat deposition [Xu *et al.* 2019b] and to the gain of meat with higher quality and nutritional value [Xu *et al.* 2019a].

Considering the documented significance of apple polyphenols on human and animal health, this study was undertaken to examine bibliometrically the total existing literature of this research field. As demonstrated in numerous previous works [Yeung *et al.* 2018, Yeung *et al.* 2019a, Yeung *et al.* 2019b, Yeung *et al.* 2020a, Yeung *et al.* 2020b], bibliometrics allows to holistically examine entire scientific areas or sub-fields to get new qualitative and quantitative insights.

Material and methods

The electronic literature database, Web of Science (WoS) Core Collection, was queried on 23 September 2020 with the following search string: TS = (apple* polyphenol*) AND (health* OR illness* OR disease* OR medic* OR pharma*). This strategy identified papers that mentioned these words and their derivatives by searching through their titles, abstracts, and keywords. The query returned with 890 papers. Basic publication and citation data were recorded by the functions called Analyze and Create Citation Report offered by the WoS platform. Full records of the 890 papers were exported to VOSviewer, a dedicated bibliometric software, for further analyses. A term map visualizing phrases recurring in >1% (n = 9) of the titles and abstracts of the 890 papers was generated to reveal which of them had higher citations per paper (CPP). A similar term map was generated to illustrate author keywords (those occurring in one paper were excluded). It should be noted that self-citations were not removed from the citation counts.

Results and discussion

The 890 papers were cited 34642 times in total (Fig. 1), meaning an average of 38.9 citations per paper (CPP) and an h-index of 81. In the 2010s, this research field has been growing steadily with 60–80 papers published each year. The earliest paper was published in 1993. It was a study reporting that apple was the third major source of flavonoids intake for elderly males behind tea and onion, and that the intake of apples was inversely related to coronary heart disease mortality [Hertog *et al.* 1993]. Most of the papers were authors' own works i.e. original articles (n = 760, 85.4%, CPP = 37.3) and the remaining were mainly reviews (n = 100, 11.2%, CPP = 62.2). The original article-to-review ratio was thus 7.6:1. This article-to-review ratio of 7.6:1 was lower than that revealed in the literature on grape and wine phenolic compounds (44.1:1) [Aleixandre-Tudo *et al.* 2019], berberine (13.6:1) [Yeung *et al.* 2020a], and resveratrol (9.5:1) [Yeung *et al.* 2019a], but higher than the one occurring in the literature on natural dietary natural products as a whole (1.5:1) [Yeung *et al.* 2018]. The comparisons implied that the apple polyphenol research field was relatively balanced in producing new experimental findings and summarizing existing results. Meanwhile, nearly all of the indexed papers were in English (97.5%).

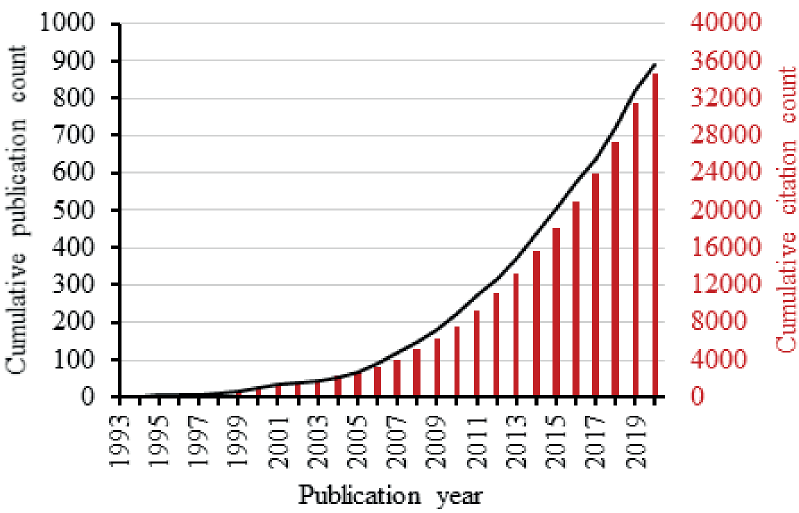

Fig. 1. Cumulative publication and citation counts.

The five most productive authors, organizations, countries, and journals are listed in Table 1. The most productive author was Professor Ettore Novellino from the University of Naples Federico II, Italy. His affiliation was also among the top 5 most

Table 1. The top-five most productive authors, organizations, countries, and journals

Item	Number of papers (% of 890)	Citations per paper (CPP)
Author		
Novellino, Ettore	13 (1.5)	11.7
Richling, Elke	13 (1.5)	45.8
Oszmianski, Jan	11 (1.2)	38.7
Rupasinghe, H. P. Vasantha	11 (1.2)	49.7
Sun-Waterhouse, Dongxiao	10 (1.1)	36.5
Organization		
INRAE (France)	28 (3.1)	134.2
New Zealand Institute for Plant Food Research Ltd	25 (2.8)	51.0
University of Naples Federico II (Italy)	20 (2.2)	27.9
Consejo Superior De Investigaciones Cientificas (CSIC, Spain)	19 (2.1)	51.3
Fondazione Edmund Mach (Italy)	17 (1.9)	27.7
Country		
China	123 (13.8)	17.3
Italy	113 (12.7)	24.8
The United States	102 (11.5)	44.5
Spain	74 (8.3)	40.1
Germany	62 (7.0)	41.0
Journal		
Journal of Agricultural and Food Chemistry	53 (6.0)	69.4
Food Chemistry	34 (3.8)	86.7
Journal of the Science of Food and Agriculture	22 (2.5)	30.9
Molecular Nutrition Food Research	22 (2.5)	36.5
Food Research International	20 (2.2)	31.4
Nutrients	20 (2.2)	23.7

productive organizations, together with 3 other European organizations and one in New Zealand. The high CPP of INRAE was due to a review paper on 93 intervention studies about the bioavailability of polyphenols in humans (3067 citations). Without counting this paper, CPP of INRAE became 25.6. China, Italy, and the United States each contributed to >10% of all papers. With China being the most productive in both the apple polyphenols and berberine research fields, the latter had heavy contributions from other Asian countries such as India, Japan, and South Korea [Yeung *et al.* 2020a]. On the other hand, the United States was the leading contributor for grape and wine phenolic compounds, dietary natural products, and resveratrol [Yeung *et al.* 2018, Aleixandre-Tudo *et al.* 2019, Yeung *et al.* 2019a]. Overall, it seemed that China and United States were consistent high-yield contributing countries to various areas of phytochemistry research.

Approximately half of the indexed papers belonged to the WoS category of food science & technology (n = 430, 48.3%, CPP = 33.0), followed by nutrition & dietetics (n = 198, 22.2%, CPP = 62.3), chemistry applied (n = 128, 14.4%, CPP =

60.2), biochemistry & molecular biology (n = 85, 9.6%, CPP = 55.8), and agriculture multidisciplinary (n = 81, 9.1%, CPP = 54.5). Most productive journals were related to food, agriculture, and nutrition (Tab. 1). Similar to the field of grape and wine phenolic compounds, *Journal of Agricultural and Food Chemistry* and *Food Chemistry* were the two most productive journals [Aleixandre-Tudo *et al.* 2019].

Figure 2 represents a term map showing the recurring terms in the titles and abstracts and the papers. Terms with higher clinical relevance, such as consumption, bioavailability, and metabolism (situated in the lower right part) had higher CPPs than lab-related terms, such as activity, content, expression, and quality. Upon closer examination of the data, "apple juice" was most frequently mentioned derivative of apple* terms (n = 78, CPP = 26.4), followed by "apple fruit" (n = 47, CPP = 30.2), apple peel (n = 36, CPP = 40.0), "apple pomace" (n = 30, CPP = 39.6), "apple extract" (n = 23, CPP = 35.6), "apple flesh" (n = 13, CPP = 54.1), "apple skin" (n = 13, CPP = 47.5), and "apple leaves" (n = 11, CPP = 19.2).

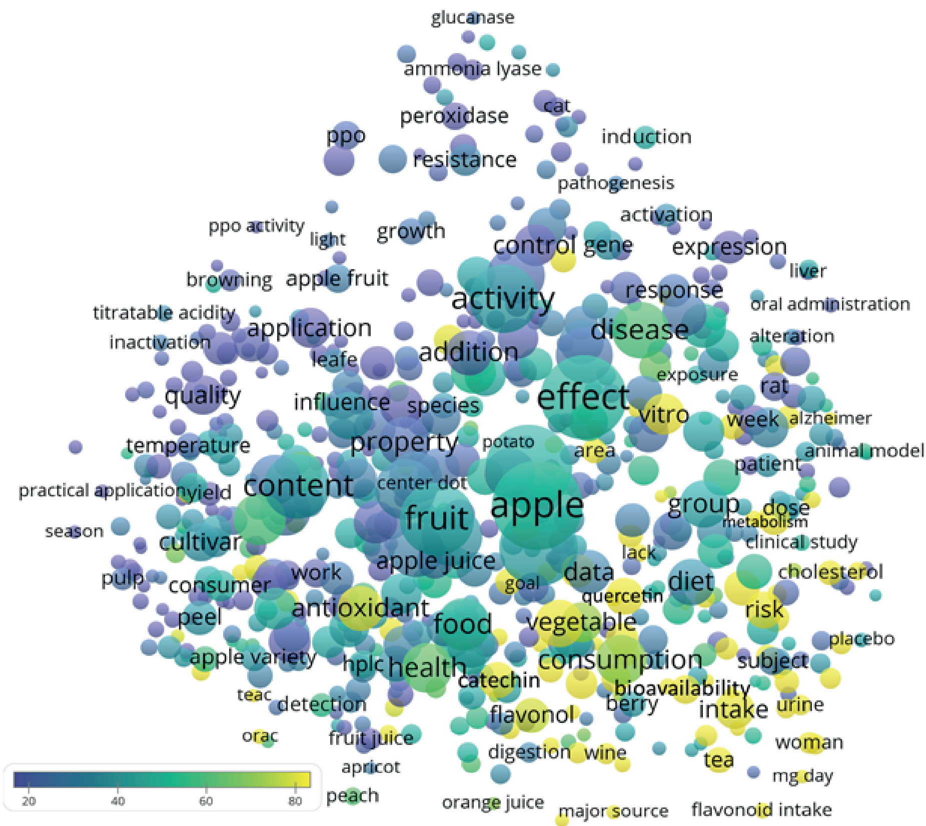

Fig. 2. Term map showing recurring phrases in the titles and abstracts of the papers. Bubble color presents the citations per paper (CPP) of the terms. Bubble size presents the number of papers. Bubble proximity presents how frequently the terms co-occurred with each other in the same papers.

Table 2. Recurring chemicals/chemical classes from the papers (n≥9)

Chemical/chemical class	Number of papers (% of 890)	Citations per paper (CPP)
Flavonoid	131 (14.7)	83.5
Quercetin	81 (9.1)	122.9
Anthocyanin	78 (8.8)	35.8
Catechin	77 (8.7)	96.5
Epicatechin	72 (8.1)	32.7
Flavonol	70 (7.9)	76.0
Procyanidin	68 (7.6)	79.2
Chlorogenic acid	61 (6.9)	42.7
Phloridzin	55 (6.2)	39.2
Dihydrochalcone	43 (4.8)	37.5
Ascorbic acid	41 (4.6)	27.9
Phloretin	35 (3.9)	31.1
Proanthocyanidin	32 (3.6)	29.1
Caffeic acid	26 (2.9)	20.5
Carotenoid	24 (2.7)	17.3
Flavanol	23 (2.6)	40.8
Tannin	23 (2.6)	31.0
Hydroxycinnamic acid	20 (2.2)	49.8
Rutin	18 (2.0)	38.1
Cyanidin	16 (1.8)	35.8
Gallic acid	16 (1.8)	28.0
Kaempferol	16 (1.8)	249.6
Resveratrol	16 (1.8)	55.2
Flavanone	15 (1.7)	162.3
Citric acid	12 (1.3)	12.9
Ferulic acid	11 (1.2)	39.1
Myricetin	11 (1.2)	368.8
Phlorizin	11 (1.2)	34.6
Beta carotene	10 (1.1)	359.7
Epigallocatechin	9 (1.0)	103.6
Lignin	9 (1.0)	12.8
Malic acid	9 (1.0)	13.3

In Table 2 are listed the recurring chemicals/chemical classes in the papers by examining the titles and abstracts. Myricetin and beta carotene had the highest CPPs. Both chemicals were involved in the 5-year study on elderly males mentioned at the beginning of the Results [Hertog *et al.* 1993].

Figure 3 represents a term map showing author keywords (keywords that occurred in one paper only were excluded). Flavonoids and antioxidant activity were recurring keywords in the center of the map. Frequently mentioned medical conditions are listed in Table 3. Cardiovascular disease was the most frequently mentioned medical condition.

The intake of apple polyphenol not only improved muscle quality and lipid metabolism in pigs [Xu *et al.* 2019a, Xu *et al.* 2019b, Xu *et al.* 2019c], but in rats it also alleviated experimental gastric damage [Lee *et al.* 2017], regulated cholesterol metabolism [Osada *et al.* 2006], reduced bone loss [Puel *et al.* 2005], and exerted

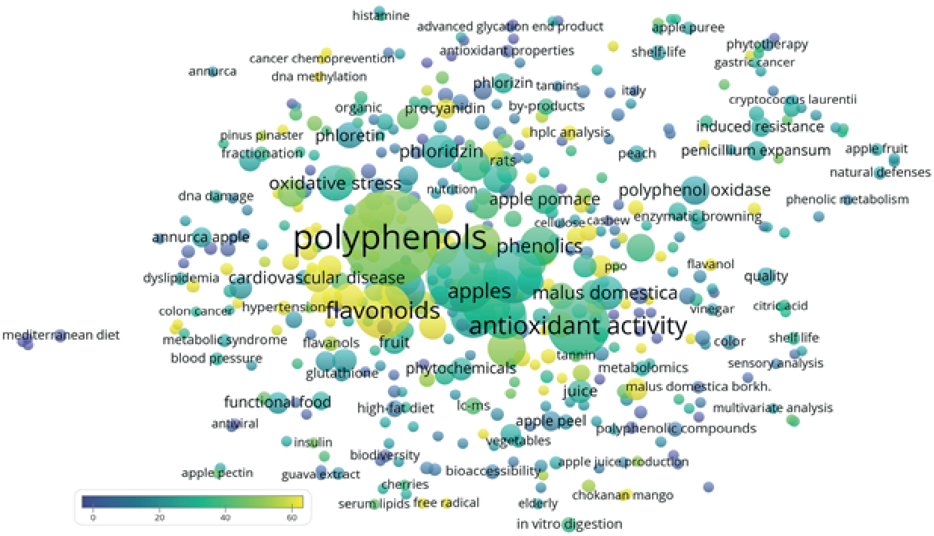

Fig. 3. Term map showing author keywords (keywords that occurred in one paper only were excluded). Bubble color presents the citations per paper (CPP) of the terms. Bubble size presents the number of papers. Bubble proximity presents how frequently the terms co-occurred with each other in the same papers.

Table 3. Frequently mentioned medical conditions (n≥3)

Medical condition	Number of papers (% of 890)	Citations per paper (CPP)
Cardiovascular disease	14 (1.6)	58.3
Atherosclerosis	8 (0.9)	22.9
Diabetes	7 (0.8)	17.4
Alzheimer's disease	5 (0.6)	23.2
Obesity	5 (0.6)	44.2
Hypertension	4 (0.4)	61.8
Dyslipidemia	3 (0.3)	24.0
Hyperlipidemia	3 (0.3)	9.3
Metabolic syndrome	3 (0.3)	21.3
Overweight	3 (0.3)	3.7

anti-tumor (and thus chemopreventive) properties [Gossé *et al.* 2005]. In mice, it was demonstrated to inhibit the development of food allergy [Akiyama *et al.* 2005]. Some of these effects were also reported in humans, e.g., reduction in total and low-density cholesterol was observed after a 12-week intake [Nagasako-Akazome *et al.* 2007].

Conclusion

The apple polyphenol papers had global contributions, particularly from China, Italy, the United States, Spain, and Germany. Many of them focused on food science

& technology, nutrition & dietetics, as well as on applied chemistry, biochemistry & molecular biology, and multidisciplinary agriculture. Some of the most frequently mentioned chemicals/chemical classes were quercetin, anthocyanin, catechin, epicatechin, and flavonol. Examples of frequently mentioned medical conditions were cardiovascular disease, atherosclerosis, diabetes, Alzheimer's disease, and obesity. The potential health benefits of apple polyphenols on humans and animals are diverse and deserve further research work.

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