

Apple polyphenols in human and animal health*

Andy Wai Kan Yeung^{1,2}, Nikolay T. Tzvetkov^{3,4}, Amr El-Demerdash^{5,6},
Olaf K. Horbanczuk⁷, Niranjana Das⁸, Vasil Pirgozliev⁹, Massimo Lucarini¹⁰,
Alessandra Durazzo¹⁰, Eliana B. Souto^{11,12}, Antonello Santini¹³, Hari Prasad
Devkota¹⁴, Md. Sahab Uddin^{15,16}, Javier Echeverría¹⁷, Dongdong Wang^{18,19},
Ren-You Gan^{20,21}, Mladen Brnčić²², Reni E. Kalfin²³, Lyubka P. Tancheva²³,
Devesh Tewari²⁴, Ioana Berindan-Neagoe^{25,26}, Silvestre Sampino²⁷,
Nina Strzałkowska²⁷, Joanna Marchewka²⁷, Artur Józwick²⁷,
Jarosław Olav Horbańczuk²⁷, Atanas G. Atanasov^{2,27**}**

¹ Oral and Maxillofacial Radiology, Applied Oral Sciences and Community Dental Care,
Faculty of Dentistry, The University of Hong Kong, Hong Kong, China

² Ludwig Boltzmann Institute for Digital Health and Patient Safety,
Medical University of Vienna, Spitalgasse 23, 1090, Vienna, Austria

³ Department of Biochemical Pharmacology and Drug Design, Institute of Molecular Biology
“Roumen Tsanev”, Bulgarian Academy of Sciences, Sofia, Bulgaria

⁴ Pharmaceutical Institute, University of Bonn, Bonn, Germany

⁵ Institut de Chimie des Substances Naturelles, ICSN-CNRS, University of Paris Saclay, France

⁶ Chemistry Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt

⁷ Department of Technique and Food Product Development, Warsaw University of Life Sciences
(WULS-SGGW) 159c Nowoursynowska, 02-776 Warsaw, Poland

⁸ Department of Chemistry, Iswar Chandra Vidyasagar College, Tripura, India

⁹ The National Institute of Poultry Husbandry, Harper Adams University, Shropshire, UK

¹⁰ CREA-Research Centre for Food and Nutrition, Via Ardeatina 546, 00178 Rome, Italy

* Authors acknowledge the support from The National Centre for Research and Development (NCBR) of Poland (project number POIR.01.01.01-00-0593/18).

**Corresponding authors: ndyeung@hku.hk, Atanas G. Atanasov: atanas.atanasov@univie.ac.at

- ¹¹ Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal
- ¹² CEB-Centre of Biological Engineering, University of Minho, Campus de Gualtar 4710-057 Braga, Portugal
- ¹³ Department of Pharmacy, University of Napoli Federico II, Via D. Montesano 49, 80131 Napoli, Italy
- ¹⁴ Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, 862-0973, Kumamoto, Japan
- ¹⁵ Department of Pharmacy, Southeast University, Dhaka, Bangladesh
- ¹⁶ Pharmakon Neuroscience Research Network, Dhaka, Bangladesh
- ¹⁷ Departamento de Ciencias del Ambiente, Facultad de Química y Biología, Universidad de Santiago de Chile, Santiago, Chile
- ¹⁸ The Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Fei Shan Jie 32, 550003 Guiyang, China
- ¹⁹ Centre for Metabolism, Obesity and Diabetes Research, McMaster University, 1280 Main St. W., Hamilton, ON Canada L8N 3Z5
- ²⁰ Research Center for Plants and Human Health, Institute of Urban Agriculture, Chinese Academy of Agricultural Sciences, Chengdu 600213, China
- ²¹ Key Laboratory of Coarse Cereal Processing (Ministry of Agriculture and Rural Affairs), School of Food and Biological Engineering, Chengdu University, Chengdu 610106, China
- ²² Faculty of Food Technology and Biotechnology, University of Zagreb, Pierottijeva 6, 10000 Zagreb, Croatia
- ²³ Department of Biological Effects of Natural and Synthetic Substances, Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria
- ²⁴ Department of Pharmacognosy, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab 144411, India
- ²⁵ Department of Functional Genomics and Experimental Pathology, The Oncology Institute “Prof. Dr. Ion Chiricuta”, 34-36 Republicii Street, 400015 Cluj-Napoca, Romania
- ²⁶ Research Center for Functional Genomics, Biomedicine and Translational Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, 23 Marinescu Street, 400337 Cluj-Napoca, Romania
- ²⁷ Institute of Genetics and Animal Biotechnology of the Polish Academy of Sciences, 05-552, Jastrzębiec, Poland

(Accepted May 27, 2021)

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) [Alexandre-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%).

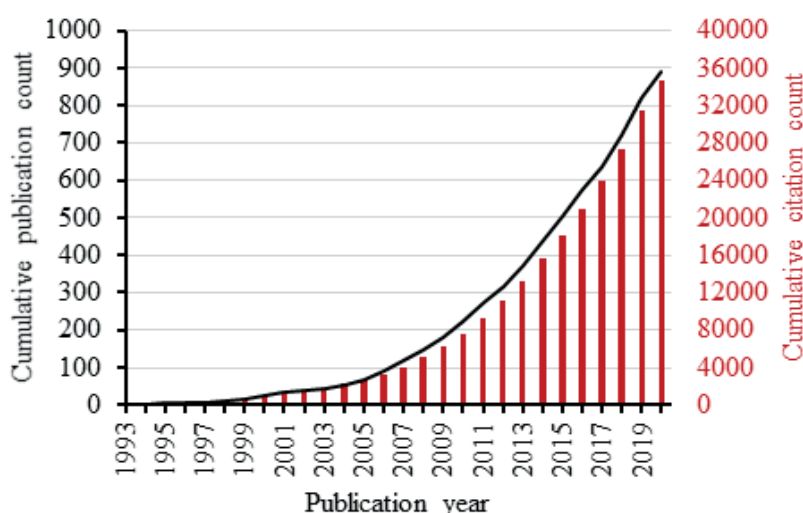


Fig. 1. Cumulative publication and citation counts.

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, Alexandre-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 [Alexandre-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).

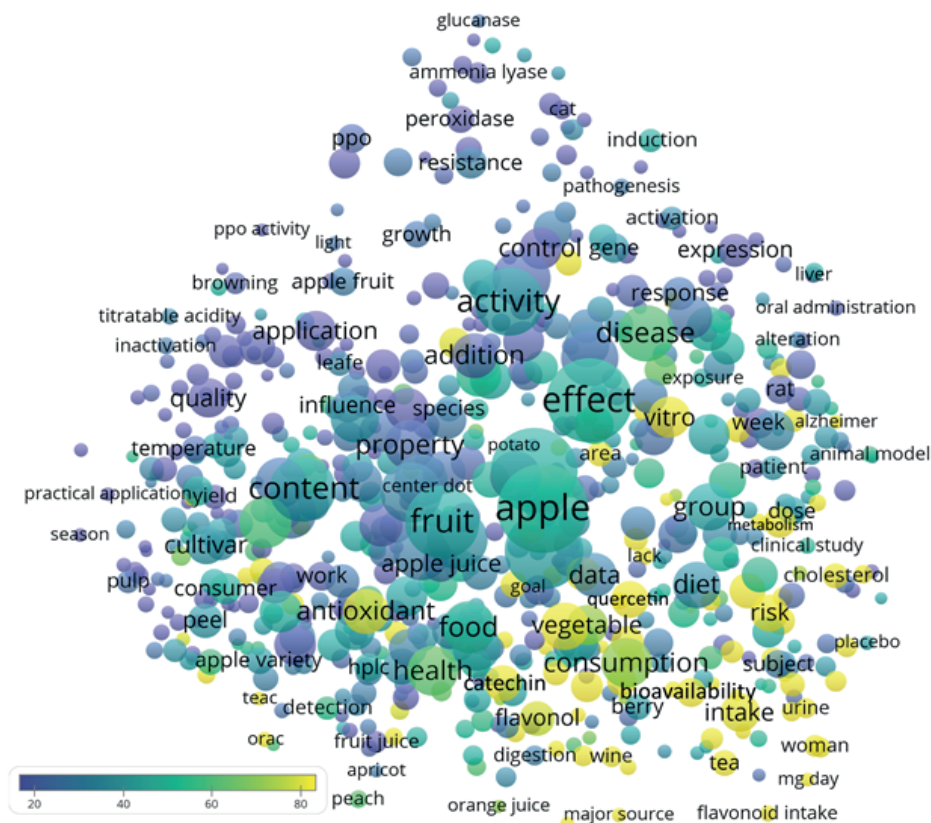


Fig. 2. Term map showing recurring phrases in the titles and abstracts of the papers. Bubble color presents the citations per paper (CPP) of the terms. Bubble size presents the number of papers. Bubble proximity presents how frequently the terms co-occurred with each other in the same papers.

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

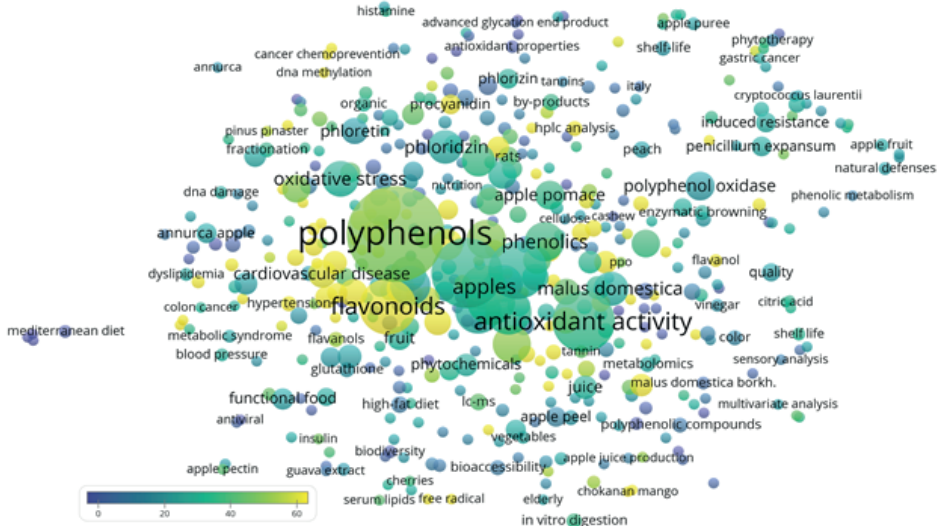


Fig. 3. Term map showing author keywords (keywords that occurred in one paper only were excluded). Bubble color presents the citations per paper (CPP) of the terms. Bubble size presents the number of papers. Bubble proximity presents how frequently the terms co-occurred with each other in the same papers.

Table 3. Frequently mentioned medical conditions ($n \geq 3$)

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.

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

- AKIYAMA H., SATO Y., WATANABE T., NAGAOKA M.H., YOSHIOKA Y., SHOJI T., KANDA T., YAMADA K., TOTSUKA M., TESHIMA R., 2005 - Dietary unripe apple polyphenol inhibits the development of food allergies in murine models. *FEBS Letters* 579, 4485-4491.
- ALEIXANDRE-TUDO J.L., CASTELLÓ-COGOLLOS L., ALEIXANDRE J.L., ALEIXANDRE-BENAVENT R., 2019 - Unravelling the scientific research on grape and wine phenolic compounds: a bibliometric study. *Scientometrics* 119, 119-147.
- ANTONIC B., JANCIKOVA S., DORDEVIC D., TREMLOVA B., 2020 - Apple pomace as food fortification ingredient: A systematic review and meta-analysis. *Journal of Food Science* [Epub ahead of print], doi: 10.1111/1750-3841.15449.
- AUCLAIR S., SILBERBERG M., GUEUX E., MORAND C., MAZUR A., MILENKOVIC D., SCALBERT, A., 2008 - Apple polyphenols and fibers attenuate atherosclerosis in apolipoprotein E-deficient mice. *Journal of Agricultural and Food Chemistry* 56, 5558-5563.
- BHUSHAN S., KALIA K., SHARMA M., SINGH B., AHUJA P.S., 2008 - Processing of apple pomace for bioactive molecules. *Critical Reviews in Biotechnology* 28, 285-296.
- BONDONNO C.P., BONDONNO N.P., SHINDE S., SHAFAEI A., BOYCE M.C., SWINNY E., JACOB S.R., LACEY K., WOODMAN R.J., CROFT K.D., 2020 - Phenolic composition of 91 Australian apple varieties: towards understanding their health attributes. *Food & Function* 11, 7115-7125.
- DEL RÍO-CELESTINO M., FONT R., 2020 - The Health Benefits of Fruits and Vegetables. *Foods* 9, 369.
- DURAZZO A., LUCARINI M., SOUTO E.B., CICALA C., CAIAZZO E., IZZO A.A., NOVELLINO E., SANTINI A., 2019 - Polyphenols: A concise overview on the chemistry, occurrence, and human health. *Phytotherapy Research* 33, 2221-2243.
- ESTRUCH R., CASAS R., ROS E., 2020 - Eat Even More Vegetables and Fruits to Protect Your Heart. *Annals of Internal Medicine* 172, 826-827.
- EUROFIR AISBL, 2020 - eBASIS: BioActive Substances in Food Information System. <http://ebasis.eurofir.org/Default.asp>. [Accessed on 9 October 2020.]
- FINGLAS P.M., BERRY R., ASTLEY S., 2014 - Assessing and improving the quality of food composition databases for nutrition and health applications in Europe: the contribution of EuroFIR. *Advances in Nutrition* 5, 608S-614S.
- GOSSÉ F., GUYOT S., ROUSSI S., LOBSTEIN A., FISCHER B., SEILER N., RAUL F., 2005 - Chemopreventive properties of apple procyanidins on human colon cancer-derived metastatic SW620 cells and in a rat model of colon carcinogenesis. *Carcinogenesis* 26, 1291-1295.
- GRASSINO A.N., BARBA F.J., BRNČIĆ M., LORENZO J.M., LUCINI L., BRNČIĆ S.R., 2018 - Analytical tools used for the identification and quantification of pectin extracted from plant food matrices, wastes and by-products: A review. *Food Chemistry* 266, 47-55.

14. HAYTOWITZ D., WU X., BHAGWAT S., 2018a - USDA Database for the proanthocyanidin content of selected foods Release 2.1. *US Department of Agriculture, Agricultural Service*,
15. HAYTOWITZ D.B., WU X., BHAGWAT S., 2018b - USDA Database for the Flavonoid Content of Selected Foods, Release 3.3. US Department of Agriculture, Agricultural Research Service.
16. HERTOGE M.G., FESKENS E.J., KROMHOUT D., HOLLMAN P., KATAN M., 1993 - Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *The lancet* 342, 1007-1011.
17. HODGSON J. M., PRINCE R. L., WOODMAN R. J., BONDONNO C.P., IVEY K.L., BONDONNO N., RIMM E.B., WARD N.C., CROFT K.D., LEWIS J.R., 2016 - Apple intake is inversely associated with all-cause and disease-specific mortality in elderly women. *British Journal of Nutrition* 115, 860-867.
18. HUA C., ZHAO J., WANG H., CHEN F., MENG H., CHEN L., ZHANG Q., YAN J., YUAN L., 2018 - Apple polyphenol relieves hypoxia-induced pulmonary arterial hypertension via pulmonary endothelium protection and smooth muscle relaxation: In vivo and in vitro studies. *Biomedicine and Pharmacotherapy* 107, 937-944.
19. HORBAŃCZUK O.K., KUREK M.K., ATANASOV A.G., BRNČIĆ M., BRNČIĆ S.R., 2019 - The effect of natural antioxidants on quality and shelf life of beef and beef products. *Food Technology and Biotechnology* 57(4), 439-447. Doi: 10.17113/ftb.57.04.19.6267.
20. HUMINIECKI L., ATANASOV A.G., HORBAŃCZUK J., 2020 - Etiology of atherosclerosis informs choice of animal models and tissues for initial functional genomic studies of resveratrol. *Pharmacological Research* 156,104598.
21. HUMINIECKI L., HORBAŃCZUK J., 2018 - The functional genomic studies of resveratrol in respect to its anti-cancer effects. *Biotechnology Advances* Doi: 10.1016/J.Biotechadv.2018.02.011.
22. HUMINIECKI L., HORBAŃCZUK J., ATANASOV A.G., 2017 - The functional genomic studies of curcumin. *Seminars in Cancer Biology* Doi.Org/10.1016/J.Semcancer.2017.04.002.
23. LARSSON S.C., VIRTAMO J., WOLK A., 2013 - Total and specific fruit and vegetable consumption and risk of stroke: a prospective study. *Atherosclerosis* 227, 147-152.
24. LEE Y.-C., CHENG C.-W., LEE H.-J., CHU H.-C., 2017 - Apple polyphenol suppresses indomethacin-induced gastric damage in experimental animals by lowering oxidative stress status and modulating the MAPK signaling pathway. *Journal of Medicinal Food* 20, 1113-1120.
25. LI CH., LI J., JIANG F., LI Y., TZVETKOV N.T., HORBAŃCZUK J.O., ATANASOV A.G., WANG D., 2021 - Vasculoprotective effects of ginger (*Zingiber officinale* Roscoe) and underlying molecular mechanisms. *Food and Function* 12, 1897-1913.
26. LI D., LIU F., WANG X., LI X., 2019 - Apple Polyphenol Extract Alleviates High-Fat-Diet-Induced Hepatic Steatosis in Male C57BL/6 Mice by Targeting LKB1/AMPK Pathway. *Journal of Agricultural and Food Chemistry* 67, 12208-12218.
27. LYU F., LUIZ S.F., AZEREDO D.R.P., CRUZ A.G., AJLOUNI S., RANADHEERA C.S., 2020 - Apple pomace as a functional and healthy ingredient in food products: A Review. *Processes* 8, 319.
28. MINK P.J., SCRAFFORD C.G., BARRAJ L.M., HARNACK L., HONG C.-P., NETTLETON J.A., JACOBS JR D.R., 2007 - Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. *The American Journal of Clinical Nutrition* 85, 895-909.
29. MOZOS I., STOIAN D., CARABA A., MALAINER C., HORBAŃCZUK J., ATANASOV A., 2018 - Lycopene and vascular health. *Frontiers In Pharmacology* 9, 521. Doi: 10.3389/Fphar.2018.00521.
30. NAGASAKO-AKAZOME Y., KANDA T., OHTAKE Y., SHIMASAKI H., KOBAYASHI T., 2007 - Apple polyphenols influence cholesterol metabolism in healthy subjects with relatively high body mass index. *Journal of Oleo Science* 56, 417-428.

31. NEVEU V., PEREZ-JIMÉNEZ J., VOS F., CRESPI V., DU CHAFFAUT L., MENNEN L., KNOX C., EISNER R., CRUZ J., WISHART D., 2010 - Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. *Database* 2010, bap024.
32. OSADA K., SUZUKI T., KAWAKAMI Y., SENDA M., KASAI A., SAMI M., OHTA Y., KANDA T., IKEDA M., 2006 - Dose-dependent hypocholesterolemic actions of dietary apple polyphenol in rats fed cholesterol. *Lipids* 41, 133-139.
33. PATURI G., BUTTS C.A., BENTLEY-HEWITT K.L., MCGHIE T.K., SALEH Z.S., MCLEOD A., 2014 - Apple Polyphenol Extracts Protect Against Aspirin-induced Gastric Mucosal Damage in Rats. *Phytotherapy Research* 28, 1846-1854.
34. PIECZYNSKA M.D., YANG Y., PETRYKOWSKI S., HORBAŃCZUK O.K., ATANASOV A.G., HORBAŃCZUK J.O., 2020 - Gut microbiota and its metabolites in atherosclerosis development. *Molecules* 29, 25(3), 594. doi: 10.3390/molecules25030594
35. PLUMB J., PIGAT S., BOMPOLA F., CUSHEN M., PINCHEN H., NØRBY E., ASTLEY S., LYONS J., KIELY M., FINGLAS P., 2017 - Ebasis (bioactive substances in food information systems) and bioactive intakes: Major updates of the bioactive compound composition and beneficial bioeffects database and the development of a probabilistic model to assess intakes in europe. *Nutrients* 9, 320.
36. POGORZELSKA-NOWICKA E., ATANASOV A.G., HORBAŃCZUK J., WIERZBICKA A., 2018 - Bioactive compounds in functional meat products. *Molecules* 31, 23(2). Pii: E307. Doi: 10.3390/Molecules23020307.
37. PUEL C., QUINTIN A., MATHEY J., OBLED C., DAVICCO M.-J., LEBECQUE P., KATI-COULIBALY S., HORCAJADA M.-N., COXAM V., 2005 - Prevention of bone loss by phloridzin, an apple polyphenol, in ovariectomized rats under inflammation conditions. *Calcified Tissue International* 77, 311-318.
38. ROTHWELL J.A., PEREZ-JIMENEZ J., NEVEU V., MEDINA-REMON A., M'HIRI N., GARCÍA-LOBATO P., MANACH C., KNOX C., EISNER R., WISHART, D. S., 2013 - Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. *Database* 2013, bat070.
39. ROTHWELL J.A., URPI-SARDA M., BOTO-ORDONEZ M., KNOX C., LLORACH R., EISNER R., CRUZ J., NEVEU V., WISHART D., MANACH C., 2012 - Phenol-Explorer 2.0: a major update of the Phenol-Explorer database integrating data on polyphenol metabolism and pharmacokinetics in humans and experimental animals. *Database* 2012, bas031.
40. SCALBERT A., 2015 - Phenol-Explorer: database on polyphenol content in foods. <http://phenol-explorer.eu>. [Accessed on 9 October 2020.]
41. SLAVIN J.L., LLOYD B., 2012 - Health benefits of fruits and vegetables. *Advances in Nutrition* 3, 506-516.
42. TU S.-H., CHEN L.-C., HO Y.-S., 2017 - An apple a day to prevent cancer formation: Reducing cancer risk with flavonoids. *Journal of food and drug analysis* 25, 119-124.
43. U.S. DEPARTMENT OF AGRICULTURE, 2020 - Food Data Central. <https://fdc.nal.usda.gov>. [Accessed on 9 October 2020.]
44. USDA, 2019 - Apples and oranges are America's top fruit choices. <https://www.ers.usda.gov/data-products/chart-gallery/gallery/chart-detail/?chartId=58322>. [Accessed on 12 September 2020.]
45. WANG D., ÖZEN C., ABU-REIDAH I.M., CHGURUPATI S., PATRA J.K., HORBAŃCZUK J.O., JÓŻWIK A., TZVETKOV N.T., UHRIN P., ATANASOV A.G., 2018 - Vasculoprotective effects of pomegranate (*Punica Granatum L.*). *Frontiers in Pharmacology* 9,544. Doi: 10.3389/Fphar.2018.00544.

46. WANG D., ZHANG L., HUANG J., HIMABINDU K., TEWARI D., HORBAŃCZUK J.O., XU S., CHEN Z., ATANASOV A.G., 2020 - Cardiovascular protective effect of black pepper (*Piper nigrum* L.) and its major bioactive constituent piperine. *Trends in Food Science & Technology* <https://doi.org/10.1016/j.tifs.2020.11.024>.
47. WILLIAMSON, G., 2017 - The role of polyphenols in modern nutrition. *Nutrition Bulletin* 42, 226-235.
48. XU X., CHEN X., CHEN D., YU B., YIN J., HUANG Z., 2019a - Effects of dietary apple polyphenol supplementation on carcass traits, meat quality, muscle amino acid and fatty acid composition in finishing pigs. *Food & Function* 10, 7426-7434.
49. XU X., CHEN X., HUANG Z., CHEN D., HE J., ZHENG P., CHEN H., LUO J., LUO Y., YU B., 2019b - Effects of dietary apple polyphenols supplementation on hepatic fat deposition and antioxidant capacity in finishing pigs. *Animals* 9, 937.
50. XU X., CHEN X., HUANG Z., CHEN D., YU B., CHEN H., HE J., LUO Y., ZHENG P., YU J., 2019c - Dietary apple polyphenols supplementation enhances antioxidant capacity and improves lipid metabolism in weaned piglets. *Journal of Animal Physiology and Animal Nutrition* 103, 1512-1520.
51. YEUNG A.W. K., AGGARWAL B., BARRECA D., BATTINO M., BELWAL T., HORBAŃCZUK O., BERINDAN-NEAGOE I., BISHAYEE A., DAGLIA M., DEVKOTA H., ECHEVERRÍA J., EL-DEMERDASH A., ORHAN I., GODFREY K., GUPTA V., HORBAŃCZUK J., MODLIŃSKI J., HUBER L., HUMINIECKI L., JÓŻWIK A., MARCHEWKA J., MILLER M., MOCAN A., MOZOS I., NABAVI S., NABAVI S., PIECZYŃSKA M., PITTALÀ V., RENGASAMY K., SILVA A., SHERIDAN H., STANKIEWICZ A., STRZAŁKOWSKA N., SUREDA A., TEWARI D., WEISSIG V., ZENGİN G., ATANASOV A., 2018 - Dietary natural products and their potential to influence health and disease including animal model studies. *Animal Science Papers and Reports* 36, 345-358.
52. YEUNG A.W.K., AGGARWAL B.B., ORHAN I.E., HORBAŃCZUK O.K., BARRECA D., BATTINO M., BELWAL T., BISHAYEE A., DAGLIA M., DEVKOTA H.P., ECHEVERRÍA J., EL-DEMERDASH A., BALACHEVA A., GEORGIEVA M., GODFREY K., GUPTA V., HORBAŃCZUK J.O., HUMINIECKI L., JÓŻWIK A., STRZAŁKOWSKA N., MOCAN A., MOZOS I., NABAVI S. M., PAJANOVA T., PITTALÀ V., FEDER-KUBIS J., SAMPINO S., SILVA A.S., SHERIDAN H., SUREDA A., TEWARI D., WANG D., WEISSIG V., YANG Y., ZENGİN G., SHANKER K., MOOSAVI M.A., SHAH M.A., KOZUHAROVA E., AL-RIMAWI F., DURAZZO A., LUCARINI M., SOUTO E.B., SANTINI A., MALAINER C., DJILIANOV D., TANCHEVA L. P., LI H.B., GAN R.Y., TZVETKOV N.T., ATANASOV A.G., 2019a - Resveratrol, a popular dietary supplement for human and animal health: Quantitative research literature analysis - a review. *Animal Science Papers and Reports* 37, 103-118.
53. YEUNG A.W.K., ORHAN I.E., AGGARWAL B.B., BATTINO M., BELWAL, T., BISHAYEE A., DAGLIA M., DEVKOTA H. P., EL-DEMERDASH A., BALACHEVA A.A., GEORGIEVA M.G., GUPTA V. K., HORBAŃCZUK J.O., JOZWIK A., MOZOS I., NABAVI S.M., PITTALÀ V., FEDER-KUBIS J., SANCHES SILVA A., SHERIDAN H., SUREDA A., WANG D., WEISSIG V., YANG Y., ZENGİN G., SHANKER K., MOOSAVI M.A., SHAH M.A., AL-RIMAWI F., DURAZZO A., LUCARINI M., SOUTO E.B., SANTINI A., DJILIANOV D., DAS N., SKOTTI E., WIECZOREK A., LYSEK-GLADYSINSKA M.W., MICHALCZUK M., HORBAŃCZUK O.K., TZVETKOV N.T., ATANASOV A.G., 2020a - Berberine, a popular dietary supplement for human and animal health: Quantitative research literature analysis—a review. *Animal Science Papers and Reports* 38, 5-19.
54. YEUNG A. W.K., SOUTO E.B., DURAZZO A., LUCARINI M., NOVELLINO E., TEWARI D., WANG D., ATANASOV A.G., SANTINI A., 2020b - Big impact of nanoparticles: analysis of the most cited nanopharmaceuticals and nanonutraceuticals research. *Current Research in Biotechnology* 2, 53-63.

55. YEUNG A.W.K., TZVETKOV N.T., DURAZZO A., LUCARINI M., SOUTO E.B., SANTINI A., GAN R.-Y., JOZWIK A., GRZYBEK W., HORBAŃCZUK J.O., MOCAN A., ECHEVERRÍA J., WANG D., ATANASOV A.G., 2020c - Natural products in diabetes research: quantitative literature analysis. *Natural Product Research* doi: 10.1080/14786419.2020.1821019. PMID: 33025819.
56. YEUNG A. W.K., TZVETKOV N.T., GUPTA V.K., GUPTA S.C., ORIVE G., BONN G. K., FIEBICH B., BISHAYEE A., EFFERTH T., XIAO J., SANCHES SILVA A., RUSSO G. L., DAGLIA M., BATTINO M., ERDOGAN ORHAN I., NICOLETTI F., HEINRICH M., AGGARWAL B.B., DIEDERICH M., BANACH M., WECKWERTH W., BAUER R., PERRY G., BAYER E.A., HUBER L.A., WOLFENDER J.-L., VERPOORTE R., MACIAS F.A., WINK M., STADLER, M., GIBBONS S., CIFUENTES A., IBANEZ E., LIZARD G., MÜLLER R., RISTOW M., ATANASOV A.G., 2019b - Current research in biotechnology: Exploring the biotech forefront. *Current Research in Biotechnology* 1, 34-40.
57. ZHANG X., XU J., XU Z., SUN X., ZHU J., ZHANG Y., 2020 - Analysis of Antioxidant Activity and Flavonoids Metabolites in Peel and Flesh of Red-Fleshed Apple Varieties. *Molecules* 25, 1968.