Animal Science Papers and Reports vol. 39 (2021) no. 3, 199-212
Institute of Genetics and Animal Biotechnology
of the Polish Academy of Sciences, Jastrzębiec, Poland

Quercetin: total-scale literature landscape analysis of a valuable nutraceutical with numerous potential applications in the promotion of human and animal health – a review*

Andy Wai Kan Yeung[1,2], Neeraj Choudhary[3], Devesh Tewari[4], Amr El-Demerdash[5,6], Olaf K. Horbanczuk[7], Niranjan Das[8], Vasil Pirgozliev[9], Massimo Lucarini[10], Alessandra Durazzo[10], Eliana B. Souto[11,12], Antonello Santini[13], Hari Prasad Devkota[14], Md. Sahab Uddin[15,16], Javier Echeverría[17], Dongdong Wang[18], Ren-You Gan[19,20], Mladen Brnčić[21], Reni E. Kalfin[22], Nikolay T. Tzvetkov[23,24], Artur Jóźwik[25], Magdalena Solka[25], Nina Strzałkowska[25], Jarosław Olav Horbańczuk[25], Atanas G. Atanasov[2,25]****

[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] Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Ludhiana, Punjab, India

[4] Department of Pharmacognosy, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab 144411, India

[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

---

*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.atanasov@univie.ac.at

[8] Department of Chemistry, Iswar Chandra Vidyasagar College, Belonia, 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

[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] Centre for Metabolism, Obesity and Diabetes Research, McMaster University, 1280 Main St. W., Hamilton, ON Canada L8N 3Z5

[19] Research Center for Plants and Human Health, Institute of Urban Agriculture, Chinese Academy of Agricultural Sciences, Chengdu 600213, China

[20] Key Laboratory of Coarse Cereal Processing (Ministry of Agriculture and Rural Affairs), School of Food and Biological Engineering, Chengdu University, Chengdu 610106, China

[21] Faculty of Food Technology and Biotechnology, University of Zagreb, Pierottijeva 6, 10000 Zagreb, Croatia

[22] Department of Synaptic Signaling and Communications, Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria

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

[24] Pharmaceutical Institute, University of Bonn, Bonn, Germany

[25] Institute of Genetics and Animal Biotechnology of the Polish Academy of Sciences, 05-552, Jastrzębiec, Poland

(Accepted July 8, 2021)

Numerous investigations on quercetin have revealed that it effectively treats and prevents different diseases, acting as an anti-inflammatory, anti-bacterial, anti-proliferative, anti-atherogenic, anti-coagulative, antioxidant, antidiabetic agent, etc. This work aimed to analyze the present research literature on quercetin in the context of human and animal health. The Web of Science Core Collection electronic database was searched with (quercetin*) AND (health* OR illness* OR disease* OR medic* OR pharma* OR drug* OR therap*). The resulted 15685 papers were bibliometrically evaluated with the aid of VOSviewer software. Besides the United States, the quercetin papers received global contributions, particularly from Asian countries such as China, India, and South Korea. Examples of frequently mentioned chemicals/chemical classes were flavonoid, kaempferol, rutin, polyphenol, and catechin. Examples of frequently mentioned medical conditions were cancer, Alzheimer’s disease, and atherosclerosis. There are numerous reported beneficial effects of quercetin on human and animal health, which warrants further research for corroboration, understanding mechanism of action, and practical application.

KEY WORDS: quercetin / cancer / atherosclerosis / diabetes / Alzheimer's disease / obesity / Web of Science / VOSviewer

Nutraceuticals are nutritional natural products widely used nowadays for improving health due to their safety, nutritional value, therapeutic effects, and physiological disease-protecting significance in the prevention of several chronic diseases, i.e., cancer, neurodegenerative diseases, metabolic syndrome cluster of health conditions, and cardiovascular diseases [Santini *et al.* 2018, Daliu *et al*. 2019, Durazzo *et al.* 2020, Santini and Cicero 2020]. These qualities overall are expected to result in enhancing longevity and life quality [Vieira *et al.* 2019, Yeung *et al*. 2020b]. The global market potential of nutraceuticals is approximately USD 117 billion [Sachdeva *et al.* 2020]. Plants are a rich source of nutraceuticals due in part to the presence of phenolic substances [Durazzo *et al.* 2018, Durazzo *et al*. 2019]. Among the most active nutraceutical ingredients available in plants are flavonoids (these polyphenolic substances extracted and concentrated to be administered in the proper pharmaceutical form, are commonly denoted as "nutraceuticals" in the scientific literature) [Tapas *et al.* 2008, Huminiecki and Horbańczuk 2017, 2018, Tewari *et al.* 2017, Mozos e*t al.* 2018, Pogorzelska-Nowicka *et al.* 2018, Santini and Novellino 2018, Wang *et al.* 2018, 2020 Durazzo *et al.* 2020, Huminiecki *et al*. 2020, Kim and Hwang 2020, Pieczyńska *et al*. 2020, Singh *et al*. 2020, Yeung *et al*. 2020c, Li *et al*. 2021]. In this context, quercetin was selected as a focus of this work as it is a phytoconstituent that belongs to the class of bioflavonoids (biosynthetically derived by phenylpropanoid pathway from phenylalanine), and is widely distributed in fruits e.g. in apples, leaves, seeds, vegetables, grains, and food supplements, as well as is well documented to exert broad health benefits [Boots *et al.* 2008, Falcone Ferreyra *et al.* 2012, Wong *et al*. 2020, Dong and Lin 2021]. In addition, it must be pointed out that quercetin is a plant flavonol that belongs to the flavonoid group of polyphenols. Numerous investigations on quercetin have revealed that it is effective in the treatment and prevention of different diseases, acting as neuroprotective, an anti-inflammatory, anti-bacterial, anti-proliferative, anti-atherogenic, anti-coagulative, antioxidant, antidiabetic agent, etc [Eid and Haddad 2017, Patel *et al.* 2018, Xu *et al*. 2019]. These actions are underlined by different mechanisms of action of quercetin, involving effects on cellular signaling and gene expression pathways, and stabilization of mast cell membranes. These actions result in decreasing histamine release from mast cells, decrease of the anaphylactic responses associated with inhibition of asthma [Lesjak *et al.* 2018, Rauf *et al.* 2018, Dabeek and Marra 2019, Batiha *et al*. 2020, Yang *et al.* 2020], reduction of oxidative stress (e.g., by neutralization of highly reactive peroxynitrite species), prevention of drug/chemical toxicity at cellular and tissue level, and increase of insulin secretion and glucose uptake, among other effects [Bule *et al*. 2019, Xu *et al.* 2019, Pingili *et al*. 2020]. In addition, quercetin is known to prevent the drug-induced hepatotoxicity caused by the first-line anti-tubercular drugs isoniazid and rifampicin, as it decreases the elevated enzyme levels of alanine aminotransferase (ALT), while also decreasing the oxidative stress caused by free radicals [Qader *et* *al.* 2014, Liu *et al.* 2018]. In recent studies, it is documented that the absorption of quercetin is increased due to the presence of conjugation with the sugar moiety [Riva *et al.* 2019, Batiha *et al.* 2020], and this is of importance in the context of some of the potential problems associated with the compound, i.e. photosensitivity, thermolability, low water solubility, and poor bioavailability. The later shortcomings of quercetin act as a barrier in drug development and formulation. Along this line, bioavailability of quercetin can for example be enhanced by the incorporation of short-chain fructo-oligosaccharides [Kaşıkcı and Bağdatlıoğlu 2016]. Furthermore, to overcome the mentioned shortcomings, diverse nanoparticles, liposomes, and cocrystal cubosomes are studied to be used as carriers of quercetin [Wang *et al.* 2016, Li *et al*. 2018, Parhi *et al.* 2020] in the context of the overall development of the nanonutraceuticals field [Yeung *et al.* 2020c]. Aside of the diverse biomedical applications for humans, quercetin is also applied as a functional dietary ingredient for the promotion of animal health. For example, in animal production quercetin is used as an immunity booster and growth promoter [Saeed *et al*. 2017, Yeung *et al.* 2021]. Safety aspects of the use of quercetin as a dietary supplement are also investigated [Andres *et al.* 2018].

Therefore, in this study, the research landscape of quercetin was studied with a bibliometric approach [Yeung *et al.* 2019b, Atanasov *et al*. 2020, Yeung *et al*. 2020a] with emphasis on gaining further insights on its role as a valuable nutraceutical ingredient with numerous potential applications in the promotion of human and animal health revealed based on the systematic investigation of scientific outputs and associated academic citations performance.

Material and methods

The Web of Science (WoS) Core Collection electronic database was searched on 21st of June 2021 with the following string: TS=((quercetin*) AND (health* OR illness* OR disease* OR medic* OR pharma* OR drug* OR therap*)). This search string identified papers mentioning these meta-words and/or their variants in their titles, abstracts, and keywords. A total of 15685 documents were identified. Basic frequency data regarding the bibliographies were computed by the built-in functions of the WoS platform. Full records of the 15685 papers were then exported to VOSviewer for further scientometric visualizations [van Eck and Waltman 2009] in the format of bubble maps with default parameters. The size, proximity, and color of the displayed bubbles reflected the frequency of appearance, co-appearance, and citations per publication (CPP) respectively. A particular term was counted once even if it appeared multiple times in a single publication. Terms from titles and abstracts that appeared in at least 1.0% (n = 157) of the publications were visualized. A similar term map was generated to illustrate author keywords that recurred in at least 0.1% (n = 16) of the papers.

Results and discussion

The quercetin research was growing rapidly during the 2010s, and since 2017 the publication count has passed 10000 papers (Fig. 1). The vast majority of all papers were original articles (n = 14195, 90.5%, CPP = 29.5) and the remaining were mostly reviews (n = 1184, 7.5%, CPP = 62.2). Original article-to-review ratio was thus 12.0:1. Compared to other similar literature sets, this ratio was lower than berberine literature

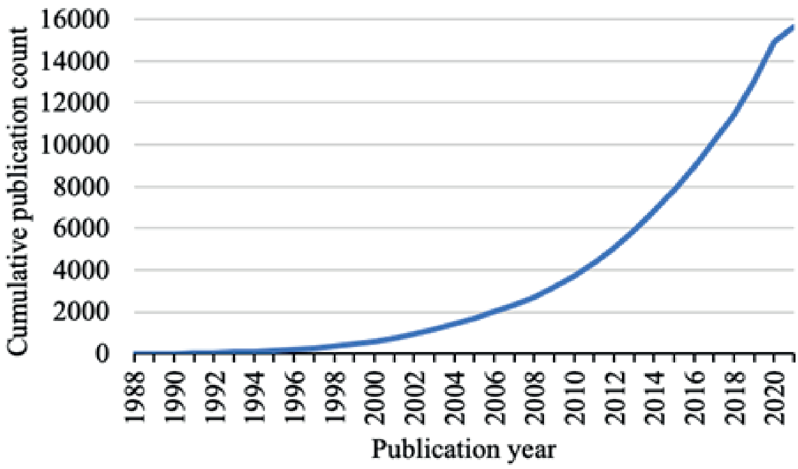

Fig. 1. Cumulative publication count of quercetin papers.

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

Item	Number of papers (% of 15685)	Citations per paper (CPP)
Organization		
Council of Scientific Industrial Research (India)	219 (1.4)	30.6
Chinese Academy of Sciences	178 (1.1)	24.3
Universidade de Sao Paulo (Brazil)	172 (1.1)	28.5
King Saud University (Saudi Arabia)	133 (0.8)	13.7
Consejo Superior de Investigaciones Cientificas (Spain)	130 (0.8)	77.5
Country		
China	2903 (18.5)	19.1
The United States	1769 (11.3)	57.6
India	1705 (10.9)	20.0
South Korea	929 (5.9)	26.2
Brazil	916 (5.8)	19.4
Journal		
Journal of Agricultural and Food Chemistry	376 (2.4)	83.7
Molecules	372 (2.4)	17.6
Journal of Ethnopharmacology	307 (2.0)	24.2
Food Chemistry	243 (1.5)	59.7
Food and Chemical Toxicology	151 (0.9)	56.3
Plos One	151 (0.9)	28.9

(13.6:1) [Yeung *et al.* 2020a] but higher than resveratrol (9.5:1) [Yeung *et al*. 2019a], apple polyphenol (7.6:1) [Yeung *et al*. 2021], and dietary natural products as a whole (1.5:1) [Yeung *et al.* 2018]. Indexed papers were mostly written in English (98.9%).

The top 5 most productive organizations, countries, and journals are listed in Table 1. Three out of the five most productive countries were from Asia, led by China. Their CPPs were comparable to that of Brazil, but less than half of the United States. Most productive authors were not analyzed because many of them had a Chinese name for which the initialized and Romanized format indexed by WoS might cause confusion, e.g. Li J, Li Y, and Li X might collectively represent many different persons [Yeung *et al*. 2019a]. The most cited paper from China was a report on using solid lipid nanoparticles as an oral delivery carrier to improve the gastrointestinal absorption of the poorly water-soluble quercetin (412 citations) [Li *et al*. 2009]. Meanwhile, the most cited paper from the United States was a report that investigated the quercetin analogs as phosphatidylinositol 3-kinase inhibitors [Vlahos *et al.* 1994].

Approximately a quarter of the indexed papers belonged to the WoS category of pharmacology and pharmacy (n = 3899, 24.9%, CPP = 28.8), followed by food science technology (n = 2545, 16.2%, CPP = 37.6), biochemistry and molecular biology (n = 2335, 14.9%, CPP = 35.5), chemistry medicinal (n = 1822, 11.6%, CPP = 24.3), and chemistry multidisciplinary (n = 1263, 8.1%, CPP = 16.4). Most productive journals were related to pharmacology and food (Tab. 1).

Figure 2 displays a term map showing the recurring terms from the titles and abstracts. Bioavailability was one of the terms with a high CPP (yellow bubble, n

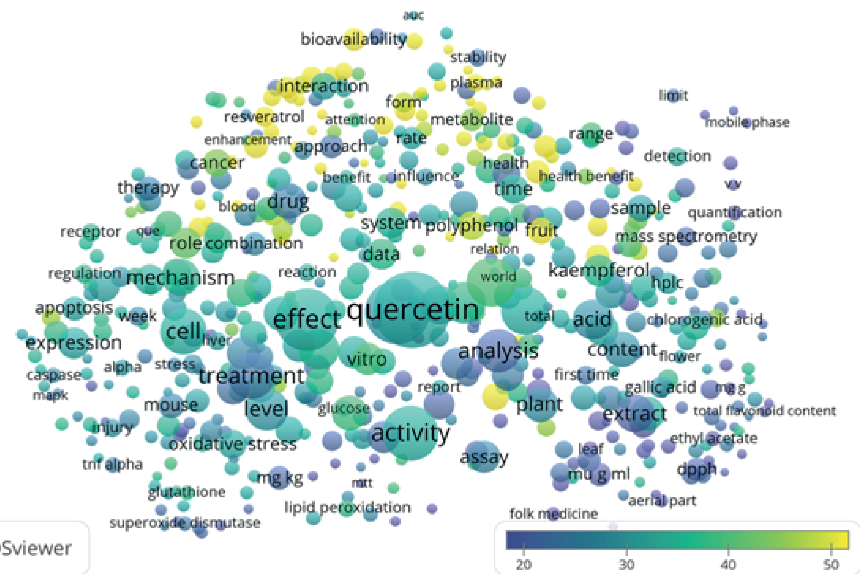

Fig. 2. Term map showing recurring terms in titles and abstracts of the quercetin papers. Bubble color indicates the citation per publication (CPP). Size indicates frequency count.

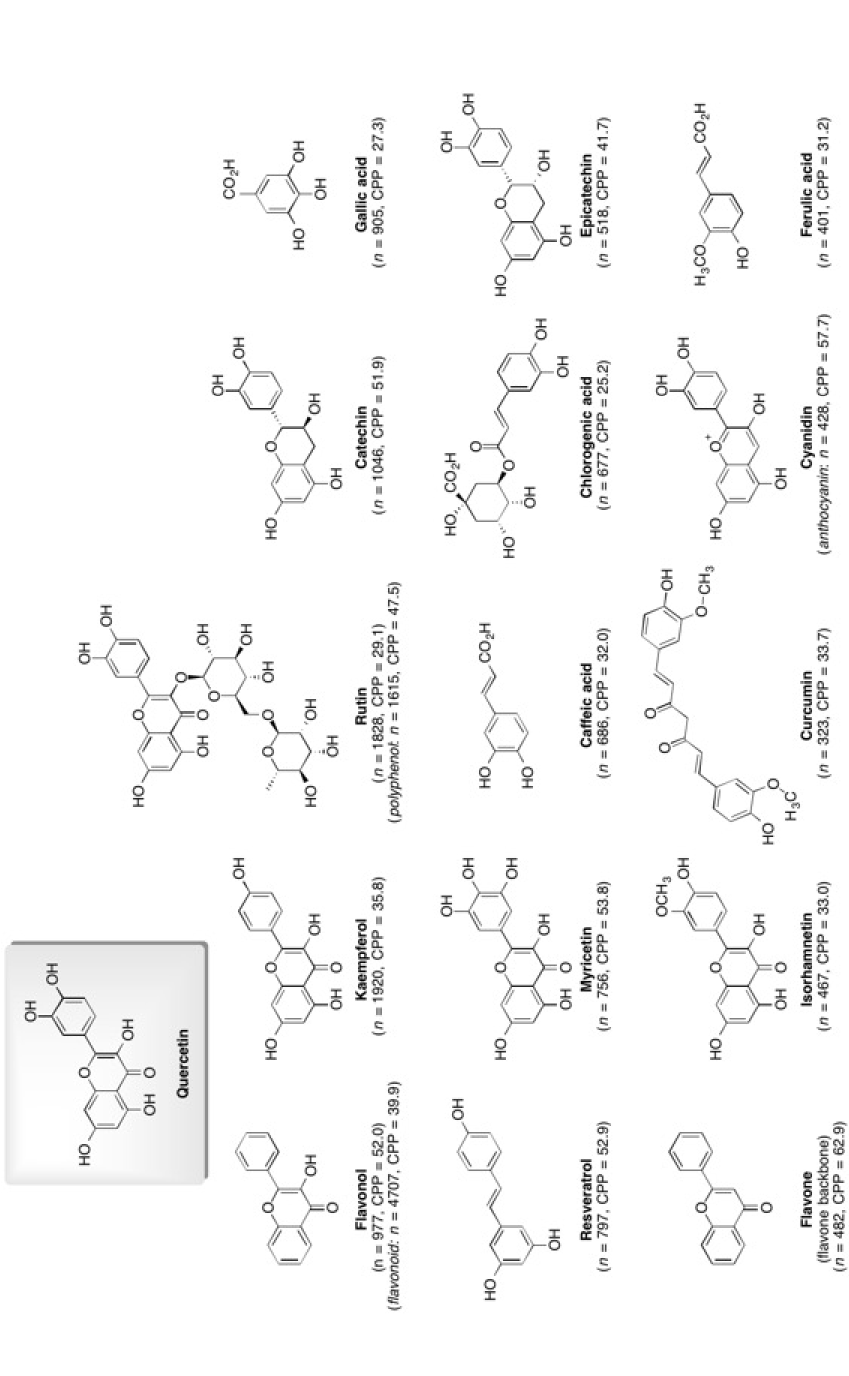

Fig. 3. Common chemicals/chemical classes mentioned in quercetin papers. In parentheses are indicated the cited compound classes (italic), number of papers (n), and citations per publication (CPP) for each chemical or representative chemical class (e.g., flavonoid, polyphenol, anthocyanin).

Table 2. Recurring chemicals/chemical classes from the papers (n≥400)

Chemical/chemical class	Number of papers (out of 15685)	Citations per paper (CPP)
Flavonoid	4707	39.9
Kaempferol	1920	35.8
Rutin	1828	29.1
Polyphenol	1615	47.5
Catechin	1046	51.9
Flavonol	977	52.0
Gallic acid	905	27.3
Resveratrol	797	52.9
Myricetin	756	53.8
Caffeic acid	686	32.0
Chlorogenic acid	677	25.2
Epicatechin	518	41.7
Flavone	482	62.9
Isorhamnetin	467	33.0
Curcumin	447	38.6
Anthocyanin	428	57.7
Ferulic acid	401	31.2

= 977, CPP = 57.3). Many terms with a high CPP were related to food sources of quercetin, such as red wine (n = 234, CPP = 135.4), apple (n = 199, CPP = 110.8), tea (n = 457, CPP = 92.7), and onion (n = 324, CPP = 83.1). Meanwhile, the recurring chemicals/chemical classes and structures of individual natural compounds are listed in Table 2 and Figure 3. One representative of these was anthocyanin, also identified as one of the most recurring compounds investigated in the grape and wine literature [Aleixandre-Tudo *et al*. 2019, Lucarini *et al*. 2021].

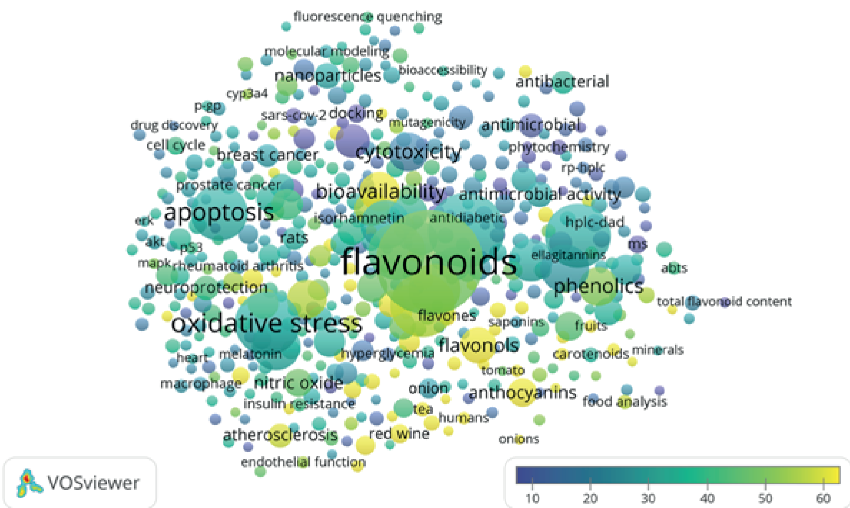

Fig. 4. Term map showing recurring author keywords of the quercetin papers. Bubble color indicates the citation per publication (CPP). Size indicates frequency count.

Figure 4 represents a term map showing recurring author keywords. Oxidative stress and apoptosis were popular keywords near the center of the map. Frequently mentioned medical conditions are listed in Table 3. Cancer and Alzheimer's disease were the most frequently mentioned medical conditions. Quercetin might promote the loss of cell viability, apoptosis, and autophagy via the modulation of several signal transduction pathways to achieve an overall anti-cancer effect [Murakami *et al.* 2008, Reyes-Farias and Carrasco-Pozo 2019]. Meanwhile, its anti-oxidative property might reduce reactive oxidative species that promote epigenetic alterations relevant to Alzheimer's disease [Zaplatic *et al.* 2019].

Table 3. Frequently mentioned medical conditions (n≥30)

Medical condition	Number of papers (out of 890)	Citations per paper (CPP)
Cancer	164	41.3
Alzheimer's disease	129	37.4
Atherosclerosis	98	57.2
Breast cancer	88	25.6
Obesity	83	22.2
Diabetes mellitus	78	16.6
Covid-19	77	7.9
Hypertension	65	41.6
Cardiovascular disease	63	60.7
Parkinson's disease	57	34.5
Prostate cancer	50	23.7
Neurodegeneration	42	38.3
Rheumatoid arthritis	38	22.5

The intake of quercetin could bring beneficial health effects in a broad array of animal models. For example, dietary quercetin could prolong the mean lifespan of *Caenorhabditis elegans* by 15% [Kampkötter *et al*. 2008], reduce the teratogenicity caused by cyclophosphamide (a medication that treats neoplastic and autoimmune diseases) in female rats [Mahabady *et al*. 2016], and reduce reproductive potential in female mice [Beazley and Nurminskaya 2016].

Conclusion

Besides the United States, the academic research on quercetin had substantial contributions from Asian and South American countries, such as China, India, South Korea, and Brazil. Many of the publications focused on pharmacology and food. Examples of frequently mentioned chemicals/chemical classes were flavonoid, kaempferol, rutin, polyphenol, and catechin. Likewise, frequently mentioned medical conditions were cancer, Alzheimer's disease, and atherosclerosis. There are numerous scientifically studied beneficial effects of quercetin demonstrated of on human and animal health, and further work focused on the nutraceutical properties of the compound is warranted.

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

REFERENCES

1. 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.
2. ANDRES S., PEVNY S., ZIEGENHAGEN R., BAKHIYA N., SCHÄFER B., HIRSCH-ERNST K. I., LAMPEN A., 2018 – Safety aspects of the use of quercetin as a dietary supplement. ***Molecular Nutrition & Food Research*** 62, 1700447.
3. ATANASOV A.G., YEUNG A.W.K., KLAGER E., EIBENSTEINER F., SCHADEN E., KLETECKA-PULKER M., WILLSCHKE H., 2020 – First, do no harm (gone wrong): Total-scale analysis of medical errors scientific literature. ***Frontiers in Public Health*** 8, 558913.
4. BATIHA G.E.-S., BESHBISHY A.M., IKRAM M., MULLA Z.S., EL-HACK M.E.A., TAHA A. E., ALGAMMAL A.M., ELEWA Y. H. A., 2020 – The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. ***Foods*** 9, 374.
5. BEAZLEY K.E., NURMINSKAYA M., 2016 – Effects of dietary quercetin on female fertility in mice: implication of transglutaminase 2. ***Reproduction, Fertility and Development*** 28, 974-981.
6. BOOTS A.W., HAENEN G.R., BAST A., 2008 – Health effects of quercetin: from antioxidant to nutraceutical. ***European Journal of Pharmacology*** 585, 325-337.
7. BULE M., ABDURAHMAN A., NIKFAR S., ABDOLLAHI M., AMINI M., 2019 – Antidiabetic effect of quercetin: A systematic review and meta-analysis of animal studies. ***Food and Chemical Toxicology*** 125, 494-502.
8. DABEEK W.M., MARRA, M. V., 2019 – Dietary quercetin and kaempferol: Bioavailability and potential cardiovascular-related bioactivity in humans. ***Nutrients*** 11, 2288.
9. DALIU P., SANTINI A., NOVELLINO E., 2019 – From pharmaceuticals to nutraceuticals: Bridging disease prevention and management. ***Expert Review of Clinical Pharmacology*** 12, 1-7.
10. DONG N. Q., LIN, H.X., 2021 – Contribution of phenylpropanoid metabolism to plant development and plant-environment interactions. ***Journal of Integrative Plant Biology*** 63, 180-209.
11. DURAZZO A., D'ADDEZIO L., CAMILLI E., PICCINELLI R., TURRINI A., MARLETTA L., MARCONI S., LUCARINI M., LISCIANI S., GABRIELLI P., 2018 – From plant compounds to botanicals and back: A current snapshot. ***Molecules*** 23, 1844.
12. DURAZZO A., LUCARINI M., SANTINI A., 2020 – Nutraceuticals in human health. ***Foods*** 9, 482.
13. 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.
14. EID H. M., HADDAD P.S., 2017 – The antidiabetic potential of quercetin: underlying mechanisms. ***Current Medicinal Chemistry*** 24, 355-364.
15. FALCONE FERREYRA M.L., RIUS S., CASATI P., 2012 – Flavonoids: biosynthesis, biological functions, and biotechnological applications. ***Frontiers in Plant Science*** 3, 222.
16. 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.
17. 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.
18. 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.
19. HUMINIECKI L., HORBAŃCZUK J., ATANASOV A.G., – 2017 – The functional genomic studies of curcumin. ***Seminar Cancer in Biology***, Doi.Org/10.1016/J.Semcancer.2017.04.002.

20. KAMPKÖTTER A., TIMPEL C., ZURAWSKI R.F., RUHL S., CHOVOLOU Y., PROKSCH P., WÄTJEN W., 2008 – Increase of stress resistance and lifespan of Caenorhabditis elegans by quercetin. ***Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology*** 149, 314-323.
21. KAŞIKCI M.B., BAĞDATLIOĞLU N., 2016 – Bioavailability of quercetin. ***Current research in nutrition and food science journal*** 4, 146-151.
22. KIM C., HWANG J.-K., 2020 – Flavonoids: nutraceutical potential for counteracting muscle atrophy. ***Food Science and Biotechnology*** 29, 1619-1640.
23. LESJAK M., BEARA I., SIMIN N., PINTAĆ D., MAJKIĆ T., BEKVALAC K., ORČIĆ D., MIMICA-DUKIĆ N., 2018 – Antioxidant and anti-inflammatory activities of quercetin and its derivatives. ***Journal of Functional Foods*** 40, 68-75.
24. LI CH., LI J., JIANG F., YUNLUN LI, TZVETKOV N.T., HORBANCZUK 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.
25. LI H., ZHAO X., MA Y., ZHAI G., LI L., LOU H., 2009 – Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles. ***Journal of Controlled Release*** 133, 238-244.
26. LI S.-J., LIAO Y.-F., DU Q., 2018 – Research and application of quercetin-loaded nano drug delivery system. ***Zhongguo Zhong Yao Za Zhi. Zhongguo Zhongyao Zazhi. China Journal of Chinese Materia Medica*** 43, 1978-1984.
27. LIU F., WANG L.-Y., LI Y.-T., WU Z.-Y., YAN C.-W., 2018 – Protective Effects of Quercetin against Pyrazinamide Induced Hepatotoxicity via a Cocrystallization Strategy of Complementary Advantages. ***Crystal Growth & Design*** 18, 3729-3733.
28. LUCARINI M., DURAZZO A., LOMBARDI-BOCCIA G., SOUTO E.B., CECCHINI F., SANTINI A., 2021 – Wine polyphenols and health: quantitative research literature analysis. ***Applied Sciences*** 11, 4762.
29. MOZOS I., STOIAN D., CARABA A., MALAINER C., HORBAŃCZUK J., ATANASOV A.G., 2018 – Lycopene and vascular health. ***Frontiers in Pharmacology*** 9, 521, Doi: 10.3389/Fphar.2018.00521.
30. MURAKAMI A., ASHIDA H., TERAO J., 2008 – Multitargeted cancer prevention by quercetin. ***Cancer Letters*** 269, 315-325.
31. PARHI B., BHARATIYA D., SWAIN S.K., 2020 – Application of quercetin flavonoid based hybrid nanocomposites: A review. ***Saudi Pharmaceutical Journal*** 28, 1719-1732.
32. PATEL R. V., MISTRY B.M., SHINDE S.K., SYED R., SINGH V., SHIN H.-S., 2018 – Therapeutic potential of quercetin as a cardiovascular agent. ***European Journal of Medicinal Chemistry*** 155, 889-904.
33. PIECZYNSKA M.D., YANG Y., PETRYKOWSKI S., HORBANCZUK O.K., ATANASOV A.G., HORBAŃCZUK J.O., 2020 – Gut microbiota and its metabolites in atherosclerosis development. ***Molecules*** 25(3):594. doi: 10.3390/molecules25030594.
34. PINGILI R.B., CHALLA S.R., PAWAR A.K., TOLETI V., KODALI T., KOPPULA S., 2020 – A systematic review on hepatoprotective activity of quercetin against various drugs and toxic agents: Evidence from preclinical studies. ***Phytotherapy Research*** 34, 5-32.
35. 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.
36. QADER G.I., AZIZ R.S., AHMED Z.A., ABDULLAH Z. F., HUSSAIN S.A., 2014 – Protective effects of quercetin against isoniazid and rifampicin induced hepatotoxicity in rats. ***American Journal of Pharmacological Sciences*** 2, 56-60.
37. RAUF A., IMRAN M., KHAN I.A., UR-REHMAN M., GILANI S. A., MEHMOOD Z., MUBARAK M.S., 2018 – Anticancer potential of quercetin: A comprehensive review. ***Phytotherapy Research*** 32, 2109-2130.

38. REYES-FARIAS M., CARRASCO-POZO C., 2019 – The anti-cancer effect of quercetin: molecular implications in cancer metabolism. ***International Journal of Molecular Sciences*** 20, 3177.
39. RIVA A., RONCHI M., PETRANGOLINI G., BOSISIO S., ALLEGRINI P., 2019 – Improved oral absorption of quercetin from quercetin phytosome®, a new delivery system based on food grade lecithin. ***European Journal of Drug Metabolism and Pharmacokinetics*** 44, 169-177.
40. SACHDEVA V., ROY A., BHARADVAJA N., 2020 – Current prospects of nutraceuticals: A review. ***Current Pharmaceutical Biotechnology*** 21, 884-896.
41. SAEED M., NAVEED M., ARAIN M., ARIF M., ABD EL-HACK M., ALAGAWANY M., SIYAL F., SOOMRO R., SUN, C., 2017 – Quercetin: Nutritional and beneficial effects in poultry. ***World's Poultry Science Journal*** 73, 355-364.
42. SANTINI A., CAMMARATA S.M., CAPONE G., IANARO A., TENORE G.C., PANI L., NOVELLINO, E., 2018 – Nutraceuticals: Opening the debate for a regulatory framework. ***British Journal of Clinical Pharmacology*** 84, 659-672.
43. SANTINI A., CICERO, N., 2020 – Development of food chemistry, natural products, and nutrition research: Targeting new frontiers. ***Foods*** 9, 482.
44. SANTINI, A., NOVELLINO E., 2018 – Nutraceuticals-shedding light on the grey area between pharmaceuticals and food. ***Expert Review of Clinical Pharmacology*** 11, 545-547.
45. SINGH L., JOSHI T., TEWARI D., ECHEVERRÍA J., MOCAN A., SAH A.N., PARVANOV E., TZVETKOV N.T., MA Z.F., LEE Y.Y., POZNAŃSKI P., HUMINIECKI L., SACHARCZUK M., JÓŹWIK A., HORBAŃCZUK J.O., FEDER-KUBIS J., ATANASOV A.G., 2020 – Ethnopharmacological Applications Targeting Alcohol. ***Frontiers in Pharmacology*** 10,1593.
46. TAPAS A.R., SAKARKAR D., KAKDE R., 2008 – Flavonoids as nutraceuticals: a review. ***Tropical journal of Pharmaceutical research*** 7, 1089-1099.
47. TEWARI D., MOCAN A., PARVANOV E.D., SAH. A.N., NABAVI S.N., HUMINIECKI L., MA Z.F., LEE Y.Y., HORBAŃCZUK J.O., ATANASOV A.G., 2017 – Ethnopharmacological approaches for therapy ff jaundice: Part II. Highly used plant species from acanthaceae, euphorbiaceae, asteraceae, combretaceae, and fabaceae families. Doi: 10.3389/Fphar.2017.00519.
48. VAN ECK N.J., WALTMAN L., 2009 – Software survey: VOSviewer, a computer program for bibliometric mapping. ***Scientometrics*** 84, 523-538.
49. VIEIRA R., SOUTO S. B., SÁNCHEZ-LÓPEZ E., LÓPEZ MACHADO A., SEVERINO P., JOSE S., SANTINI A., FORTUNA A., GARCÍA M.L., SILVA A.M., 2019 – Sugar-lowering drugs for type 2 diabetes mellitus and metabolic syndrome - review of classical and new compounds: part-I. ***Pharmaceuticals*** 12, 152.
50. VLAHOS C.J., MATTER W.F., HUI K.Y., BROWN R.F., 1994 – A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002). ***Journal of Biological Chemistry*** 269, 5241-5248.
51. WANG D., HUANG J., YEUNG A.W.K., TZVETKOV N.T., HORBAŃCZUK J.O., Willschke H., GAI Z. ATANASOV A.G., 2020 – The significance of natural product derivatives and traditional medicine for COVID-19. ***Processes*** 8(8), 937; https://doi.org/10.3390/ pr8080937.
52. WANG D., ÖZEN C., ABU-REIDAH I.M., CHGURUPATI S., PATRA J.K., HORBAŃCZUK J.O., JÓŹWIK 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.
53. WANG W., SUN C., MAO L., MA P., LIU F., YANG J., GAO Y., 2016 – The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review. ***Trends in Food Science & Technology*** 56, 21-38.
54. 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.

55. WONG S.K., CHIN K.-Y., IMA-NIRWANA S., 2020 – Quercetin as an agent for protecting the bone: A review of the current evidence. ***International Journal of Molecular Sciences*** 21, 6448.
56. XU D., HU M.-J., WANG Y.-Q., CUI Y.-L., 2019 – Antioxidant activities of quercetin and its complexes for medicinal application. ***Molecules*** 24, 1123.
57. YANG D., WANG T., LONG M., LI P., 2020 – Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine. ***Oxidative Medicine and Cellular Longevity*** 2020, 8825387.
58. 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., JÓŹWIK A., MARCHEWKA J., MILLER M., MOCAN A., MOZOS I., NABAVI S., NABAVI S., PIECZYNSKA M., PITTALÀ V., RENGASAMY K., SILVA A., SHERIDAN H., STANKIEWICZ A., STRZAŁKOWSKA N., SUREDA A., TEWARI D., WEISSIG V., ZENGIN 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.
59. 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., JÓŹWIK A., STRZAŁKOWSKA N., MOCAN A., MOZOS I., NABAVI S.M., PAJPANOVA T., PITTALA V., FEDER-KUBIS J., SAMPINO S., SILVA A.S., SHERIDAN H., SUREDA A., TEWARI D., WANG D., WEISSIG V., YANG Y., ZENGIN 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.
60. 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., ZENGIN 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 & Reports*** 38, 5-19.
61. 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.
62. 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.
63. YEUNG A.W.K., TZVETKOV N.T., EL-DEMERDASH A., HORBANCZUK O.K., DAS N., PIRGOZLIEV V., LUCARINI M., DURAZZO A., SOUTO E.B., SANTINI A., DEVKOTA H.P., UDDIN M., ECHEVERRÍA J., WANG D., GAN R.Y., BRNČIĆ M., KALFIN R., TANCHEVA L.P., TEWARI D., BERINDAN-NEAGOE I., SAMPINO S., STRZAŁKOWSKA N., MARCHEWKA J., JOZWIK A., HORBANCZUK J.O., ATANASOV A.G., 2021 - Apple polyphenols in human and animal health. ***Animal Science Papers and Reports*** 39, 105-118.

64. 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.
65. ZAPLATIC E., BULE M., SHAH S.Z.A., UDDIN M.S., NIAZ K., 2019 – Molecular mechanisms underlying protective role of quercetin in attenuating Alzheimer's disease. ***Life Sciences*** 224, 109-119.