Dietary natural products and their potential to influence health and disease including animal models

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Institute of Genetics and Animal Breeding, Jastrzębiec, Poland

Review

Dietary natural products and their potential to influence health and disease including animal model studies*

Andy Wai Kan Yeung[1], Bharat Bhushan Aggarwal[2], Davide Barreca[3], Maurizio Battino[4], Tarun Belwal[5], Olaf K. Horbańczuk[6], Ioana Berindan-Neagoe[7], Anupam Bishayee[8], Maria Daglia[9], Hari Prasad Devkota[10], Javier Echeverría[11], Amr El-Demerdash[12,13], Ilkay Erdogan Orhan[14], Keith M. Godfrey[15], Vijai Kumar Gupta[16], Jarosław O. Horbańczuk[17], Jacek A. Modliński[17], Lukas A. Huber[18], Lukasz Huminiecki[19], Artur Jóźwik[17], Joanna Marchewka[17], Mark J.S. Miller[20], Andrei Mocan[7], Ioana Mozos[21], Seyed Fazel Nabavi[22], Seyed Mohammad Nabavi[22], Magdalena D. Pieczynska[17], Valeria Pittalà[23], Kannan R.R. Rengasamy[24], Ana Sanches Silva[25,26], Helen Sheridan[27], Adrian M. Stankiewicz[17], Nina Strzałkowska[17], Antoni Sureda[28], Devesh Tewari[29], Volkmar Weissig[30], Gökhan Zengin[31], Atanas G. Atanasov[17,32,33]****

[1] Oral and Maxillofacial Radiology, Applied Oral Sciences, Faculty of Dentistry, The University of Hong Kong, Hong Kong S.A.R., China

[2] Inflammation Research Center, San Diego, CA, USA

[3] Biochemistry and Applied Biochemistry, Università degli studi di Messina, Messina, Italy

[4] Department of Clinical Sciences, Faculty of Medicine, Università Politecnica delle Marche, Ancona, Italy

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**Corresponding authors: ndyeung@hku.hk and a.atanasov.mailbox@gmail.com.

[5] Biodiversity Conservation and Management,
GB Pant Institute of Himalayan Environment and Development, India
[6] Faculty of Human Nutrition and Consumer Sciences,
Warsaw University of Life Sciences, 02-776 Warsaw, Poland
[7] Department of Pharmaceutical Botany, "Iuliu Haţieganu" University of Medicine and Pharmacy,
23 Ghe. Marinescu Street, 400337 Cluj-Napoca, Romania
[8] Lake Erie College of Osteopathic Medicine, Bradenton, FL, USA
[9] Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section,
University of Pavia, Pavia, Italy
[10] Priority Organization for Innovation and Excellence, Kumamoto University, Kumamoto, Japan
[11] Departamento de Ciencias del Ambiente, Facultad de Química y Biología,
Universidad de Santiago, Chile
[12] Centre National de La recherché Scientifique, Muséum National d'Histoire Naturelle, Molécules de Communication et Adaptation des Micro-organismes, UMR 7245 CNRS/MNHN, Sorbonne Universités, France
[13] Organic Chemistry Division, Chemistry Department, Faculty of Science, Mansoura University,
Mansoura 35516, Egypt
[14] Faculty of Pharmacy, Gazi University, Ankara, Turkey
[15] MRC Lifecourse Epidemiology Unit and NIHR Southampton Biomedical Research Centre,
University of Southampton and University Hospital Southampton NHS Foundation Trust
[16] ERA Chair of Green Chemistry, Department of Chemistry and Biotechnology,
Tallinn University of Technology, Tallinn, Estonia
[17] The Institute of Genetics and Animal Breeding, Polish Academy of Sciences,
Jastrzębiec, 05-552 Magdalenka, Poland
[18] Cell Biology, Biocenter, Innsbruck Medical University, Austria
[19] SciLifeLab, IGP, Uppsala University, Uppsala, Sweden
[20] Kaiviti Consulting, LLC, USA
[21] Discipline of Pathophysiology, Victor Babes University of Medicine and Pharmacy of Timisoara,
Timișoara, Romania
[22] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences,
P.O. Box 19395-5487, Tehran 14359-16471, Iran
[23] Department of Drug Science, University of Catania, Catania, Italy
[24] REEF Environmental Consultancy, India
[25] National Institute for Agricultural and Veterinary Research (INIAV),
Vairão, Vila do Conde, Portugal
[26] Center for Study in Animal Science (CECA), ICETA, University of Porto, Oporto, Portugal
[27] School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Ireland
[28] Research Group on Community Nutrition and Oxidative Stress (NUCOX) and CIBEROBN (Physiopathology of Obesity and Nutrition CB12/03/30038), University of Balearic Islands, Palma de Mallorca E-07122, Balearic Islands, Spain
[29] Department of Pharmaceutical Sciences, Faculty of Technology,
Kumaun University, Nainital, Uttarakhand, India
[30] Department of Pharmaceutical Sciences, Midwestern University, Glendale, AZ, USA
[31] Department of Biology, Selcuk University, Konya, Turkey
[32] Department of Pharmacognosy, University of Vienna, Vienna, Austria
[33] GLOBE Program Association (GLOBE-PA), Grandville, MI, USA

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Although biological and pharmacological effects of dietary natural products have been intensively studied, there has been no bibliometric analysis performed on this research field up to now. The current study has aimed to identify and analyze the manuscripts on dietary natural products and their potential to influence health and disease including studies using animal models. Data, including words from titles and abstracts, publication and citation data, have been extracted from Web of Science database and analyzed by the VOSviewer software. Our search has yielded 1,014 manuscripts. The ratio of original articles to reviews was identified to be 1.5:1. Over half of the manuscripts have been published since 2010. The manuscripts have been contributed by 4,301 authors from 1,445 organizations in 76 countries/territories and published in 499 journals. The results from the current study point out that scientific research focusing on the potential of dietary natural products to affect health and disease status (including animal model studies) is expanding, and suggests an increasing significance of this scientific area. With the progressive development and improvement of animal studies, it should be expected that animal models of different human diseases (especially civilization ones) would be an integral part of the research for the evaluation of pharmaceuticals originated from dietary natural products like plants or plant materials. Moreover, natural products can also be fed to animals to improve the quality of animal products, with numerous resulting functional effects.

KEYWORDS: animal models / bioactive compounds / citation analysis / dietary / food science / natural products

Dietary natural products have been extensively studied in the recent years [Weidner *et al.* 2012, Lacroix and Li-Chan 2014, Atanasov *et al.* 2015, Zhou *et al.* 2016]. Many bioactive natural products are present in common foods with considerable health effects, such as fruits, vegetables, nuts, spices, legumes and beverages [Wang *et al.* 2014, Bishayee and Sethi 2016, Sureda *et al.* 2016, Waltenberger *et al.* 2016, Huminiecki *et al.* 2017, Lipińska *et al.* 2017, Venkata *et al.* 2017, Atanasov *et al.* 2018, Belwal *et al.* 2018, Huminiecki and Horbańczuk 2018, Lipińska and Jóźwik 2018, Liu *et al.* 2018, Pogorzelska-Nowicka *et al.* 2018a, Mozos *et al*. 2018, Wang *et al*. 2018, Tewari *et al.* 2018]. With the expanding literature on the topic it is worthwhile to identify the major contributors, as well as to analyze the publishing and citation trends of the field. In the same line, another important aspect is the identification of the topics which have received more attention and thus could be considered more relevant. There are multiple aspects of bibliometric analysis in general, ranging from surveying journal editorial practice [Yeung 2017a], revealing the general landscape of a defined research field [Yeung *et al.* 2017b], examining the effect of a certain feature associated with the publication (e.g., the presence of a graphical abstract) on the citation counts [Pferschy-Wenzig *et al.* 2016], to the identification of the most cited manuscripts within a pre-defined body of literature [Yeung *et al.* 2017a]. Since no bibliometric analysis has ever been published on dietary natural products, we have rationalized that it would be beneficial to study the general landscape of this research field in order to gain an overview, e.g. revealing which health or disease conditions were most studied in relation to dietary natural products.

Therefore, in the current study, we have aimed to identify and analyze the manuscripts on dietary natural products and their potential to affect health and disease including animal model studies.

Material and methods

An extensive search was performed using the Web of Science (WoS), a multidisciplinary online database hosted by Clarivate Analytics, to identify manuscripts with the following string: TS=((diet OR dietary OR food OR feed OR nutrition) AND (health OR disease) AND ("in vivo" OR animal OR patient OR patients OR participant OR participants) AND ("natural product" OR "natural compound" OR phytochemical OR "secondary metabolite")). TS is the code for the field of "topic", which refers to the fields of title, abstract or keywords. This string searched for manuscripts that contain the pre-defined combinations of these terms or phrases in their title, abstract or keywords. We did not place restrictions on the publication year, manuscript type (e.g., research article, review, editorial, letter, etc.), or publication language.

Data Extraction

The manuscripts resulted from the literature search were evaluated and recorded for: (1) publication year; (2) journal title; (3) total citation count; (4) authorship; (5) WoS category; and (6) manuscript type. The full records and cited references of these manuscripts were imported into VOSviewer and CRExplorer for further bibliometric analyses.

VOSviewer is software that extracts and analyzes the words appearing in the titles and abstracts of manuscripts, relates them to citation counts and visualizes the results as a bubble map [van Eck and Waltman 2009]. Each bubble represents a word or a phrase. Manual inspection was conducted to exclude generic or irrelevant terms, e.g. present study, paper, information, background, etc. [Heersmink *et al.* 2011, Yeung *et al.* 2017c, Yeung 2018]. The bubble size indicates the frequency of occurrence of the words (multiple appearances in a single manuscript count as one). The bubble color indicates the averaged citation count received by manuscripts containing the word in their titles or abstracts. Two bubbles are closer to each other if the two words co-occurred more frequently. The term map visualizes terms that appeared in at least ten of the included manuscripts.

CRExplorer is software dedicated to the analysis of cited references [Marx *et al.* 2014, Comins and Leydesdorff 2016, Thor *et al.* 2016, Yeung 2017b]. We used it to identify the top five most cited references among all references made by the included manuscripts resulting from the WoS search.

We tested for possible correlation between total publication count and averaged citations per manuscript for each country. Pearson's correlation test was performed in SPSS 24.0 (IBM, New York, NY, USA). Test results were considered significant if $p<0.05$.

Results and discussion

The search, performed according to the criteria described above, resulted in 1,014 manuscripts. Over half of them were published in the year 2011 or later (Fig.

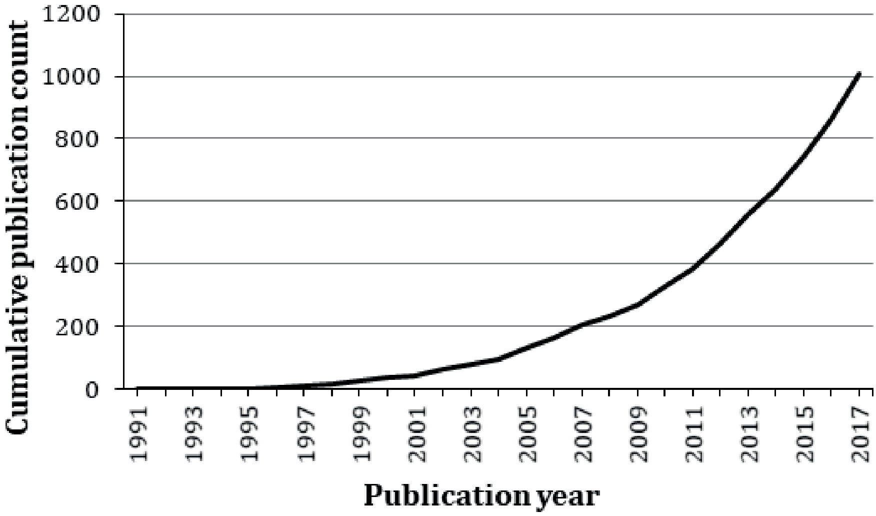

Fig. 1. The publication year of the 1,014 reported manuscripts. The numbers of manuscripts published annually in recent years have been rising steadily.

1). The numbers of original articles (*n* = 599) and reviews (*n* = 385) were in the ratio of 1.5:1. Most of the manuscripts were written in English (*n* = 987, 97.3%). The manuscripts were contributed by 4,301 authors from 1,445 organizations in 76 countries/territories and published in 499 journals. The top five contributors with regard to author, organization, country/territory and journal are listed in Table 1. The predominance of the USA and UK was consistent with previous analysis pointing their contributions to neuroimaging studies on taste and food [Yeung 2018]. The top five WoS categories associated with the analyzed publications were Food Science Technology (*n* = 220, 21.7%), Nutrition/Dietetics (*n* = 203, 20.0%), Pharmacology/Pharmacy (*n* = 166, 16.4%), Biochemistry and Molecular Biology (*n* = 141, 13.9%) and Chemistry/Medicinal (*n* = 77, 7.6%).

The predominance of the USA in publishing dietary natural product manuscripts may be partially related to its large consumer market which is in turn influenced by its government policy. The use of botanical supplements in the USA might have increased substantially after the passage of the Dietary Supplement and Health Education Act of 1994, under which the marketing of botanical supplements are allowed with few regulations as long as there are no claims about disease curing, detection or prevention [Raskin *et al.* 2002]. Using nationally representative data from the USA in 2011-2012, a study reported that 52% of USA adults have been taking dietary supplements [Kantor *et al.* 2016]. Meanwhile, the total estimated retail sales of herbal supplements in the USA have been increasing steadily since 2000 and reached US$7.5 billion in 2016 [Smith *et al.* 2017]. The growing industry and market might have fueled the research on dietary natural product. However, such connection was not fully reflected

Table 1. The top five contributors of the 1,014 manuscripts

Contributor	Number of publications (% of total)
Author	
Bishayee, Anupam	8 (0.8%)
Nabavi, Seyed Mohammad	8 (0.8%)
Daglia, Maria	7 (0.7%)
Nabavi, Seyed Fazel	7 (0.7%)
Battino, Maurizio	6 (0.6%)
Organization	
United States Department of Agriculture	34 (3.4%)
University of California	28 (2.8%)
Spanish National Research Council	22 (2.2%)
Rutgers University – New Brunswick	16 (1.6%)
University of Milan	15 (1.5%)
Country / Territory	
USA	329 (32.4%)
Italy	94 (9.3%)
China	91 (9.0%)
India	72 (7.1%)
UK	59 (5.8%)
Journal	
Molecular Nutrition and Food Research	26 (2.6%)
Journal of Agricultural and Food Chemistry	20 (2.0%)
Food and Function	18 (1.8%)
Molecules	17 (1.7%)

when we examined the list of funding sources. There was no apparent industrial entity contributing to multiple manuscripts. Meanwhile, we found specialized agencies from the list, such as the National Processed Raspberry Council (funded three studies, n = 3), California Raisin Marketing Board (n = 1), California Strawberry Commission (n=1) and Canaryseed Development Commission of Saskatchewan (n = 1). The former three were from the USA and the latter one from Canada.

Pearson's correlation test revealed that there was no significant correlation between total publication count and averaged citations per manuscript in the country level (r = 0.22, p = 0.052). Even though the USA has a much larger publication count than the second-most prolific country (Italy), the correlation was still not significant with its exclusion (r = 0.13, p = 0.283). This non-correlation is consistent with a previous report on neuroimaging studies on food [Yeung 2018].

There are three manuscripts with more than 1,000 citations, and all of them are reviews. The authors reviewed plant products such as antimicrobial agents [Cowan 1999], antioxidant properties of phenolic compounds [Rice-Evans *et al.* 1997] and the chemistry, metabolism and structure-activity of flavonoid antioxidants [Heim *et al.* 2002]. These overviews are highly relevant to many individual studies as antimicrobial and antioxidant properties are potentially beneficial to human and animal health.

By analyzing the words in the titles and abstracts of the 1,014 manuscripts, a bubble map was generated to visualize the citation data (Fig. 2). There were 688 terms that appeared in ten or more of the 1,014 manuscripts. A considerable proportion of these terms were related to human/animal health and diseases. Manuscripts containing certain terms had higher than average citation counts, such as those with wine (*n* = 17, citations per manuscript = 238), terpenoid (*n* = 15, citations per manuscript = 214), tea (*n* = 36, citations per manuscript = 136), human diet (*n* = 25, citations per manuscript = 126) and tannin (*n*=34, citations per manuscript = 120). Cancer (*n* = 268, citations per manuscript = 46), cardiovascular diseases (*n* = 116, citations per manuscript = 51) and diabetes (*n* = 119, citations per manuscript = 32) were among the major foci of the manuscripts concerning human or animal diseases.

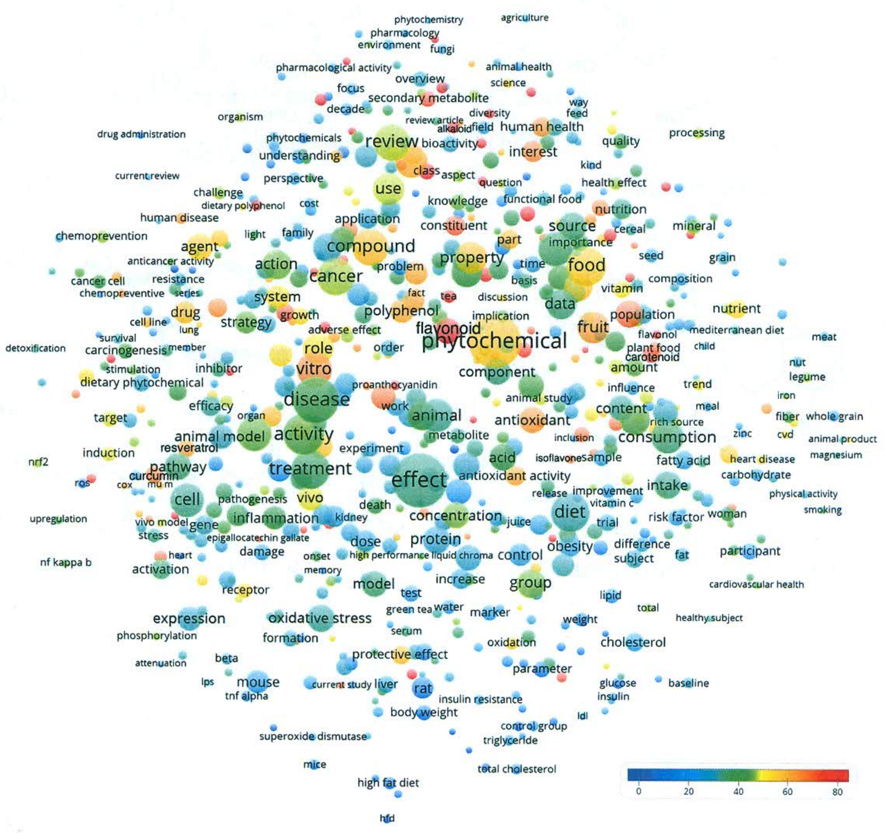

Fig. 2. Bubble map using words from titles and abstracts of the dietary natural products manuscript set. VOSviewer software was used to analyze and visualize words from titles and abstracts. There were 688 words or phrases that appeared in ten or more manuscripts. The bubble size indicates the frequency of occurrence. The bubble color indicates the averaged citation counts received by manuscripts containing the word or phrase. If two words or phrases co-occurred more frequently, the two bubbles are in closer proximity. Irrelevant terms were removed manually upon visual inspection of the initial map generated.

Some other highly cited terms of chemicals or compound classes were alkaloid (n = 33, citations per manuscript = 111), proanthocyanidin (n = 21, citations per manuscript = 104), flavonol (n = 18, citations per manuscript = 97), flavonoid (n = 128, citations per manuscript = 86), phenolic compound (n = 48, citations per manuscript = 76), carotenoid (n = 65, citations per manuscript = 73), epigallocatechin gallate (n = 10, citations per manuscript = 70), isoflavone (n = 22, citations per manuscript = 67), curcumin (n = 64, citations per manuscript = 66) and resveratrol (n = 62, citations per manuscript = 60) (Fig. 3). On average, manuscripts with these terms had > 60 citations per manuscript. Many of these compound classes commonly found in dietary natural products may have therapeutic uses. For instance, it was reported that proanthocyanidin extracted from grape seed and various parts of other fruits is useful for protection against tissue injury mediated by oxidative and free radical stresses and may have a role in cancer therapy [Bagchi *et al.* 2000, Nandakumar *et al.* 2008]. Meanwhile, epigallocatechin gallate is one of the most abundant catechins found in green tea and it has been linked to several potential health benefits with its anti-oxidative property as well as its multiple direct and indirect interactions with various cells. Interestingly, the top five references most cited by these 1,014 manuscripts were similarly focused on cancer [Jang *et al.* 1997, Surh 2003] (each cited by 33 of the 1,014 manuscripts), coronary heart disease [Hertog *et al.* 1993] (cited by 33 manuscripts) and polyphenols

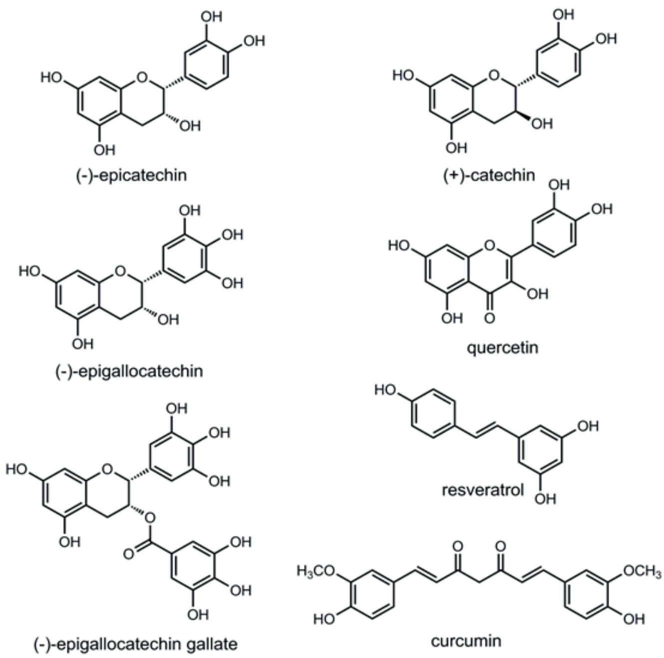

Fig. 3. Chemical structures of key single natural compounds that were often discussed in the analyzed literature set.

that may have a modulatory role in cancer and cardiovascular diseases [Manach *et al.* 2004, Manach *et al.* 2005] (cited by 49 and 31 manuscripts, respectively). The high citations of both manuscripts and references dealing with these works points to the perceived significance of the effects of dietary natural products on health and disease status. This notion has been also advocated by a number of previous literature reviews, for instance, on the effects of phytochemicals and carotenoids on human health [Dillard and German 2000, Rao and Rao 2007].

Among the most important aspects of dietary natural product research are animal studies. As depicted in Figure 2, the word "animal" is located in the center of the bubble map. In fact, animals have been commonly used as models of human diseases, especially in civilization ones to study potential therapeutic or preventive effects of natural products. For instance, resveratrol has anti-cancer and chemopreventive effects [Bishayee 2009], putative benefits for the cardiovascular system, antioxidant activity, as well as anti-diabetic and neuroprotective effects [Humiencki and Horbańczuk 2018]. Multifactorial experiments would allow for the testing and comparison of the mode of action, and testing for synergies between resveratrol and other natural products with putative anti-cancer activities [Huminiecki and Horbańczuk]. Similarly, the anticancer, antidiabetic and neuro-protective effects of green tea and its polyphenolic catechins have been demonstrated in various animal models [Zaveri 2006]. In turn, vasculoprotective effects of pomegranate (*Punica granatum* L.) can be attributed to the presence of the hydrolyzable tannins ellagitannins and ellagic acid, as well as other compounds (e.g., anthocyanins and flavonoids). For example i*n vitro* studies on animal model showed that substances derived from pomegranate reduce oxidative stress and platelet aggregation, diminish lipid uptake by macrophages, positively influence endothelial cell function, and are involved in blood pressure regulation [Wang *et al.* 2018]. This promising results should be extended with the use of others animal models such as pig and sheep.

There is scientific evidence that also lycopene may improve vascular function and contributes to the primary and secondary prevention of cardiovascular disorders. The main activity profile of lycopene studied also on animal model includes antiatherosclerotic, antioxidant, anti-inflammatory, antihypertensive, antiplatelet, anti-apoptotic, and protective endothelial effects, as well as the ability to improve the metabolic profile [Mozos *et al*. 2018]. Curcumin was also shown to decrease oxidative stress, arterial stiffness and the risk of cardiovascular events [Mozos *et al*. 2017]. In turn, curcumin has a powerful effect on gene expression profiles. The functional genomics can help us to understand how curcumin works on cancer cells. The appreciation of this fact is self-evident from the multitude of papers published in the field. At the same time, we note that these studies were mostly performed on *in vitro* cultured of cancer cell lines. It would be interesting to see more studies carried especially on the animal models for cancer chemoprevention. Moreover, according to Tewari *et al.* [2018], curcumin application may be useful for treatment of dementia symptoms, as seen in animal model studies. Furthermore, this supplement treatment with some mitochondrial antioxidants, such as α-lipoic acid and acetyl-L-carnitine has been shown to reduce both physical and mental weariness or even to restore memory function in age-related diseases, including Alzheimer disease (AD) and different types of dementia, as provided in transgenic mouse model of AD. However, there are still many unknowns in this research area that need to be clarified by planning future studies based on animal models. The scientific community needs more comprehensive research focused on identifying active ingredients of plants and investigating their mechanism of action based also on animal model studies.

It should be underlined, that to improve the translational value of animal studies that proves the anti-infective potential of natural products, there have been recommendations on the choice of pathogens, standardization of experiment procedures, endpoint parameters and efficacy criteria. With the progressive development and improvement of animal studies, it should be expected that animal models of different human diseases (especially civilization ones) must remain as an integral part of the research for the evaluation of pharmaceuticals originated from dietary natural products like plants or plant materials.

Moreover, natural product can also be fed to animals in order to improve the quality of animal products, with numerous resulting functional effects [Lipińska *et al.* 2017, Pogorzelska-Nowicka *et al.* 2018a, Pogorzelska-Nowicka *et al.* 2018b]. For instance, blends of phytogenic feed additives may exert antioxidative and antimicrobial effects in livestock as well as promote their growth [Windisch *et al.* 2008]. Moreover, adding natural antioxidants, such as avocado seed or peel extracts, or rosemary extracts, may help preserve the meat products in a better quality by reducing the lipid and protein oxidation [Falowo *et al.* 2014]. These examples illustrate that the influence of dietary natural products on health and disease's prevention is not confined to just humans, but is also applicable to animals and animal products.

In conclusion: A bibliometric analysis was performed to evaluate the manuscripts focused on dietary natural products. The obtained data indicated that the USA is the major contributor and that most of the published manuscripts were focused on nutrition, food science and pharmacology. The results from this study point out that there is a growth of the scientific research, including studies with the use of animal models, focused on the potential beneficial effects of dietary natural products to maintain and improve health status. The focus should shift to the design of experiments on animal models which better mimic effects induced by the diet containing natural products rich in bioactive compounds. With the progressive development and improvement of animal studies, it should be expected that animal models of different human diseases (especially civilization ones) would be an important and integral part of the research concerning the evaluation of pharmaceuticals originated from dietary natural products like plants or plant materials. Moreover, natural product can also be fed to animals to improve the quality of animal products, with numerous resulting functional effects.

Supplementary data: A supplementary Excel sheet is available at the journal website http://www.ighz.edu.pl/en/full-texts-pdf-format-1. It includes the terms that occurred in ten or more of the 1,014 manuscripts and their citations per manuscript.

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

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