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Resveratrol, a popular dietary supplement for human and animal health: Quantitative research literature analysis - a review

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Resveratrol is a stilbene-type bioactive molecule with a broad spectrum of reported biological effects. In this sense, the current work provides a comprehensive literature analysis on resveratrol, representing a highly-researched commercially available dietary ingredient. Bibliometric data were identified by means of the search string TOPIC=("resveratrol*") and analyzed with the VOSviewer software, which yielded 17,561 publications extracted from the Web of Science Core Collection electronic database. The ratio of original articles to reviews was 9.5:1. More than half of the overall manuscripts have been published since 2013. Major contributing countries were USA, China, Italy, South Korea, and Spain. Most of the publications appeared in journals specialized in biochemistry and molecular biology, pharmacology and pharmacy, food science technology, cell biology, or oncology. The phytochemicals or phytochemical classes that were frequently mentioned in the keywords of analyzed publications included, in descending order: resveratrol, *trans*-resveratrol, polyphenols, flavonoids, quercetin, stilbenes, curcumin, piceatannol, *cis*-resveratrol, and anthocyanins.

KEYWORDS: bibliometrics / biological activities / cancer / citation analysis / pharmacology / resveratrol / Web of Science / VOSviewer

Resveratrol (systematically named 3,5,4'-trihydroxy-*trans*-stilbene) is a phytoalexin stilbenoid [Akinwumi *et al*. 2018] mainly found in the skin of grapes and many other dietary plants such as raspberries, mulberries, pistachios and peanuts. It is hypothesized that resveratrol is produced in response to stress conditions, including injury and microbial attack [Jang *et al*. 1997, Frémont 2000, Rocha-González *et al.* 2008, Tabeshpour *et al*. 2018]. Numerous investigations have reported its potential usefulness in the prevention and treatment of cardiovascular diseases, hepatic disorders, diabetes, cancer, obesity, pain, inflammation, tissue injury, neurodegeneration, and even aging [Rocha-González *et al*. 2008, Bishayee *et al*. 2010b, Darvesh *et al*. 2010, Chachay *et al*. 2011, Sinha *et al*. 2016, Ko *et al.* 2017, Öztürk *et al*. 2017, Koushki *et al*. 2018, Pannu and Bhatnagar 2019, Springer and Moco 2019]. The antioxidant properties of resveratrol promote the reduction of arterial stiffness, which is a factor contributing to the development of cardiovascular diseases [Mozos and Luca 2017, Mozos *et al*. 2017, Wang *et al.* 2018, Uhrin *et al.* 2018]. Resveratrol has been considered responsible for the "French paradox", explaining the comparatively low incidence of coronary heart disease despite consumption of high fat diet in France, where higher amounts of red wine (rich of resveratrol) are consumed [Kopp 1998]. In relation to the latter, it has been argued that resveratrol`s bio-effects are observed at concentrations higher than the concentrations typically found in red wine, but important consideration also is the synergistic action of resveratrol with other compounds found in red wine [Chan *et al.* 2000, Kurin *et al.* 2012]. Additionally, the antidiabetic, antiviral and anti-microbial activity of resveratrol are also well documented [Koushki *et al.* 2018]. Because of its multiple potential health benefits, resveratrol is a frequently mentioned phytochemical in natural product research [Yeung *et al*. 2018a]. This compound is also present in varied and ever-growing nutraceuticals and food supplements [Santini *et al*. 2013, Andrew and Izzo 2017, Santini *et al*. 2017, Durazzo *et al*. 2018, Santini *et al*. 2018]. Resveratrol exists in two isomeric forms, i.e., the *cis*- and *trans*-isomer, both of which can be bound to glucose [Mattivi *et al*. 1995]. Trans-resveratrol is supposed to be present in grape skins, whereas *cis*-resveratrol is found in red wine, in variable concentration [López-Hernández *et al.* 2007]. Though only *trans*-resveratrol is commercially available as a purified nutraceutical, the pharmacokinetic and pharmacodynamic properties of both isomers appear to be similar [Orallo 2006]. Resveratrol has been found to activate human SIRT1 (sirtuin 1) protein, which mediates anti-proliferative and anti-inflammatory activities via gene expression alterations and metabolic pathway modulations and thus exhibits many potential beneficial health effects [Borra *et al*. 2005, Mohar and Malik 2012, Ajami *et al.* 2017, Deus *et al.* 2017, Cătană *et al*. 2018, Humieniecki and Horbańczuk 2018, Mohan *et al.* 2018]. On the other hand, the bioavailability of resveratrol is poor because of its rapid metabolism leading to high concentrations of its metabolites in plasma [Chachay *et al.* 2011, Pannu and Bhatnagar 2019].

With the large number of available publications, our literature analysis could identify major research topics, and also summarize and categorize the citation data of contributors from different levels (institutions, countries, and journals) and topics. Similar analyses have already been performed for the fields of ethnopharmacology [Yeung *et al.* 2018c], food sciences [Yeung 2018], nutraceuticals [Yeung *et al.* 2018d], neuropharmacology [Yeung *et al.* 2018e, Yeung *et al.* 2019a], and oncology [Yeung *et al.* 2018b].

The current analysis was aimed at evaluating research publications on resveratrol to identify the major contributing institutions, countries/regions, and journals. Another purpose of this work was to identify the major research topics of resveratrol literature, and reveal the chemicals/chemical classes that were frequently co-investigated and discussed along with resveratrol.

Material and methods

In December 2018, we accessed the Web of Science (WoS) Core Collection electronic database (Clarivate Analytics, Philadelphia, PA, USA) to identify publications containing the word "resveratrol" or its derivatives in the title, abstract, or keywords using for this purpose the search string: TOPIC=("resveratrol*"). Since the chemical formula of resveratrol is 3,5,4'-trihydroxy-*trans*-stilbene, we conducted an exploratory search to assess if we missed some publications that only listed the chemical formula but not the word "resveratrol" itself or its derivatives. For this purpose, we used the search string: TOPIC=("3,5,4'-trihydroxy-*trans*-stilbene") NOT TOPIC=("resveratrol*"), which yielded no results, thus confirming that our initial approach was correct. No extra restriction was considered on the search strategy, such as publication language or publication year.

Data extraction

The publications identified from the search were evaluated for (1) publication year; (2) author's affiliations; (3) country/region of the affiliations; (4) journal title; (5) WoS category; (6) publication type; (7) language; and (8) total citation count. The full records and cited references of these identified publications were extracted and analyzed by the VOSviewer software for bibliometrics.

The VOSviewer software was also applied to analyze the semantic contents of titles, abstracts, and keywords of publications in order to relate them to the citation data count and synthesize a bubble map to visualize the results [van Eck and Waltman 2009]. For the current work, we used default settings of the software for the analyses and syntheses of the bubble map. The bubble size in the bubble map indicates the frequency of occurrence (multiple appearances in a single publication count as one) of the words. Words are clustered if they co-occurred in the analyzed publications more frequently. Only words that appeared in at least 1% (n = 176) of the publications were analyzed and visualized.

Results and discussion

The literature search resulted in 17,561 publications. The earliest resveratrol-related publication indexed in WoS dated from 1976, and investigated the production of resveratrol by plants of the family Vitaceae in response to infection or injury [Langcake and Pryce 1976]. More than half of the overall publications has been published since the year 2013 of which a large number originates from China (publications since 2013 = 2,407; 72.9% of China's total publications), which reflects the increasing research interest in natural products in general [Atanasov *et al.* 2015]. The ratio of original articles (n = 13,821) to reviews (n = 1,459) was 9.5:1. Most of the publications were written in English (n = 17,348; 98.8%). Contributions came from 7,720 institutions (authors' affiliations) located in 135 countries/territories and were published in 2,751 different journals. The top five WoS categories of the publications were biochemistry and molecular biology (n = 2,850; 16.2%), pharmacology and pharmacy (n = 2,723; 15.5%), food science technology (n = 1,980; 11.3%), cell biology (n = 1,443; 8.2%), and oncology (n = 1,361; 7.8%). Top five contributors with regard to journal, institution and country/territory are listed in Table 1. In particular, we noticed that the number of publications that appeared in the journal *Molecules* largely increased after 2013 due to the introduction of its "Metabolites" section, together with its open access policy and apparent preference for Chinese researchers. Though the French National Institute of Health and Medical Research is the largest contributing institution, France was not within the top 5 countries. The large number of contributions from the USA, China and Italy was similar to their respective shares in the fields of antioxidant,

Table 1. Top five contributor journals, institutions, and countries/territories of the analyzed 17,561 publications

Contributor	Publication count (% of total)	Citation per manuscript
Journal		
Journal of Agricultural and Food Chemistry	432 (2.5%)	51.7
PLOS One	313 (1.8%)	26.7
FASEB Journal	292 (1.7%)	17.4
Food Chemistry	239 (1.4%)	30.5
Molecules	170 (1.0%)	12.3
Institution		
French National Institute of Health and Medical Research	267 (1.5%)	57.3
National Institutes of Health (USA)	244 (1.4%)	83.5
University of California	243 (1.4%)	54.2
National Research Council (Italy)	206 (1.2%)	46.5
University of Texas	198 (1.1%)	76.6
Country / Territory		
USA	4,148 (23.6%)	44.8
China	3,300 (18.8%)	15.5
Italy	1,277 (7.3%)	33.2
South Korea	1,042 (5.9%)	23.5
Spain	1,027 (5.8%)	38.9

ethnopharmacology, and natural products research [Yeung *et al.* 2018a, Yeung *et al.* 2018b, Yeung *et al.* 2018c, Yeung *et al.* 2019b].

There were 422 terms that appeared in at least 1% (n = 176) of the analyzed titles and abstracts (Fig. 1). Some major themes were related to: treatment (n = 4,555, citations per publication; CPP = 26.4), mechanism (n = 3,479; CPP = 35.0), apoptosis (n = 2,159; CPP = 33.4), cancer (n = 1,840; CPP = 39.5), diet (n = 1,021; CPP = 45.5), oxidative stress (n = 1,656; CPP = 28.9), inflammation (n = 1,179; CPP = 33.0), and antioxidant (n = 1,064; CPP = 35.7).

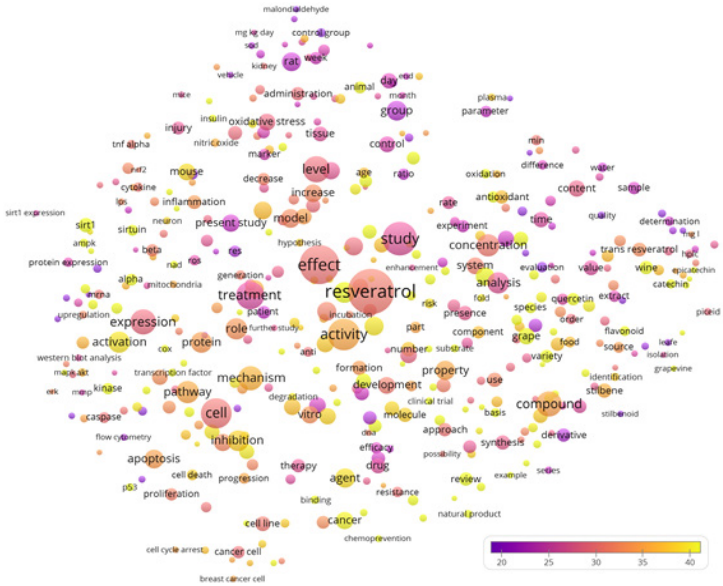

Fig. 1. Bubble map visualizing words from titles and abstracts of the 17,561 resveratrol publications. Only words that appeared in at least 1% (n = 176) of the publications' titles and abstracts were analyzed and visualized by VOSviewer software. There were 422 terms that appeared in at least 1% of the analyzed publications. The bubble color indicates the averaged citations received by publications with the specific words. The bubble size indicates the appearance frequency of the words (multiple appearances in a single manuscript count as one). Two words are closer to each other if they co-occurred more frequently in the analyzed publications.

There were 133 keywords that were used in at least 1% of the publications (Fig. 2). It could be observed that *in vitro* (n = 1,474; CPP = 26.1) was listed in more publications as a keyword than *in vivo* (n = 640; CPP = 30.3), with mice (n = 822; CPP = 23.3) and rats (n = 637; CPP = 24.7) being the most common animal models. Some of the most commonly mentioned diseases or conditions were Alzheimer's disease (n = 404; CPP = 32.5), breast cancer (n = 303; CPP = 29.9), obesity (n = 289; CPP = 24.4), atherosclerosis (n = 257; CPP = 45.1), and coronary heart disease (n = 180; CPP = 56.5). The most frequent sources of studied dietary resveratrol were red wine (n = 1,142; CPP = 47.0), grapes (n = 398; CPP = 41.0), and green tea (n = 180; CPP = 45.5). Concerning the natural sources from which resveratrol is extracted, only the plant Latin name *Vitis*

vinifera L. (*n* = 270, CPP = 32.1) was present among these 133 keywords that were used in at least 1% of the publications. Many different plant species, whose names were not found in the 133 keywords list, are also known to contain resveratrol. These include food crops like strawberry (*Fragaria* x *ananassa* (Duchesne ex Weston) Duchesne ex Rozier (Rosaceae)); raspberry (*Rubus idaeus* L. (Rosaceae)); blackberry (*Rubus* spp. (Rosaceae)); blueberry (*Vaccinium* spp. (Ericaceae)) [Schröder and Schröder 1990, Rimando *et al.* 2004, Wang *et al.* 2007, Jeong *et al.* 2016], as well as some wild plants such as *Lycium chilense* Bertero (Solanaceae) [Varela *et al*. 2016], and *Helichrysum* spp. (Compositae) [Albayrak *et al.* 2010].

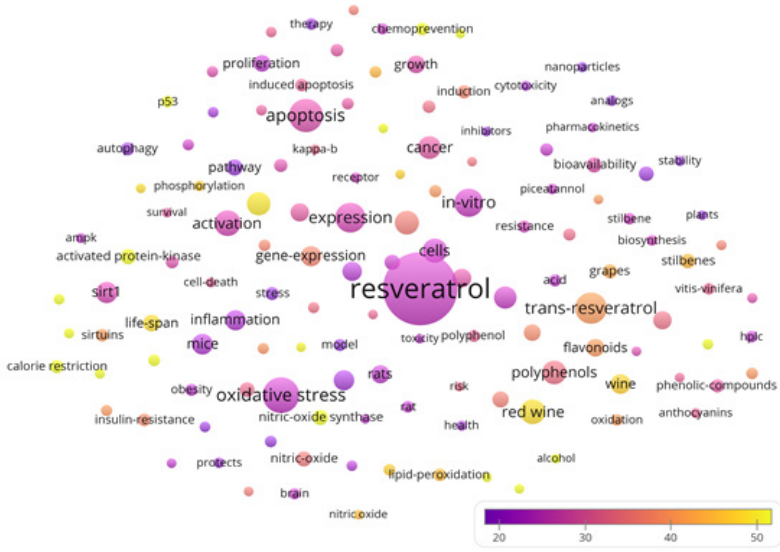

Fig. 2. Bubble map visualizing keywords of the 17,561 resveratrol publications. Only keywords (author keywords and Web of Science KeyWords Plus) that appeared in at least 1% (*n* = 176) of the publications were analyzed and visualized by VOSviewer software. There were 133 keywords that appeared in at least 1% of the analyzed publications. The bubble color indicates the averaged citations received by publications with the specific keywords. The bubble size indicates the appearance frequency of the words (multiple appearances in a single manuscript count as one). Two words are closer to each other if they co-occurred more frequently in the analyzed publications.

Phytochemicals or compound classes that were frequently mentioned in the keywords of analyzed publications included, in descending order, resveratrol (*n* = 9,524; CPP = 25.9), *trans*-resveratrol (*n* = 1,809; CPP = 39.5), polyphenols (*n* = 1,045; CPP = 33.6), flavonoids (*n* = 597; CPP = 38.9), quercetin (*n* = 520; CPP = 37.3), stilbenes (*n* = 407; CPP = 42.7), curcumin (*n* = 323; CPP = 33.7), piceatannol (*n* = 224; CPP = 25.5), *cis*-resveratrol (*n* = 215; CPP = 50.0), and anthocyanins (*n* = 213; CPP = 31.6) (Fig. 3).

In the analyzed literature set, numerous publications investigated the beneficial effect of resveratrol on animal health or animal models of disease. Among other reported

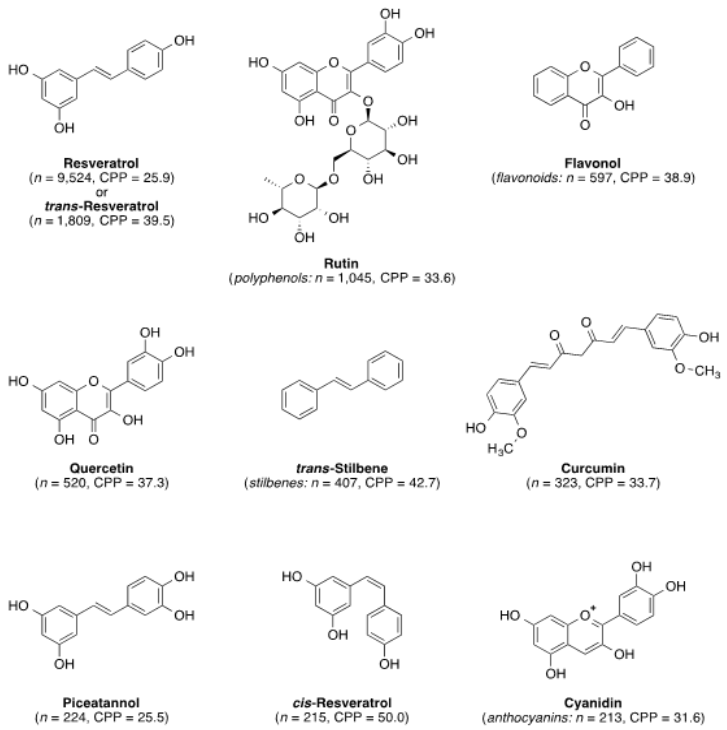

Fig. 3. Chemical structures of key single chemicals or representatives of chemical classes that were often discussed in the analyzed resveratrol-related publications.

effects, it has been found that resveratrol exerts analgesic and anti-inflammatory activities in mice and rats [Wang *et al.* 2017]. Resveratrol also improved the health and survival of mice on a high-calorie diet [Baur *et al.* 2006], which led to the inference that health-beneficial effects of resveratrol are similar to those achieved by calorie restriction (CR) and mediated through induction of autophagy, an intracellular catabolic process that maintains cell survival under stressful conditions [Dutta *et al.* 2014, Moosavi *et al.* 2018]. A combination of CR and resveratrol improved cardiovascular health in 26-month-old rats [Dutta *et al.* 2014]. In addition, resveratrol was also found to exert a protective effect against the toxicity of dioxins to which larvae of *Drosophila melanogaster* were exposed [Çolak and Uysal 2017]. On the other hand, however, resveratrol has also been associated with harms to animal health. For example, resveratrol has been linked to promoting atherosclerosis in rabbits fed with high cholesterol diet [Wilson *et al.* 1996]. Concerning its anti-cancerous effect, animal studies have yielded mixed results, depending on the route of administration, dose, tumor model, and species [Carter *et al.* 2014].

The dose of resveratrol needed for physiological adaptations in humans is different from that required for animals [Lagouge *et al*. 2006]. This may be attributable to

the difference in the metabolism rate of resveratrol between humans and animals [Hsieh and Wu 2010, Kuršvietienė *et al*. 2016]. Recent reviews have encouraged the conduction of better designed studies conducting more human clinical trials, as current evidence is scant and does not always confirm the beneficial effects reported from in vitro and animal studies [Bishayee 2009, Smoliga *et al*. 2011, Tomé-Carneiro *et al.* 2013, Singh *et al.* 2015, Berman *et al*. 2017, Ramírez-Garza *et al*. 2018]. For example, clinical studies conducted on patients diagnosed with cancer yield ambiguous results, depending on the type of cancer [Berman *et al*. 2017]. Results from a phase 2 trial of resveratrol tested on patients with mild to moderate Alzheimer's disease revealed that resveratrol was safe and well-tolerated and could penetrate the blood-brain barrier (BBB) to have effects on the central nervous system (CNS) [Turner *et al*. 2015, Terawi *et al*. 2018]. One particular problem encountered is the dose translation from animal models to humans, for which no gold standard is yet available. The body surface area normalization method rather than a simple conversion by body weight is a preferable standard [Reagan-Shaw *et al*. 2008]. A high absorption accompanied by a low bioavailability of resveratrol through oral ingestion in humans is yet another downside [Walle *et al*. 2004]. All of these factors imply that more efforts are necessary to evaluate the promising beneficial effects, especially anti-inflammatory, chemopreventive and anticancer therapeutic activities of resveratrol, observed in multiple in vitro and in vivo models [Jang *et al*. 1997, Manna *et al.* 2000, Ashikawa *et al.* 2002, Banerjee *et al.* 2002, Estrov *et al.* 2003, Aggarwal *et al.* 2004, Bhardwaj *et al*. 2007, Harikumar and Aggarwal 2008, Bishayee and Dhir 2009, Shakibaei *et al.* 2009, Bishayee *et al.* 2010a, Bishayee *et al*. 2010c, Harikumar *et al*. 2010, Gupta *et al*. 2011, Mbimba *et al.* 2012, Buhrmann *et al*. 2017, Humieniecki *et al.* 2017, Buhrmann *et a*l. 2018, Islam *et al*. 2018, Mozos *et al.* 2018, Wang *et al*. 2018].

No analysis was conducted on the authorship of resveratrol publications, as many of the most abundant authors had Chinese names, which shared the same initials, thus complicating an accurate analysis. For instance, according to the data analyzed, the most prolific author for the analyzed resveratrol publications was "Zhang Y.", which name upon a closer examination revealed to represent multiple authors: Zhang Yongqing, Zhang Yan, Zhang Yong, and a few others. Analyzing authorship by full names was also not feasible since some records only listed the authors' first names as initials.

Conclusions

The findings based on the analysis of the publications on resveratrol revealed that some of the most significant contributors came from the USA, China, Italy, South Korea, and Spain. Most of the publications focused on biochemistry and molecular biology, pharmacology and pharmacy, food science technology, cell biology, or oncology. More than 50% of them have been published since 2013, which could be attributed in part to the increased research activity in China. Frequently investigated diseases or conditions included Alzheimer's disease, breast cancer, obesity, atherosclerosis, and coronary heart

disease. This work could be used for a brief overview of resveratrol-related research landscape, in order to identify open windows for future research on resveratrol or its derivatives.

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Author contributions: AWKY and AGA conceived the work, performed data collection, analyses and drafted the manuscript. All authors critically reviewed and revised the manuscript, and approved its submission for publication in the journal *Animal Science Papers and Reports*.

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