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Berberine, a popular dietary supplement for human and animal health: Quantitative research literature analysis – a review*

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Berberine is an alkaloid with a wide range of reported beneficial health effects. The current work provides an extensive literature analysis on berberine. Bibliometric data were identified by means of the search string TOPIC=("berberin*" OR "umbellatine*"), which yielded 5,547 publications indexed in the Web of Science Core Collection electronic database. The VOSviewer software generated bubble maps to visualize semantic terms with citation results. The ratio of original articles to reviews was 13.6:1. The literature has been growing more quickly since the 2010s. Major contributing countries were China, the United States, India, Japan, and South Korea. Most of the publications appeared in journals specialized in pharmacology pharmacy, biochemistry molecular biology, chemistry, and plant science. Some of the frequently mentioned chemicals/chemical classes were alkaloid, palmatine, jatrorrhizine, coptisine, isoquinoline, and sanguinarine. The prevalent medical conditions under investigation included Alzheimer's disease, cancer, diabetes, and obesity.

KEY WORDS: alkaloid / Alzheimer's disease / berberine / citation analysis / bibliometrics / diabetes / obesity / Web of Science /VOSviewer

Introduction

Berberine (systematically named 5,6-dihydro-9,10-dimethoxybenzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizinium chloride) is an isoquinoline alkaloid found in many Berberidaceae plant species such as *Hydrastis canadensis* L., *Berberis vulgaris, Mahonia aquifolium, Xanthorhiza simplicissima,* and *Phellodendron amurense* [Imenshahidi and Hosseinzadeh 2016, Sarraf *et al.* 2019], known and widely used in traditional medicine [Jin *et al*. 2016] and for nutraceutical uses [Santini *et al.* 2017, Daliu *et al.* 2018, Durazzo *et al*. 2018]. Many potential health benefits of berberine have been reported in the earlier studies [Cicero and Baggioni 2016, Zou *et al*. 2017, Fan *et al.* 2019, Feng *et al*. 2019, Liang *et al*. 2019, Mohammadinejad *et al*. 2019, Rabiei *et al.* 2019]. For example, the oral intake of berberine may lower serum cholesterol levels *via* a post-transcriptional mechanism that is different from the mechanism of statins and red yeast rice, overall recommending it as one of the promising nutraceuticals that can be used in statin intolerant patients [Kong *et al*. 2004, Banach *et al*. 2018]. Berberine is also suitable for treating diabetes and obesity *via* the stimulation of adenosine monophosphate-activated protein kinase (AMPK) activity [Lee *et al*. 2006]. It also has anti-inflammatory effects [Kuo *et al*. 2004], and is studied in the context of cancer counteraction [Mondal *et al*. 2019]. Human serum albumin was identified as a potential drug binding site for berberine [Hu *et al.* 2009]. At the same time, berberine shows synergism with other chemical compounds. For instance, together with 5'-methoxyhydnocarpin, it shows a strong antimicrobial activity against *Staphylococcus aureus* [Stermitz *et al.* 2000]. In case of animals, berberine's anti-inflammatory activity was observed through down regulation of inflammatory cytokines in ducks infected by *Riemerella anatipestifer*, which is affecting the duck industry [Fernandez *et al*. 2017]. It was also noticed enhancement of juvenal health status of mice *Mus musculus* as expressed by the significant reductions of apoptotic cells and improvement of antioxidant biomarkers [Dkhil *et al*. 2017]. Additionally, the compound confirmed its effectiveness against ductal and invasive carcinoma in rats [Karnam *et al*. 2017] and also as a co-active agent in treatment of chicken coccidiosis [Malik *et al*. 2016]. It was also found to significantly inhibit the progress of oxidative stress, reducing apoptosis and enhancing the immunity when tested as a functional feed additive of blunt snout bream fed with high-fat diet [Chen *et al.* 2016, Huminiecki *et al*. 2017, Tewari *et al*. 2017ab, Tewari *et al*. 2018, Huminiecki and Horbańczuk 2018, Mozos *et al*. 2018, Wang *et al*. 2018]. All the above-mentioned examples illustrate the versatility of berberine in bringing health benefits, and hence, the growing literature that investigates its effects.

With many publications on the topic of berberine, a systematic bibliometric analysis can provide a summary of the research literature, so that readers and researchers can quickly grasp the essence and know the directions. Bibliometric analysis is a versatile approach, which can be used in different ways to yield diverse information ranging from, *e.g.*, characterization of the overall landscape of a given research field [Yeung *et al.* 2019c], through examining effectiveness of manuscript features such as graphical

abstracts on visibility and citations [Pferschy-Wenzig *et al*. 2016], to the analysis of the most cited manuscripts in a specified research area [Yeung *et al*. 2019d]. The current report is aimed at evaluating research publications on berberine from a bibliometric perspective. The detailed objectives of the present work are to (1) identify the major contributing institutions, countries/regions, and journals; (2) reveal the major research themes; (3) unveil the potential health benefits of berberine to animals and humans reported by the studies; and (4) report the chemicals/chemical classes that were frequently under investigation in the berberine-linked research literature.

Material and methods

In June 2019, a literature search was performed *via* the Web of Science (WoS) electronic platform (Clarivate Analytics, Philadelphia, PA, USA), with its Core Collection database chosen as the source of bibliometric data. The authors' subscription to the database allowed a search of papers published since 1956. Publications containing the word "berberine" or its derivatives in the title, abstract, or keywords were identified using the following search string: TOPIC=("berberin*" OR "umbellatine*"). We did not place additional filters to the search.

Data extraction

The publications resulting from the search have been evaluated for the following criteria: (i) publication year, (ii) institution, (iii) country/region of the institution, (iv) journal title, (v) WoS category, (vi) publication type, (vii) language, and (viii) citation count. The "Analyze" function of the WoS platform identified the most productive entities in terms of institution, country/region, journal, and WoS category. The VOSviewer software further extracted and analyzed the full records and cited references, which enables users to relate the publication and citation data to the words in the titles, abstracts, and keywords of the analyzed publications [van Eck and Waltman 2009]. A bubble map with default parameters visualizes the outcome of our work. The bubble size, proximity, and color correspond to the frequency of appearance, co-appearance, as well as averaged citations respectively. Multiple mentioning of a particular word in a publication was counted as a single appearance. Words that appeared in at least 1.0% (n = 56) of the publications have been analyzed and visualized.

Results and discussion

The literature search resulted in 5,547 publications to be analyzed, with a total number of citations of 111,999 by 54,127 citing publications, which meant that each publication received 20.2 citations *per* publication (CPP) on average. The earliest berberine publications indexed in WoS were published in 1970, and these investigated the effects of berberine on the central nervous [Shanbhag *et al.* 1970] and cardiovascular systems [Fukuda *et al.* 1970]. The literature on the topic accrued more quickly in the

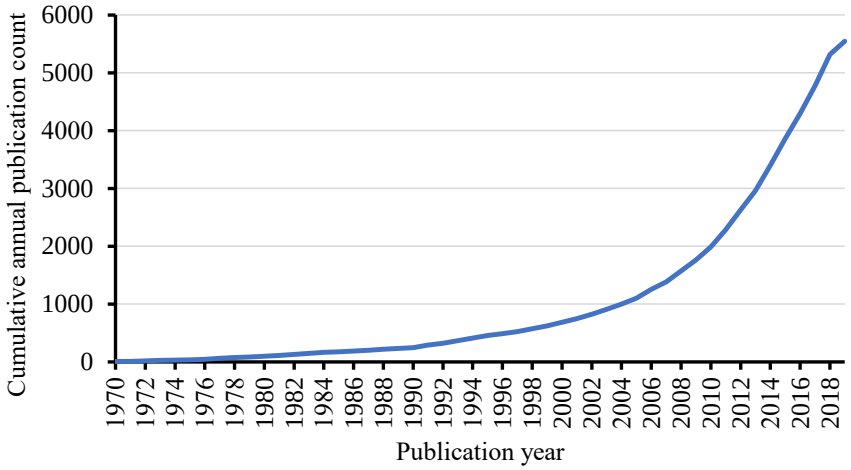

Fig. 1. Cumulative annual publication count of berberine publications.

Table 1. Top five contributing institutions, countries/regions, journals, and Web of Science categories of the berberine publications

Contributor	Publication count (% of total)	Citation *per* publication
Institution		
Council of Scientific and Industrial Research (India)	193 (3.5)	25.0
Chinese Academy of Sciences	177 (3.2)	22.2
Indian Institute of Chemical Biology	131 (2.4)	29.6
China Pharmaceutical University	124 (2.2)	15.8
Chinese Academy of Medical Sciences Peking Union Medical College	114 (2.1)	24.5
Country / Territory		
China	2,431 (43.8)	16.7
United States	645 (11.6)	31.9
India	483 (8.7)	19.3
Japan	408 (7.4)	27.1
South Korea	348 (6.3)	21.9
Journal		
PLOS One	95 (1.7)	26.3
Journal of Ethnopharmacology	84 (1.5)	33.4
Evidence-based Complementary and Alternative Medicine	75 (1.4)	7.9
Planta Medica	68 (1.2)	25.6
European Journal of Pharmacology	65 (1.2)	31.2
WoS category		
Pharmacology pharmacy	1,408 (25.4)	21.8
Biochemistry molecular biology	761 (13.7)	26.8
Chemistry medicinal	715 (12.9)	23.5
Chemistry analytical	571 (10.3)	16.1
Plant sciences	514 (9.3)	30.7

2010s as compared to the 1990s and 2000s (Fig. 1). The ratio of original articles (*n* = 4,735) to reviews (*n* = 348) was 13.6:1, which was much higher than the literature on curcumin (10.4:1) [Yeung *et al.* 2019b], resveratrol (9.5:1) [Yeung *et al.* 2019a], or dietary natural products (1.5:1) [Yeung *et al.* 2018]. English was the mainstream written language of the berberine publications (*n* = 5,378, 97.0%). The publications were contributed by over 3,400 institutions located in 101 countries/regions and published in over 1,400 journals. The top five contributors with regard to institution, country/region, journal, and WoS category are listed in Table 1. The most productive institutions were all based in China and India, the 1st and 3rd most productive countries, respectively. China contributed to nearly half of the berberine publications (43.8%). Most of these publications did not involve international collaborations (2,089/2,431, 85.9%). PLOS One was the most productive journal, and many publications were published in journals dealing with pharmacology pharmacy, biochemistry molecular biology, and chemistry.

Around 420 terms appeared in at least 1.0% (*n* = 56) of the analyzed publications' titles and abstracts (Fig. 2). Some major themes were related to treatment (n = 1,339, CPP = 22.3), mechanism (n = 1,092, CPP = 24.1), expression (n = 974, CPP = 24.1), and pathway (n = 797, CPP = 24.1). There were red bubbles of terms concerning diabetes and obesity at the lower left of the map, and terms concerning DNA-binding at the upper right. Some frequently mentioned chemicals/chemical classes were alkaloid (n = 878, CPP = 23.4), palmatine (n = 513, CPP = 21.8), jatrorrhizine (n = 261, CPP = 18.2), coptisine (n = 257, CPP = 17.8), isoquinoline (n = 257, CPP = 23.0), and sanguinarine (n = 152, CPP = 34.7) (Fig. 3). Interestingly, all these structures are closely related, strongly suggesting their implication in berberine structure-function research and discussion.

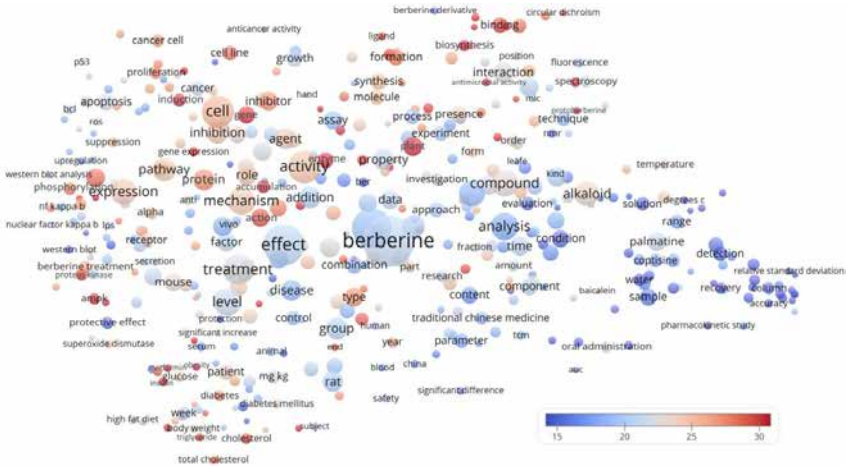

Fig. 2. Bubble map visualizing words from titles and abstracts of the 5,547 berberine publications. There were 420 terms that appeared in at least 1.0% (n = 56) of the publications' titles and abstracts and hence visualized. The bubble size, proximity, and color indicate the frequency of appearance, co-appearance, and averaged citations respectively.

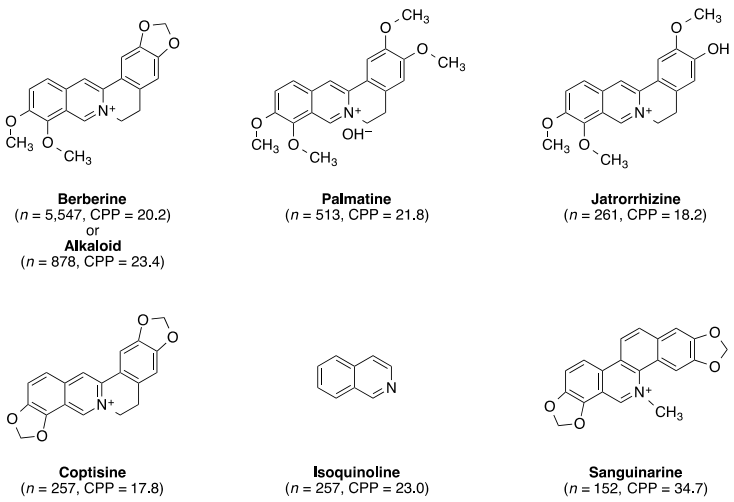

Fig. 3. Chemical structures of key single chemicals or chemical classes associated with them that were often discussed in the analyzed berberine-related publications.

There were 105 keywords appeared in at least 1.0% of the publications (Fig. 4). The keyword *in vitro* (n = 540, CPP = 22.3) was listed more frequently than *in vivo* (n = 85, CPP = 22.5), and the animal models were usually rats (n = 256, CPP = 19.4), and mice (n = 216, CPP = 20.5). Medical conditions under investigation included

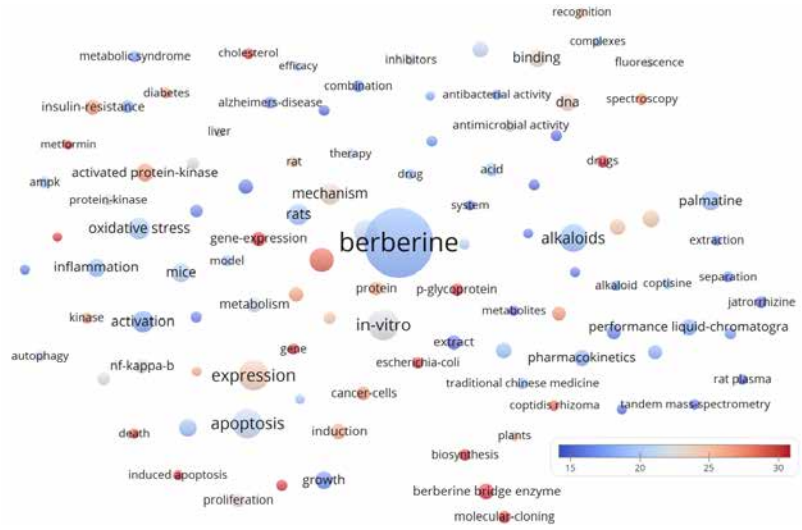

Fig. 4. Bubble map visualizing keywords of the 5,547 berberine publications. There were 105 keywords (author keywords and Web of Science KeyWords Plus) that appeared in at least 1.0% (n = 56) of the publications and hence visualized. The bubble size, proximity, and color indicate the frequency of appearance, co-appearance, and averaged citations respectively.

Table 2. Top 20 keywords listed by berberine publications

Keyword	Publication count	Citation *per* publication
In vitro	540	22.3
Expression	534	24.2
Apoptosis	515	21.1
Alkaloids	448	18.9
Cells	346	21.3
Inhibition	341	28.6
Oxidative stress	276	19.9
Activation	269	17.6
Mechanism	258	23.5
Rats	256	19.4
Palmatine	224	19.3
Mice	216	20.5
Binding	192	23.3
Inflammation	191	19.2
Activated protein kinase	186	26.7
Growth	184	16.6
Pathway	178	18.8
DNA	173	23.7
Protoberberine alkaloids	172	24.5
Pharmacokinetics	157	17.9

The word "berberine", being the most common keyword, was excluded from the list.

Alzheimer's disease (AD) (n = 78, CPP = 16.9), cancer (n = 125, CPP = 26.5), diabetes (n = 70, CPP = 27.0), and obesity (n = 94, CPP = 17.4). The 20 commonest keywords are listed in Table 2. Some of the commonest themes were apoptosis, oxidative stress, inflammation, and pharmacokinetics.

In vivo studies provided much of evidence on the potential beneficial effects of berberine on animal health. For instance, intraperitoneal injection of berberine was shown to reduce body weight and improve glucose tolerance in mice, whereas its oral administration could similarly reduce body weight and plasma triglycerides, and improve insulin action in rats [Lee *et al.* 2006, Zhang *et al.* 2009]. Oral administration of berberine also reduced blood cholesterol level in hamsters [Dong *et al.* 2010].

It was investigated that the antioxidant and anti-inflammatory effects of berberine in diabetic animals can be attributed to its modulatory effects on numerous pathways, involving adenosine monophosphate-activated protein kinase (AMPK), mitogen-activated protein kinases (MAPKs), nuclear factor erythroid 2-related factor 2 (Nrf2), and nuclear factor kappa B (NF-κB) [Li *et al.* 2014]. Also, the berberine-related prevention of weight gain in rats by berberine was associated with the changes in the expression of genes that control energy expenditure [Hu *et al.* 2014]. Besides diabetes and obesity, rats and mice studies also presented promising results that showed the nephroprotective [Domitrović *et al.* 2013], hepatoprotective [Janbaz and Gilani 2000], antidepressant [Kulkarni and Dhir 2007], and anti-cancer effects [Anis *et al.* 2001] of berberine.

Besides, berberine was also shown to improve endothelial function and arterial stiffness in healthy subjects and hypertensive rats [Zhang *et al.* 2019]. The vascular benefits of berberine were related to direct vasorelaxation and suppression of transient receptor potential vanilloid 4 channel [Wang *et al.* 2015]. Considering the effects on cardiovascular risk factors and arterial stiffness, further studies are needed to evaluate the cardiovascular benefits of berberine.

Regarding cancer, *in vitro* studies have shown that the inhibitory effects of berberine on NF-κB signaling potentiate apoptosis of cancer cells [Pandey *et al.* 2008, Muralimanoharan *et al.* 2009, Gupta *et al.* 2010]. In addition, anti-cancer effects of berberine are mediated by induction of autophagic cell death through alternating AMPK/mTOR signaling or GRP78 levels in different cancer cells [Yu *et al.* 2014, La *et al.* 2017, Moosavi *et al.* 2018].

A number of meta-analyses were published to evaluate the efficacy of berberine in improving human health. For example, a meta-analysis reported no significant difference between berberine and metformin on improving insulin resistance, glycolipid metabolism, or reproductive endocrine condition, whereas the combination of the two did not outperform metformin [Li *et al.* 2018]. Meanwhile, berberine significantly reduced the levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and increased the level of high-density lipoprotein cholesterol, without severe adverse effects [Dong *et al.* 2013, Ju *et al.* 2018]. In a meta-analyses of type-2 diabetic patients, berberine was shown to have better antidyslipidemic effect than other oral hypoglycaemics, while the combination of berberine with oral hypoglycaemics resulted in a better glycaemic control [Dong *et al.* 2012, Lan *et al.* 2015]. In the same line, Koppen *et al.* [2017], by summarizing clinical trials of studies using berberine for the treatment of hyperlipidemia and other dyslipidemias, concluded that berberine could serve as an alternative for patients who are intolerant to statins, patients resistant to starting statin therapy but who are open to alternative treatments, and for low-risk patients not indicated for statin therapy [Koppen *et al.* 2017]. Furthermore, berberine could significantly reduce the fasting plasma glucose, postprandial plasma glucose, and glycated hemoglobin levels relative to controls, though such effects became insignificant if the treatment lasted more than 90 days and for patients aged over 60 years [Liang *et al.* 2019]. Berberine also enhances cell survival and reduces cardiac ischemia/reperfusion injury. The beneficial effect of berberine is mediated by inhibiting excessive autophagy in both *in vitro* and *in vivo* models [Huang *et al.* 2015]. Recently, Xu *et al.* [2019] carried out systematic review and meta-analysis on anticancer effect of berberine based on experimental animal models of various cancers; the authors concluded that berberine exerted anti-tumor effects in a variety of tumors *in vivo*, especially breast cancer and lung cancer, whereas the evidences are insufficient for colorectal cancer and gastric cancer [Xu *et al.* 2019]. Readers should notice that the conclusions of these meta-analyses often urged for more randomized control trials to be conducted in the future due to the small sample size, small number of trials, questionable methodological quality, and unidentified risks of bias. There

was no meta-analysis on the compound's impact on other medical conditions, such as AD and cancer.

Conclusions

The publications on berberine were – apart from the United States – predominantly contributed by Asian countries, such as China, India, Japan, and South Korea. Many of the publications focused on the areas of pharmacology pharmacy, biochemistry molecular biology, chemistry, and plant science. Frequently mentioned chemicals/ chemical classes were alkaloid, palmatine, jatrorrhizine, coptisine, isoquinoline, and sanguinarine. Medical conditions under investigation included AD, cancer, diabetes, and obesity. The relevant literature underlines that berberine has multiple potential health benefits to both animals and humans. This bibliometric review gives a brief total-scale overview of the existing berberine literature and can open new horizons for designing further studies examining its bioeffects.

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

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