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

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Lycopene intake from tomatoes and other food sources has multiple potential health benefits. This report aimed to evaluate the current research literature on lycopene concerning human and animal health. The electronic Web of Science Core Collection database was searched with (lycopene*) AND (health* OR illness* OR disease* OR medic* OR pharma* OR drug* OR therap*). The resulted 3972 papers were analyzed with the aid of bibliometric software. Besides the United States, the lycopene papers received global contributions, particularly from China, Italy, India, and Spain. Examples of frequently mentioned chemicals/chemical classes were carotenoid, beta carotene, alpha carotene, beta cryptoxanthin, and alpha tocopherol. Examples of frequently mentioned medical conditions were prostate cancer, cardiovascular disease, and obesity. Published scientific articles reveal the diverse potential of lycopene in prompting human and animal health, and the knowledge on the bioactivities of this phytochemical is expected to further grow in the future.

KEYWORDS: lycopene / prostate cancer / cardiovascular disease / obesity / carotenoid / literature quantitative research analysis/ Web of Science / VOSviewer

Introduction

Nutraceuticals play a vital role in improving health, by decreasing the prevalence of various chronic diseases such as neurodegenerative-, metabolic-, cardiovascular-, liver- and respiratory diseases, and cancer [Ravichand 2015, Huminiecki *et al.* 2017, 2020, Huminiecki and Horbańczuk 2018, Wang *et al*. 2018, 2020, Singh *et al.* 2020, Yeung *et al*. 2020c, Thalkari *et al.* 2020, Mozos *et al*. 2018, 2021, Chao *et al.* 2021]. They also promote the quality and longevity of life [Tewari *et al*. 2017a, 2017b, 2018, Santini 2018, Santini and Novellino 2018, Daliu *et al.* 2019, Vieira *et al.* 2019, Durazzo *et al.* 2020a, Durazzo *et al.* 2020b, Yeung *et al.* 2020b, Wang *et al*. 2020b, Yeung *at al*. 2021b]. The global economic potential of nutraceuticals is approximated to be around USD 117 billion [Sachdeva *et al.* 2020]. Plants are abundant source of nutraceuticals and carotenoids in particular act as vital nutraceutical ingredients that help in the treatment and prevention of several diseases [Eggersdorfer and Wyss 2018, Langi *et al.* 2018, Rivera-Madrid *et al.* 2020, Yang *et al.* 2020]. In this context, lycopene has a remarkable potential as a nutraceutical agent that belongs to the class of carotenoids, and is primarily isolated from tomatoes [Naviglio *et al.* 2008a, Naviglio *et al.* 2008b, Durazzo *et al.* 2010, Górecka *et al.* 2020, Joshi *et al.* 2020]. In plants, lycopene is mainly generated by the mevalonic pathway while in microorganism it is also synthesized via the 2-C-methyl-D-erythritol 4-phosphate conversion [Li *et al.* 2020].

Lycopene is a linear polyene hydrocarbon that provides color to fruits and vegetables due to the presence of π-electron configuration in its chemical structure, and is abundant in red fruits and vegetables, for instance; apricots, watermelons, pink grapefruits, papaya, pink guavas, pumpkin, rosehips, carrots, sweet potatoes, and tomatoes [Grabowska *et al.* 2019]. Additionally, lycopene possesses numerous health benefits and displays promise in the counteraction of cancer, diabetes, obesity, liver disorders, neurological disorders, anti-inflammatory, cardiovascular disease and respiratory disorders [Chen *et al.* 2019, Paul *et al.* 2020, Tierney *et al.* 2020, Goenawan *et al.* 2021, Song *et al.* 2021]. It also decreases the risk associated with exposure to both natural toxins, including bacterial toxins and mycotoxins, and chemical toxins, including pesticides, heavy metals, as well as herbicides [Santini *et al.* 2009, Mikušová *et al.* 2010, Cimmino *et al.* 2012, Mikušová *et al.* 2013, Chen *et al.* 2015, Hedayati *et al.* 2019, Nazhand *et al.* 2020, Khan *et al.* 2021, Przybylska and Tokarczyk 2022].

Lycopene has several mechanisms of action, including regulation of signaling pathways like JNK/MAPK, AGE/RAGE, SIRT1/FoxO1/PPARγ, and PI3K/Akt [Zhu *et al.* 2020b]. Lycopene also decreased cholesterol accumulation through downregulation of SR-A mRNA expression and lipid synthesis in human monocyte-derived macrophages (HMDMs) and THP-1 macrophages, which is highly related to cardiovascular disease [Wang *et al.* 2019]. In addition, it also inhibited foam cell formation though increasing ABCA1 protein expression [Wang *et al.* 2020a]. It also inhibits peroxidation of lipids and ROS production [Lim and Wang 2020], modulates the expressions of various genes [Paul *et al.* 2020], and interferes with DNA damage, upregulating AMPK pathway and apoptosis of malignant cells [Lim and Wang 2020, Puah *et al.* 2021]. Lycopene also reduces the neuroinflammation, nuclear factor-κB [Chen *et al.* 2019, Zhu *et al.* 2020a], increases the hepatic biomarker expression of RXR-α, PPARγ and RXR-β [de Barros Elias *et al.* 2019], and protects myocardial ischemia injury by activating JNK/ERK signaling pathway [Fan *et al.* 2019]. Noteworthy, the lycopene cis-isomer exhibits better bioavailability and absorption than trans-isomer in adipose tissue and liver [Zhu *et al.* 2020b]. A problem associated with lycopene application is its insolubility in aqueous solution resulting in poor stability and bioavailability. Moreover, the lycopene extractability from the vegetable matrix and bioavailability of lycopene is affected by heat treatments [Maiani *et al.* 2009, D'Evoli *et al.* 2013]. To overcome this drawback, lycopene loaded organic nanocarriers such as liposomes, nanoemulsions, nanostructured lipid carriers, niosomes can be used to enhance its bioavailability [Souto *et al.* 2020b, a, Carvalho *et al.* 2021, Falsafi *et al.* 2021]. Thus, lycopene was formulated into nanostructured lipid carriers (NLC) with synthesized carboxymethyl oil palm for topical administration [Sharma *et al.* 2021]. The highest concentration achieved was 2.25 mg/ml for topical administration, with an encapsulation efficiency higher than 98%, and showing an initial burst release following a sustained release over 24 h. This modified release profile can be further exploited for the topical treatment of inflammatory diseases. NLC composed of cocoa butter as solid lipid and Grape seed oil as liquid lipid were loaded with lycopene obtained from watermelon *(Citrullus lanatus)* [Sirikhet *et al.*

2021]. An encapsulation efficiency as high as 80% was reported, together with a prolonged release until 48 hr. Lycopene obtained from red guava (*Psidium guajava* L.) was loaded into self-emulsifying drug delivery systems (SEDDS) and proposed for the treatment of prostate cancer. The in vivo studies resulted in no significant changes in clinical, hematological, biochemical, or histopathological parameters in orally treated mice [Vasconcelos *et al.* 2021]. The oral delivery of microemulsions composed of Transcutol HP as inner oil phase and Tween 80 as surfactant were proposed for the targeted delivery of lycopene to the brain [Guo *et al.* 2019]. The authors reported a significant increase in the lycopene bioavailability in rats when formulated as microemulsions in comparison to the control lycopene dissolved in olive oil of equivalent dose.

Besides the diverse bioeffects demonstrated on human health, lycopene has been applied for promoting animal health, *e.g.* by affecting gene expression and thereby regulating fat metabolism [Nosková *et al.* 2020, Tian *et al.* 2020], and by being used as feed supplement reducing oxidative stress and increasing lactation [Garavaglia *et al.* 2015]. Therefore, in the current study, the research landscape of lycopene was analyzed using a bibliometric approach to explore the potential roles of lycopene as a nutraceutical ingredient in promoting the health of humans and animals, based on the investigation of research outputs and coupled academic citations performance.

Methodology

On 21st of February 2022, the electronic Web of Science (WoS) Core Collection database was queried with the following search string: TS=((lycopene*) AND (health* OR illness* OR disease* OR medic* OR pharma* OR drug* OR therap*)). The system searched the title, abstract, and keyword fields of indexed publications to identify those that mentioned these words and their derivatives. The search identified a total of 3972 documents. Basic frequency data were obtained from the built-in functions of the WoS system. Full records of the 3972 papers were exported to VOSviewer for additional bibliometric visualizations [Van Eck and Waltman 2010]. With default parameters, a term map was generated to visualize the recurring terms from the titles and abstracts. The size, proximity, and color of the circles in the term map reflected the frequency of appearance, co-appearance, and citations per publication (CPP), respectively. Multiple appearances within a single publication counted as once. Recurring terms that appeared in at least 1.0% (n = 40) of the publications were visualized. A keyword map was similarly generated to illustrate author keywords that recurred in at least 0.1% (n = 4) of the papers.

Results and discussion

The lycopene research domain has been growing steadily since the 2000s, and the total number of publications is expected to surpass the mark of 4000 papers in

2022 (Fig. 1). The vast majority of all papers were original articles (n = 3286, 82.7%, CPP = 38.5) and the remaining were mostly review papers (n = 538, 13.5%, CPP = 68.9). Original article-to-review ratio was thus 6.1:1. Compared to other similar literature sets, this ratio was lower than in berberine (13.6:1) [Yeung *et al.* 2020a],

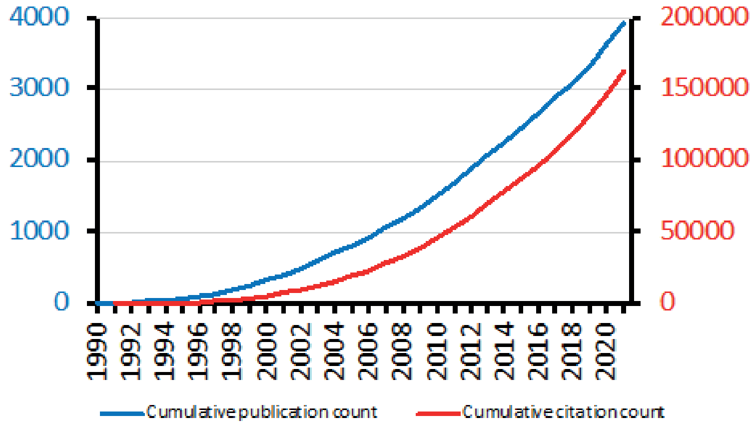

Fig. 1. Cumulative publication and citation counts of lycopene papers.

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

Item	Number of papers (% of 3972)	Citations per paper (CPP)
Author		
Erdman, John W. Jr.	37 (0.9)	61.5
Schwartz, Steven J.	36 (0.9)	65.9
Clinton, Steven K.	33 (0.8)	83.4
Willett, Walter C.	32 (0.8)	135.4
Borel, Patrick	27 (0.7)	69.0
Organization		
Harvard University	118 (3.0)	88.3
United States Department of Agriculture	118 (3.0)	74.7
University of California system	74 (1.9)	63.8
National Institutes of Health (United States)	73 (1.8)	75.6
University of Illinois system	72 (1.8)	59.4
Country		
The United States	1013 (25.5)	67.8
China	391 (9.8)	18.3
Italy	335 (8.4)	44.4
India	322 (8.1)	24.2
Spain	271 (6.8)	37.3
Journal		
Journal of Nutrition	90 (2.3)	81.7
American Journal of Clinical Nutrition	85 (2.1)	86.4
Journal of Agricultural and Food Chemistry	77 (1.9)	82.0
Food Chemistry	74 (1.9)	46.2
British Journal of Nutrition	72 (1.8)	42.0

resveratrol (9.5:1) [Yeung *et al.* 2019], apple polyphenol (7.6:1) [Yeung *et al.* 2021c], but higher than in dietary natural products literature as a whole (1.5:1) [Yeung *et al.* 2018]. Indexed papers were mostly written in English (98.0%).

The 5 most productive authors, organizations, countries, and journals are listed in Table 1. The author with the highest number of published works regarding lycopene was Professor Erdman, John W. Jr. from the University of Illinois, whose research interest was focused on the effect of dietary consumption of tomato or lycopene on cancer prevention [Clinton *et al.* 1996, Arballo *et al.* 2021]. Meanwhile, the top 5 organizations actively reporting on lycopene were all from the United States. Behind the United States, two countries from Asia and Europe entered the list. The Asian countries had lower CPPs. Finally, the top 5 journals were related to nutrition and food chemistry.

Figure 2 presents the term map that visualizes the recurring terms from the titles and abstracts. Tomato was one of the most recurring terms (n = 905, CPP = 49.2). Other notable terms were carotenoid (n = 1593, CPP = 51.5), and oxidative stress (n = 529, CPP = 40.5). Meanwhile, the recurring chemicals/chemical classes are listed in Table 2 and their chemical structures are shown in Figure 3.

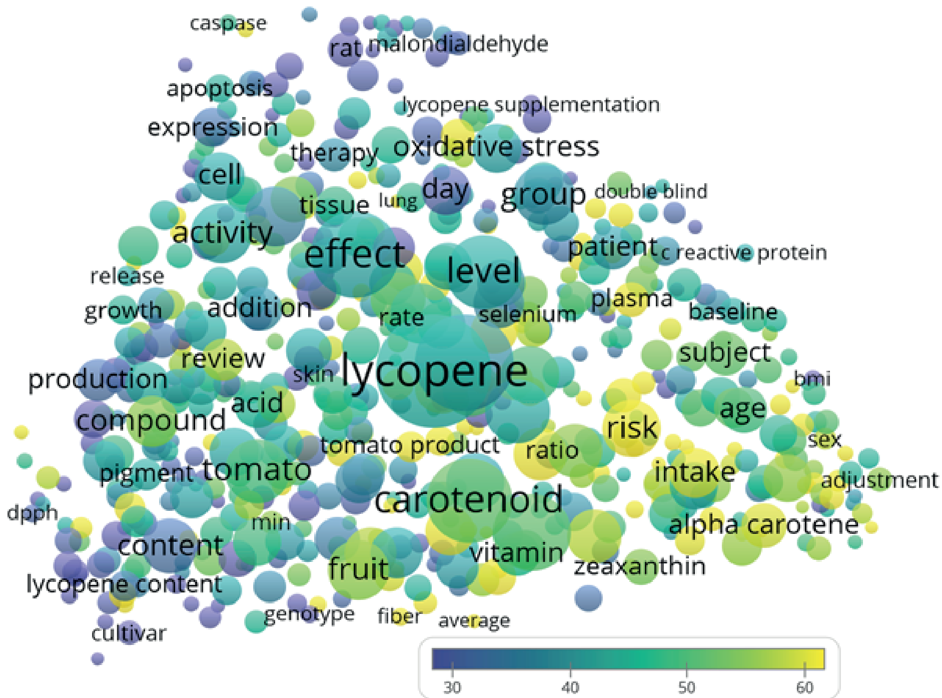

Fig. 2. Term map showing recurring terms in titles and abstracts of the lycopene papers. Circle color indicates the citation per publication (CPP). Size indicates frequency count.

Table 2. Recurring chemicals/chemical classes from the lycopene papers (n≥40)

Chemical/chemical class	Number of papers (% of 3972)	Citations per paper (CPP)
Lycopene	2878 (0.7)	42.8
Carotenoid	1593 (0.4)	51.5
Beta carotene	1308 (0.3)	51.1
Alpha carotene	438 (0.1)	58.5
Beta cryptoxanthin	364 (0.1)	55.1
Alpha tocopherol	300 (0.1)	51.4
Zeaxanthin	292 (0.1)	53.4
Flavonoid	212 (0.1)	64.7
Ascorbic acid	201 (0.1)	40.3
Malondialdehyde	134 (0.03)	32.0
Gamma tocopherol	129 (0.03)	51.2
Polyphenol	115 (0.03)	48.9
Curcumin	78 (0.02)	73.4
Resveratrol	75 (0.02)	91.2
Quercetin	70 (0.02)	48.9
Anthocyanin	59 (0.01)	31.3
Canthaxanthin	50 (0.01)	64.5
Phytofluene	48 (0.01)	44.7

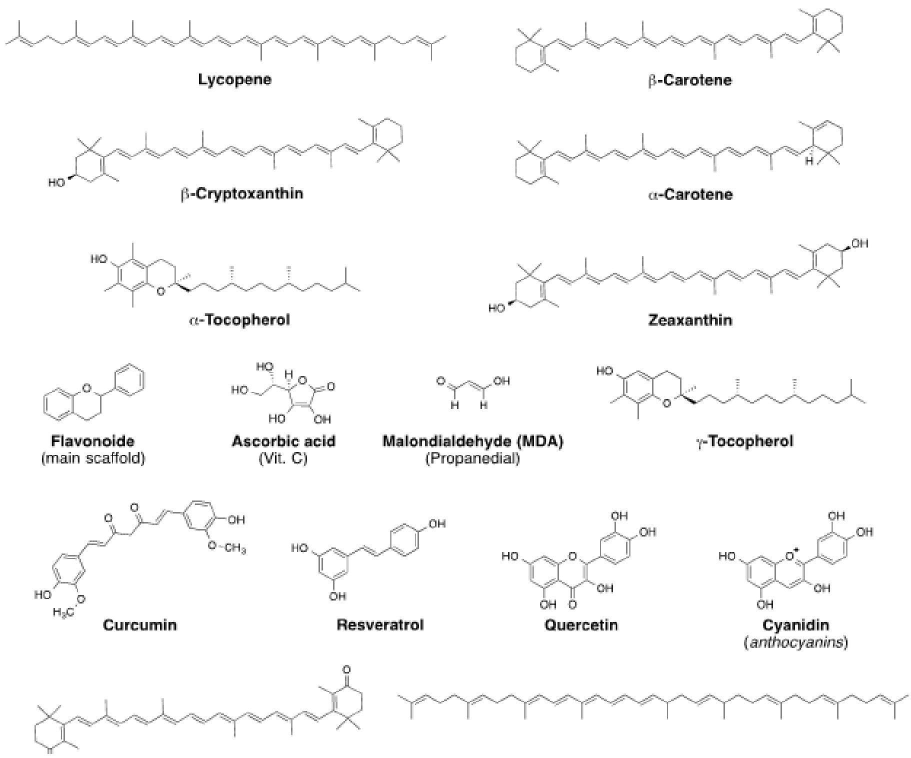

Fig. 3. Common chemicals/chemical classes mentioned in lycopene papers.

Figure 4 represents a term map showing recurring author keywords. Oxidative stress, antioxidants, and apoptosis were recurring keywords well-evident at the middle of the figure. Frequently mentioned medical conditions from the keywords are listed

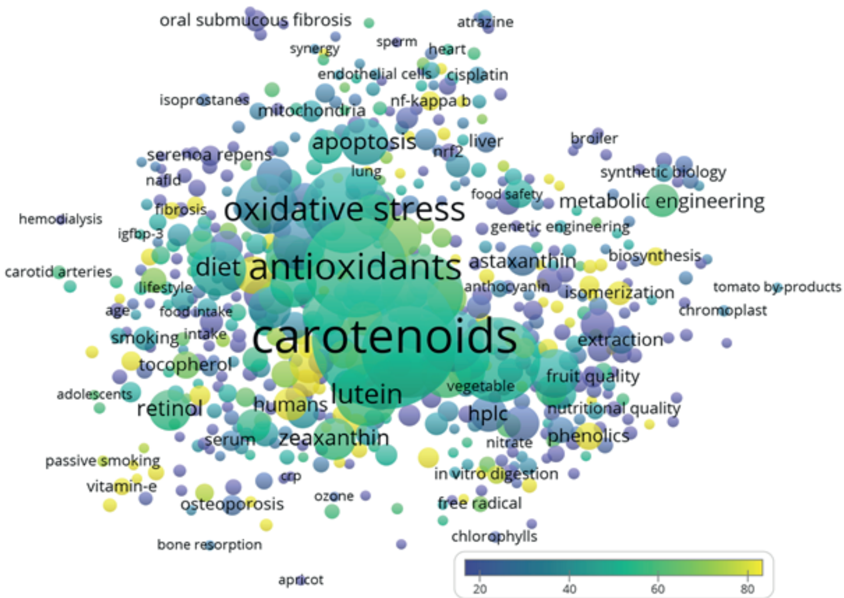

Fig. 4. Author keyword map showing recurring author keywords of the lycopene papers. Circle color indicates the citation per publication (CPP). Size indicates frequency count. The most recurring keyword "lycopene" was omitted from the figure for clarity.

Table 3. Frequently mentioned medical conditions from the author keywords (n≥10)

Medical condition	Number of papers (% of 3972)	Citations per paper (CPP)
Prostate cancer	127	34.7
Cancer	61	66.2
Atherosclerosis	51	78.6
Cardiovascular disease	40	60.9
Obesity	36	17.4
Breast cancer	27	27.0
Alzheimer's disease	19	45.3
Diabetes	19	16.3
Metabolic syndrome	18	14.7
Oral submucous fibrosis	17	6.8
Osteoporosis	16	26.3
Benign prostatic hyperplasia	11	17.3
Coronary heart disease	10	59.7
Hypertension	10	16.0
Myocardial infarction	10	80.9
Parkinson's disease	10	32.0
Stroke	10	66.6

in Table 3. Cancer, especially prostate cancer, and cardiovascular diseases were the most frequently mentioned medical conditions mentioned in the lycopene literature. Furthermore, lycopene was demonstrated to enhance the antioxidant response of prostate cells, as well as to inhibit proliferation and induce apoptosis of prostate cancer cells [Holzapfel *et al.* 2013]. Meanwhile, its potential ability to inhibit cholesterol synthesis may be beneficial to cardiovascular health [Arab and Steck 2000].

The intake of lycopene could also bring health benefits in diverse animal models. For example, dietary lycopene could correct metabolic syndrome and reverse liver injury in high-fat diet-induced obese rats [Albrahim and Alonazi 2021]. Besides oral intake, intraperitoneal administration of nanoemulsion of lycopene was found to reduce rheumatoid arthritis in animal models [Moia *et al.* 2020].

Conclusion

Besides the United States, scientific interest in lycopene has attracted substantial inputs from Asian and European countries. Many of the lycopene-related reports were published in nutrition and food chemistry journals. Examples of frequently mentioned chemicals/chemical classes in the lycopene-related literature were carotenoid, beta carotene, alpha carotene, beta cryptoxanthin, and alpha tocopherol. Examples of frequently mentioned medical conditions were prostate cancer, cardiovascular disease, and obesity. The intake of lycopene was shown to have myriad potential benefits to both human and animal health. The research literature on this phytochemical is expected to further greatly expand in the near future.

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