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Review Article

Occurrence of Tocols in Foods: An Updated Shot of Current Databases

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Tocols are present in various foods, mostly in fruits and in plant seeds. Edible oils are the most important natural dietary sources of tocopherols and tocotrienols, collectively known as tocols. Tocopherols and tocotrienols are considered beneficial for their antioxidant effect which impacts on prevention of different health conditions. This perspective is addressed to give an updated picture of the tocol occurrence in foods. Moreover, the current state of the art of tocols in updated databases is explored and commented outlining their importance and future trends.

1. Introduction

Tocols (tocopherols and tocotrienols), as shown in Figure 1, are monophenols obtained from 6-hydroxy-2-methyl-2-phytylchroman, which are applied as food additives in the food and pharmaceutical industries [1]. Some of the chemical characteristics of the tocols include their solubility in polyethylene glycol, propylene glycol, chloroform, acetone, surfactants, oils, and ethanol. They are not water soluble, while they are resistant to heat, and acid-stable, although they are instable when exposed to alkali, light, and oxygen [2].

The chemical structure of tocopherols and tocotrienols is different so that tocopherols (α, β, γ, and δ) contain a chromanol ring and a 16-carbon phytyl side chain in their structure with methylation at three positions of 5, 7, and 8 in the chromanol ring of the α-tocopherols, at two positions of 7 and 8 in the chromanol ring of the γ-tocopherols, and the positions of 8 in the chromanol ring of the δ-tocopherols. Simultaneously, the same substitution of methyl groups can be seen in the tocotrienols on the chromanol ring with unsaturation in the 16-carbon side chain having double bonds at the positions of $3'$-, $7'$-, and $11'$ [3].

There are reports on different functional features of tocopherols and tocotrienols, including anticancer [4], antiobesity [5], antidiabetic [6], and cardioprotective [7] effects. Moreover, the functions of tocotrienols and tocopherols are different, and a recent study indicated a more effective activity of the tocotrienols than that of the

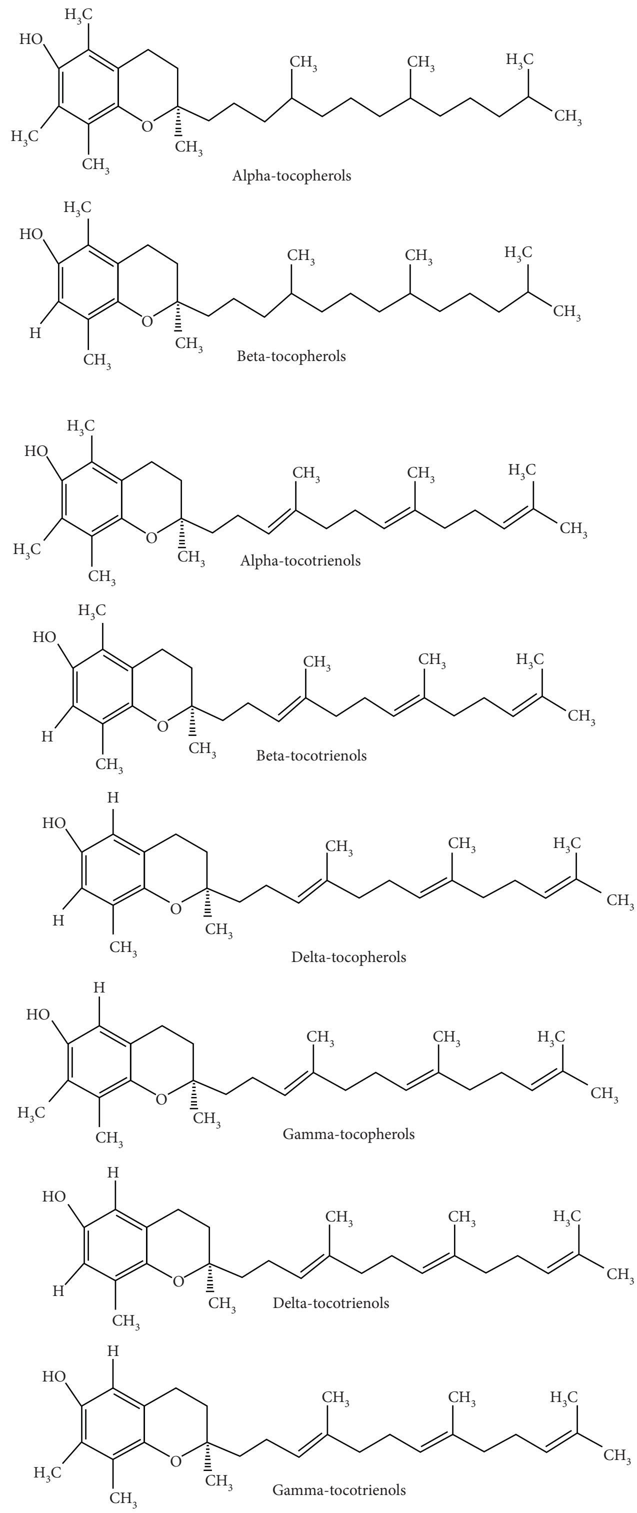

Figure 1: Structure of main tocols.

α-tocopherol in the control of chronic disorders [8]. The results of a review article on noncommunicable diseases revealed the inhibition of hormonal changes, oxidative stress, inflammatory response, and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase following the administration of tocotrienols, wherein the efficiency of tocotrienols was higher than that of tocopherol. The tocotrienols alone had a better influence on the treatment of diseases rather than the combination of tocotrienols and tocopherol [9]. Idriss et al. [10] found an *in vitro* anticancer activity for beta-tocotrienol, which was related to the induction of p53-independent apoptosis and the stop of the cell cycle G1 phase, and a higher anti-tumorigenic potential for beta-tocotrienol when compared with gamma-tocotrienol was also noted. The administration of tocotrienol-rich fraction (200 mg/kg) for about three months showed a positive impact on the myocardial antioxidative system in rats *via* new GSH synthesis [11]. The administration of gamma-tocotrienol reduced adipose tissue macrophages' recruitment and systemic and adipose inflammation in mice after a month, confirming the antiobesity activity [12].

A study aimed to investigate pharmacokinetics' impact of δ-tocotrienol at different high concentrations (750–1000 mg/d), the results of which showed Tmax value of 3–4 hours for all the isomers of tocotrienols and tocopherols, apart from α-tocopherol. According to this finding, it can be concluded that such high concentrations of tocotrienols are safe for human use especially as therapeutic agents in the management of some disorders, e.g., Alzheimer's disease, diabetes, and cancer [13]. Liang et al. produced α-tocopherol succinate modified chitosan (CS-TOS) and then encapsulated it using paclitaxel (PTX) to obtain micelles [14]. They could improve the performance and safety of PTX-loaded CS-TOS micelles via prolonged systemic circulation time and slow down the elimination rate than those of Taxol formulation. Based on the results from an *in vivo* study, the U14 tumor growth was significantly inhibited by PTX-loaded polymeric micelles, mitigating the toxicity of formulation [14].

2. Distribution of Tocols in Foods: Occurrence

Tocols are present in various foods, predominantly in fruits and plant seeds (see Table 1). Bastías-Montes et al. conducted a study to identify the tocols using the HPLC technique and reported the presence of β-sitosterol, tocotrienols, and α, β, γ, and δ-tocopherols from seed oil of Maqui berry (*Aristotelia chilensis*) fruit [15]. In a study, the two methods of direct injection and solid-phase microextraction (SPME) were combined with gas chromatography-mass spectrometry (GC-MS). The results detected α-tocopherol (LOD = 0.001 μg mL^{-1} and LOQ = 0.004 μg mL^{-1}) and α-tocopheryl acetate (LOD = 0.002 μg mL^{-1} and LOQ = 0.006 μg mL^{-1}), as well as the relative standard derivation (RSD) percent on days 4.8 and 8.8 in vegetables such as curly kale, celery, carrot, and onion [16]. The tocopherols were detected in vegetable oils using a novel flow-through column electrolytic cell for supercritical fluid chromatography system, the results of which reported 3.55 RSD percent [17]. Mezni et al. found α- and γ-tocopherols at the concentrations of 119 mg/kg and 23 mg/kg of oil, respectively, using HPLC analysis [18]. In a recent study, the yield of edible oil was 8.6 ± 1.2 g oil/100 g of guava seeds by supercritical CO_2 extraction, and then the γ-tocopherol with a concentration of 82.6 ± 3.7 mg/100 g oil was detected by the GC-MS method [19]. One of the most important products derived from fruit is Hass avocado (*Persea americana* Mill.)

Table 1: Levels of tocols in different foodstuff.

	Compound	Content	Reference
Raw foods			
Macauba fruits	α-Tocopherol	4373 μg/100 g	[29]
Cauliflower	α-Tocopherol and γ-tocopherol	23.47 mg/100 g and 74.55 mg/100 g	[30]
Yellow passion fruit (*Passiflora edulis*)	γ-Tocopherol	0.045 mg/100 g	[31]
Broccoli	Tocopherols	286 μg/g	[21]
Pitaya, jackfruit, durians, mango, and papaya fruits	α-Tocopherol	0.45, 0.20, 0.36, 0.16, and 0.26 mg/100 g DW	[32]
Oat, corn, spelt, buckwheat, wheat, rye, and rice bran	Total tocochromanol	5.5, 16.2, 15.8, 14.7, 12.8, 10.7, and 9.1 mg/100 g DW	[33]
Annatto seeds	γ–Tocotrienol, total tocotrienols	3.7 and 28.9 g/100 g extract	[34]
Barely grain	α-Tocotrienol, γ-tocotrienol, α-tocopherol, and γ-tocopherol	16.26, 4.67, 7.14, 0.55 mg/100 g DW	[35]
Einkorn wheat (*Triticum monococcum* ssp. *monococcum* L.)	α- and β-tocopherol and tocotrienol	12.2 mg/g dm, 4.79 mg/g dm, 12.7 mg/g dm, and 48.2 mg/g dm	[36]
Sesamum angustifolium	Tocopherol	7.34 mg α-TE/100 g	[37]
Hazelnuts	Tocols	41.9 mg/100g	[38]
Barley genotypes (*Hordeum vulgare* L.)	Total tocols	39.9 and 81.6 μg/g	[39]
Irish barley	α-Tocotrienol	46–58 μg/g dw	[40]
Fresh goji berries	α-Tocopherol and β-tocopherol	1.4 and 1.0 mg/100 g	[41]
Oils			
Sea buckthorn berries pulp oil	Total tocols	666–1788 mg/kg	[42]
Cold-pressed Moringa oleifera and Moringa peregrina seed oils	α-Tocopherol	139.61 and 137.89 mg/kg	[43]
Cane berry seed oils	Total tocopherols	75–290 mg/100 g	[44]
Apple, Japanese quince, and sea buckthorn seed oils	α-Tocopherol	58.77, 121.79, and 198.94 mg/100 g	[45]
Rapeseed, sunflower seed, linseed, sesame, and maize oils	α-Tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol	0.6–46.1 mg/100 g	[46]
Cold-pressed pumpkin seed (*Cucurbita pepo* L.) oil	Tocopherol and tocotrienol	94.29–97.79 mg/100 g	[47]
Soybean, corn, olive, and camellia oils	Total tocopherols	39.9 mg/100 g, 36.06 mg/100 g, 29.42 mg/100 g, and 17.72 mg/100 g	[48]
Sunflower, soybean, corn, hazelnut, peanut, and canola oils	Total tocols	488.88–913.51 mg/kg	[49]

oil, which has a great market value and is the richest source of tocopherols. Accordingly, Santana et al. extracted Hass avocado oil from dried fruit using conventional methods and then identified the α-tocopherol with the concentration of 11.6–21.0 mg/100 g using normal phase HPLC with a photondiode array detector (PDA) [20]. In another study, the analytical method of LC-APCI-MS/MS was used to detect the main compounds in 12 vegetables from the Brassicaceae family, the results of which reported total levels ranging from 1.83 to286 μg/g DW for tocopherols [21]. Niro et al. employed the HPLC method to detect the tocols (tocopherols and tocotrienols) in the cereals [22]. According to the findings, total levels of tocols were 3.80 mg/100g d.w. in millet, 3.09 mg/100g d.w. in sorghum, 5.99 mg/100g d.w. in tef, 0.36 mg/100g d.w. in wild rice, 9.10 mg/100g d.w. in quinoa (white and pigmented), 18.06 mg/100g d.w. in cañihua, 6.31 mg/100g d.w. in amaranth, and 14.43 mg/100g d.w. in chia. Labuschagne et al. used the HPLC method and reported the maximum tocol level of 59.8 mg kg^{-1} in the whole flour of South Africa's wheat [23]. Dąbrowski et al. applied the HPLC-FLD technique to detect tocols such as β/γ-tocopherols in flaxseed oils using *n*-hexane (1%, m/V) and isopropanol (0.7%) solutions [24]. Bertolín et al. [25] implemented a fast, accurate, and simple method to determine carotenoids, tocopherols, retinol, and cholesterol in ovine lyophilised meat, liver, and milk and raw samples using the UHPLC method. Another recent study developed a UHPLC-LTQ-Orbitrap-HRMS-based method to determine the nutrients in rice; as a result, 21 nutrients have been identified and reported in less than 13 min [26]. The range of regression coefficients was between 0.05 and 10 μg/mL for tocopherols, tocotrienols, and β-carotene, between 0.1 and 50 μg/mL for phospholipids, and between 0.001 and 10 μg/mL for γ-oryzanols. Besides, the limit of detection was between 0.2, and 1.9 ng/mL, the limit of quantitation was between 0.7 and 6.3 ng/mL, the relative standard deviations were between 2.3 and 9.6%, and the recoveries were between 80.6 and 109.6% for all the analytes. Moreover, the total ion current fingerprint profile showed significant differences between the brown and white rice samples. The developed method provided a convenient analytical method to identify the nutrients in rice, confirming the effectiveness of this approach for food testing [26].

Knecht et al. [27] developed and validated an HPLC-FLD method for tocochromanol (tocopherols and tocotrienols) analysis equally suitable for raw and cooked vegetables. The recent study of Wu et al. [28], reported the integrated analysis of fatty acid, sterol, and tocopherol components of seed oils obtained from four varieties of industrial and environmental protection crops, i.e., *Amygdalus pedunculata* Pall. (Amygdalus), *Elaeagnus mollis* Diels (Elaeagnus), *Xanthoceras sorbifolium* Bunge (Yellowhorn), and *Paeonia suffruticosa* Andr. (Paeonia); particularly, three tocopherol homologues, α-, γ-, and δ-tocopherols, were present in four varieties of seed oils, and *Elaeagnus* oil contains the highest α-tocopherol (7.48 mg/100 g) and γ-tocopherol (109.58 mg/100 g) content [28].

A shot of the occurrence of tocols in different foodstuffs is given in Table 1, taking into account both more and less rich sources and more and less consumed foods.

The occurrence of tocols in food groups is described here. It is worth mentioning that the reviews [50–54] summarized common and emerging dietary sources of tocols, with particular attention to oils as the major natural dietary sources of tocopherols and tocotrienols, as well as main analytical methods and effects in food and biological systems.

3. Tocols and Databases: The Current State of the Art

Nowadays, the need of the categorization of bioactive compounds is emerging. A bioactive compound can be defined as a "compound that occurs in nature, part of the food chain, that can interact with one or more compounds of the living tissue, by showing an effect on human health" as reported by Biesalski et al. [55]. Databases can be viewed as a system that can generate and collect any data, information, and documentation especially organized for a rapid search and retrieval by using a computer (Encyclopaedia Britannica) [56]. They represent tools developed to simplify the storage, retrieval, modification, and deletion of data, all this in combination with several data-processing operations [57].

The development of specialized databases of components with nutritional and nutraceutical properties [58], at a National and European level, represents a current challenge to explore better the relationship between food, nutrition, health, and environment. Researches on the relationship between diet and health have led to a great interest in all bioactive substances present with the nutrients in food, and data on these and other compounds are increasingly required in the database system. Specialized databases could be useful for planning and evaluating clinical and epidemiological research studies on biologically active food contained compounds. They may represent a crucial tool to evaluate exposure measurement and, indeed, understanding the potential benefits of substances and extracts with nutritional and nutraceutical properties [59–62]. In the formulation of complete and comprehensive harmonized databases, possible limitations, as highlighted by Scalbert et al. [63], could be given both by the diversity of the chemical features of the compounds, the numerous dietary sources, the variability in content from a source to another, and by the different extraction procedures as well as the analytical techniques and methodologies used. Moreover, additional factors that should be considered in some cases are as follows: (i) only a few compounds within a class are investigated in literature studies and (ii) there is a lack of appropriate analytical methods.

As an example, as reported by the NDA Panel of the European Food Safety Authority (EFSA) in 2015 [64], the most of food composition databases in EU countries contain values for vitamin E as α-tocopherol equivalents (α-TEs), and only two countries (Finland and Sweden) considered in the intake assessment by EFSA have vitamin E values in their food composition databases as α-tocopherol values. Food Explorer, an innovative interface for finding food composition data, allows to simultaneously search information from most of the available databases from the European Union (EU) Member States, as well as Canada, United States, New Zealand, and Japan. Searching, for example, "Vitamin E" and selecting all the 39 databases, 398 records can be retrieved [65, 66].

The eBASIS database [67, 68] contains composition data and biological effects of over 300 major European plant-derived foods organized in 24 classes of compounds (i.e., glucosinolates, polyphenols, isoflavones phytosterols, glycoalkaloids, and xanthine alkaloids).

The EuroFIR eBASIS (Bioactive Substances in Food Information Systems) is an Internet-deployed food composition and biological effects resource based on a compilation work of experts that critically evaluated data extracted from peer-reviewed literature as raw data. eBASIS could be considered as the first EU-harmonized food composition database. Concerning tocols, in eBASIS, 4 data points are present for α-tocopherols [69].

Tocols represent essential ingredients in many dietary supplements. Nowadays, a great attention is given to the use of natural substances in different fields such as nutraceutical and cosmeceutical ones [70–72].

Recently, information on the compositions reported on labels of selected dietary supplements has been collected for the development of a Dietary Supplement Label Database according to products' availability on the Italian market, including also items consumed in the last Italian Dietary Survey [73]. Five hundred and fifty-eight products were entered into the aforementioned database, giving a homogeneous picture of the major classes of food supplements consumed in Italy. It is worth underlining that, for each item, a code was assigned following the food classification system FoodEx2 developed by EFSA [74], a tool for the standardization and harmonization of the data among different countries to guarantee interoperability between different databases [75].

In particular, in Italian Dietary Supplement Label Database, tocols are present as ingredients in different categories of products containing vitamin E and, in particular, as main ingredients in vitamin only supplements [A03SL], combination of vitamin and mineral only supplements [A03SN], mixed supplements/formulations [A03TC], or as minor ingredients in formulations containing special fatty acids (e.g., omega-3 and essential fatty acids) [A03SX], protein and amino acid supplement [A03SY], and micronutrient supplement for sports people [A03SB] [73]. The ingredient vitamin E was indicated using the facet [F04.A0EXL]. The code in square brackets identify the category of products.

Moving towards the scenario of metabolic pathways and the benefits of bioactive compounds in humans, Human Metabolome Database (HMDB) has been considered, in particular, the version 4.0 [76, 77]. It is a freely available electronic database of information regarding small molecule metabolites found in the human body. It well linked chemical data, clinical data, and molecular biology/biochemistry data. In the above database, for instance, the following information is reported including metabocard for α-tocopherol (https://hmdb.ca/metabolites/HMDB0001893) and β-tocopherol (https://hmdb.ca/metabolites/HMDB0006335) reporting information on record information, metabolite identification, chemical taxonomy, ontology, physical properties, chemical spectra, biological properties, normal concentrations, abnormal concentrations, associated disorders, diseases, external links, and references.

4. Conclusion

Alongside the increasing attention towards the standardization and need of food categorization and classification, this perspective paper gives an updated shot of the occurrence of tocols in food and existing databases as useful tool in nutrition-related studies, i.e., dietary intake assessment and exposure studies.

Although the tocols and their different homologous derivates have been consuming as additives in food and pharmaceutical industries and evaluated using advanced analysis methods during the last decade, extracting and analyzing them from complex food matrices is still time-consuming and needs a significant quantity of organic solvents. Therefore, there is need for simple, fast, and green extraction protocols using environmentally friendly solvents. Despite the absence of any evidence of possible adverse effects following the use of tocols, caution should still be exercised in recommending the use of supplement containing them, with special attention to the recommended intake and dosage.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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