Nutraceuticals and Health Care

Edited by
Jasmeet Kour and Gulzar Ahmad Nayik

Nutraceuticals and Health Care

Edited by

Jasmeet Kour
Department of Food Engineering and Technology, Sant Longowal Institute of Engineering and Technology, Longowal, Sangrur, Punjab, India

Gulzar Ahmad Nayik
Department of Food Science & Technology, Government Degree College Shopian, Jammu & Kashmir, India

ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-323-89779-2

Publisher: Charlotte Cockle
Acquisitions Editor: Megan R. Ball
Editorial Project Manager: Devlin Person
Production Project Manager: Joy Christel Neumarin Honest Thangiah
Cover Designer: Greg Harris

Typeset by TNQ Technologies

Contents

7. Carotenoids

Sweta Priyadarshini Pradhan, Santwana Padhi, Monalisa Dash, Heena, Bharti Mittu and Anindita Behera

8. Curcumin

Srinivasan Krishnamoorthy, R. Paranthaman, J.A. Moses and C. Anandharamakrishnan

15. Alpha-linolenic acid

Jessica Pandohee

16. Ascorbic acid

Bharti Mittu, Zahid Rafiq Bhat, Ashish Chauhan, Jasmeet Kour, Anindita Behera and Mahaldeep Kaur

17. Phenolic acids

Md Nazmus Saqib and Md Ramim Tanver Rahman

18. Anthocyanins

Amir Gull, Mohd Aaqib Sheikh, Jasmeet Kour, Beenish Zehra, Imtiyaz Ahmad Zargar, Altaf Ahmad Wani, Surekha Bhatia and Mushtaq Ahmad Lone

Chapter 14

Tocopherol

Jinku Bora[1], Thoithoi Tongbram[2], Nikhil Mahnot[3], Charu Lata Mahanta[2] and Laxmikant Shivnath Badwaik[2]

[1]Department of Food Technology, Jamia Hamdard, New Delhi, Delhi, India; [2]Department of Food Engineering and Technology, School of Engineering, Tezpur University, Napaam, Assam, India; [3]Department of Food Technology, Rajiv Gandhi University, Rono Hills, Doimukh, Arunachal Pradesh, India

14.1 Introduction

Vitamin E was first discovered as "factor X" in 1922 while conducting experiments on the dietary factors essential for reproduction in rats (Evans & Bishop, 1922). Later, the substance was named "vitamin E" in 1924 (Sure, 1924). Subsequent expansion of research studies on vitamin E revealed the importance of it in human nutrition.

Vitamin E found in nature is composed of eight different forms known as homologues (α, β, γ, and δ forms), of which four forms are tocopherols and the other four forms are tocotrienols. The chemical differences between the four homologues of tocopherol are due to the number and position of the methyl groups in and around the chromanol ring. Tocopherols predominantly occur in seeds of higher plants, and are found in significant quantities in green tissues, and synthesized exclusively by all photosynthetic organisms. Plant-derived oils contain the four homologues of tocopherols in different relative quantities, and thus, they represent the major sources of vitamin E. Oils derived from almonds and sunflower contain a higher amount of α-tocopherol; corn oil contains a higher amount of δ-tocopherol; and oils derived from walnut contain mainly γ-tocopherol. The tocopherols are not synthesized in animals and also the interconversion of the different forms by methylation or demethylation does not take place. α-Tocopherol is the most naturally abundant form of tocopherol, due to which it is widely being used in food, pharmaceutical, and cosmetic industries.

Tocopherols, the main biologically active form of vitamin E, function as a lipophilic antioxidant that prevents the propagation of free radical chain reactions and reduces the risk of chronic diseases associated with oxidative stress in tissues (Brigelius-Flohé & Traber, 1999). Vitamin E deficiency may lead to a number of health problems such as AVED (ataxia with vitamin E deficiency), cancer, diabetes, cardiovascular diseases, and aging.

In this chapter, available literature regarding information and knowledge on the sources, chemistry, extraction, stability, safety, toxicity, and applications of tocopherols are reviewed and discussed.

14.2 Sources

Tocopherols are naturally present in a wide range of foods. Being fat-soluble, it is reasonable to understand that vegetable oils are the major sources. Nuts are another excellent source of tocopherols, even certain vegetables and fruits do have appreciable quantities. The quantities (average/range) of tocopherols present in various foods are mentioned in Table 14.1. However, the values are not strict, as different researchers have carried out tocopherol estimation using different analytical methods, moreover the cultivars or varieties considered cause variability. Processing of vegetable oils or domestic cooking methods of vegetables also tends to have an effect on tocopherol content (Diamante et al., 2021; Ergönül & Köseoğlu, 2014). Vitamin E compounds are biologically essential fat-soluble antioxidants derived from 6-chromanol. Industrially most relevant (all-rac)-α-tocopherol is generally synthesized by coupling of arenes with aliphatic precursors. Synthetic vitamin E has been developed commonly using 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (trolox) in either racemic or chiral form as the starting molecule. The commonly used derivatives of vitamin E as supplements are present in the form of esters of acetates and succinates (Nagy et al., 2013).

Nutraceuticals and Health Care. https://doi.org/10.1016/B978-0-323-89779-2.00008-9

TABLE 14.1 Sources of tocopherols in various foods/products.

Sources	Tocopherols (in mg/kg)				References
	α	β	γ	δ	
Vegetable oils					
Sunflower oil	686.5	21.6	8.4	3.7	Cruz and Casal (2018), Ergönül and Köseoğlu (2014), FAO/WHO (2002), Zhang et al. (2019)
Crude palm oil	340.5	44.6	–	174.7	
Extra virgin olive oil	281.3	5.0	10.1	–	
Wheat germ	1510–1920	310–650	0–520	–	
Rapeseed oil	331.5	41.8	243.8	–	
Soybean oil	197.3	18.5	434.3	74.8	
Corn oil	350	38	319.2	–	
Camellia oil	378	–	26	12	
Nuts					
Almonds	1132	4.04	21.4	–	Hejtmánková et al. (2018)
Walnuts	42.2	–	442	52.4	
Hazelnut	808	8.39	31.5	2.39	
Brazil nuts	162	–	427	2298	
Vegetables					
Cauliflower	27	–	78	–	Cruz and Casal (2013), Lee et al. (2020)
Broccoli	221	–	65	–	
Rocket salad	63	–	8	–	
Water cress	40	–	11	–	
Lettuce	1.47–3.64	–	4.93–6.25	–	
Fruits					
Chaenomeles varieties	7–26	1.4–6.21	0.13–4.2	0.06–1.85	Chun et al. (2006), Turkiewicz et al. (2020)
Avocadoes	26.6	0.8	6.9	0.3	
Blackberries	14.3	0.4	14.2	8.5	
Raspberries	8.5	0.9	13.9	11.5	
Other products					
Butter	32.5	–	4.2	–	Cruz and Casal (2018)
Margarine	105.3	3.5	56.0	7.5	
Fish oil supplement	11,133.6	103.6	608.4	229.3	

14.3 Extraction and characterization techniques

Various natural and food sources house tocopherol homologues (alpha, beta, gamma, and delta forms) from which they can be isolated and characterized. Isolation of tocopherols is primarily done from a wide variety of normal foods, most conveniently from cereal grain oils (corn, wheat, barley, and rye) and vegetable oils (wheat germ, soybean, cottonseed, safflower, peanut, linseed, sunflower, rapeseed, palm, etc.). The purity of tocopherol concentrate depends on the vegetable source as well as the particular type and/or combinations of available techniques used for isolation.

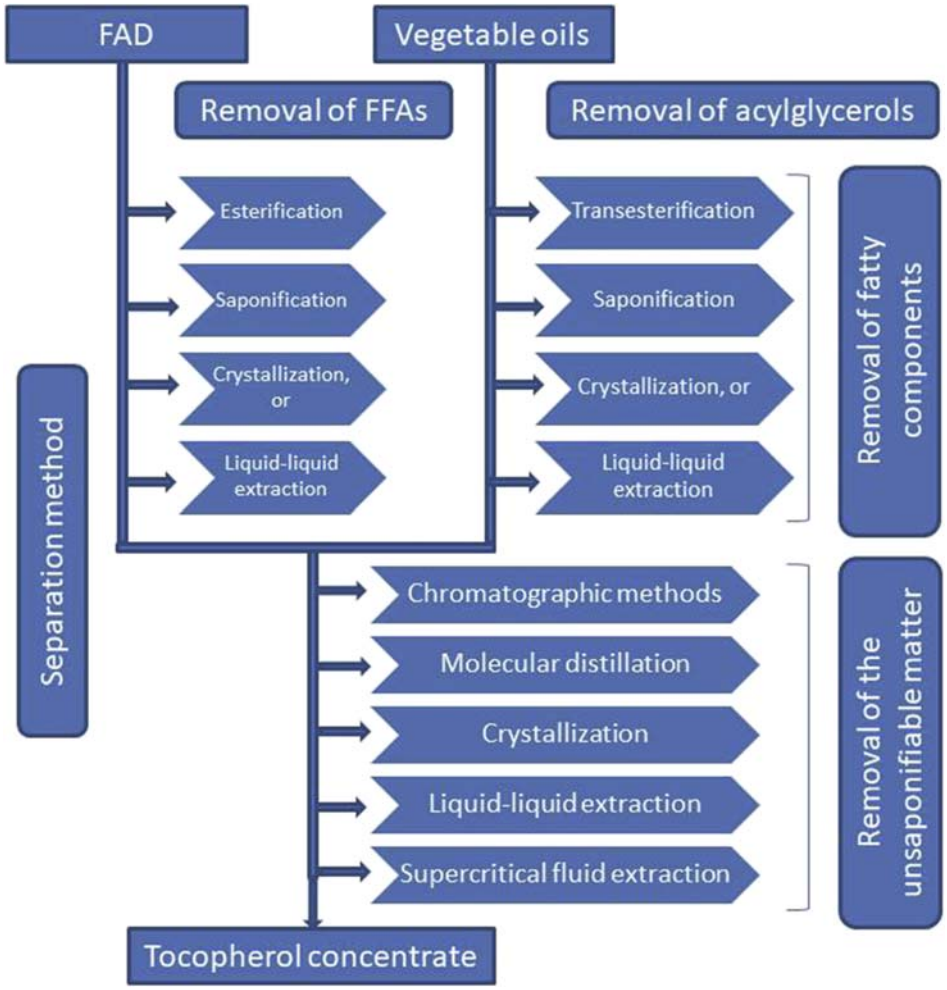


FIGURE 14.1 A brief illustrative flowchart of different tocopherol extraction methods. *Modified from Quek, S.-Y., Chu, B.-S., & Baharin, B. S. (2007). In* The encyclopedia of vitamin E *(pp. 140–152). Trowbridge, UK: Cromwell Press.*

Generally, natural tocopherol is isolated by techniques selected from extraction, saponification, distillation, esterification, ion-exchange, adsorption chromatography, precipitation of sterols, and crystallization (Fig. 14.1). Commercially, it is desirable to follow two-step isolation: first, separate and concentrate the source of tocopherol; then, isolate tocopherols from impurities present therein the concentrate.

14.3.1 Esterification and transesterification

Esterification is one of the most common steps in a series of methods used to extract tocopherols from vegetable oil sources, particularly fatty acid distillate (FAD). Commercially, FAD is an important source because it is high in tocopherol concentration and cheaply available during vegetable oil deodorization. In this method, an acid is used as a catalyst to esterify free fatty acids (FFAs) present in FAD to induce the formation of alkyl esters in an esterification process with lower alkyl alcohol in a reaction vessel. This alkyl alcohol is feed continuously into the vessel; water as a by-product is removed to prevent a backward favoring reaction, such as hydrolysis. The temperature in the reaction vessel ranges from 65 to 130 °C and the vessel is pressurized to maintain reactions in a liquid state. In the case of a vegetable oil source, transesterification is employed; an alkaline catalyst such as potassium hydroxide, sodium hydroxide, sodium methoxide, or zinc oxide is used. In both esterification and transesterification, the catalyst is withdrawn once the reaction is complete, following which the reaction mixture is cooled, washed with water, purged with nitrogen, and dried. Alkyl esters formed in this process are separated either by distillation, adsorption chromatography, liquid–liquid extraction, or other means. Alternately, esterification can also be carried out using sterols or a boric acid source (Fig. 14.2).

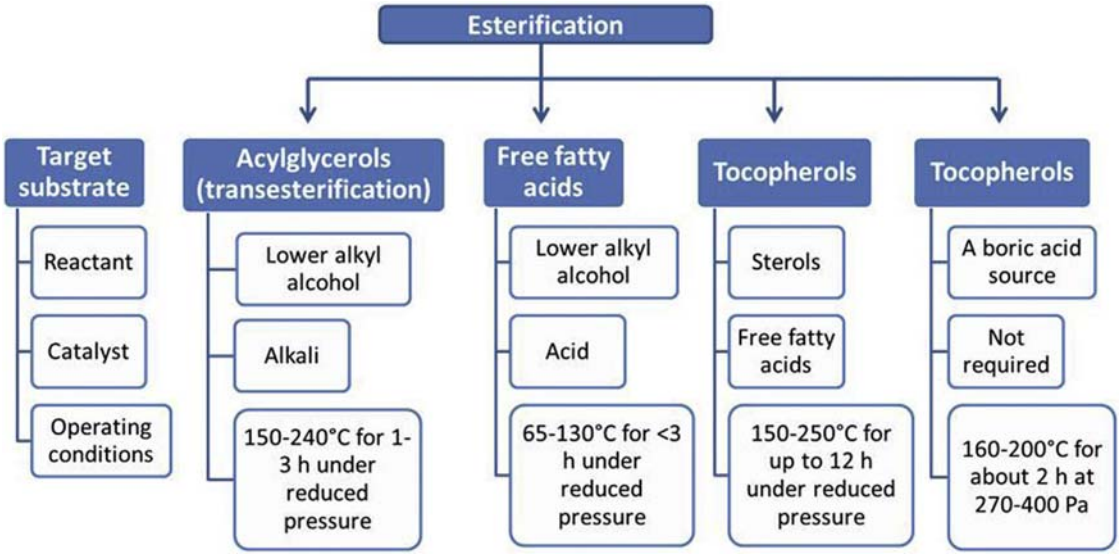


FIGURE 14.2 A demonstrative flowchart of esterification methods for tocopherol extraction. *Modified from Quek, S.-Y., Chu, B.-S., & Baharin, B. S. (2007). In* The encyclopedia of vitamin E *(pp. 140–152). Trowbridge, UK: Cromwell Press.*

14.3.2 Direct solvent extraction

A primitive, but the original method for extraction of tocopherols includes dehydration of sample with anhydrous magnesium sulfate; extraction of lipid-soluble components with isopropanol and methylene chloride; fractionation of the extracted components (vitamins) in a high-performance gel permeation chromatography (Lee et al., 1998). An improved method (Lim et al., 2007) employs hot deionized water to prepare the sample prior to treatment with anhydrous magnesium sulfate. This is followed by repeated washing with extraction solvent (e.g., hexane: ethyl acetate, 90:10 v/v with 0.01% BHT), filtration, and collection of filter cake (filtration 1). The filter cake undergoes another round of treatment with isopropanol and extracting solvent (filtration 2). The combined filtrates (from filtration 1 and 2) are diluted to volume using extraction solvent and filtered through a nylon membrane filter. A small aliquot from this filtrate is then evaporated with N_2 and it is prepared to appropriate concentration of analytes with the mobile phase.

14.3.3 Saponification

Saponification is another method used to remove fatty components from vegetable oils and FAD for extraction of tocopherol. The process is brought into effect in a lower monohydric alcohol medium using hydroxides of sodium, potassium, or calcium at reflux temperature. Back-esterification of glycerine and other ester-forming alcohols with FFAs may occur while using an aqueous alkali saponification process, which is minimal if alcoholic saponification is applied. Due to this and shorter reaction times, the latter is preferably used. The next step for the treatment of the saponified mixture is propagated in various ways (Fig. 14.3).

In a patented method, the mixture is acidulated, allowing it to settle into two phases: glycerine containing phase at the bottom, which is drawn off; and the top phase enriched with FFAs and tocopherol, which is esterified with alkyl alcohol. In another technique known as Fizet's method, alcohol is removed and to the top phase, another solvent such as methyl or ethyl formate or acetate is added for crystallization at 0 °C. The fatty acid calcium salts crystallize and are filtered off; the tocopherol-containing fraction is concentrated on a rotary evaporator from the filtrate. Also, liquid–liquid extraction is another technique used to recover tocopherol using acetone or ethyl ether from saponified FAD. Calcium chloride is added to facilitate extraction by converting sodium or potassium hydroxide to calcium soaps (metathesis), which is ground into particulates with powdering agents. Metathesis can alternatively be carried out by the addition of zinc halide (preferably the chloride) after saponification (Lee et al., 1998; Lim et al., 2007; Quek et al., 2007, pp. 140–152).

14.3.4 Distillation

Distillation is carried out as a usual follow-up step to remove lower alkyl esters postesterification (Quek et al., 2007, pp. 140–152). To avoid any undesirable loss of tocopherols during distillation, a chelating agent such as ascorbic acid, phosphoric acid, malic acid, citric acid, or tartaric acid is added to the feed prior to drying and distillation. The alkyl esters

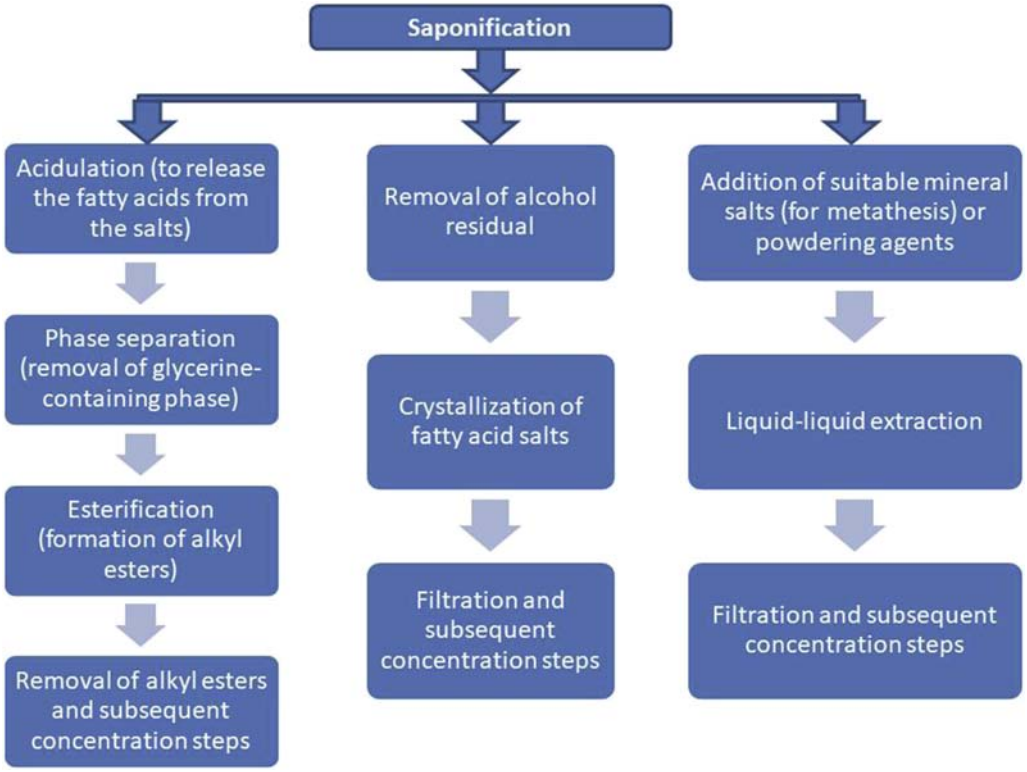


FIGURE 14.3 Concentration steps ensuing after saponification. *Modified from Quek, S.-Y., Chu, B.-S., & Baharin, B. S. (2007). In* The encyclopedia of vitamin E *(pp. 140–152). Trowbridge, UK: Cromwell Press.*

get distilled in the process, which is collected and discharged as a by-product. The tocopherols retained in the distillation column must also be cleared out in the minimum time possible to avoid deterioration losses.

14.3.5 Chromatographic methods

Ion-exchange chromatography and adsorption chromatography are the two most popularly used chromatographic techniques to isolate tocopherols from their sources (Quek et al., 2007, pp. 140–152). A highly effective method for the concentration of tocopherols is the use of ion-exchange chromatography. Tocopherols exhibit a weak acidity and therefore, bind to resins inside the column, which are strongly basic in nature; impurities like sterols, hydrocarbons, acylglycerols, pigment, and foreign basic and neutral substances elute out. It is mandatory to remove FFAs from FAD and also preferable to convert the basic resins from the usually sold Cl^- type to the OH^- anion type with larger adsorption capacity. Lower monohydric alcohol such as ethanol, methanol, or isopropanol is used to purge the column and wash out the impurities not attached to the column. To elute out the adsorbed tocopherols, an acidic solution (sulfuric, acetic, formic, or boric acid) is used. Similarly, a carbon dioxide–treated solvent is also used to selectively desorb tocopherols from the resin.

Normal phase adsorption chromatography functions using a polar stationary phase and a less polar mobile phase; the reverse applies to a reverse-phase adsorption chromatography. Both are based on the concept of hydrophilicity and lipophilicity. A typical normal phase column to isolate tocopherol from the fraction containing alkyl esters as an impurity is packed with alumina, silica gel, magnesium oxide, calcium hydroxide, silicic acid, powdered agar, or cellulose. The fatty acid alkyl esters are removed by eluting the column with a medium-chain alkyl hydrocarbon such as hexane, heptane, or petroleum ether. Tocopherol is then desorbed from the column with lower alkyl alcohol like isopropanol or a mixture with hexane. A classic example of the reverse phase is the separation of tocopherol from esterified palm oil using a reverse-phase C_{18} bonded silica gel column. Polar impurities are removed with methanol: water: acetic acid solution (90:10:0.25 by vol.) while the trapped tocopherol concentrate is extracted from the column with methanol or ethanol.

14.3.6 Liquid–liquid extraction

A binary mixture of two immiscible liquids—a polar and nonpolar solvent—is employed in this technique (Quek et al., 2007, pp. 140–152). Commonly used polar solvents include water, methanol, and acetone with strong hydroxyl or carbonyl groups; preferred nonpolar solvents such as benzene, hexane, and carbon disulfide are categorized by weakly

polar molecular structures. The immiscibility of the two-solvent system must be such that there is separation at a practical rate and the property of immiscibility must be retained even after admixture with FAD. To ensure this, emulsion breakers can be added, the extraction can be carried out in single contact, multistage contact, or countercurrent extraction. The volumetric ratio of the two solvents is an important selection parameter to decide the solubility of tocopherol in either polar or nonpolar solvent. If the design is such that tocopherol is found in the nonpolar solvent, a polar solvent (at a selected volumetric ratio) is later used to contact and dissolve tocopherol from the nonpolar solvent. Evaporation of the polar solvent yields the extracted tocopherol. Another variation of this technique devises the use of alkali to form a two-phase system to extract tocopherol: a generous amount of caustic methanol (tocopherol rich) and a nonpolar solvent (containing organic material). The two phases are separated; acid is used to neutralize caustic methanol; the resulting salt from neutralization is filtered out; the filtrate is evaporated to remove methanol. In order to avoid contamination with FFAs in the caustic methanol phase, they are necessarily removed from the starting material.

14.3.7 Crystallization

Sterols are concentrated together with tocopherols in FAD and crystallization is primarily used to separate them for high purity tocopherols (Quek et al., 2007, pp. 140–152). A process that describes the enhancement of tocopherol content after distillation of fatty acid alkyl esters uses a major amount of a low polarity organic solvent (hexane, heptane, or isooctane), a minor amount of high polarity organic solvent (methanol or ethanol), and water. A homogenous liquid mixture is generated by boiling at the atmospheric boiling point; the ratio of this solvent to the source may vary from 5:1 to 3:1 (v/w). At crystallization temperature (typically −25 to 0 °C), separation takes place with tocopherols still in the liquid phase and sterols in the solid phase, which is then removed by filtration.

This technique is also useful when applied after esterification but before distillation. Immediately after esterification, cold water is introduced into the reaction mixture containing alcohol, which is then cooled to room temperature or ≤ 5 °C. Sterol crystals are formed in this process, which can be separated by centrifugation or filtration while the fraction containing tocopherol is taken up in acetone at −20 °C. In another process, crystallization is employed to segregate tocopherols from FFAs present in palm oil. The procedure uses acetone, methanol, ethanol, or a mixture of them at −75 to −14 °C to extract tocopherols in the liquid phase. Repeated crystallization and separation of solid FFAs can improve the purity of tocopherol.

14.3.8 Enzymatic methods

Microbial lipase-catalyzed reactions are finding applications in the recovery of tocopherol from FAD (Quek et al., 2007, pp. 140–152). Hydrolysis, alcoholysis, and esterification catalyzed by specific or nonspecific lipases or inappropriate combinations can produce fatty acid esters and fatty acids from FAD. The use of 2.7%–4.3% lipase with methanol to esterify 96.5% FFAs in FAD at 50 °C and convert it to methyl esters can increase the concentration of tocopherols up to 1.7 times over the original content. Immobilized lipases present another way to produce alkyl esters; lipases from *Candida cylindracea* can be used to hydrolyze acylglycerols and lipases from *Mucor miehei* to esterify FFAs liberated by the former's action and those already present in FAD to produce butyl esters. Fractional distillation at two temperature ranges removes esters, hydrocarbons, and oxidized products at 180–230 °C for 45 min and recovers tocopherol at 230–260 °C for 15 min. *Candida antarctica* lipase is nonspecific and thermally stable; when immobilized, it can be used to hydrolyze acylglycerols in palm FAD. A distinct advantage of the use of microbial lipases is the reduction in tocopherol loses, as esterification and hydrolysis reactions are carried out at relatively low temperatures of 50–70 °C.

14.3.9 Supercritical fluid extraction

The use of SCF for extraction of tocopherol from sources such as FAD, palm oil, and olive tree leaves presents some pioneering work during the technology's early days. An extracting solvent (organic or inorganic), which is gaseous at room temperature and atmospheric pressure, is used in this technique. The solvent, when pressurized over its critical temperature, increases its density and hence its dissolving power improves. Most commonly, carbon dioxide is used, as it is nontoxic, nonflammable, highly selective in nature, and affordable. In addition, it operates at low temperature and solute–solvent separation is clearly easy. A continuous flow of CO_2 is maintained inside the reaction vessel; when the operating temperature and pressure are set, the feed oil is introduced. As extraction proceeds, the reaction mixture consists of a carbon dioxide fraction containing FFAs and another that has tocopherol and acylglycerols. The solvent is transferred into another chamber where the FFAs are separated; the solvent undergoes this repeated extraction and recirculation until

complete extraction is achieved. The effective partitioning of tocopherols and FFAs depends on the type of feed and coelution of fatty components due to dilution by higher fatty acid and acylglycerol concentration. Other forms of SCF extraction use hydrogen halide as a solvent to separate tocopherol from sources. For the separation of tocopherols from sterols, an inert organic solvent such as hexane, petroleum ether, benzene, or acetone is used to dissolve partially treated FAD. Hydrogen halide (chloride, bromide, or iodide) is introduced into the reaction mix in gaseous or liquid form at reflux temperatures for about 1 h. This produces a tocopherol-enriched liquid phase and an insoluble sterol phase (a product of sterols reacting with hydrogen halide), which can be removed by any conventional method such as filtration and centrifugation (Mendes et al., 2005; Quek et al., 2007, pp. 140−152).

14.3.10 Soxhlet extraction

Soxhlet extraction has high efficacy and is widely used. One of the earliest forms of this method uses a powdered sample: anhydrous sodium sulfate at a ratio of 1:4 (w/w). This thoroughly blended mixture is extracted in a Soxhlet apparatus containing hexane with 0.01% BHT in the dark for 4 h. The extract is then used in further analysis of tocopherol. In another approach, extraction is performed on ground sample with hexane: ethyl acetate (85:15 v/v with 0.01% BHT) under yellow light for 24 h (Lee et al., 1998; Lim et al., 2007; Ribeiro et al., 2019).

14.3.11 Cold pressing

One of the recent methods that stand out from the rest is the cold pressing method of extraction of oils from plant seeds because it is devoid of any harmful chemicals and high temperatures (Ribeiro et al., 2019). Heating, exposure to oxygen, and use of harmful chemicals degrade the composition and overall quality of extracted oil; its bioactive contents such as tocopherols get affected. Cold pressing ensures oil does not have to go through a refinement process to remove toxic chemicals even though the yield is lower than those obtained by solvent extraction methods.

14.3.12 Deep eutectic solvent extraction

This is an emerging solvent system that is gaining popularity as a green solvent due to its biodegradability, volatility, low melting point, and incombustibility — a set of unique physicochemical properties for an extraction solvent (Liu et al., 2019). Generally, deep eutectic solvent (DES) is a uniform combination of a hydrogen bond donor (HBD) and a quaternary ammonium salt set at a temperature of 60−80 °C. Commonly used HBD includes natural sources like urea, carboxylic acids, and polyols; choline chloride (ChCl) makes for role-fitting quaternary ammonium salt. Another advantage of DES as an extraction solvent is its tunability, basis of proportion, ratio, and type of components chosen.

14.3.13 Ultrasound-assisted extraction

The coupling of ultrasound with existing methods can increase the extraction of targeted compounds during sample preparations (Xu, 2008). Sound waves are used to break, disintegrate, and/or damage the natural integrity of micelles or matrix that houses the bioactive compounds, which are otherwise inaccessible by solvent due to their hydrophobic nature. A benefit of ultrasound application is the nonutilization of chemicals for breakdown (e.g., saponification) and freedom of possible chemical degradation of extracted compounds. The extraction efficiency of such assisted technique further increases due to agitation caused by the ultrasonic waves, thus increasing solvent-targeted compound interaction significantly.

14.3.14 Partition of tocopherol homologues for separate use

As per applications of the different properties of tocopherol homologues, there is sometimes demand these homologues be separated for individual usage. Analytically, some chromatographic techniques are available for separation and analysis (qualitative and quantitative), but not all of them are feasible for utilization in a commercial sense. A patented method describes the use of single-step reverse-phase liquid chromatography to execute this separation process on a commercial level. C_{18} bonded silica acts as a lipophilic reverse-phase chromatography medium and this becomes the stationary phase; the mobile phase consists of ethanol and deionized water. Polar impurities are eluted out first; tocotrienol homologues, if present, are eluted out next; the homologues of tocopherol are eluted out in the order of delta, gamma, and alpha forms. Alternatively, the tocopherol concentrate can be adsorbed on the reverse-phase C_{18} silica gel column; CO_2 SCF extraction can then be used to selectively desorb the homologues from the column.

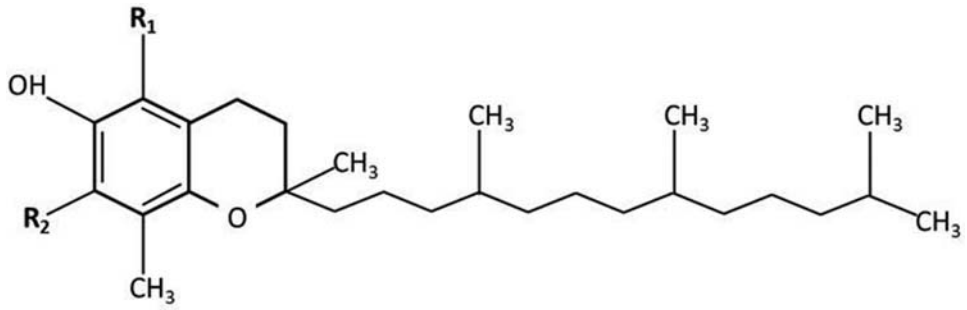
For ease of operation, the homologues can be selectively altered prior to a chromatographic run. This allows the homologues to have increased adsorption affinity toward the resins on stationary phase to varying degrees and thus provides a better chromatographic resolution of the homologues. The technique is achieved by selective deacylation of tocopherol esters by cyclic amines (in the order of delta > beta ~ gamma > alpha) and separation of these esters from free tocopherols in a column. Deacylation of delta homologue acetate undergoes rapidly within 15 min, while acetates of beta and gamma homologues take about 2 h; alpha homologue acetates are unreactive. Since cyclic amines are expensive, they can be replaced with methanol, ethanol, or propanol but the reaction requires 190–210 °C temperatures inside a pressurized vessel. To overcome this limitation, a basic catalyst such as potassium carbonate, potassium hydroxide, or sodium hydroxide that enables the deacylation reaction to happen at <100 °C (by reflux) is devised as an improved method (Quek et al., 2007, pp. 140–152).

14.4 Chemistry and biosynthesis of tocopherol

Tocopherol is the collective term for compounds that are characterized by the presence of a 6-chromanol ring structure; the compound tocol (2-methyl-2-(4′,8′,12′-trimethyltridecyl)-chromanol-6-ol) is considered the parent compound (Fig. 14.4). There is a C_{16} saturated side chain at position 2. The 6-chromanol ring structure is methylated to varying degrees at the 5, 6, and 8 positions, which gives rise to different homologues of tocopherol depending on the position and degree of methylation: alpha (trimethylated), beta and gamma (dimethylated), and delta (monomethylated) (Fig. 14.4). Three asymmetric carbons (chiral centers) are present at position 2 (chromanol ring) and at positions 4′ and 8′ (phytyl side chain).

All homologues of tocopherol, the 6-hydroxychromanols, are synthesized in plants with well-defined biosynthetic pathways present in all photosynthetic organisms (Eitenmiller & Lee, 2004; Lushchak & Semchuk, 2012). The alpha-tocopherol is documented to be present in both photosynthetic and nonphotosynthetic tissues, primarily concentrated in the chloroplasts, while the other homologues are concentrated in nonphotosynthetic tissues (chloroplasts, mitochondria, and microsomes). Biosynthesis of tocopherols happens in the chloroplasts and partitions into the chloroplast membrane (lipid phase). Generally, for most tocopherols, the phytyl tail is found embedded into the lipid membrane bilayer.

The synthesis of tocopherol occurs by the utilization of two precursors from two different pathways: homogentisic acid (HGA) and phytyldiphosphate (PDP) (Fig. 14.5). HGA (2,5-dihydroxyphenylacetate), which is obtained from the cytosolic shikimate pathway, is the precursor for the formation of the aromatic ring of tocopherol. PDP from the plastid methyl-erythritol phosphate pathway is the precursor for the tocopherol tail. HGA and PDP together conjugate to give the different homologues of tocopherol via a cascade of reactions. This condensation reaction is catalyzed by homogentisate phytyl



Tocopherol	R_1	R_2
Alpha	CH_3	CH_3
Beta	CH_3	H
Gamma	H	CH_3
Delta	H	H

FIGURE 14.4 Chemical structure of tocopherol family with number and position of methyl groups on the aromatic ring. *From Špika, M. J., Kraljić, K., & Škevin, D. (2016). Tocopherols: Chemical structure, bioactivity, and variability in Croatian virgin olive oils. In* Products from Olive Tree *(p. 317). BoD–Books on Demand.*

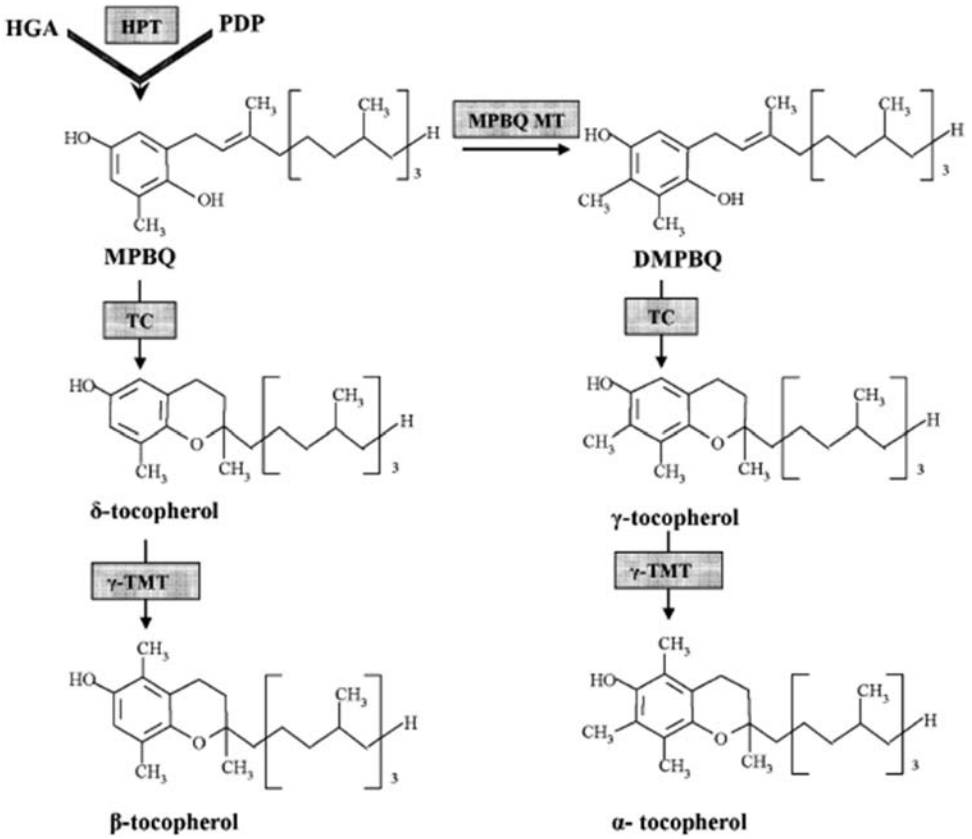


FIGURE 14.5 Tocopherol biosynthesis pathway in photosynthetic organisms. *c-TMT*, c-tocopherol methyltransferase; *DMPBQ*, 2,3-dimethyl-6-phytyl-1,4-benzoquinol; *HGA*, homogentisic acid; *MPBQ*, 2-methyl-6-phytyl-1,4-benzoquinol; *MPBQ MT*, MPBQ methyltransferase; *PDP*, phytyldiphosphate; *TC*, tocopherol cyclase. *From Lushchak, V. I., & Semchuk, N. M. (2012). Tocopherol biosynthesis: chemistry, regulation and effects of environmental factors.* Acta Physiologiae Plantarum, 34*(5), 1607−1628. https://doi.org/10.1007/s11738-012-0988-9.*

transferase (HPT) to yield 2-methyl-6-phytyl-1,4-benzoquinone (MPBQ), which is the committed step in tocopherol biosynthesis. MPBQ gets methylated by MPBQ methyltransferase (MPBQ MT) to 2,3-dimethyl-6-phytyl-1,4-benzoquinone (DMPBQ). Tocopherol cyclase (TC) acts on MPBQ and DMPBQ, and utilizes both as substrates for the formation of gamma and delta tocopherols, respectively. Finally, gamma-tocopherol methyltransferase (TMT) methylates gamma and delta tocopherols to produce alpha and beta tocopherols, respectively (Špika et al., 2016).

14.5 Mechanism of action: antioxidant properties and degradation

14.5.1 Antioxidant properties

The primary role of tocopherols is to prevent lipid peroxidation and protect lipids from it. Hence, its best source is vegetable oils, followed by other plant-based food. Tocopherols act as antioxidants by participating in oxidation chain-breaking events. They quench peroxy radicals of polyunsaturated fatty acids (PUFAs) by ending the oxidation chain reaction. This happens by the transfer of a hydrogen atom from the hydroxyl group on the chromanol ring to the PUFA peroxide radical. The "tocopherol radical" thus formed does not propagate the reaction further, but it is resonance stabilized inside the chromanol ring. It is then quickly recycled back to the corresponding tocopherol thereby allowing each tocopherol molecule to repeat this quenching process, protecting up to 10^3 to 10^6 PUFAs at lower peroxide values. Due to structural differences between the tocopherol homologues, the antioxidant activities vary in the order of: delta > beta > gamma > alpha (in vitro) and alpha > beta > gamma > delta (in vivo). This highest activity of the alpha homologue within living tissues is due to the action of hepatic alpha-tocopherol transfer protein that occurs in higher levels in plasma and tissues, allowing alpha-tocopherol to be preferentially retained and incorporated into lipoproteins. Additionally, tocopherols also react with singlet oxygen or other reactive species (ROS) as part of their antioxidant functions (Špika et al., 2016).

14.5.2 Degradation of alpha tocopherol

Tocopherols are oxidized by ROS, mainly by lipid peroxyl radicals; the mechanism can proceed differently (Fig. 14.6). Oxidation of tocopherols to tocopheryl radicals may occur by one-electron transfer, which can be rereduced to tocopherols by an ascorbate−glutathione system (Asc/GSH). In absence of ascorbate or glutathione, tocopheryl radicals can form adducts (quinones) or self-coupling products (dimers and/or trimers). In another oxidation pathway involving a two-electron transfer and singlet oxygen, tocopherols get converted to hydroperoxide, which irreversibly gets hydrolyzed to tocopherol quinone (TQ). This conversion happens in chloroplast lumen under mildly acidic conditions. TQ can be enzymatically transformed to tocopherol quinol (TQH_2), catalyzed by NADPH-dependent reactions. Both TQ and TQH_2 formed from alpha-tocopherol elucidate antioxidant properties (Špika et al., 2016).

14.6 Bioavailability

Bioavailability of food is the fraction of food ingredients placed at the disposal of tissues after ingestion. The bioavailability of tocopherols, commonly known as Vitamin E, in humans, is assessed using the level of plasma tocopherol. This availability is essential for biological activity, as this fraction will only contribute toward our physiological activities. Out of the four vitamers (homologues) of tocopherol (vitamin E), α-tocopherol is the dominant fraction present in the human body and has the highest biological activity. β- and γ-tocopherol have been shown to have reduced vitamin activity (10%−30%), whereas δ-tocopherol has no activity (Reboul, 2017). In another definition, bioavailability refers to the ingested component that becomes accessible to absorption in the gastrointestinal (GI) tract, followed by its metabolism and further distribution in the body. Bioavailability constitutes three steps: bioaccessibility, absorption, and transformation of the ingested component (vitamin E in this case). To make referencing easier, we shall use the term "vitamin E" synonymously with "tocopherol" from this point onward.

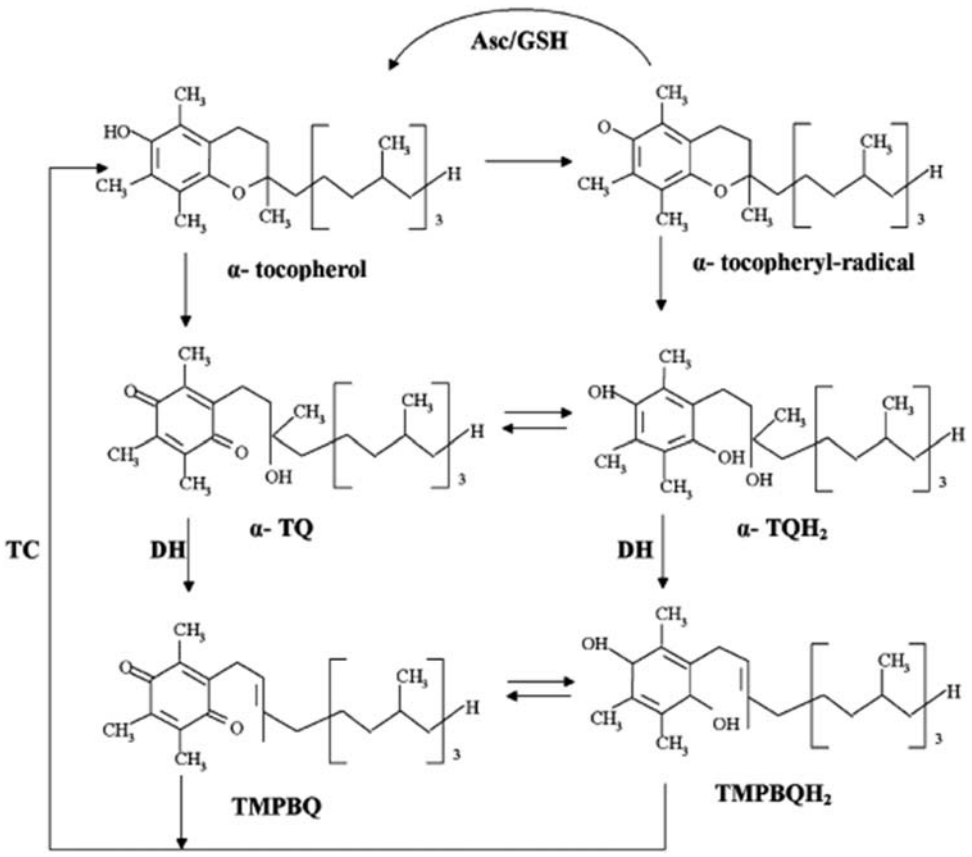


FIGURE 14.6 Possible pathway for degradation of alpha tocopherol. *α-TQ*, α-tocopherol quinone; *α-TQH2*, α-tocopherol quinol; *Asc/GSH*, ascorbate−glutathione cycle; *DH*, unknown dehydratase; *TC*, tocopherol cyclase; *TMPBQ*, 2,3,5-trimethyl-6-phytyl-1,4-benzoquinone; *TMPBQH2*, 2,3,5-trimethyl-6-phytyl-1,4-benzoquinol. *From Lushchak, V. I., & Semchuk, N. M. (2012). Tocopherol biosynthesis: chemistry, regulation and effects of environmental factors.* Acta Physiologiae Plantarum, 34*(5), 1607−1628. https://doi.org/10.1007/s11738-012-0988-9.*

Firstly, let us go through how vitamin E is metabolized in the body. Vitamin E is fat-soluble, and is shown to be associated with major lipids and absorbed mainly in the upper GI tract. However, its absorption is not very efficient. Metabolism of vitamin E in the upper GI tract includes emulsification; incorporation into the micelles; transportation through the unstirred water layer (glycocalyx); assimilation by an apical membrane of enterocytes (intestinal absorptive cells); solubilization into the intestinal lipoproteins; and secretion out of the intestinal cells into the lymph or into the portal vein. The initial phase is the dissolution of vitamin E in the lipid phase of the meal it is present in, which occurs during mastication of food. This is followed by the action of gastric enzymes (pepsin, amylase, and gastric lipase), which assist in the release of vitamin E from the food matrix. It is well established that α-tocopherol does not undergo any significant degradation or absorption in the stomach (Reboul, 2017). In the duodenum (first part of the small intestine), the digestive enzymes (proteases, amylases, and lipases) continue degrading the food matrix, thereby contributing toward further release. Here, the absorption mechanism of vitamin E is quite similar to that of dietary fats. Vitamin E requires biliary and pancreatic secretions in order to form micelles for subsequent uptake by the intestinal epithelial cells (Traber, 2007). The main site for vitamin E absorption is supposedly the midsection of the GI tract. Intestinal absorption of vitamin E is quite complex (Gagné et al., 2009); it is partly mediated by class-B type-1 (SR-B1) scavenger receptors, which are also involved in cholesterol uptake (Reboul, Richelle, et al., 2006). Other mechanisms include intracellular trafficking proteins; modulation of nuclear receptors; and activity of ATP-binding cassette transporters (Traber, 2004). The efficiency of vitamin E absorption is not similar along the intestine; the major sites are where the concentration of vitamin E in micelles and possibly vesicles is the highest. Also, the repartition of vitamin E transporters and distribution of SR-B1 scavengers are not uniform (Borel et al., 2001; Reboul et al., 2007).

The efficiency of vitamin E transportation across the intestinal wall is quite variable ranging from 10% to 95% (Borel et al., 2013; Emmanuelle Reboul, 2017). However, in one study where deuterium-labeled vitamin E was studied for absorption, the range dropped to 10%−33% (Bruno et al., 2006). There are numerous factors that modulate vitamin E bioavailability. A mnemonic term '**SLAMENGHI**" is currently in considerable use to list all factors contributing to vitamin E bioavailability (Desmarchelier et al., 2018, pp. 1181−1196). This term was initially proposed to access carotenoids bioavailability and other fat-soluble micronutrients (West & Castenmiller, 1998). Each term corresponds to one factor: **S** for "**S**pecies of vitamin E" (referring to relative bioavailability of the vitamers); **L** for "Molecular **l**inkages" (e.g., esterification of vitamin E); **A** for "**A**mount of vitamin E consumed in a meal"; **M** for "**M**atrix in which vitamin E is incorporated" (e.g., vegetable oil or supplement); **E** for "**E**ffectors of absorption" (i.e., the effect of other nutrients or drugs); **N** for "**N**utrient status of the host with respect to vitamin E levels"; **G** for "**G**enetic factors"; H for "**H**ost related factors" (viz. individual characteristics such as age, sex, pathologies, etc.); and **I** for "Mathematical **i**nteractions" (referring to interacting effects of two or more of the described factors).

Species of vitamin E—There is less number of studies regarding the variation of vitamin E species in humans. Overall, it has been reviewed by Desmarchelier et al. (2018, pp. 1181−1196) that the relative bioavailability of stereoisomers, *RRR*- and *SRR*-α-tocopherol bioavailability, presented with no significant difference in human studies. Also, α- and γ-tocopherol bioavailability carried out with a low number of human subjects did not reveal any significant difference between them as well.

Molecular linkages—Mostly, dietary vitamin E is consumed in its free form or as supplements. Supplements are usually esterified to protect the hydroxyl group against oxidation. However, no significant differences in bioavailability in human were observed for the free form or esters of succinates and acetates of tocopherols in healthy individuals (Burton et al., 1988; Cheeseman et al., 1995; Nagy et al., 2013).

Amount of vitamin E—The studies comparing nutritional doses with supplemental or pharmacological doses are currently lacking. It has been assumed that the efficiency of vitamin E absorption decreases with increased dose owing to blood saturation. On the contrary, there is no strict evidence of the same. However, one case study has shown that vitamin E levels in chylomicrons increased on the consumption of meals containing large dosages (432 or 937 IU) of α-tocopherol acetates (Borel et al., 1997).

Matrix effects—The matrix within which vitamin E is incorporated is a key factor that governs its bioavailability. Vitamin E needs to be bioaccessible, i.e., to become available for absorption. The bioaccessibility is quite variable among food matrices. For instance, in banana, lettuce, and bread, vitamin E is almost completely bioaccessible, whereas in apples and orange it is quite low (Reboul, Klein, et al., 2006). It has also been found that the addition of eggs to durum wheat pasta reduces the bioaccessibility of vitamin E from around 70%−50% (Werner & Böhm, 2011). In the case of juices blended with whole milk, an increase in bioaccessibility was observed (Cilla et al., 2012). In other studies, where oil-in-water emulsions fabricated with natural emulsifiers and long-chain triglycerides were used, better bioavailability of α-tocopherol was observed (Yang et al., 2017).

Effectors of absorption—Different authors (Desmarchelier et al., 2018, pp. 1181−1196; Reboul, 2017) have concluded from various studies that the amount of dietary fat in a food matrix facilitates vitamin E extraction, stimulates biliary secretion, and promotes micelle formation to increase its bioaccessibility. For example, consumption of toasted bread with butter or cereals with whole fat milk or raw vegetables consumed with canola oil and eggs led to better absorption of vitamin E, as compared to consuming the same without the fat components. On the other hand, the presence of certain micronutrients like vitamin C, carotenoids, and polyphenols negatively impacts intestinal absorption of tocopherol (Reboul et al., 2007). Whereas, with respect to dietary fibers intake, no adverse effects on vitamin E absorption was concluded among different studies concerning rats as well as humans (Desmarchelier et al., 2018, pp. 1181−1196). However, further studies are needed to identify the impact of various other micronutrients and draw real conclusions.

Nutrient status of the host—Vitamins being essential and large amounts of fat-soluble vitamins can lead to toxicity; it is suggested that vitamin E absorption is mediated by the vitamin E status of the host. Studies have suggested that tocopherols can modulate directly or indirectly several nuclear receptors and can act as transcriptional factors for genes encoding proteins for vitamin E uptake (Borel et al., 2013; Desmarchelier et al., 2018, pp. 1181−1196).

Genetic as well as host-related factors—The involvement of intestinal proteins/enzyme in vitamin E absorption has stimulated the hypothesis that genetic factors can modulate vitamin E absorption efficiency. Intestinal absorption of vitamin E requires normal digestive functions, and thus people with genetic diseases such as cystic fibrosis and abetalipoproteinemia suffer from impaired vitamin E absorption. Further, the effect of sex on vitamin E absorption is difficult to access in males and females, as female hormones affect lipid and lipoprotein metabolism differently (Borel et al., 2013). However, a nonsignificant difference in vitamin E levels has been observed in certain studies (Desmarchelier et al., 2018, pp. 1181−1196). Considering aging effects, it has been observed that the bioavailability of α-tocopheryl acetate is apparently lower in healthy older individuals than in younger ones (Borel et al., 1997), which were attributed to age-related altered digestive functions.

Mathematical interactions—This includes synergistic or antagonistic effects on vitamin E absorption when considering the interaction of two or more factors with one another.

Overall understanding of various factors relating to vitamin E absorption can ultimately transfer benefits leading to higher bioavailability, and one can suggest a personalized recommendation for individuals to confer potent health benefits.

14.7 Stability, safety, and toxicology

Lipid oxidation is the major cause of quality deterioration of food products and the destruction of biological membrane structures. Lipid soluble antioxidants such as tocopherols can prevent the oxidation of lipids by competing with unsaturated fatty acids for the lipid peroxy radicals. The reaction rate of tocopherol is 100,000 times faster than the lipid with the lipid peroxy radical (Niki et al., 1984). However, tocopherols themselves may degrade due to improper storage, presence of free radicals, exposure to molecular oxygen, light and elevated temperature, grossly leading to the loss of antioxidant activity, or their role as prooxidants may become available (Choe & Min, 2006; Pignitter et al., 2014). At higher concentrations, tocopherol loses their antioxidant activity or becomes prooxidants, whereas at lower concentrations they have the highest antioxidant activity. The antioxidant activity of tocopherol is inversely related to the stability of tocopherol in vegetable oil (Jung & Min, 1992). The α-tocopherol of soybean oil due to its higher antioxidant activity is destroyed faster than the γ- and δ-tocopherol of soybean oil during storage at 50 °C (Fig. 14.7). Moisture content, the types of oil, and the concentration of tocopherol homologues significantly influence the stability of tocopherol homologues (Jung & Min, 1992). The decomposition of α-tocopherol can be reduced by forming a protein−nutrient complex of α-tocopherol with β-lactoglobulin (Liang et al., 2011).

Vitamin E deficiency is a common phenomenon in humans with fat malabsorption syndromes. Primarily, α-tocopherol is administered in humans to prevent vitamin E deficiency. Tocopherols as food additives have the Generally Recognized as Safe (GRAS) status in the United States. The recommended daily intake of vitamin E is reported as 15 mg (Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids: A Report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine., 2000). However, the recommended daily intake may increase with the increase in the content of unsaturated fatty acids in a diet (Belitz & Grosch, 1999). Apparently, the adequate intake of this vitamin is not defined and may vary among the population of the world depending on the physiological conditions and diet. Vitamin E daily intake can be increased up to 300 mg without any complications (Yap et al., 2001). Even short-term high-doses and supranutritional (more than nutritionally required) doses administration of vitamin E has no reported adverse effects on health (Curtis et al., 2014; Final Report on the Safety Assessment of Tocopherol, Tocopheryl Acetate, Tocopheryl

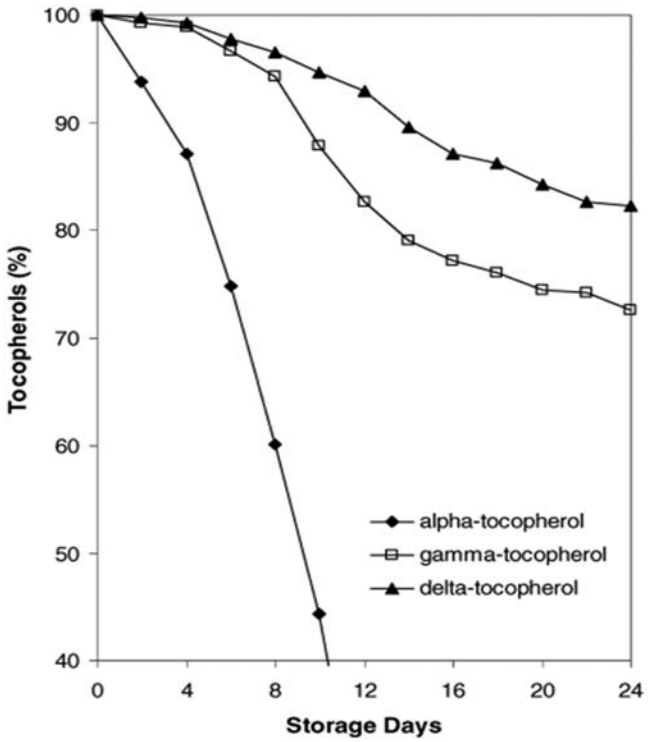


FIGURE 14.7 Degradation of α-, γ-, and δ-tocopherol in soybean oil on a storage time scale of 24 d at 50°C. *From Player, M. E., Kim, H. J., Lee, H. O., & Min, D. B. (2006). Stability of α-, γ-, or δ-Tocopherol during soybean oil oxidation.* Journal of Food Science, 71*(8), C456–C460.* https://doi.org/10.1111/j.1750-3841.2006.00153.x.

Linoleate, Tocopheryl Linoleate/Oleate, Tocopheryl Nicotinate, Tocopheryl Succinate, Dioleyl Tocopheryl Methylsilanol, Potassium Ascorbyl Tocopheryl Phosphate, and Tocophersolan, 2002). However, the risk of developing side effects in some group of patients at the risk of cardiovascular diseases such as thrombotic risk cannot be ruled out and supplementation must be considered with precautions (Final Report on the Safety Assessment of Tocopherol, Tocopheryl Acetate, Tocopheryl Linoleate, Tocopheryl Linoleate/Oleate, Tocopheryl Nicotinate, Tocopheryl Succinate, Dioleyl Tocopheryl Methylsilanol, Potassium Ascorbyl Tocopheryl Phosphate, and Tocophersolan, 2002). Therefore at present, there is no need for recommendation of higher or supranutritional doses of vitamin E which may lead to health complications in the long term. Taking into consideration with regard to what we know at present, the efficacy and supplementation of vitamin E is worth investigating.

14.8 Applications (clinical and pathological): health benefits

14.8.1 Antioxidant activity

Prolonged oxidative stress could lead to the onset of many metabolic and lifestyle-associated disorders. Such stress is caused due to an imbalance of free radical generation. Free radicals are generated as an impact of various metabolic processes in human. Widely known free radicals such as hydroxyl, superoxide anion, peroxide, singlet oxygen, nitric oxide, etc., are very reactive and capable of damaging DNA, proteins, carbohydrates, and lipids in the cell, leading to unwanted biochemical reactions (Saikia & Mahanta, 2016). These biochemical reactions later lead to serious metabolic and nonmetabolic disorders in human. However, innate defense in humans against such radicals associated damage is modulated by enzymes like superoxide dismutase, glutathione peroxidase, and micronutrients that quench or scavenge such radicals (Lobo et al., 2010), acting as antioxidants. The antioxidant activity of vitamin E (α-tocopherol) is attributed to its ability to neutralize or intercept lipid peroxyl radicals (LOO^{-}) thereby terminating the lipid peroxidation. However, vitamin E is not much of a potent scavenger of other radicals, viz., $^{\cdot}OH$ and alkoxyl radicals ($RO^{\cdot}$) (Nimse & Pal, 2015). A recent study conducted on rats demonstrated that the effectiveness of vitamin E supplementation was effective for decreasing lipid peroxidation and attenuating oxidative stress (Abdulaziz et al., 2020). Studies have also demonstrated improved oxidative stress and antioxidant status in elderly women on intakes of dietary antioxidants, such as carotenoids,

vitamin E, and vitamin C (Boaventura et al., 2020). A recent review has suggested that vitamin E supplementation may lead to increased exercise performance in athletes (Higgins et al., 2020). The same study suggested that vitamin E tends to block free radicals generated during exercise which act as signaling molecules as protection against physical stress. In action, quenching of such radicals supposedly enhances endurance during exercise or sports performance. Thus, it is simple to deduce that vitamin E intake will potentially lead to better antioxidant status in the body, possibly providing protection against health disorders (Lobo et al., 2010).

14.8.2 Antiinflammation

Inflammation is a result of an overreactive immune response to a harmful stimulus (chemical or biological). On such a stimulus, a cascade of reactions is initiated. Inflammation is characterized by the overproduction of reactive oxygen/nitrogen species and pro-inflammatory mediators, including lipid mediators, notably prostaglandins and leukotrienes, and cytokines such as TNF-α and interleukin-6 (IL-6). Chronic inflammation is a major contributor to the pathogenesis of chronic diseases such as cancer, cardiovascular diseases, rheumatoid arthritis, and asthma. Studies on tocopherols dosage on varied animal models induced with burn injury, airway inflammation, and colon inflammation have suggested a significant decrease in inflammatory factors (Jiang, 2014). Vitamin E indirectly reduces inflammation by affecting inflammatory mediators (Lewis et al., 2019). A meta-analysis study carried out by taking into consideration 33 randomized clinical trials suggested that α-tocopherol proved to be more effective in reducing serum levels of C-reactive proteins and IL-6 and overall alleviating subclinical inflammation in adults (Asbaghi et al., 2020). Studies pertaining to role of inflammation in arthritis, vitamin E supposedly retards the progression of osteoarthritis by ameliorating oxidative stress and inflammation of the joints (Chin & Ima-Nirwana, 2018).

14.8.3 Immunity

Having a strong immunity is of utmost importance. It is widely being noted owing to a prevailing scenario where outbreaks of known or unknown infections can cause a toll on human health. The healthy immune response is linked to increased immunoglobulin levels, antibody responses, lymphocyte proliferation, and interleukin (IL)-2 productions. Numerous studies on dietary supplementation on varied animal and human models have shown the immunomodulatory effect of vitamin E. Vitamin E functions as an antiinflammatory agent by modulating T cell function by directly impacting T cell membrane integrity, signal transduction, and cell division, and also indirectly by affecting other inflammatory mediators (Lewis et al., 2019). In animal studies with cows, chicken, and rats, vitamin E supplementation led to overall increased immune responses (Lee et al., 1998). However, with human subjects, multiple studies have reported increased immune function, but at levels more than dietary recommendation (Lewis et al., 2019). Still, there are other studies suggesting no significant effects on immune functions. This might possibly be due to variation in dosage, age of subjects, and determination methodologies utilized in different studies (Lee & Han, 2018). For mice model studies on wound infections with methicillin-resistant *Staphylococcus aureus*, and *Streptococcus pneumoniae* infection of the respiratory tract, vitamin E therapy resulted in good immune responses and subsequent lower microbial counts (Bou Ghanem et al., 2015; Pierpaoli et al., 2017). In humans as well, lower levels of infection in pneumonia, malaria, and the common cold have been reviewed and reported (Lee & Han, 2018). It would be beneficial to focus on further research leading to the identification of optimal doses specific to age health conditions, nutritional status, and genetic variability.

14.8.4 Cancer

Owing to its strong antioxidant nature, tocopherols are linked to reduced cancer risks. Certain studies have shown that deficiency of vitamin E is associated with increased risk in certain cancers (Wilson & Mucci, 2019). Vitamin E vitamers have been reviewed to be effective in inducing growth arrest, apoptosis, autophagy, and endoplasmic reticulum stress in cancer cells (Petronek et al., 2021). However, other studies with human subjects revealed a nonsignificant impact of vitamin E on the prevention or delay of lung cancer and pancreatic carcinoma and urinary tract cancer in humans (Petronek et al., 2021). Nevertheless, it has been suggested that vitamin E can be used as an adjuvant along with other active components such as selenium, doxorubicin for cancer prevention (Fernandes et al., 2018; Fred Gey, 1998; Wilson & Mucci, 2019). Cancer cell line and animal model studies have suggested that tocopherols help in modulating nuclear receptors such as PPARγ (by upregulation) and ERα (by downregulation) to induce cell proliferation and apoptosis in breast cancer (Das Gupta & Suh, 2016). Overall, the impact of tocopherols is minimal, and the data pertaining to its effects are rather inconsistent.

14.8.5 Metabolic disorders

Metabolic disorders constitute a cluster of medical conditions majorly including obesity, hyperglycemia, dyslipidemia, and hypertension. Vitamin E is suggested as a promising agent for the treatment of such disorders (Wong et al., 2017). The impact of vitamin E in diabetic patients has been extensively carried out. One study carried out on Finnish men and women revealed that dietary intake of vitamin E was significantly associated with a reduced risk of type II diabetes (Montonen et al., 2004). In one study with 44 women aged between 20 and 50 years, it was assessed that consumption of grape seed oil rich in tocopherols improved insulin resistance in obese women (Irandoost et al., 2013). Next, in a clinical study in type I and type II diabetic patient vitamin E supplementation was found to delay the onset of diabetic and reduce blood pressure (Baburao Jain & Anand Jain, 2012). In a recent study, vitamin E evaluation on healthy subjects from Singapore suggested that vitamin E could play a role in delaying the onset of type II diabetes (Bi et al., 2019). Dyslipidemia is characterized by increased triglycerides and lowering of low-density lipoproteins (LDLs). Studies have suggested that supplementation of tocopherols do not confer any benefits in dyslipidemia as such but supplementing with tocotrienols or tocotrienol-rich fractions resulted in significant benefits (Wong et al., 2017). On the other hand, a contrasting effect of vitamin E intake was reported in recent Mendelian randomization-based observational study, in which vitamin E was linked to elevated levels of LDL and triglycerides (Wang & Xu, 2019). Thus, future research on revaluation of the therapeutic potential of vitamin E along with an emphasis on mechanistic understanding will be necessary to better confirm and elucidate beneficial effects of vitamin E in metabolic disorders.

14.8.6 Skincare

Vitamin E has been used in dermatological applications for more than 50 years now as a potent antioxidant. Skin is subjected to damage owing to continuous solar radiations which lead to lipid peroxidation in membranes and age-related collagen cross-linking. Tocopherols are found to protect against both lipid peroxidation and collagen cross-linking. Tocopherols stabilize cell membrane by inhibiting the oxidation of arachidonic acid of membrane phospholipids. Also, the topical application of vitamin E has been reviewed to reduce erythema, sunburned cells, UV-inflicted skin damage, and photocarcinogenesis (Schagen et al., 2012). More recently, a study reported synergistic effects of vitamin E with ascorbic acid to improve skin health and brightening effects in the case of female subjects (Rattanawiwatpong et al., 2020), suggesting combinatorial therapies to be better than monotherapies. In another study, authors reported that topical formulation with phosphorylating α-tocopherol monomers better diffuse into skin epidermis thereby increased potential toward damage against UV radiations (Saleh et al., 2021). Existing studies considering preclinical and clinical studies have suggested the benefits of Vitamin E in the case of atopic dermatitis (Ehterami et al., 2019; Teo et al., 2020). Recent studies are more targeted toward enhanced delivery of α-tocopherol in the skin using nanoemulsions (Harun et al., 2021) to benefit skin health.

14.8.7 Eye health

Oxidative stress leads to oxidative damage to the eye lens and is regarded as the major factor leading to the pathogenesis of senile cataract (Nartey, 2017). A meta-analysis evaluation suggested that both dietary and supplemental intake of vitamin E could significantly be associated with reduced age-related cataract development (Zhang et al., 2015). Like other antioxidants, tocopherols are also supposed to minimize oxidative damage. In a recent study, nanomicelles consisting of inulin-D-α-tocopherol succinate bioconjugates loaded with curcumin were able to protect the blood−retina barrier against high glucose levels, thus suggesting that tocopherol can prevent diabetes-induced retinopathy (Rassu et al., 2021). The lens contains α-crystallin (a molecular chaperone) whose function is to maintain the correct folding of other protein and is also affected by oxidation. In one study, it was observed that rats injected with selenite-α-tocopherol had better α-crystallin function when supplemented with coffee. The study suggested that targeting such chaperone activity can be useful in the development of anticataract drug (Nakazawa et al., 2017). Overall, synergistic beneficial effects on eye health for tocopherols are observed with other antioxidants.

14.8.8 Liver health

Nonalcoholic fatty liver disease (NAFLD) is referred to as the accumulation of excessive fat in the liver, without alcohol consumption. It is also strongly associated with obesity and related metabolic disorders such as insulin resistance, dyslipidemia, and oxidative stress. NAFLD also leads to nonalcoholic steatohepatitis (NASH), characterized histologically

by the presence of hepatic steatosis, lobular inflammation, and hepatocyte ballooning leading to cirrhosis and hepatocarcinoma (Hadi et al., 2018; Pacana & Sanyal, 2012). A significant improvement in steatosis, inflammation, ballooning, and resolution of steatohepatitis in adult nondiabetic patients with aggressive NASH can be brought about with vitamin E therapy (Pacana & Sanyal, 2012). From numerous studies on animals, it has been concluded that vitamin E therapy could recover depleted hepatic glutathione (depletion is linked with oxidative stress and marked increase in hepatic fibrosis); ameliorate steatosis, necroinflammation, hepatic stellate cell activation, and collagen mRNA expression (triggered by increase in oxidative stress and metabolic abnormality due to NAFLD); and reduce serum transaminase levels (elevated levels are associated with NAFLD). These effects have been associated with suppressed expression of the fibrotic genes TGF-β and MMP-2, inflammatory factor COX-2, and proapoptotic genes (Bax), inhibition of factor kappa B (NFkB), and increased hepatic superoxide dismutase activity. On the contrary, multiple human clinical trials with long-term vitamin E monotherapies have reportedly shown both significant and no significant improvement on liver biochemistry and histopathology. However, long-term (>2 years) combinatorial treatment strategies such a vitamin E + ursodeoxycholic acid or vitamin E + vitamin C + atorvastatin have demonstrated overall modest benefits in liver health and histopathological improvements in majority of adults and pediatric patients (Abdel-Maboud et al., 2020; Hadi et al., 2018). On meta-analysis of a controlled clinical trial carried out, the effect of dosage and formulation variation among various clinical studies makes it difficult to ascertain their effects comparatively (Amanullah et al., 2019). Still, there is a need for further studies to comprehend the physiology of NADH/NASH which would help us to better understand and develop a targeted approach for treatments using vitamin E.

14.9 Conclusion

This chapter presents essential and relevant information on the sources, extraction, antioxidant properties, and health-benefiting properties of tocopherols, which are the most important and active forms of vitamin E. After a century of studies since its discovery, some aspects of tocopherols are still far from being completely compiled in literature, especially the nutritional recommendations, therapeutic applications, and disease prevention. Taking into account all these aspects, the research studies on this compound are gaining interest and hence, reemerged as a topic of intense research for the scientific community.

References

Abdel-Maboud, M., Menshawy, A., Menshawy, E., Emara, A., Alshandidy, M., & Eid, M. (2020). The efficacy of vitamin E in reducing non-alcoholic fatty liver disease: A systematic review, meta-analysis, and meta-regression. *Therapeutic Advances in Gastroenterology, 13*. https://doi.org/10.1177/1756284820974917, 1756284820974917.

Abdulaziz, A. B., Helmy, E.-A. S., Mohamed, H. A., & Mohamed, A.-N. I. (2020). The protective effects of vitamin E against selenium-induced oxidative damage and hepatotoxicity in rats. *Journal of Taibah University for Science, 14*(1), 709−720. https://doi.org/10.1080/16583655.2020.1769256

Amanullah, I., Khan, Y. H., Anwar, I., Gulzar, A., Mallhi, T. H., & Raja, A. A. (2019). Effect of vitamin E in non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomised controlled trials. *Postgraduate Medical Journal, 95*(1129), 601−611. https://doi.org/10.1136/postgradmedj-2018-136364

Asbaghi, O., Sadeghian, M., Nazarian, B., Sarreshtedari, M., Mozaffari-Khosravi, H., Maleki, V., Alizadeh, M., Shokri, A., & Sadeghi, O. (2020). The effect of vitamin E supplementation on selected inflammatory biomarkers in adults: A systematic review and meta-analysis of randomized clinical trials. *Scientific Reports, 10*(1). https://doi.org/10.1038/s41598-020-73741-6

Baburao Jain, A., & Anand Jain, V. (2012). Vitamin E, its beneficial role in diabetes mellitus (DM) and its complications. *Journal of Clinical and Diagnostic Research, 6*(10), 1624−1628. https://doi.org/10.7860/JCDR/2012/4791.2625

Belitz, & Grosch, W. (1999). *Food chemistry* (p. 381).

Bi, X., Loo, Y. T., Yeo, P. L. Q., & Henry, C. J. (2019). Are α-tocopherol levels associated with improved glycaemia? *Journal of Nutrition and Intermediary Metabolism, 18*. https://doi.org/10.1016/j.jnim.2020.100110

Boaventura, B. C. B., Di Pietro, P. F., Cembranel, F., Preedy, V. R., & Patel, V. B. (2020). *Chapter 14 - Oxidative stress and antioxidants in elderly women* (pp. 145−154). Academic Press. https://doi.org/10.1016/B978-0-12-818698-5.00014-6

Borel, P., Mekki, N., Boirie, Y., Partier, A., Grolier, P., Alexandre-Gouabau, M. C., Beaufrere, B., Armand, M., Lairon, D., & Azais-Braesco, V. (1997). Postprandial chylomicron and plasma vitamin E responses in healthy older subjects compared with younger ones. *European Journal of Clinical Investigation, 27*(10), 812−821. https://doi.org/10.1046/j.1365-2362.1997.1960744.x

Borel, Patrick, Pasquier, B., Armand, M., Tyssandier, V., Grolier, P., Alexandre-Gouabau, M.-C., Andre, M., Senft, M., Peyrot, J., Jaussan, V., Lairon, D., & Azais-Braesco, V. (2001). Processing of vitamin A and E in the human gastrointestinal tract. *American Journal of Physiology, Gastrointestinal and Liver Physiology, 280*(1), G95−G103. https://doi.org/10.1152/ajpgi.2001.280.1.G95

Borel, P., Preveraud, D., & Desmarchelier, C. (2013). Bioavailability of vitamin E in humans: An update. *Nutrition Reviews, 71*(6), 319−331. https://doi.org/10.1111/nure.12026

Bou Ghanem, E. N., Clark, S., Du, X., Wu, D., Camilli, A., Leong, J. M., & Meydani, S. N. (2015). The α-tocopherol form of vitamin E reverses age-associated susceptibility to streptococcus pneumoniae lung infection by modulating pulmonary neutrophil recruitment. *Journal of Immunology (Baltimore, Md. 1950), 194*(3), 1090−1099. https://doi.org/10.4049/jimmunol.1402401

Brigelius-Flohé, R. B. F., & Traber, M. G. (1999). Vitamin E: Function and metabolism. *FASEB Journal, 13*(10), 1145−1155. https://doi.org/10.1096/fasebj.13.10.1145

Bruno, R. S., Leonard, S. W., Park, S. I., Zhao, Y., & Traber, M. G. (2006). Human vitamin E requirements assessed with the use of apples fortified with deuterium-labeled α-tocopheryl acetate. *American Journal of Clinical Nutrition, 83*(2), 299−304. https://doi.org/10.1093/ajcn/83.2.299

Burton, G. W., Ingold, K. U., Foster, D. O., Cheng, S. C., Webb, A., & Hughes, L. (1988). Comparison of free α-tocopherol and α-tocopheryl acetate as sources of vitamin E in rats and humans. *Lipids, 23*(9), 834−840. https://doi.org/10.1007/BF02536201

Cheeseman, K. H., Holley, A. E., Kelly, F. J., Wasil, M., Hughes, L., & Burton, G. (1995). Biokinetics in humans of RRR-α-tocopherol: The free phenol, acetate ester, and succinate ester forms of vitamin E. *Free Radical Biology and Medicine, 19*(5), 591−598. https://doi.org/10.1016/0891-5849(95)00083-A

Chin, K. Y., & Ima-Nirwana, S. (2018). The role of vitamin E in preventing and treating osteoarthritis - a review of the current evidence. *Frontiers in Pharmacology, 9*. https://doi.org/10.3389/fphar.2018.00946

Choe, E., & Min, D. B. (2006). Mechanisms and factors for edible oil oxidation. *Comprehensive Reviews in Food Science and Food Safety, 5*(4), 169−186. https://doi.org/10.1111/j.1541-4337.2006.00009.x

Chun, J., Lee, J., Ye, L., Exler, J., & Eitenmiller, R. R. (2006). Tocopherol and tocotrienol contents of raw and processed fruits and vegetables in the United States diet. *Journal of Food Composition and Analysis, 19*(2−3), 196−204. https://doi.org/10.1016/j.jfca.2005.08.001

Cilla, A., Alegría, A., De Ancos, B., Sánchez-Moreno, C., Cano, M. P., Plaza, L., Clemente, G., Lagarda, M. J., & Barberá, R. (2012). Bioaccessibility of tocopherols, carotenoids, and ascorbic acid from milk- and soy-based fruit beverages: Influence of food matrix and processing. *Journal of Agricultural and Food Chemistry, 60*(29), 7282−7290. https://doi.org/10.1021/jf301165r

Cruz, R., & Casal, S. (2013). Validation of a fast and accurate chromatographic method for detailed quantification of vitamin E in green leafy vegetables. *Food Chemistry, 141*(2), 1175−1180. https://doi.org/10.1016/j.foodchem.2013.03.099

Cruz, R., & Casal, S. (2018). Direct analysis of vitamin A, vitamin E, carotenoids, chlorophylls and free sterols in animal and vegetable fats in a single normal-phase liquid chromatographic run. *Journal of Chromatography A, 1565*, 81−88. https://doi.org/10.1016/j.chroma.2018.06.029

Curtis, A. J., Bullen, M., Piccenna, L., & McNeil, J. J. (2014). Vitamin E supplementation and mortality in healthy people: A meta-analysis of randomised controlled trials. *Cardiovascular Drugs and Therapy, 28*(6), 563−573. https://doi.org/10.1007/s10557-014-6560-7

Das Gupta, S., & Suh, N. (2016). Tocopherols in cancer: An update. *Molecular Nutrition & Food Research, 60*(6), 1354−1363. https://doi.org/10.1002/mnfr.201500847

Desmarchelier, C., Borel, P., & Said, H. M. (2018). *Chapter 52 - Bioavailability of vitamin E*. Academic Press. https://doi.org/10.1016/B978-0-12-809954-4.00052-9

Diamante, M. S., Vanz Borges, C., Minatel, I. O., Jacomino, A. P., Basílio, L. S. P., Monteiro, G. C., Corrêa, C. R., de Oliveira, R. A., & Pace Pereira Lima, G. (2021). Domestic cooking practices influence the carotenoid and tocopherol content in colored cauliflower. *Food Chemistry, 340*, 127901. https://doi.org/10.1016/j.foodchem.2020.127901

Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids : A report of the Panel on dietary antioxidants and related compounds, Subcommittees on upper reference levels of nutrients and interpretation and uses of dietary reference intakes, and the standing committee on the scientific evaluation of dietary reference intakes, Food and Nutrition Board, Institute of Medicine. (2000). National Academy Press.

Ehterami, A., Salehi, M., Farzamfar, S., Samadian, H., Vaez, A., Ghorbani, S., Ai, J., & Sahrapeyma, H. (2019). Chitosan/alginate hydrogels containing Alpha-tocopherol for wound healing in rat model. *Journal of Drug Delivery Science and Technology, 51*, 204−213. https://doi.org/10.1016/j.jddst.2019.02.032

Eitenmiller, R. R., & Lee, J. (2004). *Vitamin E: Food chemistry, composition, and analysis*. CRC Press.

Ergönül, P. G., & Köseoğlu, O. (2014). Changes in α-, β-, γ- and δ-tocopherol contents of mostly consumed vegetable oils during refining process. *Null, 12*(2), 199−202. https://doi.org/10.1080/19476337.2013.821672

Evans, H. M., & Bishop, K. S. (1922). ON the existence OF a hitherto unrecognized dietary factor essential for reproduction. *Science, 56*(1458), 650. https://doi.org/10.1126/science.56.1458.650

FAO/WHO. (2002). *FAO/WHO expert consultation on human vitamin and mineral requirements. Chapter 9 Vitamin E, 121-131*. Rome: FAO. http://www.fao.org/3/y2809e/y2809e09.pdf. (Accessed 28 January 2021).

Fernandes, R. S., Silva, J. O., Seabra, H. A., Oliveira, M. S., Carregal, V. M., Vilela, J. M. C., Andrade, M. S., Townsend, D. M., Colletti, P. M., Leite, E. A., Cardoso, V. N., Ferreira, L. A. M., Rubello, D., & Barros, A. L. B. (2018). α- Tocopherol succinate loaded nano-structured lipid carriers improves antitumor activity of doxorubicin in breast cancer models in vivo. *Biomedicine & Pharmacotherapy, 103*, 1348−1354. https://doi.org/10.1016/j.biopha.2018.04.139

Final report on the safety assessment of tocopherol, tocopheryl acetate, tocopheryl linoleate, tocopheryl linoleate/oleate, tocopheryl nicotinate, tocopheryl succinate, dioleyl tocopheryl Methylsilanol, potassium ascorbyl tocopheryl phosphate, and tocophersolan. *International Journal of Toxicology, 21*(3_Suppl. l), (2002), 51−116. https://doi.org/10.1080/10915810290169819

Fred Gey, K. (1998). Vitamins E plus C and interacting conutrients required for optimal health. *BioFactors, 7*(1-2), 113−174. https://doi.org/10.1002/biof.5520070115

Gagné, A., Wei, S. Q., Fraser, W. D., & Julien, P. (2009). Absorption, transport, and bioavailability of vitamin E and its role in pregnant women. *Journal of Obstetrics and Gynaecology Canada, 31*(3), 210−217. https://doi.org/10.1016/S1701-2163(16)34118-4

Hadi, H. E., Vettor, R., & Rossato, M. (2018). Vitamin E as a treatment for nonalcoholic fatty liver disease: Reality or myth? *Antioxidants, 7*(1). https://doi.org/10.3390/antiox7010012

Harun, M. S., Wong, T. W., & Fong, C. W. (2021). Advancing skin delivery of α-tocopherol and γ-tocotrienol for dermatitis treatment via nanotechnology and microwave technology. *International Journal of Pharmaceutics, 593*, 120099. https://doi.org/10.1016/j.ijpharm.2020.120099

Hejtmankova, A., Taborsky, J., Kudelova, V., & Kratochvilova, K. (2018). Contents of tocols in different types of dry shell fruits. *Agronomy research, 16*(S2), 1373−1382. https://doi.org/10.15159/AR.18.148

Higgins, M. R., Izadi, A., & Kaviani, M. (2020). Antioxidants and exercise performance: With a focus on vitamin E and C supplementation. *International Journal of Environmental Research and Public Health, 17*(22), 8452. https://doi.org/10.3390/ijerph17228452

Irandoost, P., Ebrahimi-Mameghani, M., & Pirouzpanah, S. (2013). Does grape seed oil improve inflammation and insulin resistance in overweight or obese women? *International Journal of Food Sciences and Nutrition, 64*(6), 706−710.

Jiang, Q. (2014). Natural forms of vitamin E: Metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. *Free Radical Biology and Medicine, 72*, 76−90. https://doi.org/10.1016/j.freeradbiomed.2014.03.035

Jung, M. Y., & Min, D. B. (1992). Effects of oxidized α-, γ- and δ-tocopherols on the oxidative stability of purified soybean oil. *Food Chemistry, 45*(3), 183−187. https://doi.org/10.1016/0308-8146(92)90112-F

Lee, G. Y., & Han, S. N. (2018). The role of vitamin E in immunity. *Nutrients, 10*(11). https://doi.org/10.3390/nu10111614

Lee, H. W., Zhang, H., Liang, X., & Ong, C. N. (2020). Simultaneous determination of carotenoids, tocopherols and phylloquinone in 12 Brassicaceae vegetables. *LWT, 130*, 109649. https://doi.org/10.1016/j.lwt.2020.109649

Lee, J., Landen, W. O., Jr., Phillips, R. D., & Eitenmiller, R. R. (1998). Application of direct solvent extraction to the LC quantification of vitamin E in peanuts, peanut butter, and selected nuts. *Peanut Science, 25*(2), 123−128. https://doi.org/10.3146/i0095-3679-25-2-13

Lewis, E. D., Meydani, S. N., & Wu, D. (2019). Regulatory role of vitamin E in the immune system and inflammation. *IUBMB Life, 71*(4), 487−494. https://doi.org/10.1002/iub.1976

Liang, L., Tremblay-Hébert, V., & Subirade, M. (2011). Characterisation of the β-lactoglobulin/α-tocopherol complex and its impact on α-tocopherol stability. *Food Chemistry, 126*, 821−826. https://doi.org/10.1016/j.foodchem.2010.12.029

Lim, H., Woo, S., Kim, H. S., Jong, S.-K., & Lee, J. (2007). Comparison of extraction methods for determining tocopherols in soybeans. *European Journal of Lipid Science and Technology, 109*(11), 1124−1127. https://doi.org/10.1002/ejlt.200700060

Liu, W., Fu, X., & Li, Z. (2019). *Journal of Oleo Science, 68*(10), 951−958. https://doi.org/10.5650/jos.ess19146

Lobo, V., Patil, A., Phatak, A., & Chandra, N. (2010). Free radicals, antioxidants and functional foods: Impact on human health. *Pharmacognosy Reviews, 4*(8), 118−126. https://doi.org/10.4103/0973-7847.70902

Lushchak, V. I., & Semchuk, N. M. (2012). Tocopherol biosynthesis: Chemistry, regulation and effects of environmental factors. *Acta Physiologiae Plantarum, 34*(5), 1607−1628. https://doi.org/10.1007/s11738-012-0988-9

Mendes, M. F., Pessoa, F. L. P., & Uller, A. M. C. (2005). Optimization of the process of concentration of vitamin e from DDSO using supercritical CO2. *Brazilian Journal of Chemical Engineering, 22*, 83−91.

Montonen, J., Knekt, P., Järvinen, R., & Reunanen, A. (2004). Dietary antioxidant intake and risk of type 2 diabetes. *Diabetes Care, 27*(2), 362. https://doi.org/10.2337/diacare.27.2.362

Nagy, K., Ramos, L., Courtet-Compondu, M.-C., Braga-Lagache, S., Redeuil, K., Lobo, B., Azpiroz, F., Malagelada, J.-R., Beaumont, M., Moulin, J., Acquistapache, S., Sagalowicz, L., Kussmann, M., Santos, J., Holst, B., & Williamson, G. (2013). Double-balloon jejunal perfusion to compare absorption of vitamin E and vitamin E acetate in healthy volunteers under maldigestion conditions. *European Journal of Clinical Nutrition, 67*(2), 202−206. https://doi.org/10.1038/ejcn.2012.183

Nakazawa, Y., Nagai, N., Ishimori, N., Oguchi, J., & Tamura, H. (2017). Administration of antioxidant compounds affects the lens chaperone activity and prevents the onset of cataracts. *Biomedicine & Pharmacotherapy, 95*, 137−143. https://doi.org/10.1016/j.biopha.2017.08.055

Nartey, A. (2017). The pathophysiology of cataract and major interventions to retarding its progression: A mini review. *Advances in Ophthalmology & Visual System, 6*. https://doi.org/10.15406/aovs.2017.06.00178

Niki, E., Saito, T., Kawakami, A., & Kamiya, Y. (1984). Inhibition of oxidation of methyl linoleate in solution by vitamin E and vitamin C. *Journal of Biological Chemistry, 259*(7), 4177−4182.

Nimse, S. B., & Pal, D. (2015). Free radicals, natural antioxidants, and their reaction mechanisms. *RSC Advances, 5*(35), 27986−28006. https://doi.org/10.1039/C4RA13315C

Pacana, T., & Sanyal, A. J. (2012). Vitamin E and nonalcoholic fatty liver disease. *Current Opinion in Clinical Nutrition and Metabolic Care, 15*(6), 641−648. https://doi.org/10.1097/MCO.0b013e328357f747

Petronek, M. S., Stolwijk, J. M., Murray, S. D., Steinbach, E. J., Zakharia, Y., Buettner, G. R., Spitz, D. R., & Allen, B. G. (2021). Utilization of redox modulating small molecules that selectively act as pro-oxidants in cancer cells to open a therapeutic window for improving cancer therapy. *Redox Biology*, 101864. https://doi.org/10.1016/j.redox.2021.101864

Pierpaoli, E., Orlando, F., Cirioni, O., Simonetti, O., Giacometti, A., & Provinciali, M. (2017). Supplementation with tocotrienols from Bixa orellana improves the in vivo efficacy of daptomycin against methicillin-resistant *Staphylococcus aureus* in a mouse model of infected wound. *Phytomedicine, 36*, 50−53. https://doi.org/10.1016/j.phymed.2017.09.011

Pignitter, M., Stolze, K., Gartner, S., Dumhart, B., Stoll, C., Steiger, G., Kraemer, K., & Somoza, V. (2014). Cold fluorescent light as major inducer of lipid oxidation in soybean oil stored at household conditions for eight weeks. *Journal of Agricultural and Food Chemistry, 62*(10), 2297−2305. https://doi.org/10.1021/jf405736j

Quek, S.-Y., Chu, B.-S., & Baharin, B. S. (2007). *In the encyclopedia of vitamin E*. Trowbridge, UK: Cromwell Press.

Rassu, G., Pavan, B., Mandracchia, D., Tripodo, G., Botti, G., Dalpiaz, A., Gavini, E., & Giunchedi, P. (2021). Polymeric nanomicelles based on inulin D α-tocopherol succinate for the treatment of diabetic retinopathy. *Journal of Drug Delivery Science and Technology, 61*, 102286. https://doi.org/10.1016/j.jddst.2020.102286

Rattanawiwatpong, P., Wanitphakdeedecha, R., Bumrungpert, A., & Maiprasert, M. (2020). Anti-aging and brightening effects of a topical treatment containing vitamin C, vitamin E, and raspberry leaf cell culture extract: A split-face, randomized controlled trial. *Journal of Cosmetic Dermatology, 19*(3), 671−676. https://doi.org/10.1111/jocd.13305

Reboul, E. (2017). Vitamin E bioavailability: Mechanisms of intestinal absorption in the spotlight. *Antioxidants, 6*(4). https://doi.org/10.3390/antiox6040095

Reboul, E., Klein, A., Bietrix, F., Gleize, B., Malezet-Desmoulins, C., Schneider, M., Margotat, A., Lagrost, L., Collet, X., & Borel, P. (2006). Scavenger receptor class B type I (SR-BI) is involved in vitamin E transport across the enterocyte. *Journal of Biological Chemistry, 281*(8), 4739−4745. https://doi.org/10.1074/jbc.M509042200

Reboul, E., Richelle, M., Perrot, E., Desmoulins-Malezet, C., Pirisi, V., & Borel, P. (2006). Bioaccessibility of carotenoids and vitamin E from their main dietary sources. *Journal of Agricultural and Food Chemistry, 54*(23), 8749−8755. https://doi.org/10.1021/jf061818s

Reboul, E., Thap, S., Perrot, E., Amiot, M.-J., Lairon, D., & Borel, P. (2007). Effect of the main dietary antioxidants (carotenoids, γ-tocopherol, polyphenols, and vitamin C) on α-tocopherol absorption. *European Journal of Clinical Nutrition, 61*(10), 1167−1173. https://doi.org/10.1038/sj.ejcn.1602635

Ribeiro, P. P. C., Silva, D. M. de L., Dantas, M. M., Ribeiro, K. D. da S., Dimenstein, R., & Damasceno, K. S. F. da S. C. (2019). Determination of tocopherols and physicochemical properties of faveleira (*Cnidoscolus quercifolius*) seed oil extracted using different methods. *Food Science and Technology, 39*, 280−285.

Saikia, S., & Mahanta, C. L. (2016). In vitro physicochemical, phytochemical and functional properties of fiber rich fractions derived from by-products of six fruits. *Journal of Food Science and Technology, 53*(3), 1496−1504. https://doi.org/10.1007/s13197-015-2120-9

Saleh, M. M., Woods, A., Harvey, R. D., Young, A. R., & Jones, S. A. (2021). Nanomaterials fusing with the skin: Alpha-tocopherol phosphate delivery into the viable epidermis to protect against ultraviolet radiation damage. *International Journal of Pharmaceutics, 594*, 120000. https://doi.org/10.1016/j.ijpharm.2020.120000

Schagen, S. K., Zampeli, V. A., Makrantonaki, E., & Zouboulis, C. C. (2012). Discovering the link between nutrition and skin aging. *Dermato-Endocrinology, 4*(3), 298−307. https://doi.org/10.4161/derm.22876

Špika, M. J., Kraljić, K., & Škevin, D. (2016). Tocopherols: Chemical structure, bioactivity, and variability in Croatian virgin olive oils. In *Products from olive tree* (p. 317). BoD−Books on Demand.

Sure, B. (1924). Dietary requirements for reproduction: II. The existence OF a specific vitamin for reproduction. *Journal of Biological Chemistry, 58*(3), 693−709. https://doi.org/10.1016/S0021-9258(18)85329-7

Teo, C. W. L., Tay, S. H. Y., Tey, H. L., Ung, Y. W., & Yap, W. N. (2020). Vitamin E in atopic dermatitis: From preclinical to clinical studies. *Dermatology*. https://doi.org/10.1159/000510653

Traber, M. G. (2004). The ABCs of vitamin E and β-carotene absorption. *The American Journal of Clinical Nutrition, 80*(1), 3−4. https://doi.org/10.1093/ajcn/80.1.3

Traber, M. G. (2007). Vitamin E regulatory mechanisms. *Annual Review of Nutrition, 27*(1), 347−362. https://doi.org/10.1146/annurev.nutr.27.061406.093819

Turkiewicz, I. P., Wojdyło, A., Tkacz, K., & Nowicka, P. (2020). Carotenoids, chlorophylls, vitamin E and amino acid profile in fruits of nineteen Chaenomeles cultivars. *Journal of Food Composition and Analysis, 93*, 103608. https://doi.org/10.1016/j.jfca.2020.103608

Wang, T., & Xu, L. (2019). Circulating vitamin E levels and risk of coronary artery disease and myocardial infarction: A mendelian randomization study. *Nutrients, 11*(9). https://doi.org/10.3390/nu11092153

Werner, S., & Böhm, V. (2011). Bioaccessibility of carotenoids and vitamin E from pasta: Evaluation of an in vitro digestion model. *Journal of Agricultural and Food Chemistry, 59*(4), 1163−1170. https://doi.org/10.1021/jf103892y

West, C., & Castenmiller, J. (1998). Quantification of the "SLAMENGHI" factors for carotenoid bioavailability and bioconversion. *International Journal for Vitamin and Nutrition Research, 68*(6), 371−377. Internationale Zeitschrift Fur Vitamin- Und Ernahrungsforschung. Journal International de Vitaminologie et de Nutrition http://europepmc.org/abstract/MED/9857264.

Wilson, K. M., & Mucci, L. A. (2019). Diet and lifestyle in prostate cancer. *Advances in Experimental Medicine and Biology, 1210*, 1−27. https://doi.org/10.1007/978-3-030-32656-2_1

Wong, S. K., Chin, K.-Y., Suhaimi, F. H., Ahmad, F., & Ima-Nirwana, S. (2017). Vitamin E as a potential interventional treatment for metabolic syndrome: Evidence from animal and human studies. *Frontiers in Pharmacology, 8*, 444. https://www.frontiersin.org/article/10.3389/fphar.2017.00444.

Xu, Z. (2008). Comparison of extraction methods for quantifying vitamin E from animal tissues. *Bioresource Technology, 99*(18), 8705−8709. https://doi.org/10.1016/j.biortech.2008.04.065

Yang, Y., Xiao, H., & McClements, D. J. (2017). Impact of lipid phase on the bioavailability of vitamin E in emulsion-based delivery systems: Relative importance of bioaccessibility, absorption, and transformation. *Journal of Agricultural and Food Chemistry, 65*(19), 3946−3955. https://doi.org/10.1021/acs.jafc.7b00955

Yap, S. P., Yuen, K. H., & Wong, J. W. (2001). Pharmacokinetics and bioavailability of α-, γ- and δ-tocotrienols under different food status. *Journal of Pharmacy and Pharmacology, 53*(1), 67−71. https://doi.org/10.1211/0022357011775208

Zhang, L., Wang, S., Yang, R., Mao, J., Jiang, J., Wang, X., … Li, P. (2019). Simultaneous determination of tocopherols, carotenoids and phytosterols in edible vegetable oil by ultrasound-assisted saponification, LLE and LC-MS/MS. *Food Chemistry, 289*, 313−319. https://doi.org/10.1016/j.foodchem.2019.03.067

Zhang, Y., Jiang, W., Xie, Z., Wu, W., & Zhang, D. (2015). Vitamin E and risk of age-related cataract: A meta-analysis. *Public Health Nutrition, 18*(15), 2804−2814. https://doi.org/10.1017/S1368980014003115

Further readings

Granado-Lorencio, F., Olmedilla-Alonso, B., Herrero-Barbudo, C., Blanco-Navarro, I., Pérez-Sacristán, B., & Blázquez-García, S. (2007). In vitro bioaccessibility of carotenoids and tocopherols from fruits and vegetables. *Food Chemistry, 102*(3), 641−648. https://doi.org/10.1016/j.foodchem.2006.05.043

Jung, J., Gim, S. Y., Lee, C., Kim, M.-J., & Lee, J. (2017). Stability of tocopherol homologs in soybean, corn, canola, and olive oils under different moisture contents at 25°C. *European Journal of Lipid Science and Technology, 119*(6), 1600157. https://doi.org/10.1002/ejlt.201600157