

Chapter 8

Plant Tocopherols and Phytosterols and Their Bioactive Properties



Pradip Poudel, Spyridon A. Petropoulos, and Francesco Di Gioia

Abstract Tocopherols and phytosterols are plant-derived fat-soluble bioactive compounds with several health beneficial properties. Tocopherols are mainly known for their antioxidant activity, while phytosterols are well known for their capacity to lower blood cholesterol levels in the human body. Plants produce these compounds for their own protection against oxidative damages and to maintain cell integrity. Including plant-based food in the daily meal plan, especially vegetable oil, fresh vegetables, nuts, and fruits, helps to fulfill our dietary needs for tocopherols and phytosterols. After briefly describing the biochemistry, biosynthesis and the important role these two categories of compounds play in the plant physiology, this chapter provides an overview of (i) the primary plant sources of tocopherols and phytosterols, summarizing some of the factors that determine their concentration in plants; and (ii) the main health-promoting effects that have been reported recently for both categories of bioactive compounds. While more research is needed to unravel the health effects of tocopherols and phytosterols, additional research effort is needed to identify alternative low-cost sources of these valuable compounds, using, for example, by-products and waste of the agri-food industry. Future research should also focus on the development of functional food products employing sustainable biofortification techniques that may allow to enhance the content and bioavailability of tocopherols and phytosterols in commonly consumed plant and plant-derived food products.

P. Poudel · F. Di Gioia (✉)

Department of Plant Science, Pennsylvania State University, University Park, PA, USA
e-mail: pmp5548@psu.edu; fxd92@psu.edu

S. A. Petropoulos

Department of Agriculture, Crop Production and Rural Environment, University of Thessaly,
Nea Ionia, Magnissia, Greece

8.1 Introduction

Tocopherols and phytosterols are fat-soluble secondary metabolites of plant origin increasingly studied for their health beneficial properties. These compounds are generally extracted from the unsaponifiable lipid fraction of plant-based food (Ryan et al. 2007). As tocopherols and phytosterols are not synthesized in the animal body, humans fully rely on plant-based food for their daily dietary intake of these compounds. Vegetable and edible oils are particularly rich in tocopherols and phytosterols; however, they can also be found in significant amounts in nuts, fresh vegetables, and fruits. Both compounds have strong antioxidant activity because of the phenolic head and electron-donating methyl and ethyl group attached to it (Lesma et al. 2018; Wallert et al. 2019). They can scavenge free radicals through breaking the oxidation chain reaction. Further, they can protect from lipid peroxidation, oxidative stress, cancer, and neurodegenerative diseases. In addition, phytosterols are mainly known for the cholesterol-lowering ability in the blood plasma, thus preventing obesity and cardiovascular diseases (Poli et al. 2021). Including around 2–3 g of plant sterols in the daily diet could decrease low-density lipoproteins (LDL) levels by 10–15% and reduce the chance of coronary heart disease over the lifetime by 20% (MacKay and Jones 2011; Chawla et al. 2016; Yang et al. 2019). Similarly, a daily intake of 15 mg of α -tocopherol is recommended by the Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds (2000).

Tocopherols are the forms of a molecule that comprise vitamin E. Vitamin E includes eight different forms of a molecule (α -, β -, γ -, and δ -), among which four are tocopherols and other four are tocotrienols (Niki and Abe 2019). The basic tocopherols structural units contain a chromanol ring and a hydrophobic carbon chain (16 C) attached to C2 position (Niki and Abe 2019; Ali et al. 2022). The main chemical difference among α -, β -, γ -, and δ tocopherol is the number and position of the methyl group in the chromanol rings (Fig. 8.1). Alpha forms of tocopherols contain three methyl groups at C5, C7, and C8 position, while β -tocopherols contains only two methyl group at C5 and C8 position. Similarly, γ -tocopherols also contain two methyl groups at C7 and C8 positions, while δ -tocopherols only

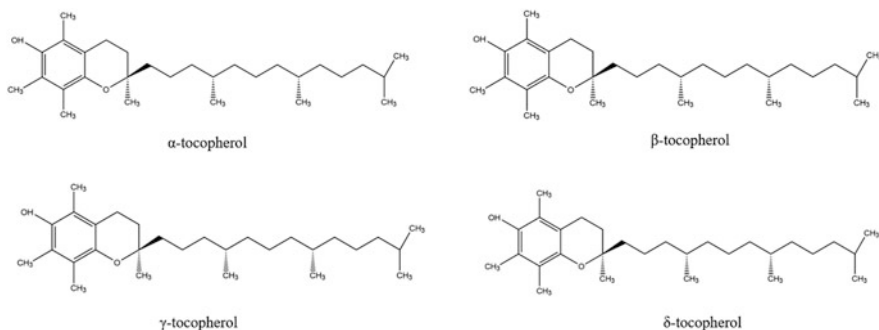


Fig. 8.1 Chemical structure of tocopherol isomers

contain one methyl group at C8 position of the chromanol ring. Because of the presence of the phenyl and electron-donating methyl group, tocopherols (vitamin E) are mainly known for their neutralizing role in lipid peroxidation and oxidative stress (Frankel 1989; Wallert et al. 2019; Bora et al. 2022). These structural differences between the different forms of tocopherols are responsible for their varying antioxidant and biological activities (Bora et al. 2022).

Among the four different isomers of tocopherol, α -tocopherol is the most abundant one based on their presence in different plants and plant-based food products. Comparatively to the other forms, α -tocopherol has higher biological activity as it is retained at high levels in plasma and body tissues (Szewczyk et al. 2021), due to the active selection by the α -tocopherol transfer protein (α -TTP) and slow degradation by the cytochrome P450. In contrast the other isomers of tocopherols are regarded as xenobiotics and are actively degenerated by the cytochrome P450 and secreted through bile and urine (Azzi 2018). This higher biological activity makes α -tocopherol the most important tocopherol and this is why it is generally recommended or referred to as vitamin E, and tocopherol level is expressed or measured in the level of α -tocopherol and α -tocopherol equivalent (EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA) 2015).

Phytosterols are another important class of bioactive compounds widely studied because of their cholesterol-lowering activity in the human body. Phytosterols comprise plant sterols and stanol naturally found in the plant cell membrane. Plant stanol and sterols have similar chemical structures, with the exception that stanols do not have a double bond in their chemical structure (Chawla et al. 2016). Hydrogenation of plant sterols results in the respective plant stanol; for example, hydrogenation of β -sitosterol results in β -sitostanol. The main function of stanols in plants is the formation of cell membrane structures. There are around two hundred different phytosterols reported, however, major phytosterols found in different sources are β -sitosterol, campesterol, and stigmasterol (Lagarda et al. 2006; Wang et al. 2018). Phytosterols have a similar structure to the cholesterol, however, they have one extra methyl or ethyl group at C24 position of the sidechain (Chawla et al. 2016). The chemical structures of the most common phytosterols (β -sitosterol, campesterol, and stigmasterol) found in plants are shown in Fig. 8.2.

Phytosterols are synthesized mainly in plants and marine animals but cannot be synthesized in the human body. Phytosterols can be found in different forms in plants, for example, free phytosterol, esterified with a fatty acid, steryl glycosides, and acylated glycosides (Yang et al. 2019). The structure and different forms of the phytosterols affect the biological activity, including their cholesterol-lowering capacity and antioxidant activity (Wang et al. 2018). Around 50% of the dietary intake of phytosterols includes β -sitosterol, however, generally, campesterol concentration is higher in blood possibly due to higher absorption in the intestine (Schött et al. 2017; Wang et al. 2018). Plant oils, vegetables, and nuts are rich sources of phytosterols; therefore, great importance is given to include these plant products in our daily diet.

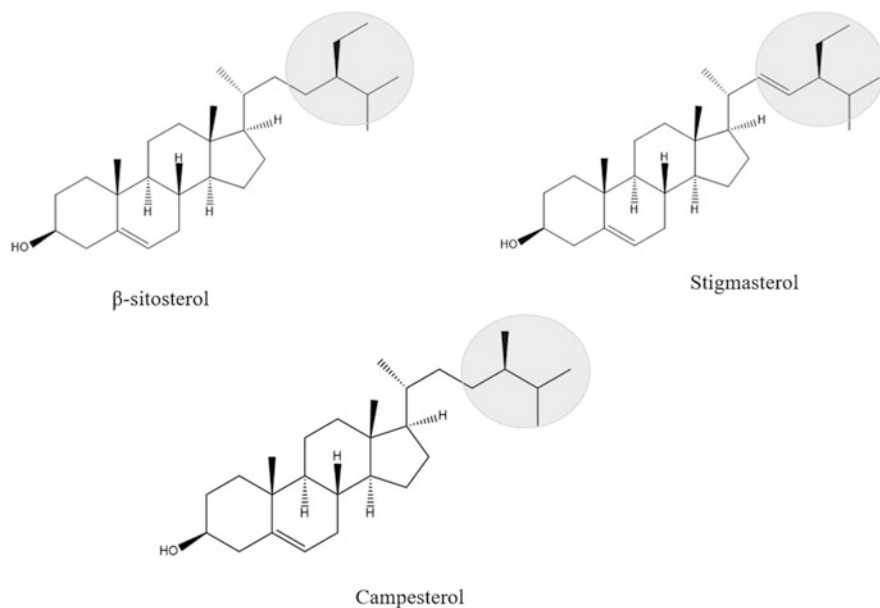


Fig. 8.2 Chemical structures of β -sitosterol, stigmasterol and campesterol

8.2 Biosynthesis and Physiological Role in Plants

The biosynthesis of tocopherols in plants involves different pathways: cytosolic shikimate, plastid methylerythritol phosphate and tocopherol-core pathways as shown in Fig. 8.3. Tocopherols derive from two precursors: 2,5-dihydroxyphenylacetate (HGA) and phytyldiphosphate (PDP) which are derived from two different pathways. The HGA forms the aromatic head of the tocopherols and is derived from the cytosolic shikimate pathway, while PDP forms the hydrophobic carbon chain of the tocopherols, and is derived from the plastid methylerythritol phosphate pathway (Lushchak and Semchuk 2012; Vinutha et al. 2017). HGA and PDP condensation is the following step forming 2-Methyl-6-phytyl-1,4-benzoquinone (MPBQ), which is catalyzed by the homogentisate phytyl transferase (VTE2). This marks the starting of the tocopherol-core pathway. Tocopherol cyclase (VTE1) converts the MPBQ to the δ -tocopherol, and from δ -tocopherol to the β -tocopherol via γ -tocopherol methyl transferase (VTE4). On the other hand, the formation of the 2,3-dimethyl-5-phytylbenzoquinonol (DMPBQ) is facilitated by the MPBQ/MSBQ methyltransferase (VTE3), and from DMPBQ to γ -tocopherol by the VTE1. Gamma-tocopherol is converted into α -tocopherol by the VTE4 (Lushchak and Semchuk 2012; Vinutha et al. 2017; Kusajima et al. 2021; Ali et al. 2022).

Tocopherols play an important role in plants both during stress and non-stress conditions. They help to maintain the integrity and fluidity of the photosynthetic cell

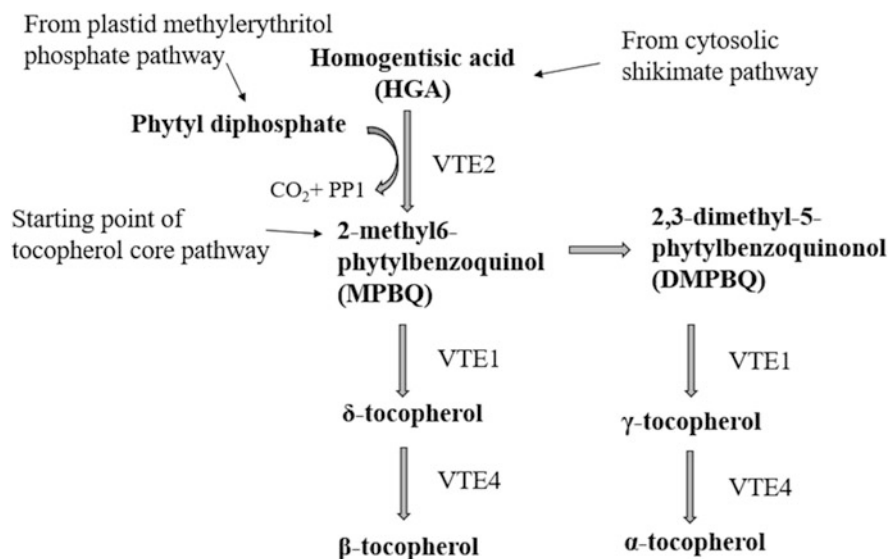


Fig. 8.3 Biosynthetic pathway of tocopherols in plants. VTE1, tocopherol cyclase; VTE2, homogentisate phytyltransferase; VTE3, MPBQ/MSBQ methyltransferase; VTE4, γ -tocopherol methyl transferase

membrane throughout the plant life cycle through its free radical quenching capacity (Sadiq et al. 2019). Biosynthesis of tocopherols may vary throughout the plant life cycle based on growth and development stages. Plants produce tocopherols in presence of various biotic and abiotic stress conditions, as a mechanism of self-protection from oxidative damages. For example, Kusajima et al. (2021) reported an increase in tocopherols concentration in *Arabidopsis thaliana* plants after the application of heat shock, through the activation of the corresponding biosynthetic pathways. Similarly, tocopherols level increased in *A. thaliana* when plants were subjected to drought stress by overexpressing VTE1 (Liu et al. 2008). Plant tocopherols levels could also increase during other environmental stress conditions determined by high light levels, salinity stress, heavy metal ion, ozone, and UV-B radiation as they play a critical role in protecting plants from oxidative damages (Lushchak and Semchuk 2012). Stahl et al. (2019) reported an increased expression of genes involved in the tocopherol's biosynthesis and increased concentration of γ -tocopherol and δ -tocopherol when they inoculated *A. thaliana* leaves with *Pseudomonas syringae*. Another important example of the antioxidant function of tocopherols in plants is given by the presence of α -tocopherol in the leaf chloroplasts. Alpha-tocopherols present in leaf chloroplasts trap the reactive oxygen species (ROS) produced during photosynthesis and further prevent the lipid peroxidation in thylakoid membranes by scavenging lipid peroxy radicals (Munné-Bosch 2005). Other than its antioxidant role in plants, tocopherols also play a role in plant cell signaling activities. Munné-Bosch (2019) have discussed the stress sensing and signaling activities of tocopherols. Tocopherols signal the accumulation of

3'-phosphoadenosine 5'-phosphate in chloroplasts which helps preventing the degradation of primary messenger RNA and promotes the production of mature messenger RNA in nucleus. According to Munné-Bosch (2019), the mechanism behind the modulation of 3'-phosphoadenosine 5'-phosphate by tocopherols is still unknown. Further, tocopherols present in vegetable oils, exert their anti-oxidation function protecting the oil from oxidation processes, thus contributing to increase the stability and shelf-life of the oil (Kamal-Eldin 2006; Mishra et al. 2021).

A recent study revealed that exogenous application of tocopherols in wheat via foliar application not only enhanced wheat tolerance to drought stress but also increased plant growth, yield, seed phenolics and flavonoids content, activity of antioxidant enzymes, and content of α -, β - and γ -tocopherols (Ali et al. 2019). Similarly, seed priming of carrots with α -tocopherol increased growth parameters, yield, chlorophyll, proline, ascorbic acid and total phenols content, and also the antioxidant activity in carrots (Hameed et al. 2021). This also suggests a potential application of tocopherols for the potential agronomic biofortification of food crops.

The biosynthesis of plant sterols is a multi-stage complex process, which mostly occurs in the endoplasmic reticulum. A simplified biosynthesis pathway of common phytosterols in plant is presented in Fig. 8.4. The biosynthesis of the plant sterols starts with acetyl-CoA, which later converts into the squalene through mevalonate (MVA) pathway (Zhang et al. 2020). It involves an important enzyme, HMGR (3-hydroxy-3-methylglutaryl-CoA reductase), which catalyzes the conversion of 3-hydroxy-3-methylglutaryl-CoA to mevalonic acid (Valitova et al. 2016). The following process is the formation of cycloartenol through the cyclization of squalene facilitated by the squalene epoxidase and cycloartenol synthase, respectively. C24 methylation of the cycloartenol is the other important process of sterol formation which is catalyzed by the SMT (C24-sterol methyltransferase). SMT has two different forms, SMT1 and SMT2, which are involved in primary and secondary methylation activities. SMT1, SMT2, and DWF1 (Dimunito/Dwarf1) catalyze the synthesis of campesterol and β -sitosterol from the cycloartenol as shown in Fig. 8.4. Conversion of the β -sitosterol to the stigmasterol is facilitated by the enzyme protein CYP710A1. Plant sterols concentration and their composition differ in different plant species, and is potentially modulated by the enzymes SMT and CYP710A (Zhang et al. 2020).

An important function of phytosterols in plants is to maintain the cell membrane integrity and fluidity (Grosjean et al. 2015). The importance of phytosterols becomes even more critical for plants during stress conditions. Plants respond to stress through different biochemical and physiological changes, which includes the increased production of phytosterols. Kumar et al. (2018) reported an increase in the sterol and sterol ester concentration in drought-stressed plants. The importance of phytosterol in seeds for storage and germination was discussed by Zhou et al. (2019). Yu et al. (2021) have reported reduced lipids droplets in seeds with lower phytosterol levels which are critical for energy storage and lipid metabolism in seeds. This suggests an important role of sterols in seed growth and development. Similarly, excess phytosterol accumulation in seeds delayed the seed germination due to thicker seed coats and irregular seed coat formation in *Arabidopsis thaliana*

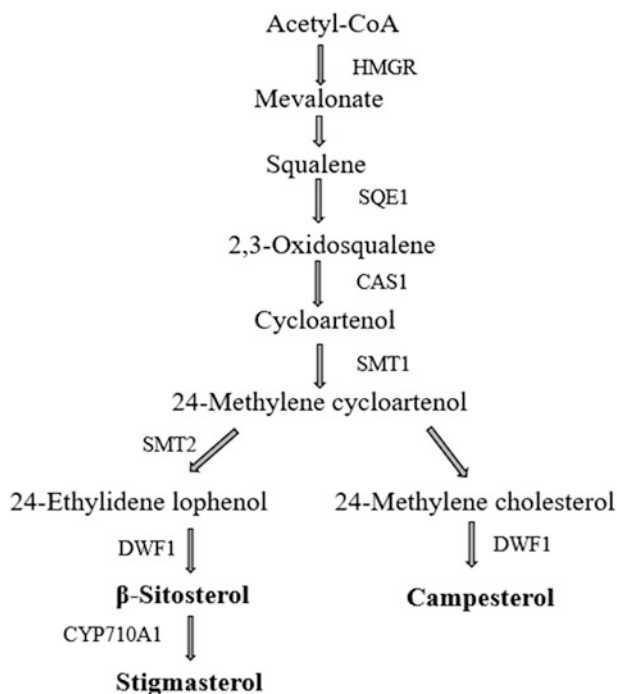


Fig. 8.4 Simplified biosynthesis pathway of plant sterols. HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; SQE, squalene epoxidase; CAS, cycloartenol synthase; SMT, C24-sterol methyltransferase; DWF, Dimunito/Dwarf1; CYP710A, cytochrome P710 A

(Shimada et al. 2021). Further, the effect of phytosterol composition on cotton fiber length and secondary cell wall deposition was studied by Niu et al. (2019) who found a decrease in fiber cell length and promotion of secondary cell wall formation in cotton with high sitosterol and a low ratio of campesterol to sitosterol. Phytosterol also helps to promote plant innate immunity against biotic stress factors. Wang et al. (2012) reported an increased resistance of the plant to external pathogens by restricting the nutrient flow to the apoplast. Maintenance of cell membrane integrity and fluidity contributes to protect plants from external stress. Other studies have also shown the potential role phytosterols plays on plant reproductive growth, seed formation, and ultimately in determining crop yield (Du et al. 2022).

8.3 Tocopherols and Phytosterol Content in Plants

Plant-derived products and foods are the major sources of tocopherols and phytosterols required for the human body, as both classes of compounds are not synthesized de novo in the human body (Chen et al. 2009; Chawla et al. 2016; Azzi 2018).

Interconversion of different forms of tocopherols through methylation and demethylation also does not take place inside the human body (Azzi 2018; Bora et al. 2022). Tocopherols are produced exclusively by photosynthetic organisms like plants, algae, and cyanobacteria, while major sources of tocopherols and phyosterols are seeds of oleaginous crops such as sunflower and canola, soybean seeds, nuts, leafy vegetables, and some fruits.

The amounts and types of tocopherols intake throughout the world are different and are influenced by different dietary habits. For example, around 70% of the vitamin E uptake from food sources in the USA is in the form of γ -tocopherol due to the consumption of high proportions of soybean and other vegetable oils like canola oil rich in γ -tocopherol (Dietrich et al. 2006). Likewise, the Mediterranean diet which is regarded as one of the healthiest dietary habits includes olive oil (extra-virgin olive oil) as an important ingredient that is rich in α -tocopherol (Shahidi and De Camargo 2016; Chatzopoulou et al. 2020). In addition, the Mediterranean diet includes different diverse vegetable species and fulfills one-tenth or more calories required by vegetables and fruits, which are rich in different micronutrients along with tocopherols. However, the bio-accessibility of the tocopherol present in vegetables is comparatively low due to the low level of lipid content, considering that the presence of fat components in the food matrix increases the bio-accessibility of the tocopherols (Azzi 2018; Bora et al. 2022). For example, raw vegetables consumed along with canola oil or eggs increase the absorption of tocopherols compared to the consumption without any fat component (Bora et al. 2022). Different commonly used vegetable oil, fresh vegetable, and fruits that are rich in tocopherols content are summarized in Table 8.1. The range of tocopherols concentration varies not only between species but also within the same species in function of the crop cultivar or variety, maturity stage, and is influenced by environmental conditions including pedoclimatic and light conditions, as well as by crop management practices and harvesting procedures (Bauernfeind and Desai 1977; Chun et al. 2006). Even in post-harvest stages, factors like vegetable processing, storage, samples preparation, and laboratory analysis procedures were found to affect tocopherols level in vegetable oil, fruits, and vegetables (Bauernfeind and Desai 1977; Chun et al. 2006; Knecht et al. 2015).

Olive oil, canola oil, and sunflower oil are commonly used and important sources of tocopherols as they contain high levels of α -tocopherols. They contain 3.7–27.7, 11.7–41.85 and 43.23–91.6 mg α -tocopherol/100 mg of oil, respectively (Table 8.1). Soybean generally contains high amounts of total tocopherols (73.61–171.5 mg/100 g oil) compared to olive (4.99–31.81 mg/100 g oil), canola (26.58–113.15 mg/100 g oil), and sunflower oil (45.3–111.48 mg/100 g oil); however, it is not considered an excellent source of tocopherols and vitamin E compared to sunflower, canola, and olive oil (Chun et al. 2006) because a large proportion of total tocopherols in soybean is in γ -tocopherol form and only a small fraction is represented by α -tocopherol. When considering what are the best sources of tocopherols and vitamin E, particular attention has been dedicated to α -tocopherol being the isomer with the highest retention in the blood plasma and tissues compared to other tocopherol isomers that are metabolized faster and are excreted out of the human

Table 8.1 Content ranges of tocopherols in different plant and plant-derived sources

Species	α -tocopherol	β -tocopherol	γ -tocopherol	δ -tocopherol	Total tocopherol (mg/100 g)	References
Vegetable and edible oils						
Sunflower oil	43.23–91.6	2.07–8.45	0–9.23	0–2.2	45.3–111.48	Grilo et al. (2014), Ergönül and Köseoğlu (2014), Ayerdi Gotor et al. (2015), Cruz and Casal (2018), Wen et al. (2020), Xu et al. (2020)
Rapeseed (canola oil)	11.7–41.85	6.43	12.2–46.07	2.68–18.8	26.58–113.15	Grilo et al. (2014), Ergönül and Köseoğlu (2014), Xu et al. (2020)
Soybean	6.96–55.73	5.3	49.52–79.91	11.83–30.56	73.61–171.5	Grilo et al. (2014), Ergönül and Köseoğlu (2014), Wen et al. (2020)
Maize oil	2.2–50.53	1.1–5.9	25.97–75.99	4.35–18.4	55–119.27	Grilo et al. (2014), Ergönül and Köseoğlu (2014), Wen et al. (2020), Xu et al. (2020)
Sesame oil	0.8–1.0	–	37.6–39.4	2.9–3.3	21.4–42.5	Xu et al. (2020)
Linseed oil	0.7	–	39.8–41.6	1.0–1.2	42.5	Xu et al. (2020)
Rice bran oil	0.59–50.3	0–5.3	0–19.4	0–8.49	3.23–62.2	Wen et al. (2020)
Cottonseed oil	44.93–63.4	–	28.45–51.8	2–2.96	62.6–111.8	Wen et al. (2020)
Hemp oil	2.61–2.65	–	61.17–61.18	3.04–3.11	66.82–66.94	Cruz and Casal (2018)
Peanut oil	13.32–36.64	–	11.33–31.45	2.28–3.83	21.97–71.9	Wen et al. (2020)
Camelia oil	12.34–20.1	–	1.3–3.9	0.48–1.92	14.12–25.92	Zhang et al. (2019), Wen et al. (2020)
Olive oil	3.7–27.7	–	0.8–2.6	0.49–1.51	4.99–31.81	Zhang et al. (2019)
Walnut oil	1.24–2.88	–	26.95–33.15	–	28.95–37.15	Maguire et al. (2004)
Hazelnut oil	27.9–34.12	–	3.14–9.1	–	31.04–43.22	Maguire et al. (2004)
Almond oil	43.47–44.43	–	1.04–1.46	–	44.51–45.89	Maguire et al. (2004)
Macadamia oil	9.78–14.68	–	–	–	9.78–14.68	Maguire et al. (2004)
Fresh vegetables						
Kale	3.4–5.8	0.06–0.12	0.3–1.3	0.02–0.04	3.78–7.26	Isabelle et al. (2010), Wen Lee et al. (2022)

(continued)

Table 8.1 (continued)

Species	α -tocopherol	β -tocopherol	γ -tocopherol	δ -tocopherol	Total tocopherol (mg/100 g)	References
Spinach	1.3–5.90	0.01–0.014	0.15–4.18	0.005–0.007	1.47–10.10	Chun et al. (2006), Kim et al. (2007), Knecht et al. (2015), Lee et al. (2018), Wen Lee et al. (2022)
Pea shoots	0.86–1.04	0.005–0.007	0.009–0.0143	Trace	0.87–1.06	Wen Lee et al. (2022)
Lettuce	0.22–0.55	0.01	0.11–0.74	–	0.32–1.06	Chun et al. (2006), Cruz and Casal 2013)
Celery	0.26–0.47	0.01–0.018	Trace	Trace	0.27–0.49	Chun et al. (2006), Kim et al. (2007), Knecht et al. (2015)
Chayote leaves	0.6–1.6	0.03–0.13	0.7–2.5	0.1–0.5	0.83–4.73	Wen Lee et al. (2022)
Turmeric leaves	3.6–6.6	0.16–0.26	1.5–3.1	0.08–0.13	5.34–10.09	Wen Lee et al. (2022)
Green Amaranthus	0.14–0.24	0.02–0.35	0.17–0.33	0.007–0.011	0.34–0.93	Wen Lee et al. (2022)
Garlic chives	2.1–2.7	0.09–0.15	0.7–1.1	0.1–0.5	2.99–4.45	Wen Lee et al. (2022)
Cassava leaves	6.9–7.3	0.06–0.1	0.13–0.29	0.002–0.006	7.09–7.67	Wen Lee et al. (2022)
Fenugreek leaves	3.03–3.21	0.014–0.016	0.01	0.01	3.06–3.25	Wen Lee et al. (2022)
Red sweet pepper	2.72–3.78	0.1–0.19	0.03–0.17	0.020–0.04	2.87–4.18	Knecht et al. (2015)
Sweet potato	0.25–0.56	0.01	–	–	0.26–0.57	Chun et al. (2006), Lee et al. (2018)
Eggplant	0.11–0.34	–	0.5–0.7	0.08–0.11	0.69–1.15	Kim et al. (2007)
Bamboo shoot	0.15–0.33	–	0.26–0.53	–	0.41–0.86	Kim et al. (2007)
Soybean sprout	0.11–1.09	–	1.62–3.96	0.15–1.99	1.88–7.04	Kim et al. (2007), Isabelle et al. (2010)
Broccoli	1.22–3.75	0.02–0.03	0.19–0.43	–	1.43–4.21	Chun et al. (2006), Knecht et al. (2015), Lee et al. (2018)
Cabbage	0.07–0.21	–	–	–	0.12–0.69	Chun et al. (2006)

Carrot	0.37–1.30	0–0.02	–	–	0.37–1.03	Chun et al. (2006), Knecht et al. (2015), Lee et al. (2018)
Coriander	5.16	–	0.06	0.007	5.23	Isabelle et al. (2010)
Cauliflower	0.08–0.16	–	0.20–0.44	0.005	0.34–0.61	Chun et al. (2006), Isabelle et al. (2010)
Cucumber	0.03	0.01	0.04	–	0.08	Chun et al. (2006)
Red chili	5.65	–	0.22	0.008	5.88	Isabelle et al. (2010)
Tomato	0.53–1.02	0.04	0.07–0.38	0.03	0.53–1.47	Chun et al. (2006), Knecht et al. (2015)
Fresh fruits						
Apple	0.04–0.38	0.01	0.04	0.01	0.04–0.44	Chun et al. (2006), Kim et al. (2007)
Grape	0.06–0.10	–	0–0.32	–	0.06–0.42	Chun et al. (2006), Kim et al. (2007)
Peach	0.11–0.94	–	0–0.04	0–0.06	0.11–1.04	Chun et al. (2006), Kim et al. (2007)
Plum	0.09–0.39	–	0–0.13	–	0.09–0.52	Chun et al. (2006), Kim et al. (2007)
Avocado	1.33–2.66	0.03–0.08	0.13–0.69	0.03	1.98–3.13	Chun et al. (2006)
Banana	0.3–0.23	–	–	–	0.06–0.24	Chun et al. (2006)
Blackberries	0.69–2.17	0.02–0.06	1.27–1.57	0.52–1.08	2.8–4.68	Chun et al. (2006)
Blueberries	0.37–0.79	–	0.29–0.47	0–0.05	0.74–1.36	Chun et al. (2006)
Cantaloupes	0.04–0.08	–	0.08–0.12	–	0.13–0.19	Chun et al. (2006)
Cranberries	1.03–1.43	–	0.04	–	1.34–1.88	Chun et al. (2006)
Grapefruit	0.1–0.22	–	–	–	0.10–0.24	Chun et al. (2006)
Kiwi	1.28–1.34	–	–	–	1.40–1.50	Chun et al. (2006)
Oranges	0.25	–	–	–	0.25	Chun et al. (2006)
Raspberries, red	0.66–1.04	0.06–0.12	1.06–1.72	0.74–1.56	3.10–3.82	Chun et al. (2006)
Dry fruits						
Walnut	2.87–5.57	0.33	42.73–45.67	4.17–6.31	50.1–57.98	Hejtmánková et al. (2018)
Hazelnuts	76.9–83.7	0.72–0.96	3.01–3.29	0.13–0.35	80.76–88.3	Hejtmánková et al. (2018)
Cashew nut	<0.5	–	6.68–12.42	0.63–0.67	7.31–13.09	Hejtmánková et al. (2018)
Pistachios	3.58–4.86	–	57.69–59.31	0.98–1.14	62.25–65.31	Hejtmánková et al. (2018)
Brazil nuts	14.4–18	–	36.29–49.11	140.1–319.5	190.79–386.6	Hejtmánková et al. (2018)

(continued)

Table 8.1 (continued)

Species	α -tocopherol	β -tocopherol	γ -tocopherol	δ -tocopherol	Total tocopherol (mg/100 g)	References
Macadamia nuts	39.4–47.6	–	17.8–19.55	0.64–0.76	57.84–67.91	Hejtmánková et al. (2018)
Pecans	1.89–11.09	–	10.5–66.9	1.12–4.48	13.51–82.47	Hejtmánková et al. (2018)
Pea nuts	26.4–28.4	–	9.46–12.94	0.56–0.69	36.42–42.03	Hejtmánková et al. (2018)

body system by the liver. However, recently the scientific community devoted more attention toward other tocopherols like γ - and δ -tocopherols, aiming to investigate further their possible antioxidant activity and physiological functions (Wagner et al. 2004; Dietrich et al. 2006; Blair 2018; Zheng et al. 2020). Oils from peanuts, cottonseeds, hazelnuts, almonds, macadamia, and rice brans are other excellent sources of α -tocopherols (Table 8.1). Other edible oils like maize oil, sesame oil, linseed oil, hemp oil, and walnut oil are richer in γ -tocopherol. In general, seed oils are the major sources of tocopherols and vitamin E for the human body. Nevertheless, people obtain significant amounts of tocopherols also through the inclusion of vegetables in their diet.

Among vegetables, leafy vegetables like kale and spinach, or sweet pepper and broccoli are major sources of α -tocopherols. Kale contains 3.4–5.8 mg of α -tocopherol per 100 g fresh weight, while spinach, sweet red pepper, and broccoli contain 1.3–5.9, 2.72–3.78, and 1.22–3.75 mg of α -tocopherol per 100 g fresh weight, respectively. Similarly, spices and condiments like red chili, coriander, turmeric leaves, cassava leaves, and fenugreek leaves are also found to have a higher level of α -tocopherol and with possible applications in diet and pharmaceutical uses as a source of tocopherols. Among fruits, avocado, cranberries, red raspberries, and kiwi (1.33–2.66, 1.03–1.43, 0.66–1.04, and 1.28–1.34 mg/100 g fresh weight, respectively) have relatively high concentration of α -tocopherols. Tree fruits like apple, peach, and plum also contain α and γ -tocopherol but at relatively lower concentrations. Further, a recent study suggested the possibility to use tree fruit leaves as a low-cost source of tocopherols (Wojdyło et al. 2022). These authors studied α -tocopherol content in the leaf of tree fruits like apples, pears, plums, and cherries. The time the leaves were collected, and the species affected the content of tocopherols more than the cultivars. Apricot leaves (203.34–260.86 $\mu\text{g/g}$ dry weight in spring and 23.83–235.62 $\mu\text{g/g}$ dry weight in autumn) had the highest tocopherols content, followed by peach, plum, and apple (Wojdyło et al. 2022). Different dry fruits and nuts are also excellent sources of tocopherols and vitamin E. Hazelnuts, macadamia nuts, and peanuts have a higher proportion of α -tocopherols, whereas walnut, cashew nuts, pistachios, Brazil nuts, and pecans have comparatively higher γ -tocopherols content.

Vegetable oils are also rich in phytosterols. Daily intake of phytosterol varies based on regional and country dietary patterns. For example, within China, total phytosterols intake varies between 257.7–473.7 mg/day in different regions (Wang et al. 2018). Similarly, the Mediterranean diet usually includes phytosterol within the range of 377–550 mg/day due to the inclusion of vegetable oil (olive oil) and a variety of vegetables. The phytosterol content in different edible and vegetable oil, fresh vegetable, and fruits are presented in Table 8.2. Concentration level widely varies as it depends on many factors like species, variety, management practices, environmental conditions, extraction, and analysis method just like for the tocopherols' level.

Rice bran oil contains the highest amount of total phytosterols among the commonly studied edible oils followed by sesame oil (Table 8.2). Rice bran oil total phytosterol concentration ranges between 1230.9 and 2392.58 mg/100 g fresh

Table 8.2 Content range of phytosterols in different plant and plant-derived sources

Species	β -sitosterol (mg/100 g)	Campesterol (mg/100 g)	Stigmasterol (mg/100 g)	Total phytosterol ^a (mg/100 g)	References
Vegetable and edible oils					
Sunflower seed oil	182.4–245.8	13.1–65.73	15.9–41.8	197–440.6	Ayerdi Gotor et al. (2015), Wang et al. (2018), Yang et al. (2019), Xu et al. (2020), Almeida et al. (2020)
Rapeseed (canola oil)	109.1–394.1	46.2–270.79	2.2–25.67	290–673	Yang et al. (2019), Xu et al. (2020), Almeida et al. (2020)
Soybean	165.3–174.89	62.4–96.7	62.81–87.28	100.4–355.67	Wang et al. (2018), Yang et al. (2019), Almeida et al. (2020)
Maize oil	251–540.62	39.6–219.02	22.9–56.72	343.1–743.65	Yang et al. (2019), Xu et al. (2020), Almeida et al. (2020)
Sesame oil	322.73–467.7	41.4–90.4	48.1–86.89	457.01–818.19	Mariod et al. (2011), Wang et al. (2018), Yang et al. (2019), Xu et al. (2020)
Linseed oil	97.3–162	33.1–65.2	16.7–26.5	171–363.5	Wang et al. (2018), Xu et al. (2020)
Rice bran oil	590.8–735.17	20.7–226.43	21.8–132.9	1230.9–2392.58	Wang et al. (2018), Yang et al. (2019)
Peanut oil	136.33–189.12	19.83–41.19	16.33–48.16	243.25–395.9	Maguire et al. (2004), Wang et al. (2018), Yang et al. (2019)
Camelia oil	48.1–50.09	16.5–16.52	22.11–23	91.78–193.5	Wang et al. (2018), Yang et al. (2019)
Olive oil	152.05–185.61	14.31–25.85	7.4–21.13	195.42–380.62	Yang et al. (2019), Almeida et al. (2020)
Walnut oil	66.2–165.23	3–31.53	0.7–32.80	80.6–379.45	Wang et al. (2018), Yang et al. (2019)
Flaxseed oil	133.42–182.16	88.32–142.72	5.03–20.21	406.08–527.38	Yang et al. (2019)
Cottonseed oil	402.8–403.8	43.6–44.2	5.2–5.4	492.4	Mariod et al. (2011)
Grapeseed oil	131.96–161.3	24.04–34.46	31.8–39.74	234.95–312.65	Yang et al. (2019)

(continued)

Table 8.2 (continued)

Species	β -sitosterol (mg/100 g)	Campesterol (mg/100 g)	Stigmasterol (mg/100 g)	Total phytosterol ^a (mg/100 g)	References
Penoy oil	240.27– 277.16	7.02–35.62	0.34–4.8	325.06– 409.32	Yang et al. (2019)
Hazelnut oil	48.5–99.1	2.5–6.67	0.6–3.81	70.0–117.99	Maguire et al. (2004), Wang et al. (2018)
Almond oil	58.2– 207.1	0.7–8.1	0–5.17	109.5– 221.87	Maguire et al. (2004), Wang et al. (2018)
Macadamia oil	45.3– 152.5	2.8–9.2	0.5–3.83	114.1– 177.04	Maguire et al. (2004), Wang et al. (2018)
Fresh vegetables					
Lettuce	29.7	2.5–29.9	0.6–6.2	25.5–50.3	Wang et al. (2018)
Celery	0.6–13.2	1.44–29	0.5–6.0	0.74–38.0	Kaloustian et al. (2008), Han et al. (2008), Wang et al. (2018)
Green pepper	26.4–45.9	3.0–4.9	14.8–26	46.8–79.6	Wang et al. (2018)
Sweet potato	22.4	23.3	15.2	85.7–195.1	Wang et al. (2018)
Eggplant	10.2–19.4	7.1–17.1	1.8–4.4	25.5–50.7	Wang et al. (2018)
Bamboo shoot	53.2–55.6	65.7–71.1	15.7–18.5	147.1–158.3	Wang et al. (2018)
Cabbage	1.5–14.5	0–1.1	0–6.8	6.89–13.4	Kaloustian et al. (2008), Wang et al. (2018)
Carrot	4.8–14	0.99–10.9	0.8–4.8	7.35–26.5	Kaloustian et al. (2008), Han et al. (2008), Wang et al. (2018)
Cauliflower	1.2–6.9	0.2–2.31	0.7–0.56	26.82–27.98	Kaloustian et al. (2008), Wang et al. (2018)
Cucumber	0.5–3.8	0.2–0.9	1.1–2.9	35.0–106.2	Han et al. (2008), Wang et al. (2018)
Onion	3.66–9.4	0.21–0.9	0.028–2.2	1.22–16.4	Kaloustian et al. (2008), Han et al. (2008), Wang et al. (2018)
Radish	3.6–23.4	0.2–1.0	1.4–8.6	6.2–35.4	Wang et al. (2018)
Tomato	2.9–6.6	0.6–7.2	1–1.9	9.6–19.1	Han et al. (2008), Wang et al. (2018)
Fruits					
Apple	0.1	ND	0.3	2.4–3.6	Wang et al. (2018)

(continued)

Table 8.2 (continued)

Species	β -sitosterol (mg/100 g)	Campesterol (mg/100 g)	Stigmasterol (mg/100 g)	Total phytosterol ^a (mg/100 g)	References
Lemon	11.9–18.7	35.8–46.2	6.5–8.1	59.4–79.8	Wang et al. (2018)
Pomelo	1–4.4	19.3–20.3	9.4–16.2	36–40	Wang et al. (2018)
Peach	0.9–11.6	0–0.5	0–1.6	1.0–13.7	Han et al. (2008), Wang et al. (2018)
Plum	0.5–0.7	0–0.2	0–0.2	0.7–0.9	Wang et al. (2018)
Blueberries	0.1–0.3	0.5–1.1	0–0.2	5.9–7.5	Wang et al. (2018)
Kiwi	13.4	1.1	2.0	17.5	Han et al. (2008)
Oranges	8.8–19.6	30.8–43	6.2–9.2	49.0–73.4	Han et al. (2008), Wang et al. (2018)
Strawberries	10.9	0.3	0.2	11.8	Han et al. (2008)

^aTotal phytosterols content is the range of sum of plant sterols reported in the cited manuscript and not the sum of the three phytosterols reported in this table

weight of oil, and β -sitosterol holds the highest share, followed by campesterol and stigmasterol. Sesame, flaxseed, maize, canola, and cottonseed oil contain total phytosterol in the range of 457.01–818.19, 406.08–527.38, 343.1–743.65, 290–673, and 492.4 mg/100 g fresh weight of oil, respectively. All the above-mentioned vegetable oils are rich in β -sitosterol followed by campesterol. Soybean oil which is the most consumed oil in North America contains 100.4–355.67 mg total phytosterols/100 g fresh weight of oil, while olive oil which is one of the main ingredients of the Mediterranean diet contains total plant sterols in the range of 195.42–380.62 mg /100 g fresh weight of oil. Other vegetable oils like sunflower, linseed, camelia, grapeseed oil, and nut oils also contain a significant amount of phytosterols (Table 8.2).

Fresh vegetables and fruits also contribute to the daily intake of phytosterols. They contain a relatively small concentration of plant sterols on a fresh weight basis, however, could play a significant role in human health due to a relatively higher consumption in the human diet compared to vegetable oil. Sweet potato, bamboo shoot, cucumber, green pepper, eggplant, and lettuce are the major phytosterol-containing vegetables (Table 8.2). Sweet potato and bamboo shoots contain 85.7–195.1 and 147.1–158.3 mg phytosterol/100 g of fresh weight, respectively, where campesterol is more abundant followed by the β -sitosterol and stigmasterol. Cucumber, green pepper, eggplant, and lettuce have phytosterol concentrations in the range of 35.0–106.2, 46.8–79.6, 25.5–50.7, and 25.5–50.3 mg/ 100 g of fresh weight, respectively. Other vegetables that are rich in plant sterols are radish, carrot, celery, cauliflower, cabbage, tomato, and onion. Among fruits commonly studied fruits such as lemon, orange, pomelo, kiwi, and strawberries contain a relatively higher amount of total phytosterols. Lemon has 59.4–79.8 mg/100 g fresh weight of total phytosterols, whereas orange, pomelo, kiwi, and strawberries have 49–73.4, 36–40, 17.5, and 11.8 mg/100 g fresh weight of total phytosterols. Other fruits rich in phytosterols are peach, blueberries, apple, and plum.

As mentioned above, several factors could affect the tocopherols and phytosterol content even within species. Genetics is a major component as varieties and cultivars of the same species could contain different levels of tocopherol and phytosterols. Radenkovs et al. (2018) evaluated the by-product of apple processing industries as possible sources of tocopherols and phytosterols and found different α -tocopherol and phytosterol levels in different *Malus* species and varieties. “Bernie Prieks” had higher δ -tocopherols (around 72% of total tocopherols) and total phytosterols. β -Sitosterol was detected in all studied *Malus* species, while other phytosterols were not identified in some species. A wide range of genetic variability on tocopherol composition is being utilized for breeding for the development of varieties with high nutritional oil quality (Rani et al. 2007). Growing environment and crop management are other factors affecting tocopherol and plant sterol concentration. For example, the level of tocopherols in sunflower seed decreased over the production year with higher average air temperature, especially during grain filling time (Ayerdi Gotor et al. 2015). In addition, a negative correlation ($r = -0.61$) has been observed between the tocopherol concentration and temperature during summer (grain filling period). Further, Zhang et al. (2007) found light during germination may have an effect on the tocopherol level in canola oil. Light increased total tocopherols, especially α -tocopherol during seed germination, compared to seeds germinated in dark conditions. In general, total tocopherols increased during germination. Further, interconversion of isomers was also seen; γ isomer changed to the α and disappearance of the δ isomer and appearance of the β isomer after two days of germination also suggest their interconversion. Total phytosterol also increased during germination in rapeseed but was higher in the presence of light than in dark conditions. Increased concentration of α -tocopherol, total tocopherols, and total phytosterols during germination suggest that oil extraction after germination could be a viable option for concentrating such beneficial phytochemicals in the oil fraction, however, there is a depletion of oil reserve during germination, and seedling growth. Shi et al. (2010) also found similar results in soybean seeds. Oil extraction two to three days after the seed soaking increased tocopherol and phytosterol levels in the soybean oil, however, their level decreases five to seven days after soaking.

Seguin et al. (2010) have reported an effect of seeding rate, row spacing, and seeding date on the tocopherols level in soybean. A seeding rate at 40 seeds/m² and wide row spacing (more than 36 cm) resulted in a higher α -tocopherol level in soybean oil. The earlier seeding date resulted in an almost 45% higher α -tocopherol concentration compared to the mid to late-May seeding. Carrera and Seguin (2016) have also mentioned the effect of irrigation and fertilization strategy on the tocopherol levels of edible oil. This suggests that tocopherols concentration in seed oil could vary based on the different management practices and growing environment. The enhanced concentration of tocopherols and phytosterols during the germination process may justify the growing interest of consumers in the consumption of sprouts and microgreens of various species that are considered rich sources of phytonutrients and bioactive compounds (Kyriacou et al. 2016; Di Gioia et al. 2017, 2021). Moreover, several factors like processing, cooking, and method of sample extraction and analysis make a major difference in the tocopherol and phytosterol levels. Naz

et al. (2011) have reported a decrease in the individual and total tocopherol levels (37.9%) during neutralization, bleaching, and deodorization processes, indicating loss of a major portion of tocopherols during oil processing. Improvement in the processing technology is needed to preserve tocopherols in the oil during processing. Heat treatment of the oil also decreases tocopherol levels. For example, higher temperatures and prolonged heating/frying/cooking time degrade tocopherols present in the oil (Kmieciak et al. 2019). However, in the case of vegetables, research has shown a higher level of tocopherols and phytosterols in slightly heated or cooked, or steamed vegetables compared to raw fresh vegetable. For example, higher tocopherols were found in steamed broccoli compared to raw and fresh broccoli (Chun et al. 2006; Kaloustian et al. 2008). This is often related to the increased extractability of the compounds, from steamed/heat treated vegetables, due to cell disruption (Knecht et al. 2015). Lee et al. (2018) compared the effect of different cooking methods (boiling vs. blanching vs. steaming vs. microwave) on the level of tocopherols in different vegetables and found that all cooking methods had higher total tocopherols levels compared to the raw vegetable; however, the effect of cooking methods varies based on the vegetable species. Steaming was better for spinach, blanching for broccoli, microwaving for sweet potato, carrot, mallow, and boiling was better for chard. Kaloustian et al. (2008) compared the phytosterols level before and after cooking (boiling) in different vegetables (cabbage, celery, red carrot, white cauliflower, yellow onion, and red pepper) and found an increase in level in all studied vegetables. Different sample extraction methods also affect the levels of tocopherols and phytosterols measured as different methods differ in their precision and sample extraction procedures (Kaloustian et al. 2008; Almeida et al. 2020). For example, the sample extraction method of acid hydrolysis resulted in a notably higher sterol value compared to alkaline saponification alone (Kaloustian et al. 2008). Different analysis methods were found to differ in their sensitivity to the plant sterol levels present (Péres et al. 2006; Xu 2008; Saini and Keum 2016).

8.4 Tocopherols and Phytosterols Health Effects

Tocopherols are mainly known for their antioxidant properties and their role in reducing cardiovascular and neurodegenerative diseases. The effect of different tocopherols on human health is summarized in Table 8.3. Due to the higher retention in human plasma and tissue compared to other tocopherols, α -tocopherol has higher biological activity, and most of the studies on tocopherols are mainly focused on α -tocopherol and its potential health benefits. Alpha-tocopherol has more prominent antioxidant activity as it contains one or two more electron-donating methyl groups in the chromanol group compared to other tocopherols. It offers protection from lipid peroxidation and various oxidative stresses. An *in vivo* study has shown the antioxidant capacity of tocopherols to be in the following order: $\alpha > \beta > \gamma > \delta$ (Bora et al. 2022). Higher antioxidant activity of the α -tocopherol inside living organisms is possibly due to the hepatic α -tocopherol transfer protein as it only recognizes

Table 8.3 Health benefits of the tocopherols

Tocopherols	Health benefits	References
α -Tocopherol	Antioxidant; neutralization of lipid peroxidation and oxidative stress	Adami et al. (2018), Wallert et al. (2019), de Carvalho et al. (2019), Villalón-García et al. (2022)
	Anti-inflammation	Wallert et al. (2019), Liu et al. (2021b), Schubert et al. (2022), Kopańska et al. (2022)
	Reduced risk of heart and cardiovascular disease	Wallert et al. (2019), Violi et al. (2022)
	Protection against neurodegenerative disease	Elfakhri et al. (2019), Berardesca and Cameli (2021), Zakharova et al. (2021)
	Antitumor activity and lung cancer	Yano et al. (2000), Tam et al. (2017), Fernandes et al. (2018)
	Protection of kidney function	Tasanarong et al. (2009, 2013), Kongkham et al. (2013), Monami et al. (2021)
	Reduced depression and anxiety	Lee et al. (2022)
	Protection of eye function	Engin (2009), Wang et al. (2011), Xin et al. (2016)
	Gene regulation	Fischer and Rimbach (2019), Gugliandolo et al. (2019)
	Improved immune system	Wu et al. (2000), Mojani et al. (2013)
β -Tocopherol	Antioxidant; protection from oxidative stress and lipid peroxidation	Brigelius-Flohé (2006), Azzi (2018)
	Increased immunity	Wu et al. (2000)
γ -Tocopherol	Antioxidant; protection from oxidative stress	Brigelius-Flohé (2006), Jiang et al. (2022)
	Anti-inflammatory activity	Lee and Lim (2019), Liu et al. (2021a), Jiang et al. (2022)
	Protection from cardiovascular disease	Masterjohn et al. (2012)
	Protection against nitrosative stress	Takahashi et al. (2006), Das Gupta et al. (2015)
	Protection against neurodegenerative disease	Pahrudin Arrozi et al. (2020)
	Anticancer	Betti et al. (2006), Smolarek and Suh (2011), Das Gupta et al. (2015), Chen et al. (2017)
	Protection against cognitive decline and dementia	de Leeuw et al. (2020)
	Gene regulation	Toricelli et al. (2013)
	Increased immunity	Wu et al. (2000)
	Protection against asthma	Wagner et al. (2007, 2008)
Protection of kidney function	Tasanarong et al. (2013)	
δ -Tocopherol	Antioxidant activity	Li et al. (2011)
	Anticancer	Betti et al. (2006), Li et al. (2011), Smolarek and Suh (2011), Chen et al. (2017), Blair (2018)
	Anti-inflammatory activity	Smolarek and Suh (2011)
	Increased immunity	Wu et al. (2000)
	Neuronal differentiation	Deng et al. (2015)

α -tocopherol, while they have maximum retention in plasma and tissue levels. In a zebrafish study, de Carvalho et al. (2019) found a reduction in oxidative stress and anxiety induced through caffeine uptake. Similarly, α -tocopherol supplementation protected human spermatozoon from induced oxidative stress (Adami et al., 2018). A study by Wallert et al. (2019) found an inhibition effect of α -tocopherol on ischemia/reperfusion injury-induced oxidative and inflammatory responses, maintaining normal cardiac function. They suggested the use of vitamin E (especially α -tocopherol) as an acute therapy for a patient with myocardial infarction. In addition, α -tocopherol is very helpful against neurodegenerative diseases like Alzheimer's disease. Neuroinflammation and oxidative stress were further found to exacerbate Alzheimer's disease progression (De Felice and Lourenco 2015; Elfakhri et al. 2019). Elfakhri et al. (2019) found a possible curating strategy for Alzheimer's disease through the administration of etodolac and α -tocopherol in a concurrent manner as they found a significant reduction in Alzheimer's disease-related pathology in the brains of mice through the α -tocopherol application. A recent study by Villalón-García et al. (2022) showed a reduction in lipid peroxidation and ROS generation in *PLA2G6*-Associated Neurodegeneration through the application of α -tocopherol. Likewise, α -tocopherol also protected the cultured cortical neurons from oxidative stress and the brain cortex of rats during cerebral ischemia/reperfusion injury (Zakharova et al. 2021). However, at higher concentrations, the antioxidant capacity of the α -tocopherol could decrease (Liu et al. 2021b). β -tocopherol, a close homologous of the α -tocopherol, is not studied much compared with other tocopherols for its health effects. In recent studies, β -tocopherol showed similar antioxidant activity and protection from lipooxidation and oxidative stress, although the efficiency was comparatively lower than α -tocopherol (Brigelius-Flohé 2006; Azzi 2018).

Despite having a good antioxidant capacity, α -tocopherol can not trap reactive nitrogen species, unlike γ -tocopherol which has an unsubstituted C-5 position making it more active to trap relative nitrogen species (Saldeen and Saldeen 2005). Therefore, γ -tocopherol could trap reactive nitrogen species and form 5-nitro- γ -tocopherol which protects the mitochondrial function more efficiently than other tocopherols (Jiang et al. 2022). In addition, Pahrudin Arrozi et al. (2020) found comparative effectiveness of γ -tocopherol to α -tocopherol on the reduction of the amyloid-beta ($A\beta$) and amyloid precursor protein (APP) contents which are higher in Alzheimer's disease patients. Further, γ -tocopherol also reduced mitochondrial permeability as suggested by the reduction in CypD protein and pro-caspase-3 protein expression, which was not seen in the α -tocopherol treatment (Pahrudin Arrozi et al. 2020). de Leeuw et al. (2020) found a positive correlation of γ -tocopherol with the presynaptic protein levels in the elderly human midfrontal cortex, suggesting an important role in preserving cognitive power and preventing dementia problems. A lower presynaptic protein level is generally used to be recognized as a clinical diagnosis of dementia. Supplementation of α and γ tocopherols could help preventing oxidative stress, the reason behind the decreasing level of presynaptic protein levels, thus protecting from dementia and deterioration of cognitive power (de Leeuw et al. 2020). A previous research suggested a better

action against myocardial infarction with the combination of α and γ -tocopherol (Hensley et al. 2004), while Deng et al. (2015) have reported a potential role of δ -tocopherol on neuronal differentiation through the l-type calcium channels.

Tocopherol also helps to protect against cancer cells. Many studies have shown the important role of γ - and δ -tocopherol against cancer cells, however, they did not find conclusive evidence of anticancer activity determined by α -tocopherol (Abraham et al. 2019; Retzlaff et al. 2021). A meta-analysis even shows a potential negative role of α -tocopherol on the effectiveness of chemo and radiotherapy further worsening the survival of cancer patients (Retzlaff et al. 2021). However, many articles have mentioned the effectiveness or lower effectiveness of α and β -tocopherol as inhibitors of cancer cells proliferation compared to the γ - and δ -tocopherol (Galli et al. 2004; Yang et al. 2012; Azzi 2018). Galli et al. (2004) compared α and γ -tocopherol and their carboxy-ethyl-hydroxychroman metabolites on prostate cancer cell proliferation and found that γ -tocopherol and its precursors were more effective in the inhibition of PC-3 growth through the downregulation of cyclin expression. Similarly, Li et al. (2011) did a comparative study of α -, γ -, and δ -tocopherol on inhibiting lung tumorigenesis through a xenograft model. δ -tocopherol was more effective in inhibiting tumor growth possibly through trapping more reactive oxygen and nitrogen species compared to γ -tocopherol while α -tocopherol was ineffective. δ -Tocopherol inhibited oxidative DNA damage and nitrotyrosine formation and further increased apoptosis in tumor cells (Li et al. 2011). Similarly, colon tumor formation was reduced by the dietary supplementation of δ - and γ -tocopherol which also suppressed markers of oxidative and nitrosative stress (Chen et al. 2017). γ - and δ -tocopherols were also effective in preventing breast cancer, while α -tocopherol was ineffective (Smolarek and Suh 2011). Despite several studies have shown the ineffectiveness of α -tocopherol in a cancer-preventing role, Mahabir et al. (2008) have found an inverse relation between α -tocopherol intake and risk of lung cancer. Increasing the intake of α -tocopherol decreased lung cancer risk by 34–54%, through the analysis of epidemiology data from 1088 patients with lung cancer cases. Nevertheless, α -tocopherol succinate has shown antitumor activity. In particular, Fernandes et al. (2018) and Tam et al. (2017) observed antitumor activity of the α -tocopherol succinate against human breast cancer cells, both in vitro and in vivo.

Tocopherols and especially α -tocopherols are involved in many gene regulatory functions (Rimbach et al. 2010; Fischer and Rimbach 2019; Gugliandolo et al. 2019). For example, Gugliandolo et al. (2019) found the modulation effect of α -tocopherol on non-amyloidogenic pathways and autophagy in an in vitro study of Alzheimer's disease. Likewise, α -tocopherol modulates the expression of selective Tumor Necrosis Factor-Alpha-Induced (TNF) genes in primary human aortic cell lines (Ranard et al. 2019). γ -tocopherol also has gene regulatory activities, and it upregulates a transglutaminase 2 (TG2) and its activity and decreases cyclin D1 and cyclin E (Torricelli et al. 2013). In this way, γ -tocopherol helps the inhibition of prostate cancer cells in humans.

α - and γ -tocopherols also protect kidney function. A meta-analysis by Monami et al. (2021) showed a reduction in the incidence of contrast-induced nephropathy

(CIN) after the treatment with α -tocopherol. Another study also found a decrease in rat renal contrast-induced nephropathy with the pretreatment with α -tocopherol (Kongkham et al. 2013). A similar result was also found by Tasanarong et al. (2013) who compared an oral administration of α - and γ -tocopherol with the placebo in patients affected by chronic kidney disease. α -tocopherol was the most effective in preventing contrast-induced acute kidney injury compared to γ -tocopherol, while both are effective against placebo. γ -tocopherols also protect against allergic rhinitis and asthma (Wagner et al. 2007, 2008). Supplementation of γ -tocopherol for four days protected from the inflammatory effect induced by allergen (Wagner et al. 2008).

Tocopherols were also found to protect eye functions as studies have shown the role of vitamin E in the prevention of cataracts and glaucoma (Tanito 2021). Orally administered α -tocopherol protected eyes from ultraviolet radiation-induced cataract in rats, however, this effect was dose-dependent (Wang et al. 2011). Similarly, α -tocopherol application as eye drops was found to prevent ocular oxidative damage improving the ocular stability and efficiency (Xin et al. 2016). According to Pastor-Valero (2013), a lower prevalence of cataracts could be associated with a higher intake of vitamin E (α -tocopherol) and vitamin C through a high consumption of fruit and vegetables following the Mediterranean diet.

The immunoregulatory role of tocopherols has also gained attention. Supplementation of tocopherols increases the function of the immune system, thus reducing the chance of infection, especially in the older population (Lewis et al. 2019). Recently Wu et al. (2000) showed a lymphocyte proliferation capacity of α , β , γ , and δ tocopherols in a mice study. In general, the order of efficiency among the four tocopherol isomers was β -tocopherol \approx δ -tocopherol $>$ γ -tocopherol $>$ α -tocopherol. Similarly, Mojani et al. (2013) reported a lymphocyte proliferation activity of α -tocopherol alone or in combination with mixed-tocotrienols. These studies suggest a potential beneficial role of tocopherols in strengthening the body immune system under different stress conditions.

Phytosterols have several health-promoting activities, including a reduction in blood cholesterol levels, antioxidant, and anti-inflammatory activities, as summarized in Table 8.4. Phytosterols help lowering the total cholesterol and low-density lipoprotein cholesterol (generally regarded as “bad cholesterol”) in blood by reducing their absorption (Lagarda et al. 2006; Trautwein and Demonty 2007; Vezza et al. 2020). The exact mechanism behind the reduction of LDL cholesterol is still under investigation, however, many theories mentioned the precipitation of cholesterol in the presence of added phytosterol and competition for absorption (MacKay and Jones 2011; Chawla et al. 2016). The efficiency of phytosterols in lowering the LDL cholesterol levels in blood plasma is higher when their intake is associated with fat intake, as bile secreted in the presence of fatty food facilitates the fat mixed micelles formation, important for plant sterols absorption (Trautwein and Demonty 2007). The same study revealed that there is cholesterol in the bile that is not completely reabsorbed in the presence of phytosterols and is later excreted in feces. Outside of the micellar phase, cholesterol is not soluble, and forms a co-crystal with unabsorbed phytosterols and they are excreted together. Cholesterol and phytosterol share the

Table 8.4 Health benefits of phytosterols

Health benefits	References
Reduced blood cholesterol level	Li et al. (2018), Reaver et al. (2019), Trautwein and Demonty (2007), Wu et al. (2014)
Anti-obesity activity	Thornton et al. (2011), Li et al. (2018), Masuzaki et al. (2019), Vezza et al. (2020)
Anti-diabetic activity	Ramalingam et al. (2020), Krishnan et al. (2021), Jayaraman et al. (2021)
Antioxidant activity and reduction of oxidative stress	Koc et al. (2021), Lesma et al. (2018), Paniagua-Pérez et al. (2008)
Anti-inflammatory activity	Othman and Moghadasian (2011), Valerio and Awad (2011), Kurano et al. (2018), Teixeira et al. (2021), He et al. (2022)
Anti-atherogenic activity	Nashed et al. (2005), Moghadasian et al. (2016), Ghaedi et al. (2020)
Anticoagulant	Salunkhe et al. (2018), Gogoi et al. (2018)
Anticancer activity	Awad et al. (2007), Jiang et al. (2019), Blanco-Vaca et al. (2019)
Immune system modulation	Paniagua-Pérez et al. (2008), Boukes and Van de Venter (2016), Le et al. (2017), Hu et al. (2017)

same transporter protein and process, there is also a competition for sterols uptake and transportation that contributes to reduce the cholesterol level in the body (Trautwein and Demonty 2007). In a randomized, placebo-controlled study, Reaver et al. (2019) reported a 10.2% decrease in low-density lipoprotein cholesterol (LDLc) through the dietary supplementation of 1.5 g/day phytosterol equivalents. Similarly, an association of lower total cholesterol and LDLc with phytosterol intake was found by Li et al. (2018). They also found a lower-body mass index, waist circumference, and prevalence of overweight/obesity in the population with higher phytosterol intake in their diet. Many other studies have also shown the inverse relationship between phytosterols intake and obesity (Vezza et al. 2020). In a diet-induced obesity mouse model, Thornton et al. (2011) found a lower mass accumulation in a high-fat diet with phytosterols. Masuzaki et al. (2019) also reported a reduced preference for a high-fat diet in mice after phytosterol intake (brown rice-specific *c*-oryzanol) through modulation in striatal dopamine D2 receptor and further changing metabolic function. They described phytosterol as a possible approach to protect against obesity and diabetes. In addition, Jayaraman et al. (2021) found β -sitosterol may play a role in the downregulation of the IKK β /NF κ B and c-Jun-N-terminal kinase (JNK) signaling pathway, which helps to reduce obesity-induced insulin resistance. Daily supplementation of 20 mg/kg of body weight of phytosterols stabilized the level of blood glucose, serum insulin, and marker of oxidative stress in high-fat diet-fed diabetic rats (Krishnan et al. 2021). A similar result was also observed by Ramalingam et al. (2020). Administering daily 15 mg/kg of body weight of β -sitosterol to rats on high-fat feeding for up to 30 days, they found lower plasma glucose and increased levels of insulin.

Further, phytosterols are also found to have antioxidant, anti-inflammatory, anticoagulant, and atherosclerotic properties. A study by Koc et al. (2021) suggests the potential use of β -sitosterol on renal and cardiac necrosis and apoptosis due to the anti-inflammatory and antioxidant properties of phytosterols which further reduce oxidative stress. Paniagua-Pérez et al. (2008) have demonstrated the antioxidant properties of phytosterols and found that β -sitosterol could trap up to 78.12% of free radicals at 250 $\mu\text{g}/\text{mL}$ of phytosterol, through DPPH assay. Lesma et al. (2018) also reported the antioxidant activity of phytosterols, γ -oryzanol, and their conjugates. Anti-inflammatory activity is the other important role of phytosterols. Teixeira et al. (2021) reported the potential anti-inflammatory effect of phytosterol as it reduced TNF- α and IL-6 in inflammation induced by lipopolysaccharide in the macrophages. Another study also found the anti-inflammatory activity of the β -sitosterol in the macrophages through the inactivation of STAT1 and NF- κ B (Valerio and Awad 2011). He et al. (2022) also reported on the anti-inflammatory role of phytosterols, which reduced lipopolysaccharides-induced inflammation of acute lung injury through the activation of the LXRs/ABCA1 pathway. Reduction in IL-6, TNF- α , and MCP-1 levels in the adipose tissue in the mice with obesity-induced chronic inflammation also shows the potential anti-inflammatory activities of phytosterols.

The anti-atherogenic role of phytosterols and their effect on cardiovascular diseases is one of the most discussed and highly controversial topics. Some studies have shown positive effects, while others have shown a detrimental effect on cardiovascular health. Moghadasian et al. (2016) reported a positive effect on atherosclerotic lesion size and severity compared to control when they supplement low-density lipoprotein receptor knockout (LDL-r-KO) mice with a wild rice and phytosterol combination. They attributed the result seen to the decrease in plasma LDL and the increase in fecal cholesterol extraction. Nashed et al. (2005) reported an anti-atherogenic activity of phytosterols and inhibition of proinflammatory cytokine production as a possible pathway for such effect in apolipoprotein E (apoE) deficient mice. apoE is the protein which plays important role in lipid transportation in plasma (Hatters et al. 2006). Further, anticoagulant activities of phytosterols were reported by Gogoi et al. (2018) and they suggested a possible use of soybean-extracted β -sitosterol to prevent thrombosis-associated cardiovascular disorder. There are some studies in which authors have discussed the possible negative effects of phytosterols on coronary atherosclerosis. In particular, a genome-wide meta-analysis by Scholz et al. (2022) revealed a detrimental effect of phytosterols on coronary artery disease (CAD). They found a positive relationship between increased serum phytosterol levels with CAD after performing a Mendelian randomization analysis. Similarly, a study on mice found an increased rate of ventricular arrhythmia, impaired cardiac function, and sudden death with the increased plasma level of phytosterols (Ge et al. 2021). Therefore, further studies, *in vivo* and *in vitro*, are required to better understand the effect of phytosterols on cardiovascular health.

Anticancer properties and immune system stimulation are other possible health benefits of phytosterols. Phytosterols may have a role in reducing cancer through the modulation of proliferation and apoptosis of tumor cells (Blanco-Vaca et al. 2019). Awad et al. (2007) observed a reduction in tumor cell growth and an increase in the transformed cell membrane in human breast cancer cells. They found an increase in

Fas protein level and caspase-8 activity and discussed them as a possible cell signaling pathway in the protection mechanism against a cancer cell. A meta-analysis by Jiang et al. (2019) also revealed an inverse relationship between phytosterols intake and cancer risk. Another commonly discussed health benefit of phytosterols is the stimulation of the immune system. Boukes and Van de Venter (2016) reported phagocytosis and increased innate immune response in the U937 leukemia cells, in vitro study, after the pretreatment with phytosterols extracted from *Hypoxis* spp. Similarly, Hu et al. (2017) also reported an increase in immunity with the phytosterols supplementation in weaned piglets. There was an increase in lymphocyte production in the mice after the administration of phytosterols in the study conducted by Paniagua-Pérez et al. (2008). A study has also shown the immunotherapeutic potential of phytosterols after observing immunosuppression activity of β -sitosterol and stigmasterol in murine cells (Le et al. 2017). Because of their multiple health beneficial effects, nowadays plant sterols have become an important part of the development of functional foods (Poli et al. 2021).

8.5 Conclusions

Tocopherols and phytosterols are plant fat-soluble bioactive compounds which play an important role in the plant physiology, ranging from the protection against oxidative stress to cell membrane stability. Tocopherols are mainly known for their antioxidant activity, while phytosterols are primarily known for their capacity to lower blood cholesterol levels in the human body. Recently, several randomized in vitro and in vivo studies have shown their multiple beneficial effects on human health. As these important bioactive compounds are not synthesized by animals and the human body, the daily recommended intake of these compounds should be fulfilled using plant and plant-derived food sources. Vegetable oil, fresh vegetables, nuts, and fruits are the primary sources of both tocopherols and phytosterols, and their regular inclusion in the diet is recommended, although the same compounds have been also successfully extracted from by-product of agri-food industry or from commonly non-edible plant portions such as the leaves of fruit trees. Considering the proven health beneficial properties of these compounds, more research is needed to identify low-cost widely available sources of tocopherols and phytosterols to enhance their availability at global scale. Further, future research work should focus on the development of plant-based functional food products investigating sustainable biofortification approaches for increasing the level of tocopherols and phytosterols in commonly consumed crops and plant products.

Acknowledgments Contributions of P. Poudel have been supported by the Strategic Networks and Initiatives Program (SNIP) Soil, Plants, and Consumers funded by the Penn State College of Agricultural Sciences. Contributions of F. Di Gioia have been supported by the Food Resilience in the Face of Catastrophic Global Events grant funded by Open Philanthropy and by the USDA National Institute of Food and Agriculture and Hatch Appropriations under Project #PEN04723 and Accession #1020664.

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