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Valorization of Natural Antioxidants for Nutritional and Health Applications

Pedro Ferreira-Santos, Zlatina Genisheva, Claudia Botelho, Cristina Rocha and José António Teixeira

Abstract

The significant increase in the world population age, 47 years in 1950 to 73 years in 2020, resulted in an increase in aging related diseases as well as in degenerative diseases. In consequence, researchers have been focusing in the development of new therapies, with a particular emphasis on the use of compounds with antioxidant properties, namely phytochemicals, such as polyphenols and carotenoids. Several *in vitro* and *in vivo* studies have demonstrated the phytochemicals antioxidant capacity. Their use is broad, as they can be part of food supplements, medicine and cosmetics. The health benefit of antioxidant phytochemicals is an indisputable question. Phytochemical properties are highly influenced by the natural matrix as well as by extraction process, which have a key role. There are several extraction methods that can be applied depending on the chemical properties of the bioactive compounds. There is a wide range of solvents with different polarities, which allows a selective extraction of the desired target family of compounds. Greener technologies have the advantage to reduce extraction time and solvent quantity in comparison to the most traditional methods. This chapter will focus on the different green extraction strategies related to the recovery of antioxidant bioactive compounds from natural sources, their nutritional and health potential.

Keywords: bioactive compounds, antioxidants, green technologies, oxidative stress, health benefits

1. Introduction

Nowadays, the awareness for the need to have a healthier lifestyle results in a higher consumption of natural organic food products and nutritionally rich antioxidants rather than synthetic and processed foods. In the past decade, an increased interest in the exploitation of natural ingredients to be used in the food and food products was observed. Researchers from all over the world are focusing on alternative sources of healthy nutrients promoting a safer and convenient diet. There is not clear evidence that synthetic antioxidants have toxic effects, although, consumer's interest is moving towards the natural products. Moreover, synthetic antioxidants and preservatives in food may lead to lipid peroxidation and deterioration of food flavor and quality [1]. Therefore, organic and sustainable processes, the identification of new phytochemicals with attractive biological activities, such as antioxidant,

anticancer, antimicrobial, among others, are a hot topic among food researchers as well as for food industry aiming to develop new functional and therapeutic products.

Natural antioxidants are mainly derived from food, plants and other living organisms, such as fruits, vegetables, flowers, cereals, mushrooms, macro and micro-algae, spices and traditional medicinal herbs [2]. It is known that exogenous antioxidants have a strong potential to inhibit oxidative stress, preventing the lipid peroxidation process, and restore the cellular homeostasis [3]. Indeed, most of the antioxidant products shown to act as potential therapeutic agents. The consumption of antioxidants is highly important not only in prevention but also as an adjunct in the treatment of various human pathologies associated with oxidative stress, such as diabetes, aging, neurological, cardiovascular, and cancer [4]. In this sense, beneficial health effects of antioxidants are directly linked to regular daily intake and bioavailability.

The issues created by the increase of the human population, together with a reduction in renewable resources, is reflected in the increase of the global demand for reuse of industrial biowastes, as well as increasing the use of underexploited resources. The growing demand for new or alternative bioactive molecules obtained by green and sustainable processes, and decreasing the quantity of biowastes are premises for the development of conscious approaches for the valorization of phytochemicals from natural sources [5, 6]. Additionally, the development and optimization of efficient and intensified process for the recovery and isolation of high value phytochemicals are important.

The current chapter is focused on appreciation of different green extraction strategies related to the recovery of high value bioactive compounds from natural sources, their potential antioxidant activity, and possible nutritional and health applications.

2. Green approach in the extraction of antioxidant compounds

The recovery of antioxidant biomolecules or extracts is an important step to enable the reuse of natural resources for subsequent application in pharmaceutical, cosmetic products, food enrichment and preservatives, supplements and nutraceuticals.

Usually, bioactive phytochemicals are obtained using solid-liquid extraction, the unit operation, and depends on several factors, including the applied extraction technique, the parameters associated with the technique (such as temperature, time, pH and the extraction solvent), and the raw materials composition [7]. Extraction process is composed by 4 essential steps: (1) raw material pre-treatment (drying, grinding, *etc.*) to increase surface contact area and solvent penetration; (2) extraction with appropriated solvent; (3) post-treatment of the obtained liquid extract (filtration, concentration, purification, *etc.*); (4) solvent removal and its reuse [8].

The extraction process, when it is not optimized, is often time and energy consuming, induces the use of huge amount of water or petroleum-based solvents (harmful for environment and consumers) and generates large quantity of waste [9]. Moreover, the resulting extract may not be safe for the consumers, as it may contain residual solvents, contaminants from raw material, or denatured compounds due to extreme extraction conditions [5]. In this sense, the extraction processes intensification/optimization is necessary. The goal of an intensified process is to obtain greater extraction efficiency, high-quality and safe extracts while reducing extraction time, energy consumption, number of unit operations, amount

Extraction technology	Concept	Advantages	Disadvantages	References
Microwave assisted extraction (MAE)	Microwaves are electromagnetic fields in the range of 300 MHz to 300 GHz. The solvent penetrates into the solid matrix by diffusion leading to cell disruption and releasing the compounds of interest from a matrix to a solvent.	Lower time of extraction; low solvent volume; effective, uniform and selective heating.	High extraction pressure might modify the chemical structures of the compounds; low penetration of radiation in bulk products; equipment more expensive.	[5, 19]
Ultrasound assisted extraction (UAE)	Ultrasound is a sound wave of 20 kHz to 100 MHz. This process produces a phenomenon called cavitation, which means that the production, growth, and collapse of the bubbles to form pores that facilitate the cell wall disruption and increased the release of intracellular compounds into the extraction medium.	Fast; low solvent usage; lower extraction temperatures; preserving heat-sensitive compounds; eco-friendly and cheap process.	Energy intensive; difficult to scale up.	[20, 21]
Pressurized liquid extraction (PLE)	This technology is based on the use of liquid solvents at temperature and pressure values above the atmospheric boiling point and below the critical point values, decreasing the viscosity of the solvent, promoting accelerated dissolution kinetics, and increasing the solutes' solubility. The process disrupts the matrix, which increases the mass transfer of the analyte from the solvent sample	Rapid extraction; reduced organic solvent consumption.	Requires sophisticated instrumentation; possible degradation of thermolabile compounds.	[22, 23]
Supercritical fluid extraction (SFE)	Supercritical extraction is characterized by changes in temperature and pressure which transform the gas in supercritical fluid.	Fast; selective extraction; no residual solvents.	High cost; energy intensive; low polarity; type of co-solvent affects the efficiency of the extraction of antioxidant compounds.	[23, 24]
High hydrostatic pressure (HHP)	This technology applies very high pressures (100–1000 MPa) at 0 °C to less than 100 °C for a short period of time. Improves mass transfer rates and increases the secondary metabolite diffusion according to phase transitions.	Time efficient, requires less solvent, convenient, eco-friendly, safe and energy efficient; does not generate waste; pure and microbiologically safe products; absence of heating, avoiding compound denaturation and ensuring the extraction of thermo-sensitive components.	Variable efficiency; high processing costs.	[25–28]

Extraction technology	Concept	Advantages	Disadvantages	References
Enzyme assisted extraction (EAE)	The matrix and enzyme solution are loaded into an extraction vessel and placed in a thermostated water bath at the certain temperature and time.	Moderate extraction conditions; eco-friendly; selectivity due to the specificity of enzymes.	Expensive cost of enzymes; activity of enzymes varying with the environmental factors; filtration and cleanup step required; time consuming.	[3, 7, 23]
Pulsed electric field (PEF)	The material is placed between two electrodes. The pulse amplitude varies from 100–300 V/cm to 20–80 kV/cm. The treatment is conducted at room temperature or slightly higher. The principle of PEF extraction is to induce the electroporation of the cell membrane, thereby increasing the extraction yield.	Improves extraction and diffusion; cell permeability; minimize loss of heat sensitive molecules; selectivity of extracted compounds.	High control of parameters associated with the process (energy input, strength, pulses, temperature, and raw material properties, <i>e.g.</i> conductivity).	[5, 9, 29, 30]
High voltage electrical discharges (HVED)	It is an effective method to damage the cell structure and the extraction of valuable cellular compounds. The first step is the formation and propagation of a coil of a needle electrode and the formation of gaseous cavities. The second stage occurs when the streamer reaches the electrode plate (phase decomposition).	Efficiency of cell destruction; low solvent consumption; low operating temperature and temperature rise.	Free radicals production, which can react with antioxidant compounds, thus decreasing their bioactivity; lower selectivity; scale-up difficulties.	[19, 22, 31]
Ohmic heating (OH)	Non-pulsed electrotechnology centered on the conversion of electric energy into thermal energy based in the Joule effect (heat is generated inside a conductive matrix). The voltage applied in the OH process normally varies between 400 and 4000 V (electric field from 0.001 to 1 kV/cm).	Fast and homogeneous heating; reduction of energy consumption and times; low water and organic solvents use; low waste generation; selectivity of extracted compounds; improves extraction and diffusion by cell permeability.	High control of parameters associated with the process (similar to PEF and HVED).	[9, 32, 33]

Table 1.
Green technologies for the extraction of antioxidant compounds from natural sources.

of water and organic solvents in the process, environmental impact, economic costs and quantity of waste generated [8].

In the last decades, the growing interest in the global ecological footprint reduction, bioeconomy control and consumer safety, has propelled the implementation of innovative and clean alternatives in the food, chemical, cosmetic and pharmaceutical industries, following the principles of green chemistry and green engineering [10, 11].

Among the various extraction factors, solvents play an important role in extraction efficiency. The reduction of hazardous solvents is also considered one of the priorities of international policies [12]. A suitable solvent is able to obtain safe and high-quality ingredients and to preserve the biological effects of the extracted compounds. Furthermore, it should be recyclable and reusable, preventing negative environmental effects.

Numerous solvents have been used for the extraction of antioxidants from foods, marine sources, medicinal plants and agroindustrial wastes [6]. The selection of solvents must be based on the chemical nature and polarity of the compounds to be extracted, since solvents with different polarities are necessary for the isolation of compounds with different chemical structure [5]. For example, most of the phenolics, flavanoids and anthocyanins are hydrosoluble antioxidants. The polar and medium polar solvents, such as water, ethanol, methanol, propanol, acetone and their aqueous mixtures, are widely used for their extraction [13–15]. Carotenoids are lipid-soluble antioxidants, and common organic solvents, such as the mixtures of hexane with acetone, ethanol, methanol, or mixtures of ethyl acetate with acetone, ethanol, methanol, have been used for extraction [16–18].

A number of new alternatives to conventional techniques (Soxhlet, heat reflux, infusion, distillation, *etc.*), have been proposed to extract target antioxidant compounds from various natural matrices. **Table 1** presents a summary of the concept, the many benefits of some innovative extraction technologies as well as challenges associated with its use in the recovery of antioxidant molecules.

In the following sections some examples of natural matrices used as sources of antioxidant compounds using clean and innovative processes will be reported.

3. Natural sources of antioxidants

Fruits and vegetables are highly recommended dietary contents, widely known for their health-promoting effects and nutritious values. They got an essential place as conventional foods in the history because of their high amount of minerals, specifically electrolytes; vitamins, mainly vitamins C and E. Several studies are also demonstrating their high phytochemical contents with antioxidant properties. Antioxidants obtained from plants, vegetables and fruits are mostly of terpenes, polyphenols, phytosterols, peptides, vitamins and minerals (**Figure 1**) [34, 35]. Antioxidant minerals, such as iron, zinc, selenium, copper, and manganese, act as cofactor of many antioxidant enzymes, absence of which may certainly disturb the activity of their enzymatic scavenging activity [2].

It has been argued that agri-food residues generated by the use of plants and their derivatives might have a negative impact on the environment when they are discarded. In developed countries, 42% of food waste is produced by households, while 39% losses occur in the food manufacturing industry, 14% in food service sector and remaining 5% in retail and distribution [36]. Waste from parts of plants such as peel, leaves, stem, seed, and roots generated from agriculture, to industrial manufacturing and processing [2]. They constitute a low-cost source of antioxidant molecules, which exhibit other biological activities, like antidiabetic, anti-obesity, antihypertensive, anticancer, and antimicrobial [13, 37, 38].

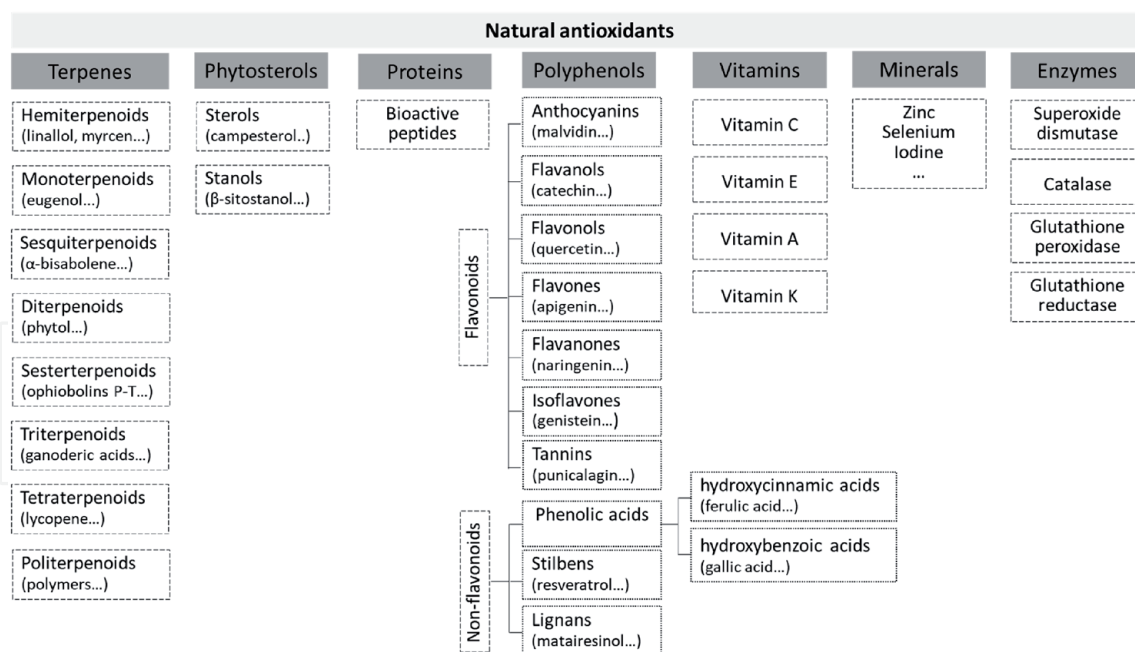


Figure 1.
Classification of natural antioxidants.

Marine biodiversity is another underexploited source of natural products. Marine resources are gaining the attention of industries such as foods, pharmaceuticals, nutraceuticals, and cosmetics because they have several interesting antioxidant molecules and other attractive biotechnological compounds (*e.g.* polysaccharides, pigments, proteins, *etc.*), making these resources a profound and renewable source to investigate novel molecules. Currently, more than 30000 structurally diverse secondary metabolites have been isolated from marine sources [39].

Algae are considered the richest source of active compounds with antioxidant activity (and other biological activities). They can be used as nutraceuticals, food additives and cosmetics. Algae are composed by a complex group of photosynthetic organisms with simple reproductive organs, which can be multicellular, known as macroalgae or seaweeds, and unicellular named as microalgae [40]. Algae produce various secondary metabolites with many antioxidant activities such as pigments (phycobiliproteins, chlorophylls and carotenoids), polyphenols (bromophenols, flavonoids, phlorotannins and phenolic acids), vitamins (β -carotene and other carotenoids), a complex of B vitamins (B1, B2, B3, B5, B6, B7 and B12), vitamin C (ascorbic acid), vitamin D and vitamin E (α -tocopherol) [40, 41]. Sulfated polysaccharides are nonanimal compounds reported to have antioxidant activities, which can be obtained from marine algae and other marine organisms from the phaeophyta group [42]. These compounds may be used as hydrocolloids and as nutraceuticals in the food industry.

Iodine (an important mineral from seaweeds), is a key element for hormones related with the thyroid, helping in the metabolism regulation [43].

Marine sponges (family Aplysinellidae) are recognized as producers of bromotyrosine derivatives, displaying a myriad of biological and pharmacological potentialities [39]. Many biological compounds previously isolated from some other marine organisms such as fish, crustaceans, and their by-products present bioactive potential.

For the past few decades, researchers and industry have been focusing their work on the use of by-products or biowastes to obtain products with high added value, using innovative and environmentally friendly processes. These products can be used as (bio)functional additives, or as a therapeutic alternative in the prevention or treatment of cardiometabolic, cancer and neurodegenerative diseases [40, 42, 44, 45].

Sources	Compounds	Technologies (Solvents)	Bioactivities	References
<i>Plants and by-products</i>				
Passion fruit peel	Carotenoids Pectin	MAE,UAE (water, Olive oil sun flower oil)	Antioxidant Antimicrobial Anticancer	[46, 47]
Vine pruning	Polyphenols	OH, MAE, (water, ethanol)	Antioxidant Anticancer	[48, 49]
Grape skins	Anthocyanins Polyphenols	OH, MAE, UAE, EAE, PLE (water, eutectic solvents)	Antioxidant	[50–55]
Colored potato	Anthocyanins	OH (water)	Antioxidant Antimicrobial Anticancer Neuroprotective	[15]
Pine bark	Polyphenols	OH, MAE, UAE, SFE (CO ₂ , water, ethanol)	Antioxidant Anticancer Antimicrobial Antihyperglycemic	[13, 56–58]
Pine nuts	Polyphenols	PLE, UAE, MAE (water)	Antioxidant	[59]
Soy beans	Proteins Isoflavones	EAE, UAE, PLE (eutectic solvents, ionic liquid, water, methanol)	Antioxidant Cardioprotective Anticancer	[60–63]
Mentha	Polyphenols Essential oil	UAE, SFE, MAE, OH (water, ethanol, methanol)	Antioxidant	[64–66]
Tomato by-products	Polyphenols Pectin Fatty acids Carotenoids	MAE, HHP, UAE, PEF, SFE, EAE (hexane, methanol, acetone, ethyl lactate)	Antioxidant Cardioprotective Antihypertensive Antidiabetic Anticancer	[67–71]
Apple peels	Pectin Polyphenols	UAE, SFE (water)	Antioxidant	[72, 73]
Apple seeds	Essential oils polyphenols	PFE, UAE, SFE (CO ₂ , water)	Antioxidant	[74–76]
Brewer's spent grains	Polyphenols, proteins	PEF, UAE, SFE (water, ethanol)	Antioxidant	[77–79]
Orange peel	Pectin Polyphenols	PEF, MAE (citric acid)	Antioxidant	[37, 80]
Moringa leaves	Polyphenols Vitamin C	PLE (water)	Antioxidant	[81]
Rapeseed oil, Guava oil,	Phytosterols, Polyphenols Tocopherols	SFE (CO ₂ , Euctetic solvents)	Anticholesterolemic Antioxidant	[82, 83]
Roselle seeds Black sesame seeds	Phytosterols	SFE (CO ₂ , ethanol)	Anticholesterolemic Antioxidant	[84, 85]
<i>Microalgae</i>				
<i>Spirulina platensis</i>	Polyphenols Carotenoids Phycobiliproteins	OH; MAE; PEF; UAS; EAE (water, ethanol)	Antioxidant Antimicrobial Anticancer Anti-inflammatory	[86–95]
<i>Heterochlorella luteoviridis</i>	Carotenoids Lipids	OH; UAE (ethanol)	Antioxidant Anti-inflammatory	[96, 97]

Sources	Compounds	Technologies (Solvents)	Bioactivities	References
<i>Chorella vulgaris</i>	Carotenoids Polyphenols	PEF; SFE (CO ₂ , Water, water: ethanol)	Antioxidant Antimicrobial Anticancer Anti-inflammatory	[98–101]
<i>Nannochloropsis</i> spp	Carotenoids Chlorophylls Polyphenols Proteins Lipids	UAE; PEF; PLE (water, ethanol, dimethyl sulfoxide)	Antioxidant UV-protective Anti-inflammatory Anticancer	[102–104]
<i>Phaeodactylum tricornerutum</i>	Proteins Pigments Lipids Carotenoids Chlorophylls Polyphenols	HVED; HHP; PLE, MAE (water, ethanol, chloroform: methanol)	Antioxidant	[17, 105]
<i>Neochloris oleoabundans</i>	Carotenoids	PLE (ethanol)	Antioxidant	[106]
<i>Macroalgae</i>				
<i>Gracilaria</i>	Sulfated polysaccharides	Maceration by liquid nitrogen (sodium acetate buffer)	Antioxidant	[42]
<i>Laminaria ochroleuca</i>	Fatty acids Polyphenols	PLE (hexane, ethyl acetate, ethanol and ethanol:water)	Antioxidant Anti-atherogenic	[107]
<i>Ascophyllum nodosum</i> <i>Laminaria japonica</i> <i>Lessonia trabeculate</i> <i>Lessonia nigrescens</i>	Polyphenols	MAE (70% methanol)	Antioxidant Anti-hyperglycemic	[108]
<i>Fucus serratus</i> <i>Laminaria digitata</i> <i>Gracilaria gracilis</i> <i>Codium fragile</i>	Polyphenols	PLE (water, ethanol/water, and methanol/water)	Antioxidant Antiproliferative	[40, 109]
<i>Palmaria palmata</i>	Proteins Peptides	EAE (water)	Antioxidant Cardioprotective Anti-inflammatory Anti-diabetic	[110, 111]
<i>Gelidium pusillum</i>	Phycobiliproteins	UAE (phosphate buffer)	Antioxidant Anticancer Anti-inflammatory	[112, 113]

MAE, Microwave assisted extraction; UAE, Ultrasound assisted extraction; PLE, Pressurized liquid extraction; SFE, Supercritical fluid extraction; HHP, High hydrostatic pressure; EAE, Enzyme assisted extraction; PEF, Pulsed electric field; HVED, High voltage electrical discharges; OH, Ohmic heating.

Table 2.

Green processes for antioxidants recovery from some plants, algae and by-products.

Table 2 shows some examples of bioactive molecules from natural sources (plants and their by-products and algae), as well as the type of technologies and solvents used in the extraction process.

Currently, phytochemicals are being used in several commercial applications, like nutraceuticals, food supplements, cosmetic products, food coloring agents, among others. As an example *Moringa Olifeira* extract is widely used in cosmetics or bath cosmetics [114]. Pycnogenol[®] is trade mark for the French pine bark extract, which is used as a food supplement with antioxidant properties [115]. Curcumin (Biocurcumax[®], BCM-95[®] CURCUGREEN[®]) is used as coloring agent for food and cosmetics, as well as a nutraceutical [116].

Multiple cosmetics companies use algae extracts and compounds in their formulations, as an active agent, or a moisturizer, excipient, gelling, thickening, dyes, pigments, preservatives, additives, aroma or fragrance agents. For example, *Gracilaria* species extracts are integrated into various commercial cosmetics, such as hydrogel soap from Sealaria[®] (Kfar Hess, Israel), facial mask by Balinique[®] (Miami, FL, USA), and hydrating cream by Thalasso[®] (Rosa Graf, Stamford, CT, USA). The *Chondrus crispus* extract enriched in sulphated polysaccharides, Gelcarin[®] (Dupont Nutrition and Biosciences, Wilmington, DEL, USA), to be used in various cosmetic products as gelling, thickener and stabilizer agent [43].

β -Carotene was the first high-value product commercially produced from a microalga *Dunaliella salina* with production starting in the 1980s by four producers—Koor Foods (Nature Beta Technology) in Israel, Western Biotechnology Ltd. and Betatene Ltd. in Australia, and Nutralite in the USA [117].

3.1 Enzymes

Antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are considered to be, the first line defense in the cells against reactive species like superoxide radical ($\cdot\text{O}_2$). SOD, CAT and GPx are indispensable in the antioxidant defense of the body [118]. SOD is an endogenous enzyme and the most powerful antioxidant in the cell. As a metalloenzyme SOD requires a metal cofactor for its activity (iron, zinc or copper). It catalyzes the conversion of two molecules of $\cdot\text{O}_2$ to hydrogen peroxide (H_2O_2). The level of superoxide dismutase decrease with the age. Moreover, the SOD deficiency was connected to a number of pathologies in both animals and humans. The daily intake of SOD supplement protect the immune system and slow down aging process. CAT is highly efficient antioxidant enzyme, located primarily in the peroxisomes but absent in mitochondria of mammalian cells. It catalyzes the reduction of H_2O_2 to water and molecular oxygen, completing the process initiated by SOD. In the mammalian mitochondria cells, where the catalase is absent, the breakdown of the hydrogen peroxide to water and oxygen is carried out by another enzyme the GPx. GPx is an intracellular enzyme, and its activity depends on the micronutrient cofactor selenium [118]. Cabbage, brussels sprouts, and broccoli are natural sources of these enzymes [118].

3.2 Proteins and peptides

The protein role in the antioxidant defense system is a result of their direct action as precursors of intracellular formation of glutathione [119]. The antioxidant potential of fruit and vegetable juices and grain products is comparable to the antioxidant potential of milk [119]. Plant proteins are considered the new source of antioxidant peptides [120]. Soy milk is soybean-derived product rich in bioactive peptides and isoflavones. It is one of the most popular milk-substitutes for individuals with lactose-intolerance [121]. Other known plant protein drinks substitutes of cow milk are rice milk and almond milk.

Bioactive peptides are present in many fermented and functional foods. The bioactive peptides usually have between 2 and 20 amino acids residues and exercise

their activities only after being released from the main protein. Bioactive peptides can display different activities, e.g. antihypertensive, antioxidant, immunomodulatory, anti-inflammatory or antimicrobial, depending on the sequence and amino acid composition [122]. Agroindustrial by-products and wastes are being used as a source of bioactive peptides. Tomato seeds, containing 28% of protein, were subjected to fermentation to obtain different size of peptides [122]. Many times in fruit processing the main generated waste is the fruit stone. The alternatives for reutilization of these type of waste are few (as fertilizers or fuels). The cherry fruit stone contain high values of protein (up to 39%), and is considered a cheap source for production of bioactive peptides [123]. The obtained peptide fractions had high antioxidant or antihypertensive activities [123]. Phycobiliproteins are water soluble protein found in Rhodophyta (red algae), Cyanobacteria (*Spirulina*), and Cryptophyta (**Table 2**). These proteins are well known for their strong antioxidant and free-radical scavenging activities [124]. Phycobiliproteins are divided in three classes phycoerythrin, phycocyanin and allophycocyanin. These proteins constitute up to 60% of the total soluble cellular protein in microalgae [125]. Phycobiliproteins have high commercial value as natural colorants in the nutraceutical, cosmetic, and pharmaceutical industries [124].

Other wastes like, peel, leaves, stem, seeds and roots are generated during harvesting, post-harvesting or processing of plants. These wastes are low-cost source of antioxidant molecules like terpenes, polyphenols, phytosterols and peptides that can exhibit different biological activities including antidiabetic, anti-obesity, antihypertensive, anticancer, antiviral and antibacterial [126].

3.3 Terpenes

Terpenes also known as terpenoids or isoprenoids are antioxidant molecules formed by the condensation of two subunits of isoprene (C_5H_8). Moreover, the terpenes are classified on the basis of the number of isoprene units (**Figure 1**). Terpenes are the main constituents of essential oils (up to 90%) and are very diverse in structure and compounds. Carotenoids are a class of natural lipid-soluble pigments that are responsible for the red, yellow, and orange colors found in various plants and microorganisms. Carotenoids are tetraterpenes (C-40) classified in two groups xanthophylls (lutein, zeaxanthin, and β -cryptoxanthin) and carotenes (α -carotene, β -carotene, and lycopene). Carotenoids are beneficial for humans and animals demonstrating antioxidant, antidiabetic, antihypertensive, anti-inflammatory and anticancer activities [33, 127–129].

3.4 Polyphenols

Polyphenol compounds are secondary metabolites produced in plants as a response to different stress conditions. Nowadays more than 8,000 polyphenols are known and more than a half correspond to the group of flavonoids. The main structure of the phenols is the benzene ring with different OH radicals. According to their chemical structure phenolic compounds can be divided in two major groups flavonoid and non-flavonoid. The non-flavonoid group includes the phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids), stilbenes and lignans. The anthocyanins, flavanols, flavonols, flavones, flavanones, isoflavones and tannins are flavonoids [5].

Flavonoid consumption is associated with a reduced risk of coronary heart disease, stroke and cancer. Rich sources of polyphenol compounds in nature are fruits and vegetables, cereals, chocolate, olive oils and beverages such as tea and wine (**Table 2**). Polyphenols are known for their strong antioxidant properties [5].

The strength of their antioxidant activity depends on their interaction with other molecules. For example the absorption of polyphenols in human body is enhanced when there is no sugar molecules attached with them. This means that tea polyphenols have higher absorption than fruit polyphenols because of the high sugar content. Normally from the total consumed amount of polyphenol only 15% -20% are absorbed in the human blood [2]. Moreover, studies demonstrated that the addition of milk to tea, a habit common in the United Kingdom, reduces the absorption of flavonols and diminish their antioxidant effect [130].

3.5 Vitamins

Vitamins obtained from fruit and vegetables also act as antioxidants. Examples are vitamin C and vitamin E. Vitamin C, that is ascorbic acid is powerful antioxidant found in citrus fruits and vegetables such as oranges, lemons, as well as tomatoes. Vitamin E is a fat-soluble vitamin found naturally in lipid-rich fruits and vegetables, such as olives, sun flower, and nuts [2].

3.6 Phytosterols

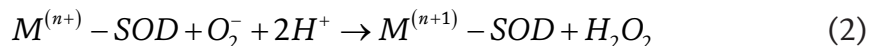
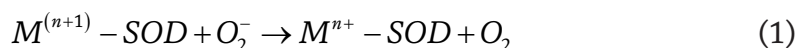
Phytosterols are natural bioactive compounds belonging to the group of triterpenes. Humans must obtain phytosterols from plant-derived foods, such as nuts, seeds, cereals and legumes, vegetable oils, soybean oil, and sunflower oil (examples in **Table 2**) [126]. The most important and abundant phytosterols are β -sitosterol (carbon structure C-29), campesterol (C-28), and stigmasterol (C-29) [126, 131]. Phytosterols have chemical structures and functions similar to cholesterol, but differ from it by an extra methyl or ethyl group at C-24 or a double bond at the C-22 position [132]. Because of the similarity in the structure, phytosterols can reduce cholesterol absorption in the small intestine and thus decreasing blood cholesterol levels. Additional known bioactivities of the phytosterols are anticholesterolemic, antidiabetic, hepatoprotective, anticancer, antioxidant, antimicrobial and anti-inflammatory [131, 133].

4. Antioxidant actions of phytochemicals

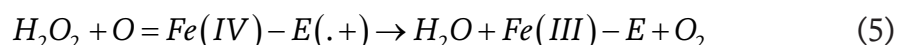
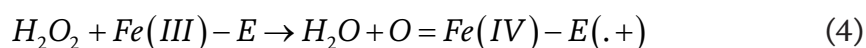
4.1 *In vitro* evidence

Oxidation is a natural phenomenon of human cells. Several important biological processes need reactive oxygen species (ROS) like superoxide radicals, hydrogen peroxide, hydroxyl radicals and singlet oxygen [134, 135]. Without them, protein phosphorylation, activation of transcriptional factors, apoptosis or cell differentiation would not occur. The problem lays on the formation/degradation imbalance of ROS and/or reactive nitrogen species (RNS) [134, 135]. The cell has intrinsic mechanisms to protect itself from excess of ROS/RNS, but only to an extent. If the threshold levels are overcome, cellular structures can be damaged like protein [134–136], lipids [134, 135, 137], polysaccharides [134, 135, 138] and nucleic acids [134, 135, 139]. Several cell mechanisms of defense against oxidative stress have been described in the literature [140, 141]. These mechanisms can be divided into enzymatic and non-enzymatic. SOD, CAT, GPx, Thioredoxin (TRX), Peroxiredoxin (PRX), Glutathione transferase (GST) are endogenous enzymatic mechanisms, while All trans retinol 2 (Vitamin A), Ascorbic acid (Vitamin C) and α -Tocopherol (Vitamin E) are non-enzymatic endogenous antioxidant mechanism [141]. SOD catalyzes the dismutation of the superoxide anion free radical into molecular oxygen

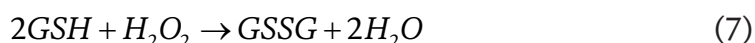
and hydrogen peroxide [141, 142] (Eqs. (1) and (2)). As described by Younus [142] this reaction is accompanied by an alternate oxidation–reduction of the metal ions present in the active site of SOD.



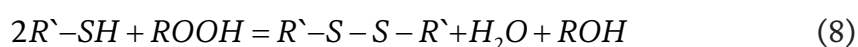
CAT can use iron or even manganese as a cofactor for its enzymatic reactions that will lead to the degradation or reduction of hydrogen peroxide to water molecules and oxygen. This enzyme competes the detoxification process that SOD initiated (Eqs. (3)-(5)) [118, 143, 144].



GTPx encompasses two independent reactions, the first one is the reduction of the enzyme by a hydroperoxide (Eq. (6)) followed by the oxidation to GSH [145].



Trx system is composed by Trx and thioredoxin reductase and NADPH. It is described that Trx uses cysteines at position 32 and 35 for the enzymatic reaction. In the first reaction (Adenosine monophosphate + sulfite + thioredoxin disulphide = 5'-adenylyl+thioredoxin) [141, 146] the N-terminal cysteine of Trx acts on the disulphide bond of the substrate protein, leading to the formation a mixed disulphide bond between Trx and the substrate protein. Following the reaction to the C-terminal cysteine of Trx on the intermediate intermolecular disulphide bond, which will form in a disulphide bond in the oxidized Trx and the breakdown of the disulphide bond in the reduce substrate (Adenosine 3',5'-bisphosphate + sulfite + thioredoxin disulphide = 3'-phosphoadenylyl sulphate+thioredoxin) [141, 146]. PRX are antioxidant enzyme with the ability to reduce hydroperoxides, organic hydroperoxides and peroxyxynitrite using Trx as electrons donor (Eq. 8) [141, 147].



The presence of ROS initiates an autocatalytic chain lipid peroxidation of polyunsaturated acids, which leads to the formation of toxic electrophilic species and free radicals. This reaction may lead to the increase of 4-Hydroxynonenal (4HNE).

GST catalyze conjugation of lipid aldehydes like 4HNE, with GSH are the major defense against oxidative stress-induced cytotoxicity (Eq. (9)) [141, 148].



It is not clear if oxidative stress is the onset of degenerative diseases [149], but it is well known that it plays a significant role in their progression, like in the case of Alzheimer's disease or vascular dementia [150]. Oxidative stress is also involved in other diseases like cancer [151, 152], cardiovascular diseases [153], metabolic disorders [154], and even on aging [149, 155]. Therefore, it is necessary to lower the ROS/RNS concentration inside the cell to minimize the effect. Antioxidants can act by different chemical mechanism: hydrogen atom transfer (HAT), single electron transfer (SET) and the ability to chelate transition metals.

Most of the commercially available anti-inflammatory and antioxidant medication present side effects [156], therefore the interest in natural antioxidants has grown considerably for the past years, being the phytochemicals a group of interest.

The characterization of molecules with antioxidant potential is complex, due to the inherent complexity of the oxidative reactions that occurs in cells [156]. There are several methods to determine the antioxidant potential of a particular substrate. **Table 3** describes some of the chemical *in vitro* methods.

The chemical characterization of phytochemicals in terms of their antioxidant capacity is only the first step. It is necessary to perform a second screening using *ex vivo* models, like LDL-cholesterol assay [165, 166], supercoiled plasmid pBR322 DNA Model [166], Haemolysis inhibition assay [167], 2',7'-dichlorofluorescein diacetate (DCFH-DA) [168].

Several studies have been made regarding the antioxidative properties of phytochemicals, as an example Ferreira-Santos *et al.* [13] demonstrated that the presence of phytochemicals in *Pinus* bark has antioxidant properties. It has been shown that extracts of *Moringa oleifera* leaves significantly reduced the ROS production inducing by H₂O₂ in HEK-293 cells [169]. Dilworth *et al.* presented similar results, it was demonstrated that the presence of *Moringa oleifera* extract results in a significant decrease of the ROS in HL60 cells after an oxidative insult [170]. Soybean peptide also demonstrated similar results, where HepG2 cells in the presence of this compound resulted in a significant decrease on ROS [171]. These are a few of the several studies that demonstrate the high potential of phytochemicals.

The third step is to evaluate these molecules *in vivo*. Pre-clinical tests using animal models and human clinical studies are required.

4.2 *In vivo* evidence

In the literature there are extensive studies regarding phytochemicals impact human health, particularly on the prevention of cardiovascular, metabolic, neurodegenerative and cancer diseases.

4.2.1 Cardiovascular and metabolic diseases

Cardiovascular diseases are associated with a multiple risk factors like hypercholesterolemia, hypertension, smoking, diabetes, poor diet, stress and physical inactivity. Usually, vegetables like spinach, citrus fruits, soybean oil, sprouts, peppers, cereals, spices, whole grain, honey, walnuts and black tea can significantly increase the hepatic antioxidant enzymes reduces the risk of cardiovascular diseases. Some

Method	Description	Determination	References
2,2-diphenyl-1-picrylhydrazyl (DPPH)	DPPH is a stable free radical that in contact with a substrate that can donate a hydrogen bond forms a non-radical molecule Diphenylpicrylhydrazine. Scavenging activity mechanism.	Colorimetric	[1]
2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS)	In the presence of antioxidant ABTS ⁺ is reduced to ABTS resulting in a decrease in color. Scavenging activity mechanism.	Colorimetric	[157, 158]
O ₂ ⁻ scavenging activity	This assay is optimized for enzymatic antioxidants and relies on the competition kinetics of O ₂ ⁻ reduction of cytochrome C (probe) and O ₂ ⁻ scavenger (sample). Not suitable for non-enzymatic antioxidants. Scavenging activity mechanism.	Fluorescence	[1]
H ₂ O ₂ scavenging activity	A common assay that claims to measure H ₂ O ₂ scavenging capacity of dietary antioxidants uses horseradish peroxidase to oxidize scopoletin to a nonfluorescent product. In the presence of antioxidants the oxidation is inhibited. Scavenging activity mechanism.	Fluorescence	[1]
Ferric ion reducing antioxidant power (FRAP)	It is based on the ability of antioxidants to reduce ferric iron. The molecule 2,3,5-triphenyl-1,3,4-triazole-2-azoniacyclopenta-1,4-diene chloride (TPTZ) is reduced to the ferrous form at a low pH. This reduction will result in a color change. Reducing power mechanism.	Colorimetric	[158, 159]
Cupric ion reducing antioxidant capacity (CUPRAC)	bis(neocuproine)copper(II) chloride (Cu(II)-Nc) chromogenic oxidizing agent can react with a polyphenol. The reactive Ar-OH from the polyphenol are oxidized to quinones and Cu(II)-Nc reduced to a highly colored Cu(I)-Nc chelate.	Colorimetric	[158, 160]
Oxygen radical absorbance capacity (ORAC)	Assay is based on the oxidation of a fluorescent probe by peroxy radicals by way of a hydrogen atom transfer (HAT) process. Peroxy radicals are produced by a free radical initiator, which quenches the fluorescent probe over time. Antioxidants present in the assay work to block the peroxy radical oxidation of the fluorescent probe until the antioxidant activity in the sample is depleted. The remaining peroxy radicals destroy the fluorescence of the fluorescent probe.	Fluorescence	[161, 162]

Method	Description	Determination	References
Total radical-trapping antioxidant potential (TRAP)	It is based on the measurement of the fluorescence decay of R-phytoerythrin during an oxidation reaction. Antioxidant activity mechanism.	Chemiluminescence quenching	[163, 164]
Thiobarbituric reactive substances (TBARS)	Lipid peroxidation inhibition.	Colorimetric Fluorescence	[1]

Table 3.
 In vitro assays to evaluate natural substrates antioxidant potential.

specific fruits, vegetables or legumes can prevent cardiovascular disease induced by oxidative stress, due to presence of unique dietary antioxidant components [34].

Already in 1999, a study comprising approximately 100 000 patients in the US evaluated over a period of 7 years the outcome of flavonoid intake. The results demonstrated that flavonoid consumption was associated with lower risk of death with cardiovascular disease [172]. Patel *et al.* described that cohort studies clearly indicate that the consumption of plant-based foods decrease the prevalence of cardiovascular diseases [173]. Zhang *et al.* examined the relation between soy food intake and the incidence of coronary heart disease in a cohort study of 75 000 and concluded that there is a clear evidence of soy food intake and reduce risk of coronary heart disease [174].

Hypertension is characterized by high blood pressure leading to cardiac and vascular problems. A study performed in hypertensive rats demonstrated that the intake of *Moringa oleifera* seed powder did not reduce blood pressure, but decreased nocturnal heart rate and improved cardiac diastolic function [175]. Another study, lycopene diet ameliorates metabolic syndrome, lowering blood pressure, maintains normal blood glucose and prevents insulin resistance, ameliorates hypertension, vascular function and improves oxidative stress [33].

Diabetes mellitus, a chronic metabolic disease, characterized by elevated levels of blood glucose and insufficiency in production and action of insulin is the seventh leading cause of death worldwide. Phytochemicals with antioxidant activity like cinnamic acids, coumarins, diterpenes, flavonoids, lignans, prophenylphenols, monoterpenes, tannins, triterpenes, *etc.* also proved beneficial to protect diabetes or protect diabetic complications [176].

4.2.2 Cancer

Similarly to cardiovascular diseases, the number of reports regarding the benefits of phytochemicals and cancer prevention and treatment are immense. Briefly, it has been reported that curcumin, a polyphenol compound that has anticancer properties, acting on cell cycle regulation, apoptosis, oncogene expression and metastasis [177]. The intake of green tea seem to help in the treatment of patients with low grade B-cell tumors [178, 179]. Another phytochemical that demonstrated positive results is *Panax ginseng* (responsible chemical groups, steroid glycosides and triterpene saponins). Clinical trials demonstrated that *P. ginseng* decreases cancer incidence and inflammation, particularly that ginseng tea decreases the risk of pharynx, larynx, esophagus cancer among others [180]. Some of the reported flavonoids (*e.g.*, catechin, apigenin, kaempferol, quercetin, *etc.*) are able to influence the deregulated processes during cancer development. Thus, flavonoids have beneficial effects on health and have the potential for the development of possible

chemoprotective therapeutic agents for the treatment of cancer. Some dietary flavonoids have antitumor activity during *in vivo* studies and also repress angiogenesis. *In vitro* studies conclude the potential of flavonoid-induced modulation of kinases with apoptosis, vascularization, cell differentiation, cell proliferation, *etc* [181]. For example, flavonoids have shown a potential effect in breast cancer as potent inhibitors of aromatase, *i.e.*, cytochrome P450 enzyme complex. Quercetin has shown decreased cell proliferation in prostate cancer and cell apoptosis by downregulation of heat-shock protein 90 (HSP90) [182].

4.2.3 Neurodegenerative diseases

Neurodegenerative diseases are highly debilitating diseases associated to oxidative stress and inflammatory processes. Several studies have been performed to validate the benefices of phytochemicals on the several neurodegenerative diseases, like Alzheimer's, Parkinson's and multiple sclerosis. Flavonoids have a specific role in central nervous system maintaining homeostasis by effecting as antianxiety, anticonvulsant, by modulating neuronal oxidative metabolism, and neurotransmitters [183]. Epigallocatechin-3-galate, a polyphenol present in the tea leaves seems to delay neurons degeneration [184]. A commercial drug which has in its composition Epigallocatechin-3-galate demonstrated to reduce amyloid plaques on an Alzheimer disease model [185, 186]. Another study demonstrated that epigallocatechin-3-galate and tea prevented the loss of cells in substantia nigra in a Parkinson Disease model [187]. In a neuronal cell culture model SH-SY5Y cells, the presence of epigallocatechin-3-galate has a protective effect [187].

In vitro studies for Parkinson's, quercetin markedly reduced the apoptosis of pheochromocytoma (PC-12) cells and hippocampal neurons. It showed increased cell viability and inhibited ROS and MDA production in H₂O₂-induced toxicity in PC-12 cells [183].

Once again curcumin demonstrates to have a positive effect in Alzheimer's disease, as it can bind to amyloid plaques by inhibiting NF- κ B [188]. A different study demonstrated that ethanolic turmeric extract (*Curcuma longa* L.) prevented oxidative stress by decreasing the plasma and brain MDA levels and increasing the SOD, CAT, and GPx enzyme activities as well as GSH levels in the brain, showing neuroprotective effects [189].

Yang *et al.* [190] reported the neuroprotective effects of *Ginkgo biloba* extract (rich in flavonol glycosides and terpene trilactones) by preventive action on neuronal cell death and enhancement of the function of brain capillary endothelial monolayers.

As an example of a carotenoid action, astaxanthin has potent antioxidant, anti-inflammatory and neuroprotective properties. Wu and coworkers [191] suggested that astaxanthin could alleviate brain aging, which may be due to attenuating oxidative stress, ameliorating hippocampus damage and increasing brain derived neurotrophic factor levels, preventing age-related neurodegenerative diseases.

5. Conclusions and future perspectives

The use of green methodologies and extraction process optimization to obtain highly value molecules with antioxidant properties, like terpenes, polyphenolic, phytosterols, and bioactive peptides, has increased for the past years. The reduction of the environmental footprint and the ability to obtain safe products with high industrial interest is fundamental for the future.

Upon extraction and purification of the added value compounds it is possible to determine their antioxidant potential by several chemical and biological processes.

Plants, algae and by-products or waste products of the food industry are an invaluable source of active molecules with antioxidant properties. It is of upmost interest the discovery/development of new therapeutical molecules for the application in several diseases. Computer-aided drug screening techniques, animal models and clinical trials should be taken into account to further develop this field of research.

There are several natural bioactive compounds already used for the treatment of different diseases (in combination with the conventional drugs), demonstrating good results.

Overall, natural antioxidant obtained from plants and marine resources have high nutritional potential and reveal a fundamental role in promoting human health, as an alternative to synthetic products.

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Conflict of interest


The authors declare no conflict of interest.

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References

- [1] Carocho M, Ferreira ICFR. A review on antioxidants, prooxidants and related controversy: Natural and synthetic compounds, screening and analysis methodologies and future perspectives. *Food Chem Toxicol.* 2013;51:15-25. Available from: <http://dx.doi.org/10.1016/j.fct.2012.09.021>
- [2] Anwar H, Hussain G, Mustafa I. Antioxidants from Natural Sources. In: Shalaby E, Azzam G, editors. *Antioxidants in Foods and Its Applications.* London: InTechOpen; 2018. Available from: <http://dx.doi.org/10.5772/intechopen.75961>
- [3] Xu DP, Li Y, Meng X, Zhou T, Zhou Y, Zheng J, et al. Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. *Int J Mol Sci.* 2017 Jan 5;18(1):96. Available from: <http://dx.doi.org/10.3390/ijms18010096>
- [4] Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP, et al. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. *Molecules.* 2015. 20(12): 21138-21156. Available from: <http://dx.doi.org/10.3390/molecules201219753>
- [5] Ferreira-Santos P, Zanuso E, Genisheva Z, Rocha CMR, Teixeira JA. Green and Sustainable Valorization of Bioactive Phenolic Compounds from Pinus By-Products. *Molecules.* 2020;25(12):2931. Available from: <https://doi.org/10.3390/molecules25122931>
- [6] Torres-Valenzuela LS, Ballesteros-Gómez A, Rubio S. Green Solvents for the Extraction of High Added-Value Compounds from Agri-food Waste. *Food Eng Rev.* 2019;12:83-100. Available from: <https://doi.org/10.1007/s12393-019-09206-y>
- [7] Wen L, Zhang Z, Sun D-W, Sivagnanam SP, Tiwari BK. Combination of emerging technologies for the extraction of bioactive compounds. *Crit Rev Food Sci Nutr.* 2020 Jun 16;60(11):1826-1841. Available from: <https://doi.org/10.1080/10408398.2019.1602823>
- [8] Chemat F, Abert-Vian M, Fabiano-Tixier AS, Strube J, Uhlenbrock L, Gunjevic V, et al. Green extraction of natural products. Origins, current status, and future challenges. *TrAC Trends Anal Chem.* 2019;118:248-263. Available from: <https://doi.org/10.1016/j.trac.2019.05.037>
- [9] Rocha CMR, Genisheva Z, Ferreira-Santos P, Rodrigues R, Vicente AA, Teixeira JA, et al. Electric field-based technologies for valorization of bioresources. *Bioresour Technol.* 2018 Apr 1;254:325-339. Available from: <https://doi.org/10.1016/j.biortech.2018.01.068>
- [10] Chemat F, Rombaut N, Meullemiestre A, Turk M, Périno S, Fabiano-Tixier A-S, et al. Review of Green Food Processing techniques. Preservation, transformation, and extraction. *Innov Food Sci Emerg Technol.* 2017;41:357-377. Available from: <https://doi.org/10.1016/j.ifset.2017.04.016>
- [11] Soquetta MB, Terra L de M, Bastos CP. Green technologies for the extraction of bioactive compounds in fruits and vegetables. *CYTA - J Food.* 2018;16(1):400-12. Available from: <https://doi.org/10.1080/19476337.2017.1411978>
- [12] Cvjetko Bubalo M, Vidović S, Radojčić Redovniković I, Jokić S. New perspective in extraction of plant biologically active compounds by green solvents. *Food Bioprod Process.* 2018 May 1;109:52-73. Available from: <https://doi.org/10.1016/j.fbp.2018.03.001>

- [13] Ferreira-Santos P, Genisheva Z, Botelho C, Santos J, Ramos C, Teixeira JA, et al. Unravelling the Biological Potential of *Pinus pinaster* Bark Extracts. *Antioxidants*. 2020 Apr 20;9(4):334. Available from: <https://doi.org/10.3390/antiox9040334>
- [14] Barba FJ, Grimi N, Vorobiev E. Evaluating the potential of cell disruption technologies for green selective extraction of antioxidant compounds from *Stevia rebaudiana* Bertoni leaves. *J Food Eng*. 2015;149:222-228. Available from: <https://doi.org/10.1016/j.jfoodeng.2014.10.028>
- [15] Pereira RN, Rodrigues RM, Genisheva Z, Oliveira H, de Freitas V, Teixeira JA, et al. Effects of ohmic heating on extraction of food-grade phytochemicals from colored potato. *LWT - Food Sci Technol*. 2016;74:493-503. Available from: <https://doi.org/10.1016/j.lwt.2016.07.074>
- [16] Andreou V, Dimopoulos G, Dermesonlouoglou E, Taoukis P. Application of pulsed electric fields to improve product yield and waste valorization in industrial tomato processing. *J Food Eng*. 2020 Apr 1;270:109778. Available from: <https://doi.org/10.1016/j.jfoodeng.2019.109778>
- [17] Zhang R, Lebovka N, Marchal L, Vorobiev E, Grimi N. Multistage aqueous and non-aqueous extraction of bio-molecules from microalga *Phaeodactylum tricornutum*. *Innov Food Sci Emerg Technol*. 2020 Jun;62:102367. Available from: <https://doi.org/10.1016/j.ifset.2020.102367>
- [18] Goula AM, Ververi M, Adamopoulou A, Kaderides K. Green ultrasound-assisted extraction of carotenoids from pomegranate wastes using vegetable oils. *Ultrason Sonochem*. 2017;34:821-830. Available from: <http://dx.doi.org/10.1016/j.ultsonch.2016.07.022>
- [19] Carbonell-Capella JM, Šic Žlabur J, Rimac Brnčić S, Barba FJ, Grimi N, Koubaa M, et al. Electrotechnologies, microwaves, and ultrasounds combined with binary mixtures of ethanol and water to extract steviol glycosides and antioxidant compounds from *Stevia rebaudiana* leaves. *J Food Process Preserv*. 2017 Oct 1;41(5):e13179. Available from: <http://doi.wiley.com/10.1111/jfpp.13179>
- [20] Okolie CL, Akanbi TO, Mason B, Udenigwe CC, Aryee ANA. Influence of conventional and recent extraction technologies on physicochemical properties of bioactive macromolecules from natural sources: A review. *Food Res Int*. 2019;116:827-839. Available from: <https://doi.org/10.1016/j.foodres.2018.09.018>
- [21] Vinatoru M, Mason TJ, Calinescu I. Ultrasonically assisted extraction (UAE) and microwave assisted extraction (MAE) of functional compounds from plant materials. *TrAC Trends Anal Chem*. 2017;97:159-178. Available from: <https://doi.org/10.1016/j.trac.2017.09.002>
- [22] Barba FJ, Zhu Z, Koubaa M, Sant'Ana AS, Orlie V. Green alternative methods for the extraction of antioxidant bioactive compounds from winery wastes and by-products: A review. *Trends Food Sci Technol*. 2016;49:96-109. Available from: <http://dx.doi.org/10.1016/j.tifs.2016.01.006>
- [23] Bonifácio-Lopes T, Teixeira JA, Pintado M. Current extraction techniques towards bioactive compounds from brewer's spent grain—A review. *Crit Rev Food Sci Nutr*. 2020;60(16):2730-2741. Available from: <https://pubmed.ncbi.nlm.nih.gov/31433199/>
- [24] Wrona O, Rafińska K, Mozenski C, Byszewski B. Supercritical fluid extraction of bioactive compounds from plant materials. *J AOAC Int*.

- 2017;100(6):1624-1635. Available from: <http://dx.doi.org/10.5740/jaoacint.17-0232>
- [25] Andrés V, Mateo-Vivaracho L, Guillamón E, Villanueva MJ, Tenorio MD. High hydrostatic pressure treatment and storage of soy-smoothies: Colour, bioactive compounds and antioxidant capacity. *LWT*. 2016;69:123-130. Available from: <https://doi.org/10.1016/j.lwt.2016.01.033>
- [26] Moreira SA, Silva S, Costa EM, Saraiva JA, Pintado M. Effect of high hydrostatic pressure extraction on biological activities of stinging nettle extracts. *Food Funct*. 2020;11(1):921-31. Available from: <https://doi.org/10.1039/C9FO02442E>
- [27] Scepankova H, Martins M, Estevinho L, Delgadillo I, Saraiva JA. Enhancement of Bioactivity of Natural Extracts by Non-Thermal High Hydrostatic Pressure Extraction. 2018;73:253-67. Available from: <https://doi.org/10.1007/s11130-018-0687-9>
- [28] Khan SA, Aslam R, Makroo HA. High pressure extraction and its application in the extraction of bioactive compounds: A review. *J Food Process Eng*. 2019;42(1):e12896. Available from: <http://doi.wiley.com/10.1111/jfpe.12896>
- [29] Azmi AA bin, Sankaran R, Show PL, Ling TC, Tao Y, Munawaroh HSH, et al. Current application of electrical pre-treatment for enhanced microalgal biomolecules extraction. Vol. 302, *Bioresource Technology*. Elsevier Ltd; 2020. p. 122874.
- [30] Puértolas E, Barba FJ. Electrotechnologies applied to valorization of by-products from food industry: Main findings, energy and economic cost of their industrialization. *Food Bioprod Process*. 2016;100:172-184. Available from: <https://doi.org/10.1016/j.fbp.2016.06.020>
- [31] Li Z, Fan Y, Xi J. Recent advances in high voltage electric discharge extraction of bioactive ingredients from plant materials. *Food Chem*. 2019;277:246-260. Available from: <https://doi.org/10.1016/j.foodchem.2018.10.119>
- [32] Sastry S. Ohmic heating and moderate electric field processing. *Food Sci Technol Int*. 2008;14(5):419-422. Available from: <https://doi.org/10.1177/1082013208098813>
- [33] Ferreira-Santos P, Aparicio R, Carrón R, Montero MJ, Sevilla MÁ. Lycopene-supplemented diet ameliorates metabolic syndrome induced by fructose in rats. *J Funct Foods*. 2020;73:104098. Available from: <https://doi.org/10.1016/j.jff.2020.104098>
- [34] Septembre-Malaterre A, Remize F, Pouchet P. Fruits and vegetables, as a source of nutritional compounds and phytochemicals: Changes in bioactive compounds during lactic fermentation. *Food Res Int*. 2018;104:86-99. Available from: <https://doi.org/10.1016/j.foodres.2017.09.031>
- [35] Fidelis M, De Moura C, Kabbas T, Pap N, Mattila P, Mäkinen S, et al. Fruit seeds as sources of bioactive compounds: Sustainable production of high value-added ingredients from by-products within circular economy. *Molecules*. 2019;24(21):1-67. Available from: <https://doi.org/10.3390/molecules24213854>
- [36] Mirabella N, Castellani V, Sala S. Current options for the valorization of food manufacturing waste: A review. *J Clean Prod*. 2014;65:28-41. Available from: <https://doi.org/10.1016/j.jclepro.2013.10.051>
- [37] Luengo E, Álvarez I, Raso J. Improving the pressing extraction of polyphenols of orange peel by pulsed electric fields. *Innov Food Sci Emerg Technol*. 2013;17:79-84. Available

from: <https://doi.org/10.1016/j.ifset.2012.10.005>

[38] Fierascu RC, Fierascu I, Avramescu SM, Sieniawska E. Recovery of Natural Antioxidants from Agro-Industrial Side Streams through Advanced Extraction Techniques. *Molecules*. 2019;24(23). Available from: <https://doi.org/10.3390/molecules24234212>

[39] El-Demerdash A, Atanasov AG, Horbanczuk OK, Tammam MA, Abdel-Mogib M, Hooper JNA, et al. Chemical diversity and biological activities of marine sponges of the genus *Suberea*: A systematic review. *Mar Drugs*. 2019;17(2):115. Available from: <https://doi.org/10.3390/md17020115>

[40] Jimenez-Lopez C, Pereira AG, Lourenço-Lopes C, Garcia-Oliveira P, Cassani L, Fraga-Corral M, et al. Main bioactive phenolic compounds in marine algae and their mechanisms of action supporting potential health benefits. *Food Chem*. 2021;341:128262. Available from: <https://doi.org/10.1016/j.foodchem.2020.128262>

[41] Geada P, Rodrigues R, Loureiro L, Pereira R, Fernandes B, Teixeira JA, et al. Electrotechnologies applied to microalgal biotechnology – Applications, techniques and future trends. *Renew Sustain Energy Rev*. 2018;94:656-668. Available from: <https://doi.org/10.1016/j.rser.2018.06.059>

[42] Alencar POC, Lima GC, Barros FCN, Costa LEC, Ribeiro CVPE, Sousa WM, et al. A novel antioxidant sulfated polysaccharide from the algae *Gracilaria caudata*: In vitro and in vivo activities. *Food Hydrocoll*. 2019;90:28-34. Available from: <https://doi.org/10.1016/j.foodhyd.2018.12.007>

[43] Morais T, Cotas J, Pacheco D, Pereira L. Seaweeds Compounds: An Ecosustainable Source of Cosmetic

Ingredients? *Cosmet*. 2021 Jan 15;8(1):8. Available from: <https://doi.org/10.3390/cosmetics8010008>

[44] Nagar S, Sharma N, Kumar S. C-Phycocyanin Extraction and Purification from *Spirulina Platensis*. 2018;8(2):60-3. Available from: <https://doi.org/10.1007/s40502-014-0094-7>

[45] Gontijo DC, Gontijo PC, Brandão GC, Diaz MAN, de Oliveira AB, Fietto LG, et al. Antioxidant study indicative of antibacterial and antimutagenic activities of an ellagitannin-rich aqueous extract from the leaves of *Miconia latecrenata*. *J Ethnopharmacol*. 2019;236:114-123. Available from: <https://doi.org/10.1016/j.jep.2019.03.007>

[46] Chutia H, Mahanta CL. Green ultrasound and microwave extraction of carotenoids from passion fruit peel using vegetable oils as a solvent: Optimization, comparison, kinetics, and thermodynamic studies. *Innov Food Sci Emerg Technol*. 2020;102547 (In Press). Available from: <https://doi.org/10.1016/j.ifset.2020.102547>

[47] Thu Dao TA, Webb HK, Malherbe F. Optimization of pectin extraction from fruit peels by response surface method: Conventional versus microwave-assisted heating. *Food Hydrocoll*. 2021;113:106475. Available from: <https://doi.org/10.1016/j.foodhyd.2020.106475>

[48] Jesus MS, Ballesteros LF, Pereira RN, Genisheva Z, Carvalho AC, Pereira-Wilson C, et al. Ohmic heating polyphenolic extracts from vine pruning residue with enhanced biological activity. *Food Chem*. 2020;316:126298. Available from: <https://doi.org/10.1016/j.foodchem.2020.126298>

[49] Jesus MS, Genisheva Z, Romaní A, Pereira RN, Teixeira JA, Domingues L. Bioactive compounds recovery optimization from vine pruning residues using conventional

- heating and microwave-assisted extraction methods. *Ind Crops Prod.* 2019;132:99-110. Available from: <https://doi.org/10.1016/j.indcrop.2019.01.070>
- [50] Pereira RN, Coelho MI, Genisheva Z, Fernandes JM, Vicente AA, Pintado ME, et al. Using Ohmic Heating effect on grape skins as a pretreatment for anthocyanins extraction. *Food Bioprod Process.* 2020;124. Available from: <https://doi.org/10.1016/j.fbp.2020.09.009>
- [51] Kwiatkowski M, Kravchuk O, Skouroumounis GK, Taylor DK. Microwave-assisted and conventional phenolic and colour extraction from grape skins of commercial white and red cultivars at veraison and harvest. *J Clean Prod.* 2020;275:122671. Available from: <https://doi.org/10.1016/j.jclepro.2020.122671>
- [52] Natolino A, Da Porto C. Kinetic models for conventional and ultrasound assisted extraction of polyphenols from defatted fresh and distilled grape marc and its main components skins and seeds. *Chem Eng Res Des.* 2020;156:1-12. Available from: <https://doi.org/10.1016/j.cherd.2020.01.009>
- [53] Cvjetko Bubalo M, Ćurko N, Tomašević M, Kovačević Ganić K, Radojčić Redovniković I. Green extraction of grape skin phenolics by using deep eutectic solvents. *Food Chem.* 2016;200:159-166. Available from: <https://doi.org/10.1016/j.foodchem.2016.01.040>
- [54] Fernández K, Vega M, Aspé E. An enzymatic extraction of proanthocyanidins from País grape seeds and skins. *Food Chem.* 2015;168:7-13. Available from: <https://doi.org/10.1016/j.foodchem.2014.07.021>
- [55] Stavikova L, Polovka M, Hohnová B, Karásek P, Roth M. Antioxidant activity of grape skin aqueous extracts from pressurized hot water extraction combined with electron paramagnetic resonance spectroscopy. *Talanta.* 2011;85(4):2233-2240. Available from: <https://doi.org/10.1016/j.talanta.2011.07.079>
- [56] Ferreira-Santos P, Genisheva Z, Pereira RN, Teixeira JA, Rocha CMR. Moderate Electric Fields as a Potential Tool for Sustainable Recovery of Phenolic Compounds from Pinus pinaster Bark. *ACS Sustain Chem Eng.* 2019;7(9):8816-8826. Available from: <https://doi.org/10.1021/acssuschemeng.9b00780>
- [57] Mellouk H, Meullemiestre A, Maache-Rezzoug Z, Bejjani B, Dani A, Rezzoug SA. Valorization of industrial wastes from French maritime pine bark by solvent free microwave extraction of volatiles. *J Clean Prod.* 2016;112:4398-4405. Available from: <https://doi.org/10.1016/j.jclepro.2015.06.129>
- [58] Seabra IJ, Dias AMA, Braga MEM, de Sousa HC. High pressure solvent extraction of maritime pine bark: Study of fractionation, solvent flow rate and solvent composition. *J Supercrit Fluids.* 2012;62:135-148. Available from: <https://doi.org/10.1016/j.supflu.2011.10.016>
- [59] Liazid A, Schwarz M, Varela RM, Palma M, Guillén DA, Brigue J, et al. Evaluation of various extraction techniques for obtaining bioactive extracts from pine seeds. *Food Bioprod Process.* 2010;88(2-3):247-252. Available from: <https://doi.org/10.1016/j.fbp.2009.11.004>
- [60] Perović MN, Knežević Jugović ZD, Antov MG. Improved recovery of protein from soy grit by enzyme-assisted alkaline extraction. *J Food Eng.* 2020;276:109894. Available from: <https://doi.org/10.1016/j.jfoodeng.2019.109894>
- [61] Bajkacz S, Adamek J. Evaluation of new natural deep eutectic solvents for

the extraction of isoflavones from soy products. *Talanta*. 2017;168:329-335. Available from: <https://doi.org/10.1016/j.talanta.2017.02.065>

[62] Magiera S, Sobik A. Ionic liquid-based ultrasound-assisted extraction coupled with liquid chromatography to determine isoflavones in soy foods. *J Food Compos Anal*. 2017;57:94-101. Available from: <https://doi.org/10.1016/j.jfca.2016.12.016>

[63] Lu W, Chen XW, Wang JM, Yang XQ, Qi JR. Enzyme-assisted subcritical water extraction and characterization of soy protein from heat-denatured meal. *J Food Eng*. 2016;169:250-258. Available from: <https://doi.org/10.1016/j.jfoodeng.2015.09.006>

[64] Patonay K, Szalontai H, Csugány J, Szabó-Hudák O, Kónya EP, Németh ÉZ. Comparison of extraction methods for the assessment of total polyphenol content and in vitro antioxidant capacity of horsemint (*Mentha longifolia* (L.) L.). *J Appl Res Med Aromat Plants*. 2019;15:100220. Available from: <https://doi.org/10.1016/j.jarmap.2019.100220>

[65] Shahsavarpour M, Lashkarbolooki M, Eftekhari MJ, Esmailzadeh F. Extraction of essential oils from *Mentha spicata* L. (Labiatae) via optimized supercritical carbon dioxide process. *J Supercrit Fluids*. 2017;130:253-260. Available from: <https://doi.org/10.1016/j.supflu.2017.02.004>

[66] Gavahian M, Farahnaky A, Farhoosh R, Javidnia K, Shahidi F. Extraction of essential oils from *Mentha piperita* using advanced techniques: Microwave versus ohmic assisted hydrodistillation. *Food Bioprod Process*. 2015;94:50-58. Available from: <https://doi.org/10.1016/j.supflu.2017.02.004>

[67] Baltacıoğlu H, Baltacıoğlu C, Okur I, Tanrıvermiş A, Yalçın M. Optimization

of microwave-assisted extraction of phenolic compounds from tomato: Characterization by FTIR and HPLC and comparison with conventional solvent extraction. *Vib Spectrosc*. 2021;113. Available from: <https://doi.org/10.1016/j.vibspec.2020.103204>

[68] Ninčević Grassino A, Ostojić J, Miletić V, Djaković S, Bosiljkov T, Zorić Z, et al. Application of high hydrostatic pressure and ultrasound-assisted extractions as a novel approach for pectin and polyphenols recovery from tomato peel waste. *Innov Food Sci Emerg Technol*. 2020;64. Available from: <https://doi.org/10.1016/j.ifset.2020.102424>

[69] Pataro G, Carullo D, Falcone M, Ferrari G. Recovery of lycopene from industrially derived tomato processing by-products by pulsed electric fields-assisted extraction. *Innov Food Sci Emerg Technol*. 2020;63:102369. Available from: <https://doi.org/10.1016/j.ifset.2020.102369>

[70] Squillace P, Adani F, Scaglia B. Supercritical CO₂ extraction of tomato pomace: Evaluation of the solubility of lycopene in tomato oil as limiting factor of the process performance. *Food Chem*. 2020;315:126224. Available from: <https://doi.org/10.1016/j.foodchem.2020.126224>

[71] Catalkaya G, Kahveci D. Optimization of enzyme assisted extraction of lycopene from industrial tomato waste. *Sep Purif Technol*. 2019;219:55-63. Available from: <https://doi.org/10.1016/j.seppur.2019.03.006>

[72] Shivamathi CS, Moorthy IG, Kumar RV, Soosai MR, Maran JP, Kumar RS, et al. Optimization of ultrasound assisted extraction of pectin from custard apple peel: Potential and new source. *Carbohydr Polym*. 2019;225:115240. Available from: <https://doi.org/10.1016/j.carbpol.2019.115240>

- [73] Massias A, Boisard S, Baccaunaud M, Leal Calderon F, Subra-Paternault P. Recovery of phenolics from apple peels using CO₂ + ethanol extraction: Kinetics and antioxidant activity of extracts. *J Supercrit Fluids*. 2015;98:172-182. Available from: <https://doi.org/10.1016/j.supflu.2014.12.007>
- [74] Wang L, Boussetta N, Lebovka N, Vorobiev E. Cell disintegration of apple peels induced by pulsed electric field and efficiency of bio-compound extraction. *Food Bioprod Process*. 2020;122:13-21. Available from: <https://doi.org/10.1016/j.fbp.2020.03.004>
- [75] Panadare DC, Gondaliya A, Rathod VK. Comparative study of ultrasonic pretreatment and ultrasound assisted three phase partitioning for extraction of custard apple seed oil. *Ultrason Sonochem*. 2020;61:104821. Available from: <https://doi.org/10.1016/j.ultsonch.2019.104821>
- [76] Montañés F, Catchpole OJ, Tallon S, Mitchell KA, Scott D, Webby RF. Extraction of apple seed oil by supercritical carbon dioxide at pressures up to 1300 bar. *J Supercrit Fluids*. 2018;141:128-136. Available from: <https://doi.org/10.1016/j.supflu.2018.02.002>
- [77] Li W, Yang H, Coldea TE, Zhao H. Modification of structural and functional characteristics of brewer's spent grain protein by ultrasound assisted extraction. *Lwt*. 2020;110582. (In Press) Available from: <https://doi.org/10.1016/j.lwt.2020.110582>
- [78] Martín-García B, Tylewicz U, Verardo V, Pasini F, Gómez-Caravaca AM, Caboni MF, et al. Pulsed electric field (PEF) as pre-treatment to improve the phenolic compounds recovery from brewers' spent grains. *Innov Food Sci Emerg Technol*. 2020;64:102402. Available from: <https://doi.org/10.1016/j.ifset.2020.102402>
- [79] Spinelli S, Conte A, Lecce L, Padalino L, Del Nobile MA. Supercritical carbon dioxide extraction of brewer's spent grain. *J Supercrit Fluids*. 2016;107:69-74. Available from: <https://doi.org/10.1016/j.supflu.2015.08.017>
- [80] Hosseini SS, Khodaiyan F, Yarmand MS. Optimization of microwave assisted extraction of pectin from sour orange peel and its physicochemical properties. *Carbohydr Polym*. 2016;140:59-65. Available from: <https://doi.org/10.1016/j.carbpol.2015.12.051>
- [81] Nuapia Y, Cukrowska E, Tutu H, Chimuka L. Statistical comparison of two modeling methods on pressurized hot water extraction of vitamin C and phenolic compounds from *Moringa oleifera* leaves. *South African J Bot*. 2020;129:9-16. Available from: <https://doi.org/10.1016/j.sajb.2018.09.001>
- [82] Narváez-Cuenca CE, Inampues-Charfuelan ML, Hurtado-Benavides AM, Parada-Alfonso F, Vincken JP. The phenolic compounds, tocopherols, and phytosterols in the edible oil of guava (*Psidium guava*) seeds obtained by supercritical CO₂ extraction. *J Food Compos Anal*. 2020;89:103467. Available from: <https://doi.org/10.1016/j.jfca.2020.103467>
- [83] Jafarian Asl P, Niazmand R, Jahani M. Theoretical and experimental assessment of supercritical CO₂ in the extraction of phytosterols from rapeseed oil deodorizer distillates. *J Food Eng*. 2020;269:109748. Available from: <https://doi.org/10.1016/j.jfoodeng.2019.109748>
- [84] Nyam KL, Tan CP, Lai OM, Long K, Che Man YB. Optimization of supercritical fluid extraction of phytosterol from roselle seeds with a central composite design model. *Food Bioprod Process*. 2010;88(2-3):239-246.

Available from: <https://doi.org/10.1016/j.fbp.2009.11.002>

[85] Botelho JRS, Medeiros NG, Rodrigues AMC, Araújo ME, Machado NT, Guimarães Santos A, et al. Black sesame (*Sesamum indicum* L.) seeds extracts by CO₂ supercritical fluid extraction: Isotherms of global yield, kinetics data, total fatty acids, phytosterols and neuroprotective effects. *J Supercrit Fluids*. 2014;93:49-55. Available from: <https://doi.org/10.1016/j.supflu.2014.02.008>

[86] Izadi M, Fazilati M. Extraction and purification of phycocyanin from *Spirulina platensis* and evaluating its antioxidant and anti-inflammatory activity. *Asian J Green Chem*. 2018;2(4):364-379. Available from: <https://doi.org/10.22034/AJGC.2018.63597>

[87] İltir I, Akyıl S, Demirel Z, Koç M, Conk-Dalay M, Kaymak-Ertekin F. Optimization of phycocyanin extraction from *Spirulina platensis* using different techniques. *J Food Compos Anal*. 2018;70:78-88. Available from: <https://doi.org/10.1016/j.jfca.2018.04.007>

[88] Martínez JM, Luengo E, Saldaña G, Álvarez I, Raso J. C-phycocyanin extraction assisted by pulsed electric field from *Arthrospira platensis*. *Food Res Int*. 2017;99:1042-1047. Available from: <https://doi.org/10.1016/j.foodres.2016.09.029>

[89] Jaeschke DP, Mercali GD, Marczak LDF, Müller G, Frey W, Gusbeth C. Extraction of valuable compounds from *Arthrospira platensis* using pulsed electric field treatment. *Bioresour Technol*. 2019;283:207-212. Available from: <https://doi.org/10.1016/j.biortech.2019.03.035>

[90] Ferreira-Santos P, Nunes R, De Biasio F, Spigno G, Gorgoglione D, Teixeira JA, et al. Influence of thermal and electrical effects of ohmic heating

on C-phycocyanin properties and biocompounds recovery from *Spirulina Platensis*. *LWT*. 2020;109491. Available from: <https://doi.org/10.1016/j.lwt.2020.109491>

[91] Pagels F, Guedes AC, Amaro HM, Kijjoo A, Vasconcelos V. Phycobiliproteins from cyanobacteria: Chemistry and biotechnological applications. *Biotechnol Adv*. 2019;37(3):422-443. Available from: <https://doi.org/10.1016/j.biotechadv.2019.02.010>

[92] Goiris K, Muylaert K, Fraeye I, Foubert I, De Brabanter J, De Cooman L. Antioxidant potential of microalgae in relation to their phenolic and carotenoid content. *J Appl Phycol*. 2012;24(6):1477-1486. Available from: <https://doi.org/10.1007/s10811-012-9804-6>

[93] Czerwonka A, Kaławaj K, Sławińska-Brych A, Lemieszek MK, Bartnik M, Wojtanowski KK, et al. Anticancer effect of the water extract of a commercial *Spirulina* (*Arthrospira platensis*) product on the human lung cancer A549 cell line. *Biomed Pharmacother*. 2018;106:292-302. Available from: <https://doi.org/10.1016/j.biopha.2018.06.116>

[94] Alshuniaber MA, Krishnamoorthy R, AlQhtani WH. Antimicrobial activity of polyphenolic compounds from *Spirulina* against food-borne bacterial pathogens. *Saudi J Biol Sci*. 2021 Jan 1;28(1):459-64. Available from: <https://doi.org/10.1016/j.sjbs.2020.10.029>

[95] Chittapun S, Jonjaroen V, Khumrangsee K, Charoenrat T. C-phycocyanin extraction from two freshwater cyanobacteria by freeze thaw and pulsed electric field techniques to improve extraction efficiency and purity. *Algal Res*. 2020;46:101789. Available from: <https://doi.org/10.1016/j.algal.2020.101789>

- [96] Jaeschke DP, Menegol T, Rech R, Mercali GD, Marczak LDF. Carotenoid and lipid extraction from *Heterochlorella luteoviridis* using moderate electric field and ethanol. *Process Biochem.* 2016;51(10):1636-1643. Available from: <https://doi.org/10.1016/j.procbio.2016.07.016>
- [97] Jaeschke DP, Rech R, Marczak LDF, Mercali GD. Ultrasound as an alternative technology to extract carotenoids and lipids from *Heterochlorella luteoviridis*. *Bioresour Technol.* 2017 Jan 1;224:753-757. Available from: <https://doi.org/10.1016/j.biortech.2016.11.107>
- [98] 't Lam GP, Postma PR, Fernandes DA, Timmermans RAH, Vermuë MH, Barbosa MJ, et al. Pulsed Electric Field for protein release of the microalgae *Chlorella vulgaris* and *Neochloris oleoabundans*. *Algal Res.* 2017;24:181-7. Available from: <https://doi.org/10.1016/j.algal.2017.03.024>
- [99] Postma PR, Pataro G, Capitoli M, Barbosa MJ, Wijffels RH, Eppink MHM, et al. Selective extraction of intracellular components from the microalga *Chlorella vulgaris* by combined pulsed electric field-temperature treatment. *Bioresour Technol.* 2016;203:80-88. Available from: <https://doi.org/10.1016/j.biortech.2015.12.012>
- [100] Cho H-S, Oh Y-K, Park S-C, Lee J-W, Park J-Y. Effects of enzymatic hydrolysis on lipid extraction from *Chlorella vulgaris*. *Renew Energy* [Internet]. 2013 Jun;54:156-160. Available from: <http://dx.doi.org/10.1016/j.renene.2012.08.031>
- [101] Wang HM, Pan JL, Chen CY, Chiu CC, Yang MH, Chang HW, et al. Identification of anti-lung cancer extract from *Chlorella vulgaris* C-C by antioxidant property using supercritical carbon dioxide extraction. *Process Biochem.* 2010;45(12):1865-1872. Available from: <https://doi.org/10.1016/j.procbio.2010.05.023>
- [102] Parniakov O, Apicella E, Koubaa M, Barba FJ, Grimi N, Lebovka N, et al. Ultrasound-assisted green solvent extraction of high-added value compounds from microalgae *Nannochloropsis* spp. *Bioresour Technol.* 2015;198:262-267. Available from: <http://dx.doi.org/10.1016/j.biortech.2015.09.020>
- [103] Parniakov O, Barba FJ, Grimi N, Marchal L, Jubeau S, Lebovka N, et al. Pulsed electric field assisted extraction of nutritionally valuable compounds from microalgae *Nannochloropsis* spp. using the binary mixture of organic solvents and water. *Innov Food Sci Emerg Technol.* 2015;27:79-85. Available from: <https://doi.org/10.1016/j.ifset.2014.11.002>
- [104] Gallego R, Bueno M, Chourio AM, Ibáñez E, Saldaña MDA, Herrero M. Use of high and ultra-high pressure based-processes for the effective recovery of bioactive compounds from *Nannochloropsis oceanica* microalgae. *J Supercrit Fluids.* 2021;167:105039. Available from: <https://doi.org/10.1016/j.supflu.2020.105039>
- [105] Gilbert-López B, Barranco A, Herrero M, Cifuentes A, Ibáñez E. Development of new green processes for the recovery of bioactives from *Phaeodactylum tricornutum*. *Food Res Int.* 2017;99:1056-1065. Available from: <https://doi.org/10.1016/j.foodres.2016.04.022>
- [106] Castro-Puyana M, Herrero M, Urreta I, Mendiola JA, Cifuentes A, Ibáñez E, et al. Optimization of clean extraction methods to isolate carotenoids from the microalga *Neochloris oleoabundans* and subsequent chemical characterization using liquid chromatography tandem mass spectrometry. *Anal Bioanal Chem.* 2013;405(13):4607-4616. Available

from: <https://doi.org/10.1007/s00216-012-6687-y>

[107] Otero P, López-Martínez MI, García-Risco MR. Application of pressurized liquid extraction (PLE) to obtain bioactive fatty acids and phenols from *Laminaria ochroleuca* collected in Galicia (NW Spain). *J Pharm Biomed Anal.* 2019;164:86-92. Available from: <https://doi.org/10.1016/j.jpba.2018.09.057>

[108] Yuan Y, Zhang J, Fan J, Clark J, Shen P, Li Y, et al. Microwave assisted extraction of phenolic compounds from four economic brown macroalgae species and evaluation of their antioxidant activities and inhibitory effects on α -amylase, α -glucosidase, pancreatic lipase and tyrosinase. *Food Res Int.* 2018;113:288-297. Available from: <https://doi.org/10.1016/j.foodres.2018.07.021>

[109] Heffernan N, Smyth TJ, FitzGerald RJ, Soler-Vila A, Brunton N. Antioxidant activity and phenolic content of pressurised liquid and solid-liquid extracts from four Irish origin macroalgae. *Int J Food Sci Technol.* 2014;49(7):1765-1772. Available from: <http://doi.wiley.com/10.1111/ijfs.12512>

[110] Mæhre HK, Jensen IJ, Eilertsen KE. Enzymatic pre-treatment increases the protein bioaccessibility and extractability in dulse (*Palmaria palmata*). *Mar Drugs.* 2016;14(11):196. Available from: <https://doi.org/10.3390/md14110196>

[111] Pimentel FB, Alves RC, Harnedy PA, FitzGerald RJ, Oliveira MBPP. Macroalgal-derived protein hydrolysates and bioactive peptides: Enzymatic release and potential health enhancing properties. *Trends Food Sci Technol.* 2019;93:106-124. Available from: <https://doi.org/10.1016/j.tifs.2019.09.006>

[112] Mittal R, Tavanandi HA, Mantri VA, Raghavarao KSMS. Ultrasound assisted

methods for enhanced extraction of phycobiliproteins from marine macroalgae, *Gelidium pusillum* (Rhodophyta). *Ultrason Sonochem.* 2017;38:92-103. Available from: <https://doi.org/10.1016/j.ultsonch.2017.02.030>

[113] Kissoudi M, Sarakatsianos I, Samanidou V. Isolation and purification of food-grade C-phycoerythrin from *Arthrospira platensis* and its determination in confectionery by HPLC with diode array detection. *J Sep Sci.* 2018;41(4):975-981. Available from: <https://doi.org/10.1002/jssc.201701151>

[114] Nizioł-Łukaszewska Z, Furman-Toczek D, Bujak T, Wasilewski T, Hordyjewicz-Baran Z. *Moringa oleifera* L. Extracts as Bioactive Ingredients That Increase Safety of Body Wash Cosmetics. *Dermatol Res Pract.* 2020;2020. Available from: <https://doi.org/10.1155/2020/8197902>

[115] Schoonees A, Visser J, Musekiwa A, Volmink J. Pycnogenol® for the treatment of chronic disorders. In: *Cochrane Database of Systematic Reviews.* John Wiley & Sons, Ltd; 2012;2:CD008294. Available from: <https://doi.org/10.1002/14651858.CD008294.pub3>

[116] Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *British Journal of Pharmacology.* 2017;174(11):1325-48. Available from: <https://doi.org/10.1111/bph.13621>

[117] Borowitzka MA. High-value products from microalgae-their development and commercialisation. *J Appl Phycol.* 2013;25(3):743-756. Available from: <https://doi.org/10.1007/s10811-013-9983-9>

[118] Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT)

and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria J Med.* 2018;54(4):287-293. Available from: <https://doi.org/10.1016/j.ajme.2017.09.001>

[119] Caroprese M, Ciliberti MG, Albenzio M, Marino R, Santillo A, Sevi A. Role of antioxidant molecules in milk of sheep. *Small Rumin Res.* 2019;180:79-85. Available from: <https://doi.org/10.1016/j.smallrumres.2019.07.011>

[120] Wen C, Zhang J, Zhang H, Duan Y, Ma H. Plant protein-derived antioxidant peptides: Isolation, identification, mechanism of action and application in food systems: A review. *Trends Food Sci Technol.* 2020;105:308-322. Available from: <https://doi.org/10.1016/j.tifs.2020.09.019>

[121] Eslami O, Shidfar F. Soy milk: A functional beverage with hypocholesterolemic effects? A systematic review of randomized controlled trials. *Complement Ther Med.* 2019;42:82-88. Available from: <https://doi.org/10.1016/j.ctim.2018.11.001>

[122] Moayedi A, Mora L, Aristoy MC, Safari M, Hashemi M, Toldrá F. Peptidomic analysis of antioxidant and ACE-inhibitory peptides obtained from tomato waste proteins fermented using *Bacillus subtilis*. *Food Chem.* 2018;250:180-187. Available from: <https://doi.org/10.1016/j.foodchem.2018.01.033>

[123] García MC, Endermann J, González-García E, Marina ML. HPLC-Q-TOF-MS Identification of Antioxidant and Antihypertensive Peptides Recovered from Cherry (*Prunus cerasus* L.) Subproducts. *J Agric Food Chem.* 2015;63(5):1514-1520. Available from: <https://doi.org/10.1021/jf505037p>

[124] Pereira T, Barroso S, Mendes S, Amaral RA,

Dias JR, Baptista T, et al. Optimization of phycobiliprotein pigments extraction from red algae *Gracilaria gracilis* for substitution of synthetic food colorants. *Food Chem.* 2020;321:126688. Available from: <https://doi.org/10.1016/j.foodchem.2020.126688>

[125] Sonani RR, Singh NK, Kumar J, Thakar D, Madamwar D. Concurrent purification and antioxidant activity of phycobiliproteins from *Lyngbya* sp. A09DM: An antioxidant and anti-aging potential of phycoerythrin in *Caenorhabditis elegans*. *Process Biochem.* 2014;49(10):1757-1766. Available from: <https://doi.org/10.1016/j.procbio.2014.06.022>

[126] Lizárraga-Velázquez C, Leyva-López N, Hernández C, Gutiérrez-Grijalva EP, Salazar-Leyva J, Osuna-Ruiz I, et al. Antioxidant Molecules from Plant Waste: Extraction Techniques and Biological Properties. *Processes.* 2020;8:1-44. Available from: <https://doi.org/10.3390/pr8121566>

[127] Park WS, Kim HJ, Li M, Lim DH, Kim J, Kwak SS, et al. Two classes of pigments, carotenoids and c-phycoerythrin, in spirulina powder and their antioxidant activities. *Molecules.* 2018;23(8):1-11. Available from: <https://doi.org/10.3390/molecules23082065>

[128] Toh DWK, Sutanto CN, Loh WW, Lee WY, Yao Y, Ong CN, et al. Skin carotenoids status as a potential surrogate marker for cardiovascular disease risk determination in middle-aged and older adults. *Nutr Metab Cardiovasc Dis.* 2020;(In Press). Available from: <https://doi.org/10.1016/j.numecd.2020.10.016>

[129] Mohamadnia S, Tavakoli O, Faramarzi MA. Enhancing production of fucoxanthin by the optimization of culture media of the microalga *Tisochrysis lutea*. *Aquaculture.* 2021;533:736074. Available from: <https://doi.org/10.1016/j.aquaculture.2020.736074>

- [130] Cloetens L, Panee J, Åkesson B. The antioxidant capacity of milk - The application of different methods in vitro and in vivo. *Cell Mol Biol*. 2013;59(1):43-57. Available from: <https://pubmed.ncbi.nlm.nih.gov/24200020/>
- [131] Miras-Moreno B, Sabater-Jara AB, Pedreno MA, Almagro L. Bioactivity of Phytosterols and Their Production in Plant in Vitro Cultures. *J Agric Food Chem*. 2016;64(38):7049-7058. Available from: <https://doi.org/10.1021/acs.jafc.6b02345>
- [132] Kritchevsky D, Chen SC. Phytosterols—health benefits and potential concerns: a review. *Nutrition Research*. 2005;25(5):413-428. Available from: <https://doi.org/10.1016/j.nutres.2005.02.003>
- [133] Ferreira-Santos P, Carrón R, Recio I, Sevilla MÁ, Montero MJ. Effects of milk casein hydrolyzate supplemented with phytosterols on hypertension and lipid profile in hypercholesterolemic hypertensive rats. *J Funct Foods*. 2017;28:168-176. Available from: <https://doi.org/10.1016/j.jff.2016.11.020>
- [134] Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative Stress: Harms and Benefits for Human Health. *Oxid Med Cell Longev*. 2017;2017. Available from: <https://doi.org/10.1155/2017/8416763>
- [135] Turrens JF. Mitochondrial formation of reactive oxygen species. *Journal of Physiology*. 2003;552(2):335-344. Available from: <https://doi.org/10.1113/jphysiol.2003.049478>
- [136] Stadtman ER, Levine RL. Protein oxidation. In: *Annals of the New York Academy of Sciences*. New York Academy of Sciences; 2000. p. 191-208.
- [137] Rubbo H, Parthasarathy S, Barnes S, Kirk M, Kalyanaraman B, Freeman BA. Nitric oxide inhibition of lipoxygenase-dependent liposome and low-density lipoprotein oxidation: Termination of radical chain propagation reactions and formation of nitrogen-containing oxidized lipid derivatives. *Arch Biochem Biophys*. 1995;324(1):15-25. Available from: <https://doi.org/10.1006/abbi.1995.9935>
- [138] Kaur H, Halliwell B. Evidence for nitric oxide-mediated oxidative damage in chronic inflammation Nitrotyrosine in serum and synovial fluid from rheumatoid patients. *FEBS Lett*. 1994;350(1):9-12. Available from: [https://doi.org/10.1016/0014-5793\(94\)00722-5](https://doi.org/10.1016/0014-5793(94)00722-5)
- [139] Ledoux SP, Driggers WJ, Hollensworth BS, Wilson GL. Repair of alkylation and oxidative damage in mitochondrial DNA. *Mutat Res - DNA Repair*. 1999;434(3):149-159. Available from: [https://doi.org/10.1016/s0921-8777\(99\)00026-9](https://doi.org/10.1016/s0921-8777(99)00026-9)
- [140] Surai PF, Kochish II, Fisinin VI, Kidd MT. Antioxidant defence systems and oxidative stress in poultry biology: An update. *Antioxidants*. 2019; 8(7):235. Available from: <https://doi.org/10.3390/antiox8070235>
- [141] Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. *World Allergy Organ J*. 2012;5(1):9-19. Available from: <https://doi.org/10.1097/WOX.0b013e3182439613>
- [142] Younus H. Therapeutic potentials of superoxide dismutase. *Int J Health Sci (Qassim)*. 2018;12(3):88-93. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5969776/>
- [143] Marklund SL. Extracellular superoxide dismutase and other superoxide dismutase isoenzymes in tissues from nine mammalian species. *Biochem J*. 1984;222(3):649-55.

Available from: <https://doi.org/10.1042/bj2220649>

[144] Chelikani P, Fita I, Loewen PC. Diversity of structures and properties among catalases. *Cell Mol Life Sci.* 2004;61(2):192-208. Available from: <https://doi.org/10.1007/s00018-003-3206-5>

[145] Dworzański J, Strycharz-Dudziak M, Kliszczewska E, Kiełczykowska M, Dworzańska A, Drop B, et al. Glutathione peroxidase (GPx) and superoxide dismutase (SOD) activity in patients with diabetes mellitus type 2 infected with Epstein-Barr virus. *PLoS One.* 2020;15(3):e0230374. Available from: <https://doi.org/10.1371/journal.pone.0230374>

[146] Lee S, Kim SM, Lee RT. Thioredoxin and thioredoxin target proteins: From molecular mechanisms to functional significance. *Antioxid Redox Signal.* 2013;18(10):1165-1207. Available from: <https://doi.org/10.1089/ars.2011.4322>

[147] Trivedi A, Singh N, Bhat SA, Gupta P, Kumar A. Redox Biology of Tuberculosis Pathogenesis. *Adv Microb Physiol.* 2012;60:263-324. Available from: <https://doi.org/10.1016/B978-0-12-398264-3.00004-8>

[148] Singhal SS, Singh SP, Singhal P, Horne D, Singhal J, Awasthi S. Antioxidant role of glutathione S-transferases: 4-Hydroxynonenal, a key molecule in stress-mediated signaling. *Toxicol Appl Pharmacol.* 2015;289(3):361-370. Available from: <https://doi.org/10.1016/j.taap.2015.10.006>

[149] Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, et al. Oxidative stress, aging, and diseases. *Clin Interv Aging.* 2018;13:757-772. Available from: <https://doi.org/10.2147/CIA.S158513>

[150] Luca M, Luca A, Calandra C. The Role of Oxidative Damage in the Pathogenesis and Progression of Alzheimer's Disease and Vascular Dementia. *V Oxid Med Cell Longev.* 2015; 2015:504678. Available from: <https://doi.org/10.1155/2015/504678>

[151] Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative Stress in Cancer. *Cancer Cell.* 2020;38(2):167-197. Available from: <https://doi.org/10.1016/j.ccell.2020.06.001>

[152] Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? *Free Radic Biol Med.* 2010; 49(11):1603-1616. Available from: <https://doi.org/10.1016/j.freeradbiomed.2010.09.006>

[153] Pignatelli P, Menichelli D, Pastori D, Violi F. Oxidative stress and cardiovascular disease: New insights. *Kardiol Pol.* 2018;76(4):713-722. Available from: <https://doi.org/10.5603/KP.a2018.0071>

[154] Sharifi-Rad M, Anil Kumar N V, Zucca P, Varoni EM, Dini L, Panzarini E, et al. Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases. *Front Physiol.* 2020;11:694. Available from: <https://doi.org/10.3389/fphys.2020.00694>

[155] Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature.* 2000;408(6809):239-247. Available from: <https://doi.org/10.1038/35041687>

[156] Chakrabarti S, Jahandideh F, Wu J. Food-derived bioactive peptides on inflammation and oxidative stress. *Biomed Res Int.* 2014;2014:608979. Available from: <https://doi.org/10.1155/2014/608979>

[157] Seeram NP, Henning SM, Niu Y, Lee R, Scheuller HS, Heber D. Catechin

and caffeine content of green tea dietary supplements and correlation with antioxidant capacity. *J Agric Food Chem.* 2006;54(5):1599-1603. Available from: <https://doi.org/10.1021/jf052857r>

[158] Alam MN, Bristi NJ, Rafiquzzaman M. Review on in vivo and in vitro methods evaluation of antioxidant activity. *Saudi Pharm J.* 2013;21(2):143-52. Available from: <https://doi.org/10.1016/j.jsps.2012.05.002>

[159] Benzie IFF, Strain JJ. Ferric reducing/antioxidant power assay: Direct measure of total antioxidant activity of biological fluids and modified version for simultaneous measurement of total antioxidant power and ascorbic acid concentration. *Methods Enzymol.* 1999;299:15-27. Available from: [https://doi.org/10.1016/s0076-6879\(99\)99005-5](https://doi.org/10.1016/s0076-6879(99)99005-5)

[160] Apak R, Güçlü K, Özyürek M, Çelik SE. Mechanism of antioxidant capacity assays and the CUPRAC (cupric ion reducing antioxidant capacity) assay. *Microchim Acta.* 2008;160:413-419. Available from: <https://doi.org/10.1007/s00604-007-0777-0>

[161] Prior RL. Oxygen radical absorbance capacity (ORAC): New horizons in relating dietary antioxidants/bioactives and health benefits. *J Funct Foods.* 2015;18:797-810. Available from: <http://dx.doi.org/10.1016/j.jff.2014.12.018>

[162] Huang D, Ou B, Hampsch-Woodill M, Flanagan JA, Prior RL. High-throughput assay of oxygen radical absorbance capacity (ORAC) using a multichannel liquid handling system coupled with a microplate fluorescence reader in 96-well format. *J Agric Food Chem.* 2002;50(16):4437-4444. Available from: <https://doi.org/10.1021/jf0201529>

[163] Moharram H, Youssef M. Methods for Determining the Antioxidant

Activity: A Review. *Alexandria J Food Sci Technol.* 2014;11(1):31-42.

[164] Číž M, Čížová H, Denev P, Kratchanova M, Slavov A, Lojek A. Different methods for control and comparison of the antioxidant properties of vegetables. *Food Control.* 2010;21(4):518-523. Available from: <https://doi.org/10.1016/j.foodcont.2009.07.017>

[165] Shahidi F, Zhong Y. Measurement of antioxidant activity. *J Funct Foods.* 2015;18:757-781. Available from: <http://dx.doi.org/10.1016/j.jff.2015.01.047>

[166] Chandrasekara A, Shahidi F. Bioactivities and antiradical properties of millet grains and hulls. *J Agric Food Chem.* 2011;59(17):9563-9571. Available from: <http://doi.org/10.1021/jf201849d>

[167] Gião MS, Leitão I, Pereira A, Borges AB, Guedes CJ, Fernandes JC, et al. Plant aqueous extracts: Antioxidant capacity via haemolysis and bacteriophage P22 protection. *Food Control.* 2010;21(5):633-638. Available from: <https://doi.org/10.1016/j.foodcont.2009.08.014>

[168] Wolfe KL, Rui HL. Cellular antioxidant activity (CAA) assay for assessing antioxidants, foods, and dietary supplements. *J Agric Food Chem.* 2007;55(22):8896-8907. Available from: <https://doi.org/10.1021/jf0715166>

[169] Vongsak B, Mangmool S, Gritsanapan W. Antioxidant Activity and Induction of mRNA Expressions of Antioxidant Enzymes in HEK-293 Cells of Moringa oleifera Leaf Extract. *Planta Med.* 2015;81(12-13):1084-1089. Available from: <https://doi.org/10.1055/s-0035-1546168>

[170] Dilworth LL, Stennett D, Omoruyi FO. Effects of Moringa oleifera Leaf Extract on Human Promyelocytic Leukemia Cells Subjected to Oxidative Stress. *J Med Food.* 2020;23(7):728-734.

Available from: <https://doi.org/10.1089/jmf.2019.0192>

[171] Yi G, Din JU, Zhao F, Liu X. Effect of soybean peptides against hydrogen peroxide induced oxidative stress in HepG2 cells: Via Nrf2 signaling. *Food Funct.* 2020;11(3):2725-37.

Available from: <https://doi.org/10.1039/C9FO01466G>

[172] McCullough ML, Peterson JJ, Patel R, Jacques PF, Shah R, Dwyer JT. Flavonoid intake and cardiovascular disease mortality in a prospective cohort of US adults. *Am J Clin Nutr.* 2012 Feb;95(2):454-464. Available from: <https://doi.org/10.3945/ajcn.111.016634>

[173] Patel H, Chandra S, Alexander S, Soble J, Williams KA. Plant-Based Nutrition: An Essential Component of Cardiovascular Disease Prevention and Management. *Curr Cardiol Rep.* 2017;19(10):104. Available from: <https://doi.org/10.1007/s11886-017-0909-z>

[174] Zhang X, Shu XO, Gao YT, Yang G, Li Q, Li H, et al. Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. *J Nutr.* 2003;133(9):2874-2878. Available from: <https://doi.org/10.1093/jn/133.9.2874>

[175] Randriamboavonjy JI, Loirand G, Vaillant N, Lauzier B, Derbré S, Michalet S, et al. Cardiac protective effects of moringa oleifera seeds in spontaneous hypertensive rats. *Am J Hypertens.* 2016;29(7):873-881. Available from: <https://doi.org/10.1093/ajh/hpw001>

[176] Bacanlı M, Dilsiz SA, Başaran N, Başaran AA. Effects of phytochemicals against diabetes. In: *Advances in Food and Nutrition Research.* Academic Press Inc. 2019;89:209-38. Available from: <https://doi.org/10.1016/bs.afnr.2019.02.006>

[177] Wilken R, Veena MS, Wang MB, Srivatsan ES. Curcumin: A review

of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. *Mol Cancer.* 2011;10:12. Available from: <https://doi.org/10.1186/1476-4598-10-12>

[178] Shanafelt TD, Lee YK, Call TG, Nowakowski GS, Dingli D, Zent CS, et al. Clinical effects of oral green tea extracts in four patients with low grade B-cell malignancies. *Leuk Res.* 2006;30(6):707-712. Available from: <https://doi.org/10.1016/j.leukres.2005.10.020>

[179] Hosseini A, Ghorbani A. Cancer therapy with phytochemicals: evidence from clinical studies. *Avicenna J phytomedicine.* 2015;5(2):84-97. Available from: <https://pubmed.ncbi.nlm.nih.gov/25949949/>

[180] Yun T-K, Choi S-Y, Yun H-Y. Epidemiological Study on Cancer Prevention by Ginseng: Are All Kinds of Cancers Preventable by Ginseng? *J Korean Med Sci.* 2001;19-27. Available from: <https://doi.org/10.3346/jkms.2001.16.S.S19>

[181] Patil VM, Masand N. Anticancer Potential of Flavonoids: Chemistry, Biological Activities, and Future Perspectives. In: *Studies in Natural Products Chemistry.* Elsevier. 2018;59:401-30. Available from: <https://doi.org/10.1016/B978-0-444-64179-3.00012-8>

[182] Aalinkeel R, Bindukumar B, Reynolds JL, Sykes DE, Mahajan SD, Chadha KC, et al. The dietary bioflavonoid, quercetin, selectively induces apoptosis of prostate cancer cells by down-regulating the expression of heat shock protein 90. *Prostate.* 2008;68(16):1773-89. Available from: <http://doi.wiley.com/10.1002/pros.20845>

[183] Kavitha R V, Kumar JR, Egbuna C, Ifemeje JC. Phytochemicals as therapeutic interventions in neurodegenerative diseases. In:

Phytochemicals as Lead Compounds
for New Drug Discovery.

Elsevier. 2019;161-178. Available
from: [https://doi.org/10.1016/
B978-0-12-817890-4.00010-X](https://doi.org/10.1016/B978-0-12-817890-4.00010-X)

[184] Velmurugan BK, Rathinasamy B,
Lohanathan BP, Thiyagarajan V, Weng CF.
Neuroprotective role of phytochemicals.
Molecules. 2018;23(10):2485. Available
from: [https://doi.org/10.3390/
molecules23102485](https://doi.org/10.3390/molecules23102485)

[185] Walker JM, Klakotskaia D, Ajit D,
Weisman GA, Wood WG, Sun GY, et
al. Beneficial effects of dietary EGCG
and voluntary exercise on behavior in
an Alzheimer's disease mouse model.
J Alzheimer's Dis. 2015;44(2):561-572.
Available from: [https://doi.org/10.3233/
JAD-140981](https://doi.org/10.3233/JAD-140981)

[186] Wobst HJ, Sharma A, Diamond MI,
Wanker EE, Bieschke J. The green tea
polyphenol (-)-epigallocatechin gallate
prevents the aggregation of tau protein
into toxic oligomers at substoichiometric
ratios. FEBS Lett. 2015;589(1):77-83.
Available from: [https://doi.org/10.1016/j.
febslet.2014.11.026](https://doi.org/10.1016/j.febslet.2014.11.026)

[187] Koh SH, Kim SH,
Kwon H, Park Y, Kim KS, Song CW,
et al. Epigallocatechin gallate protects
nerve growth factor differentiated PC12
cells from oxidative-radical-stress-
induced apoptosis through its effect
on phosphoinositide 3-kinase/Akt and
glycogen synthase kinase-3. Mol Brain
Res. 2003;118(1-2):72-81. Available
from: [https://doi.org/10.1016/j.
molbrainres.2003.07.003](https://doi.org/10.1016/j.molbrainres.2003.07.003)

[188] Zhang C, Browne A,
Child D, Tanzi RE. Curcumin decreases
amyloid- β peptide levels by attenuating
the maturation of amyloid- β
precursor protein. J Biol Chem.
2010;285(37):28472-28480. Available
from: [https://doi.org/10.1074/jbc.
M110.133520](https://doi.org/10.1074/jbc.M110.133520)

[189] Yuliani S, Mustofa, Partadiredja G.
The neuroprotective effects of an

ethanolic turmeric (*Curcuma longa* L.)
extract against trimethyltin-induced
oxidative stress in rats. Nutr Neurosci.
2019;22(11):797-804. Available from:
Available from: [https://doi.org/10.1080/
1028415X.2018.1447267](https://doi.org/10.1080/1028415X.2018.1447267)

[190] Yang X, Zheng T, Hong H, Cai N,
Zhou X, Sun C, et al. Neuroprotective
effects of Ginkgo biloba extract and
Ginkgolide B against oxygen-glucose
deprivation/reoxygenation and
glucose injury in a new in vitro
multicellular network model. Front
Med. 2018;12(3):307-318. Available
from: [https://doi.org/10.1007/
s11684-017-0547-2](https://doi.org/10.1007/s11684-017-0547-2)

[191] Wu W, Wang X,
Xiang Q, Meng X, Peng Y, Du N, et al.
Astaxanthin alleviates brain aging in
rats by attenuating oxidative stress and
increasing BDNF levels. Food Funct.
2014;5(1):158-66. Available from:
<https://doi.org/10.1039/c3fo60400d>