Chapter

Valorization of Natural Antioxidants for Nutritional and Health Applications

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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; dificult 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 applys 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, *e.g.* 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 bioactivy; lower selectivy; 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.
Geen 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 propel 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 eith 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].

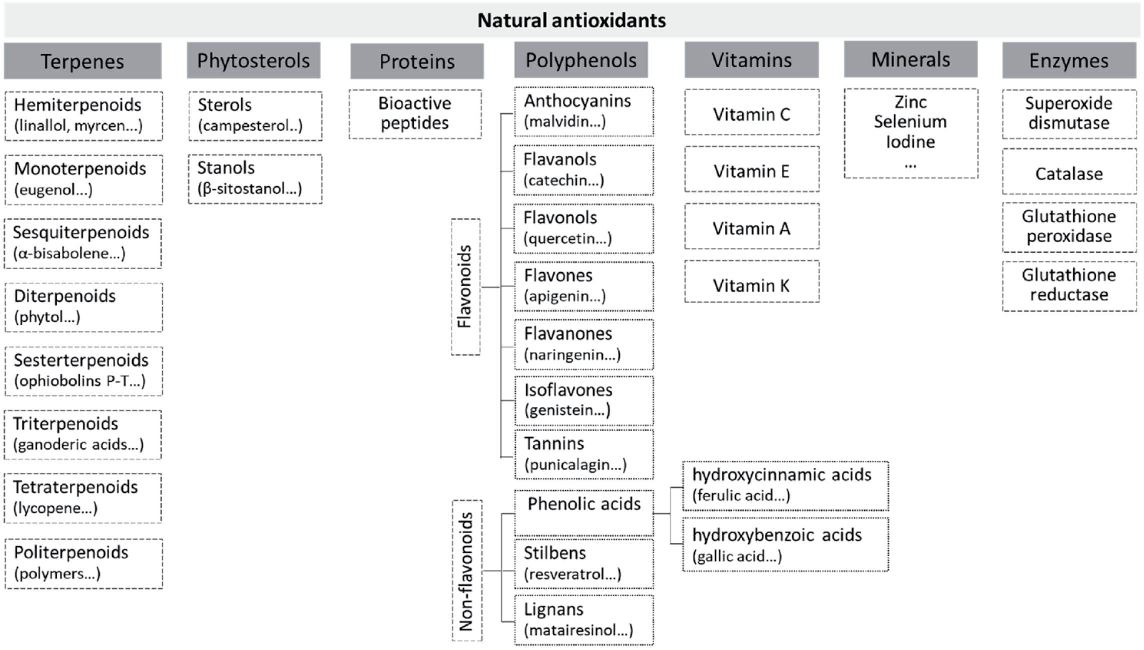

Figure 1.
Classification of natural antioxidants.

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**
Plants and by-products				
Passion fruit peel	Carotenoids Pectin	MAE,UAE (water, 0live 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]
Microalgae				
Spirulina platensis	Polyphenols Carotenoids Phycobiliproteins	OH; MAE; PEF; UAS; EAE (water, ethanol)	Antioxidant Antimicrobial Anticancer Anti-inflammatory	[86–95]
Heterochlorella luteoviridis	Carotenoids Lipids	OH; UAE (ethanol)	Antioxidant Anti-inflammatory	[96, 97]

Sources	Compounds	Technologies (Solvents)	Bioactivities	References
Chorella vulgaris	Carotenoids Polyphenols	PEF; SFE (CO_2, Water, water: ethanol)	Antioxidant Antimicrobial Anticancer Anti-inflammatory	[98–101]
Nannochloropsis spp	Carotenoids Chlorophylls Polyphenols Proteins Lipids	UAE; PEF; PLE (water, ethanol, dimethyl sulfoxide)	Antioxidant UV-protective Anti-inflammatory Anticancer	[102–104]
Phaeodactylum tricornutum	Proteins Pigments Lipids Carotenoids Chlorophylls Polyphenols	HVED; HHP; PLE, MAE (water, ethanol, chloroform: methanol)	Antioxidant	[17, 105]
Neochloris oleoabundans	Carotenoids	PLE (ethanol)	Antioxidant	[106]
Macroalgae				
Gracilaria	Sulfated polysaccharides	Maceration by liquid nitrogen (sodium acetate buffer)	Antioxidant	[42]
Laminaria ochroleuca	Fatty acids Polyphenols	PLE (hexane, ethyl acetate, ethanol and ethanol:water)	Antioxidant Anti-atherogenic	[107]
Ascophyllum nodosum *Laminaria japonica* *Lessonia trabeculate* *Lessonia nigrecens*	Polyphenols	MAE (70% methanol)	Antioxidant Anti-hyperglycemic	[108]
Fucus serratus *Laminaria digitata* *Gracilaria gracilis* *Codium fragile*	Polyphenols	PLE (water, ethanol/water, and methanol/water)	Antioxidant Antiproliferative	[40, 109]
Palmaria palmata	Proteins Peptides	EAE (water)	Antioxidant Cardioprotective Anti-inflammatory Anti-diabetic	[110, 111]
Gelidium pusillum	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 ($^{\cdot}O_2$). 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 $^{\cdot}O_2$ 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 caw 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, antidibetic, 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 enchased when there is no sugar molecules attached with them. This means that tea polyphenol 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 triterpens. 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 de 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.

$$M^{(n+1)} - SOD + O_2^- \rightarrow M^{n+} - SOD + O_2 \tag{1}$$

$$M^{(n+)} - SOD + O_2^- + 2H^+ \rightarrow M^{(n+1)} - SOD + H_2O_2 \tag{2}$$

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].

$$2H_2O_2 \rightarrow O_2 + H_2O \tag{3}$$

$$H_2O_2 + Fe(III) - E \rightarrow H_2O + O = Fe(IV) - E(.+) \tag{4}$$

$$H_2O_2 + O = Fe(IV) - E(.+) \rightarrow H_2O + Fe(III) - E + O_2 \tag{5}$$

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].

$$2GSH + ROOH \rightarrow GSSG + 2ROH + H_2O \tag{6}$$

$$2GSH + H_2O_2 \rightarrow GSSG + 2H_2O \tag{7}$$

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 peroxynitrite using Trx as electrons donor (Eq. 8) [141, 147].

$$2R`{-}SH + ROOH = R`{-}S - S - R`{+}H_2O + ROH \tag{8}$$

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].

$$RX + GSH = HX + R - S - GSH \tag{9}$$

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], Haemololysis inhibiton assay [167], 2′,7′-dichlorofluorescin 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 H_2O_2 in HEK-293 cells [169]. Dilworth *et al*. presented similar results, it was demonstrated that the presence of *Moring 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 Diphenylpicrylhhydrazine. Scavenging activity mechanism.	Colorimetric	[1]
2,2`-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS)	In the presence of antioxidant $ABTS^{\cdot+}$ is reduce to ABTS resulting in a decrease in color. Scavenging activity mechanism.	Colorimetric	[157, 158]
$O_2^{-\cdot}$ scavenging activity	This assay is optimized for enzymatic antioxidants and relies on the competition kinetics of $O_2^{-\cdot}$ reduction of cytochrome C (probe) and $O_2^{-\cdot}$ scavenger (sample). Not suitable for non-enzymatic antioxidants. Scavenging activity mechanism.	Fluorescence	[1]
H_2O_2 scavenging activity	A common assay that claims to measure H_2O_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-triaza-2-azoniacyclopenta-1,4-diene chloride (TPTZ) is reduce 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 peroxyl radicals by way of a hydrogen atom transfer (HAT) process. Peroxyl radicals are produced by a free radical initiator, which quenches the fluorescent probe over time. Antioxidants present in the assay work to block the peroxyl radical oxidation of the fluorescent probe until the antioxidant activity in the sample is depleted. The remaining peroxyl 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-phytocoerythrin 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 consuption of plant-based foods decrease the prevalence of cardiovascular diseases [173]. Zhang *et al.* examinated 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 benefices 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-κβ [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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