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processes

Review

Advances in Ascorbic Acid (Vitamin C) Manufacturing: Green Extraction Techniques from Natural Sources

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Abstract: Ascorbic acid (AA), or vitamin C, is one of the most important vitamins consumed through the diet due to its critical role in many biological processes. Although the human body cannot synthesize it, AA is essential in maintaining healthy bodily structure, acting as a cofactor of many enzymes involved in collagen synthesis and an efficient immune system. At the same time, AA is used in the cosmetic field for its antioxidant and antipigmentary properties, in the food industry as additive, and in chemical synthesis as reducing agent. AA can be chemically synthesized, produced by the oxidative fermentation of bacteria, or extracted from natural sources. This review addresses the most recent developments in its manufacture, including techniques for extracting vitamin C from plants, fruits, vegetables, algae, and leaves, and focusing on the most commonly used green methods, i.e., ultrasound-assisted extraction, microwave-assisted extraction, pressurized liquid extraction, and supercritical fluid extraction. These methods are based on mild extraction conditions, environmentally friendly solvents, low time, cost, and energy consumption. In contrast, their extraction yields are comparable to or even higher than those of conventional methods.

Keywords: ascorbic acid; vitamin C; green extraction method; ultrasound-assisted extraction; microwave-assisted extraction; pressurized liquid extraction; supercritical fluid extraction; nutraceutical

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1. Introduction

Vitamin C, or ascorbic acid (AA, C_6H_8O), is one of the most important water-soluble molecules present in foods and is involved in many biological processes of the human body. It was identified and isolated for the first time in 1928 by the Hungarian biochemist and Nobel Prize winner Szent-Györgyi, as a molecule to prevent and treat scurvy [1,2]. The term vitamin C includes two different compounds: AA in reduced form (L-ascorbic acid), which is the predominant one, and the oxidized form (L-dehydroascorbic acid, DHAA) [3].

AA is an essential nutrient for humans and animals, but it is also an important product in the pharmaceutical, cosmetics, and food industries, with a global market in 2022 around 1.24 billion [4].

Vitamin C can be produced in three different ways: it may be chemically synthesized, produced via oxidative fermentation by bacteria, or extracted from natural sources. The first patented AA production method, currently still in use, is the Reichstein method, which is based on several steps composed of six chemical syntheses and one microbial transformation with Acetobacter sp. This method has a high conversion efficiency; it uses cheap raw materials, such as glucose, and produces chemically stable intermediates. However, it involves high operating costs, multiple steps, the use of harmful solvents, and high waste disposal costs [4,5]. Another type of AA production is two-step fermentation, an evolution of the previous method with improved environmental impact, fewer toxic compounds, and lower costs [5]. This method starts from the hydrogenation of D-glucose in D-sorbitol; a first fermentation through *G. suboxydans*, *A. suboxydans*, and *G. oxydans* is needed to obtain L-sorbose, and a second using a synergic microbial culture is needed for

2-keto-L-gulonic acid synthesis; subsequent esterification and lactonization then produce vitamin C [6]. To further simplify AA production through fermentation involving fewer steps, a recent one-step fermentation method was introduced by exploiting the metabolic pathway to directly synthesize AA from glucose or sorbitol using *Saccharomyces cerevisiae*, *Erwinia herbicola*, and a mixed culture (*K. vulgare* and *G. oxydans*) [4,7–9].

In addition to these synthesis methods, AA could also be extracted from plants, fruits, vegetables, and algae. The content of vitamin C in foods is generally high (10–100 mg/100 g) compared to other compounds, probably because it is composed of sugars, which are present in all plant species [10]. Plants, fungi, and algae can synthesize AA in mitochondria and microsomal fractions, starting from D-glucose or D-galactose [11].

The richest sources of vitamin C are fruits from different parts of the world, such as the kakadu plum from Australia, camu-camu and acerola from South America, and rosehip and sea buckthorn in Europe and Asia. Star fruit, guava, black currant, kiwifruit, and strawberry are good sources of dietary AA; citrus fruits have a lower but acceptable content of vitamin C. AA is also contained in cruciferous vegetables, kale, peppers, spinach and other green-leaf vegetables, tomatoes, asparagus, and Brussels sprouts. A significant amount of AA can also be found in fresh aromatic herbs and algae, while grains, starchy roots and tubers, and animal products, i.e., meat, eggs, and dairy, contain very little AA [10,12,13]. In addition to AA from fresh vegetables and fruits, extraction of AA allows the reuse and valorization of some waste materials produced by the food industry. Every year, it generates a massive amount of waste material, such as peels and seeds, from juice and jam production, causing environmental and economic problems. However, this waste is still a rich source of bioactive compounds, allowing the combination of these valuable compounds' extraction with the recycling of waste materials from the food industry [14–17]. For instance, orange is one of the most well-known and rich sources of AA and, alongside the pulp, the peel contains three times more vitamin C than the inner, edible part of the fruit [18,19]; pomegranate peel is a rich source of tannins, flavonoids, and other phenolic compounds, and its extract, with antioxidant and antimutagenic properties, contains more AA than the fruit or the seeds [20,21].

This review aims to provide technical information about the extraction of AA from different vegetal sources and their yield, presenting a comparative overview of modern green extraction methods, i.e., microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), supercritical fluid extraction (SFE), and pressurized liquid (PLE), as alternatives to other conventional solvent extraction (CSE) methods, such as Soxhlet, hydrodistillation, and maceration.

2. Ascorbic Acid Applications

2.1. AA as Dietary Supplement

Vitamin C plays a critical role as an antioxidant and a cofactor in enzyme reactions, involved in the maintenance of healthy body structure in the skin, bones, teeth, tendons, and blood vessels; it is also involved in iron adsorption and immune response regulation [22]. Animals can synthesize this vitamin in the liver or kidneys. In contrast, humans and primates have lost this ability due to a mutation in the coding sequence of the enzyme L-gulono-gamma-lactone oxidase. Thus, its intake is derived from the diet [23,24]. The recommended daily dose is still widely debated, with variations in guidelines depending on country, region, and organization, ranging between 40 and 220 mg. This recommended intake aims to maintain the level of plasmatic AA at 50–75 µmol/L; if it decreases to under 23 µmol/L, the affected organism experiences hypovitaminosis C, with related symptoms such as fatigue, lethargy, and mood changes. If it further decreases to under 11 µmol/L, there is a vitamin C deficiency [25,26]. Besides the different guidelines' values, recommendations regarding sufficient intake are more or less the same, and fall into four categories: preventing scurvy, saturating immune cells with AA whilst limiting its urinary excretion, maintaining an adequate plasma concentration of AA by replacing its daily turnover, and optimizing individual health [27]. The levels of plasmatic AA vary with age

and gender; it is higher in children of 6 to 11 years old, then it decreases over time, and after 60 years old, it increases again. Regarding gender, it is higher in women than men [28].

AA concentrations are affected by various factors, i.e., dietary intake, absorption, distribution, oxidative decomposition, and excretion. Oral ingestion is the first route of administration of vitamin C, and in humans, it is usually stored in the skeletal muscles; healthy subjects can saturate the level of muscle AA using only a balanced diet, while diseased individuals and smokers may need supplements [29].

Vitamin C can be administered using different routes. The oral route is strictly ruled by intestinal adsorption and limited by an active transport mechanism; the intravenous route avoids the gastrointestinal passage, increasing the plasma levels until renal clearance re-establishes homeostasis. For some more peripheral applications, a topical route is preferred, to improve bioavailability [30].

In general, oral administration is the most commonly used method; thus, its homeostasis is driven by the interplay of different mechanisms: intestinal absorption by sodium-dependent vitamin C transporter 1 (SVCT1); kidney filtration and reabsorption in the proximal tubule through SVCT1; cells' internalization mediated by sodium-dependent vitamin C transporter 2 (SVCT2); and urinary excretion [12,31].

AA can be transported across membranes using three mechanisms: passive, facilitated, and active transport (Figure 1).

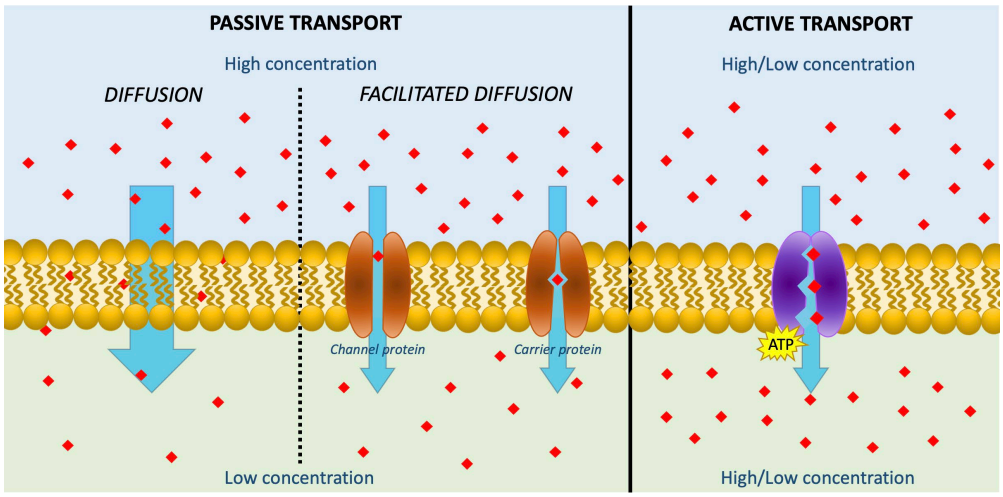

Figure 1. Schematic figure describing the transportation of AA across membranes using three mechanisms: passive diffusion, facilitated diffusion, and active transport. The red squares represent Vitamin C.

Passive diffusion is the most important transport route for small molecules; however, since AA is present primarily as a monoanion at a physiological pH, it is highly water-soluble, and the diffusion rate across membranes is very slow, even at high concentrations [32]. In contrast, in the stomach and small intestine, the acid pH (1 and 5, respectively) increases the presence of unionized AA, favoring this kind of transport mechanism [26]. Facilitated diffusion is based on carrier proteins and, as a form of passive diffusion, depends on the electrochemical gradient. For instance, thanks to its structural similarities to glucose, DHAA is absorbed through several glucose transporters, competing with glucose [33]. The presence of this AA's oxidized form is negligible in healthy individuals' blood, but its intestinal concentration is probably higher because of the lack of intracellular recycling and high food concentrations. This may explain repeated results regarding the similar bioavailability of AA and DHAA [26,34]. However, the most important mechanism for AA membrane transport is the active one, where transporters, i.e., SVCT1 and SVCT2, play a crucial role. In the distal ileum, SVCT1 mediates the transport of AA to enterocytes, and is saturable and sodium-dependent. Thus, the absorption is not linear, and the bioavailability is maximum in low doses, while it decreases when the dose increases to above 200 mg [10].

The uptake of AA by cells is mediated by SVCT2, a close analogue of SVCT1, sharing with it a 65% sequence homology. SVCT2 is more expressed in specialized cells in different organs and has a higher affinity but lower efficiency than SVCT1. The transport is unidirectional and based on electrochemical sodium gradients. Besides low efficiency, SVCT2 has high sensitivity, also working at low concentrations of AA. This aspect meets the physiological need for massive absorption of AA through SVCT1 from the gastrointestinal tract and the capacity of SVCT2 to uptake AA in the cells even at low plasma concentrations [10,26,35,36].

From the biological point of view, ascorbic acid is of great importance due to its antioxidant and radical scavenger properties, even if the biochemical bases of this behavior are still not understood. This antioxidant behavior is unusual, since AA donates a single reducing equivalent, forming monodehydroascorbate, which reacts preferentially with radicals instead of non-radical compounds [37].

Ascorbic acid and its biological potential were initially discovered for the treatment of scurvy, once a very common disease, but now classified as rare; it developed during long sea voyages, when fresh fruit and vegetable stocks ran out, and without intervention typically led to death [38,39].

AA is essential for collagen synthesis; the enzymes procollagen-proline dioxygenase and procollagen-lysine dioxygenase, involved in the cross-linking of collagen chains, require ascorbic acid. AA does not directly participate in these reactions, but since these enzymes contain Fe^{2+} as a cofactor, and it tends to oxidize to Fe^{3+}, inactivating the enzymes, AA is needed to reduce Fe^{3+} back to Fe^{2+} [37]. AA is the cofactor of eight human enzymes; three of them participate in collagen hydroxylation, specifically the synthesis of norepinephrine, the amidation of peptide hormones, and tyrosine metabolism. A further two enzymes are involved in carnitine biosynthesis. In addition, the enzymes ascorbate oxidase and ascorbate peroxidase can reduce O_2 and H_2O_2 in H_2O, using AA as a single-equivalent donor [32,37,40].

AA also plays a critical role as an antioxidant and free-radical scavenger in the non-enzymatic reduction of superoxide, hydroxyl, alkoxyl, peroxyl, tocopheroxyl and other radicals. These radicals take a single H atom from ascorbic acid, oxidizing it to monodehydroascorbate [37]. AA, as a radical scavenger, protects cells against reactive oxygen species (ROS)' oxidative damage, thanks to its ability to reduce ROS in stable ascorbate free radicals (AFR) serving as a one-electron donor. Then, NADH- and NADPH-dependent reductases reduce AFRs back to ascorbate inside cells. This scavenging property might explain AA's cytoprotective function, i.e., the prevention of the oxidation-induced DNA mutation, the protection of lipids from oxidative damage, and the maintenance of protein integrity through the repair of oxidized amino acid residues [41].

Besides its antioxidant action, AA can also exhibit pro-oxidant effects. It exerts biological protection against free transition metal ions in solutions, such as iron or copper, reducing Fe^{3+} to Fe^{2+}, then re-oxidize producing superoxide, H_2O_2, and hydroxyl radical via Fenton chemistry. Furthermore, AA oxidizes itself in monodehydroascorbate, reducing quinones to semiquinones, which can then reoxidize in superoxide. Superoxide is then reduced by AA and monodehydroascorbate in H_2O_2 [37,42].

Thanks to all these properties, vitamin C is extensively used for the prevention and/or the treatment of chronic and acute pathologic conditions like diabetes, cataracts, glaucoma, macular degeneration, atherosclerosis, stroke, heart diseases, and cancer [2].

AA is also well known as an immune system enhancer. Leukocytes accumulate AA against the gradient, resulting in an inner concentration 50 or 100 times higher than the plasma level, and their saturation could be reached with a dietary intake of ~100 mg/day, conferring a protective effect on these cells [1]. Neutrophils internalize vitamin C via SVCT2, enhancing their chemotactic and microbial killing ability and protecting them from oxidative damage. Lymphocytes accumulate AA through SVCT; even though its action in these cells is still unclear, it surely exerts an antioxidant effect. Vitamin C promotes lymphocyte proliferation, resulting in enhanced antibody production and reduced susceptibility to

cell death stimuli, i.e., exposure to toxins and chemicals. In addition, AA induces T and natural killer cell differentiation and maturation [43].

In recent years, with the outbreak of the COVID-19 pandemic, vitamin C has been proposed as a supplement in treatment and prevention protocols for its antioxidant and immune enhancer properties, but also for its safety profile and low cost [44,45].

Intravenous injection of high doses of vitamin C has a cytotoxic effect on cancer cells, and many ongoing clinical trials are exploring its safety and efficacy in treating various types of cancer as a monotherapy or combination therapy. Cancer cells are generally more sensitive to oxidative stresses than normal cells for their upregulated metabolism and defective mitochondria [46]. There are many hypotheses posited to explain the anticancer effect of vitamin C. One of them is that pharmacological concentrations of AA cause a pro-oxidant effect, stimulating the formation of hydrogen peroxide and ROS, which have a direct cytotoxic activity on cancer cells. This mechanism is even enhanced by the presence of redox-active transition metals, such as iron, inside the cancer cells. In addition, after administration, AA is oxidized in DHAA and, thanks to its structural similarities with glucose, it is internalized by the upregulated glucose transporters of cancerous cells. Once inside the cell, the DHAA is reduced back to AA at the expense of intracellular antioxidants, increasing the endogenous levels of ROS [46,47]. Another hypothesis is based on the epigenetic changes induced by AA due to its effect on 2-oxoglutarate-dependent dioxygenases, like histone and DNA demethylases [48,49]. In addition, DNA demethylation, mediated by the ten-eleven translocation enzymes activation, allows the re-expression of tumor-suppressor genes in cancer cells such as p53, promotion of stem cell differentiation, inhibition of leukemogenesis, and enhancement of DNA methyltransferase inhibitor-induced immune signals via increased expression of endogenous retrovirus transcripts. AA also plays a role in cancer treatment by enhancing chemo and radiosensitivity and decreasing the side effects by acting as a prodrug for hydrogen peroxide [50,51]. Furthermore, it can enhance the efficacy of immunotherapy, modulating cytokine generation, improving T cell responses by reverting their exhaustion-associated DNA methylation program and helping to overcome resistance to the immune checkpoint blockade [52,53].

AA has also been proposed for the treatment of patients with septic shock, and its parenteral administration with this aim has undergone many clinical trials. In addition to its antioxidant and scavenging properties, vitamin C acts as a cofactor for dopamine b-hydroxylase and tyrosine hydroxylase, increasing the endogenous production of norepinephrine, dopamine, and vasopressin, usually administered to manage hypotension refractory to catecholamines, which is a hallmark of sepsis. In addition, it may improve and preserve microvascular function, contribute to endothelial cell proliferation and apoptosis, smooth-muscle-mediated vasodilation, and endothelial barrier permeability; attenuate neutrophil necrosis; and demonstrate bacteriostatic activity [54,55].

2.2. AA in Cosmetics

Besides the oral route, ascorbic acid can also be administered topically for skin health applications, since it is involved in skin synthesis, depigmentation, and antioxidant activity.

Thanks to its high aqueous solubility, AA is available in the aqueous compartments of the cell; thus, skin application is one of its most established functions. It acts as a potent antioxidant by neutralizing and removing oxidants produced by the skin's interactions with environmental pollutants or after ultraviolet light exposure, especially in the epidermis, wherein vitamin C is more concentrated [56]. Repeated exposure to UV light reduces the availability of AA in the skin. Although it has no UV absorption spectra in the UVA (320 to 400 nm) or UVB (290 to 320 nm) range, topical administration of AA can exert a photoprotective effect against UVR due to its antioxidant and anti-inflammatory properties [30].

After wounding, the vitamin C level in the injured site decreases dramatically due to depletion generated by free oxidant radicals and its increased consumption in biological repair processes. Apart from the antioxidant action in contrasting oxidative stress, AA assists fibroblasts in producing and cross-linking a stable form of collagen, providing a

strong framework for repair; it also suppresses pro-inflammatory processes and promotes anti-inflammatory and pro-resolution effects in macrophages [57,58].

Furthermore, AA is also used in cosmetics as an antipigmentary agent, through interacting with the copper ions of tyrosinase enzymes, which converts tyrosine into melanin, thereby inhibiting its action in some conditions such as skin hyperpigmentation, melasma, or age spots [30,59].

However, AA is chemically active and unstable in aqueous media, as it is easily oxidizable or decomposable, very prone to photooxidation, and its skin absorption is limited. For these reasons, AA's topical efficacy has been improved using different approaches. The first approach is to use some hydrophobic AA precursors, which can increase AA's concentration in the cytoplasm, easily crossing the cell membrane [60], or in AA glycosides, which act as a reservoir of AA thanks to its continuous release due to enzymatic hydrolysis [61]. The second approach is the application of technologies to cosmetics, such as the encapsulation of AA inside reverse micelles, nanoparticles, or liposomal formulations, which can maintain its stability and improve its delivery to the target site [62,63].

2.3. AA Industrial Applications

AA's strong antioxidant activity has encouraged the food industry to develop some additives based on this compound. Nowadays, there are several commercial food additives derived from AA: E300, ascorbic acid; E301, sodium ascorbate; E302, calcium ascorbate; E303, potassium ascorbate; and E304, fatty acid esters of ascorbic acid (ascorbyl palmitate and ascorbyl stearate). They are used in the production and transformation phases of several foods such as beer, gelatines, jam, sweets, bread and baked products, fruit juices, wine, fishing products, and meats. AA in foods usually prevents nitrosation and oxidation, as well as the discoloration of products during storage, which could be unpleasant for the consumers but is not associated with organoleptic alterations [64,65].

In addition, AA is also used for animal feed, with the aim of body weight gain, feed efficiency, nutrient digestibility, immune response, and antioxidant status [66–68].

AA is widely used in the chemical industry as additive, as it is a weak reducing agent thus can suppress the oxidation of desired compounds [69–72]; it can also be used as a leaching agent for valuable metals [73,74].

3. Ascorbic Acid Extraction

In recent years, several methods have been developed to extract bioactive compounds from natural sources. Some of them are based on solvent extractions, i.e., Soxhlet and maceration, but they have demonstrated some drawbacks regarding environmental sustainability, economy, and energy costs. Thus, in recent decades, some alternative green techniques have started to be considered effective alternatives (Figure 2).

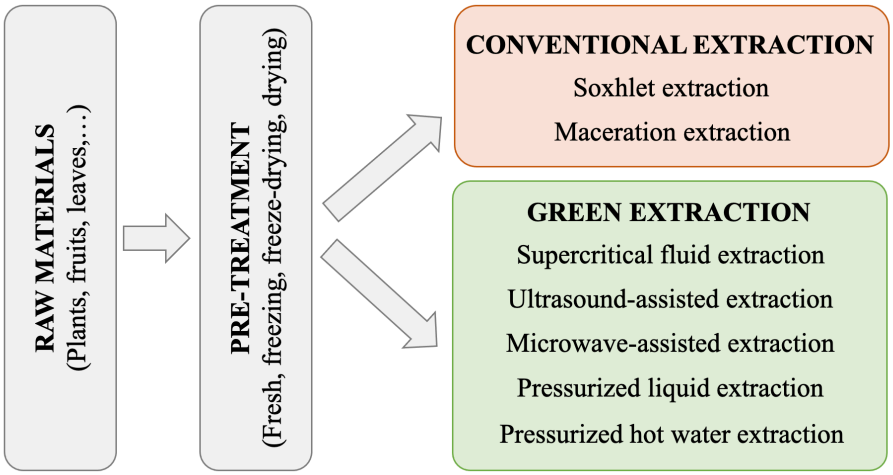

Figure 2. Conventional and green extraction methods for naturally derived compounds.

3.1. Pretreatments

The extraction process usually starts from raw materials; fruits (or parts of them, such as peel and seeds), leaves, vegetables, algae, or other plant-derived materials are collected, cleaned to discard useless parts, and washed with water. The resulting material can be used either fresh or pre-treated through freezing, freeze-drying, or heat-drying, and then milled to obtain a dry powder.

The recovery of the desired bioactive compound strongly depends on the parameters of this pretreatment step. Since AA is thermo-sensitive, high processing temperatures and long exposure at these temperatures (50–60 °C) can reduce the extraction yield [75–77]. Furthermore, the final yield of vitamin C recovery strongly depends on the method used to heat-dry the samples. For instance, microwave drying better preserves the AA sample content than infrared drying, through heating its entire volume and reducing the drying time. Additional pressure reduction during microwave drying could reduce the vitamin C oxidation, favoring better recovery of the compound [76,78]. However, comparing all the drying methods, freeze-drying seemed to be the best technique for preserving AA content if compared to conventional oven-drying or microwaves. Although there is still a small loss of vitamin C if compared to fresh samples, the mild temperatures used guarantee a higher yield than other methods [79,80].

In addition to these pretreatments, some extraction methods could be combined to enhance the final yield of vitamin C. Since AA is a heat-sensitive compound, the preferred pretreatments are the non-thermal ones. One of the most used is ultrasound (US) pretreatment, which can modify the structure of the material, but without an excessive increase in the temperature [81]. It has proven to be an excellent method of facilitating the further release of vitamin C from different materials, such as cabbage leaves [81], honeyberries [82], and cashew apples [83]. A more recent pretreatment method is the pulsed electric field (PEF) which electroporates cell membranes, facilitating the recovery of bioactive compounds with a subsequent extraction step [84].

3.2. Conventional Solvent Extraction

Conventional solvent extraction (CSE) stands as one of the most widely employed and recognized methods for solid–liquid extraction. An everyday example of this technique can be found in the preparation of tea or coffee. Its fundamental principle involves immersing raw materials, such as plants, fungi, fruits, or algae, in a suitable solvent capable of selectively gathering the desired compounds. Subsequently, solid residues are separated through centrifugation and/or filtration. The resulting extract can then serve various purposes, including as an additive, a dietary supplement, or in the formulation of functional foods [85]. CSE encompasses several techniques. Among them are Soxhlet extraction and maceration.

Soxhlet extraction, initially designed for lipid extraction and subsequently applied to various purposes, involves repeatedly passing a solvent through a small quantity of dry sample. This repetitive process aims to enhance the extraction yield. However, it is worth noting that while this method is well optimized, it comes with the disadvantage of extended extraction times and the use of substantial quantities of potentially polluting solvents.

In the maceration process, a finely ground sample is mixed with a solvent. The addition of agitation can augment the extraction yield by promoting compound diffusion and facilitating the removal of concentrated solutions from the sample's surface. This technique has found extensive use in obtaining essential oils and bioactive compounds.

The optimization of both the quantity and quality of plant-derived bioactive compounds extracted via CSE is heavily contingent upon the choice of solvent. The polarity of the target compound is the driving parameter for the solvent choice, but the molecular affinity between solvent and solute, mass transfer, use of co-solvent, environmental safety, human toxicity, and costs should also be considered [86,87]. For instance, in the case of AA, an acid extraction solution is preferable for the stabilization of the isolated vitamin C; the

most frequently used acids for this purpose are metaphosphoric acid, oxalic acid, acetic acid, ethylenediaminetetraacetic acid, and sulfuric acid [22].

Some examples of the applications of CSE for vitamin C extraction are summarized in Table 1.

Table 1. Applications of CSE for vitamin C extraction.

Parameters	Source	Pretreatment	Yield (mg/100 g)	Ref.
1:2 *w*/*v* in 95% ethanol for 24 h	Orange Tomato pomace	Fresh	59 14	[88]
1:25 in ethanol for 24 h	Grapefruit peels Lemon peels Orange peels	Freeze-dried	113 59 110	[89]
Acetic acid 1%	Oenanthe linearis Sonchus arvensis	Shed-dried	1539 1211	[86]
Citric acid 3%	Orange	Frozen	38	[11]
Ethanol, 24 h, and 160 rpm	Lead tree sprouts	Freeze-dried after 3 days of germination	180	[90]
Methanol 5%, citric acid (21 g/L) and EDTA (0.5 g/L)	Camu-camu Camu-camu seeds and peels	Spray-dried Fluid-bed dried	3510 9040	[91]
Metaphosphoric acid-acetic acid	Orange Pomelo Mandarin Lemon Lime Red grapefruit peel Green grapefruit peel White grapefruit peel	Freeze-dried	50 72 42 59 41 34 67 44	[92]
A mixture of methanol, ethanol, acetone, and water	Pomegranate peels Pomegranate pulp	Fresh	99 85	[93]

There are many patents based on the solvent extraction of ascorbic acids from fruits; some examples are reported in Table 2.

Table 2. Some examples of patents based on CSE.

Patent Number	Method Description	Ref.
EP2044849A1	Amla compounds were extracted using ethanol, and the extract was enriched by different additions of amla juice followed by vacuum concentration	[94]
EP1889616A2	AA was extracted from dog rose, acerola, and camu-camu using an aqueous solution with ethanol and a dissolved gas (CO_2), also applying a magnetic field	[95]
CN112898249A	AA was extracted from lyophilized and milled peels and pulp of kiwi fruits using an oxalic acid solution	[96]
CN114149390A	AA was extracted from golden pomelo using a debitterizing solution	[97]
CN107298663A	AA was extracted from lemon	[98]
CN111349062A	Acerola cherry juice was pre-treated with cellulase and pectinase before the CSE	[99]
CN106588839A	AA extracted from sweet persimmon with cold water	[100]
CN104292196A	AA was extracted from sweet tea powder with water in a ratio of 1:10–1:40, adding pH buffer to pH 5.0–7.0	[101]
CN104544131A	AA was extracted from ginseng fruits, ginkgo biloba extract, honeysuckle extract and sodium sulfite, using an aqueous solution of oxalic acid, hydrochloric acid and metaphosphoric acid as an extraction solution at 40–60 °C for 1–30 min	[102]

CSE gives a low yield of AA compared to other methods [77]. In addition, this process is highly time consuming, expensive, and requires the use of polluting solvents, pushing researchers toward the development of more cost-effective and greener techniques for the extraction of compounds from natural matrices [103].

3.3. Ultrasound-Assisted Extraction

Ultrasound-assisted extraction (UAE) has emerged as a promising technique for the extraction of bioactive natural compounds due to its simplicity and safety, cost and time savings, and reduced use of organic solvents. UAE utilizes ultrasound waves, which have longer wavelengths than audible ones, typically in the millimeter range. These waves cannot directly interact with the molecules in the matrix. Instead, the chemical changes they induce result from the significant energy they generate [104].

Ultrasonication (US) is employed in extractions due to the transmission of acoustic waves, which induce cavitation phenomena [105]. Specifically, the collapse of a cavitation bubble generates a microjet directed toward the plant or fruit matrix. During this process, characterized by high pressures and temperatures, cell walls are disrupted, leading to the release of cellular compounds into the surrounding solvent [77,106].

UAE is typically conducted using an ultrasonic bath operating at a frequency of at least 20 kHz. Several patents have been filed for the extraction of vitamin C using the UAE method. For instance, CN106432155A describes the extraction of AA from ephedra fruits [107], while CN106432154A details a similar process for *Pouteria caimito* [108]. The inventors of CN110623951A employed oxalic acid as an extractant solution to produce granules from *Rosa roxburghii* [109].

As previously mentioned, US can be combined with other extraction methods, either as a pretreatment or in tandem, to enhance overall yield. For example, in the case of vitamin C extraction, US can be applied before microwave treatment or following the treatment of samples with pulsed electric fields [19].

3.4. Microwave-Assisted Extraction

The Microwave-Assisted Extraction (MAE) method harnesses microwave (MW) irradiation to rapidly elevate the internal temperature and pressure of plant or fruit cells. This process takes advantage of two oscillating perpendicular fields, namely electric and magnetic fields [110]. The increase in temperature disrupts hydrogen bonds within the cells, while the rise in pressure induces physical changes, enhancing the porosity of the biological matrix. This, in turn, enables the penetration of the solvent and the extraction of internal compounds [111]. Additionally, dipole rotation, in which molecules attempt to align with the alternating MW electric field; ionic conduction; and the migration of charged compounds create friction between molecules and the medium, further facilitating extraction [112].

MAE offers several advantages over CSE, including reduced extraction time, increased yield, improved precision, and suitability for thermolabile chemical components, such as AA [103]. However, it is crucial to carefully select MAE parameters to prevent excessive temperature increase, as high MW power levels and extended exposure times can lead to the degradation of thermolabile components.

Several patents have been filed using the MAE technique. For example, the inventors of CN102023191A described a method for extracting AA from vegetables and fruits using a slightly acidic extracting solvent under a nitrogen atmosphere to prevent oxidation [113]. The inventors of CN107056734A extracted vitamin C from *folium Rubi suavissimi*. The process involved cleaning, drying, and crushing the material, followed by suspension in acidic water. The mixture was then placed in a high-pressure tank, and MAE was performed. After ultrafiltration, the resulting extract was crystallized [114].

3.5. Pressurized Liquid Extraction

Pressurized liquid extraction (PLE) is a relatively recent extraction technique, first developed in 1995 by the Dionex Corporation, Sunnyvale, CA, USA. This method combines

the interaction of solvents with matrix molecules, elevated temperatures, and high pressures to enhance the solubility and mass transfer of the desired compounds. The application of high pressure and temperature to the solvent reduces its surface tension, facilitating its penetration into the material's pores. PLE represents an evolution of CSE, significantly reducing extraction times and solvent consumption compared to traditional methods [103].

The choice of solvents in PLE is driven by the solubility of the solutes, and the physicochemical properties of the solvents (including density, diffusivity, viscosity, and dielectric constant) can be controlled by adjusting temperature and pressure. This adaptability makes PLE a versatile extraction technique [115].

One of the significant advantages of PLE is the production of extracts rich in vitamin C due to the absence of oxygen and light during the extraction process. Moreover, since the resulting extract is aqueous, it can be directly applied in the fields of food, pharmaceuticals, and cosmetics [22].

3.6. Supercritical Fluid Extraction

A fluid enters a supercritical state when it simultaneously exhibits characteristics of both a liquid and a gas phase, surpassing its critical temperature and pressure. In this state, it demonstrates unique properties, including viscosity, density, and solvation, which can be manipulated by adjusting temperature and/or pressure. These fluids serve as effective solvents due to their ability to combine the advantageous properties of both phases, facilitating the enhanced mass transfer rate of solutes during the extraction [103].

The process of supercritical fluid extraction (SFE) takes place within an extraction vessel equipped with a pressure release valve and temperature controllers, allowing for precise adjustment of the extraction parameters. Carbon dioxide (CO_2) is the preferred fluid for SFE, given its non-toxic nature, designation as generally recognized as safe (GRAS) by the United States Food and Drug Administration, cost-effectiveness, non-flammability, environmentally friendly profile, ease of removal from the final product, and moderate critical temperature (31.1 °C) and pressure (73.8 bar), which enable operation under mild conditions [116,117].

However, one drawback of SFE is the low polarity of CO_2, resulting in limited solubility of certain phenolic compounds, such as ascorbic acid (AA). To address this, co-solvents like acetonitrile, acetone, methanol, ethyl ether, ethanol, and water, which act as polarity modifiers, can be added. Ethanol is particularly favored for its low toxicity and high solubilization capacity for phenolic compounds. While water shares similar properties with ethanol, its low solubility in CO_2 necessitates its use in combination with ethanol, rather than alone [103,117,118].

The applications of SFE in the nutraceutical and food industry are driven by its sustainable and environmentally friendly characteristics, which reduce reliance on toxic organic solvents. Additionally, SFE boasts a high extraction efficiency and yields comparable to those of conventional methods.

3.7. Other Extraction Methods

In recent years, various additional environmentally friendly methods have been developed. Apart from its role as a pretreatment method, pulsed electric field (PEF) can be utilized as an alternative to other extraction techniques, such as UAE, MAE, and CSE. PEF involves the application of moderate to high electric field strengths, typically ranging from 100–300 V/cm in batch mode to 20–80 kV/cm in continuous mode extraction. As the electric field penetrates membranes, it segregates molecules based on their charge, creating repulsion forces that lead to pore formation and increased membrane permeability [115].

Two prevalent hypotheses explain the mechanisms of action for PEF. The first theory suggests that PEF accelerates chemical reactions, enhancing solvent solubility. The second theory involves electroporation, where the application of electric fields leads to the formation of pores in cell membranes. This phenomenon softens and disrupts cell membranes, facilitating the release of intracellular components [119]. PEF is an economical

and sustainable method for the recovery of intracellular bioactive compounds [115]. Its effectiveness largely depends on the selection of process parameters including field intensity, input energy, pulse number, temperature, and material properties [87].

Another effective method is progressive freeze concentration (PFC), which systematically produces ice crystals, layer by layer, on a cooled surface until a large single crystal block forms around the concentrated solution [120]. PFC stands out for its use of low temperatures, enabling the preservation of thermosensitive compounds like AA. This factor alleviates the challenges associated with thermal extractions, such as evaporation [16].

Various extraction methods for obtaining vitamin C from vegetable matrices are detailed in Table 3, which provides information on the techniques employed, the parameters used, and the resulting extraction yields.

Table 3. Green techniques for the extraction of vitamin C.

Process	Parameters	Source	Pretreatment	Yield (mg/100 g)	Ref.
MAE	1% citric acid in water, 560 W, 110 s	Cashew apples	Dried at 40 °C	239	[121]
	Ethanol–water (70:30), 540 W, 50 s	Peach waste	Frozen	108	[112]
	Methanol, 10% power, 15 min	Potato peels	Freeze-dried	144	[122]
MAE+ UAE	Ethanol and 3% metaphosphoric acid, US 37 kHz for 30 min, MW 100 W for 2 min	Cabbage leaves	Fresh	287	[81]
PEF	Ethanol 100%, 10 µs, 1000 Hz and 1.0 kV cm^{-1}	Orange peel	Freeze-dried	1029	[19]
PEF+ UAE	Ethanol 100% PEF: 10 µs, 1000 Hz and 1.0 kV cm^{-1} US: 37 kHz	Orange peel	Freeze-dried	870	[19]
PFC	−12 °C, 400 rpm, 20 min circulation time	Orange peel	Drying in oven (35 °C, 12 h) and maceration	72	[16]
PLE	Distilled water, 70 °C, 10 MPa, 3 mL/min, 2 h	Camu-camu	Freeze-drying	30,040	[22]
	Ethanol and water (70:30) pH 2.5, 2 cycles, 1500 psi	Blueberry	Fresh	17	[123]
	Ethanol and water (70:30) pH 11.5, 2 cycles, 1500 psi	Rosehip berry		109	
	Ethanol and water (70:30) pH 11.5, 2 cycles, 1500 psi	Partridgeberry		83	
SFE	Ethanol, 70 °C, 250 bar, 2–0.4 mL/min	Grapes seeds	Freeze-drying	272	[117]
UAE	Acetic acid 8%, 95 W, 35 kHz, 10 min	Parsley	/	264	[124]
	Acetone (80:20) in water for 24 h under stirring, then US for 2 h	Cashew apples	Dried at 50 °C for 48 h	388	[125]
	Ethanol 50%, 400 W for 30 min	Orange peel	/	54	[106]
		Mandarin peel		136	[126]
	Ethanol 50%, 200 W, 40 kHz for 30 min at 30 °C	Rugosa rose fruit	Freeze-dried	638	[127]
	Ethanol 100% 2 h	Grapefruit peel			
	Ethanol 100%, 37 kHz	Orange peel	Freeze-dried	1229	[19]
	Hydrochloric acid 0.1% in methanol	Genova citrus lemon	/	6013	[128]
	Water, 5 min, 50 °C, 30% amplitude, then reverse osmosis	Camu-camu	/	619	[129]
	Water, 30 min, 35 kHz, 40 °C	Turmeric	Dried at 55 °C	17	[130]

3.8. Purification of AA from Organic Solvents

The sensitivity of AA to temperature necessitates the use of gentle heating, and sometimes relatively toxic or organic solvents are commonly employed to maximize the extraction yield. Furthermore, for applications such as dietary supplements or cosmetics, it becomes essential to eliminate these solvents, as they can be harmful. This can be achieved through various methods. The first and simpler one is evaporation, which can be carried out in the case of volatile compounds, such as methanol and ethanol, using low temperatures and usually under a vacuum [131–133]. Other methods, based on the different properties of solutes and solvents, are filtration and centrifugation [134,135]. These methods can require the crystallization of the solutes to better separate them from the solvents. In some cases, acids such as metaphosphoric acid can be added to the aqueous extraction solution to protect vitamin C against oxidation and too rapid degradation, and they can be removed via precipitation in the form of insoluble salts; for instance, metaphosphoric acid is eliminated as ammonium and magnesium phosphate salts [136].

4. Conclusions

Vitamin C, also known as ascorbic acid (AA), plays a pivotal role as a vital nutrient in the human body. Its functions span a wide spectrum, acting as a cofactor for numerous enzymes, supporting collagen synthesis, and regulating immune responses. Additionally, AA finds applications in the treatment of various pathological conditions, including inflammation and sepsis, and as a supplement to enhance the effects of pharmacological treatments like chemotherapy, radiotherapy, and COVID-19 therapies. Notably, AA boasts a high safety profile, affordability, and ease of administration and distribution. Furthermore, it is widely used in the cosmetic and food industries and in chemical synthesis, which exploit its antioxidant activity and reducing abilities.

Given these remarkable properties, AA has become one of the most widely used nutraceutical products. Consequently, many industries have focused on its production and extraction. Traditionally, extraction methods from plant materials have relied on solvent-based techniques. However, these protocols involve the use of environmentally harmful solvents, lengthy extraction times, and substantial costs. This has prompted increased exploration of new, environmentally friendly, and cost-effective approaches.

Among the emerging methods, ultrasound-assisted extraction, microwave-assisted extraction, pressurized liquid extraction, and supercritical fluid extraction have gained prominence. These techniques operate under mild processing conditions, involving low temperatures necessary to avoid the degradation of vitamin C and employing aqueous or ethanol-based solvents. Physical stimuli, such as ultrasound waves or microwaves, and variations in pressure enhance the extraction process. Furthermore, these methods yield results that are comparable to or even surpass those obtained with conventional solvent extraction (CSE), while simultaneously reducing costs, time, and energy consumption. In this way, the green extraction of AA preserves the environment and protects consumers, paving the way for an even more ecologic, economic, and innovative approach. In the very near future, the world will face an environmental crisis, which will require, among the other measures, careful biowaste management and research into the valorization of new waste sources for AA extraction.

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