

Plant-Derived Citrulline: From Agricultural Sources to Functional Food Applications

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Abstract

Citrulline, a non-protein amino acid, has recently gained prominence as a valuable functional food bioactive due to its many physiological and nutritional advantages. Citrulline is predominantly found in cucurbit vegetables (like watermelon, or *Citrullus lanatus*) and is an active participant in, among other things, the metabolism of plants (primarily through nitrogen cycling) and stress tolerance in plants. In addition to its applications in plants, there has been a steady increase in recent years in the use of citrulline in food science, especially for functional foods and nutraceuticals. This review will provide an overview of citrulline, including its distribution in agricultural commodities, its biosynthesis in plants, and its physicochemical properties that may be important for use in food systems. The effect of different processing and storage conditions (both from a raw and finished product perspective) on the stability of citrulline is reviewed with an emphasis on the need for the development of improved methods to help maintain the bioactivity of citrulline in foods. Extraction, isolation, and quantification methods are summarized so that citrulline may be efficiently used in food formulations. A brief discussion of citrulline bioavailability, metabolic fate of citrulline in human beings, and the associated health benefits of citrulline (such as its role in nitric oxide production, cardiovascular support, and improved muscle metabolism) is also provided. This review examines the growing trend of utilizing citrulline in the development of new products using food technology. A wide range of viable methods for incorporating citrulline into food products is evaluated, as well as several new and innovative delivery methods. The review focuses on the use of sustainable methods to obtain citrulline, such as the use of agricultural byproducts, such as watermelon rinds, which are a particularly rich source of citrulline. Ultimately, this review shows that citrulline has considerable potential as a valuable bioactive compound that can improve food quality and enhance food production sustainability in an environmentally friendly manner.

Categories: Functional foods, Food biochemistry, Food nutrition

Keywords: citrulline, functional foods, cucurbit crops, food processing, bioavailability, nutraceuticals, sustainability

Introduction And Background

Introduction to citrulline as a functional food bioactive

Citrulline is an amino acid that does not form proteins but has recently gained popularity as a bioactive food ingredient, like other amino acids incorporated directly into proteins [1]. Citrulline exists primarily in its free form but has a major impact on the metabolism of amino acids and nitrogen balance, as well as many other metabolic processes in the body [2]. Citrulline was first discovered in watermelon (*Citrullus lanatus*), and it remains one of the best sources of citrulline in the plant food chain, which is a significant indicator of citrulline's relationship with plant-based nutrition [3].

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As it relates to nutrition and food science, citrulline is beginning to receive a greater appreciation as a nutritional component capable of enhancing health beyond its conventional use as a nutrient (i.e., food) [4]. Moreover, citrulline is the precursor for the production of arginine, and as a result, this would have a major impact on the production of nitric oxide (NO), an important signaling molecule in the body that impacts blood vessel health, immune function, and cellular communication [5]. These benefits are contributing to the use of citrulline in functional food and nutraceutical products that promote cardiovascular health, improve performance during exercise, and support metabolic health [6].

Dietary research regarding citrulline is driven by the growing interest in using naturally occurring plant-based compounds that are beneficial to human health as ingredients in food or food products [7]. Functional foods such as fruit-based drinks, enriched with citrulline, are now being researched as a possible means of delivering targeted health benefits in a natural way that is also acceptable to consumers [8]. Furthermore, since citrulline is present in many of the world's primary agricultural products, it offers potential as a sustainable source of functional ingredients in food product development [9].

In addition, the growing understanding of the extensive evidence regarding the benefits of citrulline is being reflected in its usefulness for food processing and product formulation [10]. To successfully incorporate citrulline into food products, you need to understand citrulline's stability during processing and its interaction with other food components. Citrulline also represents a growing opportunity for creating value-added products in the ever-evolving functional foods industry by bridging the gap between nutrition and health [11].

The objective of this review is to fill this knowledge gap by reviewing the literature on plant-based citrulline. There have been several literature reviews published in recent years describing particular aspects of L-citrulline, including cardiovascular benefits, exercise, NO biochemistry, sarcopenia, ageing, and use of watermelon-derived nutraceuticals. However, most of these reviews do not display any of the aspects related to agriculture, diversity of crops, extraction and purification techniques, processing and stability studies, analysis, sustainability, and food uses of citrulline-rich agro-industrial waste. This review addresses some of these aspects by providing a holistic overview of food science considering production, biosynthesis, physicochemical properties, extraction and processing, and industrial applications of plant-derived L-citrulline. Comparison of the present review with previous reviews is shown in Table 1.

Reference	Scope	Limitations	Present review contribution
[12]	Cardiovascular health and NO metabolism	Mainly clinical	Includes agricultural sources, extraction, purification, food processing, stability and functional foods
[13]	Exercise performance	Supplement-focused	Covers plant sources and food technology
[14]	Clinical supplementation	Human studies only	Includes crop sources, processing, and sustainability
[15]	Skeletal muscle and ageing	Muscle biology	Adds food science and industrial applications
[16]	Watermelon beverages	Beverage applications only	Covers extraction, purification, and food formulation
[17]	Exercise performance	Sports nutrition	Agricultural and functional food perspective
Present Review	Agriculture → Extraction → Purification → Processing → Bioavailability → Functional foods → Sustainability	Comprehensive	Integrated food science perspective

TABLE 1: Comparison of Published Reviews on L-Citrulline and the Distinct Scope of the Present Review
NO, Nitric Oxide

Review

Methodology

A narrative review was conducted in an attempt to provide a comprehensive review of the current literature on plant-derived L-citrulline, focusing on agricultural resources, extraction, processing, bioavailability, and functional food applications of L-citrulline. Literature studies were obtained through database searches such as Scopus, Web of Science, PubMed, ScienceDirect, Google Scholar, and SpringerLink. The searches were mainly conducted on the scientific literature from 2000 to April 2026 using key terms such as L-citrulline, plant-derived citrulline, cucurbit vegetables, watermelon, extraction, purification, food processing, bioavailability, functional foods, and sustainability. Peer-reviewed literature in the English language was considered on the basis of their scientific relevance to this review scope. Conference papers, patents, non-English literature, and literature not related to food applications were excluded from the review. Recent studies were preferred to be included in this review.

Chemical structure and physicochemical properties of citrulline

Citrulline (L-citrulline) is a type of amino acid that is not used in the making of protein in the body but is omnipresent in the body and is frequently added to foods [18]. L-Citrulline differs from the 20 protein-forming amino acids chemically in that its side chain contains a neutral ureido group. L-Citrulline is a non-protein amino acid, found in proteins. Such amino acids are mainly involved in nitrogen metabolism and urea cycle. L-Citrulline has a highly polar and uncharged side chain, which is responsible for its excellent water solubility [19]. Like other amino acids, citrulline consists of an α -amino group, a carboxyl group, and a side chain containing a ureido group. The unique structure allows citrulline to have a major impact on metabolism and the presence of nitrogen, while also allowing it to have many different functional characteristics within food systems [20]. The citrulline molecule also has a great deal of polarity, which makes citrulline soluble in water.

At physiological pH (around 7.0), citrulline is in solution as a zwitterion, meaning it carries two opposite charges (positive and negative). The pK_{a1} of the carboxylic group of citrulline is approximately 2.5, and the pK_{a2} of the amino group of citrulline is approximately 9.5 [21]. Due to the unique charges present on citrulline, it exists primarily as a dipolar ion in solution, which promotes its use with other polar materials in food. The isoelectric point of citrulline is around 5.9, which means that citrulline has no net electrical charge at that pH. This is an important consideration when developing food products that will contain citrulline, as it has a bearing on the way citrulline interacts with proteins, polysaccharides, and other charged materials in the food matrix [22].

L-Citrulline shows reasonable thermal stability under normal food processing conditions, particularly when the temperatures are below about 100°C, and the pH of the solution is close to neutral. However, after prolonged exposure to elevated temperatures ($\geq 120^\circ\text{C}$), high or low pH, or oxidation, citrulline degradation or incomplete recovery may occur [23]. These effects of food processing should be distinguished from biological metabolism. L-Citrulline is converted to arginine through the urea cycle by the argininosuccinate synthase and argininosuccinate lyase enzymes, while ornithine is produced metabolically. However, conversion into arginine or ornithine cannot be considered as a direct effect of food processing procedures [24].

From a physicochemical perspective, citrulline has a high level of solubility (>100 g/L in water) and a neutral taste profile, which can provide advantages when used in foods, as it will not affect the sensory qualities of the food product negatively [25]. The low reactivity of citrulline relative to reducing sugars and reactive amino acids will also help reduce its risk of participating in Maillard browning chemistry during processing [26]. Key physicochemical properties of citrulline that are important to the food system are provided in Table 2.

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S. No.	Property	Description/Value	Relevance to Food Systems
1	Chemical name	L-Citrulline	Standard nomenclature
2	Molecular formula	C ₆ H ₁₃ N ₃ O ₃	Defines composition
3	Molecular weight	175.19 g/mol	Important for formulation calculations
4	Functional group	Ureido (-NH-CO-NH ₂)	Unique structural feature
5	Solubility	Highly soluble in water (>100 g/L)	Suitable for beverages
6	pKa (carboxyl)	~2.5	Influences ionization
7	pKa (amino)	~9.5	Affects buffering capacity
8	Isoelectric point (pI)	~5.9	Important for protein interactions
9	Physical state	White crystalline powder	Ease of handling
10	Taste	Mild, neutral	No adverse sensory impact
11	Thermal stability	Stable under moderate heat	Suitable for processing
12	Reactivity	Low (non-reducing)	Minimal Maillard reaction involvement

TABLE 2: Physicochemical Properties of Citrulline Relevant to Food Applications

Natural sources of citrulline: focus on agricultural crops

Plant sources provide the majority of citrulline; however, members of the cucurbit family concentrate most of the citrulline found in plants. Of all cucurbit plants, watermelon is by far the greatest natural source of citrulline, a key contributor to dietary citrulline consumption [27,28]. The first citrulline was isolated from watermelon; however, its concentration in watermelon varies with variety, stage of ripeness, and part of the plant [29]. The highest citrulline concentration is typically found in the rind, suggesting that there is potential to utilize agricultural byproducts for additional value-added purposes [30].

There are also trace amounts of citrulline found in other cucurbit crops (cucumber, pumpkin, and bitter melon), and they are therefore foods that can be consumed to obtain some of citrulline's bioactive properties [31]. These crops are readily available and are widely grown and consumed in today's world. In addition to cucurbit vegetables, some other types of legumes, nuts, and leafy vegetables contain occasional very low levels of citrulline [32]. Still, the amount of citrulline from these food sources is not likely to be large enough to have a meaningful impact on overall daily consumption.

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L-Citrulline content is highly variable among different plant species, varieties, tissues, ripeness stages, and environmental conditions. Among agricultural products, watermelon (*Citrullus lanatus*) has been reported to be the richest source. The fruit’s rind has been found to contain higher levels of L-citrulline than its flesh. Other cucurbit crops such as cucumber, pumpkin, melon, and bitter melon contain appreciable but smaller levels of L-citrulline [33]. Table 3 summarizes selected L-citrulline concentrations in crops.

Plant Source	Plant Tissue	Representative L-Citrulline Content	Remarks
Watermelon (<i>Citrullus lanatus</i>)	Rind	Highest among plant tissues	Major agro-industrial by-product
Watermelon	Flesh	High	Primary dietary source
Watermelon	Seeds	Low–moderate	Limited studies
Melon (<i>Cucumis melo</i>)	Flesh	Moderate	Species-dependent
Cucumber (<i>Cucumis sativus</i>)	Fruit	Low–moderate	Widely cultivated cucurbit
Pumpkin (<i>Cucurbita</i> spp.)	Fruit	Low	Minor source
Bitter melon (<i>Momordica charantia</i>)	Fruit	Low	Limited quantitative reports

TABLE 3: Concentrations of Citrulline Reported in Major Agricultural Crops and Plant Tissues

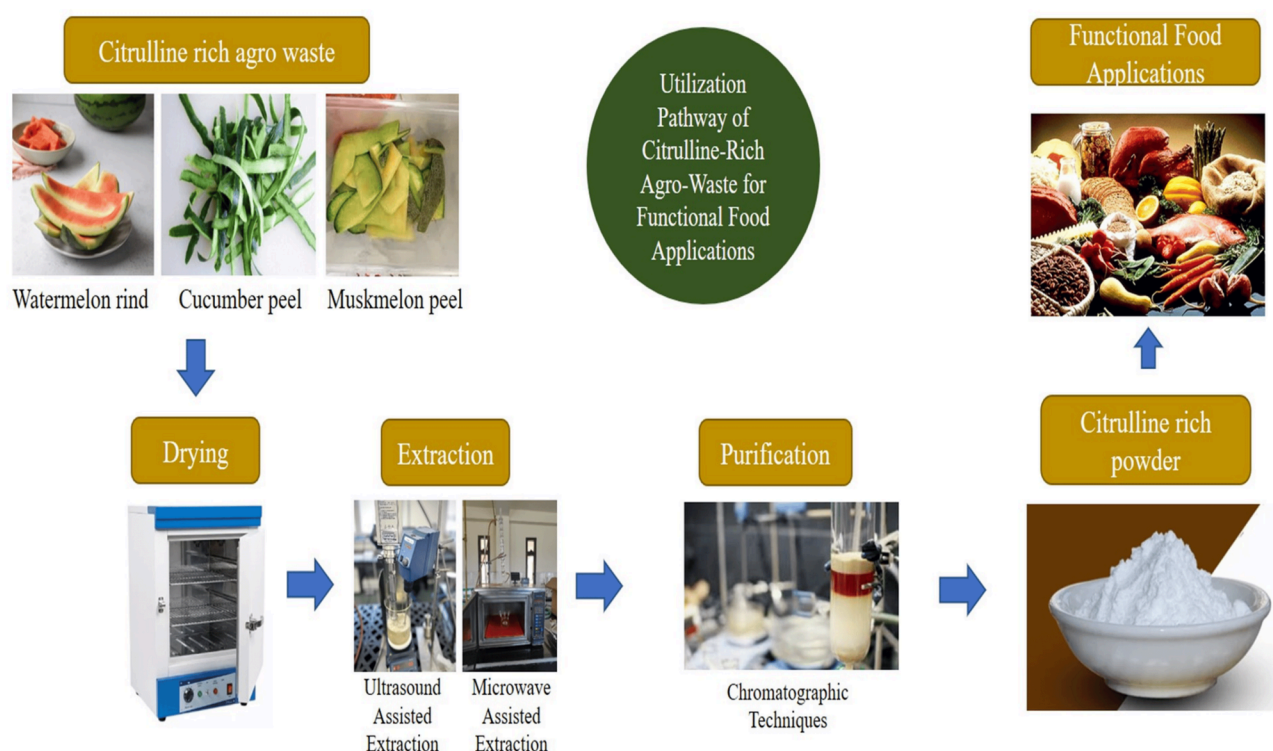


FIGURE 1: Utilization Pathway of Citrulline-Rich Agro-Waste (Watermelon Rind)

Plant tissues contain citrulline, which is distributed according to many different physiological and environmental influences [32]. Plants use citrulline to transport nitrogen and regulate osmotic pressure when they face abiotic stresses such as droughts and salinity. High levels of citrulline in crops under drought conditions may provide the potential for an agricultural method to increase citrulline in plants grown under abiotic stress due to the stresses placed on these crops [34]. In addition, the genetic variation found among different cultivars has a large influence on the amount of citrulline produced in a plant, providing an opportunity to select and breed crops for improved nutrition based on their citrulline content [35]. Agricultural by-products rich in L-citrulline, such as watermelon peel, are promising feedstocks for waste valorization in sustainable agri-food systems. The underutilized resources can be used as powders, extracts, or other functional food components. The process reduces agri-food waste and adds value to these resources in the form of economically valuable products [36]. Figure 1 depicts the potential pathways for converting citrulline-rich agricultural by-products into functional food ingredients.

Biosynthesis and role of citrulline in plants

Citrulline is an essential intermediate in plants' metabolic processes involving nitrogen. It is found mostly in the biosynthesis pathway between ornithine, citrulline, and arginine (referred to as the ornithine-citrulline-arginine biosynthesis pathway) [37]. This pathway is closely linked to the urea cycle and to the conversion of one amino acid into another [38]. The enzyme ornithine transcarbamylase (OTC) makes citrulline from ornithine and carbamoyl phosphate. This reaction serves as a primary link between nitrogen assimilation and the biosynthesis of amino acids [39]. The second step in this process involves citrulline being converted to argininosuccinate and subsequently to arginine, which is considered a major storage form of nitrogen in plants [40].

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The plant lacks the full complement of enzymes for the urea cycle. In contrast, citrulline enters several cycles related to nitrogen metabolism in plants. Citrulline is used as a nitrogen transport molecule by plants because it has a large amount of nitrogen relative to carbon. The enzymes that are involved in the metabolism of citrulline in plants are similar to those involved in the urea cycle of animals, but the physiological roles are quite different [41].

Under normal physiological conditions, glutamine and asparagine are the major nitrogen carriers among the amino acids involved in nitrogen metabolism due to their efficient assimilation and transport of nitrogen. In contrast, L-citrulline has a higher nitrogen-to-carbon ratio and therefore is an efficient nitrogen carrier, particularly under environmental stress such as drought and salinity. Citrulline not only functions as a carrier of nitrogen but also plays an important role in osmotic adjustment and stress tolerance [42].

Citrulline is now being recognized for the role it plays in helping plants to tolerate stress, and this discovery has contributed to an increased interest in the study of citrulline in plants. NO is an essential signaling molecule in plant growth, development, and stress responses. However, there is no conclusive evidence for a canonical nitric oxide synthase (NOS) similar to the enzyme in animals in higher plants [43]. The available data suggest that NO formation proceeds via several enzymatic and nonenzymatic routes, including the nitrate reductase-dependent route. However, the relationship between citrulline catabolism and NO biosynthesis in plants has to be carefully evaluated because it is not the animal citrulline-arginine-NO pathway [44]. Data show that accumulation of citrulline in plants has been observed as a response to extreme temperature, drought, salinity, high light intensity, and other abiotic stresses [45]. The role of citrulline in osmotic adjustment has also been attributed to its role as a compatible solute and osmoprotectant in response to abiotic stress. It has been generally accepted that the antioxidant effect of citrulline is mainly indirect and not due to its direct ROS scavenging activity. Citrulline contributes to the stabilization of cellular proteins and membranes, to the maintenance of the cellular redox balance, and to stress-induced antioxidant defense systems [46]. This dual role helps plants stay strong and keeps them growing even when the weather is bad.

The enhanced accumulation of citrulline has been especially evident in cucurbit crops such as watermelon, where citrulline contributes not only to stress tolerance but also to the quality and nutritional value of fruits [47]. Availability of nutrients, soil moisture, temperature, and many other environmental factors play a significant role in the accumulation of citrulline, and there is also considerable genetic variation across cultivars, which affects citrulline levels [48]. Therefore, there is potential to increase citrulline levels in crops through breeding and selection.

The biosynthesis and regulation of citrulline are two areas of research that can help develop new ways to adapt crops to stressful conditions and improve the concentration of nutrients in the food derived from plants, as discussed in Table 4 [49]. Various agronomic and biotechnological approaches have been explored in plants to increase citrulline production. Citrulline production can be improved by agronomic practices such as nitrogen optimization, deficit irrigation, and controlled abiotic stresses such as drought and salinity. Conversely, classical breeding, cultivar selection, and metabolic engineering of the enzymes of the ornithine-citrulline-arginine pathway have shown promise for increasing the citrulline content of the edible parts of plants [50].

S. No.	Step	Substrate	Enzyme	Product	Functional significance	Reference
1	Nitrogen assimilation	Ammonia	Glutamine synthetase	Glutamine	Initial nitrogen incorporation	[51]
2	Glutamate formation	Glutamine	Glutamate synthase	Glutamate	Amino donor for pathways	[52]
3	Ornithine formation	Glutamate	Ornithine aminotransferase	Ornithine	Precursor for citrulline	[53]
4	Carbamoyl phosphate synthesis	Ammonia + CO ₂	Carbamoyl phosphate synthetase	Carbamoyl phosphate	Nitrogen donor	[54]
5	Citrulline formation	Ornithine + Carbamoyl phosphate	Ornithine transcarbamylase	Citrulline	Key intermediate	[39]
6	Argininosuccinate formation	Citrulline	Argininosuccinate synthase	Argininosuccinate	Precursor to arginine	[55]
7	Arginine synthesis	Argininosuccinate	Argininosuccinate lyase	Arginine	Nitrogen storage	[56]
8	NO production	Arginine/Nitrate	Nitrate reductase-dependent and other proposed pathways	NO	Stress signaling	[57]
9	Recycling step	Citrulline	Multiple enzymes	Ornithine	Nitrogen cycling	[58]
10	Stress accumulation	—	—	Citrulline accumulation	Osmoprotection and ROS scavenging	[59]

TABLE 4: Key Enzymes and Steps Involved in Citrulline Biosynthesis in Plants

* Whether higher plants possess a canonical NO synthase, as is the case for animal systems, is still unclear. NO biosynthesis is believed to be mediated by both enzyme-mediated and non-enzyme-mediated reactions. ROS, Reactive Oxygen Species; NO, Nitric Oxide

Extraction, isolation, and quantification techniques

To use citrulline, which comes from plant materials for functional foods and nutraceuticals, it is necessary to be able to efficiently extract, isolate (remove), and quantify (measure) the citrulline from the plant material [60]. Citrulline is very polar and soluble in water; therefore, extracting citrulline will usually use either an aqueous or a hydro-alcoholic extraction method. The choice of solvent in extraction will be guided mainly by the physical and chemical characteristics of L-citrulline. L-Citrulline is a non-protein amino acid with high polarity and water solubility and is thus more soluble in aqueous and hydro-alcoholic solvent systems than in non-polar organic solvents [61]. Water is normally the most preferred solvent, because it is safe, cost-effective, and environmentally sustainable. Hydro-alcoholic solvents such as aqueous ethanol may even increase the extraction efficiency due to better solvent penetration through the plant matrix and release of intracellular metabolites [62]. The method used is determined by the type of raw plant material being used (e.g., fresh pulp, the rind of the fruit, or the dried powder of the fruit), the desired purity of the end product, and the anticipated use of the extracted citrulline [63].

Extraction Techniques

Conventional methods of extraction typically involve aqueous extraction of homogenized (ground) fruit materials (e.g., watermelon flesh or rind) using distilled water (or buffered) solvent. In addition, four key extraction parameters (i.e., the pH level, the temperature of the solvent, the solvent-to-solid ratio, and the duration the sample is in interaction with the solvent) will greatly affect the amount of citrulline obtained [64,65]. Previous studies have shown that L-citrulline extraction is commonly carried out at slightly acidic to neutral pH (about pH 5.0-7.0) as this pH will allow the stability of the amino acid while at the same time making the extraction process more efficient. This is because strongly acidic and alkaline pH can adversely affect the extraction process [66].

To improve extraction efficiencies, a growing number of advanced extraction technologies have been examined. These advanced extraction processes include the following techniques: Ultrasound-assisted extraction (UAE) [67], in which ultrasound cavitation enhances mass transfer; microwave-assisted extraction (MAE), where microwaves accelerate solvent entry into the plant material and decrease the extraction time [68]; and enzyme-assisted extraction (EAE), where enzymes can help break down cell walls and free up intracellular citrulline [69]. These advanced extraction processes offer improved extraction yields, reduced solvent use, and shorter processing times, all of which make them applicable to industrial-scale citrulline extraction. Table 5 summarizes the major methods of extracting plant-based L-citrulline, their strengths and weaknesses, and their suitability for the industry.

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Extraction technique	Advantages	Limitations	Industrial suitability
Conventional aqueous extraction	Simple, inexpensive, food-grade solvent	Longer extraction time, lower efficiency	High
Hydro-alcoholic extraction	Improved recovery of polar metabolites	Solvent recovery required	Moderate to High
Ultrasound-assisted extraction (UAE)	Short extraction time, enhanced mass transfer, reduced solvent use	Requires optimization and specialized equipment	High
Microwave-assisted extraction (MAE)	Rapid heating and improved extraction efficiency	Risk of thermal degradation if not optimized	Moderate
Enzyme-assisted extraction (EAE)	Mild conditions, environmentally friendly, improved cell wall disruption	Higher enzyme cost and longer processing time	Moderate

TABLE 5: Comparison of Different Extraction Techniques for Plant-Derived L-Citrulline

The extraction efficiency of L-citrulline is mainly controlled by the extraction conditions like solvent composition, solvent-to-solid ratio, temperature, time of extraction, and pH. The L-citrulline is very polar and water-soluble, and aqueous extractions or ethanol solutions are commonly used [70]. Previous studies reported extraction efficiencies at a solvent-to-solid ratio of 10:1 to 30:1 mL g⁻¹, a temperature of 25-60°C, and an extraction time of 30-120 minutes, depending on the type of plant matrix and extraction method used [71]. The traditional aqueous extraction usually takes a long time and UAE and MAE greatly reduce the time without compromising or even improving the efficiency of extraction. Furthermore, it has been reported that extraction at a slightly acidic to neutral pH (pH ~5.0-7.0) is effective in maintaining the stability of L-citrulline during the extraction process [60]. Therefore, the optimization of extraction parameters considering the characteristics of the plant matrix is crucial to obtain L-citrulline with high efficiency and quality in maximum yield. Generally, the selection of the L-citrulline extraction technique depends on extraction efficiency, processing time, solvent consumption, economic viability, industrial applicability, and environmental sustainability. Water-based extraction normally takes longer than other methods; however, the use of solvents that are safe to consume and the low cost still offer potential for industrial scale. Modern techniques of UAE, MAE, and EAE, in contrast, offer improved mass transfer and extraction efficiency, reduced processing time, and solvent utilization; however, their large-scale application may be restricted due to high equipment costs and process optimization.

Isolation and Purification

After the extraction of citrulline, it will generally still be in a complex of amino acids, sugars, and organic acids, and therefore, purifying citrulline will be considered necessary for either analysis or formulation purposes, not only because it has been extracted [72]. Common methods of isolating citrulline include: ion-exchange chromatography, which distinguishes amino acids based on differences in charge; high-performance liquid chromatography (HPLC), which separates citrulline from contaminants to achieve a highly purified product; and filtration techniques (ultrafiltration/nanofiltration), which partially purify citrulline. Crystallization methods are also commonly used for

preparative purification scale (i.e., to provide enough citrulline for subsequent use/analysis) [73,74]. Ion-exchange resins have proven to be highly effective at selectively binding to and eluting citrulline due to the zwitterionic nature of citrulline, allowing selective binding and elution to occur under controlled pH conditions [70].

Quantification Methods

Precise quantitation of citrulline is important for multiple reasons: quality control and product labeling, as well as research use. Analytical methods that have been used to quantify citrulline include HPLC, the most commonly used method, frequently coupled with either UV spectrophotometric or fluorescence detection after derivatization (e.g., o-phthalaldehyde) [37]. HPLC is still the most used method among the analytical methods for the determination of L-citrulline due to its high sensitivity, specificity, precision, and reproducibility. HPLC analysis can be coupled with UV, fluorescent or mass spectrometry detectors after suitable derivatization of analytes depending on the sample composition and analytical purposes [75]. This strategy allows for the successful separation of L-citrulline from structurally similar amino acids and other co-eluting compounds and is therefore applicable to the analysis of complex matrices of plants. Therefore, HPLC is regarded as the gold standard among analytical methods for the routine determination of L-citrulline in plant material. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) provides high levels of both sensitivity and specificity for very accurate quantitation of citrulline [76]. GC requires derivatization due to the non-volatility of citrulline [77].

Various spectrophotometric methods (colorimetrically/color-based methods) are used to rapidly estimate levels of citrulline, but the precision of the estimation is much lower. The most reliable methods for determining citrulline concentration in foods are HPLC and LC-MS/MS, based on reproducibility, sensitivity to low-level quantities, and compatibility with complex food matrices [78].

Effect of processing and storage on citrulline stability

Citrulline's stability is a prerequisite, as it affects the amount that is left and how functional that citrulline is in foods after processing. Citrulline is highly water-soluble and fairly stable as an amino acid, which makes it somewhat resistant to stability-related aspects associated with typical food preparation, but citrulline can become unstable by heat, acid, exposure to oxygen, or long times of processing [79].

Effect of Thermal Processing

The stability of L-citrulline can be influenced by thermal treatments such as pasteurization, blanching, drying, and cooking, according to the temperature of the thermal treatment, duration of heat treatment, oxidation conditions, water content, and the nature of the food matrix. L-citrulline is a non-protein amino acid and is normally stable under mild to moderate thermal processing conditions and has a lower tendency to undergo Maillard reactions than most of the protein amino acids [80]. However, prolonged heating under oxidizing conditions at high temperatures can cause a gradual degradation and decrease in citrulline content. Thus, the optimization of processing conditions, especially temperature and duration of the process, is important to maximize citrulline stability [81].

Effect of Drying and Dehydration

The drying technique is important for L-citrulline stability. Freeze-drying is generally considered one of the best methods for the preservation of L-citrulline, as dehydration takes place at low temperature and pressure, leading to lower losses from thermal destruction and oxidation [82]. Studies of the rind of watermelons have indicated that vacuum freeze-drying and vacuum microwave drying better preserve the physical and chemical properties of the material and its biologically active compounds than hot air drying due to the reduction of drying time and thermal effects [83]. Also, the optimization of the parameters of the spray-drying process enabled the production of very stable, thermally stable powders of citrulline with high encapsulation efficiency suitable for application as functional food ingredients. No precise data are available concerning the quantitative preservation of L-citrulline, but the results obtained demonstrate that the advanced drying technology is more efficient than traditional drying technology [84].

Influence of pH and Food Matrix

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The pH of the food matrix also influences the stability of L-citrulline. Existing studies' results show that L-citrulline is fairly stable in the food system at slightly acid to neutral pH (5.0-7.0) [85]. These conditions are often found in fruits and vegetables. However, if the food system is under highly acidic or highly basic pH, it can cause the degradation of L-citrulline or modify its recovery. Therefore, it is advisable to keep the process at a slightly acidic to neutral pH [86].

Furthermore, the stability and availability of L-citrulline are also influenced by the composition and structure of the food matrix. Watermelon peel, which has higher L-citrulline content than the flesh of the fruit, is of great interest as a functional component in the development of value-added food products [87]. Fiber, phenols, and antioxidants are present in the plant matrix, which can help to prevent oxidation and degradation during processing and storage [88]. Conversely, liquid food matrices, such as juices, have a high oxygen availability, which limits the stability of L-citrulline. Moreover, the application of watermelon components in dry powder form and functional food products has been proven beneficial for storage stability and application in nutraceuticals and functional foods.

Effect of Storage Conditions

Factors affecting stability in the storage process are temperature, light, oxygen, and moisture. The storage conditions during storage processes influence the stability of L-citrulline [89]. It was observed that keeping the fresh and processed plant-based foods at a cold temperature of approximately 4°C under refrigeration was capable of holding L-citrulline better than at room temperature (25-30°C) because of the more rapid rate of reactions leading to loss [90]. Processing the food and then freezing it (-18 to -20°C) enhances its stability in storage by reducing the chemical reactions that occur. There is no particular quantitative data on the stability of L-citrulline on storage, but it is highly recommended to store it at low temperatures to increase its stability. Foods can undergo oxidation reactions when exposed to oxygen. L-citrulline, however, is less susceptible to oxidation than most other bioactive compounds [91]. Packaging methods, such as vacuum packaging and modified atmosphere packaging (MAP), improve the stability of oxygen [92].

Processing Strategies for Improved Stability

To maximize and retain the amount of citrulline in food products would require using optimal processing methods, including using mild heat, implementing nonheat treatment (i.e., high-pressure processing), and using protective methods such as encapsulation and using proper packaging [93,94]. Utilizing these kinds of methods is critical for creating functional foods that are fortified with citrulline to ensure both the stability and bioavailability of citrulline [14]. Table 6 represents the effect of processing and storage conditions on citrulline stability.

S. No.	Processing/storage factor	Representative condition	Effect on L-citrulline	Key remarks	Reference
1	Pasteurization	60–90°C, short duration	Minimal loss	Suitable for beverages	[95]
2	High-temperature heating	>100°C, prolonged heating	Progressive degradation	Avoid prolonged heating	[96]
3	Blanching	80–100°C for short time	Slight reduction	Time-dependent	[97]
4	Freeze drying	Low temperature, reduced pressure	Highest preservation	Best drying method	[98]
5	Hot-air drying	50–70°C	Moderate loss	Temperature dependent	[99]
6	Vacuum drying/Microwave drying	Reduced oxygen, shorter drying time	Better preservation than hot-air drying	Lower thermal damage	[100]
7	pH	pH 5–7	Maximum stability	Suitable for food processing	[101]
8	Alkaline conditions	pH >8	Increased degradation	Avoid extreme pH	[102]
9	Refrigerated storage	~4°C	Improved stability	Extends shelf life	[103]
10	Frozen storage	–18 to –20°C	Highest storage stability	Long-term preservation	[104]

TABLE 6: Effect of Processing and Storage Conditions on Citrulline Stability

Bioavailability and metabolic fate in humans

L-Citrulline is a key physiologically active nonprotein amino acid, involved in several physiological processes, including nitrogen metabolism, endogenous synthesis of L-arginine, and synthesis of NO. This compound is not considered a nutritionally essential amino acid, as it can be synthesized within the organism, but its particular biochemical activity and pharmacokinetic profile have aroused much interest [12]. Citrulline, after ingestion through the mouth, is quickly and efficiently absorbed in the small intestine using sodium-dependent amino acid transporters [105]. Unlike orally administered L-arginine, L-citrulline is less subject to first-pass effect after oral administration, thus having higher bioavailability for the synthesis of L-arginine. Consequently, citrulline can be a lot more efficient substrate (precursor) for the production of endogenous arginine [106]. Oral L-arginine is subject to extensive metabolism by the enzyme arginase

in the gastrointestinal tract and liver before it reaches the bloodstream. Most L-citrulline, however, bypasses this first-pass effect. L-citrulline is absorbed by the intestine, taken up by the kidney, and efficiently converted into L-arginine by the enzymes argininosuccinate synthase (ASS) and argininosuccinate lyase (ASL) [107]. In humans, supplementation with L-citrulline has been shown to increase the blood levels of L-citrulline and L-arginine, improving the bioavailability of NO.

Absorption and Transport

After citrulline is consumed, it is efficiently absorbed into the bloodstream. Citrulline is then transported to tissues outside of the blood vascular system, with the kidney being an important organ where citrulline is converted to arginine [108]. The lack of substantial amount of metabolism of citrulline by either the gastrointestinal system or the liver leads to elevated concentrations of citrulline that are sustained within the blood [109]. Because of these factors, citrulline can showcase higher bioavailability and thus is well suited to functional food formulations that will enhance the physiological effects that occur from increased NO levels in the body [110].

Conversion to Arginine and NO Production

Citrulline is converted to arginine through an enzymatic two-step process occurring in the kidney and utilizes the following enzymes for its conversion: ASS and ASL. The arginine that was synthesized then acts as the substrate for nitric oxide synthase (NOS), causing production of NO, a key chemical messenger or signaling molecule responsible for causing vasodilation, regulating blood flow, and communicating with cells [111]. The pathway formed when citrulline is converted to arginine results in NO production, which makes up much of the health benefits obtained from citrulline intake, such as enhancing heart health and increasing your performance capacity to exercise [112].

The transformation of L-citrulline to L-arginine is a key process in the maintenance of NO homeostasis, especially when the availability of arginine in the body is reduced. Increased NO bioavailability leads to NO-dependent vasodilation via eNOS, improved endothelial function, and improved tissue perfusion and delivery of oxygen and nutrients to peripheral tissues [113]. In humans, clinical studies have demonstrated that the intake of L-citrulline increases the plasma concentrations of L-arginine and NO bioavailability, with vascular benefits. These physiological functions explain why L-citrulline is increasingly used in functional foods and nutraceuticals [114].

Tissue Distribution and Utilization

Researchers have observed citrulline and its metabolites in different tissues, including vascular endothelial cells, skeletal muscle, and immune cells [112]. Citrulline also enhances detoxification of ammonia and aids in providing nitrogen balance by serving as a precursor for the recycling of amino acids [115].

Factors Influencing Bioavailability

Many elements play a role in how well our body is capable of using citrulline (bioavailability). The main things that affect bioavailability are as follows [87]:

1. Dosage and form (whether you consume citrulline naturally or as a supplement).
2. Food matrix interactions.
3. Individual differences in metabolism.
4. Processing conditions that affect citrulline stability.

The body readily absorbs L-citrulline from natural sources such as watermelon, which then helps the body produce L-arginine. Research in humans has demonstrated that the supplementation of L-citrulline from a purified source would exert greater effects on the levels of plasma L-citrulline and L-arginine than its consumption in food due to the presence of standardized dosages. These responses will vary with the dose, formulation, duration of administration, and the subjects, such as the age, health, and activity of the study participants. The presence of L-arginine in the diet and dietary nitrate may play an important role in the metabolism of nitric oxide, as they provide complementary substrates for NO production, whereas carbohydrates, proteins, and dietary fiber in the food may affect the digestion and absorption of L-citrulline [114].

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Excretion and Safety Considerations

L-Citrulline is considered safe and well tolerated in healthy adults taking it at the usual doses used in the human trials performed. Administration of this amino acid at a daily dose of about 3 to 8 g/day for 2-6 weeks does not cause significant adverse effects. Occasionally, nausea, abdominal pain, and diarrhea have been reported in patients taking higher doses, but these effects are temporary and usually resolve on their own. Note that there is still a lack of clinical data in this population and people with severe renal impairment, hereditary urea cycle disorder and those receiving nitric oxide-modulating therapy could be at risk.

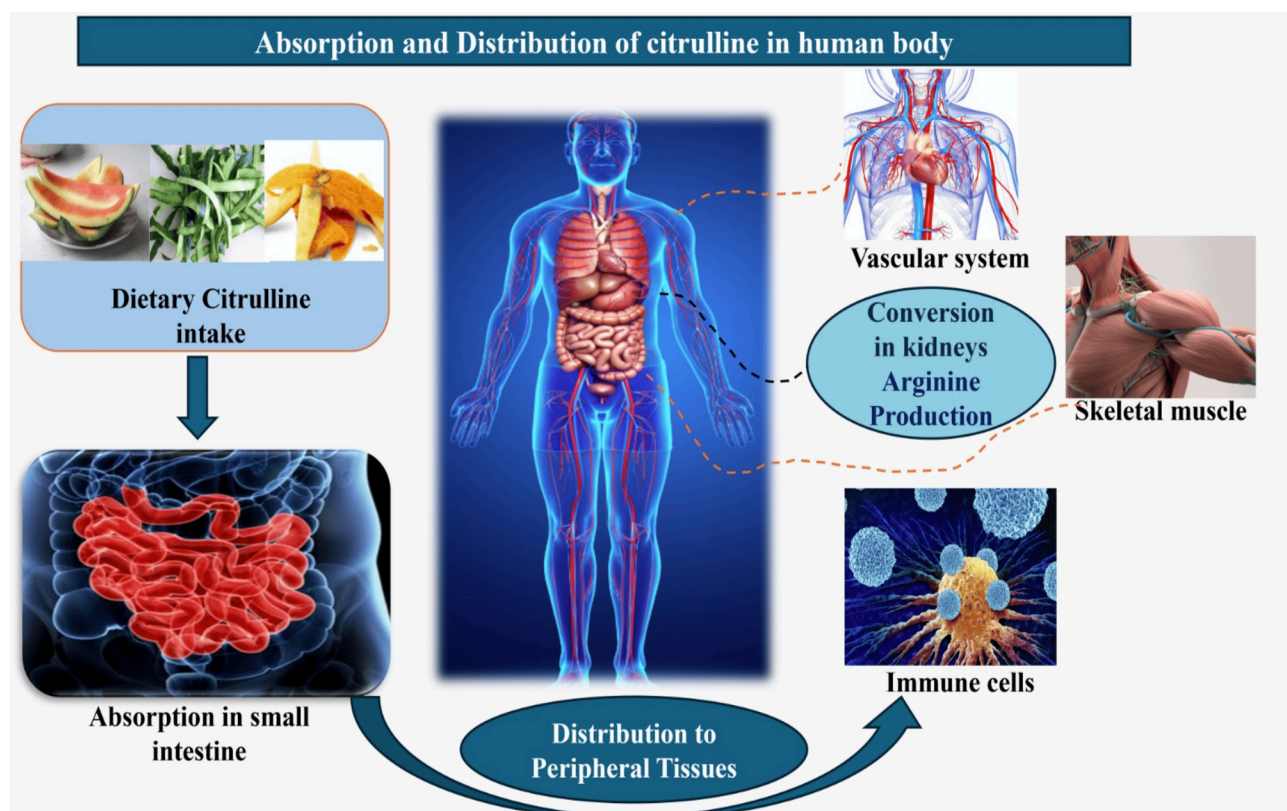


FIGURE 2: Absorption and Distribution of Citrulline in the Human Body

Figure 2 depicts the absorption, transport, and tissue distribution of citrulline following dietary intake.

Health-promoting properties of citrulline

L-Citrulline has been extensively studied for its role as a precursor of L-arginine and NO, both important mediators in the vasculature, skeletal muscle, and several physiological processes [116]. The health effects of L-citrulline have been explored *in vitro*, in animal models, in clinical trials and in systematic reviews, but the strength of evidence varies according to the health effect being studied. L-arginine and nitric oxide production are increased in plasma levels in human subjects, but other benefits claimed of L-citrulline, such as antioxidant and anti-inflammatory effects, immune modulation and metabolic effects, have only been demonstrated in experimental studies and need to be confirmed in large-scale clinical trials [117]. L-Citrulline is naturally present in cucurbit crops such as watermelon, melon, cucumber, pumpkin, and gourd.

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The potential of L-citrulline to help improve cardiovascular function has been examined due to the ability of L-citrulline to convert into L-arginine, the precursor to NO [118]. The production of NO increases vascular dilation and endothelial function, which leads to an increase in blood circulation in the blood vessels. L-citrulline supplementation has been shown in human clinical trials to be associated with improvement of endothelial function and arterial compliance, especially in those with poor vascular function. The benefits observed in terms of blood pressure and other cardiovascular functions have been inconsistent in various studies depending on dose and other factors like duration of supplementation, subject's health condition, and population under study [13].

Exercise Performance and Muscle Function

L-Citrulline has been extensively studied to assess its possible benefit for performance during exercise and skeletal muscle function [119]. Clinical data in humans suggest that supplementation with L-citrulline can improve exercise performance, as well as muscular endurance and recovery via increased NO bioavailability resulting in increased oxygen and nutrient delivery to muscle [120,121]. L-Citrulline is also involved in the removal of ammonia from the blood following prolonged or intense exercise and may therefore contribute to delayed muscle fatigue and recovery following physical activity [122]. However, heterogeneity of the described effects was observed among the clinical trials. The effectiveness of L-citrulline intake seems to be affected by such factors as dosage, duration, type of exercise, training status, and participants' characteristics.

Antioxidant and Anti-Stress Effects

L-Citrulline itself is not an antioxidant, but it may contribute to antioxidant defense through the improvement of NO availability, enhancement of endothelial function, and modulation of pathways related to oxidative stress [123]. L-Citrulline is thought to function as a ROS scavenger and osmoprotectant in plant physiology, assisting the cells of plants in avoiding oxidative damage during the abiotic stress period [124]. It is important to note, however, that the mechanisms described above cannot be directly extrapolated to human physiology. In humans, the antioxidant effect of L-citrulline is proposed to be mediated by NO metabolism and vessel function, while direct antioxidant activity has not been sufficiently proven.

Metabolic Health and Nutritional Support

L-Citrulline has also been researched for its effects on metabolic health, specifically lipid metabolism and insulin sensitivity. L-Citrulline has been associated with improvements in lipid metabolism and insulin sensitivity and thus overall metabolic health via pathways associated with NO production, amino acid metabolism, and nitrogen balance [125]. Nevertheless, there is relatively little current evidence for the effect of L-citrulline in humans, and the results are inconsistent depending on the population, the supplementation process, and the duration of the intervention used. Thus, while there is promise in the use of L-citrulline as a nutrition-based strategy in metabolic health, further research needs to be done [126].

Immune Function and Detoxification

L-Citrulline indirectly promotes immunity through its involvement in L-arginine metabolism and formation of NO, both of which are critical for proper functioning of immune cells and signaling [127]. L-Citrulline is a precursor for endogenous L-arginine, contributes to nitrogen balance, and plays a key role in physiological events related to immune system homeostasis. Moreover, the involvement of L-citrulline in the urea cycle helps in the detoxification of ammonia and thus aids in nitrogen metabolism and prevents accumulation of nitrogenous waste products [128]. However, there is not enough scientific evidence regarding the immunomodulatory effects of L-citrulline and more studies are needed to confirm the mechanism.

Applications in functional foods and nutraceutical development

Due to the upsurge in the popularity of healthy food options, citrulline has become a widely known bioactive material for the creation of functional foods and nutraceuticals [129]. The properties of citrulline, like its ease of dissolution in water, its lack of taste, and its established effect on the human body, give it numerous possible uses in different food systems

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[130]. After much research and industry interest, there has been a push to get innovative and consumer-ready products out into the marketplace using citrulline-rich plant-based raw materials.

Functional Food Applications

L-Citrulline has been used in various experimental formulations of functional foods, such as beverages, and nutraceutical products. Watermelon juice as well as beverages from watermelon rinds have gained popularity due to their natural content of L-citrulline along with vitamins, minerals, and antioxidants that allow them to be used as functional beverages [131]. At the same time, watermelon rind powder has been applied successfully in bakery products, snack bars, and beverages in order to increase their nutritional value and valorize agricultural waste [132]. In dairy products, L-citrulline containing ingredients have been considered for the development of yoghurts and fermented milk drinks, while powdered forms have been tested for use in ready-to-drink beverages and sports nutrition products. Selection of a proper formulation approach would depend on the application purpose, desired L-citrulline level, consumer acceptance, and processing requirements. Despite the evidence of technological feasibility of the formulations presented here, more studies are needed to optimize formulation properties, storage stability, and consumer acceptability of products before commercialization [133].

Some typical examples of functional food products enriched with L-citrulline that were successfully developed experimentally and are available commercially are presented in Table 7. This table highlights the flexibility of using L-citrulline-containing food ingredients, especially the watermelon-based ones, for making functional food products.

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Product/Application	L-Citrulline source	Formulation strategy	Technological challenges	Sensory/Storage characteristics
Functional beverage	Fresh watermelon juice	Direct utilization of natural L-citrulline-rich juice	Microbial stability and shelf-life limitations	Good consumer acceptance; refrigeration required
Fortified beverage/smoothie	Watermelon rind extract or powder	Addition of rind extract/powder to fruit beverages	Sedimentation and color stability	Acceptable sensory quality after formulation optimization
Bakery products	Watermelon rind powder	Partial replacement of wheat flour	Changes in texture and moisture retention	Acceptable sensory properties at optimized incorporation levels
Dairy products	L-Citrulline-rich watermelon ingredients	Fortification of yoghurt and fermented dairy products	Maintaining product texture and flavor	Good stability under refrigerated storage
Sports nutrition products	Purified L-citrulline powder	Ready-to-mix powders, protein supplements and sports drinks	Uniform dispersion and dosage standardization	High stability under dry storage conditions
Nutraceutical formulations	Purified L-citrulline	Capsules, tablets, and powdered supplements	Ingredient purity, regulatory compliance, and dosage consistency	Excellent storage stability when protected from moisture

TABLE 7: Functional Food Products Developed Using L-Citrulline-Rich Ingredients and Their Technological Characteristics

Nutraceutical and Dietary Supplement Development

Citrulline is most commonly sold as capsules, tablets, and powdered supplements in the nutraceutical industry. Generally, these products usually target cardiovascular health or sports performance. Citrulline is widely used with other bioactive substances (e.g., arginine, antioxidants, vitamins), either by itself or in combination with them. This is due to it being more biologically available than arginine, which has contributed to the popularity of products that may enhance NO production and physical performance [134]. L-Citrulline products intended for commercial purposes have to meet quality standards, purity of ingredients, labeling, and acceptable health claims as per the governing regulatory authorities for ensuring the safety of the products and building customer trust [78].

Encapsulation and Delivery Systems

Several encapsulation systems have been investigated to improve L-citrulline stability, bioavailability, and controlled release in functional foods [135]. Of these encapsulation technologies, the microencapsulation technology based on biopolymers, such as alginate, gelatin, maltodextrin, and gum arabic, is widely used because of its ease of use, lower cost, and compatibility with food systems. However, this technique has the problems of early release and insufficient

protection during processing [136]. Nanoencapsulation has benefits of better stability against degradation, improved bioavailability, and controlled release due to its tiny particle size, but problems of higher cost and processing complexity [140]. Liposomal delivery systems are effective for the delivery of water-soluble bioactive compounds due to their stability in the gastrointestinal tract and the ability to target delivery; however, the issues of physical stability and high cost of production continue to be critical problems [137]. To summarize, the selection of appropriate encapsulation systems is dependent on variables such as food application, stability during storage, processing conditions, cost of production, and controlled release [138]. Different kinds of encapsulation systems used for L-citrulline delivery in food applications are demonstrated in Table 8.

Encapsulation system	Advantages	Limitations	Suitability for food applications	References
Microencapsulation (alginate, gelatin, maltodextrin, gum arabic)	Cost-effective, easy to scale, protects during storage	Limited protection under severe processing	Functional beverages, bakery, dairy	[139]
Nanoencapsulation	High bioavailability, controlled release	High cost, regulatory concerns	Nutraceuticals, targeted delivery	[140]
Liposomes	Excellent protection of hydrophilic compounds, improved gastrointestinal delivery	Physical instability, expensive production	Functional beverages and nutraceuticals	[141]

TABLE 8: Different Types of Encapsulation Systems With Their Advantages and Limitations Used in Food Systems

Product Development and Commercial Potential

The application of agricultural waste products rich in citrulline has become increasingly popular as an environmentally friendly approach for producing value-added functional food ingredients. The use of watermelon peel, usually discarded during processing, is effective for producing powder, extract, and functional ingredients used in beverages, bakery products, bars, and sports nutrition products [142]. This approach not only adds nutritive value to foods but also helps valorize agro-waste products and is in line with the principles of the circular economy [143]. The utilization of the peels of melon and cucumber processing residues as a source of L-citrulline in nutraceutical and functional foods has also been studied besides watermelon peel. The commercial outlook is promising, but there is room for improvement [144].

Sustainability aspects and future perspectives

Increasing focus on sustainable food systems and circular economy methods has resulted in increased interest in bioactive materials, especially citrulline, because it is found naturally in many crops and industrial by-products [145]. Citrulline has strong potential as a sustainable resource, especially from plant by-products such as the watermelon rind, which is typically considered waste but has high levels of citrulline. Incorporating these by-products into food value chains will both reduce waste and promote the application of economical and environmentally sound functional ingredients [146].

Agro-Waste Valorization and Circular Economy

Using this method helps to minimize waste and increase resource efficiency while providing a new income for farmers and processors [147]. The use of green extraction technologies also improves sustainability due to reduced solvent usage, lower energy requirements, and less environmental damage [148].

Sustainable Processing and Green Technologies

Developing environmentally safe processing methods is needed to obtain high amounts of citrulline but also to minimize the impact on the environment. For example, newer technologies such as UAE, MAE, and membrane filtration can help reduce processing time and reduce dependence on chemicals in obtaining citrulline [149]. Furthermore, nonthermal processing technologies, such as HPP and cold press extraction technology, have been investigated for the production of L-citrulline-containing foods. The primary advantage of the cold press method is that the juice extraction process does not involve heat production and thus helps to preserve heat-sensitive bioactive compounds. However, HPP is primarily used after the extraction process to enhance microbial safety and extend the shelf-life of juice [150].

Crop Selection and Agricultural Strategies

Increasing the content of citrulline in crops can be an important tool for getting long-term sustainability. By selecting for high-citrulline varieties, optimizing irrigation methodologies, and managing abiotic factors affecting crops, it has been successfully proven that citrulline levels in crops can increase significantly [151]. Additionally, it has been demonstrated that regulated stress can promote increases in citrulline levels that may be used to potentially improve biofortification and enhance crops through controlled exposure to particular stressors [152].

Challenges and Research Gaps

The regulatory requirements for products containing L-citrulline vary from country to country. In the European Union, the European Food Safety Authority (EFSA) requires scientific evidence to support any health claims that are to be made before they appear on any food products. In the United States, products containing L-citrulline are generally classified as dietary supplements and are therefore regulated by the Food and Drug Administration (FDA) under the Dietary Supplement Health and Education Act (DSHEA), which requires manufacturers to ensure the safety of their products [153]. In India, the Food Safety and Standards Authority of India (FSSAI), a regulatory agency for the manufacture and sale of nutraceuticals and functional foods, governs products containing L-citrulline [154]. There are regulations governing L-citrulline products, but some of the challenges to bringing these products to market include labeling, quality standardization, dosage standardization, and developing strong clinical evidence for health claims [154,155].

While citrulline has great potential, many barriers must be overcome to fully leverage citrulline's potential for use within sustainable food systems [156], such as variability of citrulline content because of crop and growing conditions; limitations in large-scale processing and commercialization strategies; and the need for clarifying regulations surrounding the use of citrulline in functional foods. To address these challenges, researchers will need to conduct interdisciplinary studies that integrate food science, agriculture, and biotechnology.

Future Perspectives

Future studies related to citrulline should include: A focus on developing new and improved functional foods with greater stability and bioavailability [157], investigating advanced methods of delivering citrulline, such as nanoencapsulation technology [158], investigating the requirement of citrulline as an integrated component of personalized diet plans and programs [159], and investigating the increased use of citrulline in plant-based and sustainable diets. Furthermore, researchers and consumers alike must have a greater understanding of citrulline, as well as more collaboration between researchers, consumers, and the industry, in order to transfer research into successful consumer and commercial products. The alignment of citrulline research with current global issues, including nutrition safety, environmental sustainability, and health promotion, makes citrulline further relevant to today's food systems.

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Conclusions

L-Citrulline is a non-proteinogenic amino acid that has been of increasing interest to scientists in its application to functional food products and nutraceuticals due to its physiological importance in the synthesis of NO, the metabolism of L-arginine, and nitrogen balance. High levels of L-citrulline are present only in some cucurbits, especially watermelon and its products, which provide potential opportunities to develop novel functional food ingredients. The current scientific literature points to the ability of L-citrulline to raise plasma levels of L-arginine and NO availability, and even more so, clinical studies have shown potential health benefits for cardiovascular physiology, physical activity, and metabolism. However, the evidence for such health effects varies, and some of the proposed benefits need to be proven in clinical studies on humans.

The advances in green extraction methods, encapsulation techniques, and new food formulations have increased the possibilities of using L-citrulline in functional foods and nutraceuticals and have enabled the sustainable exploitation of agricultural residues such as watermelon rinds within the framework of circular economy approaches. However, there are still some difficulties, such as the development of standard methods for the extraction and analysis of L-citrulline, optimal processing conditions, product stability, harmonization of regulations, and more clinical evidence to support the health claims. More scientific work is needed on industrial-scale manufacturing, long-term safety and efficacy trials, food formulation improvements, and sustainable processing technologies to help bring L-citrulline functional foods to the market. These findings will, in total, enable the integration of L-citrulline into evidence-based functional nutrition.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Conflicts of interest: In compliance with [the ICMJE uniform disclosure form](#), all authors declare the following:

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- **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
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Data Availability Statements

Data sharing is not applicable. This work is theoretical; no datasets were generated or analyzed.

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