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Designing Next-Generation Functional Food and Beverages: Combining Nonthermal Processing Technologies and Postharvest Abiotic Stresses

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Abstract
Currently, consumers are demanding healthier foods that are at the same time fresh, safe, and long-lasting. However, traditional food processing technologies apply thermal treatments, which lead to modifications of sensory properties and losses of health-promoting compounds. Therefore, novel technologies have been increasingly researched and developed to overcome these problems, including postharvest abiotic stresses (PAS) and nonthermal processing technologies (NTPTs). PAS refer to the application of non-biological stimuli (i.e., wounding stress, modified atmospheres, UV light) to which plants respond by synthesizing secondary metabolites as a defense mechanism. Many of these secondary metabolites are nutraceuticals. On the other hand, NTPTs (i.e., high-pressure processing, ultrasound, pulsed electric fields) extend the shelf-life of foods without using high temperatures, allowing the retention of sensory, nutritional, and nutraceutical quality. Furthermore, certain NTPTs can also act as PAS, enhancing the nutraceutical content of foods through physical, chemical, and metabolic changes. This review describes the physiological response of fruits and vegetables to PAS and NTPTs and discusses their strengths and drawbacks when using them as elicitors to induce the accumulation of nutraceuticals. It presents a new concept that consists of the combined application of PAS and NTPTs to design next-generation food and beverages against chronic diseases using colon cancer as an example. Combining PAS and NTPTs is an emerging field; therefore, more research is needed to establish which combinations are most suitable and cost-effective to satisfy consumer demands.

Keywords Postharvest abiotic stress · Nonthermal processing technologies · Nutraceuticals · Next-generation foods · Colon cancer

Abbreviations

ATP	Adenosine triphosphate
H_2O_2	Hydrogen peroxide
HPP	High-pressure processing
NADPH	Nicotinamide adenine dinucleotide phosphate
NTPTs	Nonthermal processing technologies
PAL	Phenylalanine-ammonia lyase
PAS	Postharvest abiotic stresses
PEF	Pulsed electric fields
ROS	Reactive oxygen species
US	Ultrasound
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
UVC	Ultraviolet C

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Introduction

Chronic degenerative diseases such as cancer, diabetes, and cardiovascular disorders (ischemic heart diseases, stroke) are the leading causes of death worldwide [55]. These diseases could be prevented by eating healthy [54], doing exercise [8], and consuming foods rich in nutraceuticals [13]. Nutraceuticals are defined as compounds naturally present in food that provide health benefits, including the prevention and treatment of chronic diseases [14]. Fruits and vegetables are the main sources of nutraceuticals in human diet, and thus, their consumption could aid in the prevention of chronic diseases.

Due to the health benefits of nutraceuticals found in horticultural crops and the continuous awareness of consumers to eat healthier, the food industry is interested in incorporating fruits and vegetables into processed foods to enhance their nutraceutical quality. However, traditional food processing technologies apply thermal treatments to foods, which leads to losses of health-promoting compounds. Therefore, novel technologies have been increasingly researched and developed to overcome these problems, including postharvest abiotic stresses (PAS) and nonthermal processing technologies (NTPTs).

PAS refer to treatments applied after harvest such as wounding stress, modified atmospheres, phytohormones, and ultraviolet (UV) radiation among others applied to horticultural crops that induce the activation of the plant secondary metabolism. Nutraceuticals in fruits and vegetables are present as secondary metabolites, and thus, the controlled application of PAS results on their accumulation as a stress response [10]. Therefore, PAS could be applied prior to processing to overcome the thermal degradation induced by traditional processing [41]. On the other hand, NTPTs (i.e., high-pressure processing (HPP), ultrasound (US), pulsed electric fields (PEF), ultraviolet C (UVC) radiation) can extend the shelf-life of foods without the need of using high temperatures, allowing the retention of their sensory, nutritional, and nutraceutical quality. Furthermore, certain NTPTs can also act as PAS enhancing the nutraceutical content of foods through physical, chemical, and metabolic changes [24]. Thus, the proper combination of PAS and NTPTs during the design of a bioprocess could allow obtaining a processed food or beverage with high concentration of nutraceuticals and long shelf-life.

In this paper, we are referring as next-generation food and beverages to processed products that are designed to prevent chronic degenerative diseases obtained as follows: (a) raw materials (fruits and vegetables) are selected rationally to obtain a final product that contains a previously validated mixture of nutraceuticals that prevents or treats a certain chronic disease; (b) prior to processing, the horticultural crops selected are treated with PAS and/or NTPTs to increase the concentration of the nutraceuticals required in the final product; (c) the product is stabilized using NTPTs or a combination of thermal and nonthermal technologies (hurdle technology) to preserve the nutraceutical content, safety, and sensory properties.

This concept paper describes the physiological response of fruits and vegetables to PAS and NTPTs and discusses their strengths and drawbacks when using them as elicitors to induce the accumulation of nutraceuticals. Likewise, it presents the combined application of PAS and NTPTs to design next-generation food and beverages against chronic diseases, taking into consideration previous reports from our group and other research groups working actively in this emerging area.

Definitions, Strengths, and Drawbacks of PAS and NTPTs

As previously described, PAS such as wounding, UV radiation, phytohormones, and modified atmospheres applied to fruit and vegetables can induce the biosynthesis of secondary metabolites with health-promoting activity [10]. In addition to the technologies commonly known as PAS in postharvest research, certain NTPTs such as HPP, PEF, US, and UVC can also be considered PAS since they elicit the biosynthesis of secondary metabolites [24]. Indeed, there are technologies based on the application of UV radiation that appear in both categories, which can complicate their classification. However, the most common NTPTs have the potential to increase the nutraceutical content of fruits and vegetables, while not all PAS can be NTPTs, which are primarily applied to inactivate microorganisms and enhance the shelf-life of foods.

Both PAS and NTPTs have strengths and drawbacks summarized in Table 1. The main strength of PAS is that some can cause large increases of the nutraceutical content of fruits and vegetables at low or ambient temperatures in short times (hours–few days) without affecting the quality of the crops under controlled conditions. For instance, wounding stress has been reported to increase phenolic compounds by 200 to 800% in raw carrot and carrot products in 48 h at 15 °C without spoilage [3, 41, 42].

Most PAS are unable to inactivate microorganisms and enzymes that can severely affect the quality and safety of fruits and vegetables stored for a prolonged storage time. In the specific case of phenolic compounds, it has been reported that wounding is the most effective PAS to induce their stress-induced biosynthesis [23]. However, for certain tissues such as carrot, in order to observe a significant eliciting response of other PAS, such as UV radiation and phytohormones, they must be applied in wounded tissue, and only a slight response is observed when these PAS are applied in whole fruit and vegetables [21, 25, 27, 17, 19, 18, 35, 36, 48].

The strengths of NTPTs include inactivation of microorganisms and enzyme at low or moderate temperatures, which leads to the preservation of nutrients, nutraceuticals, and organoleptic properties of fruits and vegetables, and can also induce moderate nutraceutical increases under certain processing conditions described in the previous section. In contrast with PAS, for certain tissues, NTPTs such as US and PEF, can induce significant increases in nutraceuticals when applied in whole fruits and vegetables. For instance, US and PEF activated the biosynthesis of phenolics in whole carrots [12, 30],

Table 1 Strengths, drawbacks, and examples of postharvest abiotic stresses and nonthermal processing technologies

Postharvest abiotic stresses	Nonthermal processing technologies
Strengths	
• Some can cause large nutraceutical increases at low-moderate temperatures in short times without affecting quality and safety.	• Can inactivate microorganisms and enzymes at low-moderate temperatures • Can induce moderate nutraceutical increases • Can induce nutraceutical increases in whole tissue
Drawbacks	
• Most are unable to inactivate microorganisms and detrimental enzymes. • Most can severely affect quality and safety. • In most cases, wounding stress is needed before the application of other PAS to observe significant nutraceutical increases.	• In an attempt to inactivate undesirable enzymes, they can inactivate key enzymes required for nutraceutical biosynthesis. • Can be complicated finding the optimal point of undesirable enzyme inactivation and nutraceutical increase.
Examples	
• Wounding	• High hydrostatic pressure
• Phytohormones	• Pulsed electric fields
• UVA, UVB, UVC light	• Ultrasound
• Modified atmospheres	• UVC light
• Water stress	
References	
[5–7, 10, 56, 1, 21, 27, 23, 4, 48, 35, 36, 17, 19]	[49, 29, 33, 24, 45, 12, 2, 30, 52, 37, 16]

whereas US application increased the biosynthesis of glucosinolates and phenolic compounds in broccoli florets [2].

In an attempt to inactivate undesirable enzymes, NTPTs can inactivate key enzymes and slow down the metabolism of the plant tissue, which are needed for nutraceutical biosynthesis as well, causing limited nutraceutical increases or none at all depending on the conditions. For instance, to induce accumulation of phenolic compounds, the phenylpropanoid pathway needs to be activated, which requires several enzymes [23]. Therefore, finding an optimal point of inactivation of undesirable enzymes and nutraceutical increase is a complex task. Combining postharvest abiotic stresses and nonthermal processing technologies is here proposed to compensate their drawbacks allowing the design of nutraceutical-rich, highly nutritional, fresh, and safe food products.

Physiology of Stress-Induced Activation of Secondary Plant Metabolism

Plants subjected to PAS undergo a series of events that result in the activation of the secondary metabolism, and thus the accumulation of molecules with health-promoting properties. This sequence of events can be divided into an *immediate*, *early*, and *late response* depending on the time elapsed after the application of the stress [11, 24]. Taking wounding stress as an example of PAS, the *immediate response* would be the generation of oxidative stress via two main mechanisms. First, wounded cells will release adenosine triphosphate (ATP) from the cytoplasm, which binds to unwounded cell receptors. ATP binding to receptors induces the generation of reactive oxygen species (ROS) through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [46, 27]. Second, an immediate increase in cellular respiration after wounding also results in the production of ROS ([47]; [35]). Thus, the production of the primary (ATP) and secondary (ROS) wound signals is observed as an immediate stress response. The *early response* occurs few minutes after wounding (between 30 and 90 min) and consists in the generation of additional stress-signaling molecules, such as ethylene and jasmonic acid, which through a complex cross-talk with ROS, activate the expression of primary and secondary metabolic genes [9, 25, 38, 50]. Finally, in the *late response* (hours after wounding), translation of overexpressed primary and secondary metabolic genes occurs, producing enzymes that catalyze the biosynthesis of secondary metabolites, many of them with health-promoting properties [11, 23]. Other PAS such as UV radiation and hyperoxia also induce elicitation through ROS generation [27, 48]. For instance, UV radiation induce ROS formation by water ionization and increase cellular respiration [48], whereas hyperoxia increases respiration rate of the tissue [27]. In the following section, the physiological mechanisms by which NTPTs induce stress responses in horticultural crops are described, using as a basis the physiological stress response of plants to wounding stress.

How Do Nonthermal Processing Technologies Induce Stress Response in Fruits and Vegetables?

Previous reports have demonstrated that NTPTs such as HPP, US, and PEF, under certain processing conditions, can be used as abiotic elicitors to induce the biosynthesis of secondary metabolites [24]. A hypothetical model explaining the physiological mechanisms eliciting the biosynthesis of nutraceuticals in plant foods treated with NTPTs (US, HPP, and PEF) has been recently proposed by our group [24, 45]. In the model, NTPTs such as US, HHP, and PEF induce changes in cell membrane permeability, eliciting a stress response similar to wounding, which is initiated by ATP released from the cytoplasm of damaged cell membranes. ATP binding to undamaged cells generates the aforementioned immediate, early, and late wound-like responses.

The physiological model previously reported is supported by scientific evidence indicating similar physiological responses to wounding when different horticultural crops are treated with NTPTs. For instance, increased respiration rate, as well as increased phenylalanine-ammonia lyase (PAL) gene expression and activity (key enzyme in phenolic biosynthesis), and phenolic accumulation was reported in carrots treated with US (24 kHz, 20 °C, 5 min, 100 μm) and stored for 72 h at 20 °C [12]. Likewise, Ramos-Parra et al. [37] evaluated the effect of HPP treatments (50–400 MPa for 3–60 min) and storage at 4 °C on oxidative stress (H_2O_2 generation) and expression of genes related with carotenoid biosynthesis in papaya fruit. The authors reported that H_2O_2 significantly increased with the magnitude of pressure applied as well as the expression of genes related with carotenoid biosynthesis, which resulted in carotenoid accumulation. Similarly, López-Gámez et al. [30] evaluated the effect of PEF on the accumulation of phenolic content, cellular permeability, and viability of carrot cells. The authors treated carrot with different electric field strengths (0.8, 2, and 3.5 kV cm^{-1}) and number of pulses (5, 12, and 30) and observed that the largest increase (40%) in phenolics was detected after 24 h of storage (at 4 °C) of the tissue treated with 30 pulses of 0.8 kV cm^{-1} or 5 pulses of 3.5 kV cm^{-1}. This increase was attributed to destabilization of cell membranes after PEF treatment, which induced a physiological response, leading to phenolic biosynthesis [30].

An important factor to consider when using NTPTs as PAS is the processing conditions selected in order to prevent irreversible damage or plant cell death [24]. Conditions used for HPP should not exceed 200 MPa, whereas for US, high-energy and low-frequency (between 20 and 100 kHz) conditions should be selected. On the other hand, moderate intensity (0.5–5 kV/cm, 1–20 kJ/kg) PEF has been reported to elicit stress response in fruits and vegetables. An overview on the effect of different processing and storage conditions that induces stress response by US, HPP, and PEF can be further consulted in recent publications [24, 45].

In addition to US, HPP, and PEF, another promising nonthermal technology that acts as an effective abiotic elicitor is UVC. UV radiation is classified into UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm) [48]. UVA, UVB, and UVC can be used as PAS. In the specific case of UVC, it is also considered NTPT due to its germicidal effect [29]. However, in contrast with US, HPP, and PEF, the primary signal inducing the stress response in UVC-radiated fruits and vegetables would be ROS directly produced by either water ionization of the tissue or increased mitochondrial respiration [48].

It is important to consider that fruits and vegetables treated with US, HHP, or PEF undergo additional microstructural changes not induced by commonly applied PAS. For instance, as an immediate response to the treatment, cell membrane permeation occurs, resulting in higher extractability of nutraceuticals [20, 24, 26, 45]. This is positive from a nutraceutical perspective since the bioactive molecules would be more bioavailable for their absorption in humans. Figure 1 summarizes the physiological stress response of fruits and vegetables when treated with common PAS and NTPTs.

Combined Application of PAS and NTPTs to Design Next-Generation Foods and Beverages Against Chronic Diseases

The combination of common PAS with NTPTs treatments could be an effective strategy to obtain nutraceutical-rich, fresh, and safe food products. Depending on the market to reach and the target chronic disease to prevent, a proper combination of raw material, PAS and NTPTs stress, and processing conditions can be selected to satisfy the need. We have recently published a practical guide for designing effective nutraceutical combinations against chronic diseases, which can be used as a basis for designing next-generation foods and beverages [40]. In the practical guide, first nutraceuticals against a specific chronic disease are selected, and their optimum combinations are determined by in vitro studies. Thereafter, the food or beverage is designed based on the best combination of food ingredients (in most cases fruits or vegetables) that are rich in those nutraceuticals.

The major challenge of food ingredient selection is to find fruits and vegetables with high concentration of bioactive compounds that, when combining and subjected to thermal processing conditions to stabilize the food, reach the desired concentration of nutraceuticals in the final product. At this

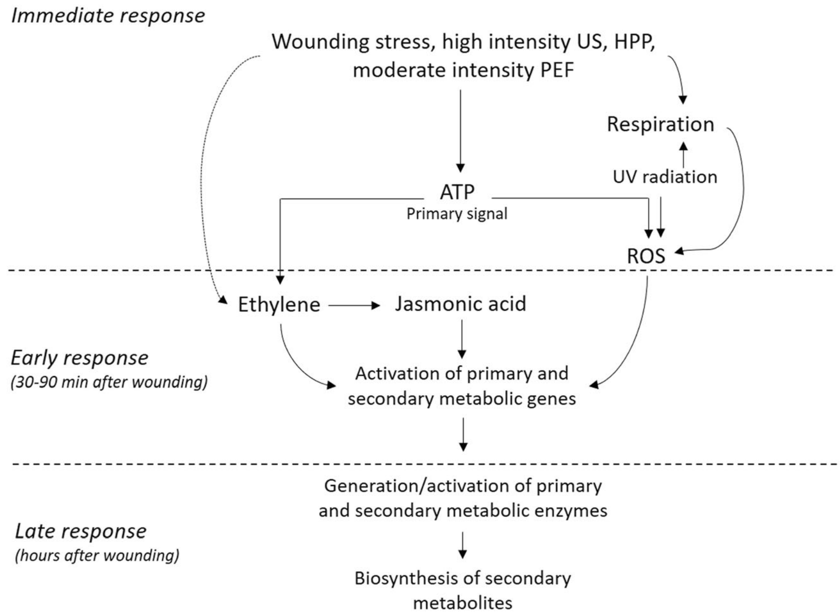

Fig. 1 Physiological stress response of fruits and vegetables when treated with common postharvest abiotic stresses (wounding stress and UV radiation) and nonthermal processing technologies (NTPTs), high-intensity ultrasound (US), high-pressure processing (HPP), and moderate intensity pulsed electric fields (PEF)

point is where planning an effective bioprocess addressing the right combination of PAS and NTPTs to enhance and preserve the concentration of nutraceuticals in horticultural crops becomes critical.

Fruits and vegetables treated with PAS and NTPTs (mild conditions) with enhanced levels of nutraceuticals can be used as raw materials for the production of food or beverages, whereas NTPTs applied alone at high-intensity conditions or combined with thermal processing can be applied in the formulated product to minimize the degradation of nutraceuticals during pasteurization, ensuring its microbial quality and safety, and enhancing its shelf-life. In this concept paper, the following scenarios or combinations of PAS and NTPTs conditions are envisioned to enhance the nutraceutical content of raw materials and to retain the content of bioactive compounds during processing to stabilize the final food or beverage:

- PAS and/or NTPTs (mild-intensity conditions) alone or combined = gives raw materials with enhanced nutraceutical properties (shelf-unstable product)
- PAS and/or NTPTs (mild-intensity conditions) + NTPT (high-intensity conditions) = gives a final product with enhanced nutraceutical properties (shelf-stable product)
- PAS + NTPT (high-intensity conditions) = gives a final product with enhanced nutraceutical properties (shelf-stable product)

To exemplify the strategy, we will use as an example a study done by our group following the protocol previously described [40] to find synergistic combinations of nutraceuticals against colon cancer [43]. In that study, we evaluated combinations of sulforaphane, dihydrocaffeic acid (a chlorogenic acid metabolite), and curcumin against human colon cancer cells, and determined that the 1:1 combination of sulforaphane and dihydrocaffeic acid exerted a synergistic effect against HT-29 colon cancer cells at 90% cytotoxicity level (doses 90:90 μM), and the combination was significantly more cytotoxic for cancer cells than normal cells.

The next step of the protocol is to find rich sources of these compounds and to make the proper combination of raw materials that provides a final food product containing 1:1 combination of sulforaphane and dihydrocaffeic acid. Thus, a bioprocess that includes the right combination of PAS and NTPT conditions to enhance and preserve the concentration of nutraceuticals in the crops selected should be determined. Dihydrocaffeic acid is a metabolite of chlorogenic acid [39, 44]. About 2/3 of the ingested chlorogenic acid reaches the colon where it is further metabolized by the colonic microbiome [15, 32, 34]. Dihydrocaffeic acid is one of the main metabolites of chlorogenic acid produced by the colonic microbiota. On the other hand, sulforaphane is an isothiocyanate present in cruciferous vegetables. Normally, sulforaphane is in the form of glucoraphanin, a glucosinolate, in intact vegetable tissue. However, when the vegetable is macerated or eaten, the enzyme myrosinase hydrolyzes glucoraphanin to sulforaphane [28]. Cooking inactivates myrosinase, resulting in the ingestion of intact glucoraphanin, which upon reaching the colon can be hydrolyzed to sulforaphane by the microbiota with thioglucosidase activity [28]. Therefore, in order to reach the 1:1 concentration of dihydrocaffeic acid and sulforaphane in the colon, it is necessary to formulate a food or beverage with high concentrations of chlorogenic acid and glucoraphanin that will be transformed into dihydrocaffeic acid and sulforaphane by the microbiota.

In the specific case of chlorogenic acid, it has been reported that the application of PAS increases its concentration in carrots. For instance, the application of wounding stress (shredding) can increase the content of chlorogenic acid from 38.2 to 803.3 mg kg^{-1} fresh weight (2002%) after storage of the tissue at 20 °C for 48 h, and the content is further increased to 1171.4 mg kg^{-1} fresh weight (2966%) when shredded carrots are stored under hyperoxia conditions (80% oxygen in the atmosphere) [27]. To obtain foods rich in chlorogenic acid, carrot tissue with increased levels of the compound has been dried, milled, and used as an ingredient in corn tortillas [41] and sausages [3]. Furthermore, using a similar approach, the bioprocess to obtain carrot juice [42] and puree [31] was modified incorporating a step of wounding stress to the raw

Table 2 Strategy to obtain next-generation food and beverages against colon cancer using the combined application of postharvest abiotic stresses (PAS) and nonthermal processing technologies (NTPTs) for designing the bioprocess

Step	Compound 1 (chlorogenic acid)	Compound 2 (glucoraphanin)	Reference/notes
1. Selection of nutraceutical combination with synergistic effect against colon cancer based on in vitro studies	Dihydrocaffeic acid (produced from chlorogenic acid by the microbiome)	Sulforaphane (produced from glucoraphanin by the microbiome)	[44] Note: The synergistic interaction occurs when the compounds are combined in a 1 to 1 proportion.
2. Selection of food ingredients rich in chlorogenic acid and glucoraphanin	Carrot	Broccoli	[22, 23]; [53]
3. Application of PAS and/or NTPTs to increase the content of nutraceuticals in the raw material	Shredded carrots stored for 48 h at 15 °C, dried and milled to produce carrot powder. Carrot slices stored for 48 h at 15 °C to produce carrot juice or puree (PAS alone)	Broccoli florets stored for 24 h at 20 °C and subsequent ultrasound treatment (20 min, frequency 24 kHz, amplitude 100 μm) (PAS and NTPT (mild-intensity conditions) combined)	[27]; [42]; [31]; [51]; [2]
4. Design the appropriate mixtures of ingredients from stressed tissue to obtain the desired (1:1) concentration chlorogenic acid and glucoraphanin	Under investigation		
5. Determine NTPT conditions applied alone or combined with thermal processing to preserve the nutraceuticals and stabilize the obtained food			
6. Perform in vitro gastrointestinal digestion studies of the food to determine the bioavailability of the nutraceuticals			
7. Perform efficacy evaluations with laboratory animals and clinical human trials			
8. Perform shelf-life studies of the obtained product			

material. The product obtained contained 3600% and 300% higher chlorogenic acid in the juice and puree, respectively, as compared with the products obtained from the non-stressed carrot.

On the other hand, for glucoraphanin, it has been reported that the application of PAS and NTPTs increases its concentration in broccoli. For instance, glucoraphanin in broccoli florets increased from 1081 to 4585 mg kg^{-1} dry weight (324%) when stored at 20 °C for 24 h [51]. Furthermore, broccoli florets treated with US (20 min, frequency 24 kHz, amplitude 100 μm) showed an immediate increase in the extractability of glucoraphanin from 262.5 to 2349.4 (795%) [2]. Thus, a suggested strategy would be to store broccoli florets at 20 °C for 24 h and then apply US (20 min, frequency 24 kHz, amplitude 100 μm), further increasing the bioavailability of glucoraphanin produced as a stress response in the raw material. As compared with carrots, no previous attempts have been performed to incorporate stressed broccoli as an ingredient or raw material in food products.

The methodology proposed herein is summarized in Table 2, using as an example the design of a food product against colon cancer. As observed, steps 1 to 3 have been already accomplished by our research group; however, steps 4 to 8 are still under investigation. The strategy presented herein for a rational design of next-generation foods against chronic diseases could be easily extrapolated to other case studies.

Conclusions and Future Trends

This paper presented a new concept dealing with the combination of PAS and NTPTs to obtain novel food and beverages with health-promoting properties. The concept is based on the proper selection of the nutraceuticals needed in the final product to exert the desirable nutraceutical properties. Once determined, a bioprocess is designed where raw materials (fruits and vegetables) rich in the nutraceuticals required are selected and further processed with PAS and NTPTs to increase the content of desirable compounds in the raw material. This step is key to overcome losses of bioactive compounds induced by traditional thermal processing, which could be ameliorated by applying NTPTs alone or combined with thermal processing to stabilize the final food product. More research is needed to determine PAS and NTPTs processing conditions that allows elicitation of secondary metabolites, as well as NTPTs that could help in the stabilization of the designed food. As research continues, new strategies incorporating the principles of PAS and NTPTs will emerge under the principles of process integration and intensification, allowing a much more efficient and economic production of nutraceutical-rich, highly nutritional, fresh, and safe foods.

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