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Title: DEVELOPMENT OF NEW CRITICAL FLUID-BASED PROCESSING METHODS FOR NUTRACEUTICALS AND NATURAL PRODUCTS

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Development of New Critical Fluid-Based Processing Methods for Nutraceuticals and Natural Products

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Abstract

The development of new supercritical fluid processing technology as applied to nutraceuticals and natural products is no longer confined to using just supercritical fluid extraction (SFE) and supercritical carbon dioxide (SC-CO_2). Recently reported advances have been focused on modifying natural products and improving functionality of an end product using newer experimental techniques and fluid phases. In this presentation four focus areas will be emphasized: (1) control of particle size /morphology and encapsulation of the nutraceutical ingredients, (2) the use of combinatorial methodology to optimize critical fluid processing, (3) application of sub-critical water as a complementary medium for processing natural products, and (4) an assessment of the current state of products and processing which use critical fluid to produce nutraceutical and natural products for the food and cosmetic marketplace. Application of the various particle formation processes conducted in the presence of critical fluid media, such as: CPF, SAS, DELOS, RESS, PGSS, and GAS, can be used to produce particles of small and uniform distribution, having unique morphologies, that facilitate rapid dissolution or sustained release of many nutraceutical ingredients. These substances have included: therapeutic spices, phystosterols, vitamins, phospholpids, and carotenoids. Accelerating the development of critical fluid processing has been the application of combinatorial methodology to optimize extraction, fractionation, and/or reactions in near-, SC-, or sub-critical fluid media. This is frequently accomplished by using sequential or multi-channel automated instrumentation that was originally designed for analytical purposes. Several examples will be provided of rapidly assessing the extraction of anthocyanins with sub-critical water and the SFE of natural products. However, differences do exist in conducting experiments on the above instrumentation vs. scaled-up continuous processes, which will be noted. Sub-critical water is finding increase use as an extraction/fractionation or reaction medium. The literature reports applications for the extraction spices, natural antioxidants (rosemary, anthocyanins, etc.), and herbal components (tea and coffee ingredients). Our studies and the literature provide adequate correlations of solute solubility in sub-critical water as well as models for the kinetics of extraction in this medium. Finally, the current state of critical fluid technology as applied to natural products and nutraceuticals will be assessed; noting specific processes, organizations, and products that exist.

1. Introduction

The nutraceutical and functional food industry continues to provide a powerful incentive for the use of compressed fluids technology, i.e., critical fluids, since such products are targeted toward the health-conscientious consumer. Public knowledge in many countries has increased to the point that nutraceutical product labeling often refers to supercritical fluid extraction (SFE) or cold pressing techniques as evidence that such products have been isolated in a "natural" or "green" manner. Depending upon the definition of a nutraceutical, the market ranges of such products is

conservatively estimated to be 3.15 - 4.6 billion dollars in the USA and range from 1.05-1.6 billion US dollars in Europa. A broader definition of "functional" food suggests their US market value between 14.2-17.6 billion US dollars, and if one assumes that 50% of the food selected for consumption is based on health or medical considerations, then the estimated value of the nutraceutical market expands to 250 billion US dollars. This is a tremendous economic incentive to apply critical fluid technology to the nutraceutical, functional food, or natural pharmaceutical market

Critical fluid processing can be used in several modes for producing nutraceutical ingredients or functional foods. Exhaustive extraction in which SC-CO_2 or a SC-CO_2-cosolvent mixture is often used to yield an extract equivalent to those obtained with organic solvent extraction or via pressing/expelling technologies as documented in the recent literature [1]. Fractional extraction, where extraction pressure, temperature, time, or the addition of a cosolvent is varied on an incremental basis, is also capable of producing extracts that are somewhat either enriched or depleted in the desired nutraceutical agent [2]. Such fluid density-based or co-solvent-assisted extractions frequently yield extracts with considerable extraneous material; indeed specifically extracting or enriching a desired solute out of natural product matrix is somewhat akin "to finding a needle in a haystack".

Table I lists some of the common and popular nutraceutical agents in use today and their application with respect to their anticipated therapeutic benefit. It should be noted that all of the nutraceuticals listed in Table I have or can be processed using critical fluids; indeed a segment of the production capacity of the over 50 critical fluid processing plants worldwide are devoted to producing such products for the nutraceutical market. Specific examples of such plants and products will be cited later.

In this contribution, we will review and report on new approaches for applying and optimizing critical fluid processing as applied to nutraceuticals and natural products. These will include (1) control of particle size, morphology, and encapsulation with compressed fluids, (2) use of combinatorial instrumentation and methodology to optimize processes, (3) further application of sub-critical water, alone and in tandem with SC-CO_2, and the current state of processes and/or products which utilize critical fluids for the production of nutraceuticals and other health-related extractives from natural products. An extension of our studies on the extraction of anthocyanins from berries using sub-critical water will also be reported.

Table I. Nutraceuticals and their therapeutic use.

Nutraceutical	Utility
Saw Palmetto	Prostate
Kava-Kava	Anxiolytic
Hawthorne	Cardiotonic
Ginseng	Tonic
Garlic	Circulatory
Ginko Biloba	Cognitive
St. John's Wort	Depression
Chamomile	Dermatological
Echinacea	Colds/Flu
Black Cohosh	Gynecological
Lutein	Optical
Flavonoids	Anti-Cancer
Isoflavones	PMS, Circulatory
Omega 3 EFA, DHA	Circulatory
Evening Primrose	Inflammation
Phytosterols	Circulatory
Tocopherols	Antioxidant
Phospholipids	Cognitive

2. Experimental

The experimental conditions for the various particle/powder production processes, comminution, and encapsulation schemes cited here have been described in the literature [3,4] However a brief description of the principles involved, particularly as related to the CPF and similar processes is provided, along with a brief description of an early process investigated by the author for producing a powdered phospholipid extract from lecithin. Likewise, the utilization of combinatorial approaches and instrumentation or techniques has been recently summarized by the

author [5]. Application of this approach to optimizing the extraction of anthocyanins from berry substrates will be described below.

2.1 Experimental apparatus for de-oiling lecithin

A device similar in principle to that used by German researchers [6] has been described by King [7] as shown in Figures 1. Figure 1 shows the general and initial design of the jet extraction system. In this laboratory-scale apparatus, the solids collection reservoir and two collector vessels were each 30.5 X 2.54 cm, 316 stainless steel tubing. The lecithin sample to be extracted is placed into the solids reservoir and extruded into the jet tube assembly with the aid of a nitrogen pressure head. This "pusher" gas flow rate is regulated by a micro-metering valve.

As described above, the SC-CO_2 interfaces with the lecithin sample in the jet tube assembly (Figure 1). It is critical that in the pictured three-way valve that the viscous sample be injected through the 0.16 cm capillary into the larger concentric tube to avoid viscous back streaming and to assure intimate contact with the SC-CO_2. The solubilized oil components are then routed through the back pressure relief valve, where the CO_2 decompression occurs, resulting in the precipitation of the oily constituents in the liquid collector. The de-oiled lecithin powder than drops into solids collection vessel. Careful control must be exercised over the relative flow rates of the pushing and extraction fluids so as to maximize the contact time between the lecithin and the extraction fluid. This can also be amplified by using longer extraction chambers which provide a long contact, or drop time, of the lecithin in the compressed CO_2 atmosphere. Further experimental details can be found in reference [7].

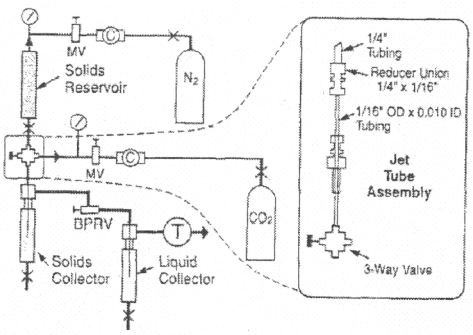

Figure 1. Details of jet extractor for de-oiling soya lecithin: BPRV = backpressure regulating valve; T = flow totalizer..

2.2 Experimental apparatus for high pressure spraying and particle formation

The experimental apparatus for high pressure spraying processes which are applicable to the production of fine particulates for the nutraceutical field is shown in Figure 2. Specific details can be found in the studies of Weidner [8]. This mixing of substrates dissolved in liquid medium in a tee with a pressurized gas is the basis of the CPF process cited later, which seems particularly suitable to producing fine powders of nutraceuticals. A third component, a powdered carrier may also be introduced into the precipitation chamber as will be discussed in the Results and Discussion section. Experimental details on the various powder formation processes applicable to nutraceuticals can be found in Proceedings of the the 6th International Symposium on Supercritical Fluids held in Versailles, France [9].

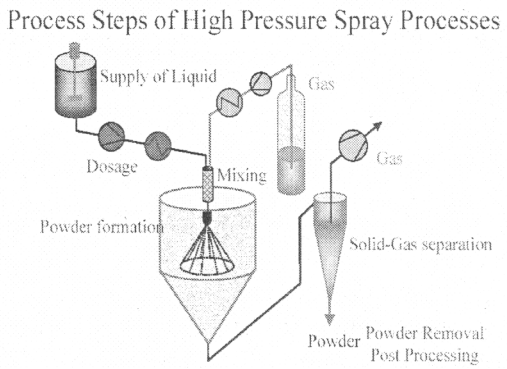

Figure 2. Generic schematic of powder forming process using a pressurized fluid – Courtesy E. Weidner

2.3 Combinatorial determination of optimal conditions for sub-critical water extraction of anthocyanins from berries.

The specific combinatorial method used in this study involved the use of a pressurized solvent extractor to test various extraction conditions with sub-critical water compositions. An ASE 300 (Dionex Corp., Sunnyvale, CA) was used to screen extraction conditions. A 34 mL extraction cell filled with approx. 9.5 g of berry pomace + diatomaceous earth (DE); 1 part DE to 3 parts of pomace was used. Each cell was extracted using 4 cycles; each cycle being collected in a separate glass bottle which was immediately cooled in an ice bath. All extractions were performed in triplicate.

A laboratory-designed extractor was also constructed and consisted of the following features: an extraction cell (46 mL) into which 24 g of pomace per run; and solvents: degassed water and

water adjusted to pH 2.3. This was a continuous flow system similar in design to that previously reported [10], except water flow was induced by applying nitrogen pressure to the water reservoir rather than using a pump. The extraction vessel and solvent-heating coil were housed in an oven and heated to 120°C. The solvent was then pumped through the system under pressure with nitrogen gas. The pressure in the system just prior to the heating coil was 20 psi and flow rates averaged 0.41 mL/min. Upon exiting the extractor, the solvent flowed through a coil submerged in a 20°C water bath, 8 – 50 mL fractions being collected. Fractions from each run were analyzed for total solids (LOD) and total anthocyanins (HPLC), on the same day as the extraction. All extractions and analyses were performed in duplicate.

3. Results & Discussion

3.1 Control of particle size, morphology, and encapsulation using compressed fluids

A number of processes exist for producing fine powders and encapsulated products that containing nutraceuticals. Space does not permit a thorough discussion of these various options, but a recent tome by York, Kompella, and Shekunov [11] should serve as an excellent reference source. If such particle formation processes are collectively viewed as a combination of critical fluid technology and particle formation technology (CF-PT), than a coupled process similar to SFE-SFF or SFE-SFC results as discussed at the previous Super Green symposium [10]. This would suggest that CF-PT could be combined to advantage with SFE to permit not only the extraction of a targeted compound, but also allow consecutive formation of a desired morphology of the target compound. Unfortunately all too often in SFE the conditions in the collection or precipitation vessel are not optimized with respect to this factor. The described experiment with a "jet extractor" [12] for de-oiling lecithin is a good example of optimizing the collection or precipitation conditions during SFE, as well as using a novel design to achieve a de-oiled phospholipid-contained powder or granule at the end of the SFE.

Table II lists some examples of CT-PT for producing nutraceutical type-ingredients. These are based on examples cited in the Proceedings of the 6th International Symposium on Supercritical Fluids [9]. The CPF process [13] seems particularly promising for nutraceutical and natural product extracts. The CPF technique usually employs carrier materials that are biologically-compatible with their consumption into the human body. Various starches, silicic acids, celluloses, sugars, and emulsifiers serve as carriers in the CPF technique. As an example, by using the appropriate carrier in the CPF process, powderized lipophilic paprika extracts can be prepared for use in water. The combination of using the CPF process with an appropriate carrier containing an additive, results in materials that can be protected from oxidation (and hence increased shelf life), and their particle size, re-dispersion, and sustained release properties controlled when incorporated into foods. These conferred properties add to the attractiveness of using CF-PT processes in the manufacture of nutraceutical ingredients.

Table II. Examples of CT-PT processes.

Technique	Application
Concentrated Powder Form (CPF), Jet Dispersion	Paparika Dispersion - Soup Powders
Semi-continuous Gas Anti-solvent Process	Cholesterol Form and Precipitation
Rapid Expansion of Supercritical Solution	Micronization of phytosterols
DELOS Crystallization	Crystallization: Stearic Acid
CPF Process	Controlled Release of Flavors and Vitamins
RESS	Encapsulation of β-sitosterol in low MW Polymer Matrix
Supercritical Anti-Solvent Process	Incorporation of cholesterol or protein in a biodegradable matrix
PGA & GAS Processes	Precipitate of beta-Carotene
Particle from Gas Saturated	Lipid Micronization of Solution (PGSS) Phosphatidylcholine and Tristearin
Supercritical Anti-Solvent Process	Biodegradable Polymers Ppt. Studies

3.2 Use of combinatorial instrumentation and methodology to optimize CF processes

Why use combinatorial technology with CF technology as applied to nutraceuticals and natural product isolation? The rationale lies in the complexity of optimizing CF processes as they apply to complex substrates which frequently occur in the nutraceutical field. The mention of the word "combinatorial" usually conjures up the image to many of the high throughput screening of synthetic compound libraries or natural products in the pharmaceutical industry. Indeed, this is probably the best known as well as time-honored application of the combinatorial method. However, recently a number of other applications for the combinatorial assessment of experimental parameters have appeared in the literature, such as: the screening of catalysts and catalytic activity, evaluation of sorbents for chromatographic selectivity, and evaluation of the composition of materials (e.g., solid state or semiconductor properties).

Combinatorial evaluation permits rapid experimentation to be enacted and the examination of many parameters which impact on the final processing conditions. Fortuitously equipment and instrumentation exists which allow use of, or the evaluation of the following:

Use of parallel or sequential methodology
Investigations on super- and sub-critical fluids
Processing modes (SFE, SFF, SFR, SFC, etc.)
Use of co-solvent or mixtures

There are now available parallel, multiple reactors which permit simultaneously the evaluation of high pressure reaction conditions simultaneously. These range from the traditional stirred autoclaves under computer monitoring and control to parallel flow reactors which are often times used in the synthesis of pharmacologically-active compounds. Also available from the analytical instrumentation field are both sequential and parallel extraction modules which can be configured to conduct not only extractions, but to evaluate sorbents as would be used in SFC, or catalysts in reactions conducted under supercritical fluid conditions (SFR). These possibilities have been described in a brief review by King [5].

Parallel assessment and optimization of processing or analysis conditions is most often done on samples having different compositions (or reactants), although in principle these can also be varied along with the external experimental conditions. For example, a commercial parallel reactor available from Argonaut Technologies (Louisville, KY) allows up to eight independent reactions to be conducted under different specific conditions simultaneously at temperatures ranging from ambient to 200°C and a pressure range extended up to 500 psig (34 bar). This approach can also be achieved by using a series of identical individual reactor modules "piggy-backed" together as in the Parr Model 5000 multiple reactor system (Parr Instruments, Moline, IL). Here it is possible to operate at pressures up to 3000 psig (204 bar) and have individual control of the reactor temperature up to 300°C for six 75 mL stirred reactors.

Sequential combinatorial possibilities using analytical SFE instrumentation have been reported by King [7]. Less well known is the possibility of using these systems for sub-critical processing and with "hot" slightly compressed liquids, such as sub-critical water. Two systems expressly designed for use with compressed liquids above their boiling points are the Dionex ASE systems and Applied Separations PSE modules. As noted in the experimental section, we have used a Dionex ASE 300 system to evaluate the use of sub-critical water as an extracting agent for flavonoids from berry substrates.

This has permitted the evaluation of the concentration of solids and total anthocyanins extracted per gram of berry pomace, as well as the concentration of anthocyanins per 100 gram of solids extracted s shown in Figures 3a-c. Here acidified water at 120°C yielded the highest quantity of anthocyanins extracted/g -pomace, 7.24 mg/g on a dry weight basis. Degassed water at 120°C on the other hand resulted in a slightly lower quantity of anthocyanin/g- pomace (6.96 mg/g on a dry basis), but a higher ratio of anthocyanin to overall extracted material (10.65g/100g-extract on a dry weight basis. These rapid combinatorial experiments also revealed that increasing the extraction temperature resulted in a faster extraction of the anthocyanins; however less total quantity of anthocyanins were extracted. HPLC results indicated that approximately the same quantity of each non-anthocyanin phenolic (chlorogenic acid and rutin) were extracted from the pomace with both degassed water and acidified water. Ellagic acid, gallic acid, catechin, *trans*-resveratrol, quercetin and caffeic, *p*-coumaric, and ferulic acids were not detected in the extracts. This suggests that sub-critical water under the reported conditions have the capability of selectively extracting various polyphenolic components. Such results permit the rapid optimization and evaluation as to the effectiveness of sub-critical water extraction for removing and concentrating anthocyanins from a variety of berry materials, such elderberry, chokeberry, cranberry, etc. Even visual observation of these highly chromaphoric extracts allows a

qualitative evaluation of the rate and completeness of the extraction as previously reported [10].

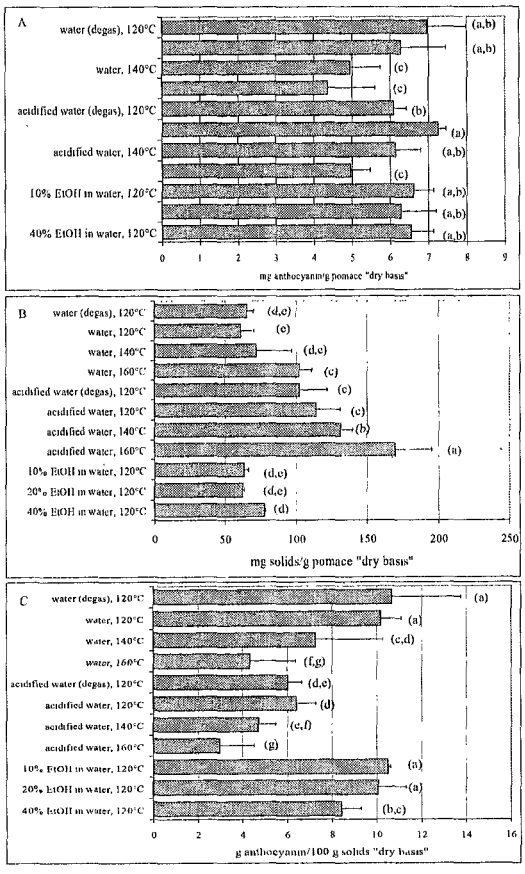

Figure 3. Anthocyanin and total solids extracted from elderberry pomace using the ASE system. A) mg anthocyanins extracted/g of pomace on a dry basis; B) mg solids extracted/g of pomace on a dry basis; C) g anthocyanins/100 g of solids on a dry basis. Error bars indicate the standard deviations (n=2). Treatments with the same letter are not significantly different based on LSD ($p<0.05$).

Caution should be exercised when extrapolating results obtained via the combinatorial approach with results on a larger scale extraction system. Results obtained on a larger scale sub-critical water extraction system tended to follow the same pattern as found with the ASE system but the extraction efficiencies were lower. For example, more anthocyanin was extracted per gram of pomace using the ASE system versus the scaled up sub-critical water extraction system. The total amounts of solids extracted were very similar between the two systems. Therefore, when the extracts were dried, samples from the ASE system contained more anthocyanin per 100 g solids than the samples produced in the larger, dynamic flow system. It should be noted that with the scaled-up extractor, that all the extractions were done at the same flow rate. However, extraction efficiencies can be sensitive to flow rates and hence higher extraction efficiencies may be obtained by changing the water flow rate through the extraction vessel.

The extraction differences observed between the two systems could be due to several factors. For one, the initial static solvent contact time differed between the two systems. The laboratory constructed system allowed for both a controlled and continuous flow of the pre-heated solvent (water); while with the configuration of the ASE system, the static time of the solvent was minimized but not be eliminated entirely. Here the pomace/solvent contact time was 5-7minutes as the ambient solvent was pumped into the vessel, pressurized, and then heated to the desired temperature. There was no solvent static time after set temp was reached.

The pressure in the two experimental systems also differed, although pressure in sub-critical water extraction is not a significant controlling variable [14]. In general it is best to operate at the minimum pressure required by the vapor-liquid equilibrium curve between the liquid and gaseous states., in order to save on energy during sub-critical water extraction. In the case of the ASE 300, it was set at 1500 psi and could not be altered; while in the case of the laboratory -made system, the operational pressure was much lower. For example, pressures of only 15-75 psig were required to ensure that the sub-critical water stayed in its liquid state over the temperature range of 120 – 160°C. It must also be recognized that a sample dispersing agent, DE, was used in the ASE 300 system while no such agent was used in the larger dynamic flow extraction system.

3.3 Application of sub-critical water extraction alone and in tandem with SC-CO_2

As has been mentioned previously, sub-critical water is complimentary to SFE using SC-CO_2 particularly as this pertains to an all natural processing platform. Sub-critical water can be substituted in many cases for ethanol ad other polar organic solvents, and is inherently a lower energy process than steam distillation. Since many sub-critical water extraction processes take place above the boiling point of water, the possibility of in-situ reduction of undesirable microbial and enzymatic activity in the substrate being processed exists.

The increasing solute solubilities that are found as the extraction temperature is raised above the boiling point of water can be predicted *a priori*

using the empirical equation developed by Clifford and Hawthorne [15]. This equation is given as:

$$\ln[x_2(T)] \approx \left(\frac{T_o}{T}\right)\ln[x_1(T_o)] + 15\left[\left(\frac{T}{T_0}\right)-1\right]^3$$

and has been applied to predict the magnitude of solute solubility increase with temperature into the sub-critical water region. Here the solute's mole fraction solubility (x_1) at a reference temperature, T_o, is used to predict the mole fraction solubility (x_2) at a higher temperature (120°C) for various polyphenolic solutes commonly found in berries and grapes (Table III) . As can be seen from Table III, this increase from 20 to 125°C is of the order of $10^1 - 10^2$, a trend that is consistent with the reported experimentally measured solute solubilities recorded for model solutes, glucose and naphathalene, which are 3.569E-01 @ 90°C and 2.949E-05 @ 65°C, respectively.

Table III. Calculated mole fraction (x) solubilities of polyphenolic compounds in sub-critical water at 120°C.

Solute	Exp. x_1	Cal'c x_2
Chlorogenic acid	5.077E-04	6.352E-03
Tannic acid	1.009E-01	3.283E-01
Gallic acid	1.163E-03	1.178E-02
Hesperiden	5.896E-07	4.117E-05
Rutin	3.685E-06	1.614E-04
Catechol	4.675E-02	1.850E-01

Exp x_1 = Experimental value in water@ 20°C

Exp x_2 = Calculated value in sub-critical water@120°C

Solute diffusion coefficients over the same temperature range vary from 10^{-7} to 10^{-6} cm^2/sec, thus the reinforcing effects of both this mass transport property and the increase in solute solubilities with temperature result in an increased extraction flux with increasing temperature. This results in very fast extractions in the sub-critical water region, thereby permitting high linear velocities of the sub-critical water (approx. 0.1 cm/sec) and short residence times through the extraction vessel [10]. This is why sub-critical extractions can be executed above the boiling point of water without deleterious damage to the extracted solutes.

There are numerous citations to the use of sub-critical water for processing natural products. These include:

Extraction of spices
Deterpenation of essential oils
Selective reaction of biomass to sugars
Hydrolysis of vegetable oils

With respect to nutraceuticals and natural products compounds, there are several studies worth citing which employ neat sub-critical water for extraction and reaction, or selective extraction in tandem with or SC-CO_2. For example, Ibanez et al. [16] , have used sub-critical water for the extraction of antioxidants from rosemary at temperatures up to 200°C. A high selectivity in his case as recorded for such compounds as carnosol, rosmanol, carnosic acid etc. as well as some flavonoids. Extraction of gypenosides (saponins) from *Gynistemnia pentaphyllum* has been studied by Chang et al. [17], who reported over 90% yields in a semi-continuous extraction system at 200 psi and 100°C. Likewise, Ozel et al. [18] have demonstrated that sub-critical water may be applicable to the extraction and fractionation of essential oils, optimal results being obtained at 150°C for the extraction of T*hymbra spicata*. In a related study, the hydrolysis of ginger bagasse has been conducted in the presence of sub-critical water by Meireles and coworkers [19] after removing the ginger essential oil by SC-CO_2 extraction. This is a good example of affecting a SFE-SFR coupled process using two different critical fluids.

Coupled SC-CO_2/sub-critical water extraction or reaction processes have also been reported in the literature. Several of these are not concerned with natural product extractions, but are focused on the extraction of components in soils and sediments to remove toxicants. Three coupled processes involving natural products are worth noting. Smith et al. [20] have applied a tandem CO_2 - H_2O process to selectively remove alkenyl phenolic compounds and polysaccharides from cashew nut shell liquid oil, and have also used pressurized CO_2 cycling to enhance the extraction yield. Tandem carbon dioxide-water processing has also been applied by Rogalinski et al. [21] to recover the essential oil and a medicinal compound, boldine, from the leaves of boldo, a plant indigenous to South America.

Another study that is specifically illustrative of the applicability of a coupled CO_2 -

H_2O process is the separation of bioactive compounds in St. John's Wort by Mannila and coworkers [22-24]. In their research, the active components hyperforin and hypercin as well as their tautomeric forms, were each fractionated individually. Hyperforin was extracted from the plant matrix using CO_2 30°C and 80 atm. Than hypercin was removed using sub-critical water at a pH = 7.0 with 1% $NaHCO_3$. For hyperfoin, 93 – 99% yields were obtained while for hypercin, 80-93% yields were recorded. In their studies it was suggested that flavonoids such as quercitin might be fractionated by using a SC-CO_2 – co-solvent mixture. As noted previously, fractionation of flavonoids can also be achieved via sub-critical water.

3.4 Current state of critical fluid technology as applied to nutraceuticals/natural products

There are a number of recognizable trends that are taking place with respect to the application of critical fluids in the nutraceutical and natural products processing/product area. These are enumerated below for further discussion:

Increase in new product offerings
Derived extracts from compressed polar solvents
Development of cosmeceuticals
Flexible strategy with respect to processing plant diversity, scale, and location
Optimization of product through SFF, SFC, CF-PT, or coupled processing

An array of "new" as well as old nutraceutical products and natural extracts are now available, and they proudly announce they are derived from SFE, SC-CO_2, or compressed fluid processing. For example, one retailing company provides an array of health-related with titles such as: "Supercritical Feverfew", "Supercritical Smoke Detoxification", "Supercritical Calming", "Supercritical Upliftment", etc. In the latter two cases, these titles are related to their St. John's Wort and kava-kava content, which are obtained by extraction with SC-CO_2. A number of retailed products have mixed compositions, where than one ingredient is obtained via SFE. Another line of SFE-derived products, available for ordering over the internet, declares on the label that these are obtained with the "ultra high technology of supercritical fluid extraction". This latter line of extracts focuses on spices and flavoring components for foods, many of which have specific health benefits.

Commercial sales are made through a number of distributors, a sampling of which is provided in Table IV in the United States . These retailers are mutually dependent on a number of key processors or toll refiners, some of which we shall note shortly. Table IV lists the name of the retailers, their location within the USA, and some of their typical SFE-derived product offerings, which are by no means exclusive.

Table IV. Commercial Retailers in the USA of Nutraceuticals and Natural Product Extracts for the Personal Health Market

Company	Location	Typical Product
Buckton, Scott	Fairfield, NJ	Lutein esters
Inter-Cal	Prescott, AZ	Saw palmetto
NuturNutra	Piscataway, NJ	Borage, oil
Sage V Foods	Los Angeles,	CO_2- defatted Products
Primal Essence	Oxnard, CA	Spices
Prostate Rx	Naples, FL	Saw palmetto
GAIA Herbs	Brevard, NC	Oregano oil
New Chapter	Brattleboro, VT	Assorted products

Occasionally the presence of a polar organic co-solvent may be noted on the labeling, and it is most frequently ethanol. Aqueous ethanolic extracts are also rather common, so it is anticipated that sub-critical water extractives will take their place in the commercial market eventually.

The above retailed products frequently have a common production source. Some of the better known processors both in the USA and world-wide are:

U.S. Nutraceuticals – Eustis, FL
Croda – Lee, United Kingdom
Norac – Edomonton, Canada
Flavex, Rehlingen, Germany
Hitex – Vannes, France
Arkopharma – Carros, France
Aromtech – Tornio, Finland
NateCO_2 - Wolnzach, Germany
GreenTek 21 – Seoul, South Korea

There are other commercial production plants located in New Zealand, several in mainland China, Taiwan, Japan, Italy, and India. Some of the these producers directly market their own extracts; for example Aromtech retails sea buckthorn and black

currant, U.S. Nutraceuticals - astaxanthin, and Arkopharma, bee pollen and pumpkin seed extract. Somewhat absent in the production of nutraceutical extracts are larger scale producers, such as the hops manufacturers whose plants and vessel sizes tend to be larger then needed in nutraceutical production.

The production of "green" extracts for use in the cosmetics industry has been somewhat slow to evolve, but a plethora of applicable natural extracts can be obtained via SFE as noted by King [2]. This is a "natural" fit for CO_2 and sub-critical water extraction since both extraction "solvents" are compatible with dermal use. Recently New Chapter has marketed "Estrotone Crème" which contains SC-CO_2 – extracted ginger, and "Zyflamed Crème" with ginger and oregano CO_2 – extracts. A blackcurrant CO_2 – extract is used in a Finnish product, a renewing eye crème, is marketed under the Lumene line of cosmetics.

With respect to the nutraceutical and natural product extractive industry, the production plant of the future will be smaller in scale, more versatile in design, and most likely located in close geographical proximity to the source of the natural product. The future critical fluid-based processing facility will permit extraction and fractionation modes to be practiced individually, or coupled to produce extracts enriched in a targeted nutraceutical or health ingredient. These plants due to their high capitalization costs for fluid containment, delivery, and heat exchange will probably be capable of processing using either supercritical or liquid CO_2, compressed consumer-friendly organic solvents, and sub-critical water. Most of these fluid types are capable of being delivered by in-common pumps or compressors.

Future plant locations will of course reflect increasing environmental concerns, a factor which makes critical fluid technology particularly appealing. As noted above, proximity to biomass or natural product source is crucial to minimize degradation of specific components. This suggests that a "mobile" processing facility which can be moved "fieldside" would be particularly appealing. Several production plants that embody critical fluids are also located at the border between two countries in order to facilitate its use on in-common agricultural or forestry feedstocks. Such plants may be in economically-disadvantaged areas, and thereby contribute to the development of sustainable communities, and hence help develop the economies of indigenous peoples.

4. Conclusions

The future would appear bright for further extension of the critical fluid technology platform towards the processing of natural products for the health food, nutraceutical, and medicinal markets. The potential for using multiple critical fluid processing steps to custom design extracts enriched in the desired nutritional or medicinal components will see increased application, particularly in the use of sub-critical water and particle formation or encapsulation techniques. Some additional benefits can also occur when using high pressure carbon dioxide or water for processing natural products, such as the deactivation of harmful microbes or enzymes, allowing sterilization or stabilization of the resultant end products, without resorting to the extreme temperatures and pressures required in ultra-high pressure food processing.

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