Journal of Advanced Pharmaceutical Sciences and Natural Products

Journal of Advanced Pharmaceutical Sciences and Natural Products (JAPSNP)

GREEN AND SUSTAINABLE EXTRACTION TECHNOLOGIES FOR BIOACTIVE NATURAL PRODUCTS: A CRITICAL COMPARISON OF ULTRASOUND, MICROWAVE, SUPERCRITICAL CARBON DIOXIDE AND NATURAL DEEP EUTECTIC SOLVENTS

Dr. Vishal Chauhan*

MAHSA University, Jln SP 2, Bandar Saujana Putra, 42610, Jenjarom, Selangor, Malaysia

Corresponding author:
Dr. Vishal Chauhan

Email: vishal@mahsa.edu.my

ABSTRACT

Four technologies dominate the literature on sustainable recovery of bioactive natural products: ultrasound-assisted extraction, microwave-assisted extraction, supercritical carbon dioxide extraction and extraction with natural deep eutectic solvents. Each is routinely described as green, and each is routinely benchmarked against maceration or Soxhlet extraction on the single axis of yield. That comparison flatters all four and discriminates between none of them. This review reads the four platforms against a common framework drawn from the principles of green extraction, mass-based metrics, published life-cycle evidence, residual-solvent regulation and the small number of studies that place two or more platforms on the same plant matrix under matched analysis. The evidence supports a narrower and more useful claim than the field usually makes. Ultrasound has the lowest energy demand and the cheapest capital entry, and its acoustic intensity attenuates on scale-up while some matrices defeat it outright. Microwave irradiation is the fastest and most productive per batch, and it consumes more than three times the electricity of ultrasound for equivalent antioxidant recovery. Supercritical carbon dioxide delivers a genuinely solvent-free lipophilic extract with unmatched regulatory standing, and recovers polar phenolics poorly without an entrainer. Natural deep eutectic solvents extract labile and poorly water-soluble compounds better than aqueous alcohols, and then hold them: reported recovery from the eutectic spans about 21 per cent by antisolvent precipitation to above 90 per cent by macroporous resin. The four platforms therefore occupy separable regions of a design space set by target polarity, thermal lability, required purity and production scale. The review sets out that mapping and names the comparison the field has still not run.

Keywords: green chemistry; plant extracts; sonication; microwaves; supercritical fluid extraction; deep eutectic solvents.

1. Introduction

Plant and marine biomass remains the most productive source of pharmacologically active chemistry available, and the operation standing between the biomass and the molecule is extraction. That operation has historically been the least examined part of the value chain. Maceration, percolation, reflux and Soxhlet extraction dominate the pharmacopoeial and industrial record, and all four share a profile of long residence times, large volumes of volatile organic solvent, sustained heating, and a waste stream whose mass exceeds the mass of product by one to two orders of magnitude.

Two pressures have made that profile untenable. The first is regulatory. Residual solvents in a pharmaceutical product are governed by a risk-based classification in which hexane and methanol sit in Class 2 with permitted daily exposures of 2.9 and 30.0 mg respectively, corresponding to concentration limits of 290 and 3000 ppm, while ethanol sits in Class 3 with no specific limit beyond good manufacturing practice [1]. Food-sector extraction is constrained separately, with propane, butane, ethyl acetate, ethanol, carbon dioxide, acetone and nitrous oxide permitted essentially without residue limits and hexane restricted to 1 mg/kg in oils and fats [2]. A process built on dichloromethane or hexane now carries a documentation and purification burden that a process built on ethanol, water or carbon dioxide does not.

The second pressure is economic. Solvent manufacture, rather than the extraction step itself, dominates the environmental burden of a conventional botanical process, contributing more than 70 per cent of the total load in comparable analyses [3]. Reducing solvent inventory is therefore the largest available lever, and it happens also to reduce cost.

Against that background, four technologies have accumulated a substantial primary literature: ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical carbon dioxide extraction (SFE-CO2) and extraction with natural deep eutectic solvents (NADES). The volume of that literature is not matched by its comparability. Most published studies benchmark one green technology against maceration or Soxhlet extraction on one matrix, report a yield advantage, and stop. Almost none report energy consumption. Very few report the mass of solvent leaving the process as waste. Fewer still place two green platforms side by side under matched conditions, and when they do the ranking often reverses depending on which analytical endpoint is chosen [4].

This review therefore does not ask which technology is greenest. It asks a question the evidence can answer: given a defined target compound class, a defined matrix and a defined production scale, which platform is defensible, and on what grounds.

1.1 Scope and evidence base

This is a critical narrative review rather than a systematic one, and it is reported as such. The literature was searched through PubMed, Europe PMC and publisher platforms, with bibliographic

records confirmed through Crossref, using the four platform names combined with terms for bioactive class, plant matrix, green metrics, life-cycle assessment, scale-up and toxicity. Work published between 2018 and 2026 was preferred, with earlier papers retained where they define a concept or a regulatory position. Priority went to primary studies reporting numerical results, to guideline documents for any limit or classification, and to studies comparing two or more platforms on a single matrix. Every source cited was retrieved and read to the extent needed to support the claim attached to it, and any figure that could not be confirmed against a retrieved record was excluded rather than approximated. Results are not pooled quantitatively, for the reason set out in Section 8: the reported outcomes are measured on incompatible scales and against incompatible functional units, and a pooled estimate over them would be a precise answer to a question nobody asked.

The four platforms differ not in degree but in the physical route by which they move a solute out of plant tissue, and Figure 1 sets those routes side by side. Ultrasound breaks the cell wall mechanically. Microwave irradiation heats from inside the tissue and bursts it. Supercritical carbon dioxide leaves the wall intact and partitions solutes by polarity. A eutectic solvent binds the solute by hydrogen bonding and then has to be persuaded to give it back. Every difference in performance discussed below follows from that first difference.

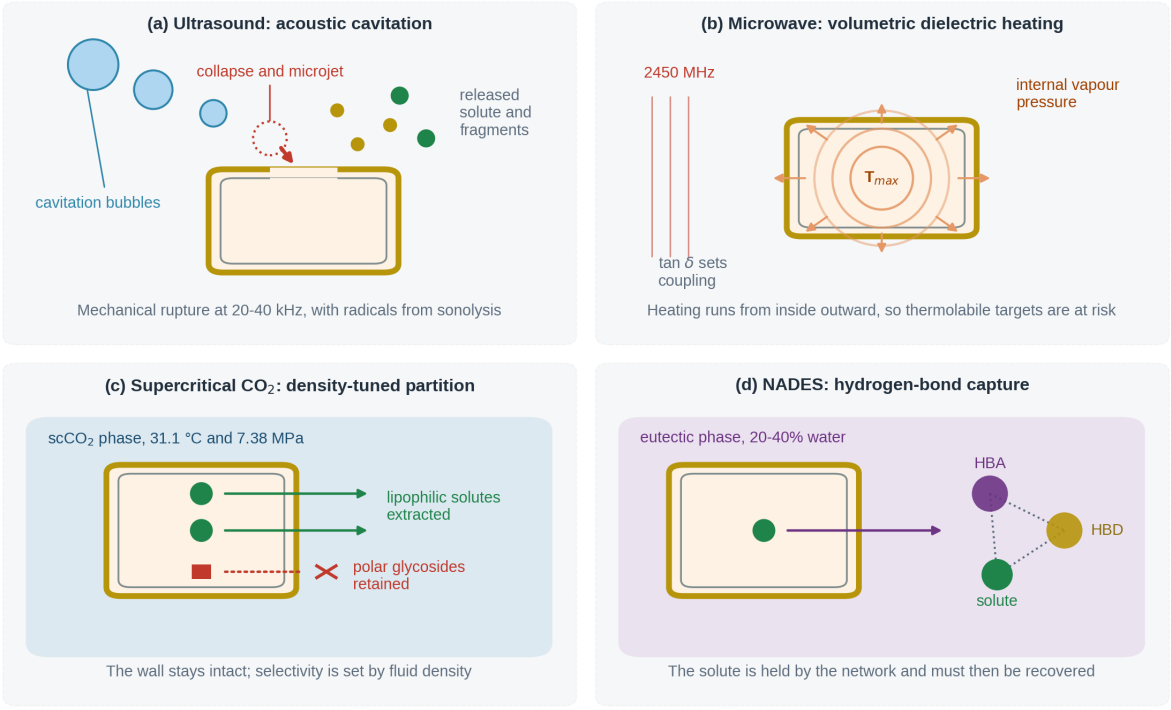

Figure 1. The four platforms enhance mass transfer by four different physical routes, and those differences determine where each one fails. (a) Ultrasound at 20 to 40 kHz drives acoustic cavitation. Asymmetric bubble collapse at the cell wall produces a liquid microjet with transient local pressure on the order of 100 MPa, which fragments the wall and releases solute, while sonolysis of water generates radicals capable of degrading the target [5]. (b) Microwave irradiation at 2450 MHz couples to the medium through dipole rotation

and ionic conduction in proportion to the loss tangent (tan delta), so heat is generated within the tissue and the thermal gradient runs outward; internal moisture superheats and ruptures the wall [6,7]. (c) Supercritical carbon dioxide above 31.1 degrees Celsius and 7.38 MPa permeates the intact wall and partitions solutes by polarity, extracting lipophilic species while polar glycosides are retained [8,9]. (d) A natural deep eutectic solvent extracts by hydrogen bonding between a hydrogen bond acceptor (HBA), a hydrogen bond donor (HBD) and the solute; the network responsible for the extraction efficiency then holds the solute, so a separate recovery step is required [10,11].

2. What "green" has to mean before technologies can be compared

The six principles of green extraction translate the general green chemistry agenda into requirements specific to biomass: renewable plant varieties, preference for water and agro-solvents, energy recovery through innovative technologies, production of co-products rather than waste, reduction in the number of unit operations, and delivery of a non-denatured, biodegradable, uncontaminated extract [12]. The sixth is the one most often neglected and the one that most sharply separates the four platforms, because it makes the state of the extract, not the mass of the extract, part of the definition of success.

Quantification rests on a small set of mass-based metrics, of which the E-factor, the mass of waste per unit mass of product, remains the most direct. It runs below 5 for bulk chemicals, between 5 and 50 for fine chemicals, and from 25 to above 100 for pharmaceuticals, which places botanical extraction firmly in the range where waste dominates the material balance [13]. Table 1 sets out the regulatory position of the solvents that matter to this comparison, since a process is only as green as the solvent it must later prove absent.

The sixth principle deserves separate emphasis, because it is the one that a yield table cannot express. An extract is a mixture, and two processes applied to the same biomass can return the same mass of the same nominal compound class in states that behave differently. Olive leaf and olive pomace processed by ultrasound and by supercritical carbon dioxide illustrate the point sharply: the ultrasonic extracts carried several times the phenolic content, and the supercritical extracts were substantially the better antimicrobials [4]. Whichever extract a developer wants, the decision cannot be made from a content assay. A green process is therefore one that delivers the extract in the state the application needs, and that criterion has to be written into the comparison before any number is collected [12].

Table 1. Regulatory position of the principal extraction solvents under the pharmaceutical residual-solvent guideline and the European food extraction-solvent Directive. PDE, permitted daily exposure.

Solvent	Pharmaceutical position (ICH Q3C(R9)) [1]	Food position (Directive 2009/32/EC) [2]
Ethanol	Class 3, low toxic potential; no specific concentration limit beyond good manufacturing practice	Part I; permitted with no residue limit
Carbon dioxide	Volatilises completely on depressurisation, so no residual-solvent specification arises	Part I; permitted with no residue limit

Ethyl acetate, acetone, propane, butane, nitrous oxide	Not tabulated here	Part I; permitted with no residue limit
Methanol	Class 2; PDE 30.0 mg per day, concentration limit 3000 ppm	Part II; 10 mg/kg
Hexane	Class 2; PDE 2.9 mg per day, concentration limit 290 ppm	Part II; 1 mg/kg in oils and fats, 10 to 30 mg/kg in protein products
Dichloromethane	Not tabulated here	Part II; 2 to 5 mg/kg
Natural deep eutectic solvent components	No dedicated classification; toxicity is a property of the specific eutectic and must be measured for each [14]	Not addressed by the Directive

A technology that doubles yield while quadrupling electricity consumption has not necessarily improved anything. The clearest demonstration comes from a multi-criteria optimisation of polyphenol recovery from beet seed by-product in which UAE and MAE were compared at a matched functional unit of antioxidant activity. Microwave irradiation delivered roughly 33 per cent more polyphenol and 23 per cent higher antioxidant activity, and reached the endpoint up to six times faster. It also required between 3.2 and 3.6 times the electricity, and carried a climate-change impact up to 12 per cent higher and an ozone-depletion impact up to 82 per cent higher [15]. Ranking the two on yield gives one answer, ranking them on impact gives the opposite, and neither ranking is wrong. Figure 2b sets out that divergence directly.

Life-cycle assessment resolves such conflicts in principle and introduces its own comparability problem in practice, because the functional unit and the system boundary are chosen study by study. An assessment of polyphenol extraction from waste biomass found electricity for heating dominant in every process examined, and reported approximately 8 kg of carbon dioxide equivalent per gram of polyphenol recovered by ultrasound, against more than five times that impact for a high-temperature alkaline solid-liquid extraction that gave higher raw yield [16]. That result and the beet seed result cannot be placed on one axis, because one is denominated per gram of polyphenol and the other per unit of antioxidant capacity. Figure 2a assembles the carbon dioxide emissions reported for two independent systems, each normalised to its own conventional benchmark, and the same caution applies across the two groups.

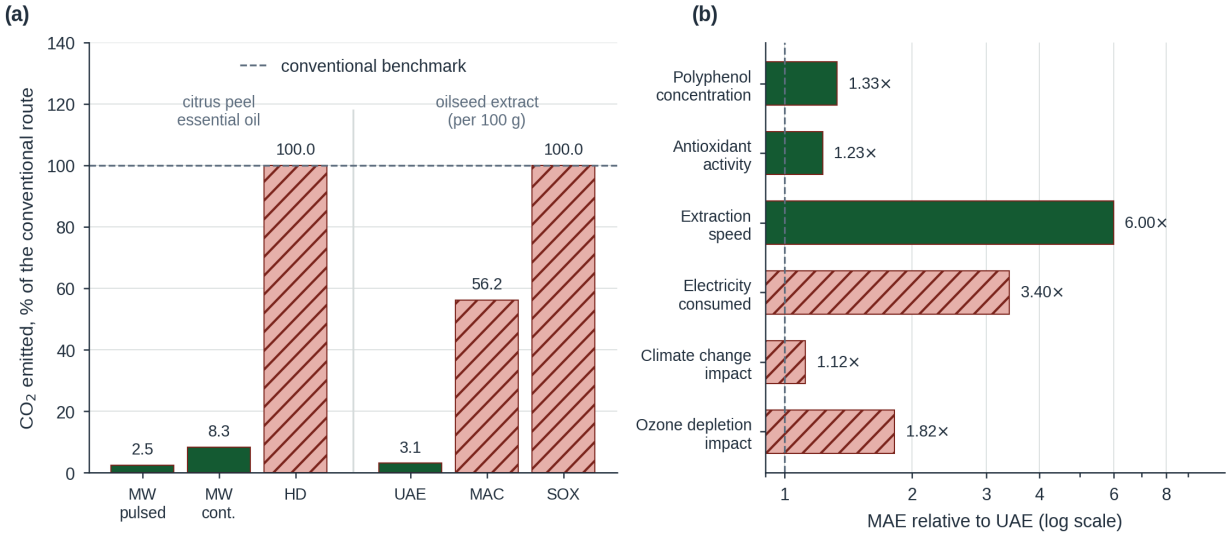

Figure 2. Higher yield and lower environmental burden are not the same axis. (a) Carbon dioxide emitted by each route, expressed as a percentage of the conventional route taken as the benchmark within each system, so that each system is read internally rather than against the other. Citrus peel essential oil: pulsed solvent-free microwave extraction (MW pulsed) 121.62 g, continuous solvent-free microwave extraction (MW cont.) 400.43 g and hydrodistillation (HD) 4800.26 g [17]. Oilseed extract, per 100 g of extract: ultrasound-assisted extraction (UAE) 200 g, maceration (MAC) 3600 g and Soxhlet extraction (SOX) 6400 g [5]. Solid dark bars are the intensified routes; hatched pale bars are the conventional benchmarks. (b) Microwave-assisted extraction expressed relative to ultrasound-assisted extraction on the same beet seed by-product at a matched functional unit of 16.6 mM Trolox equivalent antioxidant capacity, on a logarithmic scale.

Table 2. Operating characteristics of the four platforms, as established in Sections 3 to 6.

Platform	Principal mechanism	Typical operating window	Best-suited targets	Principal limitation	Largest reported scale
UAE	Acoustic cavitation, microjetting, matrix detexturation [5]	20 to 40 kHz; 30 to 45 degrees Celsius for labile targets; minutes to tens of minutes [5,18]	Phenolics, anthocyanins, polysaccharides, oils from soft matrices	Acoustic intensity falls as vessel volume rises; matrix-dependent failures; titanium transfer from probe erosion [5,19]	120 kg continuous pilot batch [19]
MAE	Dielectric volumetric heating by dipole rotation and ionic conduction [6]	2450 MHz laboratory, 915 MHz industrial; 300 to 1000 W; seconds to about 20 minutes [20,21]	Polyphenols, alkaloids, pectin, essential oils by solvent-free routes	Thermal degradation of labile targets; penetration depth caps batch vessel radius [21,22]	Continuous flow above 200 kg/h at 75 kW [21]
SFE-CO2	Density-tuned partition into a supercritical fluid, with staged depressurisation for fractionation [8]	Above 31.1 degrees Celsius and 7.38 MPa; typically 31 to 70 degrees Celsius and 50 to 480 bar [23]	Carotenoids, tocopherols, cannabinoids, essential oils, lipids	Poor recovery of polar phenolics without an entrainer; highest capital cost; feed must be dried [9,23]	Established industrial decaffeination [24]

NADES	Hydrogen bonding between HBA, HBD and solute, almost always with ultrasonic or microwave assistance [10]	Ambient to about 40 degrees Celsius; 20 to 40 per cent water [10,25]	Poorly water-soluble aglycones, alkaloids, anthocyanins	The solvent is non-volatile, so the product must be recovered by a separate operation; toxicity is formulation-specific [11,14]	No established industrial precedent

3. Ultrasound-assisted extraction

3.1 The mechanism is mechanical, and that constrains everything

Ultrasound at 20 to 40 kHz propagates through a liquid as alternating compression and rarefaction. Where the negative pressure exceeds the tensile strength of the liquid, cavitation bubbles nucleate, grow over successive cycles and collapse. Collapse near a solid boundary is asymmetric, producing a liquid microjet directed at the surface. Six distinct consequences for plant tissue have been distinguished: fragmentation, surface erosion, the sonocapillary effect, sonoporation, local shear, and detexturation of the matrix [5].

Frequency sets the scale of the event. Resonant bubble diameter falls from roughly 330 micrometres at 20 kHz to about 13 micrometres at 500 kHz, so low frequencies deliver fewer and more violent collapses suited to disrupting flexible plant tissue, while higher frequencies deliver a larger population of gentler events [5]. Frequency is therefore not a free parameter to be set by whichever bath happens to be available. Delivery geometry matters as much: a bath disperses attenuated energy through a large volume while a probe concentrates it at the tip, and bath systems are the weaker of the two on reproducibility [5].

That distinction has a direct consequence for reading the literature. A yield reported from a bath describes an average over a poorly characterised acoustic field, while a yield reported from a probe describes a small high-intensity zone near the tip and a much quieter bulk. Two studies on the same matrix, one using each geometry, are not measuring the same treatment, and comparing their optima as though they were is a common error.

3.2 Where ultrasound fails

Two failure modes recur, and both are under-reported. The first is over-processing. Anthocyanin recovery from mulberry fruit by response surface optimisation rose from 20 to 40 degrees Celsius and fell again from 40 to 60 degrees Celsius, giving a non-monotonic dose response that a study reporting only its optimum conceals entirely [18].

The second failure mode is matrix dependence severe enough to invert the comparison. Recovery of lycopene and related carotenoids from tomato processing waste by ultrasonic bath gave 420.8 micrograms of lycopene equivalent per gram of dry weight, against up to 691.3 micrograms per gram by conventional stirring, with antioxidant capacity following the same order. Ultrasound was faster, at 5 to 25 minutes against 30 to 90, and that speed did not compensate [26]. A negative result of this kind is

worth more per publication than another confirmation that a green technology beats maceration, and it is exactly the kind of result the literature under-reports.

One further concern bears on pharmaceutical use specifically. Most probe emitters are titanium alloy, and erosion of the tip transfers metal particles into the extraction medium, which is a contamination route with no counterpart in the other three platforms [5].

3.3 Scale and cost

Ultrasound scales, but its intensity does not. A stepwise transfer of olive pomace polyphenol extraction from a 0.2 kg batch at 400 W through a 2.2 kg continuous stage at 1000 W to a 120 kg continuous pilot at 2000 W maintained product concentration, reaching 3.0 g gallic acid equivalents per litre at pilot scale, 58 per cent above the conventional control. Delivered acoustic intensity nonetheless fell from 41 to 90 W/cm2 at the intermediate stage to 23 to 57 W/cm2 at pilot scale, and applied energy rose from 17 Wh to 1200 Wh [19]. The constraint is that acoustic amplitude cannot be maintained as horn diameter increases.

Energy is where the platform is strongest. Figures reported for a seed oil extraction give 0.25 kWh for ultrasound against 6 kWh for maceration and 8 kWh for Soxhlet extraction, with corresponding carbon dioxide emissions of 200, 3600 and 6400 g per 100 g of extract [5].

4. Microwave-assisted extraction

4.1 Heating from inside the matrix

Microwave energy at 2450 MHz couples to matter through dipole rotation and ionic conduction, and the efficiency of that coupling is set by the loss tangent of the medium. Measured values at 2450 MHz give 0.89 for ethanol, 0.11 for water, 0.13 for hexane and 0.04 for petroleum ether [7]. Ethanol therefore heats far more readily than water at this frequency, which is why aqueous ethanol rather than water is the default microwave extraction solvent, and why non-polar solvents require either a co-solvent or a susceptor. Absorbed energy is dissipated volumetrically, so the thermal gradient runs from inside the tissue outward, the reverse of conductive heating: residual moisture inside the cell superheats, vapour pressure rises, and the cell wall ruptures [6].

The consequences for kinetics are large. Optimised microwave extraction of Foeniculum vulgare gave 149.35 mg/g in 4 minutes, against 83.05 mg/g by Soxhlet extraction over 16 hours and 53.41 mg/g by cold maceration over 24 hours, with total phenolic content and radical scavenging following the same order [20]. Solvent-free variants exploit the same physics without any added solvent at all. An intermittent solvent-free process applied to citrus peel gave 3.51 per cent oil in 24 minutes against 3.28 per cent by hydrodistillation over 240 minutes, using 0.15 kWh against 0.44 kWh for continuous solvent-free operation, with carbon dioxide emissions of 121.6, 400.4 and 4800.3 g respectively for the intermittent, continuous and hydrodistillation

routes [17]. The order-of-magnitude gap between the microwave routes and hydrodistillation is the strongest single environmental argument available to this platform.

The reason that gap is so large is worth stating plainly. A solvent-free microwave process carries no solvent inventory at all: the water already inside the plant material is the working fluid, so the waste term in any mass-based metric collapses towards the spent biomass alone, and there is no solvent manufacture upstream to dominate the life-cycle burden [17]. The condition is restrictive. The route applies only to matrices that carry enough of their own water and to targets that are volatile enough to be carried out with the steam, which in practice means essential oils rather than phenolics. Where those conditions hold, this is the closest any of the four platforms comes to satisfying the principle of solvent replacement outright [12].

4.2 The thermal ceiling and the penetration limit

Microwave extraction is a thermal method, and the compounds most worth extracting are frequently thermolabile. Anthocyanin recovery from powdered blueberry showed degradation beginning at 41.2 degrees Celsius, and above 53.6 degrees Celsius the rate of degradation exceeded the rate of acquisition, with delphinidin, cyanidin and pelargonidin significantly reduced while malvidin was unaffected [22]. Localised hot spots arise wherever the loss tangent is heterogeneous across the matrix, and closed-vessel operation raises both the achievable temperature and the pressure hazard [6].

At 2450 MHz the penetration depth of microwave energy into an aqueous load is a few centimetres, which caps the radius of any batch vessel intended to heat uniformly. The engineering answer is to abandon the batch vessel. A continuous-flow industrial cannabis process operating at 915 MHz with up to 75 kW of applied power and a power density of 0.1 to 10 kW per kilogram of biomass has run at throughputs above 200 kg/h, recovering up to 95 per cent of the actives while eliminating separate decarboxylation and winterisation steps, at a reported capital cost of US$1000 to US$5000 per kilowatt of installed microwave power [21]. Lowering the frequency increases penetration depth; moving material through a fixed field removes the uniformity problem. Neither adjustment is available to a laboratory multimode cavity, which is why laboratory microwave results transfer to industry less predictably than the yield figures suggest.

5. Supercritical carbon dioxide extraction

5.1 A tunable solvent with a hard polarity limit

Carbon dioxide becomes supercritical above 304.1 K and 7.38 MPa, beyond which it combines gas-like diffusivity and viscosity with liquid-like density [8]. Solvating power is a function of density, and density is set by pressure and temperature, so the strength of the solvent is adjustable during a run. Two consequences follow. Fractionation becomes possible by staged depressurisation across a cascade of separators,

each releasing a different solute class, and the extract leaves the process genuinely solvent-free because the fluid evaporates on depressurisation[8].

Fractionation deserves more weight than it usually receives, because it folds a purification step into the extraction. A cascade of separators held at descending pressures releases progressively lighter or less polar fractions, so a single pass can deliver a crude extract already partly resolved into the classes a downstream process would otherwise have to separate by chromatography or by liquid-liquid partition [8]. Counted against the principle of reducing the number of unit operations, that is a real advantage, and it is invisible in any comparison that stops at total yield [12].

The limitation is equally fundamental. Supercritical carbon dioxide is essentially non-polar, and compounds above about 400 Da bearing multiple hydroxyl groups, which covers most glycosides, tannins and polysaccharides, are close to insoluble in it [9]. A direct comparison on olive leaves gave 6753 to 7410 mg gallic acid equivalents per 100 g by ultrasound against 848 to 1763 mg/100 g by supercritical carbon dioxide[4].

Ethanol as entrainer partially closes the gap, and the dose response is steep. In hemp seed oil extraction, total phenolic content rose from 30.52 mg gallic acid equivalents per kilogram with pure carbon dioxide to 294.15 mg/kg with 10 per cent ethanol and 427.77 mg/kg with 20 per cent ethanol, with total tocopherols rising from 361.16 to 654.80 mg/kg and the oxidative stability index from 9.8 to 28.0 hours [27]. Entrainer use is typically held below 10 per cent of the carbon dioxide stream [9], and it reintroduces a liquid solvent, so the solvent-free claim then requires qualification.

5.2 Selectivity is the argument, not yield

Vitamin E recovery from canola seed reached 6.91 mg per gram of oil at 15 MPa and 70 degrees Celsius but only 1.79 mg/g at 25 MPa and 50 degrees Celsius, because the higher-density condition co-extracted triglyceride and diluted the target [28]. Higher pressure raises yield and lowers purity, and the process variable that matters is the one that discriminates rather than the one that maximises. Regulatory standing is the second distinctive strength: carbon dioxide is permitted as a food extraction solvent without a residue limit [2] and leaves no residual-solvent specification to defend in a pharmaceutical process.

5.3 The costs that are not in the yield table

Three burdens are consistently understated. The first is feedstock preparation, since moisture below about 10 per cent is generally required for plant material [23]; drying is an energy cost that belongs to the extraction and is rarely accounted to it. The second is capital, because pressure vessels rated to 300 bar and above set an entry cost that no other platform in this comparison approaches.

The third is the carbon accounting itself. A cradle-to-gate assessment of supercritical decaffeination, the oldest and best-established industrial application of the technology,

attributed 3.29 kg of carbon dioxide equivalent to one kilogram of decaffeinated coffee plus recovered caffeine, of which agriculture accounted for roughly 48 per cent and the extraction step for roughly 43 per cent; the process ran at 25 MPa and 90 degrees Celsius with 97 per cent caffeine recovery over 11.5 hours for Arabica and 22 hours for Robusta [24]. The extraction step is not a rounding error, and claims that supercritical carbon dioxide extraction is carbon neutral because the fluid is recycled do not survive contact with the compression duty.

6. Natural deep eutectic solvents

6.1 Definition, structure and the role of water

Mixing a hydrogen bond acceptor with a hydrogen bond donor at a particular molar ratio can depress the melting point of the mixture far below that of either component, giving a liquid at room temperature; the original demonstration used choline chloride with urea [29]. The natural variant arose from a different question, namely whether the high intracellular concentrations of sugars, organic acids, amino acids and choline found in living cells constitute a third liquid phase alongside water and lipid, in which poorly water-soluble metabolites are stored and transported [30]. That hypothesis reframed these mixtures as biologically native media rather than synthetic curiosities.

Viscosity is the practical obstacle and water is the practical answer. Adding 25 per cent water to a glucose-choline-water eutectic reduced kinematic viscosity from 397 to 7.2 mm2/s, and a proline-choline system fell from 33 to 6.1 mm2/s against 0.7 mm2/s for water itself. Beyond about 50 per cent water the hydroxyl signals characteristic of the hydrogen bond network disappear from the nuclear magnetic resonance spectrum and solute solubility falls sharply, because the eutectic has been diluted into an ordinary aqueous solution [10]. The operating window for most extraction work therefore lies between roughly 20 and 40 per cent water, and reporting a formulation without its water content makes the result irreproducible.

6.2 What the eutectic does better, and what it does not

The advantage is compound-class specific rather than general. Citric acid-based eutectics applied to Scutellaria baicalensis raised flavonoid aglycone recovery two- to sixfold over aqueous methanol, with wogonin up 6.32-fold, while the corresponding glycosides rose only 1.5- to 1.8-fold [25]. Hydrogen bonding with a poorly water-soluble aglycone or alkaloid is where the eutectic earns its place; already-soluble glycosides gain little.

Stabilisation of labile pigments is often claimed as a second advantage, and the claim requires qualification, because extraction efficiency and post-extraction stability are separate properties of a eutectic. In pomegranate flower extraction a choline chloride-urea eutectic gave the highest anthocyanin and phenolic recovery, at 0.128 mg cyanidin-3-glucoside equivalents per gram against 0.095 mg/g for water and 0.056 mg/g for ethanol, and simultaneously the fastest degradation, with a half-life of 8.13 days at 20

degrees Celsius and a temperature coefficient of 5.31, against a half-life of 266.6 days and a coefficient of 1.217 for ethanol [31]. Optimising the first property can destroy the second.

Because viscosity limits mass transfer, eutectic extraction is almost always assisted by ultrasound or microwave irradiation [25]. A eutectic process therefore inherits the energy profile and the scale-up constraints of whichever assist technology it is paired with, which is a cost rarely carried into the comparison.

6.3 The recovery problem

A eutectic solvent has negligible vapour pressure. That is what makes it non-volatile, non-flammable and safe to handle, and it is also why the target compound cannot be recovered by evaporating the solvent, which is the standard final step in every conventional extraction [11]. This is the largest unsolved obstacle to industrial adoption, and the published record on it is thin relative to the record on extraction yield.

Three routes are in use, with markedly different performance. Macroporous resin adsorption is the most successful, recovering 93.7 per cent of Ginkgo flavonoids from a levulinic acid eutectic [32]. Antisolvent precipitation is far lossier: precipitation of curcumin from a choline chloride-lactic acid eutectic raised purity from 0.31 to 20.54 per cent but recovered only 21.49 per cent of the curcumin present [33]. Solid-phase extraction and membrane separation occupy intermediate positions, with recoveries above 90 per cent reported in favourable cases [11]. The fourth route is to avoid recovery altogether by formulating the eutectic extract directly into the final product, which is credible for a cosmetic or a nutraceutical and much harder for a pharmaceutical dosage form with an excipient specification.

Non-volatility cuts both ways in the mass balance. Because nothing evaporates, a eutectic can in principle be recovered intact and reused across cycles, which would make the solvent a fixed inventory rather than a consumable and would transform the E-factor of the process. The evidence for how many cycles survive, and for whether repeated thermal, ultrasonic or microwave exposure alters the composition or the toxicity of the recovered solvent, has not been assembled [11]. Until it is, the reuse argument is a projection rather than a finding, and the honest position is that the solvent is currently consumed.

6.4 "Natural" is not a toxicological argument

Eutectic mixtures do not inherit the safety profile of their components. Component median lethal doses between 9.71 and above 20 g/kg have been reported against 5.31 to 6.39 g/kg for the corresponding mixtures, and half-maximal effective concentrations above 2000 mg/L for choline chloride-glucose and choline chloride-glycerol against 218.7 mg/L for a choline chloride-oxalate system, with toxicity rising monotonically with acidic donor content [14]. Toxicity is a property of the specific eutectic and must be measured for each, not inferred from the provenance of the ingredients. That finding, more than any yield figure, is what a regulator will ask about first.

7. Critical comparison

7.1 What the head-to-head studies show

Only a small number of studies place two or more of these platforms on the same matrix under matched analysis, and their collective message is that the ranking depends on the endpoint chosen. Table 3 collects them.

Olive leaves and olive pomace processed by both ultrasound and supercritical carbon dioxide gave a decisive advantage to ultrasound on phenolic content in leaves and near parity in pomace. Antimicrobial activity then reversed the order entirely, with supercritical extracts inhibiting Pseudomonas savastanoi by 59 to 93 per cent against 18 to 75 per cent for ultrasonic extracts, and inhibiting a Hanseniaspora species by 64 to 97 per cent against 0 to 8 per cent[4]. The supercritical extract contained less phenolic material and more of whatever was doing the killing. A review that had ranked technologies on total phenolic content alone would have reached the wrong conclusion about which extract to develop as an antimicrobial.

Olive leaf extraction compared conventionally and by microwave, each with both classical solvents and eutectics, found the highest oleuropein concentration from conventional ethanol extraction at 70 degrees Celsius, at 29,580 mg/L, with a choline chloride-acetic acid eutectic diluted with ethanol the best of the eutectic systems, and microwave extraction delivering a comparable phenolic and antioxidant profile in far less time with far less solvent [34]. Time and solvent inventory, not concentration, were where the green platforms won.

Sequential combination outperforms either technique alone. On red onion skin waste, ultrasound gave 5.36 per cent quercetin and microwave 5.03 per cent, while ultrasound followed by microwave gave 7.66 per cent and microwave followed by ultrasound 10.32 per cent [35]. Where two mechanisms of cell disruption are complementary rather than redundant, combining them is more productive than optimising either.

Table 3. Published studies placing two or more of the four platforms on the same matrix under matched analysis. Abbreviations as in Table 2; TPC, total phenolic content; GAE, gallic acid equivalents.

Matrix	Compared	Headline result	Reference
Olive leaves and olive pomace	UAE, SFE-CO2	Leaves: TPC 6753 to 7410 against 848 to 1763 mg GAE/100 g in favour of UAE. Pomace: 7660 against 7200 mg GAE/100 g, effectively equal. Antimicrobial inhibition reversed in favour of SFE-CO2	4
Olive leaves	Conventional and MAE, each with a classical solvent and with a eutectic	Highest oleuropein 29,580 mg/L by conventional ethanol at 70 degrees Celsius; MAE gave a comparable profile in far less time and with far less solvent	34
Red onion skin waste	UAE, MAE, and both sequential orders	Quercetin 5.36 per cent by UAE, 5.03 per cent by MAE, 7.66 per cent by UAE then MAE, 10.32 per cent by MAE then UAE	35
Beet seed by-product	UAE, MAE at a matched functional unit	MAE gave 33 per cent more polyphenol and was up to 6 times faster; UAE used 3.2 to 3.6 times less electricity and carried lower climate and ozone	15

		impacts	

7.2 The selection map

Read together, the evidence supports a mapping rather than a ranking. Four properties of the problem determine the defensible choice, and Figure 3 shows the first two of them as a design space.

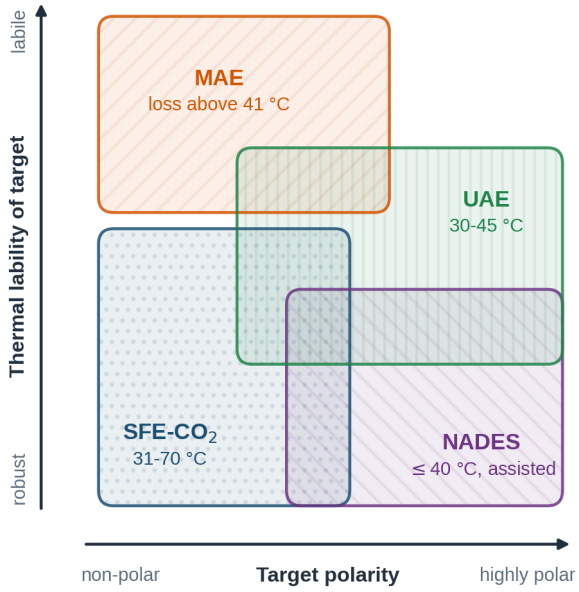

Figure 3. The four platforms occupy separable and partly overlapping regions of a design space set by target polarity and thermal lability, rather than competing for a single optimum. Each shaded region marks where the platform named within it is defensible on the evidence reviewed here; the overlaps are real and indicate conditions under which more than one platform is a reasonable choice. The annotation beneath each label is the operating range or the reported degradation threshold discussed in the text: supercritical carbon dioxide is typically operated between 31 and 70 degrees Celsius [23]; ultrasound optima for labile pigments fall between 30 and 45 degrees Celsius, above which anthocyanin degradation dominates [18]; microwave heating of powdered blueberry showed anthocyanin degradation from 41.2 degrees Celsius [22]; assisted eutectic extraction is typically run at or below 40 degrees Celsius [25].

Target polarity. Non-polar and moderately polar targets, including carotenoids, tocopherols, cannabinoids, essential oils and lipids, belong to supercritical carbon dioxide, which extracts them selectively and delivers them solvent-free. Polar phenolics, glycosides and polysaccharides do not, and forcing them into a supercritical process with a high entrainer load recovers neither the selectivity nor the solvent-free claim [9]. Aglycones and alkaloids of poor aqueous solubility are where eutectic solvents outperform aqueous alcohols by the largest margin [25].

Thermal lability. Anthocyanins degrade measurably above about 41 degrees Celsius under microwave irradiation [22] and above about 40 degrees Celsius under sonication [18]. Supercritical carbon dioxide operates routinely between 31 and 70 degrees Celsius [23] and can be run at the low end of that range, and eutectic solvents can operate close to ambient temperature. For a genuinely thermolabile target, microwave extraction is the least appropriate of the four unless residence time is measured in seconds.

Required purity and downstream form. A pharmaceutical intermediate requiring a defined residual-solvent profile favours supercritical carbon dioxide, which has no residual-solvent specification to meet [2], and disfavours a eutectic solvent that must first be separated from the product [11] and whose toxicology must be established formulation by formulation [14]. Titanium transfer from probe erosion is a specific objection to ultrasonic processing of injectable-grade material [5].

Scale and capital. Ultrasound has the lowest entry cost and a demonstrated route to 120 kg batches, at the price of falling acoustic intensity[19]. Microwave processing scales through continuous flow at reduced frequency rather than through larger vessels, at US$1000 to US$5000 per installed kilowatt [21]. Supercritical plant carries the highest capital cost but the longest industrial track record [24]. Eutectic solvent processing has no established industrial precedent, and its scale-up question is not extraction but recovery [11].

7.3 The comparison the field has not run

No published study places all four platforms on one matrix, with one analytical method, one functional unit, and reported energy and solvent inventories. Until such a study exists, every general claim about which technology is greenest, including the claims summarised here, rests on cross-study inference between experiments that differ in matrix, in solvent, in analytical endpoint and in the definition of yield.

8. Why the primary literature resists synthesis

Three reporting failures recur often enough to be structural. Energy is usually absent. Among the studies examined for this review only a minority reported electricity consumption in any form, and among those the units varied between watt-hours per batch, kilowatt-hours per kilogram of feed and kilowatt-hours per kilogram of extract, which are not interconvertible without data that is not reported. A technology whose entire claim is process intensification cannot be assessed without it.

What a usable report would contain is not demanding: the electrical energy drawn by the extraction device over the run, the mass of dry biomass charged, the mass of solvent charged and the mass recovered, and the mass of the named target compound obtained. Four numbers, all measurable on a bench, would make any two studies comparable on both an energy and a mass basis. Their routine absence is a convention rather than a technical obstacle.

Life-cycle assessments are not comparable to one another, because functional units, system boundaries and assumptions about solvent recovery differ study by study. The consequence is visible in Section 2: two careful assessments reach compatible qualitative conclusions through arithmetic that cannot be placed on one axis [15,16].

Optima are reported without the response surfaces that surround them. Non-monotonic behaviour is the norm in all four platforms, whether from degradation under sonication[18], thermal loss under microwave irradiation [22], co-

extraction of unwanted matrix at high supercritical density [28] or hydrogen-bond network collapse at high water content in a eutectic [10]. A single optimum conceals the shape of the curve and therefore conceals the robustness of the process. Negative results are scarcer still: the finding that conventional stirring outperformed ultrasound on tomato carotenoids [26] is more informative per publication than another confirmation that a green technology beats maceration, and its rarity is a publication bias with direct consequences for anyone selecting a process from the literature.

9. Future directions

Three specific pieces of work would change the state of this field more than further single-platform optimisation.

The first is a matched four-platform benchmark: one matrix carrying both polar and non-polar targets, such as grape pomace or olive leaf, processed by ultrasound, microwave, supercritical carbon dioxide and an assisted eutectic system, with a single validated chromatographic method, a functional unit defined as mass of a named compound rather than as spectrophotometric equivalents, and mandatory reporting of energy, solvent inventory and E-factor. The absence of this study is the reason Section 7.3 exists. It would also need to report the state of each extract rather than its content alone, since the olive leaf comparison shows content and activity diverging on the same material [4], and to declare its assist conditions for the eutectic arm, since a eutectic system inherits the energy profile of whichever technology is used to overcome its viscosity [25].

The second is systematic work on recovery from eutectic solvents. The extraction literature for these solvents now vastly exceeds the recovery literature, and the reported recoveries span a fourfold range between antisolvent precipitation and resin adsorption [32,33]. What is needed is a comparison of recovery routes across a common set of eutectics and target classes, with solvent reuse cycles and the toxicological consequences of thermal or ultrasonic recycling characterised [11,14].

The third is hybridisation studied as a design problem rather than as an empirical accident. Sequential microwave and ultrasound treatment approximately doubled quercetin recovery over either alone [35], and assisted eutectic systems already combine two mechanisms by necessity [25]. The open question is which pairings are complementary in mechanism and which are redundant, and that question is answerable by design of experiments rather than by trial.

10. Conclusion

The four technologies examined here are not four answers to one question. Supercritical carbon dioxide extraction is the defensible choice for non-polar targets where regulatory cleanliness governs, and the wrong choice for polar phenolics. Ultrasound is the cheapest and least energy-intensive route to intensification and the most likely to fail unpredictably on a new matrix. Microwave irradiation is the fastest and most productive per batch and the least suited to heat-

sensitive chemistry. Natural deep eutectic solvents extract difficult polar and labile compounds better than aqueous alcohols and have not yet solved the problem of giving them back.

The field's real deficiency is not technological. It is that a literature of many thousands of single-platform optimisations has produced very few comparisons capable of guiding a process choice, because energy is not reported, functional units are not standardised, and results that do not favour the newer technology are not published. A green extraction process is one whose full inventory has been measured and found favourable. Until that inventory is reported as a matter of routine, the word green in this field describes an intention rather than a finding.

Declarations

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. International Council for Harmonisation. ICH guideline Q3C (R9) on impurities: guideline for residual solvents. EMA/CHMP/ICH/82260/2006. Amsterdam: European Medicines Agency; 2024.
2. Directive 2009/32/EC of the European Parliament and of the Council of 23 April 2009 on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients (Recast). Off J Eur Union. 2009;L141:3-11.
3. Lian JZ, Liu T, Yang J, Zhu H, Chalermchotiwong N, Grain Y, et al. Sustainable extraction of bioactive compounds: a life cycle perspective on technologies, solvents, and process scale-up. RSC Sustain. 2026;4(3):1180-202. doi:10.1039/D5SU00832H
4. Gizaw Y, Benito MJ, Rivas MA, Gudino I, Cordoba MG, Casquete R. Influence of ultrasound-assisted and supercritical CO2 extraction on phytochemical profiles with antimicrobial and antioxidant functionality from olive leaves and olive pomace. Molecules. 2026;31(7):1186. doi:10.3390/molecules31071186
5. Chemat F, Rombaut N, Sicaire AG, Meullemiestre A, Fabiano-Tixier AS, Abert-Vian M. Ultrasound assisted extraction of food and natural products. Mechanisms, techniques, combinations, protocols and applications. A review. Ultrason Sonochem. 2017;34:540-60. doi:10.1016/j.ultsonch.2016.06.035
6. Tatke P, Jaiswal Y. An overview of microwave assisted extraction and its applications in herbal drug research. Res J Med Plant. 2011;5(1):21-31. doi:10.17311/rjmp.2011.21.31
7. Ibrahim NA, Zaini MAA. Solvent selection in microwave assisted extraction of castor oil. Chem Eng Trans. 2017;56:865-70. doi:10.3303/CET1756145
8. Reverchon E, De Marco I. Supercritical fluid extraction and fractionation of natural matter. J Supercrit Fluids. 2006;38(2):146-66. doi:10.1016/j.supflu.2006.03.020
9. Uwineza PA, Waskiewicz A. Recent advances in supercritical fluid extraction of natural bioactive compounds from natural plant materials. Molecules. 2020;25(17):3847. doi:10.3390/molecules25173847
10. Dai Y, Witkamp GJ, Verpoorte R, Choi YH. Tailoring properties of natural deep eutectic solvents with water to facilitate their applications. Food Chem. 2015;187:14-9. doi:10.1016/j.foodchem.2015.03.123
11. Molnar M, Gaso-Sokac D, Komar M, Jakovljevic Kovac M, Bilic Rajs B. Potential of deep eutectic solvents in the extraction of organic compounds from food industry by-products and agro-industrial waste. Separations. 2024;11(1):35. doi:10.3390/separations11010035

12. Chemat F, Vian MA, Cravotto G. Green extraction of natural products: concept and principles. Int J Mol Sci. 2012;13(7):8615-27. doi:10.3390/ijms13078615

13. Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. Green Chem. 2017;19(1):18-43. doi:10.1039/C6GC02157C

14. Lomba L, Ribate MP, Sanguesa E, Concha J, Garralaga MP, Errazquin D, et al. Deep eutectic solvents: are they safe? Appl Sci. 2021;11(21):10061. doi:10.3390/app112110061

15. Bouchez A, Vauchel P, Perino S, Dimitrov K. Multi-criteria optimization including environmental impacts of a microwave-assisted extraction of polyphenols and comparison with an ultrasound-assisted extraction process. Foods. 2023;12(9):1750. doi:10.3390/foods12091750

16. Barjoveanu G, Patrautanu OA, Teodosiu C, Volf I. Life cycle assessment of polyphenols extraction processes from waste biomass. Sci Rep. 2020;10:13632. doi:10.1038/s41598-020-70587-w

17. Xie Y, Zhang L, Wu W, Xie J, Gao B, Xiao Y, et al. Sustainable and green extraction of citrus peel essential oil using intermittent solvent-free microwave technology. Bioresour Bioprocess. 2025;12(1):48. doi:10.1186/s40643-025-00885-6

18. Zou TB, Wang M, Gan RY, Ling WH. Optimization of ultrasound-assisted extraction of anthocyanins from mulberry, using response surface methodology. Int J Mol Sci. 2011;12(5):3006-17. doi:10.3390/ijms12053006

19. Rodriguez O, Bona S, Stabler A, Rodriguez-Turienzo L. Ultrasound-assisted extraction of polyphenols from olive pomace: scale up from laboratory to pilot scenario. Processes. 2022;10(12):2481. doi:10.3390/pr10122481

20. Akhtar I, Javad S, Ansari M, Ghaffar N, Tariq A. Process optimization for microwave assisted extraction of Foeniculum vulgare Mill using response surface methodology. J King Saud Univ Sci. 2020;32(2):1451-8. doi:10.1016/j.jksus.2019.11.041

21. Radoiu M, Kaur H, Bakowska-Barczak A, Splinter S. Microwave-assisted industrial scale cannabis extraction. Technologies. 2020;8(3):45. doi:10.3390/technologies8030045

22. Sun Y, Xue H, Liu C, Liu C, Su X, Zheng X. Comparison of microwave assisted extraction with hot reflux extraction in acquirement and degradation of anthocyanin from powdered blueberry. Int J Agric Biol Eng. 2016;9(6):186-99. doi:10.3965/j.ijabe.20160906.2724

23. Yildirim M, Ersatir M, Poyraz S, Amangeldinova M, Kudrina NO, Terletskaya NV. Green extraction of plant materials using supercritical CO2: insights into methods, analysis, and bioactivity. Plants. 2024;13(16):2295. doi:10.3390/plants13162295

24. De Marco I, Riemma S, Iannone R. Life cycle assessment of supercritical CO2 extraction of caffeine from coffee beans. J Supercrit Fluids. 2018;133:393-400. doi:10.1016/j.supflu.2017.11.005

25. Oomen WW, Begines P, Mustafa NR, Wilson EG, Verpoorte R, Choi YH. Natural deep eutectic solvent extraction of flavonoids of Scutellaria baicalensis as a replacement for conventional organic solvents. Molecules. 2020;25(3):617. doi:10.3390/molecules25030617

26. Mavridis K, Todas N, Kalompatsios D, Athanasiadis V, Lalas SI. Lycopene and other bioactive compounds' extraction from tomato processing industry waste: a comparison of ultrasonication versus a conventional stirring method. Horticulturae. 2025;11(1):71. doi:10.3390/horticulturae11010071

27. Allay A, Benkirane C, Ben Moumen A, Fauconnier ML, Bouakline H, Nkengurutse J, et al. Optimizing ethanol-modified supercritical CO2 extraction for enhanced bioactive compound recovery in hemp seed oil. Sci Rep. 2025;15:8551. doi:10.1038/s41598-025-91441-x

28. Shi J, Xue S, Sun Q, Scanlon M, Yao J, Li X. Exploring selectivity of supercritical-CO2 for vitamin E extraction from canola seeds. Food Bioprocess Technol. 2025;18(3):2754-64. doi:10.1007/s11947-024-03621-8

29. Abbott AP, Capper G, Davies DL, Rasheed RK, Tambyrajah V. Novel solvent properties of choline chloride/urea mixtures. Chem Commun. 2003;(1):70-1. doi:10.1039/B210714G

30. Choi YH, van Spronsen J, Dai Y, Verpoorte R, Witkamp GJ, Hollmann F, et al. Are natural deep eutectic solvents the missing link in understanding cellular metabolism and

physiology? Plant Physiol. 2011;156(4):1701-5. doi:10.1104/pp.111.178426

31. Zieniuk B. Application of natural deep eutectic solvents (NADES) for the extraction of floral phenolics and anthocyanin degradation kinetics. Appl Sci. 2026;16(8):4036. doi:10.3390/app16084036
32. Socas-Rodriguez B, Torres-Cornejo MV, Alvarez-Rivera G, Mendiola JA. Deep eutectic solvents for the extraction of bioactive compounds from natural sources and agricultural by-products. Appl Sci. 2021;11(11):4897. doi:10.3390/app11114897
33. Sahlan M, Rosarina D, Suminar HFR, Wijanarko A, Hermansyah H, Mahida SN, et al. Microwave-ultrasound-assisted extraction coupled with natural deep eutectic solvent enables high-yield, low-solvent recovery of curcumin from Curcuma longa L. Pharmaceutics. 2025;17(7):818. doi:10.3390/pharmaceutics17070818
34. Boli E, Prinos N, Louli V, Pappa G, Stamatis H, Magoulas K, et al. Recovery of bioactive extracts from olive leaves using conventional and microwave-assisted extraction with classical and deep eutectic solvents. Separations. 2022;9(9):255. doi:10.3390/separations9090255
35. Jabbari Velisdeh Z, Najafpour Darzi G, Poureini F, Mohammadi M, Sedighi A, Perves Bappy MJ, et al. Turning waste into wealth: optimization of microwave/ultrasound-assisted extraction for maximum recovery of quercetin and total flavonoids from red onion (Allium cepa L.) skin waste. Appl Sci. 2024;14(20):9225. doi:10.3390/app14209225