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GREEN SOLVENTS IN NATURAL PRODUCT EXTRACTION: A COMPARATIVE ANALYSIS OF DEEP EUTECTIC SOLVENTS, IONIC LIQUIDS AND SUPERCRITICAL CARBON DIOXIDE

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ABSTRACT

The recovery of bioactive compounds from plant and marine biomass still depends heavily on volatile organic solvents whose toxicity, flammability and environmental persistence sit awkwardly beside a pharmaceutical industry that increasingly measures itself against sustainability targets. Three classes of alternative solvent have moved from curiosity to credible replacement over the past two decades: deep eutectic solvents and their natural subclass, ionic liquids, and supercritical carbon dioxide. Each rests on a different physical principle, and each therefore succeeds and fails against a different part of the extraction problem. This review compares the three head to head across the dimensions that decide whether a solvent reaches a manufacturing plant rather than a single publication: extraction efficiency and selectivity, green-chemistry credentials, solute recovery, scalability and capital cost, and regulatory acceptability. The central argument is that no single class is universally superior, and that framing the three as competitors obscures how neatly their strengths partition by target polarity and production scale. Deep eutectic solvents, and especially natural deep eutectic solvents, dominate the recovery of polar phenolics and offer the most convincing green profile, but pay for it in viscosity and difficult product isolation. Ionic liquids provide selectivity and tunability that neither rival matches, yet a debated toxicity record, high cost and awkward recovery keep most applications at laboratory scale. Supercritical carbon dioxide delivers solvent-free, food-grade nonpolar extracts at industrial scale but is largely blind to hydrophilic solutes without a co-solvent. The field's most productive direction is not the search for one winner but the deliberate pairing of these solvents with each other and with intensification techniques, supported by the life-cycle accounting that green claims currently lack.

Keywords: deep eutectic solvents; ionic liquids; supercritical carbon dioxide; green chemistry; natural product extraction; bioactive compounds; sustainable extraction.

1. Introduction

Natural products remain the most productive single source of pharmaceutical lead compounds, and the first step in almost every discovery or manufacturing pipeline built on them is the same: pull the molecule of interest out of a complex biological matrix and leave the rest behind. For most of the twentieth century that step meant maceration, Soxhlet extraction or percolation with hexane, dichloromethane, methanol, acetone or chloroform. These solvents are effective, cheap and well understood, which is precisely why they have been so hard to displace. They are also volatile, flammable, frequently toxic, often derived from petroleum, and responsible for a large share of the waste generated per kilogram of active ingredient in fine-chemical and pharmaceutical production. As the principles of green chemistry moved from academic slogan to industrial expectation, the solvent became the obvious target for reform, because it is usually the largest mass input to a process and the one with the clearest environmental footprint.[1]

The pressure to reform is not only environmental. Solvent residues are regulated, and pharmaceutical manufacturers must demonstrate that class-restricted solvents such as methanol, dichloromethane and hexane fall below defined limits in a finished product, which imposes analytical and processing costs that a non-toxic or non-volatile medium can avoid entirely. Solvents also account for a large fraction of a process mass balance, so the waste generated per unit of product, the figure the fine-chemical sector tracks as its environmental factor, is dominated by solvent use more than by any reagent. A solvent that is safer to handle, cheaper to dispose of, and recyclable therefore improves several ledgers at once, and that convergence of environmental, regulatory and economic incentive is what has turned solvent substitution from a niche academic interest into a mainstream industrial objective.

The response has been the concept of green extraction, articulated as a set of principles that ask process designers to reduce energy use, favour renewable feedstocks, cut solvent consumption, and eliminate hazardous and petroleum-derived media wherever a safer alternative exists.[2] Meeting those principles requires more than swapping one organic solvent for a slightly less objectionable one. It requires solvent systems built from the ground up around low toxicity, low volatility and recyclability. Three such systems have emerged as the serious contenders, and they could hardly be more different from one another in their underlying chemistry.

The first is the deep eutectic solvent, a liquid formed simply by combining a hydrogen-bond acceptor such as a quaternary ammonium salt with a hydrogen-bond donor such as urea, a sugar or an organic acid. The mixture melts far below either parent component because hydrogen bonding disrupts the crystal lattices, and the resulting fluid behaves as a tunable, largely non-volatile solvent.[3] When both components are primary plant metabolites, the fluid is termed a natural deep eutectic solvent, a

class proposed as the medium in which many poorly water-soluble metabolites are stored and transported inside living cells.[4] The second contender is the ionic liquid, a salt that is molten at or near room temperature, whose almost limitless combinations of bulky organic cation and weakly coordinating anion allow its solvent properties to be dialled to a target.[5] The third is supercritical carbon dioxide, not a designed liquid at all but a familiar gas taken above its critical point, where it acquires a liquid-like density and a gas-like diffusivity and dissolves nonpolar solutes with a selectivity that can be tuned by pressure alone.[6]

These three are routinely presented as rivals for the same job, and reviews frequently rank them as though one must eventually win. This review takes a different position. Read across the evidence, the three solvent classes do not compete so much as partition the extraction problem between them, because each is governed by a different physical variable: hydrogen-bond networks for deep eutectic solvents, ion-specific interactions for ionic liquids, and density-dependent solvating power for supercritical carbon dioxide. The purpose here is to make that partition explicit. The review sets out the chemistry and performance of each class in turn, then compares them directly across the criteria that determine industrial fate rather than laboratory novelty, and finally argues that the field's near-term progress lies in combining these solvents deliberately and in closing the gap between their green reputations and the life-cycle evidence that would justify those reputations.

2. Deep eutectic solvents

2.1 Definition and chemistry

A deep eutectic solvent is produced by mixing two or more components that associate through hydrogen bonding to give a liquid whose melting point lies well below that of any individual constituent. The founding example remains the clearest illustration of the effect. Choline chloride melts at 302 degrees Celsius and urea at 133 degrees Celsius, yet a mixture of the two in a one-to-two molar ratio is liquid at room temperature, with a melting point near 12 degrees Celsius.[3,7] The depression arises because the chloride anion of choline chloride forms strong hydrogen bonds with urea, delocalising charge and frustrating the crystallisation that each pure component would otherwise undergo. Because the interaction is between a hydrogen-bond acceptor and a hydrogen-bond donor rather than between defined ions of a single salt, deep eutectic solvents are not, strictly, ionic liquids, although the two families are often discussed together and share a low vapour pressure.[4]

The family has since expanded well beyond the original salt-and-amide combination. Contemporary classifications recognise several subclasses, including natural deep eutectic solvents built entirely from primary metabolites such as amino acids, sugars, choline and organic acids; therapeutic deep eutectic solvents in which at least one component is an active pharmaceutical ingredient; and polymeric variants.[7] The natural subclass carries the greatest weight for extraction because its components are food-grade, renewable and, in

many formulations, safe enough to leave in a finished product without a separate removal step. Surveys of the published extraction literature show how narrow the practical palette really is: choline chloride serves as the hydrogen-bond acceptor in close to a third of reported systems, while urea, glycine, lactic acid and glucose dominate the donor side.[8]

2.2 Performance in extraction

The defining strength of the deep eutectic solvent is its affinity for polar and moderately polar solutes, particularly the phenolic acids, flavonoids and anthocyanins that account for much of the antioxidant value of plant material. Because the hydrogen-bond network of the solvent can donate and accept in the same way the target molecules do, dissolution is often markedly better than in water and competitive with or superior to ethanol. The solubility gains can be large. Rutin, a flavonoid glycoside of pharmaceutical interest, dissolves fifty to one hundred times more readily in certain deep eutectic solvents than in water, a difference that translates directly into higher extraction yields and smaller solvent volumes.[7]

Applied studies bear this out across a wide range of feedstocks, and food and agricultural by-products have become a favoured proving ground because they pair a sustainability narrative with genuinely valuable residual chemistry. Natural deep eutectic solvents have recovered total phenolics from orange peel at concentrations above 2100 milligrams of gallic acid equivalent per hundred grams of dry material, and have outperformed conventional solvents in anthocyanin recovery from sour cherry by more than sixty percent.[8] For components of Ginkgo biloba, including flavonoids and terpene esters, a deep eutectic medium raised extraction rates by more than two orders of magnitude relative to a conventional approach, an increase that reflects both improved solubility and the ability to tune polarity by adjusting the component ratio.[9] The same tunability lets a formulator move a solvent from hydrophilic to hydrophobic character by choice of components, extending the reach of the class toward less polar targets that would otherwise demand an organic solvent.

2.3 Limitations

Two problems temper this picture, and both are intrinsic rather than incidental. The first is viscosity. The dense hydrogen-bond network that makes these solvents good at dissolving polar solutes also makes them thick, and high viscosity throttles mass transfer, slowing the diffusion of solute out of the plant matrix and into the bulk liquid. The effect is routinely described as the central practical obstacle to deep eutectic extraction.[7,9] It is manageable: adding a controlled amount of water, raising the temperature, or applying ultrasound or microwave energy all reduce viscosity and restore mass transfer, and because these solvents absorb microwave radiation efficiently they pair naturally with microwave-assisted extraction.[10] Each fix, though, adds a variable that must be optimised and, in the case of added water, can change the solvent's structure and selectivity.

The second problem is recovery. The very low vapour pressure that makes a deep eutectic solvent safe to handle and non-polluting also means it cannot simply be evaporated off to release the product, unlike ethanol or hexane. Isolating the target compound therefore requires antisolvent precipitation, solid-phase adsorption, back-extraction or chromatography, each of which adds cost and can compromise the clean green ledger the solvent was chosen for.[7] For applications where the loaded solvent is itself the product, as in some cosmetic and nutraceutical formulations, this ceases to matter, and that is where deep eutectic extraction has advanced fastest. Where a pure isolated compound is the goal, recovery remains the step at which the method is judged.

2.4 Water, stability and the natural context

Two further features distinguish deep eutectic solvents from the other green media and deserve mention because they shape how the class is used. The first is the pivotal role of water. Small, controlled additions of water lower viscosity and improve mass transfer, but beyond a threshold the added water disrupts the hydrogen-bond network that defines the solvent, so a deep eutectic medium diluted too far ceases to behave as one and reverts toward an ordinary aqueous mixture. Water content is therefore not an incidental variable but a formulation parameter that has to be optimised for each system, since it trades viscosity against structure and selectivity. The second feature is a stabilising effect on the extracted compounds themselves. The dense hydrogen-bond environment can protect labile bioactives such as anthocyanins and other pigments against oxidation and photodegradation, so a deep eutectic extract sometimes retains activity better on storage than an ethanolic or aqueous one.[7] This stabilisation, together with the proposal that these mixtures act as a third intracellular liquid phase in which plants store poorly water-soluble metabolites, gives the natural subclass a biological plausibility that reinforces its safety case and helps explain why so many plant metabolites dissolve in it so readily.[4]

3. Ionic liquids

3.1 Definition and the designer-solvent concept

Ionic liquids are salts that are liquid below one hundred degrees Celsius, and often at room temperature, composed entirely of ions. A bulky, asymmetric organic cation, commonly imidazolium, pyridinium, quaternary ammonium or phosphonium, is paired with an inorganic or organic anion such as chloride, tetrafluoroborate, hexafluorophosphate or bis(trifluoromethylsulfonyl)imide. The size and irregular shape of the cation prevents efficient crystal packing, so the salt stays molten far below the temperature of a conventional inorganic salt.[11] Their most-cited virtue is a negligible vapour pressure, which removes the inhalation and flammability hazards that define volatile organic solvents, together with high thermal and chemical stability.

The property that sets ionic liquids apart from every other solvent class, however, is combinatorial tunability. With a large library of

cations and an equally large library of anions, and the option of appending functional groups to either, the number of accessible ionic liquids runs to millions, and their polarity, hydrogen-bonding capacity, viscosity and miscibility can be adjusted almost continuously. This is the origin of the label designer solvent, the idea that the medium can be engineered to a specific separation rather than selected from a short shelf of fixed options.[12] For natural product extraction this means an ionic liquid can be built to favour one class of metabolite, and the resulting selectivity is real.

3.2 Performance in extraction

In practice ionic liquids have proved especially effective for solutes that conventional solvents struggle with, and alkaloids are the clearest example. The ionic character of the solvent strengthens ion-exchange and electrostatic interactions with basic nitrogen-containing metabolites, and salt effects can be exploited to drive extraction that a neutral organic solvent cannot achieve.[9] Imidazolium-based liquids have been used to recover alkaloids, phenolics and flavonoids from a range of medicinal plants, frequently in combination with microwave or ultrasound assistance that shortens extraction time and raises yield.[12] Because the solvent's properties are tunable, the same platform can be re-optimised for a new target without abandoning the underlying method, which is part of the appeal to analytical and process chemists working across many species.

A refinement that has done much to make ionic liquids practical is the aqueous biphasic system. Rather than using the neat, viscous salt as the extraction medium, a hydrophilic ionic liquid is combined with an inorganic salt or a polymer in water to form two immiscible aqueous-rich phases, and the target partitions between them. This keeps the working fluid mostly water, which lowers viscosity and cost, while the ionic liquid supplies the tunable selectivity that drives the separation. Systems of this kind have been used to concentrate and purify alkaloids, phenolics and proteins from crude plant material, and they illustrate a broader lesson: the most successful ionic-liquid processes tend to use the ions as a designed additive that steers a partition, not as a bulk solvent to be consumed in large volume.[12]

The limitation on the performance side is not efficiency but breadth of evidence. Much of the ionic-liquid extraction literature reports single-target studies under carefully optimised conditions, and there is comparatively little data on how these solvents behave with the full, competing mixture of compounds present in a real plant extract.[9] Selectivity demonstrated against a pure standard does not always survive the crowded chemistry of a genuine matrix, and this gap between model and reality is one reason the class has been slower to translate than its tunability might predict.

3.3 The toxicity and recovery problem

The green credentials of ionic liquids are the most contested of the three classes reviewed here, and honesty about that contest matters. Negligible volatility does remove air pollution and inhalation risk, which is a genuine

environmental advantage over volatile organic solvents. It says nothing, however, about aquatic toxicity or biodegradability, and here the record is mixed. Many imidazolium and pyridinium liquids, particularly those with long alkyl chains or fluorinated anions, are poorly biodegradable and toxic to aquatic organisms, and some fluorinated anions can hydrolyse to release hazardous species.[9] Describing ionic liquids as green by default is therefore not defensible; greenness has to be established for each specific ion combination, and the more benign choices often sacrifice some of the performance that made the class attractive.

Two further barriers slow industrial adoption. Cost is the first: high-purity ionic liquids are considerably more expensive to prepare than deep eutectic solvents or carbon dioxide, and preparation cost has repeatedly been named as a brake on scale-up.[9] Recovery is the second: as with deep eutectic solvents, the absence of volatility that makes an ionic liquid safe also makes it hard to separate from the product, so isolation depends on back-extraction, antisolvent addition or adsorption, and full solvent recycling, though increasingly demonstrated, adds process complexity. The combination of debated toxicity, high cost and awkward recovery is why ionic liquids, despite unmatched selectivity, remain largely a laboratory and specialty-scale technology.[9]

4. Supercritical carbon dioxide

4.1 Principles

Supercritical carbon dioxide occupies a different conceptual space from the two ionic media. It is not a purpose-built liquid but ordinary carbon dioxide held above its critical temperature of 31.1 degrees Celsius and critical pressure of 73.8 bar, roughly 7.4 megapascals.[6,13] Above that point the fluid is neither gas nor liquid: it has a density approaching that of a liquid, which gives it solvent power, and a viscosity and diffusivity closer to those of a gas, which let it penetrate a solid matrix quickly and wash out dissolved solute efficiently. The feature that makes it so useful is that this solvent power depends steeply on density, and density depends on pressure and temperature, so the operator can tune what the fluid will and will not dissolve by turning a pressure dial rather than by changing solvent.[6]

The practical advantages follow directly from the choice of carbon dioxide as the working fluid. It is non-toxic, non-flammable, inexpensive, abundant and recognised as safe for food and pharmaceutical use, and its critical temperature sits close to ambient, so thermolabile natural products are not cooked during extraction. Above all, when the extraction is finished the pressure is released, the carbon dioxide reverts to a gas and leaves the vessel, and the product is recovered with no residual solvent at all.[14] For a food ingredient, a botanical drug or a fragrance, a solvent-free extract with no removal step is a decisive commercial and regulatory advantage that neither ionic medium can offer.

4.2 Performance and the co-solvent fix

The selectivity of supercritical carbon dioxide is both its strength and its defining weakness. Pure carbon dioxide is nonpolar, so it dissolves nonpolar and weakly polar solutes readily and is excellent for essential oils, volatile aroma compounds, fixed oils, carotenoids and other lipophilic natural products, giving clean extracts free of the waxy or chlorophyll contamination that solvent extraction often carries.[14] The same nonpolarity makes it largely blind to hydrophilic, high-molecular-weight and strongly hydrogen-bonding solutes, so the phenolic glycosides and polar alkaloids that deep eutectic solvents handle so well are precisely the compounds carbon dioxide extracts poorly on its own.[9]

The standard remedy is a co-solvent, or entrainer, most often a small percentage of ethanol added to the carbon dioxide stream to raise its polarity and hydrogen-bonding capacity. Even a few mole percent of ethanol substantially extends the range of accessible solutes while keeping the extract food-compatible, and optimisation of the ethanol fraction alongside pressure and temperature is now a routine part of method development for polar-leaning targets such as the minor bioactives in seed oils.[14] The entrainer erodes the solvent-free selling point somewhat, since the ethanol must then be removed, but it does so with a benign and easily evaporated additive rather than a hazardous one, and the core extract remains far cleaner than a conventional organic-solvent product.

4.3 The cost and scope constraints

A second advantage that distinguishes supercritical carbon dioxide from batch solvent extraction is fractionation. Because solvent power tracks density, and density can be stepped down in stages by controlled reduction of pressure, a single loaded fluid stream can be separated into fractions of increasing polarity as it passes through a series of collection vessels, delivering a crude separation during the extraction itself rather than as a later purification step.[6] The performance of the process also depends heavily on the state of the feed. Particle size, moisture content and the way the matrix is packed all govern how quickly the fluid can reach and dissolve the solute, so milling and drying the biomass beforehand often matters as much as the choice of pressure and temperature, a sensitivity the operator must control for reproducible yield.[12]

The obstacle that has always defined supercritical extraction is capital cost. Operating a fluid at seventy or more bar demands high-pressure vessels, pumps, heat exchangers and safety systems, and the equipment is expensive to buy and to run relative to a stirred tank of solvent.[13,14] The economics improve with scale and with high-value products, which is why supercritical carbon dioxide has succeeded commercially in decaffeination, hop extraction, spice and fragrance production and premium botanical extracts, where the quality of a solvent-free product justifies the plant. For a low-value, highly polar target the numbers rarely work, and a cheaper ionic or eutectic medium is the rational

choice. Set against that cost, though, the process is mechanically simpler than it looks once built, and reported yield gains over conventional extraction can be large: for rose extract, a supercritical process raised yield from around 0.03 percent to 0.2 percent while delivering a cleaner product.[9]

5. Comparative analysis

Placing the three classes side by side makes the partition of the extraction problem explicit, and the summary in Table 1 organises the comparison across the criteria that decide industrial fate.[15] The comparison is best read not as a scoreboard but as a map of which solvent belongs where, and Figure 1 draws that map along the single axis that predicts most of the outcome, namely the polarity of the target solute.

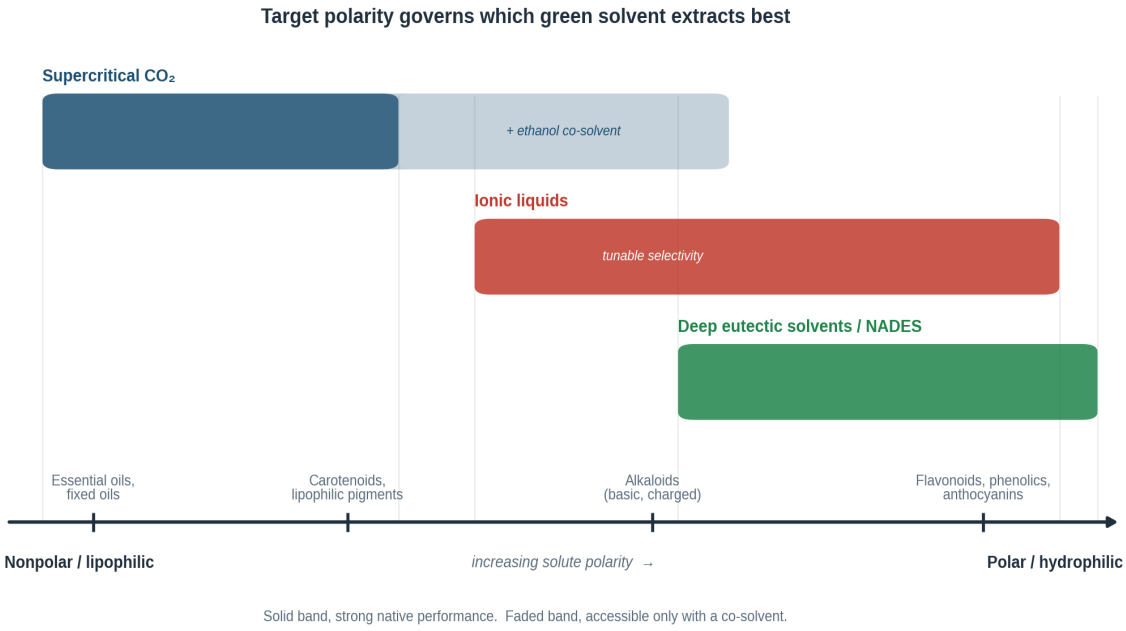

Figure 1. Target solute polarity governs which green solvent class extracts best. The horizontal axis runs from nonpolar, lipophilic solutes on the left to polar, hydrophilic solutes on the right, with representative natural product targets marked along it. Each coloured band shows the polarity range over which a solvent class performs strongly in its native form; the faded blue band shows the range that supercritical carbon dioxide reaches only when an ethanol co-solvent is added. The three classes occupy largely separate regions, which is the central argument of this review: they partition the extraction problem by target polarity rather than competing for the same solutes.

Table 1. Comparative summary of the three green solvent classes across the criteria that determine industrial adoption. Ratings are qualitative syntheses of the cited literature and are intended to guide solvent selection, not to substitute for feedstock-specific optimisation.

Criterion	Deep eutectic solvents (NADES)	Ionic liquids	Supercritical CO_2
Physical basis	Hydrogen-bond network between donor and acceptor	Salt molten near room temperature	Gas above its critical point (31.1 °C, 73.8 bar)
Best-suited targets	Polar phenolics, flavonoids, anthocyanins	Alkaloids and charged or basic metabolites	Essential oils, fixed oils, lipophilic pigments
Selectivity and tunability	Moderate, via component ratio and water content	Highest, via combinatorial ion choice	Moderate, via pressure and temperature
Green credentials	Strong for natural formulations, over 60% biodegradable	Contested, compound-specific toxicity	Strong, inert non-toxic recyclable fluid
Recovery of product	Difficult, no evaporation possible	Difficult, no evaporation possible	Automatic on depressurisation, residue-free
Scalability and maturity	Developing at food and pharmaceutical scale	Mostly laboratory and specialty scale	Industrially mature across several sectors
Capital and operating cost	Low, simple to prepare	High preparation cost	High capital cost, favoured by high-value products
Regulatory acceptability	Plausible for food-grade formulations	Weakest, poorly characterised residues	Strongest, established food and pharmaceutical use

On extraction efficiency and selectivity the answer depends entirely on the target. For polar phenolics, flavonoids and anthocyanins, deep eutectic solvents lead, with ionic liquids competitive and often superior for alkaloids and other charged or basic species, while supercritical carbon dioxide trails badly unless a co-solvent is added.[8,9] For nonpolar essential oils, fixed oils and lipophilic pigments the ranking inverts completely: supercritical carbon dioxide is the natural choice and delivers a purity the ionic media cannot match, while unmodified deep eutectic solvents and ionic liquids are ill-suited to strongly lipophilic solutes. Ionic liquids hold the unique advantage on tunable selectivity for a defined single target, a consequence of the combinatorial ion library, but that advantage is partly theoretical until it is demonstrated in a real multicomponent matrix.[9]

On green credentials the three separate cleanly, and this is where careless language does the most damage. Natural deep eutectic solvents present the most convincing profile: built from food-grade metabolites, more than sixty percent biodegradable in many formulations, low in toxicity and cheap to prepare from renewable feedstocks.[8] Supercritical carbon dioxide is arguably as green in a different sense, since its working fluid is inert, non-toxic, recyclable within the process and often a captured by-product, and it leaves no residue at all.[14] Ionic liquids are the outlier, genuinely superior to volatile organic solvents on volatility and air quality but variable and sometimes poor on aquatic toxicity and biodegradability, so their greenness cannot be assumed and must be proven ion by ion.[9]

On recovery and downstream processing the picture again splits by physical principle. Supercritical carbon dioxide wins outright, because depressurisation separates solvent from product automatically and the solvent-free extract needs no purification step.[14] Both ionic media pay for their low volatility here: neither can be evaporated, so both depend on antisolvent precipitation, adsorption or back-extraction to release the product, and both add the cost and the environmental burden of that step to their ledgers.[7,9] For deep eutectic solvents this is tolerable when the loaded solvent is itself the deliverable, and awkward when a pure compound is required.

On scalability and cost the order is clearest of all. Supercritical carbon dioxide is the most industrially mature of the three, proven at manufacturing scale across several sectors despite its capital intensity.[14] Deep eutectic solvents are inexpensive and simple to make, which favours scale-up, but high solvent consumption, viscosity and recovery keep large-scale food and pharmaceutical use still developing.[8,9] Ionic liquids are the least scalable, held back by preparation cost and recovery even as their laboratory performance impresses.[9] Table 2 collects representative applications that illustrate where each class has actually delivered rather than merely promised.

Table 2. Representative reported outcomes of green-solvent extraction, grouped by solvent class. Values are as reported in the cited sources.

Solvent class	Target and matrix	Reported outcome	Ref.
Natural DES	Total phenolics, orange peel	Above 2100 mg gallic acid equivalent per 100 g dry weight	8
Natural DES	Anthocyanins, sour cherry	More than 60% higher recovery than conventional solvent	8
Deep eutectic solvent	Flavonoids and terpene esters, *Ginkgo biloba*	Extraction rate raised more than 100-fold	9
Deep eutectic solvent	Rutin solubility	50 to 100 times higher than in water	7
Ionic liquid	Alkaloids, medicinal plants	Recovered where neutral organic solvents fail; enhanced by microwave or ultrasound assistance	12
Supercritical CO_2	Essential oil, rose	Yield raised from about 0.03% to 0.2%, with a cleaner product	9
Supercritical CO_2 with ethanol	Minor bioactives, hemp seed oil	Ethanol co-solvent enhances recovery of polar compounds	14

On regulatory acceptability, the dimension that ultimately governs whether an extract can enter a medicine or a food, the three again diverge sharply, and this criterion tends to decide close cases. Supercritical carbon dioxide has the strongest position by a wide margin: its working fluid is recognised as safe for food use, it leaves no residue to declare or limit, and its extracts already appear in approved food, flavour and botanical products, so a manufacturer adopting it inherits a settled regulatory path.[14] Natural deep eutectic solvents built from food-grade metabolites have a plausible case for the same treatment, and where the loaded solvent is

consumed as part of the product the residual-solvent question largely dissolves, but the newer and more exotic formulations still lack the toxicological dossiers that regulators expect.[7] Ionic liquids are furthest from acceptance, precisely because their toxicity is compound-specific and often poorly characterised, and a residue of a poorly biodegradable, aquatically toxic ion in a consumed product is exactly the outcome the regulatory framework exists to prevent.[9] The order on this criterion, carbon dioxide ahead of natural deep eutectic solvents ahead of ionic liquids, mirrors the order on green credentials, which is not a coincidence but a reflection of the same underlying facts about what each medium leaves behind.

The honest synthesis is the one the comparative literature itself reaches: no single technology combines all the advantages without a corresponding limitation for a complex, multicomponent natural extract.[9] A reviewer looking for a universal green solvent will not find one among these three, and the search for one is arguably the wrong question. The right question is which solvent matches a given target's polarity, a given product's purity requirement, and a given process's scale and budget, and on that question the three classes give clear and largely non-overlapping answers.

6. Discussion and future directions

The strongest conclusion to draw from the comparison is that the three solvent classes are complementary, and that their most interesting near-term applications lie in combining them rather than choosing between them. A biomass stream rarely contains only one class of target. An aromatic medicinal plant may hold a valuable essential oil and an equally valuable polar phenolic fraction, and no single solvent recovers both well. A sequential process that first strips the lipophilic fraction with supercritical carbon dioxide and then treats the spent residue with a natural deep eutectic solvent for its phenolics extracts more total value from the same feedstock than either solvent alone, and does so without introducing a hazardous medium at any stage. Framing the three as rivals obscures this, and the biorefinery logic of fractionating a feedstock into several product streams with several matched green solvents is where the field's practical payoff is largest.

A second theme is intensification. None of these solvents performs at its best under simple stirring. Deep eutectic solvents need heat, dilution or ultrasound to overcome viscosity; ionic liquids gain markedly from microwave and ultrasound assistance; and supercritical extraction is itself an intensified, pressure-driven process. The productive unit of study is therefore the solvent-plus-technique pairing rather than the solvent in isolation, and reporting that does not specify the intensification conditions is of limited use for scale-up. The literature would be more decision-relevant if it consistently paired each solvent claim with the assisted-extraction protocol behind it.

The field's most serious weakness is evidential rather than chemical, and it applies unevenly across the three classes. Green claims are made

far more often than they are measured. A solvent is called green because its components are natural or its vapour pressure is low, but a defensible sustainability judgement requires life-cycle assessment that accounts for the energy of solvent synthesis, the water and heat added to manage viscosity, the antisolvent or adsorbent consumed in recovery, and the number of times the solvent can actually be reused before its performance degrades. Comparative life-cycle data of this kind remain scarce for all three classes and almost absent for head-to-head comparisons on the same feedstock. Until that gap closes, the green label is a hypothesis rather than a finding, and the honest reviewer should treat it as such. For ionic liquids specifically, the toxicity and biodegradability question remains not just unmeasured but actively unresolved, and the class will not earn broad regulatory acceptance in food and pharmaceutical manufacturing until benign, well-characterised ion combinations are shown to retain the selectivity that justifies their use.

Three concrete lines of work would move the field fastest. First, standardised, feedstock-matched comparisons in which the same plant material is extracted by all three solvent classes under separately optimised conditions and assessed by the same yield, purity, cost and life-cycle metrics, so that the partition argued here rests on controlled data rather than on studies that are difficult to compare. Second, systematic development and toxicological characterisation of hydrophobic natural deep eutectic solvents and of demonstrably biodegradable ionic liquids, the two developments most likely to extend the polar and the selective classes, respectively, toward the targets they currently miss. Third, pilot-scale demonstration of the tandem and biorefinery configurations described above, since the case for combining solvents is currently made on paper and needs process data to become an engineering reality. Each of these is specific, achievable with existing tools, and more valuable than another single-solvent, single-target optimisation study.

7. Conclusion

Deep eutectic solvents, ionic liquids and supercritical carbon dioxide are the three credible green replacements for the volatile organic solvents that still dominate natural product extraction, and each earns its place by a different mechanism. Deep eutectic solvents, led by their natural subclass, offer the best combination of green credentials and affinity for polar bioactives, at the cost of viscosity and difficult recovery. Ionic liquids provide selectivity and tunability that nothing else matches, but a contested toxicity record, high cost and awkward isolation confine them mostly to the laboratory. Supercritical carbon dioxide delivers solvent-free, food-grade nonpolar extracts at industrial scale, limited chiefly by capital cost and by a near-blindness to polar solutes that a co-solvent only partly relieves. The single most important message of the comparison is that these are not three answers to one question but matched answers to three different questions, sorted by target polarity, purity requirement and scale. The field advances not by crowning one solvent but

by pairing each with the targets and the techniques it suits, by combining them in sequence to fractionate a feedstock fully, and by replacing the green label with the life-cycle evidence that would finally earn it.

Declarations

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