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Applications of green solvents in extraction of phytochemicals from medicinal plants: A review

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Abstract

With increasing ecological and economical concerns, Green Chemistry has become more important for “greening” of various chemical processes. Green chemistry is providing various kinds of “green” solvents that can be employed for the extraction and isolation of various therapeutically important phytoconstituents from plants. As medicinal plants form backbone of traditional system of medicine in developing countries. Medicinal plants are source of natural antioxidants such as phenols, flavonoids, alkaloids, terpenoids, sterols etc. So replacement of conventional solvents by eco-friendly green solvents for phytoextraction can revolutionize the chemical and pharmaceutical industry. Present review article focuses on the importance of various green and alternative solvents viz. supercritical fluids, subcritical water and ethyl lactate in extraction of various phytoconstituents.

Keywords: Green solvents, green chemistry, phytoextraction, SCFs, subcritical water, ethyl lactate

Introduction

Medicinal plants are important source of chemicals that can act as potent agents for treatment and prevention of various ailments. The medicinal plants possess medicinal, flavouring and aromatic values. Today, medicinal plants are finding diverse use in the society from medicine to cosmetics, herbal drinks, herbal foods and other articles in the daily uses. India with its mega-biodiversity and knowledge of rich ancient traditional systems of medicine (Ayurveda, Siddha, Unani and local health traditions) provide a strong base for the utilization of a large number of plants in general healthcare and alleviation of common ailments of the people [1]. Medicinal plants have a vast potential for their usage on large scale for their curative medicinal uses as herbal food products. The World Health Organization reported that 80% of the world population relies chiefly on traditional medicines including the use of plant extracts or active isolated phytoconstituents. Medicinal plants are relatively cheaper and easily accessible to the local population. It helps in utilization of every virtue of medicinal plants especially when they have been tested and proven to be non toxic, safe, inexpensive and culturally acceptable to the community. Herbs of similar, supporting or enhancing nature are supposed to be added to the food products for intensifying the medicinal effects.

The beneficial medicinal effects of plant materials typically results from the combinations of secondary metabolites such as alkaloids, steroids, tannins, phenolic compounds, flavonoids, resins, fatty acids and gums [2, 3]. Plant-based traditional medicine system continues to play a vital role in the health care system. Modern knowledge on medicinal plant research still contains at least 25% drugs and many others, which are synthetic analogues, built on prototype compounds isolated from medicinal plants. The ongoing growing recognition of medicinal plants is due to escalating faith in herbal medicine. Various phytochemicals isolated from different plant parts, such as stem, bark, leaves, fruits and seeds have been part of phytomedicine that induces certain physiological action on human body. The most important of these natural bioactive constituents of plants are alkaloids, tannins, flavonoids and phenolic compounds. Medicinal plants also contain large amounts of antioxidants, such as polyphenols, vitamin C, vitamin E, selenium, β-carotene, lycopene, lutein and other carotenoids, which play important roles in adsorbing and neutralizing free radicals, quenching singlet and triplet oxygen, or decomposing peroxides.

Global economic and technological growth in the 20th century, forced scientists and researchers of various arena to realize that further development of human civilization and the fulfillment of socio-economic needs of the present generation will be only possible if the natural resources are properly managed and the relationship between economic growth and caring for the environment of the present and future generations is consciously maintained.

The global chemical industry plays a fundamental role in important scientific and technological fields associated with the future of sustainable development in developed and developing countries. From the beginning, the leaders of the major chemical industries participated in the debate on the actions and changes needed to achieve goals of Sustainable Development and identified their share of responsibility towards these goals. Researchers in chemistry fields are paying attention to cope up sustainability challenges in order to minimize potential environmental and health implications of various chemicals used by them during laboratory work. The American Chemical Society (ACS) in the 1990s promoted sustainability, green chemistry, and green engineering, combined with incentives for the adoption of sustainable technologies and new regulatory strategies.[4], [5] In the last decade Green Chemistry has advanced for a great variety of research providing cutting-edge research and practical applications for a wide spectrum of chemical products. The most important research and technological fields of Green Chemistry include solutions. Among other things, reduction of global warming and use of CO_2 as a raw material for chemical synthesis, microwave, electrochemical and ultrasound synthetic methods, solvent free reactions (or water as a solvent), phytoremediation, waste management and wastewater, eco-friendly dyes and pigments, innovative food products, catalysis and biocatalysis, biopolymer technology, renewable materials, renewable energy sources, etc.

From the beginning Paul Anastas and John Warner emphasized the new principles of Green Chemistry and the new ―philosophy that has to be followed to achieve the sustainable eco-development of the chemical industry in the future. The following list of 12 principles outlines an early conception of what would make a greener chemical, process, or product [6, 7, [8].

1. **Prevention:** It is better to prevent waste than to treat or clean up waste after it has been created.
2. **Atom Economy:** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. **Less Hazardous Chemicals:** Syntheses wherever practicable, should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals:** Various chemicals that are employed during chemical processes must be highly efficient in performing desired function while minimizing their toxicity.
5. **Safer Solvents and auxiliaries substances**: Solvents, separation agents, etc must be safe for workers and the environment.
6. **Design for Energy Efficiency**. Energy requirements of chemical processes should be recognized for their environmental and economic points of view and should be minimized.

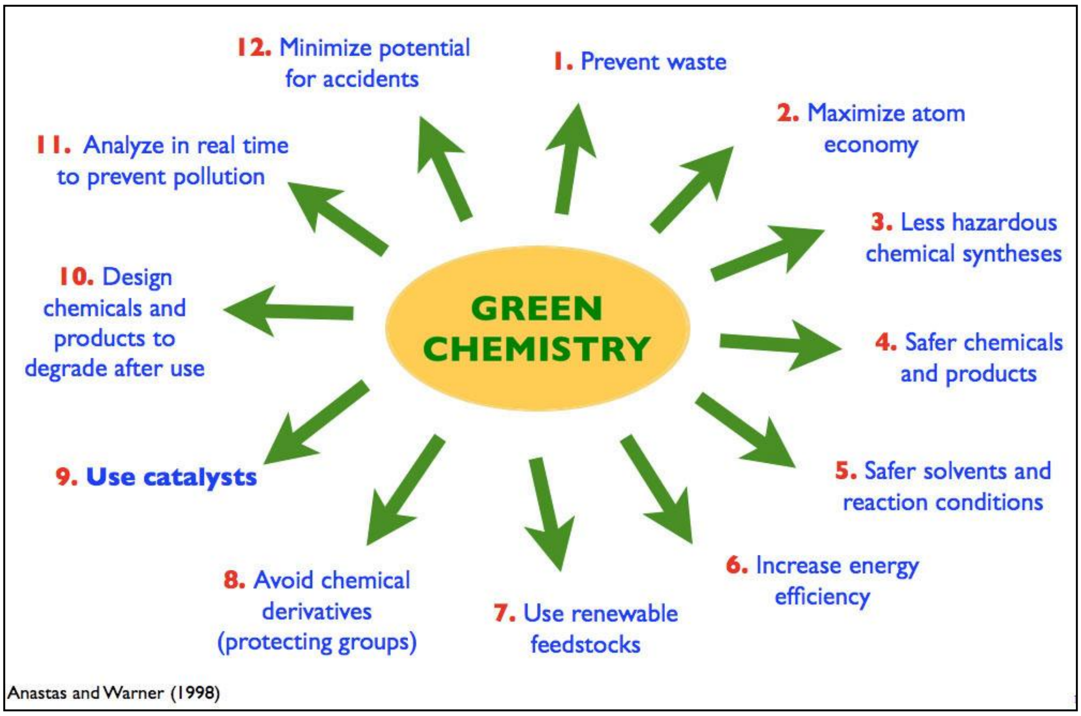

Fig 1: Twelve principles of Green Chemistry

7. **Use of Renewable Feedstocks**. Raw materials or feedstock should be renewable rather than depleting.
8. **Reduce Derivatives**. Unnecessary derivatization (blocking groups, protection/deprotection, temporary modification, etc) should be minimized or avoided if possible.
9. **Catalysis and new catalytic reagents** (enzymes, as selective as possible) are superior to stoichiometric reagents.
10. **Design Products for Degradation**: Chemical products should be designed so that at the end of chemical function they perform, they break down into biodegradable degradation products and do not persist in the environment.
11. **Real-time analysis for Pollution Prevention**: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention:** Substances and chemical process should be chosen to minimize the potential for chemical accidents.

Role of “green” solvents in extraction of phytochemicals from medicinally important plants:

Supercritical fluids as “green” solvents for extraction of phytoconstituents:

Supercritical fluid extraction (SFE) has been applied extensively by food and medical industries in recent years, since it is an environment-friendly technology that represents an alternative to conventional extraction methods and offers several advantages over conventional solvent extraction (CSE) methods [9]. The advantages of supercritical fluid extractions are:

1. Supercritical fluids have a higher diffusion coefficient and lower viscosity than liquids [10].
2. Absence of surface tension allows for their rapid penetration into the pores of heterogeneous matrices, which helps enhance extraction efficiencies [11, 12].
3. Selectivity during extraction may be manipulated by varying the conditions of temperature and pressure affecting the solubility of the various components in the supercritical fluid [12].
4. Supercritical fluid extraction does not leave a chemical residue [13].
5. Supercritical fluid extractions can use carbon dioxide gas, which can be recycled and used again as part of the unit operation.

Supercritical carbon dioxide ($scCO_2$) is the most commonly used solvent in supercritical fluid extraction. $scCO_2$ solvent has highly desirable properties such as non-toxicity, non-flammability, non-explosiveness, low cost, readily availability and ease of removal from the extracted materials [14]. Moreover, CO_2 has a low critical temperature (T_c = 31.1 °C) and technically convenient critical pressure (P_c = 73.8 bar), which would prevent degradation of thermally labile and reactive components during extraction. [15]

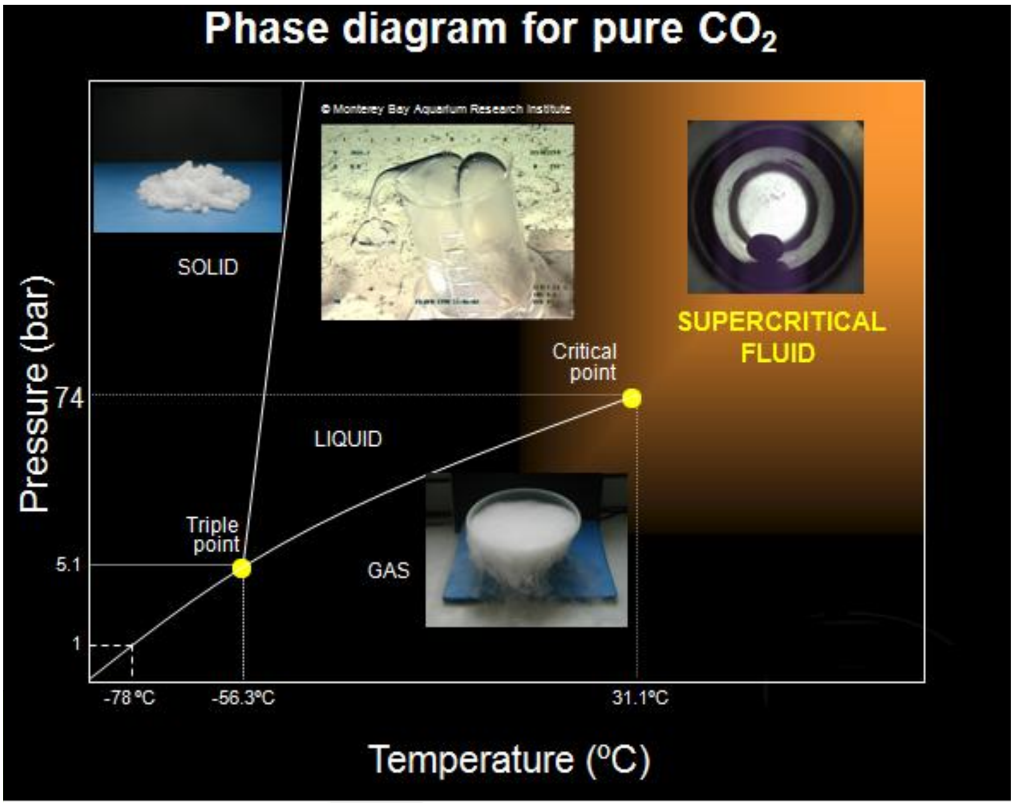

Fig 2: Phase diagram of pure carbon dioxide

In recent years much research has been done on the application of SCF in the food, pharmaceutical and environmental field. The supercritical fluid extraction (SFE) has received special attention in the fields of solid material extraction and fractionation of liquid mixtures. Supercritical fluid extraction using carbon dioxide ($scCO_2$) is a particularly suitable isolation method for isolation of the valuable components from plant materials. A natural plant extract, free from chemical alterations brought about by heat and water, and without solvent residues and other artifacts can be obtained by this method. Moreover, conventional methods are usually carried out at high temperatures, which can be responsible for the destruction of valuable substances. Additionally, the use of organic solvents can also lead to product contamination with solvent residues. SFE method is very advantageous and environmentally friendly over other conventional either solvent or enzyme extraction methods for recovering the natural oil or carotenoid. Extraction with supercritical fluids is also a unit operation that could be employed for a variety of applications including the extraction and fractionation of edible fats and oils, purification of solid matrices, separation of tocopherols and other antioxidants, clean-up of herb medicines and food products from pesticides [16, 17, 18, 19]. Supercritical fluid extraction has proved effective in the separation of essential oils and its derivatives for use in the food, cosmetics, pharmaceutical and other related industries, producing high-quality essential oils with commercially more satisfactory compositions (lower monoterpenes) than obtained with conventional hydro-distillation [20, 21, 22].

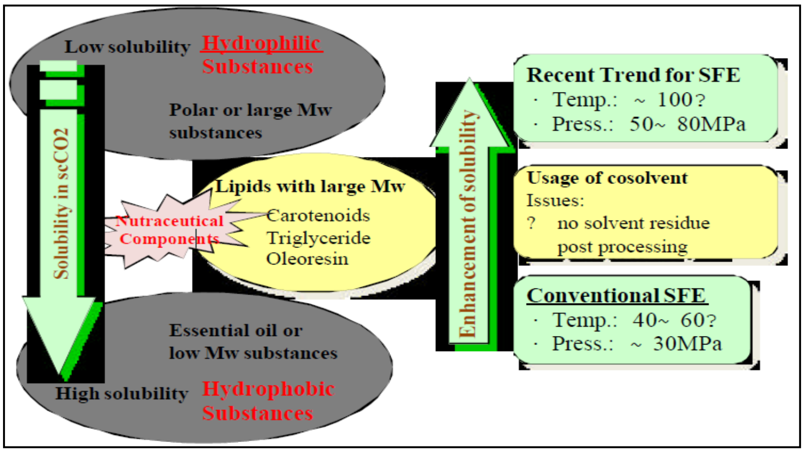

Fig 4: Supercritical fluid extraction [21]

Alkaloids are organic compounds present in many plants. They have bitter taste and toxic effects on animals and humans, but present therapeutic effects when applied in moderate doses. Alkaloids such as caffeine, morphine, emetine, pilocarpine, among others, are the active components in a variety of stimulants and medicinal products and their recovery from natural plants is of great interest to the food, pharmaceutical, and cosmetic industries. Supercritical Carbon dioxide proved to be highly selective for caffeine prompting its use as the selected solvent in the commercial decaffeination of coffee and black tea. Recent investigations have demonstrated the potential exploration of solvent and anti-solvent properties of carbon dioxide in the recovery of alkaloids such as theophylline, theobromine and pilocarpine, among others [23, 24].

Juice of *Citrus junos*, is often preferred to vinegar. After juice processing (cold pressing), a large amount of fruit pulp (mainly composed of peel) is considered waste and incurs a cost for disposal. The nonpolar components of *Citrus junos*, such as terpenoids and carotenoids, are preferentially removed by CO2 followed by extraction with a CO2-cosolvent combination that can remove the more polar components, such as flavonoids or coumarines. In this stage, the hybrid SFE system is useful for the separation of flavonoids. The separation can be controlled by adjusting the CO2 and water in the extraction field; therefore, the hybrid process can extract hydrophilic and hydrophobic components at the same operation stage. The hybrid SFE process is useful for the separation of hydrophilic flavonoids (hesperidin) and hydrophobic flavonoids (tangeretine, nobiretine) from waste citrus residue. After removal of the flavonoid components, subcritical water can be applied to isolate saccharides, followed by other compounds [21].

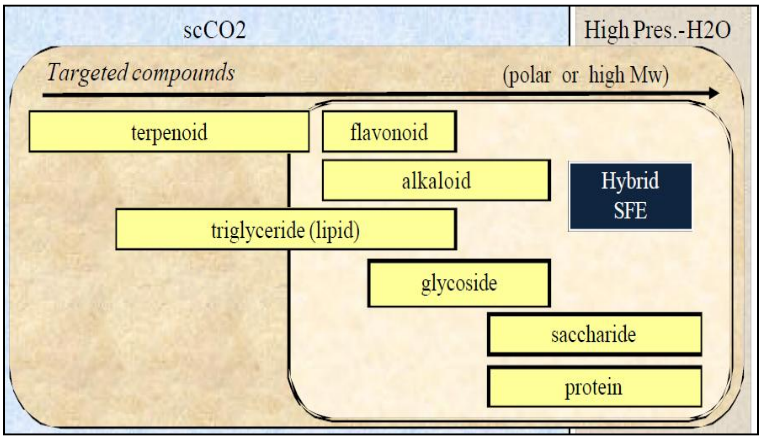

Fig 3: Green solvent processing of various phytochemicals [21]

Domadia & Vaghela reported extraction of lycopene from tomato skin in $scCO_2$ by optimizing pressure, temperature & solvent flow rate [25]. Lycopene is one of the best biological suppressants of free radicals, especially those derived from oxygen. It has the highest singlet oxygen-quenching rate of all carotenoids in biological systems [25]. Lycopene is an acyclic, open chain, unsaturated carotenoid having 13 double bonds, of which 11 are conjugated, arranged in a linear array, and has a molecular formula of $C_{40}H_{56}$ with molecular weight of 537. Lycopene present in red tomato fruits typically contains 94-96% of all-*trans*-lycopene. However, It may undergo *trans*-to-*cis* isomerization during tomato processing. It is unstable when exposed to light, heat, and oxygen. Exposure to light and heat starts isomerization from the *trans* to *cis* configurations. The *cis*-isomers of lycopene have different physical and chemical characteristics than all-*trans*-lycopene. Some of these differences include lower melting points, lower specific absorption, and a shift in the absorption maximum. Lycopene can also undergo oxidation. When exposed to oxygen with the formation of many different oxidation products. To prevent isomerization and oxidation, lycopene is kept under inert gas in lightproof containers and stored in a cool place.

Pyrrolizidine alkaloids (anti-cancer agent) were extracted from seeds of Crotalaria spectabilis by using $scCO_2$ [26]. Traditional methods for its extraction employed toxic solvents and it was difficult to isolate it from the plant material without degradation. Extraction of chemotherapeutic agents from the plant materials like maytansine and rollinia papillionela with $scCO_2$ also has been mentioned [15].

Recently use of $scCO_2$ as an alternative of hexane in soybean-oil extraction is being considered. Data on the extraction and oil composition of soybean oil have been described by Friedrich *et al*., 1984. He showed that the separation of oil from CO2-oil stream at 800 bar can be carried out by dropping the pressure by only 150 or 200 bar at 70 °C [27].

The extraction of essential oil components using solvent at high pressure, or supercritical fluids (SCF), has received much attention in the past several years, especially in food, pharmaceutical and cosmetic industries, because it presents an alternative for conventional processes such as organic solvent extraction and steam distillation. Supercritical fluid extraction allows a continuous modification of dissolution power and selectivity by changing the solvent density. It has the density of a liquid and solubilizes solids like a liquid solvent, but has a diffusion power similar to a gas and permeates through solid materials very easily. The power of solubilization increases with the density of the fluid; high densities of a supercritical fluid are possible at high pressures and allow it to dissolve large quantities of organic compounds. The dissolved compounds can be recovered from the fluid by reduction of its density, by means of decreasing the pressure or increasing the temperature. This low temperature separation process prevents the degradation of the chemical compounds of the extract due to heat, as in steam distillation [28].

A novel methods employing $scCO_2$ for concentration of aromatic constituents in lemon oil was described by Robey *et al*. [29] Product degradation and requirement of subsequent removal of solvent are the main drawbacks of conventional methods based on either steam distillation or liquid-liquid extraction. It is reported that a tenfold concentration of aromatics can be achieved in a single extraction stage with a superior result concerning the flavour compared to the conventional method. SFE appears to be a cost-effective technique in laboratory scale, but an accurate economic evaluation for large-scale units requires supplementary experiments. The advantages of SFE-CO_2 extraction over the petrol ether extraction include: low operating temperature, hence no thermal degradation of most of the labile compounds; shorter extraction period; high selectivity in the extraction of compounds; no solvent residue with negative effects on the oils quality. The essential oils of plants have usually been isolated by either hydrodistillation or solvent extraction. The disadvantages of all these techniques are: low yield, loss of volatile compounds, long extraction time, toxic solvent residues and degradation of unsaturated compounds, giving undesirable off-flavour compounds, due to heat.

Supercritical carbon dioxide ($scCO_2$) extraction of flavonoids from pomelo (*Citrus grandis* (L.) Osbeck) peel and their antioxidant activity were investigated by He *et al*. (2012). The optimal conditions for obtaining the highest extraction yield of flavonoids from pomelo peel were a temperature of 80 °C, a pressure of 39 MPa and a static extraction time of 49 min in the presence of 85% ethanol as modifier. Under these conditions, the experimental yield was 2.37%, which matched positively with the value predicted by the model. Furthermore, flavonoids obtained by $scCO_2$ extraction showed a higher scavenging activity on hydroxyl, 1, 1-diphenyl-2-picrylhydrazyl (DPPH) and 2, 2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radicals than those obtained by conventional solvent extraction (CSE). Therefore, $scCO_2$ extraction can be considered as a suitable technique for the obtainment of flavonoids from pomelo peel [30].

Subcritical water as "green" solvent for phytoextraction

The conventional methods used for extraction of phenolic compounds are soxhlet and maceration. During soxhlet, fresh solvent can repeatedly bring to contact with sample many times and the plant material is exposed to high temperature. Maceration is very sample method that is just soaking materials in solvent for long time extraction. These techniques use organic solvent (such as methanol, ethanol, ethyl acetate, ether, acetronitrile) for extraction. Low extraction efficiency and toxic solvent residues in the extracts occurs when using these technologies. Recently, Subcritical water extraction (SCW) has become an increasing alternative technology in the extraction of phenolic compounds. Subcritical water, also called pressurized (hot water), superheated water or hot liquid water, it refers to water at temperature between 100 and 374°C and at a pressure which is high enough to maintain the liquid state (below the critical pressure of 22 MPa). The most important advantages of SCW over traditional extraction techniques are shorter extraction time, lower cost of the extracting solvent, higher quality of the extraction and environment-friendly [31].

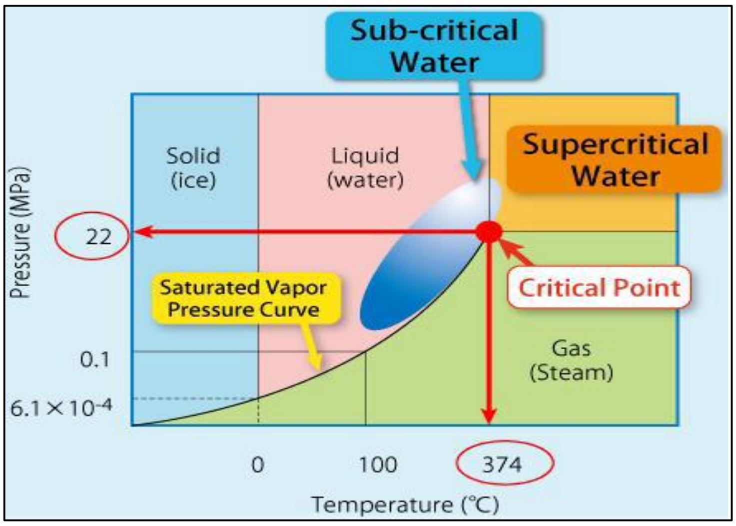

Fig 2: Phase diagram of pure water

SCW was used to extraction of polyphenolic compounds from Terminalia chebula Retz. fruits that found the amounts of extracted gallic acid (GA) and ellagic acid (EA) increased with an increasing in subcritical water temperature up to 180 °C, while the highest amount of corilagin (CG) was recovered at 120 °C. Moreover, water volumetric flow rate affected the extraction behavior and concluded the suitable flow rate for extraction of total phenolic compounds was 4 ml/min [32].

Mango peels, wastes generated from fruit can processing, are a good source of functional ingredients such as phenolic compounds that has potential antioxidant properties. This study investigated the extraction of phenolic compounds from mango peels using subcritical water extraction (SCW). Experiments were performed in a batch laboratory-built equipment (50 ml volume of vessel) immersed in oil bath and temperatures ranging from 160 to 220 °C, extraction time of 30 to 120 min., material particle sizes of 30 to 70 mesh, solid to water ratio of 1:10 to 1:50 and pH of solution 2 to 8. The highest phenolic content was obtained 50.25 mg GAE / g DW at the condition as follows: 180 °C, 90 min, solid to water ratio as 1:40 and pH 4. The amount of phenolic compounds from mango peels using SCW extraction was higher than that using soxhlet extraction at extraction time 60 min as 1.5 times [33]. SCW extraction might be an alternative green technology for phenolic compounds extraction from agricultural wastes which substitute conventional method using organic solvents. There are many important and useful applications of SFE such as the extraction of active ingredients, including various flavors and medicinal constituents from plants and animals advanced unsaturated fatty acids and fatty esters, fat-soluble vitamins etc. Other applications include the removal of unnecessary constituents, such as decaffeination and desolvation in pharmaceutical tablets [34, 35].

Application of Ethyl lactate in extraction of phytochemicals

Ethyl lactate is an agrochemical solvent being used in food, pharmaceutical and cosmetic industries. Recently, it is being widely investigated to replace the solvents employed in various synthetic processes, with the intention of making the whole process more environmentally benign. Ethyl lactate is a novel, sustainable and environmental-friendly solvent as compared to other solvents produced from petroleum industry which are toxic for human consumption. Comparably, ethyl lactate has high flash point, non-toxic, nonflammable, non-corrosive, non-carcinogenic, nonozone depleting, low volatility, low viscosity and it is completely biodegradable into CO2 and water. Studies show that ethyl lactate has a very low human and animal toxicity at wide range of concentration exposures [36]. The US Food and Drug Administration has approved the use of ethyl lactate in food and pharmaceutical products. Ethyl lactate exerts polarity in the range of acetronitrile. It is capable to form intra- and intermolecular hydrogen bonding, either as a proton donor or acceptor [37]. On top of that, it has the ability to form Van der Waals interactions in oils [38] As a result, ethyl lactate can dissolve in both aqueous and hydrocarbon solvents and it is capable to extract compounds of a wide range of polarity [39]. In pharmaceutical industry, ethyl lactate is applied to disperse biologically active compounds without destroying their pharmacological activity. Therefore, the stability of heat- and lightsensitive compounds, such as carotenoids and vitamin E in ethyl lactate should be better than in other relatively strong organic solvents. The price of ethyl lactate is becoming lower because the production itself is sustainable instead of depending on the fluctuating and increasing price of crude oil, which is non-renewable. Advancement in ethanol and lactic acid production are continuously developed to further reduce the production cost of ethyl lactate. These include the production of ethanol from cellulosic biomass and the production of lactic acid from grass juice [40, 41]. Ishida and Chapman (2009) have investigated the extraction of lycopene from dried tomato powder, lutein from corn powder and β-carotene from carrots powder using ethyl lactate. The optimal temperature and time to extract β-carotene into ethyl lactate were found to be at 30 ^{0}C and 30 min. β-carotene was suspected to degrade at 60 ^{0}C after half an hour of extraction. The use of ethanol as co-solvent was investigated as well and it was found that the concentration of ethanol was proportional to the amount of carotene extracted. Additionally, the presence of ethanol promoted isomerisation of transto cis-lycopene, leading to different extraction behaviours [42].

Strati and Oreopoulou (2011) found that ethyl lactate, other than being an environmental-friendly solvent, is the most efficient solvent to extract carotenoids (lycopene) from tomato waste at 70 ^{0}C, as compared to acetone, ethyl acetate, hexane and ethanol. Even at ambient temperature, ethyl lactate was able to extract more lycopene than other solvents at higher temperature. 30 min was found to be adequate to extract lycopene from tomato waste. Prolonged extraction was undesirable due to isomerisation and oxidation of carotenoids at high operating temperature [39]. In 2011, Villanueva *et al*. reported the use of ethyl lactate to remove up to 90% of caffeine from green coffee beans at 150 ^{0}C [43]. Ethyl lactate, limonene and ethanol were used by Bermejo *et al.* in 2013 as green solvents to extract thymol from thyme plants. After 10 min of pressurized liquid extraction, the yield achieved 83% of the yield at 20 min. Thus, 10 min was adequate to recover the thymol. With increasing temperature, thymol concentration decreased with slight improved of recovery. It might be happen due to simultaneous extraction of other competitive solutes. The concentration of thymol extracted was highest in limonene followed by ethyl lactate and ethanol. The efficiency was reported higher than conventional Soxhlet extraction and steam distillation. The recovery of thymol using pressurized liquid extraction was comparable to supercritical fluid extraction, which is vastly studied in recent years. It is also comparable to pressurized liquid extraction using organic solvents derived from petrochemical industry [44].

Conclusion

Efficient extraction of various kinds of phytochemicals by “green” solvents provide an eco-viable alternative of the conventional solvents. These green solvents even can improve the efficiency of the extraction. Heat-labile phytochemicals can be extracted without degradation. Less or non-toxicity of these solvents make chemical processes economically as well as ecologically sustainable.

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