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Extraction of phenolic compounds; A review of subcritical water method

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Abstract

In recent years, with the increase in awareness of the benefits of consuming compounds with antioxidant properties and the desire of producers and consumers to natural products, a lot of research has been done to find resources rich in natural antioxidants. Many of the antioxidant and antimicrobial properties of plant extracts are due to the presence of substances such as phenol and flavonoids and similar compounds. Natural antioxidants are found in almost all plants, microorganisms, fungi, and even animal tissues. The main group of natural antioxidants are phenolic compounds, the most important of which are tocopherols, flavonoids, and phenolic acids. Extraction is the first major step in various researches and applications. Solvent extraction technique is one of the most common extraction methods. This method was often cost-effective, time-consuming, with high solvent consumption with low extraction coefficient and adverse and harmful effects on the extracted compounds and products. For this reason, the use of various methods to accelerate and facilitate the extraction of phenolic compounds has received much attention. One of the new methods of extraction, known as green technology, is extraction by subcritical water; Which is very effective in extracting effective compounds. In this method, with increasing temperature and pressure, the physicochemical properties of water change and water becomes a fluid with a wide range of extraction of compounds with different polarities.

Keywords: Extraction, Phenolic compounds, Subcritical water

Introduction

The term natural antioxidants refers to compounds that are naturally present in animal or plant tissues. Foods are also formed during cooking or processing and can be extracted. Natural antioxidants are found in almost all plants, microorganisms, fungi and even animal tissues. The main group of natural antioxidants are phenolic compounds, the most important of which are tocopherols, flavonoids and phenolic acids. The main natural antioxidants in food are phenolic and polyphenolic compounds of plant origin, which are classified as free radical scavenging compounds and are abundant in many fruits and vegetables. The mechanism by which the antioxidant effects of these compounds occur varies depending on the compositional characteristics of the food. The overall effect of natural antioxidants depends on the binding and involvement of phenolic hydrogen, the radical antioxidant stability created during radical reactions, and the chemical degradation present in the structure. Decreases in structure are probably the most important factor in the ability of an antioxidant to participate in radical reactions and the formation of stable resonance (Mahiyan et al, 2015).The health benefits of eating plant foods are attributed in part to the presence of phenolics, which are at risk for cardiovascular disease, cancer, cataracts and degencrative diseases.

These effects are achieved by preventing the oxidation of fats, cross-linking of proteins, DNA mutations and tissue damage. Although phenolic compounds and some of their derivatives are very effective in preventing autooxidation, only some of them are allowed to be used as antioxidants in food, and food manufacturers use authorized antioxidants, which are mainly phenolic in nature, to prevent product degradation and protect their nutritional value.Phenols are one of the most important natural antioxidants and protect processed foods from oxidation (Antolovich et al, 2004). Polyphenols play an important role in protecting the body against disease. For example, in protecting body tissue against the stresses of cancers such as prostate, breast, skin and colon cancer, Oxidative LDL is effective in preventing oxidation. Phenolic antioxidants fall into the category of antioxidants that neutralize free radicals. These compounds slow down or inhibit the onset of chain reactions by reviving free radicals (alkyl), thus affecting the initial stage of autooxidation. Phenolic compounds may also inhibit the release stage of autooxidation by reacting with alkoxy or proxy radicals. For this reason, they are also called primary antioxidants or chainsaws or radical scavengers. These compounds usually provide a single electron to the free radical electron and regenerate it. Polyphenol compounds are very active in this regard (Mohamed et al, 2007). The mechanism of action of phenolic antioxidants (AH) is as follows:

$$AH + LOO^{\circ} \rightarrow A^{\circ} + LOOH \quad (1)$$

$$AH + LO^{\circ} \rightarrow A^{\circ} + LOH \quad (2)$$

$$A^{\circ} + LOO^{\circ} \rightarrow LOOA \quad (3)$$

$$A^{\circ} + LO^{\circ} \rightarrow LOA \quad (4)$$

$$A^{\circ} + L^{\circ} \rightarrow LA \quad (5)$$

The presence of ethyl group or n-butyl instead of methyl in para-situations increases antioxidant activity. While the entry of alkyl groups, especially branching groups, such as the third type of butyl radicals in the same position, reduces antioxidant activity. This delays the destruction of antioxidants under conditions of high temperatures and other conditions that are used in the preparation of cooked and fried foods. These compounds are referred to as Carry-Through or Carry-Over Antioxidants. In most cases, phenolic antioxidants at high concentrations lose their activity and act as peroxides due to the involvement of the initial stage reactions (Lee and Shibamoto, 2002).

$$AH + O_2 \rightarrow A^{\circ} + HOO^{\circ} \quad (6)$$

$$AH + LOOH \rightarrow LO^{\circ} + A^{\circ} + H_2O \quad (7)$$

Herbal antioxidants

Plants are rich sources of natural antioxidants. Herbal antioxidant compounds are generally phenolic in nature and include compounds such as tocopherols, carotenoids, phenolic acids (derivatives of benzoic acid and cinamic acid), flavonoids and di-terpenes. Oxidized plant phenolic compounds combine with proteins and other components to protect plants from tissue damage. In addition, these compounds in plants may act as defense systems against herbivores. Photosynthetic by-products may also produce high levels of oxygen, free radicals, and reactive oxygen species. In this way, plants use thousands of antioxidant compounds to survive (Korukluoglu et al, 2008).

Tocopherols

Tocopherols, the most widely used natural antioxidants in plant sources, are divided into tocopherols and tocotrienols. In each of these two groups, there are four isomers (δ, γ, β, α) with different antioxidant power (increasing the antioxidant power from alpha tocopherol to delta tocopherol). Tocopherols act as antioxidants through two primary mechanisms:

A) Mechanism of A Chain Breaking Electron Donor (CB-D)

B) Mechanism of A Chain breaking Acceptor (CB-A)

In the (CB-D) mechanism, antioxidants compete with unsaturated fatty acids (RH) for radical peroxisomal fats, thereby reducing the production of radical fat (R˚) that results from the reaction of RH to ROO˚. The second mechanism (CB-A) involves the corrosion or extinction of a single oxygen. This reaction eventually slows down the process of proliferation or oxidation of fats by itself. Tocopherols can compete effectively with RH for ROO˚ and form a stable ROOH compound by transferring a hydrogen atom to ROO˚ (Lourenço et al, 2019).

Carotenes

Carotenes, especially beta-carotene, such as tocopherols, are effective single oxygen extinguishers. Unique oxygen shutdown by beta-carotene is caused by the transfer of energy from a single oxygen to a beta-carotene. The amount of blackout depends on the number of double conjugate bonds, so that the presence of 9 or more double bonds in the building greatly increases the ability to turn off oxygen. Cartonoids with 7 or more double bonds are not effective in disabling the unpaired electrons of a single oxygen due to the inability of the conjugate chain (Fiedor and Burda, 2014).

$$1O_2 + \beta - car \rightarrow 3O_2 + 3\beta - car \quad (8)$$

Terpenoids

Terpenoids include mono-, sesqui-, di- and tri-terpenes non-volatile and sterol and carotenoid pigments. Antioxidant oil essential oils belong to the category of mono- and sesqui terpenes. And the natural antioxidants found in sage and rosemary, which include carnosic acid, carnosol, rosmanol, epirosmanol, and isorosmanol, are among the di-terpenes (McGarvey and Croteau, 1995).

Flavonoids

Flavonoids are a large group of plant phenolic compounds. They are characterized by a C6-C3-C6 carbon skeleton consisting of two aromatic rings. Aromatic rings are connected by a 3-carbon aliphatic carbon chain, usually in the form of furanose and pyranose. Types of flavonoids, including flavones, flavonols, isoflavones, and chalcones, are found in all higher classes of plant species. Flavones and flavonols are found in almost all plants, especially leaves and petals. Flavonols are more common than flavones. About 90% of flavonoids in plants are glycosides. Due to the fact that flavonoids may be in two forms of glycosides (with glucose side chains) or aglycone (without glucose side chains), they act as antioxidants by trapping superoxide anions, proximal and hydroxyl radicals, or other mechanisms such as switching off single oxygen, chelating metal ions, and inhibiting the enzyme lipoxygenase. Flavonoids are compounds with hydroxyl at the para-position in the β ring, and the double bond between the 2 and 3 positions of the C-ring is responsible for antioxidant activity. Aglycons are also more potent antioxidants than glycosides, possibly due to the lack of a hydroxyl substitution at position 3 in the C-ring (Tungmunnithum et al, 2018).

Phenolic acids

Phenolic acids have antioxidant activity. Erto-diphenols such as caffeic, hydroxytyrosol and oleuropein have more antioxidant activity than phenolic acids such as turosol. In addition, phenolic acids, which are derivatives of hydroxynamic acid (caffeic acid, ferulic acid, ciuapic acid), are more active than derivatives of hydroxydeuzoic acid (P-hydroxydeuzoic acid, vanillic acid, and 3,4-Dihydroxybenzoic acid). The antioxidant activity of hydroxyaromatic acids (phenolic acids) and their associated esters and caltons have been evaluated in relation to their structure. It has been shown that high antioxidant activity is associated with at least two adjacent hydroxyphenol groups in the molecule, and the presence of three hydroxyphenol groups is more desirable. In

addition, a carbonyl group, such as an aromatic acid, an ester, or a lactone, increases activity. The carbonyl group, separated from the aromatic ring, also enhances antioxidant activity. Cinnamic acids are more effective than benzoic acids and have the greatest effect on phenylacetic acid and phelyl propionic acid (Kiokias et al., 2020).

Antioxidants with a microbial source

Microorganisms are one of the first phenomena discovered on Earth, which are sometimes added to increase the quality of food. The antioxidant activity of ethyl acetate extracts of different species of Aspergillus, Penicillum, Rhizopus and Oryzae has been measured by thiocyanate method. Gallic acid is a phenolic compound with antioxidant power and can be obtained from microbial sources such as Aspergillus and Penicillum. Bacillus, Streptomyces, and Xanthophyllomyces are other microbial sources of antioxidant power (Stolarzewicz et al, 2013).There are several ways to extract phenolic compounds. Sample preparation steps are the same as for other materials, for example, reducing the particle size plays an important role in increasing the extraction speed. The type of phenolic compounds to be extracted, as well as the purpose of the experiment (quantitative or qualitative), determine how the extraction is performed. Soluble phenolic compounds are generally extracted using water, ethanol, methanol and acetone. The presence of some sugars in polyphenolic compounds increases their solubility in water, and therefore a mixture of the above organic solvents and water gives better results for glycosides (Tanase et al, 2019). In contrast, less polar agglutinins, such as isoflavones, flavonoids, and highly methylated flavonols, are more soluble in non-aqueous solvents. Methanol is the best solvent for the extraction of flavonoids, flavonoids, flavonoid glycosides, methoxyflavones and diflavones. The problem that can be observed is the presence of turbidity after centrifugation in the last stage, which can be solved by adding a little water to the solvent system (Iloki-Assanga et al, 2015).

A variety of extraction methods

Extraction with solvent

In the past, solvent extraction was the most common method of extraction. This method consumes a lot of solvents and requires an additional step to recover the solvent and concentrate the extract, and the method is time consuming. In addition, the solvents used are toxic. The mechanism of action in this method is the diffusion of polyphenolic compounds from the solid to the solvent phase. Two steps can be observed during solvent extraction. In the initial stage, we see the swelling of the particles of the extracted material. At this stage, the solid absorbs the solvent due to the osmotic pressure, the strength of the capillary tubes and the solubility of the ions. Also, at this stage, some of the compounds that have been released due to tissue damage during the manufacturing process are extracted directly. It is at this point that the dissolution of the compounds in the solvent takes place. In the next step, the compounds must first be released in the solid phase and then released into the liquid surrounding the solid (Zhang et al, 2018).

Factors affecting the solvent extraction process

The most important solvent for the extraction of polyphenolic compounds, methanol and water mixtures is methanol. Other solvents such as acetone, ethyl acetate and their solutions are also used, but these solvents usually reduce efficiency. The pH also determines the solubility of the various components. Increasing the temperature increases the extraction speed. The effect of temperature is to increase the permeability of the cell membrane, increase the solubility and diffusion coefficient and reduce the solubility of the solvent. At the same time, temperature has a detrimental effect on phenolic compounds, so it is not recommended to use temperatures above $25^{\circ C}$ when faced with decomposition. By increasing the extraction steps, efficiency

increases effectively. For example, if we extract a sample 4 times with 50 cc of methanol, it is much better than extracting the same sample once with 200 cc of methanol. Particle size dramatically affects extraction speed. The smaller the particle size, the better the extraction. It is recommended to use dry, frozen or lyophilized samples for extraction, because polyphenolic compounds are very sensitive to enzymatic activity. Its use is not recommended for drying samples, as it reduces the extraction capacity of some polyphenols. In this case, the compounds bind to the fibers and proteins of the plant. In addition, heat dissipation is possible. In contrast, freez drying has no effect on the polyphenolic composition. Freezing the sample before extraction, by destroying the cell wall, greatly aids the process (Boeing et al, 2014).

Microwave assisted extraction

This new method uses a combination of microwaves and conventional extraction. The mechanism of action in this method is that the waves absorbed by the sample produce heat. This heat causes the sample water to evaporate, resulting in a lot of pressure on the cell wall of the sample by water vapor and the breakdown of this wall (Jalali et al, 2019). In this way, the active compounds are easily removed from the sample. Various studies have shown that this method requires less solvent and less time, and its extraction efficiency and accuracy are higher. In this method, a suitable ratio of the desired solvent with the crushed sample is mixed. The specimen is exposed to microwaves for 4 to 12 minutes. Radiation cannot be carried out steadily because it will increase the temperature. So the sample cools with air or water after 45 to 60 seconds of irradiation (Lujan et al, 2006).

Dynamic ultrasound assisted extraction

Another method of new extraction is extraction with ultrasonic waves. Sound waves create cavitation, thereby accelerating the penetration and transmission of the desired compounds between the aqueous or solvent environment of the extractor and the solid background. On the other hand, these waves cause the decomposition of the extractive solvent and the production of oxidative energy. Therefore, with the help of these waves, better and more complete extraction is done (Vardanega et al, 2014; Jalali et al, 2019).

Solid phase extraction

This method is a simple, fast and economical alternative to liquid-solid extraction. Because it significantly reduces the consumption of organic solvents. This method is used by separating the compounds from a liquid matrix, alone or as a liquid extraction supplement. Solid phase extraction can also be used as a component for purification or purification, or it can be used for primary condensation. In this method, the liquid stream containing the desired compound is passed through a solid substrate that absorbs the substance (Berrueta et al, 1995).

Supercritical fluid extraction

This method was developed in the 1960s. Today, this method has found a special value and position for the extraction of polyphenolic compounds. The most important feature of supercritical fluid extraction is the combination of the properties of liquids and gases in the extraction of compounds. The low viscosity of the supercritical fluid increases the diffusion capacity of the material in the fluid. In addition, the supercritical fluid extraction method minimizes chemical damage and reactions, such as oxidation and isomerization, because its time is very short and it is done in the absence of light and oxygen. Critical pressure is pressure that is applied at the right temperature. In supercritical conditions, fluid is neither liquid nor real gas, but some of its properties are like gases and some are like liquids. Its penetration coefficient is closer to liquids such as gases and its density. Critical CO2 has a special place due to its advantages such as neutrality, low toxicity and non-contamination. The mechanism of

action for extraction in this method is that first the raw material is completely crushed and poured into the relevant cartridge. At the same time, the modifier is added. Depending on the compound polarity to be extracted, methanol, ethanol or aqueous-alcoholic or ethyl acetate solutions can be used as modifiers. Highly polar polyphenols usually require higher densities and higher concentrator concentrations (Capuzzo et al, 2013).

Subcritical water extraction

In this extraction method, the fluid is subjected to temperature conditions above the boiling point and below the critical point. In this case, by increasing the pressure, we put the fluid in the liquid phase. For example, water under temperature conditions between 100 and 374$^{\circ C}$, which are the boiling point and the critical point, respectively, if left in the liquid phase with increasing pressure, becomes an infrared fluid (Figure 1). Water thermodynamic properties diagrams are used to determine the pressures corresponding to the temperatures used (Figure 2). Using these diagrams, the required pressure can be determined at the studied temperature so that the water remains in the liquid state. For example, a pressure of 15 bar at 200$^{\circ C}$ or 85 bar at 300$^{\circ C}$ should be used (Zakaria and Kamal, 2016).

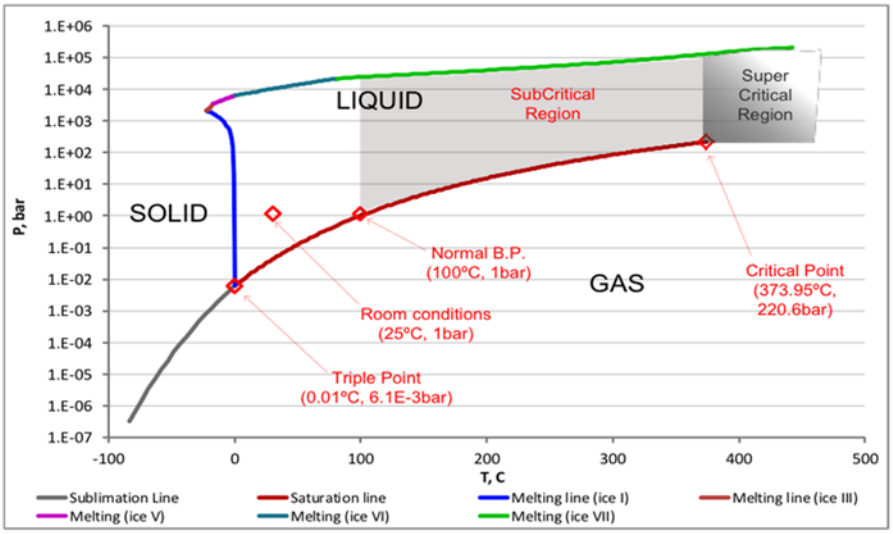

Figure 1. Subcritical water diagram

Figure (2) shows the relationship between temperature and pressure and different water states at different pressures and temperatures.

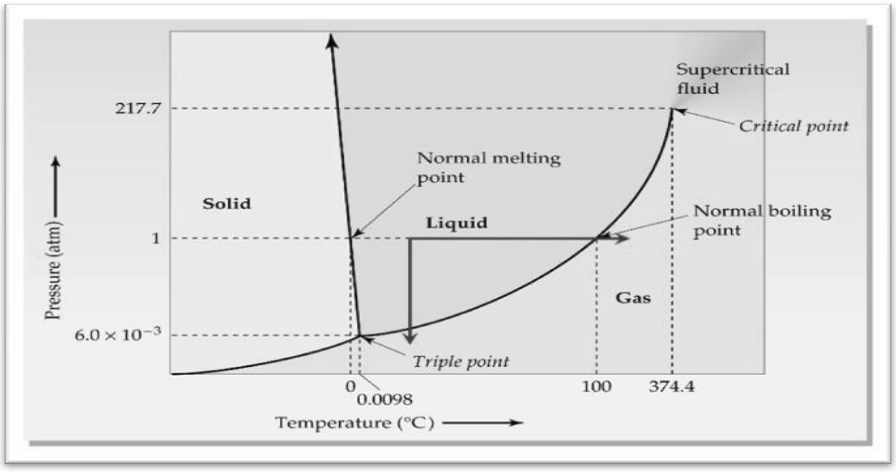

Figure 2. Water thermodynamic diagram

The table below also shows the physical properties of water at sub-critical temperatures and conditions and below.

Table 1. Physical properties of water

T °C	P bar	P kPa	ρ_L kg/m^3	ρ_V kg/m^3	H_L J/g	H_{Vap} J/g	H_V J/g	S_L J/(g·K)	S_{Vap} J/(g·K)	S_V J/(g·K)
10	0.012282	1.2282	999.65	0.00941	42.02	2477.2	2519.2	0.15109	8.7487	8.8998
20	0.023393	2.3393	998.19	0.01731	83.91	2453.5	2537.4	0.29648	8.3695	8.6660
30	0.042470	4.2470	995.61	0.03042	125.73	2429.8	2555.5	0.43675	8.0152	8.4520
40	0.073849	7.3849	992.18	0.05124	167.53	2406.0	2573.5	0.57240	7.6831	8.2555
50	0.12352	12.352	988.00	0.08315	209.34	2381.9	2591.3	0.70381	7.3710	8.0748
100	1.0142	101.42	958.35	0.5982	419.17	2256.4	2675.6	1.3072	6.0469	7.3541
150	4.7616	476.16	917.01	2.5481	632.18	2113.7	2745.9	1.8418	4.9953	6.8371
200	15.549	1554.9	864.66	7.8610	852.27	1939.7	2792.0	2.3305	4.0996	6.4302
250	39.762	3976.2	798.89	19.967	1085.8	1715.2	2800.9	2.7935	3.2785	6.0721
300	85.879	8587.9	712.14	46.168	1345.0	1404.6	2749.6	3.2552	2.4507	5.7059

Symbols:

P = absolute pressure ρ_L = liquid density ρ_V = vapor density
H_L = liquid specific enthalpy H_{Vap} = enthalpy of vaporization H_V = vapor specific enthalpy
S_L = liquid specific entropy S_{Vap} = entropy of vaporization S_V = vapor specific entropy

The following diagram shows the enthalpy and entropy of water at corresponding temperatures and pressures.

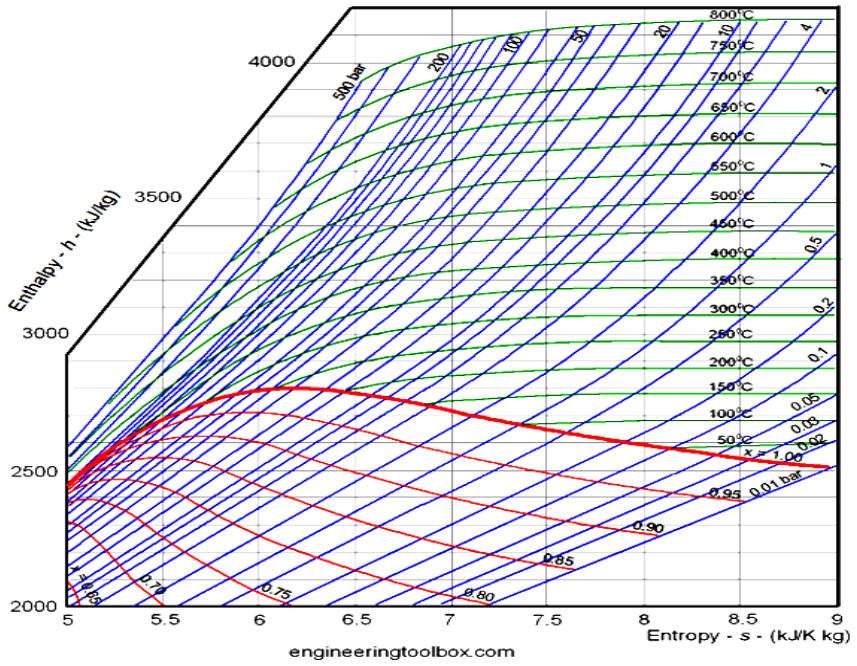

Figure 3. Enthalpy - Entropy - Temperature - Water pressure and quality diagram

Changes in the physicochemical properties of water

Water at 25$^{\circ C}$ and pressure of 0.1 MPa, is a highly polar solvent with the highest dielectric constant (ε). Under these conditions, the highest percentage of hydrogen bonds is observed in water. In this case, water is not recommended for extracting non-polar or organic compounds. In this case, the water temperature is low and has a constant density of 997 kg.$(m^3)^{-1}$, a high dielectric constant of 78.5, which is the best option for extracting salts. As the temperature rises, the polarity and dielectric constant of the water decreases, and the water becomes soluble, such as methanol, ethanol, or stonitrile, which are more capable of dissolving non-polar compounds (Roudsari et al, 2009). In subcritical conditions, the water ionization constant (Kw) also increases, so water is easily ionized to hydrogen and hydroxide ions, and as a result, the degree of hydrolysis increases (Watchararuji et al, 2008). As the temperature rises from 25 to 200$^{\circ C}$, the dielectric constant of the water decreases from 79 to 35$^{\circ C}$. Under normal conditions, ethanol has a dielectric constant of 24 or methanol has a dielectric constant of 35. The dielectric constant of water at 80, 110 and 160$^{\circ C}$ is 81, 53 and 42, respectively. Rising temperatures also reduce surface tension and viscosity, while the diffusion coefficient and mass transfer rate increase (Roudsari et al, 2009). One of the capabilities of Subcritical water extraction is that it has the ability to extract compounds with different polarities. Thus, low temperatures can be used to extract polar compounds and high temperatures can be used to extract non-polar compounds (Ibanez et al, 2003).

Conclusion

Solvent extraction was the most common method of extraction. This method consumes a lot of solvents and requires an additional step to recover the solvent and concentrate the extract, and the method is time consuming. In addition, the solvents used are toxic. Thus, new methods such as microwave assisted extraction, dynamic ultrasound assisted extraction, solid phase extraction, partial composition of phenolic compounds with supercritical fluid extraction, and subcritical water extraction can be mentioned. The use of non-critical water extraction has shown that this method is based on the use of water at temperatures between 100 and 374$^{\circ C}$ and the pressure required to keep water in a liquid state as solvent, and the high speed and the use of relatively low temperatures in this method make it a very good alternative to traditional methods of extracting plant materials.

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