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Extraction Methods of Extractive Substances from Medicinal Plant Raw Materials: Advantages and Limitations

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Medicinal plants have recently gained considerable interest, forasmuch as their use in ethnomedicine for the treatment of common diseases such as colds, fevers and other medical assumptions are now confirmed by reliable scientific investigations. Natural products are an important source of biologically active substances that can be used to develop drugs. The amount of bioactive natural compounds in natural medicines is always quite low. Today it is very important to choose the right effective and selective methods of extraction and isolation of these biologically active natural compounds. A wide range of technologies using various extraction methods is currently available. Thus, the present review paper aims to describe and compare the most commonly used methods, based on their principles, benefits, and limitations, to help assess the feasibility and cost-effectiveness of the methods.

Key words: extraction, medicinal plant raw materials, maceration, Soxhlet extraction, EMH, UAE, ASE, SLE.

Medicinal plants have recently gained considerable interest, forasmuch as their use in ethnomedicine for the treatment of common diseases such as colds, fevers and other medical assumptions are now confirmed by reliable scientific evidences. Researches on medicinal plants have been started with extraction procedures, which play a crucial role in the extraction results (for instance, yield and content of phytochemicals), as well as for further analyzes conducted. Nowadays, a wide range of technologies with different extraction methods is available. Therefore, the present review paper aims to describe and compare the most commonly used methods based on their principle, strength and limitations to help assess the suitability and cost-effectiveness of the methods.

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As of today, medicinal plants are of great importance due to their special properties as a rich source of therapeutic phytochemicals that can be used in the development of new drugs. There are reports (Venugopal & Liu, 2012) that most phytochemicals from plant sources, such as phenolic compounds and flavonoids, have a positive effect on health and cancer prevention. Interest in the use of natural sources in the development and creation of pharmaceuticals and preparations for the skin, as an alternative to conventional drugs and synthetic products, contributes to the growing interest in research and industrial use of medicinal plants (Mukherjee et al., 2011). The high content of phenolic compounds and flavonoids in medicinal plants is closely connected with their antioxidant activity, which plays a determining role in preventing the development of age-related diseases, in particular, those caused by oxidative stress.

In general, herbal medicines have been an extremely important source for the discovery of numerous medicines. For instance, morphine was the first purely natural product to be isolated, introduced into pharmacotherapy in 1826. (Merck). The first semi-synthetic pure substance of aspirin based on salicylic acid was isolated from the bark of willow *Salix alba* and manufactured in 1899 (Bayer). This was followed by the isolation of active compounds from old herbal preparations, such as digitoxin, codeine, pilocarpine, quinine and many others; some of which are still used today. Over time, after investigating "old" and "well-known" medicinal plants, numerous herbal drugs were introduced into therapy. Consequently, Silymarin extracted from *Silibum marianum* seeds is used as a hepatoprotector; Paclitaxel from *Taxus brevifolia* bark is applied in the treatment of lung, ovarian and breast cancer, as well as Artemisinin from the herb *Artemisia annua* is used for combating multiple resistances to malaria (Veeresham, 2012).

The study of medicinal plants begins with the procedures of pre-extraction and basic extraction, which is an important stage in the processing of bioactive components from plant materials. Traditional methods, such as maceration and Soxhlet extraction are commonly used in small research institutes or at the level of a small manufacturing enterprise (SME). Significant progress has been made in the treatment of medicinal plants, such as implementation of modern extraction methods, namely: extraction with microwave heating (EMH), ultrasound-assisted extraction (UAE) and supercritical liquid extraction (SLE), in which these achievements are aimed at increasing the yield at low cost. Moreover, modifications of these methods are constantly being developed. With such diversity, the choice of the correct extraction method requires careful

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evaluation. This review paper describes the principles, benefits, and limitations of commonly used methods, with examples as of recent years that will help one choose the relevant methods.

Extraction methods

Extraction is the process of separating medicinal active parts of a plant with the help of selective solvents according to standard methods (Handa et al., 2008). The purpose of the whole extraction is to separate soluble plant metabolites from insoluble cell residue. The initial crude extracts obtained by the extraction method contain a complex mixture of numerous plant metabolites, such as alkaloids, glycosides, phenolic substances, terpenoids and flavonoids. Some extracts obtained may be ready for use as pharmaceutical products in the form of tinctures and liquid extracts, however, most require further processing.

Extraction of medicinal plant raw materials is usually connected with surface phenomena in the interaction of solvent molecules with molecules of cellular structures of the sample. Along with this, the extraction process is influenced by sorption phenomena, forasmuch as most of the substances in the dried raw material are in the sorbed both in the thickness of the shell and on the surface. At another point, the duration of extraction of medicinal plant raw materials will depend on a number of factors that determine the properties of the sample. These are as follows: various physiological condition of tissues of organic matter, differences in structure of tissue of organic raw materials, the density of the cell membrane of plants, the presence of micropores and / or ultramicropores, the presence or absence of substances (protopectin, waxes, lignins, etc.) that reduce or clog the intercellular passages, etc. (Popova & Litvinenko, 1995).

Studies show that the most important parameters that affect the extraction process are the difference in concentrations; temperature; the viscosity of both the sample and the solvent; phase separation surface, hydrodynamic conditions, etc. It should also be noted that the extraction process and its efficiency depends on the technological properties of the raw material to be extracted. When selecting the extraction process, it is important to take into account the coefficients of swelling and absorption of raw materials, the ability to grind it, the volume prior and after shrinkage, humidity, etc. (Demyanenko, Breusova & Demyanenko, 2009, Bondarenko, Gladukh & Kotenko, 2011).

We propose to take a closer look at some of the commonly used extraction

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methods.

Maceration, infusion, infiltration and digestion. Maceration is a technique commonly used in winemaking and has become widespread and widely used in investigations on medicinal plants. Maceration involves soaking plant materials (coarse or powdered) in a sealed container with solvent and keeping at room temperature for at least 3 days with frequent stirring (Handa et al., 2008). Such holding with the solvent is intended to soften and destroy the cell wall of the plant and, as a consequence, to release soluble phytochemicals. After 3 days, the mixture is pressed or filtered. In this conventional method, heat is transferred by convection and conductivity, and the choice of solvents will determine the type of compound to be extracted. In case of infusing and boiling, the same principle is used as for maceration: the samples are soaked in cold or boiled water. However, the infusion maceration period is shorter and the sample is boiled in a targeted volume of water (for instance, 1:4 or 1:16) for a certain time for the decoction (Handa et al., 2008). Decocting is only suitable for extracting heat-resistant compounds from solid plant materials (for instance, roots and bark), and, as a rule, more oil-soluble compounds are formed compared to maceration and infusion. Unique equipment called a percolator is used for impregnation (infiltration) - another method that is based on a similar fundamental principle. The dried powder samples are packed in a percolator, after that boiled water is added and these samples are macerated for 2 hours. The impregnation process is usually carried out at a moderate rate (for example, 6 drops / min) until the extraction is completed before evaporation to obtain concentrated extracts (Rathi, Bodhankar & Baheti, 2006).

Advantages and limitations: This method is easy and simple to reproduce. However, the problem arises with organic waste, forasmuch as numerous different solvents are used and proper handling is required. Temperature change and solvent selection improve the extraction process, reduce the volume required for extraction, and can be introduced into the maceration technique if possible. Boiling *Centella asiatica* at 90 °C has showed an increase in phenol content and antioxidant activity, however, it has compromised the pH of the extracts due to increased extraction time (Yung, Maskat & Wan Mustapha, 2010). The solvents used in the soaking process play an important role in this method.

For example, to obtain BAR from the root of *Pelargonium sidoides*, the extracts of which are used to treat diarrhea, gastrointestinal diseases, dysmenorrhea and liver

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disease (Kayser, 2001), the maceration method is ineffective because the tannin content in the obtained extract is quite low, and the maximum value for the indicator "Dry residue" is manifested only at 48 hour (Bryda et al., 2020). With the help of a pressing element, we were able to obtain 599 ml, which is by 18,45% more than the finished extract when using traditional maceration. This is explained by the fact that the raw material of the roots is quite hygroscopic, as a result of which it absorbs a significant amount of extract into itself; due to pressing a more complete extraction of the extract is achieved. It has been experimentally confirmed (Bryda et al., 2020) that the use of the method of dynamic extraction with constant rotation of the extractor and the use of periodic circulation is more efficient and cost-effective extraction of tannins from pelargonium roots.

Soxhlet extraction or hot continuous extraction: In this method, the finely ground sample is placed in a porous bag or "thimble" made of strong filter paper or cellulose, which is in the thimble chamber of the Soxhlet apparatus (Figure 1). The extraction solvents are heated in the lower flask, evaporated into a thimble with the sample, condensed in a condenser and droped back. When the liquid reaches the siphon sleeve (Figure 1), the contents are poured into the lower flask and the process continues.

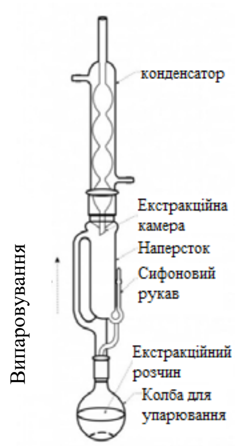

Figure 1. Traditional Soxhlet extractor

Українська	English
Випаровування	Evaporation
Конденсатор	Condenser
Екстракційна камера	Extraction chamber
Наперсток	Thimble
Сифоновий рукав	Siphon sleeve
Екстракційний розчин	Extraction solution
Колба для упарювання	Flask for evaporation

Advantages and limitations: This method requires less solvent compared to maceration (Handa et al., (2008). However, extraction in the Soxhlet apparatus has its drawbacks, namely: influence of hazardous and flammable liquid organic solvents, with potential toxic emissions during extraction; the solvents used during the extraction must be highly pure, which increases the cost of the procedure; this method is considered unfavorable for the environment and can cause the problem of contamination compared to an improved method of extraction, such as supercritical liquid extraction (SLE) (Naudé et al., 1998). There are certain requirements to samples for extraction in the Soxhlet apparatus: they must be dry and fine solids (Methods Optimization in Accelerated Solvent Extraction, 2013). In addition, numerous factors need to be considered for this method, such as temperature, solvent-sample ratio, and stirring rate (Amid, Salim & Adenan, 2010). High temperature and long extraction time during extraction in the Soxhlet apparatus increase the possibilities of thermal decomposition of extracts. For instance, the degradation of catechins in tea is observed during extraction by this method due to the applied high temperature. Alomg with this, the concentrations of both total polyphenols and total alkaloids obtained by extraction in the Soxhlet apparatus at 70 °C are reduced compared to those during maceration, which occurs at 40 °C (Chin et al., 2013, Xu et al., 2015).

Wei and co-authors obtained ursolic acid from TCM *Cynomorium (Cynomorii Herba)* with a yield of 38,21 mg / g of the sample by extraction in a Soxhlet apparatus (Wei et al., 2013).

Liquid extraction under pressure (LEP) is described by researchers as accelerated solvent extraction, enhanced solvent extraction, pressurized liquid extraction, accelerated liquid extraction and high pressure solvent extraction. As the name implies, high pressure is applied during extraction in this method. High pressure keeps the solvents in the liquid state above their boiling point, which leads to high solubility and high rate of diffusion of dissolved lipids in the solvent, as well as to high penetration of the solvent into the matrix. The application of this method dramatically reduces the extraction time and the amount of solvent used; it has better reproducibility compared to other methods.

Liquid extraction under pressure has been used successfully by researchers from the University of Macau and other institutes to extract numerous types of natural products, including saponins, favonoids and essential oil from traditional Chinese medicine (Yi, 2012, Guang-Ping et al., 2010, Xu et al., 2010, Xu et al., 2015). Some researchers believe that LEP cannot be used to extract thermolabile compounds due to the high extraction temperature, while others note that this method can be used to extract thermolabile compounds after a short extraction time. For instance, Mayer reactions occurred when LEP was used at 200 °C for the extraction of antioxidants from grape pomace (Vergara-Salinas et al., 2013). Anthocyanins are thermolabile. Gizir and co-authors have successfully used the LEP method to obtain an extract of black carrots rich in anthocyanins, forasmuch as the rate of decomposition of anthocyanins depends on time, and the conditions of LEP extraction with high temperature and short process time can overcome the lack of high temperature during extraction (Gizir, Turker & Artuvan, 2008).

Extraction with microwave heating (EMH): microwave energy for facilitating the distribution of analytes from the sample matrix to the solvent is used in this extraction method (Trusheva, Trunkova, Bankova, 2007). Microwave radiation interacts with dipoles of polar and polarized materials (for instance, solvents and sample), causing heating near the surface of the materials, and heat is transferred by conductivity. Dipole rotation of molecules induced by microwave radiation disrupts the hydrogen bond; enhances the migration of dissolved ions and promotes the penetration of the solvent into the matrix (Kaufmann & Christen, 2002). Poor heating is observed in non-polar solvents because energy is transferred only by dielectric absorption (absorption) (Handa et al., 2008). EMH can be considered as selective methods that prefer polar molecules and solvents with high dielectric constant (Table 1).

Table 1. Dielectric constant of some commonly used solvents

Solvent	Dielectric constant (20°C)
Hexane	1,89
Toluene	2,4
Dichloromethane	8,9
Acetone	20,7
Ethanol	24,3
Methanol	32,6
Water	78,5

Advantages and limitations: This technique reduces the extraction time and the volume of solvent compared to conventional methods (maceration and Soxhlet

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extraction). When using this method, an improvement in the extraction of analytes and reproducibility is observed, however, one need to carefully choose the proper conditions to avoid thermal degradation (Kaufmann & Christen, 2002). However, this method has limitations on its use towards low molecular weight phenolic compounds such as phenolic acids (gallic acid and ellagic acid), quercetin, isoflavone and trans-resveratrol, forasmuch as these molecules remained stable under microwave heating to 100 °C for 20 minutes. The use of additional EMH cycles (for instance, from 2 × 10 s to 3 × 10 s) leads to a sharp decrease in the yield of phenolic substances and flavanones, which is mainly caused by the oxidation of compounds (Trusheva, Trunkova & Bankova, 2007). The use of this method for the extraction of tannins and anthocyanins is not possible because they are potentially subject to degradation at high temperatures.

Bayramoglu and co-authors performed microwave extraction of the essential oil of *Origanum vulgare L.* without the use of solvents (Jayasena & Jo, (2013) and investigated the effect of microwave power and extraction time on the yield and composition of the product. Extraction with microwave heating without the use of solvents *Origanum vulgare L.* was compared with traditional hydrodistillation in terms of process duration, yield, composition and physical properties of the obtained essential oil. Significantly higher yields of essential oils were achieved by solvent-free microwave extraction at higher power levels compared to traditional hydrodistillation. The required extraction time was significantly reduced, while the composition of the essential oil obtained by both methods was similar.

Ultrasound-assisted extraction or ultrasonic extraction (UAE): This method involves the use of ultrasound in the range from 20 kHz to 2000 kHz (Handa et al., 2008). The mechanical effect of acoustic cavitation from ultrasound increases the surface contact between solvents and samples, as well as the permeability of cell walls. Physical and chemical properties of materials subjected to ultrasonic treatment change and the cell wall of the plant is destroyed; the release of compounds facilitates and the mass transfer of solvents into plant cells increases (Dhanani et al., 2017). This method is a simple and relatively inexpensive technology that can be used in both small and large-scale phytochemical extraction.

Advantages and limitations: The advantages of UAE mainly lie in the reduction of the extraction time and the amount of solvent used. However, the use of ultrasonic energy above 20 kHz can affect active phytochemicals through the formation of free

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radicals (Kaufmann & Christen, 2002, Handa et al., 2008).

Other extraction methods

Other methods, such as accelerated solvent extraction (ASE) and supercritical liquid extraction (SLE), are also used to extract plant materials. But these methods are less popular because of their high cost, despite the effectiveness of the methods.

Accelerated solvent extraction (ASE): ASE is an effective option for liquid solvent extraction compared to maceration and Soxhlet extraction, forasmuch as a minimum amount of solvent is used in this method. The sample is compacted with an inert material, such as sand, in a stainless steel extraction chamber (Figure 2) to prevent aggregation of the sample and blocking of the system pipeline (Methods Optimization in Accelerated Solvent Extraction, 2013, Rahmalia, Fabre &

Mouloungui, 2015).

Figure 2. Stainless steel cells with a volume of 1 ml and the schematic diagram of a packaged extraction cell with layers of cellulose filter paper, sand and a mixture of sample and sand.

Українська	English
Целюлозний фільтрувальний папір	Cellulose filter paper
Пісок	Sand
Суміш зразка та піску	Mixture of sample and sand

As is seen from Figure 2, packed cells for ASE comprise layers of a mixture of samples and sand between the cellulose filter paper and sand layers. This automated extraction technology makes it possible to control the temperature and pressure for each individual sample and requires less than an hour for extraction. Like other solvent-based methods, ASE is also critically dependent on the types of solvents selected. A solution of cyclohexane-acetone in a ratio of 6:4 V / V with 5-minute heating (50 °C) showed (Rahmalia, Fabre & Mouloungui, 2015) the highest yield of bixin from *Bixa orellana* with a purity of 68,16%. A high amount of extraction (~ 94%) of flavonoids from *Rheum palmatun* was observed when using 80% aqueous solution of methanol at ASE, which indicates the suitability of this method for

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assessing quality control (Tan, Jiang & Hu, 2014).

Supercritical liquid extraction (SLE): A supercritical liquid (SL), also known as a dense gas, is a substance that at its critical point separates the physical properties of both gas and liquid. Factors such as temperature and pressure are determinants that push a substance into a critical area. SL behaves more like a gas; however, it has the soluble features of a liquid. CO_2 is an example of SL, which is converted to SL at a temperature above 31,1 °C and a pressure of 7380 kPa. Interest in supercritical-CO_2 (SL-CO_2) extraction arises due to the excellent solubility of non-polar analytes; by the way, CO_2 is an easily available gas at a low price and has low toxicity. Although SL-CO_2 has poor solubility for polar compounds, such modifications as the addition of a small amount of ethanol and / or methanol allow it to extract polar compounds as well. SL-CO_2 also extracts analytes in the form of a concentrate, forasmuch as CO_2 evaporates at ambient temperature. The strength of SL solvents can be easily changed by changing the temperature, pressure or adding modifiers, which reduces the extraction time. Optimization of the SL-CO_2 extraction process of *Wadelia calendulacea* has made it possible to achieve optimal yield at 25 MPa, temperature 25ºC, modifier concentration 10% and extraction time only 90 minutes (Patil et al., 2013). The main disadvantage of this method is the very high initial cost of the equipment (Naudé et al., 1998).

The method outlined is an effective tool of extracting valuable components, suitable for replacing traditional methods (Asl et al., 2018, Hashemi et al., 2018) due to the lack of organic solvents and elevated temperatures, which can lead to undesirable reactions of active compounds such as hydrolysis, isomerization and oxidation, as well as inversely proportional effect on their antioxidant and antimicrobial properties. SLE of oregano leaves are offered as an effective method for concentrating and isolating antioxidant extracts to be used as functional food ingredients. The extraction process was evaluated both in terms of quality and activity of the obtained antioxidant products.

Discussion

All methods that use solvents (maceration, EMH, UAE, ASE), largely depend on the types of solvents. However, there is no significant effect of the volume of solvent used in the three methods (maceration, EMH and UAE) on biologically active compounds in poplar-type propolis in the ratio (1:10 = weight : volume) (Trusheva, Trunkova & Bankova, 2007). Herewith, the results are limited to a comparative

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assessment of the content of phenols, flavonoids and total yield.

Vongsak and co-authors proposed maceration as a widely used, convenient and less expensive method for small and medium enterprises (SMEs) compared to other modern extraction methods. However, chemical waste is a serious problem when using the maceration method compared to EMH and UAE, known as the “green method” (Dhanani et al., 2017). Although all of these extraction methods resulted in crude extracts containing a mixture of metabolites, the efficacy of these crude extracts using nanoencapsulated *Centella asiatica* demonstrated efficacy similar to that of purified (Kwon et al., 2012). This fact indicates that further isolation and purification of extracts, which is a rather complex and time-consuming procedure, is not required if proper preparation and extraction is carried out.

It is important to select the appropriate conditions for each extraction method. Some factors, such as temperature and light, need to be determined for the extraction of thermolabile compounds. For the extraction of anthocyanins from red and blue flowers, a weakly acidic solvent (0,1% HCl-methanol v / v) is used, which affects the pH during extraction (Vankar & Srivastava, 2010). It has been established (Oancea, Stoia & Coman, 2012) that hydrochloric acid in the ethanol system is more efficient than acetic acid for anthocyanin extraction. Among the following parameters, namely: solvent type, solvent strength, extraction time, stirring rate, sample-solvent ratio and temperature, which have been investigated using the factor design of the experiment, the concentration of solvent, which is a 70% ethanol solution, is the most important factor in the extraction of *Curcuma longa* (Paulucci et al., 2013). A similar observation for 70% of ethanol as the most influential parameter has been recorded in the extraction of triterpenoids from the leaves of *Jatropha curcas* (Wei et al., 2015) and phenolic extractions from *Moringa oliefera* (Vongsak et al., 2013).

Among the optimization studies, the type and strength of the solvent is the most influential parameter in almost all methods. However, it is reported that the solvent - sample ratio does not have a significant effect, which avoids the use of unnecessarily large amounts of solvents. Each optimized method is unique to an individual plant. All influencing factors (temperature, solvents, stirring rate, etc.) can enhance the extraction, however, they can cause degradation of components without proper assessment of their impact on the process. Thus, the selection of methods that have the least number of influencing factors can be a reasonable step in choosing the appropriate methods. However, if the purity of the extracts obtained is questionable, advanced extraction technologies such as SLE should be considered.

Conclusions

The use of natural products has contributed to the development of the pharmaceutical industry over the past few decades. However, labour-intensive and time-consuming extraction and separation processes have hampered the use of natural products in drug development. Forasmuch as technologies continue to evolve, more and more new automatic and rapid methods of extraction and separation of natural medicines are being developed that can meet the requirements of high-performance screening. Modern extraction methods, which are also considered as “green extraction methods”, including EMH, UAE, ASE, SLE, have been the subject of increased attention in recent years due to the high yield of extracts, selectivity, stability of target extracts and safety benefits of the process. Some of the methods outlined have even become common methods of preparing samples for analytical purposes.

All stages of extraction are equally important in the study of medicinal plants. It can be concluded that no universal extraction method is an ideal method, and each extraction procedure is unique to a particular plant species. Previously optimized methods can be used to select appropriate methods. However, the evaluation and selection of pre-extraction and extraction methods depend on the objectives of the study, samples and target compounds.

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