Comparative Study on Bioactive Constituents and Extraction Procedure of Malaysian Medicinal Plants: A Review

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ABSTRACT
This article aims to provide an overview on bioactive constituents and extraction procedure used of Malaysian medicinal plants. Search on the electronic databases including "ScienceDirect', 'Scopus, and 'Web of Science' was done based on related keywords, 'Malaysia',' medicinal plant' and 'extraction method', focusing from the year 2017 to 2020. As a result, 22 medicinal plants from 29 articles have been reviewed. Modern extraction techniques have been proven to produce a high amount of phytochemical even though the extraction yield is lower than conventional procedures. The antioxidant and antimicrobial are the must-have biological properties, as they can contribute to other therapeutic values of the plants. Further investigation on the isolation of bioactive compounds and maximum implementation into modern medicine should be further explored.

Keywords: *Bioactive constituents, extraction procedure, Malaysia plant extract, medicinal*

1. INTRODUCTION

Malaysia is listed as one of the 12 richest countries in the world in biodiversity, where its rainforest encompasses thousands of species of vascular plants. More than 2,000 trees species have been reported including the parasitic monster flower *Rafflesia arnoldii*, varieties of carnivorous pitcher plants *Nepenthes*, hundreds different species of trees in one acre of forest (herbs, shrubs, creepers) and more [1]. From those, plants containing phytochemicals are important and have been used since ancient times due to their beneficial medicinal properties and potential benefits to human health.
Phytochemical is a secondary metabolite, which is a part of nun-nutritive plants that biologically active, including phenolic, terpenoid and alkaloid [2]. It's produced in a part or all parts of the plants. There are a lot of researches has been done to characterize the active compounds that contribute to the medicinal properties of the plants [3-5]. Antioxidant, antimicrobial, anti-inflammatory, antiviral and wound healing are among the reported health benefits resulting from the presence of the secondary metabolites in the plants.
Extraction procedure plays an important part in processing the biological active phytochemical from the plant materials. The choice of solvent, suitable temperature, pressure and more need to be carefully evaluated before choosing the proper methods. Two categories of extraction methods are established and studied, conventional and modern technique. The most commonly used route is conventional extractions that have the benefit of more yield extracted. However, the disadvantages of these methods have been pointed out such as potential co-extracted of impurities, toxic solvents contaminate the sample extract during the process, a large amount of solvent is wasted, not suitable for thermolabile compounds and long extraction time [6]. The utilization of modern extraction methods, such as microwave-assisted (MAE), ultrasound-assisted extraction (UAE) and supercritical fluid extraction (SFE), in the separation process of active constituents have overcome the problems (lower cost, high yield of compounds) [4,7]. To date, the modifications on the methods are continuously advancing.
This review describes the comparative study on bioactive constituents obtained and different extraction procedure of Malaysian medicinal plants.

2. HISTORY

Medicinal plants have been tremendously used since ancient time, especially in China, India and Egypt. In Malaysia, the research has emerged from the basic phytochemical screening era to modern bioassays, toxicological and clinical studies. The research of the plants with medicinal properties was starting since 1950's, by photochemical screening. The research has been growing by years, and the collaboration with foreign institution starts to take place in 1994, after the formation of Malaysia Natural Products Society. The empowerment of local medicinal plants in 7^{th} to 10^{th} Malaysia Plans boost the research and development of the plants; also, more research funding encourages collaborations between universities and industries [8]. To date, a great amount of industrial collaborations, in term of research and commercialization can be noticed throughout Malaysia.

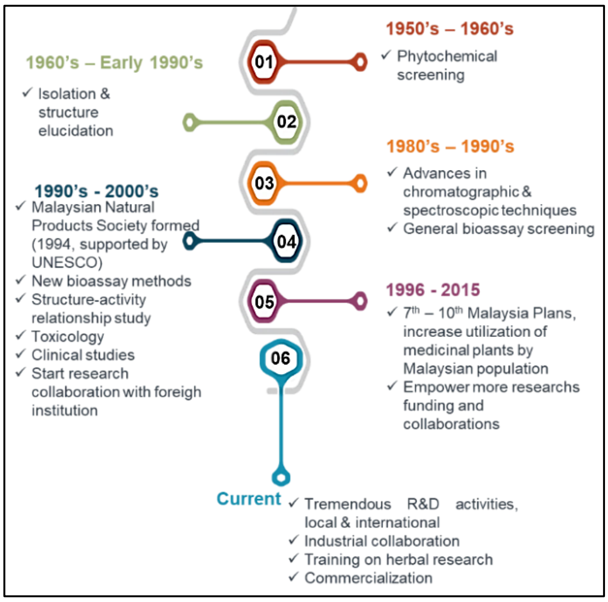

Figure 1 History of medicinal plant research and development in Malaysia

3. METHODS

The bibliographic research was performed in the following databases: ScienceDirect, Scopus, and Web of Science, where these databases were searched for relevant research articles and proceedings according to and must include at least one keyword from each of the following: (i) Malaysia, (ii) medicinal plant, (iii) extraction method, which specific word of 'extraction' should be included in the title, abstract, or keywords. The time frame was set in the range of 2017 to 2020. Even though 91 papers were yielded in the results, some of the papers were not reviewed as not related to medicinal properties, and the raw materials were not originated from Malaysia.

4. RESULTS AND DISCUSSION

The World Health Organization (WHO) define medicinal plant as a plant that contains compounds which can be used as therapeutic purposes or that can synthesize useful drugs from the metabolite. Over centuries, medicinal plants have been used worldwide to fight illness and maintain health. Interestingly, approximately 85% of the world population still rely on these traditional plants as their primary healthcare mode [9], especially rural communities in Africa, parts of Asia, Central and South America. Besides, about 50% of medicinal plants are integrated into the drug for modern usage [10]. Research on medicinal plants has been increasing significantly. Table 1 shows the summarize medicinal plants studied using different extraction procedures in Malaysia. It will be discussed based on the yields and the compounds present in the plant extracts.

4.1 Yield

Generally, from 2017 to 2020, most of the extraction methods used to obtain the valuable compounds in the plants are microwave and ultrasonic-assisted extraction (MAE and UAE). Both extraction methods are among several non-conventional methods that preferable due to its high efficiency, short extraction time and less material degradation [41]. On the other hand, conventional methods such as Soxhlet, maceration and soaking are less desirable since it requires high solvent volume and long extraction time. Moreover, the possibility of toxic materials will co-extracted is high. In term of extraction yield, the conventional method is observed to have more than modern techniques in most of the cases. It can be seen when extracting *Vernonia amygdalina* with Soxhlet and supercritical fluid extraction (SFE) [24,26]. However, the number of secondary metabolites detected using the modern technique is better. For example, asiaticoside amount extracted from *Centella asiatica* using MAE is higher than that of the maceration method [28]. Noted that SFE is less used might be due to the high cost of investment associated with high-pressure process [42].

4.2 Phytochemicals

Table 1 also shows most of the medicinal plants contain polar compounds which responsible for biological activities of the plants. According to the solubility theory of 'like-dissolve-like', more polar solvents are used for the extraction of these compounds [15,25,27,31,43]. It is important to note that plant part used as a starting material also take part in the determination of the type of solvent and

Table 1 List of medicinal plants, extraction techniques used, major compounds and their therapeutic values

Scientific Name	Local Name	Part Used	Extraction Method/Solvent	Yield	Major Compounds	Therapeutic values/ Function	Ref
Piper betle	Sirih	Leaf	UAE/ Ethanol	13.71%	Hydroxychavicol (0.012 mg/mL) Eugenol (0.067 mg/mL) Isoeugenol (9.993 mg/mL) 4-allyl-1,2-diacetoxybenzen (0.003 mg/mL)	Inhibit lipid peroxidation Antioxidant Analgesic Anti-inflammatory	[11]
			Maceration/ Ethanol	10.96%	Present of tannins and steroids		
			SFE/ CO_2	4.56%	Eugenol (8.21%)		[12]
Carica papaya Linn.	Betik	Leaf	SFE/ Ethanol	5.35%	α-tocopherol (24.67%) Squalene (7.89%) Linolenic acid (7.70%) Campesterol (4.37%) Stigmasterol (1.39%)	Antioxidant power in blood Reduce peroxidation levels Antifungal Antibacterial Larvicidal Treat dengue fever	[13]
Phaleria macrocarpa	Mahkota dewa	Fruit	UAE/ Water, Methanol, Ethanol	NA	Mangiferin (28.6 mg/g)	Antidiabetic Anti-inflammation Antioxidant	[14]
Quercus infectoria	Manjakani	Gall	Aqueous decoction	NA	Tannic acid (2233.82 ± 1.311 mg/g)	Anti-inflammation Antioxidant	[15]
			UAE (Bath-type)/ Water UAE (Probe-type)/ Water	NA	Tannic acid (9920.05 mg/kg) Gallic acid (1103.441 mg/kg) Tannic acid (10542.45 mg/kg) Gallic acid (1287.816 mg/kg)	Wound healing	[16]
Ficus deltoidea	Mas cotek	Leaf	MAHD/ Water	NA	Vitexin (33.40 ± 0.98% w/w)	Antioxidant Hypoglycemic Antinociceptive	[17]

					Isovitexin (11.38 ± 0.86% w/w)		
			Conventional	NA	Vitexin (15.0 % w/w) Isovitexin (7 % w/w)		
Eurycoma longifolia	Tongkat ali	Root	UAE/ Ultrapure water Conventional heat assisted	9.54% at 5 min 9.76% at 38 min	Eurycomanone	Treat erectile dysfunction Increase sexual desire Enhance muscular ability	[18]
			MAE/ Water	7.33%	Protein (16.878 ± 1.186%)	Improve spermatogenesis	[19]
Trigonella-Foenum Graecum	Halba	Seed	Soxhlet/ Hexane	5.55%	Linoleic acid (54.13%) Palmitic acid (16.21%)	Anti-diabetic Antimicrobial Anti-inflammation	[20]
			MAE/ Ethanol	26.03%	Linoleic acid (28.27%) 15,16-Dehydroestrone methyl ether (12.89%) Laevulic acid- trimethylsilyl ester (8.55%)	Anti-cancer Antioxidant Lower cholesterol level	[21]
Vernonia amygdalina	Pokok Afrika	Leaf	Soxhlet/ Petroleum ether (PEE), Ethyl Acetate (EAE), Methanol (ME)	Yield pattern: ME > EAE > PEE	High total flavonoid and phenolic content	Treat diabetes and other gastrointestinal problems Antioxidant Anti-inflammatory	[22]
			MAE/ Water	22.34%	Linoleic acid Palmitic acid Terpenoids Steroid glycoside	Renoprotective Anti-tumour Antioxidant Antimicrobial	[23]
			Soxhlet/ Ethanol	7.28%	Quercetin-7-O-rutinoside Kaempferol 1-galloyl-β-D-glucose kukoamine A 3,5-O-dicaffeoylquinic acid 6-gingerol	Anti-diabetic activities Ease headache Rheumatism Convulsions Insect repellent	[24]
			MAE/ Ethanol	NA	Phenolic acids		[25]

					Phenolic Aldehyde Flavonoids		
			SFE/ CO_2	1.241%	Caryophyllene (31.47%) Humulene (14.6%)		[26]
Phyllanthus niruri	Dukung anak	Stems and aerial	SFE/ Ethanol	NA	Gallic Acid Corilagin Ellagic acid	Treat ulcer, inflammation, kidney and gallbladder stones Wound healing Cure diabetes and jaundice	[27]
Centella asiatica	Pegaga	Whole plant	MAE/ Solvent-free	3.02%	Asiaticoside (158.8 μg/mL)	Anti-ulcer	[28]
			Maceration	NA	Asiaticoside (2.56 μg/mL)	Anti-amnesic	
			Soxhlet/ Methanol	NA	Asiaticoside (1-3 mg/mL)	Anti-stress	
			Subcritical water	NA	Asiaticoside (10 mg/g)	Antimicrobial	
			Enzymatic pre-treatment, microwave	NA		Regenerate brain and nerve cells Anti-Parkinson's disease treatment	
			Soxhlet/ Methanol, Ethanol, Water	7.30% (Ethanol) 5.00% (Methanol) 3.30% (Water)	Asiaticoside (27.10%)	Prevent cold-induced gastric ulcer Anti-inflammatory Antioxidant Wound healing	[29]
Alternanthera sessilis	Keremak merah	Leaf	Soxhlet/ Water, Ethanol, Ethyl acetate, Hexane	12.11% (Water) 4.55% (Ethanol) 1.81% (Ethyl acetate) 1.41% (Hexane)	Ferulic acid Rutin Quercetin Apigenin	Reduced risk of oxidative stress Free radical scavengers Anti-inflammatory Antiulcer Analgesic	[30]
		Stem	Soxhlet/ Water, Ethanol, Ethyl acetate, Hexane	22.24% (Water) 3.34% (Ethanol) 5.17% (Ethyl acetate) 0.02% (Hexane)	NA		
Persicaria tenella	Daun kesum	Plant (Fresh)	Liquid biphasic flotation/ Alcohol-Salt	9.42%	Gallic acid Rutin Cournaric acid	Antioxidant Anti-proliferative Anti-cancer	[31]

					Quercetin	Anti-inflammatory Anti-angiogenic Anti-vesicular Anti-fungal Anti-ulcer Anti-hyperlipidaemic Anti-acetylcholinesterase	
Mitragyna speciosa	Ketum	Leaf	SFE/ CO_2, Ethanol	1.36% (CO_2) 0.48% (CO_2 + Ethanol)	Palmitic acid (CO_2: 34.90%)	Treat muscle pain, fever, wounds, diarrheal, cough, hypertension Combat fatigue Enhance tolerance to hard work	[32]
Piper sarmentosum	Kaduk	Leaf	Soxhlet/ Methanol	≈10%	Dydimin Quercetin Amurensin Hesperidin Difucol	Neuroprotective Antioxidant Anticancer Antidiabetic Antiviral Antihepatotoxic Anti-inflammatory Allergenic	[33]
Clinacanthus nutans Lindau	Belalai gajah	Leaf	SFME/ Water	NA	Polyphenols	Anti-apoptotic Antioxidant	[34]
		Root	Solvent extraction/ Methanol, Ethyl acetate	NA	Lupeol (94.21%) Betulin (1.38%) Stigmasterol (1.33%)	Control menstrual pain Pain relief Treat skin rashes Treat anemia and jaundice Antidiabetic	[35]
Scurrula Ferruginea	Dedalu api merah	Leaf	Soaking/ Methanol, Acetone, Benzene Deionized water	80% Acetone >80% Methanol > 100% Methanol > Water	Phenolic compounds	Antifungal Antibacterial Treat shingles, malaria Wound healing	[36]

				>100% acetone >100% benzene		Release hypertension Protective medicine after childbirth Ease urination pain	
Bridelia stipularis	Cenderai gajah	Stem	Soxhlet/ Methanol; Fractionation/ Hexane, Chloroform, Ethyl Acetate	1.71% (Hexane) 0.63% (Chloroform) 0.34% (Ethyl acetate)	Oxalic acid (24.98%) 4-Tridecanol (6.36%)	Treat amoebic dysentery, chest pain, constipation, diarrhea, leucoderma and strangury	[37]
Momordica charantia	Peria katak	Fruit	UAE/ Aqueous ethanol	28.00 ± 2.5%	NA	Antiviral Prevent/ treat fever, polydipsia, diarrhea, colic, infections, diabetes, eczema	[38]
Piper nigrum	Black pepper	Seed	Microwave reflux extraction/ Water	NA	Piperine (5.64 w/w)	Anti-inflammatory Antibacterial	[39]
			Heat reflux technique/ Water	1.32%	Piperine (37.85%) Caryophyllene (8.97%) Sabinene (5.76%) Limonene (4.51%) β-bisabolene (1.66%)	Anti-cold Anti-rheumatic	[40]
Piper nigrum	White pepper	Seed	Heat reflux technique/ Water	1.40%	Piperine (42.29%) Caryophyllene (10.36%) Sabinene (7.94%) Limonene (6.47%) β-bisabolene (2.42%)		

UAE: Ultrasonic assisted extraction; SFE: Supercritical fluid extraction; MAHD: Microwave-assisted hydrodistillation; MAE: Microwave assisted extraction; SFME: Solvent-free microwave extraction; CO_2: Carbon dioxide; GAE: Gallic acid equivalent; QE: Quercetin equivalent; NA: No available data determination of quantity and secondary metabolites of the extract [44]. The data in the table presents that if the samples are leaf (*Piper betle*), root (*Eurycoma longifolia*), gall (*Quercus infectoria*) and stem (*Phyllanthus niruri*), the polar solvent is utilized solvent in the extraction process. Meanwhile, seed as starting material (*Trigonella-Foenum Graecum*) use non-polar solvent during the process. The observation tells that the state of the obtained extract (oil, colourless) yielded more non-polar compounds than the extracts from leaf, stems, etc. which high in viscosity and colour present. Non-polar compounds include fatty acids (linoleic acid, linolenic acid), α-tocopherol, and squalene, whereas polar compounds are phenolic, flavonoid, etc.

4.3 Choice of Extraction Methods

There are a variety of extraction methods that have been applied in the research of medicinal plants, from conventional to modern, depending on the several factors that can affect the diffusivity and solubility of the desired materials. Careful consideration on the selection of plant nature, particle size of starting materials, moisture content, solvent polarity, solvent-to-solid ration, extraction temperature, pressure and time will enhance the extraction efficiencies, as well as affecting the choice of extraction methods [45]. For instance, theoretically, smaller particle size will be yielded better yield than a larger one, and high solvent-solid-ration will increase the efficiency of the extraction process. Besides, the targeted compounds and the intended use of the final products also influence the selection of the methods [46].

There are four basic mechanisms of the extraction process discussed by Zhang et. al [43], which are: 1) solvent penetration into the solid particle, 2) solute dissolves in the solvents, 3) solute diffuse out from the solid, 4) extracted solutes are obtained. Table 2 demonstrates the principles, strengths and limitations of commonly used extraction procedures in medicinal plants researches [4,45,47-49].

Table 2 Comparison of different extraction methods use in medicinal plant researches

Extraction Methods	Principle	Strength	Limitation
Maceration, Percolation, Decoction	-Involve soaking method -Heat is transfer through convection and conduction -Target compounds depending on extraction solvent	-Easy and simple methods -Suitable for thermolabile compounds -Temperature and choice of solvent can be altered to enhance the extraction process	-Large volume of extraction solvent -Prolonged extraction time -Organic waste -May co-extracted impurities -Low extraction efficiency
Soxhlet	-Automatic continuous extraction method -Temperature is dependent on boiling point of extraction solvent	-High extraction yield -High efficiency than maceration -Complete/exhaustive extraction process	-Large volume of extraction solvent -Prolonged working time -Can cause thermal degradation due to high temperature -May co-extracted impurities -Exposure to hazardous/flammable organic solvents -Potential toxic emission -Limited to dry and finely divided solid
Microwave assisted	-Microwave generate heat by the interaction between the polar solvent and organic components in the plant matrix -Involve ionic conduction and dipole rotation mechanisms	-High yield and quality of targeted compound -Provide homogenous heating -Improved extraction rate, higher yield -Decrease in thermal degradation	-Poor efficiency for non-polar and volatile compounds, could be improved by solvent-free microwave extraction -Limited to small molecule phenolic compounds

	- Fast heating mechanism will destroy the cell walls of the plant tissues	- Selective heating of vegetal material - Less solvent and extraction time, thus decrease costs and environmental impact	
Ultrasonic assisted	- Use ultrasonic wave energy in the process (20 – 2000 kHz) - Ultrasound in the solvent produces cavitation that increases the surface contact between solute-sample and permeability of cell walls - Speed up dissolution and diffusion of the solute and heat transfer, improves extraction efficiency	- Applicable to thermolabile and unstable compounds - Less solvent and energy consumption - Low operating temperature - Short extraction time	- May produces reactive oxygen species during cavitation and cause compound degradation - Ultrasound energy > 20 kHz can affect phytochemicals through free radicals' formation
Supercritical fluid	- Use supercritical fluid (SF) as extraction solvent - SF have similar solubility to liquid, similar diffusivity to gas - Solvation properties dramatically change at a critical point with a slight change of pressure or temperature - Carbon dioxide commonly used as a solvent due to its selectivity, low critical pressure and temperature, non-toxic, suitable to extract thermolabile compound	- High yield and quality of targeted compound - Not required alternative energy source - Eco-friendly technique - Avoids degradation of thermolabile compounds - Can dissolve a wide variety of natural products - Avoid hydro solubilization or hydrolysis of sensible compounds - Suitable for the low polarity of the compound - Can be altered by the addition of co-solvent	- Major drawback is the high cost of equipment set-up/operation
Subcritical water	- Extraction process using hot water as solvent at a specific pressure to maintain the liquid state at a critical temperature between 100 - 374°C at critical pressure (1–22.1 MPa) - Provide mass transfer through diffusion and convection process - Energy supplied can interrupt the bonding of adhesive (solute-matrix) and cohesive (solute-solute) by reduction of activation energy required for the desorption process	- Dielectric constant can be varies based on various conditions - Less expensive - Can be used to extract different polarity of compounds - Continuous operation is possible	- Need high temperature to reach subcritical water state - Thermal degradation may occur at high temperature
Pressurized liquid/ Pressurized solvent/ Accelerated solvent	- Works under high pressure and temperature - Increase efficiency of the extraction process by the	- Suitable for aromatic compounds and essential oils - Suitable for a compound that stable at high temperature - Fast, clean and highly efficient	- High cost of investment - Not suitable for thermolabile compounds

	combine effects of elevated pressure - Application of pressure to remains solvent liquid state during extraction beyond its normal boiling point - Includes filtration and clean-up of compounds from solid samples that accelerate extraction of the compounds from solid particle	-Eco-friendly -Less solvent amount and time used

Also, Figure 2 summarized the preferred modern extraction methods and plant parts for different chemical classes according to Belwal et. al [47]. Table 2 and Figure 2 provides basic ideas when choosing the suitable extraction process according to the needs and objectives of the specific research.

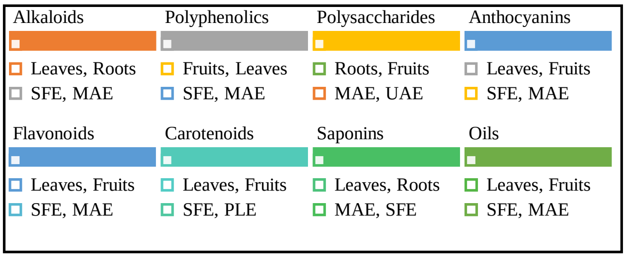

Figure 2 Preferred extraction method and plant parts for different chemical classes of phytochemicals

4.4 Bioactivities

The medicinal plant serves as pharmacological importance to human through bioactive components in the plants. To date, most studied pharmacological activities are antioxidant and antimicrobial since these are the basic properties of medicinal plants that later contributes to other biological activities as well such as anti-inflammatory, antidiabetic, analgesic and wound healing. Free radicals which exist in the body can cause cancer, heart disease, inflammation, diabetes, ageing, and more [50]. Supplementary antioxidants, for instance, phenolic compounds and terpenoids, are important alongside with barrier system in the human body. Besides, reports say that microorganisms have developed resistance to many antibiotics [51], thus the demand of medicinal plant extracts and the isolated compounds which possess antimicrobial properties against microorganisms has been increased [52].

4. CONCLUSION AND FUTURE PERSPECTIVE

This review demonstrates the researches done on Malaysian medicinal plants, including their bioactive compounds and extraction procedure implemented. There is a clear increasing pattern of interest in the extraction and compound detection of medicinal plants. Modern extraction methods are more preferable to yield high purity of the desired compounds, depending on the polarity of solvent use. Pharmacological studies revealed that the naturally occurring secondary metabolites of the plants display antioxidant and antimicrobial properties that contribute to other important therapeutic values. This review suggests further research need to be performed to determine the specific bioactive compounds which have potential in respective activities, upscaling the extraction process, more industrial collaborations as well as more integration of these plants in modern medicine. With these, it increases the income generation of the farmers and will benefit Malaysia economy besides can produce an individual with healthy wellbeing by the consumption of our natural products.

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