



Review Article

Extraction, Synthesis and Derivatization of Emodin: An Overview

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Abstract

Emodin (6-methyl-1,3,8-trihydroxyanthraquinone) is a natural anthraquinone derivative with potential pharmacological effects to be developed into a drug candidate. Emodin can be synthesized or extracted from natural products to ensure its availability. This review describes the source of emodin, existing extraction, and synthesis methods, additionally with recent methods for the synthesis of analogs and derivatives that have been performed to improve the physicochemical and pharmacological qualities of emodin.

Keywords: Emodin; Extraction and synthesis; Structure modification; Natural product

Introduction

Nature has always provided and continues to provide food and nutrients that benefit human health. Natural product compounds and their structural derivatives have made significant contributions to the drug discovery and development process. Many natural compounds or their derivatives have been discovered and developed for approval and marketing as commercial drugs. Such as taxol, vinblastine, vincristine, and topotecan, significant anticancer medicines in broad clinical use, were developed using chemicals derived from several natural products (Khazir *et al.* 2013). Several promising bioactive compounds are in clinical or preclinical trials.

Emodin is an anthraquinone-derived compound found in natural sources as a polyvalent molecule (Fig. 1). It has logP 5.3 and a molecular weight of 270.24 g/mol, with a melting point of 256-257°C (National Center for Biotechnology Information 2024). Emodin has various biological functions, such as anti-inflammatory, anti-bacterial, inhibition of oxidative stress, and even hepatoprotective solid capabilities, such as anti-fibrotic (Li *et al.* 2021; Semwal *et al.* 2021; Zheng *et al.* 2021; Ruan *et al.* 2022), and prevents renal ischemia-reperfusion injury (Lu *et al.* 2023). In addition to these, emodin has activity as an anti-cancer agent (Fang *et al.* 2019; Zhang *et al.* 2021; Zhang *et al.* 2022), a

protective effect against sepsis (Shang *et al.* 2021), potential cardiovascular therapy (Guo *et al.* 2022), and a neuroprotective effect (Leung *et al.* 2020; Li *et al.* 2021; Mitra *et al.* 2022). Natural emodin derivatives or analogs such as chrysophanol, rhein, aloe-emodin, and physcion have many pharmacological effects that have the potential to be used as therapy (Yang *et al.* 2019; Kuo *et al.* 2020; Nguyen and Kim 2020; Wen *et al.* 2021; Zhou *et al.* 2021; Feng *et al.* 2022; Karatoprak and Karatoprak 2022; Luo *et al.* 2022; Ma *et al.* 2022; Qi *et al.* 2022; Kim *et al.* 2023; Mao *et al.* 2023). With its numerous health benefits, emodin and its derivatives represent a crucial source of lead compounds in drug discovery and development research.

Unfortunately, emodin has its challenges in developing into a new drug, even though it has various potentials to be developed as a new drug. This can be seen from the large number of studies on emodin which are still in the preclinical testing stage. The challenge of developing emodin as a new drug is that this compound has low bioavailability (Sharifi-Rad *et al.* 2022) and a lack of efficient drug delivery to the required site (Zheng *et al.* 2021; Hu *et al.* 2023). Thus, in the process of developing drugs derived from nature, availability and sustainability are challenges in providing potential compounds besides concerns about their toxicity to cells or organs and bioavailability issues.

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This review summarizes the previous information on extraction methods carried out on emodin from various natural sources and chemical synthesis that have been reported. Additionally, this reviews also discusses some modification structures performed on emodin to improve its physicochemical properties and pharmacological effect. The availability in large quantities will guarantee that research on emodin can be developed more optimally using either the emodin itself or by modifying the structure.

Source of emodin

There have been several reports regarding the origins of emodin from plants. Most of the commercial emodin comes from the *Frangula* bark species with a $\geq 90\%$ purity level. More than half of plant species containing emodin come from Fabaceae, Polygonaceae, Rhamnaceae, and Hypericaceae families. Rest of them are found in Annonaceae, Asteraceae, Asphodelaceae, Chaetomiaceae, Cucurbitaceae, Eriocaulaceae, Incertae sedis, Lardizabalaceae, Myrsinaceae, and Picramniaceae families (Table 1). In fungi, emodin comes from isolates, extracted, or modified gene fungi (Table 2). Emodin from *Aspergillus nidulans*, for example, is the result of gene modification. This gene modification occurs due to the deletion process of *cclA*, a component of the COMPASS complex of *A. nidulans*, because a sequence of deletions that are targeted in the *cclA* deletion strain is created (Chiang *et al.* 2010). In other studies, emodin can be extracted from fungi like *A. flavipes*. Extraction was carried out using the growth fermentation medium that this fungus uses. The medium is then removed using a suitable solvent to obtain the intended target compound (Gong *et al.* 2022).

Extraction method of emodin

Extraction is separating or withdrawing compounds from plant parts, animal tissues or other medicinally active parts using selective solvents (Handa *et al.* 2008; Abubakar and Haque 2020). The purpose of extraction is to obtain the intended active compound at high concentrations. This compound is practically insoluble in water, soluble in alcohol, alkaline hydroxide solution, sodium carbonate solution and ammonia. For its stability, emodin is sensitive to prolonged exposure to light (National Center for Biotechnology Information 2024).

There are many kinds of emodin extraction methods, including maceration, soxhlet, reflux, molecularly imprinted polymer, ionic-liquid based extraction, sublimation assisted extraction (SAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE) and ultrasonic-assisted extraction (UAE) (Fig. 2). The selection of extraction method and solvent to be used needs to be adjusted to the type of compound to be addressed. This is so that we can obtain many compounds in the extraction process. Emodin is practically insoluble in water, soluble in alcohol, alkaline hydroxide solution, sodium carbonate solution and ammonia.

Maceration

Maceration is one of the most widely used conventional extraction methods. Unfortunately, this method has a long extraction time and low efficiency (Zhang *et al.* 2018). The work of this method is that the material to be extracted, either in the form of coarse powder, leaves, bark, or others, is placed in a container for further addition of the appropriate solvent and allowed to stand for a certain period while stirring occasionally. This method suits plant materials requiring prolonged solvent exposure (Garcia-Vaquero *et al.* 2020).

Several plants like *Cassia alata*, *Kalimeris indica*, *Momordica charantia*, *Rheum emodi*, *Picramnia sellowii*, *C. nigricans*, *C. obtusifolia*, *Rheum palmatum*, and others use the extraction method by maceration to obtain emodin. Following is a list of plant species extracted by the maceration method (Table 3). Based on Table 3, it is evident that an organic solvent is the kind employed in the extraction process for the maceration method. Some extraction techniques involve more than simply maceration; shaking is one of them (Fernand *et al.* 2008). Additionally, prior to the extraction process, studies treated samples using pre-treatment techniques such as hydrolysis and defatting (Alemayehu *et al.* 1996; Genovese *et al.* 2010; Arvindekar *et al.* 2015). For *Frangus alnus* extraction process, it is using petroleum ether to remove the nonpolar compounds until decolorization of the petroleum ether occurs so that only polar compounds are extracted (Đukanović *et al.* 2020). Based on the information gathered, it is known that some investigations into the emodin compound's extraction method are currently in the qualitative testing phase of determining its existence. Because of this, the amount of emodin extracted via the maceration procedure is not included in particular research.

Reflux

Reflux is a more efficient extraction method than maceration because it has less extraction time and solvent. This method suits thermostable compounds (Zhang *et al.* 2018). This is because the reflux method uses heating to assist the extraction process. Several plants were extracted using the reflux method including *Rumex acetosa*, *Polygonum cuspidatum*, *C. alata*, *R. emodi*, *R. palmatum* and others. Table 4 provides a list of plant species extracted by the maceration method.

Results regarding *R. emodi* treatment of acid hydrolysate and extracted using ethanol gave a higher yield of emodin when compared to no treatment (Arvindekar *et al.* 2015). In the extraction of *R. palmatum* leaves, the extraction was carried out using 80% ethanol for 90 min at a temperature of 95°C. The results obtained showed a yield of 0.97 mg/g (Wang *et al.* 2008).

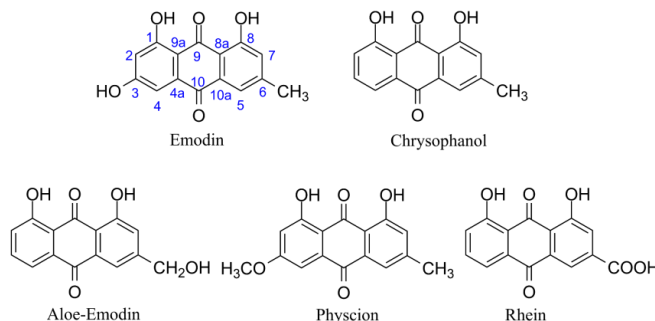
Soxhlet

Soxhlet is an extraction method that has a high level of

Table 1: Source of emodin from plants

Family	Species	Part of Uses	Reference
Annonaceae	<i>Annona muricata</i>	Leaves	(Mací <i>et al.</i> 2001)
Asteraceae	<i>Kalimeris indica</i>	The air-dried herbs	(Wang <i>et al.</i> 2019)
Cucurbitaceae	<i>Momordica charantia</i>	Leaves	(Kumari <i>et al.</i> 2017)
Fabaceae	<i>Cassia alata</i>	Root, leaves	(Angelina <i>et al.</i> 2021)
Fabaceae	<i>Cassia javanica</i>	Leaves, seed	(Chaudhuri and Chawla 1987; Khan <i>et al.</i> 2005)
Fabaceae	<i>Cassia obtusifolia</i>	Seed	(Paudel <i>et al.</i> 2019)
Fabaceae	<i>Cassia roxburghii</i>	Bark, seed, fruit (Pericarp)	(Khan <i>et al.</i> 2005)
Fabaceae	<i>Cassia tora</i> L.	Leaves	(Ko <i>et al.</i> 2021)
Fabaceae	<i>Cassia nigricans</i>	Leaves	(Ayo <i>et al.</i> 2007)
Fabaceae	<i>Senna auriculata</i>	n.d*	(Nille <i>et al.</i> 2021)
Fabaceae	<i>Senna didymobotrya</i>	Pods	(Alemayehu <i>et al.</i> 1996)
Fabaceae	<i>Senna occidentalis</i>	Leaves	(Musa 2018)
Fabaceae	<i>Senna alexandrina</i>	Aerial part	(Alam <i>et al.</i> 2022)
Fabaceae	<i>Senna septemtrionalis</i>	Pods, barks	(Alemayehu <i>et al.</i> 2010)
Hypericaceae	<i>Hypericum sampsonii</i>	Herbs	(Zhu <i>et al.</i> 2022)
Hypericaceae	<i>Hypericum perforatum</i>	<i>In vitro</i> shoot cultures	(Pradeep <i>et al.</i> 2020)
Hypericaceae	<i>Vismia laurentii</i>	n.d*	(Hussain <i>et al.</i> 2012)
Hypericaceae	<i>Vismia orientalis</i>	n.d*	(Hussain <i>et al.</i> 2012)
Polygonaceae	<i>Polygonum cuspidatum</i>	n.d*	(Wang <i>et al.</i> 2019)
Polygonaceae	<i>Polygonum multiflorum</i>	n.d*	(Liu <i>et al.</i> 2022)
Polygonaceae	<i>Rheum emodi</i>	Leaves	(Arvindekar <i>et al.</i> 2015)
Polygonaceae	<i>Rheum palmatum</i>	Leaves, Roots, Rhizomes	(Chen <i>et al.</i> 2020)
Polygonaceae	<i>Rheum tanguticum</i>	n.d*	(Wang <i>et al.</i> 2023)
Polygonaceae	<i>Rumex acetosa</i>	Aerial Part	(Liu He-chun 2019)
Polygonaceae	<i>Rumex confertus</i>	Bark	(Santos <i>et al.</i> 2016)
Rhamnaceae	<i>Rhamnus alpinus</i>	Bark	(Genovese <i>et al.</i> 2010)
Rhamnaceae	<i>Rhamnus prinoides</i>	n.d*	(Abegaz and Peter 1995)
Rhamnaceae	<i>Ventilago denticula</i>	Trunks and Barks	(Azizah <i>et al.</i> , 2020)
Rhamnaceae	<i>Ventilago leiocarpa</i>	Fresh Stem	(Lin <i>et al.</i> 1996)
Rhamnaceae	<i>Frangula alnus</i>	Bark	(Đukanović <i>et al.</i> 2020)

*Not detected


Fig. 1: Structure of Anthraquinone Analogue

efficiency with a relatively faster time and lower solvent consumption when compared to maceration methods. High temperatures and long extraction times in Soxhlet extraction increase the possibility of thermal degradation (Zhang *et al.* 2018). *R. acetosa* plants extracted by the soxhlation method gave emodin yield of 8.32% using ethanol as a solvent. Apart from that, *R. emodin* and *C. tora* also had their extraction process carried out by the soxhlation method but the solvents used were different. For *R. emodin* the extraction process uses ethanol solvent but the *R. emodin* sample is treated with acid hydrolysate. The purpose of giving acid hydrolysate is to hydrolyze anthraquinone glycosides to increase the concentration of the extracted compounds (Arvindekar *et al.* 2015). However, in *C. tora* the solvent used in this extraction method is chloroform.

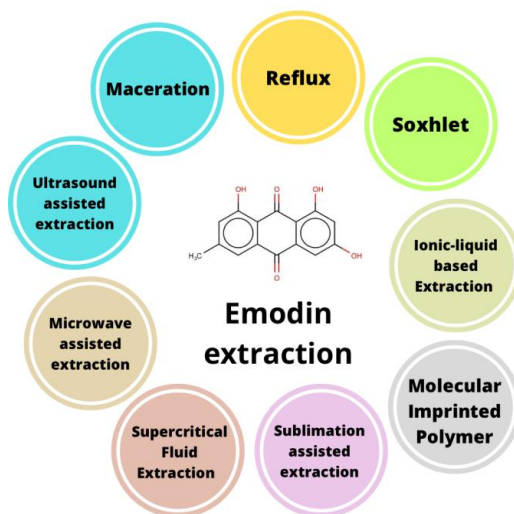
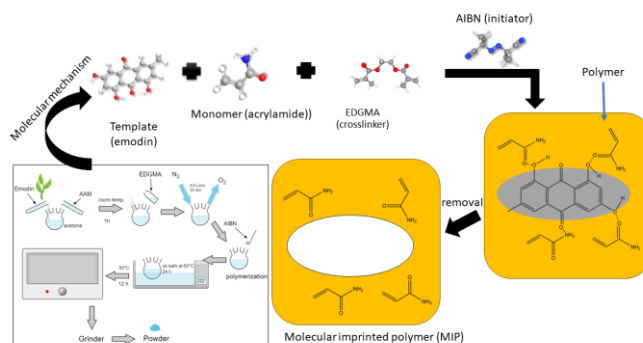
Molecularly imprinted polymer

Molecularly imprinted technology is a method that aims to prepare polymers with binding sites explicitly made for templates in shape, size, and functional groups (Fresco-Cala *et al.* 2020). Molecularly imprinted polymers (MIPs) are artificial polymers whose selectivity has been predetermined for specific analytes or a group of structurally designated species (Yang *et al.* 2014). MIPs are used in a variety of applications for separation, sensors, or catalysis (Zhuang *et al.* 2007).

In this method, the polymer chain propagation process will occur, and then the template molecule will be surrounded by compounds so that the compounds will be trapped in a three-dimensional polymer network. Furthermore, the

Table 2: Source of emodin from fungi

Family	Species	Part of Uses	Reference
Chaetomiaceae	<i>Guanomyces polythrix</i>	Fermentation broth and mycelium	(Mací et al. 2001)
Chaetomiaceae	<i>Thielavia subthermophila</i>	The mycelia of fungus <i>Thielavia subthermophila</i> isolated from <i>Hypericum perforatum</i>	(Kusari et al. 2009)
Trichocomaceae	<i>Aspergillus nidulans</i>	Agar medium	(Chiang et al. 2010)
Trichocomaceae	<i>Aspergillus awamori</i>	Culture filtrate	(Ismail et al. 2016)
Trichocomaceae	<i>Aspergillus flavipes</i>	Fermentation broth	(Gong et al. 2022)
Trichocomaceae	<i>Aspergillus terreus</i>	Mycelia	(Chen et al. 1995)

**Fig. 2:** Schematic extraction technology of emodin**Fig. 3:** Schematic synthesis of emodin by molecularly imprinted polymers (MIP)

compounds trapped in the polymer will be extracted with a suitable solvent, and then the template is removed. This method has high selectivity and better adsorption efficiency resulting in good separation results. This method can extract and separate the active ingredients from traditional ingredients (Fresco-Cala et al. 2020; Dong et al. 2021).

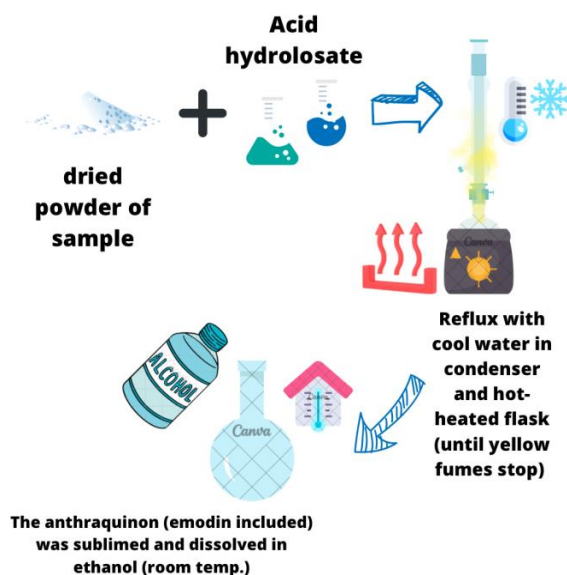
In testing the MIP method using emodin, it was found that emodin-printed polymers showed cross-activity where the emodin template had the highest IF (Fig. 3) (Zhuang et al. 2007). Then the research that was extraction of emodin from kiwi fruit root using molecularly imprinted polymers/multi-walled carbon nanotubes (MIPs/MWNTs) and the results showed that there was good site accessibility using

MIPs/MWNTs in 60 min to reach adsorption equilibrium and highly selective recognition for emodin templates. In addition, the use of the MIPs/MWNTs-SPE procedure for emodin provided satisfactory recovery results ranging from 89.2 to 93.8%. This shows that this method provides selective results in obtaining emodin from kiwi fruit roots (Yang et al. 2014). In addition, research on the *P. multiflorum* plant using the MIP method yielded maximum absorption capacities for physcion and emodin, 32.00 and 48.87 $\mu\text{mol/g}$, respectively. This research was conducted to obtain the results of the intended target compound free of other anthraquinones and able to increase the overall components of the extract (Liu et al. 2022).

Table 3: List of species using maceration method for extraction of emodin

Species	Part of Uses	Solvent	Ratio Samples (g): Solvents (mL)	Yield or Concentration of Emodin	Additional Information	References
<i>Kalimeris indica</i>	The air-dried herbs	Ethanol (40%)	16.5:1	n.d*	Three times, 2 h each time	(Wang <i>et al.</i> 2019)
<i>Momordica charantia</i>	Leaves	Methanol and distilled water	n.d*	n.d*	n.d	(Kumari <i>et al.</i> 2017)
<i>Senna didymobotrya</i>	Pods	Chloroform	n.d*	n.d*	Hydrolysed and defatted before extraction	(Alemayehu <i>et al.</i> 1996)
<i>Senna occidentalis</i>	Leaves	Ethanol (60%)	n.d*	n.d*	For 4 days	(Musa 2018)
<i>Senna septemtrionalis</i>	Pods	Chloroform	1:5.4	n.d*	Hydrolysed and defatted before extraction	(Alemayehu <i>et al.</i> 1997, 2010)
	Barks	Dichloromethane: methanol (1:1)	1:20	n.d*	For 10 h at room temperature	
<i>Rheum emodi</i>	Barks	Methanol	1:20	n.d*	For 30 minutes at room temperature	
<i>Rhamnus alpinus</i>	Leaves	Ethanol	1:20	n.d*	Hydrolysed before extraction	(Arvindekar <i>et al.</i> 2015)
<i>Ventilago denticula</i>	Bark	Methanol	1:10	0.942 mg/ml	Hydrolysed before extraction	(Genovese <i>et al.</i> 2010)
	Trunks and barks	Methanol and dichloromethane	n.d*	n.d*	For 2 days at room temperature	(Azizah <i>et al.</i> 2020)
<i>Ventilago leiocarpa</i>	Fresh stem	Ethanol	n.d*	400 mg (1.05%) from Chloroform fraction and 1.25 g (2.7%) from ethyl acetate fraction	Extract partitioned with n-hexane, chloroform, ethyl acetate and butanol	(Lin <i>et al.</i> 1996)
<i>Cassia javanica</i>	Leaves	Petroleum ether	1:5	n.d*	For 5 times	(Chaudhuri and Chawla 1987)
	Leaves	Methanol	1:5	n.d*	For 5 times	
<i>Cassia obtusifolia</i>	Seeds	Methanol	1:20	11.8%	Extraction for two days	(Yang <i>et al.</i> 2003)
<i>Rheum palmatum</i>	Leaves	Ethanol (80%)	1:30	0.94 mg/g	For 90 min	(Chen <i>et al.</i> 2020)
<i>Cassia alata</i>	Root	Ethanol	1:5	n.d*	With shaking at 110 rpm for 18 h	(Angelina <i>et al.</i> 2021)
	Root	Ethanol	1:10	26.5 ± 5.0 ppm	Shaking for 12 h at room temperature and repeated two times	(Fernand <i>et al.</i> 2008)
<i>Frangula alnus</i>	Bark	Ethanol	1:10	15,126 ± 907 µg/g (µg/g of extract dry weight)	For 24 h with moderate shaking	(Đukanović <i>et al.</i> 2020)

*Not detected

**Fig. 4:** Scheme of DHAQ extraction

Sublimation assisted extraction

For plants extracted by sublimation method is *R. emodin*. The solvent used in the extraction process is ethanol where before the sample is extracted, the sample is treated using acid hydrolysate. Then the sample was transferred in a 50 ml round bottom flask attached to a reflux condenser (>1 m long) with cold water circulating and placed in a heating mantle. The flask was heated vigorously (8-10 min), until yellow smoke stopped from the sample. On cooling to room temperature, 100 mL of ethanol was added to dissolve the

sublimated DHAQ adhering to the condenser walls and the volume was made up to 100 mL of which 0.1 mL was diluted with methanol (1:100) and subjected to HPLC (Fig. 4). The results showed that the samples treated with acid hydrolysate had higher levels than those without treatment (Arvindekar *et al.* 2015).

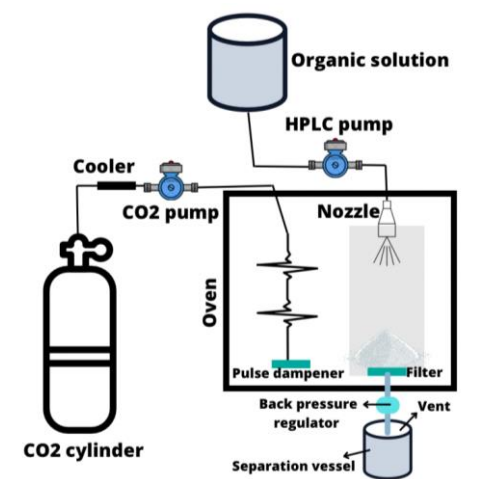
Supercritical fluid extraction

Supercritical fluid extraction or SFE (Fig. 5) is an extraction method that uses supercritical fluids, where the solvent used

Table 4: List of species using reflux method for extraction of emodin

Species	Part of Uses	Solvent	Ratio	Yield or Concentration of Emodin	Additional Information	References
<i>Cassia javanica</i>	Seed	Chloroform	1:50	51 µg/10 mL	For 4 h	(Khan <i>et al.</i> 2005)
<i>Cassia obtusifolia</i>	Seed	Methanol	1:20	170 mg (yield)	For 3 h and three times	(Paudel, Seong, <i>et al.</i> 2020)
<i>Cassia roxburghii</i>	Bark	Chloroform	1:50	20 µg/10 mL	For 4 h	(Khan <i>et al.</i> 2005)
<i>Cassia roxburghii</i>	Fruit (Pericarp)	Chloroform	1:50	45 µg/10 mL	For 4 h	(Khan <i>et al.</i> 2005)
<i>Cassia roxburghii</i>	Seed	Chloroform	1:50	20 µg/10 mL	For 4 h	(Khan <i>et al.</i> 2005)
<i>Rheum emodi</i>	Leaves	Ethanol	1:20	n.d*	Hydrolysed before extraction	(Arvindkar <i>et al.</i> 2015)
<i>Cassia alata</i>	Leaves	Methanol	1:4.3	26.5 µg/mg	Time for 8 h at 64 °C	(Pham <i>et al.</i> 2021)
<i>Polygonum cuspidatum</i>	Root	Methanol	0.1:25	13.39%±0.45	With heating for 120 min at 100°C	(Wang <i>et al.</i> 2019)
<i>Rheum palmatum</i>	Leaves	Ethanol (80%)	0.15:50	0.97 mg/g	For 90 min at 95°C	(Wang <i>et al.</i> 2008)

*Not detected

**Fig. 5:** Scheme of supercritical fluid extraction

exhibits liquid-like properties (solvent power, surface tension can be neglected) and gas-like properties (transport) (Capuzzo *et al.* 2013). The solvent that is usually used in this extraction method is CO₂ gas because it is chemically inactive, easily accessible, and economical. It can be separated from extracts, is non-toxic, and is an approved food-grade solvent. In addition, CO₂ has gas and liquid-like properties, selectivity and potential for extracting heat-sensitive compounds and low critical pressure and temperature (Uwineza and Waśkiewicz 2020). The advantages of this method when compared to other methods are higher selectivity and extraction results, better fractionation ability, and lower environmental impact (Santos *et al.* 2016). In the supercritical fluid extraction process, the most essential areas in the pressure-temperature composition space are (i) 2-phase, liquid-vapor (LV), solid-vapor (SV), or liquid-liquid (LL) equilibrium; (ii) 3 phases, liquid-liquid-vapor (LLV), solid-liquid-vapor (SLV), solid-solid-vapor (SSV) equilibrium, and sometimes; (iii) 4-phase equilibrium: solid-SCF mixture. In addition, supercritical fluid extraction solvents can break down multi-component mixtures (Castells *et al.* 2003). For plants extracted using the supercritical fluid extraction method, *Rumex emodin* was obtained, where the yield obtained was 29.9–43.8 mg/g (Santos *et al.* 2016). In another studies, *P. cuspidatum* root extraction or also called *Fallopia japonica* using the SFE method can provide higher

emodin extraction results when compared to soxhlet. The results obtained with the SFE method were 0.82 ± 0.03 mg/g, whereas with the Soxhlet method the results were 0.34 ± 0.09 mg/g. The SFE method is an acceptable technique for anthraquinone-based compounds like emodin, but, on the other, hand it is not so suitable for more polar compounds as stilbenes (Beňová *et al.* 2010).

They have studied green extraction of *P. cuspidatum* to obtain maximum yields of resveratrol and emodin by using RSM (*Response Surface Methodology*) optimization. Second-order polynomial mathematical models were developed and applied to predict the optimal extraction conditions based on temperature, pressure, and ethanol content. The result from RSM optimization is a temperature of 51.8°C, pressure of 25.34 MPa, and ethanol content of 110.83 mL/L. Under these conditions, confirmatory experiments showed that the yields of emodin and resveratrol were 2.804 ± 0.108 and 2.564 ± 0.121 mg/g, respectively. This showed that the extract has high antioxidant properties, strong free radical scavenging abilities, and good reducing abilities (Ruan *et al.* 2022).

Microwave assisted extraction

As the efficiency of extraction is demanded, the development of various methods increases. Among the techniques developed to obtain higher yield or efficiency,

ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE) got more attention due to their low instrument set-up cost at the laboratory scale and other advantages (Kala *et al.* 2016). Microwaves and ultrasound are electromagnetic waves, one is heat and the other is vibration. Microwave irradiation uses magnetic and electric fields in frequencies ranging from 300 MHz to 300 GHz, though the range 0.915 to 2.45 GHz is preferred worldwide (Leonelli *et al.* 2013). This technology works by conversion of electromagnetic energy which penetrates into chemical mixtures or substances to produce heat. The microwave irradiation acts by selective heating which is caused by the difference of permittivity values of the solvents used. The main reaction of energy transfer in the heating process includes dipole rotation and ionic conduction. The ionic conduction itself occurs when there are dipoles and displacement of charged ions present in the solvent and solute, and this is determined by their dielectric constant (Chan *et al.* 2011; Leonelli *et al.* 2013). This principle enables a significant reduction in time for extraction and offers high efficiency.

There are fundamental closed system and open systems of MAE, and various modified MAE have been developed such as nitrogen-protected microwave-assisted extraction (NPMAE), ultrasonic microwave-assisted extraction (UMAE), vacuum microwave-assisted extraction (VMAE), dynamic microwave-assisted extraction (DMAE) (Chan *et al.* 2011). The principle of heating transfer in MAE mentioned above means that the energy transfer is characteristic of microwave heating. In MAE, microwave energy is delivered through molecular interactions using an electromagnetic field to convert electromagnetic energy to thermal energy. Based on this scheme, the most important properties involved in the process of dielectric are represented in the equation: $\tan \delta = \varepsilon'' / \varepsilon'$, which $\tan \delta$ is the dielectric loss tangent, ε is complex relative permittivity, and ε' is the fundamental part that (dielectric constant) that represent proportional to the amount of energy absorbed; while ε'' , is imaginary part representing the dielectric loss or loss factor. The loss tangent property indicates the ability of a medium to dissipate input dielectric energy as heat (Vinatoru *et al.* 2017). This will then be considered when choosing a solvent so the heat will occur.

Modifying methods to improve the efficiency of an extraction is often necessary, usually by pre-treating the biomass. Such pre-treatment is selected to disrupt or weaken the cell walls or membranes of different organisms. It is described as the plant cell walls and different fungi are very resistant to disruption. This can reduce extraction yields by as much as 90% (Didion *et al.* 2023). So, the extraction by using MAE is usually pretreated before, e.g. application of ILs (*Ionic Liquids*) in sample preparation techniques, such as liquid-liquid extraction (Jin *et al.* 2011).

For emodin, Wang *et al.* (2008) studied advanced microwave-assisted extraction by assisting it with

aqueous two-phase extraction to effectively obtain emodin, piceid, and resveratrol directly from *P. cuspidatum* using ethanol/ammonium sulphate system to investigate the separation behavior of the extraction process. They showed that the addition of ethanol and ammonium sulphate increased the partition coefficient and yield. They further reported that the optimum condition of the system was 25% (w/w) ethanol and 21% (w/w) ammonium sulphate for the extraction to get an equal yield of picked, and that of resveratrol and emodin 1.1 and 1.9 times higher, respectively, than that by microwave-assisted extraction and heat reflux extraction.

Another study was done by Fan *et al.* (2019) inspired by a previous study using DES, which used the protic ionic liquid as the method in microwave-assisted extraction. They extracted emodin and rhein from *R. palmatum* and their results indicating that PILs (*Protic Ionic Liquids*) exhibit higher extraction ability compared to conventional solvents, such as trichloromethane, methanol, and deep eutectic solvents (DESSs). A DES is a homogeneous mixture of a few constituents at a specific ratio. DESs comprise hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) to form hydrogen interaction (Dai *et al.* 2021; Meenu *et al.* 2023). The PILs, 1-butyl-3-himidazolium methanesulfonate ([BHim]MeSO₃) used here was more efficient. Under the optimum extraction conditions of liquid-solid ratio, the extraction yields of emodin and rhein were 4.0 and 7.8 mg/g, respectively.

In addition to using the extraction method, the selection of the solvent used can affect the extraction results of emodin. As studied by Wang *et al.* (2020), the MAE on dry herbs *R. palmatum* using DES as a solvent produced higher yields of emodin when compared to using ethanol solvents with the same method. In this study the DES solvent used was a combination of choline chloride: citric acid with a ratio of 1:3 which produced 2.30 ± 0.15 mg/g emodin.

Ionic-liquid based extraction

Ionic liquids (ILs) are semi-organic molten salts at or close to room temperature, have melting point lower than 100°C, and are made from the association of organic cations and organic or inorganic anions (Wang *et al.* 2019). Some cations used in ILs include alkylammonium, imidazolium, phosphonium, piperidinium, pyridinium, etc., while anions are more diverse, some of which including organic and inorganic anion, such as carboxylate, halides, [BF₄], [CH₃SO₄], [CF₃SO₃], and [N(CN)₂], [SCN]. The DESs are also used which due to having similar properties with ILs such as thermodynamic characteristics, so DESs are considered as IL analogues (Dai *et al.* 2021; Meenu *et al.* 2023). This method was developed to overcome air-assisted liquid-liquid microextraction (AALLME), which uses volatile and highly toxic chlorinated solvents in the process of extraction (You *et al.* 2018).

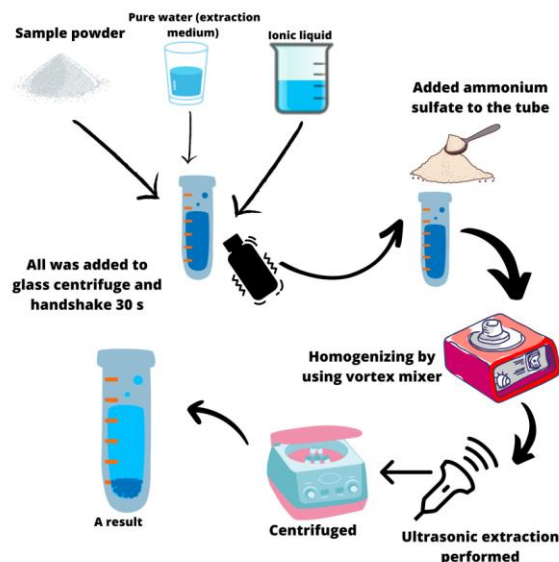


Fig. 6: Scheme of ionic liquid assisted extraction

The ILs possesses various advantages as alternative substituents for toxic, flammable, and volatile solvents, and are usually used in current extraction, especially in solid-liquid extraction (SLE) (Freire *et al.* 2010). Furthermore, the SLE, due to having ionic combinations and characteristics, can absorb and transfer electromagnetic energy such as microwave and magnetic interaction. Hence it is a viable approach to use ILs as assisting solvents in UAE or MAE or even UMAE. This approach could be preferred to get shorter extraction times and higher extraction efficiencies (Ventura *et al.* 2017). Besides UAE and MAE, ILs could be established along with any other extraction method such as IL-based ultrahigh pressure extraction (IL-UPE), IL-assisted negative-pressure cavitation extraction (NPCE), or could be alongside heat reflux extraction (HRE) (Zhang and Wang 2010; X. Liu *et al.* 2012; Bogdanov 2014; Zhang *et al.* 2018).

With the development of research in the following years, the application of ILs combined with organic, inorganic salts, alcohols, carbohydrates, and polymers was reported to form Aqueous Biphasic System (ABS) or Aqueous Two-Phase System (ATPs). ABS was used to achieve phase separation from two water-soluble compounds as the ternary system. It consists of water and two solutes, and is therefore explored to analyze the various combinations of phase-forming components (Basaiahgari and Gardas 2021). Among the study of combinations of ILs, the exciting combination was IL-salt. The addition of salt to aqueous solutions impacts the solubility of the analytes in the mixture and induces the salting-out process to enhance their partitioning and form two aqueous phases (Fig. 6; Zhang *et al.* 2014). Because of the nature of ILs, they could be modified to undergo biphasic separation with water and other substances like organic/inorganic salts, amino acids,

organic buffer, etc and conduct various possible interactions (Shukla *et al.* 2018). The advantages of IL-based ABS as the new separation technique are for the efficiency and selectivity of this method.

Another development based on ionic liquid is homogeneous liquid-liquid microextraction (HLLME) to extract various natural compounds (Wang *et al.* 2019). This HLLME combined with MAE had also been studied to extract *R. palmatum* to obtain anthraquinone (Wang *et al.* 2016). These authors used solid-liquid and liquid-liquid approaches, and the result showed that emodin yield was 3.05 ± 0.10 mg/g comparable to UAE but more efficient in the used solvent. As an approach to get a higher yield or more straightforward way to extract emodin, the liquid-liquid approach was pragmatic with microwave or ultrasonic-assisted extraction.

Wang *et al.* (2019) studied this method for emodin extraction from *P. cuspidatum* by using the alkyl-imidazole ionic liquid as extraction solvent. In this research, the concentration or condition of salt, solvent, and ultrasound-affecting-factors were determined to get the best yield of emodin. This study also compared the yield of emodin obtained with reflux, ultrasonic extraction, and pharmacopeia standard of extraction. The results showed IL-SI-LLE was slightly lower than those obtained by the Pharmacopoeia method. However, as the extraction yields obtained by the IL-SI-LLE were comparable to those obtained by UE, the operation was more straightforward, and the extraction time was shorter. Compared with HRE, when the present method was applied, much less sample, extraction solvent and extraction time were consumed. So, the IL-assisted extraction brought more efficiency in the process even though the yield was no different significantly.

As mentioned above about the ATPSs or ABSs, a study was done by Tan *et al.* (2012) using Aqueous two-phase systems (ATPSs) based on ILs and salts were applied to isolate and purify anthraquinones (AQs) from aloe leaves with the intent to purify aloe anthraquinone like aloe-emodin, emodin, etc., and used $[C_4mim]BF_4$ as the ionic liquid to form phase separation. The optimal extraction condition were 25°C temperature, 10 min equilibrium time, and pH 4.0. The maximal extraction efficiency was obtained using the $[C_4mim]BF_4/NaSO_4$ system. The main constituents observed were aloe-emodin and chrysophanol by comparing before and after the ILATPS by procedure. The results showed that the extraction efficiency of aloe-emodin and chrysophanol was 92.34 and 90.46%. Furthermore, ILATPS procedure was compared with conventional liquid–liquid extraction methods, which concluded that ILATPS was more efficient and environmentally friendly, and could be used as an alternative “greener” extraction method in isolation and purification of other natural active compounds or bio-products.

Extraction of *R. palmatum* from its roots using IL-NaY-MSPD (Ionic liquid-immobilized NaY zeolite-based matrix solid-phase dispersion) compared with UAE, HRE and methods from Pharmacopoeia showed that the IL-NaY-based MSPD can provide higher yields of compounds compared to the UAE and HRE methods. In this extraction method IL-NaY containing 25% $[C_4MIM][PF_6]$ was used as a dispersant and the emodin was obtained at 1.15 ± 0.09 mg/g. Nevertheless, the outcomes of this approach exhibited a lesser magnitude when contrasted with the technique outlined in the Pharmacopoeia. How can one acquire emodin using the method described in the Pharmacopoeia, which yields a concentration of 1.16 ± 0.11 mg/g. However, the IL-NaY-based MSPD approach significantly reduces the amount of sample, extraction solvent, and extraction time required (Chen *et al.* 2020).

Ultrasonic assisted extraction

The UAE is an extraction method with ultrasound energy and solvents used to extract target compounds from various plant matrices. Ultrasound energy itself is a mechanical wave that has a frequency of around >20 kHz or higher than the frequency range that can be heard by humans, which is around 20 Hz to 20 kHz. The existence of these ultrasound waves can put pressure on the source matrix of the compounds used so that an attractive force occurs that holds the molecules together and creates cavitation bubbles. The cavitation bubbles will collapse during the compression phase creating hot spots and local extreme conditions. So the collapse of cavitation bubbles will generate shock waves and accelerated collisions between particles causing fragmentation in the cellular structure. Fast fragmentation will cause solubilization of bioactive components in solvents due to decreased particle size, increased surface area and high mass transfer rates in the solid matrix boundary layer,

so that the target compounds are able to be extracted optimally using this extraction method (Kumar *et al.* 2021). Two main factors that can increase the efficiency of using ultrasonic waves, namely the presence of cell disturbance and effective mass transfer. In addition, the UAE is also able to shorten the duration of extraction to achieve optimal extraction efficiency (Zahari *et al.* 2020). Plants namely *P. cuspidatum*, *R. emodin*, and *R. palmatum* known to contain emodin were extracted using UAE method.

For *P. cuspidatum* plant, the emodin extraction was carried out using the usual UAE method using methanol as solvent with a yield of $12.87\% \pm 0.42$ (Wang *et al.* 2008). In another study, where this plant was extracted using the ultrasonic extraction capillary zone electrophoresis (UE-CZE) method using methanol solvent, it produced an emodin yield of 1.46%. In addition, testing using the ultrasound extraction high-performance capillary electrophoresis method with electrochemical detection (UE-CE-ED) and a solvent in the form of ethanol yielded 4.33% (Wang *et al.* 2019).

In their study, Xu *et al.* (2022), used the Ultrasonic-dispersive solid phase extraction technique (d-SPE) for emodin. Using 70% methanol to extract emodin from *P. multiflorum* plants, this technique a simple, fast, green, user-friendly, and inexpensive purification approach. The extraction results of the emodin obtained were 616.35 ± 3.24 mg/kg. The emodin was extracted and purified by d-SPE method using HC-C18 adsorbent and desorbed with acetonitrile. During the testing process, there was a linear relationship in the range of 0.3–100 mg/L for emodin with a detection limit of five analytes ranging from 0.01 to 0.08 mg/L, and recoveries in the range of 82.8–118.4%. This ultrasonic extraction method can significantly shorten the extraction time and reduce the amount of extraction solvent.

For *R. emodin* plant, the UAE process using ethanol solvent which was previously treated with acid hydrolysate was able to increase the yield level of emodin when compared to no treatment. The purpose of giving acid hydrolysate is to hydrolyze anthraquinone glycosides to increase the concentration of the extracted compounds (Arvindekar *et al.* 2015). Besides that, extraction of *R. palmatum* using the UAE method gives higher yields of anthraquinones, especially emodin, when compared to using the HRE and extraction method provided by the Ch.P (CEE) with the yield of emodin being obtained as much as 2.76 mg/g (Beňová *et al.* 2010).

For extraction from *Rhamnus* sp. namely *R. fallax*, *R. intermedia*, and *R. pumila* using the UAE method and methanol solvent respectively to produce 1.680, 0.050 and 0.339 mg/g emodin, respectively. Prior to the quantitative step, the resulting extracts were treated with a 6 M solution of HCl to hydrolyse glycosides so that more optimal extraction results could be obtained (Kosalec *et al.* 2013). Extraction of *F. japonica* or *P. cuspidatum* using the ultrasonic method can yield emodin extracts of 6.72 ± 0.25 mg/g. The solvent used in this process is a combination of methanol-water with a ratio of 50:50 v/v extracted for 30 min (Chen *et al.* 2013).

Furthermore, in the *R. Palmatum* extraction process various types of Natural Deep Eutectic Solvents (NADES) solvents were used. NADES is a mixture of two green solvents with a lower eutectic point than the eutectic point of each component of the NADES solvent. This type of solvent has more polar properties than water and has the same polarity as methanol (Liu *et al.* 2018). NADES has been widely used in the extraction of natural materials intended for various outcomes. NADES solvent extraction is proven to increase the yield of active plant metabolites. Apart from that, it can also reduce the energy consumption needed in the extraction process (Hikmawanti *et al.* 2021). Based on the results of the *R. palmatum* extraction test, the highest emodin yield was obtained from the ultrasonic extraction process using NADES solvent (a mixture of lactic acid-glucose-water with a ratio of 5:1:3) produces an emodin yield of $1.55\% \pm 0.02$ (Wu *et al.* 2018).

In others studies used RSM to maximize the yields of sennoside A, sennoside B, chrysophanol, aloe-emodin, and emodin from *S. alexandrina* (aerial parts). The optimal extraction conditions were found to be 52.1 min extraction time, 25.2 mL/g liquid to solid ratio and 64.2°C extraction temperature. The experimental values of sennoside A, sennoside B, chrysophanol, aloe-emodin, and emodin (2.237, 12.792, 1.529, 2.457 and 0.261%, respectively) agreed with those predicted (2.152, 12.031, 1.411, 2.331, dan 0.214%, respectively) by RSM models, thus demonstrating the appropriateness of the model used and the accomplishment of RSM in optimizing the extraction conditions (Alam *et al.* 2022).

Synthesis of emodin

Emodin can be synthesized by involving Friedel-Crafts acylation and Diels-Alder reaction (Yinga and Dazhao 2011) as a critical step. The starting materials for the earliest synthesis of synthetic emodin were m-cresol and 3,5-dimethoxyphthalic anhydride (Eder and Widmer 1923; With *et al.* 1924). A novel method of emodin synthesis (**8**) was developed utilizing 4-methylsalicylic acid (**1**) as the primary substrate. The process involves a sequence of chemical reactions, such as methylation and subsequent hydrolysis of the methyl ester, leading to the formation of carboxylic acid chloride (**3**). Compound **3** underwent a Friedel-Crafts acylation reaction with two steps and eight phases (Fig. 7). The researchers discovered that the utilization of lower temperature (83°C) in the steps proved to be more efficient. This stage resulted in a higher overall yield of the desired compound **8** (37%) (Chalothorn *et al.* 2019). However, there are limitations of the emodin synthesis, including the need for costly, hazardous, or regulated compounds, a complicated set-up, severe conditions, or low yields (Chalothorn *et al.* 2019). Emodin can be converted into its derivatives, such as emodic acid, amides, emodin alcohols, bromomethyl emodin, and emodin aldehydes compounds using appropriate reagents (Mitra *et al.* 2022).

Recent development in synthetic chemistry of emodin derivatives

The synthesis of emodin derivatives has garnered attention due to their diverse origins and biological roles, making it an essential natural active ingredient (Salama *et al.* 2003). Besides emodin, other anthraquinone aglycones are commonly found in natural plant sources such as chrysophanol, aloe-emodin, physcion, and rhein (Fig. 1). Chrysophanol can be synthesized from emodin by a dehydroxylation reaction in plants. In addition, physcion is also a derivative of emodin. Anthraquinone glycosides, e.g. emodin-8-glucoside, frangulin, and glucofrangulin, are formed when a sugar group such as glucose or rhamnose is attached to a C-6 or C-8 OH group by a β -glycoside bond. Then, aloe-emodin is an anthraquinone compound derived from chrysophanol via the polyketide pathway. This compound is an analogue or isomer of the compound emodin, which differs in the position of one hydroxyl group (Lu *et al.* 2019; Karatoprak and Başkal 2022; Nowak-Perlak *et al.* 2022). Physcion is a compound derived from emodin, which can be formed by transferring a methyl group to the C-6 hydroxyl of emodin. One way to make this emodin-derived compound is with the help of fungi. For example, *A. terreus* and *A. nidulans* fungi can produce physcion through microbial fermentation (Qi *et al.* 2022; Yao *et al.* 2023). Lastly, for rhein, emodin can be converted to 7-methyl rhein through their phenolic groups (Fonteneau *et al.* 2001). The further progress in the synthesis of emodin derivatives is summarized in the following section.

Acetylation and alkylation of emodin

As intermediate molecules in emodin derivatization, triacetyl-emodin (**9**) and trimethyl-emodin (**10**) have commonly been used. The reaction of emodin with acetic anhydride resulted in the acetylation of emodin to form **9** (Morooka *et al.* 1990). Paudel *et al.* (Paudel *et al.* 2019) modified the current method by replacing the strong acidic chemical H_2SO_4 with a basic pyridine in their investigation (Fig. 8). As an intermediary molecule, tri-O-acetoxyemodin (**9**) was synthesized to produce emodic acid and ω -hydroxyemodin. According to Salama *et al.* (2003), **10** showed promise under the reaction conditions for hypericin synthesis, which could be related to the acylated analogue's intrinsic instability (Obermu *et al.* 2001). A mixture of emodin with tetrabutylammonium bromide, anhydrous potassium carbonate, and dimethyl carbonate in the N,N-dimethylformamide was used to make the tri-O-methyl protected emodin derivative (Shao *et al.* 2022). Emodin modifications through alkylation were also done with reacting long-chain alkoxy groups at the 3-position (**11** and **12**) in the presence of K_2CO_3 as a catalyst (Chalothorn *et al.* 2019).

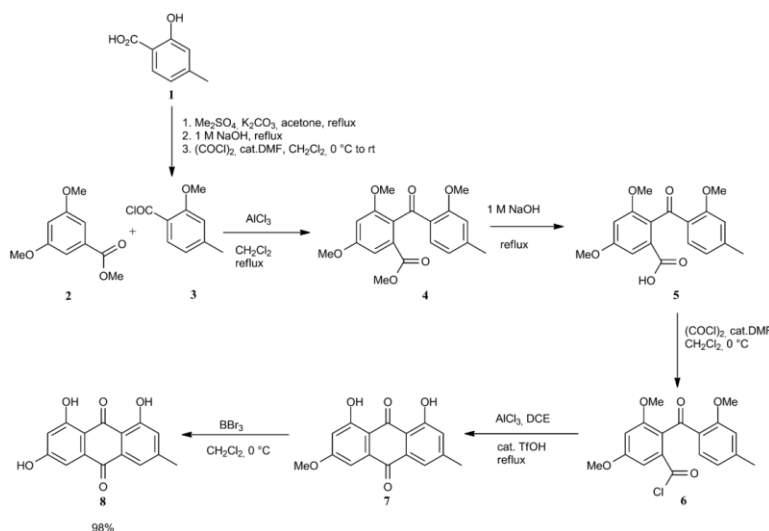


Fig. 7: Synthesis of emodin

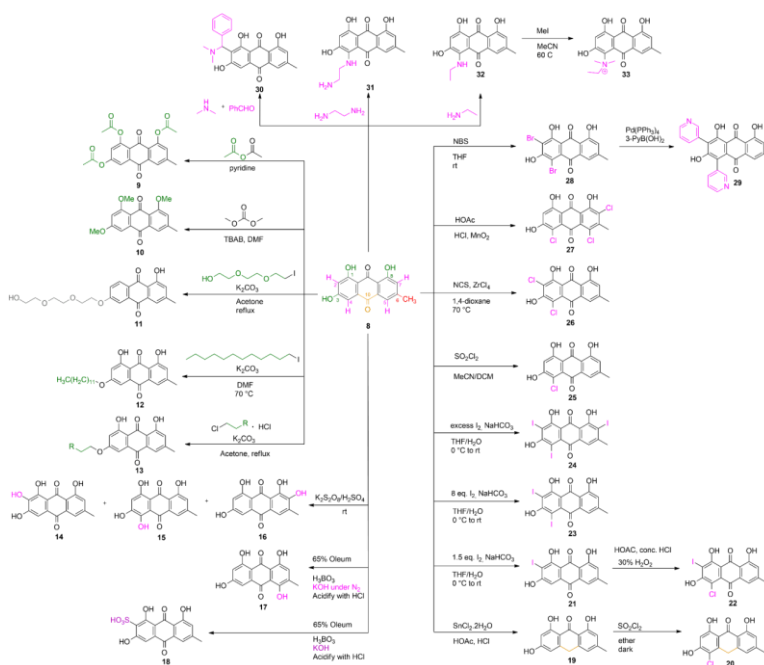


Fig. 8: Modification of emodin; an update 2012-2022

Emodine amine derivatives

The derivatives formed by the combination of tertiary amine groups and emodin were expected to be candidates for multifactor anti-Alzheimer's disease drugs, as the substituent was reported to have AChE inhibitory activities. A compound **13** was synthesized from the reaction of emodin with alkyl chloride amine in the presence of anhydrous K_2CO_3 in dried acetone (Fig. 8). According to the result (Fig. 9), compounds with various substituents exhibit an inhibitory action in the following order: piperidiny (**a**) > pyrrole alkyl (**b**) > dimethylamino (**c**) > morpholiny (**d**) (Kou *et al.* 2020).

Hydroxyemodin

Emodin underwent a reaction with metabisulfite, resulting in the formation of a combination of 2-hydroxyemodin (**14**), 4-hydroxyemodin (**15**), and 7-hydroxyemodin (**16**) (Fig. 8). These compounds were subsequently isolated using acidified silica gel column chromatography (Morooka *et al.* 1990; Paudel *et al.* 2020). Emodin, which underwent a reaction with 65% oleum and boric acid in the absence of nitrogen gas, resulted in the formation of emodin sulfuric acid (**18**) rather than 5-hydroxyemodin (**17**). During the hydroxylation, the initial attack specifically targeted the α -

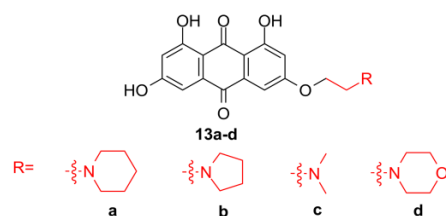


Fig. 9: Series of emodin amine derivatives

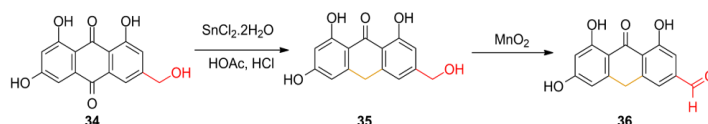


Fig. 10: Synthesis of aldehyde emodin anthrone derivate

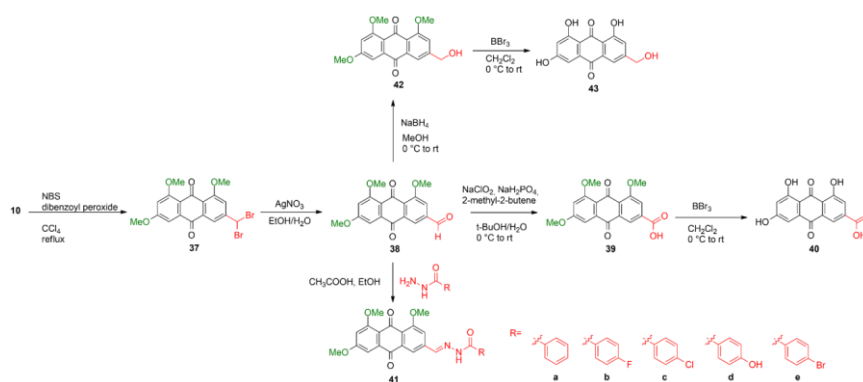


Fig. 11: Synthesis route of ω -hydroxyemodin, emodin aldehyde, emodic acid and emodin acylhydrazone derivatives

carbon of the anthraquinone system, avoiding the pre-existing hydroxylated ring (Banks *et al.* 1978).

Haloemodin

The electrophilic substitution of halogens onto the aromatic rings of emodin has resulted in the discovery of a unique class of halo-emodin. The reactions of emodin with higher mole ratios of elemental iodine resulted in the formation of 2-iodioemodin (**21**), 2,4-diiodoemodin (**23**), and 2,4,5-triiodoemodin (**24**) (Fig. 8). 2-iodine-4-chloroemodin (**22**) was achieved through 2-iodioemodin (**21**) chlorination using hydrogen peroxide in acetic acid (Duan *et al.* 2014). In their investigation, (Koerner *et al.* 2017) accomplished the first high-yielding regioselective synthesis of 2-and 4-position of chlorinated emodin. Sulfuryl chloride was used to generate 4-chloroemodin (**25**), while the reaction of emodin (**8**) with N-chlorosuccinimide (NCS) and zirconium chloride produced 2-chloroemodin. In addition, 2,4-dichloroemodin (**26**) was formed in the presence of mol N-chlorosuccinimide (NCS) and $ZrCl_4$ in dioxane solution (Obermu *et al.* 2001). Chlorinating of emodin facilitated by acid and MnO_2 resulted in the formation of 2,4,7-trichloroemodin (**27**). The bromination of emodin was

catalyzed by N-bromosuccinimide (NBS), yielding 2,4-dibromoemodin (**28**). Brominated emodin was used as an intermediate compound of **29** (Koerner *et al.* 2017).

Reduction of emodin

The synthesis of emodin anthrone (**19**) was described and modified in prior investigations (Gonçalves *et al.* 2019). The utilization of tin(II) chloride along with conc. HCl and glacial acetic acid have been identified as remarkably effective methods for emodin conversion into emodin anthrone derivatives. By adding large excess of HCl, the reduction of emodin produced a higher yield of compound **19** in the 30 min of reaction time. The reduction method was used on emodin (**8**) and ω -hydroxyemodin (**34**), yielding the corresponding compounds **19** and **35** with 90 and 92% yields, respectively. Oxidation of **35** in the presence of MnO_2 produced compound **36** with an 86% yield (Fig. 10; Liang *et al.* 2012).

Chlorination was also used to modify emodin anthracenone (Fig. 8). After treating emodin anthracenone (**19**) with sulfuryl chloride, a compound identified as the new 5-chlorinated anthracenone (**20**) was isolated. Due to separation difficulties and the inherent instability of the

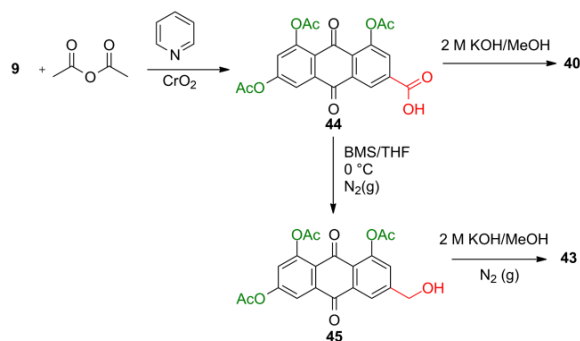


Fig. 12: Emodic acid and ω-hydroxyemodin synthesis from acetylation route

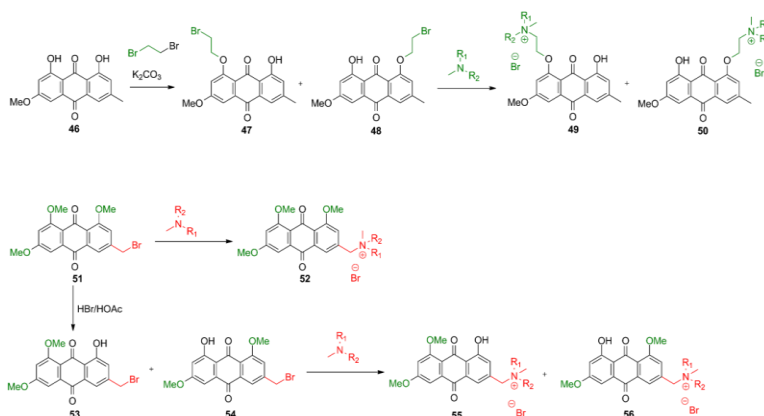


Fig. 13: Synthesis route for emodin quaternary ammonium salt derivatives

product, the attempt to synthesize 2-chlorinated anthraquinone was unsuccessful (Koerner *et al.* 2017).

Emodin ethylamine

The catalyst-free Mannich reaction was employed to substitute the C-2 position of emodin with dimethylamine and benzaldehyde, resulting in the formation of the emodin Mannich base (30) (Fig. 8). According to (Zhao *et al.* 2013), the reaction resulted in a product yield of 76% with complete combustion of the starting material. Amination at the 4-position of emodin by adding an ethylenediamine and ethylamine substituent gave analogues 31 and 32, respectively. The formation of 4-aminoemodin derivatives was achieved through the reaction of the molecule with diacetoxyiodobenzene in the presence of the suitable amine, employing the methodology previously described (Teich *et al.* 2004). The synthesis of a quaternary ammonium iodide analogue (33) was achieved via the reaction of compound 32 with iodomethane in acetonitrile at ambient temperature, resulting in a product yield of 86% (Chalothorn *et al.* 2019).

Emodin aldehyde

As a starting material for emodin alteration in the methyl

position at C-6, the emodin aldehyde derivative (38) was synthesized (Fig. 11). The bromination of tri-O-methylemodin (10) using N-bromosuccinimide and dibenzoyl peroxide as initiators, followed by oxidation with silver nitrate, yielded emodin analogues 37 and 38, respectively (Salama *et al.* 2003). Later, aldehyde was reduced with sodium borohydride, coupled with hydrazide molecule, and oxidized with sodium chlorite to produce compounds 39 and 42. After demethylation with boron tribromide, analogues 40 and 43 were formed. However, because demethylation of 38 failed, emodin aldehyde cannot be produced (Chalothorn *et al.* 2019).

In addition to the methylation pathway (Fig. 11), emodic acid (40) and ω-hydroxyemodin (43) production via acetylation have been described (Paudel *et al.* 2020). Compound 9 underwent a reaction with acetic anhydride and pyridine in the presence of CrO₂, resulting in the formation of 1,3,8-triacetyl emodic acid (44) by a similar process to the acetylation of emodin (Fig. 8). Compound 44 transformed to provide compound 40 or reduced to produce the acetylated ω-hydroxyemodin structure (45) using a solution of 2 M KOH in methanol. 45 was then subjected to de-acetylation, resulting in the formation of compound 43 (Fig. 12).

The derivatization of emodin-containing acylhydrazones, a significant subgroup of Schiff bases,

involved the dehydration of aldehyde **38** in the presence of glacial acetic acid in ethanol (Fig. 11). This process resulted in the formation of derivatives **41**. The acylhydrazone compound has broad biological properties due to the nitrogen and oxygen atom's ability to engage with receptors by hydrogen bond interaction (Takagi *et al.* 2007; Liu *et al.* 2014; Wang *et al.* 2014). Most reactions demonstrated good efficiency and resulted in the formation of the matching **41a-e** compounds with notable yields ranging from 72 to 79% (Shao *et al.* 2022).

Emodin quarternary ammonium salt derivatives

A lengthy quaternary ammonium salt side chain was added to emodin's 1- and 8-locations to assess pharmacophore positions' anticancer effects. The synthesis was started by alkylating the methylated emodin (**46**) with 1,2-dibromoethane in the presence of K_2CO_3 (Fig. 13). By treating the mixture of **47** and **48** with a sequence of tertiary amines, the corresponding quaternary ammonium salts **49** and **50** are produced. Because the separation of isomers **47** and **48** failed, **49** and **50** were synthesized in a mixture with **49** as the predominant product.

The modification was also done in the methyl group at the 6-position of emodin, while the hydroxyl groups were methylated. The synthesis of a series of compound **52** was reported by reacting the emodin with a sequence of derivate amine in chloroform. At room temperature, **51** demethylated using HBr aqueous solution, removing only one methyl by acid hydrolysis. Isomers of compounds **53** and **54** were acquired. However, their separation using column chromatography was unsuccessful. The combination underwent a reaction with a sequence of tertiary amines, forming a mixture of quaternary ammonium salts, primarily consisting of compounds **55** and **56**, with compound **55** being the prevailing product (Wang *et al.* 2012).

Conclusion

Extraction of emodin uses several commonly used methods (conventional extraction methods) such as maceration, reflux, Soxhlet, and others. The modern extraction methods are supercritical liquid extraction, sublimation, ultrasonication, and others. Some of the extraction methods that were carried out on an average did not give the overall percentage yield of emodin. The method is still to detect the presence or absence of emodin content from existing natural sources. Emodin is a promising chemical with potential for application as a novel pharmaceutical. Despite its extensive biological activity, emodin has little efficacy as a medication. Various recent modifications of emodin, including acetylation, alkylation, reduction and substitution of recognized promising groups, have been created to enhance the role of emodin in drug development.

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Author Contributions

CSM, MRI and FA wrote and prepared the manuscript. F, AM and AB reviewed the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

Not applicable.

Data Availability

Not applicable.

Ethics Approval

Not applicable to this paper.

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