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# A Review on the Extraction and Optimization of Phytochemicals from *Curcuma xanthorrhiza* Roxb

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**ABSTRACT**

**The genus Curcuma pertains to the Zingiberaceae family and consists of 70-80 species of perennial rhizomatous herbs. This genus originates in the Indo-Malayan region and it is broadly spread all over the world across tropical and subtropical areas. *Curcuma xanthorrhiza* belongs to the Zingiberaceae family is a rich source of phenolics and terpenoids with various bioactivities. This study aims to provide more information about botanical features, biological activities, essential oils, phytochemicals, ultrasound-assisted extraction, and optimization of *C.xanthorrhiza* by response surface methodology and HPLC for further advanced research. Because of its use in the medicinal and food industries, *C.xanthorrhiza* is an extremely important economic genus. *C.xanthorrhiza* rhizomes are the source of a yellow dye and have traditionally been utilized as spices and food preservers, as a garnishing agent, and also utilized for the handling of various illnesses because of the chemical substances found in them. Furthermore, Because of the discovery of new bioactive substances with a broad range of bioactivities, including antioxidants, antivirals, antimicrobials and anti-inflammatory activities, interest in their medicinal properties has increased. Lack of information concerning botanical features, biological activities, essential oils, phytochemicals, ultrasound-assisted extraction, and optimization of *C.xanthorrhiza* by response surface methodology and HPLC is the biggest problem that the researcher encountered. This review recommended that collecting information concerning the *C.xanthorrhiza* may be providing more opportunities for further advanced studies lead to avoid wasting time and use this information for further research on bioactive compounds which are beneficial in medicinal purposes.**

***Keywords-*** *Curcuma xanthorrhiza*, Ultrasound-Assisted extraction, Xanthorrhizol, Curcumin, RSM.

## I. INTRODUCTION

*Curcuma xanthorrhiza Roxb*. belongs to the Zingiberaceae family (ginger family) and originated plants of Indonesia. It is cultivated in Sri Lanka, Malaysia, the Philippines, and Thailand (Theresia *et al*., 2019). It is widely used for the traditional treatment of many illnesses in South East Asian countries, including migraines, constipation, liver problems, and inflammatory conditions. It has been reported that *C. xanthorrhiza* has utility for hepatitis, rheumatism, cancer, hypertension liver problems, diabetes, and heart disorders (Erpina *et al*., 2017). *C. xanthorrhiza* commercially has an interest in the development of new medicines for the treatment of different diseases by both research centres and medicinal companies (Anjusha & Gangaprasad, 2014).

*C. xanthorrhiza* consists of non-volatile curcuminoids and volatile essential oil (Darmawan & Pramono, 2016). Xanthorrhizol **(1)** is known as the major component of *C. xanthorrhiza* that can be extracted from either essential oil or dried powder of *C. xanthorrhiza* rhizome. It is a sesquiterpenoid-type bisabolane. This compound accounts for almost 46.3% of the whole essential oil component via hydrodistillation techniques (Devaraj *et al*., 2013; Tusek *et al*., 2018). Besides, other extraction techniques can be utilized to extract xanthorrhizol **(1)** from dried rhizome of *C. xanthorrhiza* such as ultrasound-assisted extraction (UAE), maceration, microwave-assisted extraction, Soxhlet, supercritical extraction of carbon dioxide, and

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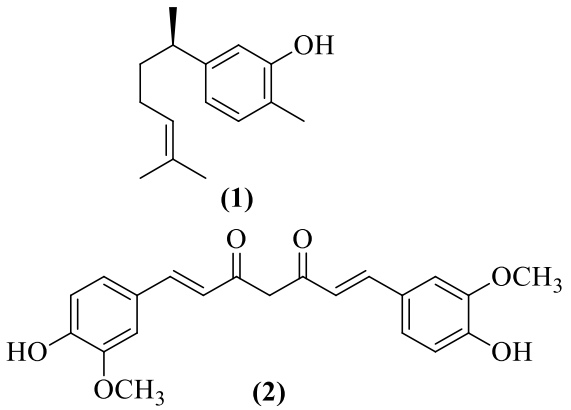
solid-phase extraction methods (Başpınar *et al*., 2017). Moreover, xanthorrhizol **(1)** is a highly potent bioactive compound capable of achieving the current need for new drug discovery (Oon *et a*l., 2015). Also, other major compounds that have been discovered from *C. xanthorrhiza* are curcuminoids mainly curcumin **(2)** (Aziz *et al*., 2018). Curcumin **(2)** is a diarylheptanoids phenolic compound which extracted from dried rhizome of *C. xanthorrhiza* using different extraction methods (Xu *et al*., 2017).




## II. METHODOLOGY

This study is a review study on extraction and optimization of phytochemicals from Curcuma. xanthorrhiza which all information have been gathered from reliable scientific sources.

## III. PRIOR APPROACH

The optimization of bioactive compounds and extraction methods are of great interest in the food and medicinal industries for further research and development. Over the years, medicinal plants in their native and processed from have been commonly used in traditional medicine, due to the various biologically active molecules found within them (Taher & Sarmidi, 2015). Extraction is the most critical step in making full use of the bioactive molecules found in medicinal plants (Başpınar *et al*., 2017).

One of the effective techniques for extracting desirable components from plant materials is ultrasonic-assisted extraction that is completely adaptable on small or large scales (i.e. on an industrial scale or laboratory scale). Conventionally, an ultrasonic tool is much simpler and easier to operate (Tatke & Rajan, 2014). Additionally, Ultrasound-assisted extraction (UAE) has been commonly utilized for the laboratories with outstanding benefits including lower energy consumption, less use of solvents, more efficient mixing, and shorter extraction time (Zhang *et al*., 2020). Alternatively, Ultrasonic-assisted extraction can be conducted at a lower temperature to prevent thermal damage during extraction and volatile components degradation during boiling (Xia *et al*., 2006).

Response surface methodology (RSM) is an effective mathematical tool commonly utilized for optimizing the experimental conditions for technical operations in many industries. RSM also has benefits for maximizing or minimizing different independent variables as it simultaneously measures the impact of various factors and their respective interplay on one or more variables (Azahar *et al*., 2017). Meanwhile, RSM is an empirical statistical experiment method design that aims at finding the optimum parameters and achieving the best response. Also, RSM helps to reduce the number of experimental trials required and reveals the relationship between independent variables to multiple regression responses (Subuki *et al*., 2018).

Quantification of phytochemicals is important to quantify and find concentration of targeted compounds from analyt. HPLC was commonly used to measure concentration of phytochemicals. The retention time of HPLC analysis was affected by several factors such as mobile phase, stationary phase, detectors and the type of columns to be used (Anggarani & Maulana, 2018). Generally, methanol and acetonitrile are commonly used in the mobile system. In addition, reversed-phase $C_{18}$ HPLC and polar organic solvents are also widely used for phytochemical compound quantification. HPLC is a system widely used in terms of simplicity, speed and high efficiency. Photodiode array detector (PDA) has many benefits, such as high selectivity, high sensitivity and fast analyses (Zhu *et al*., 2018).

## IV. OUR APPROACH

***Curcuma xanthorrhiza***

The Zingiberaceae family comprises of perennial herb plants, consisting delicate fleshy inflorescences that occur as lateral, terminal, or both. The curcuma genus is one of the Zingiberaceae family's largest genera of 120 species, commonly used as herbs, medicinal items, colorants, and ornamental plants. It is spread in Australia, China, Asia, and the South Pacific countries. One variety and twenty species from southern India were recorded (Santhoshkumar & Yusuf, 2019). The curcuma genus belongs to the Zingiberaceae family consisting of annual or perennial rhizomatous plants. The curcuma genus consists of 70 species, typically distributed overwhelm tropical and subtropical areas around the world. Out of the 70 species, approximately 40 species originated from India have been recorded. The curcuma has been naturally seen in Malaysia, Indochina, Thailand, Indonesia in India and eventually spread to northern Australia also it is widely grown in the Asia, South America, West Africa, and Australia (Kaliyadasa & Samarasinghe, 2019).

Traditionally, *C. xanthorrhiza* is a popular herbal pharmaceutical plant with its anti-cancer

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activities, anti-inflammatory, and defensive impact on liver damage (Zhang *et al*., 2015). Temulawak (*C. xanthorrhiza Roxb*.) is an Indonesian native plant. This plant is one of Indonesia's five largest herbal medicinal products to be grown and commercialized. The human being was acquainted with *C. xanthorrhiza* rhizome, which has been utilized in traditional medicinal and agro-industry as raw materials, including such natural food colours. Other drug therapy activities, such as antioxidants, antimicrobials, anti-inflammation, and anticancer have been documented in temulawak chemical compounds (Cahyono *et al*, 2018). Table 2.1 presents the taxonomy of *Curcuma xanthorrhiza* (Kumar *et al*., 2011).

**Table 1.1: The taxonomy of *Curcuma xanthorrhiza***

| Rank | Scientific Name |
|---|---|
| Kingdom | Plantae |
| Sub-kingdom | Viridaeplantae |
| Phylum | Tracheophyta |
| Division | Magnoliophyta |
| Class | Liliopsida |
| Sub-class | Commelinids |
| Superorder | Zingiberanae |
| Order | Zingiberales |
| Family | Zingiberaceae |
| Tribe | Zingiberae |
| Genus | Curcuma |
| Species | *Curcuma xanthorrhiza* |

***Botanical Description of Curcuma xanthorrhiza***

*C. xanthorrhiza* commonly referred to Indonesia as temulawak or Javanese turmeric has been found both wild and grown in Indonesia (Lin *et al*., 1996) that mainly grown on the island of Java, Indonesia (Rohaeti *et al*., 2015) Therefore, it is cultivated in Malaysia, Philippines, Sri Lanka, and Thailand. It is locally called as Temulawak in Malaysia. *C. xanthorrhiza* is a low-growth plant with a ginger-like rhizome that has an aromatic, pungent odour and bitter flavour. *C. xanthorrhiza* is native to north-eastern India and is widely grown in many parts of India, Sri Lanka, and China. It has a deep yellow rhizome with brownish-purple veins and green leaves (Anjusha & Gangaprasad, 2014; Zhang *et al*., 2015) which grows to a height of three to five feet (Kumar *et al*., 2011).

Temulawak is an herb with branched rhizome, inside orange or orange-red, outside dark yellow to reddish-brown, blades oval-oblong to oblong-lanceolate, 25 – 100 cm x 8 -20 cm, leave sheaths up to 75 cm long, green with a pale brown band around the midrib, labellum 2-2,5 cm x 1,5-2 cm, yellowish with a dark yellow median band, corolla 4-6 cm long; light red, other staminodes longitudinally folded, yellowish-white, anther with long spurs; batch pale green, coma bracts purple, inflorescence on the separate shoot,. *C. xanthorrhiza* is naturally recognized in thickets and teak forests, primarily on dense, moist, humus-rich soils up to 750 m above sea level (Sri Adi Sumiwi, 2008). The temulawak plant has usually 50 to 200 cm in height (Kaliyadasa & Samarasinghe, 2019). The plant has a group of plumb pseudo stems up to 2 m long in an underground rhizome and each pseudo stem has 40–90 cm long and 15–21 cm broad blades with about eight blade leaves. (Rajkumari & Sanatombi, 2017). Figure 2.1 and Figure 2.2 show the whole plant, leaves, flower, and rhizome of *Curcuma xanthorrhiza*.

**Figure 2.1: The whole plant of *Curcuma xanthorrhiza*** (Oon *et al*., 2015)


**Figure 2.2** (A) Leaves, (B) Flowers, and (C) Rhizomes of *Curcuma xanthorrhiza* (Oon *et al*., 2015)

***Biological Activities and Traditional Uses of Curcuma xanthorrhiza***

Pharmaceutical plants are main source of raw material for traditional medicinal systems as well as for modern medication. Today plant products are used as home remedies, through the industrialized and

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developing globe for the pharmaceutical industry. So, they perform an important fundamental proportion of the global drug market (Devaraj *et al*., 2013). Moreover, plants have an almost infinite ability to synthesize various secondary metabolites that have wide-ranging biological functions that are useful to humans. *C. xanthorrhiza Roxb*. is an important and potential pharmaceutical plant which is widely used in the local food industry and consists of diverse therapeutic values (Ab Halim *et al*., 2012). Traditionally, all cultures used plants as medicine from ancient times until today. Medicinal plants are important nowadays for the global economy (Anjusha & Gangaprasad, 2014).

In some tropical region like Malaysia and Indonesia, *C. xanthorrhiza* Roxb, commonly known as Java turmeric, has been traditionally used as a food and medicinal plant for medicinal purposes to treat diseases such as stomach diseases, liver hepatitis, rheumatism and skin inflammation. (Kim *et al*., 2014). It is used as an Indian cobra antivenin, used as a tonic, to treat digestive problems (Anjusha & Gangaprasad, 2014). As far as, Javanese turmeric is the rhizome of *C. xanthorrhiza* it is used in Indonesia and South East Asia as a food spice and as a preservative and colouring agent (Darmawan & Pramono, 2016). Many studies have demonstrated the ability of *C. xanthorrhiza* as an anticancer. Xanthorrhizole **(1)** has the potential as a chemo-preventive and anticancer agent in *C. xanthorrhiza* by showing anti-proliferation activity against MCF-7 cells. The combination of xanthorrhizol **(1)** and curcumin **(2)** can anti-proliferate breast cancer cells.

Therefore, the rhizome of temulawak is a yellow colouring source and has historically been used as spices, food preservatives, flavouring agents and home remedies to cure many diseases with chemical compounds contained (Lukitaningsih, 2020). Temulawak has been used to treat enlarged liver, hepatic disorders, chest pain, skin diseases, spleen, stomach ulcer, diabetes cough, boils, blood purifiers, and rheumatism in terms of traditional medicinal uses. Nowadays, different parts of this plant are widely consumed as cooked or raw vegetables. They are also listed as a foodstuff with a nutritional balance, as the plants are rich in, proteins, fats, starch, carbohydrates, minerals, and vitamins (Rajkumari & Sanatombi, 2017).

Essential oil is a precious natural product. It can be found in cosmetics, perfumes, aromatherapy, and nutrition, as raw as a spice (Srivastava *et al*., 2001). It was believed to have a beneficial impact in aromatherapy along with the additional aromatic compounds for several decades (George *et al*., 2015). This has also been utilized for thousands of years as food preservatives, alternative drugs, medicinal products, and natural therapies (Utami *et al*., 2014). It has different functions until today, including conferring pests and disease resistance. It is utilized in the cosmetics industry to manufacture shampoos. Lotion, cologne, cream, and other make up products (Lis-Balchin & Deans, 1997).

*C. xanthorrhiza* likewise recognized in Indonesia as “Javanese turmeric”, “Javanese ginger” or “temulawak” and “wan-salika-linthong” in Thailand which is originated to Indonesia and Malaysian Peninsula, grown in the Philippines, Sri Lanka, Thailand, Malaysia. The *C. xanthorrhiza* rhizomes are used within Indonesia as food colouring, starch sources, and colouring, cosmetics, and herbal medicine (Adams, 2007). Infusions and extracts of *C. xanthorrhiza* exist for conventional medicine causes that *C. xanthorrhiza* rhizome is used to treat, diabetes, hypertension, fevers, diarrhoea, constipation, dysentery, stomach pain, rheumatism, liver damage, haemorrhoids, skin rash, and other cancers. The dried powder or fresh rhizome of *C. xanthorrhiza* is utilized in northern Thailand for skin diseases (Dosoky & Setzer, 2018).

Meanwhile, Javanese turmeric (*C. xanthorrhiza*) has a long history of Indonesian medicinal use (Aziz *et al*., 2018) which has also displayed diuretic, anti-cancer, anti-inflammatory, antispasmodic, anti-leucorrhoea, anti-bacterial, anti-oxidant, anti-hypertensive, anti-rheumatic, anti-hepatotoxic, anti-dysmenorrhea, and antifungal effects. This decreases cholesterol, prevents migraines, constipation, and enhances the flow of milk during breastfeeding (Erpina *et al*., 2017). It is confirmed that curcuminoids and xanthorrhizol **(1)**, derived from turmeric rhizomes cause the therapeutic effect (Aziz *et al*., 2018).

Xanthorrhizol **(1)**, the major component of *C. xanthorrhiza*’s essential oil, is a sesquiterpenoid-type bisabolane. This compound accounts for almost 46.3% of the whole essential oil component via hydrodistillation technique (Zwaving & Bos, 1992). In comparison, curcuminoids have anti-inflammatory effects, is a very powerful antioxidant as well as antihypercholesterolemia and can be used to avoid cholera while xanthorrhizol **(1)** shows biological activities such as anti-inflammatory, antioxidant, anticancer, antimicrobial, antihyperglycaemic, antihypertensive, antiplatelet, nephron-protective, hepatoprotective, estrogenic (Aziz *et al*., 2018).

***Essential oils of Curcuma xanthorrhiza***

The Curcuma genus (Zingiberaceae) is a family of persistent rhizomatous plants that originate in tropical and subtropical areas. Turmeric has widely grown in tropical and subtropical places of Asia, South America, and Australia. Many species of Curcuma are medicinally used in Malaysia, Bangladesh, Nepal, India, and Thailand. The most commonly used section of the plant is the rhizome (Dosoky & Setzer, 2018). Temulawak rhizome has its essential oil that contains volatile aromatic compounds which has the essence of this plant's fragrance (Rafi *et al*., 2015). The most active constituents of the rhizome are volatile oil and non-volatile curcuminoids Several phytochemical research on turmeric oils have resulted in the discovery of sesquiterpenoids and monoterpenoids (Dosoky & Setzer, 2018).

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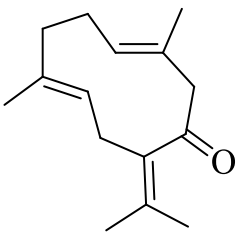
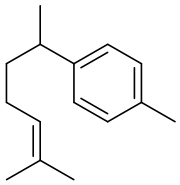
Curcuma essential oil has a broad variety of pharmacological effects, including carminative, including anti-inflammatory, anticancer, antidiarrheal, anti-proliferative, hypo-cholesterol emic, anti-diabetic, anti-hepatotoxic, antiviral, insecticidal, diuretic, anti-rheumatic, hypotensive, antioxidant, antimicrobial, larvicidal, antiviral, cyclootic antithrombotic, and anti-tyrosine effects (Li *et al*., 2014). It has also been recognized that turmeric oils improve the immune system, enhance blood circulation, speed up the removal of toxic, and promote digestion (Dosoky & Setzer, 2018). Essential oils are a complex combination of volatile and non-volatile substances formed by various parts of the natural products (Adams, 2017). This includes terpenes, sesquiterpenes, and oxygenated derivatives for volatile substances whereas it consists of fatty acids, waves, presales, and carotenoids for non-volatile substances (Schmidt *et al*., 2015). The essential oils perform different functions such as; treatment of various diseases, the flavour in food or preservation as well as in cosmetics industries can be used, in particular for the production of shower baths, lotion, shampoo, and cologne (Aziz, 2017).

The amount of essential oil is defined via the presence of the aromatic compounds in the essential oils, such as oxygenated and terpenes compounds, by the presence of aromatic compounds (Adams, 2007). The essential oil will be known as a good quality essential oil if the oxygenated compound is of high value or is a major compound (Coutinho *et al*., 2009). It is because the oxygenated substance is extremely odorous. Alcohols, aldehydes, ketones, acids, and esters are the compounds that are commonly present in the essential oils (Ranasinghe *et al*., 2003; Prijatmoko *et al*., 2018).

Monoterpenes consist of 80–88% essential oil of *C. xanthorrhiza* rhizome. Three major chemo-types have been found: (1) α-terpinolene-rich chemo-type; (2) α-curcumene-dominated chemo-type; and (3) xanthorrhizol-dominated chemo-type. Xanthorrhizol **(1)** forms 64.4% of the hydrodistilled oil obtained from *C. xanthorrhiza* fresh rhizome in India, although, just 8.0% of the oil yielded via supercritical carbon dioxide extraction (Dosoky & Setzer, 2018). The hexane extract of *C. xanthorrhiza* contained germacrone **(3)** and α-curcumene **(4)** while the dichloromethane extract contained xanthorrhizol **(1)** and curcumin **(2)** (Park *et al*., 2015).

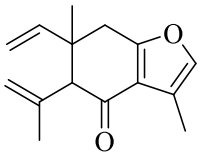



**(3)**

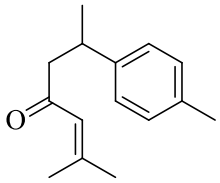


**(4)**

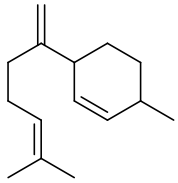
Essential oils of temulawak produced in India comprises main compounds including ar-curcumene **(4)** and xanthorrhizol **(1)** whereas Thailand consisted curzerenone **(5)**. Three recent kinds of literature studies that addressed Indonesia's major components of curcuma oil noted which include ar-turmerone **(6),** ar-curcumene **(4)**, bisabolane **(7),** and xanthorrhizol **(1)**, also curcuma oil produced in India (Zhang *et al*., 2014). Nevertheless, a study performed in the Meru Betiri National Park is placed between the city of Jember and Banyuwangi, in the southeast of Java Island has shown that *C. xanthorrhiza* oil from Meru Betiri National Park comprises of ar-turmerone **(6)**, and β-elemene **(8)**, but without any reported xanthorrhizol **(1)** and curzerenone **(5)** as the main compounds (Oktavianawati *et al*., 2018).



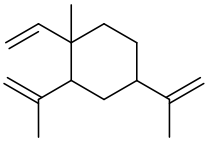

**(5)**




**(6)**



**(7)**



**(8)**

***Phytochemical Studies of Curcuma xanthorrhiza***

From ancient times until now, the curcuma genus has been shown traditional application usage over an extended history from folk medicine to food products. Further, then 70 types of turmeric are widely dispersed and extensively cultivated around the world. Curcuma was naturally spread to Malaysia, Thailand, Indonesia, India, Indochina and eventually expanded to northern Australia. Several phytochemical, pharmacological, and molecular research on different curcuma species have been performed worldwide. A concern in their medicinal properties has grown because of the new bioactive compounds discovered with a wide variety of bioactivities like antioxidants, antivirals, antimicrobials, and anti-inflammatory activities. The curcuma species rhizomes are recognized as one of the most commonly used components of chemical extractions (Kaliyadasa & Samarasinghe, 2019).

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***Diarylheptanoids from Curcuma xanthorrhiza***

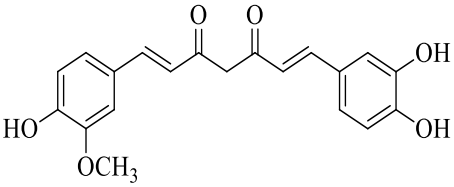
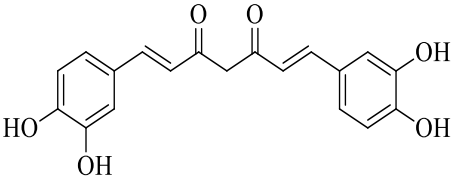
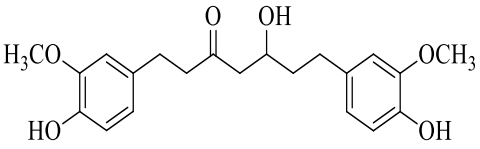
*C. xanthorrhiza* consists of volatile essential oils and non-volatile curcuminoids which are known as the active constituents of the rhizomes. The main components in curcuma oil are sesquiterpenoids and monoterpenoids (Kaliyadasa & Samarasinghe, 2019). Diarylheptanoids consist of 1,7-diphenylheptane (Lv & She, 2012). They are known as one of the major secondary metabolites in many curcuma species including *C. xanthorrhiza* (Lee *et al*., 2014). Diarylheptanoids which commonly known as curcuminoids have been classified into two groups, which are linear diarylheptanoids and cyclic diarylheptanoids (Lv & She, 2012). Therefore, both groups can be categorized into phenolic and non-phenolic diarylheptanoids (Claeson *et al*., 1993).

Phenolic compounds (diarylpentanoids, diarylheptanoids, the phenyl propene derivatives) and terpenoids (monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids) were present in the *C. longa*, and some at *C. xanthorrhiza* originally (Lukitaningsih, 2020). As a major group of compounds in *C. longa* and *C. xanthorrhiza* diarylheptanoids or curcuminoids (curcumin **(2)**, demethoxycurcumin **(9)**, bisdemethoxycurcumin **(10)**, etc.) and sesquiterpenoids were identified (Rohaeti *et al*., 2015). The relative amount of these components have been ranged from 68% to 76% for curcumin **(2)**, while demethoxycurcumin **(9)** and bisdemethoxycurcumin **(10)** ranged from 23% to 29% and 1% to 3% respectively (Cahyono *et al*., 2018).

***Terpenoids from Curcuma xanthorrhiza***

Terpenoids are a mixed group of phytochemicals comprising aromatic, non-aromatic, volatile, and non-volatile compounds that exhibit an important role in conventional herbal drugs and are known for antibacterial, antineoplastic and other medicinal products characteristic (Lee *et al*., 2014). They are classified into several groups according to the number of isoprene units which can be distinguished in the parent nucleus: monoterpenoids consist of two isoprene units with molecular formula $C_{10}H_{16,}$ sesquiterpenoids consist of three isoprene units with molecular formula $C_{15}H_{24}$ diterpenoids consist of four isoprene units with molecular formula $C_{20}H_{32,}$ triterpenoids consist of six isoprene units with molecular formula $C_{30}$ $H_{48}$ (Breitmaier, 2006). The most abundant terpenoids in the curcuma species are sesquiterpenoids (Lee *et al*., 2014). They can be classified into several groups depending on their structure which includes: bisabolane, bisaborane, cadalene, cadinane, carabrane, cuparane, curcumane, elemane, eudesmane, furanoeudesmane, germacrone, and guaiane (Ravindran *et al*., 2007; Park *et al*., 2014). Table 2.2 reports review on the phytochemical studies of *Curcuma xanthorrhiza.*

**Table 1.2: Review on the phytochemicals of *Curcuma xanthorrhiza***

| Plant Part | Group | Structure | References |
|---|---|---|---|
| Rhizome | Diarylheptanoid |  Demethoxycurcumin **(9)** | (Wang *et al*., 2018) |
| Rhizome | Diarylheptanoid |  Bisdemethoxycurcumin **(10)** | (Halder *et al*., 2016) |
| Rhizome | Diarylheptanoid |  Hexa-hydro-curcumin **(11)** | (Cahyono *et al*., 2018) |

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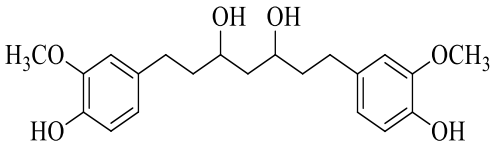
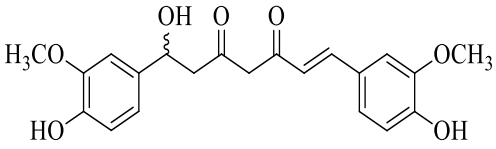
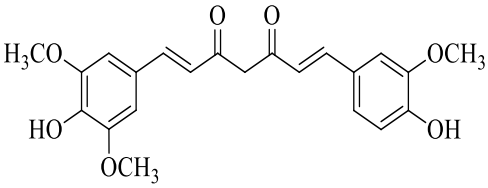
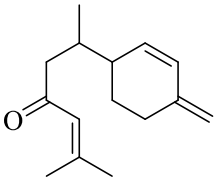
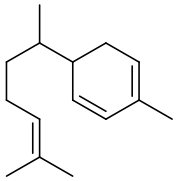
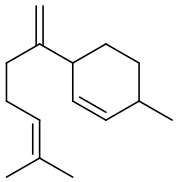
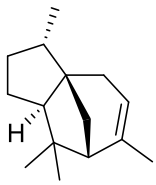
|---|---|---|---|
| Rhizome | Diarylheptanoid |  Octa-hydro-curcumin **(12)** | (Uehara *et al.*, 1987) |
| Rhizome | Diarylheptanoid |  (1E)-Hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-6-heptene-3,5-dione **(13)** | (Uehara *et al.*, 1987). |
| Rhizome | Diarylheptanoid |  1-(4-hydroxy-3,5-dimethoxy phenyl)-7-(4-hydroxy-3-methoxyphenyl) -(1E,6E)-1,6-heptadiene-3,5-dione **(14)** | (Masuda *et al.*, 1992) |
| Rhizome | Sesquiterpenoid |  β-Turmerone **(15)** | (Dosoky & Setzer, 2018) |
| Rhizome | Sesquiterpene |  Zingiberene **(16)** | (Butu *et al.*, 2014) |
| Rhizome | Sesquiterpene |  β-Bisabolene **(17)** | (Davies *et al.*, 2014) |
| Rhizome | Sesquiterpene |  α-Cedrene **(18)** | (Zhang & Fan, 2015) |

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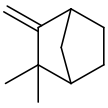
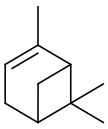
| Rhizome | Monoterpene |  Camphene **(19)** | (Volzone *et al*., 2001) |
| Rhizome | Monoterpene |  α-Pinene **(20)** | (Leite *et al*., 2007) |

***Ultrasound-Assisted Extraction Method of Curcuma xanthorrhiza***

Pharmacologically, active compounds are typically in low concentrations in herbal plants, and various efficient and specific extraction approaches were developed to extract them from the raw material. Organic solvent extraction is the most commonly used process (Giang *et al*., 2019). This method of extraction has disadvantages, for example organic solvents consumption, hazardous waste production and Limited adjustable parameters to handle extraction selectivity. Hence, the development of a more effective, easier, less chemical-intensive and less costly technique is commercially ideal for production (Salea *et al*., 2014).

On the other hand, a phytomedicine production demands the use of different processing techniques, such as extraction of active herbal components or chemical markers. For this reason, various techniques and tools can be implemented. Extraction methods such as static and dynamic maceration, convection extraction (CE), percolation, supercritical fluid extraction (SFE), microwave-assisted extractions (MAE), and ultrasound-assisted extraction (UAE) are widely used. Nevertheless, this approach can be time consuming due to specific requirements involve the use of a huge quantity of organic solvent and might have lower efficiency in extraction (Paulucci *et al*., 2013). Recently, eco-friendly extraction technique such as ultrasound-assisted extraction (UAE) has been utilized for the extraction of phenolic compounds from plants (Le *et al*., 2019).

Products extracted from pharmaceutical plants have for centuries been used as a main source of medications worldwide. Previous studies suggest that terpenoids and phenolic compounds are involved in the prevention of disease in the plant extracts. The extraction solvent is a critical factor that could significantly affect the metabolite content of the fractions and their biological activities, as bioactive compounds with different chemical properties and polarities could be obtained differently from different solvent (Weber *et al*., 2011). *C. xanthorrhiza* can be extracted with different extraction methods as summarized in the Table 2.3.

**Table 1.3: Previous reported extraction methods of *Curcuma xanthorrhiza***

| Temperature | Time | Sample: solvent | Type of solvent | Method of extraction | References |
|---|---|---|---|---|---|
| Not stated | 48h | 30g : 50 mL | Methanol | Cold Maceration | (Santhoshkumar & Yusuf, 2019) |
| 40°C | 1h | 5g : 100 mL | Ethanol | Ultrasonic Bath Sonicator | (Awin *et al*., 2016) |
| 40-50°C | 24h | 5mg : 150 mL | Methanol & Distilled water | Soxhlet | (Anjusha & Gangaprasad, 2014) |
| 50°C | 1h | 100g : 80mL | Not stated | Supercritical Carbon Dioxide | (Salea *et al*., 2014) |
| 40-45°C | 3h | 100g : 80 mL | Methanol | Cold Maceration | (Syahbirin & Nurfadilawati, 2017) |
| 78°C | 2h | 15g :750 mL | Ethanol | Cold Maceration | (Kim *et al*., 2007) |
| 60°C | 2h | 2kg:70 mL | Ethanol | Maceration & Percolation | (Rosidi *et al*., 2016) |
| Not stated | 72h | 800g : 8L | Ethanol | Cold Maceration | (Devaraj *et al*., 2010) |
| 50°C | 10 mins | 0.1g : 40 mL | Ethanol | Ultrasonic water bath | (Akter *et al*., 2018) |
| 60°C | 30 mins | 50g : | Methanol | Cold Maceration | (Ab Halim *et al*., |

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|---|---|---|---|---|---|
| | | 800 mL | | | 2012) |
| 27°C | 3 days | 50g : 1L | Ethanol | Cold Maceration | (Ab Halim *et al.*, 2012) |
| 60°C | 5 mins | 0.1g:2 mL | Methanol | Ultrasonic water bath | (Weber *et al*., 2011) |
| 25°C | 2 days | 29g : 200mL | Methanol | Cold Maceration | (Akter *et al.*, 2019) |
| Not stated | 72h | 800g : 8L | Ethanol | Cold Maceration | (Ab Halim *et al.*, 2012) |
| Not stated | 1h | 50g : 100mL | Ethanol | Ultrasonic bath | (Awin *et al*., 2019) |
| Not stated | 24h | 25g : 50mL | Ethanol | Soxhlet | (Nurcholis *et al.*, 2016) |
| 60°C | 2h | 0.5g : 25mL | Methanol | Cold Maceration | (Alafiatayo Akinola *et al*., 2014) |
| 37°C | 1 week | 1kg : 5L | Ethanol | Cold Maceration | (Ngadino *et al*., 2018) |
| Not stated | 24h | 500g : 2L | Dichloro methane | Maceration | (Weber *et al*., 2011) |

***Optimization of Ultrasound-Assisted Extraction (UAE) by Response Surface Methodology (RSM)***

Selecting the correct extraction technique would result in obtaining the maximum extract yield and simultaneously, allow targeted compounds to be extracted in plants which ultimately improve the quality of the end product. Conventional extraction methods have many drawbacks, such as longer extraction time, using expensive and harmful organic solvents, poor selectivity for extraction, and allow a post extraction process to remove solvent from the extract (Shah *et al*., 2016). However, numerous factors are involved in the effectiveness of extractions, such as a form of solvents, concentration of solvents, temperature, time, pH, and solid-liquid ratios (Azahar *et al*., 2017).

The optimum parameters can be calculated using response surface methodology (RSM) (Subuki *et al*., 2018). Response surface methodology (RSM) is one of the most commonly used experimental designs for optimization. It is a useful method since it allows the evaluation of the effects of multiple factors and their interactions on one or more response variables (Aydar, 2018). In other words, RSM is a reliable statistical method which commonly utilized to design experiments and find the optimum conditions of variables for appropriate, targeted responses. Besides, reducing the number of experimental trials needed by optimizing the extraction process and analyse the variations of all factors and responses simultaneously, and also identify the relationship between them (Shah *et al*., 2016). Furthermore, the optimal extraction parameters (temperature, time, and solid-liquid ratio) for extracting the maximum quantity of phenolic compounds from the *C. zedoaria* leaves were determined via RSM (Azahar *et al*., 2017). Typically, there are two main experimental designs utilized in the response surface methodology are Box-Behnken designs (BBD) and central composite design (CCD) (Aydar, 2018). Additionally, each of parameters has five levels which coded as +2, +1, 0, -1, -2 in the CCD design and three levels which coded as +1, 0, -1 in the BBD design (Barabadi *et al*., 2014).

Ultrasound-assisted extraction is currently gradually replacing conventional extraction methods. Ultrasound-assisted extraction can achieve a high extraction output in a very short period by spreading liquids with various polarities to create fine emulsions and speeding up the process of reaction kinetics within the reaction process. To obtain these purposes, ultrasound-assisted extraction is widely distributed in the extraction, with the advantages of saving time and preserving heat-sensitive bioactive compounds from degradation at lower overall temperatures. Various parameters, such as ultrasonic time and solvent composition may affect the ultrasonic extraction efficiency independently or jointly (Wang *et al*., 2017). Using Box-Behnken Design (BBD) response surface methodology (RSM) has been commonly known as a very powerful instrument for investigating the individual or collective effects on responses of several parameters (Wang *et al*., 2016). Besides, the desirability function (DF) can optimize one or more response performance conditions at the same time by combining several responses into one. (Wang *et al*., 2017).

Therefore, choosing the operating parameters in the optimization of ultrasonic-assisted extraction is caused by Table 2.4 displayed the numerous variables effect of the desired response which leads to finding the best optimizing parameters for ultrasonic-assisted extraction. Hence, this table can be applied as a reference to get a range of operating parameters and as a consequence to obtain the best outcome for the desired response. In the current study, the desired responses are the percentage of yield and quantification on phytochemicals from *C. xanthorrhiza.* Table 2.4 shows a review on the optimization of UAE.

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**Table 1.4: Review on the optimization of UAE**

| Part and Plant | Optimal Condition | Range of Time and Temperature | Sample: Solvent (g:mL) | Response | References |
|---|---|---|---|---|---|
| Rhizomes *C. wenyujin* | 20 min, 70% ethanol, 8mL/g | 3-24 min 30-50°C | 10 : 100 | Yield: 97.1% | (Wang *et al*., 2016). |
| Rhizomes *C. phaeocaulis* | 20 min, 80% ethanol, 8mL/g | 3-20 min 20-50°C | 10:100 | Yield: 87.09% | (Wang *et al*., 2017). |
| Leaves *C. zedoaria* | 90 min, 75% Ethanol, Ethanol: water 90:10 | 80-120 min 60- 80°C | Solvent Yield: C 70-90% | Yield: 70% | (Azahar *et al*., 2017). |
| Rhizomes *C. longa* | 15 min, ethanol, Sample:solvent rate 3.29 g :100 mL Ultrasonic: Intensity 33.63w/cm$^2$ | 5-25 min Not stated | 5: 100 | Yield: 51.47% | (Xu *et al*., 2017) |
| Rhizomes *C. longa* | 30 min, ethanol C 50 mL, particle size: 0.42nm, 60°C | 10-50min 50-90°C | 10 : 50 | Curcumin Yield: 9.051% | (Başpınar *et al*., 2017) |
| Leaves *C. zedoaria* | 92 min, ethanol C: 90: 10, 75°C | 80-120 min 60-80°C | Solvent C; 70-90 % | antioxidant %: 85.76% | (Gani *et al*., 2018) |

***Quantification of Phytochemicals from Curcuma xanthorrhiza by High-Performance Liquid Chromatography (HPLC)***

Several bioactivities have been recorded in *C. xanthorrhiza* to treat hepatitis, cancer, rheumatism, hypertension, liver disease, diabetes, antioxidant, diuretic, and hepatoprotective effects. The curcuminoids are the main compounds found in the *C. xanthorrhiza* rhizome which is considered to be responsible for these biological activities. Therefore, the concentrations of the compounds or compound groups responsible for the biological activities should be determined (Siregar *et al*., 2017).

Nevertheless, analytical techniques should be developed which can quantify major compounds (xanthorrhizol **(1)** and curcuminoids) totally and individually. Many analytical approaches for the routine curcuminoids (Hadi *et al*., 2018) and xanthorrhizol **(1)** analysis (Choi *et al*., 2017) were developed and used including thin layer chromatography-densitometry, liquid chromatography-mass spectrometry, fourier transform infrared spectroscopy, high-performance liquid chromatography using photodiode array detector, and high-performance liquid chromatography using an electrochemical detector, UV-visible detector and capillary Electrophoresis (Prabaningdyah *et al*., 2017).

High-performance liquid chromatography (HPLC) is the method of choice for separating major compounds (xanthorrhizol **(1)** and curcuminoids) in the plant. Multiple parameters including such mobile phase composition, stationary phase, column temperature, mobile phase $P^H$, and flow rate help to analyse HPLC (Prabaningdyah *et al*., 2017). HPLC usually employs different types of stationary phases, a pump that drives the mobile phase(s) and analyses through the column, and a detector that supplies the analyte with a characteristic retention time. Additional analyte-related information can also be provided by the detector (typically a photodiode array detector) (i.e. if equipped, UV / Vis spectroscopic analyte data). A pump generates the higher pressure required to bring the mobile phase through the densely packed column and analyte. The increased density results from smaller sizes of the particles. It allows greater separation on shorter-length columns and assures higher velocity (Pisoschi & Negulescu, 2011). When developing analytical methods, selection of column temperature and phase-related mobile factors during optimisation of the HPLC were considered critical (Siregar *et al*., 2017). Therefore, standard phase HPLC uses polar stationery and a non-polar, non-aqueous mobile phase which operates efficiently in non-polar solvents to distinguish analytes readily soluble whereas, the reversed HPLC phase comprises of a moderately polar aqueous mobile phase and a stationary non-polar phase. One specific stationary phase is silica that was handled via $RMe_2$ Si Cl, where R

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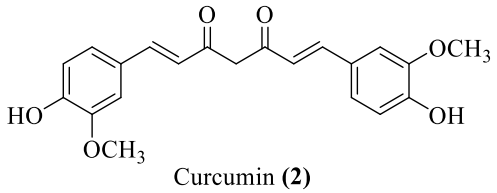
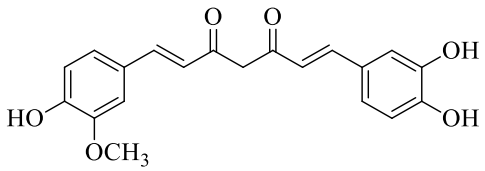
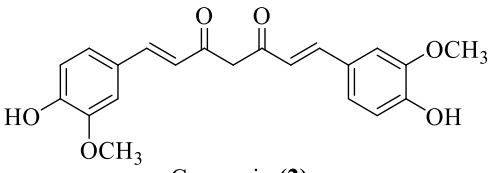
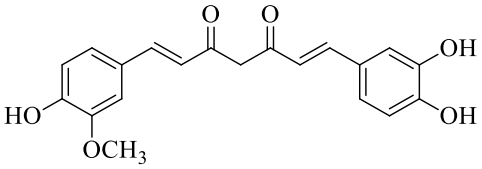
is a straight alkyl chain group like $C_{18}H_{37}$ or $C_8H_{17}$. The retention time for less polar molecules is longer whenever using these stationary phases, whereas polar molecules more easily elude (Pisoschi & Negulescu, 2011).

The HPLC conditions on the quantification of curcuminoids (Hadi *et al*., 2018) and xanthorrhizol **(1)** (Choi *et al*., 2017) compounds from *C. xanthorrhiza* was reviewed at Table 2.5. Column $C_{18}$ is one of non-polar stationary phase that creates longer retention time for less polar compounds and vice versa (Pisoschi & Negulescu, 2011). Table 2.5, therefore, shows the summary of phytochemicals from the rhizome of *C. xanthorrhiza* with ethanol or methanol extract which carried out by enormous researchers from different countries such as Malaysia (Devaraj *et al*., 2013; Devaraj *et al*., 2010) Thailand, India (Prabaningdyah *et al*., 2017), Indonesia (Siregar *et al*., 2017; Hadi *et al*., 2018), South Korea (Choi *et al*., 2017).

**Table 1.5: Review on the HPLC conditions and quantification of phytochemicals from *Curcuma xanthorrhiza***

| HPLC Conditions | Structures |
|---|---|
| **Part:** Rhizome<br><br>**HPLC instrumentation:** LC20AD (Shimadzu, Japan) equipped with a binary gradient pump 20 µl loop volume with a injector valve of Rheodyne 7725i including photodiode array (Shimadzu, SPD-M20A) detector<br><br>**Column:** $C_{18}$ column (250 x 4.6 mm i.d; 5 µm) X-Bridge<br><br>**Solvent/Flow rate/Injection volume:** The acetic acid concentration (3.00%), acetic acid ratio (51%), the mobile phase flow rate (1.05 ml/min)<br><br>**Column temperature:** (45ºC)<br><br>**Mobile phase ratio:** acetonitrile-acetic acid ( 50: 50)<br><br>**Analyte detection:** PDA detector was set at 425 nm<br><br>**References:** (Siregar *et al*., 2017<br><br>Curcumin **(2)** and Demethoxycurcumin **(9)** |  <br>Curcumin **(2)**<br>  <br>Demethoxycurcumin **(9)** |
| **Part:** Rhizome<br><br>**HPLC instrumentation:** Not stated<br><br>**Column:** Reversed-phase 18 Waters® X-Bridge (250 x 4.6 mm i.d.; 5 µm)<br><br>**Solvent/Flow rate/Injection volume:** The acetic acid concentration (4.08%), acetic acid ratio (49:51), mobile phase flow rate 1.04 mL/min, 20 uL.<br><br>**Column temperature:** (40ºC)<br><br>**Mobile phase ratio:** acetic acid 4.08%: acetonitrile (51: 49)<br><br>**Analyte detection:** detector PDA set at 425 nm<br><br>**References:** (Prabaningdyah *et al*., 2017) |  <br>Curcumin **(2)**<br>  <br>Demethoxycurcumin **(9)** |

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Curcumine **(2)** and Demethoxycurcuminis **(9)**

**Part:** Rhizome (ethanol extract)

**HPLC instrumentation:** Waters Corp., USA

**Column:** $C_{18}$ WatersXterra MS $C_{18}$ (5 µm; 4, 6×250 mm)

**Solvent/Flow rate/Injection volume:** aquabidestilata and acetonitrile (65:35 v/v) containing 1% acetic acid, not stated, 20 µL

**Column temperature**: (40ºC)

**Mobile phase ratio:** aquabidestilata and acetonitrile (65:35 v/v)

**Analyte detection:** UV-vis detector set at λ 425 nm

**Retention time (min):** 40 min

**References:** (Rohman *et al.*, 2015)

Curcumin **(2)**, Demethoxycurcuminis **(9)**, and Bisdemethoxycurcuminis **(10)**

**Part:** Rhizome (methanol extract)

**HPLC instrumentation:** LC-20A series HPLC DAD, equipped with a diode array UV detector, (Shimadzu, Tokyo, Japan)

**Column:** VP-ODS $C_{18}$ column (150 mm × 4.6 mm i.d., 4.6-µm particle size) Shim-pack

**Solvent/Flow rate/Injection volume:** methanol at concentrations of 1000 µg/mL, 1 mL/min, not stated

**Column temperature**: Not stated

**Mobile phase ratio:** 0.5% acetic acid and acetonitrile in water using a gradient elution program of 100% (A) for 30–40 min, 40–75% (A) for 0–30 min, and 0.5 % acetic acid in 45–75% acetonitrile

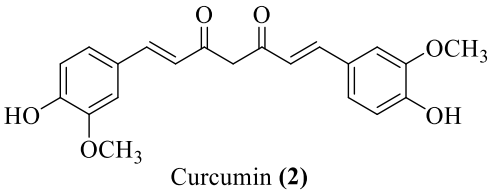
**Analyte detection**: 425nm

**References:** (Rafi *et al.*, 2015)

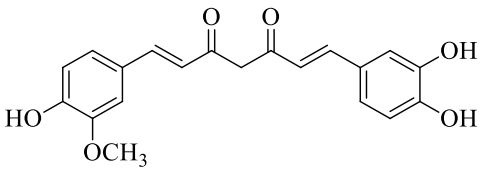
Curcumine **(2),** Demethoxycurcuminis **(9),** and Bisdemethoxycurcuminis **(10)**

**Part:** Rhizome (ethanol extract)

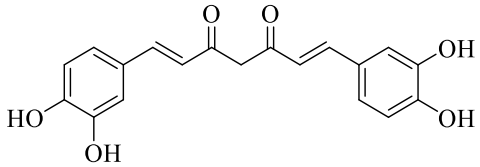
**HPLC instrumentation:** HPLC-UVD system consisted



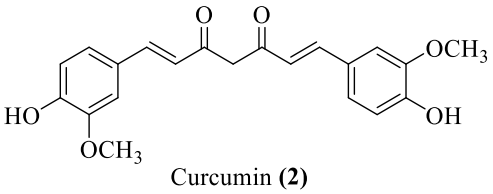
Curcumin **(2)**



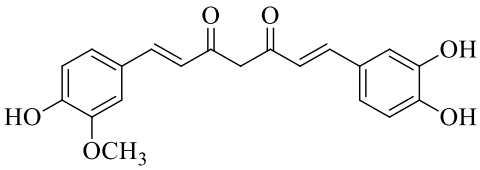
Demethoxycurcumin **(9)**



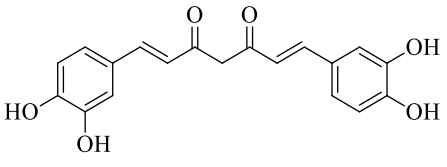
Bisdemethoxycurcumin **(10)**



Curcumin **(2)**



Demethoxycurcumin **(9)**



Bisdemethoxycurcumin **(10)**

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of a UVD detector (LabAlliance), a 20 µL Rheodyne sample injector, and a binary pump system

**Column:** Waters BioSuiteTM p $C_{18}$ column (4.6 mm×150 mm, 7 µm)

**Solvent/Flow rate/Injection volume:** Methanol, 1.0 mL/min, 20 µL

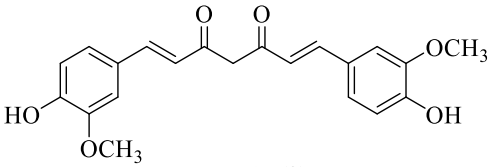
**Column temperature**: (30ºC)

**Mobile phase ratio:** methanol and run in isocratic mode

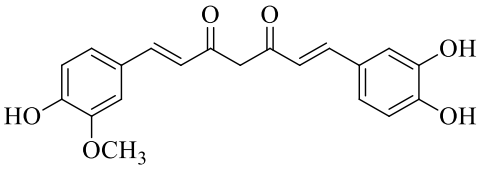
**Analyte detection:** UVD wavelength set at 420 nm

**Retention time (min):** 30 min

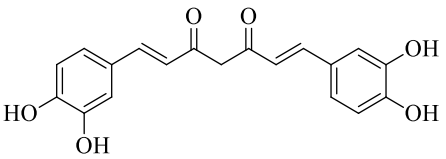
**References:** (Hadi *et al*., 2018)
Curcumine **(2),** Demethoxycurcuminis **(9)**, and Bisdemethoxycurcuminis **(10)**




Curcumin **(2)**




Demethoxycurcumin **(9)**




Bisdemethoxycurcumin **(10)**

**Part:** Rhizome (ethanol extract)

**HPLC instrumentation:** API 4000 LC/MS/MS system equipped with an electrospray ionization interface (AB SCIEX, Framingham, MA, USA)

**Column:** reversed-phase column (Agilent, Cork, Ireland; Atlantis T3, 50 × 2.1mm internal diameter, 3 m particle size)

**Solvent/Flow rate/Injection volume:** methanol solutions (100 mg/mL) of xanthorrhizol, 10 L/min, 5 µL

**column temperature:** (30ºC)

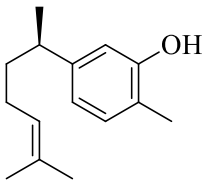
**mobile phase ratio:** 20 mM ammonium acetate aqueous solution and acetonitrile (20:80, v/v)

**Analyte detection:** Not stated

**Retention time (min):** 5 min

**References:** (Choi *et al*., 2017)

Xanthorrhizol **(1)**




Xanthorrhizol **(1)**

**Part:** Rhizome (methanol extract)

**HPLC instrumentation:** 20A series HPLC LC-equipped with a diode array UV–Vis detectors (Shimadzu, Tokyo, Japan)

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**Column:** Phenomenex $C_{18}$ column (150×4.6 mm ID, 5 µm particle size).

**Solvent/Flow rate/Injection volume**: phosphoric acid, acetonitrile, acetic acid, formic acid, and methanol,1 mL/min, 20 µL

**Column temperature:** (40ºC)

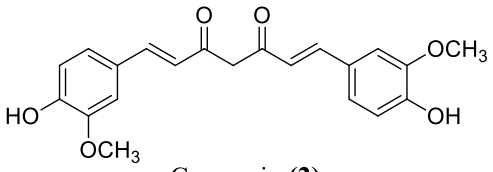
**Mobile phase ratio:** Formic acid of acetonitrile with acetonitrile 0.001% (A) and 0.001% formic acid in water with pH 6.5 (B) with a gradient elution program of 45–85% (A) for 0–60 min, and 100% (A) for 75–80 min, 85-100% (A) for 60–75 mins

**Analyte detection:** Detection wavelength224 nm for XNT and 425 nm for curcuminoids

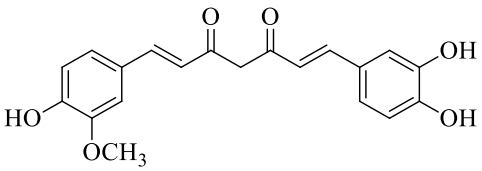
**Retention time (min):** 60-80 mins

**References:** (Erpina *et al*., 2017)

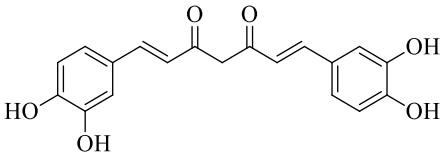
Curcumin **(2)**, Demethoxycurcuminis **(9)** Bisdemethoxycurcumin **(10)**, and Xanthorrhizol **(1)**



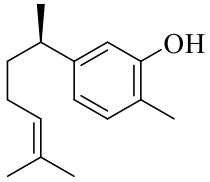

Curcumin **(2)**




Demethoxycurcumin **(9)**




Bisdemethoxycurcumin **(10)**




Xanthorrhizol **(1)**

**Part:** Rhizome (dichloromethan extract)

**HPLC instrumentation:** Not stated

**Column:** HPLC column, glass column 26 × 240 mm, 4 × 150 mm, Sepacore® cartridge

**Solvent/Flow rate/Injection volume**: Methanol, water, A) 1 mL/min, B) 10 mL/min, C) 30 mL/min, Samples: A) 100 µg in 10 µL, B/C) 500 mg in 5 mL

**Column temperature:** (40ºC)

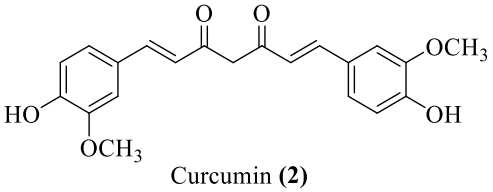
**Mobile phase ratio:** Methanol (A), water (B) both with 0.1% formic acid; gradient: 50–100% B in A)

**Analyte detection:** 220 nm

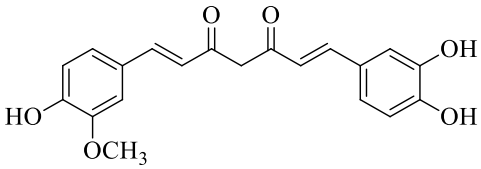
**Retention time (min):** 30, 120, 600 min

**References:** (Weber *et al*., 2011)

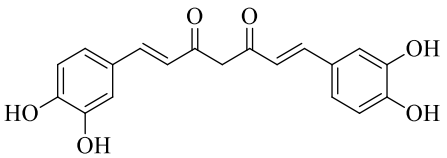
Curcumin **(2)**, Demethoxycurcuminis **(9)**




Curcumin **(2)**




Demethoxycurcumin **(9)**




Bisdemethoxycurcumin **(10)**

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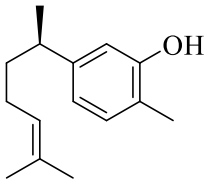
Bisdemethoxycurcuminis **(10)**, and Xanthorrhizol **(1)**




Xanthorrhizol **(1)**

## V. CONCLUSION

*Curcuma xanthorrhiza Roxb*. belongs to the Zingiberaceae family (ginger family) and originated plants of Indonesia. It is cultivated in Sri Lanka, Malaysia, Philippines, and Thailand. It is widely used for the traditional treatment of many illnesses in South East Asian countries, including migraines, constipation, liver problems, and inflammatory conditions. *C. xanthorrhiza* commercially has an interest in the development of new medicines for the treatment of different diseases by both research centres and medicinal companies.

*C. xanthorrhiza* consists of non-volatile curcuminoids and volatile essential oil. The human being was acquainted with *C. xanthorrhiza* rhizome, which has been utilized in traditional medicinal and agro-industry as raw materials, including such natural food colours. Other drug therapy activities, such as antioxidants, antimicrobials, anti-inflammation, and anticancer have been documented in *C. xanthorrhiza* chemical compounds. The optimization of bioactive compounds and extraction methods are of great interest in the food and medicinal industries for further research and development. Extraction is the most critical step in making full use of the bioactive molecules found in medicinal plants. One of the effective techniques for extracting desirable components from plant materials is ultrasonic-assisted extraction that is completely adaptable on small or large scales (i.e. on an industrial scale or laboratory scale). Conventionally, an ultrasonic tool is much simpler and easier to operate. Additionally, Ultrasound-assisted extraction (UAE) has been commonly utilized for the laboratories with outstanding benefits including lower energy consumption, less use of solvents, more efficient mixing, and shorter extraction time. Response surface methodology (RSM) is an effective mathematical tool commonly utilized for optimizing the experimental conditions for technical operations in many industries. RSM also has benefits for maximizing or minimizing different independent variables as it simultaneously measures the impact of various factors and their respective interplay on one or more variables.

Quantification of phytochemicals is important to quantify and find concentration of targeted compounds from analyt. HPLC was commonly used to measure concentration of phytochemicals. The retention time of HPLC analysis was affected by several factors such as mobile phase, stationary phase, detectors and the type of columns to be used. HPLC is a system widely used in terms of simplicity, speed and high efficiency.

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