Herbal Drug Delivery Systems

Herbal Drug Delivery Systems:

Extraction, Formulation, and Characterization

By

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Cambridge Scholars Publishing

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PREFACE

This is undoubtedly an exciting time to be studying and reading *Herbal Drug Delivery Systems*. Many herbal remedies are physiologically active chemical compounds that aren't involved in the growth and development of herbs. Maceration, infusion, and decoction, percolation, Soxhlet extraction/hot continuous extraction, microwave-assisted extraction, ultrasound-assisted extraction or sonication extraction, accelerated solvent extraction, and supercritical fluid extraction are all methods for extracting and isolating biologically active chemical compounds from herbs. Furthermore, the primary purpose of these physiologically active chemical substances is to protect the body against illness. They have toxicological and pharmacological effects in humans, suggesting that they might become a more important component of nutraceuticals and dietary supplements in the future.

Traditional and out-of-date methods of delivering herbal medicines have resulted in decreased efficacy of biologically active compounds. The main idea behind integrating drug delivery in herbal medications is oral and transdermal herbal drug delivery systems, which is a unique approach to herbal treatments. The innovative technology has the potential to increase the efficacy of herbal medications while reducing their negative effects. To treat additional illnesses, it is critical to combine oral and transdermal medication delivery methods with herbal medicines. Furthermore, advanced phytopharmaceutical research studies and solves scientific demands associated with the use of herbal medicines, such as pharmacokinetics, mechanism of action, site of action, and the precise amount necessary, among others. Herbal medications can therefore be included in new drug delivery systems.

Evaluating the formulation, processability, and stability of herbal drug delivery systems necessitates a thorough understanding of their characterizations. Characterizations may be utilized to anticipate the physical and chemical interaction as well as the stability of herbal drug

delivery systems in many applications. Many types of studies in the field of drug delivery systems have relied heavily on in vitro studies to assess the potential therapeutic value of biologically active chemical compounds, due to the ease with which they may be controlled and compared to in vivo investigations. Many factors may be assessed for medication targeting by utilizing minimal amounts of the biologically active chemical compound over large ranges in *in vitro* experiments. Evaluations can be achieved in a short period of time, and a variety of target techniques can be utilized.

This book covers a wide range of topics, including herbal medicines, herbal extractions, herbal drug delivery systems, and various characterizations and *in vitro* studies of both oral and transdermal drug delivery systems, which can be used to determine the formulation and biologically active chemical compounds of herbal formulations, as well as some case studies.

This book is also based on the author's research experience, which includes over 100 published published articles. This initial version of the book is written with great care. However, there will be some accidental inaccuracies, as well as certain topics that are left unattended or neglected. Any such comments, suggestions, and/or critiques would be greatly appreciated by the author. In the second version of this book, they will be addressed in the appropriate manner.

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In addition, none of this would have been possible without the love and encouragement of my friends. I thank them for their understanding during all of the times and for their steady love that supports me.

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CHAPTER 1

HERBAL MEDICINES

People have long used herbs and plant products to treat ailments. The traditional medical system is so deeply ingrained in people's cultures that it provides relief to more than 75 percent of the world's population. The World Health Organization is currently promoting the use of herbal medicine in developing nations, which has been practiced for millennia. There have been 3000 plants identified worldwide that can be used as medication. Every sickness has a natural treatment in the form of a plant. Drugs utilized in modern medicine are either derived from natural or synthetic. Herbs and plants found across the world, on the other hand, constitute an intriguing supply of therapeutic plants that are still being studied. They offer scientists working on new and more effective medications with therapeutic benefits and minimal side effects, the most difficult areas of pharmaceutical and medical science.

1.1 Introduction

Since the dawn of time, people have used herbs and plant products to treat illnesses. A wide range of herbs and plants, both aromatic and medicinal, may be found in several subcontinents. Botanists have identified and cataloged many different varieties of herbs. In traditional medicine, these numerous herbs and plants have been extensively used as a source of various medicines. Medicinal plants are frequently suggested as a means of treating disease and significantly improving health and well-being. The traditional medical system is so deeply ingrained in people's cultures that it provides relief to more than 75 percent of the world's population. With such a significant part of the population dependent on herbal remedies, it's important that these long-used plant products be scientifically verified for their efficacy. The World Health Organization (WHO) has encouraged underdeveloped countries to embrace herbal therapy, which has been practiced for millennia. There are 3000 plants that can be utilized as

medicine across the world. Scientific furtherance in the pharmacology and toxicology fields, which can be used as medicine, is based on natural products. The study of herbal medicine was established through the discovery of plants with healing powers in the early phases. People have been looking for medicinal plants for thousands of years, resulting in a long list of plants that may be used to treat diseases and promote good health. It may be claimed with certainty that every illness has a remedy in a plant growing in nature. Several herbs and plants have recently been discovered to be effective as single-drug treatments. Drugs utilized in modern medicine are either derived from nature or synthesized. Drugs of biological origin are made in the living cells of plants and are derived from herbs and plants. The herbs and plants found on this planet, on the other hand, constitute a fascinating source of therapeutic plants that is currently being investigated. As a result, they assist scientists in the search for new and more effective medicines with noticeable therapeutic virtues and negligible side effects with the most difficult elements of pharmaceutical and medical research.

1.2 Herbal Medicines

Many herbal medicines are biologically active chemical compounds that are not even involved in the growth and development of herbs. Maceration, infusion and decoction, percolation, Soxhlet extraction/hot continuous extraction, microwave-assisted extraction, ultrasound-assisted extraction or sonication extraction, accelerated solvent extraction, and supercritical fluid extraction are all methods for extracting and isolating biologically active chemical compounds from herbs. Furthermore, the primary purpose of these physiologically active chemical substances is to protect the body against illness. They have toxicological and pharmacological effects in humans, suggesting that they might become a more important component of nutraceuticals and dietary supplements in the future. They also aid in agricultural yields as plant and animal growth stimulants, as well as being utilized as colors, perfumes, tastes, and cosmetics (Sasidharan, Chen, Saravanan, Sundram & Latha, 2011). Table 1.1 summarizes some biologically active chemical components discovered in herbal medicines that have toxicological and pharmacological relevance.

1.2.1 Zingiber cassumunar Roxb.

Z. cassumunar Roxb. belongs to the family of Zingiberaceae or ginger, known as Plai in Thailand, Bangle in Indonesia, and Bulei in China, which is an important herbal medicine. It has traditionally been used to treat (1) joint and muscular pain and inflammation, (2) respiratory issues including asthma and cough, (3) menstrual discomfort, and (4) gastrointestinal illnesses. It has a wonderful, invigorating peppery green eucalyptus scent and is well-known for its therapeutic massage qualities. The essential oil of *Z. cassumunar* is non-toxic, non-sensitizing, and nonirritating (Han, Kim, Piao, Jung & Seo, 2021; Suksaeree, Charoenchai, et al., 2015; Suksaeree, Monton, et al., 2015). Phenylbutenoids, curcuminoids, sesquiterpenoids, benzaldehydes, quinones, and essential oils containing monoterpenoids are just a few of the compounds found in *Z. cassumunar* that have been discovered and published.

Table 1.1 Biologically active chemical compounds from herbal medicines and their medicinal uses

Phytochemicals	Examples	Medicinal uses
Alkaloids	Morphine, caffeine, berberine, codeine, piperidine, camptothecin, vinblastine, vincristine, serpentine, aceclidine, rutaecarpine, quinine, artemisinin	Diuretic, local anesthetic, bactericidal, anticancerous, antihypertensive, cholinomimetics spasmolytics, antiasthmCatics, antimalarials
Anthocyanins	3-Caffeoylquinic acid, 5-caffeoylquinic acid, polymeric procyanidins, 5-caffeoylquinic acid, procyanidins	Antioxidative, antiinfluenza, antiviral
Coumarins	Umbelliferone, aesculetin, herniarin, psoralen, imperatorin	Antidiabetic, hepatoprotective, antithrombotic, antifungal, antiviral, analgesic, anticarcinogenic

Flavonoids	Quercetin, reservaratrol kaempferol, caffeic acid, flavones, rutin, naringin, hesperidin tannic acid, gallic acid, ellagic acid	Hyperlipidemia, hyperglycemia, anticancerous, antioxidative, antiartherosclerotic
Glycosides	Amygdalin, gentiopicrin, rographolide, polygalin, cinnamyl acetate, anthraquinone	Antifungal, antibacterial, antioxidant, antidiabetic, fluid and electrolyte loss, hepatoprotective, cardioprotective
Phenols and phenolic acids	p-Hydroxybenzoic acids, protocatechuic acids, vanillic acid, syringic acid	Antioxidant, antiulcer, antidiabetic, cardioprotective, anticancerous, anti-inflammatory, neuroprotective, antiaging, hepatotprotective, antimicrobial activity
Saponins	Diosgenin and hecogenin α-hederin and hederasaponin-C	Nutraceuticals, functional foods, natural food, preservatives
Terpenoids	Isoprenoids mono- and sesquiterpenes, saponins, sapogenins, sesquiterpene lactones, tetraterpene carotenoids, β-sitosterol, artemisinin	Antimicrobial, antifungal, antiviral, antihyperglycemic, anti-inflammatory, antioxidants, antiparasitic, immune-modulatory, skin permeation enhancer
Tannins	Procyanidins, prodelphinidins, epicatechin, epigallocatechin procyanidin, or prodelphinidin	Hyperglycemia, hyperlipidemia

(I) Various isolation techniques, such as recrystallization, silica gel, reverse phase column chromatography, countercurrent chromatography, and preparative high-performance liquid chromatography, have been used to separate and report phenylbutenoids for the characteristic compounds of Z. cassumunar (Han et al., 2004; Lu, Yanbin, Sun, Wang & Pan, 2005; Matsuda et al., 2011; Nakamura et al., 2009).

The 41 phenylbutenoids discovered in Z. cassumunar are summarized and reported by Han et al., 2021 (Figure 1.1) such as (E)-4- (3′,4′-dimethoxyphenyl)but-3-en-2-ol (Panthong, Kanjanapothi, Niwatana nant, Tuntiwachwuttikul & Reutrakul, 1997), (E)-4-(20,40,50-trimethoxyphenyl)but-1,3-diene (Nakamura et al., 2009), cis-3-(3′,4′-dimethoxyphenyl)-4-[(E)-2‴,4‴,5‴-trime thoxystyryl]cyclohex-1-ene (Amatayakul et al., 1979), 3R-(3,4-dimethoxyphenyl)-4S-[(E)-3,4-dimethoxystyryl]cyclohex-1-ene (Chu et al., 2011), (E)-4-(3′,4′-dimethoxyphenyl)propenal (Lu, Yanbin, Liu, Berthod & Pan, 2008), etc. The absolute configuration data of phenylbutenoids has been established, and it is an effective reference for identifying phenylbutenoids' stereochemistry.

(II) Curcumin is a second major compound that is isolated from the rhizomes of *Z. cassumunar* (Kubo et al., 2015; Nakamura et al., 2009). Han et. al., 2021 summarizes and reports the 6 curcuminoids that are found in *Z. cassumunar* (Figure 1.2), such as cassumunins (Jitoe, Masuda & Mabry, 1994), (1E,4E,6E)-1,7-Bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one, and bisdeoxycurcumin (Li, M.-X. et al., 2019) are found in the rhizomes of *Z. cassumunar*.

(III) Two quinones are found in the rhizomes of *Z. cassumunar* and are identified as 2-methoxy-8(3,4-dimethoxyphenyl)-1,4-naphthoquinone and 2-methoxy-8(2,4,5-trimethoxyphenyl)-1,4-naphthoquinone (Figure 1.2) (Amatayakul et al., 1979; Dinter, Hänsel & Pelter, 1980).

(IV) Four phenolic compounds (Figure 1.2) are found in *Z. cassumunar* that are vanillic acid, 3,4-dimethoxybenzaldehyde, 2,4,5-trimethoxybenzaldehyde, and 1-feruloyloxy cinnamic acid (Li, M.-X. et al., 2019; Nakamura et al., 2009).

(V) Four sesquiterpenoids (Figure 1.2) are found in the rhizomes and leaves of *Z. cassumunar* that are zerumbone (Leelarungrayub & Suttajit, 2009), β-sesquiphellandrene (Nakamura et al., 2009), 4-furanodien-6-one, curzerenone, and β-sesquiphellandrene (Leelarungrayub & Suttajit, 2009).

(VI) Four monoterpenoids (Figure 1.2) are found in the rhizomes and leaves of *Z. cassumunar* that are sabinene and terpinene-4-ol (Mektrirat, Yano, Okonogi, Katip & Pikulkaew, 2020), and α-terpinene and γ-terpinene (Verma et al., 2018).

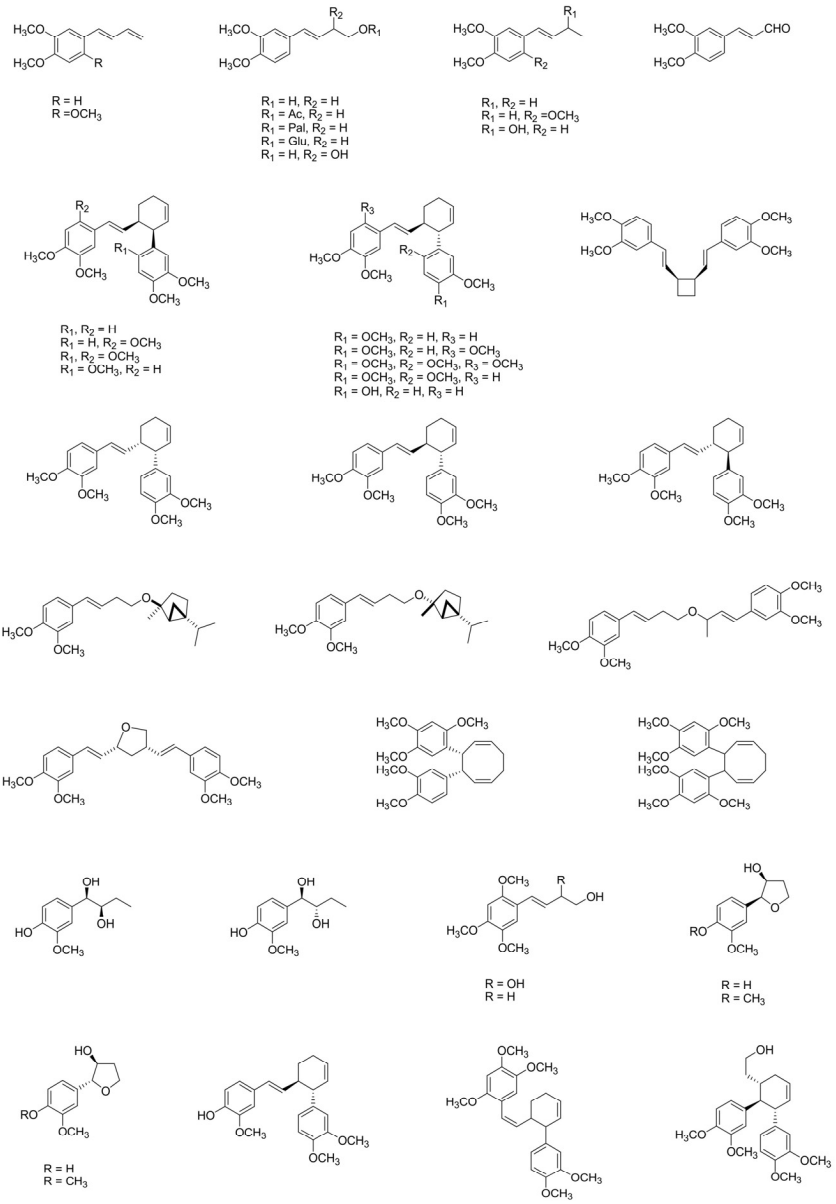

Figure 1.1 Chemical structures of phenylbutenoids isolated from *Z. cassumunar*

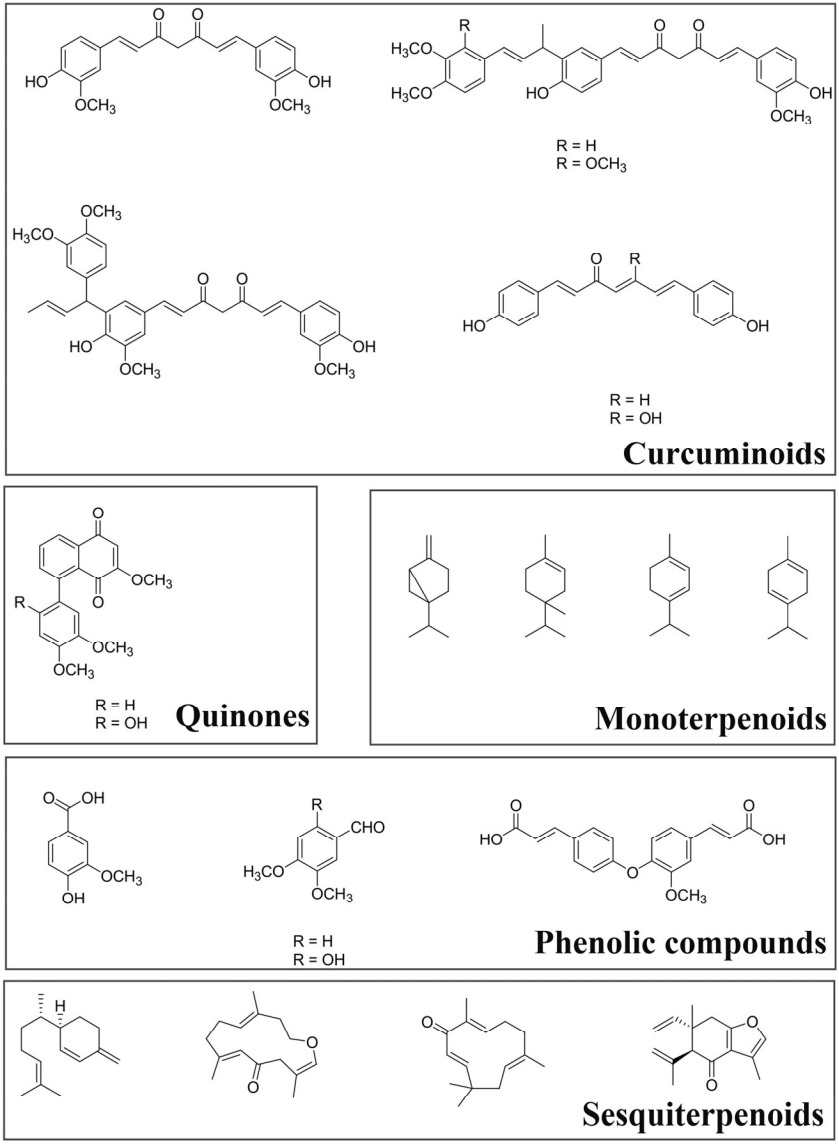

Figure 1.2 Chemical structures of curcuminoids, quinones, phenolic compounds, sesquiterpenoids, and monoterpenoids, isolated from *Z. cassumunar*

1.2.2 Kaempferia parviflora

K. parviflora is locally known in Thai as Kra-chai-dam. Its rhizome has been used as an aphrodisiac and a treatment for fungal infections, as well as allergies and gastrointestinal disorders (Kummee, Tewtrakul & Subhadhirasakul, 2008). The chemical compounds present in *K. parviflora*, such as flavonoids (Trakoontivakorn et al., 2001), terpenoids, isopimarane phenolic compounds, and diarylheptanoids (Yao, Huang, Wang & He, 2018), essential oils (Raina & Abraham, 2016) have been discovered and published.

(I) *K. parviflora* possesses a wide range of flavonoids and phenolic chemicals, which are investigated due to their high biological activity. The methoxy groups are found in specific sites in the flavonoid nuclei of *K. parviflora* rhizomes (Kobayashi, Kato, Azuma, Kikuzaki & Abe, 2015; Nakao et al., 2011) such as pyranoflavone, 2″,2″-dimethylpyrano-[5″,6″:8,7]-flavone (Chawengrum et al., 2018), flavanones (Trakoontivakorn et al., 2001), and kaempferol and kaempferide (Umar, Asmawi, Sadikun, Altaf & Iqbal, 2011).

(II) The different diarylheptanoid compounds are present in the rhizomes of *K. galanga* and have been previously described (Yao et al., 2018), but the phenolic acids, particularly methoxylated cinnamic acid derivatives, are the main isolated chemicals (Othman, Ibrahim, Mohd, Mustafa & Awang, 2006). The curcuminoid is extracted and examined from the rhizomes of *K. marginata* (Kaewkroek, Wattanapiromsakul, Kongsaeree & Tewtrakul, 2013) while the phenolic glycoside is discovered in the rhizomes of *K. previflora* (Azuma, Tanaka & Kikuzaki, 2008).

(III) From the rhizomes of *K. roscoeana* and *K. angustifolia*, seven abietanes have been identified and described (Boonsombat et al., 2017; Yeap et al., 2017). In addition, the Kaempheria species include the main diterpenoids isopimarenes, labdane, clerodane, oxygenated labdanes, clerodanes, and (12Z,14R)-labda-8(17),12-dien-14,15,16-triol (Chawengrum et al., 2018; Elshamy et al., 2019).

(IV) The volatile oils are discovered and described in *K. galanga* (Li, Y.C., Ji, Li, Zhang & Li, 2017; Panyakaew et al., 2017), as well as *K. angustiflora* and *K. marginata* (Panyakaew et al., 2017). The volatile oil of *K. galanga* is a prospective product in many countries, however, it is quite costly. Phenylpropanoids, cinnamates, and monoterpenes are the most common chemicals found in *Kaempheria* species' volatile oils (Li, Y.C. et al., 2017; Panyakaew et al., 2017). The volatile oils of *Kaempferia species* have been reported to exhibit nutraceutical (Munda, Saikia & Lal, 2018), antimicrobial (Isayeva, Kasibhatla, Rosenthal & Kennedy, 2003), and antioxidant (Sahoo, Parida, Singh, Padhy & Nayak, 2014).

1.2.3 Curcuma longa L.

C. longa L., often known as turmeric, has been used in traditional medicine to treat jaundice and other liver disorders, ulcers, parasite infections, various skin illnesses, sprains, joint inflammation, and cold and flu symptoms. *C. longa* L. is a culinary spice used in curry in various Asian nations to give it its distinct flavor and color (Tomeh, Hadianamrei & Zhao, 2019). It has been used in food to keep freshness and nutritional value, as well as to improve palatability, aesthetic appeal, and the shelf-life of perishable foods. It is a well-known herbal medicine that is used to treat a wide range of illnesses and conditions, including inflammation and infection. It is used to treat wounds, bruises, and sprains, and may be found in several products, including topical lotions and bath soaps (Jayaprakasha, Jagan Mohan Rao & Sakariah, 2005). The phenolic component and its analogs are responsible for the brilliant yellowish color of *C. longa* L.'s aromatic volatile oil. The numerous volatile oils of *C. longa* L. have been the subject of several studies (Figure 1.3)

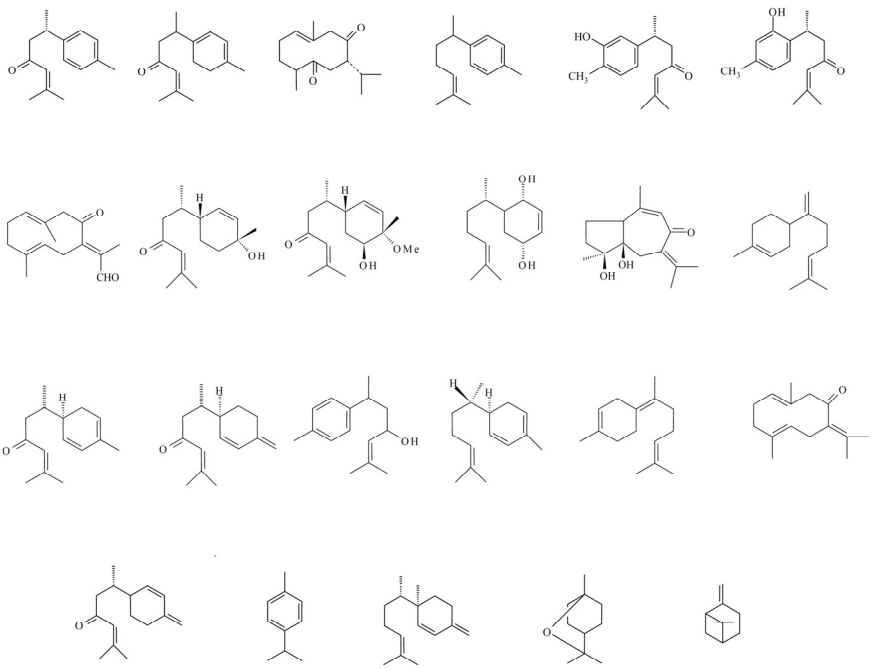

Figure 1.3 Chemical structures isolated from *C. longa* L.

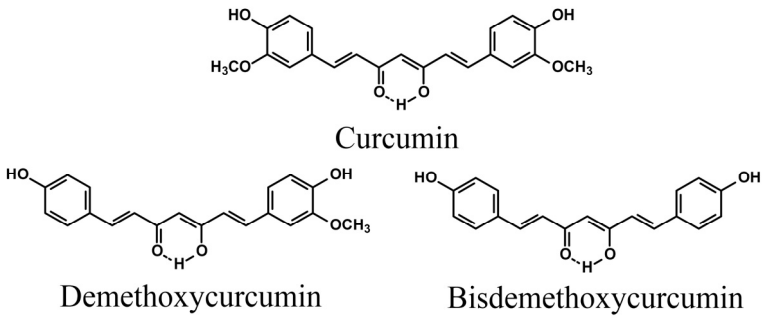

Figure 1.4 Chemical structures of curcumin, demethoxycurcumin, and bisdemethoxycurcumin

The major compound that is found in the rhizomes is a polyphenolic, called curcumin, 1, 7-bis (hydroxyl-3-methoxyphenyl)-1,6- heptadiene-3, 5-dione (Figure 1.4), which is the most important active compound responsible for the biological activity. Curcumin is not soluble in water; however, it may be dissolved in ethanol or acetone. Curcumin is unstable at pH 7.4 in a phosphate buffer, although it can be greatly improved by lowering the pH or adding glutathione, N-acetyl cysteine, or ascorbic acid. Chemical synthesis has also improved curcumin, resulting in compounds with improved antioxidant and cancer chemoprotective characteristics (Youssef et al., 2004). The natural ratios of curcumin occurring contain 5% bisdemethoxycurcumin, 15% demethoxycurcumin, and 80% curcumin (Ali, Marrif, Noureldayem, Bakheit & Blunden, 2006).

1.3 Analytical Technique and Chromatographic Fingerprint Analysis of Herbal Medicines

A method for determining a chemical or physical feature of a chemical compound, chemical element, or combination component in herbal medicine is known as analytical methodology. Analyses can be performed in several methods, from simple weighing to complex operations using highly specialized equipment.

1.3.1 Thin layer chromatography

The fundamental approach for fingerprint identification of substances in herbal medicines is thin layer chromatography. The light or fluorescence pictures are used to get the analysis and identification results. Rather, for rapid on-site monitoring with a semi-qualitative evaluation of herbal medicines, thin layer chromatography is frequently an acceptable and simple approach. Thin-layer chromatography is the method of choice for the examination of herbal medicines until instrumental chromatography technologies such as high-performance liquid chromatography and gas chromatography are developed. Thin-layer chromatography is a technique for distributing a solute between an adsorbent stationary phase and a liquid mobile phase.

1.3.2 High-performance liquid chromatography

High-performance liquid chromatography is a widely used technology that is the most effective fingerprinting analytical approach for detecting chemicals with no restrictions on whether they are volatile or stable components (Liang, X.-m. et al., 2009). The use of high-performance liquid chromatography is required to ensure that the mobile phase compositions, pH adjustment, flow rate, and pump pressure are all optimized for the separation of components in herbal medicines. Quantitative analysis employing high-performance liquid chromatography aims to separate and identify the components in herbal medicines. The identification of the major chemical components and hazardous compounds is required for the quality control of herbal medicines. High-efficiency separation is presently being developed and reported for quantitative analysis of complex samples. Table 1.2 summarizes instances of relevant research that employ hyphenated approaches for the quantitative study of herbal medicines.

Table 1.2 Techniques for quantitative analysis of herbal medicines that are hyphenated

Methods	Chemical compounds	Herbal medicines	References
High-performance liquid chromatography-Ultraviolet	(E)-4- (3′,4′-dimethoxyphenyl)-but-3-en-1-ol (compound D)	*Z. cassumunar* Roxb.	(Suksaeree, Charoenchai, et al., 2015; Suksaeree & Chuchote, 2018; Suksaeree, Monton, et al., 2015; Suksaeree, Nawathong, Anakkawee & Pichayakorn, 2017)
	Salidroside and tyrosol	*Rhodiola* L.	(Mao, Li & Yao, 2007)
	Chlorogenic acid, laminarin, and luteolin	*Chrysanthemum indicum* L.	(Zhang, Q. et al., 2007)

	Xanthone glycoside	*Anemarrhena asphodeloides* Bge.	(Wang, Lou, Zhu, Chai & Wu, 2005)
	Phenolic compounds	*S. miltiorrhiza* Bge.	(Yuan, Pan, Fu, Makino & Kano, 2005)
High-performance liquid chromatography-Mass spectrometry	Oleanolic acid and ursolic acid	*Anoectochilus roxburghii* (wall.) Lindl	(Huang, Chen, Ye & Chen, 2007)
	Flavonoids	*Citrus aurantium* L.	(Lu, Y., Zhang, Bucheli & Wei, 2006)
	Alkaloids and ecdysone	*Tinospora sagittata* (Oliv.) Gagnep.	(Shi et al., 2007)
High-performance liquid chromatography-Fluorescence detection	Tanshinol	*S. miltiorrhiza* Bge.	(Luo, Bi, Zhou, Wei & Zhang, 2001)
	Nephrotoxic and carcinogenic aristolochic acid	*Aristolochia marshuriensis* Kom.	(Chan, Lee, Liu & Cai, 2007)

1.3.3 Gas chromatography

The extremely sensitive fingerprinting analysis path of all volatile chemical components is gas chromatography. Gas chromatography is the most cost-effective approach due to the small amounts of volatile chemicals required for detection. As a function, many of the pharmacologically active ingredients in herbal medicines exist in volatile chemical forms. For studying these volatile components, gas chromatography is essential. Gas chromatography is frequently recommended for separating a wide range of chemical groups. However, it is not recommended for the research of polar, nonvolatile, or heat-sensitive chemicals (Walker, 2002). Examples of the related research work that uses gas chromatography for quantitative analysis of herbal medicines are the determination of essential oils in *Cinnamomum cassia* Presl. (Gong, Liang, Xu & Chau, 2001), curcumol; curdione; and germacrone in *Curcuma longa* L. (Deng, Ji, et al., 2006), camphor and borneol in *Chrysanthemum indicum* L. (Deng, Mao,

Yao & Zhang, 2006), eucalyptol; camphor; and borneol in *Chrysanthemum indicum* L. (Dong, Wang, Deng & Shen, 2007), etc.

1.4 Standardization of Herbal Medicines

Herbal medications describe the use of their powder, essential oils, and extracts after adopting all industrial methods and standardization. When compared to synthetic and modern pharmaceuticals, herbal medicines are best known for their safety and low cost, as well as their capacity to be made in large quantities and a wide range of therapeutic uses. There is a need to introduce a system or protocol that assures that the finished product is safe enough before it can be disseminated and sold in the market, given the current trend to industrialize herbal medicine manufacturing and processing, as well as the drying and storage process. On the other hand, quality criteria have been carefully enforced. Furthermore, the implementation of standards has elicited a varied response (Shariati et al., 2021). Herbal medication standardization is mostly summarized and required based on the following:

i) characteristics of histology, biology, and botany, as well as associated supplies and measures
ii) toxicity issues
iii) pharmacology issues
iv) all physical and chemical properties
v) pollution and contamination (radioactive, microbiology, etc.)

Herbal treatments are widely used in a variety of therapies, beverages, and meals, and some have undergone considerable study and testing. Even though herb usage is growing increasingly widespread, it is still hard to predict the results of controlled research. As a result, herbal medicines' complexity persists, necessitating a lack of uniformity in chemical analytical techniques (Liang, Y.-Z., Xie & Chan, 2004). The fundamental ideas of chemometric techniques for chemical identification are data acquisition and determining similarity and differences (Walker, 2002). The confirmation and quality control of herbal medicines are the two primary ways of standardizing herbal medicines, which explains the compound-oriented and pattern-oriented approaches, respectively (Liu et al., 2010;