Review Article

A Review: The Phytochemistry, Pharmacology, and Pharmacokinetics of *Curcumae Longae Rhizoma* (Turmeric)

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Abstract

Curcumae Longae Rhizoma (CLR) is the rhizome of *Curcuma longa* L. Pharmacological studies show that CLR can be used to treat cervical cancer, lung cancer, lupus nephritis, and other conditions. In this paper, we review botany, traditional application, phytochemistry, pharmacological activity, and pharmacokinetics of CLR. The literature from 1981 to date was entirely collected from online databases, such as Web of Science, Google Scholar, China Academic Journals full-text database (CNKI), Wiley, Springer, PubMed, and ScienceDirect. The data were also obtained from ancient books, theses and dissertations, and *Flora Reipublicae Popularis Sinicae*. There are a total of 275 compounds that have been isolated from CLR, including phenolic compounds, volatile oils, and others. The therapeutic effect of turmeric has been expanded from breaking blood and activating qi in the traditional sense to antitumor, anti-inflammatory, antioxidation, neuroprotection, antibacterial, hypolipidemic effects, and other benefits. However, the active ingredients and mechanisms of action related to relieving disease remain ill defined, which requires more in-depth research and verification at a clinical level.

Keywords: Botany, *Curcumae Longae Rhizoma*, pharmacokinetics, pharmacology, phytochemistry, traditional uses

Introduction

Curcumae Longae Rhizoma (CLR) is the irregularly oval or cylindrically shaped, dried rhizome of *Curcuma longa* L. (CLL) and belongs to the *Zingiberaceae* family. Turmeric is often used as a medicine or condiment worldwide. Its cultivation areas are mainly in the tropical regions of Asia, including India, Bangladesh, China, Thailand, and other countries.[1] In Bangladesh, people refer to it as "holud." In India where it is known as "haldi" or "golden spice," it is not only used in traditional medicine but also widely used in Hindu religious ceremonies, food, daily chemicals, and other areas.[141] People in India conventionally used turmeric as a spice and condiment and later began to use it for the treatment of anemia, measles, chickenpox, rheumatism, anorexia, rhinitis, cough, and even insect repellent. It is now an integral component of Ayurvedic medicine.[2] In China, turmeric is called *Jiang Huang* (姜黄) because of its ginger-like shape and bright yellow. Pharmacopoeia records that turmeric tastes pungent and bitter, while being mild in nature. It can enter the spleen and liver meridians and has the effect of improving blood circulation and activating qi, dredging meridians, and relieving pain. It is used in traditional Chinese medicine (TCM) to treat conditions such as chest, shoulder and arm pain, dysmenorrhea, amenorrhea, rheumatism, and swelling and pain from falls.[3] *Xin Xiu Ben Cao* (新修本草) records that "turmeric is the main confidant, which leads to stagnation, lower qi, broken blood, wind–heat removal, and carbuncle swelling elimination. The skill is stronger than Yu Jin." This means that turmeric has a positive effect on regulating blood gas, and optimal blood gas is the key to regulating meridians and exerting its efficacy.[4] CLL is a type of medicinal and edible plant, which possesses aboveground and underground parts. People usually discard the leaves and primarily use its rhizome part. Studies have shown that the leaves may have no medicinal value.[5] CLL is mainly distributed in Sichuan, the Fujian province in China,

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and is also found in Jiangxi, Hunan, Shaanxi, and Yunnan. Phytochemical studies show that CLL contains mainly phenolic turmeric acids, sterols, diterpenoids, and a few trace elements. More than 275 types of components have been identified and isolated from turmeric. Pharmacological studies have shown that CLR can be used for the treatment of various diseases and conditions – such as antitumor, anti-inflammatory, antioxidation, neuroprotection, antibacterial, and blood lipid-lowering remedies.[6-11] In addition, it can be used to treat gastrointestinal diseases – especially bile and liver diseases, sinusitis, joint pain, fatigue, sprains, boils, scabies, insect bites, and other ailments and diseases.[12]

Over the past few years, researchers in China and abroad have studied turmeric using modern technology and methods. However, clinical applications of CLR recorded in traditional medical books still require deep excavation and evaluation from a scientific perspective. The research on the aerial parts of CLL was rarely reported, and its leaves may contain some undiscovered new compounds that should be studied in more detail to avoid a waste of resources. Furthermore, investigations into the scientific mechanism underlying its therapeutic effects are incomplete, and future researchers should further study the pharmacological action mechanisms of CLR to ensure its safe clinical application. In this paper – the botany, ethnopharmacology, phytochemistry, pharmacological action, and pharmacokinetics of CLR are summarized. We not only reviewed the research progress on CLR in recent decades from various angles but also determined the inadequacies of the current studies and put forward the relevant problem-solving options to address them. We aim to provide a material basis for further development and utilization of CLR to fully tap the medicinal potential of turmeric.

Botany

CLL., a perennial herb, has long and wide leaves growing directly from the base of the plant, and its rhizomes are well developed. There are about 80 species of *Curcuma* in the world and more than 10 species in China. The earliest record of CLR can be traced back to *Xin Xiu Ben Cao* (新修本草): The roots and leaves of CLL are similar to *Curcuma wenyujin*. The buds grow in spring and bloom in summer, but it bears no fruits. The colors of the roots are yellow, blue, and white.[4] The plant has well-developed, underground, fleshy rhizomes and constitutes the medicinal parts, while the aboveground parts wither in winter.

CLL can easily be distinguished by its appearance. Images of CLL and CLR are shown in Figure 1. The morphological characteristics are as follows.[140] the rhizome is thick, and the end expands to grow into an oval- or spindle-shaped new rhizome, which is grayish brown; the rhizome is ovate and yellow inside; lateral rhizomes are cylindrical, red, and yellow; the leaf blade is elliptical or narrow, 20–45 cm in length, and 6–15 cm in width. The petiole is approximately half as long as the leaf blade sometimes several times as long. The leaf

Figure 1: Images of *Curcuma longa* L. and *Curcumae Longae Rhizoma*

sheath is wide and about the same length as the petiole. Spikes are dense and 13–19 cm in length. The total pedicel length is 20–30 cm; bracts are broadly ovoid, with each bract containing several small flowers; the top bracts are ovate or narrowly ovate, and there are no flowers in the axils. The stamens are rectangular, the filaments are flat and wide, and the lateral staminodes are long and oval. The capsule is membranous, spherical, and three-valved. The seed is oval shaped with an aril. The flowering period lasts from August to November.[13]

CLL is suited to grow in a warm and humid environment with abundant sunshine and rainfall but is unsuited to severe cold and frost, drought, and waterlogging. It is mainly distributed in tropical Asia – including China, India, and Thailand. The harvest season of turmeric is generally in the late December, at which time the rhizomes contain the highest content of curcuminoids and exhibit the best efficacy.[14]

Ethnopharmacology

Turmeric has been used in China for thousands of years and is recorded in several books of Chinese medicine. These include *Xin Xiu Ben Cao* (新修本草), *Sheng Ji Zong Lu* (圣济总录), *Pu Ji Fang* (普济方), and *Ben Cao Gang Mu Shi Yi* (本草纲目拾遗).[128-131] TCM believes that turmeric relieves pain, alleviates blood stasis, relieves depression, activates qi, benefits the gallbladder, clears the heart, eliminates body-waste stagnation, and dredges channels.[15] It can be used not only as a medicine but also as a dietary supplement. Pharmacopoeia records that it can quickly promote blood circulation and qi movement, clear channels, and relieve pain, and it can be used for the treatment of chest, shoulder, and arm pain, dysmenorrhea, amenorrhea, traumatic injury, rheumatism, and other ailments. The usual dosage is 3–10 g. The use of turmeric was recorded in the Harappa civilization as early as 3000 BC.[16] CLL is also popular in India as a medicinal plant. People use it to treat various illnesses, from arthritis to indigestion to various skin diseases.[17] In China, there are numerous records of turmeric in medical books.

The book of *Ben Cao Tu Jing* (本草图经)[132] in the Song Dynasty mentioned that CLR could treat flatulence and postpartum septicemia.

According to *Ben Cao Jing Shu* (本草经疏)[133] in the Ming Dynasty, the use of turmeric was banned if the etiology was blood deficiency, arm pain, and abdominal pain, instead of blood stasis and swelling due to qi and plastic. If people consumed it by mistake, it would negatively affect the blood and the disease would worsen.

Ben Cao Qiu Yuan (本草求原)[134] of the Jin Dynasty recorded that CLR could accelerate the movement of qi in the body. If the gas was biochemical, the body fluid would flow in the three *Yin San Yang*, while the clear one would be injected into the lung, and the turbid one would be injected into the meridian and slip into the sea. The blood would circulate on its own, to regulate the qi and disperse the knot, and then be released.

Ben Cao Gang Mu Shi Yi (本草纲目拾遗), written in the Ming Dynasty, reported that authentic turmeric is that which has been planted for more than 3 years. It can produce and develop flowers in the rhizosphere just like *Schima superba*. Rhizomes are hard and pungent, which is similar to *Curcumae Rhizoma* and *Curcumae Radix*. The smell and other characteristics of turmeric were described clearly in this book.

According to the *Ben Cao Qiu Zhen* (本草求真)[135] of the Qing Dynasty, the function of CLR is similar to that of *Curcuma aromatica, Curcuma zedoaria, Trigonobalanus,* and *Corydalis yanhusuo*. *C. aromatica* can enter the heart and purge the blood of heart cells, and *C. zedoaria* enters the liver to treat blood in qi. *Trigonobalanus* enters the liver to treat qi in blood, and *C. yanhusuo* divides qi from heart and liver blood, while qi divides blood. In addition, CLR enters the spleen, which not only cures blood in qi but also restores qi ear in the blood. *Chen Zangqi* declared that CLR was less pungent and more bitter, with a better nature than *C. aromatica.* It can quickly promote blood circulation and qi movement. It can treat suffocation and gas accumulation, blood stasis, and blood-closed carbuncles. The book also describes the differences between turmeric plants.

The medicine books of *Xin Xiu Ben Cao* (新修本草) point out that the leaves and rhizomes of CLL are like *Curcumae Radix*. CLL produces flower buds in the early spring and blooms in summer, without bearing any seeds. Roots are yellow, green, and white. The taste of the leaves is less bitter than that of the rhizomes (similar to that of *Curcumae Radix*), but the flowers are different. *C. longa*, *Curcumae Rhizoma*, and *Curcumae Radix* all come from the *Curcuma* family. They have similar basic sources but different chemical compositions and pharmacological effects. However, referring to ancient books, it has been found that they were used interchangeably in ancient times, and their relationship is confusing. Currently, despite existing literature distinguishing them using fingerprint and modern analysis methods, unified evaluation is lacking.

Turmeric is mostly used alone in practical application, but it can play a better role in combination with other herbs. These formulations follow the rule of "*Jun Chen Zuo Shi*."[142] It is more effective in reducing adverse effects and toxicity and improving the therapeutic of herbs.[143] For example, the common formulae include Qiwei Jianghuang Chaji, Jiuwei Gantai Jiaonang, Wuhuang Yangyin Keli, Huazheng Huisheng Pian, and Fengtong'an Jiaonang, which carry the functions of clearing away heat and dampness, dispelling wind and relieving itching, removing blood stasis and dredging collaterals, soothing the liver and invigorating the spleen, eliminating phlegm, and benefiting qi and nourishing yin, among other uses. It can be used for treating symptoms caused by blood stasis, frequent micturition, spontaneous perspiration, night sweats, palpitations, insomnia, obesity, depression, vexation, acne caused by damp heat and depressed skin, as well as other similar conditions. The prescriptions of CLR are summarized in Table 1.

In modern times, turmeric extract is also used in the cosmetic field because it possesses antiwrinkle and skin-beautifying effects. It is also used as an additive in food and dyes. Turmeric residue can produce turmeric starch, ferment unpleasant wine, and be directly used as feed. The comprehensive utilization of turmeric can promote the development of the food, chemical, spice, and pharmaceutical industries and therefore offers valuable economic benefits.

Phytochemistry

Several chemical components have been extracted from CLR, which have been widely investigated by researchers. To date, more than 275 compounds have been isolated and identified, including primarily phenolic compounds, volatile oils, trace elements, and other components.[18] In this section, we summarize the chemical constituents obtained.

Phenolic compounds

The main active components in CLR are phenolic compounds and volatile oils, both of which have good therapeutic and medicinal effects, and curcumin is currently the main research target. Curcumin is a type of polybasic phenolic acid compound with a β-diketone symmetrical structure, which consists of 1–2 phenolic groups, two α-, β-unsaturated ketone double bonds, one β-diketone, and a central active methylene group.[19] The 2020 version of Pharmacopoeia stipulates that the content of curcumin in turmeric should not be less than 1.0%. The first separation of curcumin compounds can be traced back to 1815, and the chemical structure of the bis-feruloyl methane component was identified in 1910.[20] At present, more than 30 kinds of natural curcumin compounds have been isolated from turmeric.[21] Among them, the highest content is found in three components, including curcumin I, curcumin II, and curcumin III.[22] Pharmacological studies show that curcumin has anticancer, anti-inflammation, and antioxidation pharmacological properties, also reduces blood lipid levels, offers neuroprotection, and provides other pharmacological protection.[23]

With a focus on "search-location-purification-identification," Li *et al*. identified a new compound with a curcumin skeleton structure from a 95% methanol extract of *Curcumae Rhizoma* named curcuterpene G (3,4‴-epoxy-5‴-C-(1α,2β,3β-bisabola-4,10-die

Table 1: Prescription of Curcumae Longae Rhizome

Preparation name	Main compositions	Formulation	Traditional and clinical uses	Reference
Qiwei Jianghuang Chaji	CLR Paridis rhizoma *Polygonum perfoliatum* L. *Chenopodium ambrosioides* L. *Solidago decurrens* Lour. *Gynostemma pentaphyllum* (Thunb.) Makino *Zingiber corallinum* Hance	Liniment	It can be used for clearing away heat and dampness, dispelling wind and relieving itching, promoting blood circulation, and eliminating acne	Chinese Pharmacopoeia (version 2020)
Jiuwei Gantai Jiaonang	CLR Notoginseng Radix Et Rhizoma Curcumae Radix *Chenopodium ambrosioides* Rhei Radix Et Rhizoma *Scutellaria baicalensis* Georgi Centipede *Dioscorea oppositifolia* L. *Schisandra chinensis* (Turcz.) Baill	Capsule	It can remove blood stasis, dredge collaterals, soothe liver, and strengthen spleen. It can be used for hypochondriac pain or stabbing pain, depression, and boredom	Chinese Pharmacopoeia (version 2020)
Wuhuang Yangyin Keli	CLR *Coptis chinensis* Franch Radix hedysari Radix rehmanniae *Scutellaria baicalensis* Georgi	Granules	It can eliminate dampness, eliminate phlegm, invigorate qi and nourish yin. Used for diabetes, which is characterized by phlegm-dampness stagnation and deficiency of both qi and yin	Chinese Pharmacopoeia (version 2020)
Fengtong'an Jiaonang	CLR Radix stephaniae tetrandrae *Tetrapanacis medulla* *Cinnamomi ramulus* Gypsum fibrosum Coix seed Papaya *Pittosporum omeiense* *Lonicera japonica* Thunb. Phellodendron Talc Weeping forsythia	Capsule	It can clear heat, promote diuresis, promote blood circulation, and dredge collaterals. It is used for arthralgia caused by damp-heat blocking collaterals, with symptoms of red swelling and pain of joints and sore muscles	Chinese Pharmacopoeia (version 2020)
Wujun Zhidan Pian	CLR *Mume fructus* Rhei Radix Et Rhizoma *Citri sarcodactylis* *Fructuscitrus aurantium* *Origanum vulgare* L. Gardenia Glycyrrhizae Radix Et Rhizoma Areca Catechu Clematis root	Tablet	It can soothe the liver, relieve depression, promote gallbladder function, remove heat, and relieve pain. Used for hypochondriac pain and bilge caused by damp-heat of liver and gallbladder	Chinese Pharmacopoeia (version 2020)
Binghuang Fule Ruangao	CLR Rhei Radix Et Rhizoma Sulfur *Scutellaria baicalensis* Georgi Glycyrrhizae Radix Et Rhizoma *Borneolum syntheticum* Menthol	Paste	It can clear away heat and dampness, promote blood circulation and dispel wind, relieve itching and diminish inflammation. Used for skin itching caused by damp-heat accumulation or blood hot air drying	Chinese Pharmacopoeia (version 2020)
Ruyi Jinhuang San	CLR Rhei Radix Et Rhizoma Phellodendron *Atractylodis rhizoma* *Magnoliae officinalis* cortex	Powder	It can clear away heat and toxic materials, reduce swelling, and relieve pain. It can be used for treating sore, swelling and pain caused by heat toxin and	Chinese Pharmacopoeia (version 2020)

Contd...

Table 1: Contd...

Preparation name	Main compositions	Formulation	Traditional and clinical uses	Reference
	Citri Reticulatae Pericarpium Glycyrrhizae Radix Et Rhizoma *Arisaematis rhizoma* *Angelica dahurica* (Fisch.ex Hoffm.) Trichosanthin		stagnation of skin, red, swollen, hot, and painful skin	
Jinto Zhitong Wan	CLR Paeoniae Radix Alba Corydalis Rhizoma Notoginseng Radix Et Rhizoma Curcumae radix *Citri sarcodactylis fructus* Glycyrrhizae Radix Et Rhizoma	Pill	It is feasible to relieve pain by qi, soothe liver and stomach, remove blood stasis, and create new life. It can be used for epigastric pain caused by stagnation of qi and blood, dysmenorrhea, and pain caused by peptic ulcer and chronic gastritis	Chinese Pharmacopoeia (version 2020)
Yuxuebi Jiaonang	CLR *Boswellia carteri* Myrrha *Carthami flos* Clematis root *Cyathulae radix* *Cyperi rhizoma* *Angelicae sinensis* Radix Salviae Miltiorrhizae Radix Et Rhizoma Chuanxiong Rhizoma Astragali Radix Praeparata Cum Melle	Capsule	It can promote blood circulation, remove blood stasis, dredge collaterals, and relieve pain. It can be used for arthralgia caused by blood stasis blocking collaterals, which is characterized by severe pain in muscles and joints, refusal to press at pain points, immobile fixation, and possible hard joints or ecchymosis	Chinese Pharmacopoeia (version 2020)
Biwen San	CLR Sandalwood *Lysimachia foenumgraecum* Hance Angelica Anisochilus carnosua L. Wall Rosae Rugosae Flos Rhizoma Nardostachyos Caryophylli Flos Radix Aucklandiae Moschus *Borneolum syntheticum* Cinnabar Menthol	Pill	It can dispel summer heat, avoid filth, induce resuscitation, and relieve pain. Used for dizziness, headache, stuffy nose, nausea, vomiting, motion sickness, and seasickness caused by summer heat evil	Chinese Pharmacopoeia (version 2020)
Jiang Huang San	CLR Angelicae Sinensis Radix Radix Aucklandiae Combined Spicebush *Evodia rutaecarpa* (Juss.) Benth.	Powder	It can cure heartache which cannot bear	Sheng Ji Zong Lu (圣济总录)[129]
Jiangqin Siwu	CLR Angelicae Sinensis Radix Radix Rehmanniae Red peony root Chuanxiong Rhizoma *Scutellaria baicalensis* Georgi Cortex Moutan Corydalis Rhizoma Cyperi Rhizoma	Decoction	Treatment of menstruation comes early, with less blood astringency and red color	Yi Zong Jin Jian (医宗金鉴)[136]
Jiang Huang Tang	CLR Persicae Semen *Magnolia denudata* Des Cortex Moutons Sappan Lignum Angelicae Sinensis Radix	Decoction	It cures all traumatic injuries	Shang Ke Fang Shu (伤科方书)[137]

Contd...

Table 1: Contd...

Preparation name	Main compositions	Formulation	Traditional and clinical uses	Reference
	Citri Reticulatae Pericarpium Sheng Xi Chuanxiong Rhizoma Radix Rehmanniae *Cinnamomum cassia* Presl *Boswellia carteri* Myrrha			
Xieriga Siweitang capsules	CLR Phellodendron Gardenia Caltrop	Capsules	It can induce diuresis and relieve damp heat. It can be used for stopping urination, frequent micturition, urgent micturition, bloody urine, and stinging bladder	The Ministry of Health of the People's Republic of China Drug Standards Mongolian Medicine Sub-volume (《中华人民共和国卫生部药品标准》蒙药分册)[138]
Sheng Jing San	CLR White Muscardine Silkworm Periostracum Cicadae Rheum officinale Baill	Powder	It can be used for warming, plague, pathogenic heat flooding inside and outside, blocking qi activity, clearing yang without rising, turbid yin without falling, causing swelling of head and face	Shang Shu Quan Shu (伤暑全书)[139]

CLR: Curcumae Longae Rhizome

ne-9-one)-(2 → 5‴)-curcumin) by using Liquid Chromatograph-Mass Spectrometer (LC-MS) analysis, MCI (Macroporous Resin) MCI pore resin, ODS-C18 reversed-phase column chromatography, and (Reversed Phase-High Performance Liquid) RP-HPLC.[24] Bai *et al*. used various column chromatography approaches to separate the yellow-pigmented compound 1,5-bis (4-hydroxyphenyl)-penta-(1E,4E)-1,4-diene-3-one from the ethanol extract of *C. longa* for the first time.[25] Cui *et al*. used silica gel column chromatography, Sephadex LH-20 gel column chromatography, and HPLC to separate 13 components from the n-butanol fraction of 95% ethanol extract of CLR, among which isocyclic demethoxycurcumin was isolated for the first time.[26] Li *et al*. reported 19 diphenyl heptanes and 3 diphenyl ketones.[18] Wei *et al*. found through HPLC comparative analysis that the aerial parts of CLL do not contain curcumin, so it may have no pharmacological value. This may be one of the reasons why ancient people abandoned it completely.[5] We summarize the phenolic compounds of CLR in Table 2, and the structures are shown in Figure 2.

Volatile oils

There are various components in CLR, of which volatile oils are one of the main active components. Its content can reach approximately 7% (ml/g) in the turmeric. Modern research shows that the volatile oil has various kinds of pharmacological activities such as antitumor, antithrombosis, antioxidation, antibacterial, and anti-inflammatory effects.[27] It has been widely used in medicine, food, cosmetics, and other fields. However, the components of volatile oil are complex. Differences in plant variety, cultivation areas, and processing and extraction methods result in marked differences in the chemical components and relative content percentage of volatile oil from CLR.[28] Yang *et al*. analyzed the chemical components of turmeric volatile oil from Sichuan, Hainan, Thailand, and Vietnam using gas chromatography-mass spectrometry (GC-MS) and identified 50 components. The investigation revealed that the content of turmeric was lower in domestic volatile oil than in that imported from Southeast Asia.[29] Qiang *et al*. extracted volatile oil using steam distillation and analyzed the components of the extracted volatile oil using headspace solid-phase microextraction combined with GC-MS. Among them, 51 components were identified, and the relative percentage of these components accounted for 98.41% of volatile oil components. At the same time, a new compound, β-cedrene, was discovered.[30] Zeng *et al*. separated and identified the ethanol extract of CLR and obtained six sesquiterpenes including turmeronol A, turmeronol B, bisabolone, 8-hydroxyl-ar-turmerone, bisabolone-9-one, (6S)-2-methyl-6-[(1R,5S) 4-methene-5-hydroxyl-2-cyclohexen-2-hepten-4-one].[31] Chen *et al*. used GC-MS to compare the volatile components extracted from dried and raw turmeric using steam distillation and Soxhlet extraction with petroleum ether as the solvent. Five common components were identified with relative content exceeding 4%: α-curcumene, aromatic ginger flavone, β-sesquiterpene, α-ginger flavone, and β-ginger flavone.[32] Gounder and Lingamallu extracted the volatile oil from CLR using fresh and dried plants (from India) and obtained 28 and 14 components, respectively, most of which were sesquiterpenes, and the main components were aromatic ginger flavone (21.0% and 30.3%), α-ginger flavone (33.5% and 26.5%), and β-ginger flavone (11.5%).[33] Zou *et al*. analyzed 71 components from the volatile oil of CLR using GC-MS, among which the main components were turmeric flavone, *Curcuma* new ketone, ginger flavone, and so on.[34] Fang *et al*. analyzed CLR from Guangdong, Sichuan, Fujian, Yunnan, and Hainan using the ultrasonic method and extracted its methanol and petroleum ether fractions. This approach yielded 47 chemical components identified using LC-MS

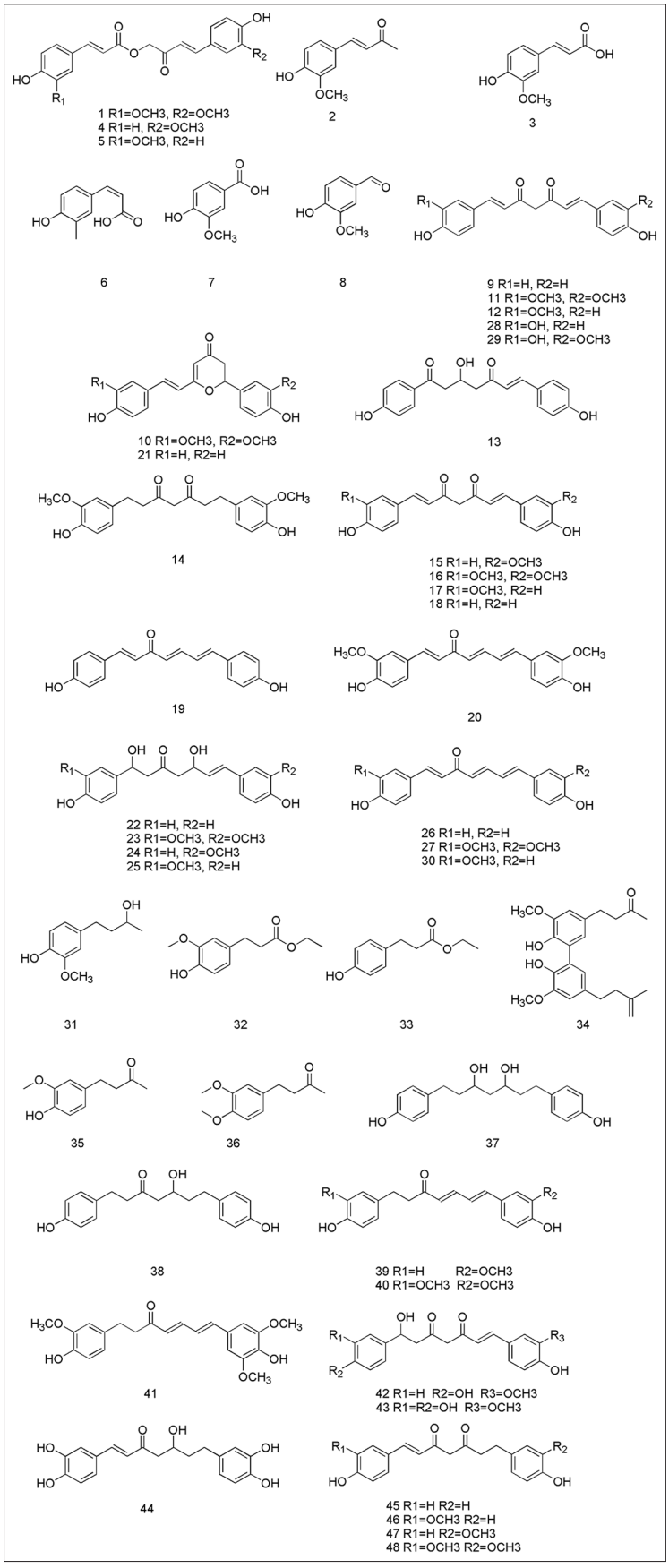

Figure 2: Structures of phenolic compounds in *Curcumae Longae Rhizoma*

Table 2: The phenolic compounds in *Curcumae Longae Rhizoma*

Compound name	Reference
Calebin-A	[97]
(*E*)-4-(4-hydroxy-3-methoxyphenyl) but-3-en-2-one	[98]
(*E*)-ferulic acid	[98]
4"-(4"'-hydroxyphenyl)-2"-oxo-3"-butenyl-3-(4'-hydroxyphenyl-3'-methoxy)-propenoate	[99]
4"-(4"'-hydroxyphenyl-3-methoxy)-2"-oxo-3"-butenyl-3-(4'-hydroxyphenyl)-propenoate	[99]
(*Z*)-ferulic acid	[98]
Vanillic acid	[98]
Vanillin	[98]
Bisdemethoxycurcumin (curcumin III)	[126]
Cyclocurcumin	[100]
Curcumin (curcumin I)	[126]
Demethoxycurcumin (curcumin II)	[126]
3-hydroxy-1,7-bis-(4-hydroxyphenyl)-6-heptene-1,5-dione	[101]
tetrahydroxycurcumin	[126]
5-hydroxyl-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadiene-3-one	[102]
5-hydroxyl-1,7-bis (4-hydroxy-3-methoxyphenyl)-4,6-heptadiene-3-one	[102]
5-hydroxyl-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-4,6-heptadiene-3-one	[102]
1,7-bis (4-hydroxyphenyl)-1-heptene-3,5-dione	[102]
1,7-bis-(4-hydroxyphenyl)-1,4,6-heptatrien-3-one	[103]
1,7-bis (4-hydroxy-3-methoxyphenyl)-1,4,6-heptatrien-3-one	[126]
1,5-epoxy-3-carbonyl-1,7-bis (4-hydroxyphenyl)-4,6-heptadiene	[105]
1,5-dihydroxy-1,7-bis (4-hydroxyphenyl)-4,6-heptadiene-3-one	[101]
1,5-dihydroxy-1,7-bis (4-hydroxy-3-methoxyphenyl)-4,6-heptadiene-3-one	[101]
1,5-dihydroxy-1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-4,6-heptadiene-3-one	[101]
1,5-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-4,6-heptadiene-3-one	[101]
1,5-bis (4-hydroxyphenyl)-penta-(1E,4E)-1,4-dien-3-one	[101]
1,5-bis (4-hydroxy-3-methoxyphenyl)-penta-(1E,4E)-1,4-dien-3-one	[98]
1-(4-hydroxyphenyl)-7-(3, 4-dihydroxyphenyl)-1, 6-heptadiene-3, 5-dione	[126]
1-(4-hydroxy-3-methoxyphenyl)-7-(3, 4-dihydroxyphenyl)-1, 6-heptadiene-3, 5-dione	[101]
1-(4-hydroxy-3-methoxyphenyl)-5-(4-hydroxyphenyl)-1, 4-pentadiene-3-one	[101]
Zingerol	[43]
Dihydroferulic acid ethyl ester	[43]
Ethyl 3-(4-hydroxy-phenyl)-propionate	[43]
Zingerone dimer [4,4'-(6,6'-dihydroxy-5,5'-dimethoxy-[1,1'-biphenyl]-3,3'-diyl) bis (butan-2-one)]	[34]
Zingiberone	[3]
4-(3,4-dimethoxyphenyl) butan-2-one	[43]
1,7-bis (4-hydroxyphenyl)-3,5-heptanediol	[126]
5-hydroxyl-1,7-bis (4-hydroxyphenyl)-3-heptanone	[126]
7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4, 6-heptadien-3-one	[126]
1,7-bis (4-hydroxy-3-methoxyphenyl)-4, 6-heptadien-3-one	[126]
1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxy-3,5-dimethoxyphenyl)-4, 6-heptadien-3-one	[126]
1- hydroxy-1-(4-hydroxy-phenyl)-7-(4-hydroxy-3-methoxyphenyl)-6-hepten-3,5-dione	[126]
1- hydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-6-hepten-3,5-dione	[126]
1-Hepten-3-one, 5-hydroxy-1,7-bis (3,4-dihydroxyphenyl)	[126]
Dihydrobisdemethoxycurcumin	[126]
Dihydrodemethoxycurcumin-A	[126]
Dihydrodemethoxycurcumin-B	[126]
Dihydrocurcumin	[126]

(Liquid Chromatograph-Mass Spectrometer) and GC-MS. On comparing the content of compounds from different habitats, it was found that there were differences in the methanol fractions, petroleum ether fractions, and contents of CLR, and the content of total ginger flavonoids in CLR decreased first and then increased with increased latitude.[35]

We summarize the volatile oil compounds of CLR in Table 3, and the structures are shown in Figure 3.

Other components

In addition to the above components, CLR contains low levels of diterpenes, saccharides, sterols, flavonoids, organic acids,

Table 3: The volatile oil components in *Curcumae Longae Rhizoma*

Compound name	Reference
α-zingiberene	[106]
α-turmerone	[107]
α-thujeneterpinolene	[106]
α-terpineol	[108]
α-terpinene	[106]
α-selinene	[109]
α-santalol	[109]
α-santalene	[109]
α-pinene	[108]
α-oxobisabolene	[110]
α-humulene	[106]
α-curcumene	[108]
Ascaridole	[111]
ar-turmerone	[125]
ar-turmerol	[112]
Aristolene	[109]
ar-curcumene	[112]
Adoxal	[109]
Acoradiene	[109]
a-bisabolol	[109]
β-turmerone	[107]
β-sesquiphellandrene	[108]
β-santalene	[109]
β-pinene	[110]
β-phellandrene	[106]
β-elemene	[110]
β-curcumene	[113]
β-bisabolene	[106]
β-atlantone	[98]
β, β-dimethylstyrene	[109]
bornyl acetate	[111]
Borneol	[106]
Bisacurone C	[114]
Bisacurone B	[114]
Bisacurone A	[115]
Bisacurone	[98]
Bisacumol	[116]
Bisabolone-9-one	[112]
Bisabolone	[99]
Bisabola-3,10-diene-2-one	[117]
Bicyclo[7.2.0]undecane, 10,10-dimethyl-2,6-bis (methylene)	[109]
Benzene, 1-methyl-4-(1-methylpropyl)	[109]
Curlone	[109]
Curcuphenol	[110]
Curcumin L	[118]
Curcumenone	[116]
Curcumenol	[116]
Curcumanolide B	[98]
Curcumanolide A	[98]
Curculonone D	[98]
Curculonone C	[98]
Curculonone B	[98]
Curculonone A	[98]
Cubebene	[106]
Corymbolone	[110]
Citronellyl pentanoate	[108]
Citronellal	[108]
Cis-ocimene	[106]
Cineole	[110]
Caryophyllene oxide	[109]
Caryophyllene	[108]
Carvone	[108]
Carvacrol	[111]
Camphor	[109]
Camphene	[106]
Dihydro-ar-turmerone	[119]
di-epi-cedrene	[109]
Dehydrozingerone	[114]
Dehydrocurdione	[116]
Dehydrocurcumene	[120]
Epiprocurcumenol	[116]
2-norpinanone	[111]
2-methyl-6-(4-hydroxyphenyl)-2-hepten-4-one	[99]
2-methyl-6-(4-hydroxy-3-methylphenyl)-2-hepten-4-one	[115]
2-methyl-6-(4-formylphenyl)-2-hepten-4-one	[99]
2-methoxy-5-hydroxybisabola-3,10-diene-9-one	[115]
2-carene	[108]
2,6-dimethyl-2,6-octadiene-1,8-diol	[109]
2, 5-dihydroxybisabola-3, 10-diene	[114]
2-(2,5-dihydroxy-4-methylcyclohex-3-enyl) propanoic acid	[115]
2, 8-epoxy-5 -hydroxybisabola-3, 10-diene-9-one	[115]
2,6,10-dodecatrien-1-ol, 3,7,11-trimethyl-	[109]
(*E, E*)-α-farnesene	[111]
(*E*)-*γ*-atlantone	[106]
(*E*)- *γ*-atlantone	[119]
(*E*)-sesquisabinene hydrate	[111]
(*E*)-chrysanthenyl acetate	[111]
(*E*)-caryophyllene	[111]
(*E*)-carveol	[111]
(*E*)-α-atlantone	[119]
Germacrone-13-al	[116]
Germacrone	[116]
Germacrene D	[108]
β-germacene	[106]
Geranyl acetate	[109]
Geraniol	[109]
Geranic acid	[109]
Geranial	[106]
γ-terpineol	[110]
γ-terpinene	[106]
γ-gurjunen epoxide	[109]
γ-elemene	[109]
γ-curcumene	[106]
γ-bisabolene	[110]
Hxadecane-1,2-diol	[110]

Contd...

Contd...

Table 3: Contd...

Compound name	Reference
Himachalene	[109]
Isoprocurcumenol	[116]
Iso-artemisia ketone	[106]
Juniper camphor	[109]
Linalool	[108]
Limonene	[111]
6-hydroxycurcumanolide A	[98]
(6*S*,7*R*)-bisabolene	[111]
(6*S*)-2-menthyl-6-[(1*R*,5*S*) -(4-methene-5-hydroxyl-2-cyclohexen)-2-hepten-4-one	[112]
(6*R*)-[(1*R*)-1,5-dimethylhex-4-enyl] -3-methylcyclohex-2-en-1-one	[98]
Myrcene	[106]
Menthol	[109]
Menthofuran	[108]
m-cymene	[106]
Nerolidyl propionate	[109]
Neryl acetate	[110]
Nerolidal	[120]
Nerol	[108]
Neral	[106]
Naphthalene, 1,2,3,4,4a, 5,6,8a-octahydro-4a, 8-dimethyl-2-(1methylethylidene)	[109]
o-cymene	[110]
Procurcumenol	[116]
Procurcumadiol	[116]
p-methylacetophenone	[120]
p-meth-8-en-2-one	[110]
p-mentha-1,4 (8)-diene	[110]
p-menth-8-en-2-one	[111]
Piperitone epoxide	[110]
Piperitone	[109]
Phellandrol	[108]
p-cymene	[108]
p-cymen-8-ol	[110]
7-*epi*-sesquithujene	[111]
R-citronellene	[110]
Sylvestrene	[110]
3-carene	[111]
3-bornanone	[109]
3,7-dimethyl-6-nonenal	[109]
3,4,5,6-tetramethyl-2,5-octadiene	[109]
4-terpinol	[112]
4-methylene-5-hydroxybisabola-2,10-diene-9-one	[115]
4-methoxy-5-hydroxy-bisabola-2,10-diene-9-one	[116]
4-hydroxybisabola-2,10-diene-9-one	[116]
4,8-dimethyl-3,7-nonadien-2-ol	[109]
4,5-dimethyl-2,6-octadiene	[109]
4, 5-dihydroxybisabola-2,10-diene	[114]
(4*S*,5*S*)-germacrone-4,5-epoxide	[116]
Turmeronol B	[99]
Turmeronol A	[115]
Trans-ocimene	[106]
Thymol	[106]

Contd...

Table 3: Contd...

Compound name	Reference
Terpinolene	[111]
Terpinen-4-ol	[110]
Teresantalol	[109]
5,9-undecadien-2-one, 6,10-dimethyl-, (*Z*)-	[109]
5-hydroxyl-ar-turmerone	[99]
Xanthorrhizol	[108]
1-*epi*-cubenol	[119]
12-oxabicyclo [9.1.0] dodeca-3,7-diene, 1,5,5,8-tetramethyl-,	[109]
1,3,8-paramenthatriene	[120]
1,10-dehydro-10-deoxy-9-oxozedoarondiol	[98]
Zingerone	[114]
Zedoaronediol	[116]
(*Z*)-β-farnesene	[111]
(*Z*)-α-bergamotene	[111]
(*Z*)-sabinol	[121]
(*Z*)-cinerone	[121]
(*Z*)--atlantone	[106]
β-Cedrene	[30]
Methacrolein	[30]
Toluene	[30]
2-Isopropenyltoluene	[30]
2-Nonanol	[30]
δ-Elemene	[30]
Germacrene B	[30]
Nonyl methyl ketone	[30]
3-Dimethyl-2,3-diphenylbutane	[30]
isoledene	[30]
3-Dimethyl-2,4-hexadiene	[30]
3,7（11）-Selinadiene	[30]
3,3,5,5-Tetramethylcyclopentene	[30]
Mesitylene	[30]
β-Elemenone	[30]
Zingiberenol	[30]
Guaiol	[30]
α-Acorenol	[30]
Curcumol	[122]
Curdione	[122]
Bisacurone D	[123]
Bisacurone E	[123]
Bisacurone F	[123]
Bisacurone G	[123]
β-Pinen	[124]
Sabinen	[124]
3-Karen	[124]

and trace elements. Afzal *et al*. isolated 4 diterpenoids and 3 triterpenoids from CLR.[36] The saccharides in CLR include 1.1% arabinose, 12% fructose, and 28% glucose. There are also acidic polysaccharides A, B, C, and D. CLR also contains sterols such as β-sitosterol, fatty acid, oleoresin, mono-dilute acid, and di-dilute acid. Flavonoids isolated and identified from CLR include dihydroflavonols, flavones, flavonols, and their aglycones myricetin, lutein, quercetin, apigenin, and

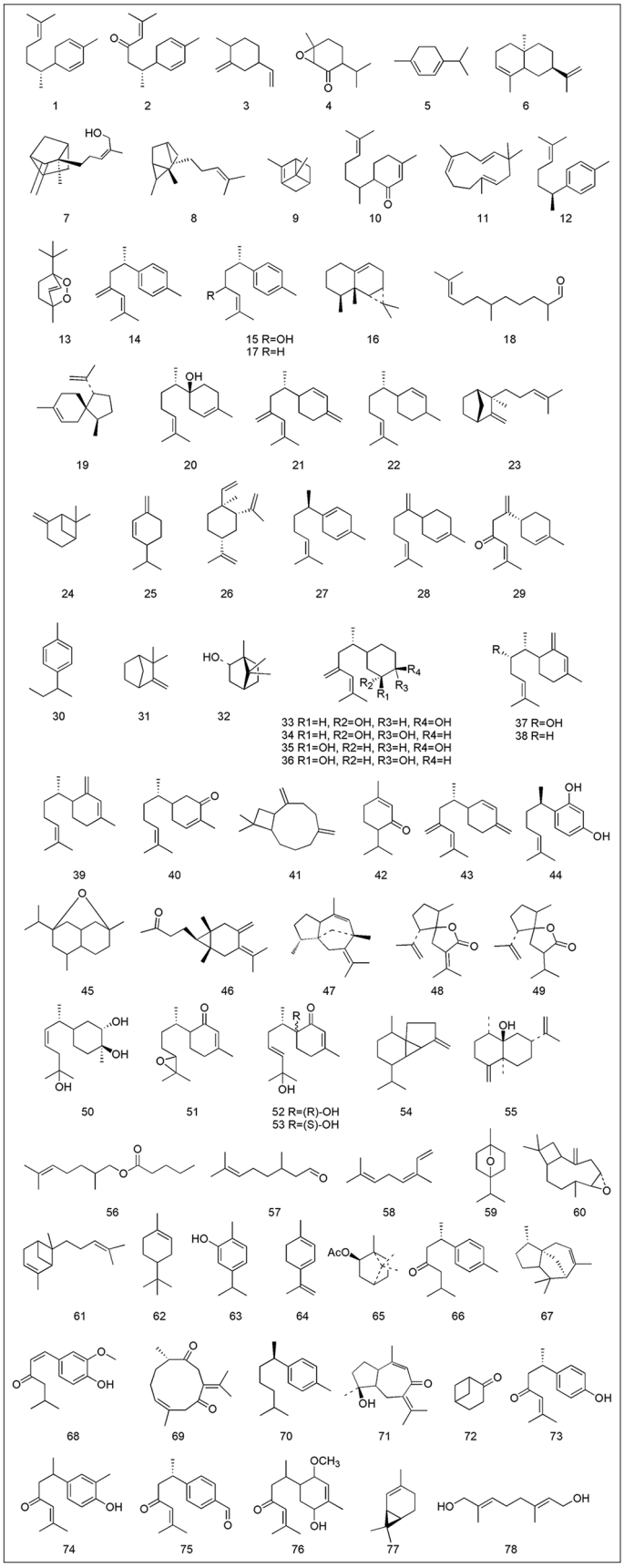

Figure 3: Structures of volatile oils in *Curcumae Longae Rhizoma*

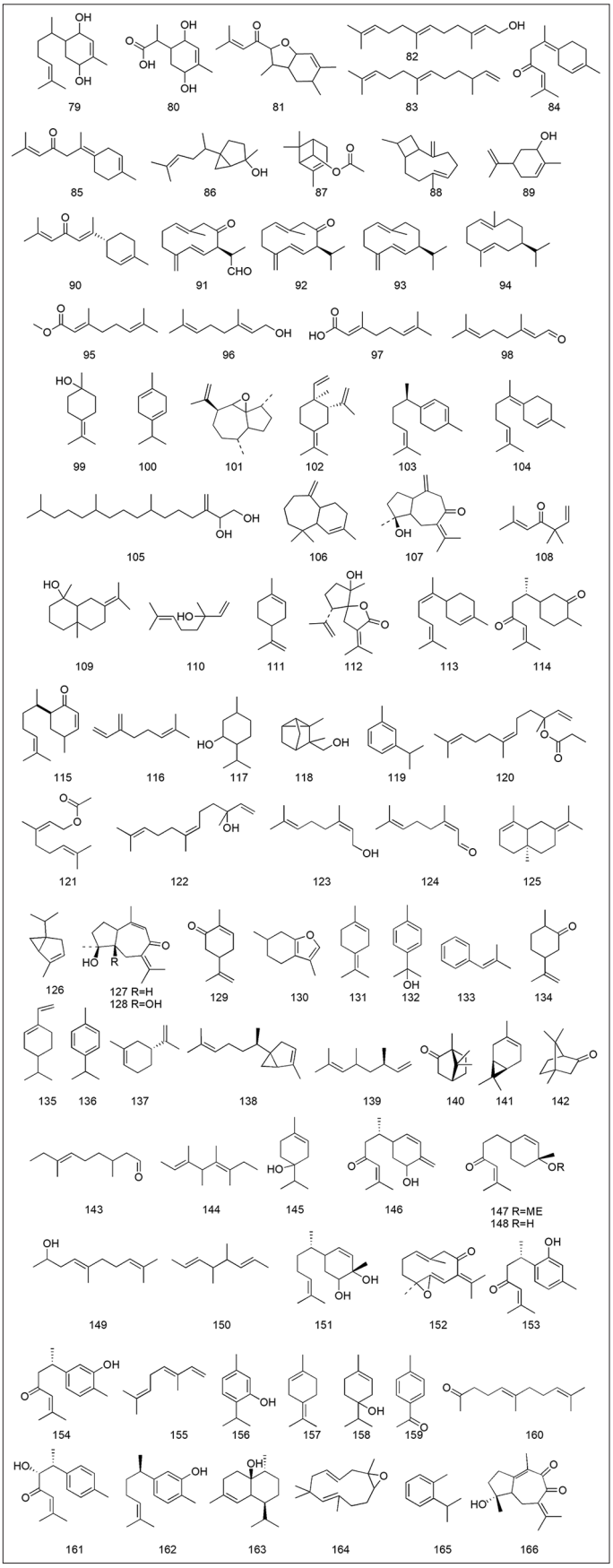

Figure 3: Contd...

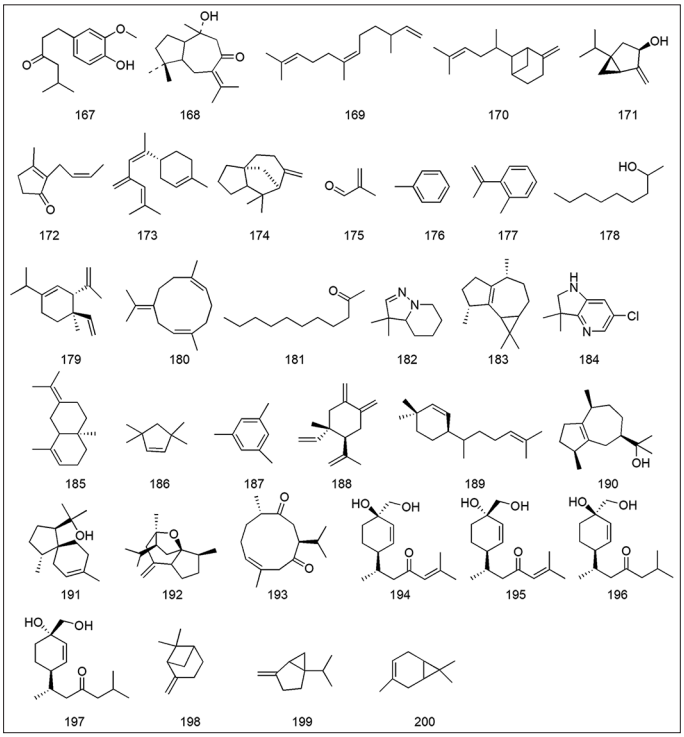

Figure 3: Contd...

kaempferol.[37-39] Furthermore, organic acids isolated from CLR include salicylic, veratric, ferulic, syringic, cinnamic, sinapic, chlorogenic, m-hydroxybenzoic, and p-hydroxybenzoic types of acids.[40] In addition, it contained succinic acid and protocatechuic acid.[41] Chen *et al*. determined 19 inorganic elements, namely Li, B, Mg, Al, P, Ca, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Sr, Ba, Cd, and Pb from turmeric using MS (Inductively Coupled Plasma-Mass Spectrometry) ICP-MS and (Inductively Coupled Plasma-atomic emission spectrometry) ICP-AES.[42] We summarize the other compounds of CLR in Table 4, and the structures are shown in Figure 4.

Pharmacology

As a natural medicine, the pharmacological activity of CLR has surpassed the category of "breaking blood and activating qi, dredging meridians, and relieving pain" in TCM theory and has become a new area of interest in natural medicine research. Published scientific literature has shown that CLR possesses antitumor, anti-inflammatory, antioxidation, neuroprotection, antibacterial, and hypolipidemic functions. Chemotherapeutic drugs take effect quickly and can rapidly affect the patient's condition. However, they may elicit adverse reactions and lead to the development of drug resistance.[144] In contrast, TCM can achieve better therapeutic effects using multichannel and multitarget strategies.[145]

Antitumor effects

In recent years, Chinese medicine has demonstrated unique advantages in treating tumors. Numerous preclinical cell and animal experiments have shown that turmeric volatile oil and curcumin have therapeutic effects on pancreatic, gastric, colorectal, prostate, liver, skin, breast, and oral cancers.[44] CLR can be used not only as a chemotherapy drug but also as a tumor-preventive drug. Its anticancer mechanism acts at various stages in the development of cancer and inhibits tumor-related factors in different ways.[45] Therefore, CLR has become a research hotspot in China and abroad.

In 1985, Kuttan *et al*. discovered that CLR could inhibit the growth of animal tumors *in vivo* and *in vitro* and determined that its antitumor active component was curcumin. It was proved that curcumin could be used as an anticancer and antimutagenic agent.[46] Subsequently, the antitumor effect of curcumin was widely studied. Experiments by Xu *et al*. revealed that curcumin inhibited the proliferation of human gastric cancer MGC803, human liver cancer Bel7402, and human erythroleukemia K562 cells and had a significant antitumor effect on mouse melanoma B16 and Ehrlich ascites carcinoma-transplanted tumor *in vivo*.[47] Chen *et al*. found that pure curcumin has certain inhibitory effects on H22 tumor cells, but the water extract of turmeric has no obvious inhibitory effect, which may be related to the difference in curcumin content in the water extract, the interference of other components on curcumin's anticancer properties, or the loss of volatile oil components with anticancer effects in the process of water extraction.[48] Sun *et al*. studied the antitumor activity of turmeric extract emulsion *in vivo* and found that the injection of turmeric oil extract emulsion inhibits the growth of tumors in transplanted melanoma-bearing and glioma-bearing mice (intracranial inoculation) in a dose-dependent manner; the effect of intravenous administration twice a day on mice with

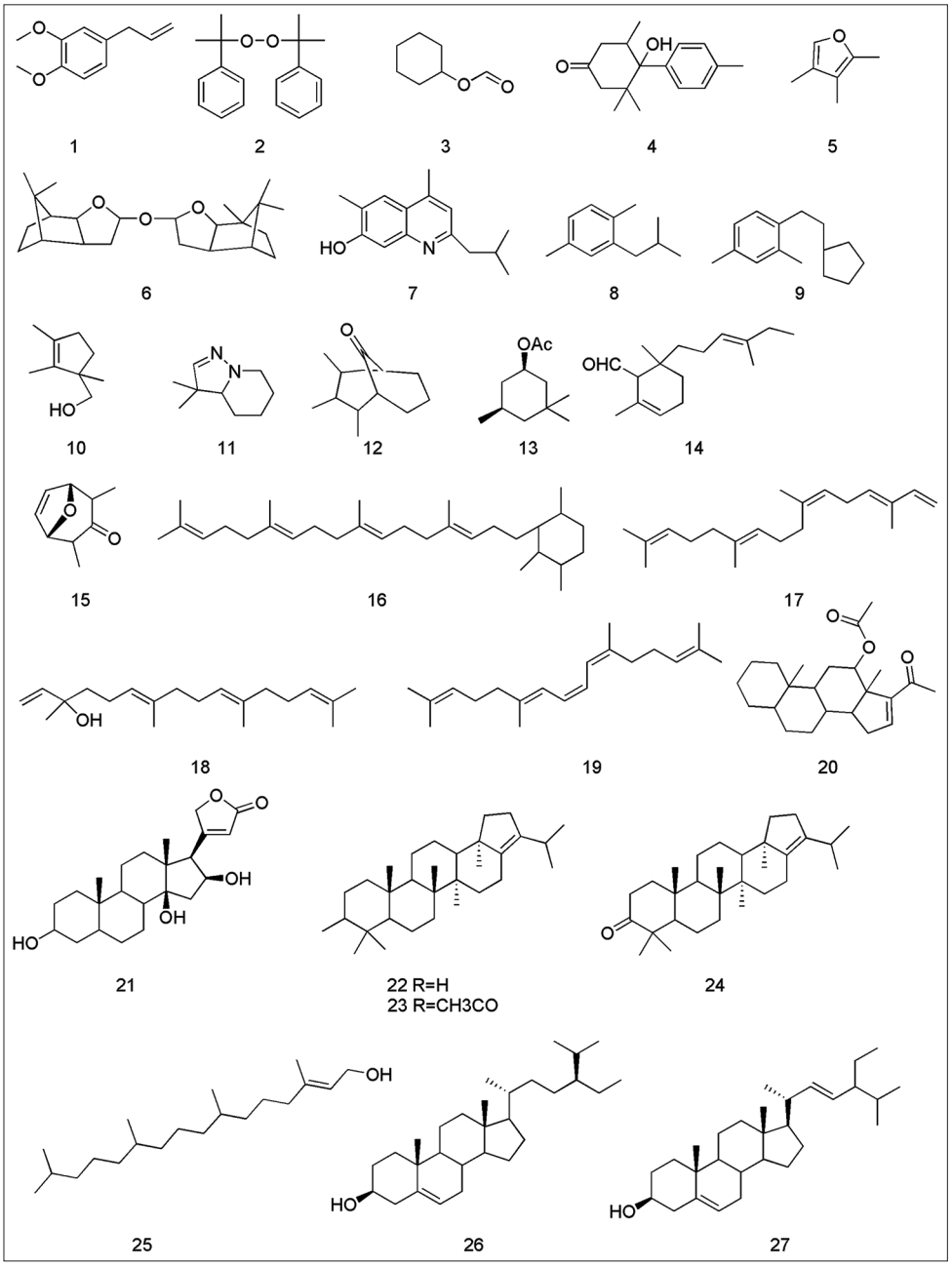

Figure 4: Structures of the other ingredients in *Curcumae Longae Rhizoma*

glioma is better, indicating that turmeric oil extract emulsion has anticancer effects and can pass the blood–brain barrier.[49] Puliyappadamba *et al*. studied the anticancer effect of curcumin on lung cancer cells and found that curcumin can downregulate nuclear factor kappa-B (NF-κB), protein kinase B (Akt), B-cell lymphoma/leukemia-2 (Bcl-2), and mitogen-activated protein kinases (MAPKs) in lung cancer cell lines H1299 (p53−/−) induced by nicotine. The activation of survival signals such as activator protein 1 and inhibitor of apoptosis protein revealed that nicotine is a harmful carcinogen, especially in patients with lung cancer with impaired tumor protein 53 status, and determined that curcumin is a potential chemopreventive agent.[50]

Qin and Chen used human umbilical vein endothelial cells (HUVECs) and chick embryo allantoic membrane-transplanted tumor as models to investigate the effect of curcumin on angiogenesis and the possible mechanism of inhibiting melanoma growth. The experimental results showed that turmeric could inhibit the migration number of HUVECs induced by vascular endothelial growth factors (VEGF) in a dose-dependent manner (8–5 μmol·L^{-1}) and inhibit angiogenesis *in vivo*. At the same time, it can inhibit the growth of melanoma B16F10 *in vivo* at 20 mg·L^{-1} by blocking the proliferation and migration of HUVECs and reducing the expression of VEGF receptor 2 and matrix metalloproteinase (MMP-2) protein.[51] Liu *et al*. discussed

Table 4: Other components in *Curcumae Longae Rhizoma*

Compound name	Reference
Methyleugenol	[109]
Dicumyl peroxide	[109]
Cyclohexyl formate	[109]
Curcuma-J	[98]
2,3,5-trimethylfuran	[109]
2,2'-oxybis [octahydro-7,8,8-trimethyl-4,7-methanobenzofuran	[109]
2-(2'-methyl-1'-propenyl)-4, 6-dimethyl-7-hydroxyquinoline	[98]
1,4-dimethyl-2-(2-methylpropyl)-benzene	[109]
1-(3-cyclopentylpropyl)-2,4-dimethy-benzene,	[109]
(1,2,3-trimethyl-cyclopent-2-enyl)-methanol	[109]
Pyrazolo[1,5-a] pyridine, 3,3a, 4,7-tetrahydro-3,3-dimethyl-, (3aS)	[109]
Bicyclo[3.3.1]nonan-9-one, 2,4-dimethyl-3-nitro- (exo)-	[109]
3,3,5-trimethyl-cyclohexanol acetate	[109]
2,6-dimethyl-6-(4-methyl-3-pentenyl)-2-cyclohexene-1-carboxaldehyde	[109]
2,4-dimethyl-8-oxabicyclo [3.2.1] oct-6-en-3-one	[109]
2,2,4-trimethyl-3-(3,8,12,16-tetramethyl-heptadeca-3,7,11,15-tetraenyl)-cyclohexanol	[109]
(E, E, E)-3,7,11,15-tetramethylhexadeca-1,3,6,10,14-pentaene	[109]
1,6,10,14-hexadecatetraen-3-ol, 3,7,11,15-tetramethyl-, (E, E)-	[109]
2,6,11,15-tetramethyl-hexadeca-2,6,8,10,14-pentaene	[109]
20-oxopregn-16-en-12-yl acetate	[109]
Gitoxigenin	[109]
hop-17 (21)-en-3-ol	[119]
hop-17 (21)-en-3-yl acetate	[119]
Hopenone I	[119]
Phytol	[110]
β-sitosterol	[98]
Stigmasterol	[98]

the effect of curcumin on dimethylhydrazine-induced colorectal cancer in rats at the cellular and organism levels. The results revealed that the cancer inhibition rate of the curcumin group was 26.46%, and the expression of peroxisome proliferator-activated receptor γ (PPARγ) was enhanced ($P < 0.05$). *In vitro*, curcumin also inhibits the proliferation of human colon cancer cell line HT29 in a dose–time-dependent manner, and the effect is stronger than that of the GW9662 intervention group, which proves that curcumin controls colorectal cancer by regulating the PPARγ pathway.[52] Tang *et al*. studied the effect of curcumin on multidrug resistance (MDR) of human gastric cancer drug-resistant cell line SGC7901/VCR. The experiment showed that SGC7901/VCR cell line was more sensitive to drugs, which may be related to the activation of caspase-3 in SGC7901/VCR cells and the decrease of P-glycoprotein (P-gp) function and expression, indicating that curcumin was an MDR regulator of drug-resistant gastric cancer cells.[53]

Esophageal cancer is the sixth most common cancer in the world. It is estimated that approximately 200,000 people in the world die from esophageal cancer annually, and the disease greatly endangers people's lives and health.[54] Wang explored the mechanism of curcumin reversing the MDR of the esophageal cancer cell line vincristine VCR. Experiments showed that a small dose of curcumin combined with vincristine VCR could significantly increase the sensitivity of Eca-109/VCR cells to VCR and effectively reverse the drug resistance of Eca-109/VCR cells. The mechanism may be by inhibiting the p38 MAPK signaling pathway. The expression of *p38 MAPK* mRNA, excision repair cross-completion gene 1 mRNA, *MDR* mRNA, p38 MAPK, p-p38 MAPK, P-gp, and other proteins were downregulated to achieve the goal.[55] Zhao *et al*. studied the anticancer effect of turmeric volatile oil on human lung cancer A549 cells. Experiments showed that turmeric volatile oil could inhibit tumor growth in a time–dose-dependent manner, which showed that the structure of tumor cells was deformed, the nucleus shrunken, the amount of apoptosis increased, and the migration ability of A549 cells *in vitro* obviously inhibited.[56] This experiment provides the possibility for exploring new antitumor candidate drugs further and offers the basis for the development and research of anticancer drugs.

Cervical cancer is a common malignant tumor which occurs in the cervical, vaginal, or transitional zone. Wei *et al*. explored the effect of curcumin on cervical cancer tumors transplanted subcutaneously within mice. The results showed that the tumor volume of mice in the experimental group was significantly reduced, the tumor quality was decreased, the NO produced by tumor cells was decreased, and the levels of the tumor marker molecules MMP-2, MMP-9, and VEGF

were all decreased ($P < 0.01$), which indicated that curcumin had antitumor protection effects on mice with subcutaneously transplanted cervical cancer that inhibited tumor growth.[57] Hong *et al*. discussed the effect and mechanism of curcumin on mice with cervical cancer from the perspective of pathway analysis. The experimental results revealed that the tumor inhibition rate of mice in the CLR group increased, while the thymus, splenic, and apoptosis indexes of tumor cells in the experimental group were higher than those in the model group, indicating that curcumin could significantly inhibit the growth of transplanted tumors in mice with cervical cancer, induce apoptosis of tumor cells, and enhance the immune function against cervical cancer in mice. The mechanism may be related to the inhibition of an epidermal growth factor receptor-signal transducer and activator of transcription 3 (STAT3) signal transduction.[58]

As already noted, CLR has the efficacy of breaking blood and activating qi, which is considered by TCM to be able to eliminate tumors. Modern pharmacological studies also show that CLR, as a candidate of anticancer drugs, has an inhibitory effect on various cancers. It can be targeted to multiple molecular pathways such as phosphate and tension homology deleted on chromosome ten (PTEN), VEGF-A, and phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) and also assists western medicines in eliminating drug resistance of tumor cells. However, most of the above studies were conducted at cell and organism level and lack clinical validation, which make the results insufficient. In follow-up studies, researchers can strengthen the related research on clinical trials or establish more experiments and animal models *in vivo* and *in vitro* to further explore the antitumor mechanism of the compounds in CLR so that it can be widely popularized and applied as an auxiliary drug in clinical antitumor treatment.

Anti-inflammation effects

Inflammation is a defensive response of the body to stimulation, which is characterized by redness, swelling, heat, pain, and dysfunction. Inflammation is subdivided into the infectious and noninfectious types. Usually, inflammation is beneficial and an automatic defense response of the human body. Sometimes, inflammation can be harmful, notably causing attacks on own tissues and inflammation in transparent tissues, among the examples. CLR is a Chinese herbal medicine and an anti-inflammatory drug recorded in the literature.[59] The anti-inflammatory effects are mainly achieved by reducing the expression and secretion of inflammatory cytokines, mediating a variety of inflammatory signaling pathways, and regulating inflammation-related cell functions.

Kim *et al*. studied the effect of curcumin on Janus tyrosine kinase-STAT (JAK-STAT) signaling pathways in activated brain microglia. They found that curcumin can inhibit the phosphorylation of JAK1 and JAK2 by increasing the phosphorylation of SRC homology 2 domain-containing tyrosine phosphatase 2 (SHP-2) and its connection with JAK1 and JAK2, thus inhibiting the JAK-STAT signaling pathway and alleviating inflammatory reaction.[60] This study found a new anti-inflammatory mechanism, which offers a novel approach for the treatment of brain injury and chronic inflammation.

Hu *et al*. studied the effect of a turmeric decoction on experimental synovitis in rats. The experimental results showed that compared with the normal group, the extent of swelling of the ankle joint in the turmeric group was significantly reduced ($P < 0.05$). In addition, congestion of synovial tissue and inflammatory cell infiltration of rats were reduced, which indicated that turmeric could improve inflammation in experimental rats.[61] However, in this experiment, the anti-inflammatory mechanism of CLR was not studied in-depth, and no positive drug group was set for comparison, which may be the point at which the experiment needed to be supplemented.

NF-κB is an important nuclear transcription factor, which plays an important regulatory role in inflammatory, stress, and immune responses.[62] Curcumin can effectively inhibit inflammation by inhibiting this pathway. Han *et al*. studied the effect of curcumin on rats with experimental autoimmune neuritis (EAN). The experimental results showed that curcumin could reduce the accumulation of inflammatory cells. Inhibition of the expression of the inflammation-related factors interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-17 in the peripheral nervous system (PNS) can change the differentiation of helper T-cells by reducing IFN-γ + CD4 + Th1 cells in the lymph nodes and spleen. The experimental results show that curcumin can be used as a candidate drug for EAN.[63] Liu *et al*. studied the effect of curcumin on lupus nephritis and its possible mechanism. The experiment showed that the levels of urinary protein, renal function indexes, selective catalytic reduction, and blood urea nitrogen in MRL/Lpr mice were significantly decreased, the level of the anti-dsDNA antibody of the systemic lupus erythematosus marker in serum was significantly decreased, and the protein expression of the nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3 (NLRP3), and caspase-1 was inhibited. The mechanism may be related to the inhibition of the NF-κB signaling pathway and the activation of the NLRP3 inflammatory corpuscle.[64]

Although curcumin demonstrates strong anti-inflammatory activity, its water solubility is poor, it is unstable under physiological conditions, it metabolizes rapidly *in vivo*, and it is easy to decompose under alkaline conditions, which leads to low bioavailability and poor effective absorption.[65] To overcome this problem, Luis *et al*. studied the anti-inflammatory effect of curcumin coated with different gel carriers on mouse ear edema induced by 12-o-tetradecanoylphorbol 13-acetate (TPA). The experimental results showed that the anti-inflammatory activity of curcumin coated with organogels was 45.9%, that of curcumin coated with nanogels was 61.8%, that of curcumin without coating, namely free curcumin (FC), was 33.2%, and that of curcumin coated with hydrogel was 28.1%.[66] The gel

system was nontoxic *in vivo* and easy to manufacture, and it also greatly improved the utilization rate of curcumin.

Symptoms of inflammation include redness, swelling, heat, and pain. As indicated, TCM believes that turmeric can activate qi and blood, dredge meridians, and relieve pain, thus eliminating inflammation. Phytochemical studies have shown that the phenylacryloyl group in curcumin compounds is essential for anti-inflammation. Pharmacological experiments show that CLR can inhibit the activity of inflammation-related enzymes such as Cox-2 and iNOS and inhibit the production of inflammatory factors such as TNF-α, IL-1, IL-1β, IL-2, IL-6, IL-8, IL-12, IL-13, IL-17, and IFN-γ. However, the above experiments lack dose-dependent studies, and the maximum safe dose and the minimum effective dose have not been studied yet. In addition, only NF-κB involved in the anti-inflammatory pathway of turmeric is mentioned. Future researchers can perform in-depth studies of the JAK2/STAT3 pathway, c-Jun N-terminal kinase/MAPK pathway, and extracellular regulated protein kinases-cAMP-response element binding protein pathway, among other similar pathways. At the same time, the anti-inflammatory effects of volatile oil components require further investigation.

Antioxidation effects

Curcumin compounds in CLR have strong antioxidant activity. Xu *et al*. homogenized the brain, heart, liver, kidney, and spleen of NIH (National Institutes of Health) NIH mice. After adding curcumin, a significant antagonistic effect emerged on lipid peroxidation of the five organs in a dose-dependent manner, indicating that curcumin has an antioxidant function.[67] However, this experiment has not been verified *in vivo*.

The antioxidant activity of curcumin is closely related to the content of glutathione (GSH) in cells. GSH is a small molecule sulfhydryl compound synthesized in cells, which has antioxidant and detoxification effects. Zheng *et al*. found that curcumin, as an antioxidant, could increase the expression of the glutamate-cysteine ligase gene, increase the intracellular GSH content, and reduce the oxidative stress reaction, thus inhibiting the activation of hepatic stellate cells.[68] The antioxidant activity of curcumin was mainly achieved by promoting GSH synthesis. This experiment elucidated a new antioxidant mechanism. However, this conclusion is drawn from the *in vitro* experiment, and it needs to be validated *in vivo*. Therefore, the effect of curcumin on (Hepatic stellate cells) HSC activation *in vivo* may not be fully reflected.

Under normal conditions, the defense system of oxides and antioxidants in organisms is balanced, thus ensuring the normal operation of metabolism. When the balance of oxide and the antioxidant defense system is destroyed, it causes oxidative stress, and intracellular oxidative stress will cause serious metabolic disorders.[69] Huang studied the effects of curcumin with a model of different concentrations on H_2O_2-induced oxidative stress in bone marrow mesenchymal stem cells. It was found that curcumin with a concentration of 12.5 μmol/L can exert the greatest antioxidative stress effect, and its mechanism may be related to activation of the mechanistic target of rapamycin (mTOR) pathway, the antiapoptosis promoting proteins Bcl-2, p-mTOR, p-P70S6K, and p-S6, and decreased expression of Bcl-2-associated X protein.[70]

Shakeri *et al*. treated asthma model rats with turmeric extract and curcumin, and the symptoms of rats were alleviated, while the levels of superoxide dismutase (SOD), catalase (CAT), and sulfhydryl groups in rats were increased, and the total number of white blood cells and lymphocytes, nitric oxide-2, nitric oxide-3, and malondialdehyde (MDA) levels were decreased. The therapeutic effect was equivalent to that of the positive drug dexamethasone, indicating that turmeric and its main component curcumin had preventive treatment potential for oxidative stress in asthma symptoms.[71] Xiao *et al*. explored the antioxidant capacity of curcumin using various differentiated rat adrenal pheochromocytoma cells (PC12 cells) as models. Experiments showed that curcumin could enhance the activities of antioxidant enzymes in cells, such as SOD, CAT, and glutathione peroxidase. It could upregulate the expression of genes to improve the total antioxidant capacity of PC12 cells, reduce the level of reactive oxygen species, and promote the redox balance of cells. Therefore, curcumin at a certain concentration could have an antioxidative effect in PC12 cells.[72]

However, the above experiments only studied the antioxidant capacity of turmeric at the cell and organism level, and researchers should continue to verify it clinically in the future. Moreover, researchers only regard curcumin as the most important antioxidant component in turmeric, which cannot reflect the complete activity of turmeric. There may be thousands of components in turmeric, including antioxidant components; further, it may contain components without antioxidant activity or those that promote oxidation. Future studies can use spectrum-effect relationships to screen out more components with antioxidant activity. In addition, studies have shown that the ethanol extract of the CLL fruit has strong antioxidant activity, but researchers have not regarded it as a medicinal part – yet, its utilization may alleviate the shortage of CLL resources. Finally, as a natural antioxidant, turmeric has the advantages of low toxicity and easy access, and it can also be added to food for use. In the future, people should pay attention to the application of turmeric as a food-borne antioxidant and further study its antioxidant functions and mechanisms, to provide a theoretical basis for the prevention and treatment of oxidative stress-related diseases.

Neuroprotective effects

Curcumin has potential applicability in brain protection and the treatment of cerebrovascular diseases. owing to its good antioxidant and anti-inflammatory effects. Zhang *et al*. studied the protective effect of curcumin on HUVEC injury induced by TNF-α. The results showed that the morphology of HUVEC treated with curcumin did not change significantly, while apoptotic bodies decreased significantly, which may be achieved by downregulating the gene expression of

caspase-3.[73] Susana *et al*. studied the protective effect of curcumin on the hemin-induced death of cerebellar granule neurons (CGNs) of the rats. The research showed that curcumin could promote the expression of heme oxygenase-1 (HO-1), glutathione transferase (GSH), and oxidized glutathione disulfide (GSSG) in CGNs, increase the activities of glutathione reductase (GR), glutathione-S transferase (GST), and SOD in CGNs, and induce translocation of nuclear factor-erythroid-factor 2-related factor 2 (Nrf2) into the nucleus to play a neuroprotective role.[74]

Depression is a kind of psychological disorder characterized by significant and lasting melancholy and lack of interest. The disease seriously affects quality of life, and in recent years, cases of depression have shown an increasing trend. Zhang *et al*. studied the antidepressant effect of curcumin on chronic, unpredictable, and mild stress (CUMS)-induced depression in a rat model. The results showed that curcumin could inhibit brain-derived neurological factor (BDNF). The decrease of postsynaptic density protein 95 (PSD-95) and synaptophysin (SYN) expression in lateral amygdala (LA) could improve depression behavior, which offers a novel perspective for the clinical treatment of depression.[75] Deng *et al*. further studied the effect of curcumin on CUMS depression in a rat model and discussed the central nervous protection of curcumin on chronic stress in rats. The experiment showed that the sugar water preference of curcumin-treated rats increased, the immobility time shortened, the serum corticosterone level decreased significantly, the expression of BDNF, PSD-95, and SYN protein in the hippocampus increased significantly, the apoptosis index in tissue sections decreased significantly, and depression-like behavior was alleviated. It proved the potential antidepressant effect of curcumin, which may be related to regulating the hypothalamic–pituitary–adrenal axis to reduce serum corticosterone levels, improving synaptic plasticity, and exerting an antiapoptosis effect.[76]

Yang *et al*. studied the neuroprotective effect of curcumin on the rat model of traumatic brain injury (TBI) caused by heavy impact. The experiment showed that compared to the solvent group, in the curcumin treatment group, the score of the modified neurological impairment scale was significantly lower ($P < 0.05$), the level of phosphorylated PI3K/AKT was significantly higher ($P < 0.05$), the injured area of the brain tissue was reduced ($P < 0.05$), and the apoptosis rate of neurons was significantly reduced ($P < 0.05$). The expression levels of LC3 and beclin-1 increased significantly ($P < 0.05$), while that of P62 decreased significantly ($P < 0.05$). The experiment showed that curcumin could significantly improve the nerve function of rats with TBI, and the mechanism may involve autophagy that is activated through the PI3K/AKT signaling pathway.[77] However, the protein related to the PI3K/AKT signaling pathway did not change significantly in this experiment, but the phosphorylation level of PI3K/AKT increased significantly, and autophagy appeared. Therefore, the mechanism of activating the PI3K/AKT signaling pathway remains to be explored.

The above experiments have proved that turmeric has neuroprotective function, and it can cure depression, brain injury, death of CGNs, and related diseases. However, due to the complexity of the human brain, and the fact that these experiments have not been verified clinically, the specific effect needs to be explored further. In addition, there were no positive or negative control groups in these experiments. Future research can employ pregabalin, nicotinamide, donepezil hydrochloride, mecobalamin, and metformin as positive controls to improve the experimental data. Furthermore, network pharmacology can be used to link the target genes of active ingredients of CLR and neurological diseases to explore more target pathways and proteins. This may lay a foundation for the treatment of neurological diseases such as Alzheimer's and Parkinson's disease.

Antibacterial effects

De *et al*. explored the bacteriostatic effect and mechanism of curcumin on *Helicobacter pylori* through *in vitro* and *in vivo* experiments and found that curcumin not only inhibited the reproduction of *H. pylori in vitro* but also reduced the stomach injury caused by *H. pylori* infection. In addition, they found that the bacteriostatic mechanism of curcumin did not always depend on the shikimate pathway, which provided a new mechanism for curcumin to resist *H. pylori* infection in the future. However, this experiment still needs clinical application.[78]

Tyagi *et al*. studied the antibacterial activity of curcumin against Gram-positive and Gram-negative bacteria. It was found that curcumin had antibacterial effects on *Staphylococcus aureus* and *Enterococcus faecalis*, *Escherichia coli*, and *Pseudomonas aeruginosa* by destroying the permeability of bacterial cell membranes in a dose–time-dependent manner, which was also related to its antioxidant and anti-inflammatory activities.[79] However, curcumin could only kill bacteria at high concentration in this study, so its effect is not strong in practical application. Therefore, we can try to modify its structure or add a coating gel to enhance its antibacterial effect in the future.

Alihosseini *et al*. studied the synergistic antibacterial activity of curcumin and ampicillin against *P. aeruginosa, S. aureus, E. coli, Corynebacterium diphtheria, Bacillus subtilis,* and methicillin-resistant *S. aureus*. Experiments showed that the antibacterial activity of solid lipid nanoparticles was enhanced and the minimum inhibition concentration was reduced. The use of nanotechnology could reduce the dosage of antibiotics and reduce the drug resistance of certain strains.[80] Li *et al*. found that curcumin glucoside, curcumin disaccharide glycoside, and curcumin had inhibitory effects on penicillin-sensitive strains, intermediate strains, and drug-resistant strains of *Streptococcus pneumoniae*, respectively, and the inhibitory areas exceeded the penicillin G group and the inhibitory areas on drug-resistant strains all exceeded 20 mm. The mechanism of action may involve the inhibition of penicillin-binding proteins, destruction of the integrity of the bacterial cell wall, and selective permeation of the envelope, which eventually leads to bacterial death.[81]

The above experiments show that curcumin in turmeric can not only inhibit and kill bacteria but may also reduce the emergence

of bacterial resistance and the side effects of western medicine. COVID-19, which broke out at the end of 2019, has evolved into a global pandemic. A large number of clinical trials are being carried out around the world, but a specific drug has not yet appeared. Studies have shown that curcumin has inhibitory effects on the homologous porcine transmissible gastroenteritis virus,[127] and because of its convenient access and minimal side effects, it may become a candidate drug for treating COVID-19.

Hypolipidemic effects

As stated before, CLR is a commonly used medicine for promoting blood circulation and removing blood stasis and has the functions of breaking blood and activating qi, dredging channels, and relieving pain. Its function of reducing blood lipids has been supported by the TCM theory, clinical application, and experimental research. Wan studied the effects of different compatibility ratios of ethanol extracts of rhubarb and turmeric on experimental mice with hyperlipidemia. Experiments showed that all three compatibility ratios had the effect of reducing blood lipids, and the compatibility ratio of rhubarb and turmeric at 1:2 was better than that of the equal ratio group and rhubarb and turmeric group at 2:1. This experiment provides some evidence for further studying the difference of the effects of Chinese medicine in combination with other drugs.[82] However, the principle of the lipid-lowering effect of rhubarb and turmeric in the experiment needs further exploration. Singh *et al*. found that turmeric volatile oil could play an antihyperlipidemic role by regulating the genes involved in lipid metabolism and transportation and PPARα. At the same time, it could regulate liver X receptor α and reduce lipid-induced oxidative stress, platelet activation, and vascular dysfunction. It could also reduce accelerated atherosclerosis, inflammation, and macrophage foam cell formation caused by arterial injury.[83]

Chen *et al*. studied the effect of propolis combined with turmeric extract on blood lipid in hyperlipidemia model rats. The results showed that propolis combined with turmeric extract in low-, medium-, and high-dose groups could reduce the contents of serum total cholesterol (TC) and serum total triglyceride (TG) in rats with hyperlipidemia, but propolis or turmeric extract alone had no significant effect. Compared with the water control group, the content of high-density lipoprotein cholesterol (HDL-C) in the middle- and high-dose groups increased significantly ($P < 0.05$). The results showed that propolis and turmeric extract were effective in lowering serum TC and serum TG, as well as increasing serum HDL-C and other hyperlipidemia-related indexes, and had obvious lipid-lowering effects.[84] This study provides a scientific basis for the clinical application and product development of propolis combined with turmeric. Statins are lipid-lowering drugs that can be taken over a long time. However, the risk of cardiovascular and cerebrovascular diseases induced by statins has gradually increased in recent years. As extracts of TCMs and natural medicines have a relatively small incidence of adverse reactions, combined drugs have gradually been used in favor of statins. Hai *et al*. studied the effect of turmeric extract combined with atorvastatin calcium on reducing blood lipid in a hyperlipidemia mice model established by a high-fat diet. The results showed that the turmeric extract group, atorvastatin calcium group, and combined group showed different degrees of blood lipid-reducing effect in the serum of mice with hyperlipidemia. The combination of turmeric extract and atorvastatin calcium was superior to a single drug in the four indexes of serum TC, TG, HDL-C, and low-density lipoprotein cholesterol (LDL-C), which may be related to their deficiency in specific pharmacodynamic indexes.[85] Further studies are necessary to verify whether the combination of turmeric extract and atorvastatin calcium can achieve the same result in the clinical treatment of hyperlipidemia.

Wen and Zou studied the effect of β-cyclodextrin inclusion with curcumin on the lipid-lowering function of patients with hyperlipidemia. After 2 months of medication-related observation on 228 patients, the related indexes were determined. After the test, the contents of serum TC, TG, and LDL-C decreased, while the HDL-C level increased. The total effective rate of auxiliary lipid-lowering was 55.3%, which indicated that the sample had an auxiliary lipid-lowering function.[86]

Others

Paraquat (PQ) is an organic heterocyclic contact defoliant and herbicide widely used in the world at present and can produce a large amount of mitochondrial peroxide and induce insulin resistance and a disorder of blood glucose metabolism. Yang *et al*. discussed the effect and pharmacological mechanism of curcumin on paraquat oxidative stress-induced insulin resistance in mice. The experimental results showed that protein kinase B (PKB) phosphorylation was enhanced, the PTEN level of the insulin signal suppressor protein was decreased, MDA level in muscle tissue and mitochondria of mice returned to normal levels, and Nrf2 nuclear translocation and its specific regulation of quinone oxidoreductase 1 (NQO-1) protein increased. The inflammatory signal inhibitory protein IκBα increased to a certain extent, which indicated that curcumin could resist the disorder of glucose metabolism caused by PQ environmental pollutants, and its effect of relieving insulin resistance in mice was related to enhancing the muscle insulin signal and activating the Nrf2 antioxidant system.[87]

CLR is often used in the treatment of rheumatism and arthralgia. Yin *et al*. studied the effect of turmeric alcohol extract on reducing uric acid in mice with hyperuricemia induced by hypoxanthine and potassium oxazine. The experimental results showed that turmeric alcohol extract of 2.6 g/kg could reduce serum uric acid, inhibit liver xanthine oxidase, and promote urine uric acid excretion, which indicated that turmeric could reduce uric acid production, promote urine uric acid excretion by inhibiting xanthine oxidase activity in the liver tissue, and treat gout.[88]

Fibrosis is a kind of pathological change in which fibrous connective tissue increases and parenchymal cells decrease in organs and tissues. Progression of fibrosis can lead to the destruction of organ structure, functional decline, and even failure.

Xue *et al*. studied the effect of curcumin on a bleomycin-induced pulmonary fibrosis model in rats. The results showed that the content of transforming growth factor beta 1 (TGF-β1) in lung tissue protein decreased to a certain extent after 200 mg/kg/day curcumin was administered, which was similar to the results of the positive drug control group – indicating that curcumin has certain preventive and therapeutic effects on pulmonary interstitial fibrosis in rats. It may be achieved by inhibiting the expression of TGF-β1 in lung tissue.[89] This experiment has good development prospects, but the formation of pulmonary fibrosis is a chronic and complex process, so the experimental results need to be tested clinically over an extended time period. Liu *et al*. found that CLR could be used to treat coronary microembolization-induced myocardial injury, which may be related to its induced decrease of myocardial apoptosis and inhibition of myocarditis reaction mediated by the Toll-like-receptor 4/myeloid differentiation factor 88/NF-κB signaling pathway.[90] In addition, turmeric is also used to treat dermatitis, gastrointestinal ulcer, retinopathy, cerebral infarction, acute lung injury, allergic rhinitis, and other diseases. The pharmacological activities of CLR are listed in Table 5.

Pharmacokinetics

Curcumin has low solubility in water, short plasma half-life, easy metabolism, and poor absorption, which leads to its low bioavailability. The study of its pharmacokinetics *in vivo* is helpful in providing a theoretical basis for the preparation and clinical application of different formulations of curcumin. Sun *et al*. studied the kinetic characteristics of curcumin liposome administered intravenously in rabbits and orally in rats. Experiments showed that curcumin liposome injection conformed to the two-compartment model, and compared with FC, it had the advantages of fast distribution, strong action, slow elimination, and long action time. Compared with curcumin suspension, the curcumin liposome oral liquid had the advantages of fast absorption, slow elimination, high concentration in blood, and wide distribution in tissues.[91] Schiborr *et al*. found that the curcumin content in the brain of mice was 4–5 $\mu g \cdot g^{-1}$ after intraperitoneal injection of curcumin for 30 min, while the curcumin content in the plasma, livers, and brains of mice in a gastric perfusion group was lower than the detection limit.[92] Zhang *et al*. measured the concentration of curcumin in rat plasma under different administration routes and calculated its bioavailability. The results showed that the elimination half-life of curcumin given by intravenous administration was 11.96 ± 2.64 min, compared with that given by intragastric administration (90.79 ± 11.55 min) and intraperitoneal injection (159.28 ± 18.12 min). The rats were administered curcumin by gavage (200 mg/kg), intraperitoneal injection (20 mg/kg), and sublingual vein (10 mg/kg), and their C_{max} values were 3.58 ± 0.58, 1.01 ± 0.12, and 0.67 ± 0.06 mg/L, respectively, with area under characteristic (AUC) readings of 86.36, 73.39, and 104.62 mg/L·min, respectively. The bioavailability of curcumin with oral administration was 4.13% and that with intraperitoneal injection was 35.07%. This shows that the absorption rate of active ingredients can be increased by changing the mode of administration of curcumin to the injection method.[93]

Huang *et al*. studied the pharmacokinetics of a curcumin-povidone solid dispersion in mice after intragastric administration. The results showed that it conformed to the two-compartment open model. Three hours following intragastric administration, the absorption rate of curcumin suspension was 11.8% ± 2.2%, while the absorption rate of curcumin solid dispersion solution achieved was 79.7% ± 2.1%. The results show that the absorption rate of the curcumin solid dispersion solution is 6.75 times higher than the curcumin suspension ($P < 0.01$).[94] The former can significantly increase the bioavailability of curcumin and the blood drug concentration is higher. Chen *et al*. created curcumin nanoparticles and compared their effects on mice with Alzheimer's disease with those of curcumin micropowder. The experimental results showed that curcumin nanoparticles effectively increased the blood concentration of curcumin, and the brain AUC and residence time increased sixfold, indicating that the new dosage form can increase the absorption of curcumin *in vivo*.[95] Lu *et al*. found that gavage administration of T_{max}, C_{max}, T½, and AUC of curcumin nanopreparation and dispersion were 120 min, 0.14 μg/mL, 2310 min, and 246.80 min·μg/ml and 30 min, 0.12 μg/mL, 1733 min, and 155.31 min·μg/ml, respectively. In contrast, C_{max}, T½, and AUC were 1.83 μg/mL, 365 min, 103.22 min·μg/ml, and 12.15 μg/mL, 6930 min, and 331.09 min·μg/ml, respectively, after intravenous injection of curcumin nanopreparation and its dispersion. This showed that the bioavailability of nanopreparation by intragastric administration was optimal and that of intravenous dispersion was ideal.[96]

Turmeric has low bioavailability *in vivo* owing to its structure and solubility characteristics. Many researchers have worked in this field and designed various dosage forms; however, a few shortcomings remain, such as high levels of traditional dosage forms and potential toxicity of new dosage forms. Therefore, the mechanism to design dosage forms with low cost, convenience, environmental protection, safety, and good kinetic characteristics in the future needs further exploration and research by pharmaceutical workers.

Conclusions and Perspectives

In this paper, the characteristics of turmeric in botany, traditional application, pharmacological activity, and pharmacokinetics were comprehensively described. More than 275 components isolated till date are summarized, and their structures are attached, which has certain comprehensive reference value. In the pharmacological aspect – the antitumor, anti-inflammatory, antioxidant, hypolipidemic, antibacterial, and neuroprotective effects of CLR were studied. This in-depth and comprehensive summary has never been reported in the literature. After decades of efforts, we have an in-depth understanding of the physicochemical and therapeutic properties of turmeric. However, with these achievements, we find that our understanding is insufficient in the research of CLR.

Table 5: The pharmacological effects of Curcumae Longae Rhizome

Pharmacological effects	Extracts/compounds	Animal/cell line	Study design	Control	Mechanism/results	Reference
Antitumor	Turmeric extract (0.4 mg/ml) curcumin (4 μg/ml)	CHO cells and Dalton's lymphoma cells	*In vivo/ vitro*	Blank	CLR can inhibit the growth of animal tumors, and its active ingredient is curcumin	[46]
	Curcumin (3.13 mg/ L-50 mg/L)	Human gastric cancer MGC803, human liver cancer Bcl7402, human erythroleukemia K562 cells, melanoma B16 and EAC	*In vivo/ vitro*	Blank	*In vitro*, curcumin has obvious killing effects on MGC803, Bel 7402, B16, K562 and K562/ADM, and can induce apoptosis of MGC 803 cells. Curcumin ig or ip has significant anti-tumor effect on mouse melanoma B16 and Ehrlich ascites carcinoma EAC	[47]
	Turmeric water extract (24, 12, 6 g/kg), curcumin (300 mg/kg)	Solid tumor of transplanted liver cancer in mice	*In vivo*	Cyclophosphamide	Curcumin has obvious anti-tumor effect, but the water extract of turmeric has no obvious anti-tumor effect	[48]
	Emulsion injection extracted from turmeric volatile oil (3-30 mg/kg)	Transplanted melanoma-bearing mice and brain glioma-bearing mice (intracranial inoculation)	*In vivo*	Podophyllotoxin, cyclophosphamide	Turmeric extract emulsion injection can inhibit the growth of tumor in transplanted mice bearing melanoma and brain glioma (intracranial inoculation), and prolong the survival process of mice in a dose-dependent manner	[49]
	Curcumin (10 μM)	lung cancer cell lines H1299, lung cancer cell lines A549	*In vitro*	None	Curcumin can down-regulate activation of NF-κB, Akt, Bcl2, MAPKs, AP1 and IAPs induced by nicotine in lung cancer cell lines H129	[50]
	Curcumin (4-15 μmol/L)	HUVECs, B16F10 cell, CAM transplanted tumor model	*In vivo/ vitro*	Blank	Curcumin can block the proliferation and migration of HUVECs cells and reduce the expression of VEGFR2 and MMP-2 protein	[51]
	Curcumin (10-60 μmol/L)	Rat colorectal cancer and human colon cancer cell line HT29 induced by dimethylhydrazine	*In vivo/ vitro*	Blank	Curcumin can prevent and treat colorectal cancer by regulating PPARγ pathway	[52]
	Curcumin (5-20 μmol/L)	Vincristine-resistant gastric carcinoma SGC7901/VCR cell line	*In vitro*	Me_2SO (vehicle control) verapamil (positive control)	Experiments show that the sensitivity of SGC7901/VCR cell line to drugs is increased, which may be related to the activation of caspase-3 in SGC7901/VCR cells and the decrease of P-gp function and expression	[53]
	Curcumin (20 μmol/L)	Esophageal cancer resistant Eca-109/VCR cells	*In vitro*	Blank	The combination of curcumin and VCR can significantly increase the sensitivity of Eca-109/VCR cells to VCR, and effectively reverse the drug resistance of Eca-109/VCR cells. The mechanism may be achieved by inhibiting p38 MAPK signaling pathway, down-regulating the expression of p38MAPK mRNA, ERCC1 mRNA, MDR mRNA and the expression of p38MAPK, p-p38MAPK, ERCC1, P-gp and other gene proteins	[55]
	Turmeric volatile oil (100 mg/L)	Human lung cancer A549 cells	*In vitro*	None	Turmeric volatile oil can deform the structure of tumor cells, shrink the nucleus, increase the number of apoptosis, and inhibit the migration ability of A549 cells *in vitro*	[56]
	Curcumin (5 g/kg)	Model mice of cervical cancer subcutaneous transplantation	*In vivo*	Cisplatin	In the treatment group, the tumor volume decreased significantly, the tumor quality decreased, the no produced by tumor cells decreased, and the levels of tumor marker molecules MMP-2, MMP-9 and VEGF decreased ($P<0.01$)	[57]
	Curcumin (120, 240 mg/kg)	Underarm inoculation of U14 tumor cells induced mouse model bearing cervical cancer	*In vivo*	Cisplatin	Curcumin can significantly inhibit the growth of transplanted tumor in cervical cancer mice, induce apoptosis of tumor cells, and enhance the immune function of cervical cancer mice. The mechanism may be related to the inhibition of EGFR-STAT3 signal transduction	[58]
	Curcumin (5-20 μM)	Rat primary microgliamurine BV2 microglial cells	*In vitro*	IFN-γ	Curcumin can inhibit the phosphorylation of JAK1 and JAK2 by increasing the phosphorylation of SHP-2 domain-containing tyrosine phosphatase 2 and its connection with JAK1 and JAK2, thus inhibiting JAK-STAT signaling pathway and alleviating inflammatory reaction	[60]

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Table 5: Contd...

Pharmacological effects	Extracts/compounds	Animal/cell line	Study design	Control	Mechanism/results	Reference
Anti-inflammation	Water decoction of turmeric (5 g/kg)	Collagen-induced arthritis rat model induced by collagen mixed with Freund's adjuvant	*In vivo*	Blank	CLR can improve the general pathological changes of experimental arthritis rats, including mental state, activity ability and joint swelling degree pathological observation showed that turmeric had a good inhibitory effect on inflammatory cell infiltration and synovial cell proliferation in synovial tissue	[61]
	Curcumin (100 mg/kg)	EAN rats	*In vivo/ vitro*	Blank DMSO	Curcumin can reduce the accumulation of inflammatory cells, inhibit the expression of IFN-γ, TNF-α, IL-1β and IL-17 in peripheral nervous system PNS, and change the differentiation of helper T-cells by reducing IFN-γ + CD4 + Th1 cells in lymph nodes and spleen	[63]
	Curcumin (100-200 mg/kg)	MRL/lpr mice	*In vivo*	Physiological saline	The levels of urinary protein, renal function indexes SCr and BUN in MRL/lpr mice were significantly decreased after curcumin treatment, and the anti-dsDNA antibody of SLE marker in serum was significantly decreased, and the protein expression of NLRP3 and caspase-1 was inhibited, which may be related to the inhibition of NF-κB signaling pathway and the activation of NLRP3 inflammatory corpuscle	[64]
	Curcumin (25 mg/g)	Ear edema induced by 12-O-TPA in mice	*In vivo*	Diclofenac	The anti-inflammatory activity of curcumin coated with organogels is 45.9%, that of curcumin coated with nanogels is 61.8%, that of curcumin without coating FC is 33.2%, and that of curcumin coated with hydrogel is 28.1%	[66]
Anti-oxidation	Curcumin (1.285-204 mg/L)	NIH mice	*In vitro*	Blank	Curcumin has a significant antagonistic effect on lipid peroxidation in five organs in a dose-dependent manner	[67]
	Curcumin (5-30 μM)	Hepatic stellate cells	*In vitro*	Blank	Curcumin, as an antioxidant, can increase the expression of glutamate-cysteine ligase gene and increase the content of glutathione in cells, thus reducing the oxidative stress and inhibiting the activation of hepatic stellate cells	[68]
	Curcumin (3.125-50 μmol/L)	Oxidative stress model of BMSCs induced by H2O2	*In vitro*	Rapamycin	12.5 μmol/L curcumin can exert the greatest anti-oxidative stress effect, and its mechanism may be closely related to activating mTOR pathway, promoting the expression of anti-apoptotic proteins Bcl-2, p-mTOR, p-P70S6K, and p-S6, and decreasing the expression of pro-apoptotic protein Bax	[70]
	Turmeric extract (0.75-3.00 mg/ml) curcumin (0.15-0.60 mg/ml)	Asthmatic rats	*In vivo*	Dexamethasone	The levels of superoxide dismutase, CATalase and sulfhydryl groups in rats increased, while the total number of leukocytes and lymphocytes, NO2, NO3, and MDA levels decreased	[71]
	Curcumin (10 μmol/L)	Rat adrenal pheochromocytoma cells	*In vivo*	None	Curcumin can enhance the activities of intracellular antioxidant enzymes SOD, CAT and GSH-Px and upregulate their gene expression to improve the total antioxidant capacity of PC12 cells, reduce the intracellular ROS level and promote the redox balance of cells	[72]
Neuroprotection	Curcumin (25-100 μg/ml)	HUVEC induced by TNF-α	*In vitro*	Blank	In curcumin group, the morphology of HUVEC cells did not change significantly, and apoptotic bodies decreased significantly, which may be achieved by down-regulating caspase-3 gene expression	[73]
	Curcumin (15 μM)	Hemin-induced cerebellar granule neurons of rats in mice	*In vitro*	Blank	Curcumin can promote the expression of HO-1, GSH, and GSSG in CGNs, increase the activities of GR, GST and SOD in CGNs, and induce Nrf2 translocation into nucleus to prevent the death of nerve cells	[74]

Contd...

Table 5: Contd...

Pharmacological effects	Extracts/compounds	Animal/cell line	Study design	Control	Mechanism/results	Reference
	Curcumin (40 mg/kg)	CUMS-induced depression rats	*In vivo*	Blank	Curcumin can prevent the decrease of BDNF, PSD-95, and SYN expression in lateral amygdala of lateral amygdala and improve depression behavior	[75]
	Curcumin (100 mg/kg)	CUMS depression rat model	*In vivo/ vitro*	Physiological saline	In curcumin treatment group, the preference of sugar water increased, the immobility time shortened, the serum corticosterone level decreased significantly, the expression of BDNF, PSD-95 and SYN protein increased significantly, the apoptosis index in tissue sections decreased significantly, and the depression-like behavior was alleviated	[76]
	Curcumin (60 mg/kg)	Establishment of rat model for controlling cortical blast injury by heavy object impact method	*In vivo*	PBS	In curcumin treatment group, the score of the modified neurological impairment scale modified neurological impairment scale was significantly lower ($P<0.05$), the level of phosphorylated PI3K/AKT was significantly higher ($P<0.05$), the injured area of brain tissue was reduced ($P<0.05$), and the apoptosis rate of neurons was significantly reduced ($P<0.05$). The expression levels of LC3 and beclin-1 increased significantly ($P<0.05$), while the expression level of P62 decreased significantly ($P<0.05$). the mechanism may be that autophagy is activated through PI3K/AKT signaling pathway	[77]
Antibacterial	Curcumin (5-50 μg/ml)	*H. pylori*-infected C57BL/6 mice, *H. pylori* strains	*In vivo/ vitro*	PBS	Curcumin can not only inhibit the reproduction of H. pylori in vitro, but also reduce the stomach injury caused by *H. pylori* infection. It is found that the antibacterial mechanism of curcumin does not always depend on shikimate pathway	[78]
	Curcumin (25 μM)	*Streptococcus aureus* and *Enterococcus faecalis, Escherichia coli* and *Pseudomonas aeruginosa*	*In vitro*	HNP-1 and nisin	Curcumin can produce antibacterial effect on *Streptococcus aureus* and *Enterococcus faecalis, Escherichia coli* and *Pseudomonas aeruginosa* by destroying bacterial membrane in a dose-time dependent manner	[79]
	Curcumin and ampicillin were combined to prepare solid lipid nanoparticles	*Pseudomonas* aeroginosa, *Streptococcus aureus, Escherichia coli, Corynebacterium diphtheria, Bacillus subtilis*, and MRSA	*In vitro*	Ampicillin	The antibacterial activity of curcumin and ampicillin was enhanced and MIC was decreased. The use of nanotechnology can reduce the dosage of antibiotics and reduce the drug resistance of strains	[80]
	Curcumin (10-15μg/ml)curcumin monoglucoside (5-10 μg/ml), curcumin diglucoside (7-10 μg/ml)	*Streptococcus pneumoniae* (penicillin-susceptible, penicillin-intermediate and penicillin-resistant)	*In vitro*	Penicillin G	Curcumin glucoside, curcumin disaccharide glycoside, and curcumin have inhibitory effects on penicillin-sensitive strains, intermediate strains and drug-resistant strains of *Streptococcus pneumoniae*, and the inhibitory areas are more than penicillin G group, and the inhibitory areas on drug-resistant strains are all over 20 mm. The mechanism of action may be related to inhibition of PBPS, destruction of the integrity of bacterial cell wall and selective permeation of envelope, which eventually lead to bacterial death	[81]
Hypolipidemic	Ethanol extract of rhubarb (0.26 g/ kg) and turmeric (0.26 g/kg)	Experimental hyperlipidemia mice	*In vivo*	Physiological saline	The compatibility effect of rhubarb and turmeric in 1:2 ratio is stronger than that of rhubarb and turmeric in 2:1 ratio	[82]
	Turmeric volatile oil (100-300 mg/kg)	Partial carotid ligation or FeCl3-induced arterial oxidative	*In vivo/ vitro*	Blank	Turmeric volatile oil can play an anti-hyperlipidemia role by regulating related genes involved in lipid metabolism and transportation and PPARα,	[83]

Contd...

Table 5: Contd...

Pharmacological effects	Extracts/compounds	Animal/cell line	Study design	Control	Mechanism/results	Reference
		injury hamster models. Human monocytic THP-1 cells			at the same time, it can regulate liver X receptor α, and reduce lipid-induced oxidative stress, platelet activation and vascular dysfunction. It can also reduce accelerated atherosclerosis, inflammation and macrophage foam cell formation caused by arterial injury	
	Propolis and turmeric extract (0.17-2 g/kg)	Hyperlipidemia model rats	*In vivo*	Camellia oil	The low-, medium-, and high-dose groups of propolis and turmeric extract can reduce the contents of TC and TG in serum of hyperlipidemia rats, but only using propolis or turmeric extract has no significant effect. The content of HDL-C in serum of middle- and high-dose groups is higher than that of water control group, and the difference is statistically significant	[84]
	Turmeric extract (50 mg/kg) combined with atorvastatin calcium (5 mg/kg)	Hyperlipidemia mouse model established by high-fat diet	*In vivo*	Blank	The serum TC, TG, HDL-C, LDL-C and other four indexes in the combination group of turmeric extract and atorvastatin calcium were better than those in the single group	[85]
	Inclusion of curcumin with β –cyclodextrin (1200 mg)	Hyperlipidemia patients	*In vivo*	Blank	In the treatment group, the serum TC, TG, LDL-C content decreased, while HDL-C level increased. The total effective rate of assisting in reducing blood lipid was 55.3%	[86]
Others	Curcumin (5 mg/kg)	Insulin resistance induced by paraquat oxidative stress in mice	*In vivo*	Physiological saline	In curcumin intervention group, PKB phosphorylation increased, PTEN level decreased, MDA level in muscle tissue and mitochondria returned to normal level, nuclear translocation of Nrf2 and NQO-1 protein content specifically regulated by nrf2 increased, and inflammatory signal suppressor protein IκBα increased to some extent	[87]
	Ethanol extract of turmeric (0.65-2.6 g/kg)	Hyperuricemia model induced by hypoxanthine and potassium oxazine in mice	*In vivo*	Tongfengding capsule	2.6 g kg^{-1} of turmeric ethanol extract can reduce SUA, inhibit XOD activity and promote UUA excretion	[88]
	Curcumin (200 mg/kg)	PF model rats with PF induced by bleomycin	*In vivo*	Prednisone acetate suspension	After curcumin was given 200 mg/(kg·day), the content of TGF-β1 in lung tissue protein decreased to a certain extent, which was similar to that of positive drug control group	[89]

CHO: Chinese hamster ovary, EAC: Ehrlich ascites carcinoma, EAN: Experimental autoimmune neuritis, TPA: Tetradecanoylphorbol 13-acetate, BMSCs: Bone marrow mesenchymal stem cells, PBS: Phosphate buffer saline, PF: Pulmonary fibrosis, CLR: Curcumae longae rhizome, HUVECs: Human umbilical vein endothelial cells, CAM: Chick embryo allantoic membrane, PPARγ: Peroxisome proliferator-activated receptor γ, MMP: Matrix metalloproteinase, VEGF: Vascular endothelial growth factors, EGFR: Epidermal growth factor receptor, STAT3: Signal transducer and activator of transcription 3, IFN-γ: Inflammation-related factors interferon-γ, TNF-α: Tumor necrosis factor-α, IL-1β: Interleukin-1β, TG: Triglyceride, MDA: Malondialdehyde, FC: Free curcumin, JAK: Janus tyrosine kinase, GSH: Glutathione, SOD: Superoxide dismutase, HUVEC: Human umbilical vein endothelial cells, CUMS: Chronic, unpredictable, and mild stress, BDNF: Brain-derived neurological factor, PSD: Postsynaptic density protein, PKB: Protein kinase B, PTEN: Phosphate and tension homology deleted on chromosome ten, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, MAPK: Mitogen-activated protein kinases

First, research on turmeric processing is rarely seen nowadays. The processing methods of turmeric in Pharmacopoeia only dealt with removing impurities, slight soaking, washing, moistening thoroughly, cutting into thick slices, and drying. Priority was given to its raw use. In ancient times, people also used a variety of other processing methods, such as simmering in wet paper, parching to dryness, parching with wine and vinegar, and soaking rice in water. Other processing methods may have been eliminated for reasons of clinical inefficacy or other reasons, which merits further discussion.

Second, curcumin compounds are the main active ingredients in CLR but have poor solubility and low bioavailability. In recent years, many researchers have focused on a drug delivery system and preparation technology to overcome the limitations and have made some progress. However, the activity of curcumin *in vivo* is closely related to the activity of its metabolites. On the basis of improving bioavailability and promoting curcumin absorption, future research should focus on the metabolites and metabolic pathways *in vivo*. At the same time, there should be studies on the new drug-loaded materials that are simple to produce and that can be used in industrial mass production.

Third, the pharmacological effects of TCM come from the chemical substances with specific activities contained in TCM. CLR, as a kind of Chinese herbal medicine, contains thousands of chemical components. At present, more than 275 components such as phenols, volatile oils, diterpenes, flavonoids, and saccharides have been identified and isolated, but this is not the end point of research into its chemical composition. Currently, most researchers concentrate primarily on the rhizomes and components such as curcumin and volatile oils. To better develop and utilize CLR and explore its potential applicability, future researchers should investigate further chemical components in the aerial parts of CLL. Although the leaf does not contain curcumin, it may contain other useful components. Investigators should also explore other components such as saccharides and flavonoids. This may provide help for research into its pharmacodynamic substances. It is believed that with the development of new technologies, new active compounds in CLR will be discovered soon.

Fourth, the pharmacological effects of CLR are extensive, but most experiments have only investigated the *in vitro* activity. The pharmacokinetics and specific mechanisms of CLR in the human body have not been uniformly demonstrated, and there are different opinions on the targets and pathways of drug action. It is hoped that future work can focus on the specific mechanisms of various pharmacological effects of turmeric. In addition, with the drug research delving thoroughly into the cellular and molecular level, it may be possible to explore and verify the biological activities of different components by combining the current transcriptomics or network pharmacology methods, which are of great significance for the development of turmeric plants and guidance on rational drug use.

Finally, there are various difficulties in fundamentally improving the quality of turmeric. For example, the research on the protection, development, and utilization of turmeric germplasm resources lacks systematic collection and collation. In addition, due to the excessive digging and destruction of the natural environment, the resources of wild medicinal plants of CLL in China are decreasing continuously. Moreover, only a single species of turmeric is cultivated by humans, so the breeding of high-quality turmeric germplasm cannot be sustained. In short, there is a lack of high-quality varieties with commercialization value in the production of turmeric. Therefore, in the future, the investigation and collection of domestic curcumin medicinal plant resources and the evaluation and screening of excellent resources should be strengthened, which is conducive to the rational development and utilization of curcumin plant reserves.

In summary, this paper reviewed CLR from the perspectives of botany, ethnopharmacology, phytochemistry, pharmacology, and pharmacokinetics, hoping to provide convenience for future researchers and to promote the development of active lead compounds and innovative drugs. It is believed that with the development of science and technology and the deepening of research, people will have a deeper understanding of turmeric.

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Conflicts of interest

There are no conflicts of interest.

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