

Curcumin

From a controversial “panacea” to effective antineoplastic products

De-Biao Xiang, PhD^a, Kai-Qiang Zhang, MS^a, Ya-Ling Zeng, MS^b, Qing-Zi Yan, MS^a, Zhe Shi, PhD^a, Qin-Hui Tuo, PhD^a, Li-Mei Lin, PhD^a, Bo-Hou Xia, PhD^a, Ping Wu, PhD^{a,*}, Duan-Fang Liao, MD, PhD^{a,*}

Abstract

Background: Curcumin, a controversial “panacea,” has been broadly studied. Its bioactivities including antioxidant, anti-inflammatory, and especially antineoplastic activities have been documented. However, due to its extensive bioactivities, some scientists hold a skeptical point of view toward curcumin and described curcumin as a “deceiver” to chemists. The objective of this study was to explore curcumin’s another possibility as a potential supplementary leading compound to cancer treatments.

Methods: Literature searches were conducted using electronic databases. Search terms such as “curcumin,” “curcumin analogues,” and so on were used. The literatures were collected and summarized. In this article, reported targets of curcumin are reviewed. The limitations of a curcumin as a therapeutic anticancer product including low bioavailability and poor targeting are mentioned. Furthermore, modified curcumin analogues and antitumor mechanisms are listed and discussed in the aspects of cell death and tumor microenvironment including angiogenesis, tissue hypoxia status, and energy metabolism.

Results: Several possible modification strategies were presented by analyzing the relationships between the antitumor activity of curcumin analogues and their structural characteristics, including the introduction of hydrophilic group, shortening of redundant hydrocarbon chain, the introduction of extra chemical group, and so on.

Conclusions: From our perspective, after structural modification curcumin could be more effective complementary product for cancer therapies by the enhancement of targeting abilities and the improvement of bioavailability.

Abbreviations: CDF = difluorinated curcumin, CN = curcumin nicotinate, CSCs = cancer stem cells, ER = endoplasmic reticulum, FGF = fibroblast growth factor, HIF-1 α = hypoxia inducible factor-1 α , LDL = low-density lipoprotein, MDR = multidrug resistance, ROS = reactive oxygen species, SREBPs = sterol regulatory element-binding proteins, STAT3 = signal transducer and activator of transcription 3, VEGF = vascular endothelial growth factor, VSMCs = vascular smooth muscle cells.

Keywords: antitumor agent, cancer treatment, curcumin, curcumin analogues, curcumin modification

1. Introduction

Curcumin, a hydrophobic polyphenol spontaneously undergoing a keto–enol tautomerism, is isolated from the rhizome of *Curcuma longa* L (Fig. 1).^[3] Multiple molecular targets of curcumin bring a vast pharmacological effects including

antioxidant, anti-inflammatory, antimicrobial, anticarcinogenic, thrombi-suppressive, hepatoprotective, cardiovascular-protective, Alzheimer-easing, hypoglycemic, and antiarthritic activities.^[1,2] Recently, it aroused a great controversy among pharmacologists and phytochemists. On the one hand, curcumin

Editor: Yung-Hsiang Chen.

DBX and KQZ contributed equally to this work.

This study was financially supported by the Construct Program of the Pharmaceutical Science Key Discipline in Hunan Province, the National Natural Science Foundation of China (81673722, 81600291, and 81773736), Natural Science Foundation of Hunan Province (2019JJ50443), and Major Projects of Hunan provincial development (S2015SS501P010).

This study does not require ethic approval, because we only analyzed data from published studies.

The work has not been published previously, and is not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript for publication.

The authors report no conflicts of interest

^a Division of Stem Cell Regulation and Application, Key Laboratory for Quality Evaluation of Bulk Herbs of Hunan Province, ^b Medical School, Hunan University of Chinese Medicine, Changsha, Hunan, China.

* Correspondence: Ping Wu, Duan-Fang Liao, Division of Stem Cell Regulation and Application, Key Laboratory for Quality Evaluation of Bulk Herbs of Hunan Province, Changsha, Hunan University of Chinese Medicine, 300 Xueshi Road, Changsha 410208, Hunan, China (e-mail: 545371528@qq.com, dfliao@hnuucm.edu.cn).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Xiang DB, Zhang KQ, Zeng YL, Yan QZ, Shi Z, Tuo QH, Lin LM, Xia BH, Wu P, Liao DF. Curcumin: from a controversial “panacea” to effective antineoplastic products. *Medicine* 2020;99:2(e18467).

Received: 30 April 2019 / Received in final form: 17 October 2019 / Accepted: 19 November 2019

<http://dx.doi.org/10.1097/MD.00000000000018467>

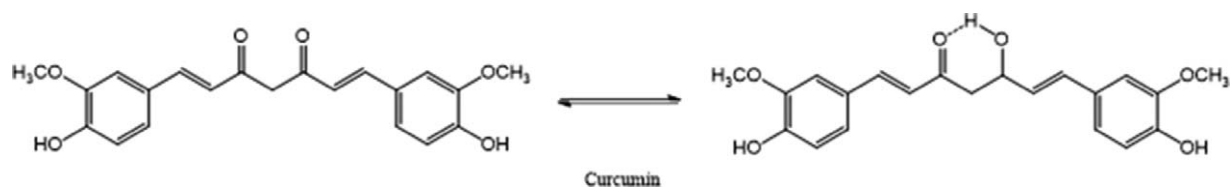


Figure 1. Chemical structure of curcumin. The α,β -unsaturated β -diketone moiety undergoes keto–enol tautomerism and forms a hydrogen bond containing 6-membered ring.

shows multiple pharmacological effects and high-dose safety feature that warrant further investigations. On the other hand, curcumin exhibits a low bioavailability.^[4–6] Moreover, vast targets inevitably bring vast unnecessary side effects. Many scientists tend to believe curcumin has been releasing a “deceptive false signal” in drug-screening tests, and they also pointed out that chemicals may hit in drug screenings but unlikely to yield a drug, and curcumin seems to be one of those “chemical frauds.”^[66] However, a most recent review argues that curcumin should not be dismissed and curcumin’s feature of multiple molecular targets is associated with modulation instead of direct inhibition. There are many animal studies and clinical trials that show the therapeutic benefits of curcumin that should not be neglected.^[67] In our opinion, it is unlikely that curcumin, as a multitarget chemical, hits a specific target without affecting others. Therefore, in this article, we summarized promising modification strategies characterized by cancer-related structural features to direct structural reforms that we hope could narrow target range to strengthen more specific effects. Modified curcumin analogues could be more effective complementary products to cancer therapies.

1.1. Search methods for identification of studies

The following electronic databases were searched: PubMed, Google Scholar, and China National Knowledge Infrastructure. The search strategy to be used in Google Scholar is shown in Table 1. The search strategies to be used in other databases are similar.

1.2. Is curcumin still worthy of further exploration?

Pharmacological study of curcumin has never been stopped ever since it was isolated from turmeric. Researchers were surprised to find that curcumin performed remarkably well in antioxidant, anti-inflammatory, and even in anticancer experiments. Curcumin has proven to be effective and has also shown a multitarget nature in mechanism studies. The vast targets of curcumin make

it an ideal basis for drug design. In this study, we have summarized the possible molecular targets of curcumin (Table 2).

Curcumin exhibits good antitumor activities. In a hen model, intake of daily dietary curcumin notably reduced the prevalence of spontaneous ovarian cancer by inhibiting NF- κ B/signal transducer and activator of transcription 3 (STAT3) signaling pathways and by inducing nuclear factor erythroid 2/heme oxygenase 1 antioxidant pathway.^[68] In human colon cancer 116 cells and cancer tissues, curcumin regulated the proliferation and apoptosis via miR-491/PEG10 pathway.^[69] In addition, as an adjuvant for antitumoral DNA-damaging drugs, curcumin induced γ -H2AX foci and decreased the expression of Rad51 to sensitize lymphoma cells to DNA-damaging agents.^[70] Also, curcumin resensitized gemcitabine-resistant pancreatic ductal adenocarcinoma cells to chemotherapy by attenuating the expression of Enhancer Of Zeste Homolog 2 Subunit of Polycomb Repressive Complex 2, a recently identified drug resistance regulating key player and its related lncRNA PVT1. In addition, curcumin-targeted cancer stem cells (CSCs) down-regulated self-renewal driving genes.^[71] Activation of Wnt/ β -catenin is critical in epithelial–mesenchymal transition and the acquisition of CSCs properties. Curcumin has been reported to reverse tobacco smoke-induced activation of Wnt/ β -catenin.^[72] Combined with other compounds or curcumin alone showed suppressive activities in cervical cancer cells by activating p53 and caspase-3.^[73] By inhibiting JAK/STAT3 signaling pathway, curcumin attenuated the normal endothelial cells transition to tumor endothelial cells to prevent tumor-microenvironment-induced angiogenesis.^[74] Numerous experimental evidences and ongoing experiment have been proving that curcumin is a promising chemopreventive natural product and worth further explorations.

1.3. Stumbling blocks between curcumin and an effective antitumor product

Curcumin exhibits an excellent antitumor activity, but there is almost no curcumin-related product clinically applied as an anticancer drug or chemopreventive medication.^[75] Poor bioavailability is the leading cause that limits the benefits of curcumin. Curcumin undergoes a spontaneous keto–enol tautomerism that makes it unstable at physiological pH. In addition, curcumin is a hydrophobic polyphenol almost insoluble in water. Slow uptake and rapid metabolism features of curcumin also limit its efficacy.^[76] Pharmacokinetic studies revealed that oral bioavailability of curcumin was only 1%.^[77]

Besides its low bioavailability issue, broad bioactivity profile of curcumin drew skepticism. A review explained its broad bioactivity profile as pan-assay interference compounds. According to the authors, multiple bioactivities of curcumin is an assay-interfered readout rather than compound–target interactions, for example, fluorescence interference, covalent labeling of proteins,

Table 1

Search strategy applied in Google Scholar database.

Number	Search terms
1	Curcumin
2	Curcumin analogues
3	Bioactivity
4	Anti-cancer
5	Bioavailability
6	Modification
7	Or 1–6

Table 2
Targets of curcumin.

	Downregulated		Upregulated		Downregulated		Upregulated	
Receptors	Androgen receptor	Death receptor 5	Transcriptional factors	Activating protein 1	Enzymes	Arylamine N-acetyltransferases-1	Glutathione S-transferase	
	Aryl hydrocarbon receptor	Endothelial protein C receptor		β-Catenin	Nuclear factor 2-related factor	ATFase	Heme oxygenase-1	
	Chemokine receptor 4	Fas receptor		CREB-binding protein	Peroxisome proliferator-activated receptor-gamma	ATPase	Src homology 2 domain-containing tyrosine phosphatase	
	Estrogen receptor alpha	Low-density lipoprotein receptor		Early growth response gene 1		Cytochrome P-450 2C8	Glutamate-cysteine ligase	
	Histamine (2)-receptor			Hypoxia-inducible factor 1		Desaturase		
	Human epidermal growth factor receptor 2			Notch 1		DNA polymerase		
	Interleukin-8 receptor			Nuclear factor-κB signal transducers		Farnesyl protein transferase		
	Inositol 1,4,5-triphosphate receptor			Activators of transcription 1 to 5		Inducible nitric oxide synthase		
	Integrin receptor			Wilms tumor gene 1		Lipoxygenase matrix metalloproteinase		
	EGF receptor		Kinases	Autophosphorylation-activated protein kinase		Quinone oxidoreductase		
Inflammatory cytokines	Interleukin (1, 2, 5, 6, 8, 12, 18)			Ca ²⁺ -dependent protein kinase	c-Jun N-terminal kinase	Ornithine decarboxylase		
	Monocyte chemoattractant protein			EGF receptor kinase		Phospholipase D		
	Migration inhibition protein			Extracellular receptor kinase		Telomerase		
	Macrophage inflammatory protein			Focal adhesion kinase		Tissue inhibitor of metalloproteinase 3		
	Tumor necrosis factor alpha			Interleukin-1 receptor-associated kinase	Adhesion molecules	Endothelial leukocyte adhesion molecule 1		
Antiapoptotic proteins	B-cell lymphoma protein 2			Janus kinase		Intracellular adhesion molecule 1		
	Bcl-xL			Mitogen-activated protein kinase		Vascular cell adhesion molecule 1		
	Inhibitory apoptosis protein 1			Phosphorylase kinase	Others	Cyclin D1	DNA fragmentation factor 40-kDa subunit	
Growth factors	Connective tissue growth factor			Protamine kinase		Multidrug resistance protein 70	Heat shock protein 70	
	Epidermal growth factor			pp60c-src Tyrosine kinase		Urokinase-type plasminogen activator	p53	
	Fibroblast growth factor			Protein tyrosine kinase				
	Hepatocyte growth factor			Protein kinase A, B, C				
	Tissue factor							
	Nerve growth factor							
	Platelet-derived growth factor							
	Transforming growth factor beta 1							
	Vascular endothelial growth factor							

Tab. 1: Possible molecular targets that curcumin might interact with.^[1,7,8] ATFase = xxx, ATPase = xxx, CREB = xxx, EGF = xxx.

metal chelation, redox reactivity, aggregation, and so on.^[78] This explanation may be plausible for experiments *in vitro*, but it is not able to explain large experimental and clinical trial data *in vivo*.^[13] We suppose curcumin, as a secondary metabolite, is structurally weak-matched with a common domain, which appears as a wide target inhibition or activation. To develop a medication, one must have a specific target, and multitarget behaviors would inevitably bring wide side effects that explained multiple activities of curcumin. When it comes to a specific disease, for example, cancer, a lot of literature documented antitumor activities of curcumin; it is unlikely that a single molecule worked on so many targets without any adverse side effects. However, it is interesting that experiments *in vivo* proved curcumin to be safe even at a very high dose.^[5,79] Possible explanations may be that either the absorption of curcumin is low or biological activities of curcumin are definite but moderate.

1.4. Current solutions for curcumin

Poor bioavailability limits the further benefits of curcumin; a lot of researchers gave their solutions. It prevented curcumin from glucuronidation to less potent metabolite curcumin glucuronides using an adjuvant piperine that is a known inhibitor of glucuronidation.^[80,81] Nanoparticle technology has been applied in curcumin delivery system. With a very small particle size, highly hydrophobic curcumin is dispersed in water to the utmost extent, which helps curcumin to get into target cells.^[82] In addition, liposome, micelles, phospholipid complexes delivery systems of curcumin have been developed to achieve a better bioavailability.^[4,83–85]

The improvement in pharmaceuticals or delivery systems of curcumin increases bioavailability indeed, but it will not change the chemical structure; curcumin still remains the “panacea” attribute. By narrowing target range to strengthen more specific effects, structural modifications of curcumin seem to be the strategy to enhance the activity as a specific anticancer product.

To strengthen pharmaceutical activities of curcumin, researchers synthesized many curcumin analogues. In a study, most of the synthesized curcumin analogues showed an increasing antioxidant activity to low-density lipoprotein (LDL) peroxidation with the increase of phenolic group number.^[9] 3'-Methoxyl in curcumin was deemed to play a role in anti-inflammatory effects; analogues that contain cyclohexanone performed superiorly, and deletion of the β -diketone moiety increased its biological stability defect that was caused by the keto-enol tautomerism.^[10] Curcumin was also found to be favorable in the treatment of Alzheimer disease. The study of structure-activity relationships revealed that it is the 2 aromatic rings that could bind with amyloid beta protein (A β) and inhibit A β aggregation but not the flexibility of the bridge between 2 aromatic rings.^[11]

In the respect of antitumor activity, modification on curcumin also has been extensively investigated. For centuries, we have been struggling with cancers, although a lot of progresses in the mechanism of tumor genesis and development have been made and there have been plenty of methods coping with different types of cancer for instance radiotherapy, chemotherapy, and other anticancer medications. However, there are many other problems, which include drug toxicities, chemoresistance, radioresistance, cancer recurrence, and so on. In previous studies, curcumin presented a great effectiveness *in vitro*, but it has hardly met expectations of the clinical demands.^[78] But as a basis for antitumor drug designs, there are 3-group sections in curcumin that have been structurally modified to yield more effective

compounds, for instance, the aromatic rings, the β -diketone moiety, and the 2 flanking double bonds. As Mosley et al in their article pointed out, mostly, the successful anticancer compounds based on curcuminoid structures retained the conjugated α,β -unsaturated ketone moieties as a Michael receptor. They observed, as cytotoxins, compounds with more than 1 conjugated carbonyl were more active than those with a single conjugated carbonyl, which indicates that a conjugated carbonyl might be the functional group against cancer cells and cancer cells are more susceptible to multiple chemical insults.^[14]

1.5. Curcumin analogues targeting cancer cells

Traditional anticancer compounds are targeting cancer cells directly. Curcumin has been documented to have direct cancer cell inhibiting effects in many cell models. Some of its analogues, therefore, have been designed to enhance the cytotoxicity directly toward cancer cells. The cytotoxicity of curcumin is mostly presumed to be related to the conjugated carbonyl, but the conjugation in curcumin tends to be unstable because of the keto-enol tautomerism. Therefore, the design strategy prefers to retain the conjugated carbonyl while avoiding the tautomerism by the deletion of the β -diketone moiety. A successful example DM-1 (Fig. 2, 15), which is a curcuminoid by a β -diketone moiety deletion based on curcumin skeleton, showed a superior toxicity to melanoma cells.^[86] A series of mono-carbonyl curcumin analogues were designed and synthesized to increase stability of curcumin, among which CA15 (Fig. 2, 16) exhibited a stronger selective toxicity toward laryngeal cancer cells compared to curcumin. Similar compounds A (Fig. 2, 17) and I (Fig. 2, 18) also showed a significant antitumor activities both in triple-negative breast cancer cells *in vitro* and in triple-negative breast cancer and leukemia xenografts *in vivo*.^[87,88] However with the alteration of α,β -unsaturated ketones, saturated curcumin or curcumin analogues, for example tetrahydrocurcumin (Fig. 2, 7), were proved to be much less potent, which further proved the importance of conjugated carbonyl in antitumor activity.^[16,24]

Based on mono-carbonyl curcumin, a designed series of piperidone curcuminoids also showed a promising outcomes in tumor inhibition.^[92] Compared to curcumin, *N*-acryloyl series (Fig. 2, 1) were found to be more cytotoxic toward murine P388 and L1210 leukemic cells and human Molt 4/C8 and CEM neoplasms.^[15] In another article, a series of α,β -unsaturated monoketone curcumin analogue based on piperidone showed remarkable cytotoxicity to leukemia cell lines.^[16]

Above all, further modifications of curcumin are basically based on mono-carbonyl curcumin or piperidone curcumin with the introduction of methyl groups, hydroxy groups, fluorine, methoxy groups, hybridization, and so. Some of the examples are listed as MC37 (Fig. 2, 19),^[89] 2,2'-fluorine mono-carbonyl curcumin (Fig. 2, 20),^[90] and Da0324 (Fig. 2, 21).^[91]

1.5.1. Curcumin analogues targeting CSCs. The CSC hypothesis accounts for the functional heterogeneity and hierarchical organization of cancerous cells. CSCs are responsible for the tumor comprising diverse cells and exhibiting a stem cell-like feature. In most cases, CSCs are drug resistant and have the abilities of self-renewal and cancer initiation to maintain the tumor existence that majorly is the reason of cancer recurrence.^[98] Recent studies on curcuminoids have presented several activities by which oncogenesis could be distinctly suppressed. It has been pointed out that 3 major signaling pathways, the Wnt/ β -catenin, sonic hedgehog, and

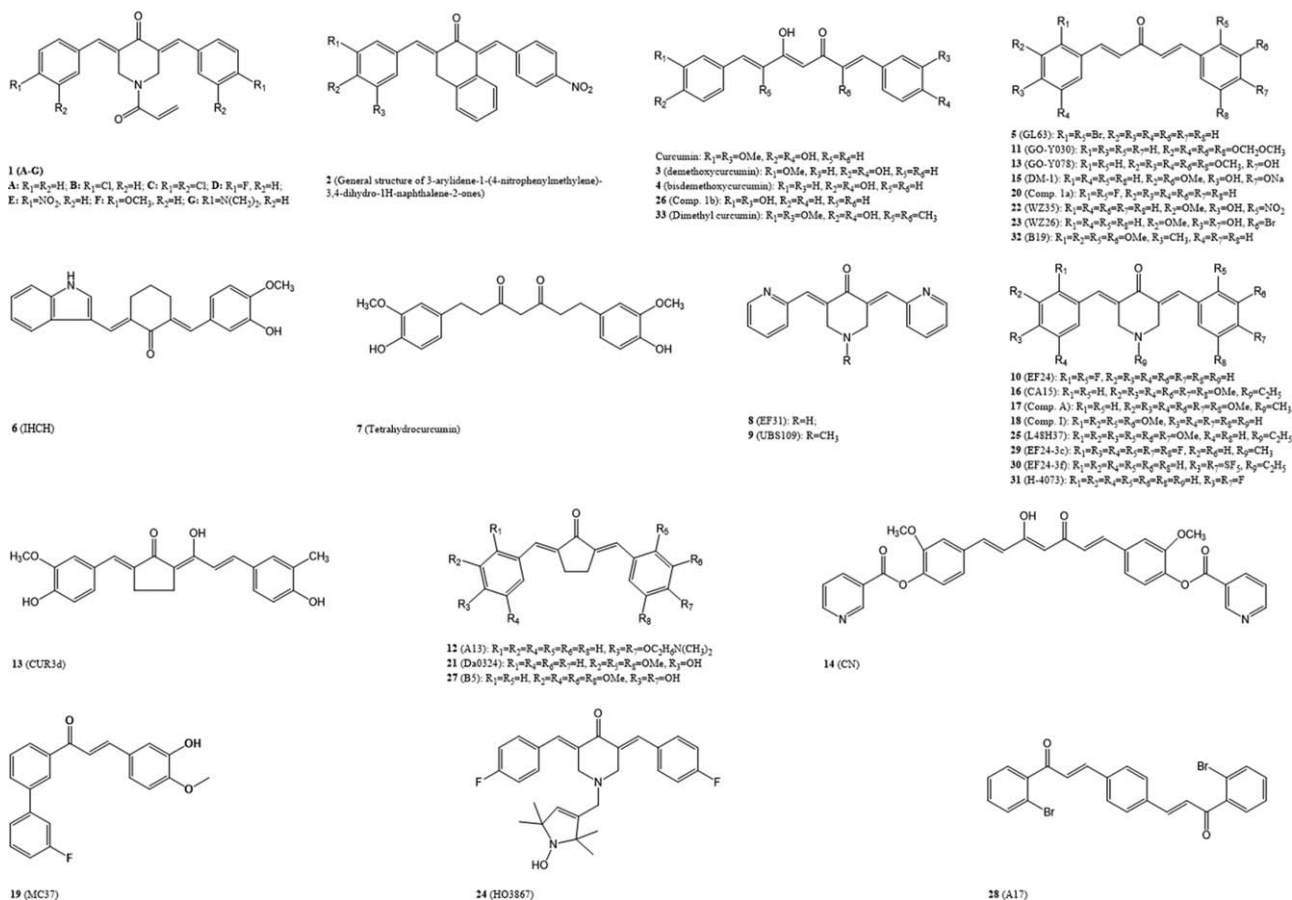


Figure 2. Potential antineoplastic curcumin analogues. Structures of curcumin and its analogues presented in this review have been reported to have the potential antineoplastic activity.

Notch 1 pathways, may be involved in curcumin blocking CSCs self-renewal through direct or indirect influences. CSCs resistance to chemotherapy and radiotherapy is considered the main reason for cancer recurrence. A strategy using a combination of CSCs-targeted curcuminoids and conventional anticancer drug therapies has been proven to be potential to attenuate tumor resistance and recurrence.^[21,26] In colorectal CSCs (ALDH⁺/CD133⁺ subpopulation of colorectal cancer cells), difluorinated curcumin (CDF) has been shown to downregulate the expression of miR-21 that would be present in high level in many cancer cells, further restore the expression of PTEN.^[27,28] Recent research also revealed its role in pancreatic cancer in which CDF accumulates 3-folds more than curcumin.^[23,30] GO-Y030 (Fig. 2, 11) and a water-soluble curcuminoid A13 (Fig. 2, 12) selectively inhibit the phosphorylation of STAT3, and then downregulate the expression of STAT3-mediated genes involved in cancer cell proliferation and survival, such as cyclin D1, Bcl-2, Bcl-XL, and putative STAT3 downstream targets, Notch 1 and Notch 3, that are essential for self-renewal and angiogenesis of stem cell.^[20,25] By increasing the expression of cleaved PARP and cleaved caspase-3, GO-Y030 also drives CSCs to apoptosis and inhibits retinoblastoma protein phosphorylation that causes cell cycle arrest at G1 to affect CSCs cell cycle.^[19,31]

1.5.2. Curcumin analogues triggering apoptosis. According to cell death morphologies, cell death includes “apoptosis,” “necrosis,” and “mitotic catastrophe.”^[99] Present experimental data of curcumin and its analogues on antitumor activity mainly

regard activating the apoptosis through ROS-mediated endoplasmic reticulum (ER) stress and mitochondrion-dependant pathways as the key to initiate cell death program. Acute ER stress in cancerous cells triggers the induction of a family of ER stress protein that promotes survival and growth of cancer cells, in which acute ER stress plays an overall protective role in its resistance to chemotherapy and radiation therapy. However, prolonged or severe ER stress impairs the protective mechanisms and triggers the cell death program.^[32,33] In intrinsic apoptosis, intracellular stress including DNA damage, cytosolic Ca²⁺ overload, and ER stress triggers pro-death or pro-survival signals to a mitochondrion-centered control mechanism. When pro-death signals prevail, mitochondrial outer membrane permeabilization occurs, which leads to a dissipation of mitochondrial transmembrane potential and arrest of mitochondrial ATP synthesis. The uncoupled respiration chains lead to reactive oxygen species (ROS) overproduction and cytochrome C released into the cytosol t induces cell apoptosis.^[99] Some studies show that curcumin triggers the accumulation of cytosolic Ca²⁺ by inhibiting the Ca²⁺-ATPase pump further increases the ER stress that induces the prolonged ER stress and activation of specific cell apoptosis by cleavage and activation of caspase and p23 cleavage, and downregulation of the antiapoptotic Mcl-1 protein.^[34,35] Some successful curcumin analogues, WZ35 (Fig. 2, 22), WZ26 (Fig. 2, 23), HO3867 (Fig. 2, 24), L48H37 (Fig. 2, 25), 2,2'-F mono-carbonyl curcumin (Fig. 2, 20), 3,3'-OH curcumin (Fig. 2, 26), and B5 (Fig. 2, 27), have been documented to induce ROS production and accumulation that activate ROS-dependent ER

stress signaling pathways or mitochondrial apoptosis pathways and finally lead to cell apoptosis.^[90,33,100,101,102,103,104,105,107,108] In addition, HO3867 and L48h37 are inhibitors of STAT3 that is closely related to tumor progression and activates gene expression of Bcl-2, considered as an important antiapoptotic protein.^[33,104] GL63 (Fig. 2, 5), WZ25, and A17 (Fig. 2, 28) can induce the expression of C/EBP homologous protein that is a direct effector of ER stress.^[36,101,109] B5 and IHCH (Fig. 2, 6) activate autophagy through the Akt and AMPK signaling pathways.^[37,108] By analyzing structures of this effective anti-apoptosis curcumin analogues, we noted that most of them are based on mono-carbonyl curcumin or piperidone curcumin, and nearly half of them are with halogen elements introduction, for example, fluorine and bromine.

1.6. Curcumin analogues influencing the tumor microenvironment

Tumor microenvironment is the cellular environment in which the tumor exists, including tumor itself, surrounding blood vessels, immune cells, fibroblasts, and so on.^[107] In the process of tumor progression and metastasis, tumor microenvironment plays an essential role.^[108] In this article, we discussed the roles of curcumin analogues from the aspects of tumor microenvironment including angiogenesis, hypoxia status, and lipid metabolism.

1.6.1. Curcumin analogues inhibiting angiogenesis. Angiogenesis known as the formation of new blood vessels plays a critical role in cancer progression. It channels the tumor metastasis and also facilitates the delivery of oxygen and nutrition and clearance of wastes to satisfy the rapid metabolisms during tumor proliferation. Therefore, for cancer treatments, inhibiting angiogenesis is another key to preventing tumors from growing and metastasizing. Angiogenesis inhibitors have been widely used in cancer treatment.^[122] As direct angiogenesis inhibitors, natural curcumin and its analogues demethoxycurcumin (Fig. 2, 3) and bisdemethoxycurcumin (Fig. 2, 4), which occur naturally and are isolated from turmeric, were proved to be active in inhibiting vascular endothelial growth factor (VEGF) and basic fibroblast growth factor-induced neovascularization, and the downregulation of VEGF and fibroblast growth factor (FGF) is mainly mediated by its inhibitory effect on NF- κ B transcription.^[23,94] Structural modifications of curcumin on antiangiogenesis aim to enhance the downregulative effect of VEGF or FGF. Some other curcumin analogues such as EF24 (Fig. 2, 10) and its fluoro and pentafluorothio analogues EF-24-3c (Fig. 2, 29) and EF-24-4f (Fig. 2, 30) had a stronger antiangiogenesis effect, some, for example, 3c even showed disruptive effect on blood vessel.^[118] Similar curcumin analogues

include UBS109 (Fig. 2, 9), EF31 (Fig. 2, 8),^[38] H-4073 (Fig. 2, 31),^[109] and B19 (Fig. 2, 32).^[97] Other than VEGFs, many components including growth factors and signal transducers also participated in tumor angiogenesis. A curcumin analogue GO-Y078 (Fig. 2, 13) showed angiogenesis-inhibiting effect not through the suppression of VEGF signaling but by actin disorganization.^[95] A unusual modification strategy dimethyl curcumin (Fig. 2, 33) by introducing methyl groups at C2 and C6 positions enhanced the antiangiogenesis activity of curcumin. Dimethyl curcumin remained β -diketone but introduced 2 methyl groups at C2 and C6 positions to resist metabolism in vivo.^[96]

1.6.2. Curcumin analogues acting under hypoxia status. In most cases, solid tumors are under hypoxia, because tumor angiogenesis results in abnormal and dysfunctional blood vessels that can hardly match with the rapid growth with a high oxygen consuming.^[58] Tissue hypoxia increases the cellular ROS and leads to ER stress.^[59] Therefore, tumor hypoxia enhances the risk of resistance to treatments.^[60] Also, hypoxia-inducible factors (HIFs) are overexpressed in cancer cells under hypoxia status, and recent research has proven that HIFs can induce relevant gene expression that contributes to self-renewal and pluripotency of CSCs, such as Oct4 and Notch 1.^[44,45] When tumor under hypoxia status, CUR3d (Fig. 2, 13) and a series of curcumin analogues can downregulate HIF-1 α .^[39] Investigations on curcumin analogues EF31 and UBS109 for their anti-pancreatic cancer activity reveal that through downregulation of HIF-1 α , heat shock proteins 90, cyclooxygenase 2, and VEGF, they also can drastically impair angiogenesis in pancreatic cancer.^[38,93]

1.6.3. Curcumin analogues regulating lipid metabolism. Lipid metabolism, an important energy metabolism pathway in organisms, plays an even more critical role in tumor's energy metabolism pathways. Because of the rapid energy-consuming rate and poor oxygen-supplying channel, tumor tissues are usually under hypoxia. Therefore, glycolysis becomes the main energy supply pathway in cancer cells. However, glycolysis still cannot be sufficient for energetic and biosynthetic requirements of tumors.^[47] Given the irregular alteration in both glucose and glutamine metabolisms, cancer cells are in need of fatty acids as extra energy sources that can be obtained by synthesis or uptake from exogenous environment. Increased dependence on lipid oxidation as their primary energy source has been observed in many tumor types.^[48,61,62] Growing evidence have confirmed that changes in lipid metabolism are closely related to the occurrence and development of tumors.^[59] Most of the enzymes required for fatty acid and cholesterol synthesis are regulated by sterol regulatory element-binding proteins (SREBPs), a transcription factor of the helix-loop-helix leucine zipper family.^[49] Overexpressed SREBP1 and SREBP2 have been found in many tumor cells.^[50] Intermediated by SREBP, mutant tumor protein p53 associates with sterol gene promoters. Hyperactivated genes break tissue architecture and finally lead to the tumorigenesis in breast cancer.^[51] In glioblastoma, the expression of LDL receptor is essential for the survival of glioblastoma.^[53] Another study illustrates that mutant epidermal growth factor receptor induces the activation of SREBP-1.^[52] SREBP1-regulated fatty acid synthase is involved in the production of lipid-signaling molecules and responsible for the multidrug resistance (MDR) during cancer treatments.^[54,55] According to all these evidence, lipid metabolic pathway could be a new perspective for cancer treatment and SREBPs could be the promising targets. Our research group has

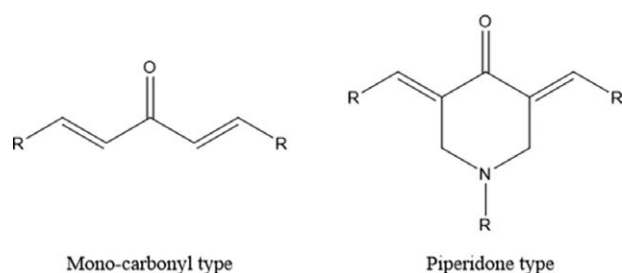


Figure 3. Promising structural modification types. Curcumin related mono-carbonyl type and piperidone type are promising structure modification starting points.

been seeking to understand and exploit the role of curcumin and curcumin analogues in cholesterol metabolism. In previous studies, we found curcumin inhibited ox-LDL-induced cholesterol accumulation in cultured vascular smooth muscle cells (VSMCs) by increasing the caveolin-1 expression and inhibiting nuclear translocation of SREBP-1.^[63] Curcumin also induced cell cycle arrest at G1/S phase and inhibited chol: M β CD-induced VSMCs proliferation via the suppression of overactivated extracellular signal-regulated kinase signaling.^[64] On the other hand, we also found curcumin could block the activation of Notch 1.^[109] In addition, a curcumin analogue curcumin nicotinate, known as CN (Fig. 2, 14), newly designed by our group has proven to significantly downregulate the expression of SREBP1 and to decrease lipid accumulation in THP-1 cells through the restoration of autophagy flux.^[56,57,59] Because curcumin and its analogues can regulate lipid synthesis and accumulation, we have been exploring whether curcumin and curcumin analogues play important roles in antitumor activity through the regulation of lipid metabolism. In our preliminary antitumor activity screening tests, CN indeed exhibited an excellent antitumor activity (unpublished data).

2. Discussion

2.1. Modification strategy of curcumin

Curcumin is a safe natural compound and has vast molecular targets, which makes it an ideal leading compound. However, to our knowledge, with a wide target range, one will not be effective enough to work as a therapeutic medicine without any side effects. As an antitumor molecule, curcumin is unlikely to be

sufficient. Therefore, it seems inevitable to narrow down the targeting spectrum of curcumin meanwhile to enhance targeting efficacy by structural modifications.

So far, the modification strategies of curcumin focus on improving the bioavailability. Curcumin is almost insoluble in water; therefore, the introduction of hydrophilic group or shortening of redundant hydrocarbon chain might be able to increase its water solubility. In addition, the spontaneous keto-enol tautomerism of curcumin makes it unstable in the process of metabolism in vivo, for which mono-carbonyl curcumin or piperidone curcumin might be more suitable for structural modification as a starting point (Fig. 3). Further modification could be the introduction of extra chemical group, for example, halogen elements; hydroxy, nitro, and methoxy groups to increase biocompatibility and bioavailability; cyclohexanone (Fig. 2, 2) to the chain between 2 aromatic rings to increase potency against MDR in tumor^[17]; and heterocycle to increase the solubility and cytotoxicity.^[40] Recent studies have also mentioned the prospect of some asymmetric curcumin analogues.^[41,42]

Modified curcumin might still not be the end. Together with the nanoparticle technology, liposome, micelles, and phospholipid complexes delivery systems, the bioavailability of curcumin analogues will be further elevated. Also, from the aforementioned successful examples, we see the potentials of curcumin analogues to work as a synergistic drug or a sensitizer of cancer chemotherapies and radiotherapies for the reasons that with different structural modification strategies, curcumin analogues can not only target cancer cells but also target tumor microenvironment (Fig. 4), for example, arresting cell cycle at G1 phase that might play a

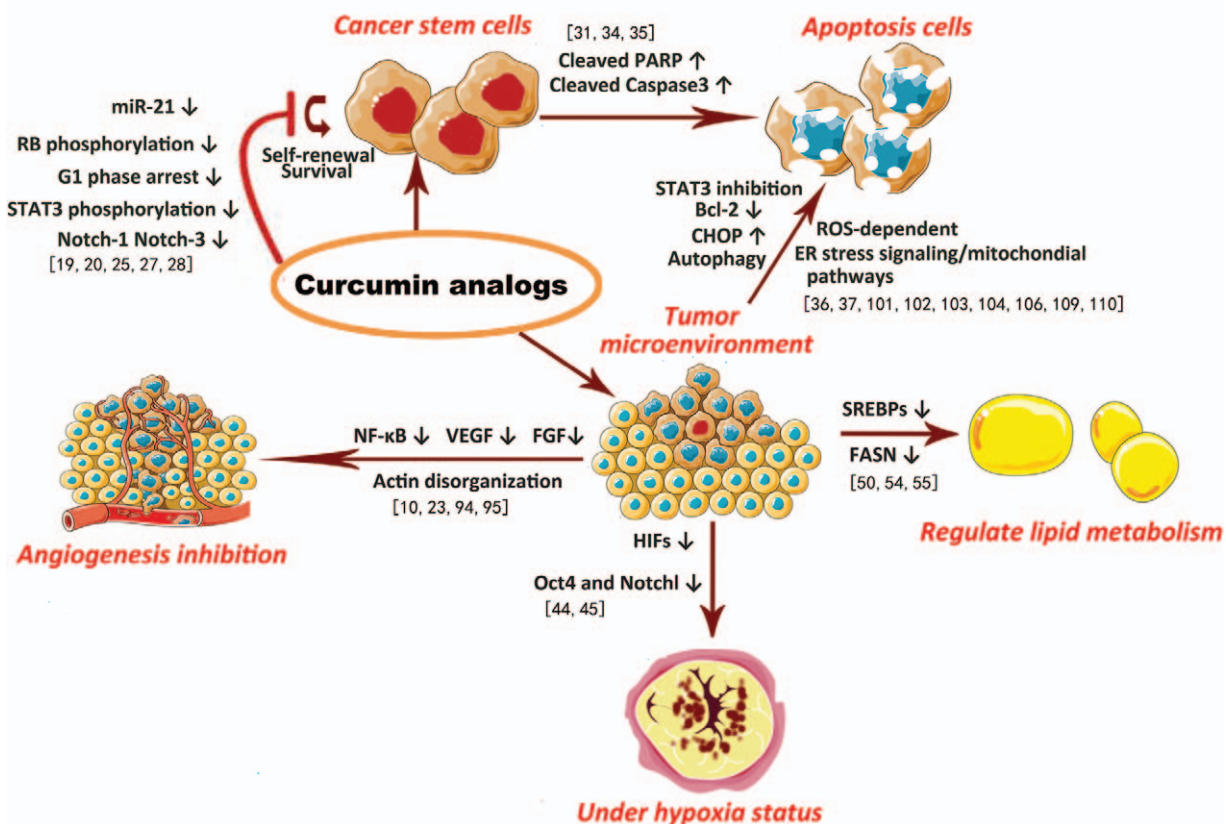


Figure 4. How curcumin analogues interrupt resistance and recurrence of cancer cells. In the aspects of cell death and tumor microenvironment including angiogenesis, tissue hypoxia status, and energy metabolism, modified curcumin analogues interrupt resistance and recurrence of cancer.

synergistic effect with radiotherapies,^[43] triggering apoptosis by ROS-mediated signaling pathways, inhibiting angiogenesis by downregulation of NF- κ B-mediated VEGF or FGF level, decreasing tissue hypoxia-induced HIFs overexpression, and regulating tumor lipid metabolism.

In summary, curcumin, as a promising compound isolated from traditional Asian dietary and medicinal plant turmeric, has drawn a massive attention. Extensive research has revealed its possible potentials for various therapeutic purposes, among which the antitumor activity has recently become a research hotspot. In cancer treatments, lots of thorny problems occur to us. Curcumin has deemed to be a multi-target agent that has its unique benefits to tumor inhibition, but its problem of low bioavailability has always been a stumbling block that have to be overcome. From our perspective, narrowing target range to strengthen more specific effects, modified curcumin analogues could be more effective. The structural modifications in our review proved to be a feasible way to improve its solubility and efficacy. Mainstream cancer therapies combined with curcumin analogues as complementary agents would be a promising therapeutic strategy, yet more curcumin analogue types and the combination remain to be further explored.

Acknowledgments

We thank all the colleagues who have helped to revise and to correct mistakes and inaccuracies in this article.

Author contributions

Conceptualization: Duan-Fang Liao.

Formal analysis: Qing-Zi Yan.

Investigation: Li-Mei Lin.

Methodology: Zhe Shi.

Software: Ya-Ling Zeng.

Supervision: Bo-Hou Xia.

Supervision: Duan-Fang Liao.

Validation: Qin-Hui Tuo.

Writing – original draft: De-Biao Xiang, Kai-Qiang Zhang, Ya-Ling Zeng, Qing-Zi Yan.

Writing – review and editing: Zhe Shi, Qin-Hui Tuo, Li-Mei Lin, Bo-Hou Xia, Ping Wu, Duan-Fang Liao.

References

- Nabavi SM, Russo GL, Tedesco I, et al. Curcumin and melanoma: from chemistry to medicine. *Nutr Cancer* 2018;1–2.
- Ahmad SS, Khan H, Danish Rizvi SM, et al. Computational study of natural compounds for the clearance of amyloid-beta: a potential therapeutic management strategy for Alzheimer's disease. *Molecules* 2019;24:E3233.
- Kunwar A, Simon E, Singh U, et al. Interaction of a curcumin analogue dimethoxycurcumin with DNA. *Chem Biol Drug Des* 2011;77:281–7.
- Yadav YC, Pattnaik S, Swain K. Curcumin loaded mesoporous silica nanoparticles: assessment of bioavailability and cardioprotective effect. *Drug Dev Ind Pharm* 2019;45:1889–95.
- Kharat M, McClements DJ. Recent advances in colloidal delivery systems for nutraceuticals: a case study-delivery by design of curcumin. *J Colloid Interf Sci* 2019;557:506–18.
- Prasad S, Tyagi AK, Aggarwal BB. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. *Cancer Res Treat* 2014;46:2–18.
- Aggarwal BB, Bhatt ID, Ichikawa H, Ravindran PN, Babu KN, Sivaraman K, et al. Curcumin—biological and medicinal properties. *Turmeric: The Genus Curcuma*. Boca Raton, FL: CRC Press; 2007;xxx.
- Qadir MI, Naqvi S, Muhammad SA. Curcumin: a polyphenol with molecular targets for cancer control. *Asian Pac J Cancer Prev* 2016;17:2735–9.
- Panahi Y, Ahmadi Y, Teymouri M, et al. Curcumin as a potential candidate for treating hyperlipidemia: a review of cellular and metabolic mechanisms. *J Cell Physiol* 2018;233:141–52.
- Liang G, Yang S, Zhou H, et al. Synthesis, crystal structure and anti-inflammatory properties of curcumin analogues. *Eur J Med Chem* 2009;44:915–9.
- Zhai P, Xia CL, Tan JH, et al. Syntheses and evaluation of asymmetric curcumin analogues as potential multifunctional agents for the treatment of Alzheimer's disease. *Curr Alzheimer Res* 2015;12:403–14.
- Haroyan A, Mukuchyan V, Mkrtchyan N, et al. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. *BMC Complement Altern Med* 2018;18:7.
- Allegra A, Innao V, Russo S, et al. Anticancer activity of curcumin and its analogues: preclinical and clinical studies. *Cancer Invest* 2017;35:1–22.
- Kálai T, Kuppusamy ML, Balog M, et al. Synthesis of N-substituted 3,5-bis (arylidene)-4-piperidones with high antitumor and antioxidant activity. *J Med Chem* 2011;54:5414–21.
- Jha A, Mohapatra P, AAlHarbi S, et al. Curcumin: not so spicy after all. *Mini Rev Med Chem* 2017;17:1425–34.
- Dimmock JR, Das U, Gul HI, et al. 3-Arylidene-1-(4-nitrophenylmethylene)-3,4-dihydro-1H-naphthalen-2-ones and related compounds displaying selective toxicity and reversal of multidrug resistance in neoplastic cells. *Bioorg Med Chem Lett* 2005;15:1633–6.
- Schmitt F, Gold M, Begemann G, et al. Fluoro and pentafluorothio analogs of the antitumoral curcuminoid EF24 with superior antiangiogenic and vascular-disruptive effects. *Bioorg Med Chem* 2017;25:4894–903.
- Kudo C, Yamakoshi H, Sato A, et al. Novel curcumin analogs, GO-Y030 and GO-Y078, are multi-targeted agents with enhanced abilities for multiple myeloma. *Anticancer Res* 2011;31:3719–26.
- Lin L, Liu Y, Li H, et al. Targeting colon cancer stem cells using a new curcumin analogue, GO-Y030. *Brit J Cancer* 2011;105:212–20.
- Ramasamy TS, Ayob AZ, Myint HH, et al. Targeting colorectal cancer stem cells using curcumin and curcumin analogues: insights into the mechanism of the therapeutic efficacy. *Cancer Cell Int* 2015;15:96.
- Wang Z, Dabrosin C, Yin X, et al. In broad targeting of angiogenesis for cancer prevention and therapy. *Semin Cancer Biol* 2015;35:S224–43.
- Pei H, Yang Y, Cui L, et al. Bisdemethoxycurcumin inhibits ovarian cancer via reducing oxidative stress mediated MMPs expressions. *Sci Rep* 2016;6:28773.
- Momtazi AA, Sahebkar A. Difluorinated curcumin: a promising curcumin analogue with improved anti-tumor activity and pharmacokinetic profile. *Curr Pharm Des* 2016;22:4386–97.
- Weng Q, Ren L, Guo L, et al. Curcumin analogue, A13, exhibits anti-leukemia effect via inhibiting STAT3. *Tumor Biol* 2016;37:9959–66.
- Reya T, Morrison SJ, Clarke MF, et al. Stem cells, cancer, and cancer stem cells. *Nature* 2001;414:105–11.
- Roy S, Yu Y, Padhye SB, et al. Difluorinated-curcumin (CDF) restores PTEN expression in colon cancer cells by down-regulating miR-21. *PLoS One* 2013;8:e68543.
- Ali S, Ahmad A, Aboukameel A, et al. Increased Ras GTPase activity is regulated by miRNAs that can be attenuated by CDF treatment in pancreatic cancer cells. *Cancer Lett* 2012;319:173–81.
- Dandawate PR, Vyas A, Ahmad A, et al. Inclusion complex of novel curcumin analogue CDF and β -cyclodextrin (1:2) and its enhanced in vivo anticancer activity against pancreatic cancer. *Pharm Res* 2012;29:1775–86.
- Zhang J, Xu K, Liu P, et al. Inhibition of Rb phosphorylation leads to mTORC2-mediated activation of Akt. *Mol Cell* 2016;62:929–42.
- Anania VG, Yu K, Gnadt F, et al. Uncovering a dual regulatory role for caspases during endoplasmic reticulum stress-induced cell death. *Mol Cell Proteomics* 2016;15:2293–307.
- Ryoo HD. Long and short (timeframe) of endoplasmic reticulum stress-induced cell death. *FEBS J* 2016;283:3718–22.
- Moore TW, Zhu S, Randolph R, et al. Liver S9 fraction-derived metabolites of curcumin analogue UBS109. *ACS Med Chem Lett* 2014;5:288–92.
- Ye H, Wei X, Wang Z, et al. A novel double carbonyl analog of curcumin induces the apoptosis of human lung cancer H460 cells via the activation of the endoplasmic reticulum stress signaling pathway. *Oncol Rep* 2016;36:1640–8.

- [34] Pan Y, Xiao J, Liang G, et al. A new curcumin analogue exhibits enhanced antitumor activity in nasopharyngeal carcinoma. *Oncol Rep* 2013;30:239–45.
- [35] Zhou GZ, Xu SL, Sun GC, et al. Novel curcumin analogue IHCH exhibits potent anti-proliferative effects by inducing autophagy in A549 lung cancer cells. *Mol Med Rep* 2014;10:441–6.
- [36] Nagaraju GP, Zhu S, Ko JE, et al. Antiangiogenic effects of a novel synthetic curcumin analogue in pancreatic cancer. *Cancer Lett* 2015;357:557–65.
- [37] Bhullar KS, Jha A, Rupasinghe HP, et al. Novel carbocyclic curcumin analog CUR3d modulates genes involved in multiple apoptosis pathways in human hepatocellular carcinoma cells. *Chem Biol Interact* 2015;242:107–22.
- [38] Gwavava P. Heterocyclic Cyclohexanone Curcumin Analogues Inhibit Growth of Ovarian Cancer Cells, In-Vitro [dissertation]. Otago, New Zealand: University of Otago; 2015.
- [39] Li Q, Chen J, Luo S, et al. Synthesis and assessment of the antioxidant and antitumor properties of asymmetric curcumin analogues. *Eur J Med Chem* 2015;93:461–9.
- [40] Kapelle IBD, Irawadi TT, Rusli MS, et al. Synthesis of asymmetric curcumin analogues from cullilawanoil using conventional and microwave method. *Procedia Chem* 2015;16:480–8.
- [41] Kriegs M, Kasten-Pisula U, Riepen B, et al. Radiosensitization of HNSCC cells by EGFR inhibition depends on the induction of cell cycle arrests. *Oncotarget* 2016;7:45122–33.
- [42] Schito L, Semenza GL. Hypoxia-inducible factors: master regulators of cancer progression. *Trends Cancer* 2016;2:758–70.
- [43] Zhang C, Zhi WI, Lu H, et al. Hypoxia-inducible factors regulate pluripotency factor expression by ZNF217-and ALKBH5-mediated modulation of RNA methylation in breast cancer cells. *Oncotarget* 2016;7:64527–42.
- [44] Bae MK, Kim SH, Jeong JW, et al. Curcumin inhibits hypoxia-induced angiogenesis via down-regulation of HIF-1. *Oncol Rep* 2006;15:1557–62.
- [45] Warburg O. On the origin of cancer. *Science* 1956;123:309–14.
- [46] Ackerman D, Simon MC. Hypoxia, lipids, and cancer: surviving the harsh tumor microenvironment. *Trends Cell Biol* 2014;24:472–8.
- [47] Jeon TI, Osborne TF. SREBPs: metabolic integrators in physiology and metabolism. *Trends Endocrinol Metab* 2012;23:65–72.
- [48] Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat Rev Cancer* 2007;7:763–77.
- [49] Freed-Pastor WA, Mizuno H, Zhao X, et al. Mutant p53 disrupts mammary tissue architecture via the mevalonate pathway. *Cell* 2012;148:244–58.
- [50] Guo D, Prins RM, Dang J, et al. EGFR signaling through an Akt-SREBP-1-dependent, rapamycin-resistant pathway sensitizes glioblastomas to antiproliferative therapy. *Sci Signal* 2009;2:ra82.
- [51] Deliang G, Felicia R, Mary Y, et al. An LXR agonist promotes glioblastoma cell death through inhibition of an EGFR/AKT/SREBP-1/LDLR-dependent pathway. *Cancer Discov* 2011;1:442–56.
- [52] Vazquez-Martin A, Colomer R, Brunet J, et al. Pharmacological blockade of fatty acid synthase (FASN) reverses acquired autotolerance to trastuzumab (Herceptin™) by transcriptionally inhibiting 'HER2 super-expression' occurring in high-dose trastuzumab-conditioned SKBR3/Tzb100 breast cancer cells. *Inter J Oncol* 2007;31:769–76.
- [53] Cheng CS, Wang Z, Chen J. Targeting FASN in breast cancer and the discovery of promising inhibitors from natural products derived from traditional Chinese medicine. *Evid Based Complement Alternat Med* 2014;2014:232946.
- [54] Gong YZ, Yao HL, Sun SW, et al. SREBP-1/caveolin-1 mediate the anti-atherosclerotic effect of curcumin nicotinate in apolipoprotein E-deficient mice. *Chin J Arterioscler* 2014;19:975–97.
- [55] Gu HF, Li HZ, Tang YL, et al. Nicotinate-curcumin impedes foam cell formation from THP-1 cells through restoring autophagy flux. *PLoS One* 2016;11:e0154820.
- [56] Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. *J Cell Sci* 2012;125:5591–6.
- [57] Zeeshan HM, Lee GH, Kim HR, et al. Endoplasmic reticulum stress and associated ROS. *Int J Mol Sci* 2016;17:327.
- [58] Vaupel P, Thews O, Mayer A, et al. Oxygenation status of gynecologic tumors: what is the optimal hemoglobin level? *Strahlenther Onkol* 2002;178:727–31.
- [59] Cairns RA, Harris IS, Mak TW. Regulation of cancer cell metabolism. *Nat Rev Cancer* 2011;11:85–95.
- [60] Kuemmerle NB, Rysman E, Lombardo PS, et al. Lipoprotein lipase links dietary fat to solid tumor cell proliferation. *Mol Cancer Ther* 2011;10:427–36.
- [61] Yuan HY, Kuang SY, Zheng X, et al. Curcumin inhibits cellular cholesterol accumulation by regulating SREBP-1/caveolin-1 signaling pathway in vascular smooth muscle cells. *Acta Pharmacol Sin* 2008;29:555–63.
- [62] Qin L, Yang YB, Tuo QH, et al. Effects and underlying mechanisms of curcumin on the proliferation of vascular smooth muscle cells induced by Chol:MβCD. *Biochem Biophys Res Commun* 2009;379:277–82.
- [63] Baker M. Deceptive curcumin offers cautionary tale for chemists. *Nature* 2017;541:144–5.
- [64] Heger M. Drug screening: don't discount all curcumin trial data. *Nature* 2017;543:40.
- [65] Sahin K, Orhan C, Tuzcu M, et al. Chemopreventive and antitumor efficacy of curcumin in a spontaneously developing hen ovarian cancer model. *Cancer Prev Res (Phila)* 2018;11:59–67.
- [66] Li B, Shi C, Li B, et al. The effects of curcumin on HCT-116 cells proliferation and apoptosis via the miR-491/PEG10 pathway. *J Cell Biochem* 2018;119:3091–8.
- [67] Zhao Q, Guan J, Qin Y, et al. Curcumin sensitizes lymphoma cells to DNA damage agents through regulating Rad51-dependent homologous recombination. *Biomed Pharmacother* 2018;97:115–9.
- [68] Yoshida K, Todden S, Ravindranathan P, et al. Curcumin sensitizes pancreatic cancer cells to gemcitabine by attenuating PRC2 subunit EZH2, and the lncRNA PVT1 expression. *Carcinogenesis* 2017;38:1036–46.
- [69] Liang Z, Lu L, Mao J, et al. Curcumin reversed chronic tobacco smoke exposure induced urocytic EMT and acquisition of cancer stem cells properties via Wnt/β-catenin. *Cell Death Dis* 2017;8:e3066.
- [70] Mukherjee S, Debata PR, Hussaini R, et al. Unique synergistic formulation of curcumin, epicatechin gallate and resveratrol, tricurin, suppresses HPV E6, eliminates HPV+ cancer cells, and inhibits tumor progression. *Oncotarget* 2017;8:60904–16.
- [71] Jin G, Yang Y, Liu K, et al. Combination curcumin and (-)-epigallocatechin-3-gallate inhibits colorectal carcinoma microenvironment-induced angiogenesis by JAK/STAT3/IL-8 pathway. *Oncogenesis* 2017;6:e384.
- [72] Siviero A, Gallo E, Maggini V, et al. Curcumin, a golden spice with a low bioavailability. *J Herb Med* 2015;5:57–70.
- [73] Liu W, Zhai Y, Heng X, et al. Oral bioavailability of curcumin: problems and advancements. *J Drug Target* 2016;24:694–702.
- [74] Zhongfa L, Chiu M, Wang J, et al. Enhancement of curcumin oral absorption and pharmacokinetics of curcuminoids and curcumin metabolites in mice. *Cancer Chemother Pharmacol* 2012;69:679–89.
- [75] Nelson KM, Dahlin JL, Bisson J, et al. The essential medicinal chemistry of curcumin: miniperspective. *J Med Chem* 2017;60:1620–37.
- [76] Singh PK, Kotia V, Ghosh D, et al. Curcumin modulates α-synuclein aggregation and toxicity. *ACS Chem Neurosci* 2012;4:393–407.
- [77] Sehgal A, Kumar M, Jain M, et al. Piperine as an adjuvant increases the efficacy of curcumin in mitigating benzo(a)pyrene toxicity. *Hum Exp Toxicol* 2012;31:473–82.
- [78] Sehgal A, Kumar M, Jain M, et al. Modulatory effects of curcumin in conjunction with piperine on benzo(a)pyrene-mediated DNA adducts and biotransformation enzymes. *Nutr Cancer* 2013;65:885–90.
- [79] Lotfi-Attari J, Pilehvar-Soltanahmadi Y, Dadashpour M, et al. Co-delivery of curcumin and chrysin by polymeric nanoparticles inhibit synergistically growth and hTERT gene expression in human colorectal cancer cells. *Nutr Cancer* 2017;69:1290–9.
- [80] Duse L, Pinnapireddy SR, Strehlow B, et al. Low level LED photodynamic therapy using curcumin loaded tetraether liposomes. *Eur J Pharm Biopharm* 2018;126:126–241.
- [81] Woraphatphadung T, Sajomsang W, Rojanarata T, et al. Development of chitosan-based pH-sensitive polymeric micelles containing curcumin for colon-targeted drug delivery. *AAPS PharmSciTech* 2018;19:991–1000.
- [82] Chávez-Zamudio R, Ochoa-Flores AA, Soto-Rodríguez I, et al. Preparation, characterization and bioavailability by oral administration of O/W curcumin nanoemulsions stabilized with lysophosphatidylcholine. *Food Funct* 2017;8:3346–54.
- [83] Oliveira ÉA, Lima DS, Cardozo LE, et al. Toxicogenomic and bioinformatics platforms to identify key molecular mechanisms of a curcumin-analogue DM-1 toxicity in melanoma cells. *Pharmacol Res* 2017;125:178–87.

- [84] Chen J, Zhang L, Shu Y, et al. Curcumin analogue CA15 exhibits anticancer effects on HEP-2 cells via targeting NF- κ B. *Biomed Res Int* 2017;2017:4751260.
- [85] Pignatelli C, Ma D, Noel M, et al. Selective targeting of cancer cells by oxidative vulnerabilities with novel curcumin analogs. *Sci Rep* 2017;7:1105.
- [86] Liang B, Liu Z, Cao Y, et al. Mc37, a new mono-carbonylcurcumin analog, induces G2/M cell cycle arrest and mitochondria-mediated apoptosis in human colorectal cancer cells. *Eur J Pharmacol* 2017;796:139–48.
- [87] Liu GY, Zhai Q, Chen JZ, et al. 2,2'-Fluorine mono-carbonyl curcumin induce reactive oxygen species-mediated apoptosis in human lung cancer NCI-H460 cells. *Eur J Pharmacol* 2016;786:161–8.
- [88] Jin R, Xia Y, Chen Q, et al. Da0324, an inhibitor of nuclear factor- κ B activation, demonstrates selective antitumor activity on human gastric cancer cells. *Drug Des Devel Ther* 2016;10:979–95.
- [89] Anthwal A, Singh K, Rawat MS, et al. Synthesis of 4-piperidone based curcuminoids with anti-inflammatory and anti-proliferation potential in human cancer cell lines. *Anticancer Agents Med Chem* 2016;16:841–51.
- [90] Rajitha B, Nagaraju GP, Shaib WL, et al. Novel synthetic curcumin analogs as potent antiangiogenic agents in colorectal cancer. *Mol Carcinogen* 2017;56:288–99.
- [91] Saberi-Karimian M, Katsiki N, Caraglia M, et al. Vascular endothelial growth factor: an important molecular target of curcumin. *Crit Rev Food Sci Nutr* 2019;59:299–312.
- [92] Sugiyama S, Yoshino Y, Kuriyama S, et al. A curcumin analog, GO-Y078, effectively inhibits angiogenesis through actin disorganization. *Anticancer Agents Med Chem* 2016;16:633–47.
- [93] Koo HJ, Shin S, Choi JY, et al. Introduction of methyl groups at C2 and C6 positions enhances the antiangiogenesis activity of curcumin. *Sci Rep* 2015;5:14205.
- [94] Sun L, Liu J, Lin SS, et al. Potent anti-angiogenic activity of B19—a mono-carbonyl analogue of curcumin. *Chin J Nat Med* 2014;12:8–14.
- [95] Suresh R, Ali S, Ahmad A, et al. The role of cancer stem cells in recurrent and drug-resistant lung cancer. *Adv Exp Med Biol* 2016;890:57–74.
- [96] Galluzzi L, Vitale I, Abrams JM, et al. Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. *Cell Death Differ* 2012;19:107–20.
- [97] Chen M, Zhou B, Zhong P, et al. Increased intracellular reactive oxygen species mediates the anti-cancer effects of WZ35 via activating mitochondrial apoptosis pathway in prostate cancer cells. *Prostate* 2017;77:489–504.
- [98] Zhang X, Chen M, Zou P, et al. Curcumin analog WZ35 induced cell death via ROS-dependent ER stress and G2/M cell cycle arrest in human prostate cancer cells. *BMC Cancer* 2015;15:866.
- [99] Zou P, Zhang J, Xia Y, et al. ROS generation mediates the anti-cancer effects of WZ35 via activating JNK and ER stress apoptotic pathways in gastric cancer. *Oncotarget* 2015;6:5860–76.
- [100] Zou P, Xia Y, Chen T, et al. Selective killing of gastric cancer cells by a small molecule targeting ROS-mediated ER stress activation. *Mol Carcinogen* 2016;55:1073–86.
- [101] Bixel K, Saini U, Kumar Bid H, et al. Targeting STAT3 by HO3867 induces apoptosis in ovarian clear cell carcinoma. *Int J Cancer* 2017;141:1856–66.
- [102] Hu Y, Zhao C, Zheng H, et al. A novel STAT3 inhibitor HO-3867 induces cell apoptosis by reactive oxygen species-dependent endoplasmic reticulum stress in human pancreatic cancer cells. *Anticancer Drugs* 2017;28:392–400.
- [103] Feng C, Xia Y, Zou P, et al. Curcumin analog L48H37 induces apoptosis through ROS-mediated endoplasmic reticulum stress and STAT3 pathways in human lung cancer cells. *Mol Carcinogen* 2017;56:1765–77.
- [104] Liu GY, Sun YZ, Zhou N, et al. 3,3'-OH curcumin causes apoptosis in HepG2 cells through ROS-mediated pathway. *Eur J Med Chem* 2016;112:157–63.
- [105] Shao FY, Du ZY, Ma DL, et al. B5, a thioredoxin reductase inhibitor, induces apoptosis in human cervical cancer cells by suppressing the thioredoxin system, disrupting mitochondrion-dependent pathways and triggering autophagy. *Oncotarget* 2015;6:30939–56.
- [106] Spill F, Reynolds DS, Kamm RD, et al. Impact of the physical microenvironment on tumor progression and metastasis. *Curr Opin Biotech* 2016;40:41–8.
- [107] Chaffer L, Weinberg RA. A perspective on cancer cell metastasis. *Science* 2011;331:1559–64.
- [108] Kumar B, Yadav A, Hideg K, et al. A novel curcumin analog (H-4073) enhances the therapeutic efficacy of cisplatin treatment in head and neck cancer. *PLoS One* 2014;9:e93208.
- [109] Sun SW, Tong WJ, Guo ZF, et al. Curcumin enhances vascular contractility via induction of myocardin in mouse smooth muscle cells. *Acta Pharmacol Sin* 2017;38:1329–39.