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Review

Curcumol: From Plant Roots to Cancer Roots

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Abstract

Natural products, an infinite treasure of bioactive scaffolds, have provided an excellent reservoir for the discovery of drugs since millennium. These naturally occurring, biologically active and therapeutically effective chemical entities have emerged as novel paradigm for the prevention of various diseases. This review aims to give an update on the sources as well as pharmacological profile of curcumol, a pharmacologically active sesquiterpenoid, which is an imperative bioactive constituent of several plants mainly from genus *Curcuma*. Curcumol has potential to fight against cancer, oxidative stress, neurodegeneration, microbial infections, and inflammation. Curcumol has been documented as potent inducer of apoptosis in numerous cancer cells via targeting key signaling pathways as MAPK/ERK, PI3K/Akt and NF-κB which are generally deregulated in several cancers. The reported data reveals multitarget activity of curcumol in cancer treatment suggesting its importance as anticancer drug in future. It is speculated that curcumol may provide an excellent opportunity for the cure of cancer but further investigations on mechanism of its action and preclinical trials are still mandatory to further validate the potential of this natural cancer killer in anticancer therapies.

Key words: Anticancer, Biological activities, Curcumol, Natural products

1. Introduction

Natural products have been a magnificent and boundless source of vast chemical diversity driving pharmaceutical industry since times [1]. Medicinal plants are extensively utilized as herbal remedies for the prevention, cure, and treatment of wide spectrum of pathological conditions [2]. Modern drug discovery from natural products is a novel approach linking molecular, biological, phytochemical, and bioassay-guided fractionation techniques [3]. Plant products-based drug discovery yet remains an imperative domain where in depth research can definitely supply novel leads against numerous biological targets [4]. Many commercially accessible drugs have their origin from plants. Plant tissue culture approach has conventionally recognized as a potential alternate source for the production of some beneficial bioactive compounds [5].

The first written record on plants dates back to 2600 B.C. which is a refined medicinal scheme in Mesopotamia consisting of around 1000 drugs derived from medicinal plants [6]. Egyptian medicinal system, a data records from 2900 B.C., is composed of 700 drugs which are mainly originated from plants [7]. Over the past 50 decades, marine system has been an imperative source of about 20,000 noteworthy chemical entities. Of these, 9 are approved drugs

while 12 are in clinical trials. All of these have been uncovered as molecules inspired from the natural products or their derivatives [8].

Numerous investigations on herbs and plants have assured their efficacy as compelling source of anticancer [3], antimicrobial [9], antiinflammatory [10], antioxidant [11], and neuroprotective agents [12, 13].

Sesquiterpenoids, saponins and diterpenoids have been abundantly found in medicinal plants, herbs and marine organisms. Due to broad range of diversity in their chemical structure, terpenes are well-known for their anticancer, antiinflammatory and neuroprotective potential in biological systems [14-18].

Till now, no one has attempted to review the anticancer activity of curcumol. Thus, this review aims to focus on the investigations associated with the pharmacological effectiveness of curcumol in various cancer types. The literatures were screened via many e-sites like PubMed, Elsevier Science Direct, Springer Link, and other related medical Journals. Keywords used for searching were "Natural products", "Curcumol", "Curcumol and its pharmacological potential", and "Anticancer".

2. Curcumol and its natural sources

Curcumol, a bioactive sesquiterpenoid, has been isolated from numerous plants of family Zingiberaceae. These plants are mostly found in Southeast Asia, China, Indonesia, India, Peru, and West Indies [19]. *Curcuma,* the most important genus of the family Zingiberaceae, encompasses approximately 100 species. Curcumol has been isolated from *C. longa* which is an imperative species of the genus *Curcuma* and is generally known as common turmeric. Curcumol was also extracted from the rhizome of *C. aeruginosae* that is effective for antiinflammatory and antioxidant activities [20]. *C. aromatic*, a well-known natural source of curcumol, has been reported for its antitumor and antimicrobial activities [21]. *C. kwangsiensis* and *C. phaeocaulis* are advantageous for their antiproliferative activities against various cancer types [22-27]. Dried roots of *C. zedoary* enriched with curcumol are documented for their effective anticancer and antiinflammatory properties [28-31]. Rhizome of various *Curcuma* species, a rich source of curcumol, serves as antimicrobial, antifibrotic, and anticancer agent [32-34]. Besides them, curcumol has also been isolated from the roots of *Astragali radix*, *C. rhizoma*, and *Fructus gardenia* which are traditionally used as anticancer agents [35, 36].

The summary of plants containing curcumol and biological activities are enlisted in Table 1. Figure 1 provides natural sources of curcumol including *Astragali radix* [36], *C. aeruginosae* [20], *C. aromatica* [21], *C. kwangsiensis* [22], *C. longa* [37], *C. phaeocaulis* [24], *C. wenyujin* [38], *C. zedoary* [28], *Fructus gardenia* [35], and *C. trichosantha* G. [39].

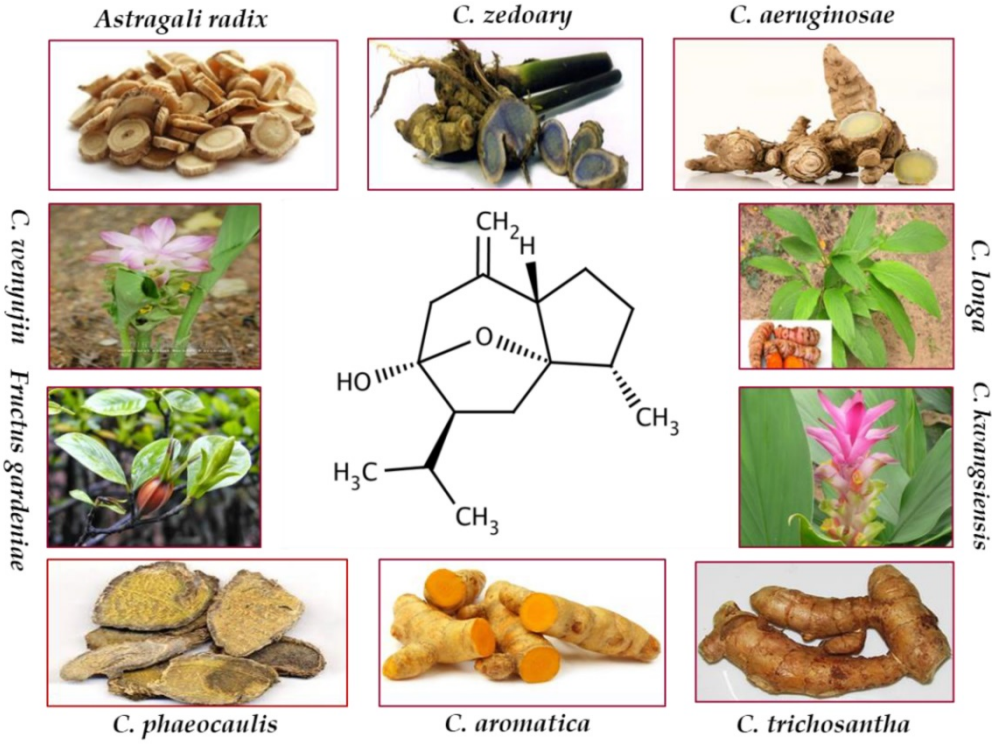

Figure 1. Chemical structure and natural sources of curcumol.

Table 1. Natural sources of curcumol.

Name of Plants		Parts used/ Extract	Disease/Function	References
Botanical Name	**Common Name**			
Astragali radix	Milkvetch root	Roots	Anticancer	[36]
Curcuma aeruginosae	Pink and blue ginger	Rhizome	Wound healing activity	[20]
Curcuma aromatica	Wild turmeric	Rhizome		[21]
Curcuma kwangsiensis	---	---	Anticancer	[22]
Curcuma longa	Common turmeric	Rhizome	Antifungal	[37]
Curcuma phaeocaulis	---	---	Antiproliferative	[24]
Curcuma wenyujin	---	---	Antitumor, antihepatic fibrosis, antioxidant, antimicrobial	[38, 40, 41]
Curcuma zedoary	White turmeric	Dried roots	Anticancer	[29]
Fructus gardenia	---	---	Anticancer	[35]
Curcuma rhizoma	---	---	---	[23]
Curcuma trichosantha G.	---	Rhizome	---	[39]

3. Biological activities of curcumol

The pharmacologically active sesquiterpenoid, curcumol, is known to possess numerous pharmacological activities like anticancer, antimicrobial, antifungal, antiviral, and antiinflammatory. This chapter intends to focus on the mechanism by which curcumol acts on apoptosis related pathways to fight against cancer development and progression.

3.1 Anticancer activities

Cancer is a multifaceted disease characterized by genetic, epigenetic, signaling, and metabolic aberrations which contribute towards the deregulation of cellular homeostasis, growth, and apoptotic cell death [42]. Currently available cancer treatments such as chemotherapies and clinical drugs have limited success as they are correlated with various toxic effects and are also expensive. Therefore, this is an ultimate need of the time to find out reliable, inexpensive, and safe alternatives [3]. Naturally occurring bioactive molecules have been extensively investigated for their chemopreventive or chemotherapeutic potential due to biosafety, lesser toxicity, and availability as dietary supplements [43]. Cancer prevention by natural entities has emerged as a novel approach to combat the burden of cancer and this field of research is expanding day by day [44].

The significance of natural products can be estimated by the fact that 80% human population is still relying on plant-derived medications. Presently, greater than 60% of anticancer drugs represent their origin from natural products such as microorganisms, plants and marine flora [45]. Dietary utilization of vegetables and fruits are associated with reduction of cancer incidences by 20% and prevention of 200,000 cancer related mortalities annually [46]. In contrary to synthetic drugs which are monotargeted, these nature-derived molecules are multitarget in action having promising potential to halt cancer development and progression [47]. Presently, there is a growing trend towards screening of extracts from natural flora for drug discovery against cancer because of their capability to prohibit carcinogenesis via modulation of various cellular signaling pathways [48].

Secondary metabolites that are derived from plants like terpenes, polyphenols, and alkaloids have been reported for their potential anticancer efficacy [49, 50]. Approximately, 55,000 terpenes have been identified from natural sources but only a limited number of entities have been screened for their anticancer potential [42]. Sesquiterpenoids, saponins, and diterpenoids as major classes of terpenes are widely known for their anticancer capabilities against broad range of cancers [15-17]. Sesquiterpenoids has been documented to act as anticancer, antiinflammatory, and neuroprotective agents in biological systems [18]. Curcumol is a guaiane type sesquiterpene lactone containing a vinylidene group along with hemiketal system [51]. Curcumol has been documented to owe potential anticancer activity against wide spectrum of cancers such as lung [52], breast [53], nasopharyngeal [54], gastric [23], liver [55], colorectal [56], and ovarian carcinoma's [57] (Figure 2).

3.1.1 Curcumol and cell cycle arrest

Since cancer represents a pathological condition with uncontrolled cellular division [58], therefore, naturally occurring bioactive entities regulating cell cycle or inhibiting mitotic divisions are affirmed to be promising candidates for chemotherapies [59, 60]. Investigations on cell cycle regulatory mechanisms have declared the fact that nature-derived chemotherapeutic entities are imperative for reinforcing the potency of targeted therapies [61]. Nature crafted molecules have pronounced ability to regulate the expression of cyclins, cyclin dependent kinases (CDKs) and various proteins and enzymatic machineries that are involved in cell cycle regulation. Naturally occurring bioactive entities regulating cell cycle or inhibiting mitotic divisions could be

promising candidates for chemotherapies [61, 62].

Curcumol has been known to arrest the cell cycle at both G2/M and G0/G1 in several cancerous cells such as lung [52], breast [53], gastric [23], nasopharyngeal [63], and liver carcinomas [55]. In A549 and H1299 carcinoma cells, combinatorial treatment of celecoxib with curcumol lead to the accumulation of cells at G0/G1 phase while population of cells in S phase was found to be dropped after the treatment. Thus, it is concluded that curcumol can reinforce the antiproliferative potential of celecoxib due to its capability of arresting cell cycle at G0/G1 phase [64]. ASTC-a-1cells treated with curcumol displayed nuclear shrinkage, membrane blebbing, membrane frilling along with G2/M cell cycle arrest [52]. SPC-A-1, TE-1, and AGS cells displayed substantial G0/G1 arrest while TE-1, AGS, and MGC-803 exhibited G2/M arrest followed by the treatment of curcumol [23, 32, 65]. Curcumol significantly prohibited growth of CNE-2 cells and caused cell cycle arresting at G0/G1 phase via increasing the expression of p21 and p27 while reducing the expression of CDKs and cyclins in a dose-dependent mode [63]. Curcumol treatment lead HepG2 cells towards G1 phase arrest mediated by mechanism activating pRB and p53 pathways which ultimately resulted in decreased cyclin A1 levels while enhanced mRNA expression level of p27KIP1, cyclin D1, CDK2, and CDK8 [55] (Table 2).

Table 2. Molecular targets of curcumol in different cancer types.

Type of cancer	Cell line	Treatment conditions		IC_{50}/Dose	Molecular targets	Cell cycle arrest	References
		No. of cells/well	Treatment time				
Lung	A549, H1299	2×10^6	24 h	30 μM	p38 MAPK↓, PI3K/Akt$^{\perp}$, caspase-3/caspase-9^{Act} CDK2↓, cyclin E↓, Bcl-xl↓, Bcl-2↓, Bad↑, Bax↑, p21↑, p-ERK↓	G0/G1	[64]
	ASTC-a-1	–	3 h, 6 h, 12h	100 μM	ΔΨm↓	G2/M	[52]
	SPC-A-1	2×10^6 cells	72 h	32.7 μM	–	G0/G1	[32]
Nasopharyngeal	CNE-2	2×10^3	24 h, 72 h	–	NCL$^{\perp}$ (Nucleolin)	–	[28]
	CNE-2	–	–	–	NF-κB↓	–	[54]
	NPC 5-8F	5×10^5	48 h	0, 0.1, 0.2, 0.4 μM/ml	N-cadherin$^{\perp}$, E-cadherin↑	–	[66]
	CNE-2	3×10^3 per well	24, 48, 72, 96 h	50 μg/ml	IGF-1R↓, GSK-3β, p-p85↓, p85↓, p-Akt↓, cyclin E↓, cyclin D1↓, CDK2↓, CDK4↓, p21↑, p27↑	G0/G1	[63]
Breast	MDA-MB-231	4×10^3	48 h, 72 h	85.0 μg/ml, 13.5 μg/ml	p73↑, Bak↑ PUMA↑	G1	[38]
	MDA-MB-231, 4T1	0.8×10^4	24 h	–	MMP-9↓, p-JNK1/2$^{\perp}$, p-Akt$^{\perp}$, NF-κB$^{\perp}$	–	[53]
	MDA-MB-231	1×10^5	24 h	20 μg/ml	eEF1A1↓	–	[67]
Gastric	AGS, MGC- 803	1.0×10^4 cells/ml	24, 48, 72 h	72.40, 64.28, 63.83 μg/ml	Bax/Bcl-2↑, PCNA↓	S, G2/M, G0/G1	[23]
	MGC-803	–	24, 48, 72 h	–	MMP↓, IDH1↓, ROS↑	G2/M	[68]
Liver	HSC-T6	–	48 h	300 μM	PARP cleavage, caspase-3^{Act}, NF-κB translocation↓, p-IκB-α$^{\perp}$, Bcl-2↓, Bcl-xl↓	–	[27]
	HepG2	–	–	–	pRB1↑, CDK2↑, cyclin D1↑, CDK8↑, p53↑, p27KIP1↑, p21WAF1↑ Wip1↑,cyclin A1↓	G1	[55]
Colorectal	LoVo	8×10^2	24, 48, 72, 96, and 120 h	0.48, 0.31, 0.24, 0.15, 0.11 μM	IGF-1R↓, p-p38 MAPK↑,CREB$^{\perp}$, Bax/Bcl-2↑, PARP-1↑, ki-67↓, Bcl-2↓, CREB1↓, Bax↑	–	[56]
	LoVo	1×10^4	24, 48, 72, 96, and 120 h	93.59 μg/ml	NF-κB↓, PTEN↑, p-p85↓, p85↓, p-Akt↓, Akt↓	–	[69]
	HCT-116	1×10^4	24, 48, 72, 96, and 120 h	76.15 μg/ml	miR-21↓	–	[69]
	SW480	1×10^4	24, 48, 72, 96, and 120 h	209.09 μg/ml	–	–	[69]
Choriocarcinoma	JEG-3	–	–	75 μg/ml	DNMT1↓, DNMT3b↓, HDAC1↓, HDAC3↓	–	[29]
Osteosarcoma	MG-63	1×10^4 cells/well	48 h	63.5 mg/l	p-JNK↑	–	[70]
Ovarian	SKOV3	–	–	–	JAK2$^{\perp}$, STAT-3$^{\perp}$	–	[57]
Bladder	EJ	5×10^3	24, 48, 72 h	12.5, 25, 50, 100 mg/ml	EZH2↓	–	[71]
	T24	5×10^3	24, 48, 72 h	12.5, 25, 50, 100 mg/ml	EZH2↓	–	[71]

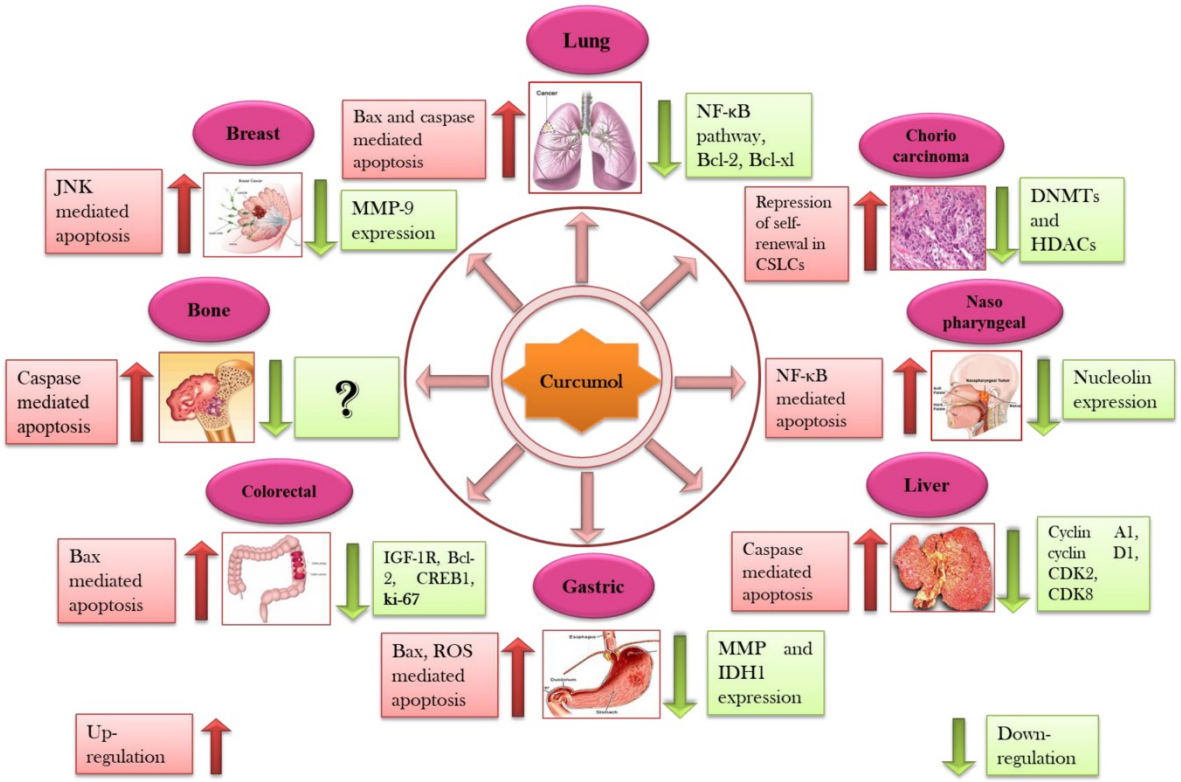

Figure 2. Cytotoxic effects of curcumol against numerous types of cancer through interruption with various cell signaling pathways (Details of different types of cancer with their molecular targets are presented in Table 2).

It can be contemplated that curcumol halt the cell cycle at G0/G1 or G2/M phase but the question that whether in G2, M, G1 or G0 phase still demands further investigation. While cyclin B and E also play crucial role in cell cycle progression, thus, further studies should also explore the role of curcumol on these cyclins. Thus, future studies are clearly needed to understand the mechanism through which curcumol cause cell cycle arrest in various cancer types.

3.1.2 Curcumol and apoptosis

Apoptosis is a synchronized form of cellular death in which various intracellular events function together to get rid of unwanted or harmful cells from human body [72]. Apoptotic cell death is considered as an important characteristic of biological events such as embryonic development, normal cellular turnover, and functioning of immune system [73]. Irregular or improper apoptosis provides a platform for the development of diseased conditions such as autoimmune responses, ischemic damage, neurodegenerative disorders, and cancer [74-76]. Intrinsic/extrinsic apoptotic pathways control apoptosis via activation of intracellular machineries of death proteases known as caspases. These activated caspases are imperative prosecutioners of programmed cell death [77]. Multiple lines of evidences have declared the fact that naturally occurring chemopreventive agents have potential to induce apoptosis in tumor cells via modulation of various molecular machineries in intrinsic and extrinsic apoptotic pathways [78-83].

Curcumol has been turned up as unique paradigm for the multitargeted prevention of cancer. Anticancer potential of curcumol has been declared to be linked with apoptosis induction via p53 regulation [55], accumulation of ROS/oxidative stress [68], reducing antiapoptotic proteins (Bcl-2, Bcl-xl) [27, 64], increasing proapoptotic proteins (Bax, Bad) [64], modulation of MAPK pathway (inhibition of p-JNK1/2, upregulation of p-p38 MAPK) [56, 64], inhibition of NF-κB [64], triggering PARP cleavage [27], activation of caspase cascade, and diminishing mitochondrial membrane potential [52] (Figure 3).

3.1.2.1 Curcumol and NF-κB pathway

NF-κB represents the superfamily of transcriptional factors that regulates the expression of various genes associated with survival, development, angiogenesis, proliferation, invasion, and metastasis [84]. This intracellular signaling cascade has potential to induce structural modification in chromatin to mediate transcription, cell cycle control, apoptosis, and cellular transformations [85]. Thus, targeting NF-κB and its regulated gene expressions offer a

promising strategy for cancer therapy [86].

Plant-derived chemical entities have been documented to induce cellular apoptosis via targeting multi-functional transcription domain NF-κB [87]. Combined treatment of celecoxib with curcumol in A549 and H1299 cancerous cells leads to the prohibition of nuclear translocation of p65 while upregulated the IκBα levels [64]. Curcumol has potential to stimulate apoptosis in CNE-2 cells via down modulation of NF-κB activity [54]. Curcumol decreased the invasive ability of MDA-MB-231 cells via prohibition of MMP-9 and suppression of Akt and JNK1/2-dependant NF-κB activity [53]. In HSC-T6 cells, curcumol effectively downregulated the nuclear translocation of NF-κB through inhibiting p-IκB-α which leads towards modulation of NF-κB associated gene expressions such as Bcl-xl and Bcl-2 [27]. Although it has been declared that curcumol induce apoptosis via NF-κB inhibition but whether it directly targets NF-κB or via its upstream pathways such as JAK or STAT-3 should be explored.

3.1.2.2 Curcumol and MAPK and PI3K/Akt pathway

MAPK pathway encompasses key signaling kinases and phosphorylation events which perform a crucial role in carcinogenesis [88]. Three subgroups of MAPK pathway: JNKs, ERKs, and p38 MAPKs carry extracellular signals which regulate cellular differentiation, apoptosis, proliferation, and invasion [88, 89]. The PI3K/Akt pathway as a regulator of multiple cellular events also plays a significant role in development of tumors and their progression [90]. Thus, MAPK and PI3K/Akt associated signaling pathways epitomize a novel target for cancer therapies.

Combined treatment of celecoxib with curcumol in A549 and H1299 cells decreased the phosphorylation level of PI3K, Akt, ERK, and p38 MAPK which accounts for the apoptotic effect of given treatment. As it is well established fact that deregulated mitogenic and PI3K pathways with their downstream pathway NF-κB have capability to inhibit apoptosis and to intensify cellular proliferation [64]. Curcumol treatment induced apoptosis in LoVo cells via phosphorylation of p38 MAPK [56]. Curcumol suppresses JNK1/2 and Akt activation because it has potential to inhibit p-JNK1/2 and p-Akt in MDA-MB-231 cells [53]. Curcumol has potential to downregulate the proliferation of colorectal cancerous cells by modulating PTEN/PI3K/Akt pathways [69]. Although it has been documented that curcumol inhibited the phosphorylation of Akt at Ser-473 but whether it can inhibit the Akt phosphorylation at Thr-308 site or not still need to be investigated.

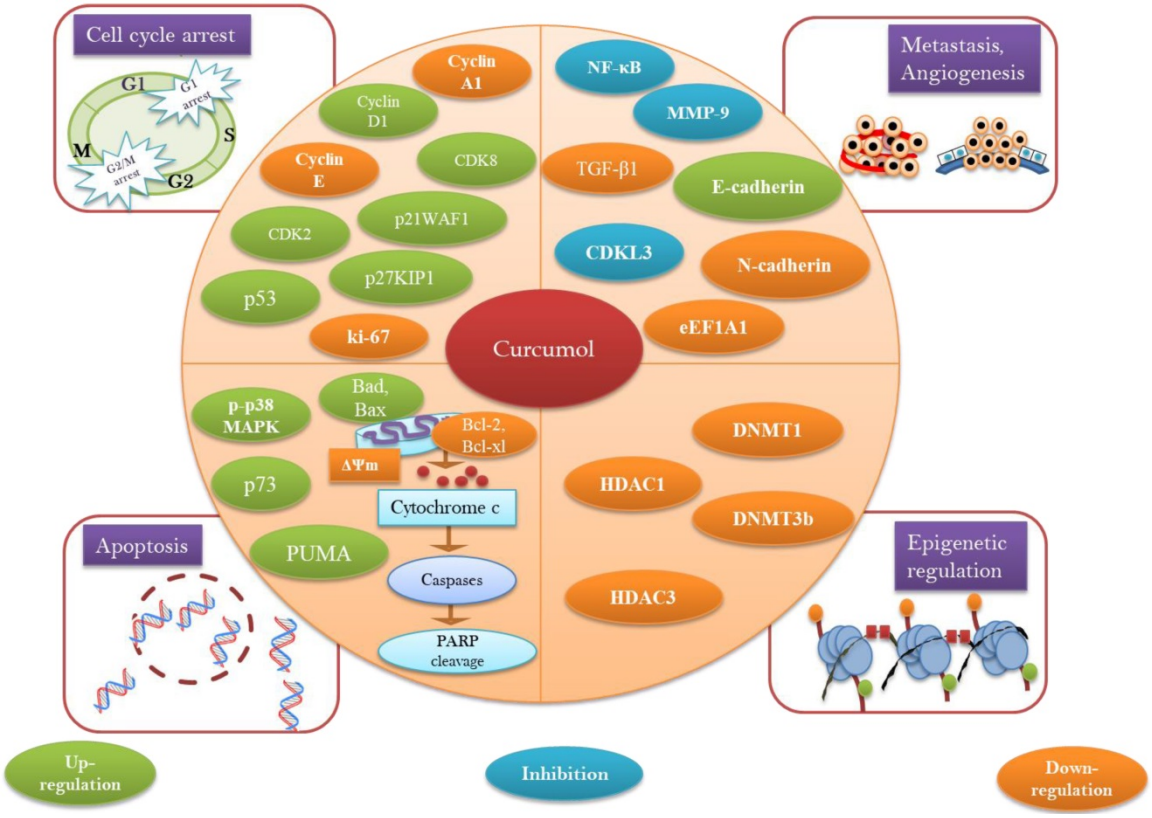

Figure 3. A diagrammatic representation of molecular targets and mechanism of action for anticancer activity of curcumol.

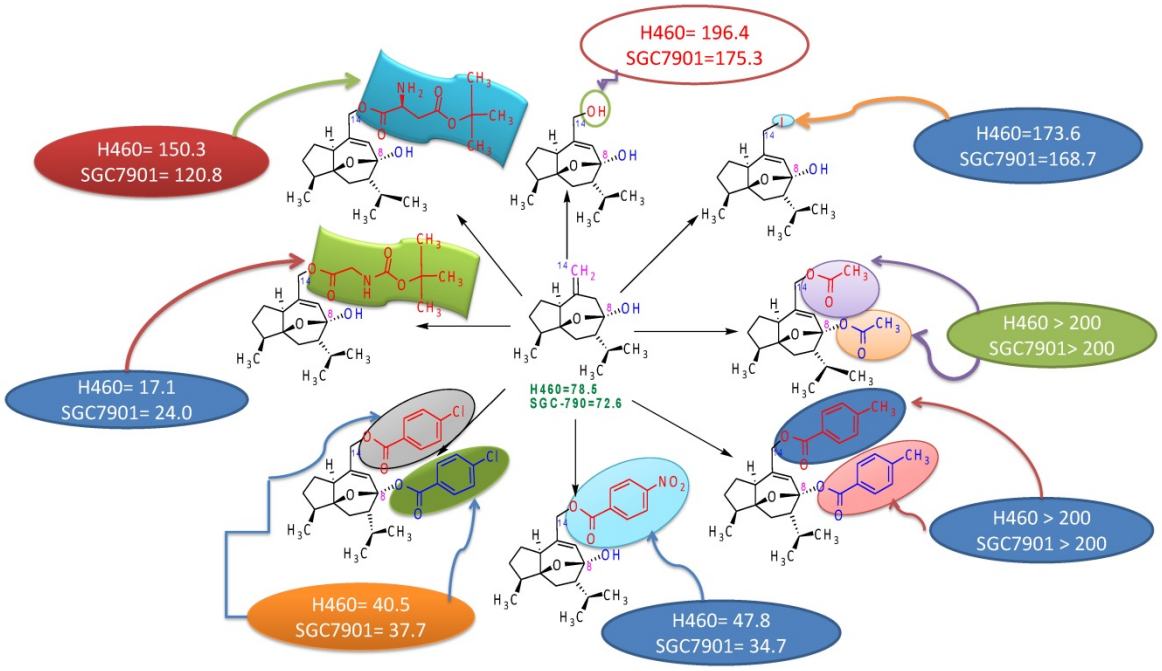

Figure 4. Structure activity relationship of curcumol.

4. *In vivo* studies and biosafety profiles

Curcumol has also been studied *in vivo* in CSLCs (cancer stem like cells) tumor-bearing mouse model induced by subcutaneous inoculation of JEG-3 cells into the left flank of mouse. Oral administration of 200 mg/kg curcumol on daily basis for 10 days resulted in significant shrinkage in both tumor volume and weight. More interestingly, curcumol treated mouse survived longer as compared to DMSO/control group. Thus, curcumol has the potential to inhibit the stemness capability of choriocarcinoma CSLCs [29]. In another study, curcumol was investigated in xenograft tumor mouse model in which cancer was induced by subcutaneous injections of NPC 5-8F cells. Administration of curcumol at the concentration of 15 μg/kg crude drug by gavage two times a day for 35 days significantly inhibited tumor growth. Curcumol treated group also showed reduced expression of TGF-β1 and N-cadherin while increased expression of E-cadherin resulting in blockage of epithelial-mesenchymal transition [66]. LoVo cells xenografted mouse model showed 70% inhibition of tumor without any loss in body weight when curcumol was administered at the dose of 80 mg/kg [56]. Combined treatment of celecoxib and curcumol for 6 days inhibited the tumor metastasis and invasion in mouse model xenografted by tail vein injection of A549 cells into nude mouse. Furthermore, researchers have clearly declared that administration of curcumol alone or in combination with celecoxib induced no distinct toxicity and no alterations in body or liver weight [64]. However, to access the biosafety profiles of curcumol, investigations affiliated with the identification of nephrotoxicity, genotoxicity and reproductive toxicity should be conducted in the future. Moreover, it is also suggested that multitudinal *in vivo* studies should be executed in future to assess the efficacy of curcumol as chemotherapeutic agent in combinatorial therapies.

5. Structure activity relationship

Studies to discover the structure-activity relationship of curcumol revealed that position-8 and position-14 are very important in improving the antitumor activity of curcumol. Electron-withdrawing groups increase the antitumor activity of curcumol as observed by comparing the activities of different derivatives of curcumol (Figure 4) [91, 92]. Presence of free hydroxyl at position-8 is responsible for increased antitumor activity but if this hydroxyl has esterified; then it led to significant decrease in antitumor activity. For example, 14-hydroxy curcumol (derivative 1) showed 196.4 activity against lung carcinoma cell line H460 and 175.3 against gastric cancer cell line SGC-790 due to presence of free hydroxyl at position-14 in place of double bond (=) in comparison to curcumol which showed activity 78.5 against lung carcinoma cell line H460 and 72.6 against gastric cancer cell line SGC-790. This comparison showed a much enhanced increment in activity by substitution of double bond with hydroxyl group. Similarly, comparison of derivative 1 with 14-iodocurcumol revealed that the substitution of hydroxyl group at position-14 by iodine led to a

decrease in antitumor activity (Figure 4).

Thus, it has been concluded that the structure-activity relationship of curcumol depends upon substituents present at position-8 and 14. The enhanced antitumor activity of curcumol is due to the presence of free hydroxyl & cyclic structure. The substitution of double bond by electron withdrawing group also led to an enhanced increment in antitumor activity [91].

6. Conclusions and future recommendations

In this article, we have focused on the progress of curcumol as anticancer agent. Collectively, data from various investigations have provided imperative clues for key role of curcumol in treatment of cancer. Curcumol exhibits wide range of toxicity against numerous cancer cell lines. This anticancer sesquiterpenoid fights against cancer development and progression by cell cycle arrest, apoptosis induction, and regulation of various signaling cascades followed by modulation of cell cycle mediators, apoptosis related proteins, transcriptional factors, protein kinases, cytokines, and growth receptors. After the critical evaluation of reported data, we found that curcumol shows most potent anticancer activity against LoVo cancerous cells with IC_{50} of 0.11 µM. Thus, it is strongly recommended to conduct further mechanistic studies because colorectal cancer is the 3rd most reported cancer of men and the 2nd in women around the world. Curcumol might serve as an attractive candidate as it has the capability to repress self-renewal of cancer stem cells. Thus, further investigations should be conducted in order to explore its potential against cancer stem cells (CSCs) because CSCs have novel therapeutic opportunity to combat with deadly diseases like cancer. As curcumol has been isolated from various traditional Chinese medicines and being an important constituent of turmeric which is a principal spice in Southeast Asia, it might turns up as safe chemotherapeutic agent in future. Moreover, curcumol possesses *in vitro* efficacy and selectivity suggesting that further *in vivo* studies, preclinical and clinical analysis should be conducted to assure the potential of curcumol for therapeutic indication. It is anticipated that assembled information will pave a new path for research community towards authentication and establishment of this natural cancer killer as a felicitous pharmacological drug in the near future.

Abbreviations

↑: Upregulation; ↓: Downregulation; ⊥: Inhibition; Act: Activation; Bax: Bcl-2-associated x protein; Bcl-2: B-cell lymphoma 2; JNK: c-Jun N-terminal kinase; JAK2: Janus kinase 2; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK: Mitogen-activated protein kinase; TNF-α: Tumor necrosis factor-α; ROS: Reactive oxygen species; CDK2: Cyclin-dependent kinase 2; Chk2: Checkpoint kinase 2; STAT-3: Signal transducer and activator of transcription 3; CDK8: Cyclin-dependent kinase 8; Cip1/p21: Cyclin-dependent kinase inhibitor p21; ERK: Extracellular signal-regulated kinase; MMP: Metalloproteinase; PI3K: Phosphatidylinositol-3-kinase; PCNA: Proliferating cell nuclear antigen (PCNA); IGF-1: Insulin-like growth factor 1; PARP1: Poly (ADP-ribose) polymerase; PUMA: p53 upregulated modulator of apoptosis (PUMA).

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Competing Interests

The authors have declared that no competing interest exists.

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