A Review of Curcumin and It's Derivatives as Anticancer Agent

Miss. Shital Nana Valkunde, Miss. Akshata Netaji Wagh, Miss. Mayuri Vijay More,
Miss. Sakshi Gangadhar Hingane, Ms. Vidhya Atole

Institute of Pharmaceutical Sciences and Research (for girls)(College Code-6914), Pune, Maharashtra, India.
Pharmaceuticals Chemistry Department.

ABSTRACT

Cancer is the second leading cause of death in the world and one of the major public health problems. Despite the great advances in cancer therapy, the incidence and mortality rates of cancer remain high. Therefore, the quest for more efficient and less toxic cancer treatment strategies is still at the forefront of current research. Curcumin, the active ingredient of the Curcuma longa plant, has received great attention over the past two decades as an antioxidant, antiinflammatory, and anticancer agent. In this review, a summary of the medicinal chemistry and pharmacology of curcumin and its derivatives in regard to anticancer activity, their main mechanisms of action, and cellular targets has been provided based on the literature data from the experimental and clinical evaluation of curcumin in cancer cell lines, animal models, and human subjects. In addition, the recent advances in the drug delivery systems for curcumin delivery to cancer cells have been highlighted.

Keywords: Curcumin, Anticancer, Structure activity relationship, Cellular pathway, Mechanism of action, Delivery system

INTRODUCTION

Cancer is the second most life-threatening disease and one of the main public health problems worldwide. In 2018, there were around 1.73 million new cases of cancer and more than 609,000 deaths in the United States alone [1]. Despite the tangible advances in cancer therapy, the reported incidence of the disease and the mortality
have not declined in the past 30 years [2]. Understanding the molecular alterations that contribute to cancer development and progression is a key factor in cancer prevention and treatment. There are several common strategies for targeting specific cancer cells to inhibit tumor development, progression, and metastasis without causing severe side effects [3]. In addition to the chemically synthesized anticancer agents, several anticancer compounds with different modes of action have been extracted from plant sources, such as Taxus brevifolia, Catharanthus roseus, Betula Alba, Cephalotaxus species, Erythroxylum previllei, Curcuma longa, and many others [4]. Among them, curcumin is the most important component of the rhizomes of Curcuma longa L. (turmeric) [5] and was extracted from turmeric plant in a pure crystalline form for the first time in 1870 [6]. Curcumin and its derivatives have received immense attention in the past two decades due to their biofunctional properties such as anti-tumor, antioxidant, and anti-inflammatory activities [7]. These properties are attributed to the key elements in the curcumin structure [8]. Due to the importance of cancer as a leading cause of death and the ongoing quest for more efficient and less toxic anticancer agents, this review has mainly focused on the anticancer activity of curcumin. The applications of curcumin in other diseases are beyond the scope of this review and have been reviewed elsewhere [4,9].

The main mechanisms of action by which curcumin exhibits its unique anticancer activity include inducing apoptosis and inhibiting proliferation and invasion of tumors by suppressing a variety of cellular signaling pathways [10]. Several studies reported curcumin’s antitumor activity on breast cancer, lung cancer, head and neck squamous cell carcinoma, prostate cancer, and brain tumors [11], showing its capability to target multiple cancer cell lines. This review focuses on the recent literature on the SAR of curcumin and its analogues and their anticancer activity in different cancer cell lines, animal models, and human clinical trials as well as different types of curcumin delivery systems that have been used for cancer therapy.

1. Curcumin
Curcumin (diferuloylmethane) is the chief component of the spice turmeric and is derived from the rhizome of the East Indian plant Curcuma longa. Curcuma longa is a member of the Zingiberaceae (ginger) family of botanicals and is a perennial plant that is native to Southeast Asia [18]. Turmeric contains a class of compounds known as
the curcuminoids, comprised of curcumin, demethoxycurcumin and bisdemethoxycurcumin (Figure 3) [19]. Curcumin is the principal curcuminoid and comprises approximately 2-5% of turmeric; it is responsible for the yellow color of the spice as well as the majority of turmeric's therapeutic effects [18]. Aside from being employed as a flavoring and coloring agent in food, turmeric has also been widely used in Ayurvedic medicine for its anti-oxidant, antiseptic, analgesic, antimalarial and anti-inflammatory properties [20]. Curcumin has been consumed as a dietary supplement for centuries and is considered pharmacologically safe [21].
Different Type of Curcumin Delivery Systems Used In Cancer Therapy

Various delivery systems for curcumin have been formulated using different nanotechnologies in order to improve curcumin properties and targetability. For the rational design of the nanoformulations, several factors should be considered in order to enhance the efficacy and improve the cellular targeting of the anticancer agents. These factors include the nanoparticle size and shape, surface properties, and nanoparticle targeting ligands, as illustrated in Figure 4. A summary of the most commonly used curcumin delivery systems is introduced in this section.
2.1. Polymeric Nanoparticles

Various polymers have been utilized to prepare nanoformulations for curcumin drug delivery to improve its biological activity. The biocompatible and biodegradable polymers are preferred in the drug delivery systems due to lower risk of toxicity. Therefore, biodegradable synthetic polymers such as PLGA (poly (D, L-lactic-co-glycolic acid) and natural polymers such as silk fibroin and chitosan have become widely used in drug delivery. PLGA-curcumin nanoformulation was found to be as effective as curcumin at 15-fold lower concentration in inhibiting mRNAs for inflammatory cytokines (CXCR3 and CXCL10) and increasing antiinflammatory cytokine interleukin-10 (IL-10) in the brain. In vivo study in rats showed that the bioavailability of curcumin-PLGA nanospheres was increased nine-fold in comparison to unprocessed curcumin administrated with alkaloid compound piperine. However, curcumin/piperine coadministration enhanced curcumin activity by inhibiting hepatic and intestinal deactivation.

2.2. Nanogels

Although hydrogels and nanogels have gained considerable attention in the past decade as a promising drug delivery system, only a few studies have investigated the curcumin-nanogel delivery in cancer therapy. There are several polymeric hydrogel nanoparticle systems that have been prepared recently using synthetic or natural polymers. Among the natural polymers, chitosan, chitin, and alginate are the most studied for the preparation of nanogels in drug delivery. On the other hand, the most commonly used synthetic polymers are polyvinyl alcohol (PVA), polyethylene oxide (PEO), polyethyleneimine (PEI), polyvinyl pyrrolidone (PVP). One of the main advantages of natural hydrogels over synthetic ones when used in drug delivery is biodegradability and biocompatibility. curcumin-loaded chitin nanogel has been used as a transdermal system for the treatment of skin cancer and has shown more specific toxicity towards human skin melanoma (A375) in comparison to human dermal fibroblast (HDF) cells without compromising the antitumor activity of curcumin. His delivery system demonstrated very high entrapment efficiency, and a significant difference in cell proliferation was observed between the cells treated with unprocessed curcumin and the cells treated with curcumin-loaded hybrid nanogel.

2.3. Liposomes

Nanoscale liposomes are emerging as one of the most useful drug delivery systems for anticancer agents. Recent advances in liposome formulations have resulted in improved treatment for drugresistant tumors and reduced toxicity. Liposome consists of a phospholipid bilayer shell and an aqueous core which makes it an ideal carrier for encapsulating both hydrophobic and hydrophilic compounds. Several liposome preparations have been utilized to encapsulate curcumin. The liposomal lipid bilayer (such as egg yolk phosphatidyl choline (EYPC), dihexyl phosphate (DHP) and cholesterol) solubilizes curcumin. This preparation was found to stabilize loaded curcumin proportionally to its content. Another work on liposomes tested coating liposomes with lipid–polymer conjugate
N-dodecyl chitosan-N-[(2-hydroxy-3-trimethylamine) propyl] (HPTMA) chloride. Positively charged nanoliposomes for curcumin delivery have also been developed by incorporating polyethylene glycol (PEG) and cationic polyethyleneimine (PEI) into the formulation. Despite low encapsulation efficiency (45%), this formulation has demonstrated twenty-fold higher cytotoxic activity than unprocessed curcumin in various cell lines, including human HepG2 hepatocellular carcinoma, A549 lung carcinoma, HT29 colorectal carcinoma, and cervical carcinoma. In liposomal gene delivery, an interesting work conducted by Fujita et al. utilized curcumin to control siRNA release. By incorporating curcumin into the liposomal formula, siRNA release showed a bell-shaped pattern due to the dose-dependent increase in liposomal permeability induced by curcumin. Curcumin-loaded liposomes were also used to inhibit the production of IL-6 in macrophages. The liposomes were prepared by mixing curcumin solution with human serum albumin (HSA) solution and subsequently adding this mixture to a lipid mixture containing 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-dipalmitoyl-sn-glycero-3-phospho-L-serine sodium salt (DPPS) and cholesterol. The designed system induced significant IL-6 suppression and reduction in the total number of macrophages.

3. Anticancer Activity Of Curcumin

One of the main causes of cancer is the loss of balance between cell proliferation and cell death. When the cells skip death due to the absence of the apoptotic signals, uncontrolled cell proliferation occurs, leading to different types of cancer. The apoptotic signals are generated through two major pathways: the intrinsic pathway and the extrinsic pathway. The intrinsic pathway works through stimulating the mitochondrial membrane to inhibit expression of anti-apoptotic proteins Bcl-2 and Bcl-XL. Curcumin disturbs the balance in the mitochondrial membrane potential, leading to enhanced suppression of the Bcl-XL protein. The extrinsic apoptotic pathway works through increasing the death receptors (DRs) on cells and triggering the tumor necrosis factor (TNF)-related apoptosis. Curcumin also contributes to this pathway by up-regulating the expression of death receptors DR 4 and DR 5. A recent work has found a new anticancer mechanism for curcumin by decreasing the glucose uptake and lactate production (Warburg effect) in cancer cells via downregulation of pyruvate kinase M2 (PKM2). Several studies have investigated the ability of curcumin and its derivatives to suppress multiple different carcinomas by interacting with different molecular targets (Figure 5).
4. In Vitro and In Vivo Studies

Curcumin has shown very promising results in suppressing cancer cell growth and proliferation in several different types of cancer, such as prostate, colorectal, breast, pancreatic, brain, head, and neck cancers. What comes next is a summary of the anticancer activity of curcumin and its derivatives in different types of cancer based on the data from in vitro studies in different cancer cell lines and animal studies.

5. Recommend Dosage of Curcumin

a) Curcumin Paste - 1/2 - 1 teaspoon or as per your requirements
b) Curcumin Oil - 2 - 5 drops or as per your requirement.
c) Curcumin Powder - 1/2 - 1 teaspoon or as per your requirement.

6. Adverse effects of Curcumin

d) nausea, vomiting, upset stomach.
e) constipation, indigestion.
f) bloating.
g) diarrhea.

7. Precaution:

a) Avoid turmeric and curcumin in individuals with bile duct obstruction, cholangitis (bile duct inflammation), Liver disease, gallstones, or any biliary disease.

b) Curcumin in food is considered safe. However, taking large amounts of turmeric and curcumin in supplement form for long periods of time may cause stomach upset and, in extreme cases, ulcers.

c) People who have gallstones or obstruction of the bile passages should talk to their doctor before taking curcumin.
8. Conclusions and Future Perspective
Curcumin, the active ingredient of the Curcuma longa extract, has been studied widely over the past few decades for its anti-inflammatory, antioxidant, anticancer, and antiandrogenic effects. Curcumin has shown considerable anticancer effects against several different types of cancer, including prostate cancer, breast cancer, colorectal cancer, pancreatic cancer, and head and neck cancer both in vitro and in vivo. Furthermore, its efficacy and safety in cancer patients either alone or in combination with other anticancer agents has been proven in several clinical studies with human subjects. Curcumin is believed to exert its anticancer activity via multiple mechanisms, interfering with different cellular pathways and inducing/inhibiting the production of various types of cytokines, enzymes or growth factors such as MAPK, EGF, NFκB, PKD1, COX-2, STAT3, TNF-α, and IκB. However, the anticancer application of curcumin has been limited mainly due to its low water solubility, which results in low cellular uptake and poor oral bioavailability, as well as low chemical stability. In order to overcome these limitations, different approaches have been made, such as structural modification and the use of drug delivery systems. The key pharmacophores contributing to the biological activity of curcumin are known to be the hydrogen donor group, the β-diketone moiety, the phenyl rings, and the substituent groups on them. Chemical modification of these moieties has led to curcumin derivatives with higher efficacy and/or enhanced water solubility or stability. In addition, various types of delivery systems have been developed for curcumin delivery to cancer cells or animal xenografts using a variety of natural or synthetic polymers, lipids, or proteins, some of which have improved the stability and/or cellular uptake of curcumin, thus giving rise to a stronger anticancer response.

9. References
1. Siegel R.L., Miller K.D., Jemal A. Cancer statistics, 2018. CA Cancer J. Clin. 2018;68:7–30. doi: 10.3322/caac.21442.

2. Gupta A.P., Pandotra P., Sharma R., Kushwaha M., Gupta S. Studies in Natural Products Chemistry. Volume 40. Elsevier; Amsterdam, The Netherlands: 2013. Chapter 8—Marine Resource: A Promising Future for Anticancer Drugs; pp. 229–325.

3. Umar A., Dunn B.K., Greenwald P. Future directions in cancer prevention. Nat. Rev. Cancer. 2012;12:835. doi: 10.1038/nrc3397.

4. Gupta A.P., Khan S., Manzoor M.M., Yadav A.K., Sharma G., Anand R., Gupta S. Chapter 10—Anticancer Curcumin: Natural Analogues and Structure-Activity Relationship. In: Atta ur
5. Alibeiki F., Jafari N., Karimi M., Peeri Dogaheh H. Potent anti-cancer effects of less polar Curcumin analogues on gastric adenocarcinoma and esophageal squamous cell carcinoma cells. *Sci. Rep.* 2017;7:2559. doi: 10.1038/s41598-017-02666-4.

6. Goel A., Kunnumakkara A.B., Aggarwal B.B. Curcumin as —Curecuminl: From kitchen to clinic. *Biochem. Pharm.* 2008;75:787–809. doi: 10.1016/j.bcp.2007.08.016.

7. Nagahama K., Utsumi T., Kumano T., Maekawa S., Oyama N., Kawakami J. Discovery of a new function of curcumin which enhances its anticancer therapeutic potency. *Sci. Rep.* 2016;6:30962. doi: 10.1038/srep30962.

8. Aggarwal B.B., Deb L., Prasad S. Curcumin differs from tetrahydrocurcumin for molecular targets, signaling pathways and cellular responses. *Molecules.* 2014;20:185–205. doi: 10.3390/molecules20010185.

9. Gera M., Sharma N., Ghosh M., Huynh D.L., Lee S.J., Min T., Kwon T., Jeong D.K. Nanoformulations of curcumin: An emerging paradigm for improved remedial application. *Oncotarget.* 2017;8:66680–66698. doi: 10.18632/oncotarget.19164.

10. Kunnumakkara A.B., Bordoloi D., Padmavathi G., Monisha J., Roy N.K., Prasad S., Aggarwal B.B. Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. *Br. J. Pharm.* 2017;174:1325–1348. doi: 10.1111/bph.13621.

11. Anand P., Sundaram C., Jhurani S., Kunnumakkara A.B., Aggarwal B.B. Curcumin and cancer: An —old-age disease with an —age-old solution. *Cancer Lett.* 2008;267:133–164. doi: 10.1016/j.canlet.2008.03.025.

12. Barry J., Fritz M., Brender J.R., Smith P.E., Lee D.K., Ramamoorthy A. Determining the effects of lipophilic drugs on membrane structure by solid-state NMR spectroscopy: The case of the antioxidant curcumin. *J. Am. Chem. Soc.* 2009;131:4490–4498. doi: 10.1021/ja809217u.

13. Tsukamoto M., Kuroda K., Ramamoorthy A., Yasuhara K. Modulation of raft domains in a lipid bilayer by boundary-active curcumin. *Chem. Commun.* 2014;50:3427–3430. doi: 10.1039/c3cc47738j.
14. Koo H.-J., Shin S., Choi J.Y., Lee K.-H., Kim B.-T., Choe Y.S. Introduction of Methyl Groups at C2 and C6 Positions Enhances the Antiangiogenesis Activity of Curcumin. *Sci. Rep.* 2015;5:14205. doi: 10.1038/srep14205.

15. Agrawal A.K., Gupta C.M. Tuftsin-bearing liposomes in treatment of macrophage-based infections. *Adv. Drug Deliv. Rev.* 2000;41:135–146. doi: 10.1016/S0169-409X(99)00061-7.

16. Chen W.-F., Deng S.-L., Zhou B., Yang L., Liu Z.-L. Curcumin and its analogues as potent inhibitors of low density lipoprotein oxidation: H-atom abstraction from the phenolic groups and possible involvement of the 4-hydroxy-3-methoxyphenyl groups. *Free Radic. Biol. Med.* 2006;40:526–535. doi: 10.1016/j.freeradbiomed.2005.09.008.

17. Ohtsu H., Xiao Z., Ishida J., Nagai M., Wang H.K., Itokawa H., Su C.Y., Shih C., Chang E., et al. Antitumor agents. 217. Curcumin analogues as novel androgen receptor antagonists with potential as anti-prostate cancer agents. *J. Med. Chem.* 2002;45:5037–5042. doi: 10.1021/jm020200g.

18. Lin L., Shi Q., Su C.Y., Shih C.C., Lee K.H. Antitumor agents 247. New 4ethoxycarbonylethyl curcumin analogs as potential antiandrogenic agents. *Bioorg. Med. Chem.* 2006;14:2527–2534. doi: 10.1016/j.bmc.2005.11.034.

19. Shi Q., Shih C.C., Lee K.H. Novel Anti-Prostate Cancer Curcumin Analogues That Enhance Androgen Receptor Degradation Activity. *Anti-Cancer Agents Med. Chem.* 2009;9:904–912. doi: 10.2174/187152009789124655.

20. Cheng M.A., Chou F.-J., Wang K., Yang R., Ding J., Zhang Q., Li G., Yeh S., Xu D., Chang C. Androgen receptor (AR) degradation enhancer ASC-J9® in an FDA-approved formulated solution suppresses castration resistant prostate cancer cell growth. *Cancer Lett.* 2018;417:182–191. doi: 10.1016/j.canlet.2017.11.038

21. Lin T.H., Izumi K., Lee S.O., Lin W.J., Yeh S., Chang C. Anti-androgen receptor ASC-J9 versus anti-androgens MDV3100 (Enzalutamide) or Casodex (Bicalutamide) leads to opposite effects on prostate cancer metastasis via differential modulation of macrophage infiltration and STAT3-CCL2 signaling. *Cell Death Dis.* 2013;4:e764. doi: 10.1038/cddis.2013.270.

22. Verderio P., Pandolfi L., Mazzucchelli S., Marinozzi M.R., Vanna R., Gramatica F., Corsi F., Colombo M., Morasso C., Prosperi D. Antiproliferative Effect of ASC-J9 Delivered by PLGA Nanoparticles against Estrogen-Dependent Breast Cancer Cells. *Mol. Pharm.* 2014;11:2864–2875. doi: 10.1021/mp500222k.

23. Qiu X., Du Y., Lou B., Zuo Y., Shao W., Huo Y., Huang J., Yu Y., Zhou B., Du J., et al.
Synthesis and identification of new 4-arylidene curcumin analogues as potential anticancer agents targeting nuclear factor-kappaB signaling pathway. *J. Med. Chem.* 2010;53:8260–8273. doi: 10.1021/jm1004545

24. Ferrari E., Lazzari S., Marverti G., Pignedoli F., Spagnolo F., Saladini M. Synthesis, cytotoxic and combined cDDP activity of new stable curcumin derivatives. *Bioorg. Med. Chem.* 2009;17:3043–3052. doi: 10.1016/j.bmc.2009.03.016.

25. Cao Y.K., Li H.J., Song Z.F., Li Y., Huai Q.Y. Synthesis and biological evaluation of novel curcuminoid derivatives. *Molecules.* 2014;19:16349–16372. doi: 10.3390/molecules191016349.