Rovedar

Journal of Laboratory Animal Research. 2023; 2(6): 72-85
DOI: 10.58803/jclr.v2i4.82
http://jlar.rovedar.com/

Systematic Review

The Use of Curcumin in the Treatment of Colorectal, Breast, Lung, and Prostate Cancers: An *in vivo* Study Update

Ghasem Dolatkhah Laein[1], Samin Safarian[1], Saba Delasaeimarvi[2], Ghazaleh Sadat Ahmadi[1], Sima Dadfar[3], Elahe Bakhshi[4], and Amir Reza Rashidzade[5*]

[1]Medical Doctor, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Medical Doctor, Shahinfar Medical Faculty-Islamic Azad University of Mashhad, Iran
[3]Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Faculty of Pharmacy, Islamic Azad University, Damghan Branch, Damghan, Iran
[5]General Surgery Resident, Mashhad University of Medical Sciences, Mashhad, Iran

*** *Corresponding author:*** Amir Reza Rashidzade, General Surgery resident, Mashhad University of Medical Sciences, Mashhad, Iran. Email: rashidzade.a@gmail.com

ARTICLE INFO

Article History:
Received: 07/10/2023
Revised: 03/11/2023
Accepted: 10/11/2023
Published: 25/12/2023

Keywords:
Anti-cancer properties
Cancer treatment
Curcumin
In vivo studies

ABSTRACT

Introduction: Cancer is one of the most prevalent and complex diseases with diverse etiology and manifestations. Curcumin is a bioactive compound found in turmeric and could have therapeutic potential for cancer due to its antitumor properties. Curcumin's properties in treating various types of cancer have been reviewed in this systematic review based on *in vivo* studies.

Materials and methods: This systematic review focused on *in vivo* studies examining Curcumin's anti-cancer properties across a broad range of cancer types. PubMed, Google Scholar, and Scopus databases were searched to identify relevant articles. Researchers selected studies evaluating Curcumin's effects on cancer progression and development based on animal models. Final analyses were conducted on the data obtained from the selected articles. The included studies were published between 2000 and 2023.

Results: The current systematic review was based on 53 articles out of 412 eligible studies, which were selected from 770 articles of literature screened from 2000 to 2023. Based on this review, *in vivo* studies have demonstrated that curcumin can potentially treat various cancers. There is evidence that curcumin has significant anti-cancer properties, including tumor growth inhibition, metastasis inhibitory activity, and angiogenesis. Several studies have demonstrated the versatility and potential of curcumin in treating cancer.

Conclusion: Curcumin has considerable cancer treatment potential, based on the *in-vivo* studies. For curcumin to be considered an effective cancer therapy, further clinical research is needed between preclinical and clinical trials.

1. Introduction

One of the most significant public health problems in the world is cancer, which is the second life-threatening disease. The United States alone has seen more than 609,000 cancer deaths in 2018, with approximately 1.73 million new cases in 2018[1,2]. Although cancer therapy has been improved in recent decades, the incidence of mortality of cancer did not decline[3,4]**.** The prevention and treatment of cancer require understanding how molecular changes contribute to its development and progression. Targeting specific cancer cells is the most common strategy for inhibiting tumor growth, metastasis, and progression without causing severe side effects[3]. In recent years, evidence has accumulated that some infectious agents are capable of causing anti-tumor effects against different types of cancers, such as *Toxoplasma gondii*, *Trypanosoma cruzi*, *Trichinella spiralis*, and *Echinococcus granulosus*[4-7]. Herbal remedies play a vital

► *Cite this paper as*: Dolatkhah Laein G, Safarian S, Delasaeimarvi S, Ahmadi GS, Dadfar S, Bakhshi E, Rashidzade AR. The Use of Curcumin in the Treatment of Colorectal, Breast, Lung, and Prostate Cancers: An *in vivo* Study Update. Journal of Lab Animal Research. 2023; 2(6): 72-85.

role in veterinary medicine and medicine, offering natural solutions for inflammation and infectious diseases [8]. As well as chemically synthesized anti-cancer agents, several anti-cancer compounds have been extracted from plants with different modes of action, including *Taxus brevifolia, Betula alba, Erythroxylum previllei, Catharanthus roseus, Curcuma longa, Cephalotaxus*, *Phytosomes* species[9-13]. Curcumin is an essential component in turmeric plant rhizomes[14]. Curcumin and its derivatives have had bifunctional properties in the past two decades, such as antioxidant and anti-inflammatory effects[15]. The anti-cancer properties of curcumin have been demonstrated *in vitro* and *in vivo* at all stages of cancer growth, including the disease's promotion and initiation[16]. It is difficult for curcumin to cross the cell membrane since it forms hydrophobic and hydrogen bonding interactions with the membrane lipids. As a result, curcumin levels remain very low throughout the cytoplasm[17]. Curcumin nano formulated can overcome these challenges and increase their bioavailability. There is a strong correlation between nanodrug entrapment and the structure used to carry the nanodrugs during manufacturing[18]. They play an essential role in drug distribution, affecting the release profile from a transporter in terms of volume and magnitude[19]. Encapsulation efficiency gauges the absorption or trapping of bioactive compounds in nanostructures. It also indicates the speed of medication binding, correlating with the drug-to-carrier ratio. According to studies, nanotherapeutic increase curcumin's function *in vitro* and *in vivo* polymers, cyclodextrins, micelles, liposomes, conjugates, dendrimers, and nanostructures[20-22]. The first focus was on enhancing the absorption rate constant of curcumin[22]. Later, they emphasized targeting curcumin in diseased areas using antibodies, peptides, or aptamers[23]. A study was conducted to investigate the oral bioavailability of curcumin encapsulated within biodegradable poly (lactic-co-glycolic acid) nanomaterials, and it found that nano curcumin was nine times more effective than unencapsulated curcumin in treating various conditions[24]. Studies have also shown that nano curcumin is effective against liver and cardiac diseases, brain tumors, and cancerous lesions[25, 26]. A wide range of pharmacological properties of curcumin have been reported in recent studies, including its benefits against type II diabetes, Alzheimer's disease, multiple sclerosis, rheumatoid arthritis, and atherosclerosis[27-30]. Curcumin suppresses thrombosis and inhibits the replication of human immunodeficiency virus (HIV) and platelet aggregation[31]. Curcumin prevents liver damage, cataract development, pulmonary toxicity, and fibrosis by enhancing wound healing[32-34]. According to studies, curcumin is an effective treatment and prevention agent for a wide range of cancers, including gastrointestinal, breast, melanoma, hematological, colorectal, lung, neurological, head and neck, and sarcoma[35-37]. This systemic review aimed to investigated the immunomodulatory effects of curcumin in cancer treatments.

2. Materials and Methods

The purpose of this study is, using a systematic review methodology to highlight the immunomodulatory properties of curcumin, with the latest research suggesting its effectiveness in the treatment of various types of cancer. Data bases such as SID, MagIran, ScienceDirect, Google Scholar, PubMed, Scopus, and Web of Science, used to extract the findings from those studies. Several databases were searched extensively, and results were selected based on keywords. Keywords included curcumin, *in vivo*, and cancer. Other search terms used in this study were "colorectal cancer," "lung cancer," "turmeric extract," and "prostate cancer," "breast cancer,". The reference lists of systematic reviews and relevant articles were reviewed to ensure the search was comprehensive. A standardized form for data extraction was used, including study characteristics (author, study design publication year), experimental details (such as treatment durations, animal models, curcumin dosages), outcomes of interest (such as tumor size molecular pathways, apoptosis rates,), and other side effects. The current systematic review was based on 53 articles out of 412 eligible studies selected from 770 articles of literature screened from 2000 to 2023. A systematic review excludes unpublished data, duplicate papers, and abstracts of congress proceedings (Figure 1).

3. What is curcumin?

Turmeric is a rhizome from *Curcuma longa Linn* herb that has many uses for preventing and treating disease[38]. There are numerous curcuminoids in turmeric powder, including bisdemethoxycurcumin (3%), demethoxycurcumin (17%), curcumin (77%), and others (3%)[39]. Curcumin is a polyphenol (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)[40]. Curcumin treats a wide range of diseases, including asthma, allergies, coughs, bronchial hyperactivity, sinusitis, anorexia, coryza, and hepatitis[41]. Many studies show its anti-inflammatory, antioxidant, anti-infectious, hepatoprotective, thrombosuppressive, cardioprotective, chemopreventive, anti-arthritic, and anticarcinogenic properties[42, 43]. Curcumin has also modulated several molecular targets in the body. Curcumin and its analogs have also been found in the *Costus speciosus, Curcuma mangga, Curcuma zedoaria, Curcuma phaeocaulis, Curcuma xanthorrhiza, Curcuma aromatic, Zingiber cassumunar plants*, and *Etlingera elatior*[44].

3.1. Bioavailability of curcumin

Even though curcumin has excellent potential for treating cancer diseases, its bioavailability, and low solubility in water have limited its clinical development. Clinical trials have indicated that when curcumin is administered orally for 8 grams daily, it rapidly transforms into metabolites, resulting in a low level of free curcumin in plasma (5ng/mL)[45]. Numerous efforts have been made to improve curcumin's solubility, stability, and bioavailability. Chemical synthesis or Chemical modifications of its analogs have been adopted as a strategy for achieving derivatives of curcumin. The molecule's oxyphenyl and carbon chain

components are crucial for its anti-tumor effects. Many studies have focused on chemically changing the abovementioned key sites, obtaining promising results[46, 47]. For instance, reduced viability of MCF-7 cells and increased oral bioavailability of the compound have been reported[48].

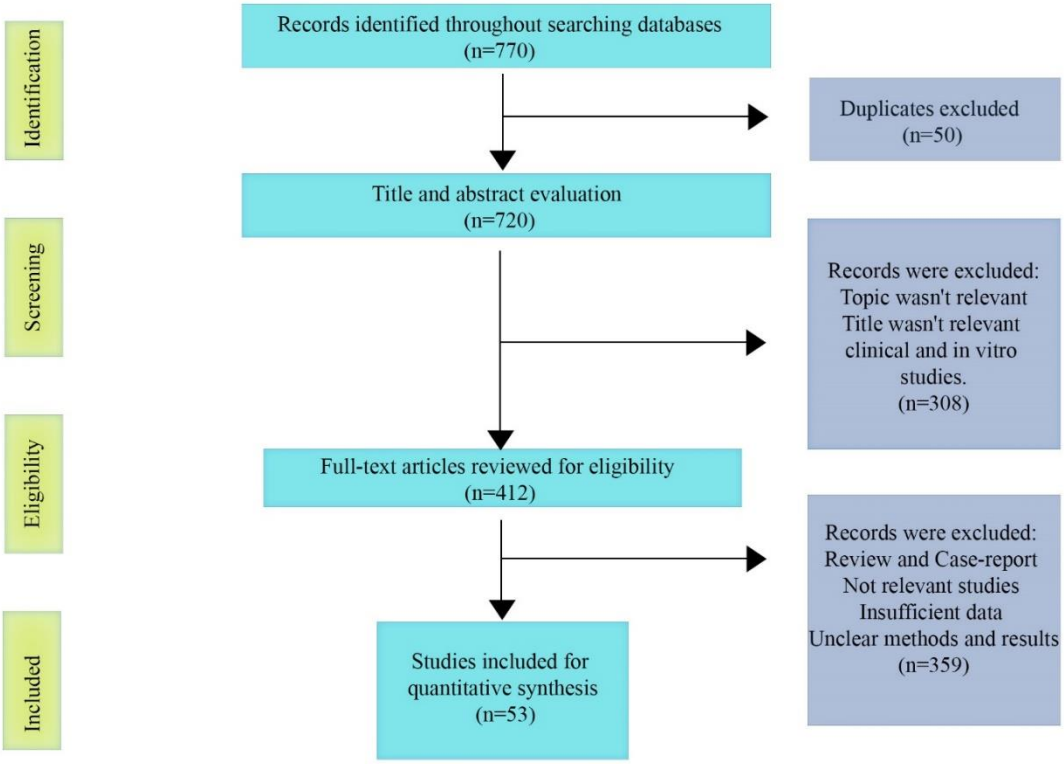

Figure 1. The methodology of the current systematic review to extract information from relevant studies published in national and international databases.

There has been evidence that two promising nano curcumin formulations, LipocurcTM (liposomal curcumin for infusion) and Meriva® have increased the bioavailability of curcumin and improved clinical outcomes in patients with pancreatic cancer and lymphocytic leukemia[49-51]. In 50 chronic myeloid leukemia patients, curcumin and imatinib (tyrosine kinase inhibitor) were evaluated for their therapeutic effects[52]. The mixed treatment was more effective than imatinib alone, although further research is needed to confirm its properties.

4. Mechanism of curcumin as an anti-cancer agent

4.1. Curcumin and adhesion molecules

An imbalance between cell death and proliferation is a major contributor to cancer, as uncontrolled cell proliferation, with cells evading death, can lead to various types of cancer[53]. Apoptotic signals are generated through extrinsic and intrinsic pathways. The intrinsic pathway inhibits the expression of B-cell lymphoma 2 (Bcl-2), and B-cell lymphoma-extra-large by induction of the mitochondrial membrane[54]. There is evidence that curcumin can disrupt the balance of mitochondrial membrane potential, thereby increasing the suppression of Bcl-xL in the mitochondria[55]. Alternatively, the extrinsic apoptotic pathway induces apoptosis associated with stimulating Death Receptors (DRs) and Tumor Necrosis Factor (TNF). As part of this pathway, curcumin is responsible for upregulating the expression of DR4 and DR[56]. Studies *in vivo* have suggested that curcumin and its derivatives can stimulate apoptosis in various cell lines by suppressing or downregulating intracellular transcription factors[57, 58]. The transcription factors involved in these pathways include Cyclooxygenase II (COX-2), Matrix Metalloproteinase-9 (MMP-9), Nuclear Factor-Kappa B (NF-κB), Signal Transducer and Activator of Transcription 3 (STAT3), Activator Protein 1 (AP-1), and nitric oxide synthase[59, 60]. Additionally, curcumin may exert its anti-cancer effect by inhibiting lactate production and glucose uptake in cancer cells by inhibiting Pyruvate Kinase M2 (PKM2)[61]. A method of suppressing PKM2 was effective by inhibiting the Mammalian Target of Rapamycin-Hypoxia-Inducible Factor 1α (mTOR-HIF1α)[62]. Curcumin induces apoptosis in CL-5 xenograft tumors and reduction in cyclin D1, Mesenchymal Epithelial Transition Factor (c-Met), Akt, and Epidermal Growth Factor Receptors (EGFRs)[63, 64]. Curcumin reduced lung-cell invasion and metastasis by upregulating HLJ1 expression in cancer cells[65]. Along with the activity of curcumin on Nuclear Factor-κB (NF-κB) and STAT3 signaling cascades, curcumin also suppressed cell cycle arrest and cell proliferation and induced apoptosis by modulating other transcription factors, including Notch-1, Erg-1, PPAR-α, p53, Hif-1, β-catenin, and AP-1[66, 67]. Researchers have demonstrated that curcumin inhibits the

phosphorylation of Focal Adhesion Kinase (FAK) and increases the expression of multiple Extra Cellular Matrix (ECM) components, which play a role in the metastasis and invasion of cancer cells[67]. These findings suggest that curcumin inhibits the action of FAK by suppressing its phosphorylation sites, improving cell adhesion, and ultimately preventing cancer cells from migrating and detaching[68]. According to one study by Zhou et al.[69], curcumin-associated compounds (containing benzyl piperidone moieties) showed activity in various cancer cell lines. They also found that some of these compounds inhibited the phosphorylation of extracellular signal-regulated kinases (Erk) 1/2 and phosphorylation of Akt. As a result of FAK suppression, cell adhesion was increased, eventually contributing to curcumin's anti-invasive properties. Curcumin reduced the expression of CD24 in colorectal cancer cells in a dose-dependent[70]. The expression of E-cadherin was increased by curcumin, which suppressed epithelial-mesenchymal transition. A study in colorectal cancer cells has shown that curcumin inhibits metastasis by downregulating CD24, FAK, and Sp-1 expression and stimulating E-cadherin expression[71]. Apoptosis in hepatocellular carcinoma cells and epithelial ovarian tumor cells may be triggered by the curcumin analog B19, and autophagy and endoplasmic reticulum (ER) stress may play a significant role in the process[72, 73]. It has been suggested that autophagy suppression may increase apoptosis induced by curcumin analogs by causing severe ER stress[74]. Curcumin analogs also induce autophagy and ER stress in ovarian cancer cell lines[75].

Several extracellular matrix components, which play an essential role in invasion and metastasis, are enhanced by curcumin, including FAK phosphorylation[76]. Curcumin may inhibit metastasis in colorectal cancer by down-regulating Sp-1, FAK, and CD24 and increasing E-cadherin expression[77].

4.2. Curcumin and endoplasmic reticulum

The Endoplasmic Reticulum (ER) is crucial to proteins' cellular synthesis and maturation. Various pathological conditions have been shown to interfere with the homeostasis of the ER and impair protein folding, causing an imbalance in the capacity and load of the ER to fold proteins and resulting in the accumulation of misfolded and unfolded proteins[78]. The condition is commonly referred to as ER stress. The autophagy pathway is a conserved proteolysis pathway in eukaryotes[79]. In addition to being an essential survival mechanism under metabolic stress, autophagy plays a critical role in protein homeostasis[80]. Protease-associated degradation and autophagy-activated autophagy are two pathways by which the proteasome degrades ubiquitinated proteins. In addition to regulating cellular homeostasis, autophagy has been shown to prevent cell damage and protect cells from nutrient deprivation[81]. Recent studies have demonstrated that unfolded protein response signaling may also significantly impact interactions within the microenvironment of cancer cells[82, 83]. It has been shown that folding proteins, autophagy, and ER stress-induced apoptosis are associated with cancer cell proliferation[84]. Anti-cancer treatments may activate this signaling pathway, possibly enhancing cancer cell death or chemotherapy resistance[85]. According to recent data, curcumin analog B19 induces apoptosis through ER stress and autophagy in epithelial ovarian tumor cells and hepatocellular carcinoma cells[86]. As a result of severe ER stress caused by autophagy inhibition, curcumin analogue-induced apoptosis may be increased. Curcumin analogs may induce apoptosis, ER stress, and autophagy *in vitro* in ovarian cancer cells[75]. A recent study found that curcumin inhibited the growth of gliomas by activating autophagy, a type II programmed cell death[74].

4.3. Curcumin and Sp-1

The transcription factor Sp-1 is highly expressed in breast, gastric, and thyroid tumor cells[87]. Studies showed that this transcription factor can interact with both a co-activator and co-repressor and, as a result, activate multiple specific biological functions, including the cell cycle and carcinogenesis[88, 89]. It is essential for interacting nuclear factors with proteins and binding sequence-specific DNA binding. Several housekeeping genes, including urokinase plasminogen activator receptors (uPARs), vascular epithelial growth factors (VEGF), epithelial growth factor receptors (EGFR), and urokinase plasminogen activator (uPA), are known to influence cell differentiation, metastasis, and tumor angiogenesis[90, 91]. Further, inhibiting Sp-1 and its housekeeping genes may provide a valuable hypothesis for preventing metastases, formation, and invasion[65, 67]. As reported in a recent study, curcumin inhibits Sp-1 activation and downstream genes, such as ADEM10, calmodulin (CALM), SEPP1, and EPHB2, according to a concentration-dependent mechanism in colorectal cancer cell lines[92]. According to other studies, curcumin suppresses Sp-1 activity in bladder cancer cells and reduces Sp-1 DNA binding activity in Non-small cell lung carcinoma (NSCLC)[93].

5. Anti-cancer activity of curcumin

The imbalance between cell proliferation and death, caused by the absence of apoptotic signals, contributes to various types of cancer as cells undergo uncontrolled proliferation[94]. Studies *in vivo* have demonstrated that curcumin and its derivatives inhibit or downregulate the activity of intracellular transcription factors, thereby causing apoptosis in different cell lines[95]. Several studies have identified curcumin and its derivatives as potential anti-cancer agents by interacting with various molecular targets[92, 96]. It has been shown that it can suppress the growth and proliferation of cancer cells in a variety of cancer types, including breast, prostate, lung, and colorectal cancer[97]. The following section summarizes data from *in vitro* and animal studies reporting curcumin and its derivatives' anti-cancer effects.

5.1. Prostate cancer

Both *in vitro* and *in vivo*, curcumin has demonstrated a solid ability to inhibit prostate cell proliferation and induce

apoptosis through interference with several cellular pathways, including Epidermal Growth Factor Receptors (EGFRs), Mitogen-Activated Protein Kinases (MAPKs), and nuclear factor κ (NFκB)[98]. A recent study has revealed that curcumin can activate Protein kinase D1 (PKD1), which attenuates oncogenic signaling by β-catenin and MAPK, ultimately inhibiting prostate cancer[99]. The PKD1 expression was significantly downregulated after prostate cancer transitioned from an androgen-dependent to an androgen-independent state, as well as to affect prostate cancer invasion and motility through its interaction with E-cadherin[100]. Thus, it has been considered as a potential new therapeutic target for the treatment of cancer in general as well as prostate cancer in particular[101]. Other curcumin derivatives have also been shown to have anti-cancer properties against prostate cancer in addition to curcumin[37, 102, 103]. As can be seen in Figure 2, DNA complexes conjugated with metallocurcumin exhibited significant toxicity against prostate cancer cells (LNCaP, DU145, PC3, 22Rv1, and TRAMP-C1)[104].

5.2. Colorectal cancer

As the third most common form of cancer, colorectal cancer ranks third behind lung and prostate cancer[105]. Although colorectal carcinoma patients undergo surgery and chemotherapy to remove tumor tissue, more than half suffer recurrences. There was a reduction in M (1) G levels

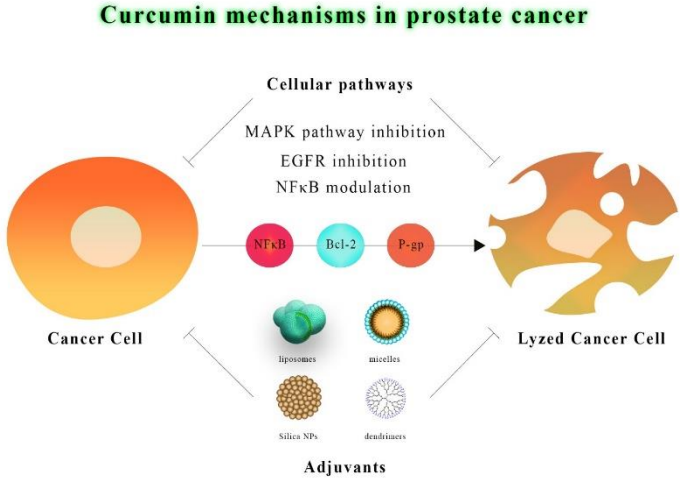

Figure 2. Curcumin's multilayered impact on prostate cancer. The figure highlights the modulation of crucial cellular pathways such as mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR), and nuclear factor κ (NFκB) by curcumin, showcasing its multi-faceted effects on prostate cancer cells. The diagram further details the activation of Protein Kinase D1 (PKD1) by curcumin, elucidating its role in attenuating oncogenic signaling, particularly in the context of β-catenin and MAPK pathways. Additionally, the figure represents the specific action of curcumin in enhancing androgen receptor degradation in androgen-dependent prostate cancer. Furthermore, the visual illustrates the toxic impact of Metallo-curcumin conjugated DNA complexes on prostate cancer cells, providing a comprehensive overview of the diverse strategies employed by curcumin in combating prostate cancer at the molecular level.

in cancer colorectal cells when curcumin was administered without affecting COX-2 protein levels[106]. Additionally, curcumin treatment inhibited AP-1 (activator protein) from binding to the *miR-21* promoter, inhibiting overexpression of miR-21 in colorectal cancer cells [107]. Through *miR-21* gene regulation, curcumin inhibited tumor tissue growth by arresting the cell cycle in the G2/M phase in HCT 116 colorectal cancer cells[107]. According to an *in vivo* study conducted on mice with colorectal cancer, curcumin was more effective than radiation therapy when combined with radiation as it can target Nuclear Factor (NF)[108].

5.3. Breast Cancer

There has been an alarming increase in breast cancer death rates among women over the past few decades[109]. According to a meta-analysis of 21 retrospective studies, breast cancer recurrence rates are still high despite chemotherapy, lumpectomy, radiation therapy, and endocrine therapy[110]. As a result, more effective therapeutic strategies are still needed. According to a study involving MCF-7 breast cancer cells and MCF-10A human mammary epithelial cells, curcumin treatment substantially reduced telomerase activity[111]. This effect was correlated with curcumin's ability to downregulate hTERT but not via the c-Myc mRNA pathway. Curcumin's effects on matrix metalloproteinases (MMPs), cell proliferation regulation proteins, and nuclear factor-B have been evaluated in BT-483 and MDA-MB-231 breast cancer cell lines[112]. After treatment with curcumin, it was observed that cyclic D1 levels in MDA-MB-231 cells and CDK4 levels in BT-483 cell lines decreased. Similar to previous studies on other breast cancer cell lines, this study confirms that curcumin inhibits proliferation by downregulating NF-B. The combination of arabinogalactan and curcumin-induced apoptosis in MDA-MB-231 cells by increasing ROS levels, disrupting mitochondrial membranes, and decreasing glutathione levels[113, 114]. Additionally, curcumin inhibits breast tumor growth by overexpressing the *p53* gene and reducing levels of antigen ki-67 [115]. Moreover, curcumin has also been shown to inhibit the production of inflammatory cytokines CXCL1/2 in MDA-MB-231 cells[116]. As a result of curcumin inhibiting CXCL1 and 2, multiple metastasis-promoting genes, such as CXCR4, are inhibited. Furthermore, dimethyl curcumin (ASC-J9) inhibits several types of steroid receptors, which may be effective in treating estrogen-dependent breast cancer[117, 118].

5.4. Lung cancer

A lung cancer diagnosis is one of the most common cancer diagnoses among men and the third most common among women[119]. In addition to surgery, chemotherapy, radiation therapy, and immunotherapy are all standard treatments for lung cancer[120]. A study of the therapeutic potential of turmeric in lung cancer therapy showed that it acts on a Wnt/β-catenin-dependent pathway in the human lung cancer cell line A549[121]. In the same cell line, curcumin suppresses the expression of Vascular Endothelial Growth Factor (VEGF) and NF-κB expression[122]. In lung cancer cells, Curcumin inhibited the Enhancer of Zest Homolog 2 (EZH2) expression, decreasing Notch 1 expression[123]. Various

studies have demonstrated that curcumin inhibits cell proliferation, increases apoptosis, and prevents the G2/M phase of Non-Small-Cell Lung Cancer (NSCLC). Furthermore, curcumin produces Reactive Oxygen Species (ROS), which activates the DNA damage signaling pathway[124]. In a recent study, a low dose of curcumin was administered to NSCLC cells for an extended period. Metastatic and invasion potential of the cancer cells was significantly suppressed in curcumin at doses range of 0.25-0.5 M[125]. Using curcumin derivatives against NSCLC cells with ALK rearrangements has also shown promising results, even when those cells become resistant to ALK inhibitors[126]. Cancer cells are sensitive to chemotherapeutic agents due to the extracellular signal-regulated kinase pathway (ERK). Curcumin's selective targeting of it causes a 75% reduction in the expression of ERK ½[127, 128]. Phosphoinositide 3-kinase (PI3K)/Akt-dependent pathways are associated with cell proliferation and apoptosis in several cancer cell lines, but the available data regarding the relationship between PI3K/Akt pathways and apoptosis are inconsistent[129]. Some drugs induce apoptosis in cancer cells by stimulating this pathway, while others inhibit it. The new curcumin derivative T59 has been shown to activate PI3K/Akt and induce apoptosis in lung cancer cells[130]. However, another study found that curcumin, combined with Paris Saponin 2 (PS2), inhibited the PI3K-Akt pathway and induced apoptosis[131].

6. Potential side effects of curcumin

According to the US Food and Drug Administration (FDA), curcumin is "generally safe." The literature does not indicate any significant side effects associated with curcumin[132]. It has been documented that some of the side effects are reversible, including allergic dermatitis[133]. According to the results of dose-escalation studies, consuming up to 12 grams of curcumin daily has no adverse effects[134]. When curcumin was administered to patients with solid tumors orally at 900 mg/day for eight weeks, no adverse effects were reported except mild gastrointestinal discomfort[135]. Patients with breast cancer also reported no adverse effects from taking 6 grams of curcumin every day for seven weeks, and prostate cancer patients reported no adverse effects from 3 grams of curcumin taken daily for nine weeks[136]. The curcumin compound also exhibits a strong ability to chelate iron[137]. As a result of long-term curcumin supplementation in mice, iron depletion was enhanced when low-iron diets were fed to the mice[138]. In addition, curcumin is an anticoagulant and is likely to cause bleeding time to increase in patients taking anticoagulants[139]. While curcumin has no overt adverse effects, several P450 subtypes, including CYP2C9 and CYP3A4, have been reported to be inhibited by this compound[140]. Therefore, curcumin may interact with other medications, such as antibiotics, antidepressants, and anticoagulants. A warfarin and clopidogrel pharmacokinetics study in Wistar rats found that curcumin increased the elimination half-life and distribution volume of norfloxacin[141].

7. Therapeutic activity of curcumin nanoformulations

Several curcumin nanoformulations have been developed so far. Most nanoformulations have improved curcumin's solubility and bioavailability while protecting it from hydrolysis inactivation[142]. Most nanoformulations focus on intracellular delivery and long-term drug retention, while some concentrate on prolonged circulation and retention. Nanoformulations used to improve the retention and circulation of drugs within the body, whereas others have been developed to enhance intracellular delivery[143].

7.1. Liposomes

A liposome is a spherical vesicle composed of multiple or single phospholipid bilayers that closely resemble the structure of a cell membrane[144]. The liposome is a perfect delivery vehicle for biologically active substances *in vitro* and *in vivo*[145]. Liposomes provide several advantages, including excellent stability, controlled distribution, easy preparation, high biodegradability, biocompatibility, targeting specific cells, flexibility, better solubility, and minimal toxicity[146]. Therefore, scientists consider liposomes to be the most effective drug-carrier system, and they are preferred by many. The number and size of bilayers influence liposomal drug capsulation in the liposome. Thus, the size of the vesicle is a crucial factor in estimating liposome circulation time. The diameter of liposomes ranges from 2.5 to 25 mm[147]. According to numerous studies, liposomes help dissolve curcumin in phospholipid bilayers, allowing curcumin to be dispersed across aqueous media and enhancing curcumin's effectiveness[148]. Moreover, liposomal drugs accumulate mainly in the bone marrow, spleen, lung, liver, and other tissues and organs. As a result, the side effects of drugs are further reduced, and their therapeutic index is improved. According to Dhule et al. 2012, liposomal curcumin demonstrated powerful anti-cancer effects *in vitro* and *in vivo* against breast cancer cell lines MCF-7 and KHOS OS[149]. Research has examined curcumin liposomes' biochemical processes and antitumor activity in PC-3 human prostate cancer cells. Compared to free CUR, liposomes of CUR had a lower survival rate in PC-3 cells. Liposomes also absorbed curcumin more efficiently, resulting in a longer and higher fluorescence intensity than in the control group. In addition, reverse transcription-polymerase chain reaction and western blot analyses were used to determine messenger RNA (mRNA) and matrix metalloproteinase-2 (MMP-2) levels. According to experiments, curcumin liposomes can facilitate the absorption of drug-loaded liposomes to enhance cytotoxic effects in PC-3 cells. MMP-2-mRNA levels and proteins decreased gradually after curcumin liposome concentrations increased along with MMP-2-mRNA levels. The MMP-2 concentration was simultaneously downregulated in PC-3 cells. Additionally, Tefas et al. 2017 formulated liposomes with Curcumin and doxorubicin, reducing cell proliferation in C26 murine colon cancer cells

and demonstrating enhanced cytotoxicity compared to free Curcumin[150].

An *in vitro* study has shown that liposomal curcumin stimulates apoptosis and dose-dependent growth suppression in two human colorectal cancer cell lines (including Colo205 and LoVo cells) by producing poly (ADP-ribose) polymerase and 3 (4,5-dimethylthiazol-2-yl)-5 (3 carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium salt)[151]. Similarly, curcumin-encapsulated liposomes were highly encapsulating, predominantly polydisperse, and smaller in particle size. The use of blue light-emitting diodes (BLED) combined with curcumin liposome nanocarriers (LIP-CUR) was found to generate excellent anti-cancer effects and bioactivity (BLED-PDT)[152]. The study showed that aqueous-soluble F127-CUR is capable of mediating curcumin's anti-cancer action and can facilitate BLED-PDT-mediated apoptosis as well as mediating its anti-cancer action. The BLED-PDT activity of aqueous-soluble F127-CUR was higher in cancer cells than in those receiving free curcumin. Based on these findings, liposomes might be an effective carrier for curcumin[63].

7.2. Nanoparticles

A nanoparticle's diameter ranges from 1 to 100 nm, which makes it useful for drug delivery because of its unique biological, physical, and chemical properties[153]. Nanoparticles are a thousand times smaller than average cells in the human body. The encapsulation of drugs within nanoparticles can enhance their solubility and pharmacokinetic properties, allowing them to be released, controlled, and targeted. Curcumin has been used with solid lipid, albumin, gold, magnetic, and polymer-based nanoparticles to improve therapeutic effects[154].

7.3. Conjugates

The conjugate complex is created when two or more molecules are combined, especially by a covalent bond. A hydrophilic polymer and small molecule conjugation of curcumin increases its solubility and oral bioavailability. In a study published by Manjuand Sreenivasan, curcumin conjugated with hyaluronic acid reduced the effects of gold nanoparticles (AuNPs) and improved their aqueous stability[155]. According to Muangnoi et al.[156], a curcumin-glutaric acid prodrug (CURDG) was created via ester linkages and evaluated in mouse cancer models. The gold nanoparticle–PVP–curcumin conjugate (PVP–C–AuNPs) has been shown to hinder the aggregation of Aβ (1–6) while facilitating prolonged drug release and enhancing curcumin bioavailability[157]. The bioavailability of curcumin can be enhanced by piperine (an alkaloid derived from black pepper). Further, this alkaloid enhances compound absorption by forming brush borders on the intestinal lining[158]. Piperine also inhibits UDP glucuronosyl transferases and cytochrome p450s, which may affect cell metabolism. The action of piperine is also exerted on p-glycoproteins[159]. Using piperine combined with curcumin significantly increased serum levels of curcumin in humans and animals by 2,000 times because of the extensive absorption and bioavailability. Several polycurcumins have been reported to be cytotoxic to cancer cells. However, there have been reports that polyacetal-based polycurcumins are more cytotoxic toward MCF-7 breast cancer cell lines and the SKOV-3 and OVCAR-3 ovarian cancer cells. Cancerous cells can also rapidly absorb them, where polyacetal-based polycurcumin is hydrolyzed and released as active curcumin. According to *in vitro* studies, it inhibited the G0/G1 phase of the cell cycle in SKOV-3 cells and stimulated the apoptosis of those cells partly via the caspase-3 pathway. The intravenous administration of polyacetal-based polycurcumin resulted in significant antitumor activity against SKOV-3 intraperitoneal xenografts[160].

7.4. Cyclodextrins (CD)

α-, β-, and γ-CDs are multi-component hybrid, soluble carrier systems for non-covalently bound drugs. These bucket-shaped oligosaccharides consist of 6 (α-), 7 (β-), or 8 (γ-) D-glucopyranose units linked via an α-1, 4-glycosidic bond to form macrocycles.Numerous researchers have demonstrated the role of CD in the delivery of curcumin in recent years[161]. The β-CD, γ-CD, and their derivatives were widely used due to their easy synthesis and low cost in the delivery of drugs and adaptability. Yallapu et al.2010 demonstrated a significant increase in CUR distribution and therapeutic value in prostate cancer cells compared to unformulated CUR using a β- CD-facilitated curcumin drug delivery system[162]. Zhang et al. 2016 observed that the formulation of cyclodextrin with curcumin (CD15) caused lung cancer cells to experience cell cycle arrest and increased apoptosis compared to curcumin alone[163]. Moreover, the experimental findings of this study indicated that CD15 enhances curcumin delivery and is effective in treating lung cancer. Nanoparticles were developed by hyaluronic acid, sulfobutyl-ether-β-cyclodextrin, and chitosan, without or with curcumin, and used to treat intestinal epithelial cells and colorectal cancer[164]. According to the results of a study, curcumin nanoparticles were more stable and more effective at encapsulation. Additionally, it reduced the potency of curcumin as a cytotoxic agent in normal intestinal epithelial cells and reduced the proliferation of cancer cells. In retinitis pigmentosa, Curcumin and CD complexes mediated increased solubility and prolonged drug release. The findings assisted in formulating eye drops that are derived from natural phytochemicals. Zhang et al.[163] investigated the effects of curcumin-CDs on cellular uptake and anti-cancer activity. Compared to free curcumin, curcumin-CDs provided improved delivery of

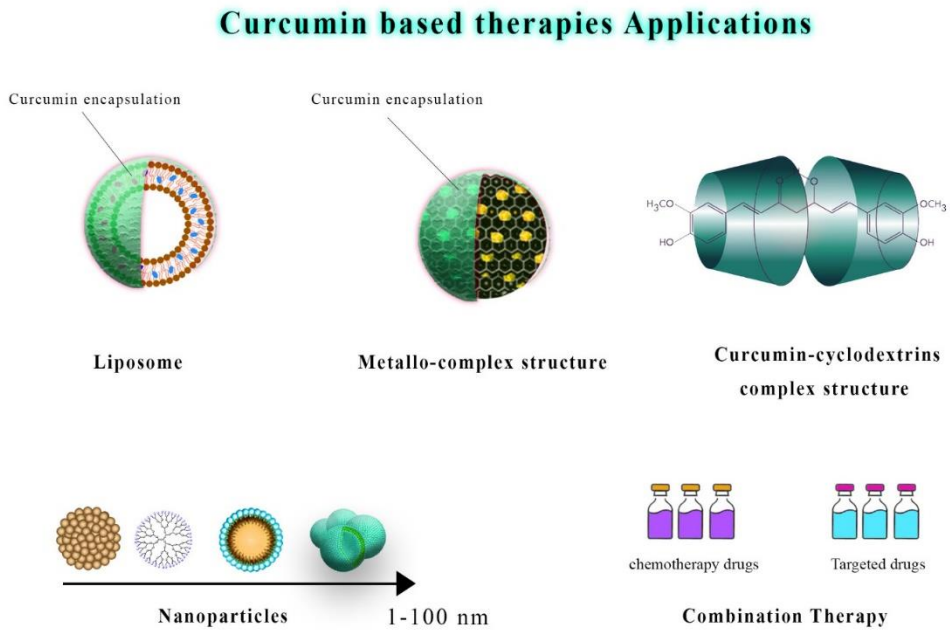

Figure 3. Curcumin in combination therapy for enhanced cancer treatment

curcumin and increased curcumin's therapeutic efficacy *in vivo* and *in vitro*[163]. Therefore, curcumin -CDs inhibit CyclinE-CDK2 combinations, increase the p53/p21 signaling cascade, and elevate Bax/caspase-3 expression to induce G1-phase arrest and cellar apoptosis through the regulation of MAPK/NF-B signaling pathways. According to these findings, curcumin-CDs can improve the delivery of CUR to tumors and its therapeutic potential[163].

7.5. Metallo-Complexes

The palladium (II) complexes of curcumin (CUR) displayed potent antitumor activity against HeLa, A549 and MCF-7 cancer cells[165]. Furthermore, further studies revealed that these complexes perturbed mitochondrial membrane potential, causing tumor cells to undergo apoptosis, and the cell cycle was arrested in the S phase. A study by Vellampatti et al.2018 found that metallo-CUR-conjugated DNA complexes exhibited significant toxic effects on prostate cancer cells compared to pristine DNA[104]. A further study evaluated the cellular uptake of these complexes and found that DNA complexes containing Cu2+/Ni2+-CUR displayed brighter fluorescence than those containing Zn2+-CUR (Figure 3).

Illustrations depicting key aspects of curcumin-based therapies. In the first set, liposomal structures are detailed, emphasizing their phospholipid bilayer composition, curcumin encapsulation, targeted delivery to specific cells, and *in vivo* effects, showcasing reduced side effects and improved therapeutic index compared to free curcumin. The second set focuses on nanoparticles, showcasing their varied structures, drug delivery capabilities, and widespread use in improving curcumin's therapeutic applications. The third set explores cyclodextrins, highlighting their bucket-shaped structures, role in curcumin delivery systems, and formation of water-soluble complexes, potentially enhancing curcumin's efficacy. The fourth set delves into metallo-complexes, outlining their structures, potent antitumor actions, ROS-dependent cascades, and cellular uptake mechanisms. Finally, the combination therapy set illustrates the conceptual framework, synergistic effects, cellular-level interactions, and potential clinical applications of combining curcumin with other therapeutic agents, offering a comprehensive view of the multi-faceted landscape of curcumin-based treatments.

8. Future challenges

While considerable effort has been made to improve curcumin's biological and physicochemical properties, several issues remain regarding the compound's bioavailability, specificity, and potency to the target tissues[166]. Curcumin's pharmacological properties have not been significantly improved using medicinal chemistry approaches, nor have its derivatives demonstrated more potency than curcumin itself [17]. Because curcumin and its derivatives have low potency, higher doses need to be administered to achieve a therapeutic response, which results in increased adverse effects and poor patient compliance[167]. Efficacy and solubility are also challenging to balance, and in most cases, one is sacrificed for the other during structural modification[168]. Many structural modifications enhance curcumin's efficacy, reduce its solubility, and make it more hydrophobic[169, 170]. To overcome this problem, it is required to conduct more studies. Various approaches have been used to improve curcumin's cellular uptake and efficacy, but most of these formulations have been at the proof-of-concept stage instead of clinical testing[171, 172]. Before these curcumin

delivery systems can reach the pharmaceutical market, no clinical studies are designed to evaluate their safety and efficacy. Furthermore, most drug delivery systems developed for curcumin do not target a specific tissue. Curcumin delivery systems still need to be improved to enhance their selectivity for specific tumor types[173, 174]. As a result of tissue-specific delivery, curcumin concentrations are enhanced in the target tissue, resulting in improved efficacy (with lower doses) and fewer side effects[175, 176].

9. Conclusion

This systematic review examined the availability of *in vivo* studies on using curcumin in treating colorectal, breast, lung, and prostate cancer. According to the combined evidence presented in the included studies, curcumin is potentially effective against various types of cancer, highlighting its numerous anti-cancer properties. Researchers have found that curcumin inhibits tumor growth, induces apoptosis, suppresses angiogenesis, and modulates several cellular signaling pathways against cancer. Considering its broad spectrum of action, curcumin may be used as a complementary treatment and an adjunct therapy for these common types of cancer. Although there were some limitations to this systematic review, it is important to acknowledge those limitations and challenges. As a result of this systematic review, curcumin has the potential to be a promising anti-cancer agent against colorectal, lung, prostate, and breast. It is essential to approach these results with cautious optimism to recognize the need to conduct further rigorous research to reduce the gap between preclinical promise and clinical application. It is clear that curcumin has excellent potential as a cancer treatment agent, and further study of its potential is warranted to achieve more effective and holistic cancer treatments.

Declarations

Competing interests

The authors declare no conflict of interest.

Authors' contributions

Amir Reza Rashidzad primarily carried out the conceptualization of the project, while the initial writing and preparation of the original draft involved the collaborative efforts of Ghasem Dolatkhah Laein, Samin Safarian, and Saba Delasaeimarvi. Subsequently, the project underwent thorough review and editing, with contributions from Ghazale Sadat Ahmadi, Sima Dadfar, and Elahe Bakhshi. The project was self-funded, and Amir Reza Rashidzade supervised its development.

All authors checked and approved the final version of the manuscript for publication in the present journal.

Funding

The authors received no funding to perform the study.

Ethical considerations

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68(1): 7-30. DOI: 10.3322/caac.21442
1. Qasemi A, Lagzian M, Bayat Z. Cancer and COVID-19: a double burden on the healthcare system. Iran Red Crescent Med J. 2023; 25(2): e2662. DOI: 10.32592/ircmj.2023.25.2.2662
2. Lee YT, Tan YJ, Oon CE. Molecular targeted therapy: Treating cancer with specificity. Eur J Pharmacol. 2018; 834: 188-196. DOI: 10.1016/j.ejphar.2018.07.034
3. Sadr S, Ghiassi S, Lotfalizadeh N, Simab PA, Hajjafari A, Borji H. Antitumor mechanisms of molecules secreted by Trypanosoma cruzi in colon and breast cancer: A review. Anti-cancer Agents Med Chem. 2023; 23(15):1710-1721. DOI: 10.2174/1871520623666230529141544
4. Sadr S, Borji H. Echinococcus granulosus as a promising therapeutic agent against triple-negative breast cancer. Curr Cancer Ther Rev. 2023; 19(4): 292-297. DOI: 10.2174/1573394719666230427094247
5. Sadr S, Yousefsani Z, Simab PA, Alizadeh AJR, Lotfalizadeh N, Borji H. Trichinella spiralis as a potential antitumor agent: An update. World Vet J. 2023; 13(1): 65-74. DOI: 10.54203/scil.2023.wvj7
6. Asouli A, Sadr S, Mohebalian H, Borji H. Anti-Tumor Effect of Protoscolex Hydatid Cyst Somatic Antigen on Inhibition Cell Growth of K562. Acta Parasitol. 2023: 1-8. DOI: 10.1007/s11686-023-00680-3
7. Ghaniei A, Ghafouri SA, Sadr S, Hassanbeigi N. Investigating the preventive effect of herbal medicine (*Allium sativum*, *Artemisia annua*, and *Quercus infectoria*) against coccidiosis in broiler chickens. J World's Poult Res. 2023; 13(1): 96-102. DOI: 10.36380/jwpr.2023.10
8. Tomeh MA, Hadianamrei R, Zhao X. A review of curcumin and its derivatives as anti-cancer agents. Int J Mol Sci. 2019; 20(5): 1033. DOI: 10.3390/ijms20051033
9. Vipasha S, Hardeep K, Tarun K, Tullika M. Traditional Indian herb Catharanthus roseus used as cancer treatment: a review. Int J Pharmacogn Phytochem Res. 2016; 8(12): 1926-1928. Available at: https://www.semanticscholar.org/paper/Traditional-Indian-Herb-Cathranthus-roseus-Used-as-Vipasha-Hardeep/caa1ced679c15e707b7eecae267515cd90f984f2
10. Sultana S, Munir N, Mahmood Z, Riaz M, Akram M, Rebezov M, et al. Molecular targets for the management of cancer using Curcuma longa Linn. phytoconstituents: A Review. Biomed Pharmacother. 2021; 135: 111078. DOI: 10.1016/j.biopha.2020.111078
11. Eckelbarger JD, Wilmot JT, Epperson MT, Thakur CS, Shum D, Antczak C, et al. Synthesis of antiproliferative Cephalotaxus esters and their evaluation against several human hematopoietic and solid tumor cell lines: uncovering differential susceptibilities to multidrug resistance. Chem-Eur J. 2008; 14(14): 4293-4306. DOI: 10.1002/chem.200701998
12. Saeed M, Sadr S, Gharib A, Lotfalizadeh N, Hajjafari A, Simab PA, et al. Phytosomes: A Promising Nanocarrier for Enhanced Delivery of Herbal Compounds in Cancer Therapy. J Lab Anim Res. 2022;1(1): 26-32. DOI: 10.58803/jlar.v1i1.8
13. Ochwang'i DO, Kimwele CN, Oduma JA, Gathumbi PK, Mbaria JM, Kiama SG. Medicinal plants used in treatment and management of cancer in Kakamega County, Kenya. J Ethnopharmacol. 2014; 151(3): 1040-1055. DOI: 10.1016/j.jep.2013.11.051
14. Luo W, Bai L, Zhang J, Li Z, Liu Y, Tang X, et al. Polysaccharides-based nanocarriers enhance the anti-inflammatory effect of curcumin. Carbohydr Polym. 2023: 120718. DOI: 10.1016/j.carbpol.2023.120718
15. Lv ZD, Liu XP, Zhao WJ, Dong Q, Li FN, Wang HB, et al. Curcumin induces apoptosis in breast cancer cells and inhibits tumor growth *in vitro* and

in vivo. Int J Clin Exp Pathol. 2014; 7(6): 2818.
Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097278/
16. Salem M, Rohani S, Gillies ER. Curcumin, a promising anti-cancer therapeutic: a review of its chemical properties, bioactivity and approaches to cancer cell delivery. RSC Adv. 2014; 4(21):10815-29. DOI: 10.1039/c3ra46396f
17. Ipar VS, Dsouza A, Devarajan PV. Enhancing curcumin oral bioavailability through nanoformulations. Eur J Drug Metab Pharmacokinet. 2019; 44: 459-480. DOI: 10.1007/s13318-019-00545-z
18. Zhao Y-Z, Lu C-T, Zhang Y, Xiao J, Zhao Y-P, Tian J-L, et al. Selection of high efficient transdermal lipid vesicle for curcumin skin delivery. Int J Pharm. 2013; 454(1): 302-309. DOI: 10.1016/j.ijpharm.2013.06.052
19. Sun M, Su X, Ding B, He X, Liu X, Yu A, et al. Advances in nanotechnology-based delivery systems for curcumin. Nanomedicine. 2012; 7(7):1085-1100. DOI: 10.2217/nnm.12.80
20. Drbohlavova J, Chomoucka J, Adam V, Ryvolova M, Eckschlager T, Hubalek J, et al. Nanocarriers for anti-cancer drugs-new trends in nanomedicine. Curr Drug Metab. 2013; 14(5): 547-564. DOI: 10.2174/1389200211314050005
21. Hafez Ghoran S, Calcaterra A, Abbasi M, Taktaz F, Nieselt K, Babaei E. Curcumin-based nanoformulations: A promising adjuvant towards cancer treatment. Molecules. 2022; 27(16): 5236. DOI: 10.3390/molecules27165236
22. Yallapu MM, Nagesh PKB, Jaggi M, Chauhan SC. Therapeutic applications of curcumin nanoformulations. AAPS J. 2015; 17: 1341-56. DOI: 10.1208/s12248-015-9811-z
23. Flora G, Gupta D, Tiwari A. Nanocurcumin: a promising therapeutic advancement over native curcumin. Crit Rev Ther Drug Carrier Syst. 2013; 30(4). DOI: 10.1615/CritRevTherDrugCarrierSyst.2013007236
24. Hassanizadeh S, Shojaei M, Bagherniya M, Orekhov AN, Sahebkar A. Effect of nano-curcumin on various diseases: A comprehensive review of clinical trials. Biofactors. 2023. DOI: 10.1002/biof.1932
25. Bhat A, Mahalakshmi AM, Ray B, Tuladhar S, Hediyal TA, Manthiannem E, et al. Benefits of curcumin in brain disorders. BioFactors. 2019; 45(5): 666-689. DOI: 10.1002/biof.1533
26. Den Hartogh DJ, Gabriel A, Tsiani E. Antidiabetic properties of curcumin II: evidence from *in vivo* studies. Nutrients. 2019; 12(1): 58. DOI: 10.3390/nu12010058
27. Chin D, Huebbe P, Pallauf K, Rimbach G. Neuroprotective properties of curcumin in Alzheimer's disease-merits and limitations. Curr Med Chem. 2013; 20(32) :3955-3985. DOI: 10.2174/09298673113209990210
28. Bagherniya M, Darand M, Askari G, Guest PC, Sathyapalan T, Sahebkar A. The clinical use of curcumin for the treatment of rheumatoid arthritis: A systematic review of clinical trials. Studies Biomark New Targets Aging Res Iran: Focus Turmeric Curcumin. 2021: 251-263. DOI: 10.1007/978-3-030-56153-6_15
29. Peng Y, Ao M, Dong B, Jiang Y, Yu L, Chen Z, et al. Anti-inflammatory effects of curcumin in the inflammatory diseases: Status, limitations and countermeasures. Drug Des Devel Ther. 2021: 4503-4525. DOI: 10.2147/DDDT.S327378
30. Gandapu U, Chaitanya R, Kishore G, Reddy RC, Kondapi AK. Curcumin-loaded apotransferrin nanoparticles provide efficient cellular uptake and effectively inhibit HIV-1 replication *in vitro*. PLoS One. 2011; 6(8): e23388. DOI: 10.1371/journal.pone.0023388
31. Asai A, Miyazawa T. Dietary curcuminoids prevent high-fat diet-induced lipid accumulation in rat liver and epididymal adipose tissue. J Nutr. 2001; 131(11): 2932-2935. DOI: 10.1093/jn/131.11.2932
32. Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Annu Rev Nutr. 2010; 30: 173-199. DOI: 10.1146/annurev.nutr.012809.104755
33. Jagetia GC, Aggarwal BB. "Spicing up" of the immune system by curcumin. J Clin Immunol. 2007; 27: 19-35. DOI: 10.1007/s10875-006-9066-7
34. Rahmani AH, Al Zohairy MA, Aly SM, Khan MA. Curcumin: a potential candidate in prevention of cancer via modulation of molecular pathways. BioMed Res Int. 2014. DOI: 10.1155/2014/761608
35. Gupta MK, Vadde R, Sarojamma V. Curcumin-a novel therapeutic agent in the prevention of colorectal cancer. Curr Drug Metab. 2019;20(12):977-987. DOI: 10.2174/1389200220666191007153238
36. Mbese Z, Khwaza V, Aderibigbe BA. Curcumin and its derivatives as potential therapeutic agents in prostate, colon and breast cancers. Molecules. 2019; 24(23): 4386. DOI: 10.3390/molecules24234386
37. Labban L. Medicinal and pharmacological properties of Turmeric (Curcuma longa): A review. Int J Pharm Biomed Sci. 2014; 5(1): 17-23. Available at:
https://www.semanticscholar.org/paper/Medicinal-and-pharmacological-properties-of-longa)%3A-Labban/ad02e6a362cc2c127527caa3ea81721d30b88b20
38. Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, et al. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. Carcinogenesis. 2007; 28(8): 1765-1773. DOI: 10.1093/carcin/bgm123
39. Chen WF, Deng SL, Zhou B, Yang L, Liu ZL. 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. 2006; 40(3): 526-535. DOI: 10.1016/j.freeradbiomed.2005.09.008
40. Shanmugam MK, Rane G, Kanchi MM, Arfuso F, Chinnathambi A, Zayed M, et al. The multi-faceted role of curcumin in cancer prevention and treatment. Molecules. 2015; 20(2): 2728-2769. DOI: 10.3390/molecules20022728
41. Qadir MI, Naqvi STQ, Muhammad SA, Qadir M, Naqvi ST. Curcumin: a polyphenol with molecular targets for cancer control. Asian Pac J Cancer Prev. 2016; 17(6): 2735-2739. PMID: 27356682
42. Shanmugam MK, Kannaiyan R, Sethi G. Targeting cell signaling and apoptotic pathways by dietary agents: role in the prevention and treatment of cancer. Nutr and Cancer. 2011; 63(2): 161-173. DOI: 10.1080/01635581.2011.523502
43. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. The molecular targets and therapeutic uses of curcumin in health and disease. 2007:1-75. DOI: 10.1007/978-0-387-46401-5_1
44. Kunati SR, Yang S, William BM, Xu Y. An LC-MS/MS method for simultaneous determination of curcumin, curcumin glucuronide and curcumin sulfate in a phase II clinical trial. J Pharm Biomed Anal. 2018; 156:189-198. DOI: 10.1016/j.jpba.2018.04.034
45. Zhao S, Pi C, Ye Y, Zhao L, Wei Y. Recent advances of analogues of curcumin for treatment of cancer. Eur J Med Chem. 2019; 180: 524-535. DOI: 10.1016/j.ejmech.2019.07.034
46. Krall N, Da Cruz FP, Boutureira O, Bernardes GJ. Site-selective protein-modification chemistry for basic biology and drug development. Nature Chemistry. 2016; 8(2): 103-113. DOI: 10.1038/nchem.2393
47. Liu C, Yang X, Wu W, Long Z, Xiao H, Luo F, et al. Elaboration of curcumin-loaded rice bran albumin nanoparticles formulation with increased *in vitro* bioactivity and *in vivo* bioavailability. Food Hydrocolloids. 2018; 77: 834-842. DOI: 10.1016/j.foodhyd.2017.11.027
48. Ranjan AP, Mukerjee A, Helson L, Gupta R, Vishwanatha JK. Efficacy of liposomal curcumin in a human pancreatic tumor xenograft model: inhibition of tumor growth and angiogenesis. Anti-cancer Res. 2013; 33(9): 3603-3609. PMID: 24023285
49. Golombick T, Diamond TH, Manoharan A, Ramakrishna R. The effect of curcumin (as Meriva) on absolute lymphocyte count (ALC), NK cells and T cell populations in patients with stage 0/1 chronic lymphocytic leukemia. 2015; 6 (7): 566-571. DOI: 10.4236/jct.2015.67061
50. Bolger GT, Licollari A, Tan A, Greil R, Vcelar B, Greil-Ressler S, et al. Pharmacokinetics of liposomal curcumin (Lipocurc™) infusion: Effect of co-medication in cancer patients and comparison with healthy individuals. Cancer Chemother Pharmacol. 2019; 83: 265-275. DOI: 10.1007/s00280-018-3730-5
51. Ghalaut VS, Sangwan L, Dahiya K, Ghalaut P, Dhankhar R, Saharan R. Effect of imatinib therapy with and without turmeric powder on nitric oxide levels in chronic myeloid leukemia. J Oncol Pharm Pract. 2012; 18(2):186-190. DOI: 10.1177/1078155211416530
52. Loftus LV, Amend SR, Pienta KJ. Interplay between cell death and cell proliferation reveals new strategies for cancer therapy. Int J Mol Sci. 2022; 23(9): 4723. DOI: 10.3390/ijms23094723
53. Tuorkey M. Curcumin a potent cancer preventive agent: Mechanisms of cancer cell killing. Interv Med Appl Sci. 2014; 6(4): 139-146. DOI: 10.1556/imas.6.2014.4.1
54. Zhou Q-M, Sun Y, Lu Y-Y, Zhang H, Chen Q-L, Su S-B. Curcumin reduces mitomycin C resistance in breast cancer stem cells by regulating Bcl-2 family-mediated apoptosis. Cancer Cell Int. 2017; 17(1):1-13. DOI: 10.1186/s12935-017-0453-3
55. Obaidi I, Cassidy H, Ibanez Gaspar V, McCaul J, Higgins M, Halász M, et al. Curcumin sensitizes kidney cancer cells to TRAIL-induced apoptosis via ROS mediated activation of JNK-CHOP pathway and upregulation of

DR4. Biology. 2020; 9(5): 92. DOI: 10.3390/biology9050092
56. Reuter S, Eifes S, Dicato M, Aggarwal BB, Diederich M. Modulation of anti-apoptotic and survival pathways by curcumin as a strategy to induce apoptosis in cancer cells. Biochem Pharmacol. 2008; 76(11): 1340-1351. DOI: 10.1016/j.bcp.2008.07.031
57. Shehzad A, Lee J, Lee YS. Curcumin in various cancers. Biofactors. 2013; 39(1): 56-68. DOI: 10.1002/biof.1068
58. Hahn YI, Kim SJ, Choi BY, Cho KC, Bandu R, Kim KP, et al. Curcumin interacts directly with the Cysteine 259 residue of STAT3 and induces apoptosis in H-Ras transformed human mammary epithelial cells. Sci Rep. 2018; 8(1): 6409. DOI: 10.1038/s41598-018-23840-2
59. Lee W-H, Loo C-Y, Young PM, Traini D, Mason RS, Rohanizadeh R. Recent advances in curcumin nanoformulation for cancer therapy. Expert Opin Drug Deliv. 2014; 11(8): 1183-1201. DOI: 10.1517/17425247.2014.916686
60. Monteiro F, Shetty SS. Natural antioxidants as inhibitors of pyruvate kinase M2 in Warburg phenotypes. J Herbal Med. 2023; 42: 100750. DOI: 10.1016/j.hermed.2023.100750
61. Siddiqui FA, Prakasam G, Chattopadhyay S, Rehman AU, Padder RA, Ansari MA, et al. Curcumin decreases Warburg effect in cancer cells by down-regulating pyruvate kinase M2 via mTOR-HIF1α inhibition. Sci Rep. 2018; 8(1): 8323. DOI: 10.1038/s41598-018-25524-3
62. Kabir MT, Rahman MH, Akter R, Behl T, Kaushik D, Mittal V, et al. Potential role of curcumin and its nanoformulations to treat various types of cancers. Biomolecules. 2021; 11(3): 392. DOI: 10.3390/biom11030392
63. Lee JY, Lee YM, Chang GC, Yu SL, Hsieh WY, Chen JJ, et al. Curcumin induces EGFR degradation in lung adenocarcinoma and modulates p38 activation in intestine: the versatile adjuvant for gefitinib therapy. PloS One. 2011; 6(8): e23756. DOI: 10.1371/journal.pone.0023756
64. Chen HW, Lee JY, Huang JY, Wang CC, Chen WJ, Su SF, et al. Curcumin inhibits lung cancer cell invasion and metastasis through the tumor suppressor HLJ1. Cancer Res. 2008; 68(18): 7428-7438. DOI: 10.1158/0008-5472.CAN-07-6734
65. Hackler Jr L, Ózsvári B, Gyuris M, Sipos P, Fábián G, Molnár E, et al. The curcumin analog C-150, influencing NF-κB, UPR and Akt/Notch pathways has potent anti-cancer activity *in vitro* and *in vivo*. PloS One. 2016;11(3):e0149832. DOI: 10.1371/journal.pone.0149832
66. Chen CC, Sureshbabul M, Chen HW, Lin YS, Lee JY, Hong QS, et al. Curcumin suppresses metastasis via Sp-1, FAK inhibition, and E-cadherin upregulation in colorectal cancer. Evid based Complement Altern Med. 2013. 541695. DOI: 10.1155/2013/541695
67. Choe SR, Kim YN, Park CG, Cho KH, Cho DY, Lee HY. RCP induces FAK phosphorylation and ovarian cancer cell invasion with inhibition by curcumin. Exp and Mol Med. 2018; 50(4): 1-10. DOI: 10.1038/s12276-018-0078-1
68. Zhou D-Y, Zhang K, Conney AH, Ding N, Cui X-X, Wang H, et al. Synthesis and evaluation of curcumin-related compounds containing benzyl piperidone for their effects on human cancer cells. Chem and Pharma Bull. 2013; 61(11): 1149-1155. DOI: 10.1248/cpb.c13-00507
69. Fan X, Zhu M, Qiu F, Li W, Wang M, Guo Y, et al. Curcumin may be a potential adjuvant treatment drug for colon cancer by targeting CD44. Inte Immunopharma. 2020; 88: 106991. DOI: 10.1016/j.intimp.2020.106991
70. Xu S, Jiang B, Wang H, Shen C, Chen H, Zeng L. Curcumin suppresses intestinal fibrosis by inhibition of PPARγ-mediated epithelial-mesenchymal transition. Evid Based Complementary Altern Med. 2017. DOI: 10.1155/2017/7876064
71. Limonta P, Moretti RM, Marzagalli M, Fontana F, Raimondi M, Montagnani Marelli M. Role of endoplasmic reticulum stress in the anti-cancer activity of natural compounds. Int JMol Sci. 2019; 20(4): 961. DOI: 10.3390/ijms20040961
72. Zhou T, Ye L, Bai Y, Sun A, Cox B, Liu D, et al. Autophagy and apoptosis in hepatocellular carcinoma induced by EF25-(GSH) 2: a novel curcumin analog. PloS One. 2014; 9(9): e107876. DOI: 10.1371/journal.pone.0107876
73. Aoki H, Takada Y, Kondo S, Sawaya R, Aggarwal BB, Kondo Y. Evidence that curcumin suppresses the growth of malignant gliomas *in vitro* and *in vivo* through induction of autophagy: role of Akt and extracellular signal-regulated kinase signaling pathways. Mol Pharmacol. 2007; 72(1): 29-39. DOI: 10.1124/mol.106.033167
74. Qu W, Xiao J, Zhang H, Chen Q, Wang Z, Shi H, et al. B19, a novel monocarbonyl analogue of curcumin, induces human ovarian cancer cell apoptosis via activation of endoplasmic reticulum stress and the autophagy signaling pathway. Int J Bio Sci. 2013; 9(8): 766. DOI: 10.7150/ijbs.5711
75. Deng Y, Verron E, Rohanizadeh R. Molecular mechanisms of anti-metastatic activity of curcumin. Anti-cancer Res. 2016; 36(11): 5639-5647. DOI: 10.21873/anticanres.11147
76. Jalili Nik M, Soltani A, Moussavi S, Ghayour-Mobarhan M, Ferns GA, Hassanian SM, et al. Current status and future prospective of Curcumin as a potential therapeutic agent in the treatment of colorectal cancer. J Cell Physio. 2018; 233(9): 6337-6345. DOI: 10.1002/jcp.26368
77. Clarke R, Cook KL, Hu R, Facey CO, Tavassoly I, Schwartz JL, et al. Endoplasmic reticulum stress, the unfolded protein response, autophagy, and the integrated regulation of breast cancer cell fate. Cancer Res. 2012;72(6):1321-1331. DOI: 10.1158/0008-5472.CAN-11-3213
78. Duprez J, Jonas JC. Role of activating transcription factor 3 in low glucose-and thapsigargin-induced apoptosis in cultured mouse islets. Biochem Biophys Res Commun. 2011; 415(2): 294-299. DOI: 10.1016/j.bbrc.2011.10.048
79. Marciniak SJ, Ron D. Endoplasmic reticulum stress signaling in disease. Phys rev. 2006; 86(4): 1133-1149. DOI: 10.1152/physrev.00015.2006
80. He L, Zhang J, Zhao J, Ma N, Kim SW, Qiao S, et al. Autophagy: the last defense against cellular nutritional stress. Adv Nutr. 2018; 9(4): 493-504. DOI: 10.1093/advances/nmy011
81. Ramirez MU, Hernandez SR, Soto-Pantoja DR, Cook KL. Endoplasmic reticulum stress pathway, the unfolded protein response, modulates immune function in the tumor microenvironment to impact tumor progression and therapeutic response. Int J Mol Sci. 2019; 21(1): 169. DOI: 10.3390/ijms21010169
82. Bartoszewska S, Collawn JF, Bartoszewski R. The role of the hypoxia-related unfolded protein response (UPR) in the tumor microenvironment. Cancers. 2022; 14(19): 4870. DOI: 10.3390/cancers14194870
83. Sisinni L, Pietrafesa M, Lepore S, Maddalena F, Condelli V, Esposito F, et al. Endoplasmic reticulum stress and unfolded protein response in breast cancer: the balance between apoptosis and autophagy and its role in drug resistance. Int J Mol Sci. 2019; 20(4): 857. DOI: 10.3390/ijms20040857
84. Kim R. Recent advances in understanding the cell death pathways activated by anti-cancer therapy. Cancer. 2005; 103(8):1551-1560. DOI: 10.1002/cncr.20947
85. Shakeri A, Zirak MR, Hayes AW, Reiter R, Karimi G. Curcumin and its analogues protect from endoplasmic reticulum stress: Mechanisms and pathways. Pharmacol res. 2019; 146: 104335. DOI: 10.1016/j.phrs.2019.104335
86. Vizcaíno C, Mansilla S, Portugal J. Sp1 transcription factor: A long-standing target in cancer chemotherapy. Pharmacol and therap. 2015; 52: 111-124. DOI: 10.1016/j.pharmthera.2015.05.008
87. Battaglia S, Maguire O, Campbell MJ. Transcription factor co-repressors in cancer biology: roles and targeting. Int J Cancer. 2010; 126(11): 2511-2519. DOI: 10.1002/ijc.25181
88. Siddappa M, Wani SA, Long MD, Leach DA, Mathé EA, Bevan CL, et al. Identification of transcription factor co-regulators that drive prostate cancer progression. Sci Rep. 2020; 10(1): 20332. DOI: 10.1038/s41598-020-77055-5
89. Leupold J, Yang H, Colburn N, Asangani I, Post S, Allgayer H. Tumor suppressor Pdcd4 inhibits invasion/intravasation and regulates *urokinase receptor* (*u-PAR*) gene expression via Sp-transcription factors. Oncogene. 2007; 26(31): 4550-4562. DOI: 10.1038/sj.onc.1210234
90. Zannetti A, Del Vecchio S, Carriero MV, Fonti R, Franco P, Botti G, et al. Coordinate up-regulation of Sp1 DNA-binding activity and urokinase receptor expression in breast carcinoma. Cancer res. 2000; 60(6): 1546-1551. Available at: https://aacrjournals.org/cancerres/article/60/6/1546/507319/Coordinate-Up-Regulation-of-Sp1-DNA-binding
91. Vallianou NG, Evangelopoulos A, Schizas N, Kazazis C. Potential anti-cancer properties and mechanisms of action of curcumin. Anti-cancer res. 2015; 35(2): 645-651. PMID: 25667441
92. Lou Z, O'Reilly S, Liang H, Maher VM, Sleight SD, McCormick JJ. Down-regulation of overexpressed sp1 protein in human fibrosarcoma cell lines inhibits tumor formation. Cancer res. 2005; 65(3): 1007-1017. DOI: 10.1158/0008-5472.1007.65.3
93. Matès JM, Segura JA, Alonso FJ, Márquez J. Intracellular redox status

and oxidative stress: implications for cell proliferation, apoptosis, and carcinogenesis. Arch toxicol. 2008; 82:273-299. DOI: 10.1007/s00204-008-0304-z
94. Wang M, Jiang S, Zhou L, Yu F, Ding H, Li P, et al. Potential mechanisms of action of curcumin for cancer prevention: focus on cellular signaling pathways and miRNAs. Int J bio sci. 2019; 15(6): 1200. DOI: 10.7150/ijbs.33710
95. Aggarwal BB, Kumar A, Bharti AC. Anti-cancer potential of curcumin: preclinical and clinical studies. Anti-cancer res. 2003; 23(1/A): 363-398. PMID: 12680238
96. Panda AK, Chakraborty D, Sarkar I, Khan T, Sa G. New insights into therapeutic activity and anti-cancer properties of curcumin. J Exp pharmacol. 2017: 31-45. DOI: 10.2147/JEP.S70568
97. Termini D, Den Hartogh DJ, Jaglanian A, Tsiani E. Curcumin against prostate cancer: current evidence. Biomolecules. 2020; 10(11): 1536. DOI: 10.3390/biom10111536
98. Sundram V, Chauhan SC, Ebeling M, Jaggi M. Curcumin attenuates β-catenin signaling in prostate cancer cells through activation of protein kinase D1. PloS one. 2012; 7(4): e35368. DOI: 10.1371/journal.pone.0035368
99. Syed V, Mak P, Du C, Balaji K. β-catenin mediates alteration in cell proliferation, motility and invasion of prostate cancer cells by differential expression of E-cadherin and protein kinase D1. J cell biochem. 2008; 104(1): 82-95. DOI: 10.1002/jcb.21603
100. Abd. Wahab NA, H. Lajis N, Abas F, Othman I, Naidu R. Mechanism of anti-cancer activity of curcumin on androgen-dependent and androgen-independent prostate cancer. Nutrients. 2020; 12(3): 679. DOI: 10.3390/nu12030679
101. Chen QH. Curcumin-based anti-prostate cancer agents. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2015; 15(2): 138-156. DOI: 10.2174/1871520615666150116102442
102. Belluti S, Orteca G, Semeghini V, Rigillo G, Parenti F, Ferrari E, et al. Potent anti-cancer properties of phthalimide-based curcumin derivatives on prostate tumor cells. International journal of molecular sciences. 2018; 20(1): 28. DOI: 10.3390/ijms20010028
103. Vellampatti S, Chandrasekaran G, Mitta SB, Lakshmanan VK, Park SH. Metallo-curcumin-conjugated DNA complexes induces preferential prostate cancer cells cytotoxicity and pause growth of bacterial cells. Sci rep. 2018; 8(1): 14929. DOI: 10.1038/s41598-018-33369-z
104. Mattiuzzi C, Sanchis-Gomar F, Lippi G. Concise update on colorectal cancer epidemiology. Ann Transl Med. 2019; 7(21). DOI: 10.21037/atm.2019.07.91
105. Goel A, Boland CR, Chauhan DP. Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. Cancer lett. 2001; 172(2): 111-118. DOI: 10.1016/S0304-3835(01)00655-3
106. Mudduluru G, George-William JN, Muppala S, Asangani IA, Kumarswamy R, Nelson LD, et al. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. Biosci rep. 2011; 31(3): 185-197. DOI: 10.1042/BSR20100065
107. Kunnumakkara AB, Diagaradjane P, Guha S, Deorukhkar A, Shentu S, Aggarwal BB, et al. Curcumin sensitizes human colorectal cancer xenografts in nude mice to γ-radiation by targeting *nuclear factor-κB-regulated* gene products. Clin Cancer Res. 2008; 14(7): 2128-2136. DOI: 10.1158/1078-0432.CCR-07-4722
108. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. Eur J cancer. 2010; 46(18): 3219-3232. DOI: 10.1016/j.ejca.2010.07.043
109. Harness JK, Davies K, Via C, Brooks E, Zambelli-Weiner A, Shah C, et al. Meta-analysis of local invasive breast cancer recurrence after electron intraoperative radiotherapy. Ann Surg Oncol. 2018; 25: 137-147. DOI: 10.1245/s10434-017-6130-x
110. Ramachandran C, Fonseca HB, Jhabvala P, Escalon EA, Melnick SJ. Curcumin inhibits telomerase activity through human telomerase reverse transcritpase in MCF-7 breast cancer cell line. Cancer lett. 2002; 184(1): 1-6. DOI: 10.1016/S0304-3835(02)00192-1
111. Liu Q, Loo WT, Sze S, Tong Y. Curcumin inhibits cell proliferation of MDA-MB-231 and BT-483 breast cancer cells mediated by down-regulation of NFκB, cyclinD and MMP-1 transcription. Phytomedicine. 2009; 16(10): 916-922. DOI: 10.1016/j.phymed.2009.04.008
112. Rauf A, Imran M, Orhan IE, Bawazeer S. Health perspectives of a bioactive compound curcumin: A review. Trends Food Sci Technol. 2018; 74: 33-45. DOI: 10.1016/j.tifs.2018.01.016
113. Fabianowska-Majewska K, Kaufman-Szymczyk A, Szymanska-Kolba A, Jakubik J, Majewski G, Lubecka K. Curcumin from turmeric rhizome: A potential modulator of DNA methylation machinery in breast cancer inhibition. Nutrients. 2021; 13(2): 332. DOI: 10.3390/nu13020332
114. Farghadani R, Naidu R. Curcumin: modulator of key molecular signaling pathways in hormone-independent breast cancer. Cancers. 2021; 13(14): 3427. DOI: 10.3390/cancers13143427
115. Bachmeier BE, Mohrenz IV, Mirisola V, Schleicher E, Romeo F, Höhneke C, et al. Curcumin downregulates the inflammatory cytokines CXCL1 and-2 in breast cancer cells via NFκB. Carcinogenesis. 2008; 29(4): 779-789. DOI: 10.1093/carcin/bgm248
116. Allegra A, Innao V, Russo S, Gerace D, Alonci A, Musolino C. Anti-cancer activity of curcumin and its analogues: preclinical and clinical studies. Cancer invest. 2017; 35(1): 1-22. DOI: 10.1080/07357907.2016.1247166
117. Karthikeyan A, Senthil N, Min T. Nanocurcumin: A promising candidate for therapeutic applications. Fron Pharmaco. 2020; 11: 487. DOI: 10.3389/fphar.2020.00487
118. Torre LA, Siegel RL, Jemal A. Lung cancer statisticsTransl Lung Cancer Res Subsets. 2016:1-19. DOI: 10.1007/978-3-319-24223-1_1
119. Memon H, Patel BM. Immune checkpoint inhibitors in non-small cell lung cancer: A bird's eye view. Life sci. 2019; 233: 116713. DOI: 10.1016/j.lfs.2019.116713
120. Wang J-Y, Wang X, Wang X-J, Zheng B-Z, Wang Y, Liang B. Curcumin inhibits the growth via Wnt/β-catenin pathway in non-small-cell lung cancer cells. Eur Rev Med Pharmacol Sci 2018; 22(21): 7492-7499. DOI: 10.26355/eurrev_201811_16290
121. Li X, Ma S, Yang P, Sun B, Zhang Y, Sun Y, et al. Anti-cancer effects of curcumin on nude mice bearing lung cancer A549 cell subsets SP and NSP cells. Oncol Lett. 2018; 16(5): 6756-6762. DOI: 10.3892/ol.2018.9488
122. Wu GQ, Chai KQ, Zhu XM, Jiang H, Wang X, Xue Q, et al. Anti-cancer effects of curcumin on lung cancer through the inhibition of EZH2 and NOTCH1. Oncotarget. 2016; 7(18): 26535. DOI: 10.18632/oncotarget.8532
123. Wang C, Song X, Shang M, Zou W, Zhang M, Wei H, et al. Curcumin exerts cytotoxicity dependent on reactive oxygen species accumulation in non-small-cell lung cancer cells. Future Oncol. 2019; 15(11): 1243-1253. DOI: 10.2217/fon-2018-0708
124. Smagurauskaite G, Mahale J, Brown K, Thomas AL, Howells LM. New paradigms to assess consequences of long-term, low-dose curcumin exposure in lung cancer cells. Molecules. 2020; (2): 366. DOI: 10.3390/molecules25020366
125. Bland AR, Bower RL, Nimick M, Hawkins BC, Rosengren RJ, Ashton JC. Cytotoxicity of curcumin derivatives in ALK positive non-small cell lung cancer. Eur J Pharmacol. 2019; 865: 172749. DOI: 10.1016/j.ejphar.2019.172749
126. Li X, He S, Tian Y, Weiss RM, Martin DT. Synergistic inhibition of GP130 and ERK signaling blocks chemoresistant bladder cancer cell growth. Cell signall. 2019; 63: 109381. DOI: 10.1016/j.cellsig.2019.109381
127. Xin J, Jue W, Huifen S, Ran R, Kai X, Xiangming T, et al. Curcumin co-treatment ameliorates resistance to gefitinib in drug-resistant NCI-H1975 lung cancer cells. J Tradit Chin Med. 2017; 37(3): 355-360. DOI: 10.1016/S0254-6272(17)30071-7
128. Gao X, Li X, Ho C-T, Lin X, Zhang Y, Li B, et al. Cocoa tea (Camellia ptilophylla) induces mitochondria-dependent apoptosis in HCT116 cells via ROS generation and PI3K/Akt signaling pathway. Food Res Int. 2020; 129: 108854. DOI: 10.1016/j.foodres.2019.108854
129. Zhou GZ, Li AF, Sun Y-H, Sun GC. A novel synthetic curcumin derivative MHMM-41 induces ROS-mediated apoptosis and migration blocking of human lung cancer cells A549. Biomed Pharmacother. 2018; 103:391-398. DOI: 10.1016/j.biopha.2018.04.086
130. Zoi V, Galani V, Lianos GD, Voulgaris S, Kyritsis AP, Alexiou GA. The role of curcumin in cancer treatment. Biomedicines. 2021; 9(9): 1086. DOI: 10.3390/biomedicines9091086
131. Kumar A, Harsha C, Parama D, Girisa S, Daimary UD, Mao X, et al. Current clinical developments in curcumin-based therapeutics for cancer and chronic diseases. Phytother Res 2021; 35(12): 6768-6801. DOI: 10.1002/ptr.7264
132. Lamb SR, Wilkinson SM. Contact allergy to tetrahydrocurcumin. Contact Dermat. 2003; 48(4): 227. DOI: 10.1034/j.1600-0536.2003.00062.x
133. Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, et al.

Dose escalation of a curcuminoid formulation. BMC complement alter med. 2006; 6(1): 1-4. DOI: 10.1186/1472-6882-6-10
134. Panahi Y, Saadat A, Beiraghdar F, Nouzari SMH, Jalalian HR, Sahebkar A. Antioxidant effects of bioavailability-enhanced curcuminoids in patients with solid tumors: A randomized double-blind placebo-controlled trial. J Function Foods. 2014; 6:615-622. DOI: 10.1016/j.jff.2013.12.008
135. Hejazi J, Rastmanesh R, Taleban F, Molana S, Ehtejab G. A pilot clinical trial of radioprotective effects of curcumin supplementation in patients with prostate cancer. J Cancer Sci Ther. 2013; 5(10): 320-324. DOI: 10.4172/1948-5956.1000222
136. Jiao Y, Wilkinson IV J, Pietsch EC, Buss JL, Wang W, Planalp R, et al. Iron chelation in the biological activity of curcumin. Free Rad Bio Med. 2006; 40(7): 1152-1160. DOI: 10.1016/j.freeradbiomed.2005.11.003
137. Jiao Y, Wilkinson IV J, Di X, Wang W, Hatcher H, Kock ND, et al. Curcumin, a cancer chemopreventive and chemotherapeutic agent, is a biologically active iron chelator. Am J Hematol. 2009; 113(2):462-469. DOI: 10.1182/blood-2008-05-155952
138. Kim DC, Ku SK, Bae JS. Anticoagulant activities of curcumin and its derivative. BMB rep. 2012; 45(4):221-226. DOI: 10.5483/BMBRep.2012.45.4.221
139. Wang Z, Sun W, Huang CK, Wang L, ia MM, Cui X, et al. Inhibitory effects of curcumin on activity of cytochrome P450 2C9 enzyme in human and 2C11 in rat liver microsomes. Drug Dev Ind Pharm. 2015; 41(4): 613-616. DOI: 10.3109/03639045.2014.886697
140. Liu AC, Zhao LX, Lou HX. Curcumin alters the pharmacokinetics of warfarin and clopidogrel in Wistar rats but has no effect on anticoagulation or antiplatelet aggregation. Planta medica. 2013; 79(11): 971-977. DOI: 10.1055/s-0032-1328652
141. Naksuriya O, Okonogi S, Schiffelers RM, Hennink WE. Curcumin nanoformulations: a review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. Biomaterials. 2014; 35(10): 3365-3383. DOI: 10.1016/j.biomaterials.2013.12.090
142. Khan AA, Mudassir J, Mohtar N, Darwis Y. Advanced drug delivery to the lymphatic system: lipid-based nanoformulations. Int J nano. 2013: 2733-2744. DOI: 10.2147/IJN.S41521
143. Dwivedi C, Sahu R, Tiwari SP, Satapathy T, Roy A. Role of liposome in novel drug delivery system. J Drug Deliv Ther. 2014; 4(2): 116-129. DOI: 10.22270/jddt.v4i2.768
144. Sadr S, Poorjafari Jafroodi P, Haratizadeh MJ, Ghasemi Z, Borji H, Hajjafari A. Current status of nano-vaccinology in veterinary medicine science. Vet Med Sci. 2023;9(5): 2294-2308. DOI: 10.1002/vms3.1221
145. Moballegh Nasery M, Abadi B, Poormoghadam D, Zarrabi A, Keyhanvar P, Khanbabaei H, et al. Curcumin delivery mediated by bio-based nanoparticles: a review. Molecules. 2020; 25(3): 689. DOI: 10.3390/molecules25030689
146. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, et al. Liposome: classification, preparation, and applications. Nanoscale res lett. 2013; 8: 1-9. DOI: 10.1186/1556-276X-8-102
147. Chang M, Wu M, Li H. Antitumor activities of novel glycyrrhetinic acid-modified curcumin-loaded cationic liposomes *in vitro* and in H22 tumor-bearing mice. Drug Deliv. 2018; 25(1): 1984-1995. DOI: 10.1080/10717544.2018.1526227
148. Dhule SS, Penfornis P, Frazier T, Walker R, Feldman J, Tan G, et al. Curcumin-loaded γ-cyclodextrin liposomal nanoparticles as delivery vehicles for osteosarcoma. Nanomedicine in cancer: Jenny Stanford Publishing; 2017. 265-295. DOI: 10.1201/b22358-10
149. Tefas LR, Sylvester B, Tomuta I, Sesarman A, Licarete E, Banciu M, et al. Development of antiproliferative long-circulating liposomes co-encapsulating doxorubicin and curcumin, through the use of a quality-by-design approach. Drug Des Devel Ther. 2017:1605-1621. DOI: 10.2147/DDDT.S129008
150. Li L, Ahmed B, Mehta K, Kurzrock R. Liposomal curcumin with and without oxaliplatin: effects on cell growth, apoptosis, and angiogenesis in colorectal cancer. Mol cancer therap. 2007; 6(4): 1276-1282. DOI: 10.1158/1535-7163.MCT-06-0556
151. Vetha BSS, Kim EM, Oh PS, Kim SH, Lim ST, Sohn MH, et al. Curcumin encapsulated micellar nanoplatform for blue light emitting diode induced apoptosis as a new class of cancer therapy. Macromol Res. 2019; 27(12): 1179-1184. DOI: 10.1007/s13233-019-7168-3
152. Biswas AK, Islam MR, Choudhury ZS, Mostafa A, Kadir MF. Nanotechnology based approaches in cancer therapeutics. Advances in Natural Sciences: Nanosci Nanotech. 2014; 5(4): 043001. DOI: 10.1088/2043-6262/5/4/043001
153. Rudramurthy GR, Swamy MK, Sinniah UR, Ghasemzadeh A. Nanoparticles: alternatives against drug-resistant pathogenic microbes. Molecules. 2016; 21(7): 836. DOI: 10.3390/molecules21070836
154. Manju S, Sreenivasan K. Conjugation of curcumin onto hyaluronic acid enhances its aqueous solubility and stability. J Colloid Interface Sci. 2011; 359(1):318-325. DOI: 10.1016/j.jcis.2011.03.071
155. Muangnoi C, Jithavech P, Ratnatilaka Na Bhuket P, Supasena W, Wichitnithad W, Towiwat P, et al. A curcumin-diglutaric acid conjugated prodrug with improved water solubility and antinociceptive properties compared to curcumin. Biosci, biotechnol, biochem. 2018; 82(8): 1301-1308. DOI: 10.1080/09168451.2018.1462694
156. Brahmkhatri VP, Sharma N, Sunanda P, D'Souza A, Raghothama S, Atreya HS. Curcumin nanoconjugate inhibits aggregation of N-terminal region (Aβ-16) of an amyloid beta peptide. New J Chem. 2018; 42(24): 19881-19892. DOI: 10.1039/C8NJ03541E
157. Meghwal M, Goswami T. Piper nigrum and piperine: an update. Phytoth Res. 2013; 27(8): 1121-1130. DOI: 10.1002/ptr.4972
158. Srinivasan K. Black pepper and its pungent principle-piperine: a review of diverse physiological effects. Critical reviews in food science and nutrition. 2007; 47(8): 735-748. DOI: https://doi.org/10.1080/10408390601062054
159. Tang H, Murphy CJ, Zhang B, Shen Y, Van Kirk EA, Murdoch WJ, et al. Curcumin polymers as anti-cancer conjugates. Biomaterials. 2010; 31(27): 7139-7149. DOI: 10.1016/j.biomaterials.2010.06.007
160. Ntoutoume GMN, Granet R, Mbakidi JP, Brégier F, Léger DY, Fidanzi-Dugas C, et al. Development of curcumin-cyclodextrin/cellulose nanocrystals complexes: New anti-cancer drug delivery systems. Bioorganic Med Chem Lett. 2016; 26(3): 941-945. DOI: 10.1016/j.bmcl.2015.12.060
161. Yallapu MM, Jaggi M, Chauhan SC. β-Cyclodextrin-curcumin self-assembly enhances curcumin delivery in prostate cancer cells. Colloids and surfaces B: Biointerfaces. 2010; 79(1): 113-125. DOI: 10.1016/j.colsurfb.2010.03.039
162. Zhang L, Man S, Qiu H, Liu Z, Zhang M, Ma L, et al. Curcumin-cyclodextrin complexes enhanced the anti-cancer effects of curcumin. Environ Toxicol Pharmacol. 2016; 48: 31-38. DOI: 10.1016/j.etap.2016.09.021
163. Abruzzo A, Zuccheri G, Belluti F, Provenzano S, Verardi L, Bigucci F, et al. Chitosan nanoparticles for lipophilic anti-cancer drug delivery: Development, characterization and *in vitro* studies on HT29 cancer cells. Colloids and Surfaces B: Biointerfaces. 2016; 145: 362-372. DOI: 10.1016/j.colsurfb.2016.05.023
164. Li Y, Gu Z, Zhang C, Li S, Zhang L, Zhou G, et al. Synthesis, characterization and ROS-mediated antitumor effects of palladium (II) complexes of curcuminoids. Euro J Med Chem. 2018; 144: 662-671. DOI: 10.1016/j.ejmech.2017.12.027
165. Abd El-Hack ME, El-Saadony MT, Swelum AA, Arif M, Abo Ghanima MM, Shukry M, et al. Curcumin, the active substance of turmeric: its effects on health and ways to improve its bioavailability. J Sci Food Agric. 2021; 101(14): 5747-5762. DOI: 10.1002/jsfa.11372
166. Ahmad MZ, Alkahtani SA, Akhter S, Ahmad FJ, Ahmad J, Akhtar MS, et al. Progress in nanotechnology-based drug carrier in designing of curcumin nanomedicines for cancer therapy: current state-of-the-art. Journal of drug targeting. 2016; 24(4): 273-293. DOI: 10.3109/1061186X.2015.1055570
167. Rodrigues FC, Kumar NA, Thakur G. The potency of heterocyclic curcumin analogues: An evidence-based review. Pharmacol Res. 2021; 166: 105489. DOI: 10.1016/j.phrs.2021.105489
168. Zheng B, McClements DJ. Formulation of more efficacious curcumin delivery systems using colloid science: enhanced solubility, stability, and bioavailability. Molecules. 2020; 25(12): 2791. DOI: 10.3390/molecules25122791
169. Sabet S, Rashidinejad A, Melton LD, McGillivray DJ. Recent advances to improve curcumin oral bioavailability. Trends Food Sci Technol. 2021; 110:253-266. DOI: 10.1016/j.tifs.2021.02.006
170. Stanić Z. Curcumin, a compound from natural sources, a true scientific challenge-a review. Plant Foods Hum Nutr. 2017; 72:1-12. DOI: 10.1007/s11130-016-0590-1
171. Maleki Dizaj S, Alipour M, Dalir Abdolahinia E, Ahmadian E, Eftekhari A, Forouhandeh H, et al. Curcumin nanoformulations: Beneficial nanomedicine against cancer. Phytother Res. 2022; 36(3): 1156-1181. DOI: 10.1002/ptr.7389
172. Khan S, Imran M, Butt TT, Shah SWA, Sohail M, Malik A, et al. Curcumin

based nanomedicines as efficient nanoplatform for treatment of cancer: new developments in reversing cancer drug resistance, rapid internalization, and improved anti-cancer efficacy. Trends Food Sci Technol. 2018; 80: 8-22. DOI: 10.1016/j.tifs.2018.07.026

173. Batra H, Pawar S, Bahl D. Curcumin in combination with anti-cancer drugs: A nanomedicine review. Pharmacol Res. 2019; 139: 91-105. DOI: 10.1016/j.phrs.2018.11.005
174. M Yallapu M, Jaggi M, C Chauhan S. Curcumin nanomedicine: a road to cancer therapeutics. Curr pharmaceut design. 2013; 19(11): 1994-2010. DOI: 10.2174/138161213805289219
175. Hardwick J, Taylor J, Mehta M, Satija S, Paudel KR, Hansbro PM, et al. Targeting cancer using curcumin encapsulated vesicular drug delivery systems. Curr pharmaceut design. 2021; 27(1):2-14. DOI: 10.2174/1381612826666200728151610