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Review Article

Curcumin as a Chemotherapy Compound for Treatment of Breast Cancer: A Review

Mohammad Reza Kasaai*

Department of Food Science and Technology, Sari Agricultural Sciences and Natural Resources University, Sari, Mazandaran, Iran

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Abstract

Breast cancer (BCA) is one of the most common cancers worldwide, with a high rate of incidence and mortality. This review provides global information on BCA therapy using curcumin. Chemotherapy, as an effective treatment for different stages of BCA, and curcumin, generally regarded as safe compound and an alternative to synthetic drugs, have been described for the treatment of BCA. A few parameters, including nano-curcumin versus bulk curcumin and its encapsulated form versus its corresponding free form, have been discussed. Curcumin, a safe and edible compound with antitumor properties, is a promising medicinal compound for the treatment of BCA. Encapsulation of curcumin enhances its stability and anticancer efficiency. Nano-curcumin exhibits superior properties when compared to its bulk counterparts, leading to notable interactions and effects.

Introduction

Breast cancer (BCA) is the most common malignant tumor among adult females. It is considered the second most common type of cancer next to lung cancer, accounting for 30% of malignancy cases and 15% of cancer deaths in women.[1–3] Most BCA cases have been identified in women, leading to hereditary implications.[4–6] According to the World Health Organization's statistical analysis in 2019,[7] BCA is a commonly diagnosed cancer worldwide, accounting for 11.7% of cancer deaths, surpassing lung cancer (11.4%).

The major types of BCA include: (i) Luminal A BCA (cell lines MCF-7, T-47D); (ii) Luminal B BCA (cell lines BT-47, ZR-75-1); (iii) Human epidermal growth factor receptor 2 $(HER2)^+$ BCA (cell lines HCCC-1954, SK-BR-3); and (iv) triple-negative BCA (TNBCA) (MDA-MB-231, MDA-4648, BT-549) cells.[8–11] Based on a number of references investigated in this study, curcumin appears to show more efficacy in triple-negative breast cancer (TNBCA) models compared to other BCA subtypes. The MCF-7 BCA cell line could be considered the second most responsive after TNBCA.[12–15]

Chemotherapy is one of the most effective treatments for different cancers, including BCA. In most cases, the preparation of chemotherapeutic agents, which are often cytotoxic, requires strict safety protocols. This typically involves preparation in a controlled environment, such as: (a) a biological safety cabinet by trained personnel; (b) appropriate personal protective equipment to minimize exposure risks; (c) application of particular techniques and equipment to uphold sterility during preparation; and (d) prevention of exposure to cytotoxic agents for both patients and healthcare workers.[6,16,17]

Curcumin, being edible, possessing several useful properties, and non-toxic, finds applications in healthcare, pharmacy, and medicine.[18,19] Curcumin exhibits antitumor properties and has been used to treat BCA.[12,20,21] Both low water solubility and bioavailability of curcumin are major challenges for its applications in all types of cancer therapies, including BCA. Water solubility and bioavailability of curcumin in cancer therapies were improved by encapsulation. The therapeutic effects of curcumin on cancer cells and inhibition of cell proliferation were enhanced by encapsulation. No adverse effects were detected on normal cells.[22–25] Use of suitable chemotherapy techniques and strategies aids in managing adverse effects in patients undergoing treatment.[23,26]

The innovation presented in this manuscript addresses the issue of low bioavailability of coarse-sized curcumin. Enhanced bioavailability is achieved through the application of nanotechnology and nano-encapsulation techniques to improve the delivery and effectiveness of curcumin in BCA treatment. The results of nano-curcumin versus bulk curcumin were compared qualitatively. This review provides global information on the therapy of BCA with curcumin. Nano-curcumin versus its bulk form, and encapsulated curcumin versus its free form, have been compared and evaluated.

Keywords: Breast cancer; Curcumin; Nanocurcumin challenges; Nanotechnology; Encapsulation; Antitumor; Therapy.

***Correspondence to:** Mohammad Reza Kasaai, Department of Food Science and Technology, Sari Agricultural Sciences and Natural Resources University, Km. 9, Farah Abad Road, Sari, Mazandaran 48181-68984, Iran. ORCID: https://orcid.org/0000-0003-0442-0662. Tel: +98-11-33687901-5, E-mail: reza_kasaai@hotmail.com

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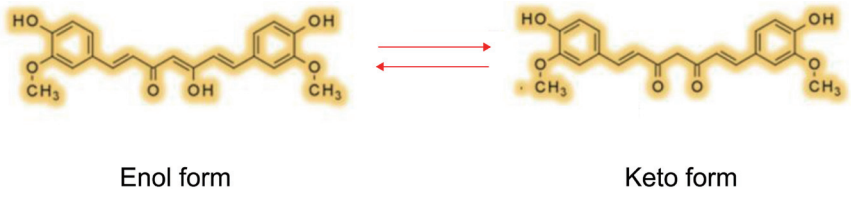

Fig. 1. Chemical structure of curcumin in both enol and keto forms. The structure of curcumin in a variety of solvents is as follows: (i) in organic solvents such as chloroform; (ii) mixtures of dimethyl sulfoxide (DMSO) and water; and (iii) buffered aqueous solution with pH 3–9. Curcumin exists in two forms: (1) enol or hydroxyl form in organic solvents; and (2) keto or carbonyl form in water or aqueous solution. [Reproduced from Fig. 1a of Payton *et al*., 2007[33]]

General aspects

Chemical structure of curcumin

Curcumin is extracted from the turmeric rhizome (*Curcuma longa L.*) roots, belongs to the group of curcuminoids, and is a member of the ginger family.[12,27–30] Curcumin is a natural plant-based phenolic compound. Curcumin, with a hydrophobic nature, a chemical formula of $C_{21}H_{20}O_6$, and a molecular weight (M_w) of 368.130 g·mol^{-1}, is a phenolic pigment (orange-yellow color). It is a diketone tautomer and also exists in enolic form. Its enol form is soluble in organic solvents, whereas its keto form is soluble in water.[31–33] Its molecular structure in enol and keto forms is illustrated in Figure 1.

The results of nuclear magnetic resonance spectroscopy illustrate that it exists in enol–keto tautomer forms.[33] This result is consistent with previous studies.[34] Keto-enol tautomerism is an equilibrium between two isomers: the keto (aldehyde or ketone) form converts into the enol form through the migration of a hydrogen to a double bond. The equilibrium is reversible.[35]

Properties of curcumin

Curcumin is a food additive and is generally recognized as safe by the U.S. Food and Drug Administration.[36] Curcumin is slightly soluble in water and soluble in organic solvents. Low aqueous solubility, low bioavailability, and absence of potent and selective target activity limit its applications.[31,32] It exhibits antioxidant, anti-inflammatory, and cancer chemo-preventive activities, including BCA.[12,34,37] Curcumin serves as a chemosensitizer in chemotherapy and, as a photosensitizer, supports photodynamic therapy without evaluating the effect of curcumin separately.[22,25,38,39]

Curcumin is recognized for its beneficial therapeutic attributes, which encompass anti-inflammatory, antioxidant, and anticancer effects. It has been shown to be effective against multiple cancer types, particularly BCA.[12,28] A few studies indicate that curcumin obstructs the migration, proliferation, adhesion, and invasion of BCA cells.[12,21] Additionally, it combats cancer by triggering apoptosis and limiting both cell survival and proliferation.[30]

Curcumin has been incorporated into dietary supplements and is generally considered safe for consumption from a pharmacological standpoint.[20] It demonstrates anti-cancer and anti-inflammatory properties.[12,28] It has shown positive effects against various types of cancer, including BCA. Some research studies indicate that curcumin inhibits BCA cell migration, reduces proliferation rates, and affects adhesion and invasion.[18–21]

Considering that curcumin is a potent antioxidant, there is evidence that nutritional supplements containing antioxidants can reduce oxidative damage from chemotherapy and radiotherapy, but may also reduce the efficacy of radiotherapy.[36,40] *In vitro* and *in vivo* research suggest that the interactions between curcumin and different chemotherapeutic agents may diminish effectiveness, which is contingent upon the dosage and timing of curcumin administration.[38] A study has shown that the use of antioxidant supplements before or during chemotherapy or radiotherapy is associated with an increased risk of recurrence and mortality, a higher overall mortality rate, and reduced recurrence-free survival among patients with BCA.[41]

Relationship between the chemical structure of curcumin and its anticancer activity

An *in vitro* study revealed that its diketo moiety (see Fig. 1) regulates redox modulation activity. Furthermore, the diketo moiety plays a crucial role in the interaction of curcumin with cellular proteins. The anticancer effects of curcumin and its derivatives have largely been linked to their redox-modulating properties and their ability to engage with various signaling proteins, suggesting that altering the structure of the diketo moiety could enhance efficacy. In fact, the introduction of isoxazole and pyrazole groups at the diketo moiety of curcumin has demonstrated an increase in its anticancer effectiveness. Additionally, methoxy substitution in the phenolic moiety of curcumin has also shown a significant boost in its anticancer properties. In conclusion, targeted structural modifications on curcumin may serve as an effective strategy to optimize its anticancer activity.[42]

Nano-curcumin demonstrates its anti-cancer properties via various mechanisms, such as the promotion of apoptosis, interruption of the cell cycle, and alteration of cancer-associated signaling pathways. Its capacity to enhance the sensitivity of cancer cells to standard therapies underscores its promise as a supplementary treatment alternative.[37]

Breast cancer

The estimated incidence and mortality of breast cancer

The estimated incidence and mortality of BCA worldwide in 2022 are presented in Table 1.[43–45] The information was derived from a recent reference.[46] Data were collected from GLOBOCAN 2022, including new incidence and mortality cases (the age-standardized incidence rate and the age-standardized mortality rate) of BCA across 21 United Nations regions and 185 countries. The incidence and mortality rates of BCA differ markedly between countries, underscoring the necessity to revise the global burden of female BCA, which encompasses present trends and future forecasts.[3,46,47]

BCA is a heterogeneous disease that exhibits variability at multiple levels, including genetic, epigenetic, transcriptomic, and proteomic.[48] Clinically, BCA is categorized into three primary subtypes based on the status of progesterone receptor, estrogen receptor, and HER2.[4,5]

Table 1. The estimated incidence and mortality of breast cancer worldwide in 2022

Age range	Incidence		Mortality	
	Case (number)	ASIR (per 10^5 person)	Case (number)	ASMR (per 10^5 person)
All ages	2,296,840	46.80	666,103	12.70
<40 years	246,060	8.10	48,700	1.60

ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate.

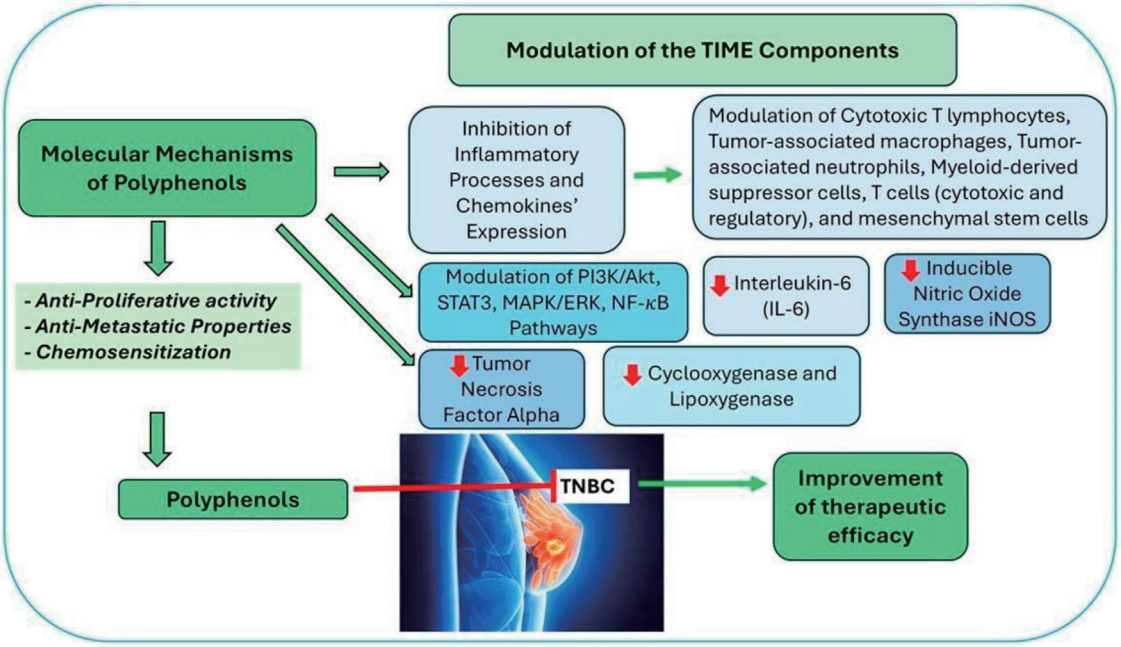

Fig. 2. A schematic diagram showing anticancer mechanisms and nano-delivery pathways on TNBCA cells for polyphenol compounds such as curcumin. The figure describes the effect of polyphenols on the expression of several proteins and on the modulation of signaling pathways, leading to improvement in therapeutic efficacy. Red arrows indicate a decrease in activation of signaling pathways or a reduction of protein expression. [Reproduced from Fig. 2 of Hilliard *et al*., 2025.[49] This article is distributed under the terms of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/ licenses/by/4.0/). Licensee: MDPI, Basel, Switzerland.] TIME, tumor immune microenvironment; TNBC/TNBCA, triple negative breast cancer.

A typical mechanistic pathway for polyphenols such as curcumin in BCA treatment is presented in Figure 2.[49]

Applications of curcumin in breast cancer

A few applications of curcumin in BCA, highlighting the clinical efficacy from both observational and interventional studies, are presented in Table 2. Curcumin acts as an anti-cancer drug specifically targeting BCA by causing cell cycle arrest during the G2/M phase [(G2/M phase: interval between the completion of deoxyribonucleic acid (DNA) synthesis and the beginning of DNA segregation)]. Furthermore, it has been shown to increase the levels of the apoptotic protein Bax (a member of the Bcl-2 gene family) while

Table 2. Applications of curcumin in breast cancer, including clinical efficacy from observational and interventional studies

Item	Results in BCA	References
Clinical efficacy observation	Curcumin exhibits antitumor properties via inhibition of the PI3K/Akt signaling pathway; Curcumin reduced cell viability with a dose-dependent passway in both wild-type and Bcl-2 + MCF-7 BCA cells	43
Clinical efficacy observation	(a) Curcumin diminishes the activation of the EGFR signaling pathway; (b) it diminishes the levels of EGFR proteins on the cell membrane, and (c) it decreases the sensitivity to its ligands	44,45
Clinical efficacy intervention	(i) Curcumin obstructs angiogenesis, growth, and cell proliferation, while facilitating senescence; (ii) curcumin induces autophagy and apoptosis in BCA cells; and (iii) curcumin contributes to BCA therapy	43
Clinical efficacy intervention	Curcumin plays a crucial role in cell proliferation and tumor development and hinders the proliferation of tumor cells	44,45

BCA, breast cancer.

decreasing the expression of the proliferative protein Akt-mTOR and the anti-apoptotic protein BCL2.[15]

For cancer cells, the AKT/mTOR pathway is important in invasion and migration. Numerous proteins can exert their effects by regulating AKT/mTOR upstream molecules or the pathway itself, indicating that the pathway is an effective target for cancer therapy.[5]

Curcumin enhances the apoptosis of BCA cells by activating the ROS-signaling pathway through the regulation of BCL2 gene expression.[50] The main challenge of chemotherapy with curcumin is poor prognosis.[51] Curcumin has demonstrated the ability to disrupt the proliferation of BCA cells and their invasion by inhibiting the regulation of genes and promoting NF-κB. At the same time, it adversely affects the molecular target involved in BCA cell proliferation, which is the HER2, a tyrosine kinase receptor associated with epidermal growth factor receptor. In BCA cell proliferation, NF-κB (a proinflammatory transcription factor) plays a crucial role. Additionally, another significant molecular target is the transcription factor Nrf2.[52,53] Molecular docking analyses revealed that curcumin exhibits favorable binding affinities at the TGFβ3 binding pocket, establishing significant interactions, including hydrogen bonds with residues.[20]

Targeted nano-formulations with cancer theragnostics capabilities (the combination of diagnosis and therapy) demonstrated enhanced internalization and accumulation in triple-negative (MDA-MB-231) BCA cells via both passive and active targeting. Increased penetration and uptake of targeted NPs in tumor spheroids resulted in boosted anticancer activity. Uptake and cytotoxicity tests demonstrated that targeted nano-delivery systems yielded more cell death than non-targeted NPs, with greater uptake and penetration in tumor spheroids, leading to enhanced anticancer efficacy.[54] Targeted drugs deliver more anticancer agents to cancer cells than non-targeted ones.[55]

Passive targeting of a formulation occurs through two effects: (a) enhanced permeability and retention effect of drugs; and (b) dictated physical properties (size, size distribution, and shape) of the carrier or nanocarrier (NC). Active targeting of a formulation or nano-formulation is performed through: (i) surface functionalization of drugs; and (ii) incorporation of carriers with target-specific ligands and/or receptors, leading to enhanced anticancer efficacy. The selection of a carrier or NC plays a significant role in anticancer efficacy. Suitable selection of carriers or NCs with optimal size, size distribution, structural architecture, and surface properties results in improvements in solubility, circulation half-life, and bio-distribution.[54,56]

The combination of nano-drug deliveries with different mechanisms of action in both passive and active targeting can benefit the treatment of chemo-resistant triple-negative breast cancer tumor tissues. This combination is a desirable candidate for more advanced *in vivo* cancer therapy.[54]

A certain number of safety data can be found in a review article. This review concluded that curcumin, alone or in combination with other drugs, can be used as an effective drug(s) for cancer therapy through the modulation of growth factors, enzymes, transcription factors, kinases, inflammatory cytokines, and pro-apoptotic proteins (by upregulation) and anti-apoptotic proteins (by downregulation).[44]

The clinical advancement of curcumin is hindered by its limited bioavailability and poor solubility in water and aqueous solution. Clinical trials have shown that when curcumin is administered orally at a dosage of 8 $g \cdot day^{-1}$ to humans, it rapidly transforms into metabolites, leading to a minimal concentration of free curcumin in plasma (<2.5 $ng \cdot mL^{-1}$).[57] In a phase I clinical trial, curcumin was administered alone to 15 patients with colorectal cancer in an oral formulation. The researchers noted no toxicity, although two patients experienced significant diarrhea, and two others exhibited stable disease after two months of curcumin therapy.[58] A clinical trial of curcumin monotherapy in 25 patients with advanced pancreatic cancer using an oral formulation was conducted. Despite the low plasma concentrations of curcumin (22–41 $ng \cdot mL^{-1}$), two patients demonstrated clinical biological activity. Notably, one patient maintained stable disease for over 18 months, while another experienced a brief but significant tumor regression of 73%.[59] The therapeutic efficacy of curcumin combined with imatinib, a tyrosine kinase inhibitor, was assessed in 50 patients with chronic myeloid leukemia, revealing that the combination treatment was more effective than imatinib alone.[60] Oral administration of exosomal-curcumin as a nano-formulation (exosomes from bovine milk) in Sprague–Dawley rats demonstrated that exosomal curcumin improved curcumin bioavailability as well as antiproliferative activity in multiple cancer cell line models, including BCA, lung, and cervical cancer, compared with free curcumin, and *in vivo* in nude mice bearing the cervical CaSki tumor xenograft.[61] Exosomes are extracellular microvesicles with a particle size of 30–100 nm and carry a cargo of proteins, lipids, RNA, and DNA. Exosomes have potential as NCs for delivering curcumin.[61] Anti-cancer efficacy of lipid NPs containing siRNA was improved against HPV16 E6/E7 combined with cisplatin in a xenograft model of cervical cancer.[62]

Limitations, challenges, and solutions to overcome them in applications of curcumin in breast cancer treatments

The pharmacokinetic properties of curcumin limit its clinical applications as follows: (i) low aqueous and water solubility; and (ii) rapid metabolism and elimination from the body, with low intestinal absorption rates, leading to a short biological half-life and low bioavailability.[18,63–65] However, absorption of curcumin can vary significantly among individuals.[66] Due to its low bioavailability, high doses are necessary when using pure curcumin. Conversely, higher doses with enhanced bioavailability must be evaluated in terms of safety.[38]

The pharmacokinetic challenges have led to significant research efforts focused on innovative delivery systems designed to enhance the therapeutic efficacy of curcumin in cancer treatments. Strategies for enhancement involve the integration of curcumin with additives such as piperine, a key element found in black pepper, which boosts bioavailability by 2,000%. Several methods to enhance bioavailability include: (a) the formulation of curcumin into phospholipid complexes and liposomes; (b) nanotechnology, which has emerged as a feasible solution to these challenges; and (c) encapsulation of curcumin.[38,67,68]

In the case of BCA, the diverse characteristics of breast tumors and the development of treatment resistance remain considerable obstacles for clinicians and researchers, even with notable progress in the cancer field.[69,70]

Different nano-formulations as NCs for curcumin delivery in BCA include liposomes, polymeric NPs, solid lipid NPs, inorganic NPs, nanostructured lipid carriers (NLCs), HSA NPs, nanoemulsions, micelles, and carbon nanotubes.[54,71–76] A detailed description of different nano-formulations used for curcumin delivery in cancers, particularly BCA, is presented in Table 3.[71–74,76,77–79]

Various NP formulations, including polymeric NPs, lipid-based NPs, and inorganic NPs, highlight their roles in improving the pharmacokinetics of curcumin and pharmacodynamic profiles.[68] Curcumin with nano-formulations has the potential to enhance

Table 3. Different nano-formulations used for curcumin delivery in cancers, particularly BCA, and their efficacy outcomes

Nanocarrier (NC) types	Nano carriers	Properties and efficacy of outcomes	References
Polymeric nanogels	Poly(acrylamidoglycolic acid)-gelatin	(a) Bioavailability and solubility of curcumin in aqueous solution improved (encapsulation efficiency was 42–48%); (b) anticancer activity of encapsulated curcumin was superior to its free form; and (c) the DDS can be used at least to treat colorectal cancer	77
A complex nano carrier	Folic acid (FA)-ZnO-3 mercaptopropionic acid (MPA)-βcyclodextrin nanostructures) was synthesized for aqueous delivery of curcumin to enhance its targeting, bioavailability, and release profile	(i) The NC was synthesized to improve the solubility of curcumin and enhance its targeting, bioavailability, and release profile; (ii) the encapsulated system enhanced cytotoxic activity against MDA-MB-231 and MDA-MB-468 BCA cells; and (iii) the nanostructure system enhanced anticancer activity and cellular uptake of curcumin in BCA	72
Polymeric NPs	Folate decorated poly-D,L-lactic-co-glycolic acid (PLGA) NPs	Two drugs (gemcitabine, curcumin) co-encapsulated into the complex NPs to treat BCA; *in vitro* and biological studies demonstrated that their co-administration into the folate decorated Poly-D,L-lactic-co-glycolic acid (PLGA) NPs system resulted in an improvement in BCA therapeutic efficacy	78
Solid lipid NPs (SLNPs)		Curcumin-loaded SLNs exhibited stronger cytotoxicity against BCA cells and higher cellular uptake efficiency; SLNPs induced higher apoptosis rates compared to the free form of curcumin; and (2) these nano-formulations with superior chemotherapeutic efficacies compared to the free form of curcumin have potential for BCA treatments	74,79
Liposomes		Two drugs (curcumin-docetaxel) co-encapsulated into the liposomes; the co-delivery systems enhanced antitumor efficacy in MCF-7 BCA models, with improved pharmacokinetic parameters (increased half-life and mean residence time) compared to free drugs	73,76
Polymeric NPs, Carbon nanotubes, or liposomes		Enhance the bioavailability and therapeutic efficacy of curcumin	76
Human serum albumin (HAS) NPs	HAS NPs	(a) Curcumin and piperine were encapsulated into HAS NPs either as individual or combined drugs; (b) the cytotoxicity experiments demonstrated that the higher ability of curcumin-piperine encapsulated in HSA-NPs against BCA MCF-7 cells in comparison with curcumin alone; and (c) the encapsulated combined drugs in HSA-NPs with adequate efficiencies can be used for both drug deliveries in BCA treatment with synergistic effects	71

BCA, breast cancer; DDS, d rug delivery system.

pharmacokinetics, facilitate targeted delivery, and augment therapeutic efficacy against tumors.[38,68] Organic NPs are composed of biocompatible and biodegradable materials, making them ideal carriers for curcumin. These systems include liposomes, polymers, micelles, emulsions, and nanogels.[38,68] Liposomes are spherical vesicles formed by phospholipid bilayers that encapsulate curcumin within their lipid core. They protect curcumin from degradation, improve solubility, and facilitate targeted delivery. Liposomes have been extensively used in cancer therapy due to their ability to accumulate in tumors via enhanced permeability and retention effects.[80] Additionally, their surface can be modified with targeting ligands to enhance specificity for cancer cells. General information on the applications of emulsions, nanoemulsions, and micelles in various medical contexts, including cancer therapy, can be found elsewhere.[81]

To overcome the limitations of curcumin caused by its low solubility in water and aqueous solutions, it has been encapsulated in NPs with various carriers. Biomacromolecules have emerged as vital agents for disease treatment, including antibodies.[82] High digestive stability of protein Z helps improve the bioavailability of curcumin. The thermostability and photostability of curcumin with protein Z were improved through interactions between protein Z and curcumin. Curcumin binds with protein Z via the hydrophobic region of protein Z, resulting in stronger binding activity compared to the free form of curcumin. Thermal, photo, and digestive stability of curcumin were significantly improved by using the protein Z–curcumin nanocomposite. The relative bioavailability of curcumin was increased by 305% using the protein Z–curcumin nanocomposite.[83] Encapsulation of curcumin into composite NPs (d = 145 nm) of lactoferrin–epigallocatechin gallate–hyaluronic acid improved the bioavailability and cellular uptake of curcumin.[84] Poor water solubility and low bioavailability were also improved using nanotechnology and nano drug delivery systems, including lipid-based NPs, polymeric NPs, micelles, and nanogels (see Table 3).[85]

Applications of nanotechnology and nano-curcumin in breast cancer therapy

To overcome the challenge of low bioavailability of curcumin, nanotechnology has emerged as a promising approach to enhance the delivery and efficacy of curcumin in cancer therapy. Curcumin NPs, encompassing organic, inorganic, and carbon-based types, have demonstrated a remarkable ability to improve its bioavailability and stability.[26] Curcumin-based NPs enable precise and targeted delivery to cancer cells, minimize off-target effects, and improve therapeutic effectiveness, making them an attractive option for cancer treatment.[86]

A study involving BCA patients treated with nano-curcumin at a dose of 80 mg·day^{-1} for two weeks demonstrated a reduction in radiation-induced skin reactions, pain, and adverse effects.[87] Gum Arabic–curcumin micelles and alginate–curcumin–Au NPs diminished cell viability and increased cytotoxic effects in MCF-7 BCA cells. Alginate served as a stabilizing agent for AuNPs, functioning as carriers for curcumin.[88,89] Numerous clinical studies have explored the safety, pharmacokinetics, and therapeutic potential of curcumin, especially regarding its application in cancer treatment and various other human conditions. Curcumin has shown considerable promise in clinical environments, demonstrating the capacity to stop or even avert the progression of cancer cells. Numerous clinical trials have indicated that nano-curcumin is effective in the treatment of different types of cancer. Additionally, the use of nano-curcumin reduces cancer treatment adverse effects. Nano-curcumin, an advanced curcumin formulation, improves absorption and has medicinal advantages. It enhances patient compliance and general quality of life by inhibiting tumor development, increasing treatment efficacy, and reducing adverse effects. The enhanced pharmacokinetics of nano-curcumin make it more efficient than conventional treatments.[90,91]

In the realm of BCA, curcumin has demonstrated efficacy in both estrogen receptor-positive and TNBCA types.[14] In laboratory settings, curcumin has been found to diminish cell proliferation, trigger apoptosis, and impede the dissemination of BCA cells. In live models, curcumin inhibited tumor growth in experimental BCA scenarios.[12] Clinical trials indicate that curcumin can halt the progression of BCA and lower tumor markers when used in conjunction with docetaxel.[92] Additionally, curcumin alleviates the adverse effects associated with standard cancer treatments, including radiation dermatitis.[93,94] Novel formulations, including nanoemulsifying drug delivery systems, have demonstrated potential in improving oral bioavailability.[95] Although intravenous administration guarantees greater bioavailability and immediate effects on tumor cells, it is more invasive and costly than oral delivery.

Both *in vitro* and *in vivo* studies show that curcumin exhibits antitumoral and antiproliferative properties in relation to BCA.[96] The concurrent use of curcumin alongside other chemotherapeutic agents markedly enhances apoptosis in cancer cells. Positive outcomes have been recorded with the intravenous delivery of curcumin in instances of advanced and metastatic BCA.[97,98] Nanoemulsions that incorporate keratin and curcumin improve absorption by BCA cells and produce cytotoxic effects.[99]

Oral intake of curcumin presents difficulties owing to its limited solubility in water and diminished bioavailability.[100] Various strategies have been devised to improve the bioavailability and therapeutic effectiveness of curcumin, such as combining it with other substances and employing encapsulation methods for its delivery.[101,102]

Curcumin exhibits antitumor properties, especially in the treatment of BCA. It plays a role in various biological mechanisms that collectively contribute to a decrease in tumor size, highlighting its promise as a versatile agent in BCA treatment. Curcumin is involved in several biological processes synergistically.[15,45,76,103]

Encapsulation of curcumin

Encapsulation of curcumin enhances the stability and efficiency of the anticancer properties of bulk curcumin. The encapsulation of curcumin into polymeric NPs allows the administration of hydrophobic curcumin drugs in an aqueous dispersion.[23,28,104,105] The encapsulated curcumin in HSA NPs was more efficient than the free form of curcumin for BCA treatment. HSA-curcumin NPs were initially fabricated by dissolution. The procedure of dissolving polymeric NPs in a solvent considers pH, ionic strength, and solute-solvent ratio. The HSA-curcumin NPs were subsequently conjugated with a peptide that binds to programmed death ligand 1 (as confirmed by Fourier transform infrared and UV–visible spectroscopy). Curcumin-loaded calcium carbonate NPs, encapsulated in lipids and L-arginine, exhibited enhanced cytotoxicity compared with the free form of curcumin. Encapsulated anticancer compounds such as curcumin improve the therapeutic effectiveness of the free form and facilitate targeted drug delivery.[106,107] pH-sensitive materials have potential applications in biology, biotechnology, and medicine because they are sensitive in biological media.[108]

There are pH differences between many tissues and cellular compartments of the human body.[109,110] For instance, pH values throughout the digestive tract range from pH 2 in the stomach to pH 7 in the colon. Moreover, tumor tissues possess pH values 0.5–1 units lower than surrounding normal tissues, due to metabolic glycolysis and lactic acid production. At the cellular level, there are pH differences among cellular compartments such as lysosomes (pH 4.5–5), endosomes (pH 5.5–6), and the cytosol (pH 7.4). Furthermore, microorganisms, directly or via enzyme release, and wounds themselves can be either acidic or alkaline depending on the biological environment. Hence, NCs are designed for specific defined pH values. They can target a specific area in the body, releasing their encapsulated drugs with maximum therapeutic impact and minimum adverse effects.[105,107] This has made pH-responsive carriers a very interesting pathway for drug delivery systems.[111–113]

Curcumin encapsulated in HSA-based lipoprotein NPs enhanced its delivery and anticancer efficacy for the treatment of BCA, specifically the MDA-MB-231 cancer line. Curcumin-dioleoyl phosphoethanolamine-HSA NPs were synthesized, characterized, and assessed for their cytotoxic effects on murine (4T1) and human BCA (MDA-MB-231) cell lines. The encapsulated NPs demonstrated greater efficiency compared with the free form of curcumin. Curcumin encapsulated in gamma-cyclodextrin liposome NPs showed significant potential for cancer treatment.[114,115]

NLCs improved oral delivery of curcumin. Encapsulated curcumin into NLCs was prepared using a warm microemulsion technique (dispersing warm microemulsion in cold water under magnetic stirring), followed by coating particle surfaces with mucoadhesive polymers (polyethylene glycol 400, polyvinyl alcohol, and chitosan).[116] NLCs can be drug delivery systems with the following advantages over conventional carriers: (a) improved drug loading as well as drug release capacity; (b) increased solubility; (c) enhanced storage stability; (d) improved permeability and bioavailability; and (e) prolonged half-life of loaded compounds. These nano-carriers can be used in cancer therapy.[116,117] The bioavailability of an orally administered drug depends on its solubility in the gastrointestinal tract and its permeability across cell membranes.[118] Curcumin quantum dots encapsulated into positively charged polymer NPs (Eudragit RS 100) significantly inhibited BCA cells, whereas normal cells were not affected by the encapsulated systems. Experimental results showed that only ~10% of

BCA cells and ~11% of colon cancer cells survived under the encapsulated system.[119]

Future perspectives

Key research gaps and recommendations for future research, as well as possible/estimated solutions to overcome challenges, were derived in this study as follows:

1. There exists a notable disparity between basic research and therapeutic applications. Solution to overcome the existing gap: "Use of innovative techniques such as gene editing, humanized mouse models, 3D bioprinting, and patient-derived organoids". The application of these experimental models enhances existing preclinical or clinical results. These models provide comprehensive insight into cancer biology by simulating the intricate nature of human diseases.
2. There exists a significant amount of experimental data *in vitro*. However, there are no effective links between *in vitro* investigators and clinical experts. Solution to overcome this: "Collaboration between research groups and clinical experts in pre-clinical and clinical sectors."
3. Production of curcumin on a large scale and its commercialization are major issues. Solution to overcome this: "Develop appropriate technologies and nanotechnology approaches for large-scale curcumin production."
4. Safety issues of nano-curcumin applications are major challenges for clinical trials and clinical applications. Recommendations to address this: (a) find effective solutions to enhance the rate of practical and clinical applications; and (b) perform laboratory research and evaluate experimental results to determine the safety level and the quantity of curcumin required for pre-clinical and clinical treatments in specific cases, in order to assess its safety and effectiveness in clinical environments.

Conclusions

Curcumin is safe and exhibits antitumor properties, but its low bioavailability in conventional and free forms necessitates high-dose consumption. Utilizing high doses may lead to adverse effects. Studies conducted *in vitro* and *in vivo* have shown that treatment with nanocurcumin is more effective than with its bulk form. The anticancer efficacy of the free form of curcumin can be enhanced by encapsulation. The slow release of curcumin to cancer cells results in superior efficacy. Various formulations of curcumin as NPs (liposomes, lipid-based NPs, polymeric NPs, micelles, emulsions, and metal-based NPs) enhance its absorption and efficacy, while providing controlled release and protecting it from degradation. Encapsulated polyphenols such as curcumin in a suitable NC may be utilized for the treatment of BCA patients diagnosed with the TNBCA type. Before clinical application of polyphenol compounds, their safety and antitumor efficacy on TNBCA should be confirmed *in vitro* and through pre-clinical studies.

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Conflict of interest

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Author contributions

MRK is the sole author of the manuscript.

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