Curcumin Nanocarriers with a Focus on Cellular Uptake Studies – An Innovative Cancer Therapy

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Abstract

Once a dye, curcumin (CUR) has transformed into a versatile therapeutic agent with antioxidative, anti-inflammatory, and anticancer properties. Despite its potent anticancer effects, CUR encounters challenges such as poor solubility and a short circulation half-life. To address this, researchers utilize nanocarriers like nanoparticles, liposomes, and micelles for efficient CUR delivery. With its multifaceted anticancer activity, CUR holds promise as a cancer therapeutic. Recent studies concentrate on crafting nanocarriers tailored for size, charge, and functionalization, offering adaptable tools for combinational cancer therapy. The synergistic combination of CUR with chemotherapy, magnetic nano hyperthermia, or photodynamic therapy amplifies the efficacy of malignancy treatment. The investigation into CUR-loaded nanocarriers, whether used alone or in combination with other modalities, aims to enhance cancer treatment outcomes, highlighting the diverse potential of curcumin in contemporary therapeutic strategies. This research underscores the importance of combinational drug delivery therapies, providing a renewed perspective on the versatile applications of curcumin in modern medicine.

Significance | Using curcumin nano carriers could provide several benefits in combating the cancers.

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1. Introduction

Turmeric have a well-established historical chronicle as herb and coloring agent. This yellow poly phenolic compound obtained from the tuber of *Curcuma longa* L. has been in recent for pharmaceutical activities. Curcuminoids plays a key role among the minor turmeric ingredients. The primary components of Curcuminoids are curcumin, dimethoxy-curcumin, and bisdemethoxycurcumin. Additionally, more than 50 curcuminoids are present which includes bisabocurcumin, curcumalongin, cyclocurcumin, and terpecurcumin. Curcumin, the most dominant compound of Curcuminoids showed an array of therapeutic properties which includes arthritis, cardiovascular disease, inflammatory bowel disease, and certain cancers. Which has been well illustrated in Figure1.

Which has actually envisaged a new role to Curcumin shifting it use from traditional textile dying to medicinal ways. Curcumin has the capacity to ameliorate the inflammatory response which can effectively reduce the inflammation and its associated symptoms (Karthikeyan et al. 2020; Jakubczyk et al. 2020; Satyabhama et al. 2022). Aside from its anti-inflammatory properties, Curcumin has also been recognized for its antioxidant effects, which help to neutralize liberated along with oxidants inside the anatomy (Jakubczyk et al. 2020). These entities are known to cause oxidative stress, linked to numerous occasional ailments as cardiac complaint, neurodegenerative disorders, and cancer (Satyabhama et al.2022). By scavenging free radicals and

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reducing oxidative stress, Curcumin protects cells from oxidative damage, supporting overall cellular health (Karthikeyan et al.2020). This antioxidative efficacy has contributed to its potential for combating age-related diseases and conditions associated with oxidative damage (Vaiserman et al. 2020). Moreover, Curcumin exhibits promising neuroprotective properties, making it a subject of interest in neurological research (Silvestro et al. 2021). Beyond its effects on inflammation, oxidation, neuroprotection, cardiovascular health, infections, and so on, one of the most up- and –coming prospect of Curcumin activities has the potential as a cancer-fighting agent. Preclinical studies have demonstrated Curcumin potential to inhibit malignant tumor magnification, brings about cell death, and suppress tumor progression (Hatcher et al. 2008) . It exerts multiple mechanisms of action that can contribute to malignant prohibition along with medicaments. Firstly, in the presence of Curcumin the swelling along with proliferation of malignant tumor is inhibited by intervention with their signaling pathways (Almatroodi et al. 2021). Additionally, Curcumin exhibits anti-angiogenic qualities, which can inhibit the creation of new blood vessels that provide nutrients to tumors, thereby preventing their growth and metastasis (Bhandarkar et al. 2007). Furthermore, Turmeric have been developed to possess anti-metastatic properties, effectively inhibiting the ability of cancer cells to occupy, along with increase toward further tissues (Wang et al.2018). The probable multi-targeted mechanism of Turmeric in cancer therapeutics makes it a fascinating candidate for further investigation in clinical trials. However, its activity is hindered by certain drawbacks, including low water solubility (hydrophobic nature), instability at physiological pH, short circulation half-life, and rapid metabolism in the intestines

and liver (resulting in limited absorption and rapid breakdown). These factors collectively restrict the bioavailability and effectiveness of its delivery (Zheng et al. 2020; Zhang et al. 2022). When administered orally or intravenously, Curcumin tends to form aggregates or precipitates in aqueous environments, resulting in low bioavailability (Chou et al. 2021). This limits its absorption and distribution in the body, reducing its therapeutic efficacy. However, they are easy to digest in the gut when present in nanoform. To address this challenge, few drug delivery system have been developed which includes adjuvants, liposomes, niosomes, self-nano emsulfying drug delivery system (SNEDDS)and combinational therapy with Curcumin-loaded Nano carriers. Although, a variety of methods have developed, the use of nanoparticle has emerged as the standard techniques for its targeted drug delivery,conjugation of nanoparticles with conventional pharmaceuticals and surface modification of nanoparticles by prodrug (such as a polymer backbone) conjugation, etc., the use of nanoparticles has emerged as the standard technique for the treatment of disease . Ayubi, M.; Karimi, M.; Abdpour, S.; Rostamizadeh, K.; Parsa, M.; Zamani, M.; Saedi, A. Magnetic nanoparticles decorated with PEGylated curcumin as dual targeted drug delivery: Synthesis, toxicity and biocompatibility study. Mater. Sci. Eng. C 2019, 104, 109810.

A comparative analysis of traditional form of curcumin and curcumin loaded nanocarriers has been described in a tabular to give an insight in to the need of the review manifesting the relevance of the study Table 1.

The review places a strong emphasis on the pharmacological actions of Curcumin with particular attention to the underlying mechanisms that support its anticancer properties. Recently, Curcumin was placed within the PAINS (pan-assay interference compound) category. PAINS primarily mediates interactions that are not covalent and exhibit varying degrees of binding affinity.(Nelson, K. M et al., 2017 & Zinatloo, A. S et al., 2014). Curcumin and its nanoforms have several medical uses due to their wide range of energy binding options. sLiposomes, micelles, polymeric nanoparticles, and lipid-based nanoparticles are examples of nanocarriers that are often utilised for the Deliveries of Curcumin are talked about in short. As the curcumin nanoforms have higher pharmacokinetic activities than the natural form, they have more functional capabilities. Curcumin that has been nano encapsulated is more bioavailable and promotes a faster metabolism. When curcumin is delivered as a nanoform, the drug's efficiency of transport to the site of action is boosted. Furthermore, the analysis sheds insight on current initiatives in creating Curcumin co-delivery systems in addition to a mix of other therapeutic approaches (photodynamic therapy, hyperthermia, etc.) to create a more potent strategy for treating cancer by combining different techniques. This review has touched upon novel aspects of curcumin nano formulations and the various aspects in which it has contributed to cancer therapy. Much emphasis has been given to immunomodulation by curcumin which is going to be a novel approach in cancer treatment. We searched the web of science, ekb.eg, Google Scholar, Pub Med, and Science Direct using keywords like "turmeric," "curcumin," "antioxidant," and "anticancer" in order to gather the data for this review. (El-Saadony et al. 2023).

2. Anti-Neoplastic Activity of Curcumin

Curcumin exhibits a wide range of actions on cancer cells, encompassing several processes like epigenetic control of gene expression, apoptosis induction, cell cycle regulation, cell signalling pathway modification, angiogenesis inhibition, immune response stimulation, metastasis suppression, and strong transcriptional inhibition (Figure.2) and Table 2.

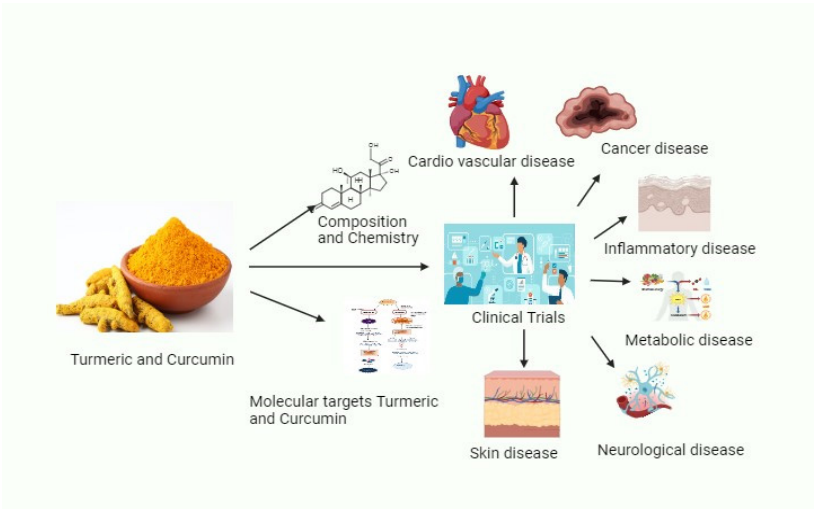

Figure 1. Pharmacological Activities of Curcumin.

Table 1: Depicting the enhanced properties of nano Curcumin over the traditional One

Features	Traditional form of Curcumin	Nano Form of Curcumin
Bioavailability	Poor	Enhanced
Stability	Degradable	Stable
Site Specific Delivery	Limited ability	More Specific
Sustained Release	Immediate	Sustained release prolong over a time
Therapeutic efficacy	Less	More

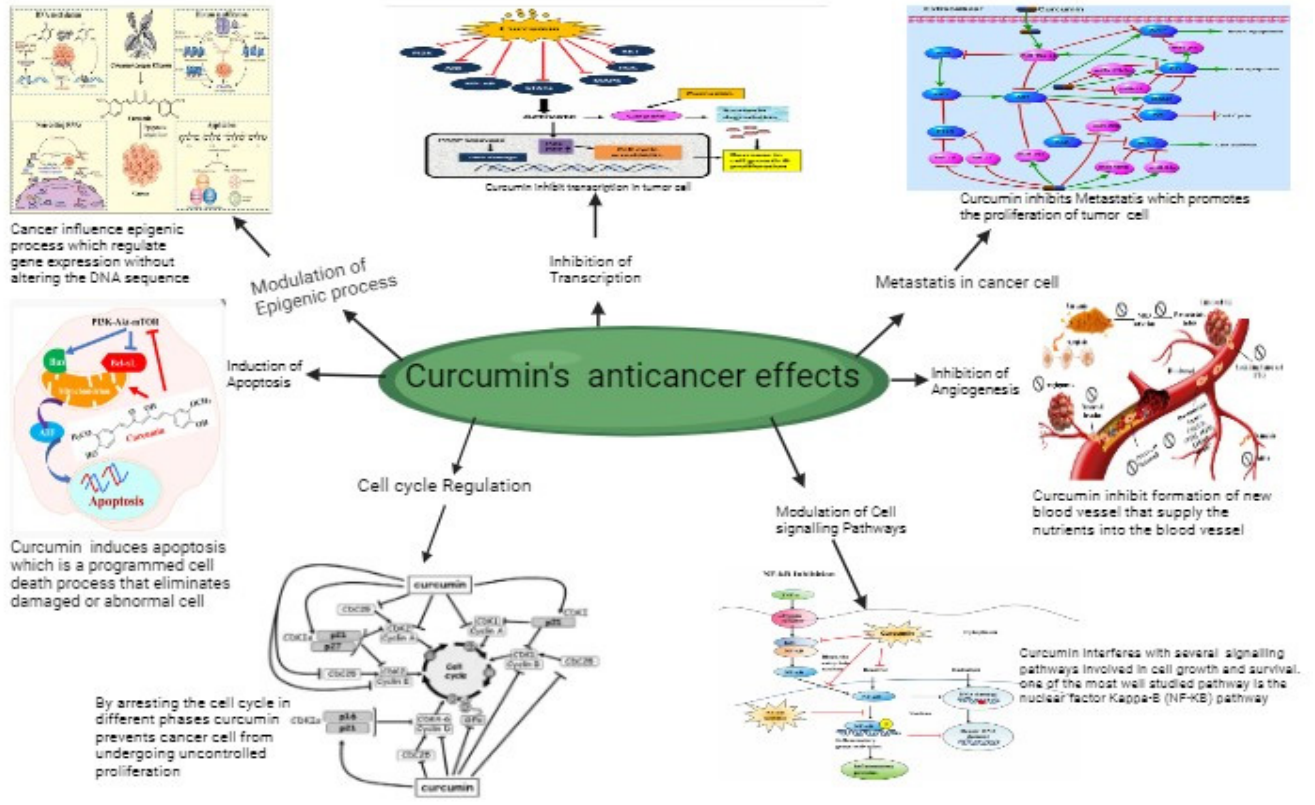

Figure 2. Anticancer activities of Curcumin

Table 2. Depicting antitumor activity and mechanism of action of curcumin in board range of cancer.

Types of Cancer	Mechanism	References
Oesophageal Cancer	Curcumin diminished NF-kB and its corresponding downstream targets through modifying Notch-1 signalling. VEGF, MMP-9, Bcl2, and cyclin D1 in oral squamous cell carcinomas.	Ghasemi et al.2019
Adenocarcinoma	turmeric initiate restraint of tissue to drop NF-KB, metalloproteinases -1(TIMP) and COX-1, AP-1, and -2, Fibroblast growth factor (FGF), VEGF, TGF-b, Cyclin E, IL-6, and -11, MMP-2, MMP-13 and MMP-9.	Anand et al.2008
Brain cancers	Turmeric initiate programming cell death in man glioblastoma T98G cells in mingling at the edge of receptor-mediated pathways.	Kuo et al. 2019
Bone cancer	Turmeric decrease cytokines and NF-kB but had no impact on p38 MAPK activation in *vivo* gum tissue from an experimental periodontal disease.	Guimarães et al.2011
Thymic cancer	Curcumin mediates thymic protection through a variety of methods, including the neutralisation of the repairing of NF-kB action, malignant-influence oxidative stress along with the retraining of the TNF-signalling pathway.	Han et al. 2020
Pulmonary cancer	Turmeric improvise the appearance of the malignant extinguish DNA J like heat shock amino acid 40(HLJF), by switch on JNK/Jon D pathways, which invasion, inhibited and metastasis in human beings alveolus malignancy cells.	Chen et al. 2008
Ovarian Cancer	Human being's gonad carcinoma cell lines SKOV3ip1, HeyA8, and HeyA8-MDR are inhibited by curcumin in athymic mice, preventing the development of ovarian cancer. Curcumin reduced Angiogenesis, micro vessel density, associated enhanced malignant cell proliferation death in the in vivo SKOV3ip1 and HeyA8 models.	Zhao et al. 2019
Cervical Cancer	In cervical cancer cells, curcumin decreases the production of E6 and E7 amount respect to time. In cervical carcinoma cells, curcumin reduced the expression of COX-2 and AP-1, suppressed IkBa phosphorylation and degradation, and blocked NF-kB activation.	Divya et al.2006
Bladder Cancer	Turmeric inhibits proliferation of tissues within the G2/M phase by upregulating Bax and p53 and downregulating Bcl2. Curcumins inhibit urothelial malignancies in a rat bladder cancer model.	Khan et al. 2020
Renal Cancer	In CakI cells downregulation of the BCL2, IAP, BCL-XL, Akt pathways along with Caspase-3 activation, DNA breakage and phospholipase C-cleavage induce death.	Hashemi et al.2022
Prostate Cancer	LNAap prostate tumor cell, curcumin reduces the number of micro vessels which inhibits their growth and prevents Angiogenesis by in vivo study.	Termini et al.2020
Ductal Carcinoma	curcumin inhibits the production of COX-2, PGE2, and IL-8, which are NF-kB -regulated gene products.	Nagaraju et al. 2019
Hepatoma	In hepatoma cell lines, curcumin inhibits the production of the Chk1, which is polypeptide promotes death as well as ceases the development of the cell cycle in the G2/M phase. During the treatment of HepG2 cells, it increases ROS and lipid peroxidation, which leads to DNA damage and growth arrest.	Soni et al. 2020
Stomach adenocarcinoma	Stomach carcinoma was inhibited by the downregulation of cyclin D1 from G1 to S phase of stomach cancer cells and also lowering the p21 activated kinase 1 along with human epidermal growth factor 2 produces by a receptor.	Cai et al. 2009
Bowel Cancer	DNA fragmentation, cell shrinkage and chromatin condensation reveals curcumin therapy, stops the spread of stimulates apoptosis and colon tumor cell lines by triggering growth detention by via caspase by means of advancement of gene which is a DNA damage inducible (DDIT3) at Mrna levels and the protein in the colon cancer cell lines -3 inhibits c—MYC, suppresses the generation of cyclin D and cyclin B, interruptions cell cycle progression, and promotes division of cells regulation 2 activation.	Shishodia et al.2007
Intestinal Cancer	Curcumin reduced the expression of b-catenin in Min/ mice's red blood cells.	Allegra et al.2020
Leukemia	Curcumin upregulated the production of P27kipl, P21wafl, and pRb while downregulating cyclin D3, disrupting the altering cell development and the cancer cell cycle is in the G0/G1 phase. Turmeric influence programming cell death in CLL-B cells by inhibiting STAT3, AKT, and NF-KB, and Myeloid cell leukemia.	Kouhpeikar et al.2019
Lymphoma	Through the production of ROS, the consequent release of cytochrome c, and modulation of the Bax protein, curcumin reduced NF-kB activity.	Wang et al. 2019
Multiple Myeloma	Curcumin inhibits the phosphorylation of STAT3 by IL-6 and subsequent nuclear translocation of STAT3.	Han et al. 2020

These complex effects/interactions ultimately shift the balance towards mortality or potent inhibition of cancer cell proliferation, highlighting the potential of Curcumin for cancer therapy.

Curcumin and its nanoforms exhibit anti-tumor properties against diverse forms of cancer (Figure 3). Curcumin regulates the tumour microenvironment and, consequently, the growth of tumours via influencing different signalling pathways. illustrates a few of the chemical processes and associated molecules that curcumin and its nanoform affect. These molecules' activities are controlled by processes like cell death, cell cycle progression, protein kinase activity, transcription factor expression,. The cancer cells underwent caspase- and mitochondria-mediated cell death as a result of the curcumin-loaded NPs. (Mundekkad et al., 2023)

2.1. Inhibition of oxidative stress in anticancer therapy

Curcumin's ability to bring about an equity in redox imbalance is an important aspect of its anticancer activity (Abadi et al. 2022). Oxidative stress arises from an inequality between the production of reactive oxygen species (ROS) and the body's capacity to oppose them through antioxidant defense mechanisms. ROS possess a high reactivity and have the potential to cause damage to many biological constituents, such as DNA, amino acid, and lipids (Juan et al. 2021). This oxidative damage has a major role in the initiation and spread of cancer (Klaunig et al. 2018). By eliminating ROS and free radicals, curcumin reduces oxidative stress and functions as a strong antioxidant. Research has demonstrated that Curcumin immediately neutralises a range of ROS. Hydroxyl radicals, singlet oxygen, and superoxide anion, among others (Ak et al. 2008). By giving away an electron or by stabilising these reactive substances with hydrogen atoms, Curcumin stops them from harming cellular structures. constructions (Indira Priyadarsini et al.2013). Based on a comprehensive review of facts about curcuminoid supplements in lowering oxidative stress; on all the examined indicators of oxidative stress, such as plasma levels of catalase and superoxide dismutase, lower levels of lipid peroxidation and glutathione (GSH) (Sahebkar et al.2015). Furthermore, the activities of catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD)—all naturally occurring antioxidant enzymes are enhanced by biomolecule curcumin (Bratovcic et al.2020). By changing dangerous ROS into less reactive forms, these enzymes are essential to the body's defence against oxidative stress (Bai et al.2022). Curcumin increases the endurance and function of these enzymes, increasing the antioxidant capacity of cells (Karimi et al. 2022). By altering signalling pathways related to redox equilibrium, Curcumin has the ability to indirectly prevent oxidative damage in addition to its direct antioxidant actions. The fundamental element erythroid 2-associated component 2 (Nrf2) pathway, for instance, can be activated by Curcumin (Huang et al.2018). One sequence- specific- DNA- binding factor that controls the formulation towards chromosome affiliated to detoxification and antioxidants is called Nrf2(Tsuchida et al.2017). Curcumin stimulates Nrf2, which causes other cytoprotective proteins and antioxidant enzymes to be upregulated. In cancer cells, this Nrf2 activation aids in the restoration of redox equilibrium and the prevention of oxidative stress (Ghareghomi et al. 2021). Curcumin aids in shielding cells from oxidative harm, including lipid peroxidation, protein oxidation, and DNA damage, by lowering oxidative stress (Samarghandian et al.2017). This is especially important for cancer treatment since cancer cells frequently show greater levels of oxidative stress than healthy ones. Curcumin may assist in preserving the integrity of cellular constituents, averting genetic instability, and advancing the general health of cells by blocking oxidative stress. It is important to remember that Curcumin has several ways of acting in cancer treatment, of which its antioxidant activity is only one. Because of its versatility, it can target several pathways involved in the initiation and spread of carcinoma. Due to its antioxidant, anti-inflammatory and other qualities, Curcumin is a good fit for integrative cancer therapy methods.

2.2. Inhibition of NF-kB activation

Turmeric have been convey to suppress the triggering towards significant element -kappa B (NF-kB), a primary translation element associated with swelling, immune response, and cancer progression. NF-kB is efficient for regulating the declaration of various genes involved in cell survival, inflammation, angiogenesis, and metastasis. Rahmani et al. showed that Curcumin suppresses NO generation, IL-2 production, and lipopolysaccharide (LPS)-induced NF-kB while enhancing NK cell cytotoxicity (Rahmani et al. 2018). (Yodkeeree et al. 2010) demonstrated that dimethoxy-curcumin successfully suppressed MDA, invasion and migration happen Breasts malignancy MB-231 cells by targeting NF-kB [57]. Curcumin prevents NF-kB activation through the possible channels listed below: a) IkB kinase (IKK) inhibition: Turmeric have the potential to prevent IKK activation, which is the process by which an enzyme complex phosphorylates and destroys the inhibitor of NF-kB (IkB). Normally, IkB attaches itself to NF-kB to stop it from moving into the nucleus and activating target genes. Curcumin inhibits IKK, which prevents IkB from being phosphorylated and degraded and, as a result, inhibits NF-kB activation. b) Curcumin has the ability to directly attach to NF-kB's DNA-binding domain, inhibiting the protein's ability to connect with target gene promoters. This binding stops NF-kB from attaching to DNA and starting the transcription of genes linked to the development of inflammation and cancer. c) Alteration of signalling pathways associated with NF-kB: Curcumin has the ability to alter signalling pathways prior

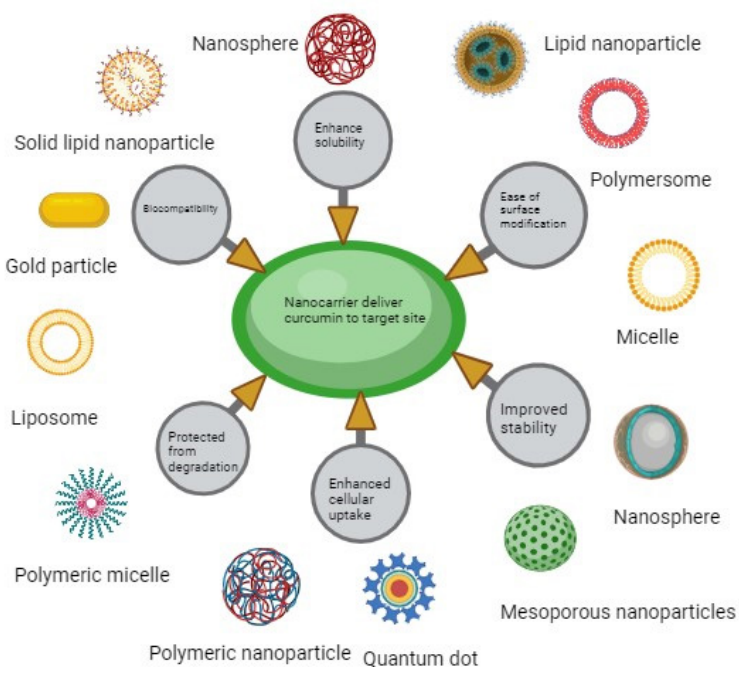

Figure 3. Different Nanocarriers for Curcumin encapsulation and delivery

to NF-kB activation. It has been demonstrated, for instance, to prevent the activation of protein kinase C (PKC), which is important due to the trigger of NF-kB. Additionally, curcumin prevents Akt from becoming phosphorylated and activated, which is a crucial signalling molecule that encourages NF-kB activity. Through focusing on these upstream signalling pathways, CUR successfully reduces the downstream consequences of NF-kB activation. It is significant to note that cellular environment, treatment concentration, and time are some of the variables that might affect how CUR affects NF-kB (Katsori et al. 2015).

Furthermore, CUR's low bioavailability could restrict its potential to directly affect NF-kB in vivo. The usage of formulations or combination medicines, for example, are being investigated as approaches to increase CUR's bioavailability and maximise its therapeutic potential in targeting NF-kB and related pathways in cancer.

3. Antioxidant activity, redox reactions, and metal chelation

The antioxidant properties of CUR rely heavily on the presence of either the hydroxyl (OH) group or the methylene (CH_2) group within the 1,3-diketone structure. As a result, CUR's antioxidant mechanisms mainly involve transferring hydrogen atoms from phenolic groups and hydrogen radicals from the CH_2 group of the diketone (Akter et al. 2023). Phenolic compounds can neutralize free radicals or act as antioxidants by donating hydrogen atoms from their phenolic rings, effectively counteracting these radicals (Jung et al. 2023). In other words, the presence of multiple phenolic groups enhances CUR's antioxidant capacity, allowing it to scavenge a wide range of reactive species and protect against oxidative damage. CUR's remarkable antioxidant effectiveness is significantly attributed to 3 various dexterous groups (α,β-unsaturated double bond, β-diketone, and aromatic o-methoxy phenolic group) (Parthiban et al.2022). Previous studies suggest that CUR's antioxidant mechanism primarily involves the Hydrogen-Atom Transfer (HAT) process for quenching radicals, with less involvement of the Mechanisms of sequential proton loss electron transfer (SPL-ET) and single electron transfer (SET) (Barzegar 2012; Barzegar et al.2011).

Furthermore, the phenolic groups can participate in redox reactions, acting as electron donors or acceptors. These redox reactions can influence the cellular redox balance and modulate signaling pathways involved in cell growth, inflammation, and cancer progression. Besides, the diketone moiety is responsible for CUR's ability to scavenge free radicals and neutralize ROS. The β-diketone structure undergoes redox reactions, donating electrons to radicals and stabilizing them. This antioxidant effect assists in defending cells against the oxidative damage created by ROS, which is responsible for a number of disease processes, including cancer (Parthiban et al.2022; Barzegar 2012; Barzegar et al.2011).

In general, Curcumin actively participates in the neutralization of diverse oxidants, encompassing hydroxyl radicals, singlet oxygen, hydrogen peroxide, and superoxide anions. This prevents damage to molecules that are in motion or present within tissues (Sachithanandam et al.2022). (Hsieh et al.2017) demonstrated that blocking the phenolic category be a dexterous design to extend the circulation time Curcumin in the body. In addition, Curcumin diketone moiety can also chelate metal ions, such as iron and copper. Chelation involves the formation of stable complexes between the metal ions and curcumin. This property is important because metal ions can catalyze the endurance of oxidants and contribute to decomposition strain. By chelating metal ions, Curcumin helps to inhibit their pro-oxidant effects and reduces oxidative damage (Agrawal et al.2019). All of the aforementioned mechanisms are essential for managing cancer and improving Curcumin anticancer properties. Some of the cases that were treated with Curcumin or its composite are listed below.

3.1 Colon cancer

The work by (Aromokeye et al.2022) was centred on the advancement of colon cancer and also looked at potential molecular explanations for this anti-colon cancer action. Even while the individual medications only marginally lowered the frequency in human cancer of the colon incidences CL-188 unit at the chosen dosages, the pairwise combination screening combination of luteolin (LUT) at 30 M and curcumin (Cur) at 15 M (C15L30) significantly inhibited the proliferation of these cells This result was observed in additional DLD-1 colon cancer cells, suggesting that C15L30 may inhibit multiple types of colon cancer cells in a synergistic manner.

3.2 Lung cancer

Curcumin nanoparticles based on Carboxyl methyl chitosan(CMCS) improve the results of medicinal values. With the ability to precisely regulate medication release based on pH and ROS levels, CMCS has the potential to targeting pulmonary malignancies that exhibit the receptor for transferrin (TfR). This outcome regarding research disclose that the drug loading capabilities of docetaxel (DTX) and curcumin were 6.48% and 7.82 percent, respectively. High concentrations (up to 500 g/mL) did not compromise excellent biosafety. More importantly, the T7-CMCSBAPE-DTX/CUR (CBT-DC) complicated illusive superior malignancy in vitro and in vivo compared to DTX (Zhu et al.2021).

3.3 Prostate cancer

The impact of EGFR-mediated signalling upon the PC-3 as well as the DU145 cells' activation of ERK were also studied. The results showed that EGFR is overexpressed in PC-3 and DU145 cells, and that EGFR expression and ERK activation were decreased by chemotherapeutic medications or curcumin. The results demonstrated that curcumin treatment, like chemotherapy

medications (paclitaxel, ziceptele, and docetaxel), decreased DU145 and PC-3 cell viability in an amount based on approach. The impact of EGFR-mediated activation in the DU145 along with PC-3 cells has an impact on ERK activation was also studied. The results showed that EGFR is overexpressed in PC-3 and DU145 cells, and that EGFR expression and ERK activation were decreased by chemotherapeutic medications or curcumin (Boccellino et al.2022).

4. Nanocarriers for Curcumin encapsulation and delivery

Nanocarriers (NCs) are recognized as superior options for transporting natural bioactive substances such as Curcumin, which face limitations due to its tiny duration in circulation, inadequate bioaccumulation, and minimum dissolved in aqueous surroundings (Senturk et al.2023). The incorporation of Curcumin into NCs has many benefits that considerably increase its therapeutic potential. Firstly, NCs enhance the solubility of Curcumin, preventing aggregation or precipitation and facilitating its systemic delivery in aqueous media (Chuan et al. 2015). Secondly, NCs provide protection from enzymatic and physical degradation, ensuring the stability of Curcumin during circulation and storage within the body (Wezgowiec et al.2021). Thirdly, these carriers enable the manage along with comfort deliver of Curcumin, prolonging its presence in the bloodstream and enhancing its bioavailability (Asif et al.2023). NCs can be strategically designed to facilitate the precise transport of Curcumin to specific tissues or cells, thereby decrease down regulation efficacy along with inducing s therapeutic effectiveness, especially in the context of cancer therapy (Senturk et al.2023; Senturk et al.2021). Furthermore, NCs allow for combination therapies by co-delivering Curcumin with other therapeutic agents, resulting in synergistic effects and improved anticancer efficacy (Zhang et al.2016; Liu et al.2016). As a result, a range of NCs, including liposomes, micelles, polymeric NPs, lipid-based NPs, etc., have been explored and optimized to amplify the conveyance along with restorative benefit of Curcumin (Figure 3.).

By leveraging the advantages of NCs, researchers aim to get control of the challenges corelated with Curcumin's low emulsifiable and short half-life, paving the way for improved clinical applications of Curcumin as an effective anticancer agent. Extensive studies has been dedicated to incorporating Curcumin within nano-delivery systems, including polymeric nanoparticles and micelles, lipid-based nanoparticles like liposomes and solid lipid nanomaterial, aminoacid nanomaterial, silica-based nanomaterial (Pan et al.2020; Li et al.2014) etc. These research determines the promising results, emphasizing the potential of nanocarriers to improve Curcumin delivery and therapeutic outcomes. Here are some notable findings:

4.1 Polymeric nanoparticles: A number of polymers, including chitosan, enhance the prohibited mobility or persistence duration, NCs including poly (lactic-co-glycolic acid) (PLGA), poly (lactic acid) (PLA), polyethylene glycol (PEG), along with polyvinyl alcohol (PVA) have been successfully used of Curcumin. These NCs showed enhance dissoluble along with strength of Turmeric, leading to enhanced cellular uptake and cytotoxicity against cancer cells corelate to free Turmeric (Udompornmongkol et al.2015). Alizadeh et al. showed that Curcumin-loaded polymeric nanocarriers (oleoyl chloride-methoxy-PEG) could significantly inhibit the proliferation of hepatocellular carcinoma cells (Alizadeh et al.2015). Additionally, polymeric NCs enabled the sustained release of Curcumin, prolonging its presence in the target tissue, and improving therapeutic effects (Chen et al.2019).

4.2 Phospholipid-based nanocarrier: It has also been possible to administer curcumin via lipid-based nanoparticle, such as nanostructured lipid carriers (NLCs) along with solid lipid nanoparticles (SLNs). The lipophilic nature of Curcumin is compatible with lipid-based nanoparticles, allowing for efficient encapsulation and dispatch to site specific (Chirio et al.2019). (Khan et al.2020) demonstrated that as the lipid ratio increased in lipid-polymer hybrid nanoparticles, the encapsulation efficiency of Curcumin increased from roughly 60% to 80% . The modification of surface characteristics of SLNs can confer distinctive attributes to these nanoparticles, such as enhanced targeting capabilities (Paliwal et al.2020) and improved bioavailability. Tri-stearin and PEGylated emulsifiers, for instance, were utilized in the fabrication of SLNs with the aim of improving the oral bioavailability of Curcumin (Ban et al.2020). Furthermore, Curcumin-loaded lipid-based NPs exhibited improved cellular uptake, increased cytotoxicity, and enhanced antitumor activity across different cancer types (Venkatas et al.2022; Wang et al.2018; Sun et al.2013).

4.3 Liposomes: Liposomes are lipid-based vesicles that can encapsulate hydrophobic substances like CUR within their aqueous core or lipid bilayer (Bnyan et al.2018). Liposomes offer advantages such as biocatalysis, stability, and ease of surface modification for targeted delivery. Mahmud et al. showed that when the molar ratio of Curcumin to lipids was 0.05/10, Curcumin-loaded liposomes displayed a high degree of stability with a remarkable 96% Curcumin encapsulation efficiency (Mahmud et al.2016). These Curcumin-loaded liposomal formulations exhibited strong carcinoma activity against panchromatic malignant cells (AsPC-1 and BxPC-3) but were less toxic to a normal cell line. Furthermore, targeted liposomes, modified with specific ligands, showed enhanced cellular uptake, and improved tumor-targeting capabilities (Feng et al.2017). According to (Jiang et al.2018) in lung cancer cell lines, modified

liposomes with arginine, glycine, and aspartic acid peptide (RGD) and co-loaded with paclitaxel and Turmeric increased biological absorption along with carcinoma action in comparison to unmodified liposomes .

4.4 Micelles: Biocompatible micelles are prefabricated composition formed by amphiphilic molecules, capable of solubilizing hydrophobic substances like Curcumin in their hydrophobic core (Askarizadeh et al.2020). (Kumbar et al.2022) found that Turmeric -nano micelles had much better cytotoxicity and cellular absorption than native Curcumin in cisplatin-impenetrable oral carcinoma cell lines (Zhao et al.2015) demonstrated that RGD-modified Curcumin-loaded polymeric micelles improved cellular absorption in both human umbilical vein endothelial cells (HUVEC) and mouse melanoma cell lines (B16) .These RGD-modified Curcumin-loaded polymeric micelles also exhibited a stronger inhibitory effect on tumor growth in B16 tumor-bearing mice as compared to non-RGD-modified micelles.

Overall, research has continuously demonstrated that Curcumin's delivery and therapeutic effects are improved by nanocarriers, including as liposomes, micelles, and polymeric or lipid-based nanoparticles. The solvability, constancy, along with bioassay of Turmeric are intensify by these nanocarriers, enabling targeted administration to tumour tissues and cells. Additionally, in preclinical research, they have shown enhanced cytotoxicity and better cellular absorption of Curcumin, indicating their potential for clinical translation in enhancing Curcumin's therapeutic effectiveness as an anticancer drug.

5. Combination therapy with CURCUMIN -loaded Nanocarriers

Combining Curcumin-loaded nanocarriers with other cancer treatment modalities such as chemotherapy, emission therapy, biological therapy, magnetic nano hyperthermia, photodynamic therapy, and targeted therapy has the potential to attain a more effective system for carcinoma therapy.

5.1. Co-delivery of CURCUMIN

It is increasingly recognized that the combined administration of drugs helps in combating various diseases such as cancer, multidrug resistance, osteoarthritis and others. This approach offers the advantages of synergistic drug action, reduced drug-related toxicity, and resolution of bioavailability issues (Patra et al.2018). Therefore, coloading with other medications can boost the low solubility medicine Curcumin's bioavailability and pharmacological action. A synergistic cytotoxic impact that might overcome drug resistance was achieved by the mass of polymers in which carcinoma medicines be supplied adjoining Turmeric (Alven, et al.2020). The combination of Curcumin or Curcumin-loaded NCs with other agents can improve the effectiveness of cancer treatment through various mechanisms:

5.2 Increased cytotoxicity: Cancer cells have been shown to become more sensitive to chemotherapeutic drugs when they are treated with curcumin (Kubczak et al. 2021). Curcumin can modulate numerous specified route elaborate in drug resistance, such as inhibition of drug efflux pumps and modulation of apoptosis-related proteins. When curcumin-loaded nanocarriers are co-administered with chemotherapeutic agents, they can enhance the cytotoxic effects of the agents and overcome drug resistance, leading to improved cancer cell killing. (Chen et al.2020) demonstrated the efficacy of synergistic combination therapy by developing a nanocarrier for the co-administering of cabazitaxel (CTX) and Turmeric to cure prostate carcinoma. The application of liposomes co-loaded with paclitaxel and Curcumin outcome in a complementary restorative outcome for targeted chemotherapy, leading to a greater ability to stop lung cancer cells from proliferating lines (Jiang et al. 2018). Also, it has been shown that Curcumin-loaded PLGA nanospheres have a significant potential for clinical application as an adjuvant therapy for prostate cancer (Rodrigues et al. 2019). Thus, combination therapy that uses Curcumin as an adjuvant medication put into nanoparticles may enhance Curcumin's use in clinical settings. (Wu et al. 2021).

5.3 Reduction of chemotherapy side effects: Chemotherapeutic drugs often have dose-limiting toxicities, which can lead to adverse side effects. Curcumin has been demonstrated to possess protective property against chemotherapy-induced toxicity. (Salahshoor et al.2016) showed that Turmeric tested its preservative impact again liver toxicity. Therefore, by combining Curcumin-loaded nanocarriers with chemotherapy, the therapeutic efficacy can be maintained or even improved, while potentially reducing the side effects associated with high chemotherapeutic drug doses.

5.4 Synergistic mechanisms of action: Curcumin has been shown to exhibit diverse mechanisms of action that complement the mechanisms of chemotherapy drugs. For example, according to Wang et al. (2019), curcumin has the ability to reduce angiogenesis, cause apoptosis, prevent cell division, and alter inflammatory pathways. In comparison to treatment with free FU/Curcumin and medication alone, the aggregate cure of 5-Fluorouracil (5-FU)/Turmeric co-loaded anticipate to large intestine carcinoma cells shown higher synergistic therapeutic efficacy that included cytotoxicity, cell cycle arrest, and apoptosis. (Sadeghi-Abandansari et al. 2021). As a result, when combined with agents, Curcumin-loaded nanocarriers can exert synergistic effects, targeting multiple pathways simultaneously and enhancing the overall therapeutic response.

5.5 Overcoming multidrug resistance: Multidrug resistance (MDR) is a common challenge in chemotherapy, where cancer cells develop resistance to multiple drugs. Curcumin has shown promise in overcoming inhibition of drug efflux leads to MDR.pumps and modulation of drug resistance-related proteins (Lopes-Rodrigues et al. 2016). Compared to cells express aside PI3K restraint alone, murine leukemia cells mediated with a amalgam of PI3K liability along with turmeric expressed less P-glycoprotein. Consequently, it was discovered that Curcumin may inhibit P-glycoprotein synthesis in murine leukaemia cell lines (Choi et al.2008). The possibility of defeating MDR and regaining chemotherapy sensitivity can be increased by adding Curcumin-loaded nanocarriers to chemotherapy regimens.

Numerous preclinical and clinical investigations have examined the synergistic effects of nanocarriers loaded with curcumin in conjunction with other chemotherapeutic medications. Improved tumour regression, higher survival rates, and less toxicity related to chemotherapy have all been reported as benefits of these research. All things considered, combining curcumin-loaded nanocarriers with other drugs is a viable approach to enhancing the effectiveness of cancer treatment. Through the use of Curcumin's distinct characteristics and nanocarriers' drug delivery capacities, this collaborative strategy holds promise for augmenting chemotherapy effectiveness, surmounting drug resistance, mitigating adverse effects, and opening up novel paths for tailored and focused cancer treatment (Hafez et al.2022).

6. Combination of Curcumin-loaded nanocarriers with magnetic nano hyperthermia

The nanoparticles are heated under control (Senturk et al.2023; Senturk et al. 2019) To produce heat at the intended location, it may also be utilised in conjunction with a amplitude towards origin, such as radiofrequency hyperthermia (Senturk et al.2021), ultrasonic hyperthermia (Sheybani et al.2020), magnetic fluid hyperthermia (Kharat et al. 2020), etc. A potential method for improved cancer treatment is the combination of Curcumin with magnetic nano hyperthermia, a method that produces localised heat by using magnetic nanoparticles. (Rao et al.2014) enlarge melting-impassive Turmeric-loaded compound NPs for prostate malignancy carcinoma (PC-3). The anticancer potential of Curcumin-loaded polymeric nanoparticles is notably increased by mild hyperthermia, leading to a reduction of over 7-fold in its inhibitory concentration to decrease cell viability in PC-3 cells. When Curcumin is combined with magnetic nano hyperthermia, several synergistic effects can be achieved:

6.1 Enhanced heat-mediated cytotoxicity: Turmeric have been shown to soften carcinoma cells to hyperthermia-induced cytotoxicity. Hyperthermia increases the susceptibility of cancer cells to the cytotoxic effects of Curcumin by disrupting cellular membranes, inhibiting DNA repair mechanisms, and inducing apoptosis. The combination of Curcumin and magnetic nano hyperthermia can lead to synergistic cytotoxic effects, resulting in improved cancer cell killing. In a study, a glioma-targeting exosome that co-loaded Turmeric along with superparamagnetic iron oxide nanoparticles (SPIONs) was created. This exosome demonstrated effective passage through the blood-brain barrier (BBB), leading to targeted imaging and a synergistic therapeutic effect, utilizing SPION-induced hyperthermia and Curcumin-based treatment (Jia et al.2018). A combination of Curcumin and hyperthermia treatment in murine Lewis's lung carcinoma cells promoted apoptosis. Additionally, the co-treatment in the *in vivo* model prevented tumor growth, reduced angiogenesis, and promoted apoptosis (Tang et al. 2013).

6.2 Improved curcumin delivery and bioavailability: Magnetic nanoparticles can serve as carriers for Curcumin, allowing for targeted delivery to the tumor site. The nanoparticles can be loaded with Curcumin and guided to the tumor through an extracellular fascination area. Nanocarriers targeting the folate receptor for fascination-boosted turmeric transportation have the ability to selectively implement ameliorative envoy to cancer cells while avoiding side effects (Purushothaman et al. 2019).

This targeted delivery enhances Curcumin's accumulation within the tumor, improving its therapeutic efficacy. Although hyperthermia enhances the flexibility of the malignant vessels, and it may additionally enhance the uptake of nanomaterials in the cancerous cells. (Mahmoud et al. 2022). On the other hand, the application of hyperthermia can trigger that liberation as regards turmeric from the NPs. The heat generated by the magnetic nanoparticles can induce the disruption of the carrier matrix or trigger the phase transition of the thermosensitive materials (Nguyen et al 2021), leading to the controlled release of Curcumin. The combination of Curcumin with hyperthermia have be explore in preclinical studies, demonstrating improved therapeutic outcomes in various cancer models (Jia et al.2018). These studies have shown enhanced tumor regression, increased Curcumin uptake, and improved survival rates compared to monotherapy approaches.

A comparative met analysis has been carried out to depict the previous work and present studies to give a schematic representation of the study over the previous ones Table 3.

7. Current Status

Current research efforts in Curcumin-loaded nanocarriers are focused on improving their design, effectiveness, and safety in order to maximize their potential for clinical translation. Currently, some of the emerging trends and future directions are being discussed.

Table 3. Showing comparative analysis between Previous work and Present study.

Previous Work	Present Study
Curcumin's low bioavailability,which seems to be mostly caused by poor absorption, fast metabolism, and rapid elimination, is one of the main issues with taking it orally by itself. Hewlings, S. J., & Kalman, D. S. (2017).	In the present work due emphasis has been given to nanocarriers to encapsulate Curcumin for its enhanced bioavailability.
Mansouri et al have mentioned about the prevention of activitation of *NFkappaB* as major cause of cancer cure by curcumin.(Clinical effects of curcumin in enhancing cancer therapy: A systematic review. Mansouri(2020).	Detailed illustrations has been chucked out showing Curcumin prevention of NF-kB activation through the possible channels listed below: a) IkB kinase (IKK) inhibition: b) Curcumin has the ability to directly attach to NF-kB's DNA-binding domain, inhibiting the protein's ability to connect with target gene promoters.c) Alteration of signalling pathways associated with NF-kB: Curcumin has the ability to alter signalling pathways prior to NF-kB activation.
Excellent antioxidant and free-radical quenching characteristics of curcumin are key factors in the compound's ability to suppress the early phases of carcinogenesis. Wilken et al (2011).	An elaborative description has been presented about Antioxidant and its mechanisms. CUR's antioxidant mechanisms mainly involve transferring hydrogen atoms from phenolic groups and hydrogen radicals from the CH_2 group of the diketone
Combining nanocurcumin with already available conventional medications in combination therapy will undoubtedly deliver more favorable results, Mundekkad et al. (2023).	Combination therapy with CURCUMIN -loaded nanocarriers has been assigned a separate point and elaborated described under 5.

7.1 Optimization of Nanocarriers properties: Researchers are exploring various approaches to optimize the design and properties of nanocarriers for Curcumin delivery. This includes fine-tuning the size, shape, surface charge, and stability of the nanocarriers to achieve optimal drug loading, controlled release, and enhanced tumor penetration. Improved tumour targeting, treatment effectiveness, and real-time monitoring are other goals being pursued by developing multifunctional nanocarriers with integrated targeting ligands, stimuli-responsive components, and imaging agents.

7.2 Overcoming biological barriers: Efforts are being made to overcome biological barriers that hinder efficient drug delivery, such as the extracellular matrix, physiological barriers like the blood-brain barrier (BBB) and tumor microenvironment. Techniques include adding certain ligands or peptides to the surface of improved nanocarrier their ability to penetrate and accumulate inside tumour tissues. To get beyond these obstacles, combination strategies are also being investigated, such as the codelivery of Curcumin with permeability-enhancing substances or the application of physical methods like magnetic guiding or ultrasound.

7.3 Theranostic:

Nanocarriers loaded with curcumin can behave as theranostic agents, allowing for both therapeutic and diagnostic applications. The natural fluorescence of Curcumin makes it possible to image and track the distribution and administration of drugs in real time. The nanocarriers can offer improved imaging capabilities by adding more imaging or contrast chemicals, enabling precise tumour visualisation and treatment response monitoring. The theranostic potential of dendrimer-Au hybrid structures loaded with Curcumin was examined in research. According to the results, Curcumin-loaded PEGylated Au dendrimers are effective CT imaging probes and have a high therapeutic index against colorectal cancer and good X-ray attenuation (Alibolandi et al. 2018). By permitting therapy modifications, giving real-time feedback on treatment efficacy, and enhancing patient outcomes, this theranostic technique can support personalised medicine.

7.4 Drug delivery to inaccessible sites

Therapeutic drugs may be delivered via nanocarriers, particularly those carrying Curcumin, to previously unreachable tumour locations. There are the possibilities of creating neurocarriers capable of carrying Curcumin across the blood-brain barrier.

Additionally, by getting beyond the physiological obstacles of the tumour, such as a thick extracellular matrix or a low blood supply, nanocarriers might enhance medication penetration and accumulation within the tumour. Its capacity to transport CUR to difficult tumour sites expands its therapeutic range and creates new therapeutic options for the medication towards malignancy.

7.5 Prevention and adjuvant therapy

Curcumin-loaded nanocarriers may also be used as adjuvant treatment and in the prevention of cancer. Because of Curcumin chemo preventive qualities, which include its anti-inflammatory and antioxidant actions, it is a potential treatment for cancer prognosis. Effective preventative measures can be made possible by improving the bioavailability and stability of Curcumin by administering it via nanocarriers. Furthermore, CUR loaded nanocarriers can be used to traditional therapies as adjuvants to increase their effectiveness and lessen their negative effects.

8. Research gap and future perspectives

While research has been done on the signalling pathways that curcumin and its nanoform influence in human diseases, much more is needed about the dosage and potential harmful effects of curcumin nanoform administration. The entire therapeutic profile of nanocurcumin is yet to be determined. However, mapping shows a a great deal of promise in this field to identify new targets, pathways, and therapeutic combinations that will improve the molecule's profile and aid in the creation of new medications to treat a variety of illnesses. While research has been done on the signalling pathways that curcumin and its nanoform influence in human diseases, much more has to be discovered about the dosage and potential harmful effects of curcumin nanoform administration. The full therapeutic profile of nanocurcumin has not yet been determined, but there is a great deal of promise in this field to identify novel targets, pathways, and therapeutic combinations that will improve the molecule's profile and aid in the creation of new medications to treat a range of illnesses. (Mundekkad et al., 2023)

Better outcomes will undoubtedly come from combination therapy combining nanocurcumin with currently available conventional medications. Advanced forms of curcumin, like niosomes and cubosomes (lyotropic liquid crystalline lipid nanoparticles), can lessen the drawbacks of employing curcumin as a cancer treatment by encasing hydrophilic and hydrophobic drugs and shielding the carrier drug from deterioration on a physical, chemical, and even biological level.

9. Conclusion

The employment of CUR-loaded nanocarriers has unclogged new opportunities to enhance the delivery and effect of Curcumin as an efficient antitumor medication. However, translating this potential into clinical applications requires concerted efforts to address existing challenges and optimize various aspects of nanocarriers technology. These includes overcoming biological barriers, implementing combination therapies with synergistic approaches and improving theranostic abilities. To evaluate the long term safety, pharmacokinetics and therapeutic effects of CUR-loaded nanocarriers, extensive preclinical and clinical studies are

required. However, with continued advances in nanotechnology and targeted drug delivery systems, CUR-containing nanocarriers have the potential to revolutionize cancer treatment by providing targeted, effective and personalized therapeutic options.

Author contribution

K.B. developed the hypothesis and wrote the initial draft, P.M. contributed to data curation and analysis, H.B.S. contributed to conceptualization and supervision. K.B. and I.J.D. were credited for comprehensive edit, which was then reviewed and approved by all authors.

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Competing financial interests

The authors have no conflict of interest.

References

Abadi, A. J., Mirzaei, S., Mahabady, M. K., Hashemi, F., Zabolian, A., Hashemi, F., ... & Sethi, G. (2022). Curcumin and its derivatives in cancer therapy: Potentiating antitumor activity of cisplatin and reducing side effects. Phytotherapy Research, 36(1), 189-213.

Agrawal, N. D., Nirala, S. K., Bhadauria, M., Srivastava, S., & Shukla, S. (2019). Protective potential of Moringa oleifera Lam. along with curcumin and piperine against beryllium-induced alterations in hepatorenal biochemistry and ultramorphology in rats. Indian Journal of Biochemistry and Biophysics (IJBB), 56(1), 70-80.

Ak, T., & Gülçin, I. (2008). Antioxidant and radical scavenging properties of curcumin. Chemico-biological interactions, 174(1), 27-37.

Akter, T., Zahan, M. S., Nawal, N., Rahman, H., Tanjum, T. N., Arafat, K. I., ... & Uddin, M. J. (2023). Potentials of curcumin against polycystic ovary syndrome: Pharmacological insights and therapeutic promises. Heliyon,9,1-16.

Alibolandi, M., Hoseini, F., Mohammadi, M., Ramezani, P., Einafshar, E., Taghdisi, S. M., ... & Abnous, K. (2018). Curcumin-entrapped MUC-1 aptamer targeted dendrimer-gold hybrid nanostructure as a theranostic system for colon adenocarcinoma. International journal of pharmaceutics, 549(1-2), 67-75.

Alizadeh, A. M., Sadeghizadeh, M., Najafi, F., Ardestani, S. K., Erfani-Moghadam, V., Khaniki, M., ... & Mohagheghi, M. A. (2015). Encapsulation of curcumin in diblock copolymer micelles for cancer therapy. BioMed research international, 2015,1-14.

Allegra, A., Di Gioacchino, M., Tonacci, A., Musolino, C., & Gangemi, S. (2020). Immunopathology of SARS-CoV-2 infection: immune cells and mediators, prognostic factors, and immune-therapeutic implications. International journal of molecular sciences, 21(13), 1-13.

Almatroodi, S. A., Syed, M. A.,...& Rahmani, A. H. (2021). Potential therapeutic targets of Curcumin, most abundant active compound of turmeric spice: Role in the management of various types of cancer. Recent patents on anti-cancer drug discovery,16(1), 3-29.

Alven, S., & Aderibigbe, B. A. (2020). Efficacy of polymer-based nanocarriers for co-delivery of curcumin and selected anticancer drugs. Nanomaterials, 10(8), 1-28.

Anand, P., Sundaram, C., Jhurani, S., Kunnumakkara, A. B., & Aggarwal, B. B. (2008). Curcumin and cancer: an "old-age" disease with an "age-old" solution. Cancer letters, 267(1), 133-164.

Aromokeye, R., & Si, H. (2022). Combined Curcumin and Luteolin synergistically inhibit Colon Cancer Associated with Notch1 and TGF-β signaling pathways in cultured cells and xenograft mice. Cancers, 14(12), 1-14.

Asif, H. M., Zafar, F., Ahmad, K., Iqbal, A., Shaheen, G., Ansari, K. A., & Ghaffar, S. (2023). Synthesis, characterization and evaluation of anti-arthritic and anti-inflammatory potential of curcumin loaded chitosan nanoparticles. Scientific Reports, 13, 1-10.

Askarizadeh, A., Barreto, G. E., Henney, N. C., Majeed, M., & Sahebkar, A. (2020). Neuroprotection by curcumin: A review on brain delivery strategies. International Journal of Pharmaceutics, 585, 1-59.

Ayubi, M.; Karimi, M.; Abdpour, S.; Rostamizadeh, K.; Parsa, M.; Zamani, M.; Saedi, A. Magnetic nanoparticles decorated with PEGylated curcumin as dual targeted drug delivery: Synthesis, toxicity and biocompatibility study. Mater. Sci. Eng. C 2019, 104, 109810.

Bai, L., Xu, D., Zhou, Y. M., Zhang, Y. B., Zhang, H., Chen, Y. B., & Cui, Y. L. (2022). Antioxidant activities of natural polysaccharides and their derivatives for biomedical and medicinal applications. Antioxidants, 11(12), 1-31.

Ban, C., Jo, M., Park, Y. H., Kim, J. H., Han, J. Y., Lee, K. W., ... & Choi, Y. J. (2020). Enhancing the oral bioavailability of curcumin using solid lipid nanoparticles. Food chemistry, 302, 125328.

Barzegar, A. (2012). The role of electron-transfer and H-atom donation on the superb antioxidant activity and free radical reaction of curcumin. Food chemistry, 135(3), 1369-1376.

Barzegar, A., & Moosavi-Movahedi, A. A. (2011). Intracellular ROS protection efficiency and free radical-scavenging activity of curcumin. PloS one, 6(10), 1-7.

Bhandarkar, S. S., Arbiser, J. L. (2007). Curcumin as an inhibitor of angiogenesis. The molecular targets and therapeutic uses of curcumin in health and disease, 595,185-195.

Bnyan, R., Khan, I., Ehtezazi, T., Saleem, I., Gordon, S., O'Neill, F., & Roberts, M. (2018). Surfactant effects on lipid-based vesicles properties. Journal of pharmaceutical sciences, 107(5), 1237-1246.

Boccellino, M., Ambrosio, P., Ballini, A., De Vito, D., Scacco, S., Cantore, S., ... & Di Domenico, M. (2022). The role of curcumin in prostate cancer cells and derived spheroids. Cancers, 14(14), 1-18.

Bratovcic, A. (2020). Antioxidant enzymes and their role in preventing cell damage. Acta Sci. Nutr. Health, 4, 1-7.

Cai, X. Z., Wang, J., Xiao-Dong, L., Wang, G. L., Liu, F. N., Cheng, M. S., & Li, F. (2009). Curcumin suppresses proliferation and invasion in human gastric cancer cells by down-regulation of PAK1 activity and cyclin D1 expression. Cancer biology & therapy, 8(14), 1360-1368.

Chen, H. W., Lee, J. Y., Huang, J. Y., Wang, C. C., Chen, W. J., Su, S. F., & Yang, P. C. (2008). Curcumin inhibits lung cancer cell invasion and metastasis through the tumor suppressor HLJ1. Cancer research, 68(18), 7428-7438.

Chen, X. P., Li, Y., Zhang, Y., & Li, G. W. (2019). Formulation, characterization and evaluation of curcumin-loaded PLGA-TPGS nanoparticles for liver cancer treatment. Drug design, development and therapy,13, 3569-3578.

Chen, Y., Deng, Y., Zhu, C., & Xiang, C. (2020). Anti-prostate cancer therapy: aptamer-functionalized, curcumin and cabazitaxel co-delivered, tumor targeted lipid-polymer hybrid nanoparticles. Biomedicine & Pharmacotherapy, 127, 1-8.

Chirio, D., Peira, E., Dianzani, C., Muntoni, E., Gigliotti, C. L., Ferrara, B., ... & Gallarate, M. (2019). Development of solid lipid nanoparticles by cold dilution of microemulsions: curcumin loading, preliminary in vitro studies, and biodistribution. Nanomaterials, 9(2), 1-17.

Choi, B. H., Kim, C. G., Lim, Y., Shin, S. Y., & Lee, Y. H. (2008). Curcumin down-regulates the multidrug-resistance mdr1b gene by inhibiting the PI3K/Akt/NFκB pathway. Cancer letters, 259(1), 111-118.

Chou, Y. T., Koh, Y. C., Nagabhushanam, K., Ho, C. T., & Pan, M. H. A natural degradant of curcumin, feruloyl acetone inhibits cell proliferation via inducing cell cycle arrest and a mitochondrial apoptotic pathway in HCT116 colon cancer cells. Molecules, 2021,26(16), 1-16.

Chuan, L. I., Zhang, J., Yu-Jiao, Z. U., Shu-Fang, N. I. E., Jun, C. A. O., Qian, W. A. N. G., ... & Shu, W. A. N. G. (2015). Biocompatible and biodegradable nanoparticles for enhancement of anti-cancer activities of phytochemicals. Chinese journal of natural medicines, 13(9), 641-652.

Divya, C. S., Pillai, M. R. (2006) Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFκB and AP-1 translocation, and modulation of apoptosis. Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center, 45, 320-332.

El-Saadony, M. T., Yang, T., Korma, S. A., Sitohy, M., El-Mageed, A., Taia, A., & Saad, A. M. (2023). Impacts of turmeric and its principal bioactive curcumin on human health: Pharmaceutical, medicinal, and food applications: A comprehensive review. Frontiers in Nutrition, 9, 1-34.

Feng, T., Wei, Y., Lee, R. J., & Zhao, L. (2017). Liposomal curcumin and its application in cancer. International journal of nanomedicine,12, 6027-6044.

Ghareghomi, S., Rahban, M., Moosavi-Movahedi, Z., Habibi-Rezaei, M., Saso, L., & Moosavi-Movahedi, A. A. (2021). The potential role of curcumin in modulating the master antioxidant pathway in diabetic hypoxia-induced complications. Molecules, 26(24), 1-26.

Ghasemi, F., Shafiee, M., Banikazemi, Z., Pourhanifeh, M. H., Khanbabaei, H., Shamshirian, A., & Mirzaei, H. (2019). Curcumin inhibits NF-kB and Wnt/β-catenin pathways in cervical cancer cells. Pathology-Research and Practice, 215(10), 1-21.

Guimarães, M. R., Coimbra, L. S., de Aquino, S. G., Spolidorio, L. C., Kirkwood, K. L., Rossa Jr, C. (2011). Potent anti-inflammatory effects of systemically administered curcumin modulate periodontal disease in vivo. Journal of periodontal research, 46(2), 269-279.

Hafez Ghoran, S., Calcaterra, A., Abbasi, M., Taktaz, F., Nieselt, K., & Babaei, E. (2022). Curcumin-based Nano formulations: A promising adjuvant towards cancer treatment. Molecules, 27(16), 1-29.

Han, Z., Zhang, J., Zhang, K., & Zhao, Y. (2020). Curcumin inhibits cell viability, migration, and invasion of thymic carcinoma cells via downregulation of microRNA-27a. Phytotherapy Research, 34(7), 1629-1637.

Han, Z., Zhang, J., Zhang, K., Zhao, Y. (2020). Curcumin inhibits cell viability, migration, and invasion of thymic carcinoma cells via downregulation of microRNA-27a. Phytotherapy Research, 34(7), 1629-1637.

Hashemi, M., Mirzaei, S., Barati, M., Hejazi, E. S., Kakavand, A., Entezari, M., & Sethi, G. (2022). Curcumin in the treatment of urological cancers: Therapeutic targets, challenges and prospects. Life Sciences,309, 1-16.

Hatcher, H., Planalp, R., Cho, J., Torti, F. M., Torti, S. V. (2008). Curcumin: from ancient medicine to current clinical trials. Cellular and molecular life sciences, 65, 1631-1652.

Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A Review of Its Effects on Human Health. Foods (Basel, Switzerland), 6(10),92. https://doi.org/10.3390/foods6100092

Hsieh, M. T., Chang, L. C., Hung, H. Y., Lin, H. Y., Shih, M. H., Tsai, C. H., ... & Lee, K. H. (2017). New bis (hydroxymethyl) alkanoate curcuminoid derivatives exhibit activity against triple-negative breast cancer in vitro and in vivo. European Journal of Medicinal Chemistry, 131, 141-151.

Huang, T., Zhao, J., Guo, D., Pang, H., Zhao, Y., & Song, J. (2018). Curcumin mitigates axonal injury and neuronal cell apoptosis through the PERK/Nrf2 signalling pathway following diffuse axonal injury. Neuroreport, 29(8), 661-667.

Indira Priyadarsini, K. (2013). Chemical and structural features influencing the biological activity of curcumin. Current pharmaceutical design, 19(11), 2093-2100.

Jakubczyk, K., Drużga, A., Katarzyna, J., & Skonieczna-Żydecka, K. (2020). Antioxidant potential of curcumin—A meta-analysis of randomized clinical trials. Antioxidants, 9(11), 1-13.

Jia, G., Han, Y., An, Y., Ding, Y., He, C., Wang, X., & Tang, Q. (2018). NRP-1 targeted and cargo-loaded exosomes facilitate simultaneous imaging and therapy of glioma in vitro and in vivo. Biomaterials, 178, 302-316.

Jiang, K., Shen, M., & Xu, W. (2018). Arginine, glycine, aspartic acid peptide-modified paclitaxel and curcumin co-loaded liposome for the treatment of lung cancer: in vitro/vivo evaluation. International journal of nanomedicine,13, 2561-2569.

Jiang, K., Shen, M., & Xu, W. (2018). Arginine, glycine, aspartic acid peptide-modified paclitaxel and curcumin co-loaded liposome for the treatment of lung cancer: in vitro/vivo evaluation. International journal of nanomedicine, 2561-2569.

Juan, C. A., Pérez de la Lastra, J. M., Plou, F. J., & Pérez-Lebeña, E. (2021). The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. International Journal of Molecular Sciences, 22(9), 1-21.

Jung, J., Ku, M., Jeong, S., Yoon, N., Park, J. H., Youn, H. S., ... & Seo, S. (2023). Antioxidative Impact of Phenolics-Loaded Nanocarriers on Cytoskeletal

Network Remodelling of Invasive Cancer Cells. ACS Applied Materials & Interfaces, 15(29), 34462-34474.

Karimi, A., Pourreza, S., Vajdi, M., Mahmoodpoor, A., Sanaie, S., Karimi, M., & Tarighat-Esfanjani, A. (2022). Evaluating the effects of curcumin nanomicelles on clinical outcome and cellular immune responses in critically ill sepsis patients: A randomized, double-blind, and placebo-controlled trial. Frontiers in Nutrition, 9, 1-12.

Karthikeyan, A., Senthil, N., Min, T. (2020). Nanocurcumin: A promising candidate for therapeutic applications. Frontiers in Pharmacology, 11,1-24.

Katsori, A. M., Palagani, A., Bougarne, N., Hadjipavlou-Litina, D., Haegeman, G., & Vanden Berghe, W. (2015). Inhibition of the NF-κB signaling pathway by a novel heterocyclic curcumin analogue. Molecules, 20(1), 863-878.

Khan, K., Quispe, C., Javed, Z., Iqbal, M. J., Sadia, H., Raza, S., & Sharifi-Rad, J. (2020). Resveratrol, curcumin, paclitaxel and miRNAs mediated regulation of PI3K/Akt/mTOR pathway: go four better to treat bladder cancer. Cancer Cell International, 20, 1-19.

Khan, M. M., Madni, A., Tahir, N., Parveen, F., Khan, S., Jan, N., ... & Khan, M. I. (2020). Co-delivery of curcumin and cisplatin to enhance cytotoxicity of cisplatin using lipid-chitosan hybrid nanoparticles. International Journal of Nanomedicine,15, 2207-2217.

Kharat, P. B., Somvanshi, S. B., Khirade, P. P., & Jadhav, K. M. (2020). Induction heating analysis of surface-functionalized nanoscale CoFe2O4 for magnetic fluid hyperthermia toward noninvasive cancer treatment. ACS omega, 5(36), 23378-23384.

Klaunig, J. E. (2018). Oxidative stress and cancer. Current pharmaceutical design, 24(40), 4771-4778.

Kouhpeikar, H., Butler, A. E., Bamian, F., Barreto, G. E., Majeed, M., & Sahebkar, A. (2019). Curcumin as a therapeutic agent in leukemia. Journal of cellular physiology, 234(8), 12404-12414.

Kubczak, M., Szustka, A., & Rogalińska, M. (2021). Molecular targets of natural compounds with anti-cancer properties. International Journal of Molecular Sciences, 22(24), 1-27.

Kumbar, V. M., Muddapur, U., Bin Muhsinah, A., Alshehri, S. A., Alshahrani, M. M., Almazni, I. A., ... & Shaikh, I. A. (2022). Curcumin-encapsulated nanomicelles improve cellular uptake and cytotoxicity in cisplatin-resistant human oral cancer cells. Journal of Functional Biomaterials, 13(4), 1-22.

Kuo, Y. C., Wang, L. J., Rajesh, R. (2019). Targeting human brain cancer stem cells by curcumin-loaded nanoparticles grafted with anti-aldehyde dehydrogenase and sialic acid: Colocalization of ALDH and CD44. Materials Science and Engineering: C, 102, 362-372.

Li, H., Zhang, N., Hao, Y., Wang, Y., Jia, S., Zhang, H., ... & Zhang, Z. (2014). Formulation of curcumin delivery with functionalized single-walled carbon nanotubes: characteristics and anticancer effects in vitro. Drug delivery, 21(5), 379-387.

Liu, Z., Zhu, Y. Y., Li, Z. Y., & Ning, S. Q. (2016). Evaluation of the efficacy of paclitaxel with curcumin combination in ovarian cancer cells. Oncology letters, 12(5), 3944-3948.

Lopes-Rodrigues, V., Sousa, E., & Vasconcelos, M. H. (2016). Curcumin as a modulator of P-glycoprotein in cancer: challenges and perspectives. Pharmaceuticals, 9(4), 1-11.

Mahmoud, K., Swidan, S., El-Nabarawi, M., & Teaima, M. (2022). Lipid based nanoparticles as a novel treatment modality for hepatocellular carcinoma: A comprehensive review on targeting and recent advances. Journal of Nanobiotechnology, 20(1), 1-42.

Mahmud, M., Piwoni, A., Filiczak, N., Janicka, M., & Gubernator, J. (2016). Long-circulating curcumin-loaded liposome formulations with high incorporation efficiency, stability and anticancer activity towards pancreatic adenocarcinoma cell lines in vitro. PloS one, 11(12), 1-23.

Mansouri, K., Rasoulpoor, S., Daneshkhah, A., Abolfathi, S., Salari, N., Mohammadi, M., ... & Shabani, S. (2020). Clinical effects of curcumin in enhancing cancer therapy: A systematic review. BMC cancer, 20, 1-11.

Mundekkad, D.; Cho, W.C. Applications of Curcumin and Its Nanoforms in the Treatment of Cancer. Pharmaceutics 2023, 15, 2223. https://doi.org/10.3390/pharmaceutics15092223

Nagaraju, G. P., Benton, L., Bethi, S. R., Shoji, M., & El-Rayes, B. F. (2019). Curcumin analogs: Their roles in pancreatic cancer growth and metastasis. International Journal of Cancer, 145(1), 10-19.

Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F., & Walters, M. A. (2017). The essential medicinal chemistry of curcumin: Mini perspective. Journal of medicinal chemistry, 60(5), 1620-1637.

Nguyen, N. M., Vu, D. M., Tran, M. D., & Ta, V. T. (2021). On-demand release of drug from magnetic nanoparticle-loaded alginate beads. Journal of Analytical Methods in Chemistry, 2021,1-7.

Paliwal, R., Paliwal, S. R., Kenwat, R., Kurmi, B. D., & Sahu, M. K. (2020). Solid lipid nanoparticles: A review on recent perspectives and patents. Expert opinion on therapeutic patents, 30(3), 179-194.

Pan, R., Zeng, Y., Liu, G., Wei, Y., Xu, Y., & Tao, L. (2020). Curcumin–polymer conjugates with dynamic boronic acid ester linkages for selective killing of cancer cells. Polymer Chemistry, 11(7), 1321-1326.

Parthiban, A., Sivasankar, R., Rajdev, B., Asha, R. N., Jeyakumar, T. C., Periakaruppan, R., & Naidu, V. G. M. (2022). Synthesis, in vitro, in silico and DFT studies of indole curcumin derivatives as potential anticancer agents. Journal of Molecular Structure, 1270, 1-30.

Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. D. P., Acosta-Torres, L. S., ... & Shin, H. S. (2018). Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology, 16(1), 1-33.

Purushothaman, B. K., Maheswari, P. U., & Begum, K. M. S. (2019). Magnetic assisted curcumin drug delivery using folate receptor targeted hybrid casein-calcium ferrite nanocarrier. Journal of Drug Delivery Science and Technology, 52, 509-520.

Rahmani, A. H., Alsahli, M. A., Aly, S. M., Khan, M. A., & Aldebasi, Y. H. (2018). Role of curcumin in disease prevention and treatment. Advanced biomedical research, 7,1-9.

Rao, W., Zhang, W., Poventud-Fuentes, I., Wang, Y., Lei, Y., Agarwal, P., ... & He, X. (2014). Thermally responsive nanoparticle-encapsulated curcumin and its

combination with mild hyperthermia for enhanced cancer cell destruction. Acta Biomaterialia, 10(2), 831-842.

Rodrigues, F. C., Kumar, N. A., & Thakur, G. (2019). Developments in the anticancer activity of structurally modified curcumin: An up-to-date review. European journal of medicinal chemistry, 177, 76-104.

Sachithanandam, V., Lalitha, P., Parthiban, A., Muthukumaran, J., Jain, M., Misra, R., ... & Ramesh, R. (2022). A comprehensive in silico and in vitro studies on quinizarin: A promising phytochemical derived from Rhizophora mucronata Lam. Journal of Biomolecular Structure and Dynamics, 40(16), 7218-7229.

Sadeghi-Abandansari, H., Pakian, S., Nabid, M. R., Ebrahimi, M., & Rezalotfi, A. (2021). Local co-delivery of 5-fluorouracil and curcumin using Schiff's base cross-linked injectable hydrogels for colorectal cancer combination therapy. European Polymer Journal, 157, 1-13.

Sahebkar, A., Serban, M. C., Ursoniu, S., & Banach, M. (2015). Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials. Journal of functional foods, 18, 898-909.

Salahshoor, M., Mohamadian, S., Kakabaraei, S., Roshankhah, S., & Jalili, C. (2016). Curcumin improves liver damage in male mice exposed to nicotine. Journal of traditional and complementary medicine, 6(2), 176-183.

Samarghandian, S., Azimi-Nezhad, M., Farkhondeh, T., & Samini, F. (2017). Anti-oxidative effects of curcumin on immobilization-induced oxidative stress in rat brain, liver and kidney. Biomedicine & Pharmacotherapy, 87, 223-229.

Satyabhama, M., Priya Dharshini, L. C., Karthikeyan, A., Kalaiselvi, S., & Min, T. (2022). The Credible Role of Curcumin in Oxidative Stress-Mediated Mitochondrial Dysfunction in Mammals. Biomolecules, 12(10), 1-15.

Senturk, F. (2023). Hyperthermia efficacy of PEGylated-PLGA coated monodisperse iron oxide nanoparticles. Hittite Journal of Science and Engineering, 10(2), 153-159.

Senturk, F., & Cakmak, S. (2023). Fabrication of curcumin-loaded magnetic PEGylated-PLGA nanocarriers tagged with GRGDS peptide for improving anticancer activity. MethodsX, 10, 1-11.

Senturk, F., Çakmak, S., & Ozturk, G. G. (2019). Synthesis and characterization of oleic acid coated magnetic nanoparticles for hyperthermia applications. Natural and Applied Sciences Journal, 2(2), 16-29.

Senturk, F., Cakmak, S., Kocum, I. C., Gumusderelioglu, M., & Ozturk, G. G. (2021). GRGDS-conjugated and curcumin-loaded magnetic polymeric nanoparticles for the hyperthermia treatment of glioblastoma cells. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 622, 1-15.

Senturk, F., Kocum, I. C., & Guler Ozturk, G. (2021). Stepwise implementation of a low-cost and portable radiofrequency hyperthermia system for in vitro/in vivo cancer studies. Instrumentation Science & Technology, 49(6), 629-641.

Sheybani, N. D., Batts, A. J., Mathew, A. S., Thim, E. A., & Price, R. J. (2020). Focused ultrasound hyperthermia augments release of glioma-derived extracellular vesicles with differential immunomodulatory capacity. Theranostic, 10(16), 7436-7447.

Shishodia, S., Chaturvedi, M. M., & Aggarwal, B. B. (2007). Role of curcumin in cancer therapy. Current problems in cancer, 31(4), 243-305.

Silvestro, S., Sindona, C., Bramanti, P., Mazzon, E. (2021). A state of the art of antioxidant properties of curcuminoids in neurodegenerative diseases. International Journal of Molecular Sciences, 22(6), 1-27.

Soni, V. K., Shukla, D., Kumar, A., & Vishvakarma, N. K. (2020). Curcumin circumvent lactate-induced chemoresistance in hepatic cancer cells through modulation of hydroxycarboxylic acid receptor-1. The International Journal of Biochemistry & Cell Biology, 123, 1-30.

Sun, J., Zhao, Y., Hu, J. (2013). Curcumin inhibits imiquimod-induced psoriasis-like inflammation by inhibiting IL-1beta and IL-6 production in mice. PloS one, 8, 1-9.

Tang, J. C., Shi, H. S., Wan, L. Q., Wang, Y. S., & Wei, Y. Q. (2013). Enhanced antitumor effect of curcumin liposomes with local hyperthermia in the LL/2 model. Asian Pacific Journal of Cancer Prevention, 14(4), 2307-2310.

Termini, D., Den Hartogh, D. J., Jaglanian, A., Tsiani, E., (2020). Curcumin against prostate cancer: current evidence. Biomolecules, 10, 1-40.

Tsuchida, K., Tsujita, T., Hayashi, M., Ojima, A., Keleku-Lukwete, N., Katsuoka, F., ... & Yamamoto, M. (2017). Halofuginone enhances the chemo-sensitivity of cancer cells by suppressing NRF2 accumulation. Free Radical Biology and Medicine, 103, 236-247.

Udompornmongkol, P., & Chiang, B. H. (2015). Curcumin-loaded polymeric nanoparticles for enhanced anti-colorectal cancer applications. Journal of biomaterials applications, 30(5), 537-546.

Vaiserman, A., Koliada, A., Zayachkivska, A., Lushchak, O. (2020). Curcumin: A therapeutic potential in ageing-related disorders. Pharma Nutrition, 14, 30051-30057.

Venkatas, J., Daniels, A., & Singh, M. (2022). The Potential of Curcumin-Capped Nanoparticle Synthesis in Cancer Therapy: A Green Synthesis Approach. Nanomaterials, 12(18), 3201.

Wang, M., Jiang, S., Zhou, L., Yu, F., Ding, H., Li, P., ... & Wang, K. (2019). Potential mechanisms of action of curcumin for cancer prevention: focus on cellular signalling pathways and miRNAs. International journal of biological sciences, 15(6), 1200-1214.

Wang, M., Jiang, S., Zhou, L., Yu, F., Ding, H., Li, P., ... & Wang, K. (2019). Potential mechanisms of action of curcumin for cancer prevention: focus on cellular signaling pathways and miRNAs. International journal of biological sciences, 15(6), 1200-1214.

Wang, W. H., Chen, J., Zhang, B. R., Lu, S. J., Wang, F., Peng, L., & Sun, Y. Z. (2018). Curcumin inhibits proliferation and enhances apoptosis in A549 cells by downregulating lncRNA UCA1. Die Pharmazie-An International Journal of Pharmaceutical Sciences, 73(7), 402-407.

Wang, W., Chen, T., Xu, H., Ren, B., Cheng, X., Qi, R., ... & Chen, C. (2018). Curcumin-loaded solid lipid nanoparticles enhanced anticancer efficiency in breast cancer. Molecules, 23(7), 1-13.

Wezgowiec, J., Tsirigotis-Maniecka, M., Saczko, J., Wieckiewicz, M., & Wilk, K. A. (2021). Microparticles vs. macroparticles as curcumin delivery vehicles: Structural studies and cytotoxic effect in human adenocarcinoma cell line (LoVo). Molecules, 26(19), 1-19.

Wilken, R., Veena, M. S., Wang, M. B., & Srivatsan, E. S. (2011). Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Molecular cancer, 10(1), 1-19

Wu, Q., Ou, H., Shang, Y., Zhang, X., Wu, J., & Fan, F. (2021). Nanoscale formulations: incorporating curcumin into combination strategies for the treatment of lung cancer. Drug Design, Development and Therapy, 2695-2709.

Yodkeeree, S., Ampasavate, C., Sung, B., Aggarwal, B. B., & Limtrakul, P. (2010). Demethoxycurcumin suppresses migration and invasion of MDA-MB-231 human breast cancer cell line. European journal of pharmacology, 627(1-3), 8-15.

Zhang, J., Huang, Y., Xu, J., Zhao, R., Xiong, C., Habu, J., & Luo, X. (2022). Global publication trends and research hotspots of curcumin application in tumor: A 20-year bibliometric approach. Frontiers in Oncology, 12, 1-15.

Zhang, Y., Yang, C., Wang, W., Liu, J., Liu, Q., Huang, F., ... & Liu, J. (2016). Co-delivery of doxorubicin and curcumin by pH-sensitive prodrug nanoparticle for combination therapy of cancer. Scientific reports, 6(1), 1-12.

Zhao, L., Yang, C., Dou, J., Xi, Y., Lou, H., & Zhai, G. (2015). Development of RGD-functionalized PEG-PLA micelles for delivery of curcumin. Journal of biomedical nanotechnology, 11(3), 436-446.

Zhao, M. D., Li, J. Q., Chen, F. Y., Dong, W., Wen, L. J., Fei, W. D., & Zheng, C. H. (2019). Co-delivery of curcumin and paclitaxel by "core-shell" targeting amphiphilic copolymer to reverse resistance in the treatment of ovarian cancer. International journal of nanomedicine,14, 9453-9467.

Zheng, B., McClements, D. J. (2020). Formulation of more efficacious curcumin delivery systems using colloid science: enhanced solubility, stability, and bioavailability. Molecules, 25(12), 1-25.

Zhu, X., Yu, Z., Feng, L., Deng, L., Fang, Z., Liu, Z., ... & Zheng, Y. (2021). Chitosan-based nanoparticle co-delivery of docetaxel and curcumin ameliorates anti-tumor chemoimmunotherapy in lung cancer. Carbohydrate Polymers, 268, 1-18.

Zinatloo, A. S., & Taheri, Q. N. (2014). Inverse miniemulsion method for synthesis of gelatin nanoparticles in presence of CDI/NHS as a non-toxic cross-linking system.)