ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2023 August 15; 15(8): 1317-1504

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 15 Number 8 August 15, 2023

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Clinical and Translational Research

Case Control Study

World Journal of Gastrointestinal Oncology

Monthly Volume 15 Number 8 August 15, 2023

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
August 15, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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ARTICLE PROCESSING CHARGE
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ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2023 August 15; 15(8): 1342-1348

DOI: 10.4251/wjgo.v15.i8.1342

ISSN 1948-5204 (online)

MINIREVIEWS

Research progress on drug delivery systems for curcumin in the treatment of gastrointestinal tumors

Xin Wu, Yang Yang

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Iruarrizaga-Lejarreta M, Spain; Sledzinski T, Poland

Received: May 11, 2023
Peer-review started: May 11, 2023
First decision: May 31, 2023
Revised: June 11, 2023
Accepted: July 11, 2023
Article in press: July 11, 2023
Published online: August 15, 2023

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Abstract

Curcumin is a natural compound with a diketone structure, which can control the growth, metastasis, recurrence, neovascularization, invasion, and drug resistance of gastrointestinal tumors by inhibiting nuclear factor κB, overexpression of tumor cells, vascular endothelial growth factor, *etc*. However, due to the low bioavailability of curcumin formulation, it did not fully exert its pharmacological effects, and its application and development in the treatment of various malignant tumors are still limited. This review summarizes the research on drug delivery systems of curcumin combating digestive tract tumors in order to further reduce the toxic side effects of curcumin-containing drugs and fully exert their pharmacological activities, and improve their bioavailability and clinical value.

Key Words: Curcumin; Digestive tract tumors; Delivery system; Water-soluble; Solubility

Core Tip: Curcumin can control the growth, metastasis, recurrence, neovascularization, invasion, and drug resistance of gastrointestinal tumors by inhibiting nuclear factor κB, overexpression of tumor cells, and vascular endothelial growth factor. It is important to clarify the application value of curcumin by different drug delivery systems to optimize the treatment of gastrointestinal tumors.

Citation: Wu X, Yang Y. Research progress on drug delivery systems for curcumin in the treatment of gastrointestinal tumors. *World J Gastrointest Oncol* 2023; 15(8): 1342-1348
URL: https://www.wjgnet.com/1948-5204/full/v15/i8/1342.htm
DOI: https://dx.doi.org/10.4251/wjgo.v15.i8.1342

INTRODUCTION

As the detection rate of advanced gastrointestinal tumors continues to rise, combination chemotherapy regimens, such as paclitaxel, capecitabine, and cisplatin, have become necessary to prolong patient survival[1,2]. However, many chemotherapy drugs have poor tumor selectivity and often have severe toxic side effects, which can damage the immune system's defense and regulatory functions and even make patients unable to tolerate subsequent treatments or develop drug resistance[3,4]. Moreover, the cost of chemotherapy combined with molecular targeted therapy is high, and patients have a low acceptance rate, making it unsuitable for widespread clinical use[5]. Compared with conventional chemotherapy and targeted therapy, curcumin biological formulations not only have low cost and high safety but also have anti-cancer, anti-virus, immune and inflammation regulation, and anti-cardiovascular fibrosis characteristics. Curcumin has therapeutic value in a variety of diseases such as esophageal cancer, gastric cancer, pancreatic cancer, biliary tract disease, rheumatic disease, and psoriasis[6,7]. However, as curcumin has poor water solubility, unstable properties under neutral and alkaline pH conditions, and strong photo-degradation, its pharmacological effects have not been well exerted [8,9]. Therefore, to develop a more scientific and efficient curcumin drug formulation, we performed a detailed analysis of the drug delivery systems for curcumin to increase its bioavailability and enhance its effectiveness against gastrointestinal tumors (Table 1, Figure 1).

CURCUMIN DRUG DELIVERY SYSTEMS

Polymer

Micelles polymer micelles are a thermodynamically stable colloidal solution with a shell-core structure. The core can carry hydrophobic drugs and effectively reduce the degradation loss of drugs, enhance the drug permeability and retention, and thus increase the concentration of drugs in the target site or accumulate the drugs in specific areas, thereby strengthening their killing effect on tumor cells and significantly reducing the toxic side effects on normal cells and tissues[10,11]. Compared with traditional drug delivery systems, curcumin micelles can not only improve the uptake rate of drugs by tumor cells but also select appropriate micelles based on the specific conditions and related symptoms of tumor patients, such as bioadhesive micelles, active targeting micelles, pH-sensitive micelles, and reversal of multidrug-resistant micelles[12]. In immunotherapy of osteosarcoma, Jin *et al*[13] found that dichloroacetic acid mitochondrial-targeted polymer micelles could induce cell apoptosis by initiating the mitochondrial oxidative stress response, enhancing immunity, and inhibiting the tumor microenvironment. In addition, by designing the hydrophobic core of polymer micelles and the hydrophobic membrane of the vesicles, the shell-core structure becomes a photocatalyst, which can effectively avoid the attack of photodynamic oxygen on enzymatic substances, keep the enzyme in an active state, and thus enhance the biocompatibility and activity of the delivery system[14]. It should be noted that comprehensive tests on encapsulation efficiency, particle size, drug loading, and drug release rate within 48 h are required to prepare curcumin polymer micelles to the fullest extent possible to overcome its poor water solubility and maximize its anti-tumor effects.

Liposome

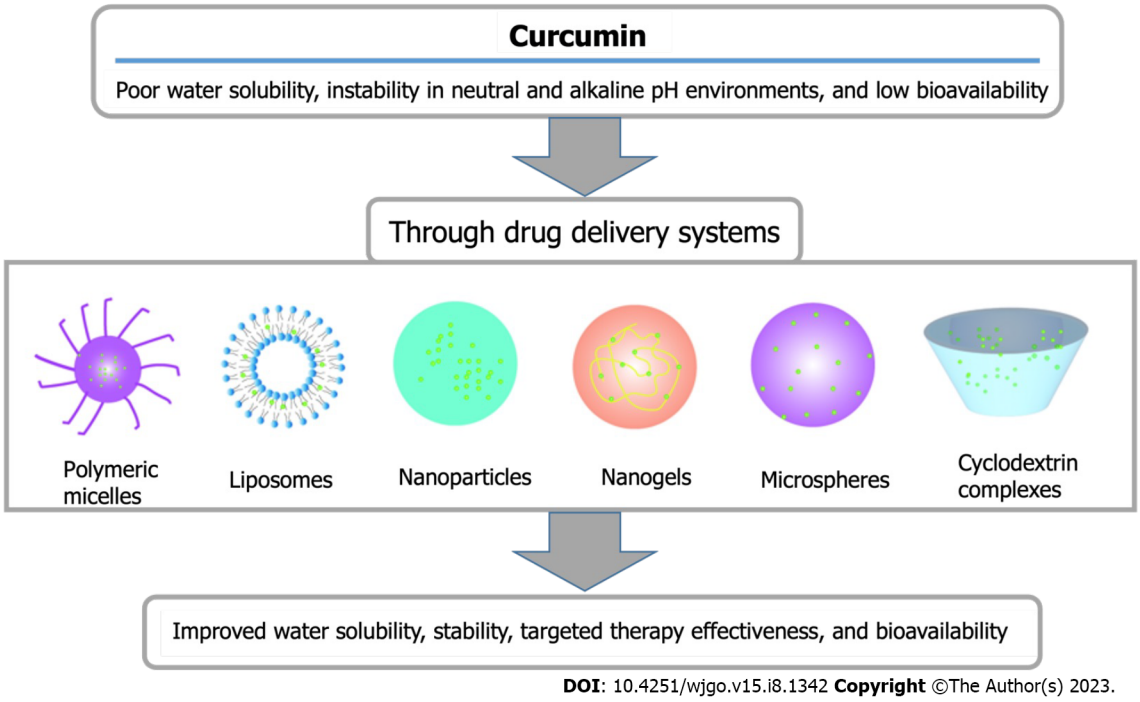
Liposomes are lipid bilayer microvesicle carriers that can encapsulate multiple drugs and have good targeting and lymphatic directionality. Compared with ordinary carriers, they can not only delay renal metabolism, reduce drug toxicity but also serve as passive targeted drugs for the reticuloendothelial system, thus protecting the liver and improving drug efficacy[15]. In a mouse experiment, Li *et al*[16] compared several different curcumin drug delivery systems and found that mice given curcumin liposomes had greater improvements in hepatic steatosis than control group mice or mice given curcumin suspensions, and smaller abdominal adipocytes. In the study of digestive tract tumors, curcumin analogs, unlike non-steroidal anti-inflammatory drugs, have important value in regulating the cancer gene pathway, and cause fewer adverse reactions such as mucosal bleeding and gastrointestinal ulcers[17]. When curcumin acts on gastric or colorectal cancer, it can regulate the cell's anti-inflammatory, anti-cell apoptosis and antioxidant mechanisms through signal pathways such as DNA methylation, nuclear factor-erythroid 2-related factor 2, and histone modification, thus regulating the transcription of factors, such as heme oxygenase-1, Bcl-2, Bcl-xL, delaying tumor progression, and achieving multi-organ protection[18,19].

Microsphere

Microspheres, also known as microcapsules, are miniature spherical capsules made of polymeric materials that encapsulate or adsorb solid or liquid drugs. Their outer shell can mask the unpleasant odor of drugs, prevent contraindications in complex formulations, and reduce the stimulatory effects of chemotherapy drugs on the gastrointestinal mucosa [20]. The most commonly used microencapsulation method in clinical practice is to develop sustained-release and

Table 1 Summary of drug delivery systems

Drug delivery system	Structure	Advantage	Disadvantage	Common types
Polymer	Shell-core structure	Hydrophobic, high and precise drug concentration with low side effects	Poor water solubility	Bioadhesive micelles, active targeting micelles, *etc.*
Liposome	Lipid bilayer microvesicle carriers	Diversity, targeting, lymphatic targeting, liver protection, *etc.*	High cost	Unilamellar liposomes, multilamellar liposomes, liposome gel, *etc.*
Microsphere	Shell-core structure	Covering bad odors, avoiding incompatible combinations, high stability and safety	Relatively short duration and relatively large drug dosage	Conventional injection microspheres, occlusive microspheres, magnetic microspheres, *etc.*
Nanoparticle (NPs)	Shell-core structure	Amphiphilic, controllable loading effect, long half-life, *etc.*	Low solubility of inorganic NPs	Lipophilic NPs, nanocapsules, nanospheres, and inorganic NPs, *etc.*
Nanogel	Intramolecular cross-linked polymer	Anti-fouling, antibacterial, targeting, small size, easily penetrating cells, *etc.*	No obvious disadvantage	pH-responsive hydrogels, hyaluronic acid hydrogels, copolymer hydrogels
Cyclodextrin	Bimolecular complex	High water solubility, low toxicity, high stability	No obvious disadvantage	α-cyclodextrin, β-cyclodextrin, partially methylated-β-cyclodextrin, *etc.*



DOI: 10.4251/wjgo.v15.i8.1342

Figure 1 Curcumin improvement through drug delivery systems.

targeted drugs to control disease progression or symptoms. Some microspheres can also embed live cells and biologically active blood substances to prevent them from denaturing or becoming ineffective[21]. Researchers extracted proteins from lotus seeds and used them to encapsulate curcumin[22]. They found that at a concentration of 50mg/mL, the encapsulation rate of curcumin was 86.32%. After digestion in the gastrointestinal tract, the cumulative release rate of curcumin-LSP was 64.3%, while that of curcumin-LSP-pectin particles was 72.4%. Moreover, the dissolution rate of curcumin-LSP-pectin particles was relatively higher. Thus, microencapsulated compounds have a higher application value.

Nanoparticle

Nanoparticles (NPs) can penetrate into membrane cells, spread along nerve synapses and lymphatic vessels, and selectively accumulate in different cells and some cell structures[23]. According to their different shell-core structures and materials, NPs are divided into multiple drug delivery systems, such as lipophilic NPs, nanocapsules, nanospheres, and inorganic NPs. Their carriers can be hydrophobic or hydrophilic compounds, as well as small molecules, biomacromolecules, proteins, and vaccines[24]. Moreover, by adjusting the composition, stability, reactivity, and surface charge of NPs and carriers, the loading effect and release kinetics of drugs can be precisely controlled[25]. Lushchak *et al*[26] pointed out that nanoparticles carrying various plant bioactive compounds had a longer half-life than traditional

formulations and could improve the permeability of epithelial cells and delayed cellular aging. Nabila *et al*[27] used nanolipid technology to prepare nano-curcumin and compared it with curcumin solution, proving that nano-curcumin had greater antiviral potential. It is worth noting that inorganic NPs synthesized from materials, such as gold, iron oxide, and silicon dioxide, have unique value in diagnosis, arterial imaging, photothermal therapy, and sonodynamic therapy. However, due to their toxicity and low solubility, the clinical application of such NPs still has certain limitations[28]. Dutta *et al*[29] coated the anionic surfactant sodium dodecyl sulfate (SDS) on the surface of hydrophobic Fe_3O_4 (oleic acid modified) nanoparticles to prepare a surface-active agent-stabilized, highly water-dispersible Fe_3O_4 magnetic nanocarrier (SMNC) capable of simultaneously carrying hydrophobic and hydrophilic anticancer drugs. Doxorubicin is adsorbed onto the surface of the nanocarrier by electrostatic interactions, while curcumin is encapsulated in the hydrophobic intermediate layer between oleic acid and SDS. The drug carrier has high drug loading capacity, good sustained release performance, and good cellular uptake ability. In addition, the drug carrier exhibits excellent heating ability under an alternating magnetic field and can be used as an effective heat source for hyperthermia.

Nanogel

Nanogel is a type of intramolecular cross-linked polymer with a particle size generally within 1000 nm. It has an internal network structure and can be dispersed into nanoscale hydrogel particles in aqueous solutions[30]. It can also be used as anti-fouling and antibacterial surface coatings, reducing the adhesion of bacteria and viruses on medical materials. The pH in the normal physiological environment of the body differs significantly from that outside the tumor cells, resulting in a significant redox potential difference between the inside and outside of the cells. However, monodispersed nanoscale hydrogels can respond specifically and accurately to the pH and redox potential differences between tumor tissues and normal tissues, creating conditions for targeted delivery of drugs to cancer sites[31,32]. Chemotherapy combined with immunotherapy is currently a popular method for treating mid-to-late-stage tumors. Its main goal is to promote the death of immunogenic cells, activate the powerful function of the immune system, and achieve the purpose of inhibiting tumor growth and improving the immunosuppressive tumor microenvironment[33]. Ma *et al*[34] prepared mannitol nanogels based on polyβ-amino esters to treat breast cancer and found that it could overcome the limitations of immunotherapy. Therefore, nanogels can achieve specific co-delivery of tumor drugs.

Cyclodextrin

Cyclodextrin is a cyclical oligosaccharide derived from starch. By appropriately modifying it chemically, amorphous or partially crystalline derivatives such as α-cyclodextrin, β-cyclodextrin, partially methylated-β-cyclodextrin, *etc.*, can be formed, which can significantly improve its water solubility and greatly reduce its gastrointestinal toxicity[35]. Among them, the inclusion complex of hydroxypropyl-β-cyclodextrin and curcumin has not only a high inclusion rate and high solubility, but also a 2.8-fold increase in bioavailability compared to ordinary curcumin preparations, and the concentration in the brain increases by 38.7-fold, showing a significant antiepileptic effect[36]. In addition, Chen *et al*[37] showed that curcumin-cyclodextrin complex has a protective effect on H2O2-induced LO2 cell damage, can effectively inhibit the overexpression of caspase-3, and alleviate liver, kidney, brain and skeletal muscle damage. This indicates that preparing curcumin-cyclodextrin inclusion complexes according to the chemical and biological properties of drugs can alleviate liver, kidney, and nerve toxicities during anti-tumor chemotherapy. In the study of curcumin solubility, the antioxidant activity of curcumin inclusion complexes formed with β-cyclodextrin and polyvinylpyrrolidone (PVP) was (96.02 ± 2.46)%, while the antioxidant activity of pure curcumin was only (58.02 ± 2.21)%. This shows that designing curcumin-β-cyclodextrin complexes with PVP can further improve the *in vivo* activity of curcumin[38].

CLINICAL RESEACH PROGRESS

Developing drug delivery systems for curcumin, such as micelles, complexes, solvent-free pH-driven capsules, and gels, to fully enhance its effectiveness and develop therapeutic or functional products, has become one of the choices to promote overall health and increase tumor remission rates[39]. However, despite the current clinical research in gastrointestinal tumors, the efficacy of curcumin remains uncertain (Table 2)[40-43]. In addition to the studies shown in the table, Hipólito-Reis *et al*[44] demonstrated that by reducing the release and production of inflammatory mediators using curcumin, curcumin can lower cell proliferation, blood vessel growth, invasion, and adhesion, or regulate cell apoptosis, lipid metabolism mechanisms, *etc.*, which can effectively improve the occurrence and development of endometriosis and achieve long-term control or clinical cure[45,46]. Meanwhile, the invasion and proliferation of tumor cells can also promote the secretion of multifunctional chemokines such as TNF-α, IL-6, IL-8, IL-10, decrease pain thresholds, and promote inflammatory exudation and necrosis of local lesions. Therefore, Nanavati *et al*[47] believe that supplementing 90-5000 mg curcumin daily can effectively improve subjective pain perception and increase the body's antioxidant capacity.

CONCLUSION

The anti-tumor effect of curcumin is closely related to multiple mechanisms. When it acts on the signaling pathway of various cytokines, it can exert different regulatory functions, thereby regulating immunity and inflammation, protecting cells, and inhibiting tumor growth. For specific cancer patients, the development of curcumin delivery systems can

Table 2 Clinical study of curcumin effects on gastrointestinal tumors

Cancer type	Study category	No.	Dosage regimen	Results
Colorectal cancer [37]	Phase II, randomized double-blind study	22	Capecitabine 825 mg/m^2, *Bid*; curcumin 4 g, *Bid*	Curcumin does not increase the remission rate of patients
Esophageal cancer [38]	Controlled trial	1	Group A: 20 μg/mL curcumin-containing culture; Group B: 2 μg/mL Vincristine-containing culture; Combined group: 20 μg/mL curcumin+2 μg/mL vincristine-containing culture	Curcumin reverses multidrug resistance of esophageal cancer cells
Metastatic colorectal cancer [39]	Phase IIa, randomized controlled trial	28	Control group: FOLFOX[1]; Research Group: FOLFOX + curcumin 2 g/d	Curcumin plus FOLFOX regimen significantly improves chemotherapy tolerance and safety
Advanced gastric cancer[40]	Randomized controlled trial	56	Control group: FOLFOX; Research Group: FOLFOX + curcumin 25 μmol/L, 1/d	Curcumin plus FOLFOX regimen significantly improves clinical remission rate and reduces toxic side effects

[1]FOLFOX is a chemotherapy regimen consisting of oxaliplatin, leucovorin, and 5-fluorouracil. Taking FOLFOX4 as an example, on the first and second day, intravenous infusion of oxaliplatin 85 mg/m^2 is administered for 2 h; intravenous infusion of leucovorin 200 mg/m^2 for 2 h; and 5-fluorouracil is given at 400 mg/m^2 as an initial intravenous bolus followed by a continuous infusion of 600 mg/m^2 for 22 h. This medication regimen is repeated every 2 wk.

significantly enhance the targeting and long-circulating effects of the drugs. Polymer micelles, liposomes, and microspheres have considerable advantages, but this article did not provide a detailed analysis of their drawbacks, and it is not entirely clear how to choose the material and type of drug delivery systems. Therefore, in future research, the application value of curcumin by different drug delivery systems needs to be further analyzed to optimize the treatment of gastrointestinal tumors.

FOOTNOTES

Author contributions: Wu X and Yang Y contributed equally to the conception, design, and literature search; Wu X drafted the manuscript and prepared the table and figure; Yang Y modified and revised the manuscript.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Country/Territory of origin: China

ORCID number: Yang Yang 0009-0003-0997-3693.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

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