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REVIEW

Nanoparticle Drug Delivery Systems for α-Mangostin

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Abstract: α-Mangostin, a xanthone derivative from the pericarp of *Garcinia mangostana* L., has numerous bioactivities and pharmacological properties. However, α-mangostin has low aqueous solubility and poor target selectivity in the human body. Recently, nanoparticle drug delivery systems have become an excellent technique to improve the physicochemical properties and effectiveness of drugs. Therefore, many efforts have been made to overcome the limitations of α-mangostin through nanoparticle formulations. Our review aimed to summarise and discuss the nanoparticle drug delivery systems for α-mangostin from published papers recorded in Scopus, PubMed and Google Scholar. We examined various types of nanoparticles for α-mangostin to enhance water solubility, provide controlled release and create targeted delivery systems. These forms include polymeric nanoparticles, nanomicelles, liposomes, solid lipid nanoparticles, nanofibers and nanoemulsions. Notably, nanomicelle modification increased α-mangostin solubility increased more than 10,000 fold. Additionally, polymeric nanoparticles provided targeted delivery and significantly enhanced the biodistribution of α-mangostin into specific organs. In conclusion, the nanoparticle drug delivery system could be a promising technique to increase the solubility, selectivity and efficacy of α-mangostin as a new drug candidate in clinical therapy.

Keywords: *Garcinia mangostana*, solubility, controlled release, targeted delivery, nanoparticle formulations, physicochemical properties

Introduction

α-Mangostin, a xanthone derivative compound isolated from *Garcinia mangostana* L. peel extract, has myriad pharmacological effects: antibacterial, antifungal, anti–inflammatory, antiallergic, antioxidant and anticancer activities.[1–5] The anticancer activity indicates that α-mangostin might serve as a potent anticancer agent in lung, stomach, colon, cervical, pancreatic, prostate, mammary gland, chondrosarcoma, renal, skin, tongue mucoepidermoid and breast cancers.[6–18] However, α-mangostin has low solubility in water (2.03 x 10^{-4} mg/L at 25ºC), and many efforts have been made to improve it: structure modification, co-solvation, solid dispersion, emulsion, complexation and nanoparticle drug delivery systems.[19–21] Additionally, α-mangostin and other cytotoxic drugs generally have limitations that influence their effectiveness, including a first fast metabolism reaction, an efflux reaction induced by transporter intercellular, fast drug release and a non-specific target site.[22–24]

Drug bioavailability is an important parameter to determine how successful the drug molecules pass through in pharmacological phases such as biopharmaceutics, pharmacokinetics, and pharmacodynamics.[25] To achieve the maximum bioavailability, drug solubility is one of the primary factors that can increase the drug bioavailability.[26] Currently, nanoparticle drug delivery systems are the most commonly used technique for nanomedicine-mediated treatment of diseases. Their nanosize can enhance

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solubility by providing a large surface area, which increases the penetration rate into a cell membrane and provides a controlled release system with passive or active targeting. This effect can serve as a cancer drug delivery system.[27–29] This system becomes a promising method to overcome the limitations of α-mangostin. Several types of nanoparticles have been formulated for the α-mangostin compound, including nanolipids, nanopolymerics, nanomicelles, nanoliposomes, nanofibers and metal nanoparticles.[19,20,30-34] The results are substantial, with significantly improved solubility for α-mangostin. Therefore, controlled and targeted drug delivery systems can be created by modified nanoparticle technology.

There are numerous published α-mangostin studies; however, they are usually limited and only discuss its pharmacological properties and bioactivities. Dermawan et al tried to predict the increase in α-mangostin solubility using a cyclodextrin inclusion complex. The inclusion complex formation energy values for all α-mangostin/cyclodextrins were obtained using the semi-empirical PM7 method. No researchers have performed experiments to prove the results of this in silico study.[35] Taken together, we believe that our review concerning nanoparticle drug delivery systems for α-mangostin, which relates to its solubility and selectivity properties, will broaden the spectrum of α-mangostin utilisation and allow for improved efficacy.

Methodology

This review is based on the literature obtained from Scopus, PubMed and Google Scholar using the keyword "nanoparticle formulation of α-mangostin", "nanoparticle drug delivery of α-mangostin", and "α-mangostin nanoparticle." We excluded opinions, reviews and unrelated topics such as pharmacological properties and bioactivities. The databases are limited to obtain the specific topic in pharmaceutical formulation. The flowchart of the methodology is shown in Figure 1.

α-Mangostin

Mangosteen (*G. mangostana*), the queen of tropical fruits, grows in tropical rainforests of Malaysia, Thailand and Indonesia. α-Mangostin (Figure 2) is the major compound of mangosteen peel extract; it is a xanthone derivative with the chemical name 1,3,6-trihydroxy-7-methoxy-2,8-bis (3-methyl-2-butenyl)-9H-Xanten-9-0n (Table 1). Its pharmacological activities are diverse: antibacterial, anti-allergic, anti-fungal, anti–inflammatory activity, antioxidant and anticancer.[1–5]

Previous studies demonstrated that α-mangostin can act against cancer cells via multiple pathways,[38–41] including inhibiting fatty acid synthase, signalling human epidermal growth factor receptor 2 (HER2)/phosphatidylinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK).[6,42] Notwithstanding its excellent bioactivity, α-mangostin has limited solubility in water (2.03×10^{-4} mg/L at 25ºC). These problems become a basic consideration for developing α-mangostin with better efficacy.

Nanoparticle Drug Delivery Systems for α-Mangostin

Recent Nanoparticle Formulations for Improved Water Solubility, Modified Release and Targeted Drug Delivery

Nanomedicine, a nanotechnology application, has an important role in clinical therapy. Due to its nanosize (10^{-9} m), the large surface area of the nanocompounds enhances the surface contact with its solvent and improves the solubility or dissolution rate of slightly water-soluble compounds.[43] Nanomedicine therapeutic interventions can be highly specific at the intermolecular scale to allow for curing diseases or repairing damaged tissues, such as nerves, muscles or bones. Liposomes, dendrimers, solid lipid nanoparticles, polymeric nanoparticles, silicon or carbon materials, metal and magnetic nanoparticles are examples of nanocarriers that have been formulated as drug delivery systems.[44] A nanoparticle drug delivery system is a promising modification technique due to the combination of physics and chemical sciences. It is a proven, favourable technique to overcome the limitation of drugs with the poor solubility in water and provide the targeted drug delivery system.[45]

Table 2 and Figure 3 describe the various nanoparticle formulations that have made this technique a promising multifunctional drug delivery system. Nanoparticles are formulated as dendrimers, solid lipid nanoparticles, metal nanoparticles and liposomes, among others. They are commonly used to deliver drugs to specific targets, including cells, receptors and genes. The important aspects of the formulation depend on the selection of the right excipient, which play a crucial role in delivering active drug substances to the intended target. Folic acid (FA), mesenchymal stem cells (MSCs), mannose, hyaluronic acid, poly(lactic-co-glycolic acid) (PLGA) and chitosan conjugated with copolymers are the main excipients used to deliver active, high-affinity pharmaceutical ingredients. Nanoparticle formulations can also enhance absorption and

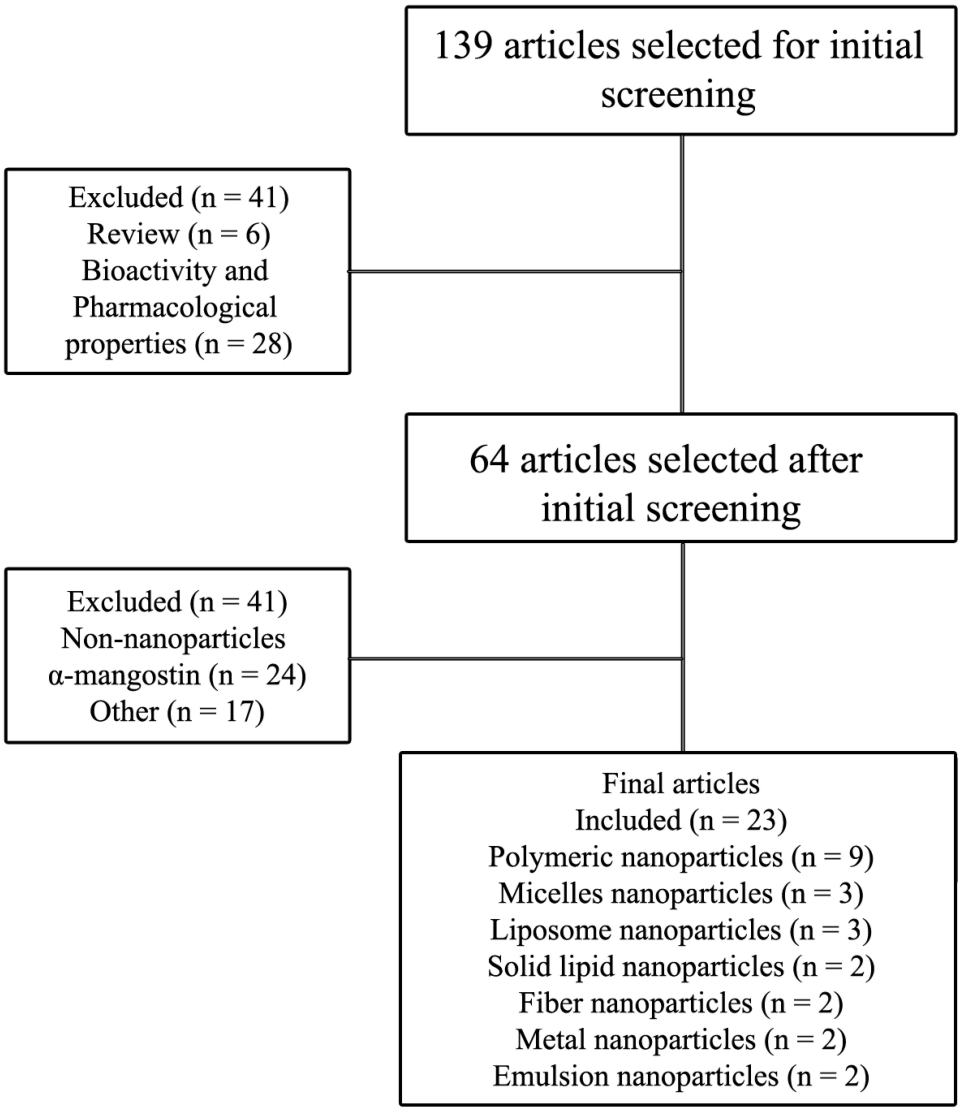

Figure 1 Flowchart of the methodology used in this review.

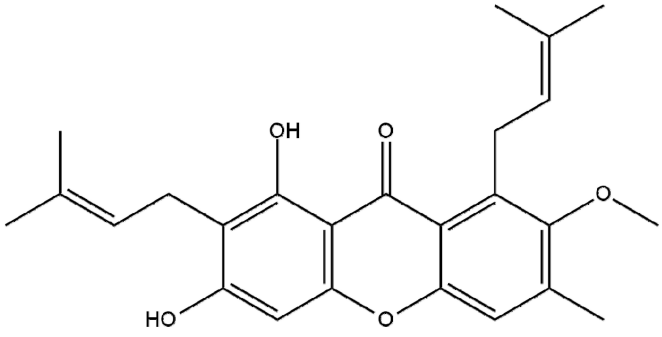

Figure 2 Chemical structure of α-Mangostin.

the penetration rate as a function of small particle size, membrane transport, cellular uptake and bioadhesive interactions with the cell membrane.[71,72] Finally, a drug's bioavailability can be improved by nanoparticle formulations, a phenomenon consistent with the enhanced solubility, dissolution and absorption rate.[73]

Table 1 Chemical and Physical Properties of α-Mangostin[36,37]

Property	Description
Chemical names	1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-enyl)xanthen-9-one
Physical state Colour/form	Solid Faint yellow to yellow powder
Molecular formula	$C_{24}H_{26}O_6$
Molecular weight	410.466 g/mol
Melting point Solubility	180–181°C Soluble in ethanol; in water, 2.03 x 10^{-4} mg/L at 25°C
Log Kow	7.71 (estimated)
Stability/shelf life	Stable under normal temperatures and pressures
Decomposition	Nitrogen oxide, carbon monoxide, irritating and toxic fumes and gases, carbon dioxide, nitrogen
Dissociation constants	pKa 1 = 3.68 (primary carbonyl) pKa 2 = 7.69 (secondary carbonyl) pKa 3 = 9.06 (tertiary carbonyl)
Henry's Law constant	2.05 x 10^{-16} atm m^3/mol at 25°C

Polymeric Nanoparticles of α-Mangostin

Polymeric nanoparticles are generally used to solve the limitation of poorly soluble drugs, provide controlled release and targeted drug delivery. Several studies have been reported related to polymeric nanoparticle formulations for α-mangostin (Table 3). The first polymeric nanoparticle formulation of α-mangostin was reported in 2011; it included biodegradable PLGA copolymers. In that study, α-mangostin was encapsulated in PLGA using colloidal extraction solvent evaporation. The PLGA α-mangostin nanoparticle was less cytotoxic to the A549 lung cancer cell line compared to free α-mangostin. These results suggest that PLGA nanoparticles can be used as a microcarrier system for the delivery of α-mangostin as a passive tumour-targeting agent.[74] Another study from the same year reported an α-mangostin polymeric nanoparticle using PLGA with chitosan biopolymer. Interestingly, the formulation without chitosan was more toxic to A549 cells. The authors speculated that the mechanism of action is mediated by the high-affinity property of chitosan biopolymer can target the nanoparticle drug delivery system targeted in lung cancer tissues.[75]

Verma et al also examined PLGA with α-mangostin as a drug payload. The authors aimed to improve the bioactivity of α-mangostin against pancreatic cancer. They prepared the nanoparticle using a double emulsion solvent evaporation method. Impressively, the nanoparticle system inhibited the proliferation of pancreatic cancer stem cells (CSCs) and pancreatic cancer cell lines and had no effect on normal human pancreatic ductal epithelial (HPNE) cells. Moreover, the nanoparticle inhibited colony formation, motility, migration and the invasion-induced apoptotic mechanism in vitro and in vivo.[42]

Another polymeric nanoparticle formulation used poly (ethylene glycol)-poly(L-lactide) (PEG-PLA) as a matrix for α-mangostin. The authors aimed to use this formulation for Alzheimer's disease. The nanoparticle was prepared by emulsion/solvent evaporation techniques. The particle size, zeta-potential and entrapment efficiency of the nanoparticle were 94.26 ± 4.54 nm, −32 ± 0.43 mV and 50.47 ± 1.96%, respectively. In vitro, the drug was rapidly released in the first 24 h (approximately 50%), followed by a slow, continuous release until 72 h and 100% release by 96 h. These results demonstrated a significant improvement of the pharmacokinetic and biodistribution profiles of nanoparticle compared to free α-mangostin.[76]

Ethyl cellulose-methyl cellulose (EC-MC), a natural polymer from cellulose groups, was designed for α-mangostin polymeric nanoparticle formulation as an anti-acne therapy in a cosmeceutical form. The system was designed as a nanoreservoir system to achieve an extended release profile using a spray drying technique. In this study, the particle size, polydispersity and loading capacity were 300–500 nm, 0.111 ± 0.024 and 41.90 ± 0.79%, respectively. The nanoparticle formation exhibited lower skin irritation compared to controls. Approximately 80–100% of α-mangostin was released over more than 7 days. Impressively, the anti-acne activity of the nanoparticle system significantly decreased the acne severity index (ASI) value and inflammatory lesions ($P < 0.05$) compared to control.[77]

Another study developed a nanoparticle system based on chitosan/alginate and genipin (GP) as a crosslinker prepared using the ionotropic gelation method. The system aimed to achieve a controlled release system and increase the antitumor activity of α-mangostin. Cytotoxicity and antitumor activity studies confirmed that an increase in GP concentration significantly reduced cell viability and induced apoptosis in colorectal adenocarcinoma cells.[78]

Table 2 Recent Nanoparticle Formulations for Improved Water Solubility, Modified Release and Targeted Drug Delivery

No	Types of Nanoparticle	Excipients	Main Objective	Ref.
1	Nanoparticle-orodispersible films	Vinylpyrrolidone-vinyl acetate copolymer/HPMC-Glycerol	Modify the disintegration time and dissolution rate of drug particles loaded into ODFs	[46]
2	IL-polymer nanoparticle	PLGA/PVA	Formulate a hybrid IL-nanoparticle system to deliver a poorly soluble drug	[47]
3	Crystalline nanoparticle	HPC-dioctyl sulfosuccinate 141 Na	Improve solubility	[48]
4	Nanoparticle antisolvent crystallisation	Poloxamer 188 and solupus	Improve solubility and dissolution rate	[49]
5	Polymeric nanoparticle	Eudragit® RL 100	Sustained release system	[50]
6	Gold (Au) nanoparticle	Au/Carrageenan oligosaccharide	pH-triggered anticancer drug release	[51]
7	Solid lipid nanoparticle	Decosanoic acid	Sustained release system	[52]
8	Polymeric nanoparticle	PLGA/hyaluronic acid	Controlled release and targeted drug delivery	[53]
9	Receptor-responsive nanoparticles	Amino terminal fragment (ATF) of human serum albumin (HSA)	Targeted to the urokinase receptor	[54]
10	Theranostic nanoparticle (metal nanoparticle)	Au/bovine serum albumin	Drug-dependent release and targeted drug delivery	[55]
11	Curdlan nanoparticle	Cyclodextrin	Intracellular release	[56]
12	Thermosensitive nanoparticle hydrogel (polymeric nanoparticle)	Amphiphilic copolymer poly(ε-caprolactone-co-1,4,8-trioxa [4.6]spiro-9-undecanone)-poly(ethylene glycol)-poly(ε-caprolactone-co-1,4,8-trioxa [4.6]spiro-9-undecanone)	Sustained co-delivery and early local treatment drug delivery for peri–implantitis	[57]
13	Semi-solid prodrug nanoparticles	Polymer-surfactant	Long-acting delivery	[58]
14	Integrin-based nanoparticle (liposome)	Lipoid S100, cholesterol, mPEG2000-DSPE and Mal-PEG2000-DSPE	Targeted drug delivery for hepatic stellate cells	[59]
15	Nanoparticle-conjugated microbubble	1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[succinyl (polyethylene glycol)-2000] (DSPE-PEG2k-NHS) and albumin	Targeted drug delivery for liver tumours	[60]
16	Silica nanoparticle (solid lipid nanoparticle)	(3-mercaptopropyl)-trimethoxysilane (MPTMS), β-mercaptoethylamine (MEA), Triton X-100 and tetraethyl orthosilicate (TEOS)/indocyanine green (ICG)	Targeted drug delivery for breast cancer cells	[61]
17	Self-assembling nanoparticle (poly-lysine dendrimer)	Polyglutamic acid (PGA)-polylysine/folic acid hydrate	Targeted drug delivery for breast cancer cells	[62]
18	Nano-hybrids	Bovine serum albumin (BSA), *N*-(3-dimethylaminopropyl), *N*′-ethylcarbodiimide hydrochloride (EDC·HCl), *N*-hydroxysuccinimide (NHS), phospholipid complex, cadmium chloride ($CdCl_2 \cdot 2.5H_2O$), thioglycolic acid (TGA), and D-mannose.	Tumour-targeted drug delivery	[63]
19	Copper (Cu) nanoparticle (metal nanoparticle)	$FeCl_3$, and $CuCl_2$	In vivo–targeted molecular imaging	[64]

(*Continued*)

Table 2 (Continued).

No	Types of Nanoparticle	Excipients	Main Objective	Ref.
20	Fe_3O_4 nanoparticle (metal nanoparticle)	Fe_3O_4 (iron oxide)/mesenchymal stem cells (MSC)	Targeted delivery for lung cancer	[65]
21	Hollow Au nanoparticle (metal nanoparticle)	Human placental Au/MSCs	Targeted drug delivery	[66]
22	HSA nanoparticle	HSA/FA-*N*-hydroxysuccinimide (NHS)	Targeted to the folic acid receptor	[67]
23	Au nanoparticle (metal nanoparticle)	Tetrachloroauric acid ($HAuCl_4$)-mono protected poly(ethylene glycol)-amino poly(ethylene glycol) undecyl mercaptan/chitosan low molecular weight	Targeted treatment for acute renal failure	[68]
24	Hybrid nanocarriers (liposomes)	Dipalmitoyl phosphatidylcholine (DPPC) and 1-oleoyl-2-[12-biotinyl(aminododecanoyl)]-sn-glycero-3-phosphocholine	Targeted to hepatocellular carcinoma cell lines	[69]
25	Folate-modified nanoparticle (polymeric nanoparticle)	FA, methoxy poly(ethylene glycol)-poly(lactide) (MPEG-PLA) and DOTAP	Targeted gene delivery system	[70]

Nguyen et al demonstrated that nanoparticles with β-cyclodextrin (β-CD) improved the solubility and enhanced the cytotoxic activity of α-mangostin, with a minimal inhibitory concentration (IC_{50}) of 8.86 and 9.86 µg/mL for LU-1 (human lung adenocarcinoma) and HL-60 (human promyelocytic leukaemia), respectively.[79] Another α-mangostin complex with β-CD was fabricated with grafted-chitosan. The system was prepared using high shear mixing techniques. The system exhibited a high of entrapment efficiency (>75%) and anti–inflammatory activity. The inclusion complex of α-mangostin and quaternised cyclodextrin grafted chitosan (QCD-g-CS) influenced cytokine

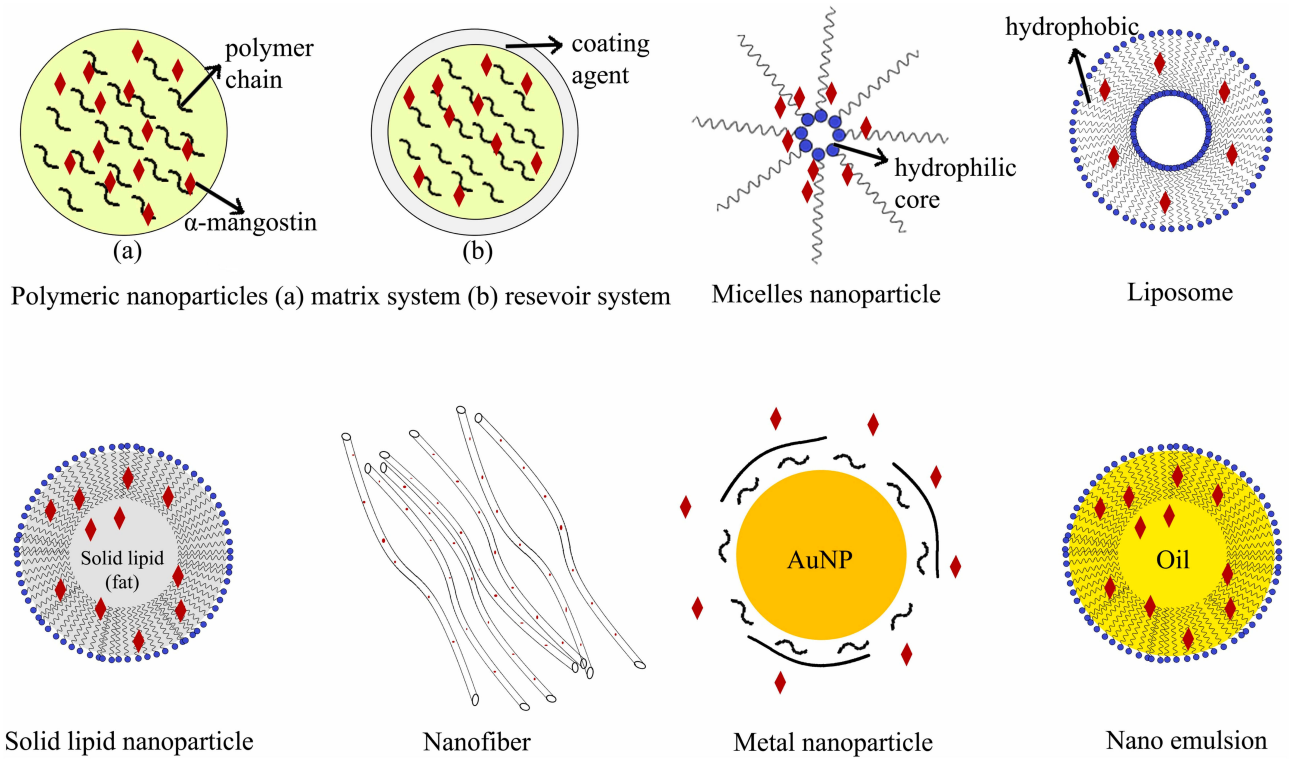

Figure 3 Nanoparticle drug delivery systems for α-mangostin.

Table 3 Nanoparticle Formulations of α-Mangostin

Formulations	Ingredients	Methods	Ref.
Polymeric Nanoparticles	PLGA	Colloidal extraction solvent evaporation	[74]
	Chitosan, PLGA	Colloidal extraction solvent evaporation	[75]
	PEG, PLA	Emulsion/solvent evaporation techniques	[76]
	PLGA	Double emulsion solvent evaporation method	[42]
	EC-MC	Spray drying	[77]
	Chitosan, alginate and genipin	Ionotropic gelation method	[78]
	β-cyclodextrin	Inclusion complex technique	[79]
	β-cyclodextrin-chitosan	Inclusion complex	[80]
	β-cyclodextrin	Inclusion complex	[81]
Nanomicelles	PVP	Solvent evaporation method	[82]
	MPEG and PLA	Single-step self-assembly method	[83]
	MPEG and PCL	Self-assembly method	[84]
Liposome nanoparticles	Transferrin	Thin film hydration	[85]
	Soya lecithin	Phase separation coacervation method	[86]
	Cholesterol, Tween 60 and ethanol	Film hydration method	[87]
Solid lipid nanoparticles	Lavender essential oil and cetyl palmitate	Hot and high-pressure homogenisation techniques	[88]
	PLGA and CD44 thioaptamer	Nanoprecipitation combined with self-assembly	[89]
Nanofibres	Thiolated chitosan	Electrospinning	[90]
	PVP	Electrospinning	[91]
Metal nanoparticles	Ag (silver)	Chemical reaction by using silver nitrate (AgNO3)	[92]
	Gold, PEI, cyclodextrin and tanshinone	Chemical reaction using polyethyleneimine (PEI)	[93]
Emulsion nanoparticle	Captex 200 P, Tween 80, carbopol 90 and silica	Solid self-emulsification	[94]
	Oleic acid, isopropyl myristate, Cremophor EL, Tween 80, carboxymethylcellulose sodium	Self-microemulsion	[31]

secretion and inhibited inflammation during the first hour (60% inhibition). After 3 h, there was almost total inhibition (95%).[80] Additionally, nanoparticles of a water-soluble β-CD and α-mangostin presented cytotoxic activities against A549 lung cancer cells, with an IC_{50} of 2.34 μg/mL.[81]

Nanomicelles

A micelle is an amphipathic molecule in water and suitable as a drug delivery carrier for drugs with high lipophilicity. The first nanomicelle for α-mangostin was generated by Aisha et al α-Mangostin in solid dispersion nanomicelles, combined with polyvinylpyrrolidone (PVP) as a main polymer, was produced by the solvent evaporation method. The solubility of α-mangostin markedly increased 10,000 fold, from 0.2 ± 0.2 pg/mL to 2743 ± 11 pg/mL. Self-assembly of anionic nanomicelles around α-mangostin was observed by transmission electron microscopy and dynamic light scattering; the diameter size was 99–127 nm. The nanomicelle uptake was mediated by endocytosis, a finding that indicated intracellular delivery of α-mangostin that could be associated with potential cytotoxicity (IC_{50} of 8.9 ± 0.2 μg/mL).[82]

In another study, α-mangostin nanomicelles with methoxypoly(ethylene glycol)-poly(lactide) (MPEG-PLA) were developed by a single-step self-assembly method for malignant glioma. In vitro and in vivo assays showed that the α-mangostin/MPEG-PLA nanoparticles inhibited cell growth and induced apoptosis—with cleaved caspase expression, DNA fragmentation, downregulation of anti-apoptotic molecules and up-regulation of apoptotic molecules. This study also successfully investigated the process of programmed cell death in malignant glioma cells after treatment with α-mangostin/MPEG-PLA.[83]

Yang et al recently generated α-mangostin with methoxypoly(ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL) as an anti-melanoma agent. The system had a sustained release profile, high solubility, strong toxicity to tumour cells and low toxicity to non-tumour cells. Additionally, MPEG-PCL inhibited melanoma cell proliferation, induced apoptosis via intrinsic and extrinsic pathways, suppressed growth cells and restrained angiogenesis. These data suggest that α-mangostin/MPEG-PCL nanomicelles are promising potential chemotherapy agents for the treatment of melanoma.[84]

Liposome Nanoparticles

Liposome nanoparticle (nanoliposome) is a liposome with particle size around 80–300 nm. Liposome nanoparticles can improve the physicochemical properties and performance of drugs due to their capability to deliver a drug. Chen developed a liposome, with α-mangostin as a drug payload using transferrin, with the thin-film hydration method. On the intercellular distribution assay, liposomes presented a time-dependent property; approximately 210 Ω/cm^2 α-mangostin crossed the blood–brain barrier (BBB), with horseradish peroxidase (HRP) permeability less than 5%.[85]

Chin et al developed an α-mangostin niosome to improve the skin permeation rate of α-mangostin. Proniosome was prepared with soya lecithin using a phase separation coacervation method. The system enhanced skin permeation of α-mangostin 1.8–8.0 fold compared to control. It also improved viable epidermis/dermis (VED) of the α-mangostin compound, where α-mangostin deposition in the VED layer was increased 2.5–2.9 fold compared to control. Moreover, the addition of spans and soya lecithin improved the solubility of α-mangostin in water.[86]

Another niosome formulation from Limpapayom et al utilised cholesterol, Tween 60 and ethanol as the main carrier system. The system was prepared by film hydration; the particle size was 213 ± 26.47 nm, polydispersity index (PDI) was 0.23 ± 0.19 and zeta potential was −12.67±0.90 mV. Subsequently, the noisome/α-mangostin was prepared in cream and serum forms with 2.5–5% α-mangostin. The particle size, PDI and zeta potential were 600–700 nm, 1.11 ± 0.01 and 0.58 ± 0.04 mV, respectively. A skin permeation study confirmed that about 10–40% of α-mangostin released over more than 24 h.[87]

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) are spherical carrier composed of single or double lipid layer on the surface, and solid layer in the core of the system. The complex system of SLN can provide an excellent drug control released. However, only two journals publication reported regarding solid lipid nanoparticle formulation of α-mangostin. Yostawonkul et al designed a nanostructure lipid carrier for α-mangostin (AM-NLC) by hot and high-pressure homogenisation techniques for non-surgical castration of male animals. Lavender essential oil and cetyl palmitate were the carrier system in this study. AM-NLC increased the activity of caspase-3 and caspase-7 and induced germ cell degeneration within the seminiferous tubules. Shrunken tubules were greatly depleted of germ cells. Additionally, the use of AM-NLC reduced the levels of pro-inflammatory mediators (nitric oxide and tumour necrosis factor α).[88]

Bonafe et al developed a lipid nanoparticle formulation to increase the activity of α-mangostin in disaggregation of MCF-7 cells. PLGA and CD44 thioaptamer used as the main carrier. A nanoparticle that contained 0.5 μg/mL α-mangostin induced disaggregation of multicellular tumour spheroid (MCTS). There was a similar dissociation effect when MCTS were cultured in matrix gel under the same conditions for 48–72 hrs. Moreover, the system with the lower α-mangostin concentration triggered damage, denoted as a substantial reduction in the MCTS size and density. The reduced spheroid expansion implied that a significant number of cells died or were in cell cycle arrest.[89]

Nanofibers

Nanofiber is widely used for site-specific drug released to achieve the desired therapeutic effects. Nanofiber has a diameter range around 150 nm and length 50–200 μm. Nanofibers could potentially overcome the limitation of α-mangostin. A nanofibre combined with chitosan thiolated with the electrospinning method had excellent mucoadhesive

properties. Additionally, the α-mangostin nanofibre improved the bactericidal rate.[90] Another nanofibre formulation was prepared using polyvinylpyrrolidone (PVP) as a carrier matrix for the active compound. The PVP nanofibre (387–586 nm) was prepared using an electrospinning apparatus. The preparation exhibited antioxidant activity, and the use of high voltage in the electrospinning technique did not apparently damage the molecular structure of α-mangostin. In vitro, α-mangostin release increased from 35% to over 90% in 60 min.[91]

Metal Nanoparticles

Metal nanoparticle is a metal with particle size around 1–100 nm. Several studies reported that metal nanoparticles have a bioactivity as anticancer agent and a high affinity with the cancer cells. Silver α-mangostin nanoparticles were formulated in a perfect spherical shape. These nanoparticles significantly inhibited the growth of the bacteria *Escherichia coli* and *Bacillus subtilis* and the fungus *Aspergillus niger*. Additionally, the presence of α-mangostin substantially reduced the silver ions in the silver nanoparticle system.[92]

Gold α-mangostin nanoparticles were also formulated; they comprised polyethylenimine (PEI) and cyclodextrin. Tanshinone was used as competitor drug payload in this study. The α-mangostin gold nanoparticles improved the loading efficiency approximately 15–50%, with an IC_{50} of 17.5 μM and 6.0 μM for PC-3 and DU145 cell lines, respectively. Comparatively, the tanshinone gold nanoparticles were very active against these cells, with a 40% improvement in the IC_{50} value for both PC-3 and DU145 cells.[93]

Emulsion Nanoparticles

Emulsion nanoparticle (nanoemulsion), a colloidal particulate system, consists of oil, water, and surfactant with high kinetic stability, low viscosity, and optically transparent. In the last decade, nanoemulsion has become a promising lipophilic drugs delivery system. Solid self-emulsification is one common modification technique to enhance the solubility and dissolution rate of α-mangostin. Droplet particles obtained from this system (using liquid-self-emulsifying drug delivery system [liquid-SEDDS]) were 106.9 ± 24.3 nm. The droplet was further converted to the solid state (solid-SEDDS) using Aeroperl 300 and Sylysia 350 silica. Solid-SEDDS with Aeroperl 300 had better flowability compared to solid-SEDDS with Sylysia 350. Based on the characterisation of X-ray diffraction (XRD) and differential scanning calorimetry (DSC) analysis, the solid-SEDDS exhibited an amorphous form. The dissolution test indicated that approximately 18.82% and 7.71% of α-mangostin was released from solid-SEDDS with Aeroperl 300 and Sylysia 350, respectively, within 60 min. However, only 0.26% of the intact α-mangostin dissolved.[94]

The mechanism for the improved α-mangostin solubility in emulsion was due to self-microemulsion; the particle diameter size was 24.6 nm and the encapsulation efficiency was 87.26%. These factors increased the area under the curve of α-mangostin by 4.75 fold compared to the free form. The preparation also increased α-mangostin distribution in lymphatic organs. Overall, self-microemulsion as a nano delivery system can promote the digestive tract absorption of α-mangostin and provide a specific distribution. The targeted system and high oral bioavailability of α-mangostin with self-microemulsion provides excellent performance for clinical drug efficacy.[31]

Perspective

In drug development, nanoparticle technology represents physical modifications intended to ameliorate solubility problems. Currently, nanotechnology can be applied for drug delivery systems, such drug controlled release,[95] delayed release and sustained release.[96] These nanoparticle formulations are the most commonly used in drug delivery systems.[97] Our objective review highlighted that the nanoparticle technology in nanomedicine applications is divided into three general classifications: increased water solubility, controlled release and targeted drug delivery. As mentioned before, nanotechnology can be used to recover the solubility problem of drugs through multiple pathways and mechanisms. Firstly, particle size reduction in nanotechnology improves the drug solubility by expanding the surface area of particles.[98,99] Secondly, the use of high water-soluble excipients as the main base of nanoparticles increase the solubility of drugs mediated by hydrogen bonding interaction between excipients and water molecules.[100,101] On the other hand, the use of surface-active agent (surfactant) in nanotechnology also enhances the solubility of high lipophilicity drugs through interfacial tension reduction.[102,103]

Considering the effects of therapy with a dose and frequency of administration that is efficient, nanoparticle technology can be utilised to provide controlled and targeted drug delivery systems, especially for cancer therapy, to increase selectivity, mitigate potentially harmful side effects and even cause death in normal cells. The physicochemical properties

of α-mangostin, especially its poor water solubility profile and its low selectivity on the target cells, limits its therapeutic applicability. Therefore, nanoparticle formulations are one option to resolve these limitations.

Numerous nanoparticle formulations have been described, including polymeric nanoparticles, solid lipid nanoparticles, nanofibers, nanomicelles and metal nanoparticles. In general, these formulations aim to increase the solubility of compounds that are poorly soluble in water through particle size modification to obtain a larger surface area. On the other hand, the type of nanoparticle and ingredients also influences the solubility of a compound. Polymeric nanoparticles are formulated with the polymer as a base for the formulations and are often made for further examinations.

Nanoparticle formulations have been developed using various nanocarriers with different techniques. Each nanocarriers are formulated by considering the aims of the studies such as to provide solubility improvement with hydrophilic polymer as a carrier,[104] to provide control released system with pH-sensitive polymers or thermal-sensitive polymers,[105,106] and to prevent protein degradation with liposome protection.[107] In some cases, the nanocarrier is combined with targeting mediators to gain the nanoparticle targeted drug delivery system into specific target.[108]

Nanoparticles that mediate passive or active targeted delivery are generally prepared with ingredients that have a high affinity to the target and low affinity towards normal cells, for example, PLGA. PLGA is a copolymer formed from the combination of polymer polylactic acid (PLA) and polyglycolic acid (PGA). Research showed that PLGA has a high affinity to cancer cells, including hepatic cancer,[109] prostate cancer[110] and lung cancer cells,[111] and many cell lines, including human umbilical vein endothelial cells,[112] H1299,[113] COS-7 and Cf2th.[114] This high affinity allows PLGA to provide drug delivery systems or genes into the target-specific tissues or organs. Ultimately, consideration of nanoparticle shape and the materials used in the formula requires careful and thoughtful attention, especially with regards to the desired use and destination.

Conclusion

Many techniques have been considered to improve α-mangostin's water solubility, of which nanoparticle formulations have become the most widely performed. This formulation provides many advantages. Overall, nanoparticle formulations improve α-mangostin's water solubility and affect its biopharmaceutical, pharmacokinetic and pharmacodynamic aspects. Additionally, nanoparticle technology for α-mangostin can be a promising for controlled release and passive and active targeting. This system should help to maximise the efficacy of α-mangostin in a drug delivery system.

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Disclosure

The authors report no conflicts of interest in this work.

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