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Review Article

Unravelling Alpha-Mangostin as a Promising Anticancer Agent: An Overview of Therapeutic Effects, Molecular Mechanisms, and Strategies to Improve Treatment Outcomes

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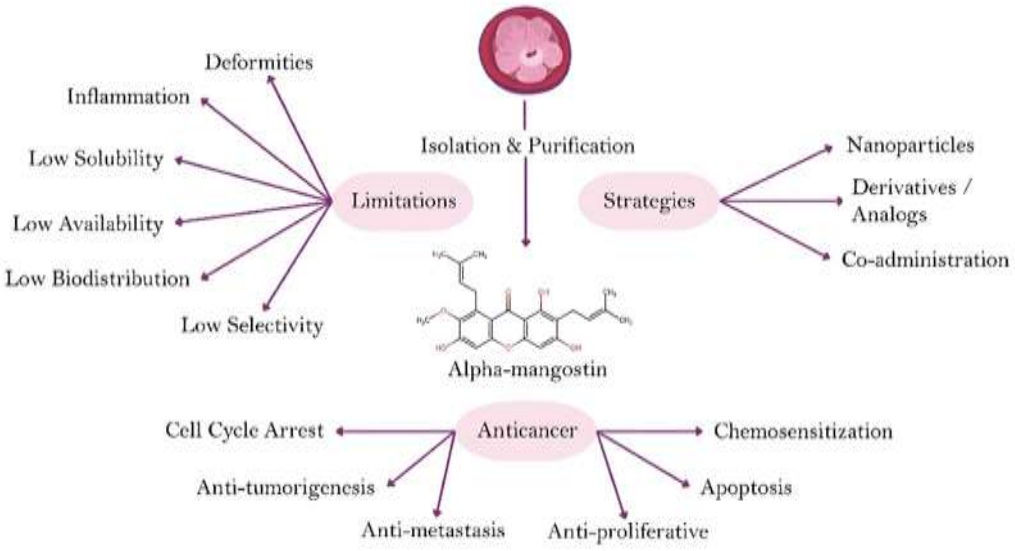
Abstract: Cancer represents a significant global health concern, contributing to a high number of fatalities in the 21st century, with projections indicating a continuous spike in cancer cases. Although chemotherapy is an established cancer treatment, it is often associated with adverse effects and chemoresistance. Thus, alternative therapies like natural products that can address these limitations of chemotherapy are crucial. Alpha-mangostin (AM), derived from the mangosteen fruit, has widely demonstrated potent anticancer and enhanced chemosensitivity properties by regulating oncogenic signaling pathways, including *phosphoinositide 3-kinase/protein kinase B* (PI3K/Akt), *nuclear factor-κB* (NF-κB), and

mitogen-activated protein kinase (MAPK) pathways. This review discusses the current anticancer status of AM in preclinical studies and associated molecular mechanisms. It also further identifies the challenges and strategies to enhance the anticancer activity of AM. AM has shown strong anticancer effects in preclinical studies across multiple cancer types, including breast, cervical, ovarian, colorectal, pancreatic, prostate, and lung cancers. It induces apoptosis, causes cell cycle arrest, and inhibits the proliferation of cancer cells. AM also reduces cancer progression and metastasis by targeting key signaling pathways, demonstrating broad therapeutic potential. To overcome the limitations of AM, such as low bioavailability and limited clinical evidence, strategies like nanotechnology, chemical modification, and combination with chemotherapeutic agents have been proposed. These approaches aim to enhance AM's therapeutic potential. However, further research is needed to assess its pharmacokinetics, safety, and clinical efficacy. Future studies should also focus on improving delivery systems and conducting rigorous clinical trials to support AM's use in integrative cancer therapy.



Graphical abstract. Alpha-mangostin exerts anticancer effects by regulating cell cycle arrest, inhibiting tumorigenesis, metastasis, and cell proliferation, inducing apoptosis, and enhancing chemosensitivity. However, its therapeutic potential is limited by low solubility, bioavailability, and biodistribution, which could be improved through nanoparticle encapsulation, derivative synthesis, or combination with other chemotherapeutic agents.

Keywords: alpha-mangostin, anticancer, chemotherapy, toxicity, nanotechnology, *Garcinia mangostana* L. (Clusiaceae), SDG 3 Good health and well-being

1. Introduction

Cancer remains a major global health challenge in the 21st century, accounting for approximately 1 in 6 deaths worldwide and contributing to nearly 30% of premature non-communicable disease (NCD) deaths among individuals aged 30–69 years. It ranks among the top three causes of death in 117 out of 183 countries [1,2]. In 2023, an estimated 609,820 cancer-related deaths were projected to occur in the United States, highlighting the urgent need for effective interventions [3]. In 2020, nearly 10 million cancer-related deaths were recorded worldwide, highlighting the growing global burden of cancer and the urgent need for improved prevention and treatment strategies [4]. The global cancer burden is projected to increase to 29.5 million new cases and 16.5 million deaths by 2040, highlighting the critical demand for innovative therapeutic strategies [5].

Today, novel modalities, such as targeted drug therapy, immunotherapy, and personalized medicine, have emerged, promising more precise and effective interventions than ever before. Chemotherapy has been widely considered the cornerstone of cancer treatment and is used to remove tumor burden and improve patients' outcomes by targeting rapidly dividing cells [6,7]. It has served a great purpose over the past few decades and has remained the preferred treatment option for advanced-stage malignancies [8]. Moreover, the use of nanoparticle-based delivery methods, targeted antibodies, aptamer functionalization, and specific drugs such as Herceptin has shown promising results in the treatment of breast cancer (BC), showcasing their potential in enhancing therapeutic efficacy and improving patient outcomes in the near future [9-11].

Chemotherapeutic drugs, commonly referred to as cytotoxic agents, have been widely employed in cancer treatment. However, their efficacy often comes with significant adverse effects, impacting patients' quality of life, and prolonged treatments can lead to toxicity, potentially causing organ failure [8,12,13]. Furthermore, chemotherapeutic drugs have been associated with multi-drug resistance (MDR), a major challenge in oncology that significantly reduces treatment efficacy and contributes to poor clinical outcomes [14,15]. Common mechanisms contributing to chemoresistance include increased drug efflux via transporters such as P-glycoprotein, enhanced DNA repair capacity, and alterations in drug targets, which collectively reduce the effectiveness of chemotherapy. Several anticancer drugs have been associated with significant adverse effects; for instance, doxorubicin is known to cause cardiotoxicity, while doxorubicin, cisplatin, and 5-fluorouracil have also been linked to cognitive impairments, potentially through mechanisms involving hippocampal inflammation and altered thyroid hormone levels [15,16].

Preclinical and some clinical studies have reported that certain phytochemicals may be less toxic and exhibit multi-targeting potential against various malignancies. They have also been shown to enhance tumor cell sensitivity to chemotherapy, potentially reducing treatment-associated toxicity [15,17]. Examples of clinically relevant phytochemicals include curcumin and resveratrol, which have shown promising anticancer and chemosensitizing effects in various cancers. They exert anticancer activities by modulating multiple cellular pathways involved in apoptosis, proliferation, migration, invasion, angiogenesis, and metastasis and by enhancing the efficacy of conventional chemotherapy, especially in treatment-resistant cases [15,18,19]. Chemosensitization is a widely used approach, whereby a drug's activity is augmented using other drugs to suppress chemoresistance. Combination chemotherapy improves traditional drug therapy by reducing chemoresistance-related proteins, genes, and pathways while simultaneously changing cancer's molecular target [15,17].

Mangosteen pericarps have been used for medical treatments in various countries, including Malaysia, Indonesia, Philippines, and Thailand [20]. Traditionally, pericarps have been used in treating wound infections, ulcers, dysentery, and abdominal pain. Alpha-mangostin (AM) is the most abundant xanthone naturally found in *Garcinia mangostana L*. from the Clusiaceae family [21]. It has been studied extensively, revealing numerous pharmacological properties, including anticancer, antidiabetic, and neuroprotective effects. The chemical structure is characterized by prenyl and hydroxyl groups, contributing significantly to its biological activity [22]. Compared with other xanthones, AM has been the most widely investigated, with strong evidence supporting its selective cytotoxicity, multitargeted molecular mechanisms, and therapeutic potential, making it the most suitable candidate for focused evaluation in this review.

AM has demonstrated selective cytotoxic activity *in vitro* and has been shown to affect various stages of cancer cell development by inducing cell cycle arrest and apoptosis in multiple human cancer cell lines [23]. For instance, AM induces apoptosis in BC cells by inhibiting Akt activation, affecting the *phosphoinositide 3-kinase/protein kinase B* (PI3K/Akt) signaling pathway, leading to apoptosis. It can also trigger apoptosis by regulating B-cell lymphoma 2 **(**Bcl-2) proteins and activating caspase-3. AM inhibits metastasis by downregulating matrix metalloproteinase 2/9 (MMP-2/9) expression [24]. Notably, AM's multitargeted activity offers a novel therapeutic angle by simultaneously addressing key unmet needs in oncology, such as drug resistance, systemic toxicity, and the limited accessibility of current precision therapies, while complementing existing treatment strategies.

Nonetheless, the treatment efficacy of AM is hindered by its hydrophobic properties [23]. As a result, AM accumulates poorly in target organs and has low bioavailability. This limitation can be resolved by incorporating nanoparticles and liposomes, modifying AM's chemical structure, and combining AM with other chemotherapeutic agents to enhance targeted localization and cellular uptake within cancer cells.

Another issue is the lack of clinical trials and most toxicity research is still in the preclinical stages, including *in vitro* and *in vivo* studies. Clinical data are currently inadequate for AM to be incorporated safely into clinical practice. In summary, this review aims to highlight the anticancer properties of AM and associated molecular mechanisms, as well as its limitations as a potential treatment option in cancer. It also discusses the biosynthesis of AM, their biosafety and toxicity profiles, and potential strategies to overcome the issues and limitations of AM.

2. Isolation and purification of alpha-mangostin

Since the first isolation of AM from dried mangosteen peels in 1855 [25], various methods have been developed to purify it. Patented and reported, isolating AM involves a range of processes tailored to specific sources of the compound, like the pericarp, rind, stem bark, and skin of the mangosteen plant. Thus, several methods have been employed to isolate and purify AM, each with varying degrees of efficiency, purity, and environmental considerations.

As reported by Van Quang *et al.*, the AM extract can be prepared from the powdered form of the peel [26]. The powder is dissolved in ethanol and left to extract for three days before it is subsequently dried. The dried extract is then rehydrated with water and n-hexane, forming an n-hexane layer, which is isolated and again dried for further use. This layer is packed into a column, fractionated, and crystallized to obtain pure AM. The purity is then verified using techniques like Thin-Layer Chromatography, High-Performance Liquid Chromatography, and Total Phenolic Content analysis. Another method by Idawati *et al.* involves directly soaking the mangosteen rinds in 96% ethanol, which allows for a higher yield (4.27%) in comparison to alternative techniques [27]. However, the downside of this method is that it requires more solvent and longer extraction times. On the other hand, Soxhlet extraction, another technique used for small-scale applications, also utilizes ethanol but results in lower yields and requires more specialized equipment.

There have been more sophisticated methods, including acid alcohol extraction, which is often followed by chromatographic purification. These techniques allow for high

purity (≥99%), but they can be costly and involve complex steps. Acid alcohol extraction offers advantages such as lower reagent use and faster processing, but poses environmental risks and temperature sensitivity [28]. Additionally, modern methods like green solvent extraction paired with chromatography have been developed to enhance the environmental sustainability of the process, achieving a purity of 98.34% while using ethanol as a green solvent [29]. In all, each synthesis method's efficiency and scalability depend on the balance between yield, purity, and operational complexity, making each suitable for different scales of production, from small-scale laboratory extractions to industrial applications. In comparative terms, direct ethanol soaking achieves the highest reported yield (4.27%) but with moderate purity, Soxhlet extraction gives lower yields with similarly modest purity, whereas acid alcohol and green solvent methods provide lower yields but consistently high purity (≥98–99%). This highlights a trade-off between maximizing recovery and achieving high-grade AM suitable for downstream applications.

3. Biosynthesis of alpha-mangostin

3.1. Structural characteristics of alpha-mangostin

AM is a natural xanthone derivative, an aromatic, and oxygenated heterocyclic compound, isolated from the pericarp of the mangosteen fruit. It is structurally based on the xanthone core (dibenzo-γ-pyrone or 9H-xanthen-9-one), which has the molecular formula of $C_{13}H_8O_2$, while AM itself has the molecular formula $C_{24}H_{26}O_6$ due to its additional functional groups [30]. The term "xanthone" originates from the Greek word "xanthós," which means yellow and was created by Schmid to describe the yellow tint of a chemical isolated from the mangosteen pericarp (*Garcinia mangostana L.*), a tropical fruit of the Clusiaceae (or Guttiferae) family [25].

Furthermore, its structure features two rings, with the A-ring derived from the acetate pathway and the B-ring derived from the shikimic acid pathway. These variations in xanthone derivatives arise from differences in substituents and their positions on the core structure, leading to a range of configurations and increased complexity in the molecule. AM possesses hydroxyl groups at positions 1 and 3 and prenyl groups at positions 2 and 8. γ-Mangostin shares a similar backbone but includes an additional methoxy group at position 6. Meanwhile, β-mangostin contains hydroxyl groups at positions 3 and 6 and a prenyl group at position 2 [31] as shown in Figure 1.

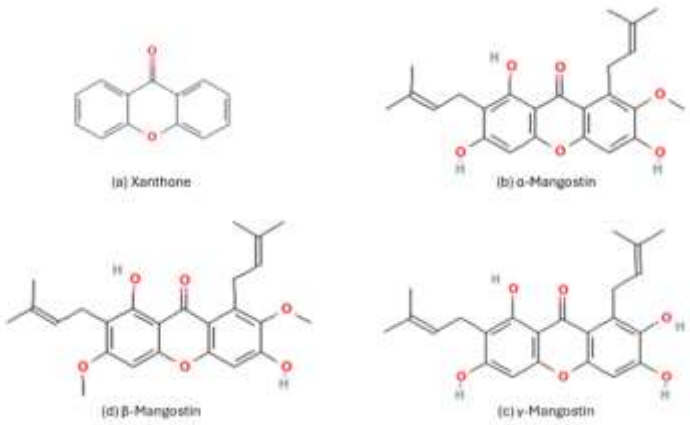


Figure 1. (clockwise from top left) Chemical structures of (a) xanthone and its derivatives: (b) alpha(α)mangostin, (c) gamma(γ)-mangostin, and (d) beta(β)-mangostin.

3.2. Biosynthesis of alpha-mangostin

According to Badiali et al., the most effective precursor of Mangostin is m-hydroxybenzoicacid, followed by other precursors, such as benzoic acid, cinnamic acid, and benzophenone [31]. An intermediate benzophenone is produced by the m-hydroxybenzoic acid produced by phenylalanine, which has reacted with three units of acetate. The xanthone moiety is produced by this oxidative reaction. Moreover, the oxidative coupling can occur in two methods, which depend on whether the benzophenone is folded to the para or ortho position of the hydroxyl group, resulting in the formation of 1,3,7-substituted mangostin or 1,3,5-trihydroxyxanthone.

Xanthones in plants are synthesized through the shikimate pathway, with the acetate (or polyketide) pathway also playing a contributory role. The shikimate pathway operates in both green and non-green plastids, allowing it to function independently of light conditions [31]. Xanthone biosynthesis generally involves the conversion of precursor compounds from glycolysis (phosphoenolpyruvate) and the pentose phosphate pathway (erythrose 4-phosphate) into shikimate. This complex process ultimately leads to the formation of L-phenylalanine through various enzymes and intermediates, crucial for generating benzophenone intermediates like 2,3',4,6-tetrahydroxybenzophenone (2,3',4,6-tetraHBP) [32]. According to Badiali *et al*., the enzymes shikimate dehydrogenase (SKD) and shikimate kinase (SK) are activated, prompted by a Ca2+-mediated H_2O_2 response, resulting in an increase in xanthone production, supporting the role of xanthones as defensive metabolites [31]. In the phenylalanine-dependent pathway, shikimate is converted to phenylalanine through a series of reactions that occur in both the plastid and the cytosol. Phenylalanine, synthesized from chorismate, the final product of the shikimate pathway, is then transported

to the cytosol via the plastidial cationic amino acid transporter (pCAT). For instance, exchanging the C-3 and C-6 with aminoethyl derivatives increased the antioxidant activity, but substituting them with methyl, propanediol, acetate, or nitrile decreased it [33].

3.3. The physicochemical properties of alpha-mangostin

1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one, or commonly known as AM, $C_{24}H_{26}O_6$, is a naturally occurring xanthone derivative with a molecular weight of approximately 410.5 g/mol and a melting point around 180-181°C. It is sparingly soluble in water (2.03×10^{-4} mg·L^{-1} at 25 °C) but exhibits good solubility in organic solvents like ethanol and dimethyl sulfoxide. In powder form, AM presents as a faint yellow to yellow color and remains stable under normal conditions (20°C, one atm). Due to its tricarbonyl structure, AM has three dissociation constants (pKa) of 3.68, 7.69, and 9.06. The AM molecule contains hydroxyl and prenyl groups, both contributing to its lipophilicity, influencing its interaction with biological membranes and its bioavailability [34].

4. Pharmacokinetic profile

AM has been demonstrated to be rapidly absorbed from the gastrointestinal tract and distributes extensively across tissues in dose-independent linearity. Notably, it has been proven to cross the blood-brain barrier, as evident by the detection in brain homogenate [35]. Moreover, enhancing the bioavailability of AM has been the focus of recent research. For instance, *in vivo* studies have proven that co-administering polyphenols, such as those with mangostin extract, significantly improves their pharmacokinetic properties. When administered as a mangostin extract, AM shows higher plasma concentration (C_{max}), longer time to reach maximum concentration (T_{max}), and extended half-life, indicating improved bioavailability and sustained presence in the systemic circulation. For instance, when administered at the dose of 100 mg/kg of mangostin extract (equivalent to ~36 mg/kg of AM) in mice, the C_{max} reached 357 ng/mL at 1 hour with a half-life of 8.2 hours, and area under the curve (AUC) from 0–24 hours (AUC_{Last}) and area under the curve from 0-inf (AUC_{inf}) with values of 2,807 nmol/hr and 2,980 nmol/hr, respectively [36].

The linearity of AM's pharmacokinetics has been further corroborated by dose-proportionality studies, revealing a strong correlation between dose and AUC, with consistent systemic clearance across varying doses [35]. Additionally, clinical data have provided valuable insights into the pharmacokinetic profile of AM in humans. Kondo *et al.* reported a significant increase in plasma AM levels following the consumption of Vemma formulation containing the mangostin extract (standardized AM content not specified), with a C_{max} of

3.12 ± 1.47 ng/mL observed after 1 hour [37]. The concentration declined to one-third of the C_{max} by the 4th and 6th hours and remained stable for the whole duration. Beyond absorption and clearance, other pharmacokinetic parameters of AM have been investigated extensively. For instance, Hidayat *et al*. reported that human intestinal absorption (HIA) rates of 90-99% for AM and its derivatives, indicating high bioavailability [38]. Moreover, AM exhibits medium permeability across cell membranes, as evidenced by its CaCo-2 score, as well as a high affinity for plasma protein binding with values exceeding 90%, suggesting that AM is bound to plasma proteins in circulation. Taken together, these pharmacokinetic features highlight both opportunities and challenges for AM's druggability: its ability to cross the blood–brain barrier and high intestinal absorption support therapeutic potential, whereas poor solubility, extensive plasma protein binding, and rapid clearance underscore the need for enabling formulations (e.g., nanoparticles, liposomes, or co-administration strategies) to improve oral bioavailability and sustain systemic exposure. However, systematic data on AM's metabolic and clearance pathways are still scarce. To date, there is no comprehensive profiling of hepatic metabolism, biotransformation routes, or elimination kinetics, representing an important gap that must be addressed to facilitate clinical translation.

5. Biosafety and toxicological profile of alpha-mangostin

To date, there have yet to be any human clinical trials conducted to analyze the anticancer properties of AM. Thus, studies analyzing the adverse reactions of AM are mostly derived from animals.

The following studies investigated the safety of AM through two different administrative routes; the first study used the oral route [39], while the other was carried out through intraperitoneal injection [40]. The rats that were treated with AM orally did not display any toxicity or mortality throughout the whole study [39]. When comparing the weights and food intake of the rats treated with AM and the control group, there were no notable differences. According to research done by Zielinska *et al.*, it demonstrated that the LD_{50} of AM was 150 mg/kg, as the mice administered with 150 mg/kg AM through intraperitoneal injection exhibited mortality after 3 days [41]. Another study carried out on fertilized embryos of zebrafish showed that there was an 80% mortality rate when the embryos were treated with 2 µM of AM. It was also discovered that when the embryos were treated with 4 µM of AM, all larvae were found to be mortal. Furthermore, there were phenotypic defects and malformations that were observed when zebrafish embryos were examined at 120 hpf (hours post fertilization). At 2 µM, the remaining zebrafish larvae that survived showed malformations in their development, such as head deformities, oedema of yolk, and lack of a

bladder. Furthermore, the effects of AM on hepatogenesis suggested that AM exhibited toxic effects toward both their cardiovascular system and bone development at a concentration of 8 μM [42].

In conclusion, the biosafety and toxicity of AM have been tested in preclinical studies, but are limited to a few. In some studies, AM is found to not impose any toxic effects, while other research states otherwise, due to the toxicity testing models' variation. Given the inconsistent results, lack of preclinical toxicity testing, and lack of clinical trials, there is a need for further research on the safety of AM before it can be administered to humans for medical use.

6. Preclinical Anticancer Activities of Alpha-Mangostin and Associated Molecular Mechanisms

AM demonstrates significant preclinical anticancer activities across various cancer types by inducing apoptosis, inhibiting cell proliferation, suppressing metastasis, and overcoming chemoresistance. These effects are mediated through diverse molecular mechanisms, including caspase-dependent and -independent pathways, modulation of key signaling pathways, and inhibition of epithelial-mesenchymal transition (EMT). AM synergistically enhances the efficacy of standard chemotherapeutic agents while mitigating associated effects. The detailed molecular mechanisms underlying these effects are summarized in Table 1 and Table S1.

6.1. Breast cancer

BC is the most diagnosed cancer among women, and several studies have demonstrated promising anticancer activities of AM in modulating cell survival and inhibiting metastasis [43]. Studies in BC cell lines, such as MCF-7, MDA-MB-231, and T47D, have highlighted these effects [44].

AM has been shown to induce apoptosis in BC cells by modulating several key molecular pathways, including both caspase-dependent and -independent mitochondrial pathways by targeting various key factors. AM-induced apoptosis through promoting the interaction of Modulator of Apoptosis 1 (MOAP-1) with activated Bcl-2-associated X protein (act-BAX), releasing Apoptosis-inducing factor (AIF), and disrupting mitochondrial membrane potential (MMP), subsequently contributes to BAX oligomerization, cytochrome c release, and caspase activation [45-48]. Additionally, AM also modulates apoptosis via the PI3K/Akt signaling pathway by either degrading Retenoid X Receptor Alpha (RXRα/tRXR)

or human epidermal growth factor receptor 2 (HER2) inactivation, both of which block Akt phosphorylation. This inhibition prevents the suppression of pro-apoptotic proteins like BAX and Bcl-2-associated death promoter (BAD), triggering apoptosis [47,49,50]. By increasing the phosphorylation of p38 and c-Jun N-terminal kinases (JNK) while decreasing the levels of phosphorylated extracellular signal-regulated kinases-1/2 (ERK1/2) and cellular rapidly accelerated fibrosarcoma (c-Raf), AM promotes the expression of C/EBP homologous protein (CHOP) and transcription factor Jun coupled with protein c-Fos (c-Jun), which leads to cell apoptosis [49]. Moreover, research by Huang *et al*. highlighted that AM induced endoplasmic reticulum (ER) stress and autophagy in MDA-MB-231 cells [44]. Prolonged ER stress with the activation of unfolded protein response (UPR) pathways can trigger both autophagy and apoptosis. Since autophagy serves as a survival mechanism for cancer proliferation, inhibiting autophagy under ER stress conditions enhances the cytotoxic effects. Several studies have also reported that AM-induced apoptosis through inhibiting Fas Cell Surface Death Receptor (FAS) activity and expression, subsequently leading to Poly (ADP-ribose) polymerase (PARP) cleavage and further promoting apoptosis [24,44,51].

Beyond inducing apoptosis, AM has also been shown to inhibit cancer cell proliferation by targeting two key genes related to cell growth, such as *KCNH1* and *CCND1*. In both BC MCF-7 and T-47D cells, AM significantly downregulated *KCNH1*, resulting in a decrease in cell proliferation. Similarly, AM suppressed *CCND1* expression to induce cell cycle arrest in the G1 phase [52]. Other studies have indicated that AM induces cyclin D1-dependent cell cycle arrest in the S and G2/M phases in MDA-MB-231 and MCF-7 cells, respectively [24,46]. AM's anti-proliferative effects are also associated with its influence on the ER signaling pathway, where it suppresses ER phosphorylation, reduces ER expression, inhibits *CYP19A1* activity, functioning as an ER antagonist [49,52]. AM has also been found to inhibit E2-stimulated cell proliferation and downregulate Erα expression [47]. Additionally, it enhances IKKα and Src expression, which in turn decreases nuclear factor-κB (NF- κB) RelA (p65) and c-Rel expression, thereby inhibiting both cell proliferation and inflammation in BC cells [49]. *In vivo* studies have further shown that AM inhibits tumor proliferation by reducing the levels of proliferating cell nuclear antigen (PCNA) while increasing p53 expression, leading to a significant reduction in tumor volume in rats injected with LA7 cells [53].

Besides, AM has shown potential anti-metastatic effects by inactivating Focal adhesion kinases (FAK) specifically through the reduction of Tyr397 phosphorylation in MCF-7 and MDA-MB-231 cells. FAK mediates signaling pathways, such as PI3K/Akt and mitogen-activated protein kinase (MAPK) pathways, which are associated with cell

proliferation, metastasis, and cell adhesion [51]. AM disrupts matrix metalloproteinase-2/7 (MMP2/7) activity in MCF-7 cells, likely through ERK1/2 inactivation, which reduces the DNA-binding activity of NF- κB and activator protein 1 (AP-1), inhibiting cell migration and invasion [30,54]. Moreover, AM downregulates pY705 and pyruvate kinases isoenzyme (PKM2) levels in BC cell lines, inhibiting signal transducer and activator of transcription 3 (STAT3)-driven proliferation, migration, and invasion [43].

AM has shown potential in overcoming chemoresistance in BC. Recent research highlights that combining 4'-hydroxytamoxifen with AM has a synergistic anti-proliferative effect, particularly by inhibiting *Baculoviral IAP Repeat Containing 5* (*BIRC5*) gene expression, which enhances cancer cell sensitivity to treatment. This combination not only improves the effectiveness of therapy but also helps to prevent the development of tamoxifen-induced endometrial cancer and to reduce electrical disturbances in the myocardium [52]. Another study demonstrated that combining AM with doxorubicin has additive effects, lowering cell viability, inhibiting retinal dehydrogenase (RALDH) activity in MCF-7 tumor spheroids, and mitigating some of the central nervous system side effects caused by doxorubicin. Mechanistically, doxorubicin was found to inhibit *PARP1* and *PARP2* and downregulate *BRCA1* and *BRCA2* expression, thereby amplifying AM-induced DNA damage and enhancing its cytotoxic effects [55]. All these findings suggest AM's potential as a promising therapeutic agent for BC treatment.

6.2. Cervical cancer

In addition, AM has shown a significant therapeutic potential in cervical cancer (CIN). Studies have reported that it induces intrinsic or mitochondrial apoptosis by reducing the levels of procaspase-3, procaspase-9, anti-apoptotic proteins, myeloid cell leukemia-1 (Mcl-1), and Bcl-2 while increasing cleaved caspase-3, PARP, and BAX in HeLa and SiHa cells [56,57]. The anti-proliferative effects of AM are attributed to the suppression of Z-Val-Ala-Asp-fluoromethylketone (Z-VAD), breakdown of MMP, production of intracellular reactive oxygen species (ROS), and activation of p38 [57,58]. AM is also involved in the apoptosis Signal-Regulating Kinase 1(ASK1)-mediated pathway, ASK1/MKK3/6/p38 signaling pathway, increasing the phosphorylation of ASK1 and MKK3/6, leading to mitochondrial damage and apoptosis *in vitro*, as observed HeLa and SiHa cells. In an *in vivo* study, this pathway contributes to tumor suppression by activating caspase-3 [57].

According to Diaz *et al.*, AM exerts cytotoxic effects on CIN cell lines with various human papillomavirus (HPV) subtypes (including HeLa, SiHa, CaSki, and C33a), showing

stronger inhibitory effects on cells with higher HPV16 copies, such as SiHa and CaSki cells [59]. AM impairs cell proliferation by downregulating *E6*- and *E7-HPV16* oncogenes and *KCNH1* in both *in vitro* and *in vivo* models. Besides, AM reduces stemness markers (e.g., Sox2, Oct-4, CK-14, and Nanog) and inhibits sphere formation in SiHa and HeLa cells [56]. Additionally, AM enhances treatment efficacy by increasing cell sensitivity through the upregulation of interleukin (IL-6) expression in CaSki cells [59]. When combined with cisplatin, AM produces synergistic effects and significantly enhances cisplatin's cytotoxicity both *in vitro* and *in vivo* by promoting apoptosis, inducing cell cycle arrest, and reducing tumor growth. AM can also act as a renoprotective agent to mitigate cisplatin-induced nephrotoxicity. However, this combination also markedly increases the effectiveness of cisplatin against cancer stem cells (CSCs) in HeLa and SiHA cells [56,60]. Notably, AM significantly elevates vimentin gene expression, suggesting its potential to prevent HPV viral infection [59].

Overall, AM exhibits strong anticancer activities in CIN. Its ability to target key signaling pathways, such as ASK1/MKK3/6/p38, and to synergize with chemotherapeutic agents highlights its potential as a multifaceted therapeutic candidate for improving treatment outcomes.

6.3. Ovarian cancer

In various ovarian cancer (OC) cell lines, AM induces dose-dependent cytotoxicity and reduces cell proliferation [61,62]. It triggers apoptotic cell death characterized by morphological changes, such as membrane blebbing, plasma membrane rupture, and nuclear condensation, through a caspase-dependent pathway. Moreover, the apoptosis is accompanied by a reduction in MMP and an increase in ROS levels.

AM also targets m-TOR/PI3K/Akt signaling pathway by inhibiting the phosphorylation of key proteins, thereby decreasing cell proliferation [63]. Notably, AM treatment significantly upregulates the *Cyclooxygenase 2* (*COX2*) gene in SKOV-3 cells, indicating its involvement in inflammation [61]. Additionally, AM induces cell cycle arrest at the G2-M phase, to exert its anti-proliferative effects. Studies have shown that AM affects exosome release from OC cells, thus reducing exosome quantity and altering the tumor microenvironment [62]. Furthermore, AM has been found to downregulate the expression of genes associated with metastasis, including those involved in cell adhesion (*APC*, *CD44*), extracellular matrix molecules (*MMP2*, *MMP10*), cell cycle regulators (*TP53*, *BRMS1*), and

cell growth markers (*MDM2*, *VEGFA*), highlighting its role in modulating the tumor microenvironment [64].

In all, in OC, AM exerts beneficial effects by inducing apoptosis, inhibiting proliferation mainly through mTOR/PI3K/Akt signaling suppression, and arresting the cell cycle at G2-M phase. AM modulates the tumor microenvironment by reducing exosome release and downregulating metastasis-associated genes, further highlighting its potential as a therapeutic agent for OC.

6.4. Colorectal cancer

Preclinical studies have explored the anticancer activities of AM in various colorectal cancer (CRC) cell lines via different mechanisms of action, including the induction of apoptosis and cell cycle arrest, and inhibition of CSC characteristics. AM induces apoptosis in CRC cells through both extrinsic (Fas receptor) and intrinsic (mitochondrial) pathways via the activation of cleaved caspase-3, -8, and -9 [63,65-67]. Lee *et al*. further reported that this AM-induced apoptosis involved the cleavage of PARP and was marked by the upregulation of BAX and the downregulation of Bcl-2, particularly when AM was encapsulated in poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol) (PECE) nanoparticles [67]. AM was also shown to induce cell cycle arrest at the G1 phase in HCT116 cells and the G2-M phase in HT29 and SW48 cells, with concomitant downregulation of proliferation-related genes (e.g., *CCND1*, *PCNA*) and upregulation of cell cycle inhibitors (e.g., *CDKN2B*). The anticancer property of AM is also evident in affecting genes involved in the DNA damage response and EGR/NF-κB pathways [68].

AM inhibits CRC progression by downregulating key proteins in the Notch signaling pathway, including Notch1, Notch2, Jagged1, Hes1, Nicastrin, and Dll4, which are crucial for CSC maintenance, drug resistance, and metastasis, thereby reducing CSC growth and chemoresistance [69,70]. This effect is enhanced when combined with chemotherapy agents (e.g.,5 fluorouracil (5-FU)). In addition to its cytotoxic effects, AM has been shown to inhibit CSC population by downregulating CSC markers (e.g., $CD44^+$, $CD133^+$, Musashi) and pluripotency-maintaining factors (e.g., Oct-4, Sox-2, c-Myc, Nanog), leading to a reduction in CSC self-renewal capacity, tumorigenicity, and ultimately decreasing metastasis and recurrence [65,71,72]. Besides, AM increases oxidative stress in CRC cells to induce DNA damage as indicated by the elevated markers, 8-hydroxyguanosine (8-OH-G), and 4-hydroxynonenal (4-HNE), which inhibit the growth of SNUC5 and 5-FU-resistant SNUC5 cells [73]. AM also impedes EMT by inducing E-cadherin expression and suppressing N-

cadherin, reducing cell migration, invasion, and metastatic potential [65]. In a study by Rech *et al.* , AM impaired cancer cell motility and invasion through the downregulation of mRNA expression of MMP-2, MMP-9, and intercellular adhesion molecule 1 (ICAM-1) [66]. *In vivo* studies have further demonstrated tumor size reduction with AM treatment, and AM synergistically enhances the antitumor efficacy of 5-FU [63,71].

AM has shown anticancer activities in CRC through the modulation of key apoptotic pathways, disruption of tumor progression mechanisms and enhancement of chemosensitivity, positioning it as a new approach for future therapies.

6.5. Pancreatic cancer

The combined effects of AM on pancreatic cancer (PaC) highlight its potential as a therapeutic agent targeting cell proliferation, metastasis, and CSC characteristics, as evident in both *in vitro* and *in vivo* studies. AM induces a caspase-dependent apoptotic pathway by increasing the expression of cleaved caspase-3 and cleaved PARP proteins while decreasing the expression of Bcl-2 [74-77]. Interestingly, AM can inhibit the proliferation of ASPC1, PANC1, and BxPC3 cells by suppressing the PI3K/Akt pathway, reducing Akt phosphorylation at Ser47, and inhibiting NF-κB signaling via reduced pNF-κB/p65Ser552 and IKKγ and IKK protein levels. It also blocks STAT3 activation, induces G0/G1, S, and G2/M phase cell cycle arrest, and reduces cyclin D1 levels [74,75]. In terms of invasion and metastasis, AM inhibits PaC cell migration by upregulating E-cadherin and downregulating mesenchymal markers, such as vimentin and N-cadherin, along with suppressing EMT transcription factors like *Snail* and *Slug* [74,76,77]. It has also been reported that AM reduces the mRNA and protein levels of MMP-2 and MMP-9 and increases the expression of tissue inhibitor of metalloproteinases 1 (TIMP1), a natural MMP inhibitor [74,75].

In pancreatic CSCs, AM inhibits pluripotency-maintaining factors, including c-Myc, Oct4, Nanog, and Sox2, and reduces self-renewal capacity and invasion potential by targeting the Shh signaling pathway and Gli transcriptional targets (i.e., Gli1, Gli2, Patched1, Patched2) [76,77]. AM also impacts pancreatic stellate cells (PSCs) by inhibiting hypoxia-driven secretion of IL-6, VEGF-A, and SDF-1, thereby suppressing EMT and invasion in both PSCs and Panc-1 cells by restraining hypoxia-induced hypoxia-inducible factor 1α (HIF-1α) stabilization and *GLI1* expression. Besides, AM inhibits cancer-associated fibroblast (CAF) activation and extracellular matrix (ECM) deposition, further contributing to the suppression of tumor metastasis [78]. *In vivo* studies have further supported these findings that AM reverses EMT by inducing a cadherin switch and inhibiting EMT-related

transcription factors, thereby limiting PaC metastatic spread [76]. Xu *et al.* reported that oral administration of AM in nude mice resulted in the suppression of the growth of tumor xenografts, suggesting that AM is a potential drug for adjuvant therapy or an alternative medicine for the management of PaC [74]. Intriguingly, additional *in vivo* research further highlights AM effectively suppresses tumor growth and limits metastasis in PaC [74-76]. Inhibition of CSCs properties, induction of apoptosis and modulation of critical pathways associated with the metastasis and invasion highlight AM's potential as an effective therapeutic agent for PaCs.

6.6. Prostate cancer

In vitro studies using prostate cancer (PC) cell lines (e.g., LNCaP, 22Rv1, and VCaP) have revealed the anti-proliferative effects of AM through its modulation of androgen receptor (AR) signaling and the ER stress pathway [79,80]. AM suppresses androgen signaling pathway by upregulating binding immunoglobulin protein (BiP) expression, which facilitates the degradation and ubiquitination of AR and its splice variant AR-V7, resulting in the downregulation of AR and AR-V7 target genes, including *FOX1*, *KLK2*, *TMPRSS2*, *HOXB13*, and *EDN2* [80]. Additionally, AM induces ER stress, as indicated by the increased levels of ER stress marker proteins (e.g., phosphorylated protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1(IRE1), CHOP, and spliced X-box binding protein 1 (XBP-1), which leads to ER destabilization and subsequent caspase activation in 22Rv1 and LNCaP cells. Interestingly, CHOP appears to have a protective effect against AM actions in 22Rv1 cells, whereas CHOP knockdown via siRNA increased AR levels in LNCaP cells, potentially contributing to LNCaP's resistance to AM-induced apoptosis. This differential response may be attributed to the varying AR profiles of the cell lines, with 22Rv1 being androgen-independent and LNCaP being androgen-dependent [79].

6.7. Lung Cancer

In vitro studies on human non-small cell lung cancer (NSCLC) A549 cells have proved significant anticancer activities of AM. AM inhibits A549 cell proliferation by inducing intracellular structural damage, such as vacuolization, swelling, and karyorrhexis [81]. Similar findings were reported by Phan *et al.* that AM also reduced the surface rigidity of cancer cells. AM promotes ROS accumulation by downregulating the nicotinamide phosphoribosyltransferase/nicotinamide adenine dinucleotide (NAMPT/NAD) pathway, resulting in NAD pool depletion and increased oxidative stress [81,82]. AM further compromises antioxidant defenses by reducing total glutathione (GSH) levels while

enhancing the activity of antioxidant enzymes, such as catalase and glutathione peroxidase, at lower doses and disrupts redox homeostasis, which enhances oxidative stress-induced cytotoxicity, leading to structural damage of cancer cells [83]. Besides, AM promotes apoptosis by increasing the expression of caspases 3, 6, 7, and 9 (key components of the intrinsic apoptotic pathway) and enhancing the phosphorylation of p38 and p53, both of which engage in cellular stress responses and DNA damage regulation. Moreover, AM downregulates cell cycle regulators, including cyclin D1 and CDK4, leading to disruptions in cell cycle progression [81]. In a study by Zhang *et al.*, AM was shown to modulate the BAX/Bcl-2 ratio, favoring pro-apoptotic signaling and further promoting apoptosis [83]. AM inhibits cell migration and invasion, further emphasizing its therapeutic potential in the treatment of lung cancer (LC) [82,83].

6.8. Other cancers

AM has also exhibited anti-proliferative, anti-metastatic, and sensitizing effects in hepatocellular carcinoma (HCC) models. It induces both intrinsic and extrinsic apoptotic pathways while inhibiting metastasis by reducing MMP-2 and MMP-9 levels in both parental and anoikis-resistance HepG2 cells. AM suppresses anoikis resistance by inactivating the Akt and ERK pathways, leading to cell death. AM also impedes the progression of EMT by preventing E/N-cadherin switch and downregulating EMT-related proteins [84].

In an *in vitro* study using gallbladder cancer (GBC) cell lines (e.g., GBC-SD and NOZ), AM suppressed cell proliferation, induced apoptosis, and arrested the cell cycle. These effects are associated with the upregulation of BAX and the downregulation of *PCNA* and *BCL-2* genes. It also inhibited lipogenesis by downregulating key markers involved in fatty acid synthesis, including SREBP1, FASN, and ACC. In nude mice xenografted with NOZ cells, AM potentiates the gemcitabine-induced inhibition of tumor growth, improving chemotherapy efficacy in GBC [85].

AM has shown potential as a therapeutic option for oral cancer (OR) as well, demonstrating promising anticancer activities. The mucoadhesive film containing AM reduces the HPV-16 pseudovirus infection at the attachment step and enhances cell migration, which is beneficial to promote wound healing. Additionally, the AM film exhibits strong anti-inflammatory properties, suggesting its use in controlling inflammation and promoting the healing of oral potentially malignant disorder lesions, thereby preventing the risk of progression to oral squamous cell carcinoma [86]. When combined with recombinant human tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), AM shows a

cytocidal effect on SAS cells derived from human oral squamous cell carcinoma. This combination therapy inhibits oral squamous cell carcinoma cell proliferation by inducing apoptosis through the caspase-dependent mitochondrial pathway, specifically activating caspases-3, -7, and -9, and causing S/G2/M cell cycle arrest that is accompanied by cytochrome c release from mitochondria [87]. These findings suggest that AM can be a promising therapeutic option for treating oral squamous cell carcinoma and help overcome TRAIL-resistant cancer cells.

Research on the effects of AM in gastric cancer (GC) has also highlighted its potent anticancer activities. AM has been shown to inhibit Bcl-2 expression while upregulating BAX in SGC7901 and SGC7901/CDDP cells. It also promotes the release of cytochrome c and AIF in BGC-823 and SGC-7901 cells to promote mitochondrial apoptosis [88,89]. Moreover, AM regulates the STAT3 signaling pathway to suppress apoptosis and proliferation by inhibiting STAT3-mediated expression of anti-apoptotic proteins, including Bcl-2 and Mcl-1 [89]. According to Li and Zeng, AM enhances the sensitivity of drug-resistant GC cells to cisplatin by targeting the Epstein-Barr Virus Induced 3 (EBI3)/STAT3 signaling pathway and cisplatin-induced autophagy [88]. AM downregulates the expression of EBI3 protein, thereby inhibiting the downstream STAT3 pathway. Additionally, AM increases the levels of autophagy-related proteins (e.g., LC3-II/I and Beclin1) while downregulating p62 expression to promote cisplatin-induced autophagy.

For skin cancer (SC), an *in vivo* study using Institute of Cancer Research (ICR) female mice with 7,12-Dimethylbenz[a]anthracene (DMBA)/12-O-Tetradecanoylphorbol-13-acetate (TPA)-induced tumors demonstrated that AM exerted therapeutic effects by reducing inflammation, inhibiting the expression of pro-inflammatory factors IL-1β, IL-4, and IL-18, and promoting the anti-inflammatory factor IL-10. In this study, AM induced apoptosis by upregulating pro-apoptotic proteins, such as BAX, BAD, cleaved caspase-3, and cleaved PARP, while downregulating anti-apoptotic proteins (e.g., Bcl-2 and Bcl-xl). Additionally, AM enhanced autophagy by increasing the expression of LC3, LC3-II, and Beclin1 and reduced the expression p62 and LC3-I. Additionally, AM inhibited tumor proliferation by suppressing the PI3K/Akt/mTOR pathway, leading to decreased levels of phosphorylated PI3K, Akt, and mTOR [90].

Overall, AM exhibits broad-spectrum anticancer activities across various cancers by inducing apoptosis, suppressing cell proliferation, inhibiting metastasis, targeting cancer stem cell properties, and enhancing the efficacy of conventional therapies, making it a promising candidate for future therapeutic application.

Table 1. Preclinical anticancer activities and molecular mechanisms of α-mangostin in breast, cervical, ovarian, colorectal, pancreatic, prostate, and lung cancers. Note that "-" indicates the data is unavailable.

Cancer Type	Preclinical Type	Preclinical Model	Treatment Period (Dosage)	Half-Maximal Inhibitory Concentration (IC_{50})	Therapeutic Effect	Molecular Mechanism	Reference
BC	*In vitro*	Human ER+ BC cell lines (MCF-7 and T-47D)	AM (1-20 μM), combined with 4-hydroxytamoxifen (4-OH-TMX)(1×10^{-11} M – 1×10^{-5} M)	AM - MCF-7: 3.53 μM (CI not available) μMT-47D: 7.15 μM (CI not available) 4-OH-TMX MCF-7: 2.44 μM (CI not available) μMT-47D: 0.1584 μM (CI not available)	Enhanced anti-proliferation effects and cell sensitivity to treatment	Inhibited oncogenic KCNH1, CCND1, and BIRC5 gene expression	[52]
BC	*In vitro*	Human BC cells (MCF-7 and MDA-MB-231)	24 h (0.5-5 μM)	-	Induced cell death via STAT3 pathway, migration, invasion, and cell proliferation	Inhibition of STAT3 signaling reduced hnRNPA1 and PKM2 expression, modulated EMT markers (↓MMP2, ↑E-cadherin), and suppressed proliferation (↓Ki67 in both cell lines; ↓BrdU in MCF-7 only)	[43]
BC	*In vitro*	Human BC cells (MDA-MB-231)	24 h and 72 h (2.5, 5, and 10 μM)	~ 23 μM (CI not available)	Enhanced immune system ability to target and attack cancer cells	Inhibited immune checkpoint ligand: ↓PD-L1 expression; Blocked glycosylation	[91]
BC	*In vivo*	Sprague-Dawley rats with LA7 cells	Twice a wk for 4 wks (30 and 60 mg/kg)	-	Decreased tumor volume; Improved mammary gland structure; Induced apoptosis; Improved antioxidant activity; Anti-proliferation	↓tumor markers (CEA, CA 15-3, ALT, ALP, LDH); Reduced mitotic events, facilitated tissue reorganization, intra-tumor vascularization and tumor tubules; ↑SOD and GPx, while↓CAT and LPx levels; ↓PCNA while↑p53 expression	[53]

BC	*In vitro*	Human Breast epithelial cancer cells (MCF-7) and cisplatin-resistant clone of MCF-7 (MCF-7 CR)	Cell viability: 12, 24, and 48 h (10, 20, and 30 µM)	24 h: MCF-7: 3.288 µM (CI not available) MCF-7 CR: 2.534 µM (CI not available)	Induced apoptosis mediated by interaction of MOAP-1 with AM activated BAX	↑MOAP-1 – BAX oligomerization, ↓BCL-XL, cytochrome c release, and caspase activation	[45]
BC	*In vitro*	Human BC (MCF-7, MDA-MB-231 and SKBR3)	48 h (1.2, 5, 10, 20, and 40 µM)	MCF-: 9.69 µM (CI not available) MDA-MB-231: 11.37 µM (CI not available) SKBR3: 7.46 µM (CI not available)	Induced anti-proliferation and apoptosis; Caused blockade of cell cycle via RXRα/cyclin D1 pathway; Anti-metastasis	Cleavage of PARP protein; Degraded RXRα/tRXR and inhibited activation of Akt – activate caspase-3; ↓RXRα, ↓cyclin D1 – cell arrest in S and G0/G1 phase, reduced migrated and invasion ability of MDA-MB-231 cells	[24]
BC	*In vitro*	Human BC cell (MCF-7 and MDA-MB-231) and MCF-7 MCTs	48 h (0.5 – 20 µg/ml), combined with doxorubicin	AM - 29.7 µM Doxorubicin - 50.5 mM (CI not available) Doxorubicin + AM - 8.70 mM (CI not available)	Additive effect on MCTs dissociation; Enhanced in reducing cell viability; Reduced cell stemness	Doxorubicin inhibited PARP1 and PARP2, ↓BRCA1 and BRCA2 – amplify AM-induced cell damage; AM bind with Jagged/Delta to Notch receptor, ↓sirtuin-2 and RALDH activity	[55]
BC	*In vitro*	Human Breast cancer cell (MCF-7 and MDA-MB-231)	24 h (0, 1, 2, and 4 µM)	-	Promoted autophagy; Induced apoptosis via promoting ER stress	↑LC311/LC31 and p62 expression; ↑ UPR markers (IRE1, ATF6, PERK), CHOP and BIP – caused ER stress, ↓mitochondrial membrane potential, caused mitochondrial stress/damage	[44]
BC	*In vitro*	Human BC cell (MCF-7 and MDA-MB-231)	Cell viability: 48 h (0.1 - 15 µg/ml) Spheroid Volume: 24 and 48h (0.1 – 30 µg/ml)	24 h: MDA-MB-231: 1.05 µg/ml (CI not available) MCF-7: 1.64 µg/ml (CI not available)	Decreased cell viability and induced apoptosis; Modulated spheroid size and density; Reduced cell motility	↑caspase activity; ↓spheroid size (0.5 – 5 and 15 – 30 µg/ml) while intermediate concentrations (8 – 10 µg/ml) increased in volume size, while greater density obtained with highest doses	[54]

				48 h: MDA-MB-231: 1.03 µg/ml (CI not available) MCF-7: 1.60 µg/ml (CI not available)			
BC	*In vitro*	Human BC cell (MDA-MB-468, AU565, SKBR3 and T47D)	MTT assay: 4, 8, 12, 16, 20, and 24h (7.5, 15, and 30 µM) Colony formation: 3 and 6 h (15 and 30 µM) Cell cycle: 12 h (0, 15, and 30 µM)	T47D: 7.5 µM (CI not available) SKBR3: 23.88 µM (CI not available) MDA-MB-231: 22.23 µM (CI not available) AU565: 43.63 µM (CI not available)	Inhibited colony formation; Induced apoptosis via intrinsic and MAPK pathway; Inhibition of cell proliferation and cell survival through Erα pathway; Apoptosis induction via inhibition of HER2 activation and PI3K/Akt signaling pathway	↓Mcl-1, ↑BAX/Bcl-2 ratio – ↑mitochondrial membrane permeability, release of cytochrome c and caspase activation; Induced p-p38 and p-JNK1/2, ↓p-ERK1/2 and p-c-Raf – suppress MEK1 and MEK2, inactivated ERK1/2; ↑IKKα and Src expression, ↓NF-κB p65 and c-Rel expression, activated CHOP and c-Jun expression, while suppress c-Myc expression; Activated dephosphorylation of p-HER2 – inactivate RAS/Raf1/MEK/ERK and PI3K/Akt, inhibited p-Akt at Ser473 and Thr308; ↓p-Ser104/106 and Ser118 of Erα	[49]
BC	*In vitro*	Human BC cell (MCF-7 and MDA-MB-231)	48 h (1, 5, and 10 µM)	-	Induced apoptosis of E2-treated MCF-7 cells; Inhibited E2-stimulated cell proliferation	↑chromatin condensation, apoptotic body formation and accumulation of sub-G1 phase cells, ↓pro-caspase-7, -8, -9 , Bid and Bcl-2, ↑PARP cleavage, ↑p53 and BAX, and release of AIF; ↓ERα expression – caspase-7 activation	[47]
BC	*In vitro*	Human BC cell (MCF-7 and MDA-MB-231)	24 h (0, 1, 2, 3, 4, 6, 8, and 10 µM)	24 h:	Induced apoptosis via PI3K/Akt signaling	↑PARP cleavage and pro-apoptotic protein BAX, ↓anti-apoptotic protein Bcl-2 – ↑BAX/Bcl-2 ratio favors apoptosis; ↓p-Akt,	[51]

				MCF-7 cells: 3.57 µM (CI not available) MDA-MB-231 cells: 3.35 µM (CI not available)	pathway and FAS; Anti-metastatic	↑p-ERk1/2 - Inhibited FAS expression and activity, ↓intracellular fatty acid; ↓Tyr^{397} phosphorylation of FAK	
BC	*In vitro*	Human normal breast cell (MCF-10 A), Human BC cells (MCF-7)	24 h (5, 10, and 20 mg/ml)	48 h: MCF-7: 2.74 µM (CI not available) MDA-MB-231: 2.26 µM (CI not available) MCF-7 cells: 10.26 µg/mL (CI not available) MCF-10A: > 30 µg/ml (No cytotoxicity) (CI not available)	Induced apoptotic morphologic features - Blebbing, nuclear chromatin condensation, increased cell permeability; Induced cell cycle arrest; Induced apoptosis via NF-κB pathway	↓MMP-2, MMP-9, Bcl-2, XIAP, while↑cytochrome c in cytosol and BAX, cleavage maturation of caspase-7, -9 and -8, PARP cleavage and ROS formation; Halted cell cycle progression in G0/G1 phase, diminished cells in both S and G2/M phases; Inhibited TNF-α, ↓NF-κB translocation	[46]
BC	*In vivo*	Rat with LA7 mammary adenocarcinoma cells	Orally twice a wks for 28 d (30 and 60 mg/kg/day)	-	Reduced tumor size	-	[46]
CIN	*In vitro*	Human CIN cell (HeLa, SiHa, CaSki, C33a)	48 h (Respectively IC_{50} values)	C33a: 5.35 µM (CI not available) HeLa: 5.00 µM (CI not available) SiHa: 4.32 µM (CI not available) CaSki: 3.77 µM (CI not available)	Inhibited cell proliferation; Modified cell cycle distribution; Anti-inflammatory effect; Enhanced treatment efficacy	Inhibited KCNH1 gene expression – promotes G1-phase cell cycle arrest; Inhibited E6-HPV16 and E7-HPV16 oncogene, ↑SubG1 phase cells, while ↓G1 phase cell in HeLa and SiHa cell lines; Inhibited TNFα gene expression; ↑IL-6 expression	[59]

CIN	*In vivo*	Athymic nude mice with SiHa and CaSki cells	4 wks (8 mg/kg/day) 24 h (0-30 µM)	-	Reduced tumor growth in mice with SiHa cells	-	[59]
CIN	*In vitro*	Human CIN cell (HeLa, SiHa)	24h AM (0-30 µM) + cisplatin (30 µM)	-	Reduced cell viability; Inhibited sphere-forming ability and stemness marker; Induced mitochondrial apoptosis	↓surface CD49f, cellular stemness marker (Sox2, Oct4, CK-17 and Nanog); ↓pro-caspase-3, -9, anti-apoptotic Mcl-1 and Bcl-2, while ↑ cleaved caspase-3, cleaved PARP and pro-apoptotic BAX – mitochondrial depolarization, apoptosis	[56]
CIN	*In vivo*	BALB/c-nude mice with SiHa cells	24h AM (0-30 µM) + Cisplatin (30 µM) Oral gavage every 3 d AM (40 mg/kg) + cisplatin (3 mg/kg)	-	Reduced tumor growth	Reduced surface CD46f, cellular stemness marker (Sox2, Oct4, CK-17 and Nanog) and proliferative marker (Ki-67)	[56]
CIN	*In vitro*	Human CIN cell (HeLa, SiHa)	24 h (0, 10, 20, and 30 µM)	-	Induced mitochondrial apoptotic pathway; Induced apoptosis via ROS	↓pro-caspase-9,-3, pan-caspase inhibitor Z-VAD, MMP, Bcl-2 and ↑cleaved caspase-3, cleaved PARP, BAX, cytochrome c; Enhanced ROS formation, ↑pASK1, p-MKK3/6, p-p38 – ASK/MKK3/6/p38 signaling cascade	[57]
CIN	*In vivo*	Mouse xenograft with HeLa cells	Every wk 20 or 40 mg/kg	-	Reduced tumor growth, volume and weight	Via ASK1/p38 mediated caspase activation:↑p-ASK1, p-p38, cleaved PARP, cleaved-caspase-3 in tissue sections	[57]
CIN	*In vitro*	Human CIN cell (HeLa and CaSki)	Cell viability: 24, 48, and 72 h Proliferation: 24h (12, 24, and 36 µM) Others: 24, 48, and 72 h	HeLa: 24.54 µM (CI not available) Ca Ski: 51.73 µM (CI not available)	Inhibited colony formation and cell proliferation; Induced apoptosis morphology – cell blebbing and nuclear chromatin condensation; Induced cell cycle arrest; Induced apoptosis via	Arrest cells in G2/M phase; ↑active caspase 3/7 and 9, ROS levels, ↓MMP – ↑ plasma membrane permeability, cytochrome c release, caspase activation	[58]

CIN	*In vitro*	Human CIN cell (HeLa)	24 h AM (0 – 80 µM) + cisplatin (0 – 120 µM)	AM: 19.1 µM (CI not available) Cisplatin: 29.7 ± 1.3 μM (CI not available) Combined: not available	intrinsic pathway and promotion of ROS Reduced cell viability; Enhanced cisplatin cytotoxicity; Enhanced cell cycle arrest in G2/M phase; Protective effect against cisplatin-induced nephrotoxicity	-	[60]
OC	*In vitro*	Human OC cell (A2780, TOV-21G and SKOV-3)	24 h (3.125 – 200 µM)	A2780:47.74 µM (CI not available) SKOV-3:25.03 µM (CI not available) TOV-21G:59.96 µM (CI not available)	Reduced the amount of exosome released from tumor cells; Altered the microenvironment of tumor cells	-	[62]
OC	*In vitro*	Human OC cell (A2780, TOV-21G and SKOV-3)	24 h	SKOV- 3:12.5 µM (CI not available) TOV-21G: 29.98 µM (CI not available)	Regulated the expression of genes involved in metastasis of exosomes	Cell adhesion molecules genes -↓APC, CDH1 and ↑CD44, FXYD5, ECM molecules - ↓MMP2, MMP10, TIMP2 and TIMP3, Cell cycle regulators - ↓TP53, BRMS1 and HRAS, Cell growth and proliferation - ↑MDM2, IL18, VEGFA, CCL7 and CXCL12 and apoptosis markers changes	[64]
OC	*In vitro*	Human OC cell (OVACAR-3)	12, 24, and 48 h (0 - 200 µM)	-	Reduced the rate of proliferation; Suppression of colony formation with increasing doses; Induced membrane blebbing, plasma membrane rupture, cellular disintegration and nuclear condensation; Induced apoptosis; Inhibited cell migration and invasion; Targeted m-TOR/PI3K/Akt signaling pathway	↓Bcl-2 expression and ↑caspases-3,-8,-9 expression, suppressed MMP and enhanced ROS production; Reduced phosphorylation of PI3K, AKT and m-TOR	[92]

OC	*In vitro*	Human OC cell (SKOV-3)	24, 48, and 72 h (2.466 µM after 24h 2.977 µM after 48 h 3.062 µM after 72 h)	Induced morphological changes – spindle-shaped cells and cell shrinkage; Induce late apoptosis and necrosis; Caused cell cycle arrest at G2/M phase	Altered the activity of caspase -↑caspase; Apoptosis-associated gene - ↑Bcl-2 expression and Inflammation-associated gene - ↑COX2 expression	[61]	
CRC	*In vitro*	Human CRC cells (HCT116 and HCT29)	Cell viability assay: 48h or 72h (0-10 µM, encapsulated in PLGA nanoparticles)	-	Induced apoptosis; Inhibited cell motility, migration and invasion; Inhibited cancer cell growth	Regulated EMT markers – ↑E-cadherin expression, ↓N-cadherin, Snail and Slug expression; Inhibited Notch signaling pathway -↑Notch1, Notch2, Jagged1, Hes1, Nicastrin and Dll4 expression	[65]
CRC	*In vitro*	Human CRC CSCs (CD133+ /CD44+ / LGR5+)	Colonosphere assay: 7d (0 - 10 µM)	-	Inhibited colony and spheroid formation in CSCs; Inhibited cell motility, migration and invasion; Inhibited self-renewal capacity of CRC CSCs	Regulated stem cell markers –↓CD133, CD44, Musashi and LGR5 and regulated pluripotency maintaining factors – ↓Oct-4, Sox-2, KLF-4, c-Myc and Nanog; Regulated EMT markers – ↓Snail, Slug and Zeb1 expression; Inhibited Notch signaling pathway -↑Notch1, Notch2, Jagged1, Hes1 and Dll4 expression	[65]
CRC	*In vitro*	Human colon cancer cells (HCT116, HT29, and SW48)	Flow cytometry assay: 48 h (25 µM)	HCT116: 13.8 umol/L (CI not available) HT29: 7.7 umol/L (CI not available) SW48: 7.7 umol/L (CI not available)	Induced apoptosis in a caspase-dependent pathway; Caused cell-cycle arrest at G1/G2/M phase; Induced DNA damage response	Regulation of proliferation-associated genes – ↓CCND1, CCNA2, PCNA expression and cell-cycle inhibitors -↑CDKN2B expression; Activated EGR/NF-κB pathways - ↑NF-κB, EGR, and GADD45 expression	[68]
CRC	*In vitro*	Human CRC cells (SW620 and HT29)	Colosphere assay: 14 d (0 - 2.5 µM)	-	Suppressed colosphere formation at low-doses; Inhibited CSCs population and suppressed 5-FU induced CSCs formation	Decreased CSC markers - ↓CD133+CD44+ cells; Downregulated Notch signaling pathway - ↓Notch1, NICD1, Hes1, and Hey1	[71]

CRC	*In vivo*	Male Balb/c mice xenografted with HT29 cells	Thrice a wk for 18d (5mg/kg) + 5-FU (0 mg/kg)	-	Reduced tumor size and CSC markers	Synergistic interaction with 5-FU	[71]
CRC	*In vitro*	Human CRC cells (SNUC5 and 5-fluorouracil resistant variant, SNUC5/5-FUR)	24-48 h (20 μM)	-	Suppressed cell growth; Induced apoptosis	Induced intracellular oxidative stress - ↑8-OH-G and ↓4-HNE; Induced cleavage of cleavage of caspase-3, caspase-8, caspase-9, PARP and cytochrome c release	[73]
CRC	*In vitro*	Human CRC cells (Caco-2, HT-29, and LoVo)	24 h (200 – 3.13 μM)	Caco-2: 7.5 μM (CI not available) HT-29: 19.9 μM (CI not available) LoVo: 17.9 μM (CI not available)	Induced apoptosis; Impaired clonogenicity; Reduced cell adhesion to ECM and angiogenesis; Inhibited invasion and metastasis	Impaired the interaction with endothelial HMEC-1 cells; ↓ MMP-2, MMP-9 and ICAM-1 mRNA expression	[66]
CRC	*In vitro*	Human CRC cells (HCT26 and HCT116)	24 h or 48 h, encapsulated in PECE nanoparticles	-	Induced apoptosis and suppressed proliferation	Regulated the expressions of caspase-dependent pathways - ↓procaspase-3, pro-caspase-8 and pro-caspase-9 and ↑cleaved-caspase-3 and regulated the expression levels of Bcl-2 family proteins - ↓Bcl-2, and ↑BAX expression	[63]
CRC	*In vivo*	Female Balb/c mice xenografted with CT26 cells	Over 15 d (50 mg/kg)	-	Induced angiogenesis and suppressed tumor growth; Inhibited pulmonary and abdominal metastasis	-	[63]
PaC	*In vitro; In vivo*	Human PaC cells (PANC-1); Female Balb/c mice xenografted with PANC_1 cells	24 h (10 μM and 20 μM), encapsulated in CAFs-targeting biodegradable polymer coated with CREKA peptide nanoparticles; 1wk (10 mg/kg every 2d)	-	Reduced cancer-associated fibroblasts (CAFs) activation and ECM deposition	Blocked TGF-β/Smad signaling pathway	[78]

PaC	*In vitro*	Human pancreatic stellate cells (PSCs) from normal pancreas tissues and human PaC cells (PANC-1)	24 h (16 μM)	-	Inhibited PSC activation; Inhibited EMT and invasion; Abolished hypoxia-activated SDF-1, VEGF-A, and IL-6 secretion	Induced hypoxia-driven ROS; Restrained hypoxia-enhanced HIF-1α stabilization and GLI1 expression	[93]
PaC	*In vitro*	Human pancreatic cells (AsPC-1, MIA PaCa-2, and PANC-1) and isolated pancreatic CSCs	Cell viability assay: 48 or 72 h (0 – 10 μM); Tumor Spheroid assay: 7 d; Cell Migration and invasion assay: 48 h	19 μM (CI not available)	Inhibited cell proliferation; Inhibited pluripotency maintaining factors; Inhibited self-renewal capacity of CSCs; Inhibited colony formation and induce apoptosis; Inhibited cell motility, migration and invasion and EMT	↓c-Myc, Oct-4 and Nanog expression; Inhibited the Shh signaling pathway and Gli transcriptional target proteins - ↓Gli1, Gli2, Patched 1 and Patched 2 expression; ↑E-cadherin expression and ↓Slug expression	[76]
PaC	*In vivo*	KPC (PdxCre;LSLKrasG12D;LSL-Trp53R172H) mice, genetically engineered mice to be genotyped for the presence of Kras, p53, and Cre27	Once per day, 5 d per wk for 10 wks (20 mg/kg)	-	Inhibited cancer growth, development; Inhibited metastasis	Induced stem cell population within the tumor -↓CD24, CD133, c-Myc, Nanog expression and Oct4 and inhibited Shh pathway - ↓Gli targets Bcl-2, XIAP and cyclin D1 expression; ↑E-cadherin expression and ↓N-cadherin, Slug, Snail and Zeb1 expression	[76]
PaC	*In vitro*	Human PaC cells (AsPC-1 and PANC-1) and isolated pancreatic CSCs	24 to 48 h (0 – 10 μM)	-	Inhibited cell proliferation and induced apoptosis; Inhibited self-renewal capacity, spheroid and colony formation; Regulated pluripotency-, cell survival- and cell cycle-related genes; Inhibited cell motility, migration, invasion and EMT	Facilitated the inhibition of Shh pathway components and Gli target proteins - ↓Gli1, Gli2, Patched1, Patched2 expression and↓Bcl-2 and cyclin D1 expression; Inhibited the expression of pancreatic CSC markers - CD24, CD44 and CD133 and pluripotency maintaining factors - Nanog, Oct4, Sox2, KLF4 and c-Myc; Inhibited binding of Nanog to its target genes (Cdk2, Cdk6, FGF4, c-Myc and Oct4) and Nanog transcription; ↑E-cadherin expression and ↓N-cadherin, Slug and Snail expression	[77]

PaC	*In vitro*	Human pancreatic cells (BxPc-3, Panc-1)	6, 12, 24, and 48 h (0 – 32 μM)	-	Induced apoptosis; Induced cell cycle arrest at G0/G1 phase; Inhibited the migration and invasion	↓Anti-apoptosis Bcl-2 protein expression and ↑cleaved caspase 3 expression; ↓cyclin-D1 protein level and the activity of PI3K/Akt pathway by inhibiting the phosphorylation of Akt at ser47; ↓MMP-2 and MMP-9 protein and mRNA expression and↑epithelial marker - E-cadherin expression and↓ mesenchymal markers – vimentin and N-cadherin	[74]
PaC	*In vivo*	Male balb/c mice xenografted with BxPc-3 cells	5 d per wk for 1month (50 or 100 mg/kg)	-	Suppressed the tumor growth	-	[74]
PaC	*In vitro*	Human pancreatic cells (PL-45, BxPc-3, Panc-1, ASPC1)	24 h (5–30 μM)	13–17 μM (CI not available)	Decreased intracellular ROS levels; Induced apoptosis; Inhibited IL-6 induced proliferation; Caused cell cycle arrest at G0/G1 phase and inhibited cell invasion and colony formation	↑cleaved PARP protein expression and ↓ expression of total PARP protein and inhibited activation of NF-κB signaling pathway - ↓protein levels of IKKγ and IKK β; Inhibited constitutive activation of Stat3; Induced ↓ expression of MMP9, cyclin D1, gp130, and Bcl3, and ↑ TIMP1 expression	[75]
PaC	*In vivo*	Athymic nude mice xenografted with ASPC1 cells	5 d per wk for 8 wks (6 mg/kg)		Suppressed the orthotopic tumor growth	Inhibited phosphorylation of both Stat3 and NF-B	[75]
PC	*In vitro*	Human PC cells (LNCaP, 22Rv1, and VCaP)	48 h (0 – 100 μM)	5–30 μM (CI not available)	Promoted apoptosis and inhibited nuclear translocation; Promoted ubiquitination and degradation of AR and AR-V7 via the proteasome; ↓mutant AR protein expression and ↑cell stress proteins PERK and BiP	↓expression of AR and AR-V7 target genes FOXA1, KLK2, TMPRSS2, HOXB13, and EDN2 genes; Promoted a protein-protein interaction between AR and BiP	[80]
PC	*In vivo*	Male nude athymic xenografted with 22Rv1cells	-	-	Slowed tumor growth	↓expression of AR and AR-V7 regulated genes - TMPRSS2 and EDN2	[80]

PC	*In vitro*	Human PC cells (LNCaP, 22Rv1)	24 h (7.5 and 15μM)	-	Inhibited proliferation and increased apoptosis; Promoted endoplasmic reticulum (ER) stress; Upregulated CHOP mRNA	↑cleaved caspase expression; ↑ER stress markers - phosphorylated PERK, IRE1, CHOP and spliced XBP-1	[79]
PC	*In vivo*	Athymic nude mice xenografted with 22Rv1cells	2 times per wk throughout the study (35 and 70 mg/kg)	-	Inhibited tumor growth	-	[79]
LC	*In vitro*	Human non-small cell lung cancer (NSCLC) cells (A549)	24 h (6, 8, and 10 μg/ml)	-	Inhibited cell proliferation and induced intracellular ROS accumulation; Damaged the integrity of intracellular structures - vacuolization, swelling and karyorrhexis; Promoted apoptosis; Altered cell cycle distribution	Downregulated NAMPT/NAD signaling pathway; ↑cleaved caspases 3,6,7 and 9 expression; Promoted phosphorylation of p38 and p53 and ↓expression of cyclinD1 and CDK4	[81]
LC	*In vitro*	Human non-small cell lung cancer (NSCLC) cells (A549)	24 h (0 – 50 μM)	10 μM (CI not available)	Induced apoptosis; Inhibited migratory activity; Induced ROS generation	↑ BAX/Bcl-2 ratio; Downregulated antioxidant machinery - ↓total GSH-levels and the activity of catalase and glutathione peroxidases	[83]

7. Issues and strategies to improve the therapeutic outcomes of alpha-mangostin

The hydrophobic nature of AM contributes to its poor water solubility, bioavailability, retentivity in target organs [94,95], selectivity [95,96] toward cancer cells, and a short half-life post administration [97]. It has been reported that intracellular transporters initiate first-pass metabolism of AM, efflux reactions stimulate rapid AM excretion [96], and low penetration of AM into solid tumors is reported [54]. Hence, an efficient delivery system is required to tackle the drawbacks of the current AM formulation to maximize its optimal delivery to achieve active targeting [82].

7.1. Nanotechnology for drug delivery to achieve active tumor targeting and avoid off-target toxicity

Nanotechnology catalyzes the formation of the AM-nanoparticle (NP) complex, boosting AM dispersibility, bioavailability, specificity, binding affinity, entrapment efficiency (EE), and biodistribution [94]. NPs increase AM solubility threefold and enhance apoptosis and cytotoxicity compared to unbound AM. Nanoformulation creates NPs in various forms (Fig 2) that encapsulate AM in their internal cavity [34], significantly improving its distribution profile [94]. Table 2 summarizes the therapeutic effects of the different forms of NPs.

An important factor affecting the therapeutic performance of AM-loaded NPs is their interaction with biological systems. Upon administration, plasma proteins rapidly adsorb onto NP surfaces, forming a protein corona. This process, known as opsonization, can change the NP's size, charge, and surface properties, marking them for recognition and clearance by the reticuloendothelial system (RES) or mononuclear phagocyte system (MPS). Consequently, rapid clearance reduces tumor accumulation and therapeutic efficacy. To overcome these challenges, NPs are often coated with polyethylene glycol (PEG) or other "stealth" polymers, which reduce protein adsorption and opsonization, prolong circulation time, and enhance accumulation in tumor tissues via the enhanced permeability and retention (EPR) effect. Optimization of NP surface properties, including PEG density, chain length, and core composition, can minimize RES/MPS uptake and off-target toxicity, thereby improving biodistribution, safety, and overall anticancer efficacy of AM-loaded nanocarriers [98-100].

In addition to biological performance, practical manufacturability is essential for the translational potential of AM-loaded nanoparticles. Scalable production methods, such as

emulsion, nanoprecipitation, or microfluidic approaches, should be considered to ensure consistent batch-to-batch quality. Lyophilization with appropriate cryoprotectants can enhance NP stability, maintain particle size and entrapment efficiency, and facilitate long-term storage. Moreover, optimizing formulation parameters for shelf-life and storage conditions is critical to preserve nanoparticle integrity, prevent aggregation, and ensure reproducible therapeutic efficacy during distribution and clinical use [101,102].

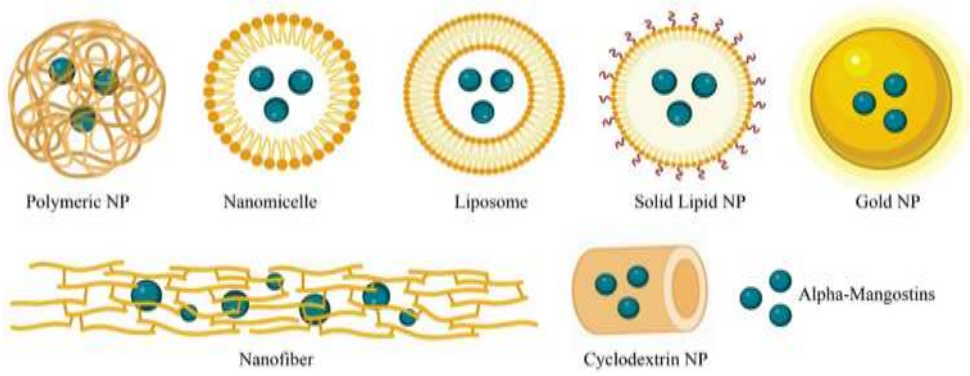


Figure 2. Here depict the different forms of AM-loaded NPs. Image created using BioRender.

7.1.1. Polymeric Nanoparticle

Polymeric NPs refer to particles sized 1 to 1000 nm loaded with active compounds entrapped within or surface-anchored onto the polymeric core [41]. Polymeric NPs exhibit improved entrapment efficacy [103] and the release profile of AM [41]. Chitosan is a versatile biopolymer matrix in which AM is encapsulated, forming chitosan polymeric NP (CNP) through ionic gelation. The cationic properties of chitosan facilitate binding to the anionic cell membrane, providing mucoadhesive features and controlled release of AM. Hence, nanocarriers, such as CNP, have the potential to enhance the physicochemical properties of AM for further manipulation as an anticancer agent [103].

7.1.2. Cyclodextrin Nanoparticle

α-Cyclodextrin (CD), β-CD, and γ-CD are oligosaccharides composed of six, seven, and eight glucopyranose subunits, respectively, in their ring structure [104]. Among these, β-CDs are the most practical in the pharmaceutical industry due to their truncated cone shape structure with optimal cavity space to accommodate hydrophobic AM. β-CD derivatives modification with substituents at the hydroxyl group showed notable water solubility boosts compared to the parent molecules. The presence of polar functional groups on the CD molecules results in better adsorption of the encapsulated AM on the polar head groups of

the lipid membrane, thereby enhancing its solubility to aid drug transportation across the lipid bilayer via passive diffusion [105] and achieve dynamic equilibrium rapidly [106].

7.1.3. Nanofiber

Nanofibers are one-dimensional nanomaterials [34], with a diameter in the nanometer range [107]. The utilization of nanofiber systems as local anticancer drug delivery devices [108] is growing popular, as it offers great specificity in delivering drugs to the tumor microenvironment, prolonged drug concentration at the target site [109], desired porosity, large outer surface ratio, etc. Pham *et al.* demonstrated that AM-loaded silk fibroin NPs enhanced AM's stability up to threefold and could penetrate the cell effectively via surface adsorption and endocytosis through the binding of two amino acids on the N-terminal of fibroin to surface receptor integrin, which is overexpressed in breast and colon cancer cells [97]. The results indicated that silk fibroin NPs enhanced the IC_{50} of AM, making it an effective AM carrier in cancer regimens [34].

7.1.4. Nanomicelles

Nanomicelles are colloidal dispersed nanostructures, commonly 10 to 100 nm, with a hydrophobic pocket and a hydrophilic cover [110]. Due to their nano-sized and amphiphilic characteristics, polymeric micelles can preferably circumvent renal clearance and reticuloendothelial system entrapment, facilitating the build-up within tumor tissues by enhancing permeability and retention (EPR) effect. By tailoring block copolymers to incorporate chemistries responsive to biological conditions, polymeric micelles offer targeted drug release through site-specific activation, reversible stabilization, and intracellular trafficking, compromising AM's poor specificity in cancer cells [111].

7.1.5. Liposomes

Liposomal NPs are lipid bilayer vesicles that deliver hydrophobic and hydrophilic bioactive [112] and are usually 30 nm to micrometer in scale [113]. AM liposome directs AM actions on body-sensitive sites [114]. Its amphiphilic nature of phospholipid to cell membrane permits passage through barriers, distribution in tissues, and elimination from organs, whereas the presence of cholesterol stabilizes the liposomal structure. Its accessibility to the tumor microenvironment can be achieved by surface modification with specific antibodies for cancer-targeting effects or by conjugating certain biomaterials with PEGylated liposomes. Moreover, the electrostatic charges on the particle surface, known as zeta potential, are a

substantial factor for liposome absorption onto the cell surface and can provide insights into the stability, circulation time, and biocompatibility of the NPs [115].

7.1.6. Solid Lipid Nanoparticle

Solid lipid nanoparticles (SLNs) are colloidal delivery systems constructed from lipids that remain solid at room temperature, with sizes ranging from 50 to 500 nm [116]. SLNs offer the advantage of controlled and targeted release by binding surface solid lipids with appropriate ligands and polymers. Furthermore, SLNs display lower adverse effects and sustained release due to the characteristics of solid lipid and submicron-sized nanoparticles. The elution kinetics of SLNs is dependent on the internal and external stimuli by temperature transition [117] and the electrostatic attraction depletions at lower pH microenvironment of cancer tissues [118].

7.1.7. Gold Nanoparticle

Gold nanoparticles (AuNPs) can easily be coupled, because they can form stable chemical bonds with S-and N-containing groups, thus permitting specific binding to organic ligands or polymers to exert desired function and performance. Surface modifications of AuNPs can increase their biocompatibility, targeting, and drug-delivery capabilities [119,120]. In 2020, Amina and Guo showed that AuNPs could infiltrate the blood vessels and penetrate organelles to access and target the tumor site [121]. The liberation of drugs from AuNPs was mediated by internal and external stimuli, including pH, glutathione (GSH), enzymes, and light. A low pH in the cancer microenvironment and short wavelength light trigger drug discharge from AuNPs, enzymes selectively release drugs through the EPR effect, while GSH is an effective stimulus for drug dispersion *in vivo*. All the evidence supports that AuNPs are effective candidates as drug carriers.

7.2. Modification of the structure of mangostin

β-mangostin (BM) and γ-mangostin (GM) , structural information presented in Table 3, are natural derivatives of AM extracted from the mangosteen pericarp, and both possess unique biological and pharmacological properties [138], proposing that BM exhibited potent anticancer activity against multiple cancer types, including hepatocellular carcinoma and leukemia. Additionally, BM suppresses the JNK2/AP1/Snail expression, eliciting anti-metastatic potential against CIN HeLa cells [139] and can inhibit hepatocellular carcinoma cell growth through activation of MEK1/2, ERK1/2, MEK4, and JNK1/2 signaling pathways [44]. GM also demonstrated anticancer [140], anti-inflammatory [141], and apoptotic activity [142]

through ROS production in CRC HT29 cells [141]. Panaxanthone, composed of roughly 75% to 85% AM and 5% to 15% GM restricts malignant growth and restrains metastasis when administered in a mammary cancer-positive murine model [143].

Rech *et al.* unveiled that the potent and active xanthone derivatives obtained through alteration of the chemical structure of the xanthone ring can potentially decrease the invasiveness of colon cancer by suppressing HCT-116 cell proliferation and inducing cell cycle arrest [66]. Tran *et al*. synthesized the novel derivative of AM via the acetylation by halogen of benzoyl at C-3 and C-6, leading to the conclusion that the phenol groups positioned on C-3 and C-6 are associated with antiproliferative activity, functioning as a booster for AM's anticancer activity [144]. In addition, Chi *et al*. designed a series of AM analogues, as shown in Table 4, and discovered improved anticancer properties against a panel of five human cancer cell lines, including HL-60, SMMC-7721, A-549, MCF-7, and SW480 [145].

Table 2. Demonstrates the different types of nanocarrier and their therapeutic potentials.

Type	Nanocarrier	Therapeutic Descriptions	Reference
Polymeric NPs	Dendrimer-bound AM	Display therapeutic effects on cancer cell lines.	[95]
	α-MNG-PLGA	Halt cell proliferation, promotes apoptosis, and has high antioxidant activity in SC.	[122]
	AM-CSNPs	Conjugated with trastuzumab against HER2 achieved high docking scores, manifesting its efficacy in BC treatment. AM-CS-NPs mediate the sustainable dissemination of AM for 12 hours and improve total release over 20 hours.	[23,123]
CDs	DM-βCD	AM/DM-βCD complex readily disseminates unbound AM across the lipid bilayer into the inner membrane and can potentially permeate into the submembrane.	[105]
	βCD	Form stable and spontaneous inclusion complex, AM/βCD, with improved physicochemical properties and increased solubility. The biodistribution test also indicates the high tendency of AM accumulation in tumors, highlighting its active tumor-targeting properties.	[34,106]
	γ-CD	AM/γ-CD complex yielded a higher entrapment efficiency and solubility.	[104]
Nanofibers	PVP/GME	DPPH assay captured high antioxidant activity by PVP/GME composite nanofiber mats.	[124]
	AM-CS-PEO	The average diameters of the electrospun AM-CS-PEO nanofibers mimic the natural ECM. FTIR analysis also confirmed the presence /of hydrogen bonds between the components, AM, CS, and PEO,	[125]

		providing insights into the structural stability, compatibility, and functional performance of the AM-loaded nanofibers.	
	PVA/AM	AM solubility in pH buffer solutions was significantly increased through PVA/AM nanofibers. The antioxidant ability of PVA/AM was markedly increased in an AM concentration-dependent manner.	[126]
	AM/MPEG-PCL	Impede melanoma cell multiplication, trigger both intrinsic and exogenous apoptosis in vitro, suppress tumor growth, restrain angiogenesis in vivo, and exert lower cytotoxicity in non-tumor cell lines relative to free AM.	[127]
Nanomicelles	AM/MPEG-PLA	Synthetic AM/MPEG-PLA blocks caspase expression, facilitates DNA fragmentation, promotes programmed cell death, influences the downregulation and up-regulation of anti-apoptotic molecules and apoptotic molecules, respectively, and decreases the proliferation and vascularization of malignant glioma cells.	[128]
	PVP	Endocytosis-mediated permeation of AM targeting human colon cancer HCT16 cells was increased in the presence of PVP.	[129]
	AM-loaded liposome	It efficiently and sustainably releases AM and has a cytotoxic effect against Hep-G2 cells.	[130]
Liposomes	Tf-modified liposome	Transport AM across the blood-brain barrier in the Tf-modified liposome group and improve brain delivery of AM.	[131]
	Fabricated AM-loaded liposome	Fabricated AM-loaded liposome composing membranous SBA and Toc facilitate entry of AM, and attenuate the cell viability of cancer spheroids by approximately 30% after 12 hours and 18.9% post-treatment 36 hours.	[132]
	Tf-LPHN	Facilitates AM uptake more efficiently than free AM in MCF-7, A549, and B16-F10 cell lines.	[133]
SLNs	S100-coated NPs	Augment AM and resveratrol loading, inhibiting AM release in the upper GIT and promoting colon-targeted delivery.	[134]
	AM-CD44 TA	AM coupled with CD44 TA induced dissociation of MCTSs by MCF-7 cells, at a 10 times lower dosage compared to free AM.	[34]
	Aptamer/AuNPs	The modification of AuNPs with aptamer favours the formation of a CEA-aptamer duplex, resulting in colour changes of AuNPs due to salt-induced aggregation in the existence of CEA. With its high sensitivity towards CEA, Aptamer/AuNP is used as a cancer biomarker.	[135]
AuNPs	AuNPs/PEI/CD	Proved that AuNPs/PEI/CD present 15% and 50% improvement in cytotoxicity against PC cell lines (PC-3 and DU145) relative to free AM.	[136]
	GC-AuNPs	Cellular uptake of GC-AuNPs by immune cells subsequently migrates to sentinel lymph node metastases in breast tumour-bearing mice, highlighting its potential in micrometastases detection.	[137]

Table 3. Chemical structures of AM, BM, and GM. Image created using ChemSpace (Chemical search - draw chemical structure | Chemspace (chem-space.com).

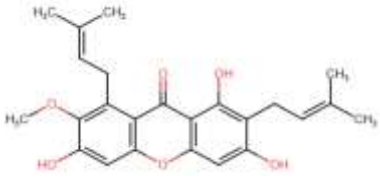
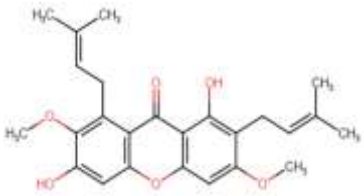
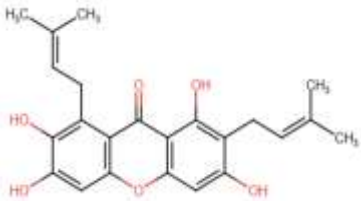
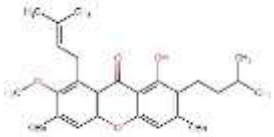
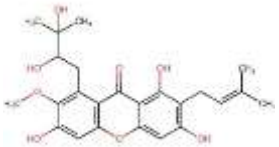
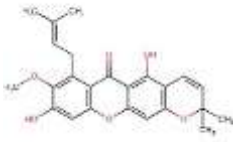
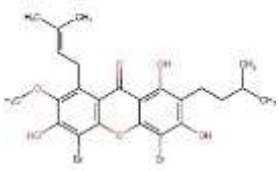
AM	BM	GM
 [142]	 [30]	 [30]

Table 4. Information on the type of modification of AM and the chemical formula of the synthetic analogs. Image created using ChemSpace (Chemical search - draw chemical structure | Chemspace (chem-space.com).

Modification Site	Carbon Position	Reaction Type	Example Chemical Structure	Therapeutic Properties
Phenolic hydroxyl group	1,3,6	Alkylation		Growth inhibitory effect and cytotoxic activity [145].
Isopentene group	2,8	Oxidation		Antiproliferative activity [146].
Phenol group	3,6	Acetylation		Enhanced selectivity antiproliferative activity [144].
Free vacant site	4,5	Halogenation		Growth inhibitory effect and cytotoxic activity [145].

7.3. Combination Treatment with Chemotherapeutic Agents

Cisplatin, a chemotherapy agent used in cancer regimens [146], exhibits therapeutic potential in combination with AM to reduce the recurrence of cisplatin-related side effects and inhibit tumor growth [147], induce programmed cell death, and mitochondrial depolarization [56]. AM plus cisplatin displays synergistic and additive effects in A2780, SKOV-3, and TOV-21G OC cells [62]. Besides, treatment of 5-FU with AM presents anti-tumor effects [71,148], while cisplatin with AM upregulates the activity of caspases-3, -9, and PARP in an *in vivo* xenograft mouse model [56]. The combination treatment of TRAIL and AM promotes apoptosis in human oral squamous carcinoma cells through the mitochondrial pathway [87]. The antineoplastic effects of AM and doxorubicin combination have been evaluated, implying its potential as a co-adjuvant for conventional cancer drugs [52,149]. The pairing of AM with doxorubicin suppresses the RALDH enzymatic activity in MCF-7 cell monolayers [55], multicellular tumor spheroids [54] and generates a potent cytotoxic effect [55]. Furthermore, conjunctional use of AM with additional xanthones has been reported to decrease P-glycoprotein activity and enhance AM absorption [36]. Additionally, the co-treatment of AM with dorsomorphin or 3-MA mediates the autophagy-directed clearance of α-Syn, conferring neuroprotective impacts [150].

AM's therapeutic potential is not limited to the coupling of AM with cancer drugs alone but possesses several benefits when incorporated into chemotherapy, such as increasing chemotherapy sensitivity [151]. AM-loaded crosslinked fibroin nanoparticles (FNP) fully exhibit consistent apoptotic and cytotoxic activities as compared to free-status AM in breast and colon cancer chemotherapy [97,152]. Moreover, the administration of AM in immune cytokine therapy functions as a sensitizer in controlling TRAIL-induced apoptosis [153]. These discoveries confirmed that optimizing AM's anticarcinogenic ability through dual therapy with conventional cancer drugs is possible.

8. Conclusion

AM has shown great potential as a natural anticancer drug in both *in vitro* and *in vivo* studies. Its biological properties have been widely documented, with preclinical studies showing significant action against a variety of cancer types, including breast, cervical, ovarian, colorectal, and pancreatic. AM has been demonstrated to trigger apoptosis, prevent metastasis, and overcome chemoresistance. This was mediated through diverse molecular mechanisms (caspase-dependent/-independent, key signaling pathways, and EMT), highlighting its significance as cancer therapeutics. Despite these promising findings, AM's pharmacokinetic profile presents challenges, especially due to its poor solubility, limited

bioavailability, and short half-life, which restrict its practicability and usefulness in clinical applications. These pharmacokinetic limitations reduce AM's absorption and systemic exposure, thereby limiting its therapeutic efficacy and consistent clinical outcomes. Although pre-clinical investigations show a positive biosafety profile, there is a lack of human evidence on its toxicity and safety. Specifically, early-phase clinical trials such as phase I studies are needed to evaluate AM's safety, tolerability, and pharmacokinetic profile in humans, followed by phase II and III trials to assess its efficacy and optimal dosing regimens. These clinical investigations will provide clearer guidance on its therapeutic potential and safety for human use. Meanwhile, various strategies, such as nanoparticle-based drug delivery systems, chemical modifications to improve solubility, and co-administration with chemotherapy, have been explored to overcome these limitations. These strategies can reduce off-target toxicities while enhancing AM's bioavailability. However, more comprehensive clinical studies are essential to confirm these findings and establish AM as a viable option in cancer treatment. Taken together, while AM holds great potential as an anticancer agent, further extensive research studies are required to optimize its pharmacokinetic properties and validate its safety and efficacy to be an established drug in the market for commercial use in humans.

Supplementary Materials: Supplementary materials are provided.

Author Contributions: YSW - Conceptualization, review & editing. XK, TZS, JL, WXT, MKE, AA, YLW - Writing original draft, writing & editing. MFL, MFCY, LCM – Writing, review & editing.

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Conflicts of Interest: The authors declare that there are no conflicts of interest.

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