Review

α-Mangostin from the mangosteen (*Garcinia mangostana*) fruit for prostate cancer

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ABSTRACT

Xanthones from the mangosteen are a collection of bioactive compounds derived from the *Garcinia mangostana* L. The fruit of the mangosteen has been widely studied for its medicinal properties with multiple reports describing its anticancer properties. Despite recent advancements in treatment of prostate cancer, therapeutic resistance driven by the AR-V7 splice variant remains a significant challenge. This review elucidates the ability of mangosteen xanthones to exhibit anti-proliferative and apoptotic activity in prostate cancer models. Mechanistic studies reveal that α-mangostin, the most abundant xanthone in the mangosteen, induce degradation of both AR, AR mutant and AR-V7 helping to overcome therapeutic resistance. Studies show that this AR and AR-V7 degradation is associated with modulation of ER chaperone protein BiP, leading to ubiquitination and proteasomal degradation. α-Mangostin has been shown to activate UPR sensor proteins including PERK, IRE1 and CHOP. Beyond the AR signaling pathway, α-mangostin has been reported to inhibit tumor progression, induce cell cycle arrest, and promote apoptosis via inhibition of cyclin-dependent kinases (CDKs). Preclinical animal studies highlight the efficacy and safety profile of α-mangostin demonstrating prostate tumor inhibition without adverse toxicity on normal cells. Pharmacokinetic parameters indicate that α-mangostin is well tolerated and safe in both preclinical and human clinical trials. In summary, understanding the mechanism of action and identifying direct molecular target of α-mangostin is important for development of novel anti-cancer agents and further clinical studies are required to evaluate its efficacy in chemotherapy.

1. Introduction

Mangosteen (*Garcinia mangostana L.*) is a tropical tree belonging to the Clusiaceae family native to Southeast Asia. This evergreen tree species is widely distributed across Indonesia, Myanmar, Thailand, Malaysia, Sri Lanka, India, and the Philippines. The fruit consists of a white internal pulp surrounded by a dark purple rind also known as an exocarp (Figure 1). The white edible portion is noted for its sweet flavor and pleasant aroma. This seasonal fruit is produced typically in the fall season beginning in August. Ethyene production leads to rapid ripening and hardening of the pericarp. During this process the pericarp turns dark purple while the aril or fruit pulp ripens, becoming soft and juicy

(Ovalle-Magallanes et al., 2017). Traditional uses can be traced back at least 200 years that include infusions and decoctions of the peels and seeds to treat gastrointestinal and urinary tract infections, anti-scorbutic, laxative, anti-fever agent (Wang et al., 2017). Modern uses include treating diarrhea, abdominal pain, fever, inflammatory and immunological diseases including arthritis (Wang et al., 2017). Notably, the majority of these beneficial compounds are found in the fruit's pericarp, the thick outer rind, which has been reported to exhibit antioxidant activity 20 times higher than that of the fruit's edible flesh (Oh et al., 2020). These benefits are attributed to the phytochemicals known as xanthones with estimates suggesting the pericarp has 20 times higher antioxidant activity than the edible portion.

Figure 1. Mangosteen fruit (*Garcinia mangostana*) photographed in Bankgkok, Thailand.

The historical and more recent scientific analysis of the mangosteen has expanded the mangosteen market for overall health and wellness (Insights, 2025). In 2024 the global mangosteen market was estimated to be between $406 million USD with projection to exceed $700 million USD by 2035. The United States and Canada account for nearly 31% of the global mangosteen market. Approximately only 30% of the fruit is edible with approximately 240,000 tons of by products that same year. These by products contain a rich source of compounds that have health promoting properties (Oh et al., 2020). These benefits are attributed to the phytochemicals known as xanthones with estimates suggesting the pericarp has 20 times higher antioxidant activity than the edible portion.

The phytochemicals present in the mangosteen that received the most interest for their health promoting properties are isoprenylated xanthones. These secondary metabolites are distributed throughout all parts of the plants; however, they are most abundant in the pericarp surrounding the edible portion (Aizat et al., 2019). More than 70 xanthones have been isolated and identified from the mangosteen plant. The structure consists of a flat planar molecule that includes a tricylcyclic aromatic ring with different functional groups attached to the A and C rings including methoxy, hydroxyl, and isoprenyl groups. More recent studies have focused on α-mangostin, the most abundant xanthone in the mangosteen, along with several others that include β-Mangostin, γ-mangostin, garcinone D and E, and gartanin (Figure 2).

2. Prostate cancer

Prostate cancer (PCa) is one the most diagnosed cancer in men worldwide, with estimation of more than 1.46 million new diagnosis and 375,000 death every year (Kratzer et al., 2025, Schafer et al., 2025). Androgen receptor (AR) is a key driver in progression and development of prostate cancer (Dai et al., 2023). AR is a ligand dependent transcription factor comprising of N-terminal domain (NTD), a DNA-binding domain (DBD), and a hinge region, and a ligand binding domain (LBD). In normal prostate cells, testosterone is converted to 5α-dihydrotestosterone (DHT), and when DHT binds with AR, it triggers conformational change that allows AR to translocate from cytoplasm to the nucleus with the help of chaperone proteins including heat shock proteins (HSPs). In the nucleus, AR dimerizes and binds with androgen response elements (ARE) in the promoter site of target genes, promoting the transcription of AR target genes including prostate specific antigen (PSA), KLK3, TMPRSS2 (Dai et al., 2023, Li et al., 2025).

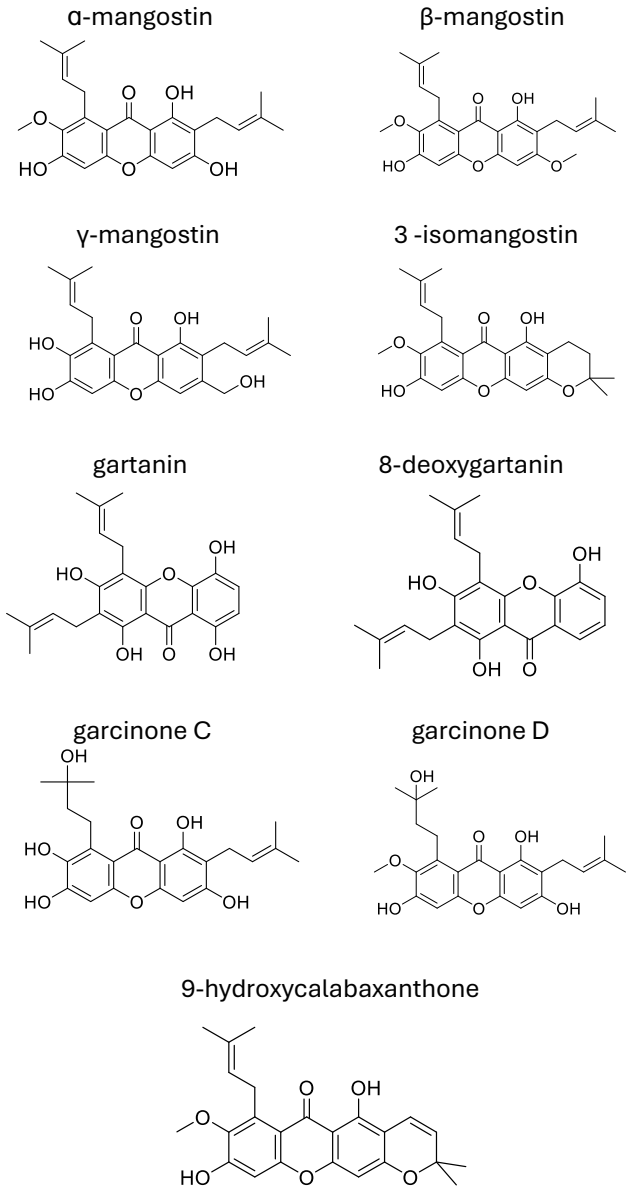

Figure 2. Selected xanthones from the mangosteen (*Garcinia mangostana*).

Androgen deprivation therapy (ADT) is the first line treatment for prostate cancer. However, the response to ADT is not effective followed by recurrence of castration-resistant prostate cancer (CRPC). AR is frequently overexpressed in CRPC despite castrate level of serum testosterone (Nishiyama et al., 2004). The development of second-generation anti-androgens including enzalutamide as a competitive inhibitor that binds to AR (Tran et al., 2009). Similarly, development of abiraterone acetate as an irreversible inhibitor of CYP17A1, which is a precursor for potent androgen biosynthesis was a pivotal milestone in the development of AR targeting agents (Haidar et al., 2003). Despite translational success of second-generation anti androgens, eventually most patients experienced prostate cancer progression and therapeutic resistance. Investigation into the resistance mechanism of primary AR targeted therapies as well as in CRPC, led to identification of point mutation (T878A) in the LBD of AR. Collectively, studies have shown that therapeutic resistance with second generation anti androgens led to somatic AR mutations in LBD including T878A, F877L, L702H and are present in ~15-20% of CRPC cases (Veldscholte et al., 1990, Robinson et al., 2015, Conteduca et al., 2017). Another mechanism implicated in CRPC as well as abiraterone and enzalutamide resistance is expression of AR splice variants (ARVs) (Nakazawa et al., 2014, Ware et al., 2014). 39% of patients treated with enzalutamide and 19% of patients treated with abiraterone had detectable AR-V7 in circulating tumor cells (Antonarakis et al., 2014). Most of the current AR targeted therapies act directly binding to the LBD and thus do not act on ARVs without LBD. Targeting other AR domains has been attractive strategy, including development of NTD inhibitors. EPI-506 is a covalent NTD inhibitor and was in phase I clinical trials of patients with mCRPC resistant to second-generation anti-androgens, however attributed to poor bioavailability (Maurice-Dror et al., 2022). These therapeutic limitations have shifted focus toward protein degradation strategies. Proteolysis-targeting chimera (PROTAC) consisting of heterobifunctional molecules containing ligand that binds to target protein and a second ligand that recruits E3 ligase for proteasomal degradation. Several small molecule PROTAC has been developed to target AR and AR-V7, however only one PROTAC drug MTX-23 has been developed for targeting AR-V7. But still effectiveness of MTX-23 ($DC_{50} \approx 2$ μM for AR) is much less effective than AR-FL PROTAC drugs (DC_{50} <1 nM for AR), could be because of AR DBD protein structure (Lee et al.,

2021). However, there is still an unmet need for compounds that target AR-V7.

2.1 Natural products and prostate cancer

Natural products consist of chemically diverse and plethora of bioactive compounds, which provides unique opportunities in discovering novel compounds that promote AR and AR-V7 degradation. Several natural products have been identified to degrade AR protein via ubiquitination and proteasome-mediated degradation leading to disruption of AR downstream transcriptional factors (Tan et al., 2022). Celastrol, a naturally derived bioactive compound from *Triptergium wilfordii* have been reported to recruit the ubiquitin ligase UBE3A and promote the degradation of AR, AR-V7 and glucocorticoid receptor (GR) to suppress PCa growth and development. Further, data showed that celastrol facilitates the direct interaction between UBE3A and AR/AR-V7 to promote AR ubiquitination (Tan et al., 2022). Previously, celastrol was reported as an HSP90 inhibitor that induced disruption of HSP90 complex (Chadli et al., 2010). Nobiletin, a polymethoxylated flavonoid derived from the peel of citrus fruits exerted anti-prostate cancer activity via inducing G0/G1 phase arrest and enhanced the enzalutamide sensitivity in AR-V7 positive PCa cells. This effect involved interactions between AR-V7 and two deubiquitinases USP14 and USP22 (Liu et al., 2021). Rutaecarpine, a novel compound isolated from Chinese medicine *Evodia rutaecarpa* have shown to induce AR-V7 degradation via K48-linked ubiquitination. Mechanistically, rutaecarpine induces formation of AR-V7-GRP78 complex which subsequently recruits E3 ligase SIAH2 to promote ubiquitination of AR-V7 (Liao et al., 2020).

2.2 Mangosteen xanthones and Prostate cancer

Our previous studies have shown that α-mangostin, a most abundant xanthone from mangosteen decreased PCa cell viability in androgen dependent (LNCaP cells), androgen independent and androgen sensitive (22Rv1 cells), androgen independent (DU145 and PC3 cells) (Johnson et al., 2012). Interestingly, we found that α-mangostin treatment promoted ER stress markers in PCa cells including PERK, IRE1, CHOP and XBP-1. However, we did not observe increased ER stress in normal prostate epithelial cells (Li et al., 2013, Li et al., 2014). Furthermore, we have shown that α-mangostin promotes apoptosis in PCa cells and inhibits nuclear translocation. We observed significant decrease in the expression of AR target genes including FOXA1, KLK2, TMPRSS2, HOXB13, and EDN2 in 22Rv1 cells. Interestingly, we found that α-mangostin induced AR and AR-V7 degradation promoting ubiquitination and proteasome-mediated degradation. Mechanistically, we found that α-mangostin induced AR mutant and AR-V7 degradation via activation of ER chaperone protein BiP (Binding Immunoglobulin Protein). SPR analysis showed that α-mangostin directly bind to BiP, and BiP is the direct molecular target. We showed that α-mangostin decreased AR and AR-V7 protein expression and AR target genes in tumor tissue samples (Nauman et al., 2023). One of the studies with mangosteen fruit extract (MFE) showed that it induced apoptosis in prostate cancer cells and significantly increased the Unfolded protein response (UPR) pathway compared to α-mangostin (Li et al., 2013). We were further interested to explore if other xanthones in MFE could have potential anti-prostate cancer activity. Gartanin, is an isoprenylated xanthone that have shown to promote AR degradation along with modulation of ER stress markers including BiP, PERK, IRE1 and CHOP. Utilizing cell free and cell-based FRET assays, we found that gartanin interacted with the ligand-binding domain through a solely antagonist interaction (Li et al., 2016).

The discovery of α-mangostin, natural product that can degrade both AR and AR-V7 by modulating ER chaperone BiP protein provides a new therapeutic strategy to treat advanced prostate cancer. BiP, also known as glucose-regulated protein 78kD (GRP78) is a multifunctional protein with several roles beyond its well-known role in UPR pathway. BiP is mainly located in the ER, however it is known to translocate to other cellular compartments including cytoplasm, nucleus, cell surface, mitochondria and secreted in cellular fluid (Casas, 2017). As an ER chaperone

protein, BiP modulates AR signaling, promotes cell survival and contributes to chemotherapy or castration resistance. BiP expression is upregulated in metastatic CRPC based on *in vitro* and patient data (Pootrakul et al., 2006). Activation of AR by DHT potently activated BiP expression in both LNCaP and LNCaP-CR cells (Tan et al., 2011). This indicates that AR activation enhances ER stress protein BiP expression in both cytoplasm and cell membrane contributing to AR stability and therapeutic resistance. Though BiP upregulation in untreated cancer has adaptive mechanism that maintains AR/AR-V7 folding and promotes cells survival. In contrary, natural products including α-mangostin shift pro-survival state of BiP into pro-apoptotic state. Under these conditions, BiP could not maintain AR/AR-V7 stability, and eventually activates UPR pathway including PERK, IRE1 and CHOP which has been shown by our group earlier (Li et al., 2013). Further, our study has shown that α-mangostin induces AR and AR-V7 degradation by enhancing ubiquitination of AR and AR-V7 and induces degradation via proteasome (Nauman et al., 2023). This study highlights that therapeutically induced ER stress can switch BiP function and eventually promoting degradation.

3. Mangosteen xanthones and Cyclin-dependent kinases

Despite advancement in development of second-generation anti-androgens, prostate cancer is a second leading cause of cancer-related death in men in United States. Studies have shown that there is a growing interest in targeting and identifying new molecular pathways in therapeutic resistance prostate cancer. One of the keys signaling pathways often dysregulated in several cancers, including drug resistance prostate cancer is cyclin-dependent kinases (CDKs). CDKs is a family of serine/threonine kinases, and its dysregulation has been implicated in cancer initiation, progression, and growth. There are 20 known CDK families, and among them CDK1, CDK2, CDK3, CDK4, CDK6 and CDK7 are involved in cell cycle progression (Farjami et al., 2025, Siskin et al., 2025). Among them, CDK2/4/6 inhibitors either monotherapy or in combination has been studied in metastatic castration-resistant prostate cancer (mCRPC) (Freeman-Cook et al., 2021, de Kouchkovsky et al., 2022, Merseburger et al., 2022, Siskin et al., 2025). However, different mechanisms of resistance of these CDK4/6 inhibitors have led to active search of novel therapeutics. Our group conducted a structure activity relationship (SAR) using nine different xanthones isolated from mangosteen for inhibition of CDK2/Cyclin E1 and CDK4/Cyclin D1 activity. Nine xanthones including α-mangostin, β-mangostin, γ-mangostin, gartanin, 8-desoxygartanin, garcinone C and garcinone D, 9-hydroxycalabaxanthone, and 3-isomangostin were utilized in a cell free biochemical assay. Among them, α-mangostin was shown to inhibit CDK4/Cyclin D1 and a key functional group differences for the CDK4/Cyclin D1 inhibitory activity was explained. Similarly, α-mangostin and γ-mangostin were strongest CDK2 inhibitor with hydroxyl and isoprenyl groups contributing to the CDK2 inhibitory effect (Johnson et al., 2012, Vemu et al., 2019, Nauman et al., 2021).

4. Pharmacokinetics and efficacy of α-mangostin

There are limited studies on the pharmacokinetic profile of α-mangostin. Our group conducted pharmacokinetic study of α-mangostin in male C57BL/6 mice (Ramaiya et al., 2012). A single dose of 100 mg/kg of α-mangostin in cottonseed oil was administered and level of α-mangostin was detected. Previously we have reported the area under curve (AUC) was 5,736 nmol/L and the plasma concentration was 1,382 nmol/L. Monoglucuronide and diglucuronide metabolites of α-mangostin were detected in the plasma sample. Our group was interested in determining pharmacokinetic properties of α-mangostin when administered as a part of a mangosteen fruit extract. C57BL/6 mice were orally administered with 100 mg/kg of mangosteen fruit extract, which is equivalent to 36 mg/kg of pure α-mangostin. The plasma samples were analyzed for over 24 h and the α-mangostin in mangosteen extract showed an 75% increase in C_{max}, 25% increase in AUC and 64% increase in half-life ($t_{1/2}$) compared to

pure α-mangostin. The pharmacokinetics as well as absorption and stability of α-mangostin was improved when administered as a mangosteen extract (Petiwala et al., 2014).

Pharmacokinetics of α-mangostin were reported in rats with α-mangostin (1.025, 4.100 and 16,400 mg/kg) administered both intravenously and orally. α-Mangostin was rapidly absorbed followed by slower elimination for both intravenous and oral routes, showing linear pharmacokinetics. When 16.4 mg/kg was administered orally, there was high accumulation in liver, small and large intestines, lungs, kidneys, and fat. α-Mangostin was also detected in brain homogenates, suggesting oral administration of α-mangostin could cross the blood brain barrier (BBB) (Zhao et al., 2016, Kalick et al., 2023).

The study in healthy human volunteers with consumption of 130 mg of xanthones in 60 mL of 100% mangosteen juice showed that both serum and urine contained both free and sulfated/ glucuronidated xanthones. These xanthones included α-mangostin, γ-mangostin, garcinone D, garcinone E, 8-deoxygatanin, and gartanin. Among 10 healthy volunteers, the variability difference was observed in measured C_{max} (113 ± 107 nmol/L) and T_{max} (3.7 ± 2.4 h) (Chitchumroonchokchai et al., 2012).

CONCLUSION

In summary, mangosteen xanthones, particularly α-mangostin and gartanin showed anti-prostate cancer activity by decreasing cell viability, promoting apoptosis, and arresting the G1 cell cycle through inhibition of CDK2/Cyclin E1 and CDK4 pathways. α-Mangostin induced AR and AR-V7 degradation via activation of BiP and UPR stress proteins including PERK, IRE1, ATF6 and CHOP. Preclinical studies showed in vivo efficacy of α-mangostin in their ability to reduce tumor and decrease AR mutant and AR-V7 expression. However, there is limited study with pharmacokinetics parameters of α-mangostin and other mangosteen xanthones including solubility and systemic exposure. Future studies could focus on combination therapy of α-mangostin with standard anti-androgens therapy, exploring other mangosteen xanthones for AR and AR-V7 degradation, and define if BiP is the direct molecular target of α-mangostin by mapping its binding site linking BiP's direct engagement in AR and AR-V7 degradation.

Conflicts of interest

The authors do not declare any conflicts of interest.

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