KEMAS 20 (4) (2025) 841-847

Jurnal Kesehatan Masyarakat

http://journal.unnes.ac.id/nju/index.php/kemas

The Ins and Outs of Alpha-mangostin's Potential as An Antimalarial

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Article Info

Article History:
Submitted Januari 2025
Accepted April 2025
Published: April 2025

Keywords:
alpha-mangostin chitosan alginate nanoparticles; ED_{50}; antimalarial activity; in vivo; berghei malaria

DOI
https://doi.org/10.15294/kemas.v20i4.19307

Abstract

Malaria drug resistance, including to development of resistance against artemisinin-based treatments, poses a major challenge to elimination efforts. Alpha-mangostin, an antioxidant with *in vitro* antimalarial activity, is hindered by its poor solubility. This study explores the antimalarial effects of water-soluble alpha-mangostin chitosan-alginate nanoparticles (ACAN) in mice with berghei malaria. Mice were treated with various doses of ACAN, compared to alpha-mangostin in polyethylene glycol (PEG), as well as in corn oil (ACO) and chloroquine as a standard. Growth inhibition rates were assessed, revealing no inhibition in the PEG and normal control (NC) groups, while ACO was less active. The effective dose 50 (ED_{50}) of ACAN was 264.5 mg/kg BW, containing only 15.87 mg of alpha-mangostin, suggesting that alpha-mangostin in ACAN may offer promising *in vivo* antimalarial activity. Further investigation is needed.

Introduction

Human malaria remains a significant problem in several countries due to its severity and challenges related to therapy, particularly for *Plasmodium falciparum.* In many tropical and subtropical regions, malaria continues to be a leading cause of disease and death (Chora *et al*., 2022). In 2020, there were 241 million reported cases of malaria, resulting in 627,000 deaths globally (WHO, 2021). Artemisinin-based combination therapy (ACT) is the treatment of choice due to the parasite's resistance to conventional drugs. However, signs of parasite resistance, especially partial resistance to ACT, are beginning to emerge in several countries, leading to slower responses to treatment (Hassett & Roepe, 2019; WHO, 2021). Resistance to ACT occurs against both artemisinin and its partner drugs through various mechanisms of action (Siddiqui *et al*., 2021). This issue poses a significant obstacle to achieving malaria elimination targets, highlighting the need for new antimalarial drugs.

Garcinia mangostana L. rind exhibits antioxidant activity (Susy Tjahjani *et al*., 2014) and has shown antimalarial activity *in vitro* (S. Tjahjani, 2017). Alpha-mangostin, one of the most abundant xanthones in *Garcinia mangostana* L. rind (John *et al*., 2021), not only has antioxidant properties but also demonstrates strong antimalarial activity, as shown in our previous *in vitro* studies (Susy Tjahjani & Widowati, 2013). Previous research has indicated that alpha-mangostin can act against *Plasmodium falciparum* by inhibiting its cysteine protease enzyme (Kuncoro *et al*., 2018). The extract of *Garcinia mangostana* L. rind, which is abundant in alpha-mangostin, demonstrates the ability to inhibit several proteins involved in the glycolysis process of the parasite (Chaijaroenkul *et al*., 2014).

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pISSN 1858-1196
eISSN 2355-3596

Additionally, there may be specific benefits to using antioxidants as antimalarials, as malaria itself induces oxidative stress in the host (Vasquez *et al*., 2021). However, the very poor solubility of alpha-mangostin in various safe solvents poses a challenge for *in vivo* studies, because low solubility is a critical factor affecting bioavailability, particularly for oral administration (Savjani *et al*., 2012).

Chitosan-eudragite nanoparticles enhance the solubility of alpha-mangostin and may improve its bioavailability, especially for oral use (Herdiana *et al*., 2020). According to another study, other alpha-mangostin nanoparticles, i.e., alpha-mangostin chitosan alginate nanoparticles, not only exhibit greater water solubility but also show promise for enhancing the performance and physicochemical properties of alpha-mangostin (Wathoni *et al*., 2019). Additionally, alpha-mangostin diluted in vegetable oil is absorbed quickly and distributed throughout the bodies of experimental animals (Zhao *et al*., 2016). Water-soluble organic solvent formulations, such as those containing polyethylene glycol, may also be utilized due to their chemical and physical stability (van der Vossen *et al*., 2017). *Plasmodium berghei* in mice is commonly used as a model for malaria caused by *Plasmodium falciparum* in humans. This study aimed to explore the antimalarial activity of alpha-mangostin chitosan-alginate nanoparticles (ACAN) in comparison to the antimalarial activity of alpha-mangostin mixed with other solvents, such as corn oil as well as 1-2 polyethylene glycol 400 (PEG 400) - distilled water (6/4, v/v) solution, to identify the most suitable oral preparation against *Plasmodium berghei*-infected mice.

Methods

Frozen Anka strain *Plasmodium berghei* was obtained from the Eijkman Institute for Molecular Biology. Alpha-mangostin was sourced from Biopurify Phytochemicals Ltd., Chengdu, China. The 46 male Swiss Webster mice aged 7-8 weeks, weighing 20-25 g, were procured from the School of Life Science and Technology, Bandung Institute of Technology (ITB). Chloroquine, used as a control drug, was obtained from Sigma-Aldrich. Other materials, including polyethylene glycol, chitosan, alginate, TPP (sodium tripolyphosphate), ethanol (96%), and citric acid, were also sourced from Sigma Aldrich. Alpha-mangostin, chitosan, and alginate were prepared in 0.1% solutions, while TPP was prepared in a 1% solution. Alginate and TPP were dissolved in distilled water, while alpha-mangostin was dissolved in 96% ethanol, and chitosan was diluted in 1% acetic acid. Alphamangostin, chitosan, TPP, and alginate were mixed in a volume ratio of 1:10:2:1 consecutively and slowly, with each step involving stirring, sonication, and pyrolysis (Muchtaridi *et al*., 2023).

This study received ethical approval from the Ethical Committee of the Faculty of Medicine, Maranatha Christian University (certificate number: 144/KEP/XI/2022). A true experimental study with a completely randomized design was used. After a one-week adaptation period under laboratory condition (23-24°C, 60-70% relative humidity, 12-hour light/dark cycle) with ad libitum access to food and water, mice were randomly divided into nine groups with five replicates per group: normal control without any treatment (NC), chloroquine control 20 mg/kg BW (Chloroquine), ACAN at doses of 100, 250, 500 mg/kg BW (ACAN1, ACAN2, ACAN3), 500 mg/kg BW alpha-mangostin in PEG (PEG), and alpha-mangostin in corn oil at doses of 125, 250, 500 mg/kg BW (ACO1, ACO2, ACO3). Each treatment group was housed in a hygienic cage. Chloroquine was diluted in a 0.5% hydroxypropyl methyl cellulose solution in aquadest, while ACAN was diluted in a 0.5% sodium carboxymethyl cellulose solution.

Frozen parasites were thawed and injected intraperitoneally and aseptically into a donor mouse. Parasitemia was monitored daily via thin blood smears from the tail aseptically, fixed in methanol, and stained with Giemsa, then parasitized red blood cells (pRBC) among 1,000 red blood cells (RBC) were counted under a light microscope to find out the parasitemia percentage. Once parasitemia reached 5-10%, the mouse was ethically euthanized using carbon dioxide (CO2), and the blood was taken by cardiac puncture. Each experimental mouse was injected intraperitoneally with 10^7 of these pRBC in 200 µL phosphate-buffered saline

(PBS). After reaching parasitemia around 2%, treatments were administered orally (200 µL) once daily for four days, as per Peters' 4-day suppressive test (Peters *et al*., 1975). The parasitemia percentage was calculated daily starting from day 0. At day 4 (the 5th day), the percentage of parasite growth inhibition was calculated using the formula: (parasitemia percentage of NC - parasitemia percentage of treatment group) / parasitemia percentage of NC x 100%. Mice were euthanized as previously described. Statistical analysis: Probit analysis was performed to determine the dose required to inhibit 50% of parasite growth (ED_{50}=effective dose 50). A lower ED_{50} indicates a more active antimalarial drug.

Results and Discussion

ACAN was successfully produced and was the same product as previously used (Muchtaridi *et al*., 2023) and the alpha-mangostin content in the nanoparticles was measured at 6%. The average of daily parasitemia percentage from NC, chloroquine, ACAN, and PEG groups was calculated, and the percentage of growth inhibition at day 4 (the 5th day) was summarized in Table 1.

Shown in Table 1, at day 4, the chloroquine group exhibited 100% parasite growth inhibition, while the PEG group showed only 4.2% inhibition (similar to NC). Notably, at equivalent doses, ACAN3 produced significantly higher inhibition than PEG, despite containing only 0.6% alpha-mangostin. Probit analysis revealed an ED_{50} of 264.5 mg/kg BW for ACAN, equating to 15.87 mg of alpha-mangostin. This is higher than the ED_{50} for chloroquine (1.4 mg/kg BW) (Mazhari *et al*., 2018) and artesunate (1.8 mg/kg BW) orally (Lombard *et al*., 2013). However, the presence of only 15.87 mg alpha-mangostin suggests strong potential antimalarial properties of the ACAN (Habte & Assefa, 2020). The average of daily parasitemia percentage for the NC and ACO groups was also calculated, with growth inhibition percentage at day 4 presented in Table 2. The ACO1 group exhibited 0.43% inhibition (negligible), while ACO3 demonstrated 27.14% inhibition, with an ED_{50} > 500 mg/kg BW.

Alpha-mangostin shows promising antimalarial activity against the *Plasmodium falciparum* 3D7 strain *in vitro* (S. Tjahjani *et al*., 2018; Susy Tjahjani & Widowati, 2013). It inhibits *Plasmodium falciparum* development,

Table 1: Parasitemia Percentage Average from Each of the NC, Chloroquine, ACAN, and PEG Groups Every Day and Percentage of Growth Inhibition at Day 4 (the 5th day)

Treatment group	% Parasitemia					% growth	% growth inhibition
	D0	D1	D2	D3	D4		
NC	**2.06** ±0.15	**6.22** ±0.40	**9.03** ±0.67	**10.14** ±0.71	**13.80** ±0.79	100	0
Chloroquine	**2.00** ±0.16	**2.18** ±0.26	**1.18** ±0.08	**0.14** ±0.11	**0.00** ±0.00	0.00	100
ACAN1	**2.04** ±0.23	**4.78** ±0.89	**7.96** ±0.63	**8.84** ±1.49	**8.34** ±1.86	60.43	39.57
ACAN2	**2.00** ±0.34	**4.84** ±0.56	**7.32** ±0.38	**8.56** ±0.40	**7.32** ±0.79	53.04	46.96
ACAN3	**2.02** ±0.24	**3.92** ±0.56	**7.20** ±0.67	**7.86** ±0.48	**6.30** ±0.95	45.65	54.35
PEG	**1.98** ±0.30	**6.2** ±0.38	**8.96** ±0.81	**10.44** ±0.49	**13.22** ±0.85	95.80	4.20

Table 2: Parasitemia Percentage Average from Each of the NC and ACOs Groups Every Day and Percentage of Growth Inhibition at Day 4 (the 5th day)

Treatment Group	% Parasitemia					% Growth	% Growth Inhibition
	D0	D1	D2	D3	D4		
NC	**2.15** ±0.33	**7.08** ±0.90	**10.38** ±1.08	**12.60** ±1.06	**15.13** ±0.85	100	0
ACO1	**1.90** ±0.16	**6.36** ±0.82	**11.46** ±1.48	**14.44** ±0.69	**15.06** ±1.73	99.57	0.43
ACO2	**2.10** ±0.32	**6.50** ±1.22	**10.14** ±1.96	**12.56** ±1.34	**12.34** ±2.81	81.59	18.41
ACO3	**1.98** ±0.19	**6.76** ±0.59	**10.10** ±1.25	**11.64** ±1.89	**11.02** ±2.14	72.86	27.14

leading to globin accumulation due to cysteine protease inhibition (Kuncoro *et al*., 2018) going to a parasite's death. Other studies indicate that several parasite glycolysis pathway proteins may also be targets of antimalarial activity of *Garcinia mangostana* L. rind extract (Chaijaroenkul *et al*., 2014) and alpha-mangostin is one of the most xanthone-containing contained in *Garcinia mangostana* L rind extract (John *et al*., 2021). However, *in vivo* results for alpha-mangostin against *Plasmodium berghei* have varied. As indicated in Table 1, parasitemia in the PEG group closely matched that of the NC group, even at a 500 mg/kg BW dose, with minimal growth inhibition. This may stem from the limited bioavailability of alpha-mangostin via oral administration, potentially due to poor gastrointestinal absorption. Similar conclusions were drawn by Upegui *et al*., who recommended modifications to enhance the therapeutic efficacy of alpha-mangostin (Upegui *et al*., 2015). Alpha-mangostin is also very insoluble in various safe solvents.

The same limited efficacy was observed with corn oil as a solvent, with an ED_{50} > 500 mg/kg BW, indicating very weak antimalarial activity (Habte & Assefa, 2020). In contrast, the nano formulation (ACAN) displayed superior antimalarial activity with an ED_{50} of 264.5 mg/kg BW. This formulation contains 6% alpha-mangostin, equating to 15.87 mg alpha-mangostin per 264.5 mg ACAN. The size of ED_{50} indicates its potential as an antimalarial. The low ED_{50} suggests potential for development as an antimalarial drug, i.e., if ED_{50} < 5-25 mg/kgBW (Sari *et al*., 2015). This indicates that alpha-mangostin in ACAN may exhibit significant antimalarial activity and warrants further investigation at higher doses or alternative administration routes.

The chitosan-alginate nanoparticles improve alpha-mangostin's water solubility and may enhance bioavailability and drug delivery. Moreover, advanced nanotechnologies offer a promising solution to reduce biological variability to counteract varied efficacy and safety, which becomes a challenge in drug design. These technologies may also be implicated in personalized medicine (Zhuo *et al*., 2024). Prior studies, such as the use of nano dendrimer G2 loaded with chloroquine, also showed that nanotechnology can enhance the activity and solubility of antimalarial drugs (Elmi *et al*., 2022). There are many other benefits of using nanotechnology for better drug design. Alpha-mangostin potentially also has many health benefits besides as an antimalarial, antioxidant, and anti-inflammatory, i.e, neuroprotective effect, antimicrobial, and anti-cancer property against many cancers: breast, colon, lung, pancreatic, hepatocellular, prostate cancer, also against leukemia by several mechanisms of action. But the lower water solubility and poor target selectivity become a challenge (Alam *et al*., 2023). Nanotechnology may also improve the performance of alpha-mangostin against it to overcome the poor drug-receptor interaction, poor bioavailability because of poor solubility, and potential systemic toxicity. The core and the surface of the nanoparticle may facilitate the drug delivery, and that's why they enhance therapeutic efficacy (Herdiana *et al*., 2021).

One of the components of ACAN is alginate. It is a product of brown algae or bacteria, and it is non-toxic, biodegradable, cheap, and safe to be consumed. It is a natural polysaccharide that has no immunogenic effect (Paques *et al*., 2014). Alginate may replace lactose for drug encapsulation because lactose may become a potentially allergenic agent. There is abundant alginate material in nature because of a large amount of algae in the marine environment. It also has many health benefits, such as enhancing insulin delivery and improving insulin resistance for diabetes management, a well-known weight loss treatment to enhance satiety, and most importantly thing is that alginate also has antioxidant activity (Puscaselu *et al*., 2020) which closely correlates with malaria pathogenesis and severity (Vasquez *et al*., 2021). Chitosan is another nanoparticle component of the ACAN. It has been reported that it has a low, non-toxic effect. Against humans, the toxicity has not been reported (Zoe *et al*., 2023). So, it is wise to have a toxicity test, especially an acute toxicity test, for this ACAN *in vivo*.

Alpha-mangostin's antioxidant properties (Susy Tjahjani & Widowati, 2013) may also provide added benefits in managing oxidative stress associated with malaria,

which closely correlates with disease severity (Vasquez *et al*., 2021). So, alpha-mangostin in ACAN acts as an antimalarial as well as an antioxidant, and it may potentially become an ideal combination. Another study also reported that antioxidant supplementation is recommended for malaria therapy (Gomes *et al*., 2022). It has great antioxidant activity through several mechanisms: as a direct free radical scavenger to purge several free radicals, such as peroxynitrite, singlet oxygen, as well as indirectly through the activation of the Nrf2 pathway to enhance endogenous enzymatic antioxidant production (Chen *et al*., 2018).

Because of the low enough ED_{50} of alpha-mangostin in the ACAN, which means a potential of antimalarial activity, it is recommended that further studies to determine the ED_{100} and studies using larger animals (such as primates) be carried out. For every new drug or new formulation of a drug, the toxicity needs to be kept in mind. According to previous studies, the oral LD_{50} (lethal dose 50) of alpha-mangostin in rats is between 1,250 - >2,000 mg/kgBW (Setyawati *et al*., 2023) and the therapeutic index is >10 (Tamargo *et al*., 2015). It means that alpha-mangostin itself is nearly a non-toxic compound, and this encourages further studies of it. Furthermore, as mentioned above, the toxicity test of alpha-mangostin in a new formulation (nanoparticle formulation) also needed to be studied, especially the acute toxicity test. Limitation of the Study: Since oxidative burst and several antimalarial drugs produce oxidative stress to kill the parasites (Vasquez *et al*., 2021). It is important to carefully consider whether administering an antimalarial drug with antioxidant activity would interfere with its antimalarial effects and reduce the parasite-killing efficacy, especially when it is used in combination with other antimalarial drugs.

Conclusion

Alpha-mangostin, when it is prepared in nanoparticles (specifically, alpha-mangostin chitosan-alginate nanoparticles), has been shown as the most suitable oral preparation antimalarial against *Plasmodium berghei*-infected mice with a low ED50. That's why further studies are needed to develop it.

Acknowledgments

We would like to thank the Directorate General of Higher Education, Research, and Technology, the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia, and Maranatha Christian University for supporting the research grant and research facility.

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