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Effectiveness of mangosteen rind (*Garcinia mangostana* Linn.) and chitosan polymers as an antimicrobial

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Abstract
Some researchers have conducted a research relating to the pharmacological effects of mangosteen rind; it was found that the xanthon compounds contained in mangosteen rind have varied pharmacological effects. From the studies that have been conducted, it is proven that mangosteen rind has many benefits and potential for treatment, one of which is as an antimicrobial. Chitosan is a derivative of chitin, commonly found in invertebrates such as Crustacea sp and cuticle insects. Chitosan has good potential in supporting the preparation of drug preparations, both in the form of tablets, hydrogels, microparticles and nanaoparticles. Chitosan is a biopolymer that has extraordinary properties, namely non-toxic, easily found, good biodegradation and biocompatibility, and can increase the bioavailability of drug preparations as well. Chitosan can be used in the manufacture of pharmaceutical preparations that has purpose to prevent or treat a disease because chitosan is known to have antimicrobial properties.
Mangosteen rind (*Garcinia mangostana* L) and chitosan are proven to have antimicrobial activity. However, mangosteen rind and its derivatives have low solubility. The increasing of solubility can be done by designing it into the form of nanoparticles using chitosan polymers that have good physical chemical characteristics so that they can be used as polymers that can act as drug delivery in anticancer, antifungal and antibacterial treatment. The addition of chitosan is used as a conductor and protective drug, so that the drug is not easily degraded due to environmental conditions in the patient's body and can work specifically on the target work of the drug.

Keywords: alpha mangostin, chitosan, antimicrobial

Introduction
Mangosteen (*Garcinia mangostana* L) is a type of fruit that grows in Asian regions such as Malaysia, Myanmar, Thailand, India, Sri Lanka and the Philippines. Mangosteen is called the 'queen of fruits' because this plant has a unique taste [15]. Mangosteen contains xanthones, a phenolic compound that has many medical benefits and has been reported as a powerful antioxidant compound [47]. Currently, Mangosteen (*Garcinia mangostana* L) has been used as one of the natural ingredients that is being widely studied by scientists related to pharmacological activities and has potential as a drug. The potential is in the mangosteen rind as there are compounds that can provide pharmacological effects for the body that contains more than 300 kinds of species from several classes of bioactive compounds such as xanthon, triterpenoids, flavonoids and benzofenon [4].
Some researchers have conducted a research relating to the pharmacological effects of mangosteen rind. In the research that has been done, it is found that xanthon compounds contained in mangosteen rind have varied pharmacological effects [34]. Xanton compounds found in mangosteen rind are not only as anticancer [1], but also analgesic [7], antimalarial [13], antimicrobial, antituberculosis [42], treatment of diarrhea, trauma, skin infections and wounds [50], dysentery, suppurating, and chronic ulcer [41], antimalarial [13], antimicrobial, antituberculosis [42], cardioprotective [10], antioxidant [49, 10], anti-inflammatory [4], anticonvulsant [21], antifungal [16], antibacterial inhibitors [10, 39], hepatoprotective [8], neuroprotective [46], and immunomodulating effects [43].
Mangosteen rind contains abundant xanthon compounds in the form of: α-mangostin, β-mangostin, γ-mangostin, gartanin, 8-deoxygartanin, and mangostanol [27]. The main and most common constituent found in *Garcinia mangostana* L., the xanthon group, is α-mangostin [5]. The α-mangostin compound in ripe mangosteen has twice the content compared to unripe mangosteen [19]. One of xanthon derivatives is alpha mangostin. Alfa mangostin has a molecular weight of 410.46 g / mol, in the form of yellow crystals with a melting point of 180-182Oc [30] and has anticancer [17], antifungal [16] antibacterial [17], anti-inflammatory [12]. kelaruta alpha mangostin and other xanthan derivatives are bad in water so modifications are made in the form of nanoparticles. Nanoparticles is one of the nanotechnology that has become a major industrial innovation recently that has created many applications in products available to consumers on an industrial scale [28]. Nanotechnology has been developed in research on pathologies in various cancers and various diseases. The concept of nanotechnology aims to target networks at the molecular level [44].
Several studies that have been carried out in an effort to modify the *Garcinia mangostana* pericarp using polymers as nanocariers made from natural and synthetic polymers have received most of the attention because of the stability and ease of surface modification [14]. They can be specially made to achieve controlled drug release and localization of specific diseases by adjusting the polymer characteristics and surface chemistry [45].

Chitosan is a derivative of chitin, commonly found in invertebrates such as Crustacea sp and cuticle insects, some fungi, green algae and yeast [2]. Chitosan is a unique biopolymer and has extraordinary properties, both in terms of biodegradation and biocompability. Extraordinary properties in chitosan can be caused by the presence of primary amines which are quite long. In addition, chitosan has both nonionic hydrophobic and cationic hydrophilic functions. Chitosan is degraded in the body by a reaction between chitonase and lysozyme. The advantages of this chitosan have become one of the interesting factors to be applied in the biomedical and pharmaceutical fields. Currently, research on chitosan in the pharmaceutical field continues to grow rapidly. Some research that has been done, has applied chitosan as an active ingredient or an additional ingredient (excipien) in pharmaceutical preparations in the form of tablets, hydrogels, nanoparticles and microparticles. As an active ingredient, chitosan can be used in the manufacture of pharmaceutical preparations aimed at preventing or treating a disease, because it is known that chitosan has antibacterial properties [38]. Generally the addition of chitosan is used as a conduit and protective drug, so that the drug is not easily degraded due to environmental conditions in the patient's body and can work specifically on the target of drug action [25].

Chitosan has been used in the pharmaceutical field since the 1990s, and has attracted the interest of researchers and industrialists to make it more effective in the therapeutic system. Structurally, chitosan consists of N-acetyl-D-glucosamine and D-glucosamine with one amino group (NH_2) and two hydroxyl groups (OH) in each glycosidic unit [9]. Chitosan has been widely used in many pharmaceuticals and materials applications due to its non-toxic, biodegradable and biocompatible nature [23].

Garcinia mangostana as an antimicrobial

Isolate *Garcinia mangostana* -02 displayed the strongest antibacterial activity against gram-positive bacteria. The Minimum Inhibitory Concentration (MIC) of the crude ethyl acetate extracts of isolate RGM02, inhibited *S. aureus* (MIC 25 µg/ml), B. subtilis (MIC 50 µg/ml), M. luteus (MIC 25 µg/ml), E. coli (MIC 200 µg/ml), *S. typhi* (MIC 200 µg/ml) and P. aeruginosa (MIC 100 µg/ml), respectively [33]. penelitian lain mengenai aktivitas *Garcinia mangostana* terhadap antimkroba juga dilakukan oleh [36], dimana alpha mangostin, isolated from the stem bark of *Garcinia mangostana* L., was found to be active against vancomycin resistant Enterococci (VRE) and methicillin resistant Staphylococcus aureus (MRSA), with MIC values of 6.25 and 6.25 to 12.5mg/ml, respectively. Penelitian yang telah dilakukan showed synergism between a-mangostin and gentamicin (GM) against VRE, and a-mangostin and vancomycin hydrochloride (VCM) against MRSA. Further studies showed partial synergism between a-mangostin and commercially available antibiotics such as ampicillin and minocycline. These findings suggested that alpha mangostin alone or in combination with *Garcinia mangostana* against VRE and in combination with VCM against MRSA might be useful in controlling VRE and MRSA infections.

Research on the bacterium *Staphylococcus aureus* has also been carried out. Methicillin-resistant Staphylococcus aureus (MRSA) is a major nosocomial pathogen which causes severe morbidity and mortality worldwide. Seventeen Thai medicinal plants were investigated for their activity against MRSA. *Garcinia mangostana* was identified as the most potential plant, and its activity was traced to the prenylated xanthones, α-mangostin (MIC and MBC values of 1.95 and 3.91 µg / ml, respectively) [6, 20, 29].

Garcinia mangostana, along with four known xanthones: 9-hydroxycalabaxanthone, parvifolixanthone C, alpha mangostin and rubraxanthone. Compounds alpha mangostin and rubraxanthone had weak to moderate activity against *Escherichia coli* and *Staphylococcus aureus*, while demonstrated promising action against Bacillus cereus with MICs 0.25, 1.0, and 1.0 mg/mL, respectively. The tested compounds were inactive against Candida albicans. However, they showed selective antifungal potential toward *Aspergillus fumigatus*. Compounds mangostana xanthones and alpha mangostin possessed quorum-sensing inhibitory activity against *Chromobacterium violaceum* ATCC 12472 [24]. Evaluasi turunan *Garcinia mangostana*, alpha mangostin ditemukan to be a potent inhibitor of acid production by *S. mutans* UA159, active against membrane enzymes, including the F(H+)-ATPase and the phosphoenolpyruvate – sugar phosphotransferase system. Alpha mangostin also inhibited the glycolytic enzymes aldolase, glyceraldehyde-3-phosphate dehydrogenase, and lactic dehydrogenase. Glycolysis by intact cells in suspensions or biofilms was inhibited by alpha mangostin at concentrations of 12 and 120 µmol·L–1, respectively, in a pH-dependent manner, with greater potency at lower pH values. Other targets for inhibition by α-mangostin included (i) malolactic fermentation, involved in alkali production from malate, and (ii) NADH oxidase, the major respiratory enzyme for S. mutans. The overall conclusion is that α-mangostin is a multitarget inhibitor of *mutans streptococci* [26].

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Chitosan as antimicrobial

Chitosan, a hydrophilic biopolymer industrially obtained by

N-deacetylation of chitin, can be applied as an antimicrobial agent. The current review of 129 references describes the biological activity of several chitosan derivatives and the modes of action that have been postulated in the literature. It highlights the applications of chitosan as an antimicrobial agent against fungi, bacteria, and viruses and as an elicitor of plant defense mechanisms [32]. Chitosan has exhibited high antimicrobial activity against a wide variety of pathogenic and spoilage microorganisms, including fungi, and Gram-positive and Gram-negative bacteria [11], Chitosan-mediated inhibition is affected by several factors can be classified into four types as intrinsic, environmental, microorganism and physical state, according to their respective roles [18]. The polycationic structure of chitosan is a prerequisite for antibacterial activity. As environmental pH is below the pKa of chitosan and its derivatives, electrostatic interaction between the polycationic structure and the predominantly anionic components of the microorganisms' surface (such as Gram-negative lipopolysaccharide and cell surface proteins) plays a primary role in antibacterial activity [48].

The combination of *Garcinia mangostana* and chitosan as antimicrobials

This research aims to determine the characteristics of chitosan taken from tiger-shrimp-shell waste (Peneaus monodon) with the addition of mangosteen-rind extract in terms of shape, color, odor, spread ability and viscosity and determine the effect of adding mangosteen-rind extract to wound healing in male rats, Wistar. This study is a pure experimental research with a randomized directional pattern design. A total of 7 male Wistar rats were treated with 7 groups of wounds randomly. Group I (Bioplacenton control) was given bioplacenton. Group II (chitosan control) was given 2% chitosan gel. Group III (extract control) was given mangosteen rind extract gel with a concentration of 3%. Groups IV, V, and VI (combination gel treatments) were given a combination of chitosan 2% gel with 1% mangosten rind extract concentration; 2% and 3%. Within 7 days after the giving of the wound and the application of the gel, the scab, the redness of the wound and the diameter of the wound were measured to determine the effect caused. The data obtained is processed by statistical tests. The result has showed that the addition of mangosteen rind extract on 2% chitosan gel increased viscosity, changed its color to dark brown color without the specific odor and reduced the spread ability of the gel. There was no difference in the wound healing process in wounds with 2% chitosan gel or chitosan combination gel and mangosteen-rind extract in male Wistar rats. The research that has been conducted [37] on the efficacy of alpha mangostin combined with chitosan for the maintenance of oral hygiene and reduction of bacterial growth that causes dental caries, where polyvinyl alcohol (PVA) was chosen as a polymer polymer muadhesif states that alpha mangostin compounds combined with chitosan polymers can be used as an antimicrobial. The antibacterial activity of quaternized β-CD grafted-chitosan (QCD-g-CS), alpha mangostin, and inclusion complex with different entrapment efficiencies were assessed by measuring the minimum inhibition concentrations (MIC) for microbial growth against *S. mutans* ATCC 25177 and *C. albicans* ATCC 10231 which showed S. mutans had a higher sensitivity to the presence of QCD-g-CS and inclusion complexes than *C. albicans* [31]. In the research conducted shows an increase in wound healing using a combination of Chitosan-ethylenediaminetetraacetic acid / polyvinyl alcohol (CS-EDTA / PVA) and *Garcinia mangostana* extract using electrospinning [3]. The effect of combined chitosan and mangosteen-rind extract has also been investigated for its activity against Propionibacterium acnes, by testing the inhibitory activity of Propionibacterium acnés and showing that the antiacne preparations tested have good stability, efficacy, physics, chemistry and microbiology [35]. Tests on gram-positive bacteria (*S. aureus* and *B. cereus*) and 1 bacterium are gram-negative (S. flexineri) have been carried out by Sitti, *et al*. 6 nm [40] by using pericarp *Garcinia mangostana* chitosan combination in which the highest inhibition in bacteria is combination with nano seize 213.6 nm [40].

Conclusion

Mangosteen rind and its derivatives have low solubility. Increasing the solubility of alpha mangostin compounds is carried out by being designed in the form of nanoparticles using chitosan polymers that have been investigated to have good physical chemical characteristics so that they can be used as polymers that can act as drug delivery in treatment. The addition of chitosan is used as a conduit and protective drug, so that the drug is not easily degraded due to environmental conditions in the patient's body and can work specifically on the target work of the drug. Utilization of alpha mangostin compounds combined with chitosan polymers can be used as a treatment, especially for antimicrobials, seen from several studies that have been done.

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