Alpha-Mangostin and Gamma-Mangostin Isolated from Mangosteen (*Garcinia mangostana* L.) as Promising Candidates against SARS-CoV-2: A Bioinformatics Approach

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Abstract

The world is endangered by the COVID-19 pandemic caused by SARS-CoV-2, people are dying in thousands every day, and without an actual treatment, it seems that bringing this global health problem to a quit is impossible. Natural products have been in constant use since ancient times and are proven by time to be effective. Medicinal plants from Indonesia may lead to the discovery of the novel drugs. Mangosteen or *Garcinia mangostana* L. is a native tropical fruit from Southeast Asia and is known to contain bioactive compounds. Interestingly, the main xanthone derivatives are alpha-mangostin and gamma-mangostin, these compounds have a variety of pharmacological activities such as antiviral activity. In summary, this study showed potential pharmacological benefits of alpha-mangostin and gamma-mangostin isolated from mangosteen against SARS-CoV-2. Thus, mangosteen exhibits as a valuable plant and a candidate for future drug development to fight SARS-CoV-2. However, further trials, such as *in vitro* and *in vivo* evaluation, are needed to prove the validity of these findings.

Keywords: *Alpha-mangostin, COVID-19, Gamma-mangostin, Garcinia mangostana L., SARS-CoV-2.*

Introduction

Indonesia is covered by many vegetations, including tropical rain forests. In addition, Indonesia is one of the top five countries in the world that has high plant diversity, including approximately 6,000 medicinal plants[1,2,3,4,5]. Consequently, Indonesia is rich in medicinal plants used by its population in curing many diseases. On the other hand, there has been around 92 million people globally who have been infected by SARS-CoV-2 (the causative agent of COVID-19) and more than 2 million deaths as the fast result of this pandemic. In Indonesia, there are more than one million cases and more than 25,000 deaths. Data was retrieved from Johns Hopkins University online website that tracks COVID-19 cases in real-time[6].

Mangosteen or *Garcinia mangostana* L. is appertain to the family of Clusiaceae and genus *Garcinia*. *Garcinia* is a large genus which consists of around 400 species originated from East India and Southeast Asia, including Indonesia[7]. Pratiwi *et al*. stated that the mangosteen production centers in Java are Blitar, Purwakarta, Bogor, Banyuwangi, Subang, Ciamis, Sukabumi, Cilacap, Purworejo, and Banjarnegara[8]. Moreover, based on the morphological and cytological studies, it can be suggested that mangosteen originates from Southeast Asia. As a matter of fact, mangosteen is a plant that has been used as traditional medicine for hundreds of years worldwide[9].

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Mangosteen contains bioactive compounds such as xanthones, tannins, and some vitamins. In fact, mangosteen's pericarp has many important benefits for health. The main compounds in the content of mangosteen's pericarp are xanthones; such as alpha-mangostin, gamma-mangostin, beta-mangostin, and so on. The main xanthone derivative, such as alpha-mangostin and gamma-mangostin, have a variety of pharmacological activities such as antiviral activity[10,11,12].

Materials and Methods

Data retrieval

We extracted phytocomponents of mangosteen from PubChem, an open chemistry database at the National Institutes of Health (NIH), USA. We revealed the Canonical SMILES of alpha-mangostin and gamma-mangostin and submitted them to the SwissADME web server for further analysis.

Table 1. Alpha-mangostin and gamma-mangostin revealed from the PubChem database.

Compounds	Formula	Molecular Weight	IUPAC Name	Canonical SMILES
Alpha-mangostin	C24H26O6	410.46 g/mol	1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-enyl)xanthen-9-one	CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C(=C(C(=C3)O)OC)CC=C(C)C)O)C
Gamma-mangostin	C23H24O6	396.43 g/mol	1,3,6,7-tetrahydroxy-2,8-bis(3-methylbut-2-enyl) xanthen-9-one	CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C(=C(C(=C3)O)O)CC=C(C)C)O)C

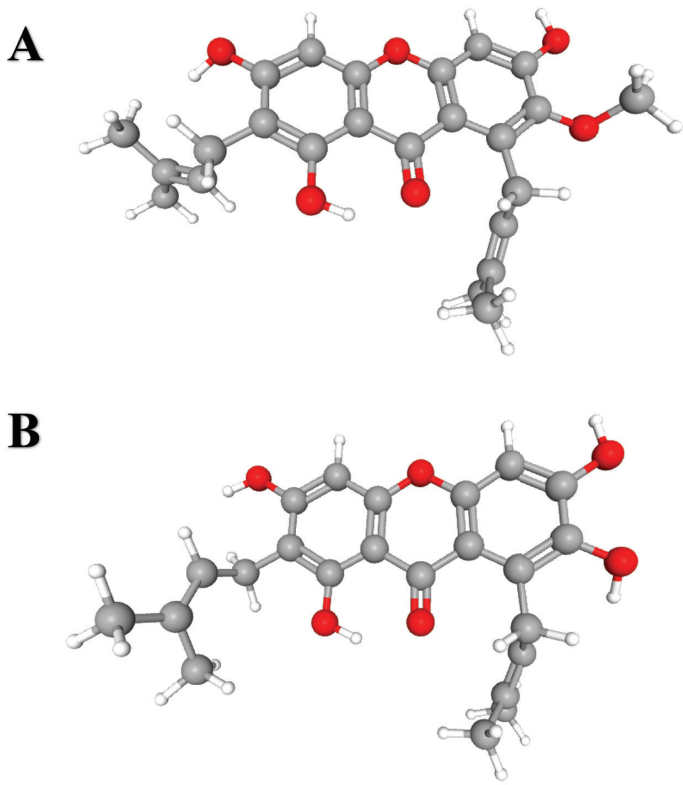

Figure 1. Chemical structures of alpha-mangostin (A) and gamma-mangostin (B) isolated from mangosteen.

Pharmacokinetics and drug-likeness predictions

In the present study, we predicted the pharmacokinetic properties and druglike nature of the phytocomponents using the SwissADME web server and identified gastrointestinal absorption prediction for oral drug probability[13] and Lipinski parameter for the drug-likeness prediction based on Lipinski *et al*.[14]

Biological activity prediction

We performed PASS (Prediction of Activity Spectra for Substances) web resource as a strong potential tool to predict the biological activity. This web resource estimates the predicted activity spectrum of a compound as probable activity (Pa)[13].

Results and Discussion

We successfully revealed pharmacokinetics, drug-likeness, biological activity predictions of alpha-mangostin and gamma-mangostin from mangosteen as presented in Table 2 and Figure 2. In addition, phytochemical screening, based on ethnomedicinal data, is considered as an effective approach for the discovery of new therapeutic agents. The major bioactive secondary metabolites of mangosteen are xanthone derivatives. The major constituents from the xanthone fraction in mangosteen were found to be alpha-mangostin and gamma-mangostin. More than 60 other xanthones were isolated from its different plant parts, including 3-isomangostin, β-mangostin, gartanin, mangostanin, 1-isomangostin, garcinone B, 9-hydroxycalabaxanthone, mangostanol, mangostinone demethylcalabaxanthone, 8-deoxygartanin, and garcinone D[1,10]. The majority of investigations are focused on the extraction and structure elucidation of xanthones from the pericarp of mangosteen. Recently, the presence of these compounds in the stem, seed, and heartwood was reported by many researchers[2,15].

Table 2. Pharmacokinetics, drug-likeness, biological activity predictions of alpha-mangostin and gamma-mangostin.

Compound	Pharmacokinetics Prediction (Gastrointestinal Absorption)	Drug-likeness Prediction (Lipinski)	Antiviral Activity Prediction
Alpha-mangostin	High	Yes	Herpesvirus (0.423) and rhinovirus (0.390)
Gamma-mangostin	High	Yes	Herpesvirus (0.453), rhinovirus (0.393), picornavirus (0.311), influenza (0.267), cytomegalovirus or CMV (0.244), hepatitis B (0.235), poxvirus (0.231), and HIV (0.191)

Mangosteen is an important medicinal plant in traditional medication system. Studies of mangosteen's pharmacological properties has started since the 1990's. Mangosteen is an important medicinal plant in the family of Clusiaceae. In the recent history, this plant is reported for its various medicinal properties. In Asia, the pericarp of mangosteen is used as antimicrobial, antiparasitic agents, and for wound healing. The pericarp decoction of mangosteen is administered to relieve gonorrhea and diarrhea.

Mangosteen stem bark and leaves are recognized to have anti-inflammatory properties for many skin disorders. In the Philippines, leaves and bark is adopted as a medication for diarrhea and various urinary problems. In Thai traditional medicine, the pericarp is used as the medication of skin infections and wounds. In addition, mangosteen root stew is used by women to treat menstrual disorders. Moreover, mangosteen has also been used for medical purposes in Caribbean and Latin America, for example as a digestive aid in Brazil[16]. Traditional medicinal properties of mangosteen are employed for hemorrhoids, tuberculosis, mycosis, fever, abdominal pain, leucorrhoea, and convulsants[10].

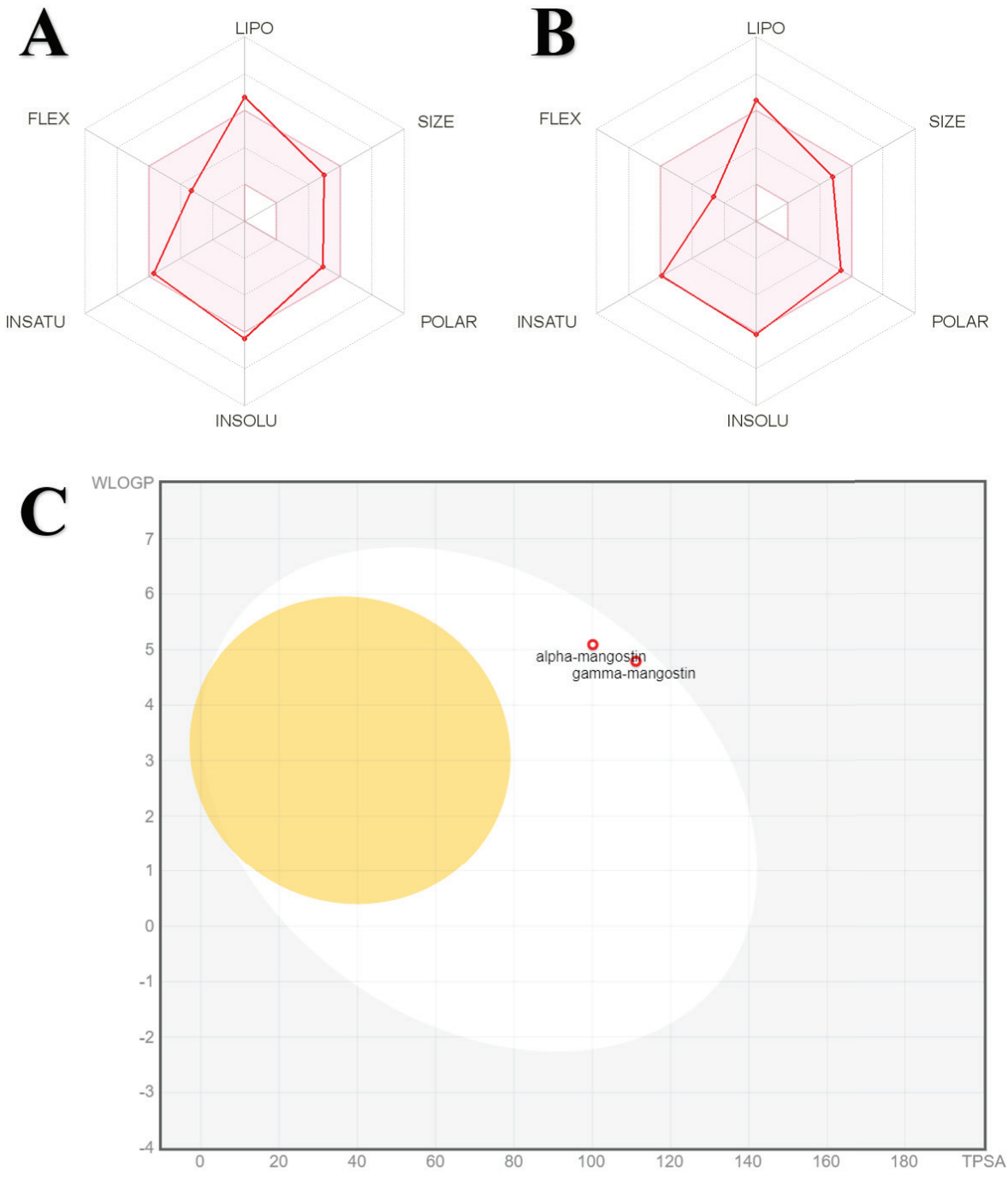

Figure 2. Radar-like representation of the drug-likeness of alpha-mangostin (A) and gamma-mangostin (B) predicted by SwissADME web server. BOILED-Egg plot to globally estimate their gastrointestinal absorption and brain penetration, two major ADME behaviors impacting pharmacokinetics (C).

In addition, alpha-mangostin and gamma-mangostin from mangosteen inhibited HIV-1 with IC_{50} values of 5.1 and 4.8 μM, respectively[17]. Vlietinck *et al*. discovered the role of α-mangostin as a non-competitive inhibitor of HIV-1 protease by inhibiting the HIV virus replication cycle[18]. Patil *et al*. performed *in vitro* and *in vivo* studies, and revealed that α-mangostin, a xanthonoid from *Garcinia mangostana*, is a promising natural antiviral compound against chikungunya virus[19]. Moreover, a study by Tarasuk *et al*. stated that alpha-mangostin inhibits both dengue virus production and cytokine/chemokine expression[20]. In line with this, Sugiyanto *et al*. and Yongpitakwattana *et al*. demonstrated the inhibitory effect of alpha-mangostin to dengue virus replication and cytokines expression in human peripheral blood mononuclear cells and dendritic cells. In addition, gamma-mangostin reported to inhibit hepatitis C virus and SARS-CoV-2[21,22].

Bioinformatics provide more efficient target discovery and validation approaches, thus helps ensure that more drug candidates are successful during the approval process, making it more cost-effective[23]. Notably, the work of Lipinski *et al*. analyzed orally active constituents to describe physicochemical ranges for high probability opportunities as an oral drug. This called Rule-of-five delineated the relationship between pharmacokinetics and physicochemical parameters. Lipinski's rule of 5 helps in distinguishing drug-like and non-drug like molecules. It predicts a high probability of success or failure due to drug-likeness for molecules complying with 2 or more of the following rules, such as molecular mass less than 500 Dalton, high lipophilicity, less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors, molar refractivity should be between 40-130[14].

In the present study, an attempt was made to investigate a more extensive pharmacological appearance of phytoconstituents by the application of PASS web resources. The proposed *in silico* method extends further to generate novel bioactivities of selected phytochemical leads, related side-effects, and their mechanisms. In addition, the recent version of PASS predicts approximately 3750 pharmacological activities, specific toxicities, biochemical mechanisms of action, and metabolic terms on the basis of the structural formula of drug-like substances with average fidelity ~95%[24]. This might be further validated through *in vitro* as well as *in vivo* trials. In line with this, the present study revealed the use of PASS in exploring hidden pharmacological potential of alpha-mangostin and gamma-mangostin as an antiviral (Figure 3).

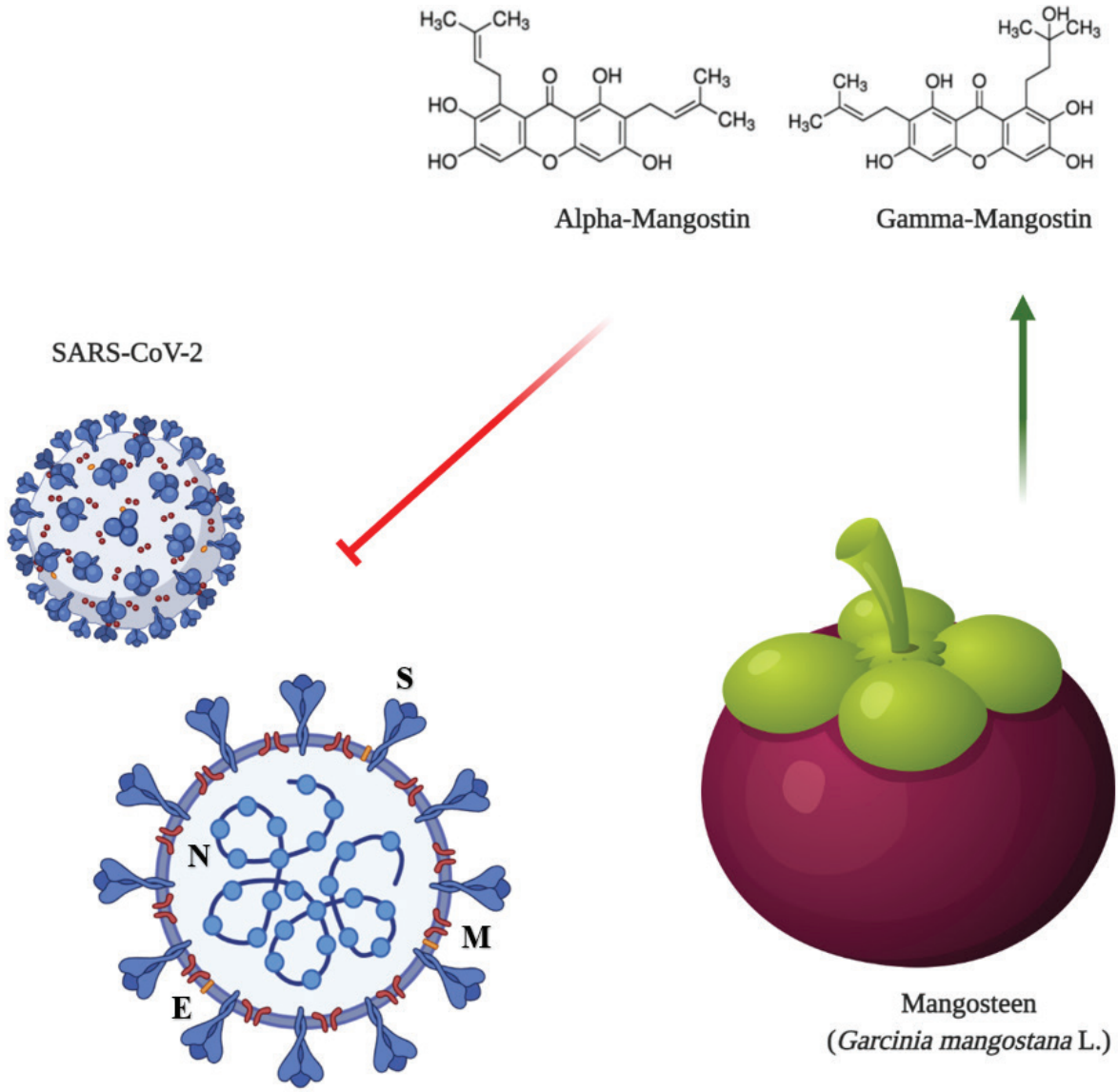

Figure 3. Alpha-mangostin and gamma-mangostin isolated from mangosteen as a promising candidate against SARS-CoV-2. E: Envelope protein, M: Membrane protein, N: Nucleocapsid phosphoprotein, and S: Spike protein. This figure created in BioRender.

Conclusion

In summary, this study showed the potential pharmacological benefits of alpha-mangostin and gamma-mangostin isolated from mangosteen against SARS-CoV-2. Thus, mangosteen exhibits as a valuable plant and establishes as a candidate for future drug development to fight SARS-CoV-2. However, further trials, such as *in vitro* and *in vivo* evaluation, are needed to prove the validity of these findings.

Conflict of Interest : The authors declare that they have no conflict of interest.

Source of Funding : This study supported by the Ministry of Education, Culture, Research and Technology of the Republic of Indonesia.

Acknowledgements: We thank Rr. Putri Amaristya Purwono for editing the manuscript. The author would like to declare my sympathy to the victims of COVID-19. Tribute goes to the frontliners

worldwide, especially in Indonesia. Additionally, Arif Nur Muhammad Ansori would specifically like to highlight the ongoing and unwavering support of Yulanda Antonius.

Ethical Approval: No ethical approval needed.

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