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FULL PAPER

A spotlight on gamma-mangostin: exploring its potential as antiviral agents

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The global health landscape has seen an upsurge in viral diseases, underlining the urgency for novel antiviral therapies. This mini-review illuminates the potential antiviral capabilities of gamma-mangostin, a xanthone derivative derived from the pericarp of the *Garcinia mangostana* fruit. Gamma-mangostin's mechanisms of action are multifaceted, displaying inhibitory effects on viral entry into host cells, disrupting essential cell signalling pathways for viral replication, and enhancing the host's immune response via antiviral cytokine stimulation. This compound has demonstrated significant *in vitro* efficacy against numerous viruses, including Influenza A virus, Herpes simplex virus, and Hepatitis C virus, and emerging preliminary research suggests potential utility against SARS-CoV-2. Its broad-spectrum antiviral properties and low cytotoxicity earmark gamma-mangostin as a promising candidate for future antiviral agent development. However, rigorous investigation is required to determine its pharmacokinetics, bioavailability, and safety profile. With the escalating burden of viral diseases, gamma-mangostin could represent an important tool in the armamentarium for disease management, contingent upon further study. This review provides an overview of current research into gamma-mangostin's antiviral potential and the challenges to its therapeutic development.

KEYWORDS

Gamma-mangostin; Garcinia mangostana; antiviral; virus.

Introduction

The escalating incidence of viral diseases worldwide underscores the urgency of developing potent and effective antiviral agents. Conventional synthetic antiviral drugs often face limitations such as resistance development, restricted antiviral spectrum, and harmful side effects. Thus, the exploration for novel therapeutics with broad-spectrum antiviral activities and minimal adverse effects remains a critical research avenue [1-3].

Naturally derived compounds have demonstrated remarkable potential as antiviral agents, leveraging millennia of evolutionary interactions between plants, their pathogens, and their environment. These compounds, inherent in the complex matrices of botanicals, represent an untapped wealth of chemical diversity that could potentially be harnessed for therapeutic application against a wide array of viral diseases [2,3].

Among these natural compounds, the xanthone derivative gamma-mangostin, found in the pericarp of the mangosteen (*Garcinia mangostana*) fruit, has gained particular attention. This Southeast Asian native fruit, often referred to as the "Queen of Fruits," has been widely used in traditional medicine due to its numerous health-promoting properties, including anti-inflammatory, antibacterial, antioxidant, and anticancer activities [4-6].

Recent scientific studies have started to shed light on the potential antiviral properties of gamma-mangostin. This bioactive compound has shown remarkable antiviral activities against several viral species, demonstrating its capability to interfere with viral attachment, penetration, replication, and even stimulate the host's immune response [1,2]. These findings suggest that gamma-mangostin could play a critical role in the on-going battle against viral diseases. Its potential to inhibit the life cycle of various viruses in multiple stages, along with its immune-modulating effects, make it a promising candidate for further research and development as an antiviral agent [3-5]. However, despite the promising *in vitro* results, comprehensive understanding of gamma-mangostin's pharmacokinetics, bioavailability, and safety profile is still in its nascent stages. The translatability of the *in vitro* efficacy to *in vivo* models and subsequently to clinical application requires rigorous, detailed investigation [6,7].

This mini-review aims to summarize and discuss the current knowledge on gamma-mangostin's antiviral properties, its mechanisms of action, efficacy against various types of viruses, and the challenges and future prospects in its development as a potential antiviral agent. It is hoped that such a review could provide new insights and encourage further research on this promising natural compound in the quest for new antiviral therapies.

Antiviral mechanisms of gamma-mangostin

Gamma-mangostin, a naturally occurring xanthone derivative, has demonstrated intriguing antiviral potential across several studies. In the growing quest for antiviral therapeutics, understanding the mechanisms by which gamma-mangostin exercises its antiviral action is critical [8-10].

The initial barrier to viral infection is the viral entry into host cells, a process involving attachment and fusion with the host cell membrane. A key mechanism of action for gamma-mangostin appears to be at this early stage. Gamma-mangostin, by binding to viral surface proteins, can inhibit the attachment and subsequent fusion of the virus with the host cells. This effectively reduces the number of viruses able to gain entry into host cells, thus limiting the spread of the virus [11,12].

Beyond impeding viral entry, gamma-mangostin has also demonstrated potential in disrupting the replication cycle of viruses (Figure 1). Many viruses, once inside a host cell, hijack cellular mechanisms to reproduce. Gamma-mangostin has shown promise in

disrupting these processes, preventing the successful replication of the viral genome and the assembly of new viral particles. This curtails the life cycle of the virus, thereby inhibiting its proliferation [13,14].

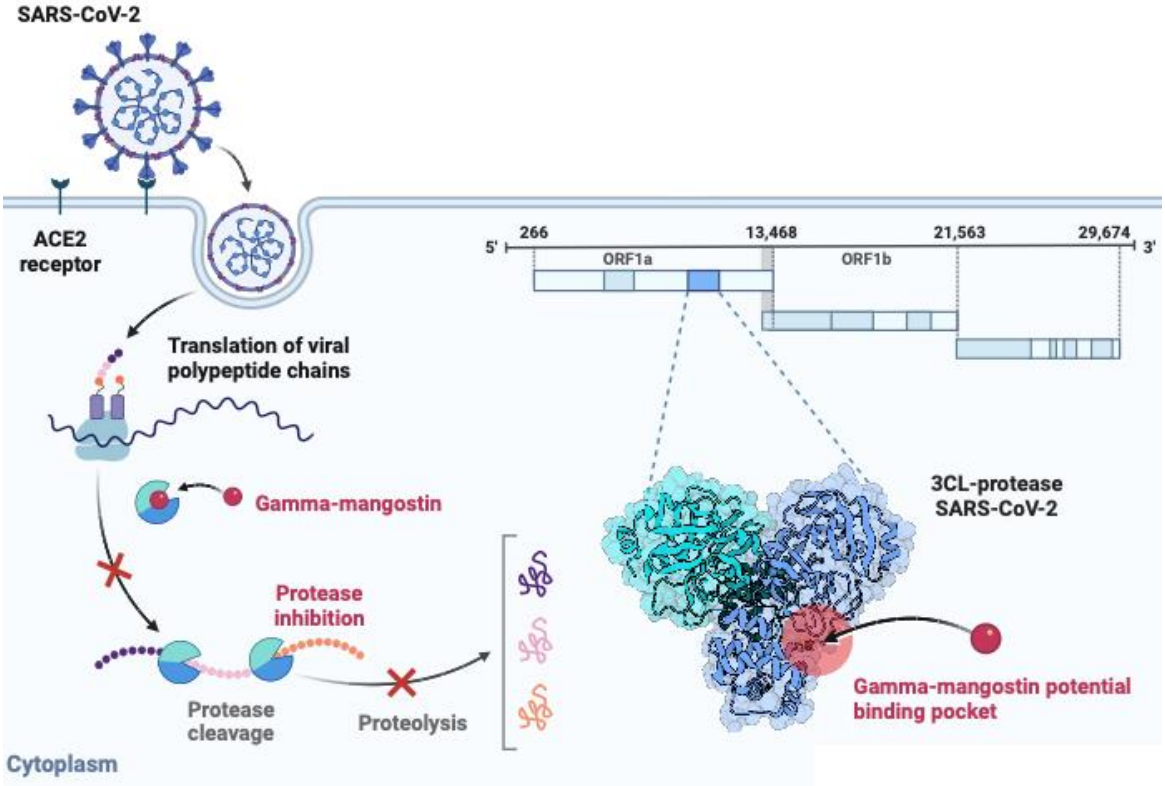

FIGURE 1 Gamma-mangostin demonstrated potential in disrupting the replication cycle of viruses (SARS-CoV-2)

Additionally, gamma-mangostin is believed to modulate cell signalling pathways that are crucial to viral replication. It may inhibit the activation of key proteins in these pathways, thus effectively impairing the virus's ability to reproduce within the host cell. This represents another avenue by which the compound exerts its antiviral effect [15,16].

An important facet of the antiviral response is the role of the immune system in recognizing and eliminating the virus. Gamma-mangostin may also enhance the host's antiviral immune response. It is thought to stimulate the production of antiviral cytokines, proteins that mediate and regulate immune responses. These cytokines can enhance the body's defence against the virus, further aiding in the control of viral infections [13-15].

Though the aforementioned mechanisms paint a promising picture of gamma-mangostin's antiviral potential, it is important to note that these mechanisms are often based on *in vitro* studies. The *in vivo* antiviral activity of gamma-mangostin, particularly its impact on viral infection and progression in a living organism, warrants further research [16,17].

In conclusion, gamma-mangostin holds promise as a potent antiviral agent, showing multifaceted mechanisms of action against various viral species. These mechanisms offer the prospect of gamma-mangostin being a broad-spectrum antiviral agent with efficacy against different viruses. However, additional studies are essential to further unravel the intricate mechanisms and validate these antiviral activities *in vivo* [18,19].

Efficacy against various viruses

The exploration for novel antiviral agents has led scientists to the pericarp of the mangosteen fruit, where gamma-mangostin resides. This natural compound has shown significant promise against a range of viral pathogens, offering hope for broad-spectrum antiviral applications [20-22].

Investigations into the activity of gamma-mangostin against the Influenza A virus have yielded promising results. Influenza, an acute respiratory infection, affects millions of individuals globally each year. Gamma-mangostin's ability to inhibit the entry and replication stages of this virus provides a strong basis for its consideration as a potential treatment for Influenza [23-25].

Furthermore, studies examining the activity of gamma-mangostin against the Herpes simplex virus, a widespread virus causing oral and genital lesions have reported encouraging outcomes. By preventing the virus from entering host cells and disrupting its replication process, gamma-mangostin has shown potential as a viable treatment option for managing Herpes simplex infections [22,24].

Hepatitis C, a major cause of liver disease, poses a significant health challenge globally. Research conducted on the Hepatitis C virus has shown that gamma-mangostin may interfere with the replication cycle of this virus, demonstrating potential efficacy against this disease [20-22].

In addition, gamma-mangostin's potential extends to emerging viral threats. Preliminary research suggests that it may hold potential against SARS-CoV-2, the causative agent of COVID-19. Though the studies are at a nascent stage, any potential for combating this global pandemic warrants significant interest [23,24].

Furthermore, gamma-mangostin's antiviral activity extends beyond human pathogens. Studies have indicated its efficacy against feline infectious peritonitis virus, a fatal viral disease in domestic cats. This also highlights the compound's potential in the field of veterinary medicine [25-27].

These findings suggest a broad-spectrum antiviral effect of gamma-mangostin, which is an exciting prospect. However, it is crucial to remember that much of the current research on gamma-mangostin's antiviral effects is conducted *in vitro* [25,26].

Translating *in vitro* antiviral activity to effective *in vivo* applications is a complex process. Factors such as bioavailability, metabolism, potential toxicity, and pharmacokinetics need to be considered, all of which require thorough investigation [27-29].

Moreover, for a better understanding of gamma-mangostin's potential as an antiviral agent, well-designed animal, and human studies are essential. The observations from such studies will help assess the real-world applicability of gamma-mangostin as an antiviral agent [30].

Gamma-mangostin, with its broad-spectrum antiviral activity, holds great promise in the fight against viral diseases. However, extensive research, including well-controlled *in vivo* studies and clinical trials, is needed to fully realize its potential.

Potential for future development

The journey of gamma-mangostin from the tropical forests of Southeast Asia to the realm of antiviral research is an intriguing one. Its potent antiviral activity against various viruses, as revealed by numerous *in vitro* studies, indeed marks gamma-mangostin as a promising candidate for future antiviral drug development [31-33].

However, the transition from *in vitro* success to clinical application is not without hurdles. One major challenge lies in the pharmacokinetic properties of gamma-mangostin. As a naturally occurring compound, its absorption, distribution, metabolism, and excretion in the human body require thorough investigation. Understanding these properties is vital in determining the effective dosage,

route of administration, and potential side effects of gamma-mangostin as an antiviral agent [34-36].

The bioavailability of gamma-mangostin is another area that needs extensive research. The efficacy of a drug does not only depend on its ability to fight a disease-causing agent, but it also should be able to reach the target site in the body in sufficient concentration. Researchers need to determine how well gamma-mangostin is absorbed and distributed in the body to exert its antiviral effects [37-39].

The potential toxicity of gamma-mangostin, particularly at the effective antiviral concentrations, is an important aspect that needs consideration. Any adverse effects associated with its use must be carefully assessed against its potential therapeutic benefits. Rigorous preclinical toxicity studies are essential before gamma-mangostin can progress to clinical trials [40].

While current research has provided valuable insights into the antiviral activity of gamma-mangostin, there is a considerable gap in our understanding of its mechanism of action. Detailed molecular studies are required to elucidate the precise targets and pathways gamma-mangostin affects in its fight against viruses. Understanding these mechanisms will be crucial for optimizing its antiviral potential and minimizing potential side effects [41-43].

Despite these challenges, the development of gamma-mangostin as an antiviral agent is promising. Its broad-spectrum antiviral activity, combined with its potential for modulating immune responses, places it as a potential cornerstone in the treatment of viral diseases [44,45].

Efforts should be also directed towards the sustainable sourcing and production of gamma-mangostin. As a compound derived from the pericarp of the mangosteen fruit, sustainable cultivation of the plant, and efficient extraction methods should be developed to ensure a reliable supply of this potential antiviral agent [46-48].

In the face of the on-going global health challenges posed by viral diseases, the development of effective antiviral agents has never been more critical. Gamma-mangostin, with its promising antiviral properties, stands as a beacon of hope in this endeavour [49-51].

With continued research and development, and a careful consideration of the challenges ahead, gamma-mangostin could well be on its way to becoming an important tool in our antiviral armamentarium. However, as with any potential therapeutic, it is crucial that we remain guided by the principles of rigorous scientific inquiry and unwavering commitment to patient safety and efficacy [50-53].

While the road to the clinical application of gamma-mangostin is indeed challenging and long, the potential reward - a novel, effective, and broad-spectrum antiviral agent - makes this journey worth undertaking.

Conclusion

As the world grapples with the pervasive threat of viral diseases, the search for novel and effective antiviral agents remains a crucial task. Gamma-mangostin, a xanthone derivative from the pericarp of *Garcinia mangostana*, has emerged as a promising candidate, demonstrating *in vitro* antiviral efficacy against a diverse array of viruses. Despite the current gaps in understanding its detailed mechanism of action, bioavailability, and potential toxicity *in vivo*, the prospect of developing this natural compound into a broad-spectrum antiviral agent is intriguing and holds immense potential. However, it is crucial that this path is tread with rigorous scientific research and a patient-centric approach, ensuring both the efficacy and safety of gamma-mangostin as a future therapeutic agent. The journey ahead is challenging, but with unwavering dedication to research and innovation, gamma-mangostin could indeed illuminate a new path in the global battle against viral diseases.

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Conflict of Interest

The authors have no conflict of interest.

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References

[1] (a) S. Suksamrarn, N. Suwannapoch, W. Phakhodee, J. Thanuhiranlert, P. Ratananukul, N. Chimnoi, A. Suksamrarn, Antimycobacterial activity of prenylated xanthones from the fruits of Garcinia mangostana, *Chem. Pharm. Bull.*, **2003**, *51*, 857-859. [Crossref], [Google Scholar], [Publisher] ,)b(A. Zarei, R. Amirkhani, M. Gholampour, H. Tavakoli, A. Ramazani, Natural compounds as strong SARS-CoV-2 main protease inhibitors: computer-based study, *J. Med. Pharm. Chem. Res.*, **2023**, *5*, 969-986. [Crossref], [Pdf], [Publisher] ,)c(M. Ahmeid, S. Essa, E.R. Jasim, Evaluating the level of vitamin D in Iraqi covid-19 patients and its association with biochemical parameters, *J. Med. Pharm. Chem. Res.*, **2023**, *5*, 126-135. [Pdf], [Publisher]) ,d (S. Rezaei, B. Naghipour, M. Rezaei, M. Dadashzadeh, S. Sadeghi, Chemical evaluation of gastrointestinal, coronary and pulmonary complications in patients admitted to the intensive care unit, *J. Med. Pharm. Chem. Res.*, **2022**, *4*, 557-566. [Crossref], [Pdf], [Google Scholar], [Publisher] ,)e(M.A.H. Roni, M.G. Mortuza, Rozina, ,., R.K. Shaha, S. Hoque, A. Kumer, Identification of SARS-CoV-2 inhibitors from alkaloids using molecular modeling and in silico approaches, *J. Med. Nanomater. Chem.*, **2023**, *In Press*, 252-266. [Crossref], [Pdf], [Publisher] ,)f(V.R. Lakshmidevi, D. Reeja, A.R. Rajan, B. Vinod, Advanced spectrum of imidazole derivatives in therapeutics: a review, *J. Chem. Rev.*, **2023**; *5*, 241-262. [Crossref], [Pdf], [Publisher] ,)g(E. Edache, H. Dawi, F. Ugbe, 3D-QSAR, molecular docking, molecular dynamics simulations and structural studies of some selected inhibitors of the glycoprotein (GPC) of lassa virus, *J. Appl. Organomet. Chem.*, **2023**, 3, 224-244. [Crossref], [Pdf], [Google Scholar], [Publisher]

[2] P. Moongkarndi, N. Kosem, O. Luanratana, S. Jongsomboonkusol, N. Pongpan, B. Sudatis, Antiproliferation, antioxidation and induction of apoptosis by *Garcinia mangostana* (mangosteen) on SKBR3 human breast cancer cell line, *J. Ethnopharmacol.*, **2004**, *90*, 161-166. [Crossref], [Google Scholar], [Publisher]

[3] V.T. Nguyen, T. Tran, T. Van Vo, Antiviral activity of garcinol and its derivatives against

influenza A virus *in vitro* and *in vivo*, *Bioorg. Med. Chem. Lett.*, **2012**, 22, 3919-3923. [Crossref], [Google Scholar], [Publisher]

[4] S. Ben-Shabat, L. Yarmolinsky, D. Porat, A. Dahan, Antiviral effect of phytochemicals from medicinal plants: Applications and drug delivery strategies, *Drug Deliv. Transl. Res.*, **2020**, *10*, 354–367 [Crossref], [Google Scholar], [Publisher]

[5] S. Tewtrakul, C. Wattanapiromsakul, W. Mahabusarakam, Effects of compounds from *Garcinia mangostana* on inflammatory mediators in RAW264.7 macrophage cells, *J. Ethnopharmacol.*, **2009**, *121*, 379-382 [Crossref], [Google Scholar], [Publisher]

[6] S.Y. Tsai, P.C. Chung, E.E. Owaga, I.J. Tsai, P.Y. Wang, J.I. Tsai, T.S. Yeh, R.H. Hsieh, Alpha-mangostin from mangosteen (*Garcinia mangostana* Linn.) pericarp extract reduces high fat-diet induced hepatic steatosis in rats by regulating mitochondria function and apoptosis, *Nutr. Metab.*, **2016**, *13*, 1-10 [Crossref], [Google Scholar], [Publisher]

[7] L.G. Chen, L.L. Yang, C.C. Wang, Anti-inflammatory activity of mangostins from Garcinia mangostana. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*, **2008**, *46*, 688–693 [Crossref], [Google Scholar], [Publisher]

[8] M. Karim, W. Lo C, S. Einav, Preparing for the next viral threat with broad-spectrum antivirals, *J. Clin. Investig.*, **2023**, *133*, e170236. [Crossref], [Google Scholar], [Publisher]

[9] C. Xu, G. Sun, G. Yuan, α-Mangostin suppresses the viability and epithelial-mesenchymal transition of pancreatic cancer cells by downregulating the PI3K/Akt pathway, *Biomed. Res. Int.* **2020**, *2020*, 2726931. [Crossref], [Google Scholar], [Publisher]

[10] X. Zhu, J. Li, H. Ning, , Z. Yuan, Y. Zhong, S. Wu, J.Z .Zeng, α-Mangostin induces apoptosis and inhibits metastasis of breast cancer cells via regulating RXRα-AKT signaling pathway, *Front. Pharmacol.*, **2021**, *12*, 739658. [Crossref], [Google Scholar], [Publisher]

[11] V. Minervini, C.P. France, Effects of opioid/cannabinoid mixtures on impulsivity and memory in rhesus monkeys, *Behav. Pharmacol.*, **2020**, *31*, 233–248. [Crossref], [Google Scholar], [Publisher]

[12] R. Watanapokasin, F. Jarinthanan, Y. Nakamura, N. Sawasjirakij, A. Jaratrungtawee, S. Suksamrarn, Effects of α-mangostin on apoptosis induction of human colon cancer, *World J. Gastroenterol.*, **2011**, *17*, 2086–2095. [Crossref], [Google Scholar], [Publisher]

[13] X. Tu, C. Li, W. Sun, X. Tian, Q. Li, S. Wang, X. Ding, Z. Huang, Suppression of Cancer Cell Stemness and Drug Resistance via MYC Destabilization by Deubiquitinase USP45 Inhibition with a Natural Small Molecule, *Cancers*, **2023**, *15*, 930. [Crossref], [Google Scholar], [Publisher]

[14] D. Chatterjee, N. Vhora, A. Goswami, A. Hiray, A. Jain, A. S. Kate, In-silico and in-vitro hybrid approach to identify glucagon-like peptide-1 receptor agonists from anti-diabetic natural products, *Nat. Prod. Res.*, **2023**, *37*, 1651–1655. [Crossref], [Google Scholar], [Publisher]

[15] R. Li, B.S. Inbaraj, B.H. Chen, Quantification of xanthone and anthocyanin in mangosteen peel by UPLC-MS/MS and preparation of nanoemulsions for studying their inhibition effects on liver cancer cells, *Int. J. Mol. Sci.*, **2023**, *24*, 3934. [Crossref], [Google Scholar], [Publisher]

[16] S. Wang, Q. Zhang, M. Peng, J. Xu, Y. Guo, Design, synthesis, biological evaluation, and preliminary mechanistic study of a novel mitochondrial-targeted xanthone, *Molecules*, **2023**, *28*, 1016. [Crossref], [Google Scholar], [Publisher]

[17] E. Marchese, V. Orlandi, F. Turrini, I. Romeo, R. Boggia, S. Alcaro, G. Costa, In silico and in vitro study of antioxidant potential of urolithins. *Antioxidants*, **2023**, *12*, 697. [Crossref], [Google Scholar], [Publisher]

[18] A. Chouni, S. Paul, A comprehensive review of the phytochemical and pharmacological potential of an evergreen plant garcinia cowa. *Chem. Biodivers.*, **2023**, *20*,

e202200910. [Crossref], [Google Scholar], [Publisher]
[19] Y. Niu, Q. Li, C. Tu, N. Li, L. Gao, H. Lin, Z. Wang, Z. Zhou, L. Li, Hypouricemic Actions of the Pericarp of Mangosteen in Vitro and in Vivo, *J. Nat. Prod.*, **2023**, *86*, 24–33. [Crossref], [Google Scholar], [Publisher]
[20] A. Cruz-Gregorio, A. K. Aranda-Rivera, O. E. Aparicio-Trejo, O.N. Medina-Campos, E. Sciutto, G. Fragoso, J. Pedraza-Chaverri, α-Mangostin induces oxidative damage, mitochondrial dysfunction, and apoptosis in a triple-negative breast cancer model, *Phytotherapy Research: PTR*, **2023**, *37*, 3394–3407. [Crossref], [Google Scholar], [Publisher]
[21] R. Ahmadian, M. R. Heidari, B.M. Razavi, H. Hosseinzadeh, Alpha-mangostin protects PC12 cells against neurotoxicity induced by cadmium and arsenic, *Biol. Trace Elem. Res.*, **2023**, *201*, 4008–4021. [Crossref], [Google Scholar], [Publisher]
[22] Y.H. Lee, P.L. Hsieh, S.C. Chao, Y.W. Liao, C.M. Liu, C.C. Yu, α-Mangostin inhibits the activation of myofibroblasts via downregulation of linc-ROR-mediated TGFB1/smad signaling, *Nutrients*, **2023**, *15*, 1321. [Crossref], [Google Scholar], [Publisher]
[23] Y.J. Wu, S.S. Zhang, Q. Yin, M. Lei, Q.H. Wang, W.G. Chen, T.T. Luo, P. Zhou, C.L. Ji, α-Mangostin inhibited M1 polarization of macrophages/monocytes in antigen-induced arthritis mice by up-regulating silent information regulator 1 and peroxisome proliferators-activated receptor γ simultaneously, *Drug Des. Devel. Ther.*, **2023**, *17*, 563–577. [Crossref], [Google Scholar], [Publisher]
[24] B. Lawal, A.T. Wu, C.H.M. Chen, G.T.A.S. Y. Wu, Identification of INFG/STAT1/NOTCH3 as γ-Mangostin's potential targets for overcoming doxorubicin resistance and reducing cancer-associated fibroblasts in triple-negative breast cancer, *Biomed. Pharmacother.*, **2023**, *163*, 114800. [Crossref], [Google Scholar], [Publisher]
[25] T.T. Le, N.T. Trang, V.T.T. Pham, D.N. Quang, L.T. Phuong Hoa, Bioactivities of β-mangostin and its new glycoside derivatives synthesized by enzymatic reactions, *R. Soc. Open Sci.*, **2023**, *10*, 230676. [Crossref], [Google Scholar], [Publisher]
[26] M.T. Khayat, K.A. Mohammad, G.A. Mohamed, D.S. El-Agamy, W.M. Elsaed, S.R.M. Ibrahim, γ-Mangostin abrogates AINT-induced cholestatic liver injury: Impact on Nrf2/NF-κB/NLRP3/Caspase-1/IL-1β/GSDMD signaling, *Life Sci.*, **2023**, *322*, 121663. [Crossref], [Google Scholar], [Publisher]
[27] X. Li, M. Geng, Y. Peng, L. Meng, S. Lu, Molecular immune pathogenesis and diagnosis of COVID-19, *J. Pharm. Anal.*, **2020**, *10*, 102-108. [Crossref], [Google Scholar], [Publisher]
[28] Y. Cai, J. Zhang, T. Xiao, H. Peng, S.M. Sterling, R.M. Walsh Jr, S. Rawson, S. Rits-Volloch, B. Chen, Distinct conformational states of SARS-CoV-2 spike protein, *Science*, **2020**, *369*, 1586-1592. [Crossref], [Google Scholar], [Publisher]
[29] M.A. Marra, S.J. Jones, C.R. Astell, R.A. Holt, A. Brooks-Wilson, Y.S. Butterfield, J. Khattra, J.K. Asano, S.A. Barber, S.Y. Chan, A. Cloutier, The genome sequence of the SARS-associated coronavirus, *Science*, **2003**, *300*, 1399-1404. [Crossref], [Google Scholar], [Publisher]
[30] F. Wu, S. Zhao , B. Yu, Y.M. Chen, W. Wang, Z.G. Song, Y. Hu, Z.W. Tao, J.H. Tian, Y.Y. Pei, M.L. Yuan, A new coronavirus associated with human respiratory disease in China, *Nature,* **2020**, *579*, 265-269. [Crossref], [Google Scholar], [Publisher]
[31] A.N.M. Ansori, V.D. Kharisma, A.A. Parikesit, F.A. Dian, R.T. Probojati, M. Rebezov, P. Scherbakov, P. Burkov, G. Zhdanova, A. Mikhalev, Y. Antonius, N.I. Sumantri, T.H. Sucipto, R. Zainul, P.M.R. Fadhil, Bioactive compounds from mangosteen (Garcinia mangostana L.) as an antiviral agent via dual inhibitor mechanism against SARS-CoV-2: an in silico approach, *Pharmacogn. J.*, **2022**, *14*, 85-90. [Crossref], [Google Scholar], [Publisher]
[32] V.D. Kharisma, A.N.M. Ansori, Y. Antonius, I. Rosadi, A.A.A. Murtadlo, V.

Jakhmola, M. Rebezov, N. Maksimiuk, E. Kolesnik, P. Burkov, M. Derkho, P. Scherbakov, M.E. Ullah, T.H. Sucipto, H. Purnobasuki, Garcinoxanthones from Garcinia mangostana L. against SARS-CoV-2 infection and cytokine storm pathway inhibition: A viroinformatics study, *J. Pharm. Pharmacogn. Res.*, **2023**, *11*, 743-756. [Crossref], [Google Scholar], [Publisher]

[33] L. Zhang, D. Lin, X. Sun, U. Curth, C. Drosten, L. Sauerhering, S. Becker, K. Rox, R. Hilgenfeld, Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors, *Science*, **2020**, *368*, 409-412. [Crossref], [Google Scholar], [Publisher]

[34] W. Dai, B. Zhang, X.M. Jiang, H. Su, J. Li, Y. Zhao, X. Xie, Z. Jin, J. Peng, F. Liu, C. Li, Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease, *Science,* **2020**, *368*, 1331-1335. [Crossref], [Google Scholar], [Publisher]

[35] D. Wrapp, N. Wang, K.S. Corbett, J.A. Goldsmith, C.L. Hsieh, O. Abiona, B.S. Graham, J.S. McLellan, Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, *Science,* **2020**, *367*, 1260-1263. [Crossref], [Google Scholar], [Publisher]

[36] J. Shang, G. Ye, K. Shi, Y. Wan, C. Luo, H. Aihara, Q. Geng, A. Auerbach, F. Li, Structural basis of receptor recognition by SARS-CoV-2, *Nature*, **2020**, *581*, 221-224. [Crossref], [Google Scholar], [Publisher]

[37] R.J. Khan, R.K. Jha, G.M. Amera, M. Jain, E. Singh, A. Pathak, R.P. Singh, J. Muthukumaran, A.K. Singh, Targeting SARS-CoV-2: a systematic drug repurposing approach to identify promising inhibitors against 3C-like proteinase and 2′-O-ribose methyltransferase, *J. Biomol. Struct. Dyn.*, **2021**, *39*, 3203-3221. [Crossref], [Google Scholar], [Publisher]

[38] Y. Gao, L. Yan, Y. Huang, F. Liu, Y. Zhao, L. Cao, T. Wang, Q. Sun, Z. Ming, L. Zhang, J. Ge, Structure of the RNA-dependent RNA polymerase from COVID-19 virus, *Science*, **2020**, *368*, 779-782. [Crossref], [Google Scholar], [Publisher]

[39] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, *Cell researc.,* **2020**, *30*, 269-271. [Crossref], [Google Scholar], [Publisher]

[40] L.U. Setyawati, W. Nurhidayah, N.K. Khairul Ikram, W.E. Mohd Fuad, M. Muchtaridi, General toxicity studies of alpha mangostin from *Garcinia mangostana*: A systematic review, *Heliyon*, **2023**, *9*, e16045. [Crossref], [Google Scholar], [Publisher]

[41] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, M.A. Müller, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, *Cell,* **2020**, *181*, 271-280.e8. [Crossref], [Google Scholar], [Publisher]

[42] C. Kong, L. Jia, J. Jia, γ-mangostin attenuates amyloid-β42-induced neuroinflammation and oxidative stress in microglia-like BV2 cells via the mitogen-activated protein kinases signaling pathway, *Eur. J. Pharmacol.*, **2022**, *917*, 174744. [Crossref], [Google Scholar], [Publisher]

[43] Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, Y. Zhao, B. Zhang, X. Li, L. Zhang, C. Peng, Y. Duan, Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors, *Nature*, **2020**, *582*, 289-293. [Crossref], [Google Scholar], [Publisher]

[44] C. Ding, Z. Song, A. Shen, T. Chen, A. Zhang, Small molecules targeting the innate immune cGAS–STING–TBK1 signaling pathway. Acta pharmaceutica Sinica. B, **2020**, *10*, 2272–2298. [Crossref], [Google Scholar], [Publisher]

[45] A. Mullard, COVID-19 vaccine development pipeline gears up. *Lancet.*, **2020**, *395*, 1751-1752. [Crossref], [Google Scholar], [Publisher]

[46] J.Y. Baek, K. Jung, Y.M. Kim, H.Y. Kim, K.S. Kang, Y.W. Chin, Protective Effect of γ-mangostin Isolated from the Peel of Garcinia mangostana against Glutamate-Induced Cytotoxicity in HT22 Hippocampal Neuronal Cells, *Biomolecules*, **2021**, *11*, 170. [Crossref], [Google Scholar], [Publisher]

[47] T. Tang, M. Bidon, J.A. Jaimes, G.R. Whittaker, S. Daniel, Coronavirus membrane fusion mechanism offers a potential target for antiviral development, *Antiviral Res.*, **2020**, *178*, 104792. [Crossref], [Google Scholar], [Publisher]

[48] S.P. Chen, S.R. Lin, T.H. Chen, H.S. Ng, H.S. Yim, M.K. Leong, C.F. Weng, Mangosteen xanthone γ-mangostin exerts lowering blood glucose effect with potentiating insulin sensitivity through the mediation of AMPK/PPARγ. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, **2021**, *144*, 112333. [Crossref], [Google Scholar], [Publisher]

[49] S. Ozono, Y. Zhang, H. Ode, K. Sano, T.S. Tan, K. Imai, K. Miyoshi, S. Kishigami, T. Ueno, Y. Iwatani, T. Suzuki, SARS-CoV-2 D614G spike mutation increases entry efficiency with enhanced ACE2-binding affinity. *Nature communications*, **2021**, *12*, 848. [Crossref], [Google Scholar], [Publisher]

[50] T.Y. Pramana, B. Wasita, V. Widyaningsih, R. Cilmiaty, S. Suroto, A. Mudigdo, B. Purwanto,The ethanol extract of Garcinia mangostana L peel reduces the isoniazid-induced liver damage in rats, *Bali Medical Journal*, **2021**, *10*, 156–159. [Crossref], [Google Scholar], [Publisher]

[51] R.S. Indharty, I. Japardi, A.M. Siahaan, S. Tandean, Mangosteen extract reduce apoptosis via inhibition of oxidative process in rat model of traumatic brain injury, *Bali Medical Journal*, **2019**, *8*, 227–232. [Crossref], [Google Scholar], [Publisher]

[52] P.S. Hu, N.Y. Hsia, W.C. Chien, M.C. Mong, T.C. Hsia, H.M. Chang, Y.C. Wang, W.S. Chang, D.T. Bau, C.W. Tsai, Protective effects of gamma-mangostin on hydrogen peroxideinduced cytotoxicity in human retinal pigment epithelial cells, *In Vivo*, **2022**, *36*, 1676–1683. [Crossref], [Google Scholar], [Publisher]

[53] A.T. Wu, Y.C. Yeh, Y.J. Huang, N. Mokgautsi, B. Lawal, T.H. Huang, Gamma-mangostin isolated from garcinia mangostana suppresses colon carcinogenesis and stemness by downregulating the GSK3β/β-catenin/CDK6 cancer stem pathway, *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, **2022**, *95*, 153797. [Crossref], [Google Scholar], [Publisher]

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