α-MANGOSTIN/CLOVE OIL-INCORPORATED LAURIC ACID-BASED SOLVENT REMOVAL-INDUCED IN SITU FORMING MATRICES

Thawatchai Phaechamud[1], Prapansak Toungsuwan[2], and Jongjan Mahadlek[1,*]

Received: January 15, 2023; Revised: June 29, 2023; Accepted: July 06, 2023

Abstract

Typically, the bacteria in periodontal pocket of periodontitis disease are capable of producing a number of virulence factors, which are directly toxic to host tissues or immune cells, or indirectly damage host tissues via induction of inflammatory cytokines. The eradication of these microbes from periodontal pocket is one of crucial processes of periodontitis treatment. The α-mangostin from *Garcinia mangostana* Linn has the most potent antibacterial activity with less tendency to acquire resistance; therefore, it is interesting for using as active compound for periodontitis treatment. This study focuses on the development of in situ forming matrices (ISM) involving 50% w/w lauric acid, 5% w/w clove oil and different α-mangostin amount in NMP for periodontal drug delivery. Physicochemical properties of ISM were investigated including pH, density, viscosity, surface tension, in vitro matrix formation, and injectability. Antimicrobial activities of formulated ISM against three standard microbes were evaluated using agar cup diffusion methods. The pH and density of all α-mangostin and clove oil-loaded 50% w/w lauric acid matrices was 4.40±0.04 to 4.78±0.20 and 0.960±0.000 to 0.963±0.001 g/cm^3, respectively. The increasing α-mangostin amounts significantly increased the viscosity of prepared formulation and injection force. All formulations had low viscosity that it was easy to injection and spreadable in the periodontal pockets. After contact PBS pH 6.8, they transformed as matrix and the hydrophobic manner of clove oil retarded a solvent exchange. These prepared formulations showed the antimicrobial activities against *Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 25922, and *Candida albicans* ATCC 17011. Hence, they are the potential systems for periodontal drug delivery.

Keywords: **α-mangostin; clove oil; in situ forming matrices; lauric acid; solvent removal**

[1] *Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand. E-mail: Phaechamud_t@su.ac.th; Mahadlek_j@su.ac.th[*]*

[2] *Faculty of Education, Silpakorn University, Nakhon Pathom 73000, Thailand. E-mail: Toungsuwan_p@su.ac.th*

[*] *Corresponding author*

DOI: https://doi.org/10.55766/sujst-2023-05-e02594

Suranaree J. Sci. Technol. 30(5):030136(1-7)

Introduction

The solvent removal-induced in situ forming matrices (ISM) are the liquid preparations transforming into semisolid or solid matrices after injection and exposure to aqueous environment (Chantadee *et al*., 2020). Lauric acid (Figure 1(a)) is a hydrophobic fatty acid found in human body and that it has the desired properties such as hydrophobicity, biocompatibility and low toxicity (Shuai *et al*., 2020). Thus, it is appealing to the use as matrix former in this system. Lauric acid has been widely used in pharmaceutical field that could improve the physicochemical properties of pharmaceutical formulation such as enhancing the drug dissolution, permeability, absorption and controlling drug release (Chantadee *et al*., 2019a). N-methyl-2-pyrrolidone (NMP) (Figure 1(b)) is a polar organic solvent that utilized in Atridox® for treatment of periodontitis. It is a water miscible and has many advantages such as biodegradability, biocompatibility, thermal stability and low toxicity both orally and parenterally (Sanghvi *et al*., 2008).

Periodontitis is an infectious disease caused by Gram-negative anaerobic bacteria such as *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* (Sanghvi *et al*., 2008). Antimicrobial drugs have been used to reduce bacteria for periodontitis treatment such as tetracycline, doxycycline, metronidazole, etc. However, there are several disadvantages of using antimicrobial drugs, including allergy, diarrhea, nausea, and vomiting (Walker *et al*., 2004).

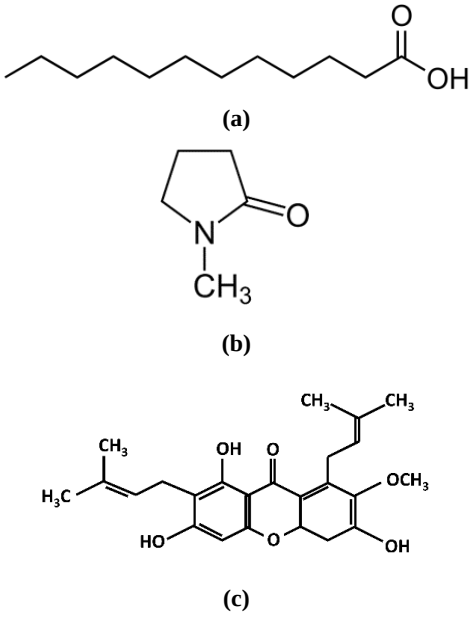

Figure 1. Structure of lauric acid (A), NMP (B) and α-mangostin (C)

Garcinia mangostana Linn. (mangosteen) is the gueen of fruits in Thailand. It has been used for treatment of diarrhea, abdominal pain, fever, skin irritation, anti-acne. The main compounds in the fruit are xanthones that possess several activities such as anti-oxidant, anti-bacterial, cytotoxicity, and anti-proliferative (Ovalle-Magallanes *et al*., 2017). α- Mangostin (Figure 1(c)) is one of the main prenylated xanthones in mangosteen that exhibits anti-oxidant activity, anti-inflammatory and anti-microbial activity and anti-cancer properties (Al-Massarani *et al*., 2013; Narasimhan *et al*., 2017). The α-mangostin could be used for periodontitis treatment because it reduces inflammatory cytokines (IL-6 and IL-8) in human gingival fibroblasts (HGFs) and protein in lipopolysaccharide (LPS) of *P. gingivalis* which is the important pathogen that plays an important role in mediating inflammation and stimulating production of pro-inflammatory cytokines by immune and inflammatory cells (Yiemwattana and Kaomongkolgit, 2015). The MIC and MBC for *P. gingivalis* were 20 and 40 μg/ml, respectively (Torrungruang *et al*., 2007). It has been reported that the 1,4-benzopyrone skeletal and isoprenyl side chains of α-mangostin show an important role in its antimicrobial activity (Phitaktim *et al*., 2016). α-Mangostin disrupted the cytoplasmic membranes of organisms leads to rapid onset of bactericidal activity (Sivaranjani *et al*., 2019). The xanthone scaffold of γ-mangostin exhibited potent anti-microbial activity against Gram-positive bacteria (Zou *et al*., 2013). Phenol groups on C3 and C6 of α-mangostin were critical to anti-proliferative activity and C4 modification was capable to improve both anti-cancer and drug like properties (Fei *et al*., 2014).

Clove oil has been applied in dentistry and presents antifungal and antibacterial properties (Nisar *et al*., 2019; Kheawfu *et al*., 2021). The clove oil could slowly exchange the solvent and prolong the doxycycline hyclate release from *in situ* Eudragit® RS matrices (Phaechamud *et al*., 2018).

From the numerous research about the anti-microbial activities of α-mangostin against *P.gingivalis* thus α-mangostin is a dramatic natural compound for utilizing as an adjunct to periodontitis treatment in the clove oil-loaded lauric-based solvent removal-induced ISM systems that the preparation and evaluation of solvent removal-induced ISM containing α-mangostin has not been

mentioned previously. This research will be novelty delivered α-mangostin to the periodontal pocket using ISM systems.

This study focuses on the development of α-mangostin and clove oil-loaded lauric acid-based solvent removal-induced ISM for periodontal delivering systems. The physicochemical properties of these systems were tested involving pH, viscosity, density, *in vitro* matrix formation, injectability, surface tension, and antimicrobial activities

Table 1. Formulation of the ISM comprising various amounts of α-mangostin

Formula	Amount (% w/w)			
	α-Mangostin	Lauric acid	Clove oil	NMP
50LN	-	50	-	50.0
1aM50L5CN	1.0	50	5	44.0
2.5aM50L5CN	2.5	50	5	42.5
5aM50L5CN	5.0	50	5	40.0
50LN	-	50	-	50.0

Materials and Methods

Luaric acid was sourced from Pacific Oleochemicals Sdn Bhd, Malaysia. Clove oil was purchased from CT Chemical Ltd. (Bangkok, Thailand). NMP was obtained from Fluka, Switzerland. α-Mangostin was recieved from Sanyuan Longsheng Biological Technology Co., Ltd. (Shaanxi, China).

Preparation of ISM

The ISM systems were formulated and the composition formula are summarized in Table 1. The 50% w/w lauric acid (L) was dissolved in N-methyl-2-pyrrolidone (N). The clove oil (C) (5% w/w) and α-mangostin (aM) at 1, 2.5, and 5% w/w were added in L solution and stirred until the solutions were clear.

Evaluation of physicochemical properties

pH, density, and viscosity

The pH values of the formulations were measured using a pH meter (Mettler Toledo, USA). The density was measured by using a pycnometer. Brookfield DV-III Ultra Programmable Rheometer (Middleboro, USA) with spindle CP-40 was employed at 25°C and 250 s^{-1} to evaluate viscosity of the formulations. All measurements were performed in triplicate.

Surface tension

The wetting behaviour of formulations was measured using a pendant drop method (First Ten Angstroms, USA) at a rate pump out of 2.6 µL/sec (n=3).

Injectability test

This intrapocket drug delivery aims to inject the developed formulation for periodontitis treatment; therefore, the measurement for the ability to expel the dosage form through a needle is necessary. Therefore, the injectability of fabricated ISM formulations was undertaken using a texture analyzer in a compression mode (TA.XT Plus, Stable Micro Systems, Godalming, UK) by adding the formulation into 1-mL polypropylene syringes coupled with 27-gauge needles. The finished prepared syringe was clamped to a stainless-steel stand. Then the upper probe of the machine was moved downward at a constant speed of 1.0-mms^{-1}, and a force of 0.1 N was applied to compress to the syringe barrel base. The area under resulting curve was measured as work of injection (N.mm). The triplicate test was conducted for each sample.

In vitro matrix formation behavior

Phase separation and changes in turbidity were investigated through visual inspection of the systems while injecting into buffer solution. The matrix formation was observed macroscopically by injection prepared formulations through PBS pH 6.8 (5-mL) in the glass test tube and the formulation was put into the syringe equipped with a 18-G needle. The prepared formulation was injected and then photographed at various times (0, 1, and 5 min).

Antimicrobial activity studies

The antimicrobial activities of the formulations against Gram positive bacteria such as *Staphylococcus aureus* ATCC 6538, Gram negative bacteria such as *Escherichia coli* ATCC 25922, and fungi such as *Candida albicans* ATCC 17011 were investigated. The microbial cultures were adjusted to a final concentration of 1.0×10^8 CFU/mL and swabbed on agar plates. The sterilized cylinder cups were gently placed on the surface of the swabbed media agar. The prepared ISMs were filled into these cylinder cups (8 mm diameter and 10 mm height) and subsequently incubated at 37°C for 48 hours. Finally, their antimicrobial activities were measured using the standard ruler and indicated as the diameter (mm) of the inhibition zone (n=3).

Statistical analysis

Statistical analysis was determined by one-way analysis of variance (ANOVA). The multiple comparisons were subjected to a post hoc test ($p<0.05$).

Results and Discussion

pH, density, viscosity, and surface tension

The pH, density, and viscosity of the 50% w/w lauric acid-based ISM comprising 5% w/w clove oil and different α-mangostin amounts are shown in Figure 2. The pH of all α-mangostin and clove oil loaded lauric acid ISM was 4.40±0.04 to 4.78±0.20 (Figure 2(a)). The increasing α-mangostin amounts did not significantly affect pH values of the prepared formulations ($p<0.05$). The NMP showed the high pH value of 11.28±0.23. The density of NMP was 1.03 g/cm^3. The lower density of all formula was evident as 0.960±0.000 to 0.963±0.001 g/cm^3 (Figure 2(b)) since lauric acid had a low density of 0.82±0.08 g/cm^3 (Kahwaji *et al*., 2017). In addition, the viscosity of all formula was low in a range of 12.29±0.36 to 14.83±0.23 cPs. (Figure 2(c)). The increasing of α-mangostin amounts significantly increased the viscosity of prepared formulation ($p<0.05$) because of the lower solvent amount in prepared formulation. All formulations had low viscosity indicating their easiness for injection and spreadability in the periodontal pockets. The prepared formulation should have a suitable viscosity to remain in the site of the periodontal pocket (Mei *et al*., 2017). Viscosity affected the properties of formulations such as the manners of solvent removal and rate of diffusion due to its resistance to diffusion (Phaechamud and Setthajindalert, 2018). Furthermore, the surface tension of formula was in the range of 34.44±0.49 to 35.20±0.59 mN/m (Figure 2(d)). The increasing of α-mangostin amounts did not significantly affect the surface tension ($p>0.05$). However, it was reported that α-mangostin interrupted the coadhesive force of solvent (Li *et al*., 2009) Injectability.

The low injection force was used to expel all formulations (1.36±0.15 to 1.80±0.06 N) (Figure 3(a)), or the low work of compression in the range of 18.10±0.85 to 24.03±0.29 (Figure 3(b)). The injection force and the work of compression without sample was 1.32±0.07 N and 3.71±0.14 J, respectively. The injection force and work of compression of the formula increased with an increased amount of α-mangostin ($p<0.05$). The criteria of injection force values for the ease to apply to periodontal pocket was lower than 50 N (Rungseevijitprapa and Bodmeier, 2009). Form the above data, it showed that all formulations were easily injected with slight force through the 27-G needle. Phase transition behaviour

The sol state of the 50% w/w lauric acid-based ISM comprising 5% w/w clove oil and different

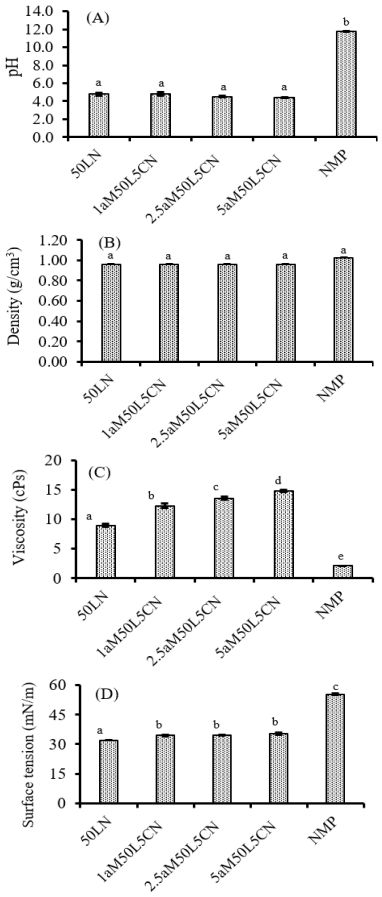

Figure 2. pH (a), density (b) and viscosity (c) and surface tension (d) of ISM (n=3). The values followed by different letters (a<b<c<d<e) in each response signify the significant difference ($p<0.05$)

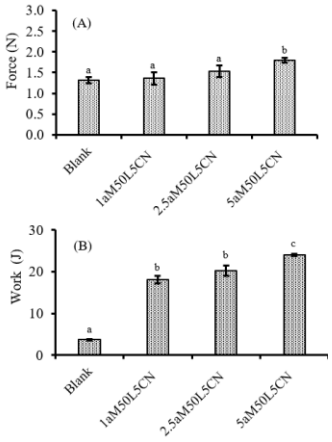

Figure 3. Injectability of ISM (n=3); (a) force, and (b) work. The values followed by different letters (a<b<c) in each response indicate the significant difference ($p<0.05$)

α-mangostin amounts in NMP was transformed to the opaque solid like state when swapped with PBS pH 6.8 as shown in Figure 4. It has been reported that the 35% w/w lauric acid in NMP could not be formed as matrix after contact to PBS pH 6.8 (Senarat *et al*., 2019). The matrix formation of 50% w/w lauric acid in NMP was slowly after contact with water phase (Chantadee *et al*., 2019b). The high polarity of drug induced the more exchange between drug molecule in systems with medium (Thakur *et al*., 2014). The schematic diagram of solvent exchange of α-mangostin-fatty acid-based ISM is shown in Figure 5. The α-mangostin/clove oil-incorporated lauric acid-based solvent removal-induced in situ forming matrices including α-mangostin, clove oil, lauric acid and NMP was liquid formulation. Lauric acid could not dissolve in water but dissolve in organic solvent (NMP). When the α-mangostin/clove oil-incorporated lauric acid-based in NMP was contacted with phosphate buffer solution pH 6.8, the solvent removal was occurred. NMP was removed and exchanged with phosphate buffer solution pH 6.8. The lauric acid matrix was formed to opaque solid like state and α-mangostin dissolved in NMP was carried out the ISM system. Therefore, this formed opaque solid like state could be a retarded matrix of α-mangostin.

Antimicrobial activities

The formula demonstrated antimicrobial activities against *S. aureus* ATCC 6538, *E. coli* ATCC 25922, and *C. albicans* ATCC 17011 as shown in Figure 6. The addition of 5% w/w clove oil in the 50% w/w lauric acid-based ISM did not significantly altered antimicrobial activities of prepared formulation against all microbes ($p>0.05$). The antimicrobial activities of the α-mangosteen-loaded lauric acid-based ISM comprising 5% w/w clove oil against *S. aureus* ATCC 6538, and *C. albicans* ATCC 17011 was not significantly changed when increasing α-mangostin amounts from 1%w/w to 5% w/w ($p>0.05$) whereas the antimicrobial activities of the prepared formula against *E.coli* ATCC 25922 was significantly decreased when the α-mangostin amounts was increased from 1% w/w to 5% w/w ($p<0.05$). The clear zone of the prepared formulation was decreased since the solvent exchange was retarded via the lauric-clove oil matrix. The α-mangostin has been shown to possess antibacterial activity, especially against Gram-positive bacteria (Ghasemzadeh *et al*., 2018). Several research have been demonstrated the antibacterial, antifungal and antiviral activities of α-mangostin (Ibrahim *et al*., 2014). The α-mangostin did not improve the antimicrobial activities of formulation because the matrix formation could retard α- mangostin release. NMP had the highest antimicrobial activities against *C. albicans* ATCC 17011. It has been reported that NMP improved the permeability of cell membranes. NMP molecule can bring the drug molecule into the presence of a polar aqueous environment resulting in an increase in drug solubility (Sanghvi *et al*., 2008). The clove oil slowed the solvent exchange and prolonged the doxycycline hyclate release from in situ Eudragit® RS matrices (Phaechamud *et al*., 2018). Hence, it described that the α-mangostin inhibited microbes, while NMP enhanced cell permeability and clove oil retarded solvent exchange.

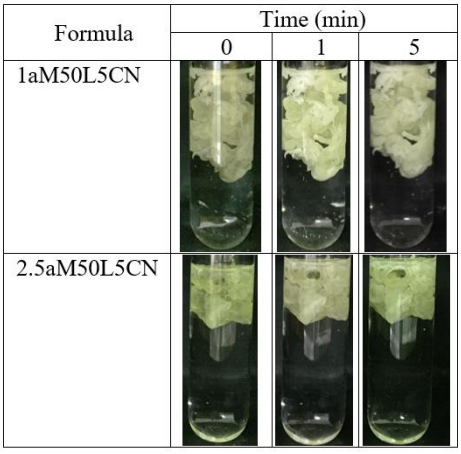

Figure 4. Digital photographs of ISM after exposure to phosphate buffer pH 6.8

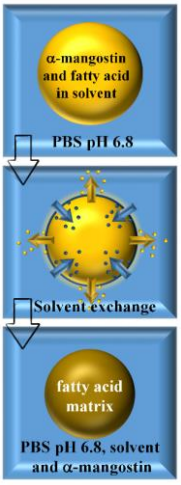

Figure 5. Schematic diagram of solvent exchange of α-mangostin/clove oil-incorporated lauric acid-based solvent removal-induced in situ forming matrices

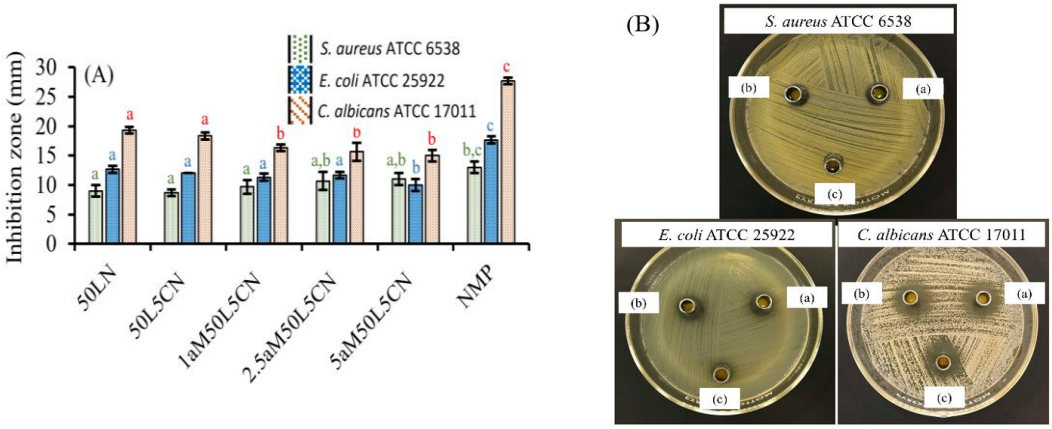

Figure 6. Inhibition zone diameter of tested formulations against microbes (a) and clear zone images of ISM (b); (a) 1aM50L5CN, (b) 2.5aM50L5CN, and (c) 5aM50L5CN. The values followed by different letters (a<b<c) in each microbe indicate the significant difference ($p<0.05$)

Conclusions

This research revealed that the ISM containing 50%w/w lauric acid, 5 %w/w clove oil and different α-mangostin amount in NMP was suitable for periodontal drug delivery. The increasing of α-mangostin amounts significantly increased the viscosity of prepared formulation and injection force. However, all formulations had low viscosity that it was easy to injection. They formed as matrix after exposure to aqueous phase. The clove oil could retard solvent exchange. These prepared formulations showed the antimicrobial activities against three standard microbes. Nevertheless, the α-mangostin release from ISM and the antimicrobial activities against *P. gingivalis* should be investigated in further experimental.

Acknowledgement

This research was financially supported by Thailand Science Research and Innovation (TSRI) National Science, Research and Innovation Fund (NSRF) and also Silpakorn University Research, Innovation and Creativity Administration Office. The authors wish to thank Faculty of Pharmacy, Silpakorn University for facilities.

References

Al-Massarani, S.M., El-Gamal, A.A., Al-Musayeib, N.M., Mothana, R.A., Basudan, O.A., Al-Rehaily, A.J., Farag, M., Assaf, M.H., El-Tahir, K.H., and Maes, L. (2013). Phytochemical, antimicrobial and antiprotozoal evaluation of Garcinia mangostana pericarp and α-mangostin, its major xanthone derivative. Molecules, 18(9):10,599-10,608. https://doi.org/10.3390/molecules180910599

Chantadee, T., Lertsuphovanit, N., and Phaechamud, T. (2019a). Application of fatty acid for pharmaceuticals. Thai Bulletin of Pharmaceutical Sciences, 14:1-11.

Chantadee, T., Santimaleeworagun, W., Phorom, Y., and Phaechamud, T. (2020). Saturated fatty acid-based in situ forming matrices for localized antimicrobial delivery. Pharmaceutics, 12(9):808. https://doi.org/10.3390/pharmaceutics12090808

Chantadee, T., Santimaleeworagun, W., Phorom, Y., and Phaechmud, T. (2019b). Mixed solvent-lauric acid solvent-exchange induced in situ forming gel. Key Eng Mater, 819:195-201. https://doi.org/10.4028/www.scientific.net/KEM.819.195

Fei, X., Jo, M., Lee, B., Han, S.B., Lee, K., Jung, J.K., Seo, S.Y., and Kwak, Y.S. (2014). Synthesis of xanthone derivatives based on α-mangostin and their biological evaluation for anti-cancer agents. Bioorganic and Medicinal Chemistry Letters, 24(9):2062-2065. https://doi.org/10.1016/j.bmcl.2014.03.047.

Ghasemzadeh, A., Jaafar, H.Z.E., Baghdadi, A., and Tayebi-Meigooni, A. (2018). Alpha-mangostin-rich extracts from mangosteen pericarp: optimization of green extraction protocol and evaluation of biological activity. Molecules, 23(8):1852. https://doi.org/10.3390/molecules23081852

Ibrahim, M.Y., Hashim, N.M., Mariod, A.A., Mohan, S., Abdulla, M.A., Abdelwahab, S.I., and Arbab, I.A. (2014). α-Mangostin from Garcinia mangostana Linn: An updated review of its pharmacological properties. Arabian Journal of Chemistry, 9(3):317-329. https://doi.org/10.1016/j.arabjc.2014.02.011

Kahwaji, S., Johnson, M.B., Kheirabadi, A.C., Groulx, D., and White, M.A. (2017). Fatty acids and related phase change materials for reliable thermal energy storage at moderate temperatures. Solar Energy Materials and Solar Cells, 167:109-120. https://doi.org/10.1016/j.solmat.2017.03.038

Kheawfu, K., Pikulkaew, S., Rades, T., Müllertz, A., Gersdorff, L.V., Jørgensen, L., and Okonogi, S. (2021). Design and optimization of self-nanoemulsifying drug delivery systems of clove oil for efficacy enhancement in fish anesthesia. Journal of Drug Delivery Science and Technology, 61:102241. https://doi.org/10.1016/j.jddst.2020.102241

Li, G.L., Zheng, L.Q., and Xiao, J.X. (2009). Synthesis and surface activities of organic solvent-soluble fluorinated surfactants. Journal of Fluorine Chemistry, 130(7):674-681. https://doi.org/10.1016/j.jfluchem.2009.05.006

Mei, L., Huang, X., Xie, Y., Chen, J., Huang, Y., Wang, B., Wang, H., Pan, X., and Wu, C. (2017). An injectable in situ gel with cubic and hexagonal nanostructures for local treatment of chronic periodontitis. Drug Delivery, 24(1):1,148-1,158. https://doi.org/10.1080/10717544.2017.1359703

Narasimhan, S., Maheshwaran, S., Abu-Yousef, I.A., Majdalawieh, A.F., Rethavathi, J., Das, P.E., and Poltronieri, P. (2017). Anti-bacterial and anti-fungal activity of xanthones obtained via semi-synthetic modification of α-mangostin from Garcinia mangostana. Molecules, 22(2):275. https://doi.org/10.3390/molecules22020275

Nisar, T., Yang, X., Alim, A., Iqbal, M., Wang, Z.C., and Guo, Y. (2019). Physicochemical responses and microbiological changes of bream (Megalobrama ambycephala) to pectin based coatings enriched with clove essential oil during refrigeration. International Journal of Biological Macromolecules, 124:1,156-1,166. https://doi.org/10.1016/j.ijbiomac.2018.12.005

Ovalle-Magallanes, B., Eugenio-Pérez, D., and Pedraza-Chaverri, J. (2017). Medicinal properties of mangosteen (Garcinia mangostana L.): A comprehensive update. Food and Chemical Toxicology, 109(1):102-122.

Phaechamud, T. and Setthajindalert, O. (2018). Antimicrobial in-situ forming gels based on bleached shellac and different solvents. Journal of Drug Delivery Science and Technology, 46:285-293. https://doi.org/10.1016/j.jddst.2018.05.035

Phaechamud, T., Thurein, S.M., and Chantadee, T. (2018). Role of clove oil in solvent exchange-induced doxycycline hyclate-loaded Eudragit RS in situ forming gel. Asian Journal of Pharmaceutical Sciences, 13(2):131-142. https://doi.org/10.1016/j.ajps.2017.09.004

Phitaktim, S., Chomnawang, M., Sirichaiwetchakoon, K., Dunkhunthod, B., Hobbs, G., and Eumkeb, G. (2016). Synergism and the mechanism of action of the combination of α-mangostin isolated from Garcinia mangostana L. And oxacillin against an oxacillin- resistant Staphylococcus saprophyticus. BMC Microbiology, 16(1): 195. https://doi.org/10.1186/s12866-016-0814-4

Rungseevijitprapa, W. and Bodmeier, R. (2009). Injectability of biodegradable in situ forming microparticle systems (ISM). European Journal of Pharmaceutical Sciences, 36(4-5):524-531. https://doi.org/10.1016/j.ejps.2008.12.003

Sanghvi, R., Narazaki, R., Machatha, S.G., Yalkowsky, S.H. (2008). Solubility improvement of drugs using N-methyl pyrrolidone. AAPS PharmSciTech, 9(2):366-376. https://doi.org/10.1208/s12249-008-9050-z

Senarat, S., Chantadee, T., Santimaleeworagun, W., Phorom, Y., and Phaechamud, T. (2019). Alpha-mangostin phase inversion induced in situ forming gel. Key Engineering Materials, 819:202-208. https://doi.org/10.4028/www.scientific.net/KEM.819.202

Shuai, C., Yang, W., Feng, P., Peng, S., and Pan, H. (2020). Accelerated degradation of HAP/PLLA bone scaffold by PGA blending facilitates bioactivity and osteoconductivity. Bioactive Materials, 6(2):490-502. https://doi.org/10.1016/j.bioactmat.2020.09.001

Sivaranjani, M., Leskinen, K., Aravindraja, C., Saavalainen, P., Pandian, S.K., Skurnik, M., and Ravi, A.V. (2019). Deciphering the antibacterial mode of action of alpha-mangostin on Staphylococcus epidermidis RP62A through an integrated transcriptomic and proteomic approach. Frontiers in Microbiology, 10:150. https://doi.org/10.3389/fmicb.2019.00150

Thakur, R.R., McMillan, H.L., and Jones, D.S. (2014). Solvent induced phase inversion-based in situ forming controlled release drug delivery implants. Journal of Controlled Release, 176:8-23. https://doi.org/10.1016/j.jconrel.2013.12.020

Torrungruang, K., Vichienroj, P., and Chutimaworapan, S. (2007). Antibacterial activity of mangosteen pericarp extract against periodontal pathogens. Journal of the Dental Association of Thailand, 57(5):240-246.

Walker, C.B., Karpinia, K., and Baehni, P. (2004). Chemotherapeutics: antibiotics and other antimicrobials. Periodontology 2000, 36(1):146-165. https://doi.org/10.1111/j.1600-0757.2004.03677.x

Yiemwattana, I. and Kaomongkolgit, R. (2015). Alpha-mangostin suppresses IL-6 and IL-8 expression in P. gingivalis LPS-stimulated human gingival fibroblasts. Odontol, 103(3):348-355. https://doi.org/10.1007/s10266-014-0160-7

Zou, H., Koh, J.J., Li, J., Qiu, S., Aung, T.T., Lin, H., Lakshminarayanan, R., Dai, X., Tang, C., Lim, F.H., Zhou, L., Tan, A.L., Verma, C., Tan, D.T.H., Chan, H.S.O., Saraswathi, P., Cao, D., Liu, S., and Beuerman, R.W. (2013). Design and synthesis of amphiphilic xanthone-based, membrane-targeting antimicrobials with improved membrane selectivity. Journal of Medicinal Chemistry, 56(6):2,359-2,373. https://doi.org/10.1021/jm301683j