THE ISOLATION OF XANTHONES FROM TRUNK LATEX OF *Garcinia mangostana* Linn. AND THEIR ANTIMICROBIAL ACTIVITIES

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Received October 6, 2014; Accepted March 1, 2015

ABSTRACT

*α-Mangostin (**1**), β-mangostin (**2**) and gartanin (**3**) have been isolated from the trunk latex of Garcinia mangostana Linn. and investigated for their antimicrobial activities against Bacillus subtilis, Enterococcus faecalis, Micrococcus luteus, Salmonella typhosa, Staphylococcus epidermidis, Streptococcus mutans and Vibrio cholerae. The significant antibacterial activity showed by α-mangostin (**1**) against Bacillus subtilis, Enterococcus faecalis. Staphylococcus epidermidis and Vibrio cholerae, but all compounds showed no activity to inhibit the growth of Micrococcus luteus and Streptococcus mutans.*

Keywords: *Garcinia mangostana Linn.; trunk latex;* α-*mangostin; β-mangostin; gartanin*

ABSTRAK

*Telah diisolasi α-mangostin (**1**), β-mangostin (**2**) dan gartanin (**3**) dari getah batang tumbuhan manggis (Garcinia mangostana* Linn.*) dan telah dilakukan uji antibakteri terhadap bakteri Bacillus subtilis, Enterococcus faecalis, Micrococcus luteus, Salmonella typhosa, Staphylococcus epidermidis, Streptococcus mutans dan Vibrio cholerae. α-Mangostin (**1**) menunjukan aktivitas antibakteri yang signifikan terhadap bakteri Bacillus subtilis, Enterococcus faecalis, Salmonella typhosa, Staphylococcus epidermidis dan Vibrio cholerae, tetapi semua senyawa tidak aktif menghambat pertumbuhan bakteri Micrococcus luteus* dan *Streptococcus mutans.*

Kata Kunci: *Garcinia mangostana* Linn.*; getah manggis; α-mangostin; β-mangostin; gartanin*

INTRODUCTION

Garcinia mangostana Linn. (mangosteen), family Guttiferae has been cultivated for centuries in tropical areas of the world. The tree is presumed to have originated from Southeast Asia or Indonesia and has largely remained indigenous to Malay Peninsula, Myanmar, Thailand, Cambodia, Vietnam and the Moluccas [1]. It has also been known to be of good medicinal value and is traditionally used in folk medicines for treatment of abdominal pain, diarrhea, dysentery, infected wounds, suppuration, chronic ulcer, leucorrhoea and gonorrhea [2].

Various studies from different part of *G. mangostana* have been carried out. From young fruit peel Suksamrarn et al. reported the presence of 1,6-dihydroxy-7-methoxy-8-(3-methylbut-2-enyl)6'6,6'-dimethyl pyrano(2',3':3,2)xanthone, demethylcalabaxanthone, 8-desoxygartanin, gartanin, *α*-mangostin, *β*-mangostin, *γ*-mangostin, garcinone B, garcinone C, garcinone D, garcinone E, mangostenone C, mangostenone D, mangostenone E, mangostanol, 11-hydroxy-1-isomangostin, mangostinone, thwaitesixanthone and mangostanin [2]. From mature fruit peel Jung et al. found 8-hydroxycudraxanthone G and mangostingone [7-methoxy-2-(3-methyl-2-butenyl)-8-(3-methyl-2-oxo-3-butenyl)-1,3,6-trihydroxyxanthone and other 12 known's xanthones [3]. From stem bark, Dharmaratne et al. obtained *α*-mangostin, *β*-mangostin, *γ*-mangostin, from root bark found *α*-mangostin, *β*-mangostin, 3-hydroxy-4-geranyl-5-methoxybiphenyl and *β*-sitosterol and from young fruit latex found *α*-mangostin, *β*-mangostin, *γ*-mangostin, methoxy-*β*-mangostin and garcinon E [4]. From seeds and fruit pulp Suksamrarn et al. found 1,7-dihydroxy-2-(3-methylbut-2-enyl)-3-methoxyxanthone, 2-isoprenyl-1,7-dihydroxy-3-methoxyxanthone, 1,7-dihydroxy-8-(3-methylbut-2-enyl)-6', 6'-dimethylpyrano (2',3':3,2)-xanthone and trapezifolixanthone [5]. Beside that, several compounds have been found in other parts of *G. mangostana* and mainly individual xanthones were reported to have a great variety of pharmacological activities including antioxidant, antifungal, antibacterial, cytotoxic, antiinflammation, antihistamine, anti-HIV and other activities [6].

Several antibacterial testing on these xanthones against some pathogenic bacteria such as *Mycobacterium tuberculosis* [2], *Staphylococcus aureus* both normal and *Staphylococcus aureus*

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penicillin-resistant strains [7], VRE (*Vancomycin resistat Enterococci*) [8] and MRSA (Methicilin resistant *Staphylococcus aureus*) [9], *Bacillus subtilis*, *Pseudomonas aeruginosa, Salmonella thypimurium* [10] have also been done before.

However, so far there is no work reported on the chemical constituents of the trunk latex of *G. mangostana*. Furthermore, fast growing interest to search a new source of xanthones has increased lately. So, in our present work we tried to isolate the major compounds of the trunk latex of *G. mangostana*. Interestingly, in our work we found that the major compounds isolated from trunk latex of *G. mangostana* gave significant antibacterial activity against *Bacillus subtilis, Enterococcus faecalis, Staphylococcus epidermidis* and *Vibrio cholerae*.

EXPERIMENTAL SECTION

Materials

Plant material: 100 g dry trunk latex of *G. mangostana* was collected at Kubang Landai, Batu Sangkar, West Sumatera on August 2013.

Testing microbes: *Bacillus subtilis* ATCC 6633, *Enterococcus faecalis* ATCC 29212, *Micrococcus luteus* ATCC 10240, *Salmonella typhosa* NCTC 786, *Staphylococcus epidermidis* ATCC 12228, *Streptococcus mutans* ATCC 25175 *and Vibrio cholerae* Inaba were provided by Indonesian Food and Drug Administration (BPOM) Padang and Pekanbaru offices and Microbiology Laboratory of Medical Faculty of Andalas University and were pre-cultured before being used.

All solvents were distilled before being used, nutrient agar (NA) (Merck), paper disc (Whatman), dimethyl sulfoxide (DMSO) (Merck) and chloramphenicol (Sigma). TLC was carried out using silica gel $60F_{254}$ (Merck) and visualized under UV light (254 nm). Column chromatography was performed on silica gel 60 (0.063-0.200 nm) (Merck).

Instrumentation

Melting points were measured on a Sybron Thermolyne Melting Point Apparatus MP-12615 and are uncorrected. FT-IR Spectra was on Perkin Elmer FT-IR Frontier. UV Spectra was recorded on Shimadzu Spectrometer UV-Vis Pharmaspec 1700. ^{1}H and ^{13}C-NMR spectra were recorded with an Agilent DD2 system (Agilent Technologies, Santa Clara, CA, USA) operating at 500 (^{1}H) and 125 (^{13}C) MHz using residual and deuterated solvents as reference standards. High-resolution mass spectra were obtained on ESI-TOF waters LCT premier XE mass spectrometer (Milford, MA, USA).

Procedure

Extraction and isolation

One hundred g dry trunk latex of *G. mangostana* was dissolved in ethyl acetate (EtOAc, 500 mL), filtered and evaporated *in vacuo* to give brown gum (86 g). The latex was practically soluble in EtOAc except for small parts of wood and bark. This was dissolved in EtOAc then precipitated by addition of hexane to give yellow amorphous solid, then recrystallized from ethanol-water to give pale yellow plates of *α*-mangostin (**1**) (2.5 g).

All uncrystallized fractions (73 g) were combined and pre-adsorbed on SiO_2 then column chromatographed on the same adsorbent and eluted with step gradient polarity solvents started from hexane, hexane-dichloromethane, dichloromethane-EtOAc, EtOAc-MeOH and MeOH to give ten subfractions (GM 1-10). Fraction GM1-2 (23 g) was recrystallized from EtoAc-Hexane then EtOH-Water to give *α*-mangostin (**1**) (5.98 g) then all of mother liquor of this fraction were combined, rechromatographed as above with isocratic solvent hexane-EtOAc (4:1). Fractions eluted from the column were monitored on TLC and fractions that gave similar TLC pattern were combined to give more of *α*-mangostin (440 mg) and six subfractions (GM 11-17). Other crystalline subfractions were combined and recrystallized from EtOAc-Hexane then EtOH-water to give yellowish needles. Based on its spectroscopic data this compound identified was as *β*-manggostin (**2**) (11.1 mg).

Subfraction GM 13 was rechromatographed on SiO_2 eluted with isocratic solvents hexane-EtOAc (9:1). Major fractions that showed similar behavior on TLC were combined then recrystallized from dichloromethane-hexane to give yellow needles of gartanin (**3**) (16 mg).

***α*-mangostin (1).** Pale yellow plates; MP: 180-181 °C. IR (KBr) (cm^{-1}): 3418, 3239, 2962, 1639, 1373, 1238, 1169, 1050, 946, 839. UV λ_{max} MeOH nm (log ε): 315 (4.23), 243 (4.41), 204 (4.44). ^{1}H-NMR (Table 1) and ^{13}C-NMR (Table 2). TOF MS-ES *m/z*: 409.1647 (M^{-1}).

***β*-mangostin (2).** Yellowish needles; MP: 166-168 °C. IR (KBr) (cm^{-1}): 3384, 2933, 1645, 1600, 1482, 1456, 1381, 1281, 1148, 1169, 939, 882. UV λ_{max} MeOH nm (log ε): 347(4.48), 315(4.87), 258 (4.98), 244(5.05), 203 (5.12). ^{1}H-NMR (Table 1) and ^{13}C-NMR (Table 2). TOF MS-ES *m/z*: 423.1801 (M^{-1}).

Gartanin (3). Pale yellow needles; MP: 165-167 °C. IR (KBr) (cm^{-1}): 2970, 2908, 1626, 1580, 1486, 1381, 1282, 1177, 1073, 966, 829. UV λ_{max} MeOH nm (log ε): 351 (4.14), 319 (4.19), 283 (4.32), 257 (4.47), 243 (4.51),

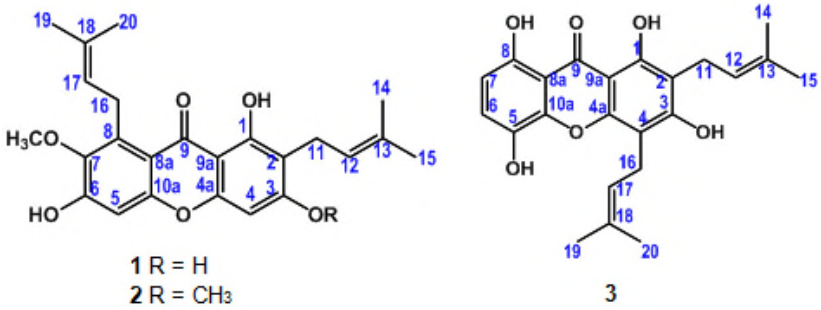

Fig 1. Structures of compounds **1-3**

Table 1. ^{1}H-NMR (500 MHz) spectral data of isolated xanthones **1-3** and their references

Position	Compound 1 ($CDCl_3$)	*α*-mangostin [12] ($CDCl_3$)	Compound 2 (Aseton)	*β*-mangostin [13] ($CDCl_3$)	Compound 3 ($CDCl_3$)	Gartanin [12] ($CDCl_3$)
1	13.78, *s* (OH)	13.80, s (OH)	13.65, *s* (OH)	13.42, *s* (OH)	12.34, *s* (OH)	12.34, *s* (OH)
3	6.15, s (OH)	6.12, br (OH)	-	-	6.59, *s* (OH)	6.58, *s* (OH)
4	6.3, *s*	6.27, s	6.52, *s*	6.24, *s*	-	-
4a	-	-			-	-
5	6.83, *s*	6.81, s	6.87, *s*	6.74, *s*	5.1, s (OH)	5.02, br *s* (OH)
6	6.3, s (OH)	6.27, s (OH)	-	-	7.22, *d* (*J*=8.5 Hz)	7.22, *d* (J=7 Hz)
7	-	-	-	-	6.66, *d* (*J*=9Hz)	6.63, *d* (*J*=7 Hz)
8	-	-	-	-	11.26, *s* (OH)	11.25, *s* (OH)
11	3.46, *d* (*J*=7.5 Hz)	3.45, *d* (*J*=7.3 Hz)	3.32, *d* (*J*=7.5 Hz)	3.37, *d* (*J*=7.2 Hz)	3.46, *d* (*J*=7 Hz)	3.46, *d* (*J*=6 Hz)
12	5.29, *t* (*J*=7 Hz)	5.25, *t* (*J*=7.3 Hz)	5.28, *d* (*J*=6.5 Hz)	5.17, *d* (*J*=7.2 Hz)	5.26, *m* (*J*=7 Hz)	5.23
14	1.77, *s*	1.75, *s*	1.83, *s*	1.75, *s*	1.86, *s*	1.8, br *s*
15	1.83, *s*	1.81, *s*	1.65, *s*	1.62, *s*	1.76, *s*	1.86, br *s*
16	4.09, *d* (*J*=6.5 Hz)	4.07, *d* (*J*=7.0 Hz)	4.13, *d* (*J*=6.5 Hz)	4.09, *d* (*J*=7.2 Hz)	3.52, *d* (*J*=6.5)	3.51, *d* (*J*=6 Hz)
17	5.29, *t* (*J*=7 Hz)	5.28, *t* (*J*=7.3 Hz)	5.21, *d* (*J*=7.5 Hz)	5.18, *t* (*J*=7.2 Hz)	5.26, *m* (*J*=7 Hz)	5.23, *t* (*J*=6 Hz)
19	1.84, *s*	1.82, *s*	1.64, *s*	1.61, *s*	1.79, *s*	1.86, br *s*
20	1.69, *s*	1.67, *s*	1.77, *s*	1.72, *s*	1.86, *s*	1.8, br *s*
3-OMe	-	-	3.8, *s*	3.82, *s*	-	-
7-OMe	3.8, *s*	3.79, *s*	3.97, *s*	3.80, *s*	-	-

203 (4.79). ^{1}H-NMR (Table 1) and ^{13}C-NMR (Table 2). TOF MS-ES *m/z*: 395.495 (M^{-1}).

Antimicrobial properties

Before being used each bacterium was grown separately in nutrient agar (NA) (Merck) and incubated at 37 °C for 24 h. These cultures were used for antimicrobial assay by modified agar disc diffusion method of Kirby and Bauer [11]. Single colony of the respective testing bacterium was transferred into NA medium and incubated for 24 h. Culture suspension in sterile NaCl 0.9% with 25% transmittant were respectively swabbed onto agar medium. Each compound (1-3) was prepared to the concentration of 2, 1, 0.5, 0.25, 0.125, 0.0625 mg/mL in DMSO. Each 10 µL of the above solution was dropped onto the paper disc (Whatman, 5 mm diameter) and carefully put onto culture media and the test was done in triplicate. Control disc contained chloramphenicol 30 µg/paper disc was similarly prepared in DMSO. Each plate was incubated at 37 °C for 24 h. Inhibition zones (including the diameter of disc) were measured and recorded and the inhibition results were reported as means of the triplo data.

RESULT AND DISCUSSION

TLC profile of the trunk latex *G. mangostana* under UV light (254 nm) showed only the presence of one major spot of *α*-mangostin, two minor less polar spots and one minor more polar spot compared to that of *α*-mangostin (**1**). Isolation work on this EtOAc soluble

Table 2. ^{13}C-NMR (125 MHz) spectral data of isolated xanthones **1-3.**

Position	Compound 1 ($CDCl_3$)	*α*-mangostin [12] ($CDCl_3$)	Compound 2 (Aseton)	*β*-mangostin [13] ($CDCl_3$)	Compound 3 ($CDCl_3$)	Gartanin [12] ($CDCl_3$)
1	160.6	160.6	160.5	159.7	158.1	158
2	108.4	108.4	111.1	111.5	109.5	109.5
3	161.6	161.6	164.6	163.5	161.6	161.6
4	93.5	93.3	89.9	88.8	105.8	105.8
4a	154.5	155.1	156.2	154.4	152.5	152.7
5	101.6	101.5	102.7	101.5	135.7	135.7
6	155.1	154.5	156.3	155.6	122.8	122.8
7	142.6	142.5	144.6	142.5	109.8	109.8
8	137	137	138.1	137	153.8	153.9
8a	112.2	112.2	112.1	112.3	107.1	107
9	182	182	182.9	181.9	184.7	184.7
9a	103.6	103.6	104.2	103.8	102.2	102.0
10a	155.8	155.8	157.6	155.2	142.8	142.2
11	21.5	21.4	21.9	21.3	21.9	21.1
12	121.4	121.4	124.7	122.3	121.8	121.0
13	132.2	135.9	131.5	132	133.9	136.5
14	25.8	25.9	25.9	25.8	25.7	25.9
15	18.2	18.2	18.3	18.2	17.9	18.0
16	26.6	26.6	26.9	31.2	21.6	22.1
17	123.1	123.5	123.3	123.2	120.9	121.8
18	135.8	132.2	131.5	131.7	136.3	133.9
19	17.9	17.9	17.9	17.8	17.9	18.0
20	25.9	25.8	25.9	26.7	25.9	25.9
3-OMe	-	-	56.5	55.8	-	-
7-OMe	62.1	62.1	61.4	62	-	-

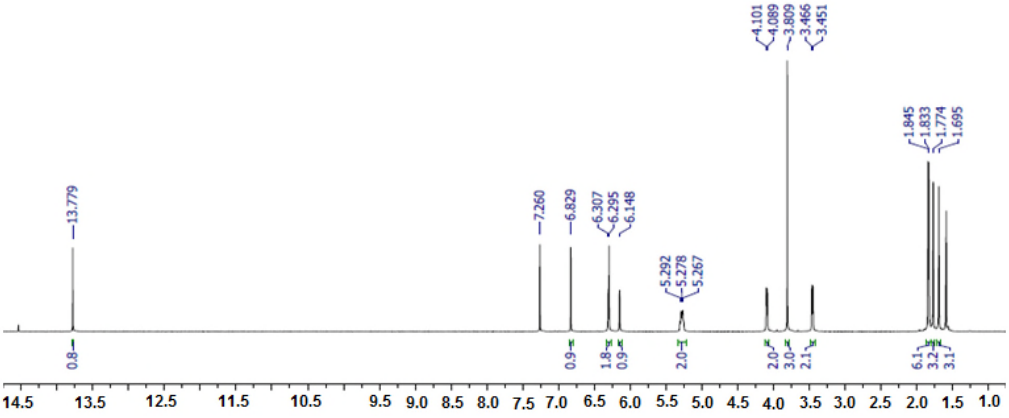

Fig 2. Spectrum ^{1}H NMR of compound 1

fraction of the trunk latex gave the two minor less polar compounds in a very small quantity compared to that of *α*-mangostin. Attempt to isolate another more polar minor compound was unsuccessful because the amount was too small to isolate. Identification of the isolated compounds was done by spectroscopic method particularly ^{1}H and ^{13}C-NMR.

The characteristics of xanthone molecules of isolated *α*-mangostin (**1**), *β*-mangostin (**2**) and gartanin (**3**) were readily showed by the presence of xanthone chromophore ultraviolet absorption at (UV λ_{max} (log ε): 350 nm (shoulder), 315 nm (4.23); 347 nm (4.48), 315 nm (4.87) and 351 nm (4.14), 319 nm (4.19), respectively. Infrared spectra also showed characteristics of xanthones hydrogen bond of hydroxyl protons attached to either C_1 or C_8 (cm^{-1}); 3418, 3418 and 3600 and 3400 to carbonyl function of C_9 respectively. The highly deshielded signals of hydroxyl protons attached to C_1 due to hydrogen bond to carbonyl oxygen of C_9 of above compounds were clearly observed by the presence of sharp ^{1}H-NMR signals at 13.779, 13.653 and 12.337 ppm respectively.

The presence of *α*-mangostin as major components in the trunk l atex was already detected by

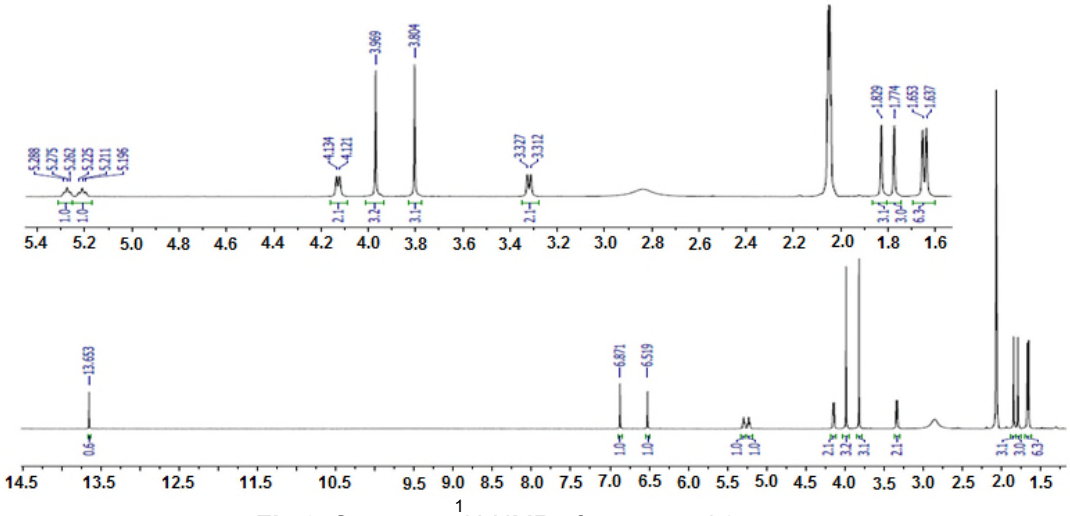

Fig 3. Spectrum ^{1}H-NMR of compound 2

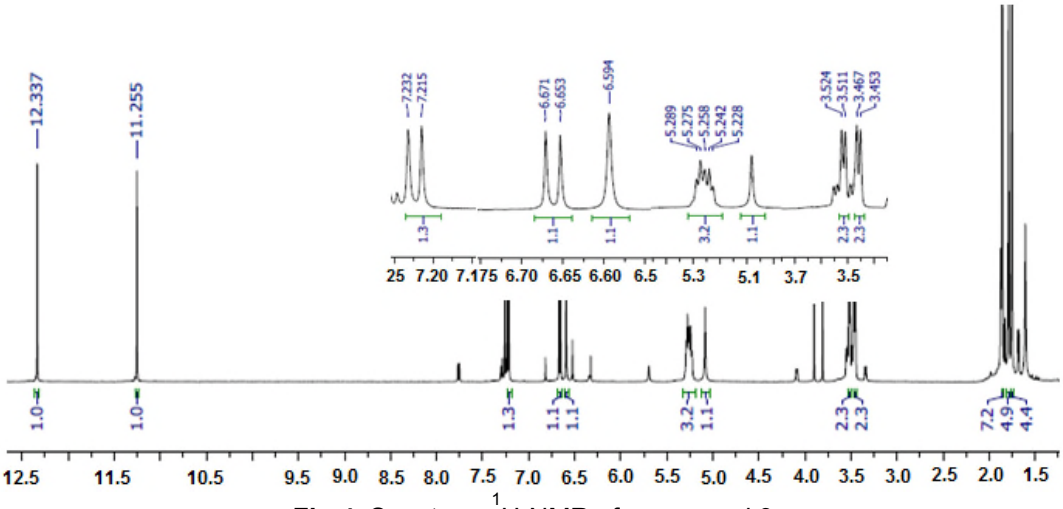

Fig 4. Spectrum ^{1}H-NMR of compound 3

comparison of its TLC profile with that of available dichloromethane fraction of methanolic extract of fruit pericarp of *G. mangostana* which was wellknown for its major constituents a-mangostin. Based on the comparison of its spectorscopic data to those of reported data in literature particularly ^{1}H and ^{13}C (Table 1 and Table 2) compound (**1**) was identified as well-known *α*-mangostin [12].

The ^{1}H-NMR spectrum of compound (2) looked very similar to that of *α*-mangostin (1), except that instead of having one methoxyl group it had two at (d, ppm, multplicity) 56.30 (3H, s) and 61.4 (3H, s). Other ^{1}H-NMR signals such as 4 methyl signals of prenyl group (d, ppm, multiplicity) : C_{14} (25.9, 3H, s), C_{15} (18.3, 3H, s), C_{19} (17.9, 3H, s) and C_{20} (25.9, 3H, s), as well as its 2 aromatic protons attached to C_4 (6.52, 1H, s) C_5 (6.87, 1H, s), all very similar to that of *α*-mangostin (**1**). In addition, all ^{13}C signals as well as its molecular ion (M^{-1}) at m/z 423.18 which agreed with empirical formula $C_{26}H_{28}O_6$ and compared to reported data in the literature particularly its ^{1}H and ^{13}C-NMR spectra (Table 1 and Table 2) it was concluded that compound (**2**) was identified as known *β*-mangostin [13].

The ^{1}H-NMR of compound (**3**) showed different ^{1}H-NMR pattern compared to the above two compounds. Only the presence of two aromatic protons was observed (*d*, ppm, multiplicity, coupling constant); 7.22 (d, 1H, J 7 Hz) and 6.63 (d, 1H, J 7 Hz) which coupled to each other with coupling constant 7 Hz, indicating the presence of *ortho*-coupling of protons H_6 and H_7. The presence of two prenyl functions were also obvious by the signals of 4 methyl group (d, ppm, multiplicity); 25.7, (3H, s), 17.9 (3H, s), 25.9 (3H, s), 17.90 (3H, s). There is no methoxyl signals were detected. Together with its ^{13}C chemical shifts and its molecular ion (M^{-1}) at m/z 395.495, this compound was identified as known compound gartanin [12].

Table 3. Inhibition of isolated xanthones against *B. subtilis*

C	Concentration (µg/disc)						
	20	10	5	2.5	1.25	0.63	+ (30)
	Zone inhibition (mm)						
1	18	17	16	15	13	10	25
2	11	10	9.7	9.3	9	8	28
3	12	10	8	-	-	-	27

C = Compound Number;
\+ = Positive control (Chloramphenicol)

Table 4. Inhibition of isolated xanthones against *E. faecalis*

C	Concentration (µg/disc)						
	20	10	5	2.5	1.25	0.63	+ (30)
	Zone inhibition (mm)						
1	21	19	17	12	10	7	29
2	16	14	9.7	8.5	7	-	30
3	-	-	-	-	-	-	29

Table 7. Inhibition of isolated xanthones against *V. cholerae*

C	Concentration (µg/disc)						
	20	10	5	2.5	1.25	0.63	+ (30)
	Zone inhibition (mm)						
1	20	18	16	15	12.5	11	28
2	13	12	11	9.7	8	7	30
3	15	13	11	10.5	9	7	30

Traditionally the fruit pericarps of *G.mangostana* in West Sumatra is used for various purposes particularly for skin infections, wound healing as well as throat and gastrointestinal infection. As part of our continuing search for antimicrobial compounds from Sumatran medicinal plants [14], we decided to check the antimicrobial activity of those isolated compounds using different variety of standard testing pathogenic bacteria as in Table 7.

The decoction of pericarps of *G. mangostana* was reported to be active against *Escherichia coli, Vibrio cholerae* and *Salmonella typhi,* the crude water extract was active against *Streptococcus faecalis, Vibrio cholerae* [5]. Crude *G. mangostana* extract also showed inhibition toward the growth of *Propionibacterium acnes* and *Staphylococcus epidermidis.* Some antibacterial activity of *α*-mangostin towards *E. faecalis, B. subtilis* and *S. typhosa* using different strains of the above microbes has also been reported before [15]. However, since the main components of the pericarps of *G. mangostana* is *α*-mangostin and following the above important traditional use of *G. mangostana,* we decided to continue the study of its trunk latex chemical constituents to explore another source of *α*-mangostin as well to check their antimicrobial activity by using available different standard pathogenic testing microbes.

Our antibacterial experiments results showed that *α*-mangostin (**1**), *β*-mangostin (**2**) and gartanin (**3**) inhibited the growth of *V. cholerae* significantly, while *α*-

Table 5. Inhibition of isolated xanthones against *S. epidermidis*

C	Concentration (µg/disc)						
	20	10	5	2.5	1.25	0.63	+ (30)
	Zone inhibition (mm)						
1	17	15	13	12	11	10	23
2	11	10	7	-	-	-	22
3	11	9	8	7.3	7	7	23

Table 6. Inhibition of isolated xanthones against *S. thyposa*

C	Concentration (µg/disc)						
	20	10	5	2.5	1.25	0.63	+ (30)
	Zone inhibition (mm)						
1	10	-	-	-	-	-	29
2	-	-	-	-	-	-	30
3	8.3	7.5	7	-	-	-	29

mangostin (**1**), *β*-mangostin (**2**) were also active inhibited the growth pathogenic gastrointestinal bacteria *B. subtilis, E. faecalis* and *V. cholerae.*

The above results showed that the traditional use of the decoction of fruit pericarps of *G. mangostana* to treat gastrointestinal infections caused by *B. subtilis, E. faecalis* and *V. cholerae* can now be understood. This preliminary result also indicated that *α*- and *β*-mangostin which were also the main component of xanthones in the pericarps of *G. mangostana* showed inhibition toward the growth *S. epidermidis* that caused acne. Based on the above results, it seems that the antibacterial activity of xanthones of *G. mangostana* might be worth investigated further.

CONCLUSION

The isolated compounds from trunk latex of *G. mangostana* were identified as *α*-mangostin, *β*-mangostin and gartanin. *α*-Mangostin gave significant activity to inhibit the growth of *B. subtilis, E. faecalis*, *S. typhosa, S. epidermidis* and *V. cholerae*. While gartanin gave significant activities against *V. cholerae* and moderate activities against *B. subtilis, S. typhosa and S. epidermidis. β*-mangostin gave significant activities against *B. subtilis, E. faecalis* and *V. cholera* and moderate activities against *S. epidermidis,* but there were no inhibition toward *M. luteus* and *S. mutans*.

ACKNOWLEDGEMENT

We are grateful to DP2M-DIKTI-Kemendiknas “Hibah Kompetensi 2013-2014” (to DA) for supporting the preliminary study of *G. mangostana*. We thank Indonesian Food and Drug Administration (BPOM) Padang and Pekanbaru and The Microbiology

Laboratory of Medical Faculty of Andalas University for providing testing microbes. We thank Prof. Dr. Yana Maolana Syah from Institut Teknologi Bandung for obtaining NMR and MS Spectroscopic data.

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