JKKI
SCIENTIA EST BASIC VITAE

Jurnal Kedokteran dan Kesehatan Indonesia

Indonesian Journal of Medicine and Health

Journal homepage : www.journal.uii.ac.id/index.php/JKKI

Potency of Xanthone Derivatives as antibacterial agent against Methicillin-Resistant Staphylococcus Aureus (MRSA)

Isnatin Miladiyah*[1], Farida Juliantina Rachmawaty[2]

[1]Pharmacology Department Faculty of Medicine, Islamic University of Indonesia
[2]Microbiology Department Faculty of Medicine, Islamic University of Indonesia

Review Article

ABSTRACT

ARTICLE INFO

Keywords:
Xanthone
Antibacterial effect
Methicillin-Resistant Staphylococcus aureus (MRSA)
Bacteria's cell membrane damage

***Corresponding author:**
isnatin@gmail.com

DOI : 10.20885/JKKI.Vol8.Iss2.art8

History:
Received: March 27, 2017
Accepted: June 3, 2017
Online: June 15, 2017

Antibiotic resistance is increasing worldwide and becoming a serious problem for the treatment of patients and also affecting their economy. One instance of bacteria that is resistant to the antibiotic is Methicillin-Resistant Staphylococcus aureus (MRSA). MRSA infections are fatal and even deadly. Some MRSA strain has shown resistance towards currently available antibacterial agents. To overcome this, we need new compound alternatives. One of the compounds currently being developed is xanthone derivatives. Xanthones can be found in many kinds of plants, including Garcinia mangostana , in which the active compounds are mangostanin and α-mangostin. Xanthones is effective against several types of Gram-positive and Gram-negative bacterias, including Staphylococcus species. Some studies have shown that xanthone derivatives are effective against Staphylococcus aureus, including MRSA. One of the proposed mechanisms of xanthone's antibacterial activity is the involvement of the bacteria's cytoplasmic membrane. Xanthone amphiphilic compounds are capable of disrupting bacterial membrane through a mechanism called interfacial activity models. Xanthone can also act as the antioxidant and by inducing the release of lipoteichoic acid (LTA) from the cell wall of MRSA. LTA is the main constituent of the cell wall of Gram-positive bacteria, which are covalently bonded to the outside of peptidoglycan. This structure is important for cell division and bacterial osmotic protection. Thus, it is believed that the mechanism of action of xanthones involved damaging bacterial cell membrane.

Resistensi antibakteri yang semakin meningkat menjadi masalah serius dalam penanganan pasien dan berdampak secara ekonomi. Bakteri yang mengalami resisten di antaranya adalah Methicillin-Resistant Staphylococcus aureus (MRSA). Infeksi oleh MRSA dapat berakibat fatal hingga menimbulkan kematian. Saat ini MRSA sudah mulai menunjukkan adanya resistensi terhadap beberapa antibakteri yang tersedia. Untuk mengatasi hal tersebut, diperlukan alternatif senyawa baru yang dapat mengatasi infeksi MRSA. Salah satu senyawa yang dikembangkan adalah turunan xanthone. Xanthone terdapat pada beberapa macam tanaman, di antaranya Garcinia mangostana dengan senyawa aktif mangostanin, α-mangostin. Xanthone efektif terhadap beberapa jenis bakteri Gram positif dan Gram negatif. Genus Staphylococcus termasuk bakteri Gram positif yang sensitif terhadap senyawa xanthone. Beberapa penelitian menunjukkan bahwa selain efektif terhadap Staphylococcus aureus, xanthone juga potensial untuk digunakan pada MRSA. Senyawa xanthone amphiphilic mampu mengganggu membran bakteri melalui mekanisme yang disebut interfacial activity model. Mekanisme lain diduga bekerja dengan cara menginduksi pelepasan lipotheicolic acid (LTA) dari dinding sel MRSA. LTA adalah penyusun utama dinding sel bakteri Gram positif,

yang berikatan secara kovalen dengan bagian luar peptidoglikan, yang penting dalam pembelahan sel dan proteksi osmotik bakteri. Dengan demikian, diduga bahwa mekanisme kerja xanthone melibatkan kerusakan dinding sel dan membran sel bakteri.

INTRODUCTION

1. Antimicrobial resistance

Antimicrobial resistance especially antibacterial is not a new-found phenomenon, and it has become an increasingly serious health concern. World Health Organization (WHO) stated that antimicrobial resistance us one of the most vital public health problem.[1] Data has shown that the yearly mortality rate caused by antimicrobial resistance infections are 23.000 in America, 25.000 in the Europe Union, and 58.000 in India.[2] These findings have stimulated a lot of global surveillance action.[1,3-5]

Antimicrobial resistance has caused a significant delay of effective treatment course for infectious diseases, and often times even caused patients to fail to receive proper treatment. Many advancements in the medicine world, for instance, the presence of chemotherapy for cancer and organ transplantation, are very dependent on an effective anti-infection. This also has implications not only medically but also economically. In addition to that, other disadvantages that can not be counted, like chronic pain, hindrance in daily activities, and psychological costs.[6] The estimation of yearly expenses caused by antimicrobial resistance in America had reached 55 billion dollars and in Europe 1,5 billion euro, in which the 900 million euro was due to inpatient treatment and loss of productivity at work.[4,7]

General data in some countries showed that the incidence of antimicrobial resistance including multidrug resistance (MDR) both in the hospital and community settings are constantly increasing.[6] This resistance is complex and multifactorial. Nonetheless, irrational antimicrobial usage is still thought to be the most important factor.[7] Unnecessary antibacterial prescription, as well as unstandardized dosage, contributes 50% overall antimicrobial usage.[4] The lack of regulation of antimicrobial utilization in other non-medical sectors, for instance, farming, is causing this issue to become more complex.[7]

The discovery of antibacterial as one kind of antimicrobial agent that can eradicate bacterial were considered a revolution of health sector during the 20th centuries.[8] The history of antibacterial agents begun in 1928, when Alexander Fleming accidentally discovered penicillin for the first time. In 1929, Fleming wrote about penicillin for the first time, however at that time penicillin was not used for medical purposes, until a team from Oxford University did so in the 1940s.[9] In the next phase, the precence of many kinds of antimicrobial agents had saved so many lives from infectious diseases, which in the pre-antibiotic era was incurable.[10]

The existence of antimicrobial agents is limited and non-renewable, which human beings will always need.[10] This had been proven in 1947, only 4 years after penicillin was mass-produced, *Staphylococcus aureus* (S. aureus) resistance to penicillin had been reported.[8] Bacterial can develop antibacterial resistance through several mechanisms, for instance through inhibiting pathway, modifying site of action, efflux mechanism, drug-target mutation, and membrane permeabilities modification.[11]

Considering the importance of antibacterial agents in the treatment process and its irreplaceable role, guidelines for rational use of antibacterial was made, one of which is published by Infectious Diseases of Society of America (IDSA) and Society of Healthcare Epidemiology of America.[7] Other guidelines include those published by The Antibiotic Stewardship and Resistance Working Groups of the International Society for Chemotherapy, for the public settings and hospital settings.[12,13] These guidelines are a form of strategical effort to optimize the effective use of antibacterial, lessen the occurrence of side effects, minimizing treatment cost, and finally preventing bacterial resistance.[7]

The increase of antibacterial resistance happens not only inside hospital settings but

also in the community. Some of this resistance are different depending on the region 5. In western countries, methicillin-resistant *Staphylococcus aureus* (MRSA), *Vancomycin-resistant enterococci* (VRE), *Escherichia coli* and β-lactamase *Klebsiella pneumonia* (ESBL), and *carbapenem-resistant Enterobacteriaceae* (CRE) are the most commonly seen. Among those antibacterial-resistant bacterias, MRSA is the most common pathogen found in the hospitals in Asia.[8]

2. Methicillin-resistant S. aureus (MRSA)

Among all gram positive bacterias, S. aureus draws more public interest due to a very rapid resistance occurrence both in the hospitals and communities. The spreading of its resistant strain was also very massive.[10] This bacteria was first reported to be resistant to penicillin only 4 years after penicillin mass-production.[8] Before 1950, *S. aureus* had been resistant to penicillin-alternatives antibacterial like *erythromycin*, *streptomycin*, and *tetracycline*. In 1959, methicillin was found as an alternative for infections caused by *S. aureus*. However, only two years after methicillin was introduced, an occurrence of resistance was reported.[14] The high incidence of infection caused by MRSA demands penicillin-alternative medicines as treatment options, which price are far more expensive.[1]

2.1 Epidemiology

On the early reports, MRSA was still limited in hospital settings and rarely occurred in the community. The occurrence of resistant-strain was first reported in the early 1990s in Australia, and after a few years occurred in the Europe, United State, Latin America, and Asia.[14] Infections caused by MRSA are the most commonly found infection in hospital settings, attacking approximately 80.000 individuals every year, 11.000 of which are deadly. This infection usually occurs during hospital stay or not long after hospitalization.[4] In Asia, between 2004-2006, an infection caused by MRSA in hospital setting was 67,5% and in the community was 25,5%.[15] In the US, until late 1980s MRSA infections in the hospital was around 8-22%, however, this number increased by 60% in 2003. Similar findings were found in Latin America and other Asia Pacific region, where in early 2000s MRSA infection in hospital settings reached more than 50%.[14]

Overall, the occurrence of MRSA infections in a various country are decreasing for around 30%, however, there are still some health service facilities with high incidence level, amounting to 50% or even 60%.[14] In contrary to the decreasing occurrence of MRSA infections inside the hospital, within the last decade, MRSA infection in the community (individuals who are not exposed to hospital settings) are increasing. The pattern of this infections is different from those in the hospital setting, including the strain of the MRSA.[4] The types of MRSA in the community have different genotypes from the resistant strain in the hospital and are still sensitive to some beta-lactam antibacterial, for instance, gentamycin, ciprofloxacin, and trimethoprim-sulfamethoxazole.[14] The occurrence of multiple drug resistance (MDR) to MRSA in the community is lower than in the hospital.[15]

2.2 The mechanism of Resistance

MRSA is resistant to almost all β-lactam antibacterial, which include group of penicillin (penicillin, dicloxacillin, nafcillin, oxacillin, all.) and cephalosporin.[16] This group of antibacterial works by inhibiting the synthesis of cell wall especially during the formation of peptidoglycan, which made the bacterial cell walls to become vulnerable and lysis easily. The β-lactam groups contribute as a pseudosubstrate that assimilates the active sides of bacterial penicillin-binding protein (PBP), thus inhibiting the cross-linking process of peptidoglycan polymer.[17] Most S. aureus resistance against β-lactam antibacterial is due to PBP changes.[18]

The resistance of MRSA is believed to be caused by mec (mecA, mecB, dan mecC) gene, that code a specific protein called PBP2A as a form of PBP changes. PBP2A is an additional PBP excluding the four existing PBP (PBP 1-4) in native S. *aureus*.[18] The affinity of PBP2A against β-lactam antibacterial is lower than S.

aureus endogen PBP and can substitute the function of PBP.[19] The lack of inhibition against peptidoglycan cross-linking polymers would keep the bacterial cell walls intact even with the administration of β-lactam.[17] This condition will defend the survival of MRSA in a high concentration β-lactam environment.[18]

The mecA gene is located on the *Staphylococcal cassette chromosome* (SCC)mec, which is a mobile genetic element (MGE) in the *Staphylococcus genus* that can interchange between species.[20] The acquisition of bacterial resistance happens through excision and integration with the mediation ofspesific recombinase gene called ccrAB and/or ccrC, and after that the SCCmec would be integrated into Staphylococcus chromosome.[16] Therefore, it can be concluded that SCCmec has a substantial role in virulence coding, immune escape mechanism, and antibacterial resistance gene.[21]

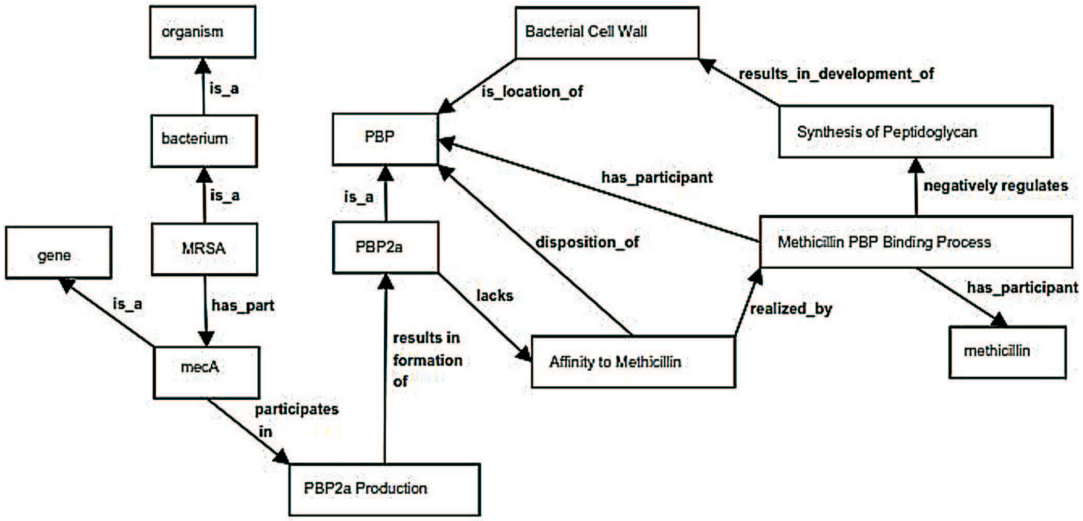


Figure 1. The scheme of Resistency in MRSA.[22]

Currently, there are eleven types of SCCmec (type I-XI) in various countries, with different intrinsic characteristic and predomination among countries.[16] For instance, SCCmec III is the most dominant types in countries like Arab, Indonesia, Thailand, Vietnam, China, Singapore, and India, which is also a type that showed resistance against cefoxitin, cephazolin, gentamycin, erythromycin, tetracycline, clindamycin, and cotrimoxazole.[23]

Since 1996, the occurrence of infections caused by MRSA has increased, and accompanied with decreasing sensitivity for vancomycin (vancomycin-*intermediate S. aureus*) in the Europe, Asia, and America. Furthermore, in 2002, there was also reports about vancomycin-resistant S. aureus/VISA.[24] VISA was also found to be resistant to teicoplanin, an antibacterial similar to vancomycin, a glycopeptide antibacterial that inhibits the synthesis of cell wall.[25] Due to these similarities, the term glycopeptide-intermediate S. aureus/GISA is more preferred.[24] Decreasing sensitivity of S. aureus against glycopeptides antibacterial is mediated by tcaA, which is a gene whose expression would affect the sensitivity of MRSA against vancomycin and teicoplanin. When the gene expression is high, *S. aureus* will be more sensitive towards vancomycin and teicoplanin, and vice versa.[26]

2.3 Methicillin-susceptible S.aureus(MSSA) versus Methicillin-resistant S. aureus (MRSA)

Until now, the difference in pathogenicity and virulence of MSSA and MRSA are still poorly described. Clinical data showed that hospitalization period, mortality rate, and treatment cost is higher in MRSA infection when compared to MSSA.[20] The general comparison of clinical aspects between MRSA and MSSA can be seen in Table 1.

Table 1. The comparison of clinical aspects between MSSA and MRSA

Parameter	MSSA	MRSA	p value	Reference point
1. Outcome patients	n = 433	n = 382		Significance p<0,001
• Patients died due to infection	22 (5,1%)	45 (11,8%)	< 0,001	[27]
• Patients with bacteremia and without spreading infection				
■ Total patients	406/433 (93,8%)	355/382 (92,9%)	< 0,001	[27]
■ Death	12/406 (3,0%)	35/355 (9%)	< 0,001	[27]
2. Local Patients	n = 80	n =159		Significance p<0,01
• abscess	23 (28,7%)	80 (50,3%)	< 0,01	[28]
• pneumonia with complication	2/13 (15,4%)	12/17 (70,6%)	< 0,01	[28]
3. Virulency, SCCmec subtype, and antibacterial resistance factor	n = 88	n = 104		Significance p<0,05
• SCCmec type III	28 (31,8%)	67 (64,4%)	0,001	[23]
• entE	63 (71,6%)	88 (84,6%)	0,019	[23]
• etb	14 (15,9%)	1 (1%)	0,000	[23]
• vancomycin resistance	3 (3,4%)	31 (29,8%)	0.001	[23]
• resistance gene distribution qacA/B	24/200 (12%)	186/297 (63%)	significance	[29]

Note:
MRSA = *methicillin-resistant Staphylococcus aureus*, MSSA = *methicillin-susceptible Staphylococcus aureus,* SCCmec = *Staphylococcal cassette chromosome mec*

This table shows the clinical importance of MRSA compared to MSSA, where MRSA is significantly causing longer hospitalization period, higher mortality rate, and more expensive treatment cost. This indicates how important an effective treatment against MRSA really is so that morbidity can be reduced.

2.4 Alternative treatment for MRSA

The high resistance of MRSA against β-lactam is causing an emerging needs of second-line medicine. The alternative therapy for MRSA based on WHO standard includes linezolid (the 1970s) and daptomycin (1980s).[2] Except for these two medicines, another alternative like tigecycline, telavancin, and ceftaroline is also still being developed.[30]

Vancomycin which was previously used as the drug of choice for MRSA is now being substituted due to increasing resistance. Unlike β-lactam antibacterial, the resistance of *S. aureus* against vancomycin and other glycopeptides antibacterials needed 40 years to develop.[14] This drug also needs a therapeutic drug monitoring (TDM) in its usage due to high nephrotoxicity.[30]

Resistance against alternative antibacterial agents like linezolid and daptomycin had been reported before. Resistance against linezolid caused by RNA subunit 23S methylation due to chloramphenicol/florfenicol resistance (cfr) gene, would cause an alteration of ribosomal binding.[30] The cause of resistance to daptomycin

is an enzyme called lysyl- phosphatidylglycerol (LPG) synthetase, that increases the synthesis of total LPG, a similar mechanism with resistance towards vancomycin.[14] Antibacterial that can still be used for MRSA with the decrease of sensitivity towards vancomycin, daptomycin, and linezolid, include quinupristin/dalfopristin, TMP-SMX, and telavancin, both as single drugs or combination with other antibacterial.[31]

The occurrence of resistance towards alternative antibacterials for MRSA implicates the need for further development of other compounds that targets MRSA increasing occurrence. One potential compound that can be developed as antibacterial agent for MRSA is xanthone.

3. The potential of xanthone development as an anti-MRSA compound

3.1 Xanthone in vitro analysis of anti-MRSA activity

Discovering new treatment course can be done by utilizing traditional herbal medicine or its synthetic compounds. Some new anti-infection drugs that originated from the nature has been approved by the Food and Drug Administration (FDA) since 2005, for instance doripenem, tigecyclin, telavancin, retapamulin, and monobactam aztreonam.[11] Xanthone derivatives compounds are good antimicrobial candidates, due to their antibacterial, antiviral, and antifungal characteristic. Not only as an antimicrobial spectrum, xanthone is also effective as antitumor, antioxidant, antiallergy, and anti-inflammatory.[32]

Xanthone derivatives (9H-xanthene-9-one) are a group of oxygen-containing heterocyclic compounds (Figure 2). The main structure of xanthone includes a planar tricyclic frame where one pyran ring fused with the two accompanying rings thus called dibenzo-γ-pyrone.[33] Natural xanthone can be divided based on its additional binding groups, for instance, simple oxygenated xanthone, glycosylated xanthone, prenylated xanthone, and so on.[34]

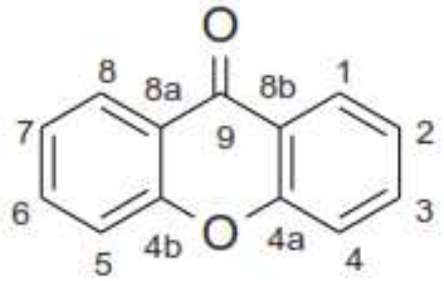


Figure 2.The main structure of xanthone[33]

As an antibacterial, xanthone is effective against a lot of gram positive and gram negative bacterias. Xanthone-sensitive gram positive bacterial include *Staphylococcus*, *Peptostreptococcus*, and *Streptococcus*. Xanthone-sensitive gram negative bacterial include Escherichia coli and Pseudomonas aeruginosa 34. Some studies showed that xanthone is not only effective against Staphylococcus aureus, but also potential against MRSA. Natural in vitro activity of xanthone against MRSA is summarized in Table 2.

Table 2 shows that the anti-MRSA activities of xanthone are different among plants in Garcinia genus. The best activities are found in α-mangostin compound (Figure 3) from Garcinia mangostana with MIC less than 2 μg/mL. While the lowest activity was found in Garcinia staudtii with MIC more than 15 μg/mL. Anti-MRSA activities of natural xanthone depend on its binding functional group. Some functional group that contributes in anti-MRSA properties of xanthone include methoxy in C-7 and hydroxy in C-5 as in Figure 4; H-5, 6-OH, prenyl C-8, as well as dimethyl chromene ring in C-2 and C-3 as seen in Figure 5 ; free prenyl in C-4 and hidroxy in C-5 and C-7 as seen in Figure 6; isoprenyl as seen in Figure 7(40).[35,36,40,42] The elimination of isoprenyl group can eliminate anti-MRSA activity.[11]

Table 2. Natural activity of xanthone against MRSA

Plants	Active compound	Method	MRSA isolats	MIC (µg/mL)	Reference
Garcinia cowa	garciniacowone	macrodilution	SK1	2	[35]
	cowanol	macrodilution	SK1	2	[35]
	mangostanin	microdilution	SK1	4	[36]
Garcinia mangostana	α- mangostin	macrodilution	DM21455	1,56	[37]
	α- mangostin	macrodilution	clinical isolated	1,95	[38]
	α- mangostin	microdilution	clinical isolated (9 strain)	6,25-12,5	[39]
	α- mangostin	macrodilution	DM21455	0,39	[11]
			9808R	0,78	
	α- mangostin	macrodilution	DM21455	0,39	[40]
			9808R	1,56	
Garcinia hanburyi	morrelic acid	disk diffusion assay	SFA300	12,5 (µM)	[41]
Garcinia staudtii	Staudtii xanthone A	agar-well-diffusion	NM*	16	[42]
Calophyllum brasiliense	1,3,5,6-tetrahydroxy-2-(3,3-dimethylallyl) xanthone	microdilution	3208 (no production of β-lactamase)	2	[43]
			80401 (produce β-lactamase)	4	

*NM: not mentioned

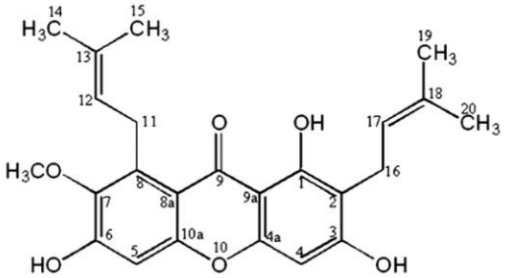


Figure 3. The structure of α-mangostin from *G. mangostana*[38]

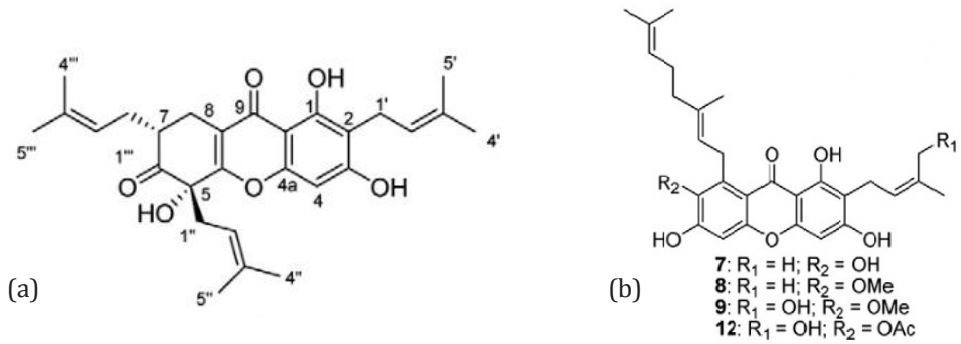
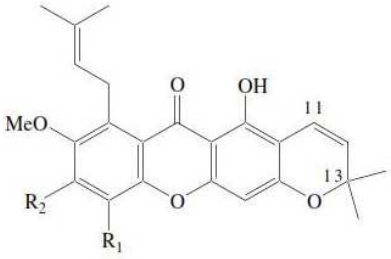
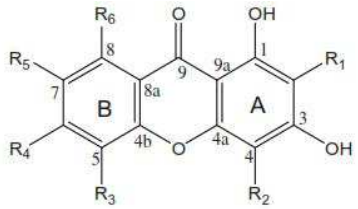


Figure 4. The structure of garciniacowone (a) and cowanone (b) from *G. gowa*[35]



3: R_1 = prenyl , R_2 = OH
11: R_1 = H, R_2 = OH
12: R_1 = H, R_2 = OMe

Figure 5. The structure of mangostanin (compound 11) from *G. Cowa*[36]



1 $R_1 = R_2$ = prenyl; $R_3 = R_5$ = OH; $R_4 = R_6$ = H
5 $R_1 = R_6$ = prenyl; $R_2 = R_3$ = H; R_4 = OH; $R_5 = OCH_3$
8 $R_1 = R_2$ = prenyl; $R_3 = R_6$ = OH; $R_4 = R_5$ = H

Figure 6. The structure of staudtii xanthone A (compound 1) from *G. staudtii*[42]

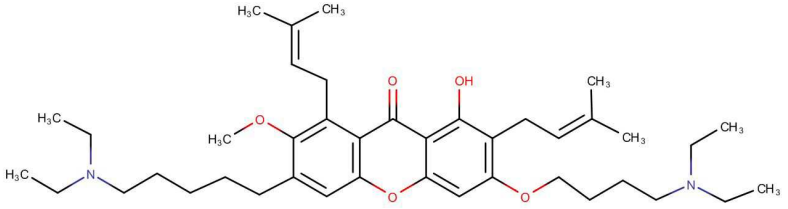


Figure 7. The structure of α-mangostin with additional isoprenyl group[40]

Not only that it has high anti-MRSA activity, α-mangostin from *G. mangostana* (AM-0016) also has much lower hemolytic activity (membranolytic) in rabbit's eritrocytes thus it is not toxic to normal tissue.[37] The results from quantitative structure-activity relationship analysis of some modified α-mangostin group show that the substitution of N-ethyl group produces better inhibitory activity (MIC 0,39-3,125 µg/mL), while longer natural N-propyl or alkylamin substitution produce lesser anti MRSA activity, with MIC ≥ 12,5 µg/mL (Table 3). The order of anti-MRSA activity and hemolytic is non isoprenyl or non hydrogenized compounds< hydrogenized isoprenyl < isoprenyl. This research found that isoprenyl groups has more contribution on anti-MRSA activity, as well as affecting the hemolytic properties.[11]

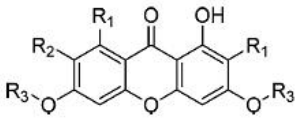
3.2 The antibacterial mechanism of xanthone compounds against MRSA

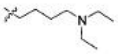
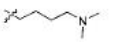
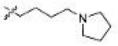
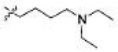
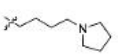
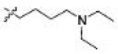
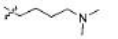
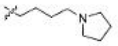
The antibacterial mechanism of xanthone derivatives against MRSA is currently still unclear. One of the posibility of its target mechanism is through bacterial cytoplasmic membrane. α-mangostin induces potential membrane disipation teice faster in two times Minimum Inhibitory Concentration (MIC), and thus causing a leakage of bacterial intracellular components.[37] Amphiphilic xanthone compound can disrupt bacterial membrane through a mechanism called interfacial activity model.[11] This mechanism depends on a balance between hidrophobik and electrostatic interaction of peptides, water, and lipid, and is also the basic mechanism of antimicrobial peptide/AMP.[44]

Model interfacial activity contributes in the development of new AMP antibacterial agents, especially for bacterias who has been resistant. Most AMP works by damaging bacterial cell membrane so that bacterias are more prone to antibacterial agents.[45] This is why the utilization of xanthone is combined with other antibacterials that has been proven effective against MRSA and are sinergistic in nature.[39]

Xanthone is also presumed to work as anti-

Table 3. α-mangostin compound from G. mangostana and its selectivity



Compound	R_1	R_2	R_3	MIC	HC50	Selectivity
1		OCH_3	H	2	9.0	4.5
2c		OCH_3		0.39	19.6 ± 3	50.4
4a		OCH_3		3.125	32.1 ± 3	10.3
5a		OCH_3		12.5	28.9 ± 2	2.3
7	H	H	H	> 50	> 200	NA[a]
8a	H	H		> 50	> 200	NA
8b	H	H		> 50	> 200	NA
9		OCH_3	H	> 50	38.0 ± 3	NA
10a		OCH_3		3.125	48.6 ± 3	15.6
10b		OCH_3		12.5	60.7 ± 4	4.9
10c		OCH_3		25	34.8 ± 3	1.4

MRSA by inducing the release of lipotheicolic acid (LTA) from MRSA cell wall. LTA is the main compound in the cell wall of Gram positive bacterias that bind convalently with the outer part of peptidoglikan which is important in cell protection.[46] The damage of LTA will ease the work of other antibacterial agents to eradicate target bacterias. Xanthone ability as an antioxidant is also presumed to contribute to its role against MRSA.[47] An antioxidant compounds are able to interact with the cell membrane of targeted microorganism, through its ability to bind with extracellular protein, soluble protein, and bacterial cell wall. MRSA as a Gram positive bacteria will be easier to eradicate by antioxidant compound because it only has one layer cell wall, while Gram negative bacteria has more layers of cell walls.[48] Nonetheless, mamalian cell walls can also be affected by antioxidant, thus an anlysis of Xanthone's possible toxicity in normal cells is needed, for instance in erythrocyte.

All the mechanisms mentioned above leads to bacterial cell wall and membrane damage, which highly depends on Xanthone ability to penetrate the cell wall. Thus,currently, the development of xanthone as anti MRSA is more directed to design and development of smaller molecules with higher membran selectivity to lessen the toxicity against normal mamalian cells.[49] Some efforts that has already been done is adding a lipophylic functional groups, like those in xanthone amphiphilic compound, which produce higher anti MRSA activity with lower membrane selectivity and lower toxicity.[11]

CONCLUSION

The development of MRSA in hospitals and community settings, as well as the emergence of resistancu against currently used anti MRSA antibacterials (linezolid and daptomycin) triggers continuous new research on possible anti MRSA, including xanthone. Various in vitro studies showed the ability of xanthone derivates to inhibit the growth of MRSA and its selective antibacterial nature (non-toxic to normal cells). The mechanism of action of xanthone derivates as anti-MRSA is still unclear, but it is presumed to involve bacterial cytoplasmic damage and

through antioxidant activity. By discovering the structures that contributes in antibacterial activities of xanthone derivates, further xanthone development as antibacterial is possible by modifying those structures, for instance, by adding a lipophylic functional groups .

REFERENCES

1. World Health Organization. Antimicrobial resistance: Global Reports of surveillance. WHO Publ. 2014. Geneva: WHO, 2014
2. Chaudhary AS. PERSPECTIVE A review of global initiatives to fi ght antibiotic resistance and recent antibiotics ' discovery. Acta Pharm Sin B. 2016;6(6):552–6
3. European Centre for Disease Control and Prevention. Annual epidemiological report: Antimicrobial resistance and healthcare-associated infections 2014. Stockholm: ECDC, 2015
4. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Georgia: CDC, 2013
5. Lai C, Lee K, Xiao Y, Ahmad N, Veeraraghavan B, Thamlikitkul V, et al. High burden of antimicrobial drug resistance in Asia. Integr Med Res. 2014;2(3):141–7
6. World Health Organization. The evolving threat of antimicrobial resistance: Options for action. Geneva: WHO, 2015
7. Hwang AY, Gums JG. The emergence and evolution of antimicrobial resistance : Impact on a global scale. Bioorg Med Chem. 2016;24:6440–5
8. Zhu Y, Cleaver L, Wang W, Podoll JD, Walls S, Jolly A, et al. Tetracyclic indolines as a novel class of b -lactam-selective resistance-modifying agent for MRSA. Eur J Med Chem. 2017;125:130–42
9. Alharbi SA, Wainwright M, Alahmadi TA, Salleeh H Bin, Faden AA., Chinnathambi A. What if fleming had not discovered penicillin? Saudi J Biol Sci. 2014;21(4):289–93
10. Carlet J, Collignon P, Goldmann D, Goossens H, Gyssens IC, Harbarth S, et al. Society's failure to protect a precious resource: Antibiotics. The Lancet. 2011;378(9788):369–71
11. Koh JJ, Zou H, Lin S, Lin H, Soh RT, Lim FH, et al. Nonpeptidic Amphiphilic Xanthone Derivatives: Structure-Activity Relationship and Membrane-Targeting Properties. J Med Chem. 2016;59:171–93.
12. Levy-hara G, Amábile-cuevas CF, Gould I, Hutchinson J, Abbo L, Saxynger L, et al. "Ten commandments" for the appropriate use of antibiotics by the practicing physician in an outpatient setting. Front Microbiol. 2011;2:1–7.
13. Levy-hara G, Kanj SS, Pagani L, Abbo L, Endimiani A, Wertheim HFL, et al. Ten key points for the appropriate use of antibiotics in hospitalised patients: a consensus from the Antimicrobial Stewardship and Resistance Working Groups of the International Society of Chemotherapy. Int J Antimicrob Agents. 2016;48(3):239–46
14. Stryjewski ME, Corey GR. Methicillin-resistant Staphylococcus aureus: An evolving pathogen. Clin Infect Dis. 2014;58(Suppl 1):10–9.
15. Song JH, Hsueh PR, Chung DR, Ko KS, Kang CI, Peck KR, et al. Spread of methicillin-resistant Staphylococcus aureus between the community and the hospitals in Asian countries: An ANSORP study. J Antimicrob Chemother. 2011;66:1061–9.
16. Liu J, Chen D, Peters BM, Li L, Li B, Xu Z, et al. Staphylococcal chromosomal cassettes mec (SCCmec): A mobile genetic element in methicillin-resistant Staphylococcus aureus. Microb Pathog. 2016;101:56–67
17. Roemer T, Schneider T, Pinho MG. Auxiliary factors: A chink in the armor of MRSA resistance to β-lactam antibiotics. Curr Opin Microbiol. 2013;16(5):538–48
18. Tang SS, Apisarnthanarak A, Hsu LY. Mechanisms of β-lactam antimicrobial resistance and epidemiology of major community- and healthcare-associated multidrug-resistant bacteria. Adv Drug Deliv Rev. 2014;78:3–13
19. Gómez P, Lozano C, González-Barrio D, Zarazaga M, Ruiz-Fons F, Torres C. High prevalence of methicillin-resistant Staphylococcus aureus (MRSA) carrying the mecC gene in a semi-extensive red deer (Cer-

vus elaphus hispanicus) farm in Southern Spain. Vet Microbiol. 2015;177:326–31.
20. Rozgonyi F, Kocsis E, Kristóf K, Nagy K. Is MRSA more virulent than MSSA? Clin Microbiol Infect. 2007;13:843–5.
21. Lindsay JA. Evolution of Staphylococcus aureus and MRSA during outbreaks. Infect Genet Evol. 2014;21:548–53
22. Goldfain A, Smith B, Cowell LG. Towards an ontological representation of resistance: The case of MRSA. J Biomed Inform. 2011;44(1):35–41
23. Fooladi AAI, Ashrafi E, Tazandareh SG, Koosha RZ, Rad HS, Amin M, et al. The distribution of pathogenic and toxigenic genes among MRSA and MSSA clinical isolates. Microb Pathog. 2015;81:60–6.
24. Appelbaum PC. Reduced glycopeptide susceptibility in methicillin-resistant Staphylococcus aureus (MRSA). Int J Antimicrob Agents. 2007. p. 398–408.
25. Kato Y, Suzuki T, Ida T, Maebashi K, Sakurai M, Shiotani J, et al. Microbiological and clinical study of methicillin-resistant Staphylococcus aureus (MRSA) carrying VraS mutation: changes in susceptibility to glycopeptides and clinical significance. Int J Antimicrob Agents. 2008;31:64–70.
26. Maki H, Mccallum N, Bischoff M, Berger-bächi B, Wada A. tcaA Inactivation Increases Glycopeptide Resistance in Staphylococcus aureus. Antimicrob Agents Chemother. 2004;48(6):1953–9.
27. Melzer M, Eykyn SJ, Gransden WR, Chinn S. Is methicillin-resistant Staphylococcus aureus more virulent than methicillin-susceptible S. aureus? A comparative cohort study of British patients with nosocomial infection and bacteremia. Clin Infect Dis. 2003;37(November):1453–60
28. Ochoa TJ, Mohr J, Wanger a, Murphy JR, Heresi GP. Community-associated methicillin-resistant Staphylococcus aureus in pediatric patients. Emerg Infect Dis. 2005;11(6):966–8.
29. Mayer S, Boos M, Beyer A, Fluid AC, Schmitz FJ. Distribution of the antiseptic resistance genes. J Antimicrob Chemother. 2001;47:896–7.
30. Gould IM, David MZ, Esposito S, Garau J, Lina G, Mazzei T, et al. New insights into meticillin-resistant Staphylococcus aureus (MRSA) pathogenesis, treatment and resistance. Int J Antimicrob Agents. 2012;39:96–104.
31. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52:1–38.
32. Pedraza-Chaverri J, Cárdenas-Rodríguez N, Orozco-Ibarra M, Pérez-Rojas JM. Medicinal properties of mangosteen (Garcinia mangostana). Food Chem Toxicol. 2008;46:3227–39.
33. Yang Z-M, Huang J, Qin J-K, Dai Z-K, Lan W-L, Su G-F, et al. Design, synthesis and biological evaluation of novel 1-hydroxyl-3- aminoalkoxy xanthone derivatives as potent anticancer agents. Eur J Med Chem. 2014;85:487–97
34. Pinto MMM, Sousa ME, Nascimento MSJ. Xanthone derivatives: new insights in biological activities. Curr Med Chem. 2005;12:2517–38.
35. Siridechakorn I, Phakhodee W, Ritthiwigrom T, Promgool T, Deachathai S, Cheenpracha S, et al. Antibacterial dihydrobenzopyran and xanthone derivatives from Garcinia cowa stem barks. Fitoterapia. 2012;83:1430–4.
36. Panthong K, Pongcharoen W, Phongpaichit S, Taylor WC. Tetraoxygenated xanthones from the fruits of Garcinia cowa. Phytochemistry. 2006;67:999–1004.
37. Koh JJ, Qiu S, Zou H, Lakshminarayanan R, Li J, Zhou X, et al. Rapid bactericidal action of alpha-mangostin against MRSA as an outcome of membrane targeting. Biochim Biophys Acta - Biomembr. 2013;1828(2):834–44
38. Chomnawang MT, Surassmo S, Wongsariya K, Bunyapraphatsara N. Antibacterial Activity of Thai Medicinal Plants against Methicillin-resistant Staphylococcus aureus. Fitoterapia. 2009;80(2):102–4

39. Sakagami Y, Iinuma M, Piyasena KGNP, Dharmaratne HRW. Antibacterial activity of α-mangostin against vancomycin resistant Enterococci (VRE) and synergism with antibiotics. Phytomedicine. 2005;12:203–8.
40. Li J, Liu S, Koh JJ, Zou H, Lakshminarayanan R, Bai Y, et al. A novel fragment based strategy for membrane active antimicrobials against MRSA. Biochim Biophys Acta - Biomembr. 2015;1848(4):1023–31
41. Chaiyakunvat P, Anantachoke N, Reutrakul V, Jiarpinitnun C. Caged xanthones: Potent inhibitors of global predominant MRSA USA300. Bioorg Med Chem Lett. 2016;26(13):2980–3
42. Ngoupayo J, Tabopda TK, Ali MS. Antimicrobial and immunomodulatory properties of prenylated xanthones from twigs of Garcinia staudtii. Bioorg Med Chem. 2009;17(15):5688–95
43. Yasunaka K, Abe F, Nagayama A, Okabe H, Lozada-Pérez L, López-Villafranco E, et al. Antibacterial activity of crude extracts from Mexican medicinal plants and purified coumarins and xanthones. J Ethnopharmacol. 2005;97:293–9.
44. Wimley WC. Describing the Mechanism of Antimicrobial Peptide Action with the Interfacial Activity Model. ACS Chem Biol. 2010;5:905–17.
45. Vishnepolsky B, Pirtskhalava M. Prediction of linear cationic antimicrobial peptides based on characteristics responsible for their interaction with the membranes. J Chem Inf Model. 2014;54:1512–23.
46. Joung DK, Mun SH, Choi SH, Kang OH, Kim SB, Lee YS, et al. Antibacterial activity of oxyresveratrol against methicillin-resistant Staphylococcus aureus and its mechanism. Exp Ther Med. 2016;12:1579–84.
47. Santos CMM, Freitas M, Ribeiro D, Gomes A, Silva AMS, Cavaleiro J a. S, et al. 2,3-Diarylxanthones as strong scavengers of reactive oxygen and nitrogen species: A structure-activity relationship study. Bioorg Med Chem. 2010;18:6776–84.
48. Araújo MGDF, Hilário F, Vilegas W, dos Santos LC, Brunetti IL, Sotomayor CE, et al. Correlation among antioxidant, antimicrobial, hemolytic, and antiproliferative properties of Leiothrix spiralis leaves extract. Int J Mol Sci. 2012;13:9260–77.
49. Shagufta, Ahmad I. Recent insight into the biological activities of synthetic xanthone derivatives. Eur J Med Chem [Internet]. Elsevier Masson SAS; 2016;116:267–80