Journal of Applied Pharmaceutical Science Vol. 10(05), pp 142-157, May, 2020
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2020.10519
ISSN 2231-3354

Marine sponge compounds with antiplasmodial properties: Focus on *in vitro* study against *Plasmodium falciparum*

Baso Didik Hikmawan[1], Subagus Wahyuono[2], Erna Prawita Setyowati[2*]

[1]Master of Pharmaceutical Science Program, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia
[2]Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia

ARTICLE INFO

Received on: 09/10/2019
Accepted on: 18/02/2020
Available online: 06/05/2020

Key words:
Bioactive compounds, drug development, antimalarial, marine natural product, *Porifera*.

ABSTRACT

Malaria continues to be a major cause of morbidity and mortality in many tropical countries. The lack of progress in drug discovery and the spread of drug resistance become the reason behind this. *Porifera* (sponges) is a potential source of novel bioactive compounds to provide future drugs against malaria. In this review, we summarized 243 isolated molecules belonging to 35 different genera that active against *Plasmodium falciparum* from published paper until March 2019. The molecules were classified into potent, good, moderate, low, and inactive based on their IC_{50}, and among observed bioactive metabolites, there were 57 marine sponge molecules reported to act as potent antiplasmodium against various strains of *P. falciparum* including drug resistance and nondrug resistance. Table 2 represents the list of isolated compounds with "potent" antimalarial activity. The class of the listed compounds includes manzamine alkaloid, guanidine alkaloids, bispyrroloiminoquinone alkaloids, pyrroloiminoquinone alkaloids, ingamine alkaloids, bromotyrosine alkaloids, sesquiterpenoids, diterpene formamides, aminoimidazole, β-galactosylceramides, β-lactam, meroterpene, trisoxazole macrolides, peroxides, thiazine alkaloids, and sterols. With this up-to-date review, we attempt to present new perspectives for the rational discovery of novel sponge metabolites that can be used as lead compounds in antimalarial drug development.

INTRODUCTION

Malaria is the most life-threatening and infectious disease caused by *Plasmodium* parasites such as *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium malariae*. Among those protozoans, *P. falciparum* is considered to be responsible for most severe diseases and most fatal cases. The World Health Organization (2018) stated in the year of 2017 that more than 99% of estimated malaria cases in the WHO African Region followed by the WHO regions of the Western Pacific (71.9%), the Eastern Mediterranean (69%), and Southeast Asia (62.8%) were caused by this most prevalent malaria parasite. In the same period, the WHO reported approximately 219 million cases of malaria occurred worldwide including 435,000 deaths. Nowadays, malaria continues to be a major cause of morbidity and mortality in tropical countries. It is further aggravated by an increase in a number of multidrug-resistant strains of *Plasmodium* accompanied by a lack of progress in the development of vaccines and drug discovery. As a consequence, the search of new agent that actives against malaria becomes urgent needs (Antony and Parija 2016; Burrows *et al*., 2011; Cui *et al*., 2015; Dondorp *et al*., 2000; Noedl *et al*., 2008).

Marine ecosystems are the largest part of the biosphere. More than 70% of the Earth's surface is covered by water, and several theories believe that the life on earth originated from the ocean. In certain marine ecosystems such as coral reefs or the deep-sea floor, scientists estimate that the diversity of marine biota is even greater than the biota inhabiting tropical rainforests. Many immotile or slow-moving marine invertebrates, which usually do not have physical protection such as shells or thorns, will produce secondary metabolites as a form of defense mechanism from the environment and other creatures in the ocean (Ebada *et al*., 2008). These compounds attract the attention of researchers from various fields such as chemistry, pharmacology, biology, and ecology. This

*Corresponding Author
Erna Prawita Setyowati, Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia.
E-mail: erna_prawita @ ugm.ac.id

statement is supported by the fact that the number of new bioactive constituents isolated from marine biota has been increasing in the past three decades (332 compounds were isolated in 1984, and 1490 new compounds were isolated in 2017) (Blunt *et al*., 2016; Carroll *et al*., 2019).

Exploration of secondary metabolites from marine organisms is expected to provide new active substituents against various diseases (Newman and Cragg, 2007). Several studies have managed to isolate metabolites from marine microorganisms, green, red, and brown algae, phytoplankton, *Cnidaria*, *Bryozoa*, molluscs, tunicates, echinoderms, mangroves, sponges, and itertidal plants which have proven to have pharmaceutical properties such as acetylcholinesterase inhibitor, radical scavenging activity, cytotoxicity, antimicrobial, anticancer, antitumor, hemolytic, anti-inflammatory, antiparasitic, antimalarial, and antifungal (Blunt *et al*., 2016; D'Ambrosio *et al*., 1996; Fattorusso and Taglialatela-Scafati 2009; Orhan *et al*., 2010; Rama Rao and Faulkner 2002; Setyowati *et al*., 2009; 2017a; 2017b).

From the perspective of drug discovery, a marine sponge is one of the invertebrate organisms which is interesting to be explored due to its potency producing new compounds (Anjum *et al*., 2016). The lack of physical defense of sponges resulting in secondary metabolites is estimated to vary depending on their habitats. Metabolite compounds isolated from sponges are highly diverse such as alkaloids, esters, fatty acids, glycosides, ketones, lipids, macrolides, peptides, peroxides, quinones, terpenoids, and polyketides and have shown many biological activities, in which one of them is antimalaria (Blunt *et al*., 2016; 2017; 2018; Carroll *et al*., 2019). These kinds of compounds have been found to interfere with pathogenesis at many distinct points; therefore, this can be beneficial in developing selective antimalarial drugs (Sipkema *et al*., 2005)

The aim of this review is to summarize compounds isolated from marine sponges which exhibit *in vitro* antiplasmodial properties, to identify the compounds with potent activity based on their IC_{50} values, and to highlight the most important functional groups of the compounds related to their potent activity against various strains of *P. falciparum*. One of the advantages of an *in vitro* study is that the study could thoroughly illustrate an effect of structural features of tested compounds to their activity with no interference from other factors such as biological system which can be found on *in vivo* study. Therefore, it can be used to generate more potent derivatives of the compounds to develop selective antimalaria drugs that work in blood-stage *P. falciparum*.

METHOD

A systematic search was accomplished to find all publications related to the theme until March 2019 in PubMed and Google Scholar. The keywords used to search the articles were "*Plasmodium falciparum*, sponge, antimalarial" or "*Plasmodium falciparum*, sponge, antiplasmodial." The data included in the review were primary articles in English about *in vitro* antimalarial study of pure compounds isolated from marine sponges against *P. falciparum* as shown in Table 1. The articles obtained were then removed if they are review articles, conference articles, and thesis, and there are no data available to be retrieved. All the synthetic compounds derived from naturally occurring metabolites in sponge are not mentioned in this review. Variables assessed in this review include sponge species/genus, isolated compound, strain of *P. falciparum*, region/country of origin, and effect on parasite growth inhibition.

EXPLORATION OF MARINE SPONGE METABOLITES FOR ANTIPLASMODIAL ASSAY

Among marine invertebrates, a sponge is the most dominant source for discovering natural products that have been used as lead compound to develop therapeutic drugs (Perdicaris *et al*., 2013). However, the study done in the investigation of marine sponge metabolites for antimalarial activity is relatively low compared to those of antitumor and anticancer. From literature published until March 2019, we included 50 primary articles for the review (Table 1). We identified that 35 different genera have been studied for their antiplasmodial activities and found that the most frequently studied genera were genus *Agelas*, *Plakortis*, and *Xestospongia* from different locations. Although many bioactive compounds have been isolated from marine sponges (Blunt *et al*., 2016; 2018; Carroll *et al*., 2019), the evaluation of their antiplasmodial activity is still relatively low. Figure 1 shows the number of studies that have been done on the examination of *in vitro* antiplasmodium of isolated compounds from marine sponge.

Overall, the number of publications from year to year shows fluctuation pattern. The highest number of the published papers was in the year of 2010 with 10 articles, followed by six publications in 2009 and 2012. In regard to the number of publications from 2013 to March 2019, it seemed to be stuck at one to three studies each year. This indicates that exploration trend of marine sponge metabolites for antiplasmodial activity diminished from 31 published papers during the period of 1992–2010 to 21 publications during the period of 2011–March 2019. One of the reasons behind the trend is that many scientists are interested in microbiological sample investigations for marine natural product exploration including bacteria and fungi sponge associated, making the detriment of sponge-derived compounds (Carroll *et al*., 2019; Thomas *et al*., 2010).

Various ecological studies have shown that secondary metabolites produced by sponges often serve defensive purposes to protect them from threats such as predator attacks, microbial infections, biofouling, and overgrowth by other sessile organisms (Paul and Puglisi, 2004; Paul *et al*., 2006). Therefore, compounds isolated from the same sponge species are more likely to be different if their habitat is distinct due to the ecological response (Mani *et al*., 2012). Moreover, a review done by Qaralleh (2016) found out that among 27 species of genus *Neopetrosia*, there are only nine species which have been chemically studied thus far. These facts disclose significant opportunities to do the chemical constituent exploration from not only genus *Neopetrosia* but also the other genus. In terms of collection site of the sponges, Australia, Bahamas, Indonesia, and Thailand were the most explored site so far for the search of compounds which exhibit *in vitro* antiplasmodium (*P. falciparum* strains). Other sponges were collected from Turkey, Vanuatu, Madagascar, Caledonia, Fiji, China, Japan, Alaska, Jamaica, Solomon Island, Puerto Rico, Papua New Guinea, and others (Table 1).

Table 1. Summarized data of isolated compounds which have been tested for their antiplasmodial activity.

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
1	*Acanthella klethra*	Axisonitrile 3	D6	0.61	Pelorus Island, Queensland, Australia	(Angerhofer *et al*., 1992)
			W2	0.07		
		Axisothiocyanate 3	D6	46.85		
			W2	11.81		
		The eudesmane compound A[a]	D6	8.50		
			W2	2.32		
		The eudesmane compound B[b]	D6	16.17		
			W2	2.22		
		The eudesmane compound C[c]	D6	>37.96		
			W2	>37.96		
2	*Acanthostrongylophora ingens*	(+)-8-hydroxymanzamine A	D6	0.03	Papua New Guinea	(Samoylenko *et al*., 2009)
			W2	0.04		
		(+)-manzamine A	D6	0.04		
			W2	0.05		
		(+)-8-hydroxymanzamine A hydrochloride	D6	0.04		
			W2	0.06		
		(+)-manzamine A hydrochloride	D6	0.01		
			W2	0.01		
3	*Acanthostrongylophora* sp.	Manzamine A	D6	0.01	Knife Cape Manado, Indonesia	(Rao *et al*., 2006)
			W2	0.01		
		(+)-8-hydroxymanzamine A	D6	0.01		
			W2	0.01		
		Manzamine Y	D6	0.74		
			W2	1.50		
		Manzamine E	D6	6.02		
			W2	8.43		
		6-hydroxymanzamine E	D6	1.36		
			W2	1.50		
		Manzamine F	D6	1.34		
			W2	2.93		
		12,34-oxamanzamine A	D6	8.97		
			W2	na		
		Ent-12,34-oxamanzamine F	D6	1.45		
			W2	1.90		
		12,28-oxamanzamine A	D6 and W2	na		
		12,28-oxa-8-hydroxy-manzamine A	D6 and W2	na		
		12,34-oxamanzamine E	D6 and W2	na		
		12,28-oxamanzamine E	D6 and W2	na		
		12,34-oxa-6-hydroxymanzamine E	D6 and W2	na		
4	*Acanthostrongylophora* sp.	Manzamine A N-oxide	D6	0.02	Manado, Indonesia	(Rao *et al*., 2004)
			W2	0.02		
		3,4-dihydromanzamine A-N-oxide	D6	2.82		
			W2	6.53		
		Manzamine J	D6	2.36		
			W2	1.36		
		6-deoxymanzamine X	D6	2.30		
			W2	2.48		

(Continued)

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
		Manzamine X	D6	1.64		
			W2	3.44		
		Neo-kauluamine	D6	1.46		
			W2	2.41		
		Ircinal A	D6	5.82		
			W2	7.51		
		Ircinal A	D6 and W2	na		
5	*Agelas* cf. *mauritiana*	Agelasine J	FcB1	6.60	Solomon Islands	(Appenzeller *et al*., 2008)
		Agelasine K	FcB1	8.30		
		Agelasine L	FcB1	18.00		
6	*Agelas gracilis*	Gracilioethers A	ItG	28.22	Oshima-Shinsone, Japan	(Ueoka *et al*., 2009)
		Gracilioethers B	ItG	1.56		
		Gracilioethers C	ItG	31.02		
7	*Agelas oroides*	24-ethyl-cholest-5α-7-en-3-α-ol	K1	38.82	Go¨kc¸eada, Turkey	(Tasdemir *et al*., 2007)
		4,5-dibromopyrrole-2-carboxylic acid methyl ester	K1	>176.73		
		4,5-dibromopyrrole-2-carboxylic acid (free base)	K1	>185.95		
		4,5-dibromopyrrole-2-carboxylic acid (salt)	K1	136.37		
		(E)-oroidin (free base)	K1	10.02		
		(E)-oroidin (salt)	K1	16.25		
		3-amino-1-(2-aminoimidazoyl)-prop-1-ene	K1	53.56		
		Taurine	K1	>399.52		
8	*Agelas dispar*	Longamide B	K1	21.19	Little San Salvador Island	(Scala *et al*., 2010)
9	*Agelas longissima*	Longamide A	K1	>64.53	Little San Salvador Island	(Scala *et al*., 2010)
		Agelongine	K1	32.97		
10	Genus Agelas (*A. conifera*, *A. clathrodes*, *A. longissima*, and *A. dispar*)	Sceptrin	K1	17.86	Little San Salvador Island	(Scala *et al*., 2010)
		Hymenidin	K1	40.43		
		Dispacamide B	K1	4.11		
		Dispacamide D	K1	>58.45		
11	*Aplysinella strongylata*	19-hydroxypsammaplysin E	3D7	6.40	Tulamben Bay, Bali, Indonesia	(Mudianta *et al*., 2012)
		Psammaplysin K	3D7	nat 10 µM		
		Psammaplysin L	3D7	nat 10 µM		
		Psammaplysin M	3D7	nat 10 µM		
		Psammaplysin N	3D7	nat 10 µM		
		19-hydroxypsammaplysin P	3D7	nat 10 µM		
		Psammaplysin T	3D7	nat 10 µM		
		Psammaplysin V	3D7	nat 10 µM		
12	*Axinyssa djiferi*	Axidjiferosides (mix-A, -B, -C)	FcB1	0.53	Senegalese coasts, Keur Bamboung	(Farokhi *et al*., 2013)
13	*Axinella verrucosa*	Stevensine	K1	12.61	Calvi Bay, Corsica	(Scala *et al*., 2010)
		Spongiacidin B	K1	3,34		
		Bromoaldisin	K1	>82.08		
		Dibromopalau'amine	K1	1.48 µg/ml		
		Bromopyrrolohomoarginin	K1	>20 µg/ml		
		Manzacidin A	K1	>20 µg/ml		

(Continued)

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
14	*Biemna laboutei*	Netamine K	not available	2.40	Salary Bay, Madagascar	(Gros *et al*., 2014)
		Mirabilin A	not available	20.70		
15	*Biemna laboutei*	Netamine O	not available	16.99	Salary Bay, Madagascar	(Gros *et al*., 2015)
		Netamine P	not available	32.62		
		Netamine Q	not available	8.37		
		Netamine H	not available	na		
		Netamine I	not available	na		
		Netamine N	not available	na		
		Netamine C	not available	na		
		Netamine F	not available	na		
16	*Callyspongia fibrosa*	24*S*-24- methyl-cholestane 3β,6β,25-triol-25-O-acetate	3D7	54.81	The Gulf of Mannar, Western Bay of Bengal, India	(Prakasa Rao *et al*., 2010)
			K1	54.02		
		24*S*-24-methyl-cholestane-3β,5α,6β,25-tetraol-25-monoacetate	3D7	30.10		
			K1	20.54		
		24S-24-methyl-cholestane-3β,6β,8β,25-tetraol-25-O-acetate	3D7	48.46		
			K1	44,44		
		24S-24-methyl-chelestane-3β,5α,6β,12β,25-pentaol-25-O-acetate	3D7	48,48		
			K1	47,75		
17	*Clathria calla*	Norbatzelladine L	FcB1	0.40	Island of Martinique	(Laville *et al*., 2009)
		Clathriadic acid		2.30		
18	*Cymbastela cantharella*	Girolline	FcB1	0.21	Caledonian sponge	(Benoit-Vical *et al*., 2008)
			W2	0.11		
			FcM29	0.13		
			F32	0.08		
19	*Cymbastela hooperi*	(1S,3S,4R,7S,8S,11S,12S,13S,15R,20R)-7-Formamido-20-isocyanoisocycloamphilectane	FCR3F86	0.58	Not available	(Wright and Lang-Unnasch, 2009)
			W2	1.75		
			D6	2.34		
		(1S,3S,4R,7S,8S,11S,12S,13S,15R,20R)-7,20-Diformamidoisocycloamphilectane	FCR3F86	41.05		
		(1S*,3S*,4R*,7S*, 8S*,12S*,13S*)-7-formamidocycloamphilect-11(20)-ene	FCR3F86	na		
		(1R*,3S*,4R*,7S*,8S*,12S*,13S*)-7-formamidoamphilecta-11(20),14-diene	FCR3F86	na		
		(1S*,3S*,4R*,7S*,8S*,12S*,13S*)-7-formamidoamphilecta-11(20),15-diene	FCR3F86	na		
20	*Desmapsamma anchorata*	sulfated polysaccharides	3D7	66.3 µg/ml	Not available	(Marques *et al*., 2016)
21	*Diacarnus megaspinorhabdosa*	Diacarnuperoxide M	W2	4.20	Xisha Islands	(Yang *et al*., 2010)
			D6	5.60		
		Diacarnuperoxide N	W2	3.00		
			D6	6.60		
		(+)-2, 3, 6-epihurghaperoxide	W2	1.60		
			D6	2.20		
		(+)-2,3,6-epihurghaperoxide acid	W2	4.90		

(Continued)

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
			D6	7.30		
		(-)-muqubilin A	W2	5.60		
			D6	8.60		
		Nuapapuin A	W2	5.50		
			D6	8.10		
		Diacarperoxide A	W2	1.90		
			D6	2.00		
22	*Fascaplysinopsis reticulata*	8-oxo-tryptamine	3D7	50.52	Passe Bateau, Mayotte	(Campos *et al*., 2019)
		(E) and (Z)-6-bromo-20-demethyl-30-N-methylaplysinopsin	3D7	24.01		
		6,6'-bis-(debromo)-gelliusine F	3D7	na		
		6-bromo-8,1'-dihydro-isoplysin A	3D7	na		
		5,6-dibromo-8,1'-dihydro-isoplysin A	3D7	na		
		tryptamine	3D7	na		
23	*Hyattella* sp.	psammaplysin G	Dd2	98% iotga 40 µM	Hervey Bay, Sponge Garden, Queensland, Australia	(Yang *et al*., 2010)
		psammaplysin F	Dd2	1.40		
24	*Hymeniacidon* sp	monamphilectine A	W2	0.60	Mona Island, Puerto Rico	(Avilés and Rodríguez, 2010)
25	*Hyrtios cf. erecta*	homofascaplysin A	K1	0.04	Fiji	(Kirsch *et al*., 2000)
			NF54	0.07		
		fascaplysin	K1	0.16		
			NF54	0.11		
26	*Hyrtios erectus*	smenotronic acid	Dd2	3.51	Chuuk Island, Federated States of Micronesia	(Ju *et al*., 2018)
		ilimaquinone	Dd2	2.11		
		pelorol	Dd2	0.80		
27	*Ircinia* sp.	tryptophol	K1	31.51	Aegean Sea, Turkey	(Orhan *et al*., 2010)
		4-hydroxy-3-tetraprenyl-phenylacetic acid	K1	7.77		
		demethylfurospongin-4	K1	32.23		
		dorisenone D	K1	1.03		
		11β-acetoxyspongi-12-en-16-one	K1	3.02		
28	Genus *Latrunculia* (later identified as *Latrunculia* (L.) *hamanni* sp. nov. (Kelly *et al*., 2016))	discorhabdins A	D6	0.05	Aleutian Islands	(Na *et al*., 2010)
			W2	0.05		
		discorhabdins C	D6	2.80		
			W2	2		
		dihydrodiscorhabdin C	D6	0.17		
			W2	0.13		
29	*Lendenfeldia dendyi*	Four polybromidated diphenyl ethers[d]	D6	na	Papua New Guinea	(Radwan *et al*., 2015)
			W2	na		
30	*Mycophora* sp.	Crambescidin 800	FCR3	0.24	Not available	(Lazaro *et al*., 2006)
			3D7	0.16		
31	*Monanchora arbuscula*	norbatzelladine A	FcB1	0.20	island of Martinique	(Laville *et al*., 2009)
		dinorbatzelladine A	FcB1	0.90		
		dinordehydrobatzelladine B	FcB1	0.80		
		dihomodehydrobatzelladine C	FcB1	4.50		

(Continued)

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
		batzelladine A	FcB1	0.30		
		batzelladine L	FcB1	0.30		
		ptilomycalin A	FcB1	0.10		
32	*Monanchora unguiculata*	Unguiculin A	3D7	12.89	Mitsio Islands, Madagascar	(Campos *et al*., 2019)
		Ptilomycalin E	3D7	0.35		
		Ptilomycalin F	3D7	0.23		
		Ptilomycalins G + H	3D7	0.46		
		Crambescidin 800	3D7	0.52		
		Fromiamycalin	3D7	0.24		
33	New Caledonian Sponge	Alisiaquinones A	FcMC29	8.50	the Norfolk Rise (New Caledonia)	(Desoubzdanne *et al*., 2008)
			FcB1	7.40		
			F32	9.10		
		Alisiaquinones B	FcMC29	2.60		
			FcB1	8.40		
			F32	7.10		
		Alisiaquinones C	FcMC29	0.08		
			FcB1	0.21		
			F32	0.15		
		Alisioaquinol	FcMC29	7.90		
			FcB1	6.40		
			F32	9.90		
34	*Pachastrissa nux*	Kabiramide J	K1	0.31	Koh-Tao, Surat-Thani Province and Chumphon Islands National Park, Chumphon Province, Thaland	(Sirirak *et al*., 2011)
		Kabiramide K	K1	0.39		
		Kabiramide B	K1	1.67		
		Kabiramide C	K1	4.79		
		Kabiramide D	K1	1.87		
		Kabiramide G	K1	na		
35	*Pachastrissa nux*	Kabiramide L	K1	2.60	Chumphon Islands National Park, Thailand	(Sirirak *et al*., 2011)
		Kabiramide I	K1	4.50	Koh Tao, Surat Thani Province, Thailand	
36	*Petrosid Ng5 Sp5*	Ingamine A	D6	0.20	Not available	(Fattorusso *et al*., 2010)
			W2	0.16		
		22(S)-hydroxyingamine A	D6	0.47		
			W2	0.30		
		Dihydroingenamine D	D6	0.18		
			W2	0.30		
37	*Plakortis* cfr. *simplex*	Manadoperoxide A	D10	6.88	Bunaken Marine Park of Manado, Indonesia	(Fattorusso *et al*., 2010)
			W2	3.74		
		Manadoperoxide B	D10	6.76		
			W2	3.69		
		Manadoperoxide C	D10	4.54		
			W2	2.33		

(Continued)

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
		Manadoperoxide D	D10	10.38		
			W2	7.93		
38	*Plakortis halichondrioides*	Epiplakinic acid F methyl ester	W2	0.01	Mona Island, Puerto Rico	(Jiménez-Romero *et al*., 2010)
		Epiplakinidioic acid	W2	0.95		
		Epiplakinic acid F	W2	7.93		
		Plakortolide J	W2	na		
		Plakortolide F	W2	na		
39	*Plakortis lita*	Thiaplakortones A	3D7	0.05	Melville Passage, Tydeman Reef, Queensland, Australia	(Davis *et al*., 2012)
			Dd2	0.01		
		Thiaplakortones B	3D7	0.65		
			Dd2	0.09		
		Thiaplakortones C	3D7	0.31		
			Dd2	0.17		
		Thiaplakortones D	3D7	0.28		
			Dd2	0.16		
40	*Plakortis simplex*	Plakortin	D10	1.26	Berry Island (Bahamas)	(Fattorusso, 2002)
			W2	0.73		
		Dihydroplakortin	D10	1.12		
			W2	0.76		
		Plakortide E	D10	na		
			W2	na		
41	*Plakortis sp.*	Plakortide F	D6	1.35	Discovery Bay, Jamaica	(Gochfeld and Hamann, 2001)
			W2	1.10		
		Plakortone G	D6	15.09		
			W2	17.10		
42	Genus *Pseudoceratina*	Psammaplysin H	3D7	0.41	Not available	(Xu *et al*., 2011)
		Psammaplysin G	3D7	5.22		
		Psammaplysin F	3D7	1.92		
43	*Pseudoceratina* sp.	Ceratinadin E	K1	0.90	Okinawa, Japan	(Kurimoto *et al*., 2018)
			FCR3	0.67		
		Ceratinadin F	K1	>8.16		
		Psammaplysin F	K1	5.16		
			FCR3	3.35		
44	*Pseudoceratina sp.*	Methyl (2,4-dibromo-3,6-dihydroxyphenyl) acetate	FcB1	12	Rowa islands, Banks Territory (Vanuatu)	(Lebouvier *et al*., 2009)
45	*Smenospongia aurea*	6'-chloroaureol	D6	9.74	Discovery Bay, Jamaica	(Hu *et al*., 2002)
		Isoplysin A	D6	3.54		
		6-bromo-2'-de-N-methylaplysinopsin	D6	3.45		
		6-bromoaplysinopsin	D6	1.02		
		Makaluvamine O	D6	3.52		
		Aureol	D6	na		
		Aureol acetate	D6	na		
		2'-de-N-methylaplysinopsin	D6	na		
		N-3'-methylaplysinopsin	D6	na		
		N-3'-ethylaplysinopsin	D6	na		

(Continued)

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
46	*Spongia* sp.	Squalene	K1	2.82 µM	Aegean Sea, Turkey	(Orhan *et al*., 2010)
		Furonospinulosin-1	K1	31.53 µM		
		Furospongine 1	K1	42.42 µM		
		2-(hexaprenylmethyl)-2-methylchromenol	K1	>34.19 µM		
		Heptaprenyl-p-quinol	K1	>33.28 µM		
		12-epi-deoxoscalarin	K1	17.37 µM		
		4-hydroxy-3-octaprenylbenzoic acid	K1	2.29 µM		
		furospinulosin-2	K1	8.30 µM		
47	*Spongosorites* sp.	Nortopsentin A	3D7	0.46	Lucaya, Bahamas	(Alvarado *et al*., 2013)
48	*Stylissa caribica*	Stevensin	D6	4.65	Columbus Park, Jamaica	(Mohammed *et al*., 2006)
		oroidin	D6	3.08		
		Stylisin 1	D6	na		
		Stylisin 2	D6	na		
		Phakellistatin 13	D6	na		
		sceptrin	D6	na		
49	*Stylissa* cf. *massa*	8-isocyanato-15-formamidoamphilect-11(20)-ene	K1	8.85	Koh-Tao, Surat-Thani Province, Thailand (10°7.569′ N, 99°48.665′ E)	(Chanthathamrongsiri *et al*., 2012)
		8-isothiocyanato-15-formamidoamphilect-11(20)-ene	K1	8.07		
		8-isocyano-15-formamidoamphilect-11(20)-ene	K1	0.52		
		7-formamidoamphilect-11(20),15-diene	K1	na		
50	*Suberea ianthelliformis*	Araplysillin I	FcB1	4.5	Anuta Paina Island (Malaita)	(Mani *et al*., 2012)
			3D7	4.6		
		Araplysillin II	FcB1	34.2		
		Araplysillin N20-formamide	FcB1	3.6		
			3D7	7.0		
		Araplysillin IV	FcB1	27.6		
		Araplysillin V	FcB1	50.5		
		Araplysillin VI	FcB1	37.4		
	Suberea ianthelliformis	Aerophobin I	FcB1	59.0	New Georgia Island	(Mani *et al*., 2012)
		Aerophobin II	FcB1	24.9		
			3D7	19.9		
		Purealidin Q	FcB1	3.6		
		Araplysillin N20-hydroxyformamide	FcB1	5.0		
			3D7	4.1		
	Suberea ianthelliformis	Aerothionin	FcB1	3.4	North West of Nggela Island	(Mani *et al*., 2012)
			3D7	4.2		
		Homoaerothionin	FcB1	2.8		
			3D7	4.0		
		11,19-Dideoxyfistularin 3	FcB1	2.1		
			3D7	0.9		
		11-Hydroxyfistularin 3	FcB1	2.1		
			3D7	2.6		
		Aplysinone D	FcB1	1.0		
			3D7	3.1		

(Continued)

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
51	*Verongula rigida*	Purealidin B	NF54	23.2% iotga 5 µM	Urabá Gulf, Caribbean Sea, Colombia (8°40′14″N, 77°21′28″W)	(Galeano *et al*., 2011)
		11-hydroxyaerothionin	NF54	8.0% iotga 5 µM		
		Aeroplysinin	NF54	35.3% iotga 5 µM		
		Dihydroxyaerothionin	NF54	7.9% iotga 5 µM		
		Purealidin R	NF54	7.1% iotga 5 µM		
		3,5-dibromo-N,N,N-trimethyltyraminium	NF54	na		
		3,5-dibromo-N,N,N,O-tetramethyltyraminium	NF54	na		
		19-deoxyfistularin 3	NF54	na		
52	*Xestospongia exigua*	Araguspongine C	D6	1.4	Bayadha, Saudi Arabian Red Sea coast	(Orabi *et al*., 2002)
			W2	0.58		
		(+)- Araguspongine K	D6	na		
			W2	na		
		(+)- Araguspongine L	D6	na		
			W2	na		
53	*Xestospongia sp.*	Kaimanol	3D7	0.36	Kaimana, West Papua, Indonesia	(Murtihapsari *et al*., 2019)
		Saringosterol	3D7	2.50×10^{-4}		
54	*Xestospongia* sp.	Xestoquinone	FcB1	3	Malvoror reef, Vanuatu	(Laurent *et al*., 2006)
55	genus Xestospongia	Halenaquinone	FcB1	>30	South Pacific	(Longeon *et al*., 2010)
			3D7	>30		
		3-Ketoadociaquinone A	FcB1	1.08		
			3D7	1.67		
		3-Ketoadociaquinone B	FcB1	3.89		
			3D7	4.12		
		Tetrahydrohalenaquinone A	FcB1	>29		
			3D7	>29		
		Tetrahydrohalenaquinone B	FcB1	>29		
			3D7	>29		
		Halenaquinol sulfate	FcB1	>24		
			3D7	>24		
		Xestosaprol C methylacetal	FcB1	>21		
			3D7	>21		
		Orhalquinone	FcB1	9.22		
			3D7	10.94		
56	*Zyzzya* sp.	Tsitsikammamine C	3D7	0.01	Rodda Reef, Queensland, Australia	(Davis *et al*., 2012)
			Dd2	0.02		
		makaluvamines J	3D7	0.02		
			Dd2	0.02		
		makaluvamines G	3D7	0.04		
			Dd2	0.04		
		makaluvamines L	3D7	0.04		

(Continued)

No	Organisms	Isolated compound	*Pf* Strain	IC_{50} (µM)	Origin	Ref.
			Dd2	0.02		
		makaluvamines K	3D7	0.40		
			Dd2	0.30		
		Damirone A	3D7	1.88		
			Dd2	0.36		
		Damirone B	3D7	12.25		
			Dd2	3.80		

[a] Compound 3 in the original article (Angerhofer *et al*., 1992); [b] Compound 4 in the original article (Angerhofer *et al*., 1992); [c] Compound 3 in the original article (Angerhofer *et al*., 1992); [d] Compound 1, 2, 3, and 4 in the original article (Radwan *et al*., 2015) nat = not active at (inhibition of parasite growth); na = not active; iotga = inhinition of the growth at

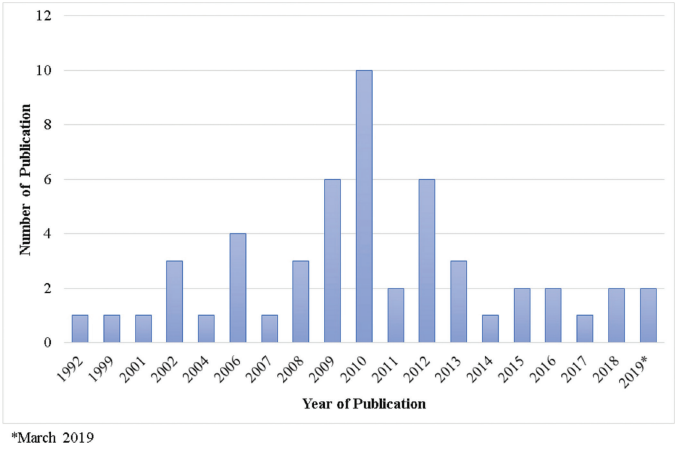

Figure 1. Distribution of conducted studies about marine sponge metabolite exploration for *in vitro* antiplasmodium.

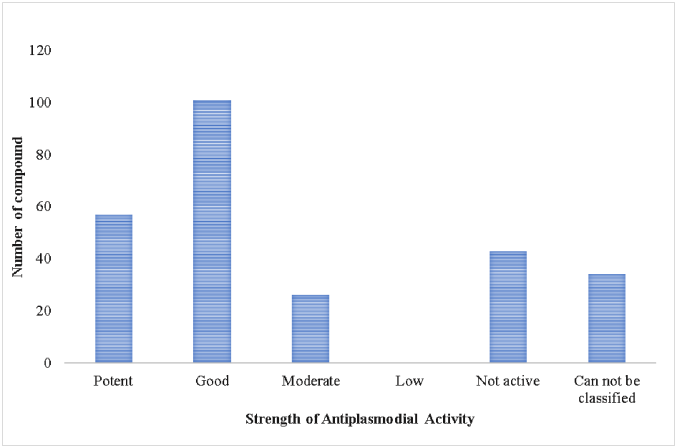

Figure 2. Classification of the isolated compounds activity according to their IC_{50} values.

CLASSIFICATION OF ANTIPLASMODIAL ACTIVITY OF ISOLATED COMPOUND FROM SPONGES

In this review, we give an overview of the bioactive metabolites recently isolated from marine sponges that have shown activity in *in vitro* study against *P. falciparum*. To compare the IC_{50} values, the units in µg/ml and nM were converted to µM. All the isolated compounds were then classified based on their IC_{50} values by following the definition of Batista *et al*. (2009), who grouped compounds into potent activity: IC_{50} < 1 µM, good activity: IC_{50} of 1–20 µM, moderate activity: IC_{50} of 20–100 µM, low activity: IC_{50} of 100–200 µM, and inactive: IC_{50} >200 µM (Batista *et al*., 2009). To be noted, the mechanism of the *in vitro* continuous cultures of *P. falciparum* approach is only related to the inhibition of growth in erythrocytic stages of the parasite (Chin *et al*., 1979). Consequently, this IC_{50}-based classification would exclude compounds that may have other specific mechanism of action. It would be wise to re-evaluate "not active compounds" with other assay or holistic approach such as the reverse pharmacology technique (Simoes-Pires *et al*., 2014).

As shown in Figure 2, among observed bioactive metabolites, there were 57 different compounds that have potent activity, 101 with good activity, and 26 compounds with moderate activity against various strains of *P. falciparum.* Some of the compounds could not be classified because, in the highest tested concentration, their activity was low or inactive and some reports use inhibition concentration instead of IC_{50}, making it incomparable. In regard to the dependency of IC_{50} to plasmodium strains, it seems that antiplasmodial activity of some isolated compounds did not depend on chloroquine/drug sensitivity of the strain (Fattorusso *et al*., 2010; Longeon *et al*., 2010; Mani *et al*., 2012).

The class of compounds which exhibit potent antiplasmodial activity includes manzamine alkaloid (Rao *et al*., 2004; 2006; Samoylenko *et al*., 2009), guanidine alkaloids (Campos *et al*., 2017; Laville *et al*.,2009), bispyrroloiminoquinone alkaloid (Davis *et al*., 2012), pyrroloiminoquinone alkaloids (Na *et al*., 2010), ingamine alkaloids (Ilias *et al*., 2012), sesquiterpenoids (Angerhofer *et al*., 1992), diterpene formamides (Wright and Lang-Unnasch, 2009), aminoimidazole (Benoit-Vical *et al*., 2008), β-galactosyl ceramides (Farokhi *et al*., 2013), β-lactam (Avilés and Rodríguez, 2010), meroterpene (Desoubzdanne *et al*., 2008), trisoxazole macrolides (Sirirak *et al*., 2011), peroxides, thiazine alkaloids (Davis *et al*., 2012), bromotyrosine alkaloids (Kurimoto *et al*., 2018; Xu *et al*., 2011), and sterols (Murtihapsari *et al*., 2019).

FUNCTIONAL GROUP IN POTENT ANTIPLASMODIAL ACTIVITY

Some marine isonitriles show various biological activities such as antimalarial, antitubercular, antifouling, and antiplasmodial effect. Marine isonitriles differ from terrestrial isonitriles in terms of their biosynthetic pathways. Most of the marine compounds containing isonitrile were derived from terpenoid, whereas terrestrial isonitriles originate from α-amino acids (Emsermann

Table 2. List of isolated compounds with potent antiplasmodial activity based on IC_{50} measurement.

No.	Isolated Compound	*P. falciparum* strain
1	Axisonitrile 3	D6 and W2
2	(+)-8-hydroxymanzamine A	D6 and W2
3	(+)-manzamine A	D6 and W2
4	(+)-8-hydroxymanzamine A hydrochloride	D6 and W2
5	(+)-manzamine A hydrochloride	D6 and W2
6	Manzamine A	D6 and W2
7	Manzamine Y	D6
8	Manzamine A N-oxide	D6 and W2
9	Axidjiferosides	FcB1
10	Norbatzelladine L	FcB1
11	Girolline	FcB1; W2; FcM29; and F32
12	(1S,3S,4R,7S,8S,11S,12S,13S,15R,20R)-7-Formamido-20-isocyanoisocycloamphilectane	FCR3F86
13	Monamphilectine A	W2
14	Homofascaplysin A	K1 and NF54
15	Fascaplysin	K1 and NF54
16	Pelorol	Dd2
17	Discorhabdins A	D6 and W2
18	Dihydrodiscorhabdin C	D6 and W2
19	Crambescidin 800	FCR3 and 3D7
20	Norbatzelladine A	FcB1
21	Dinorbatzelladine A	FcB1
22	Dinordehydrobatzelladine B	FcB1
23	Batzelladine A	FcB1
24	Batzelladine L	FcB1
25	Ptilomycalin A	FcB1
26	Ptilomycalin E	3D7
27	Ptilomycalin F	3D7
28	Ptilomycalin G + H	3D7
29	Fromiamycalin	3D7
30	Alisiaquinone C	FcMC29; FcB1; and F32
31	Kabiramide J	K1
32	Kabiramide K	K1
33	Ingamine A	D6 and W2
34	22(S)-hydroxyingamine A	D6 and W2
35	Dihydroergotamine D	D6 and W2
36	Epiplakinic acid F methyl ester	W2
37	Epiplakinidioic acid	W2
38	Thiaplakortone A	3D7 and Dd2
39	Thiaplakortone B	3D7 and Dd2
40	Thiaplakortone C	3D7 and Dd2
41	Thiaplakortone D	3D7 and Dd2
42	Plakortin	W2
43	Dihydroplakortin	W2
44	Psammaplysin H	3D7
45	Ceratinadin E	FCR3
46	Nortopsentin A	3D7
47	8-isocyano-15-formamidoamphilect-11(20)-ene	K1
48	11,19-Dideoxyfistularin 3	3D7
49	Araguspongine C	W2
50	Kaimanol	3D7
51	Saringosterol	3D7
52	Tsitsikammamine C	3D7 and Dd2
53	Makaluvamine J	3D7 and Dd2
54	Makaluvamine G	3D7 and Dd2
55	Makaluvamine L	3D7 and Dd2
56	Makaluvamine K	3D7 and Dd2
57	Damirone A	Dd2

et al., 2016). Axisonitrile-3 (1) is a sesquiterpene derived from chloroform fraction of sponge *Acanthella klethra* containing isonitrile group which appears to be crucial for activity since the corresponding isothiocyanate derivative compound 2 (moderate activity) is less active than 1 (potent activity) (Angerhofer *et al*., 1992). The eudesmane compounds 3 and 4 which contain isothiocyanate still showed good antiplasmodial activity, whereas the reversal of the stereochemical configuration between 4 and 5 exhibits a significant change on their antiplasmodial effect (see Figure 3).

The manzamines are a group of marine alkaloids characterized by a fused and bridged tetra- or pentacyclic ring system attached to a β-carboline moiety. Since manzamine was isolated in different genus of sponges, it is thought that manzamine is actually produced by associated microorganism. An interesting review had been done by Fattorusso and Taglialatela-Scafati (2009) who described the key role of the eight member rings as well as other functional groups that affect the antiplasmodial activity of manzamines; therefore, we will not discuss it in this review.

A mixture of new glycosphingolipids named axidjiferoside A (6), axidjiferoside B (7), and axidjiferoside C (8) shows a potent antiplasmodial activity (Figure 3). Compounds 6, 7, and 8 were isolated from Senegal marine sponge *Axinyssa djiferi* (Farokhi *et al*., 2013). These compounds contain sphingolipid structure which are found in ceramide analogs, PPMP (d,1-threo-1-phenyl-2-palmitoylamino-3-morpholino-1-propanol), and PDMP (1-phenyl-2-decanoylamino-3-morpholino-1-propanol). These analogs are known to inhibit the parasite sphingomyelin synthase activity and block parasite development by preventing the formation of the tubovesicular network that extends from the parasitophorous vacuole to the red cell membrane and delivers essential extracellular nutrients to the parasite (Labaied *et al*., 2004; Zhang *et al*., 2010).

Bioactive guanidine alkaloids including norbatzelladine A (9), dinorbatzelladine A (10), batzelladine A (11), dinordehydrobatzelladine B (12), norbatzelladine L (13), and batzelladine L (14) are potent against the growth of *P. falciparum*. The aromatization in the tricyclic core of 11 (compared to 9 and 8) did not change the antimalarial activity. Batzelladine A, with one bicyclic and one tricyclic guanidine core, has similar properties with 9, 13, and 14 in terms of the activity against *P. falciparum* strain FcB1, where 13 and 14 have two tricyclic guanidine cores. The reduction of bicyclic core in dihomodehydrobatzelladine C seems to affect its activity to be less active than 9–12 (Figure 3).

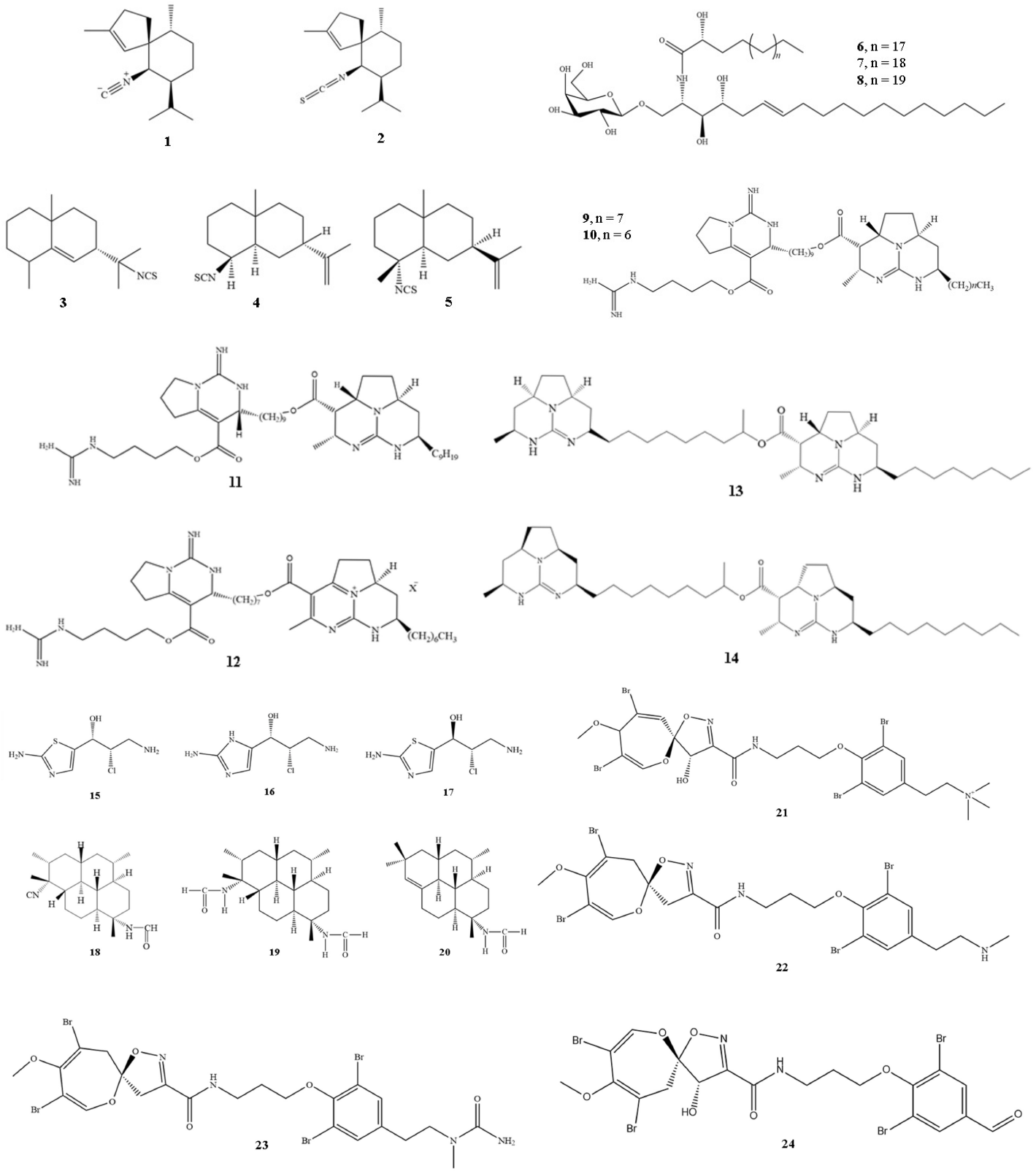

Figure 3. Structure of antimalarial compounds (Angerhofer *et al*., 1992; Benoit-Vical *et al*., 2008; Farokhi *et al*., 2013; Mudianta *et al*., 2012; Wright and Lang-Unnasch 2009; Xu *et al*., 2011).

Girolline (15), 2-aminoimidazole derivative, isolated from *Cymbastela cantharella* showed a potent activity against *P. falciparum* strains, whereas its analogs 5-deazathiogirollines (16 and 17) were considered to be inactive (Benoit-Vical *et al*., 2008). This indicates that imidazole ring in 15 plays an important role in the antiplasmodial activity.

Sponge *Cymbastela hooperi* sp. nov. described by Soest *et al*. (1996) produces a plethora of chemical compounds structurally related to diterpene isonitrile derivatives which exhibit significant *in vitro* antimalarial activity. (1S, 3S,4R,7S,8S,11S,12S,13S,15R,20R)-7-Formamido-20-isocyanoisocycloamphilectane (18), (1*S*,3*S*,4*R*,7*S*,8*S*,11*S*,12*S*,13*S*,15*R*,20*R*)-7,20-Diformamidoisocycloamphilectane (19), and (1*S**,3*S**,4*R**,7*S**,8*S**,12*S**,13*S**)-7-Formamidocycloamphilect-11(20)-ene (20) were new diterpene formamides which were isolated from *C. hooperi* (Figure 3). Compound 18 is a unique molecule since it contains both formamide and isonitrile functionalities where such a feature is rarely found in natural product. Based on its IC_{50} against *P. falciparum* FCR3F86, this substituent is classified into potent (Wright and Lang-Unnasch, 2009). The lack of isonitrile in the structure of 19 decreases the activity to be moderate. This finding is supported by the activity of compound 1 that possesses isonitrile too (Angerhofer *et al*., 1992).

Psammaplysin H (21) derived from sponge genus *Pseudoceratina* is also included in the potent activity group against *P. falciparum* 3D7 with IC_{50} 0.41 µM. This activity is more likely caused by the presence of quaternary amine in the R group at C-20 (see Figure 3). However, the secondary amine at the same position in psammaplysin F (22) reduced antimalarial activity 4-fold lower than compound 21. In addition, when the alkyl amine is substituted with a urea at C-20 in Psammaplysin G (23), the activity decreased to have IC_{50} 5.99 µM (Xu *et al*., 2011). Consistently, the loss of amine substituent in psammaplysin K (24) dispelled the antiplasmodial activity (Mudianta *et al*., 2012).

CONCLUSION

Data presented in the review indicate that marine sponges could be used as sources for lead compounds in drug discovery program including the development of non-resistance antimalarial drugs in this case. The summarized "potent" isolated compounds highlight the most promising candidates which include manzamine alkaloids, guanidine alkaloids, bispyrroloiminoquinone alkaloid, pyrroloiminoquinone alkaloids, ingamine alkaloids, sesquiterpenoids, diterpene formamides, aminoimidazole, β-galactosyl ceramides, β-lactam, meroterpene, trisoxazole macrolides, peroxides, thiazine alkaloids, bromotyrosine alkaloids, and sterols. A holistic approach for their pharmacological evaluation is still needed since *in vitro P. falciparum* assay could only evaluate a specific mechanism of action for antiplasmodium. To reproduce the compounds for their further evaluation, the possibility of bioengineering or/and bacterial fermentation could be worth.

ACKNOWLEDGMENT

The author would like to acknowledge the funding support from UGM No: 3040/UN1/DITLIT/DIT-LIT/LT/2019.

REFERENCES

Alvarado S, Roberts BF, Wright AE, Chakrabarti D. The Bis(Indolyl)Imidazole alkaloid nortopsentin A exhibits antiplasmodial activity. Antimicrob Agents Chemother, 2013; 57(5):2362–4.

Angerhofer CK, Pezzuto JM, König GM, Wright AD, Sticher O. Antimalarial activity of sesquiterpenes from the marine sponge *Acanthella klethra*. J Nat Prod, 1992; 55(12):1787–9.

Anjum K, Abbas SQ, Shah SAA, Akhter N, Batool S, ul Hassan SS. Marine sponges as a drug treasure. Biomol Therap, 2016; 24(4):347–62.

Antony HA, Parija SC. Antimalarial drug resistance: an overview. Trop Parasitol, 2016; 6(1):30–41.

Appenzeller J, Mihci G, Martin M-T, Gallard J-F, Menou J-L, Boury-Esnault N, Hooper J, Petek S, Chevalley S, Valentin A, Zaparucha A. Agelasines J, K, and L from the Solomon Islands marine sponge *Agelas* cf. *mauritiana*. J Nat Prod, 2008; 71(8):1451–4.

Avilés E, Rodríguez AD. Monamphilectine A, a potent antimalarial β-lactam from marine sponge *Hymeniacidon* sp: isolation, structure, semisynthesis, and bioactivity. Org Lett, 2010; 12(22):5290–3.

Batista R, De Jesus Silva Júnior A, De Oliveira A. Plant-derived antimalarial agents: new leads and efficient phytomedicines. Part II. Non-alkaloidal natural products. Molecules, 2009; 14(8):3037–72.

Benoit-Vical F, Saléry M, Soh P, Ahond A, Poupat C. Girolline: a potential lead structure for antiplasmodial drug research. Planta Med, 2008; 74(4):438–44.

Blunt JW, Carroll AR, Copp BR, Davis RA, Keyzers RA, Prinsep MR. Marine natural products. Nat Prod Rep, 2018; 35(1):8–53.

Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR. Marine natural products. Nat Prod Rep, 2016; 33(3):382–431.

Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR. Marine natural products. Nat Prod Rep, 2017; 34(3):235–94.

Burrows JN, Chibale K, Wells TNC. The state of the art in anti-malarial drug discovery and development. Curr Top Med Chem, 2011; 11(10):1226–54.

Campos P-E, Pichon E, Moriou C, Clerc P, Trépos R, Frederich M, Voogd ND, Hellio C, Gauvin-Bialecki A, Al-Mourabit A. New antimalarial and antimicrobial tryptamine derivatives from the marine sponge *Fascaplysinopsis reticulata*. Marine Drugs, 2019; 17(3):167.

Campos P-E, Wolfender J-L, Queiroz EF, Marcourt L, Al-Mourabit A, Frederich M, Bordignon A, Voogd ND, Illien B, Gauvin-Bialecki A. Unguiculin A and Ptilomycalins E–H, antimalarial guanidine alkaloids from the marine sponge *Monanchora unguiculata*. J Nat Prod, 2017; 80(5):1404–10.

Carroll AR, Copp BR, Davis RA, Keyzers RA, Prinsep MR. Marine natural products. Nat Prod Rep, 2019; 36(1):122–73.

Chanthathamrongsiri N, Yuenyongsawad S, Wattanapiromsakul C, Plubrukarn A. Bifunctionalized amphilectane diterpenes from the sponge *Stylissa* cf. *massa*. J Nat Prod, 2012; 75(4):789–92.

Chin W, Moss D, Collins WE. The continuous cultivation of *Plasmodium fragile* by the method of Trager-Jensen. Am J Trop Med Hyg, 1979; 28(3):591–2.

Cui L, Mharakurwa S, Ndiaye D, Rathod PK, Rosenthal PJ. Antimalarial drug resistance: literature review and activities and findings of the ICEMR network. Am J Trop Med Hyg, 2015; 93(3 Suppl):57–68.

D'Ambrosio M, Guerriero A, Pietra F, Debitus C. Leucascandrolide A, a new type of macrolide: The first powerfully bioactive metabolite of calcareous sponges (*Leucascandra caveolata*, a new genus from the coral sea). Helvetica Chimica Acta, 1996; 79(1):51–60.

Davis RA, Buchanan MS, Duffy S, Avery VM, Charman SA, Charman WN, White KL, Shackleford DM, Edstein MD, Andrews KT, Camp D, Quinn RJ. Antimalarial activity of pyrroloiminoquinones from the Australian marine sponge *Zyzzya* sp. J Med Chem, 2012; 55(12):5851–8.

Desoubzdanne D, Marcourt L, Raux R, Chevalley S, Dorin D, Doerig C, Valentin A, Ausseil F, Debitus C. Alisiaquinones and alisiaquinol, dual inhibitors of *Plasmodium falciparum* enzyme targets from a new caledonian deep water sponge. J Nat Prod, 2008; 71(7):1189–92.

Dondorp AM, Kager PA, Vreeken J, White NJ. Abnormal blood flow and red blood cell deformability in severe malaria. Parasitol Today (Regul Ed), 2000; 16(6):228–32.

Ebada SS, Edrada RA, Lin W, Proksch P. Methods for isolation, purification and structural elucidation of bioactive secondary metabolites from marine invertebrates. Nat Protoc, 2008; 3(12):1820–31.

Emsermann J, Kauhl U, Opatz T. Marine isonitriles and their related compounds. marine drugs, 2016; 14(1):16.

Farokhi F, Grellier P, Clément M, Roussakis C, Loiseau P, Genin-Seward E, Kornprobst JM, Barnathan G, Wielgosz-Collin G. Antimalarial activity of axidjiferosides, new β-galactosylceramides from the African sponge axinyssa djiferi. Marine Drugs, 2013; 11(12):1304–15.

Fattorusso C, Persico M, Calcinai B, Cerrano C, Parapini S, Taramelli D, Novellino E, Romano A, Scala F, Fattorusso E, Taglialatela-Scafati O. Manadoperoxides A−D from the Indonesian sponge *Plakortis* cfr. *simplex*. Further insights on the structure−activity relationships of simple 1,2-dioxane antimalarials. J Nat Prod, 2010; 73(6):1138–45.

Fattorusso E, Taglialatela-Scafati O. Marine antimalarials. Marine Drugs, 2009; 7(2):130–52.

Fattorusso E. Activity against *Plasmodium falciparum* of cycloperoxide compounds obtained from the sponge *Plakortis simplex*. J Antimicrob Chemother, 2002; 50(6):883–8.

Galeano E, Thomas OP, Robledo S, Munoz D, Martinez A. Antiparasitic bromotyrosine derivatives from the marine sponge verongula rigida. Marine Drugs, 2011; 9(10):1902–13.

Gochfeld DJ, Hamann MT. Isolation and biological evaluation of filiformin, plakortide F, and plakortone G from the caribbean sponge *Plakortis* sp. J Nat Prod, 2001; 64(11):1477–9.

Gros E, Al-Mourabit A, Martin M-T, Sorres J, Vacelet J, Frederich M, Aknin M, Kashman Y, Gauvin-Bialecki A. Netamines H–N, Tricyclic alkaloids from the marine sponge *Biemna laboutei* and their antimalarial activity. J Nat Prod, 2014; 77(4):818–23.

Gros E, Martin M-T, Sorres J, Moriou C, Vacelet J, Frederich M, Aknin M, Kashman Y, Gauvin-Bialecki A, Al-Mourabit A. Netamines O-S, Five new tricyclic guanidine alkaloids from the madagascar sponge *Biemna laboutei*, and their antimalarial activities. Chem Biodivers, 2015; 12(11):1725–33.

Hu J-F, Schetz JA, Kelly M, Peng J-N, Ang KKH, Flotow H, Leong CY, Ng SB, Buss AD, Wilkins SP, Hamann MT. New antiinfective and human 5-HT2 receptor binding natural and semisynthetic compounds from the Jamaican sponge *Smenospongia aurea*. J Nat Prod, 2002; 65(4):476–80.

Ilias M, Ibrahim MA, Khan SI, Jacob MR, Tekwani BL, Walker LA, Samoylenko V. Pentacyclic ingamine alkaloids, a new antiplasmodial pharmacophore from the marine sponge petrosid Ng5 Sp5. Planta Med, 2012; 78(15):1690–7.

Jiménez-Romero C, Ortiz I, Vicente J, Vera B, Rodríguez AD, Nam S, Jove R. Bioactive Cycloperoxides isolated from the Puerto Rican sponge *Plakortis halichondrioides*. J Nat Prod, 2010; 73(10):1694–700.

Ju E, Latif A, Kong C-S, Seo Y, Lee Y-J, Dalal SR, Cassera MB, Kingston DGI. Antimalarial activity of the isolates from the marine sponge *Hyrtios erectus* against the chloroquine-resistant Dd2 strain of *Plasmodium falciparum*. Zeitschrift für Naturforschung C, 2018; 73(9–10):397–400.

Kelly M, Sim-Smith C, Stone R, Samaai T, Reiswig H, Austin W. New taxa and arrangements within the family latrunculiidae (Demospongiae, Poecilosclerida). Zootaxa, 2016; 4121(1):1.

Kirsch G, König GM, Wright AD, Kaminsky R. A new bioactive sesterterpene and antiplasmodial alkaloids from the marine sponge *Hyrtios* cf. *erecta*. J Nat Prod, 2000; 63(6):825–9.

Kurimoto S, Ohno T, Hokari R, Ishiyama A, Iwatsuki M, Ōmura S, Kobayashi J, Kubota T. Ceratinadins E and F, new bromotyrosine alkaloids from an Okinawan marine sponge pseudoceratina sp. Marine Drugs, 2018; 16(12):463.

Labaied M, Dagan A, Dellinger M, Gèze M, Egée S, Thomas SL, Wang C, Gatt S, Grellier P. Anti-plasmodium activity of ceramide analogs. Malar J, 2004; 3:49.

Laurent D, Jullian V, Parenty A, Knibiehler M, Dorin D, Schmitt S, Lozach O, Lebouvier N, Frostin M, Alby F, Maurel S, Doerig C, Meijer L, Sauvain M. Antimalarial potential of xestoquinone, a protein kinase inhibitor isolated from a Vanuatu marine sponge *Xestospongia* sp. Bioorg Med Chem, 2006; 14(13):4477–82.

Laville R, Thomas OP, Berrué F, Marquez D, Vacelet J, Amade P. Bioactive guanidine alkaloids from two Caribbean marine sponges. J Nat Prod, 2009; 72(9):1589–94.

Lazaro JEH, Nitcheu J, Mahmoudi N, Ibana JA, Mangalindan GC, Black GP, Howard-Jones AG, Moore CG, Thomas DA, Mazier D, Ireland CM, Concepcion GP, Murphy PJ, Diquet B. Antimalarial activity of Crambescidin 800 and synthetic analogues against liver and blood stage of plasmodium sp. J Antibiot, 2006; 59(9):583–90.

Lebouvier N, Jullian V, Desvignes I, Maurel S, Parenty A, Dorin-Semblat D, Doerig C, Sauvain M, Laurent D. Antiplasmodial activities of homogentisic acid derivative protein kinase inhibitors isolated from a Vanuatu marine sponge *Pseudoceratina* sp. Marine Drugs, 2009; 7(4):640–53.

Longeon A, Copp BR, Roué M, Dubois J, Valentin A, Petek S, Debitus C, Bourguet-Kondracki M-L. New bioactive halenaquinone derivatives from South Pacific marine sponges of the genus *Xestospongia*. Bioorg Med Chem, 2010; 18(16):6006–11.

Mani L, Jullian V, Mourkazel B, Valentin A, Dubois J, Cresteil T, Folcher E, Hooper JN, Erpenbeck D, Aalbersberg W, Debitus C. New antiplasmodial bromotyrosine derivatives from *Suberea ianthelliformis* lendenfeld, 1888. Chem Biodivers, 2012; 9(8):1436–51.

Marques J, Vilanova E, Mourão PAS, Fernàndez-Busquets X. Marine organism sulfated polysaccharides exhibiting significant antimalarial activity and inhibition of red blood cell invasion by Plasmodium. Sci Rep, 2016; 6(1):24368.

Mohammed R, Peng J, Kelly M, Hamann Mark T. Cyclic heptapeptides from the Jamaican sponge *Stylissa caribica*. J Nat Prod, 2006; 69(12):1739–44.

Mudianta IW, Skinner-Adams T, Andrews KT, Davis RA, Hadi TA, Hayes PY, Garson MJ. Psammaplysin derivatives from the Balinese marine sponge *Aplysinella strongylata*. J Nat Prod, 2012; 75(12):2132–43.

Murtihapsari M, Salam S, Kurnia D, Darwati D, Kadarusman K, Abdullah FF, Herlina T, Husna MH, Awang K, Shiono Y, Azmi MN, Supratman U. A new antiplasmodial sterol from Indonesian marine sponge, *Xestospongia* sp. Nat Prod Res, 2019; 1–8.

Na M, Ding Y, Wang B, Tekwani BL, Schinazi RF, Franzblau S, Kelly M, Stone R, Li X-C, Ferreira D, Hamann MT. Anti-infective discorhabdins from a deep-water Alaskan sponge of the genus *Latrunculia*. J Nat Prod, 2010; 73(3):383–7.

Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. J Nat Prod, 2007; 70(3):461–77.

Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM. Evidence of artemisinin-resistant malaria in western Cambodia. N Engl J Med, 2008; 359(24):2619–20.

Orabi KY, El Sayed KA, Hamann MT, Dunbar DC, Al-Said MS, Higa T, Kelly M. Araguspongines K and L, new bioactive bis-1-oxaquinolizidine *N*-Oxide Alkaloids from red sea specimens of *Xestospongia exigua*. J Nat Prod, 2002; 65(12):1782–5.

Orhan I, Şener B, Kaiser M, Brun R, Tasdemir D. Inhibitory activity of marine sponge-derived natural products against parasitic protozoa. Marine Drugs, 2010; 8(1):47–58.

Paul VJ, Puglisi MP, Ritson-Williams R. Marine chemical ecology. Nat Prod Rep, 2006; 23(2):153–80.

Paul VJ, Puglisi MP. Chemical mediation of interactions among marine organisms. Nat Prod Rep, 2004; 21(1):189–209.

Perdicaris S, Vlachogianni T, Valavanidis A. Bioactive natural substances from marine sponges: new developments and prospects for future pharmaceuticals. Nat Prod Chem Res, 2013; 1(3):114.

Prakasa Rao TS, Sarma NS, Murthy YLN, Kantamreddi VSSN, Wright CW, Parameswaran PS. New polyhydroxy sterols from the marine sponge *Callyspongia fibrosa* (Ridley & Dendly). Tetrahedron Letters, 2010; 51(27):3583–6.

Qaralleh H. Chemical and bioactive diversities of marine sponge *Neopetrosia*. Bangladesh J Pharmacol, 2016; 11(2):433–52.

Radwan MM, Wanas AS, Fronczek FR, Jacob MR, Ross SA. Polybrominated diphenyl ethers from the marine organisms *Lendenfeldia dendyi* and *Sinularia dura* with anti-MRSa activity. Med Chem Res, 2015; 24(9):3398–404.

Rama Rao M, Faulkner DJ. Isotactic polymethoxydienes from the Philippines sponge *Myriastra clavosa*. J Nat Prod, 2002; 65(8):1201–3.

Rao KV, Donia MS, Peng J, Garcia-Palomero E, Alonso D, Martinez A, Medina M, Franzblau SG, Tekwani BL, Khan SI, Wahyuono S, Willett KL, Hamann MT. Manzamine B and E and Ircinal A related alkaloids from an Indonesian *Acanthostrongylophora* sponge and their activity against infectious, tropical parasitic, and Alzheimer's diseases. J Nat Prod, 2006; 69(7):1034–40.

Rao KV, Kasanah N, Wahyuono S, Tekwani BL, Schinazi RF, Hamann MT. Three new manzamine alkaloids from a common Indonesian sponge and their activity against infectious and tropical parasitic diseases. J Nat Prod, 2004; 67(8):1314–8.

Samoylenko V, Khan SI, Jacob MR, Tekwani BL, Walker LA, Hufford CD, Muhammad I. Bioactive (+)-Manzamine A and (+)-8-Hydroxymanzamine a tertiary bases and salts from *Acanthostrongylophora Ingens* and their preparations. Nat Prod Commun, 2009; 4(2):185–92.

Scala F, Fattorusso E, Menna M, Taglialatela-Scafati O, Tierney M, Kaiser M, Tasdemir D. Bromopyrrole alkaloids as lead compounds against protozoan parasites. Marine Drugs, 2010; 8(7):2162–74.

Setyowati EP, Jenie UA, Sudarsono, Kardono LBS, Rahmat R. Theonellapeptolide Id: structure identification of cytotoxic constituent from *Kaliapsis* sp. Sponge (Bowerbank) collected from West Bali Sea Indonesia. J Biol Sci, 2009; 9(1):29–36.

Setyowati EP, Pratiwi S, Hertiani T, Samara O. Bioactivity of Fungi Trichoderma reesei associated with sponges *Stylissa flabelliformis* collected from National Park West Bali, Indonesia. J Biol Sci, 2017a; 17(8):362–8.

Setyowati EP, Pratiwi SUT, Purwantiningsih P, Samara O. Antimicrobial activity and identification of fungus associated *Stylissa flabelliformis* sponge collected from Menjangan Island West Bali National Park, Indonesia. Indonesian J Pharm, 2017b; 29(2):66.

Simoes-Pires C, Hostettmann K, Haouala A, Cuendet M, Falquet J, Graz B, Christen P. Reverse pharmacology for developing an anti-malarial phytomedicine. The example of *Argemone mexicana*. Int J Parasitol Drugs Drug Resist, 2014; 4(3):338–46.

Sipkema D, Franssen MCR, Osinga R, Tramper J, Wijffels RH. Marine sponges as pharmacy. Mar Biotechnol, 2005; 7(3):142.

Sirirak T, Kittiwisut S, Janma C, Yuenyongsawad S, Suwanborirux K, Plubrukarn A. Kabiramides J and K, Trisoxazole macrolides from the sponge *Pachastrissa nux*. J Nat Prod, 2011; 74(5):1288–92.

Soest RWM van (Amsterdam U (Netherlands) I for S and PB, Desqueyroux-Faundez R, Wright AD, Koenig GM. *Cymbastela hooperi* sp. nov. (Halichondrida: Axinellidae) from the Great Barrier Reef, Australia. Bulletin van het Koninlijk Belgisch Instituut voor Natuurwetenschappen – Biologie, 1996. [ONLINE]. Available via http://agris.fao.org/agris-search/search.do?recordID=BE1997001470 (Accessed 31 January 2020).

Tasdemir D, Topaloglu B, Perozzo R, Brun R, O'Neill R, Carballeira NM, Zhang X, Tonge PJ, Linden A, Rüedi P. Marine natural products from the Turkish sponge Agelas oroides that inhibit the enoyl reductases from *Plasmodium falciparum*, *Mycobacterium tuberculosis* and *Escherichia coli*. Bioorg Med Chem, 2007; 15(21):6834–45.

Thomas TRA, Kavlekar DP, LokaBharathi PA. Marine drugs from sponge-microbe association—a review. Marine Drugs, 2010; 8(4):1417–68.

Ueoka R, Nakao Y, Kawatsu S, Yaegashi J, Matsumoto Y, Matsunaga S, Furihata K, Soest RWM van, Fusetani N. Gracilioethers A−C, Antimalarial metabolites from the marine sponge *Agelas gracilis*. J Org Chem, 2009; 74(11):4203–7.

World Health Organization. World malaria report, 2018. [ONLINE]. Available via http://www.who.int/malaria/publications/world-malaria-report-2018/en/ (Accessed 3 July 2019).

Wright AD, Lang-Unnasch N. Diterpene Formamides from the tropical marine sponge *Cymbastela hooperi* and their antimalarial activity *in vitro*. J Nat Prod, 2009; 72(3):492–5.

Xu M, Andrews KT, Birrell GW, Tran TL, Camp D, Davis RA, Quinn RJ. Psammaplysin H, a new antimalarial bromotyrosine alkaloid from a marine sponge of the genus *Pseudoceratina*. Bioorg Med Chem Lett, 2011; 21(2):846–8.

Yang X, Davis RA, Buchanan MS, Duffy S, Avery VM, Camp D, Quinn RJ. Antimalarial bromotyrosine derivatives from the Australian marine sponge *Hyattella* sp. J Nat Prod, 2010; 73(5):985–7.

Zhang K, Bangs JD, Beverley SM. Sphingolipids in parasitic protozoa. Adv Exp Med Biol, 2010; 688:238–48.

How to cite this article:
Hikmawan BD, Wahyuono S, Setyowati EP. Marine sponge compounds with antiplasmodial properties: Focus on *in vitro* study against *Plasmodium falciparum*. J Appl Pharm Sci, 2020; 10(05):142–157.