Saudi Journal of Biological Sciences 29 (2022) 217–227

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Review

Promising antiparasitic agents from marine sponges

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ARTICLE INFO

Article history:
Received 18 May 2021
Revised 17 August 2021
Accepted 22 August 2021
Available online 26 August 2021

Keyword:
Marine sponges
Novel antiparasitic drugs
Potent activity
Bioactive compounds

ABSTRACT

Parasitic diseases especially those prevail in tropical and subtropical regions severely threaten the lives of people due to available drugs found to be ineffective as several resistant strains have been emerged. Due to the complexity of the marine environment, researchers considered it as a new field to search for compounds with therapeutic efficacy, marine sponges represents the milestone in the discovery of unique compounds of potent activities against parasitic infections. In the present article, literatures published from 2010 until March 2021 were screened to review antiparasitic potency of bioactive compounds extracted from marine sponges. 45 different genera of sponges have been studied for their antiparasitic activities. The antiparasitic activity of the crude extract or the compounds that have been isolated from marine sponges were assayed *in vitro* against *Plasmodium falciparum*, *P. berghei*, *Trypanosoma brucei rhodesiense*, *T. b. brucei*, *T. cruzi*, *Leishmania donovani*, *L. tropica*, *L. infantum*, *L. amazonesis*, *L. major*, *L. panamesis*, *Haemonchus contortus* and *Schistosoma mansoni*. The majority of antiparasitic compounds extracted from marine sponges were related to alkaloids and peroxides represent the second important group of antiparasitic compounds extracted from sponges followed by terpenoids. Some substances have been extracted and used as antiparasitic agents to a lesser extent like steroids, amino acids, lipids, polysaccharides and isonitriles. The activities of these isolated compounds against parasites were screened using *in vitro* techniques. Compounds' potent activity in screened papers was classified in three categories according to IC_{50}: low active or inactive, moderately active and good potent active.

Contents

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2021.08.068
1319-562X/

1. Introduction

Parasitic diseases still endanger the accomplishment of current medicine for the last seven to eight decades. Particularly, the development of anti-infective drug resistance has represented a major load on global health and economics (Fitchett, 2015; Levy and Marshall, 2004). Drug resistance combined with lack of progress in the development of vaccines or resistant reversal agents has further aggravated the situation. In addition, several factors limit the utility of existing drugs in areas where they are really needed, for instance high cost, poor compliance, low efficacy and toxicity (Nwaka and Hudson, 2006). Therefore, the discovery and development of novel, safe and effective anti-infective drugs from new sources is an extremely urgent task.

Marine environment (more than 70% of the planet's surface) with its apparently infinite biodiversity is a promising source of bioactive compounds. About 30,000 compounds of marine source have been identified. Since 2008, more than 1000 compounds are being discovered every year. These compounds are generally characterized by their chemistry, complexity, diversity, and species source (Kiuru et al., 2014). Among the great biodiversity of ocean and sea, marine sponges have been one of the key resources for natural, bioactive compounds with potential therapeutic activity. This is due to the fact that sponges produce a wide variety of secondary metabolites with unique structural properties (Bisaria et al., 2020). Phylum Porifera (Sponges), the oldest multicellular animals are sessile aquatic organisms, filter feeders, without body symmetry. There are more than 9372 valid species including marine and non-marine species according to the World Porifera Database (Van Soest et al., 2018). They are located in all the seas and at different depths, adapting multiple forms and playing an important role in biogeochemical cycling (Bell, 2008).

As the majority of the sponges are soft and sessile; they become an easy target of marine predators. Therefore, as a survival strategy, sponges produce a variety of chemical compounds, including terpenes, sterols, fatty acids, alkaloids, peroxides, cyclic peptides, amino acid derivatives, and unusual nucleosides, to deter predators from preying upon them (Thomas et al., 2010). Also, sponges secrete defensive materials to keep small plants and animals from settling upon them (Hertiani et al., 2010). These bioactive compounds exhibited immunosuppressant, antitumor, antifungal, antiviral, antibacterial, anti-inflammatory and antiparasitic properties (Costantino et al., 1999; Elhady et al., 2016; Martins et al., 2014; Sagar et al., 2010; Santos et al., 2015; Vik et al., 2007; Xue et al., 2004). Moreover, approximately 800 antibiotic substances have been extracted from marine sponges (Torres et al., 2002). Therefore, Marine sponges have been considered as a drug treasure house (Anjum et al., 2016).

Amongst the few marine-derived drugs already on the market, there are two drugs derived from marine sponges; the first was Halaven® (Eribulin mesylate) isolated from the sponge *Halichondria okadai* which inhibiting the microtubule assembly and used in the treatment of patients with breast cancer and liposarcoma (Aseyev et al., 2016; Schöffski et al., 2016). The second is Cytosar-u® (cytarabine), its original natural product was isolated from the sponge *Cryptotheca crypta*, and this drug used in treatment of myeloid and meningeal Leukemia and other types of Leukemia (Pereira et al., 2019; Schwartsmann et al., 2001). However, there were no marine-based drugs have been developed for parasitic disease from sponges or other marine organisms.

The parasitic diseases malaria, leishmaniasis, American trypanosomiasis (Chagas disease), African trypanosomiasis (sleeping sickness), schistosomiasis, and others in tropical and sub-tropical regions are responsible for morbidity and mortality of million people in these regions. Malaria transmitted to people through biting of infected female *Anopheles* mosquitoes. The *Plasmodium* species that cause malaria in humans are: *P. falciparum*, *P. malariae*, *P. vivax*, *P. ovale*, *P. knowlesi*. In 2019, the WHO African Region was home to 94% of malaria cases and deaths. Human African trypanosomiasis (HAT), or sleeping sickness, is caused by trypanosome parasites; the intermediate hosts of the parasites are tsetse flies. African trypanosomiasis caused by two subspecies of *Trypanosoma brucei*, namely *T. b. gambiense* in West and Central Africa, and *T. b. rhodesiense* in East Africa. In 2019, <1000 cases were found. This few number of cases does not reflect a lack of control efforts as in general active and passive screening has been maintained at similar levels; around 2.5 million people screened per year. As for American trypanosomiasis (Chagas disease) is caused by *T. cruzi*. More than 6 million people worldwide are infected with *T. cruzi*. This disease is found mainly in endemic areas of 21 continental Latin American countries; an estimated 75 million people at risk of infection. American trypanosomiasis transmitted to humans when come into contact with the stool of infected intermediate host triatomine bugs. Furthermore, there are more than 20 *Leishmania* species caused leishmaniasis; the intermediate host is female phlebotomine sandfly. There are three main forms of the disease: cutaneous leishmaniasis, visceral leishmaniasis, also known as kala-azar, and mucocutaneous leishmaniasis. More than one billion people are at risk of infection. Concerned with Schistosomiasis, more than 700 million people live in endemic areas and the disease affects about 240 million people worldwide. The infection is prevalent in tropical and sub-tropical areas of the world. Lastly, Schistosomiasis is caused by parasitic blood worm, *Schistosoma*; the infection is acquired when human come into contact with the infective stages, cercariae which swim freely in fresh water. There are two types of schistosomiasis: Urogenital schistosomiasis which caused by *S. haematobium* (adult worms live in the venous plexuses of the urinary tract) and intestinal schistosomiasis which caused by one of the following organisms *S. mansoni*, *S. japonicum*, *S. intercalatum*, *S. mekongi* and *S. guineensis* (adult worms live in the veins draining of the intestine). Most of the eggs deposited by females are trapped in the tissues and the body's reaction to them can cause massive damage (WHO). This article aimed to review antiparasitic properties of bioactive compounds extracted from marine sponges that can be used to generate more potent selective and specific novel antiparasitic drugs.

2. Methods

A systematic search was done to find all articles published in English and related to the present review subject from 2010 until March 2021 in PubMed and Google Scholar. The keywords used to search were "antiparasitic, marine sponge, antiprotozoal", and "antiparasitic, marine sponge, anthelminthic". The review articles, conference articles, and thesis were excluded with regard to extracted agents; synesthetic and semi-synesthetic compounds and those isolated from sponge-associated organisms were not considered in the present article. Variables assessed in the present review include sponge species/genus, region/country of origin, isolated compound, species/strain of parasite and the dose that cause growth inhibition.

3. Results

By screening literatures published from 2010 until March 2021, 52 articles were included for this review, 46 deals with the antiparasitic activities of the extracted compounds from the sponges and 7 deals with antiparasitic activities of the sponges' crud extracts; the paper of Ilias et al. (2012) was counted with the first and second group of articles because it was concerned with the study of the

Table 1
Antiparasitic activity of Marine sponges' crude extracts.

Target parasite	Extract type	Concentration IC_{50} μg/mL	Spongy	Country	References
Leishmania major Promastigotes stages	aqueous extract	3.02	*Sarcotragus* sp.	Tunisia	(Ben Kahla-Nakbi et al., 2010)
	ethyl acetate extract	8.49			
	dichloromethane extract	1.39			
	aqueous extract	264.67	*Ircinia spinosula*		
	ethyl acetate extract	16.09			
	dichloromethane extract	47.38			
D6 *P. falciparum*	organic extract	0.09 μg/mL	*Petrosid Ng5 Sp5*	Australia	(Ilias et al., 2012)
W2 *P. falciparum*		0.086 μg/mL			
Leishmania donovani promastigote stages		1.19 μg/mL			
D6 *P. falciparum*	dichloromethane	12	*Negombata*	Red Sea, Egypt	(Eltamany et al., 2014)
W2 *P. falciparum*	extract	24	*corticata*		
Leishmania donovani promastigotes		74			
Plasmodium berghei	Organic extract	42.3	*Mycale laxissima*	Boca de Calderas, Havana, Cuba	(Mendiola et al., 2014)
		52	*Clathria echinata*		
		60.3	*Agelas cerebrum*		
T. cruzi trypomastigotes	organic extracts	10.80	*Amphimedon*	Atlantic Ocean, Rio de Janeiro, Brazil	(Andrade et al., 2015)
	aqueous extracts	0.57	*viridis*		
T. cruzi amastigotes	organic extracts	44.85			
	aqueous extracts	21.37			
T. cruzi epimastigote	acetone extracts	124.7	*Tethya ignis*	Brazil and Spain	(de Paula et al., 2015)
		109.9	*Tethya rubra*		
		23.4	*Dysidea avara*		
		67.3	*Mycale angulosa*		
		28.6	*Condrosia reniformes*		
T. cruzi amastigotes		7.2	*Tethya ignis*		
		44.5	*Tethya rubra*		
		40.3	*Dysidea avara*		
		55.5	*Mycale angulosa*		
		82.6	*Condrosia reniformes*		
T. cruzi Trypomastigote		EC_{50} 6.3	*Tethya ignis*		
		EC_{50} 33.3	*Tethya rubra*		
		EC_{50} 1.1	*Dysidea avara*		
		EC_{50} 3.8	*Mycale angulosa*		
		EC_{50} 0.6	*Condrosia reniformes*		
P. falciparum	–	3.26 μM	*Biemna laboutei*	Madagascar	(Gros et al., 2015)

effects of the crude extract and isolated compounds of Australian marine sponge *Petrosid Ng5 Sp5* on chloroquine-sensitive (D6) and -resistant (W2) strains of *Plasmodium falciparum* and promastigote stages of *Leishmania donovani*. The results of antiparasitic activity of marine sponges' crude extracts against *L. major*, *L. donovani*, *T. cruzi*, *P. berghei* and D6 and W2 strains of *P. falciparum* were summarized in Table 1. Antiparasitic activity of extracted compounds from marine sponges against protozoan and helminthic parasites were listed in Table 2. Promising isolated compounds with potent antiparasitic activity based on IC_{50} measurement were included in Table 3.

4. Discussion

In these articles, 45 different genera of sponges have been studied for their antiparasitic activities; the most frequently studied genus was *Plakortis* from different localities. The genera *Ircinia*, *Pandaros*, *Haliclona*, *Aplysinella*, *Diacarnus*, *Pseudoceratina*, *Monanchora* and *Hyrtios* have been studied in two different articles. These sponges were collected from different localities all over the world; the most explored sites were Australia, Indonesia, Brazil, Madagascar and China. Moreover, sponges were also collected from other localities such as Japan, India, Turkey, Egypt, Tunisia, Cuba and Spain. The secondary metabolites produced by sponges serve defensive purposes to protect them from predator attacks, biofouling, microbial infections and overgrowth by other aquatic sessile organisms (Paul et al., 2006). Therefore, compounds extracted from the same sponge species are more likely to be different if their habitat is distinguished due to the ecological response (Mani et al., 2012). Thus, it is important to mention the source of sponges to expect the variations in the extracted compounds obtained.

The antiparasitic activity of the crude extract or the compounds that have been isolated from marine sponges were assayed in vitro against *Plasmodium falciparum*, *P. berghei*, *Trypanosoma brucei rhodesiense*, *T. b. brucei*, *T. cruzi*, *Leishmania donovani*, *L. tropica*, *L. infantum*, *L. amazonesis*, *L. major*, *L. panamesis*, *Haemonchus contortus* and *Schistosoma mansoni*. The majority of articles screened (71%) were concerned with the antiparasitic activities against *P. falciparum* alone (73%) or *P. falciparum* and other parasites (27%). Different strains of *P. falciparum* were used in these studies: drug resistance strains (W2, K1, Dd2, 3D7, FcM29, FCB1) and drug sensitive strains (D6, D10, FcR3). This can be explained in the light of nearly half of the world's population was at risk of malaria in 2019; most cases and deaths occur in sub-Saharan Africa; there were an estimated 229 million cases of malaria in 2019, and the estimated number of malaria deaths was about 409,000 (WHO).

Along the period of survey, the number of publications fluctuated from year to year, the highest number of papers was recorded in 2010 (10 papers), followed by that recorded in 2014 (9 papers), then 2015 (6 papers) and 2016 (6 papers). Only four papers were recorded in 2018 and 2013. Four papers were recorded in 2011;

Table 2
Antiparasitic activity of Marine sponges extracted compounds.

Target parasite	Extracted compounds	Chemistry	Concentration IC_{50}	Spongy	Country	References
T. brucei rhodesiense	dibromopalau'amine	Bromopyrrole alkaloids	0.46 μg/mL*	*Axinella* sp. and *Agelas* sp.	–	(Scala et al., 2010)
	longamide B		1.53 μg/mL*			
	Sceptrin		9.71 μg/mL**			
	spongiacidin B		13.58 μg/mL***			
T. cruzi	longamide B		33.03 μg/mL***			
L. donovani	dibromopalau'amine		1.09 μg/mL*			
	longamide B		3.85 μg/mL**			
K1 *P. falciparum*	spongiacidin B		1.09 μg/mL*			
	dispacamide B		1.34 μg/mL*			
	dibromopalau'amine		1.48 μg/mL*			
T. brucei rhodesiense	demethylfurospongin-4	Terpenoids	4.90 μg/mL**	*Spongia* sp. and *Ircinia* sp.	Turkey	(Orhan et al., 2010)
	4-hydroxy-3-tetraprenylphenylacetic acid		0.60 μg/mL*			
	heptaprenyl-p-quinol		3.54 μg/mL**			
	diterpenes dorisenone D		2.47 μg/mL*			
	tryptophol		5.89 μg/mL**			
T. cruzi	heptaprenyl-p-quinol		4.08 μg/mL**			
	11β-acetoxyspongi-12-en-16-one		4.51 μg/mL**			
L. donovani	furospongin-1		4.08 μg/mL**			
	4-hydroxy-3-octaprenylbenzoic acid		5.60 μg/mL**			
	11β-acetoxyspongi-12-en-16-one		0.75 μg/mL*			
	tryptophol		9.60 μg/mL**			
K1 *P. falciparum*	furospinulosin-2		3.51 μg/mL**			
	furospongin-4		7.51 μg/mL**			
	4-hydroxy-3-octaprenylbenzoic acid		1.57 μg/mL*			
	squalene		1.16 μg/mL*			
	diterpenes dorisenone D		0.43 μg/mL*			
	11β-acetoxyspongi-12-en-16-one		1.09 μg/mL*			
	12-epi-deoxoscalarin		7.48 μg/mL**			
	tryptophol		5.08 μg/mL**			
T. b. rhodesiense	pandaroside G	Steroidal Saponins	0.78 μM*	*Pandaros acanthifolium*	Caribbean Sea	(Regalado et al., 2010)
	pandaroside G methyl ester		0.038 μM*			
L. donovani	pandaroside G		1.3 μM**			
	pandaroside G methyl ester		0.051 μM*			
T.b. brucei	11,12-didehydro-13-oxo-plakortide Q	Cyclic Polyketide Peroxides	0.049 μM*	*Plakortis* sp.	Australia	(Feng et al., 2012)
	10-carboxy-11,12,13,14-tetranor-plakortide Q		0.940 μM*			
Dd2 *P. falciparum*	psammaplysin F	Bromotyrosine alkaloid	1.4 μM**	*Hyattella* sp.	Hervey Bay, Australia	(Yang et al., 2010)
3D7 *P. falciparum*			0.87 μM*			
W2 *P. falciparum*	monamphilectine A	diterpenoid β-lactam alkaloid	0.60 μM*	*Hymeniacidon* sp.	Mona Island, Puerto Rico	(Avilés and Rodríguez, 2010)
D6 *P. falciparum*	discorhabdins A	Pyrroloiminoq-uinone alkaloids	0.05 μM*	*Latrunculia* sp.	Aleutian Islands	(Na et al., 2010)
	discorhabdins C		2.80 μM**			
	dihydrodiscorhabdin C		0.17 μM*			
W2 *P. falciparum*	discorhabdins A		0.05 μM*			
	discorhabdins C		2.00 μM**			
	dihydrodiscorhabdin C		0.13 μM*			
D10 *P. falciparum*	Manadoperoxide A	endoperoxyketal polyketides manadoperoxides	6.88 μM**	*Plakortis cfr. simplex*	Bunaken Marine Park of Manado, Indonesia	(Fattorusso et al., 2010)
	Manadoperoxide B		6.76 μM**			
	Manadoperoxide C		4.54 μM**			
	Manadoperoxide D		10.38 μM**			
W2 Plasmodium falciparum	Manadoperoxide A		3.74 μM**			
	Manadoperoxide B		3.69 μM**			
	Manadoperoxide C		2.33 μM**			
	Manadoperoxide D		7.93 μM**			
W2 *P. falciparum*	epiplakinic acid F methyl ester	Cycloperoxides	4 μg/mL**	*Plakortis halichondrioides*	Mona Island, Puerto Rico	(Jiménez-Romero et al., 2010)
	plakortolide J		>10 μg/mL**			
	epiplakinidioic acid		0.3 μg/mL*			
	polyketides epiplakinic acid F		3 μg/mL**			
	Plakortolide F		>10 μg/mL**			
3D7 *P. falciparum*	Haliclonacyclamine A	Piperidine alkaloid	0.7 μM*	*Haliclona* spp.	Solomon Islands	(Mani et al., 2011)
FCB1 *P. falciparum*			0.11 μM*			
L. donovani	acanthifolioside A (1)	steroid glycosides	8.5 μM**	*Pandaros acanthifolium*	Martinique Island	(Regalado et al., 2011)
	acanthifolioside D (4)		5.7 μM**			
	acanthifolioside E (5)		9.4 μM**			
	acanthifolioside F (7)		5.7 μM**			

Table 2 (*continued*)

Target parasite	Extracted compounds	Chemistry	Concentration IC_{50}	Spongy	Country	References
P. falciparum	acanthifolioside A (1),		7.6 μM**			
	acanthifolioside F (7)		9.2 μM**			
T. b. rhodesiense	acanthifolioside F (7)		6.4 μM**			
T. cruzi	aeroplysinin-1 (1)	Bromotyrosine	10 μM**	*Verongula rigida*	Columbia	(Galeano et al., 2011)
P. falciparum	purealidin B (7)		5 μM**			
L. panamensis	11-hydroxyaerothionin (8)		10 μM**			
3D7 *P. falciparum*	psammaplysin H	Bromotyrosine alkaloid	0.41 μM*	*Pseudoceratina sp.*	–	(Xue et al., 2004)
	psammaplysins G		5.22 μM**			
	psammaplysins F		1.92 μM**			
T. b. rhodesiense	manadoperoxide B	Manadoperoxides	0.003 μg/mL*	*Plakortis cfr. lita*	Indonesia	(Chianese et al., 2012)
	manadoperoxide C		0.678 μg/mL*			
	manadoperoxide F		0.792 μg/mL*			
	manadoperoxide G		1.84 μg/mL*			
	manadoperoxide H		0.315 μg/mL*			
	manadoperoxide I		0.062 μg/mL*			
	manadoperoxide K		0.087 μg/mL*			
L. donovani	manadoperoxide B		0.589 μg/mL*			
	manadoperoxide C		3.24 μg/mL**			
	manadoperoxide F		5.73 μg/mL**			
	manadoperoxide G		3.22 μg/mL**			
	manadoperoxide H		2.44 μg/mL*			
	manadoperoxide I		0.633 μg/mL*			
	manadoperoxide K		1.89 μg/mL*			
3D7 *P. falciparum*	psammaplysins, 19-hydroxypsammaplysin E	Bromotyrosine alkaloid	6.4 μM**	*Aplysinella strongylata*	Indonesia	(Mudianta et al., 2012)
FCB1 *P. falciparum*	Araplysillin I	Bromotyrosine alkaloid	4.5 μM**	*Suberea ianthelliformis*	Solomon Islands, South Pacific	(Mani et al., 2012)
	Araplysillin I (1) salt		5.3 μM**			
	Araplysillin N20-formamide		3.6 μM**			
	Araplysillin N20-hydroxyformamide		5.0 μM**			
	Purealidin Q		3.6 μM**			
	Aerothionin		3.4 μM**			
	Homoaerothionin		2.8 μM**			
	Aplysinone D		1.0 μM**			
	11,19-Dideoxyfistularin 3		2.1 μM**			
	11-Hydroxyfistularin 3		2.1 μM**			
3D7 *P. falciparum*	Araplysillin I		4.6 μM**			
	Araplysillin I (1) salt		4.5 μM**			
	Araplysillin N20-formamide		7.0 μM**			
	Araplysillin N20-hydroxyformamide		4.1 μM**			
	Aerothionin		4.2 μM**			
	Homoaerothionin		4.0 μM**			
	Aplysinone D		3.1 μM**			
	11,19-Dideoxyfistularin 3		0.9 μM*			
	11-Hydroxyfistularin 3		2.6 μM**			
T. brucei brucei	Iotrochamides A	N-cinnamoyl-amino acids	3.4 μM**	*Iotrochota* sp.	Australia	(Feng et al., 2012)
	Iotrochamides B		4.7 μM**			
3D7 *P. falciparum*	Tsitsikammamine C	bispyrroloiminoquinone alkaloid	0.013 μM|*	*Zyzzya* sp.	Australia	(Davis et al., 2012)
	Makaluvamines J		0.025 μM*			
	Makaluvamines G		0.036 μM*			
	Makaluvamines L		0.04 μM*			
	Makaluvamines K		0.039 μM*			
	Damirones A		1.88 μM**			
	Damirones B		12.25 μM**			
Dd2 P. falciparum	Tsitsikammamine C		0.018 μM*			
	Makaluvamines J		0.022 μM*			
	Makaluvamines G		0.039 μM*			
	Makaluvamines L		0.021 μM*			
	Makaluvamines K		0.3 μM*			
	Damirones A		0.36 μM*			
	Damirones B		3.8 μM**			
D6 *P. falciparum*	ingamine A	pentacyclic ingamine alkaloids	0.09 μg/mL*	*Petrosid Ng5 Sp5*	Australia	(Ilias et al., 2012)
	22(S)-hydroxyingamine A		0.22 μg/mL*			
	dihydroingenamine D		0.078 μg/mL*			
W2 *P. falciparum*	ingamine A		0.072 μg/mL*			
	22(S)-hydroxyingamine A		0.14 μg/mL*			
	dihydroingenamine D		0.057 μg/mL*			
L. donovani	ingamine A		5.98 μg/mL**			
	22(S)-hydroxyingamine A		5.83 μg/mL**			
	dihydroingenamine D		3.12 μg/mL**			
3D7 *P. falciparum*	Thiaplakortone A.	Thiazine Alkaloids	0.051 μM*	*Plakortis lita*	Australia	(Davis et al., 2013)
Dd2 *P. falciparum*			0.006 μM*			

(*continued on next page*)

Table 2 (*continued*)

Target parasite	Extracted compounds	Chemistry	Concentration IC_{50}	Spongy	Country	References
FcM29 *P. falciparum*	Plakortide U	Endoperoxide	0.3 μg/ml*	*Plakinastrella*	Fiji Islands,	(Festa et al.,
	Plakortides R	polyketides	1.62 μg/ml*	*mamillaris*	Melanesia, South	2013)
	Plakortides T		19.1 μg/ml***		Pacific Ocean	
T. b. rhodesiense	manadoperoxide B (1)	Endoperoxide	0.003 μg/ml*	*Plakortis cfr. lita*	Indonesia	(Chianese
	12-isomanadoperoxide B (2)	polyketides	0.011 μg/ml*			et al., 2013)
	manadoperoxidic acid B (3)		1.87 μg/ml*			
FCB1 *P. falciparum*	Glycosphingolipids:	glycosphingolipids	0.53 μM*	*Axinyssa djiferi*	Senegal	(Farokhi et al.,
	axidjiferoside-A, -B and -C					2013)
D10 *P. falciparum*	Endoperoxide polyketide 1	Endoperoxide	3.89 μM**	*Plakortis simplex*	China	(Chianese
	Endoperoxide polyketide 2	polyketides	4.05 μM**			et al., 2014)
	Endoperoxide polyketide 3		1.77 μM**			
	Endoperoxide polyketide 5		6.18 μM**			
	Endoperoxide polyketide 7		5.12 μM**			
W2 *P. falciparum*	Endoperoxide polyketide 1		2.91 μM**			
	Endoperoxide polyketide 2		2.70 μM**			
	Endoperoxide polyketide 3		1.56 μM**			
	Endoperoxide polyketide 5		4.98 μM**			
	Endoperoxide polyketide 6		11.4 μM**			
	Endoperoxide polyketide 7		4.10 μM**			
T. bruci	plakortide E	Endoperoxide	5 μM**	*Plakortis halichondrioides*	Bahamas	(Oli et al., 2014)
D6 *P. falciparum*	norditerpene diacarperoxide J	Norditerpene	1.6 μM**	*Diacarnus*	China	(Yang et al.,
W2 *P. falciparum*		endoperoxides	1.8 μM**	*megaspinorhabdosa*		2014a)
T. brucei brucei	24-vinyl-cholest-9-ene-3β	Steroids	21.56 μM***	*Haliclona simulans*	Ireland	(Viegelmann
	24-diol, 20-methyl-pregn-6-		4.58 μM**			et al., 2014)
	en-3β-ol,5α,8α-epidioxy					
	24-methylenecholesterol		9.01 μM**			
L. donovani	Scalarane sesterterpene,	Norditerpene	32.9 μg/mL***	*Hyrios* sp.	Paracel islands	(Yang et al.,
	sesterstamide	endoperoxides				2014a)
P. falciparum	Netamine K	Tricyclic Alkaloids	2.4 μM**	*Biemna laboutei*	Madagascar	
H. contortus	6-N-acyladenine alkaloid,	Alkaloid	LD99 31 μg/mL***	*Phoriospongia* sp.	Australia	(Farrugia
	phorioadenine A					et al., 2014)
P. falciparum	Sesquiterpene isonitrile 7,20-	Isonitriles	0.013 μM*	*Cymbastela hooperi*	–	(Young et al.,
	diisocyanoadociane					2015)
3D7 *P. falciparum*	isocyanide amphilectane-type	isocyanide	0.044 μM*	*Svenzea flava*	Caribbean Sea	(Avilés et al.,
	diterpenes monamphilectines B	amphilectane-type				2015)
	isocyanide amphilectane-type	diterpenes	0.043 μM*			
	diterpenes monamphilectines C					
T. cruzi	Monalidine A	Guanidine and	8 μM**	*Monanchoraarbuscula*	Brazil	(Santos et al.,
trypomastigotes	Batzelladine D	Pyrimidine Alkaloids	64 μM***			2015)
	Batzelladines F		5 μM**			
	Batzelladines L		2 μM**			
	Norbatzelladine L		7 μM**			
L. infantum	Monalidine A		2 μM**			
promastigotes	Batzelladine D		2 μM**			
	Batzelladines F		4 μM**			
	Batzelladines L		2 μM**			
	Norbatzelladine L		2 μM**			
P. falciparum	Netamines O	Tricyclic Guanidine	16.99 μM**	*Biemna laboutei*	Madagascar	(Gros et al.,
	Netamines P	Alkaloids	32.62 μM***			2015)
	Netamines Q		8.37 μM**			
3D7 *P. falciparum*	sulfated polysaccharides	sulfated polysaccharides	66.3 μg/ml***	*Desmapsamma anchorata*	–	(Marques et al., 2016)
W2 *P. falciparum*	norterpene cyclic peroxides1	Norterpene cyclic	4.2 μM**	*Diacarnus*	Xisha Islands,	(Yang et al.,
	norterpene cyclic peroxides2	peroxides	3.0 μM**	*megaspinorhabdosa*	South China Sea	2016)
	norterpene cyclic peroxides 3		1.6 μM**			
	norterpene cyclic peroxides4		4.9 μM**			
	norterpene cyclic peroxides5		5.6 μM**			
	norterpene cyclic peroxides6		5.5 μM**			
	norterpene cyclic peroxides7		1.9 μM**			
D6 *P. falciparum*	norterpene cyclic peroxides1		5.6 μM**			
	norterpene cyclic peroxides2		6.5 μM**			
	norterpene cyclic peroxides 3		2.2 μM**			
	norterpene cyclic peroxides4		7.3 μM**			
	norterpene cyclic peroxides5		8.6 μM**			
	norterpene cyclic peroxides6		8.1 μM**			
	norterpene cyclic peroxides7		2.0 μM**			
T. b. rhodesiense	ircinin-1 (1)	Linear	97 μM***	*Ircinia oros*	Gökçeada,	(Chianese
	ircinin-2 (2)	Furanosesterterpenoids	65 μM***		Northern Aegean	et al., 2017)
	ircinialactam E (3)		130 μM***		Sea, Turkey	
	ircinialactam F (4)		130 μM***			
T. cruzi	ircinin-1 (1)		120 μM***			
	ircinin-2 (2)		110 μM***			
	ircinialactam E (3)		–			
	ircinialactam F (4)		–			

Table 2 (*continued*)

Target parasite	Extracted compounds	Chemistry	Concentration IC_{50}	Spongy	Country	References
L. donovani	ircinin-1 (1)		31 μM***			
	ircinin-2 (2)		28 μM***			
	ircinialactam E (3)		120 μM***			
	ircinialactam F (4)		95 μM***			
P. falciparum	ircinin-1 (1)		58 μM***			
	ircinin-2 (2)		56 μM***			
	ircinialactam E (3)		95 μM***			
	ircinialactam F (4)		>100 μM***			
3D7 *P. falciparum*	8-oxo-tryptamine (4)	Guanidine	8.8 μg/mL**	*Monanchora unguiculata*	Madagascar	(Campos et al., 2017)
	mixture of (E) and (Z)-6-bromo-20-demethyl-30-N-methylaplysinopsin (6, 7)	Alkaloids	8.0 μg/mL**			
3D7 *P. falciparum*	pseudoceratidine 1	Bromopyrrole Alkaloids	1.1 μM**	*Tedania braziliensis*	Brazil, Rio de Janeiro state	(Parra et al., 2018)
	pseudoceratidine derivative 4 + 5		5.8 μM**			
	pseudoceratidine derivative 16		4 μM**			
	pseudoceratidine derivative 23		2 μM**			
	pseudoceratidine derivative 25		2 μM**			
	pseudoceratidine derivative 31		7 μM**			
	pseudoceratidine derivative 50		3 μM**			
L. infantum promastigote	pseudoceratidine derivative 20		24 μM***			
	pseudoceratidine derivative 23		19 μM**			
	pseudoceratidine derivative 27		24 μM***			
	pseudoceratidine derivative 42		20 μM***			
	pseudoceratidine derivative 50		23 μM***			
L. amazonesis promastigote	pseudoceratidine derivative 20		19 μM**			
	pseudoceratidine derivative 23		44 μM***			
	pseudoceratidine derivative 27		43 μM***			
	pseudoceratidine derivative 42		76 μM***			
	pseudoceratidine derivative 50		18 μM**			
T. cruzi epimastigote	pseudoceratidine derivative 20		7 μM**			
	pseudoceratidine derivative 27		24 μM***			
Dd2 *P. falciparum*	smenotronic acid (1)	Sesquiterpenods	3.51 μM**	*Hyrtios erectus*	Chuuk Island, Federated States of Micronesia	(Ju et al., 2018)
	ilimaquinone (2)		2.11 μM**			
	pelorol (3)		0.8 μM*			
T. b. brucei	Hyrtiodoline A	alkaloid	48 h (IC50 = 15.26 μmol/L) and 72 h (IC50 = 7.48 μmol/L)	*Hyrtios* sp.	Egypt	(Shady et al., 2018)
FCR3 *P. falciparum*	Ceratinadins E	Bromotyrosine Alkaloids	0.77 μg/mL*	*Pseudoceratina* sp.	Japan	(Kurimoto et al., 2018)
	Psammaplysin F		2.45 μg/mL *			
K1 *P. falciparum*	Ceratinadins E		1.03 μg/mL			
	Psammaplysin F		3.77 μg/mL**			
3D7 *P. falciparum*	kaimanol	Sterol	0.359 μM *	*Xestospongia* sp.	Indonesia	(Murtihapsari et al., 2021)
	saringosterol		0.00025 μM*			
3D7 *P.falciparum*	8-oxo-tryptamine (4)	Tryptamine alkaloids	8.8 μg/mL**	*Fascaplysinopsis reticulata*	Mayotte (Indian Ocean)	(Campos et al., 2019)
	mixture of (E) and (Z)-6-bromo-20 -demethyl-30 -N-methylaplysinopsin (6, 7)		8.0 μg/mL**			
D10 *P. falciparum*	avarone	sesquiterpene quinone avarone	2.74 μM**	*Dysidea avara*	Turkey	(Imperatore et al., 2020)
	Thiazoavarone		0.38 μM*			
	avarol		0.96 μM*			
W2 *P. falciparum*	avarone		2.09 μM**			
	Thiazoavarone		0.21 μM*			
	avarol		1.10 μM**			
P. falciparum gametocytes from a 3D7 transgenic line	avarone		15.53 μM**			
	Thiazoavarone		15.01 μM**			
	avarol		9.30 μM**			
promastigote stage of *L. infantum*	avarone		28.21 μM***			
	Thiazoavarone		8.78 μM**			
	avarol		7.42 μM**			
promastigote stage of *L. tropica*	avarone		20.28 μM***			
	Thiazoavarone		9.52 μM**			
	avarol		7.08 μM**			
amastigote stage of *L. infantum.*	avarone		7.64 μM**			
	Thiazoavarone		4.99 μM**			
	avarol		3.19 μM**			
S. mansoni schistosomula	avarone		42.77 μM***			
	Thiazoavarone		5.90 μM**			
	avarol		33.97 μM***			
C2C4 *T. cruzi*	bisaprasin	Bromotyrosine Alkaloids	19 μM**	*Aplysinella rhax*	Fiji Islands	(Oluwabusola et al., 2020)
3D7 *P. falciparum*			29 μM***			

*** inactive, ** moderately active, * good potent active.

Table3
List of isolated compounds with potent antiparasitic activity based on IC_{50} measurement.

	Extracted compounds	Target parasites/strains	References
1	dibromopalau'amine	*T. brucei rhodesiense*, *L. donovani*, K1 *P. falciparum*	(Scala et al., 2010)
2	longamide B	*T. brucei rhodesiense*	
3	spongiacidin B	K1 *P. falciparum*	
4	dispacamide B	K1 *P. falciparum*	
5	4-hydroxy-3-tetraprenylphenylacetic acid	T. *brucei rhodesiense*	(Orhan et al., 2010)
6	diterpenes dorisenone D	*T. brucei rhodesiense*, K1 *P. falciparum*	
7	11β-acetoxyspongi-12-en-16-one	*L. donovani*, K1 *P. falciparum*	
8	4-hydroxy-3-octaprenylbenzoic acid	K1 *P. falciparum*	
9	squalene	K1 *P. falciparum*	
10	pandaroside G	*T. b. rhodesiense*	(Regalado et al., 2010)
11	pandaroside G methyl ester	*T. b. rhodesiense*, *L. donovani*	
12	11,12-didehydro-13-oxo-plakortide Q	*T.b. brucei*	(Feng et al.. 2010)
13	10-carboxy-11,12,13,14-tetranor-plakortide Q	*T.b. brucei*	
15	monamphilectine A	W2 *P. falciparum*	(Avilés and Rodríguez, 2010)
16	discorhabdins A	D6 *P. falciparum*, W2 *P. falciparum*	(Na et al.. 2010)
17	dihydrodiscorhabdin C	D6 *P. falciparum*, W2 *P. falciparum*	
18	epiplakinidioic acid	W2 *P. falciparum*	(Jiménez-Romero et al.. 2010)
19	Haliclonacyclamine A	3D7 *P. falciparum*, FCB1 *P. falciparum*	(Mani et al. 2011)
20	manadoperoxide B	*T. b. rhodesiense*, *L. donovani*	(Chianese et al., 2012)
21	manadoperoxide C	*T. b. rhodesiense*	
22	manadoperoxide F	*T. b. rhodesiense*	
23	manadoperoxide G	*T. b. rhodesiense*	
24	manadoperoxide H	*T. b. rhodesiense*, *L. donovani*	
25	manadoperoxide I	*T. b. rhodesiense*, *L. donovani*	
26	manadoperoxide K	*T. b. rhodesiense*, *L. donovani*	
27	Tsitsikammamine C	3D7 *P. falciparum*, Dd2 *P. falciparum*	(Davis et al., 2012)
28	Makaluvamines J	3D7 *P. falciparum*, Dd2 *P. falciparum*	
29	Makaluvamines G	3D7 *P. falciparum*, Dd2 *P. falciparum*	
30	Makaluvamines L	3D7 *P. falciparum*, Dd2 *P. falciparum*	
31	Makaluvamines K	3D7 *P. falciparum*, Dd2 *P. falciparum*	
32	Damirones A	Dd2 *P. falciparum*	
33	ingamine A	D6 *P. falciparum*, W2 *P. falciparum*	(Ilias et al., 2012)
34	22(S)-hydroxyingamine A	D6 *P. falciparum*, W2 *P. falciparum*	
35	dihydroingenamine D	D6 *P. falciparum*, W2 *P. falciparum*	
36	Thiaplakortone A.	3D7 *P. falciparum*, Dd2 *P. falciparum*	(Davis et al., 2013)
37	Plakortide U	FcM29 *P. falciparum*	(Festa et al., 2013)
38	Plakortides R		
39	manadoperoxide B (1)	*T. b. rhodesiense*	(Chianese et al., 2013)
40	12-isomanadoperoxide B (2)		
41	manadoperoxidic acid B (3)		
42	Glycosphingolipids: axidjiferoside-A, -B & -C	FCB1 *P. falciparum*	(Farokhi et al., 2013)
43	• Sesquiterpene isonitrile 7,20-diisocyanoadociane	*P. falciparum*	(Young et al., 2015)
44	isocyanide amphilectane-type diterpenes monamphilectines B	3D7 *P. falciparum*	(Avilés et al., 2015)
45	isocyanide amphilectane-type diterpenes monamphilectines C		
46	psammaplysin H	3D7 *P. falciparum*	(Xu et al., 2011)
47	pelorol (3)	Dd2 *P. falciparum*	(Ju et al., 2018)
48	Ceratinadins E	FCR3 *P. falciparum*	(Kurimoto et al., 2018)
49	Psammaplysin F		
50	kaimanol	3D7 *P. falciparum*	(Murtihapsari et al., 2021)
51	saringosterol		
52	Thiazoavarone	D10 *P. falciparum*, W2 *P. falciparum*	(Imperatore et al., 2020)
53	avarol		
54	Thiazoavarone		

whereas in 2016, 2017, 2019 and 2020 only two papers were recorded in each. The seven publications concerned with the antiparasitic activities of crude extract were published in 2010, 2014 and 2015, and the forty seven publications concerned with the antiparasitic activities of extracted compounds were published all over the period of survey; this reflects the interest of authors to study the antiparasitic effect of extracted compounds rather than the crude extract to save a step towards the drug discovery.

The majority of antiparastic compounds extracted from marine sponges were related to alkaloids: diterpenoid β-lactam alkaloid (Avilés and Rodríguez, 2010), Pyrroloiminoquinone alkaloids (Na et al., 2010), bromotyrosine alkaloid (Kurimoto et al., 2018; Mani et al., 2012; Mudianta et al., 2012; Oluwabusola et al., 2020; Xu et al., 2011; Yang et al., 2010), pentacyclic ingamine alkaloids (Ilias et al., 2012), thiazine alkaloids (Davis et al., 2013), tricyclic alkaloids (Gros et al., 2014), guanidine and pyrimidine Alkaloids (Gros et al., 2015), tryptamine alkaloids (Campos et al., 2019), purines (Farrugia et al., 2014) and piperidine (Farrugia et al., 2014). In addition, peroxides represents the second important group of antiparasitic compounds extracted from sponges (Chianese et al., 2012; Chianese et al., 2014; Chianese et al., 2013; Fattorusso et al., 2010; Feng et al., 2010; Festa et al., 2013; Jiménez-Romero et al., 2010; Oli et al., 2014; Yang et al., 2014a; Yang et al., 2014b), followed by terpenoids (Avilés and Rodríguez, 2010; Chianese et al., 2017; Ju et al., 2018; Orhan et al., 2010). Some substances have been extracted and used as antiparasitic agents to a lesser extent like Steroids (Murtihapsari et al., 2021; Regalado et al., 2011; Regalado et al., 2010; Viegelmann et al., 2014), amino acids (Feng et al., 2012), lipids (Farokhi et al., 2013), polysaccharides (Marques et al., 2016) and Isonitriles (Young et al., 2015). The activities of these isolated compounds against parasites were screened using *in vitro* techniques. This is a starting point and a step ahead of target-based screen technique in the drug discovery sequence, and since it is already known to kill

the parasite, the cellular permeability problem has been settled (Nweze et al., 2021).

In the present article compounds' potent activity in screened papers was classified in three categories according to IC_{50}. If it was in μM: IC_{50} > 20 μM considered low active or inactive, IC_{50}1–20 μM classified moderately active, IC_{50} < 1 μM considered good potent active (Batista et al., 2009). If it was in μg/ml: IC_{50} > 10-μg/ml considered inactive, IC_{50} 3–10 μg/ml classified moderately active, IC_{50} < 3 μg/ml considered good potent active (Ioset et al., 2009). The total number of extracted antiparasitic compound assayed in the screened articles was 147; the compounds were labeled in Table 2 according to the previous classification and those with good potent activity were 54 compounds and listed in Table 3.

Although, there are many promising anti-parasites compounds isolated from marine sponges, however there are also many obstacles in the way of converting them into effective drugs, starting from ethics and policies associated with samples collection and followed by sample supply, shortcomings of traditional bioassay-guided fractionation approaches, compatibility of some samples to high-throughput screening (HTS) techniques, and the duration, cost, efforts and processes needed before any of these compounds can be approved as an effective drug (Mayer et al., 2020). In more details, in the natural environment like marine habitat -apart from culturable microbes- accessing, collecting or recollecting of some samples is a challenge. For example, when a promising crude extract is identified from marine animals like a sponge or other, more samples are usually required to get enough crude extract for further investigations of the compound/compounds. If the chemical synthesis is not yet established or achievable for the isolated pure compounds, more quantity is required before proceeding the preclinical studies and clinical trials (García-Vilas et al., 2016). In addition, factors like the site of sample collection, season, genotype, differences related to an organism like age, and environmental stress to which the organism exposed, apparently affect the repeatability or reproducibility, thereby limiting the progression of the identified compounds to the next phase of drug development. However, the utilization of molecular biology techniques in isolation and expression of key genes, and semi- or total synthesis of the promising compounds, it will represent a real breakthrough in overcoming a large part of sampling problems (Nweze et al., 2020). Another challenges faces the drug discovery from natural marine habitat was the trouble of lack of unanimity in terms of fractions collection, isolation and structural elucidation of the bioactive compounds and other bioassay-guided fractionation. Nevertheless, some of these challenges may be overcome with the continuous advancement in chemical analysis techniques such as spectrometry (e.g., mass spectrometer), chromatography (e.g., gas chromatography, thin layer chromatography, high performance layer chromatography), and spectroscopy (e.g., ultraviolet, evaporative light scattering, refractive index, nuclear magnetic resonance), and researchers believe that the techniques could greatly renovate bioactivity guided fractionation, especially for complex extracts (Blockley et al., 2017; Choudhary et al., 2017).

5. Conclusion

This work reviewed the antiparasitic properties of natural compounds and crude extracts from marine sponges in most recently-published articles. Considering the many antiparasitic activities observed for all crude extracts and natural compounds described here, it can be stated that in fact there are optimistic perspectives on the continuing investigation of marine sponges for the treatment of parasitic infections, and they will certainly lead the scientific community to the discovery of more new efficient molecular templates and effective drugs for these diseases. Parasitic diseases specially neglected tropical diseases such as malaria, african trypanosomiasis, Chagas' disease, leishmaniasis and schistosomiasis have a detrimental impact on the world's poor peoples. Unfortunately communities suffering from these diseases have not offered a market gainful enough to attract any notable investment in research and development for new drugs. Therefore, this work intends to draw the attention of parasitologists to take their role in the efforts required for the development of novel antiparasitic drugs as part of the intensive efforts of the global scientific community to solve this economic and humanitarian problem.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Thanks to the Deanship of Scientific Research, King Khalid University for funding this article under grant no. (G.R.P./166/42).

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