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Review

Promising antiparasitic agents from marine sponges

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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. amazonensis*, *L. major*, *L. panamensis*, *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 IC₅₀: low active or inactive, moderately active and good potent active.

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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; Schwartzmann 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, anthelmintic”. 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' crude 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
<i>Leishmania major</i> Promastigotes stages	aqueous extract ethyl acetate extract dichloromethane extract	3.02 8.49 1.39	<i>Sarcotragus</i> sp.	Tunisia	(Ben Kahla-Nakbi et al., 2010)
D6 <i>P. falciparum</i> W2 <i>P. falciparum</i> <i>Leishmania donovani</i> promastigote stages	aqueous extract ethyl acetate extract dichloromethane extract organic extract	264.67 16.09 47.38 0.09 µg/mL 0.086 µg/mL 1.19 µg/mL	<i>Ircinia spinosula</i> <i>Petrosid Ng5 Sp5</i>	Australia	(Ilias et al., 2012)
D6 <i>P. falciparum</i> W2 <i>P. falciparum</i> <i>Leishmania donovani</i> promastigotes <i>Plasmodium berghei</i>	dichloromethane extract Organic extract	12 24 74 42.3 52 60.3	<i>Negombata corticata</i> <i>Mycale laxissima</i> <i>Clathria echinata</i> <i>Agelas cerebrum</i>	Red Sea, Egypt Boca de Calderas, Havana, Cuba	(Eltamany et al., 2014) (Mendiola et al., 2014)
<i>T. cruzi</i> trypomastigotes	organic extracts aqueous extracts	10.80 0.57 44.85	<i>Amphimedon viridis</i>	Atlantic Ocean, Rio de Janeiro, Brazil	(Andrade et al., 2015)
<i>T. cruzi</i> amastigotes	aqueous extracts	21.37			
<i>T. cruzi</i> epimastigote	acetone extracts	124.7 109.9 23.4 67.3 28.6	<i>Tethya ignis</i> <i>Tethya rubra</i> <i>Dysidea avara</i> <i>Mycale angulosa</i> <i>Condrosia reniformes</i>	Brazil and Spain	(de Paula et al., 2015)
<i>T. cruzi</i> amastigotes		7.2 44.5 40.3 55.5 82.6	<i>Tethya ignis</i> <i>Tethya rubra</i> <i>Dysidea avara</i> <i>Mycale angulosa</i> <i>Condrosia reniformes</i>		
<i>T. cruzi</i> Trypomastigote		EC ₅₀ 6.3 EC ₅₀ 33.3 EC ₅₀ 1.1 EC ₅₀ 3.8 EC ₅₀ 0.6	<i>Tethya ignis</i> <i>Tethya rubra</i> <i>Dysidea avara</i> <i>Mycale angulosa</i> <i>Condrosia reniformes</i>		
<i>P. falciparum</i>	–	3.26 µM	<i>Biemna laboutei</i>	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 IC₅₀ 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*, *Haliciona*, *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, biofoul-

ing, 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. amazonensis*, *L. major*, *L. panamensis*, *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
<i>T. brucei rhodesiense</i>	dibromopalau'amine	Bromopyrrole alkaloids	0.46 µg/mL*	<i>Axinella</i> sp. and <i>Agelas</i> sp.	–	(Scala et al., 2010)
	longamide B		1.53 µg/mL*			
	Sceptrin		9.71 µg/mL**			
	spongiacidin B		13.58 µg/mL***			
<i>T. cruzi</i>	longamide B	Terpenoids	33.03 µg/mL***	<i>Spongia</i> sp. and <i>Ircinia</i> sp.	Turkey	(Orhan et al., 2010)
<i>L. donovani</i>	dibromopalau'amine		1.09 µg/mL*			
	longamide B		3.85 µg/mL**			
<i>K1 P. falciparum</i>	spongiacidin B		1.09 µg/mL*			
	dispacamide B		1.34 µg/mL*			
	dibromopalau'amine		1.48 µg/mL*			
<i>T. brucei rhodesiense</i>	demethylfurospingon-4		4.90 µg/mL**			
	4-hydroxy-3-		0.60 µg/mL*			
	tetraprenylphenylacetic acid					
	heptaprenyl-p-quinol		3.54 µg/mL**			
	diterpenes dorisenone D		2.47 µg/mL*			
	tryptophol		5.89 µg/mL**			
<i>T. cruzi</i>	heptaprenyl-p-quinol		4.08 µg/mL**			
	11β-acetoxyspongi-12-en-16-one		4.51 µg/mL**			
<i>L. donovani</i>	furospingon-1	Steroidal Saponins	4.08 µg/mL**	<i>Pandaros</i> <i>acanthifolium</i>	Caribbean Sea	(Regalado et al., 2010)
	4-hydroxy-3-		5.60 µg/mL**			
	octaprenylbenzoic acid					
	11β-acetoxyspongi-12-en-16-one		0.75 µg/mL*			
	tryptophol		9.60 µg/mL**			
<i>K1 P. falciparum</i>	furospinulosin-2		3.51 µg/mL**			
	furospingon-4		7.51 µg/mL**			
	4-hydroxy-3-		1.57 µg/mL*			
	octaprenylbenzoic acid					
	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**			
<i>T. b. rhodesiense</i>	pandaroside G	Cyclic Polyketide Peroxides	0.78 µM*	<i>Plakortis</i> sp.	Australia	(Feng et al., 2012)
	pandaroside G methyl ester		0.038 µM*			
<i>L. donovani</i>	pandaroside G		1.3 µM**			
	pandaroside G methyl ester	Bromotyrosine alkaloid	0.051 µM*	<i>Hyattella</i> sp.	Hervey Bay, Australia	(Yang et al., 2010)
<i>T.b. brucei</i>	11,12-didehydro-13-oxo-plakortide Q		0.049 µM*			
	10-carboxy-11,12,13,14-tetranor-plakortide Q		0.940 µM*			
<i>Dd2 P. falciparum</i>	psammaplysin F	diterpenoid β-lactam alkaloid	1.4 µM**	<i>Hymeniacidon</i> sp.	Mona Island, Puerto Rico	(Avilés and Rodríguez, 2010)
<i>3D7 P. falciparum</i>			0.87 µM*			
<i>W2 P. falciparum</i>	monamphilectine A		0.60 µM*			
<i>D6 P. falciparum</i>	discorhabdins A	Pyrroloiminoq-uinone alkaloids	0.05 µM*	<i>Latrunculia</i> sp.	Aleutian Islands	(Na et al., 2010)
	discorhabdins C		2.80 µM**			
	dihydrodiscorhabdin C		0.17 µM*			
<i>W2 P. falciparum</i>	discorhabdins A	endoperoxyketal polyketides manadoperoxides	0.05 µM*	<i>Plakortis</i> cfr. <i>simplex</i>	Bunaken Marine Park of Manado, Indonesia	(Fattorusso et al., 2010)
	discorhabdins C		2.00 µM**			
	dihydrodiscorhabdin C		0.13 µM*			
<i>D10 P. falciparum</i>	Manadoperoxide A	Cycloperoxides	6.88 µM**	<i>Plakortis</i> <i>halichondrioides</i>	Mona Island, Puerto Rico	(Jiménez-Romero et al., 2010)
	Manadoperoxide B		6.76 µM**			
	Manadoperoxide C		4.54 µM**			
	Manadoperoxide D	Piperidine alkaloid	10.38 µM**	<i>Haliclona</i> spp.	Solomon Islands	(Mani et al., 2011)
<i>W2 Plasmodium falciparum</i>	Manadoperoxide A		3.74 µM**			
	Manadoperoxide B		3.69 µM**			
	Manadoperoxide C	steroid glycosides	2.33 µM**	<i>Pandaros</i> <i>acanthifolium</i>	Martinique Island	(Regalado et al., 2011)
	Manadoperoxide D		7.93 µM**			
<i>W2 P. falciparum</i>	epiplakinic acid F methyl ester		4 µg/mL**			
	plakortolide J	Piperidine alkaloid	>10 µg/mL**	<i>Haliclona</i> spp.	Solomon Islands	(Mani et al., 2011)
	epiplakinidioic acid		0.3 µg/mL*			
	polyketides epiplakinic acid F		3 µg/mL**			
<i>3D7 P. falciparum</i>	Plakortolide F	steroid glycosides	>10 µg/mL**	<i>Pandaros</i> <i>acanthifolium</i>	Martinique Island	(Regalado et al., 2011)
<i>FCB1 P. falciparum</i>	Haliclonacyclamamine A		0.7 µM*			
			0.11 µM*			
<i>L. donovani</i>	acanthifolioside A (1)	steroid glycosides	8.5 µM**	<i>Pandaros</i> <i>acanthifolium</i>	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
<i>P. falciparum</i>	acanthifolioside A (1), acanthifolioside F (7)		7.6 μM^{**} 9.2 μM^{**}			
<i>T. b. rhodesiense</i> <i>T. cruzi</i>	acanthifolioside F (7) aeroplysinin-1 (1)	Bromotyrosine	6.4 μM^{**} 10 μM^{**}	<i>Verongula rigida</i>	Columbia	(Galeano et al., 2011)
<i>P. falciparum</i> <i>L. panamensis</i> 3D7 <i>P. falciparum</i>	purealidin B (7) 11-hydroxyaerotherionin (8) psammaplysin H psammaplysin G psammaplysin F	Bromotyrosine alkaloid	5 μM^{**} 10 μM^{**} 0.41 μM^* 5.22 μM^{**} 1.92 μM^{**}	<i>Pseudoceratina sp.</i>	–	(Xue et al., 2004)
<i>T. b. rhodesiense</i>	manadoperoxide B manadoperoxide C manadoperoxide F manadoperoxide G manadoperoxide H manadoperoxide I manadoperoxide K	Manadoperoxides	0.003 $\mu\text{g/mL}^*$ 0.678 $\mu\text{g/mL}^*$ 0.792 $\mu\text{g/mL}^*$ 1.84 $\mu\text{g/mL}^*$ 0.315 $\mu\text{g/mL}^*$ 0.062 $\mu\text{g/mL}^*$ 0.087 $\mu\text{g/mL}^*$	<i>Plakortis cfr. lita</i>	Indonesia	(Chianese et al., 2012)
<i>L. donovani</i>	manadoperoxide B manadoperoxide C manadoperoxide F manadoperoxide G manadoperoxide H manadoperoxide I manadoperoxide K		0.589 $\mu\text{g/mL}^*$ 3.24 $\mu\text{g/mL}^{**}$ 5.73 $\mu\text{g/mL}^{**}$ 3.22 $\mu\text{g/mL}^{**}$ 2.44 $\mu\text{g/mL}^*$ 0.633 $\mu\text{g/mL}^*$ 1.89 $\mu\text{g/mL}^*$			
3D7 <i>P. falciparum</i>	psammaplysin, 19-hydroxy-psammaplysin E	Bromotyrosine alkaloid	6.4 μM^{**}	<i>Aplysinella strongylata</i>	Indonesia	(Mudianta et al., 2012)
FCB1 <i>P. falciparum</i>	Araplysin I Araplysin I (1) salt Araplysin N20-formamide Araplysin N20-hydroxyformamide Purealidin Q Aerotherionin Homoaerotherionin Aplysinone D 11,19-Dideoxyfistularin 3 11-Hydroxyfistularin 3	Bromotyrosine alkaloid	4.5 μM^{**} 5.3 μM^{**} 3.6 μM^{**} 5.0 μM^{**} 3.6 μM^{**} 3.4 μM^{**} 2.8 μM^{**} 1.0 μM^{**} 2.1 μM^{**} 2.1 μM^{**}	<i>Suberea ianthelliformis</i>	Solomon Islands, South Pacific	(Mani et al., 2012)
3D7 <i>P. falciparum</i>	Araplysin I Araplysin I (1) salt Araplysin N20-formamide Araplysin N20-hydroxyformamide Aerotherionin Homoaerotherionin Aplysinone D 11,19-Dideoxyfistularin 3 11-Hydroxyfistularin 3		4.6 μM^{**} 4.5 μM^{**} 7.0 μM^{**} 4.1 μM^{**} 4.2 μM^{**} 4.0 μM^{**} 3.1 μM^{**} 0.9 μM^* 2.6 μM^{**}			
<i>T. brucei brucei</i>	Istrochamides A Istrochamides B	N-cinnamoyl-amino acids	3.4 μM^{**} 4.7 μM^{**}	<i>Istrochota sp.</i>	Australia	(Feng et al., 2012)
3D7 <i>P. falciparum</i>	Tsitsikammamine C Makaluvamines J Makaluvamines G Makaluvamines L Makaluvamines K Damirones A Damirones B	bispyrroloiminoquinone alkaloid	0.013 μM^* 0.025 μM^* 0.036 μM^* 0.04 μM^* 0.039 μM^* 1.88 μM^{**} 12.25 μM^{**}	<i>Zyzzya sp.</i>	Australia	(Davis et al., 2012)
Dd2 <i>P. falciparum</i>	Tsitsikammamine C Makaluvamines J Makaluvamines G Makaluvamines L Makaluvamines K Damirones A Damirones B		0.018 μM^* 0.022 μM^* 0.039 μM^* 0.021 μM^* 0.3 μM^* 0.36 μM^* 3.8 μM^{**}			
D6 <i>P. falciparum</i>	ingamine A 22(S)-hydroxyingamine A dihydroingamine D	pentacyclic ingamine alkaloids	0.09 $\mu\text{g/mL}^*$ 0.22 $\mu\text{g/mL}^*$ 0.078 $\mu\text{g/mL}^*$	<i>Petrosid Ng5 Sp5</i>	Australia	(Ilias et al., 2012)
W2 <i>P. falciparum</i>	ingamine A 22(S)-hydroxyingamine A dihydroingamine D		0.072 $\mu\text{g/mL}^*$ 0.14 $\mu\text{g/mL}^*$ 0.057 $\mu\text{g/mL}^*$			
<i>L. donovani</i>	ingamine A 22(S)-hydroxyingamine A dihydroingamine D		5.98 $\mu\text{g/mL}^{**}$ 5.83 $\mu\text{g/mL}^{**}$ 3.12 $\mu\text{g/mL}^{**}$			
3D7 <i>P. falciparum</i> Dd2 <i>P. falciparum</i>	Thiaplakortone A.	Thiazine Alkaloids	0.051 μM^* 0.006 μM^*	<i>Plakortis lita</i>	Australia	(Davis et al., 2013)

(continued on next page)

Table 2 (continued)

Target parasite	Extracted compounds	Chemistry	Concentration IC ₅₀	Spongy	Country	References
FcM29 <i>P. falciparum</i>	Plakortide U	Endoperoxide	0.3 µg/ml*	<i>Plakinastrella</i>	Fiji Islands,	(Festa et al., 2013)
	Plakortides R	polyketides	1.62 µg/ml*	<i>mamillaris</i>	Melanesia, South Pacific Ocean	
	Plakortides T		19.1 µg/ml***			
<i>T. b. rhodesiense</i>	manadoperoxide B (1)	Endoperoxide	0.003 µg/ml*	<i>Plakortis cfr. lita</i>	Indonesia	(Chianese et al., 2013)
	12-isomanadoperoxide B (2)	polyketides	0.011 µg/ml*			
	manadoperoxidic acid B (3)		1.87 µg/ml*			
FCB1 <i>P. falciparum</i>	Glycosphingolipids:	glycosphingolipids	0.53 µM*	<i>Axinyssa djiferi</i>	Senegal	(Farokhi et al., 2013)
	axidjiferoside-A, -B and -C					
D10 <i>P. falciparum</i>	Endoperoxide polyketide 1	Endoperoxide	3.89 µM**	<i>Plakortis simplex</i>	China	(Chianese et al., 2014)
	Endoperoxide polyketide 2	polyketides	4.05 µM**			
	Endoperoxide polyketide 3		1.77 µM**			
	Endoperoxide polyketide 5		6.18 µM**			
	Endoperoxide polyketide 7		5.12 µM**			
W2 <i>P. falciparum</i>	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**			
<i>T. bruci</i>	plakortide E	Endoperoxide	5 µM**	<i>Plakortis halichondrioides</i>	Bahamas	(Oli et al., 2014)
D6 <i>P. falciparum</i>	norditerpene diacarpoxide J	Norditerpene	1.6 µM**	<i>Diacarnus</i>	China	(Yang et al., 2014a)
W2 <i>P. falciparum</i>		endoperoxides	1.8 µM**	<i>megaspinothabdosia</i>		
<i>T. brucei brucei</i>	24-vinyl-cholest-9-ene-3β	Steroids	21.56 µM***	<i>Haliclona simulans</i>	Ireland	(Vieglmann et al., 2014)
	24-diol, 20-methyl-pregn-6-en-3β-ol, 5α,8α-epidioxy		4.58 µM**			
	24-methylenecholesterol		9.01 µM**			
<i>L. donovani</i>	Scalarane sesterterpene, sesterstamide	Norditerpene endoperoxides	32.9 µg/mL***	<i>Hyrios</i> sp.	Paracel islands	(Yang et al., 2014a)
<i>P. falciparum</i>	Netamine K	Tricyclic Alkaloids	2.4 µM**	<i>Biemna laboutei</i>	Madagascar	
<i>H. contortus</i>	6-N-acyladenine alkaloid, phorioadenine A	Alkaloid	LD99 31 µg/mL***	<i>Phoriospongia</i> sp.	Australia	(Farrugia et al., 2014)
<i>P. falciparum</i>	Sesquiterpene isonitrile 7,20-diisocyanoadociane	Isonitriles	0.013 µM*	<i>Cymbastela hooperi</i>	–	(Young et al., 2015)
3D7 <i>P. falciparum</i>	isocyanide amphilectane-type diterpenes monamphilectines B	isocyanide amphilectane-type diterpenes	0.044 µM*	<i>Svenzea flava</i>	Caribbean Sea	(Avilés et al., 2015)
	isocyanide amphilectane-type diterpenes monamphilectines C		0.043 µM*			
<i>T. cruzi</i> trypomastigotes	Monalidine A	Guanidine and Pyrimidine Alkaloids	8 µM**	<i>Monanchoraarbuscula</i>	Brazil	(Santos et al., 2015)
	Batzelladine D		64 µM***			
	Batzelladines F		5 µM**			
	Batzelladines L		2 µM**			
	Norbatzelladine L		7 µM**			
<i>L. infantum</i> promastigotes	Monalidine A		2 µM**			
	Batzelladine D		2 µM**			
	Batzelladines F		4 µM**			
	Batzelladines L		2 µM**			
	Norbatzelladine L		2 µM**			
<i>P. falciparum</i>	Netamines O	Tricyclic Guanidine Alkaloids	16.99 µM**	<i>Biemna laboutei</i>	Madagascar	(Gros et al., 2015)
	Netamines P		32.62 µM***			
	Netamines Q		8.37 µM**			
3D7 <i>P. falciparum</i>	sulfated polysaccharides	sulfated polysaccharides	66.3 µg/ml***	<i>Desmapsamma anchorata</i>	–	(Marques et al., 2016)
W2 <i>P. falciparum</i>	norterpene cyclic peroxides1	Norterpene cyclic peroxides	4.2 µM**	<i>Diacarnus megaspinothabdosia</i>	Xisha Islands, South China Sea	(Yang et al., 2016)
	norterpene cyclic peroxides2		3.0 µM**			
	norterpene cyclic peroxides3		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 <i>P. falciparum</i>	norterpene cyclic peroxides1		5.6 µM**			
	norterpene cyclic peroxides2		6.5 µM**			
	norterpene cyclic peroxides3		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**			
<i>T. b. rhodesiense</i>	ircinin-1 (1)	Linear	97 µM***	<i>Ircinia oros</i>	Gökçeada, Northern Aegean Sea, Turkey	(Chianese et al., 2017)
	ircinin-2 (2)	Furanosesterterpenoids	65 µM***			
	ircinialactam E (3)		130 µM***			
	ircinialactam F (4)		130 µM***			
<i>T. cruzi</i>	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
<i>L. donovani</i>	ircinin-1 (1) ircinin-2 (2) ircinialactam E (3) ircinialactam F (4)		31 μM^{***} 28 μM^{***} 120 μM^{***} 95 μM^{***}			
<i>P. falciparum</i>	ircinin-1 (1) ircinin-2 (2) ircinialactam E (3) ircinialactam F (4)		58 μM^{***} 56 μM^{***} 95 μM^{***} >100 μM^{***}			
3D7 <i>P. falciparum</i>	8-oxo-tryptamine (4) mixture of (E) and (Z)-6-bromo-20-demethyl-30-N-methylaplysinopsin (6, 7)	Guanidine Alkaloids	8.8 $\mu\text{g/mL}^{**}$ 8.0 $\mu\text{g/mL}^{**}$	<i>Monanchora unguiculata</i>	Madagascar	(Campos et al., 2017)
3D7 <i>P. falciparum</i>	pseudoceratidine 1 pseudoceratidine derivative 4 + 5 pseudoceratidine derivative 16 pseudoceratidine derivative 23 pseudoceratidine derivative 25 pseudoceratidine derivative 31 pseudoceratidine derivative 50	Bromopyrrole Alkaloids	1.1 μM^{**} 5.8 μM^{**} 4 μM^{**} 2 μM^{**} 2 μM^{**} 7 μM^{**} 3 μM^{**}	<i>Tedania braziliensis</i>	Brazil, Rio de Janeiro state	(Parra et al., 2018)
<i>L. infantum</i> promastigote	pseudoceratidine derivative 20 pseudoceratidine derivative 23 pseudoceratidine derivative 27 pseudoceratidine derivative 42 pseudoceratidine derivative 50		24 μM^{***} 19 μM^{**} 24 μM^{***} 20 μM^{***} 23 μM^{***}			
<i>L. amazonensis</i> promastigote	pseudoceratidine derivative 20 pseudoceratidine derivative 23 pseudoceratidine derivative 27 pseudoceratidine derivative 42 pseudoceratidine derivative 50		19 μM^{**} 44 μM^{***} 43 μM^{***} 76 μM^{***} 18 μM^{**}			
<i>T. cruzi</i> epimastigote	pseudoceratidine derivative 20 pseudoceratidine derivative 27		7 μM^{**} 24 μM^{***}			
Dd2 <i>P. falciparum</i>	smentronic acid (1) ilimaquinone (2) pelorol (3)	Sesquiterpenoids	3.51 μM^{**} 2.11 μM^{**} 0.8 μM^{*}	<i>Hyrtios erectus</i>	Chuuk Island, Federated States of Micronesia	(Ju et al., 2018)
<i>T. b. brucei</i>	Hyrtiodoline A	alkaloid	48 h (IC ₅₀ = 15.26 $\mu\text{mol/L}$) and 72 h (IC ₅₀ = 7.48 $\mu\text{mol/L}$)	<i>Hyrtios</i> sp.	Egypt	(Shady et al., 2018)
FCR3 <i>P. falciparum</i>	Ceratinadins E Psammaplysin F	Bromotyrosine Alkaloids	0.77 $\mu\text{g/mL}^{*}$ 2.45 $\mu\text{g/mL}^{*}$	<i>Pseudoceratina</i> sp.	Japan	(Kurimoto et al., 2018)
K1 <i>P. falciparum</i>	Ceratinadins E Psammaplysin F		1.03 $\mu\text{g/mL}$ 3.77 $\mu\text{g/mL}^{**}$			
3D7 <i>P. falciparum</i>	kaimanol saringosterol	Sterol	0.359 μM^{*} 0.00025 μM^{*}	<i>Xestospongia</i> sp.	Indonesia	(Murtihapsari et al., 2021)
3D7 <i>P. falciparum</i>	8-oxo-tryptamine (4) mixture of (E) and (Z)-6-bromo-20 -demethyl-30 -N-methylaplysinopsin (6, 7)	Tryptamine alkaloids	8.8 $\mu\text{g/mL}^{**}$ 8.0 $\mu\text{g/mL}^{**}$	<i>Fascaplysinopsis reticulata</i>	Mayotte (Indian Ocean)	(Campos et al., 2019)
D10 <i>P. falciparum</i>	avarone Thiazoavarone avarol	sesquiterpene quinone avarone	2.74 μM^{**} 0.38 μM^{*} 0.96 μM^{*}	<i>Dysidea avara</i>	Turkey	(Imperatore et al., 2020)
W2 <i>P. falciparum</i>	avarone Thiazoavarone avarol		2.09 μM^{**} 0.21 μM^{*} 1.10 μM^{**}			
<i>P. falciparum</i> gametocytes from a 3D7 transgenic line	avarone Thiazoavarone avarol		15.53 μM^{**} 15.01 μM^{**} 9.30 μM^{**}			
promastigote stage of <i>L. infantum</i>	avarone Thiazoavarone avarol		28.21 μM^{***} 8.78 μM^{**} 7.42 μM^{**}			
promastigote stage of <i>L. tropica</i>	avarone Thiazoavarone avarol		20.28 μM^{***} 9.52 μM^{**} 7.08 μM^{**}			
amastigote stage of <i>L. infantum</i>	avarone Thiazoavarone avarol		7.64 μM^{**} 4.99 μM^{**} 3.19 μM^{**}			
<i>S. mansoni</i> schistosomula	avarone Thiazoavarone avarol		42.77 μM^{***} 5.90 μM^{**} 33.97 μM^{***}			
C2C4 <i>T. cruzi</i> 3D7 <i>P. falciparum</i>	bisaprasin	Bromotyrosine Alkaloids	19 μM^{**} 29 μM^{***}	<i>Aplysinella rhax</i>	Fiji Islands	(Oluwabusola et al., 2020)

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

Table3List of isolated compounds with potent antiparasitic activity based on IC₅₀ measurement.

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

nes (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 : $IC_{50} > 20 \mu M$ considered low active or inactive, $IC_{50} 1-20 \mu M$ classified moderately active, $IC_{50} < 1 \mu M$ considered good potent active (Batista et al., 2009). If it was in $\mu g/ml$: $IC_{50} > 10 \mu g/ml$ considered inactive, $IC_{50} 3-10 \mu g/ml$ classified moderately active, $IC_{50} < 3 \mu g/ml$ 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.

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