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MINI-REVIEW

Insights into the anti-infective properties of prodiginines

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Abstract

Prodiginines are a large family of tripyrrole alkaloids that contain natural members produced by various bacteria and non-natural members obtained from chemical synthesis, enzymatic synthesis, and mutasynthesis. These compounds have attracted a great deal of attention due to their wide range of fascinating properties including anti-infective, anticancer, and immunosuppressive activities. In consideration of the great need for novel and effective anti-infective agents, this review is mainly focused on the current status of research on the anti-infective properties of prodiginines, highlighting their antibacterial, antifungal, antiprotozoal, anti-larval, and antiviral activities. Additionally, the multiple mechanisms by which prodiginines exert their anti-infective effects will also be discussed.

Keywords Prodiginines · Antibacterial · Antifungal · Antiprotozoal · Anti-larval · Antiviral

Introduction

Since the accidental discovery of penicillin in 1928, anti-infective drugs, particularly antibiotics, have opened new avenues for the treatment of infectious diseases caused by pathogens (Laxminarayan et al. 2016; Singh et al. 2017). The use of these drugs has reduced mortality associated with infectious diseases and rapidly increased human life expectancy (Laxminarayan et al. 2016; Singh et al. 2017). The use of anti-infective drugs in animal husbandry has also been demonstrated to be an important way to prevent infectious disease in animals and to improve the quality of animal products (Cheng et al. 2014). However, due to the inappropriate use of antibiotics in recent decades, the incidence of multidrug-resistant pathogens is increasing continuously; these pathogens are becoming a major public health threat (Blair et al. 2015; Brown and Wright 2016; Bassegoda et al. 2018). Therefore, it is of great importance to search for novel and effective anti-infective agents.

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The secondary metabolites of microorganisms are a prolific source of bioactive substances. Many of these compounds have been proven to be anti-infective agents, such as streptomycin, erythromycin, and cephalosporin (Katz and Baltz 2016). Prodigiosin is a natural red pigment that is isolated from the ubiquitous bacterium *Serratia marcescens* and has been identified as a secondary metabolite with a linear tripyrrole structure (Bennett and Bentley 2000; Soliev et al. 2011). It is responsible for the mysterious "bleeding bread" and "bloody polenta" phenomena throughout history (Bennett and Bentley 2000; Fürstner 2003). In addition to prodigiosin, a series of prodigiosin-like compounds, such as undecylprodigiosin, metacycloprodigiosin, and cycloprodigiosin are reported as secondary metabolites by several other bacteria including *Streptomyces coelicolor*, *Saccharopolyspora*, *Zooshikella rubidus*, and *Hahella* (Stankovic et al. 2014; Williamson et al. 2006). Furthermore, a number of new prodigiosin analogues have been obtained by chemical synthesis (Fürstner 2003; Hu et al. 2016; Nisha et al. 2015), enzymatic synthesis (Chawrai et al. 2008; You et al. 2018), and mutasynthesis (Klein et al. 2017). All of these compounds are grouped as prodiginines because they contain a common tripyrrole skeleton (Fig. 1).

In recent years, the studies on prodiginines have received an increasing amount of attention (Fig. 2), due to the impressive biological properties of prodiginines, including their antibacterial, antifungal, antimalarial, immunosuppressive, and anticancer activities (Darshan and Manonmani 2015; Nisha et al. 2015; Stankovic et al. 2014). Specifically, prodiginines

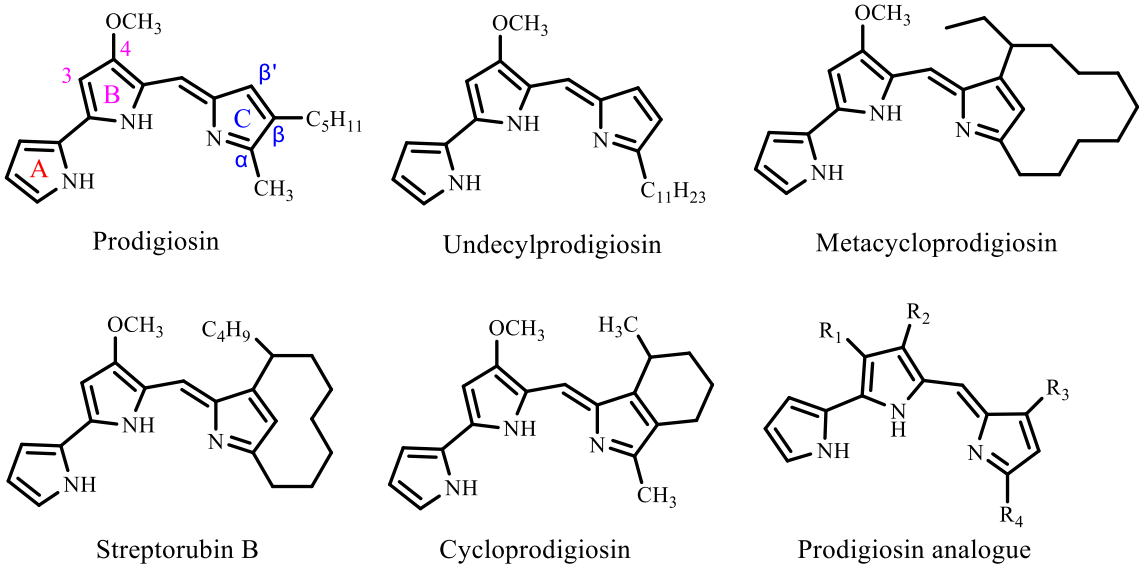


Fig. 1 Examples of prodiginines

have shown cytotoxicity against several human cancer cell lines, such as breast cancer cells (Wang et al. 2016), colorectal cancer cells (Prabhu et al. 2016), and leukemia cells (Liu et al. 2013). A synthetic prodiginine, obatoclax, has been used in multiple phase I and II clinical trials for the chemotherapy of various types of cancer (Nguyen et al. 2007; Paik et al. 2010). Several excellent reviews have been published focusing on the anticancer activities of prodiginines (Montaner and Perez-Tomas 2003; Pandey et al. 2009; Perez-Tomas et al. 2003; Perez-Tomas and Vinas 2010). Therefore, the antibacterial activities of prodiginines have been overshadowed by their promising anticancer activities. In fact, the anti-infective properties of prodiginines are remarkable. In this review, we aim to provide a concise overview of the current knowledge regarding the anti-infective properties of prodiginines. Antibacterial, antifungal, antiprotozoal, anti-larval, and antiviral activities will be covered. The anti-infective mechanisms of action of the prodiginines will also be discussed.

Antibacterial activity of prodiginines

Antibacterial activity is one of the most important anti-infective properties of prodiginines. To the best of our knowledge, the first report of the antibacterial activity of prodiginines can be traced back to 1949, which reported that old cultures of *Micrococcus prodigiosus*, an early name for *S. marcescens*, could completely inhibit the growth of *Vibrio cholera* (Abraham and Florey 1949). However, the identity of the antibacterial substance was not confirmed in this initial report. In 1971, a study conducted by Gerber evaluated the antibacterial activities of four prodiginine pigments (prodigiosin, nonylprodiginine, cyclononylprodiginine, and methylcyclodecylprodiginine) against 18 microorganisms using the agar-streak dilution method. The results demonstrated that prodigiosin had bacteriostatic activities against most of the tested microorganisms, including *Staphylococcus aureus*, *Mycobacterium smegmatis*, and *Nocardia asteroids*, while the

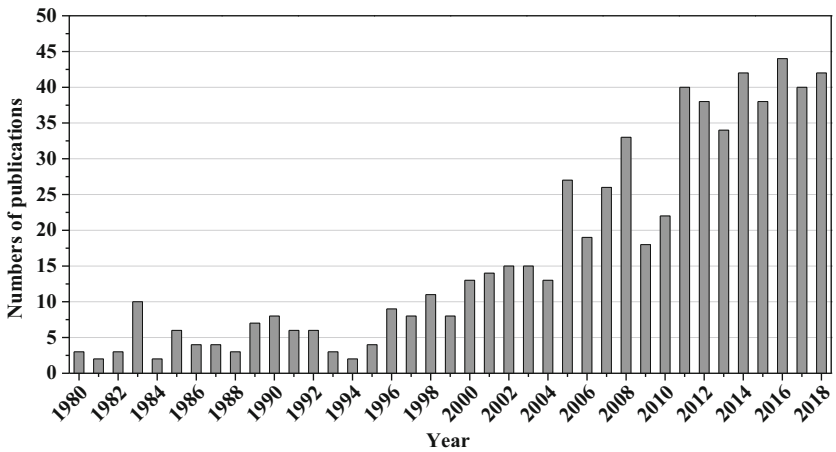


Fig. 2 Number of publications per year indexed in PubMed when searching the terms "Prodigiosin OR prodiginine" (5 Nov 2018)

other prodiginines had similar, but weaker, activity (Gerber 1971; Gerber 1975b). However, the focus of research on the prodiginines shifted to their promising anticancer and immunosuppressive activities over the next few decades. However, recently, a growing number of studies have been performed regarding the antibacterial activity of prodiginines. Tables 1, 2, and 3 summarize the published findings on the antibacterial properties of prodiginines ranging from 2011 to the present.

As shown in Tables 1, 2, and 3, prodiginines exhibited considerable antibacterial activity against both Gram-negative and Gram-positive microorganisms such as *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Micrococcus luteus*. The minimal inhibitory concentrations (MIC) of prodiginines against these bacteria were between 5 and 150 μg/mL. It is well recognized that compounds with MICs ≤ 100 μg/mL are considered noteworthy (Cushnie and Lamb 2011). Therefore, prodiginines with MICs ≤ 100 μg/mL are regarded as promising antibacterial agents and those with MICs ≤ 10 μg/mL are especially attractive for researchers.

The antibacterial activities of natural prodiginines are shown in Table 1. The antibacterial properties of prodigiosin have been more extensively studied than those of other prodiginines. Gondil et al. reported the antibacterial activity of prodigiosin from *S. nematodiphila* RL2 against four bacterial pathogens (*Listeria* sp., *Pseudomonas* sp., *Yersinia* sp., and *Shigella* sp.) by demonstrating zones of inhibition (Gondil et al. 2017). Sumathi et al. confirmed that *P. aeruginosa* and *E. coli* were more susceptible to prodigiosin than *Klebsiella pneumoniae* (Sumathi et al. 2014). Furthermore, a recent report demonstrated that the antibacterial activity of prodigiosin could be enhanced by combining with biosurfactants. The MIC of prodigiosin against *Corynebacterium glutamicum* was decreased from 2.56 to 0.005 μg/mL in the presence of 16 μg/mL N-myristoyltyrosine (Hage-Hülsmann et al. 2018). In addition to prodigiosin, undecylprodigiosin isolated from *Streptomyces* sp. JS520 exhibited growth inhibition against *M. luteus* and *B. subtilis*, with MIC values of 50 μg/mL for both species (Stankovic et al. 2012). Cycloprodigiosin from *Zooshikella rubidus* S1-1 exhibited antimicrobial properties against *E. coli*, *Salmonella* serovar Typhimurium, *B. subtilis*, and *S. aureus*, with zones of growth inhibition of 10.6, 9.3, 9.2, and 10.0 mm in diameter, respectively, that appeared when 50 μg of this compound was applied to paper disc (Lee et al. 2011). Moreover, the antibacterial activity was also reported when prodiginines were used as fibrous dye. Alihosseini showed that the dyed wool fabrics had the ability to kill approximately 50% of the *S. aureus* and *E. coli* applied within 16 h of the contact time (Alihosseini et al. 2008). Lee et al. also showed that when silk and cotton fabrics were dyed with red pigment extract solution from *Z. rubidus* S1-1, the growth rates of *E. coli* and *S. aureus* were reduced from 91.37 to 96.98% and from 96.62 to 99.98%, respectively (Lee et al. 2011).

In addition to natural prodiginines, synthetic prodiginines also exhibit antibacterial activity toward several bacteria (Table 2). A prodigiosin analogue with methylation at the C-ring (Fig. 1) showed significantly better activities against Gram-positive bacteria than prodigiosin itself (Marchal et al. 2013). However, the presence of either a conjugated carbonyl moiety or a pendant carboxylate group at the C-ring was detrimental to the activity against Gram-positive bacteria (Marchal et al. 2013). Recently, a novel prodigiosin analogue was obtained by enzymatic synthesis in our laboratory. This compound exhibited excellent antimicrobial properties against *S. aureus*, *B. subtilis*, and *E. coli* with half maximal inhibitory concentration (IC_{50}) values of 0.62, 0.73, and 4.12 μg/mL, respectively (You et al. 2018). Moreover, four cyclic prodiginines were produced using a mutasynthesis approach based on the feeding of an artificial precursor analog to a recombinant strain of *Pseudomonas putida* KT2440, in which the biosynthetic pathway is blocked in an early key step (Klein et al. 2018). The IC_{50} of cyclic prodiginines against *E. coli* were > 5.0 μM whereas *B. subtilis* and *C. glutamicum* exhibited the highest susceptibility (IC_{50}; 0.1–1.1 μM).

Among the species of prodiginine-inhibited bacteria, *S. aureus* attracted our attention because it is one of the most common human pathogens and is a major cause of hospital-acquired infections. The emergence of multidrug-resistant *S. aureus* has increased the difficulty of their treatment (Haddad Kashani et al. 2018). The biological activities of prodiginines against *S. aureus* have been reported in several studies (Table 3). Suryawanshi et al. tested the antibacterial activity of prodigiosin against *S. aureus*, *S. typhi*, *E. coli*, and *B. subtilis*. The results indicated that *S. aureus* appeared to be more sensitive to prodigiosin (MIC, 5 μg/mL) than *E. coli* (MIC, 23 μg/mL) (Suryawanshi et al. 2014). Lee et al. evaluated the capability of prodigiosin and cycloprodigiosin extracted from *Z. rubidus* S1-1 to inhibit the growth of *S. aureus*, *B. subtilis*, *E. coli*, and *S. enterica* using the disc diffusion method. The results showed that *S. aureus* was significantly inhibited by both prodigiosin and cycloprodigiosin. This study also suggested that cycloprodigiosin had higher antimicrobial activity toward *S. aureus* than prodigiosin (Lee et al. 2011).

For methicillin-resistant *S. aureus* (MRSA), a specific strain that is resistant to β-lactam antibiotics, prodiginines also exhibit good antibacterial activity. The results from Ji and co-workers indicated that prodigiosin isolated from *Serratia* sp. PDGS 120915 inhibited the growth of MRSA with an MIC value of 32 μg/mL (Ji et al. 2015). Moreover, the synergistic effects of prodigiosin in combination with a β-lactam antibiotic against MRSA were confirmed by Ji and co-workers, who showed that the use of 32 μg/mL prodigiosin reduced the

Table 1 Antibacterial activity of natural prodiginines

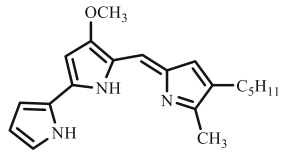
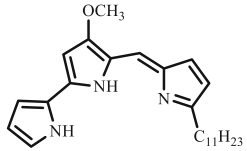
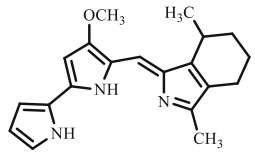
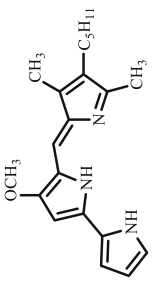
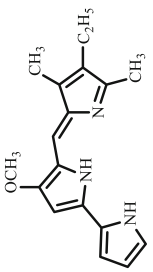
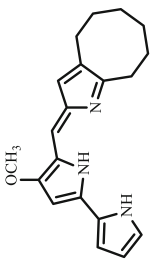
Compound	Structure	Source	Active against	MIC/IC_{50}/inhibition zone	Reference
Prodigiosin		*Serratia marcescens* NPLR1	*Escherichia coli*	MIC 132 μg/mL	Sumathi et al. 2014
			Salmonella typhi	MIC 128 μg/mL	
			Proteus vulgaris	MIC 54 μg/mL	
			Pseudomonas aeruginosa	MIC 124 μg/mL	
			Klebsiella pneumoniae	MIC 144 μg/mL	
			Bacillus subtilis	MIC 90 μg/mL	
Prodigiosin		*Serratia marcescens*	*Pseudomonas aeruginosa*	MIC 13 μg/mL	Suryawanshi et al. 2014
			Escherichia coli	MIC 23 μg/mL	
			Salmonella typhi	MIC 5 μg/mL	
			Bacillus subtilis	MIC 10 μg/mL	
Prodigiosin		*Serratia marcescens* NMCC 75	*Escherichia coli*	IC_{50} 0.17 μg/mL	Suryawanshi et al. 2015b
Prodigiosin		*Serratia marcescens* CMST 07	*Pseudomonas*	MIC 100 μg/mL	Priya et al. 2013
			Alteromonas	MIC 12.5 μg/mL	
			Gallionella	MIC 25 μg/mL	
			Bacillus sp.	MIC 100 μg/mL	
Prodigiosin		*Vibrio* sp.	*Escherichia coli*	MIC 103.4 μg/mL	Danevčič et al. 2016b
Prodigiosin		*Vibrio ruber*	*Bacillus* sp.	MIC 5–7 μg/mL	Danevčič et al. 2016a
Prodigiosin		*Pseudomonas putida* strain pig-r2	*Corynebacterium glutamicum*	MIC 2.56 μg/mL	Hage-Hülsmann et al. 2018
Prodigiosin (combined with N-myristoyltyrosine)			*Corynebacterium glutamicum*	MIC 0.005 μg/mL	
Prodigiosin (10 μg)		*Serratia marcescens*	*Escherichia coli*	6-mm inhibition zone	Arivizhivendhan et al. 2018
			Bacillus cereus	6-mm inhibition zone	
			Clostridium botulinum	7-mm inhibition zone	
			Vibrio vulnificus	2-mm inhibition zone	
			Salmonella enterica	5-mm inhibition zone	
Prodigiosin (50 μg)		*Zooshikella rubidus* S1-1	*Escherichia coli*	8.6-mm inhibition zone	Lee et al. 2011
			Salmonella serovar Typhimurium	8.0-mm inhibition zone	
			Bacillus subtilis	7.9-mm inhibition zone	
Prodigiosin (50 μg/ml)		*Serratia nematodiphila* darsh1	*Pseudomonas aeruginosa*	12.5-mm inhibition zone	Darshan and Manonmani 2016
			Escherichia coli	11.5-mm inhibition zone	
			Bacillus cereus	10.5-mm inhibition zone	
Prodigiosin (300 μg)		*Serratia marcescens* UFPEDA 398	*Enterococcus faecalis*	22-mm inhibition zone	Lapenda et al. 2015
			Streptococcus pyogenes	14-mm inhibition zone	
Undecylprodigiosin		*Streptomyces* sp.	*Bacillus subtilis*	MIC 50 μg/mL	Stankovic et al. 2012
			Micrococcus luteus	MIC 50 μg/mL	
Cycloprodigiosin (50 μg)		*Zooshikella rubidus* S1-1	*Escherichia coli*	10.6-mm inhibition zone	Lee et al. 2011
			Salmonella serovar Typhimurium	9.3-mm inhibition zone	
			Bacillus subtilis	9.2-mm inhibition zone	

Table 2 Antibacterial activity of synthetic prodiginines

Compound	Structure	Source	Active against	MIC/IC_{50}/inhibition zone	Reference
Prodigiosene		Methylation at the C-ring of prodigiosin	*Staphylococcus warneri* Vancomycin-resistant *Entrococcus faecium* *Proteus vulgaris*	IC_{50} 0.44 μg/mL IC_{50} 0.57 μg/mL IC_{50} 2.1 μg/mL	Marchal et al. 2013
Prodigiosin analogue		Enzymatic synthesis	*Escherichia coli* *Bacillus subtilis*	IC_{50} 4.12 μg/mL IC_{50} 0.73 μg/mL	You et al. 2018
Cyclic prodiginines		Mutasynthesis	*Escherichia coli* *Bacillus subtilis* *Corynebacterium glutamicum*	IC_{50} 5.0 μM IC_{50} 0.6 μM IC_{50} 0.1 μM	Klein et al. 2018

MICs of ampicillin against two standard MRSA strains (KCCM 40510 and 40511) from 512 to 0.5 μg/mL (Ji et al. 2015). Another study from Japan demonstrated that streptorubin B, a prodigiosin-like compound from *Streptomyces* sp. strain MC11024, significantly affected the growth rate of MRSA N315 at 4 μg/mL (Suzuki et al. 2015). Additionally, a synthetic compound called prodigiosene, which is methylated at the C-ring, showed significantly better activity against MRSA than prodigiosin. The IC_{50} value of this compound toward MRSA (0.6 μM) was similar to the control antibiotic vancomycin (0.7 μM) (Marchal et al. 2013). Otherwise, this compound also exhibited high activity against vancomycin-resistant *Enterococcus faecium* (IC_{50} = 1.7 μM) (Marchal et al. 2013).

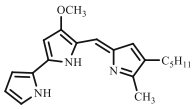
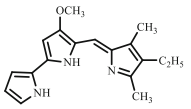
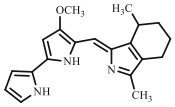
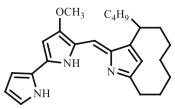
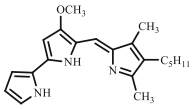
Prodigiosin also showed excellent activity toward oxacillin-resistant *S. aureus* (ORSA). Lapenda et al. investigated the antibacterial activity of prodigiosin against 20 clinical isolates of ORSA. The results showed that ORSAs were inhibited by prodigiosin with MIC values of 1–8 μg/mL, and that these strains exhibited greater sensitivity to prodigiosin than the standard antibiotic oxacillin, for which the lowest MIC was 128 μg/mL (Lapenda et al. 2015).

Antifungal activity of prodiginines

Pathogenic fungi pose a major threat to humans (Kohler et al. 2017). Some pathogenic fungi cause disease in healthy people, but most fungal infections occur in patients with an underlying serious illness (Kohler et al. 2017). Moreover, fungal infections also occur in animals and plants, which may cause declines in the populations of amphibians and reductions in crop yields (Fones et al. 2017). The antifungal activity of prodiginines provides a new strategy for the treatment of fungal infections. In 1949, the antifungal effects of prodigiosin were discovered by Lack, who demonstrated that the growth of *Coccidioides immitis* was inhibited after 48 h of exposure to a prodigiosin solution (Lack 1949). Recently, prodigiosin produced by endophytic *S. marcescens* MSRBB2 was demonstrated as an allelochemical that specifically inhibits coexisting endophytic fungi (Eckelmann et al. 2018). An overview of the existing studies analyzing the antifungal effects of prodiginines against different fungi is displayed in Table 4.

Dermatophytes are a group of filamentous fungi that cause superficial mycosis in animals and humans (Gupta et al. 2017). These fungi have the ability to utilize keratin as a nutrition source for their growth, which enables them to infect keratin-rich tissues such as skin, nails, and hair. Therefore, the therapeutic efficacy of antifungal agents toward dermatophytes depends not only on their antifungal activities but also on their pharmacokinetic properties in such tissues (Gupta et al. 2017). The effects of prodiginines on dermatophytes have been assessed in multiple studies. Nakashima et al.

Table 3 Antibacterial activity of prodiginines against *Staphylococcus aureus*

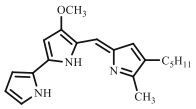
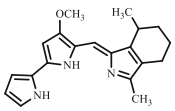
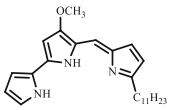
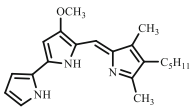
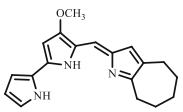
Compound	Structure	Source	Active against	MIC/IC_{50}/Inhibition zone	Reference
Prodigiosin		*Serratia marcescens*	*Staphylococcus aureus*	MIC 5 μg/mL	Suryawanshi et al. 2014
Prodigiosin		*Serratia marcescens* NMCC 75		IC_{50} 0.22 μg/mL	Suryawanshi et al. 2015b
Prodigiosin (50 μg)		*Zooshikella rubidus* S1-1		8.5-mm inhibition zone	Lee et al. 2011
Prodigiosin (50 μg/ml)		*Serratia nematodiphila* darsh1		16.5-mm inhibition zone	Darshan and Manonmani 2016
Prodigiosin (300 μg)		*Serratia marcescens* UFPEDA 398		35-mm inhibition zone	Lapenda et al. 2015
Prodigiosin analogue		Enzymatic synthesis		IC_{50} 0.62 μg/mL	You et al. 2018
Cycloprodigiosin (50 μg)		*Zooshikella rubidus* S1-1		10.0-mm inhibition zone	Lee et al. 2011
Prodigiosin		*Serratia sp.*	Methicillin-resistant *Staphylococcus aureus*	MIC 32 μg/mL	Ji et al. 2015
Streptorubin B		*Streptomyces* sp. strain MC11024		MIC 32 μg/mL	Suzuki et al. 2015
Prodigiosene		Methylation at the C-ring of prodigiosin		IC_{50} 0.2 μg/mL	Marchal et al. 2013

demonstrated that a prodigiosin analogue (PG-L-1) produced by a γ-proteobacterium was able to inhibit the growth of nine clinically isolated strains of *Trichophyton* spp. with MIC values ranging from 0.2 to 3.125 μg/mL. This study also demonstrated that the antifungal activity of PG-L-1 was approximately 3.8 times greater than that of bifonazole in the stratum corneum. The explanation for this might be that PG-L-1 can remain in an active form in the stratum corneum due to its relatively low keratin affinity. Hence, it has been suggested that PG-L-1 is a promising candidate for a clinically applicable topical antifungal drug that may be useful for the treatment of dermatophytosis (Nakashima et al. 2005). El-Bondkly et al. showed that prodigiosin-like pigments (PLPs) had potent antifungal activity against clinical dermatophyte isolates of *Trichophyton*, *Microsporum*, and *Epidermophyton*. Among these dermatophytes, *Microsporum* strains were highly sensitive to PLPs (MIC, 2.0–5.6 μg/mL), while *E. floccosum* exhibited the highest resistance toward prodigiosin (MIC, 41.5 μg/mL) (El-Bondkly et al. 2012). The results from another investigation evaluating the antifungal activity of prodigiosin on *Microsporum canis*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes* were mainly in agreement with those obtained previously. However, the MIC values of prodigiosin against these fungi (115–350 μg/mL) were much higher than those of the PLPs (Sumathi et al. 2014).

The yeast *Candida albicans* is both a prevalent commensal colonizer in mammals and the most common fungal pathogen in humans (Noble et al. 2017). *C. albicans* infections such as disseminated candidiasis and chronic mucocutaneous candidiasis are commonly present in cases of dysfunction of the local defense immune system (Kashem and Kaplan 2016). The fungicidal activity of prodigiosin against *C. albicans* was first analyzed in 1967 (Castro et al. 1967). Low concentrations of prodigiosin (80 μg/mL) showed no antifungal effects against *C. albicans* and *Cryptococcus neoformans* in agar diffusion studies. However, an IC_{50} value of prodigiosin against *C. albicans* (22 μg/mL) was obtained using a tissue culture method (Castro et al. 1967). Recently, the results from Lee and co-workers indicated that prodigiosin and cycloprodigiosin from *Z. rubidus* S1-1 had antifungal properties against *C. albicans*, with zones of growth inhibition of 7.6, and 8.8 mm, respectively (Lee et al. 2011). Stankovic et al. showed that undecylprodigiosin was active against two *C. albicans* species, with MIC values ranging from 100 to 200 μg/mL (Stankovic et al. 2012). Furthermore, a methylated analogue of prodigiosin exhibited increased activity against *C. albicans* compared to the natural compound (Marchal et al. 2013).

Batrachochytrium is the fungal pathogen known to cause chytridiomycosis, which threatens amphibian populations worldwide. In an in vitro study, prodigiosin showed

Table 4 Antifungal activity of prodiginines

Compound	Structure	Source	Active against	MIC/IC_{50}/Inhibition zone	Reference
Prodigiosin (50 μg)		*Zooshikella rubidus* S1-1	*Candida albicans*	7.6-mm inhibition zone	Lee et al. 2011
Prodigiosin		*Serratia marcescens* NPLR1	*Aspergillus niger*	MIC 230 μg/mL	Sumathi et al. 2014
			Trichoderma viridae	MIC 85 μg/mL	
			Penicillium chrysogenum	MIC 475 μg/mL	
			Microsporum canis	MIC 350 μg/mL	
			Candida albicans	MIC 315 μg/mL	
			Fusarium moniliforme	MIC 210 μg/mL	
			Trichophyton rubrum	MIC 115 μg/mL	
			Trichophyton mentagrophytes	MIC 120 μg/mL	
Prodigiosin		*Serratia marcescens*	*Aspergillus flavus*	MIC 10 μg/mL	Suryawanshi et al. 2014
			Fusarium oxysporium	MIC 8 μg/mL	
			Penicillium notatum	MIC 21 μg/mL	
			Cladosporium	MIC 18 μg/mL	
Prodigiosin		*Serratia marcescens*	*Didymella applanata*	IC_{50} 808 μg/mL	Duzhak et al. 2012
Prodigiosin		Commercial product	*Batrachochytrium dendrobatidis*	IC_{50} 1.2 μg/mL	Woodhams et al. 2018
			Batrachochytrium salamandrivorans	IC_{50} 8.8 μg/mL	
Prodigiosin		*Streptomyces* sp.	*Epidermophyton floccosum*	MIC 41.5 μg/mL	El-Bondkly et al. 2012
			Microsporum gypseum	MIC 4.9 μg/mL	
			Microsporum ajelloi	MIC 2.0 μg/mL	
			Microsporum ferrogenium	MIC 5.4 μg/mL	
			Microsporum cookie	MIC 2.3 μg/mL	
			Microsporum racemosum	MIC 5.6 μg/mL	
			Trichophyton rubrum	MIC 11.9 μg/mL	
			Trichophyton mentagrophytes	MIC 8.2 μg/mL	
			Trichophyton longfeuseus	MIC 8.1 μg/mL	
			Trichophyton semmie	MIC 5.8 μg/mL	
			Trichophyton tonsurance	MIC 13.5 μg/mL	
Cycloprodigiosin (50 μg)		*Zooshikella rubidus* S1-1	*Candida albicans*	8.8-mm inhibition zone	Lee et al. 2011
Undecylprodigiosin		*Streptomyces* sp.	*Candida albicans* ATCC10231	MIC 100 μg/mL	Stankovic et al. 2012
			Candida albicans ATCC10259	MIC 200 μg/mL	
Prodigiosene		Methylation at the C-ring of prodigiosin	*Candida albicans*	IC_{50} 3.4 μg/mL	Marchal et al. 2013
Cyclic prodiginines		Mutasynthesis	*Saccharomyces cerevisiae*	IC_{50} 0.4 μM	Klein et al. 2018
			Pichia pastoris	IC_{50} 1.7 μM	

significant growth inhibition against *B. dendrobatidis* and *B. salamandrivorans*, with IC_{50} values of 3.8 and 27.3 μM, respectively (Woodhams et al. 2018).

Prodiginines also have antifungal effects on crop pathogens, as was shown for *Didymella applanata* (Duzhak et al. 2012). *D. applanata* is the phytopathogenic fungus that causes spur blight, which is one of the most severe diseases in raspberry plants. It was found that the soil bacterium *S. marcescens* was an efficient antagonist (competitor) of *D. applanata*. An in-depth study showed that prodigiosin from *S. marcescens* could inhibit the growth of *D. applanata* at concentrations as low as 0.9 nmol/mL. Hence, the ability to produce prodigiosin may provide *S. marcescens* with a considerable competitive advantage during its competition with *D. applanata* (Duzhak et al. 2012). Meschke et al. found that undecylprodigiosin from *Streptomyces lividans* strongly

reduced microsclerotia formation when added to the growing *Verticillium dahlia*, which is an ascomycete fungus that causes the vascular wilt of many field and horticultural plants worldwide. It was also demonstrated that the presence of *S. lividans* led to an efficient reduction of *V. dahlia* hyphae and microsclerotia on the roots of developing *Arabidopsis thaliana* (Meschke et al. 2012). A study by Huerta-Palacios and colleagues explored the mechanisms by which *S. marcescens* CFFSURB2 exerts biocontrol of *Mycosphaerella fijiensis*, the ascomycete fungus that causes the black Sigatoka disease of banana (Gutierrez-Roman et al. 2015). They found that the prodigiosin from *S. marcescens* CFFSURB2 caused germ tube deformation and reduced germ tube growth of *M. fijensis*. The combination of prodigiosin with chitinases mostly exhibited a synergistic antifungal effect (Gutierrez-Roman et al. 2015). These results indicate that prodiginines can be used as antifungal agents to combat crop diseases and that prodiginine-producing bacteria can be used as effective agents for the biological control of crop diseases.

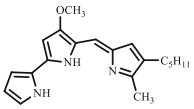
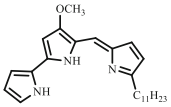
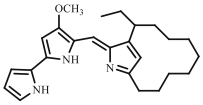
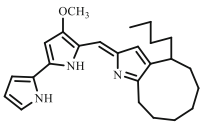
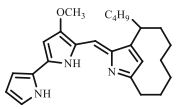
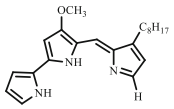
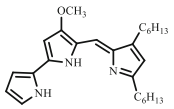
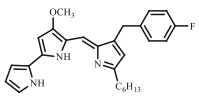
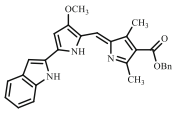
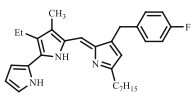
Antiprotozoal activity of prodiginines

Malaria is an infectious disease caused by parasitic protozoa (*Plasmodium* spp.), which usually occurs in tropical and subtropical regions. It was responsible for 445,000 deaths and more than 200 million infection cases in 2016 (Ashley et al. 2018). Although a number of drugs, ranging from natural drugs such as artemisinin and quinine, to synthetic drugs such as chloroquine and mefloquine, have been developed to treat malaria, the development of resistance to antimalarial agents is one of the main factors underlying the need for the search for effective novel antimalarial compounds (Baragana et al. 2015; Kancharla et al. 2011). The antimalarial activities of prodiginines have been assessed in multiple studies (Table 5). Initially, in vivo data from a study performed over half a century ago indicated that prodigiosin could prolong the average survival times of malaria-infected mice at a dose of 40 mg/kg body weight (Castro 1967). Subsequently, the antimalarial activity of five prodiginines, including undecylprodiginine, metacycloprodigiosin, butylcycloheptylprodiginine, cyclononylprodiginine, and methylcyclodecylprodiginine, against *Plasmodium berghei* KBG173 was investigated in vivo. It was reported that the lifetime of *Plasmodium*-infected mice increased from 6 to 8 days to 18–20 days under the treatment of methylcyclodecylprodiginine (Gerber 1975a). In an in vitro study, natural prodiginines, namely, prodigiosin, undecylprodiginine, metacycloprodiginine, and streptorubin B, demonstrated remarkable antimalarial activity against *Plasmodium falciparum* strain D6, with IC_{50} values of 8, 7.7, 1.7, and 7.8 nM, respectively (Kancharla et al. 2011). Specifically, combinations of prodigiosin with metal nanoparticles exhibited significant decreases in their IC_{50} values toward *P. falciparum* (2.7- to 3.1-fold) (Rahul et al. 2015). Among these natural prodiginines, metacycloprodiginine was consistently observed to be the most potent antimalarial compound, which exhibited the lowest IC_{50} values with much weaker cytotoxicity (Isaka et al. 2002; Kancharla et al. 2011).

Efforts to improve antimalarial activity through synthetic modifications have been successful when using prodigiosin as a scaffold. Kancharla and colleagues demonstrated that the C_6-C_{11} alkyl chain length at either the α- or β'-position of the C-ring (Fig. 1) is required for the antimalarial activity of monoalkylated prodiginines (Kancharla et al. 2011). The β'-C_8 alkyl monosubstituted and α-C_{11} alkoxy monosubstituted prodiginine analogues exhibited moderate inhibitory activity, with IC_{50} values of 4.6 and 5.7 nM, respectively, against *P. falciparum* strain D6 (Kancharla et al. 2014; Kancharla et al. 2011). The dialkylated analogues that had substituents at both the α and β' positions showed potent in vitro antimalarial activity, with IC_{50} values of 1.7–5.3 nM against *P. falciparum* strain D6, which demonstrated that they are more active than the monoalkylated prodiginines. More significantly, analogues containing one alkyl and one aryl substituent at positions α and β', exhibited the most potent antimalarial activity, with IC_{50} values of 0.9–1.3 nM against *P. falciparum* strain D6. The in vivo antimalarial activities of these analogues were evaluated in a *Plasmodium yoelii* murine patient infection by oral administration. The results showed that each analogue reduced parasitemia by more than 90% after 25 (mg/kg)/day dosing, and provided a cure in some cases (Kancharla et al. 2011). Based on the data from Kancharla et al., the structural features influencing their antimalarial activity of prodiginines were analyzed utilizing several methods, such as comparative molecular similarity indices analysis (CoMSIA), comparative molecular field analysis (CoMFA), genetic algorithms (GA), and ordered predictors selection (OPS) (de Campos and de Melo 2014; Mahajan et al. 2012; Masand et al. 2013; Singh et al. 2013). The analyses revealed that the lipophilicity, hydrogen donor/acceptor, and steric factors of prodiginines all play a critical role in their antimalarial activity (Mahajan et al. 2012).

Subsequently, Kancharla et al. assessed the importance of the B-ring pyrrole of prodiginines (Fig. 1) for their antimalarial activity. It was reported that the B-ring can be substituted with short alkyl substituents at either the 4-position (replacement of OMe) or 3- and 4-positions without impacting potency. An analogue that has 3-ethyl and 4-methyl substituents on the B-ring and α-alkyl and β'-alkylaryl substituents on the C-ring was synthesized, with an IC_{50} value of 5.9 nM against the chloroquine-resistant *P. falciparum* strain 7G8 (Kancharla et al. 2015). The importance of the A-ring pyrrole (Fig. 1) for antimalarial activity was investigated via substitution with other aromatic and non-aromatic groups by Marchal et al. (2014). They found that the presence of a nitrogen atom in the A-ring is needed for good antimalarial activity. Otherwise,

Table 5 Antiprotozoal activity of prodiginines

Compound	Structure	Source	Active against	Increase survival time (days) for malaria-infected mice/IC_{50}	Reference
Prodigiosin		*Serratia marcescens*	*Plasmodium berghei*	6.3 days	Castro 1967
Prodigiosin		*Serratia nematodiphila*	*Plasmodium falciparum*	IC_{50} 1.1 μg/mL	Rahul et al. 2015
Prodigiosin		*Serratia marcescens*	*Trypanosoma cruzi* SN-3 *Trypanosoma cruzi* AF-1c7	2.7 μM 2.2 μM	Genes et al. 2011
Prodigiosin		NM	*Plasmodium falciparum*	IC_{50} 8 nM	Kancharla et al. 2011
Undecylprodiginine		*Streptomyces* sp.	*Plasmodium berghei*	1.5 days	Gerber 1975a
Undecylprodiginine		*Streptomyces coelicolor*	*Plasmodium falciparum*	IC_{50} 7.7 nM	Kancharla et al. 2011
Metacycloprodigiosin		*Streptomyces* sp.	*Plasmodium berghei*	9.3 days	Gerber 1975a
Metacycloprodigiosin		*Streptomyces spectabilis*	*Plasmodium falciparum*	IC_{50} 5 ng/mL	Isaka et al. 2002
Metacycloprodigiosin		*Streptomyces longisporus*	*Plasmodium falciparum*	IC_{50} 1.7 nM	Kancharla et al. 2011
Butylcycloheptylprodiginine		*Streptomyces* sp.	*Plasmodium berghei*	7.5 days	Gerber 1975a
Heptyl prodigiosin	NM	Alpha-proteobacteria	*Plasmodium falciparum*	NM	Lazaro et al. 2002
Streptorubin B		*Streptomyces coelicolor*	*Plasmodium falciparum*	IC_{50} 7.8 nM	Kancharla et al. 2011
Prodigiosin analogue		C_8 alkyl monosubstituted at β'-position of C-ring	*Plasmodium falciparum*	IC_{50} 4.6 nM	
Prodigiosin analogue		C_6 alkyl dialkylated at both α- and β'-position of C-ring	*Plasmodium falciparum*	IC_{50} 1.7 nM	
Prodigiosin analogue		C_6 alkyl substituted at α-position of C-ring and aryl substituted at β'-position of C-ring	*Plasmodium falciparum*	IC_{50} 0.9 nM	
Prodigiosin analogue		Modification of A-ring and C-ring	*Plasmodium falciparum*	IC_{50} 5.6 μM	Marchal et al. 2014
Prodigiosin analogue		Modification of B-ring and C-ring	*Plasmodium falciparum*	IC_{50} 5.9 nM	Kancharla et al. 2015

NM: not mentioned.

the complexation of prodiginines with dibutyl tin improved their antimalarial activity, which exhibited IC_{50} values mostly in the nanomolar range (Marchal et al. 2014).

Chagas disease, also known as American trypanosomiasis, is another protozoal infection and is caused by the parasite *Trypanosoma cruzi* (Perez-Molina and Molina 2018). This disease mainly occurs in Central and South America. Since the 1960s, only two drugs, benznidazole and nifurtimox, have been available for the clinical treatment of this infection (Campo et al. 2018). Thus, there is an urgent need for new

therapeutic agents against this disease. The antitrypanosomal activity of prodiginines against *T. cruzi* was reported for the first time in the 1950s. The growth of *T. cruzi* was inhibited completely after a 24-h exposure to 10 μg/mL of prodigiosin (McRary et al. 1953). A study comparing incubations of *T. cruzi* with *S. marcescens* RPH, a prodigiosin producer, and *S. marcescens* DB11, a non-prodigiosin-producing strain, showed that only the prodigiosin-producing RPH killed *T. cruzi*. This suggested that prodigiosin is an important factor for the trypanolytic action of the bacteria (Azambuja et al. 2004). The results from another in vitro experiment showed that prodigiosin exhibited higher trypanocidal activity than rotenone, 2-thenoyltrifluoroactone, potassium cyanide, and antimycin A. The IC_{50} values of prodigiosin against *T. cruzi* SN-3 and *T. cruzi* AF-1c7 were 2.7 and 2.2 μM, respectively. This suggested that prodigiosin could be a potential drug for Chagas disease (Genes et al. 2011).

Anti-larval activity of prodiginines

Mosquitoes are the main vectors of several globally important vector-borne diseases including malaria, yellow fever, dengue, and filariasis. Mosquito control is considered an important measure to control these diseases. In the last century, mosquito control strategies have been mainly based on the use of chemical insecticides such as temophos, malathion, and dichloro-diphenyl-trichloroethane (DDT), which might have adverse effects on human health and the environment (Wilke and Marrelli 2015). Therefore, new mosquito control measures are needed. Microbial control agents offer alternatives to chemical control as they can be more selective than chemical insecticides. In vitro study of crude extracted prodigiosin produced by *S. marcescens* NMCC46 exhibited remarkable larvicidal activity against *Aedes aegypti* and *Anopheles stephensi*. The LC_{50} (50% larval mortality) values of second, third, and fourth instars of *A. aegypti* were 41.65, 139.51, and 103.95 ppm, respectively, and 51.12, 105.52, and 133.07 ppm for *A. stephensi* (Patil et al. 2011). Recently, the effects of purified prodigiosin against the larval and pupal stages of *A. aegypti* and *A. stephensi* were analyzed. Purified prodigiosin displayed LC50 values of 14–27 μg/mL against early second, third, and fourth instars and pupal stages of *A. aegypti*. LC_{50} values for *A. stephensi* were found to be 19.7–32.2 μg/ml. Therefore, pure prodigiosin may prove to be an efficient larvicidal agent for mosquito control for the larval and pupal stages of *A. aegypti* and *A. stephensi* (Suryawanshi et al. 2015a).

Plant-parasitic nematodes are worm-shaped microscopic animals that attack the majority of economically important crops, such as banana and brinjal (Holbein et al. 2016). Prodigiosin from *S. marcescens* was reported to be an efficient nematocidal agent against the juvenile stages of *Radopholus similis* and *Meloidogyne javanica* (Rahul et al. 2014). A larvicidal assay demonstrated that the LC_{50} values of prodigiosin against *R. similis* and *M. javanica* (83 and 79 mg/mL, respectively) were significantly lower than the positive control copper sulfate (LC_{50} values, 380 and 280 mg/mL, respectively). Moreover, prodigiosin exhibited complete inhibition of the hatching ability of nematode eggs.

Prodigiosin also has insecticidal activity, as was shown for *Drosophila* larvae (Liang et al. 2013). *Drosophila* is a valuable model for the investigation of host-pathogen interactions. Prodigiosin was demonstrated to inhibit the growth of *Drosophila melanogaster*, with an LC_{50} value of 230 ppm.

Antiviral activity of prodiginines

Bombyx mori nucleopolyhedrovirus (BmNPV) is an enveloped double-stranded DNA virus that belongs to the alphabaculovirus genus of the baculovirus, a large family of viruses that infect arthropods, predominantly the silkworm. Its infection causes losses as high as 70% of total sericultural production annually (Feng et al. 2018). More recently, the antiviral activity of prodiginines against BmNPV was recognized in in vitro systems (Zhou et al. 2016). The budded virus of BmNPV production in BmNPV-infected cells was strongly reduced upon treatment with 10 nM prodigiosin. The amount of viral DNA in prodigiosin-treated cells was as low as 3.0, 1.3, and 5.7% of that in untreated cells at 48, 72, and 96 h postinfection, respectively. The transcription levels of three viral genes, including the early gene *ie-1*, late gene *vp39*, and very late gene *p10*, were significantly inhibited by prodigiosin treatment. Therefore, prodigiosin was considered to be an inhibitor of the DNA replication and transcription of BmNPV. Moreover, prodigiosin treatment was found to successfully prevent BmNPV-mediated cell membrane fusion, which can block viral cell-to-cell transmission. These results suggested that prodiginines might be a new group of antiviral compounds.

Anti-infective mechanisms of action of prodiginines

Information on the molecular mechanisms of the anti-infective activities of prodiginines is still in its infancy, and elucidation of the molecular mechanisms of prodiginines is the subject of rigorous research. Although the mechanisms have not been exhaustively determined, studies have revealed that the anti-infective activities of prodiginines are brought about by a combination of one or more distinct mechanisms. The possible mechanisms revealed in recent studies will be discussed in the following paragraphs.

The principal mode of anti-infective activity is to cause the disruption of the cell membrane. The results from Danevčič et al. showed that *B. subtilis* cells were lysed immediately after treatment with prodigiosin in the middle of the exponential phase. Subsequent experimental

investigations revealed that prodigiosin interferes with cytoplasmic membrane function and increases its permeability, which is associated with autolysis in *B. subtilis*. Thus, the bacteriolytic activity of prodigiosin is due to the induction of autolysins. However, this mode of action of prodigiosin on *B. subtilis* cells depends on the growth phase. Prodigiosin has bacteriolytic activity during exponential growth, whereas in the stationary phase it has bacteriostatic activity (Danevčič et al. 2016a). The effects of prodigiosin on *E. coli* were explored by the same research group. They found that the cytoplasmic membrane of *E. coli* was not disintegrated while the outer membrane was damaged after prodigiosin treatment (Danevčič et al. 2016b). Another study from Suryawanshi et al. provided further insights into the effects of prodigiosin on the cell membrane of *S. aureus*. The results showed that prodigiosin caused leakage of intracellular substances, including K^+ ions, sugars, amino acids, and proteins. Scanning electron microscopy indicated that the surfaces of prodigiosin-treated *S. aureus* cells were heterogeneous and highly textured with white dots whereas the cells in the control were homogeneous and smooth (Suryawanshi et al. 2017). The formation of hallows was also observed on the outer membrane of *E. coli* and *Bacillus cereus*. This result may be related to the breakdown of typical membrane biodynamics (Darshan and Manonmani 2016). These findings suggest that prodigiosin is a hydrophobic stressor that is able to disrupt the plasma membrane via a chaotropicity-mediated mode of action (Suryawanshi et al. 2017).

Biofilm inhibition is another mode of anti-infective activity exhibited by prodiginines (Kimyon et al. 2016; Suzuki et al. 2015). Biofilms are surface-associated communities of bacteria typically embedded in an extracellular polymeric matrix, which consist of polysaccharides, proteins, lipids, nucleic acids (DNA and RNA), and metabolites. Biofilms pose a substantial health risk and contribute not only to many chronic and recurrent infections but also to physical and chemical protection of the bacterial cells as well as protection from antimicrobials (Rabin et al. 2015). Results obtained by Suzuki et al. suggested that streptorubin B from *Streptomyces* sp. strain MC11024 may be an inhibitor of bacterial biofilm formation. The biofilm formation of methicillin-resistant *S. aureus* (MRSA) N315 was reduced to less than 30% at 1 μg/mL of streptorubin B (Suzuki et al. 2015). Kimyon and colleagues explored the mechanism of the inhibitory effect of prodigiosin against *P. aeruginosa*. They found that prodigiosin and a prodigiosin/copper(II) complex exhibited strong RNA and dsDNA cleaving properties via H_2O_2 production. *P. aeruginosa* cell surface hydrophobicity and biofilm integrity were significantly altered due to the cleavage of nucleic acids by prodigiosin or the prodigiosin/copper(II) complex. These results suggest that prodigiosin inhibits *P. aeruginosa* biofilm development by producing reactive oxygen species (Kimyon et al. 2016). A study from Darshan and Manonmani also showed a significant increase in the level of reactive oxygen species in prodigiosin-treated *B. cereus* and *E. coli* cells (Darshan and Manonmani 2016). In addition, they demonstrated that DNA was damaged in these two species of bacterial cells when they were incubated overnight in the presence of 50 μg/mL of prodigiosin. This DNA damage mechanism involving oxidative damage may contribute to the programmed cell death-like activity against bacterial pathogens.

Evidence has also been presented for two new mechanisms of action. These are inhibition of protein synthesis and inhibition of RNA synthesis (Danevčič et al. 2016b). The total protein content in prodigiosin-treated *E. coli* cells did not change with incubation, whereas there was a significant twofold increase in total protein content after 2 h of incubation in the control cells. The total RNA level of *E. coli* cells also remained constant after prodigiosin treatment. These results suggest that prodigiosin may interfere with de novo protein synthesis and the transcription process in *E. coli*. In addition, prodigiosin was also able to inhibit the production of CO_2 in *E. coli* by fourfold at the end of incubation, indicating its interference with cellular respiration (Danevčič et al. 2016b).

However, another mechanism found to be effective against *T. cruzi* occurs when prodigiosin acts as a trypanocidal agent (Genes et al. 2011). It is reported that prodigiosin can cause mitochondrial dysfunction in *T. cruzi*. Parasite respiration was inhibited by more than 80% after prodigiosin treatment, indicating that the mitochondrial function is altered and that oxidative phosphorylation does not take its normal course. Otherwise, prodigiosin induced a significant hyperpolarization of the mitochondria after 1 h of treatment, suggesting that prodigiosin could act on an early stage of an apoptotic-like cell death pathway.

The mechanism of action of prodigiosin against mosquito larvae was further investigated by Suryawanshi and coworkers, who demonstrated that prodigiosin can inhibit the activities of several enzymes involved in mosquito larvae metabolism (Suryawanshi et al. 2015a). The activities of esterases, acetylcholine esterases, phosphatases, and proteases in fourth instar larvae of *A. aegypti* were decreased by 95.1, 70, 12, and 36%, respectively, upon prodigiosin treatment. In addition, the function of carbonic anhydrase and H + -V-ATPase, which control the pH of the anterior midgut and caeca, was also affected by prodigiosin. After prodigiosin treatment, the pH of the anterior midgut fell to 6, which may result in decreased nutrient uptake and may be responsible for larvae death.

Taken together, these results indicate that there are multiple mechanisms by which prodiginines exert their anti-infective properties, including cell membrane damage, biofilm inhibition, protein and RNA synthesis inhibition, mitochondrial dysfunction, and enzyme activity inhibition.

Conclusion

The prodiginine family has attracted a great deal of attention due to their comprehensive and enthralling biological potential. In this review, the anti-infective effects of prodiginines against bacteria, fungi, protozoa, larvae, and viruses were summarized and discussed. In general, prodiginines are considered to affect pathogenic organisms via multiple mechanisms of action, substantiating their roles as attractive candidates for further development. A crucial aspect of the anti-infective effects of prodiginines is the translation of their promising activities into clinically relevant strategies. In this regard, the safety and tolerability of prodiginines are important issues that need to be addressed before approval for clinical use. Studies with mammalian cell lines have shown that prodigiosin has a slightly toxic effect on the viability of Vero cells, human lymphocytes, and peripheral blood mononuclear cells with IC_{50} values of 6.49 μM (equal 2 μg/mL), > 12 μM (equal 3.8 μg/mL), and 241 μM (equal 78 μg/mL), respectively (Genes et al. 2011; Rahul et al. 2015). These IC_{50} values are higher than those of prodigiosin against some bacteria and fungi. Due to significant toxic effects in the effective dose range, prodiginines are not still clinically suitable anti-infective agents so far. Importantly, changes in the substituent groups on the prodiginine skeleton lead to reduced toxicity in murine splenic lymphocytes (Kancharla et al. 2011). Hence, further development that selectively increases anti-infective activities while reducing cytotoxic effects remains a challenge for future research in this field.

Another crucial factor impeding the clinical development of prodiginines is their high synthetic cost (Nisha et al. 2015). Efforts in obtaining novel prodiginines through chemical synthesis, enzymatic synthesis, and mutasynthesis are ongoing (Hu et al. 2016; Klein et al. 2018; You et al. 2018). However, the development of simple and concise routes for efficient prodiginine production that are also environmentally friendly is indeed desirable. Although there is still a long way to go before prodiginines can be routinely administered as anti-infective drugs in patients, the exciting findings of the past years should stimulate further research of prodiginines that may ultimately translate into their use in future therapeutic applications.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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