



Insight into the anti-cancer and anti-viral therapeutic properties of biological active molecule prodigiosin

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Abstract

Bioactive compounds from natural sources play an important role as an immunomodulator in diseases such as cancer, inflammatory and viral diseases. Immunomodulator functions to regulate the immune system and defends against infectious foreign particles. Naturally occurring bioactive compounds have been shown to boost the immunity and increase the anti-cancer immune response, as well as in cancer patients. Prodigiosin is reported as an anticancer agent and effective against multiple tumor cell lines and also combat to viral diseases. Innate cytotoxicity is one of the main problems linked with the use of immunosuppressants, especially in oncology that leads scientists toward the application of combined regimens. In this perception, prodigiosin offers an interesting perspective of combinatorial applications. However, the major devastating limitation associated with its use is an infectious strain: *Serratia marcescens* source linked with a few harmful pathologies in mammals. The present article will review the potential roles of prodigiosin as a key player of immunomodulator in different immune cells such as T and B lymphocytes, macrophages, dendritic cells and natural killer cells as well as antiviral activity.

Key words anticancer, antiviral, immunomodulator, immunosuppressant, prodigiosin

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Introduction

Global health estimates by World Health Organization in 2019 declared that cancer is the primary reason behind deaths almost in one hundred and thirty-five countries [1]. There were 19 million new cases of cancer reported in 2020 according to Global Burden of Cancer (GLOBOCAN), there is also an estimation of its increase up to 47% (28 million) by 2040 [2]. Research and understanding of the biochemical mechanism of tumors have immensely facilitated researchers in the progress of targeted drug treatment, however, tumor cells show multidrug resistance (MDR) as an important aspect of clinical burden because of tumor heterogeneity [3, 4]. Naturally occurring bioactive compounds obtained from microorganisms and plants have a significant role as an immunomodulator in diseases such as cancer, cardiovascular (CVDs), inflammatory disease and diabetes mellitus [5, 6]. After understanding the complicated interaction between tumor cells and the immune system, researchers investigate the use of bioactive compounds as immunomodulators [7]. Immunomodulator functions to regulate the immune system and defends against infectious foreign particles such as bacteria and viruses. It also plays a significant role in quenching abnormal functioning of the immune system in case of immune-related disorders [8]. Naturally occurring bioactive compounds have been shown to boost the immunity and increase the anti-cancer immune response *in vitro*, as well as in cancerous patients. For instance, secondary metabolites of blueberries comprise various chemopreventive compounds, which boost the functionality of those cells that act as natural killers (NK) and deprived the extent of infiltrating neutrophils in colorectal cancer (CRC) [9]. There are many bioactive natural compounds such as β -glucans, resveratrol, polysaccharide K (PSK), Epigallocatechin gallate (EGCG), curcumin, carotenoids, etc. which act as an immunomodulator by enhancing the activity of NK and inhibiting myeloid-derived suppressor cells (MDSCs) [10]. Bacterially derived tumor immunomodulators especially have gained much more attention because of their distinctive and abundant bioactivities, mechanism of action and advantages of stimulating the immunity of the host against tumors [11].

Prodigiosin (PG) is a red-colored pigment belonging to the "prodiginines" group of bacterial secondary metabolites found in gram-negative bacteria *Serratia marcescens* [12]. Some examples of bacterial prodigiosin are shown in **Figure 1**. Prodigiosin is a proven anticancer agent and declared most effective against multiple tumor cell lines along with cells that have multi-drug resistance showing a small or negligible effect on normal cell lines [13]. PG not only acts as an anti-cancerous and immunomodulatory agent but also has the potential to kill parasites, insects, and microbes [14]. By viewing all the aspects of Prodigiosin potential against various therapeutic activities there is a keen attention of researchers towards the use of PG as an anticancer agent during the last few decades. It was seen that PG significantly inhibits the mammalian target of the rapamycin (mTOR) mechanism along with angiogenesis. It causes cycle quenching and apoptosis in tumor cell lines with little or no toxicity to normal healthy cells [15]. Innate cytotoxicity is one of the main problems linked with the use of immunosuppressants, especially in oncology, that leads scientists toward the application of combined regimens. In this perception, PG offers an interesting perspective of combinatorial applications. It has a synergistic effect when used in combination with cyclosporin A and acts as an additive when applied with rapamycin, showing its distinctive properties and prospects in the development and use as an immunosuppressant [16, 17].

Though with its widespread anti-cancerous activities, there are no such investigations on its metabolic reprogramming and immunomodulating properties, the information available is only

related to a relevant compound known as prodigiosin 25-C [18]. Although PG has therapeutic potential in the discipline of biomedicines there is still no PG-derived medicine available in the market because of some limitations which restrict its entry into the field of medicine. The major and devastating limitation associated with its use is its source, which is an infectious strain: *Serratia marcescens*, linked with a few harmful pathologies in mammals [19]. The other includes deprivation of genetic evidence, systematic production of prodigiosin in the laboratory and metabolic linkages of other microorganisms that produce prodigiosin. Various studies have been conducted regarding the impact of prodigiosin on breast cancers. Given that proteins play an important role in either activating or suppressing the pathways involved in various types of cancers, it is important to prioritize interlinkage studies between prodigiosin and proteins linked to a particular pathway. These studies are crucial for comprehending the underlying mechanisms behind any type of cancer. The procedures and techniques used in research have significantly improved over time. These developments enable more in-depth analyses of the prodigiosin's characteristics and processes. We may take advantage of these developments to learn more about the effects and prospective uses of prodigiosin by assessing the existing research in this field. In this review, we review methodology, sources of prodigiosin and its biosynthetic pathway. Besides, the immunomodulator role of prodigiosin in different immune cells such as T and B lymphocytes, macrophages, dendritic cells and natural killer cells and its immunosuppressive and antiviral activity will also be covered.

Review methodology

Online information services such as TRIP database Science Direct and PubMed/MEDLINE have been searched for PG-related information. The pre-clinical studies comprised molecular mechanisms and bioactivities such as antitumor/antiproliferation/cytotoxic/antiviral of isolated and chemically synthesized prodigiosin and its derivatives. High-impact factors related to prodigiosin have been composed since December 2021. The following terms were used for the search: "Prodigiosin", "Prodigiosin/sources", "Prodigiosin/production", "Pathology", "Prodigiosin/isolation and purification", "Prodigiosin/therapeutic use", "Prodigiosin/anticancer", "Prodigiosin/antiviral", "Prodigiosin/cell cycle", "Tumor Cell Line". The previous research published in the English language was collected, which contains various resources based on prodigiosin and its derivatives with similar scientific names, the kind of bioassay performed, the nature of cell line analyzed, with molecular mechanism of action used in trial-based pharmacological studies.

Sources of Prodigiosin

Prodigiosin appears is an ubiquitous bioactive compound and has been reported with a great biodiversity of producers having a vast production yield. It has been shown that derivatives of *Alteromonas*, *Saccharopolyspora*, *Pseudomonas*, *Vibrio*, *Actinomyces* and *Streptomyces* were also searched to produce this red pigment or its mixture, in addition to the most known prodigiosin-producing strains; *Serratia* and *Streptomyces* [20]. A reverberation in marine microbiology and thirst for extreme habitats have resulted in a significant range of microorganisms and extremophiles present in the marine ecosystem, notably members of the family *Pseudoalteromonas* and *Hahellaceae* to be a source of prodigiosin [21]. Schloss and co-workers have reported that the first source of prodigiosin found in cold Alaskan soil among β -proteobacteria which is the psychrotrophic strain of *Janthino bacterium lividum* [22]. The production yield of bacterial PG has

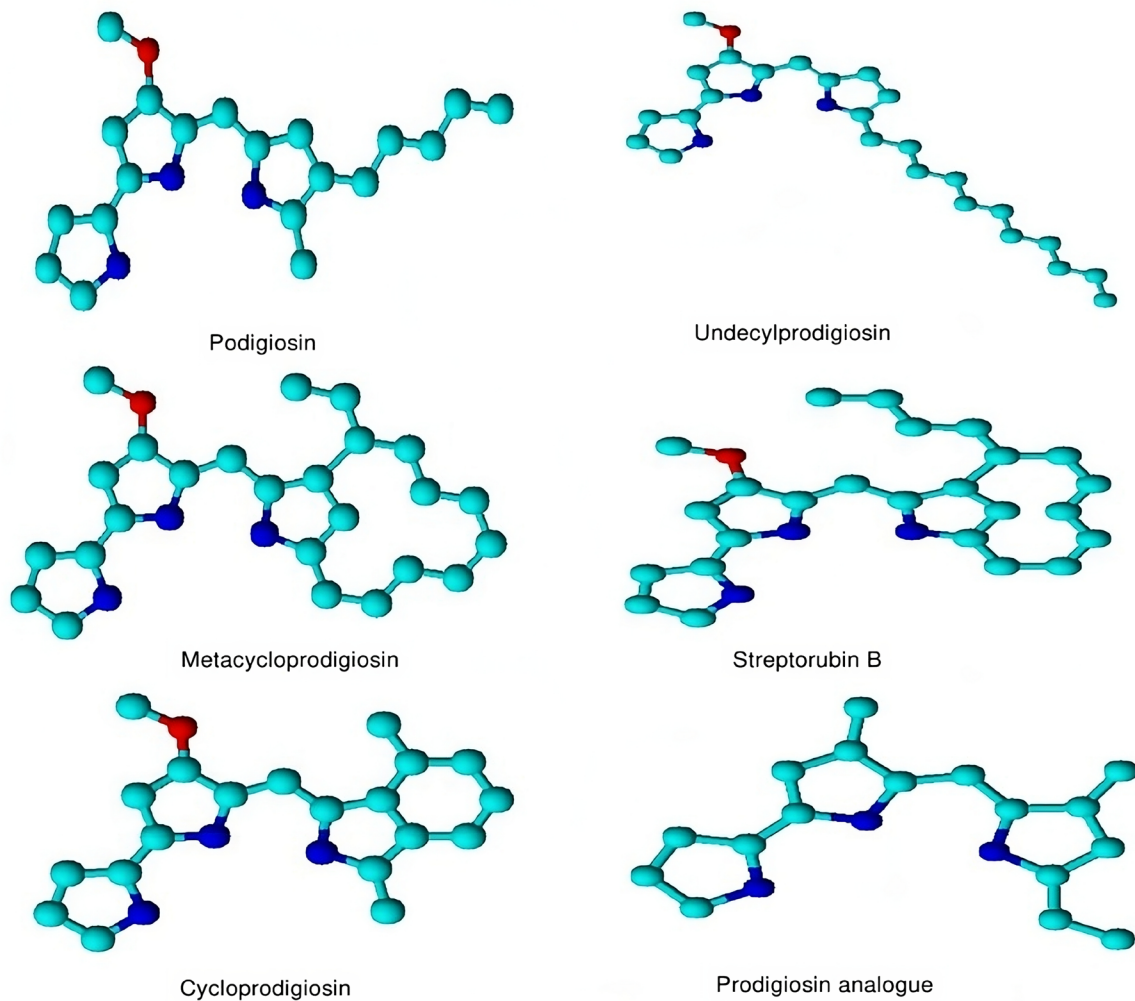


Figure 1. Some compounds of bacterial prodigiosin. Molecular modeling of 3D structures designed by the ChemDraw tool.

greatly been affected by nutritional as well as physicochemical factors including temperature, pH, nitrogen, carbon and dissolved oxygen sources, agitation, and inorganic salts [23]. Another major factor that seems to influence the production of PG is the composition of the culture medium, for example, complex media in comparison to more defined media reported to have relatively higher prodigiosin yield and support better pigment production. Complex media included peanut seed broth, nutrient broth, and LB broth [24].

Generally, carbohydrates were seen to be a poor nutrient source for prodigiosin synthesis because glucose has been described as a suppressor of PG production in *S. marcescens* [25]. The suppressing impact associated with glucose in the undecyl synthesis of prodigiosin has also been reported in *Streptomyces* [24]. Along with the C source, the kind of N₂ source in the media and the carbon-to-nitrogen ratio also affect PG synthesis. Su and co-workers had recent reports and specified a precise and accurate concentration of inorganic phosphates and peptone for the synthesis of PG by *S. marcescens* up to the levels of 2.4 g l⁻¹ using response surface methodology. They also evaluated the significance of glycine and sucrose for even higher production yields [26]. In the same way, Chen and coworkers acquired an increased PG production of approximately 15.6 g l⁻¹ by *S.*

marcescens C3 performing a statistically designed experiment. They defined carbon to nitrogen proportion as 6: 4 (starch: peptone) and use immobilization methodology [27]. Up till now, the best source of PG production, which is *S. marcescens*, has not been extensively implemented for its commercial usage. This might be due to the disadvantage linked with this cunning living being which is a harmful human pathogen and associated with many outbreaks and nosocomial diseases [28]. However, the other traditional industrially proven strains such as *Streptomyces* may be found to be a better candidate for the high-level synthesis and optimization of prodigiosin (Figure 2).

Biosynthesis of Prodigiosin

There is a total of 14 genes with a size of 20,960 bp in the pig cluster genetic makeover. In Sma 274, the genes are organized in the direction of pigA, pigB, pigC, pigD, pigE, pigF, pigG, pigH, pigI, pigJ, pigK, pigL, pigM and pigN [29]. In Sma 274 the pig genes are fringed by the cueR and copA genes. The exact location of the cueR gene is 488bp up from the starting gene of the pig cluster, also a space of 183bp separates copA gene from pigN. In Sma274, this gap between both copA and pigN proposed that copA gene expression is independent of pigN. An activator of copA has

been reported within this space of 183bp and a terminator that can terminate all 14 genes transcription in pig cluster [29]. The findings which use BPROM (Softberry) software showed that this activator most commonly provides a binding region for various transcriptional sites such as fis protein, repressor protein lexA, arginine repressor 2 (argR2), RNA polymerase sigma factor 15 (rpoD15), integration host factor (ihf) (Yip, unpublished) and C- reactive protein (crp) [30]. In Sma 374, for the synthesis of prodigiosin a bifurcated mechanism is needed to be proposed that synthesizes the two most important key regulators namely 2-methyl-3-n- amyl pyrrole (MAP) and 4-methoxy-2,2'-bipyrrole-5- carbaldehyde (MBC) [31, 32].

It has previously been seen that there are 12 out of 14 genes in pig clusters are designated and characterized through the cross-feeding-based study of individual gene mutants [33]. Genes that were allocated to produce the mono pyrrole moiety, MAP were pigB, pigD and pigE, whereas the genes accountable for the production of bipyrrole moiety MBC, were pigA, pigF, pigG, pigH, pigI, pigJ, pigM and pigN. The gene pigC performs the function of encoding the enzyme for terminal condensing of both MAP and MBC for the final synthesis of prodigiosin. There are sequence similarities between the N and C terminal domains of pigC gene with that of phosphoryl transferase moiety and the binding sites of ATP of pyruvate phosphate dikinase enzymes, respectively [29]. According to BLASTP analysis, it was seen that pyruvate phosphate dikinase PEP/pyruvate binding domain is present in both PigC and pyruvate phosphate dikinase of bacteria *S. marcescens* with 99% similarity. This enzyme is specialized in catalyzing the binding of MBC and MAP together with a core catalytic site for the synthesis of PG [32]. The task assigned for pigK and pigL genes is presently unidentified, but it was assumed that pigK might be involved in the folding of other Pig enzymes and act as a molecular chaperone in the biosynthesis of MBC. Moreover, PigL, which is known to be a 4'- phosphopantetheinyl

transferase, could take part in the phosphopantetheinylation reaction in the MBC mechanism [33].

Prodigiosin as immunomodulators

Innate bioactivity of red pigment prodigiosin against several strains of bacteria, larvae, algae and other parasites has greatly been attaining the attention of today's research [34]. This pigment and its derivatives are mostly known because of their ability to act as an immunomodulator and have cytotoxic potential against several tumor cell lines [35] Prodigiosin has the potential of enhancing the working of immunotherapy by improving multiple immune system cells for example T lymphocytes and various other proteins in the TME (e.g., programmed death ligand-1 [PD-L1]) [36]. In tumor cells, DNA replication may be associated with gene mutation and increased gene instability which results in the formation of neoantigens that induce an immune reaction [37]. Despite the immunogenic target expression, failure in immune surveillance assists tumor growth and progression (**Table 1**) [38].

Anti-cancer activity

A number of studies have been performed to evaluate the role of PG in cancer treatment and prevention (**Table 2**). Proapoptotic anti-cancer activity of prodigiosin has been observed and described to provoke cellular stresses such as DNA impairment, cell cycle blockage and fluctuations in intracellular pH, all of which can influence apoptosis (**Figure 3**) [39]. Initial studies had reported that PG stimulates apoptosis in tumor cell line independent of its mechanism of action. The phenomenon of apoptosis induction has been seen in various individual tumor cells, in hepatocellular carcinoma xenografts, in tissue culture and human primary tumor cells [40]. Mitochondrial dysfunction and ATP depletion is widely used and acknowledged anticancer pathway [41]. Francisco et

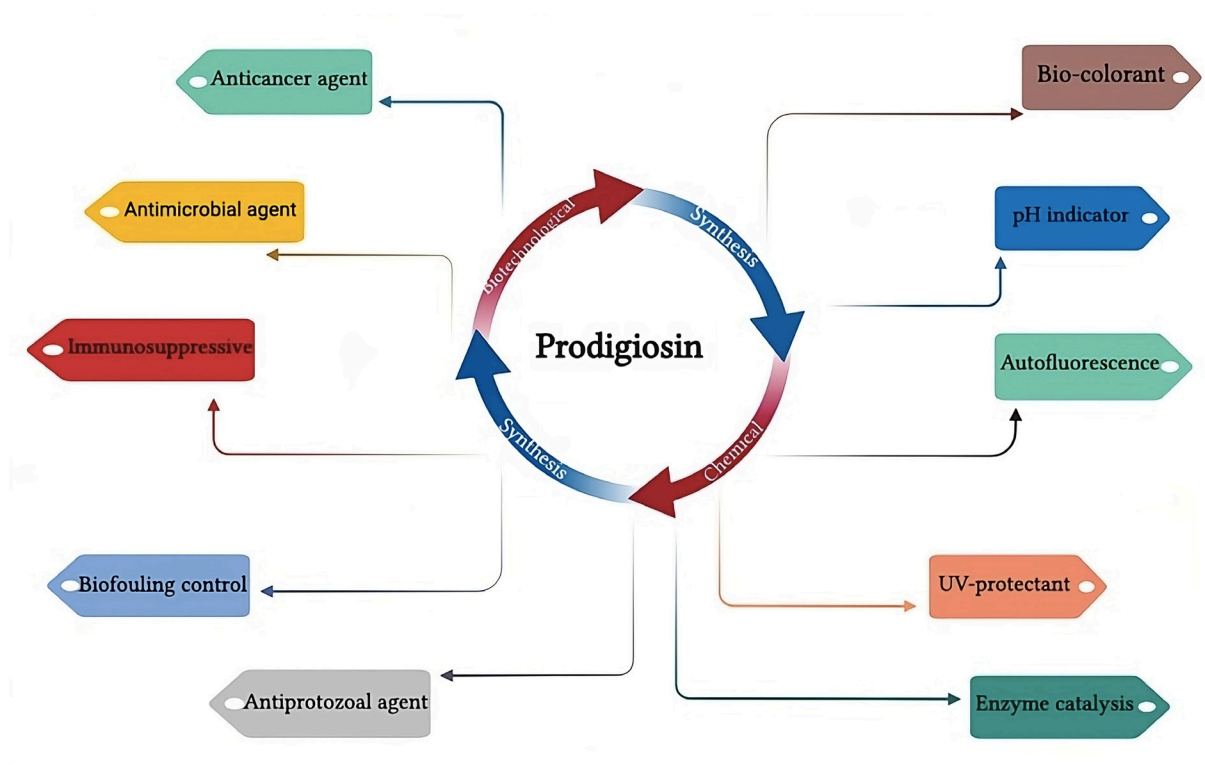


Figure 2. Prodigiosin synthesis pathways and its different biological applications.

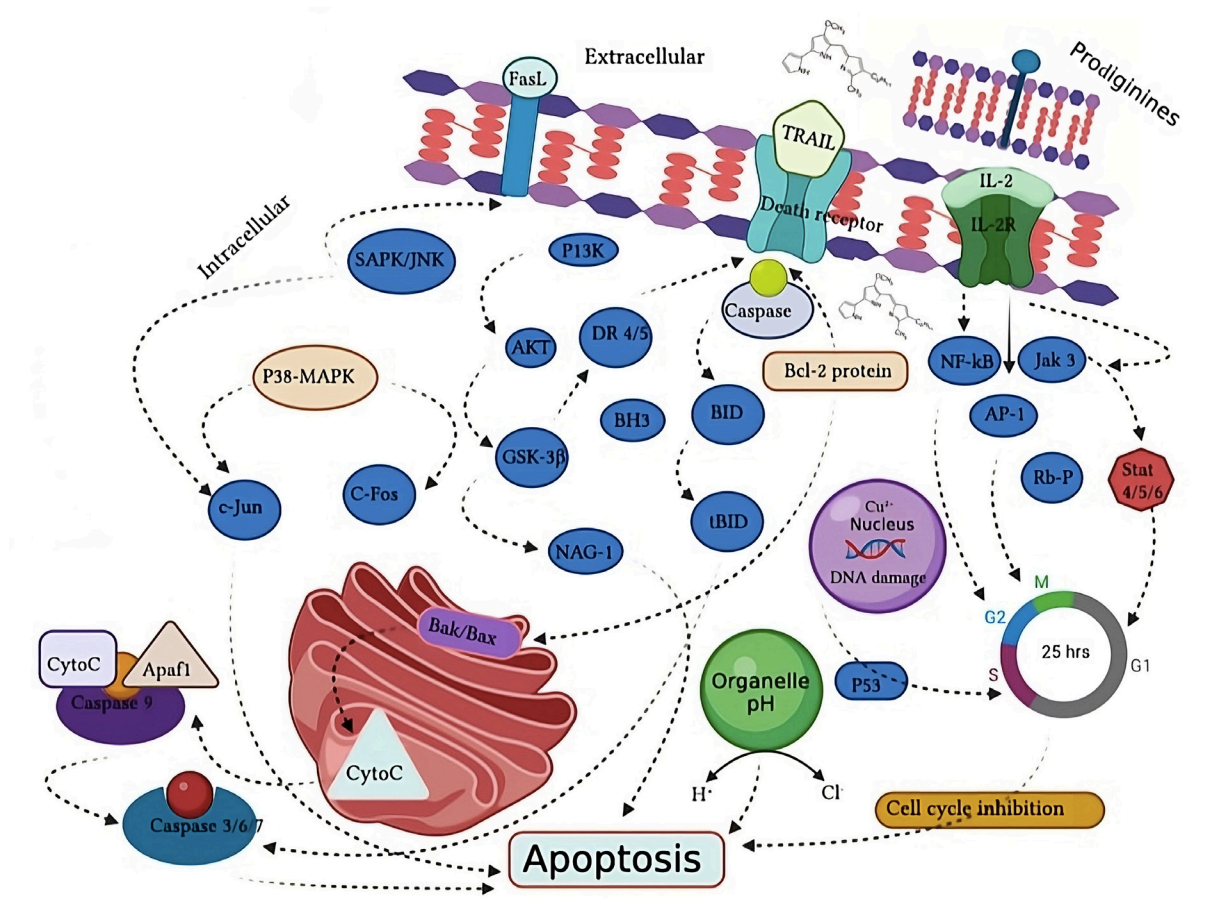


Figure 3. Prodigiosin prospective pathway of apoptosis induction in cancer cell. The prospective prodigiosin apoptosis induction pathway has been described in four different ways such as signal transduction, cell cycle blockage, intracellular acidification and DNA impairment. Figure designed by the adobe illustration tool.

al. (2007) reported that PG act as a hydrogen acceptor which could eradicate intracellular pH concentration leading towards disconnection of transport in the electronic chain of proton to ATP synthase of mitochondria, therefore initializing ATP reduction followed by apoptotic cytotoxicity in neuroblastoma cell lines [42]. Llagostera et al., (2003) also described the mitochondrial mechanism-dependent cytochrome C release which leads toward PG-induced apoptosis in lung tumor cell lines [43].

Interestingly, PG was seen when it was treated with breast tumor cell lines; estrogen receptor-positive (MCF-7) and negative (MDA-MB-231) and the MCF-7 cells which show multidrug-resistant (MDR). In this study, it was observed that PG acts as an apoptotic inducer following the mitochondrial mechanism producing cytotoxicity on the three cell lines in a time and dose-dependent manner. Although PG has negligible or no effect on MCF-7 tumor cell lines, therefore it is diminishing the reality that PG might act as a substrate for MDR transporter fragments [40]. In the era of mitochondrial pathway-dependent apoptosis, there are some studies suggesting another mechanism comprising double-stranded DNA cleavage that leads to apoptosis in cancer cell lines. It has also been observed that this red pigment stimulated H^+ / Cl^- symporter protein by uncoupling of vacuolar H^+ ATPase as it has the potential of electrostatically binding with negatively charged Cl^- molecule inducing proton paired transport of halides in transmembrane. This phenomenon of binding suggests that PG has proven to be a promising pH activator to target tumor cell lines with enhanced intracellular pH gradients [44]. The apoptotic

induction of prodigiosin was examined on the gastric cancerous cell of humans (HGT-1) resulting in a continued deprivation in cell feasibility initiated by apoptotic cell death. Other morphological changes occur in carcinoma cell lines when treated with PG, for example, shrinking of cells, condensing of chromatin, etc [45].

In vitro and in vivo studies of treating PG against lung cancer cells including doxorubicin-resistant (Dox-R) and doxorubicin-sensitive (Dox-S). Similar kind of results was obtained for PG cytotoxic potential against these cells and a maximal half concentration $10 \mu M$. The phenomenon of apoptosis was categorized as autophagy, but also apoptotic features were observed by a subpopulation of cells. Moreover, tumors present in the mice trachea were mitigated showing a clear induction of cytotoxicity with PG treatment in lung cancer cells of both Dox-R and Dox-S [46]. PG-induced cell deaths in breast tumor cell lines were seen using the cell culture technique as well as in vivo methodology. The results indicated that PG has the potential of blocking Wnt/ β -catenin signaling, which has a significant role in breast cancer propagation and development and hence controls cancer cell growth, invasion, and migration [47].

PG was treated against both ovarian cell lines (over-expressing BCRP, MDR1, or MRP2 pumps) their non-MDR type cell lines and multidrug-resistant human gastric cell line. It was observed that this red pigment induced a similar cytotoxic impact to the parental cell lines with negligible difference in comparison with mitoxantrone, daunorubicin and cisplatin. In addition to this FACS analysis described that prodigiosin cannot be exported out

Table 1. In vitro anticancer activity of bacterial prodigiosin against human cell lines.

Compound	Cell line	Feedback	Ref
Prodigiosin	Human colon cancer/HT29, DLD-1	Induces apoptosis in colon cancer	[92]
	Human neuroblastoma/LAN-1, IMR-2, SH-SY5Y	Enhance antitumor agents in the treatment of neuroblastoma	[42]
	Human breast carcinoma/MCF-7, MDA-MB-231	Apoptosis induced by PG in the MCF-7-MR cell line generates stable fragments of human type-I cytokeratins	[93]
	Human lung carcinoma/A549, NCI-H460	PG induces apoptosis in both caspase-dependent and caspase-independent pathways	[43]
	Human leukemia/U937, Jurkat-T, NSO	Caspases were activated in apoptotic cells	[94]
Undecylprodigiosin	Human lung carcinoma/A549	Induces significant cytotoxic activities against A-549	[95]
	Human breast carcinoma/BT-20, MCF-7, MDA-MB-231	Induces p53-independent apoptosis	[96]
Metacycloprodigiosin	Human lung carcinoma/A549, SPCA4	Induces significant cytotoxic activities against A-549 and SPCA4	[96]
Cycloprodigiosin	Human breast carcinoma/MDA-MB-231	cPrG · HCl treatment suppressed the growth of human breast cancer cell lines by inducing apoptosis	[97]
	Human leukemia/HL-60	cPrG · HCl through apoptosis and differentiation induction may be useful in leukemia treatment	[98]

of human epithelial ovarian and gastric cancer cells unlike that of mitoxantrone or daunorubicin which can be efficiently transferred by the ABC pumps [48]. Those findings were indicating that prodigiosin was not performing the function of substrate for MDR receptor protein and due to this reason, it could be a significant tool to treat tumor cell lines that overexpress MDR transporters.

Another study suggested potent anticancer activities of pure prodigiosin which is isolated from the marine chitin's fermentation against HepG2, A549, WiDr and MCF-7 cell lines. The IC50 values were compared with the well-known allopathic anticancer drug Mitomycin C which is 2.75-fold, 1.67-fold and 3.25-folds more efficient as compared to this drug [49]. A study was conducted to treat purified PG on human prostate tumor cell lines (PC3) and choriocarcinoma (JEG3). In an in vitro analysis prodigiosin induced apoptosis in JEG3 cell lines in a dose-dependent manner. Moreover, an interesting phenomenon of dose and time-dependent JEG3 and PC3 tumor cell growth inhibition was seen via vivo assay. It was assumed that this pigment activated a cell death response majorly due to the mitochondria-cytochrome c release mechanism with the production of caspase- and caspase-9 stimulation following the poly (ADP-ribose) polymerase (PARP) proteolysis [50]. Another study reported a similar kind of mechanism of action related to prodigiosin treatment against GLC4, its derivative doxorubicin-resistant GLC4/ADR and two small cell lung carcinoma (SCLC) cell lines. A dose-dependent apoptotic effect was seen produced by cytochrome C release, caspase cascade trigger and breakage of PARP. In addition to this, the study described that the red pigment can reduce the phenotype

which showed multidrug resistance because it has no variations among the two cell lines [51].

The combined effect of prodigiosin was studied with purine analog PU-H71, which is perfectly soluble in water and is considered to have a greater affinity towards tumor cell lines and is in phase I clinical trial testing. The study was conducted against triple-negative breast cancer MDA-MB-231 cells in a dose-dependent manner. The IC50 values for prodigiosin (2.1 μ M) and PU-H71 (157.88 nM) were determined based on the percentage of inhibition, indicating that they were capable of killing 50% of the MDA-MB-231 cells. Moreover, when combining half of the IC50 values for both drugs, the highest percentage of inhibition (75.14%) was observed in comparison to other patterns. The combined impact of both components also causes morphological changes in terms of a higher quantity of floating cells, with a more spherical shape of the cell. These morphological changes were associated with greater cytotoxicity in comparison with untreated cells and cells treated with DMSO, indicating a collaborative effect that was described by the CI method (CI = 0.7). This collaborative effect was seen among both modules due to the increased level of caspase 3, 8, and 9 which is relevant to apoptosis induced by PG. Additionally, a significant reduction in the levels of Heat shock protein 90 (HSP90 α) was seen which is a small chaperone family and is regarded as the crucial activator for the transcription of proteostasis and expression levels related to PU-H71 action [52].

PG can inhibit cell proliferation of cholangiocarcinoma (CCA) by suppressing the phenomenon of autophagy which is SNAREs-dependent, showing that it might be a promising drug to be used

Table 2. Antitumor mechanisms of prodigiosin.

Organ	Cell Line	Mechanism	IC ₅₀	Ref
Lung	95-D	Inhibiting migration, downregulating RhoA gene expression and protein levels, upregulating cell aggregation	5.0 μM	[99]
	A549	PI3K-p85/Akt/mTOR; PKB/SKP2/p27, upregulating p27 ^{KIP1} expression	0.42 μM	[46]
	CL1-5	PKB/SKP2/p27, stabilizes p27 ^{KIP1} through transcriptional repression	0.42 μM	[100]
	GLC4	Intrinsic apoptosis, upregulating cytochrome c release and activating caspase cascade	-	[45]
	GLC4/ADR	Intrinsic apoptosis, upregulating PARP cleavage	-	[101]
	H23	PKB/SKP2/p27	0.42 μM	[100]
Colorectal	DLD1	c-Jun/DNp73/p73/apoptosis; Lysosomal acidification, upregulating apoptosis	>1.6 μM	[102]
	HCT116	c-Jun/DNp73 p73 activation, accumulation of LC-3B- II and SQSTM	4.0 μM	[103]
	HT29	p21/cell cycle blockage/ intrinsic apoptosis, upregulating caspase 3 and P53 protein levels	-	[92]
	SW480	c-Jun/DNp73 p73 activation, downregulating lysosomal activity by accumulating EGFP-LC3 puncta	-	[104]
	SW-620	Apoptosis, upregulating caspase level	0.273 μM	[105]
	Blood	B-CLL	Apoptosis, downregulating vacuolar ATPase	0.116 μM
CCRF-CEM		MMP-9, upregulating caspase-3 and apoptosis, downregulating proliferation rate and viable cell number	-	[107]
HL-60		Genomic damage/apoptosis PKC/PTP1B/PP2A	9.7 μM	[83]
Jurkat		TopoI inhibition/ p27/p21/cdk2/cyclin-E/apoptosis PKC/p38/MAPK, downregulating number of viable cells	4.48 μM	[108]
K562		PKC/PTP1B/PP2A, increases caspase 3, caspase 8, caspase 9	2.5 μM	[109]
NSO		Apoptosis, acts in the absence of P53	15–30 μM	[42]
Ramos		No significant toxicity, apoptosis and decrease in normal cells	9.36 μM	[110]
T-ALL		MMP-9, upregulation of caspase-3 and accumulation of P53, downregulation of survivin protein levels and number of viable cells	-	[110]
U937		PKC/PTP1B/PP2A	0.7 μM	[84]
Brain	GBM8401	ER stress/autophagy, reduce cell viability	-	[111]
	IMR-32	ATP production	0.7 ± 0.1 μM	[112]
	LAN-1	ATP production	1.5 ± 0.1 μM	[113]
	SH-SY5Y	ATP production	1.5 ± 0.2 μM	[113]
	SK-N-AS	ATP production	7.0 ± 0.5 μM	[113]
	U87MG	ER stress/autophagy, reduce cell viability	-	[113]

Table 2. Antitumor mechanisms of prodigiosin (Continued).

Organ	Cell Line	Mechanism	IC ₅₀	Ref
Breast	MCF-7	Genomic damage/ER stress; Akt/GSK-3b/NAG-1, upregulating caspase 3, caspase 7 levels, reduces surviving transcriptional levels	4.0 μM	[112]
	MCF-7 MR	Type I cytokeratin	-	[114]
	MDA-MB-231	ER stress; Wnt/b-catenin; JNK/MAPK/RAD51, upregulating caspase 3, caspase 7, caspase 8 levels, reduces RAD51 mRNA expression	-	[115]
	MDA-MB-468	Inhibit Wnt/b-catenin, induces apoptosis, reduces cell viability, proliferation	-	[116]
	T47D	Cell cycle blockage/ER stress; JNK/MAPK/RAD51, increase caspase 3 and Bax expression levels	-	[47]
Oral	OECM1	Akt/mTOR/beclin-1/autophagy, arresting cell cycle in G0/ G1 phase	-	[92]
	SAS	Akt/mTOR/beclin-1/autophagy, arresting cell cycle in G0/ G1 phase	-	[117]
Skin	SK-MEL-28	mTORC1/2 inhibition, cell cycle arrest at G0/ G1 phase, increase apoptosis and DNA damage	4.51 μM	[117]
	SK-MEL-5	mTORC1/2 inhibition, activates the mitochondrial apoptotic pathway, disrupts MCL-1/BAK complexes	1.02 μM	[118]
Liver	HepG2	Survivin, changes cellular morphology to apoptotic types	10-39 μg/mL	[118]
Nasopharyngeal	CNE2	Cell cycle arrest, blocked autophagy	-	[119]
Prostate	PC3	Intrinsic apoptosis, downregulate cell and tumor growth	-	[120]
Trophoblast	JEG3	Intrinsic apoptosis, upregulate caspase 3, caspase 9 levels and P53 expression levels	>10 μg/mL	[50]
Uterus	Hela	Intrinsic apoptosis, antiproliferative effects	0.5–2.1 mg/mL	[50]
Stomach	HGT-1	Microtubule alteration, increase apoptosis and decrease cell viability	3.1 μM	[101]

as a chemotherapeutic agent for advanced CCA [53]. Treatment of PG with a concentration of 30-100 mg/mL for 4–7 hours against THP-1 cells decreased cell viability. Tumor cells after prodigiosin treatment when compared with non-tumor epithelial Vero normal kidney cell lines, showed that normal cell lines are not susceptible to PG doses [54]. PG showed in vivo anti-cancerous activity in BALB/c mice against Lewis lung carcinoma-induced tumors. After 28 days of treatment with PG tumor volume decreased by 34.18% [55].

T lymphocytes

Regardless of their use as an antigen-directed antitumor cytotoxic molecule, prodigiosin also triggers T cells over activation (i.e., T cell exhaustion) that induces T cell senescence with deficiencies in effector role and propagation which either avoid or control tumor [56, 57]. The continuous exposure to antigens, assists cancer escape immune surveillance and causes dysfunction of T cells leading towards multiple inhibitory receptors on dysfunctional T cells such as PD-1 [58]. It was investigated through in vitro and in vivo protocols that prodigiosin only targets and inhibits the propagation and T cells immune functioning with no effect on B-cells [59].

However, there is still insufficient information available to say confidently whether prodigiosin impedes the functioning of T cells directly or indirectly. In an analysis, it was observed that PG also prevents graft versus host disease (GvHD) by depriving expression of IL-2R α in the IL-2/IL-2R signaling pathway to stop T-cell stimulation. It also suspended the proliferation of autoimmune diabetes mellitus causing little or no toxicity to mice [60]. PG 25-C (a relevant compound) can directly attack the stimulated CD8⁺ T cells by limiting the pH increase associated with intracellular organelles which are mainly needed by cytotoxic T lymphocytes (CTLs) for proper functionality [61]. PG is known to be an efficient compound in an immunosuppressive TME mainly characterized by T cell dysfunction. Moreover, it could also be a significant moiety for T cells related immunological analyses. The research on the level of T-cell obstruction, when treated with PG is important because inhibition of defective T cell is the main root of autoimmune diseases, whereas tumor mainly arises due to inhibition of T-cells to a greater extent [62].

B lymphocytes

There is little information on the effects of prodigiosin on

B cells irrespective of its existing consent regarding its immunosuppressive function on T-cells [63]. In breast cancers, B cells constitute 40% of tumor-infiltrating lymphocytes (TILs) and they comprise 25% of all cells in other cancers [64]. B cells have both effects on tumor growth and inhibition, for example, they obstruct tumors by stimulating T cell responses and regulate tumor growth by supporting immune complex formation or immunosuppression via complement activation [65]. Prodigiosin repressed polyclonal B cell propagation, Epstein Barr virus (EBV) and human peripheral blood lymphocytes (PBLs) immortalization. The distinctive prodigiosin response on T and B cells might be endorsed to the source of the cells used for experimental analysis. For instance, human cells reported selective inhibition of T-cell propagation in comparison to mice cells [66]. In addition to this B cells are miscellaneous and assorted which have the potential to increase T cell antitumor activity and it might assist carcinogenesis through angiogenesis, inflammation, and immunosuppression [64].

Macrophages

Current knowledge supports the major function of PG in moderating tumor-associated macrophages (TAMs). Drafted macrophages linked with the Tumor microenvironment (TME) are transformed into TAMs some kind of immunosuppressive macrophages which encourages “tumor tolerance” by destroying the production and functionality of antitumor T cells [67]. Solid tumors, for instance, breast and prostate cancer had storage of TAMs which deal with insignificant disease prediction [68]. PG acts as a pro-apoptotic drug and has significant therapeutic potential against both vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). It could also control cancer proliferation by impeding the production of tumor-associated macrophage penetration and M2 polarization [69]. Involvement of phosphatidylinositol 3-kinase (PI3K/Akt) mechanism in the stimulation of tumor-associated macrophages and the PG inhibitory effect on this pathway, presented that this red pigment might control recruitment of TAM and stimulate apoptosis related to tumor necrosis factor (TNF) [70]. Metastasis could also be mediated by TAMs-produced matrix metalloproteinase-9 (MMP-9) and VEGF in primary lung cancer tissues of the TNBC mouse model [71]. Prodigiosin control matrix metalloproteinase-9 (MMP-9) which secretes β VEGF responsible for the stimulation of cancer growth and angiogenesis associated with TAM [72].

Prodigiosin might also have the potential to disrupt the functionality of nicotinamide adenine dinucleotide phosphate oxidase (NOX) released by TAMs or deprive its activation in the TME, controlling carcinogenesis related to oxidative stress. TAMs release cytokines and chemokines (e.g., TNF- α , prostaglandin E2 [PGE2] and interleukins [ILs]) that explicit NOX2 and assist carcinogenesis, that sustains metastasis, tumor genesis, and immunological tolerance [73]. Prodigiosin Equivalent block stimulation of NOX by interfering with the transfer of Rac protein and p47phox to the cell membrane of mouse macrophage cell line [74]. Prodigiosin decreases metastasis by targeting NOX2 to permit future research, taking into account various factors such as a source of reactive oxygen species (ROS), susceptibility to ROS toxicity, sensitivity to ROS-induced immunosuppression, tumor cells, effector cells and cancer propagation stage. Macrophage M1 stimulation through IFN- γ is significantly important in immune functionality and plays a role in damaging tissue culture by proinflammatory cytokines [75]. For instance, the transformation of TAMs into immunostimulatory cells is controlled by IFN- γ , suggesting the antitumor immunotherapy's efficiency by producing T cells effector in ovarian tumors [66].

Dendritic cells

Prodigiosin might also moderate TADC's immune functions via PGE2 in the same way as TAMs. Despite that DCs activate an antitumor T-cell immune feedback, malignant tumors acquire other kinds of DCs with lowered relocation and storage in lymphoid organs leading to immunosuppressant T cells. Higher levels of PGE2 switched the immunostimulatory DCs into immunosuppressant T cells to decrease the progression of antitumor T cells by stimulating PD-L1 [76]. Prostaglandin E2 (PGE2) blocks MHC II illustration and activates IL-10 via EP2 and EP4 receptors, diminishing dendritic cells antigen performance initiated through the COX-2/EP3 signaling [77]. The prodigiosin immune-regulatory mechanism of actions on tumor-associated macrophages described previously showed that it can distress dendritic cells in the Tumor microenvironment. PG could alternate TAM-initiated mitigation of tumor antigen-presenting behaviors and tumoricidal due to the established metabolic crosstalk occurring in dendritic cells [78].

Natural killer cells

Regulated natural killer cells eradicate cancer through death receptor-stimulated killing, cytokine generation (i.e., IFN- γ) and granule exocytosis, which mediate other immune cells [79]. Nevertheless, PGE2 per se trades off NK cell activities (e.g., tumor lysis) for metastases development via activated EP2 and EP4 receptors [80]. PGE2 controls the NK cell's functionality through various processes, for example by restraining IFN- γ assembly and ILs-produced IFN- γ expression in natural killer cells through EP2 receptors or reducing natural killer receptors via cAMP/PKA mechanism [76]. EP4 antagonist prostaglandins E2-stimulated natural killer cell destruction by shielding IFN- γ induction by natural killer cells, suppressing lung and breast cancer metastases [81]. PG could have an immunoregulatory function since the reciprocal natural killer-dendritic cells crosstalk is obstructed by prostaglandins E2 via cytokine and chemokine modulation [82].

Immunosuppressive activity

As an immunosuppressant, the potential of members from the prodiginine family to block the cell cycle has been oppressed, at non-apoptotic doses. PG was observed to lower graft versus host disease (GvHD) with no significant symptoms of toxicity in mice modules. Prodigiosin also delayed the progression of autoimmune diabetes mellitus. There was also inhibition of graft versus host disease and collagen-produced arthritis by prodigiosin in mice modules [60]. Different types of PGs like metacycloprodigiosin, Undecylprodigiosin and cyclo-prodigiosin, all have the potential to selectively prevent T cell propagation. However, in vitro, cytotoxicity with different levels was seen. PGs have been presented to inhibit the cell cycle at various phases. The diverse biological activities have been ascribed to their distinct assemblies and/or mechanism of action [83].

Prodigiosin prevents Jurkat T cell proliferation in humans during the G1/S phase. The function of PG in the late G1 stage was represented by reduced expression of cdk2, cyclin E, and cdk4, all of which are shown to be expressed during the mid to late G1 stage of the cell cycle. Moreover, PGs have the potential to lower retinoblastoma Rb protein phosphorylation, which is considered an important initiator for the development of the S phase from the G phase [63]. In leukemic Jurkat cells, inhibition of cyclin E, cdk2, p27, p21, and Rb phosphorylation was also seen followed by apoptosis [83]. Prodigiosin has also the capability to interfere with the accumulation of p53 and the production of NAG - 1, in the breast tumor cells (Mcf - 7) in humans [84]. Prodiginines do not interfere with IL-2 expressions, which makes

a complicated structure with its receptor (IL-2R), leading towards another significant turning point in T cell propagation. In addition, numerous kinds of activities related to given PGs have been shown at this stage in the cell cycle.

Anti-viral activity

The antiviral potential of PG has little investigation. However, it was seen that PG has the potential to inhibit signal transduction processes which are known to be important for viral infection, due to which there is an increasing trend in today's research toward the evaluation of PG as an antiviral drug [85]. An in-silico experiment was performed via homology modeling and molecular docking analysis against various viruses to evaluate the antiviral effect of PG. The study analyzed the potential of PG against diverse viral proteins from different viruses such as hepatitis C virus (HCV), hepatitis B virus (HBV), influenza A virus (H1N1) and human immunodeficiency virus (HIV). The study reported that prodigiosin has significant antiviral potential against the hepatitis B virus, human immune deficiency virus, and H1N1 but not for the hepatitis C virus. Even though, these results needed further investigations and research through in vivo and in vitro analysis [86].

The earliest analysis which demonstrated the antiviral effect of prodigiosin was described by Zhou and his coworkers [87]. The researchers investigated the capability of prodigiosin to reduce infection in silkworm BmN cells caused by Bombyx mori nucleopolyhedrovirus (BmNPV). They tested in vitro cell models for human DNA virus predicted to be effective for finding the antiviral drug. The findings showed that prodigiosin at a concentration that is non-cytotoxic to normal cells (300 nM) is shown to have a strong toxic effect on BmN cells. Certainly, PG with concentration (300 nM) deprived the formation of occlusion bodies (OB) that showed the ultimate lytic phase of BmNPV, and production of budded virus. An experiment performed indicated that prodigiosin showed both cytotoxic and antiviral potential against BmNPV and BmNPV infected cells, respectively in time and dose-dependent manner. The antiviral effect of PG in a concentration (10-300 nM) dependent manner was employed for analysis, the pathway followed by PG for antiviral activity comprised of transcription of genes i-e; early (ie-1) gene, which involved in DNA replication, late (vp39) gene, that takes part in capsid formation and very late (p10) gene which plays role in OB production followed by DNA replication of the virus. After exposure of these three genes ie-1, vp39, and p10 to 100 nM prodigiosin for 72 hours, gene expression was repressed 55 to 100-times, indicating that PG can inhibit gene transcription in viruses and hence decrease both OB and BV generation.

Interesting research was conducted to evaluate the antiviral effect of prodigiosin against Herpes simplex virus (HSV) 1 and 2 reported by Suryawanshi et al. [17]. The results described that human corneal epithelial (HCE) cells infected by HSV-1 infection are strongly inhibited by 2.5 μ M PG, which is a physiologically significant in vitro model. PG with a concentration as low as 0.3 μ M inhibited protein synthesis, gene transcription, virus replication and egress of infective virus molecules. In vivo analysis in a mice module, BALB/c suggested that PG also has the potential to lower corneal HSV-1 infection. The mice were poisoned with HSV-1 infection and topically treated with prodigiosin, a standard drug Trifluoro thymidine (TFT) used to treat ophthalmic HSV infection and dimethyl sulfoxide as blank with a concentration of 50 μ M of both drugs, employed after two days for continuous seven days. Prodigiosin showed significant protection in mice against the development of disease at a level comparable to standard drugs. Additionally, the prophylactic potential of prodigiosin against HSV disease was assayed in HCE cell lines.

The researchers found that prodigiosin produced a prophylactic effect, but it had no concern with virus entry, suggesting that prodigiosin only affects the signaling mechanism of the host after the cells got infected by the virus. More, precisely, they evaluated that prodigiosin induced its antiviral effect via inhibiting apoptosis and suppression of NF- κ B and Akt signaling which are responsible for host cell existence and is stimulated during infection caused by HSV.

Another study performed on the prodigiosin-derived compound known as obatoclax was reported to have an antiviral effect against alphaviruses like Semliki Forest (SFV) and Chikungunya (CHIKV) viruses [88]. The action pathway of obatoclax was proposed to inhibit the viral combination with cells stimulated by endosomal pH neutralization. Moreover, obatoclax antiviral activity on SARS-Cov-2 indicated the inhibition of replication in epithelial cell cultures. It was seen that the pathway for inhibition was also ascribed mainly due to a decrease in endosomal pH and diminishing activities of cathepsin and furin; enzymes responsible for viral fusion protein stimulation [89, 90].

A dose-dependent in vitro and ex vivo PG analysis against the HSV-1 virus described that PG inhibits replication of the virus. In vivo activity on HSV-1 ocular infection found that PG plays a protective role against disease development. Histopathological studies described that PG preserved the corneal integrity and no inflammation of epithelial cells. The mechanistic study demonstrated that PG inhibits pro-viral host factors including NF κ B/protein kinase B (AKT). These findings represent the evidence that during infection, prodigiosin worked out by inhibiting dysregulation of multiple signaling mechanisms, it also interferes with the host system to lower replication of the virus and proliferation [91].

The potato virus Y (PVY) is a plant virus that causes remarkable crop losses globally, particularly in Solanaceae crops. Researchers have determined a strain of the plant growth-promoting rhizobacterium (PGPR), *Serratia marcescens*-S3, which has the potential to control PVY replication in *Nicotiana benthamiana*. Underlying, there is a lack of inclusive studies demonstrating the underlying mechanism. In a recent experiment designed by Ge M et al. (2022), it was observed that the ubiquitination of NbHsc70-2 plays a pivotal role in provoking induced systemic resistance (ISR) by *Serratia marcescens*-S3. Following treatment with *S. marcescens*-S3, the protein level of NbHsc70-2 was significantly reduced. Inhibition of ubiquitination led to the increased aggregation of NbHsc70-2 in plants and reduced the *S. marcescens*-S3-mediated resistance to PVY. Moreover, transgenic *Nicotiana benthamiana* plants, NbHsc70-2KO and NbHsc70-2USM, were developed using CRISPR-Cas9 technology to knock out and ubiquitinate NbHsc70-2, respectively. *S. marcescens*-S3 was found to have a remarkable impact on reducing the inhibition of NbHsc70-2 protein aggregation in NbHsc70-2KO and NbHsc70-2USM plants. Importantly, the virulence of PVY was more noticeable in NbHsc70-2USM plants compared to the plants with the wild-type genotype. These findings express that *S. marcescens*-S3 enhances the ubiquitination process of NbHsc70-2, leading to the suppression of NbHsc70-2 molecular chaperone recruitment and hence reducing the replication as well as infection of PVY [121].

In a recent experiment conducted by Song K et al. (2023), the researchers investigated the *Micropterus salmoides* rhabdovirus (MSRV), the most lethal viral pathogen in largemouth bass farming, which poses a threat to the survival and health of bass fry. The experiment focused on observing a red-pigmented bacterial strain, *Serratia marcescens* MS01, present in the gut of *M. salmoides*. However, the researchers discovered that methanol extracts of sediment (SED) from *S. marcescens* MS01 showed extremely efficient anti-MSRV potential. At a concentration of

30 mg/L, SED effectively lowered the virulence of MSR/V, with the inhibition rate of glycoprotein and nucleoprotein expression reaching 99% in GCO cells. Furthermore, SED inhibited MSR/V-induced oxidative stress and enhanced the potential of antioxidant enzymes in CAT and SOD. Subsequent purification, activity analysis, and multi-spectroscopic identification suggested that prodigiosin played a significant role in inhibiting MSR/V in SED. These outcomes recommend that SED or prodigiosin have the potential to be employed as promising antiviral approaches against MSR/V in aquaculture farms [122].

Future potential

It has been reported that PG has a wide range of biological activities. This attractive versatile red pigment is warrant of continued development to discover the more potentials of this molecule. The derivatization of the linear tri-pyrrole structure of PG with the addition of complex functional groups to derive novel compounds in the pyrrolic family to enhance and specify their biological activities are in recent trends. Moreover, PG combined with other biomolecules such as amino acids and proteins to synthesize new compounds with complex structures and novel properties is gaining attention. New trends in molecular docking and modeling seem to be very interesting aspects to find in-silico bioactivities of PG for a specific disease. The orientation selection for the bonding with other biomolecules or active surfaces is a very attractive tool to investigate selective bonds and the ability of stable complex formation.

Further investigations on PG are required to confirm the compensatory mechanism for tumor inhibition and to know whether it may render B-cells proliferation or antitumorogenic activity. Additional information is needed to evaluate the provocative function of PG in inhibiting T-cell stimulation by curbing the expression of IL-2R α in the IL-2/IL-2R signaling pathway. Limited research on prodigiosin encapsulation via nanoparticles reported that it might be an excellent alternative in tumor therapy, adding that this is an important area to focus on in future research to find fruitful results in cancer treatment. In conclusion, more deep analysis is needed to evaluate more functionalities in prodigiosin and the basis for its miscellaneous profiles regarding bioactivities in biomedical sciences.

Conclusion

The use of prodigiosin could be a new platform for the rational design of biotechnological products. In this review, the crosstalk between the different immune cells demonstrated the potential role of prodigiosin as a key player of immunomodulators. During viral infections, some findings represent that prodigiosin inhibited the dysregulation of multiple signaling mechanisms and interferes with the host body to restrict viral replication. However, the immense spectrum of biological activities of prodigiosin fabricates this molecule an interesting candidate to develop unique alternatives to overpass the tumor microenvironment and multidrug resistance in different diseases and control the spreading of microorganisms.

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Data availability

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Competing interests

None.

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