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TREATMENT AND PROPHYLAXIS - REVIEW

Selenium and protozoan parasitic infections: selenocompounds and selenoproteins potential

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Abstract

The current drug treatments against protozoan parasitic diseases including Chagas, malaria, leishmaniasis, and toxoplasmosis represent good examples of drug resistance mechanisms and have shown diverse side effects. Therefore, the identification of novel therapeutic strategies and drug compounds against such life-threatening diseases is urgent. According to the successful usage of selenium (Se) compounds-based therapy against some diseases, this therapeutic strategy has been recently further underlined against these parasitic diseases by targeting different parasite´s essential pathways. On the other hand, due to the important functions played by parasite selenoproteins in their biology (such as modulating the host immune response), they can be also considered as a novel therapeutic strategy by designing specific inhibitors against these important proteins. In addition, the immunomodulatory potentiality of these compounds to trigger T helper type 1 (Th1) cells and cytokine-mediated immune response for the substantial induction of proinflammatory cytokines, thus, Se, selenoproteins, and parasite selenoproteins could be further investigated to find possible vaccine antigens. Herein, we collect and present the results of some studies regarding Se-based therapy against protozoan parasitic diseases and highlight relevant information and some viewpoints that might be insightful to advance toward more effective studies in the future.

Keywords Selenium · Se-nanoparticles · Se supplementation · Therapy · Protozoan parasitic diseases

Introduction

Drug efficacy against protozoan parasites is variable among species and genus and some of them are only active in the acute phase of the infection with potential side effects of the used compounds. Accordingly, the programs to

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control parasitic diseases such leishmaniasis, toxoplasmosis, malaria, and Chagas are facing huge challenges due to ineffective therapies and drug resistance (Andrews et al. 2014). Therefore, the threat of such diseases remains a priority of public and global health. All these issues prompted scientists to continuously look for novel therapeutic drugs, and selenium (Se)-based/containing compounds (selenocompounds) have shown promising results in this sense for many infectious and parasitic diseases (Brindha 2021; Chuai et al. 2021; Da Silva et al. 2014; Kieliszek and Lipinski 2020; Letavayová et al. 2006; Steinbrenner et al. 2015).

Se trace element plays important role in human health, due to its anti-inflammatory, pro-immune, and antioxidant properties (Bai et al. 2017; Hariharan and Dharmaraj 2020). Se exerts its biological effects mostly through its incorporation into selenoproteins, which have the inclusion of at least one selenocysteine residue in its sequence driving Se toward its biological functions and also decreases cytotoxicity effects (Bartolini et al. 2017). Se atom has unique physicochemical properties leading for example to selenoproteins show higher catalytic efficiency or higher nucleophilicity which have significant biological relevance (Arnér 2010, 2020). The biological properties of Se are important once incorporated into selenoproteins. Most selenoproteins are involved in redox systems with the potentiality to react with molecular oxygen and thiols to develop crucial homeostatic processes in different cells and tissues but also with signaling pathways, accordingly, selenoproteins functions are affected by the balanced cellular level of Se/or Se-related biomolecules (selenocompounds). Thus, these compounds may influence the redox homeostasis and cell signaling potentially impacting regulatory elements (Bartolini et al. 2017; Kurokawa and Berry 2013). Selenocompounds known as Se-containing molecules are described in various therapeutic strategies. Se dioxide and selenites in the form of sodium selenite have been suggested as the most studied inorganic selenocompounds. Other compounds including methylseleninic acid, isoselenazolones, selenoureas, diselenides, selenocarbonyl derivatives, selenocyanates and isoselenocyanates, selenoxides, selenazoles, and selenadiazoles, as well as Se-containing amino acids (selenocysteine, selenocystine, selenomethionine and methylselenocysteine), have been also considered organic selenocompounds which could be used in Se therapy/supplementation (Bartolini et al. 2017).

The host immune response might be affected by Se and selenoproteins (Se supplementation) on the immune cells (Fig. 1) (Bae and Kim 2020; Nelson et al. 2016; Sperk et al. 2020; Sun et al. 2017; Xia et al. 2021) or selenoproteins expressed by immune cells (Huang et al. 2012). There are several studies demonstrating that sufficient Se levels even achieved by Se supplementation regulate or decrease the level of inflammatory cytokines (Daeian et al. 2014; Kudva et al. 2015; Zhou et al. 2014). For instance, an adequate level of Se contributes to optimal levels of interleukin 6 (IL-6), both in health and disease. The increased expression of IL-6 in SARS-CoV-2 infected cells revealed a potential link between decreased selenoprotein expression and

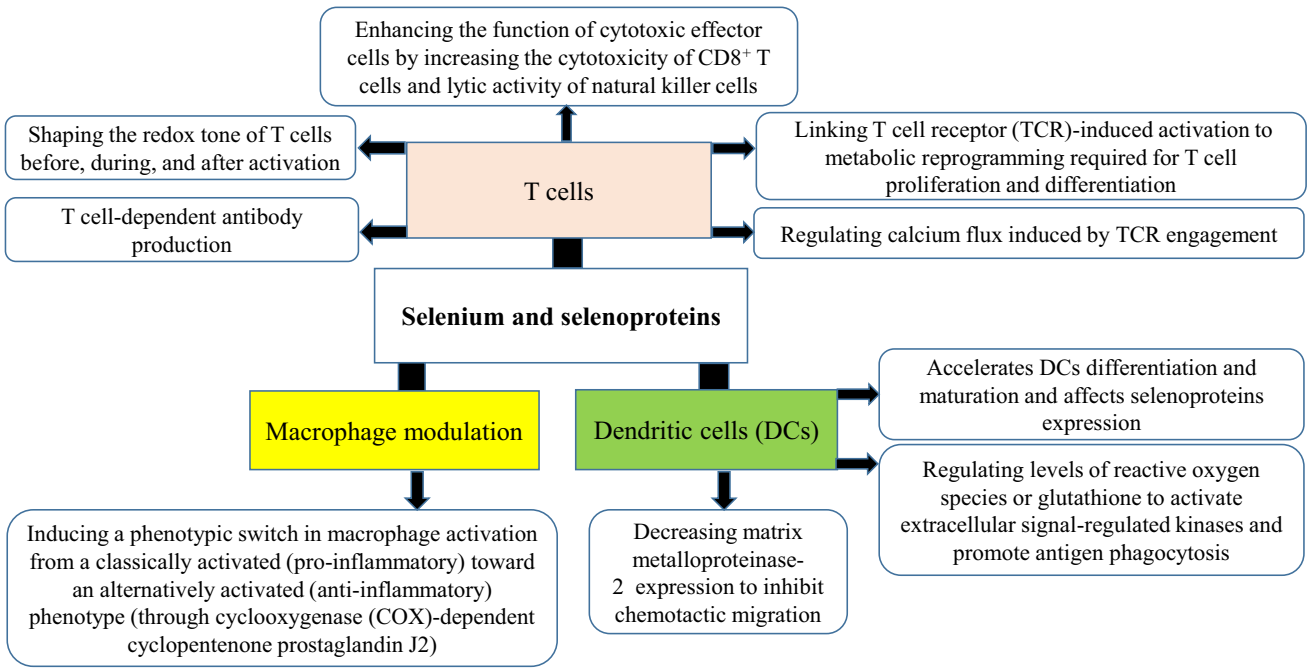

Fig. 1 The regulatory effects of Se and selenoproteins on the immune cells

COVID-19-associated inflammation (Zhang et al. 2020). In addition, selenocompounds/selenoproteins have been found to be inhibitors of the nuclear factor-kappa β (NF-κβ), as the coordinator of inflammatory cytokines (such as IL-6) activation (Zhang et al. 2020). This information highlights that Se adequacy prevents excessive cytokine activation in infectious and inflammatory conditions. Contrarily, Se deficiency led to a reduction in selenoproteins gene expression and further affected cytokines levels (low expression levels of IL-2, IL-1β, IL-6, interferon alpha (IFN-α), IL-17, and high expression levels of IL-8, IL-10, IFN-γ, IFN-β, and tumor necrosis factor alpha (TNF-α) in the Se-deficient animal models compared to the control groups) (Khoso et al. 2019).

Furthermore, Se, selenocompounds, and selenoproteins seem to modulate the immune response and consequently increase host defense against oxidative stress (antioxidant defense, redox signaling, and redox homeostasis) (Da Silva et al. 2014; Guillin et al. 2019). It is well known that the ability of different intracellular pathogens to encounter host-derived reactive species is remarkably related to the potential capacity of their antioxidant networks at the beginning of invasion, which consequently influence the balance toward pathogens survival, proliferation, and virulence over redox-dependent control of infection (Mesías et al. 2019; Piacenza et al. 2019). During parasitic infection, the immune system can generate oxidant molecules as defense mechanism that may lead to an oxidative stress status if these are not sufficiently counteracted by the antioxidant system (van de Crommenacker et al. 2012). Therefore, the selenoproteins are vital enzymes involved in overcoming the oxidative stress induced through the excessive generation of reactive oxygen species (ROS) (Avery and Hoffmann 2018).

Accordingly, Se, selenocompounds, and selenoproteins deficiency may lead to an unbalanced immune system and subsequent pathogenesis progression in the host (Amankwah and Han 2018; Khatiwada and Subedi 2021; Yazdi et al. 2015; Zhang et al. 2021). Thus, the supplementation or treatment with these compounds might be beneficial for the control or elimination of several pathologies such as protozoan parasitic infectious diseases.

Selenocompounds modulating the host immune system during protozoan parasitic infections

It has been shown that Se and selenocompounds significantly improve the efficiency of the host immune system´s function (innate and adaptive) against pathogens (Parnham 2011; Yazdi et al. 2015), including protozoan parasites. It seems that the possible mechanisms of action of such compounds in vivo include their anti-apoptotic activity and their protection against cellular damage during intracellular protozoan parasitic infections through the alteration of lipid peroxidation and endogenous antioxidant enzymes (Alkhudhayri et al. 2020; Sheneni et al. 2018).

In Chagas disease patients, low Se levels seemed to be a biological marker for the pathology and was reported to be related to the progression of *Trypanosoma cruzi* infection (Rivera et al. 2002). On the other hand, Se supplementation has been suggested as a potential therapeutic option to modulate the inflammatory, immunological, and antioxidant responses involved in cardiac and intestinal disorders caused by this pathogen (do Brasil et al. 2014; Gomez et al. 2002; Jelicks et al. 2011). In addition, since the titer of anti-*T. cruzi* immunoglobulin G (IgG) is directly correlated with the parasitic load, Se derivatives have recently demonstrated their effects as potential anti-chagasic agents, by decreasing the levels of IgG detected in serum from infected mice during the acute phase (Martín-Escolano et al. 2021a).

Se deficiency induced lower expressions of *IL-2* and *IL-4* which might contribute to the severity of the parasitic diseases such as that caused by *Cryptosporidium parvum* (Wang et al. 2009). Moreover, it had been speculated that the enhancement of the immune response by non-toxic dosage Se supplementation may also play a role on the inhibition of *C. parvum* infection in the murine model (Huang and Yang 2002).

Interestingly, in acute experimental toxoplasmosis, sodium selenite and diphenyl diselenide may decrease protein oxidation and lipid peroxidation, facilitating a beneficial immunological balance between the production of pro- and anti-inflammatory cytokines. Thus, the administration of organic and inorganic Se derivatives in combination with the common chemotherapy against toxoplasmosis reduced the exacerbated immune response (Barbosa et al. 2014). Currently, the use of nanotechnology and nanoparticles (NPs) has improved the therapeutic strategies in different pathologies including parasitic diseases (Barazesh et al. 2018; Kirtane et al. 2021; Nafari et al. 2020). The large surface-volume ratio of NPs facilitates a number of interactions with biological molecules and pathogens, and the easy penetration of those NPs into cells compare to other particles highly suggests the application of these formulations (Khan et al. 2019). SeNPs have also demonstrated effects against murine toxoplasmosis during both, therapeutic and prophylactic treatment by increasing mRNA levels of *TNF-α*, *IL-12*, *IL-10*, *IFN-γ*, and inducible nitric oxide synthase (*iNOS*) gene levels (Keyhani et al. 2020a; Keyhani et al. 2020b).

Evidences have shown decreased levels of Se in sera of patients with cutaneous and canine leishmaniasis (Souza et al. 2014; Taghipour et al. 2021). Since this trace element exerts a major regulatory function in the immune system, and host immune responses against leishmaniasis, its level alterations can be associated with the clinical symptoms of

patients with different forms of leishmaniasis (Souza et al. 2014; Taghipour et al. 2021). For the treatment of cutaneous leishmaniasis, the combination of Se with glucantime and anfotericine B has demonstrated a higher activity than each drug alone mainly by increasing *IL-12* and decreasing *IL-10* gene expression (Mostafavi et al. 2019a; Mostafavi et al. 2019b).

SeNPs have shown higher anti-parasitic, anti-oxidant, and anti-inflammatory effects than free sodium selenite against murine coccidiosis. This activity occurs through the regulation of the expression of pro-inflammatory cytokines (*IL-1β*, *IL-6*, *IFN-γ*, and *TNF-α*) and protective glycoproteins genes in the jejunum (Alkhudhayri et al. 2018). Similarly, SeNPs were able to reverse the imbalance in the antioxidant status and to reduce apoptosis of jejunal cells during *Eimeria* infection (Alkhudhayri et al. 2020).

In overall, Se and selenocompounds significantly improve the host immune system´s responses toward the elimination of the parasitic infections. Nevertheless, it has been shown in animal models infected with *T. cruzi* that the treatment with selenocompounds (sodium selenate) induced a serologic decrease of pro-inflammatory cytokines (IL-12, TNF, and IFN) and a reduction of B-lymphocytes in splenic cells (de Freitas et al. 2018). Therefore, it would be interesting to understand the link between the host immunological status and the use of Se derivatives/selenocompounds for the treatment of parasitic diseases especially under concrete physiological conditions.

Selenocompounds/Se derivatives targeting protozoan proteins involved in vital biological pathways

Besides their capability to regulate the immune responses during parasitic infections, Se/selenocompounds derivatives have also the ability to directly target such pathogens (Keyhani et al. 2020b; Shakibaie et al. 2020). One of the Se derivative´s mechanisms of action seems to be the alteration of pathways allowing the parasites to overcome the oxidative stress. Se supplementation through sodium selenite revealed an anti-coccidian effect of Se in vitro through the formation of free radicals, since this effect was reversed by the addition of free-radical scavengers to the cell culture. This statement was reinforced in vivo supporting an enhanced immune response produced by Se supplementation in mice (Huang and Yang 2002). Based on the low activity of the enzymes involved in antioxidant pathway in *C. parvum* oocysts, the effect was likely caused by free-radical production.

New organo-Se compounds bearing the sulfonamide moiety have displayed leishmanicidal activities by inhibiting the β-isoform of carbonic anhydrase from *Leishmania donovani chagasi*, which is considered a specific and promising therapeutic target against these pathogens since the host cells lack such an isoform (Al-Tamimi et al. 2019; Cabrera et al. 2021). Similarly, trypanothione reductase (TryR), catalyzing the reduction of trypanothione disulfide to trypanothione in trypanosomatids, remains a promising target due to its important role in the protection against ROS and its absence in vertebrates. Based on the analogy of sulfur and Se, diselenide and selenocyanate derivatives have been proposed as new TryR inhibitors (Baquedano et al. 2016; Etxebeste-Mitxeltorena et al. 2020; Garnica et al. 2020). Among selenourea derivatives of diselenides series, 1,1´-(4,4´-Diselanediylbis(4,1-phenylene))bis(3-hexylselenourea) demonstrated an inhibitory activity of *L. infantum* TryR (Díaz et al. 2019). Furthermore, the inhibition of Fe superoxide dismutase (Fe-SOD) has been suggested as an additional mechanism of action of these compounds on parasites in vitro (Etxebeste-Mitxeltorena et al. 2020; Martín-Escolano et al. 2021a; Mosolygó et al. 2019).

SeNPs have evidenced apoptotic effect against *Leishmania* promastigotes by increasing mRNA levels of metacaspase (Mostafavi et al. 2019a, 2019b) and by DNA fragmentation (Beheshti et al. 2013), the most important alterations that occur in programmed cell death (Raina and Kaur 2012; Zhang et al. 2005). Regarding *Giardia*, the lytic activity of SeNPs against cysts was found to be similar to that of metronidazole (Malekifard et al. 2020). Among other pathways, metronidazole causes DNA fragmentation and consequently, trophozoite death (Gardner and Hill 2001). Thus, this mechanism of action (DNA fragmentation) might be responsible for the death of *Giardia* cysts in SeNPs-based therapies. However, additional studies will be useful to clarify the activity of selenocompounds and derivatives including SeNPs against intestinal protozoan.

Furthermore, parasite death has been observed using Se derivatives that lead to mitochondrial membrane depolarization and bioenergtic collapse in *T. cruzi* and consequently, the reduction of DNA replication and RNA transcription rates (Martín-Escolano et al. 2021a; Martín-Escolano et al. 2021b). Moreover, molecules involved in cell cycle such as proliferating cell nuclear antigen (PCNA), mini-chromosome maintenance complex (MCM4), or Topoisomerase-II (TOP2) have been described as targets of Se derivatives compounds in *Leishmania* parasites (Fernández-Rubio et al. 2015; Fernández-Rubio et al. 2019).

Other vital metabolic pathways may be altered by selenocompounds. Diselenides derivatives have proven antiparasitic effect against African trypanosomes affecting the highly dependent parasite glucose metabolism (Franco et al. 2017). Furthermore, the ergosterol biosynthesis pathway has been also reported as a molecular target for *T. cruzi*, Se-containing analogues of WC-9 might act as parasite squalene synthase inhibitors (Chao et al. 2017). All these current data suggest that further investigations are needed to better understand

the mechanisms of action of selenocompounds and derivatives during host cell protozoan parasitic infections.

The parasitic selenoproteome: a promising therapeutic target and potential source for vaccine antigens

It is well known that pathogenic trypanosomatids have conserved the machinery responsible for selenocysteine biosynthesis and its incorporation in selenoproteins (Manhas et al. 2016). In addition, only three selenoproteins containing a redox center selenocysteine-based have been reported in trypanosomatids (da Silva et al. 2020). However, regarding the African *Trypanosoma*, it seems that those selenoproteins were not required for infectivity and acute infection progression in mice, and null-mutants showed similar sensitivity to stress conditions and to drugs targeting these enzymes than wild-type strains (Aeby et al. 2009; Bonilla et al. 2016). Moreover, the ablation of enzymes participating in selenoproteins synthesis caused a higher sensitivity to endoplasmic reticulum stressors, one of those selenoproteins containing selenocysteine in its redox domain demonstrated to be dispensable for *T. brucei* (da Silva et al. 2020). Accordingly, since most selenoproteins are important redox enzymes containing a catalytic selenocysteine residue, the selenoproteome of the protozoan parasites could link with critical functions and vital mechanisms in these parasites (Lobanov et al. 2006b). In addition, further studies on parasites' selenoproteome might shed some light on the biology of these proteins (Lobanov et al. 2006a; Lobanov et al. 2006b; Röseler et al. 2012).

On the other hand, selenocompounds and selenoproteins might improve the immune system, and the parasite´s adaptation to these compounds could then take place by expressing specific proteins (such as parasite's selenoproteins) in their structures/proteome or, by adapting the uptake of Se from the aforementioned compounds to the parasite selenoproteins synthesis pathway (Kalantar et al. 2021; Rashidi et al. 2020a). Furthermore, high levels of selenoproteins have been related to the impairment of immune system functions, so it has been postulated that the overexpression and release of selenoproteins by some protozoan parasites such as *Leishmania* might be involved in suppression of the host innate immunity (Rashidi et al. 2020a). Consequently, the expression of different proteins including selenoproteins in protozoan parasites proteome might be considered a defensive strategy against Se-based compounds. All of the aforementioned information further highlights the crucial and potential biological function of parasites' selenoproteome, which could be aimed as promising therapeutic targets in the treatment of parasitic diseases. The analysis of the selenoproteome expression in parasites exposed to selenocompounds remains an interesting challenge.

Methods for the identification and expression of selenoproteins can increase our information concerning selenoproteins functions. The targeting of reactive selenocysteine residues with electrophilic probes, along with progression in computational and experimental Se detection in proteomic samples, has recently developed the scope of questions significantly that can be addressed in selenoproteomics (Peeler and Weerapana 2019). Consequently, proteomic approaches might be appropriate tools for the identification of selenoproteins involved in parasite pathways facilitating the modification of the host immune responses (Bennett and Robinson 2021; Herbison et al. 2019; Sperk et al. 2020). Accordingly, a few studies based-proteomic and genomic techniques have identified the expression of several selenoproteins and key derivatives in the proteome of some protozoan parasites (Lobanov et al. 2006a, 2006b; Novoselov et al. 2007; Rashidi et al. 2020b; Röseler et al. 2012). Bioinformatics tools have also facilitated the identification of various selenoproteins through selenoproteins genome finding in different organisms (Fig. 2) (Santesmasses et al. 2020).

Thioredoxin glutathione reductase (TGR) is a parasite selenoprotein required for the survival of schistosomes in the mammalian host. Consequently, selenoproteins inhibitors were recently designed and applied against schistosomiasis. Interestingly, such inhibitors were active against all important species and development stages and immature worms. It seems that some of these inhibitors may induce a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in TGR, leading to the generation of superoxide and hydrogen peroxide (Lyu et al. 2020). Altogether, experimental data confirm that by targeting or inhibiting selenoproteins, novel effective therapeutic strategy may be developed against protozoan parasites (Andrade and Reed 2015). Most of the selenoproteins are responsible for the protection against oxidative damage through redox activities. Moreover, Se-independent homologues of these proteins have been characterized in protozoan parasites (except in *C. parvum*). For instance, *C. parvum* parasite completely lacks selenoproteins, but the glutathione peroxidase (with cysteine instead of selenocysteine in its active site) had been described (Kang et al. 2014). So, this enzyme is not inhibited by potassium cyanide, a known selenoprotein inhibitor which exerts its activity by releasing the Se atom from the enzyme active site.

Auranofin, the first oral gold salt approved by the United States Food and Drug Administration (FDA) to treat rheumatoid arthritis, has demonstrated anti-parasitic activity thanks to its monovalent gold molecule inhibiting parasitic enzymes involved in the control of the redox metabolism (Andrade and Reed 2015; Angelucci et al. 2009; Ilari et al. 2012). By analyzing the crystal structure of *Schistosoma*

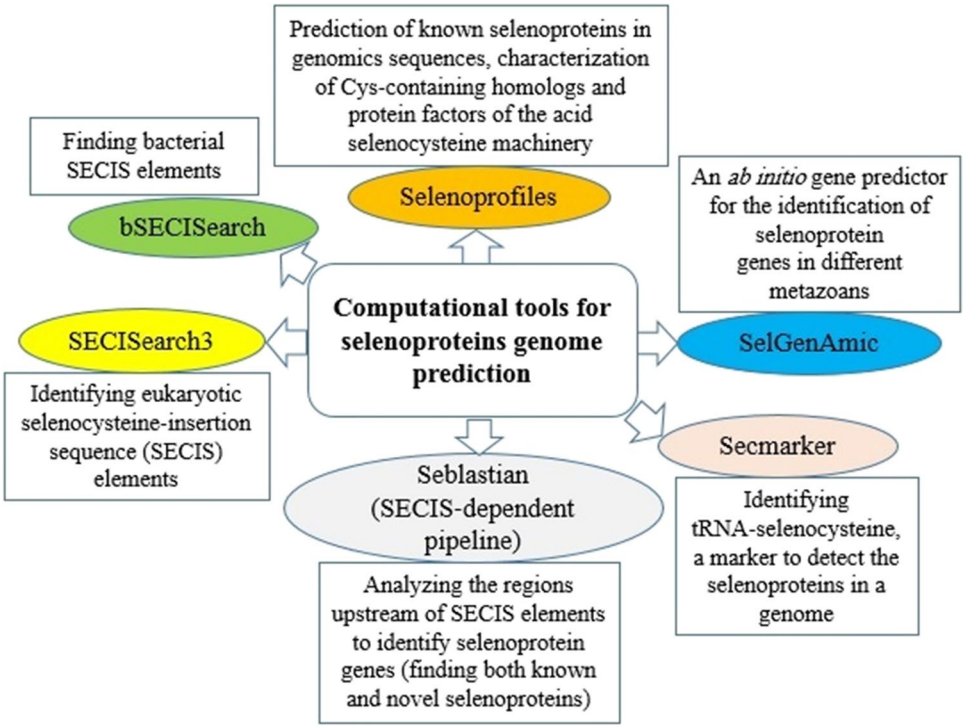

Fig. 2 Bioinformatics tools to discovery/analyze selenoproteins genome

mansoni thioredoxin-glutathione reductase, Agelucci et al. suggested a role of selenocysteine in gold transference from the compound to the cysteine couple of the TGR from the parasite. In fact, the gold-compound was less active against the enzyme from the same family lacking the selenocysteine in its active site (Angelucci et al. 2009). Since, selenoproteins have been described in several protozoan parasites (Lobanov et al. 2006b), the auranofin antiparasitic activity may be related to its activity as selective selenoproteins inhibitor. However, this compound also showed to be active against the *L. infantum* thrypanothione reductase (TR), which lacks selenocysteine motif in its active site by a mechanisms involving the cysteine residues of the protein and trypanothione binding site of the protein instead selenoproteins (Ilari et al. 2012). Similarly, *C. parvum* that lacks selenoproteins has shown to be sensitive to auranofin (Debnath et al. 2013). Auranofin-treated *Entamoeba histolytica* trophozoites were shown to be more sensitive to oxidative stress. Additional assays demonstrated that the thioredoxin lacking selenocysteine from these parasites was also the target of this gold-compound (Andrade and Reed 2015; Parsonage et al. 2016). Since auranofin showed to be more active against selenocysteine-containing proteins, further experiments are needed to determine the role of Se in the mechanism action of compounds targeting selenoproteins in protozoan parasites.

There is not enough information regarding the development of selenoproteins as vaccine candidates against parasitic diseases. However, due to the immunomodulatory potentiality of these compounds to trigger T helper type 1 (Th1) cells and cytokine-mediated immune response for substantial induction of proinflammatory cytokines (Dharmalingam et al. 2021), Se, selenoproteins, and parasite selenoproteins could be further investigated to find possible vaccine antigens in the parasitology field. The immunogenic nature of selenoproteins from protozoan parasites was explored by using a DNA vaccine encoding a Se-dependent glutathione reductase (GR) from *Toxoplasma gondii*. In the immunized mice, the humoral response showed significant higher titters of total IgG, IgA, and IgM, and the provoking cellular immune response was confirmed by an increment of IFN-γ, IL-4, IL-17, and transforming growth factor beta 1 (TGF-β1) cytokines compared with the control group. These results suggest that TgGR could induce humoral and cellular protective immune responses and an acceptable level of resistance against toxoplasmosis (Hassan et al. 2014). Moreover, it has been demonstrated that a dietary supplementation with Se compounds may potentially improve the immunogenicity and protective efficacy of some types of vaccines used against viral infections marked by the production of higher levels of specific antibodies and lower viral infection levels in the Se compounds-treated groups (Shojadoost et al. 2020). Therefore, such strategy might be also evaluated in vaccination strategies against parasitic infections.

The Se/selenocompounds-based protective and preventive therapy

The protective role of Se has been well described in cancers and antioxidant activity of this compound and its effects on cellular redox status has been suggested as the most related strategy (Björnstedt and Fernandes 2010; Kuršvietienė et al. 2020; S Darvesh and Bishayee 2010). In addition, Se-based protective and preventive therapy has shown satisfactory results in other pathologies such as euthyroid nodular goiter (Turan and Turksoy 2021), acute ischemic stroke (Mirończuk et al. 2021), or infectious diseases caused by bacteria (Kim et al. 2012), virus (Kieliszek and Lipinski 2020), and parasites (Hooper et al. 2014; Volpato et al. 2018).

Se deficiency can promote mutations, propagation, and virulence of viruses especially RNA viruses. Se might be beneficial through restoration of host antioxidant capacity and critical lymphocyte counts for the cytotoxic immune response, decrease of apoptosis, endothelial cell damages and platelet aggregation, and finally improvement of the clinical symptoms (Hiffler and Rakotoambinina 2020; Notz et al. 2021). Recent data indicate that sodium selenite probably induced an efficient protection against severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection (COVID-19). This chemical compound can oxidize thiol groups in the virus protein disulfide isomerase (PDI) leading to unsuccessful virus penetration into the non-infected cell membrane as well as infectivity restriction (Kieliszek and Lipinski 2020). Thus, since the Se supplementation-based protective therapy was found effective against intracellular pathogens such as viruses, its potential for preventing intracellular protozoan parasites to reduce the risk or modulate resistance to infectious diseases could be also evaluated.

It was shown that Se provided by Se supplementation can increase the function of cytotoxic effector cells and may also be important for maintaining T cell maturation and functions, as well as for T cell-dependent antibody production (Bae and Kim 2020). The initial immune status of the host (before infection) is critical for the development of clinical manifestations during parasitic infectious disease and Se-supplementation in the diet may be essential in maintaining the immune response. For instance, it has been reported a decrease of Th1 and Th2 cytokines in mice feed with Se deficient diet during *C. parvum* infection compared to their levels in animals feed with adequate amounts of this essential element (Wang et al. 2009). Mineral compounds subcutaneously administered including Se increased the number of leukocytes and immunoglobulins serum levels in new-born lambs and heifers, inducing protection against coccidiosis and giardiasis (Cazarotto et al. 2018; Volpato et al. 2018). Similarly, sufficient Se supply in mice caused a substantial lowering of fecal shedding of oocysts from mice, while Se-deficient diet was associated with an accelerated expulsion of oocysts, presumably due to an impaired development of parasites in the jejunum (Dkhil et al. 2014).

Se-based NPs have also demonstrated preventive effects on the protozoan parasitic diseases. The number of tachyzoites was significantly lower in mice which had orally received SeNPs before being infected by *Toxoplasma* than in the control group. The expression levels of *IFN-γ TNF-α, IL-12, IL-10*, and *iNOS* considerably increased in the treated group, illustrating the improvement of the immune system, especially the cellular immunity, which caused resistance to the infection (Shakibaie et al. 2020). On the other hand, Se supplementation had been suggested in the prevention of right ventricle chamber dilatation and reversion of *T. cruzi*-induced acute and chronic cardiomyopathy in mice (de Souza et al. 2010).

Se, Se derivatives, and selenocompounds-based therapy against protozoan parasitic infections

In agreement with the aforementioned information, many in vivo and in vitro studies have attempted to develop Se, Se derivatives, and selenocompounds-based therapy strategy against different protozoan parasitic diseases. Table 1 presents the potential treatments against parasitic protozoan infections with these compounds, highlighting their role on both, the host and the parasite.

Interestingly, selenocompounds are also involved in the regulation of exacerbated immune responses and chronic inflammation (Huang et al. 2012). Since both, the deficiency and high Se supplementation, can cause physiologic alterations such as immune-related disturbances in the human body, the control of the therapeutic doses remains crucial. Thus, the adverse effects of long-term selenocompounds-based therapy/Se supplementation are an important issue that should be undertaken in therapeutic strategies and clinical trials by these compounds. In fact, Se has a narrow therapeutic window and its toxicity margins are critical (Khurana et al. 2019). Therefore, although the results of most of these in vivo and in vitro studies (Table 1) have been successfully reported as an alternative strategy instead of the current drugs, their toxicity should not be negligible. More investigations are needed to determine the therapeutic window allowing the prevention of protozoan parasitic diseases without exhibiting toxicity in the host. New strategies could involve the use of nanocarriers, such as NPs, to increase the selenocompounds solubility, permeability, bioavailability, and consequently might be indirectly helpful

Table 1 In vitro and in vivo effects of Se/selenocompounds-based therapy against protozoan parasites

Protozoan parasites	Se compounds	Efficacy		Possible mechanism of action	References
		In vitro	In vivo		
L. tropica	Niosomal combination of Se coupled with Amphotericin B, and Glucantime	Leishmanicida (promastigote and amastigote)	Decreasing the levels of IL-10 and increasing IL-12 (as Th1 activator)	Increased expression of metacaspase in promastigotes (inducing apoptosis)	(Mostafavi et al. 2019a, 2019b)
L. major	Methylseleno-Imidocarbamates			Inducing nitric oxide production, potent effect on the cell cycle (inducing arrest in G1)	(Fernández-Rubio et al. 2015)
	Isoselenocyanate derivatives			Reduced expression of *Leishmania*' genes involved in the cell cycle (*TOP2*, *PCNA*, and *MCM4*), increase of cells in the G1 phase and reduction of cells in the S phase	
L. major* and *amazonensis	Naphthalamide isoselenocyanate-6 (NISC-6)	Leishmanicida (amastigote)			(Fernández-Rubio et al. 2019)
L. infantum	Selenocyanate and diselenide derivatives containing amide moiety	Leishmanicida (amastigote)		Targeting parasite trypanothione reductase	(Baquedano et al. 2016; Etxebeste-Mitxeltorena et al. 2020)
	Heteroaryl Selenocyanates and Diselenides				
	Selenourea derivatives of Diselenides				(Díaz et al. 2019)
	3,5-Dimethyl-4-isoxazoyl selenocyanate (a compound with good intestinal permeability)		Reducing parasite load in liver (99.2%), spleen (91.7%) and bone marrow (61.4%)		(Alcolea et al. 2021)
L. donovani* and *infantum	Organoselenium bearing sulfonamide moiety	Leishmanicida (amastigote)		Parasite Carbonic Anhydrase inhibitors	(Al-Tamimi et al. 2019)
	Organic Se compounds				(Cabrera et al. 2021)
L. infantum* and *braziliensis	Se	Leishmanicida (promastigote and amastigote)		Inhibiting Fe-SOD	(Martín-Montes et al. 2017)
L. tropica, major* and *donovani	SeNPs		Reducing the leishmanial-lesions size	Inducing apoptosis in promastigotes	(Beheshti et al. 2013; Mahmoudvand et al. 2014; Soflaei et al. 2014)

Table 1 (continued)

Protozoan parasites	Se compounds	Efficacy		Possible mechanism of action	References
		In vitro	In vivo		
T. gondii	Se-containing analogues of WC-9	Activity against tachyzoites			(Chao et al. 2017)
	Sulfamethoxazole/Trimethoprim supplemented with diphenyl diselenide and sodium selenite		Reducing IFN-γ and increasing IL-10 (preventing excessive tissue damage)	Protective mechanism through the balance between pro- and anti-inflammatory cytokines	(Barbosa et al. 2014)
	Diphenyl diselenide		Decreasing thiobarbituric acid reactive species (TBARS) levels in infected mice and increasing the Glutathione S transferase (GST) activity in the brain	Protective action as antioxidant	(Machado et al. 2016)
	SeNPs		Increasing mRNA levels of inflammatory cytokines (*TNF-α*, *IL-12*, *IL-10, IFN-γ*) and *iNOS*, decreasing parasite load in infected tissues and mortality rate (up to 100%)		(Keyhani et al. 2020b; Shakibaie et al. 2020)
Giardia deodenalis		Same effect and more cytotoxicity compared to Metronidazole in killing of cysts			(Malekifard et al. 2020)
Eimeria papillata			Decreasing the numbers of meronts, gamonts, and developing oocysts, regulating the expression of pro-inflammatory cytokines (*IL-1β*, *IL-6*, *IFN-γ* and *TNF-α*) and protective glycoproteins genes in the jejunum	Reversing the disturbance of the redox status in infected cells (antioxidant property), reducing the Bax and caspase-3 expression (anti-apoptotic property)	(Alkhudhayri et al. 2020; Alkhudhayri et al. 2018)
T. cruzi	Selenocompounds (derivative 26), Selenocyanate and Diselenide derivatives	Trypanocidal		Mitochondrial membrane depolarization, inhibition of nucleic acid levels, Fe-SOD enzyme inhibition (cell death induction by bioenergetics collapse)	(Martín-Escolano et al. 2021a; Martín-Escolano et al. 2021b)
	Selenocyanate derivatives (analogues of WC-9)	Trypanocidal		Inhibitor of parasite squalene synthase	(Chao et al. 2019)
	Selenides-1,2,3-triazoles	A possible effective compound (further in vitro and in vivo studies are needed)			(Brasil et al. 2020)

Table 1 (continued)

Protozoan parasites	Se compounds	Efficacy		Possible mechanism of action	References
		In vitro	In vivo		
T. brucei	Se + Zinc		Increasing protection against cellular damage	Regulating lipid peroxidation and endogenous antioxidant enzymes	(Sheneni et al. 2018)
	Diglycosyl diselenides	Trypanocidal		Altering glucose metabolism in parasites, interference with the redox homeostasis	(Franco et al. 2017)
C. parvum	Se		Decreasing number of oocysts in feces and a longer survival time in infected mice	Se-compounds reactions with thiols (glutathione) and enhanced levels of superoxide and hydrogen peroxide	(Huang and Yang 2002)

in decreasing the drugs (selenocompounds) side effects/toxicity (Khan et al. 2019; Yetisgin et al. 2020). Table 1 also confirms SeNPs potentials in comparison with other compounds. The recently shown hepatoprotective actions and antioxidant properties of plant-based SeNPs and the use of such compounds as an important therapeutic strategy against diabetes, various cancer cells, viral infections, bacterial diseases, and parasitic infections (malaria and leishmaniasis) also highlight the great potential of novel selenocompounds based on NPs for the management of parasitic diseases (Ikram et al. 2021). As a possible larvicidal mechanism of action for plants-based SeNPs in a dose-dependent manner in malaria and leishmaniasis (Suganya et al. 2014), these compounds could denature the special sulfur-containing proteins and phosphorus-containing compounds like DNA and also leads to the denaturation of vital organelles consequently decrease membrane permeability, reduces or disrupt adenosine 5'-triphosphate (ATP) synthesis which finally leads to cell death (Krishnan et al. 2020; Sowndarya et al. 2017). Although further experiments are needed to compare the advantages and side effects/toxicity of plants-based SeNPs in comparison with other forms of SeNPs and other selenocompounds in treatment approaches, the integration of plant-based SeNPs in experimental therapeutic strategies against protozoan parasite can provide more details regarding the therapeutic properties of such compounds.

Besides their toxicity, other factors need to be considered such as the costs and time needed for the synthesis of selenocompounds. Therefore, alternatives to the novo synthesis of selenocompounds should be explored. For example, those compounds synthetized and tested against other pathologies such as cancer are now tested in models mimicking these parasitic diseases (Fernández-Rubio et al. 2019). Currently, another successful approach widely extended is the use of in silico methods to identify and validate both new compounds and therapeutic targets (Peña-Guerrero et al. 2021). As mentioned, these methods have been used to study the selenoproteome of protozoan parasites (Lobanov et al. 2006a, b; Röseler et al. 2012) and the likely organic selenocompounds target (Cabrera et al. 2021). In addition, the complex life cycles of protozoan parasites are key factors to be analyzed during the development of reliable models of study. The characterization of selenoproteins in the infective stage or the effect of selenocompounds on immune response remain difficult since the current in vivo experimental models are not the natural hosts of the pathogens.

It would be interesting to use additional techniques including proteomics and metabolomics to study the role of the selenoproteins in the life cycle of these parasites, the protection against conventional and new treatments, as well as drug resistance. Furthermore, the effects of such compounds depend on the Se chemical form administered. For example, organic selenocompounds do not produce Se accumulation

in cells, and therefore the oxidative stress caused by Se accumulation can be prevented (Shalini and Bansal 2007). However, when dealing with intracellular parasites, compounds must exert their activities within hosts' cells, so the accumulation should be assessed. There are in silico methods developed to predict the bioavailability of chemical compounds and to choose the administration route. Further experiments must be performed to analyze the pharmacokinetic features of selenocompounds. Besides the low effectiveness of the current therapy and the lack of proper vaccines, the emergence of drug resistant strains has become a priority for the control and elimination of these diseases. The combination therapy remains a good option since previous results had been successful (Hallett et al. 2004; Lopez-Velez et al. 2010; van Griensven et al. 2010). Therefore, for the treatment of infections caused by protozoan parasites, the administration of selenocompounds in combination with other chemical compounds is a promising strategy and should continue to be explored (Mostafavi et al. 2019a, b).

Conclusions and future directions

Many examples demonstrate the re-emergence of protozoan parasitic diseases mainly due to the lack of effective treatments and vaccines but also for the appearance of parasite drug resistance So, the selective drug discovery is an important task encountering a number of barriers hampering its proper advance to find new anti-parasite compounds impacting both human and animal health in many countries (Guarner 2019; Haldar et al. 2018; Mills 2020). In this sense, selenoproteins and selenocompounds have been poorly studies in protozoan parasites and here we emphasize its usefulness for the modulation of host inflammatory responses, their role as candidates for novel drug therapies against many life-threatening protozoan parasitic diseases.

As previously demonstrated, Se-based therapies appear promising therapeutic strategies to fight against diseases caused by protozoan parasites through the targeting of different essential pathways of the parasite. The identification of the effective targets for these compounds in the parasites proteomes may lead to the improvements of the designed drug´s efficacy and might be further helpful to understand the mechanism of action of Se compounds against parasites. On the other hand, since parasites selenoproteins play vital functions in the biology of the parasites, they can be also considered as novel therapeutic targets to design specific inhibitors against these important proteins. Although the therapeutic aspects of Se, Se-compounds, and selenoproteins have been highlighted, physiological Se levels in patient's sera or selenoproteins expressed in pathogens might be also suggested as biomarkers and predictors of infection and disease progress.

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Declarations

Competing interests The authors declare no competing interests.

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