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Review

Effects of Iron-Fortified Foods on the Nutritional Status of Children Residing in Regions Vulnerable to Parasitic Diseases: A Systematic Review

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ABSTRACT: Parasitic infections (PIs) remain a public health concern among school-age children living in areas of greater socioeconomic vulnerability, especially in Brazil, Russia, India, China, and South Africa. PIs can promote nutritional deficiencies, increasing the risk of anemia and impaired physical and cognitive development. Thus, fortified foods have been considered as a promising strategy for improving the nutritional status of children and preventing PI complications. This systematic review aimed to present the effects of iron-fortified foods for deworming and improving blood parameters in schoolchildren residing in areas that are vulnerable to PIs. This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines of randomized clinical trials addressing the use of fortified foods and micronutrients in children living in areas endemic for PIs. The PubMed, LILACS, Scopus, and Cochrane databases were searched to identify articles published between 2000 and 2020. A total of 153 records were retrieved from the databases, 10 of which were considered eligible for this study. On the basis of our analysis, most of the selected studies showed that the inclusion of fortified foods in the diet improved blood and infectious parameters. Therefore, fortified foods can be used as an important tool for controlling the adverse outcomes of PIs among children living in areas of greater vulnerability. However, more studies on this topic are needed to provide more evidence and consolidate strategies using iron-fortified food.

Keywords: child, food, fortified, nutritional status

INTRODUCTION

Parasitic infections (PIs) are associated with nutritional and cognitive impairments, including anemia, growth retardation, and poor school attendance, among schoolchildren (Nga et al., 2011). In sub-Saharan Africa, East Africa, and Southeast Asia, low socioeconomic development and neglected diseases are associated with the high risk of child mortality (Stein et al., 2004; Nagahawatte and Goldenberg, 2008). Compared with adults, schoolchildren are more vulnerable to PIs because they have an immature immune system and inadequate personal hygiene and healthcare practices (Harhay et al., 2010; Mahmud et al., 2015). Malaria is one of the most relevant PIs that is caused by *Plasmodium falciparum*; it accounts for approximately 24% of all cases of anemia in sub-Saharan Africa (Glinz et al., 2017). Moreover, 50% of the mortality of underweight children worldwide has been attributed to malnutrition associated with iron, vitamin A, and zinc deficiencies (Caulfield et al., 2004). Adequate nutrition is an important factor for the risk assessment and prognosis of PIs. An unfavorable nutritional status contributes to the development of PIs, which, in turn, can lead to poor nutritional outcomes, forming a vicious cycle (Werneck et al., 2011).

Identifying tangible strategies for improving the situation of these populations is challenging as their low income impedes their ability to afford an adequate diet and effective interventions for the treatment and prevention of PIs (Prentice et al., 2017). The addition of nutrients to food sources such as cereals, salt, and milk has been shown to be an effective and sustainable option for ensuring adequate nutrient intake and preventing the occurrence of PIs (Le et al., 2006). Food fortification is a

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potential method to treat micronutrient deficiencies and has been used to eliminate nutritional deficiencies related to diseases such as pellagra and rickets (Berner et al., 2014). However, the effects of food fortification have shown conflicting results. While some studies found that iron-fortified foods can improve nutritional parameters, other studies did not (Le et al., 2007; Aimone et al., 2017; Teshome et al., 2017). Thus, the effectiveness of fortified foods in improving the nutritional status of children remains unknown. Therefore, the present study conducted a systematic review to determine the effects of iron-fortified foods for deworming and improving blood parameters (e.g., serum iron, hemoglobin concentration, serum ferritin, transferrin receptor) among schoolchildren residing in areas of greater vulnerability.

METHODS

Protocol and registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) and registered in PROSPERO (https://www.crd.york.ac.uk/prospero/): CRD42022360580.

Literature search

The PubMed (https://www.pubmed.gov), LILACS (using the Virtual Library of Health, https://bvsalud.org), Scopus (using Capes Periodicals, https://www.scopus.com), and Cochrane (https://www.cochranelibrary.com) electronic databases were searched for relevant articles published between 2000 and 2020. The descriptors ("helminths" and/or "parasitosis") and ("micronutrients" and/or "fortified foods") were used for the search. Moreover, filters were used for randomized trials to assess the mechanisms and interventions regarding the use of fortified foods to improve nutritional status in children.

Article selection process

Following the PRISMA recommendations, two researchers independently selected articles based on the eligibility criteria. Differences of opinions regarding the selection of any article were resolved through discussion until a consensus was reached. The titles and abstracts of articles were assessed initially, followed by full-text analysis. Two independent reviewers performed data extraction of the articles included based on the inclusion and exclusion criteria. The authors, year of publication, type of study, number of individuals involved in the study, study setting, intervention period, infections in the study population, fortified food, type of intervention performed, study objectives, and main outcomes were extracted, and the results are summarized in Table 1.

Inclusion and exclusion criteria

Controlled and randomized trials that were published between 2000 and 2020 and used fortified foods and micronutrients in children living in areas of greater socioeconomic vulnerability were included. Meanwhile, trials involving case reports, experimental studies, literature reviews, and systematic reviews were excluded. In addition, studies that did not correlate fortified foods with parasitosis and/or a change in nutritional status were excluded.

Quality appraisal

The risk of bias was appraised using the Cochrane Risk of Bias 2 tool (RoB 2 tool) (Sterne et al., 2019) for randomized trials. The RoB 2 tool considers five domains for each randomized trial: bias arising from the randomization process, bias because of deviations from the intended intervention, bias because of missing outcome data, bias in the measurement of the outcome, and bias related to selective outcome reporting. The five types of bias were classified as "low risk" (+), "high risk" (−), or "some concerns" (!) for each study included.

RESULTS

Selected articles and their characteristics

A total of 153 studies were obtained from the database search, eight of which were duplicates and thus removed. In the second stage, the titles and abstracts of the studies were reviewed based on the pre-established inclusion criteria, and 13 studies were considered potentially eligible. During full-text analysis, two articles did not meet one of the inclusion criteria as they did not involve a strategy that was applied to schoolchildren. Thus, 10 studies were selected for the systematic review (Fig. 1). Each study was comprehensively analyzed, and the results are presented in Table 1.

Effectiveness of fortified foods on blood parameters in schoolchildren

The selected articles showed the effectiveness of fortified foods in improving the blood parameters of schoolchildren residing in areas that are highly vulnerable to PIs. Some of the parameters that were investigated after using fortified foods included hemoglobin, hematocrit, ferritin, serum iron, and transferrin levels. Glinz et al. (2017) found an improvement only in hemoglobin levels using iron-fortified cereals, whereas Abizari et al. (2012), Le et al. (2007), and Egbi et al. (2015) found that fortified foods improved more than one blood parameter. Among these studies, Abizari et al. (2012) assessed the effects of iron-fortified cowpea meal and found increased hemoglobin, ferritin, serum iron, and transferrin levels after consumption. Le et al. (2007) showed that iron-fortified instant

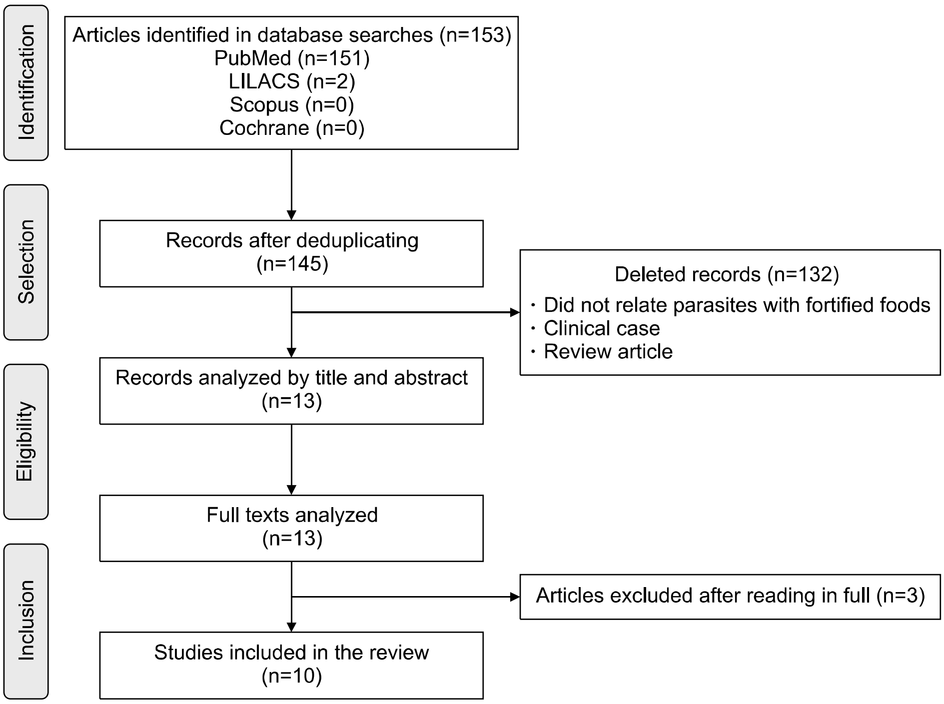

Fig. 1. Flowchart of the article selection process based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

noodles improved hemoglobin and serum iron levels. Meanwhile, Egbi et al. (2015) found increased hemoglobin and ferritin levels after using vitamin C-fortified cowpea meal and fishmeal. By contrast, Jinabhai et al. (2001), Rohner et al. (2010), and Teshome et al. (2017) tested crackers and cornmeal porridge fortified with iron and found no improvement in blood parameters or anemia frequency. Table 1 shows a description and the analysis results of the aforementioned studies.

Effectiveness of fortified foods for deworming

Nga et al. (2011), Abizari et al. (2012), Aimone et al. (2017), and Kugo et al. (2018) investigated the effectiveness of fortified foods for deworming in schoolchildren. *Ascaris lumbricoides*, *Trichuris trichiura*, *Ancylostoma duodenale*, and *P. falciparum* were the etiological agents that were identified in the analyzed population. All these studies reported a reduction in parasitemia after using fortified foods. However, Le et al. (2007) did not find satisfactory results with regard to the use of fortified foods as a therapeutic option. Table 1 shows a description and the analysis results of the aforementioned studies.

Risk of bias appraisal

None of the 10 articles included in this review had a high risk of bias. However, concerns were found in the articles by Abizari et al. (2012), Egbi et al. (2015), and Aimone et al. (2017) because of a lack of information regarding the randomization process and in the article by Egbi et al. (2015) because of selective outcome reporting, as no specific analysis plan of the results was mentioned in the methods section (Fig. 2).

DISCUSSION

In developing countries, PIs caused by intestinal helminths and protozoa are among the most prevalent infections, with high morbidity and mortality rates (Houweling et al., 2016). These diseases are an important public health concern worldwide, especially in poor regions that have no access to basic hygiene conditions (GBD 2016 DALYs and HALE Collaborators, 2017; Abe et al., 2019; Harvey et al., 2020). PIs can trigger nutritional changes, such as reduced serum levels of vitamins A and C (Crompton, 1992; Crompton and Whitehead, 1993; Hlaing, 1993; Stephenson, 1993), which increase the risk of anemia (WHO, 2016; Molla and Mamo, 2018). Moreover, they can stimulate anthropometric changes, including growth retardation and weight loss (Sanchez et al., 2013; Yoseph and Beyene, 2020).

Despite the progress of chemoprophylaxis-based control programs in the last decade (Bockarie et al., 2013), this strategy poses risks of adverse reactions (Boussinesq et al., 2003). Thus, the use of fortified foods, which can be used to control infectious diseases in malnourished populations, is a safer and more accessible strategy for controlling PIs and preventing their adverse outcomes (Zancul, 2004).

This systematic review evaluated the results of food fortification to promote deworming and improve blood parameters in schoolchildren living in areas that are highly vulnerable to PIs. Studies with interesting results regarding the effectiveness of food fortification in schoolchildren were identified. Abizari et al. (2012) showed that iron fortification through beans can increase hemo-

Table 1. Summary of the results regarding the effect of fortified foods on the nutritional status of children residing in regions vulnerable to parasitic diseases

Reference	Type of study	n	Local (country)	Period (month)	Infection	Fortified food	Study group	Objective	Result
Kugo et al., 2018	Placebo-controlled trial	326	Kenya	4	Ascariasis, trichuriasis, and hookworm	Porridge+papaya seed+Fe (GP1: 40 mg)	Comparison between groups: 1. fortified food; 2. albendazole; 3. control	Design alternatives for treating parasites that are easy to implement and have low resistance rates	Porridge fortified with iron and added papaya seeds reduced the *Ascaris lumbricoides* egg count by 63.9% (P<0.002) and increased the mean Hb count by 2 g/dL (P<0.001)
Aimone et al., 2017	Cluster-randomised trial	1,943	Ghana	5	Malaria	Powder +micronutrients +Fe	Comparison between groups: 1. micronutrient fortified powders containing vitamins and minerals with iron; 2. micronutrient fortified powders containing iron-free vitamins and minerals	Identify the response to *Plasmodium falciparum* infection in children supplemented or not with iron	Children carrying *P. falciparum* who did not receive iron-fortified food at the beginning of the study were more likely to have parasitemia at the end (OR, 2.86). An improvement in serum iron status was observed in the group that received the fortified food
Glinz et al., 2017	Cluster-randomised trial	378	Ivory Coast	9	Malaria	Cereals+Fe (GP2: 2 mg-GP4: 3.8 mg)	Comparison between groups: 1. control; 2. FC with NaFeEDTA+FeFum 3. IPT: sulfadoxine-pyrimethamine+amodiaquine; 4. FC with NaFeEDTA+FeFum+IPT; 5. FC with NaFeEDTA+FePP	To evaluate the effectiveness of iron-FC to combat anemia in preschool children in a malaria endemic region	The prevalence of iron deficiency anemia decreased markedly both in the group of children who received FeFum (32.8% to 1.2%, P<0.001) and in those who received FePP (23.6% to 3.4%, P<0.001)
Teshome et al., 2017	Double-blind randomised trial	315	Kenya	1	Malaria	Powder with cornmeal porridge (GP1: 3 mg-GP2: 12.5 mg)	Comparison between groups: 1. powder with vitamin A and zinc, 11 other micronutrients, 3 mg of iron (NaFeEDTA); 2. powder with 12.5 mg of iron (FeFum); 3. placebo	To evaluate the effectiveness of fortification with a daily dose of iron NaFeEDTA and FeFum for improving hematimetric and inflammatory status	The proposed fortification promoted a slight increase in Hb concentration, indicating that fortification with iron-containing micronutrients offers some benefit. However, no improvement in serum iron levels, anemia status and inflammation status was found
Egbi et al., 2015	Placebo-controlled trial	150	Ghana	6	Malaria	Black-eyed peas/fish flour+juice	Comparison between groups: 1. fish meal and vitamin C; 2. vitamin C; 3. control	To evaluate the effectiveness of fortified food served with a drink rich in vitamin C in improving serum iron and Hb levels	Fortified fishmeal and vitamin C-rich drink improved Hb levels and reduced the prevalence of anemia (P<0.05)

Table 1. Continued 1

Reference	Type of study	n	Local (country)	Period (month)	Infection	Fortified food	Study group	Objective	Result
Abizari et al., 2012	Double-blind, controlled trial	241	Ghana	7	Malaria	Black-eyed pea flour+Fe (10 mg)	Comparison between groups: 1. black-eyed pea flour with 10 mg Fe/meal like NaFeEDTA; 2. unfortified black-eyed pea flour	To test the effectiveness of NaFeEDTA-fortified black-eyed pea meal in improving iron status in children	Flour fortified with NaFeEDTA resulted in improvement in Hb, serum ferritin, serum iron and transferrin receptor reduction. Fortification resulted in a 30% and 47% reduction in the prevalence of iron deficiency and iron deficiency anemia, respectively
Nga et al., 2011	Placebo-contolled trial	510	Vietnam	4	Ascariasis, trichuriasis, and hookworm	Cookie+Fe and other multimicro-nutrients	Comparison between groups: 1. albendazole; 2. fortified cookies+albendazole; 3. fortified cookies; 4. placebo	The present study investigated the impact of multi-micronutrient fortification in combination with deworming in a school-based approach on growth, cognitive function and parasite burden among Vietnamese school-aged children and whether the combination of the two interventions was more beneficial than either intervention alone	Children who received albendazole with fortified food had the lowest parasite load after four months

Table 1. Continued 2

Reference	Type of study	n	Local (country)	Period (month)	Infection	Fortified food	Study group	Objective	Result
Rohner et al., 2010	Double-blind, randomized, placebo-controlled trial	591	Ivory Coast	6	Ascariasis, malaria, trichuriasis, and hookworm	Biscuits+Fe electrolytic (20 mg)	Comparison between groups: 1. placebo; 2~4. exclusive administration of cookie with Fe (20 mg) or albendazole (400 mg)+ praziquantel (40 mg/kg) or sulfadoxine (500 mg)+pyrimethamine (25 mg), respectively; 5. administration of biscuits with Fe (20 mg) associated with albendazole (400 mg)+praziquantel (40 mg/kg); 6. administration of albendazole (400 mg)+praziquantel (40 mg/kg) associated with sulfadoxine (500 mg)+pyrimethamine (25 mg); 7. administration of biscuits with Fe (20 mg) associated with sulfadoxine (500 mg)+pyrimethamine (25 mg); 8. association of biscuit with Fe (20 mg), albendazole (400 mg)+ praziquantel (40 mg/kg) and sulfadoxine (500 mg)+ pyrimethamine (25 mg)	To evaluate the effectiveness of iron supplementation in relation to anthelmintic treatment and IPT of malaria to improve anemia and nutritional status	Among treatments, only regular administration of anthelmintic medications improved anemia rates ($P<0.03$). The use of fortified iron did not reduce the rate of anemia in children
Le et al., 2007	Placebo-contolled parallel trial	425	Vietnam	6	Ascariasis, trichuriasis, and hookworm	Instant noodles	Comparison between groups: 1. pasta fortified with Fe; 2. mebendazole	To evaluate changes in Fe status and anemia in anemic schoolchildren subjected to the use of Fe-fortified pasta	Iron fortification improved anemia and Fe status in anemic schoolchildren and reduced *Trichuris* rates after the study. On the other hand, deworming, despite reducing the prevalence of worm infection, had no effect on anemia rates and Fe status
Jinabhai et al., 2001	Double blind randomized placebo controlled trial	579	South Africa	4	Ascariasis, schistosomiasis, trichuriasis, and hookworm	Cookie+Fe (GP1 and GP4: 5 mg)	Comparison between groups: 1. albendazole (400 mg)+fortified biscuit (vitamin A and iron); 2. albendazole (400 mg)+fortified cookies (vitamin A); 3. unfortified deworming cookies; 4. fortified biscuits (vitamin A and iron); 5. fortified biscuits (vitamin A); 6. unwormed, unfortified cookies	Compare the efficiency of anthelmintic treatment with the combination of anthelmintic+biscuit fortification with Fe and vitamin A in improving nutritional and cognitive status ($P<0.05$)	Vitamin A fortification improved serum retinol levels, but Fe fortification did not bring significant improvement in hematimetric status. There were no significant effects on the cognition and education of the sample

GP, group; FC, fortified cereal; NaFeEDTA, sodium iron(III) ethylenediaminetetraacetate; FeFum, ferrous fumarate; IPT, intermittent preventive treatment; FePP, ferric pyrophosphate; Hb, hemoglobin; OR, odds ratio.

Reference	D1	D2	D3	D4	D5	Overall
Kugo et al., 2018	+	+	+	+	+	+
Aimone et al., 2017	!	+	+	+	+	+
Glinz et al., 2017	+	+	+	+	+	+
Teshome et al., 2017	+	+	+	+	+	+
Egbi et al., 2015	!	+	+	+	!	+
Abizari et al., 2012	!	+	+	+	+	+
Nga et al., 2011	+	+	+	+	+	+
Rohner et al., 2010	+	+	+	+	+	+
Le et al., 2007	+	+	+	+	+	+
Jinabhai et al., 2001	+	+	+	+	+	+

+ Low risk
! Some concerns
− High risk

D1 Randomization process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Fig. 2. Risk of bias summary. Review authors' judgments in each risk of bias domain for each article are included.

globin and serum iron levels and reduce transferrin receptors. The reduction in transferrin receptors is related to homeostatic mechanisms that ensure the efficient and precise regulation of intracellular iron levels in the occurrence of an increase in serum iron (Tong et al., 2002). In the studies by Le et al. (2007) and Glinz et al. (2017), the fortification of pasta and cereals with iron, respectively, effectively reduced the prevalence of iron-deficiency anemia in children living in areas that are highly vulnerable to PIs. A recent study also observed a reduction in the prevalence of anemia in children who received iron fortification (Tchum et al., 2021). The WHO encourages weekly iron supplementation to prevent iron-deficiency anemia in children living in areas of greater vulnerability (WHO, 2011, 2018).

Egbi et al. (2015) found an improvement in hemoglobin levels and a reduction in the prevalence of anemia when using vitamin C-fortified fishmeal to prevent liver damage because of excessive iron intake during treatment (He et al., 2018).

By contrast, Jinabhai et al. (2001), Rohner et al. (2010), and Teshome et al. (2017) investigated the effects of crackers and cornmeal porridge fortified with iron. They found that fortification did not improve blood parameters. These results may be explained by the fact that PIs induce inflammation of the intestinal epithelium, thereby preventing iron absorption. In such cases, pharmacotherapeutic treatment may be more effective in decreasing iron loss and anemia occurrence by reducing intestinal inflammation (Hotez et al., 2004; Ganz, 2006; Collings et al., 2013).

Our systematic review also identified studies that showed the benefits of fortified foods in reducing parasite load and controlling PIs. This is because micronutrients contribute to immune defense and a balanced diet contributes to a more effective immune response (Koithan and Devika, 2010). Le et al. (2007), Nga et al. (2011), Aimone et al. (2017), and Kugo et al. (2018) found promising results with regard to the use of fortified foods for deworming. Kugo et al. (2018) assessed the effects of iron-fortified corn porridge and papaya seeds and found a 63.9% reduction in the egg count of *A. lumbricoides*. The effects of iron fortification also seem to contribute to a reduction in *P. falciparum* infections. Aimone et al. (2017) showed that children with malaria who did not receive iron supplementation at the beginning of the study were more likely to have parasitemia at the endpoint. This micronutrient appears to exert an indirect effect on parasitic agents because of its role as an enzyme cofactor, which is necessary for regulating the proliferation of components of innate and adaptive immunity (Puig et al., 2017; Cronin et al., 2019). Le et al. (2007) showed that iron-fortified pasta was effective in deworming, leading to a 29% reduced frequency of individuals infected with *T. trichiura* and a 24% reduced prevalence of children with high immunoglobulin E levels. Nga et al. (2011) showed the effectiveness of cookies fortified with multiple micronutrients, including iron, in reducing the parasite load of *A. lumbricoides* and *Trichuris*. The mechanisms of iron contribute to deworming by regulating intracellular metabolism and the mechanisms of action of defense cells. Aside from regulating mitochondrial oxidative phosphorylation in macrophages, iron increases the proliferation and expansion of T and B lymphocytes (Cronin et al., 2019), which induce cell proliferation and increase cells' phagocytic activity (Pereira et al., 2019). Furthermore, iron has been described to induce a greater production of antibodies in individuals with viral infection (Jiang et al., 2019). Despite the beneficial effects of iron on immune response cells, iron levels in fortified foods must be controlled because excess amounts can induce oxidative stress and cell death (Vanoaica et al., 2014). By contrast, Jinabhai et al. (2001), Rohner et al. (2010), and Teshome et al. (2017) found no significant changes in deworming with the use of fortified foods. They found that only anthelmintic treatment was effective in reducing the parasite load.

The results of the present systematic review highlight the possible benefits of fortified foods, especially those fortified with iron, in improving blood parameters and promoting deworming in children with PIs. Our findings suggest that iron-fortified foods may overcome the absorption deficit of this micronutrient in the presence of intestinal mucosal inflammation (Fig. 3). PI-induced mucosal inflammation promotes interleukin-6 production by macrophages, with a consequent increase in hepcidin

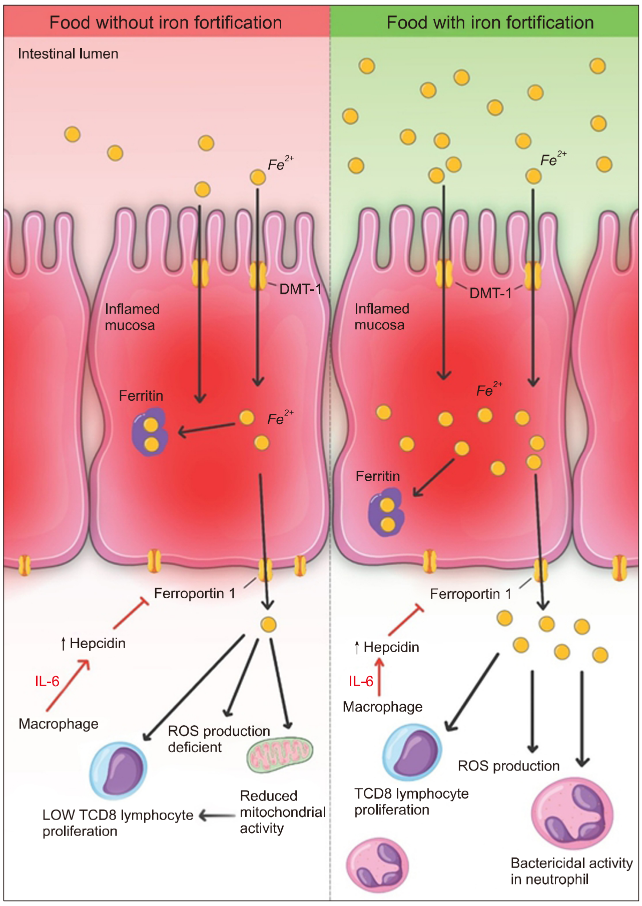

Fig. 3. Changes in iron absorption in an inflamed intestine because of parasites and adverse outcomes for the body. The figure presents a hypothetical mechanism that explains the influence of iron-fortified foods on the immune response based on the work of Ganz (2006) and Cronin et al. (2019). DMT-1, divalent metal transporter 1; IL-6, interleukin-6; ROS, reactive oxygen species; TCD8, CD8 T lymphocyte.

production. This regulatory protein appears to suppress the expression of ferroportin-1, which reduces the absorption and bioavailability of serum iron (Ganz, 2006). Thus, while individuals with PI inflammation who do not eat iron-fortified foods may have a loss in iron availability, those who eat fortified foods will have access to a high intestinal iron concentration, increasing its supply and absorption by enterocytes and its diffusion into the blood. The increased availability of iron can minimize the risks of blood-related conditions, such as iron-deficiency anemia, and increase deworming power by regulating the immune system's effector activity (e.g., lymphocyte clonal expansion, cell proliferation, increased phagocytic activity, and increased reactive oxygen species production) and inducing a greater production of antibodies that can fight against the parasite (Cronin et al., 2019). In individuals with lower iron levels, immune cell proliferation becomes deficient, phagocytic capacity is reduced because of a decrease in reactive oxygen species production, and mitochondrial energy is reduced, generating less cellular activity in the fight against the pathogen.

The studies included in this review had a low risk of bias, especially with regard to randomization and conduction of the study. This finding is of fundamental importance because it refers to the standardization and blinding of the researchers, which enables greater reliability of the data obtained.

However, considering the small number of research groups and published papers on the effects of fortified foods, especially in children, more human studies addressing this issue are needed. Despite the different results that were obtained, the use of iron-fortified foods appears to have beneficial effects, such as improving blood parameters (e.g., serum iron, hemoglobin concentration, and anemia status) in schoolchildren with PIs. Thus, an increase in the number of studies published on the subject will provide more solid evidence to reach a scientific consensus regarding this intervention.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: AWDC, FCVS, LDS. Analysis and interpretation: AWDC, FCVS, LDS, SJP, BLF. Data collection: AWDC, FCVS, LDS, MRL. Writing the article: AWDC, FCVS, LDS, MRL. Critical revision of the article: BNE, RSG, TARG, SJP, BLF. Final approval of the article: BNE, RSG, TARG. Statistical analysis: SJP, BLF, TARG. Obtained funding: BNE, RSG, TARG. Overall responsibility: BNE, RSG, TARG.

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