The Impact of Tannin Consumption on Iron Bioavailability and Status: A Narrative Review[1,2]

Nicole M Delimont, Mark D Haub, and Brian L Lindshield*

Department of Food, Nutrition, Dietetics, and Health, Kansas State University, Manhattan, KS

Abstract

Iron deficiency remains a global health issue, and antinutritional factors, such as tannins, are often cited as contributors to the high prevalence of deficiency. Despite this, tannin-rich diets may have potential beneficial cardiovascular and cancer-fighting properties because of the antioxidant activity of tannins. Furthermore, epidemiologic studies and long-term trials involving participants who consumed diets rich in antinutritional factors, particularly tannins, conflict with single-meal bioavailability studies. The purpose of this narrative review is to determine the effect of tannins on iron bioavailability and status and establish whether adaptation to tannins reduces the antinutritional effects of tannins over time. We also aimed to compare tannins used in iron studies. Common themes related to iron bioavailability and iron status with tannin consumption were collected and collated for summary and synthesis based on models and subjects used. Overall, there was dissonance between iron bioavailability and status in studies. Single-meal studies with hydrolyzable and oligomeric catechin and epicatechin tannins (tea and tannic acid) generally support reductions in bioavailability related to tannin consumption but not consumption of condensed tannin, which are more commonly found in food. Long-term animal model, epidemiologic, and multimeal studies generally do not support changes in iron status related to tannin intake. Studies suggest that long-term tannin consumption may impact iron status in a different manner than single-meal studies or bioavailability iron models predict. Furthermore, iron bioavailability studies that use condensed tannins, which are more commonly consumed, may better predict mealtime iron bioavailability. More research is needed to develop representative antinutritional iron studies and investigate mechanisms underlying the adaptation to tannins and other antinutritional factors that occur over time. CDN 2017;1:1–12.

Introduction

Iron deficiency is common worldwide, and nearly 1 billion people suffer from iron-deficiency anemia (IDA) (1). Adequate iron stores are required for normal growth and development, and IDA has been associated with loss of productivity; reduced cognitive functioning (2); increased prematurity; and perinatal, childhood, and maternal mortality (3). Whereas the WHO approximates that IDA contributes to 3% of all disability life-years lost, more recent estimates suggest that 2013 economic losses related to IDA in Indian children aged 6–59 mo alone were nearly $24 billion (4). Populations with a higher prevalence of IDA include women, children, people consuming a vegetarian or meatless diet, and those consuming insufficient amounts of iron in developing countries (1), and an estimated 30–40% of women and children <5 y of age develop IDA without iron fortification (1). Despite prevalence rates and multiple initiatives aimed at improvement of IDA, an estimated 29% of nonpregnant women were anemic in 2011, a reduction of only 4% from 1995 (5).

The absorption, incorporation, and use of iron in the body is a strictly regulated process in which the homeostatic regulation of iron is primarily mediated through absorption and recycling (6). Nearly 90% of iron stores are retained through senescent RBC recycling; nutritional intake accounts for the remaining 10% (7). Although a multitude of genetic- and disease-related factors influence the pathophysiology and prevalence of IDA (6), interest

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*To whom correspondence should be addressed. E-mail: blindsh@k-state.edu.

in its treatment has been largely focused on readily modifiable factors, such as nutritional enhancement and iron absorption inhibitors. Inhibitors found in diets rich in legumes and grains (termed "antinutritional factors") are particularly criticized as contributors to the high prevalence of deficiency in developing and low-income countries (8, 9), despite the cited health benefits of diets rich in these staples (10, 11). Antinutritional factors such as tannins and phytates in cereals have been found to negatively affect the bioavailability of minerals such as iron when consumed in large quantities (12, 13). It is accepted that tannins reduce iron availability before absorption through the formation of insoluble antinutritional-mineral complexes (14), and reported exacerbation of IDA by foods high in phytates or tannins is common (15–17). Single-meal studies have confirmed iron bioavailability inhibition with phytate (12, 18, 19) and tannin (20–22) consumption.

The term "tannin" denotes a broad class of compounds that can be further classified into hydrolysable tannins or the more commonly consumed condensed tannins (also known as proanthocyanidins) (23) (**Figure 1**). The ability of tannins to precipitate proteins has been linked to the sensation of astringency (24), and plant tannin content is linked to insect, animal, and mold resistance (25). It may be these defense mechanisms that lead to the antioxidant (26), cancer-fighting (27), and cardiovascular benefits (28) derived from the antioxidant properties of tannin-rich foods, such as wine and tea. Considering both the potential detrimental and beneficial properties of tannins, a dichotomy exists between limiting the tannin consumption of those at risk of IDA and the potential health benefits derived from tannin-rich diets.

Because of the iron absorption inhibition of tannins, prudent food system and agricultural efforts have been made to reduce the tannin content of grains, legumes, and foods in an effort to enhance the iron status of those consuming them (29). Despite this, there is a wealth of information that refutes conventional ideology that tannins contribute to chronic changes in iron deficiency. In studies that have supported a reduction in bioavailability through tannin consumption, individual iron absorption has been highly variable (30, 31), and the majority of individuals who consume diets with high concentrations of tannins, as well as antinutritional factors in general, have reported normal iron status (32, 33). Furthermore, the removal of antinutritional factors has not been shown to improve iron bioavailability (34), nor have diets rich in tannin content (35, 36).

Evidence suggests that individuals can adapt to antinutritional factors over time. Repeated consumption of antinutritional factors has been shown to blunt reductions in iron bioavailability in animal (37–39) and clinical (40, 41) models alike. Interestingly, tannins administered per rectum (42) or topically (43) have been linked to hepatotoxicity, whereas oral consumption of condensed tannins has not, suggesting that inherent defense mechanisms may exist that respond to tannin consumption over time. Although adaptation to antinutritional factors may be plausible, it is not currently well understood whether *1*) tannins at commonly consumed amounts are linked to changes in iron status, *2*) short-term tannin-mediated reductions in iron bioavailability continue over time, *3*) tannins alone (rather than consumed with phytates) reduce iron status, and *4*) single-meal study inhibition concentrations result in meaningful reductions in iron status. The focus of this review is to explore the effects of tannins on iron bioavailability and status.

Methods

Interventional and epidemiologic studies that examined the relation between tannin consumption and iron bioavailability or iron status were identified through PubMed, Web of Science, and Google Scholar databases with the use of the search terms "iron availability and/or iron bioavailability" and "tannin and/or polyphenol and/or antinutritional factors," "iron" [Mesh] and "bioavailability" [Mesh] and "tannin" [Mesh], "polyphenol," and iron bioavailability. Terms also included were "sorghum and/or tea" because of the common citation of these tannin-containing factors on iron bioavailability. In addition, the method of snowball article collection (citations from relevant journal articles) was also used.

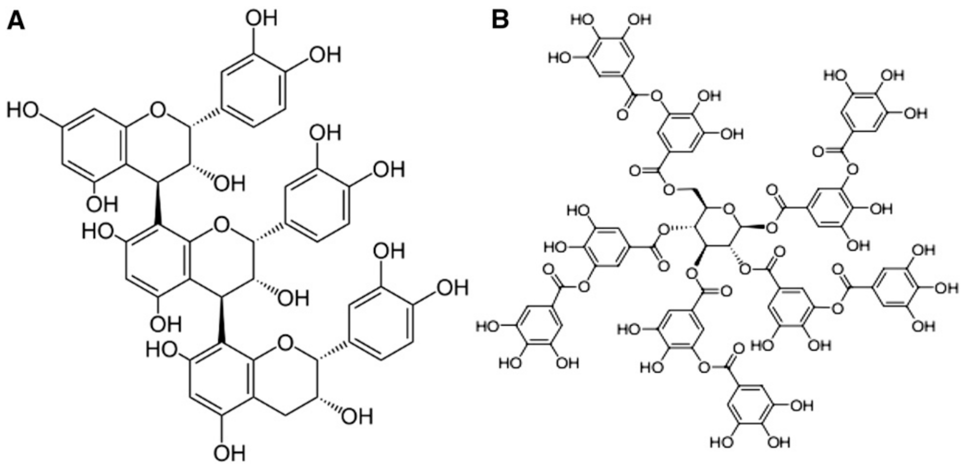

Figure 1 Condensed tannin (A). Tannic acid (B). Panel A is reproduced from https://commons.wikimedia.org/wiki/File:Tannic_acid.svg. Panel B is reproduced from https://commons.wikimedia.org/wiki/File:Procyanidin_C1.svg. Both images are in the public domain.

In vivo articles were included that gave some indication of bioavailability and iron status at the end of the study. Studies excluded were ecological, rather than human nutrition application, in vitro, or focused on special populations (genetically defined illness), or did not attempt to quantify the effects of tannins alone when consumed with other antinutritional factors.

Results

The original search terms generated 497 articles, which were narrowed first by inclusion of ≥2 search terms (*n* = 217). Exclusions for in vitro studies (*n* = 133), review articles (*n* = 38), and specialized populations (*n* = 9) were conducted during abstract reviews. A second abstract review excluded studies for manual combing of duplicates (*n* = 34). A full article review of the 64 remaining studies was conducted, and further exclusion for noniron outcomes (*n* = 13), as well as lack of direct assessment of the effects of tannins on iron status (*n* = 16), were applied. In total, 37 studies were reviewed (**Figure 2**).

Animal studies

Animal studies that used tea to measure the inhibition of iron status or bioavailability often exceeded or met amounts that could be expected in common consumption. For example, 1 cup of tea may contain ∼25–80 mg tannins per 150 mL (21, 22), and 3 cups of tea/d would mean consumption of anywhere from 75 to 240 mg tannins/d. Most studies exceeded this, especially when accounting for allometric dosing in animals. Many studies that have isolated the influence of tannin consumption over time without confounding antinutritional factors have been in animals. Without confounding factors, comparison of tissue-level iron depletion or repletion, and direct comparison between bioavailability and iron status with tannin consumption was possible.

Studies that support reduced iron bioavailability and/or iron status in animals consuming tannins over time

Studies that support reductions in iron bioavailability and/or iron status in animal models have typically used tannic acid or tea as study interventions (**Table 1**). The consumption of 100 g green tea polyphenols/L compared with water consumption in rats over 8 wk (46) resulted in a significant reduction in hepatic iron and hemoglobin (25% and 10%, respectively), although food intake was also significantly reduced. In a 28-d pig study, consumption of 125, 250, 500, or 1000 mg tannic acid/kg in feed resulted in a significant and linear depletion of serum iron concentrations, as well as hemoglobin. In this study, there was a significant decline in erythrocyte counts, hemoglobin, and hematocrit seen in the control group that was similar to the groups consuming 125, 250, and 500 mg/kg diet, and mean corpuscular volume was unaffected by tannic acid consumption (45). Interestingly, there were significant reductions in gain-to-feed ratios seen on days 0–14 that were normalized during days 15–28, suggesting adaptation to the diets over time. Serum and hepatic iron concentrations were significantly reduced in rats that consumed diets containing 5%, 10%, 15%, or 20% tannic acid/kg for 3 wk (44), but there were no significant differences in other tissue iron concentrations, body weight gain, or food intake with increasing tannin doses. Despite reductions in iron stores, rats that consumed tannic acid in weeks 2 and 3 had nonsignificant improvements in hematocrit concentrations, possibly suggesting adaptation or demand-facilitated increases in uptake to blunt iron losses. Another depletion-repletion rat study that used a bean ragout meal with green or black tea compared with water for 14 d found that iron bioavailability and change in hemoglobin decreased significantly with tea intake when iron and food intake were similar, but hepatic iron and total hemoglobin concentrations were not significantly different at study end (47). In a study that examined the effects of a habituated compared with a black tea–naïve diet on iron bioavailability in rats (*n* = 6), iron bioavailability, along with final body weight and food consumption, of rats consuming a powdered

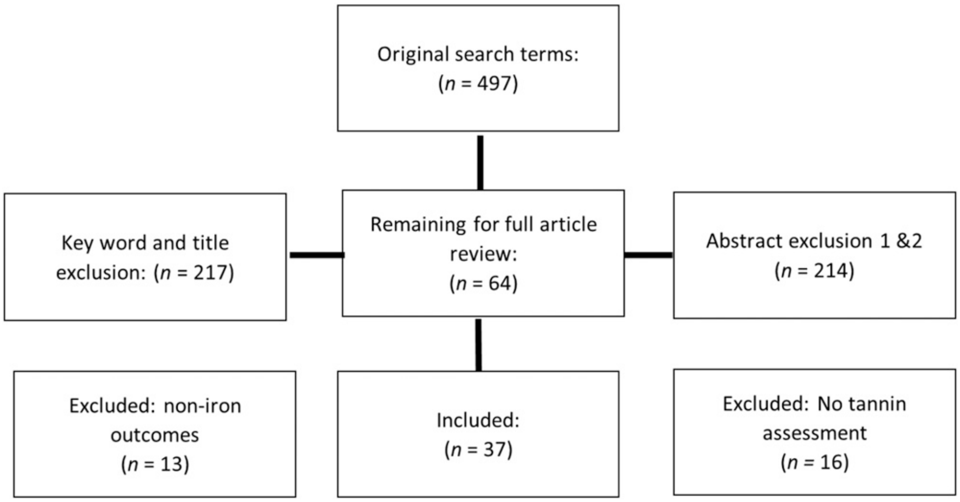

Figure 2 Inclusion and exclusion criteria for review. Articles were excluded on the basis of key terms, in vitro analysis, lack of tannin assessment in dietary analysis, and analysis of noniron outcomes.

Table 1 Studies reporting reductions in iron bioavailability in animal models

Reference	Subjects, *n*	Model	Intervention	Tannin type	Intervention length	Outcome
44	6	Rat	5, 10, 15, and 20 g tannin/kg diet vs. control	Tannic acid	3 wk	Significant linear reduction in hemoglobin (≤27%) and hepatic (≤61%) iron concentrations with tannic acid consumption.
45	9	Pig	125, 250, 500, and 1000 mg tannin/kg diet vs. control	Tannic acid	4 wk	Significant linear reduction in hemoglobin (≤21%; $P = 0.028$) and serum (29%, $P = 0.12$) iron concentrations with tannic acid consumption.
46	7	Rat	100 g tea consumption vs. 100 g tea (beverage) with various concentrations of aluminum and control	Green tea	8 wk	Significant reduction in hemoglobin (11.0 vs. 10.0 g/L; 9% reduction) and hepatic (750 vs. 250 μg/liver; 71% reduction) iron with tea consumption vs. control.
47	8	Rat	Green or black tea decoction with bean ragout meal vs. meal alone	Green or black tea	14 d	Significant depletion of hemoglobin (−1.1 and −0.95 g/L with black and green tea, respectively) and iron bioavailability (19.6% and 14.9% with black and green tea, respectively) vs. control during the study. Normal hepatic iron in tea groups vs. control (65, 89.4, and 66.3 μg/g in control, black tea, and green tea groups).
48	6	Rat	Black tea powdered diet as 25 g/kg vs. control	Black tea	12 d	Significant reduction (26%) in iron absorption vs. control, although there was a significant increase over time (24% vs. 42% at baseline and end line in tea consumers). No reduction in hepatic iron concentrations.

black tea diet was significantly reduced compared with control, although hepatic iron stores were normal (48). In the group consuming tea long term, food intake and iron bioavailability from baseline to end line significantly improved over time, suggesting adaptation.

Studies that support no differences in iron bioavailability or status with tannin consumption over time

Many animal studies have not reported differences in iron status after the consumption of tannin-rich diets by these animals (**Table 2**). In iron-replete and -depleted rats that consumed a diet containing 20 mg condensed tannin/kg body weight plus phytoferritin for 4 wk in a hemoglobin depletion-repletion model, a significant reduction in hemoglobin, weight gain, and serum iron in the rats that consumed condensed tannins plus phytoferritin compared with the rats that consumed phytoferritin alone was observed (50). Despite reductions in overall iron absorption, ferritin was not reduced, rats were not iron deficient, and they achieved iron repletion that was similar to control while consuming condensed tannins with adequate iron intake. Food intake was not measured in this study. It is important to note that anemic rats that consumed condensed tannins died by study end, pointing to toxicity at the daily dose of 20 mg/kg. In both 16-d and 30-d rat studies that compared 0.35%, 1.17%, or 3.50% black tea consumption or a green tea oral and powdered diet (daily dose of 20 mg/kg) with control diets, there were no differences in tissue iron concentrations or hemoglobin at study end (38, 49). In the study that used a green tea challenge, iron absorption was similarly unchanged among tea consumers compared with control without changes in body weight or feed intake (38). A study in weanling rats looked at differences in iron availability with condensed tannin in habituated compared with naïve rats. There were no significant differences between habituated and naïve rats' iron status at study end (51). A 4-wk hemoglobin depletion-repletion study in piglets that consumed meals with significantly different tannin amounts from red or white bean feed found no differences in hemoglobin, hemoglobin repletion-efficiency (hemoglobin replaced per iron intake), or weight gain at endpoint (36). Interestingly, this study did find initial downward trends in hemoglobin repletion efficiency on day 7 (49.9% compared with 55.6% in red compared with white bean consumers, respectively) that were compensated for by endpoint, potentially indicating adaption to tannin consumption over the study period. In pigs that consumed polyphenol-rich diets containing grape meal or hops compared with a control diet for 4 wk, there were no significant differences in plasma iron, total iron binding capacity, transferrin saturation, tissue iron, or fecal iron compared with control (52).

Human studies

Although many studies have linked tannin consumption to iron bioavailability, there is a paucity of human studies directly examining the relation between tannin intake and iron status. Studies are presented by their methodology to accurately portray the information available from the design. Single-meal studies that used tea often used a standard dose of 150–300 mL tea, whereas the majority of studies that used condensed polyphenols exceeded the 75–240 mg polyphenol/d that could be expected with tea consumption 3 times/d (21, 22).

Table 2 Studies reporting no or inconsistent reductions in iron bioavailability or iron status in animal models[1]

Reference	Subjects, *n*	Model	Intervention	Tannin type	Intervention length	Outcome
49	6	Rat	Control vs. various types of tea in food	Black tea	16 d	No significant differences in iron absorption or hepatic iron vs. control.
38	6	Rat	Green tea diet or gavage vs. control	Green tea	30 d	No significant differences in iron absorption (3.7% vs. 5.6% over time and 43% vs. 63% in control vs. tea, respectively; $P = 0.292$) or hepatic iron (60.9 vs. 54.2 μg Fe/g liver, control vs. tea, respectively; $P = 0.521$) vs. control.
50	10	Rat	Meal with phytoferritin vs. condensed tannins (PA) and phytoferritin	Condensed tannins	4 wk	Significant reduction in hemoglobin (11.9 vs. 10.0 g/L, respectively) and serum iron (10.33 vs. 21.43 μmol/L, respectively) for control vs. proanthocyanidins. Iron repletion and ferritin (23.4 vs. 20.98 ng/mL, respectively) not significantly different from no-proanthocyanidin group.
51	7	Rat	Meals consisting of casein, soy, chickpea, or red kidney bean flour	Condensed tannins	1 wk	No significant differences in iron retained, total hemoglobin in rats consuming meals containing various amounts of polyphenols vs. control; no differences in iron retention between high- and low-tannin kidney bean meals.
52	16	Pig	Grape meal– and hops-based diets vs. control	Condensed tannins	4 wk	No significant differences in iron, TIBC, transferrin, hepatic iron, and fecal iron between groups.
36	8	Pig	Red- vs. white-bean meals	Condensed tannins	4 wk	No significant difference in hemoglobin/hemoglobin repletion efficiency in white and red beans (26% vs. 30%, respectively).

[1] PA, proanthocyanidins; TIBC, total iron binding capacity.

Epidemiologic studies

The majority of epidemiologic studies that included isolated tannin-iron interactions focused on tea consumption and did not find an influence of tea consumption on iron status (**Table 3**). One study collected two 24-h recalls from 173 premenopausal parous Indian women, and found that in multiple regression analysis, tannin intake was not a significant regression factor correlated with anemia (53). Similarly, tea consumption in 2573 French men (*n* = 954) and women (*n* = 1639) had no influence on iron status (55). Another cross-sectional study with 157 Indian participants did not find differences in anemia prevalence between men and women who consumed diets that contained high and low tannin amounts (54). Notably, condensed tannin and polyphenol consumption varied widely in these studies (from 36 mg tannin/d to >5000 mL tea/wk); however,

Table 3 Epidemiologic study outcomes related to iron status[1]

Reference	Subjects, *n*	Intervention	Analysis	Tannin type	Conflation of phytates	Iron status affected?
53	173	Two 24-h recalls	Multiple regression	Dietary tannin including tea and other polyphenols	Yes	No IDA correlated with tannin intake. No significant effect in regression model.
54	143	24-h diet recall	Multiple regression	Dietary tannin including tea and other polyphenols	Yes	No significant IDA correlation with tannin intake.
55	1639	Three 24-h diet recalls, venous blood draw	Multiple regression	Black, green, and herbal tea	Yes	IDA or marginal iron status not correlated with tannin intake (ferritin 48, 50, and 49 vs. 50, 47, and 46 μg/L in control group and regular black, green, and herbal tea drinkers, respectively; $P = 0.71$, 0.34, and 0.36 in premenopausal women with green, black, and herbal tea, respectively).

[1] IDA, iron-deficiency anemia.

Table 4 Single-meal bioavailability studies showing reductions in iron bioavailability with tannin consumption[1]

Reference	Subjects, *n*	Iron status	Population	Intervention	Tannin type	Outcome
20	10	Replete	Women	Control meal with water vs. meal with tea	Black tea	Significant reduction in iron bioavailability by 20%.
56	10	Replete and depleted	Men and women	Oregano, spinach, coffee, tea, or tannic acid vs. control	Black tea, tannic acid, polyphenols/condensed tannin	Tannic acid significantly reduced iron bioavailability; oregano, tea, and coffee percentage inhibited bioavailability by >60%, which was less than their respective equivalent tannic acid doses. Spinach reduced bioavailability by 30% despite tannic acid equivalents similar to its tannic acid, tea, coffee, and oregano counterparts.
57	6 (C), 13 (I)	Replete	Men and women	High- vs. low-availability meal in vegetarians vs. nonvegetarians	Polyphenols/condensed tannin	Significant impairment of iron absorption from low-bioavailability meals in vegetarian and nonvegetarian consumers. Similar iron bioavailability between vegetarians (1.4% vs. 14.9% in bran vs. whole-wheat rolls, respectively) and nonvegetarians (22.3% vs. 2.2%) despite higher average phytate intake in vegetarian group.
22	10	Replete and depleted	Women	Meal with black tea or ascorbic acid, or control meal	Black tea	Significant reduction in iron bioavailability with tea consumption (18.2% vs. 7.1% in control vs. 150 mL tea drinkers, respectively, and 19.7% vs. 5.6% in control vs. 300 mL tea drinkers, respectively), not dependent on polyphenol burden (1 vs. 2 cups tea).
58	8	Replete and depleted	Men and women	10 different beverages	Black tea, herbal tea, cocoa, or coffee	Significant reduction in iron bioavailability with tannin consumption (tea); range in reductions for tea vs. water: 3–27%, dependent on whether food consumed.
59	13	Replete and depleted	Men and women	Control breakfast vs. coffee or tea	Black tea, polyphenols	Significant reduction in bioavailability with tea or coffee consumption vs. control (60–90% reduction vs. control; average 10% less iron absorbed).
60	22	Replete	Women	Control meal vs. meal with tea	Black tea	Nonsignificant differences in iron absorption with tea consumption (reduction 1.7%), although effects of tea noted with ascorbic acid consumption (20% reduction vs. ascorbic acid alone).
61	8	Replete	Women	Broccoli with tannic acid (500 mg) or broccoli alone	Tannic acid	Significant reduction (10% vs. 0.3%) in iron absorption for broccoli meal vs. broccoli + tannic acid meal.

(Continued)

Table 4 (*Continued*)

Reference	Subjects, *n*	Iron status	Population	Intervention	Tannin type	Outcome
31	14 (C), 15 (I)	Replete	Women	Control meal with 5 mg $FeSO_4$ vs. tannic acid, phytic acid, or pectin	Tannic acid	16–25% significant reduction in iron absorption with tannic acid vs. no tannin consumption.
62	10 (C), 16 (I)	Replete	Women	Bread baked with tannic acid (12–884 mg) vs. control	Tannic acid	Significant reduction in iron absorption ratio and serum iron with consumption of tannic acid in bread (average reduction of iron absorbed, 3–10%).
16	10 (C), 11 (I)	Replete	Men	Meal with varying amounts of tannin-rich condiment [yod kratin (a vegetable); 0–584 tannic acid equivalents] to control	Polyphenols/condensed tannins	10% significant reduction in iron bioavailability with highest tannin content meal vs. control.

[1] C, control; I, intervention.

none of them found an impact from tannin consumption amounts on iron status.

Single-meal studies

Since the 1970s, researchers have found statistically significant reductions in iron absorption measurements with tannin consumption in single meal studies. The majority of these studies have been in iron-replete individuals, both male and female, who consumed a meal with tannin compared with a meal alone. Almost all single-meal bioavailability studies use radioactive iron, most use hemoglobin incorporation, and fewer use direct measurement of iron absorption through AUC serum iron concentrations to understand iron uptake. In addition, most studies have used iron absorption ratios to compare tannin-containing meals with control.

In premenopausal anemic and nonanemic Indian women ($n = 10$) who consumed either 200 mL black tea or warm tap water with a control meal on 2 consecutive days reduced iron absorption by 21%, although this inhibition was reduced when tea was consumed with milk (20). Since then, these findings have been supported in a variety of foods, but generally, reductions in iron bioavailability with tannin consumption are linked to consuming black tea (**Table 4**) (22, 56–63). These studies all reported notable iron absorption variability between participants. Furthermore, iron absorption between studies varied, from as little as 1% (64) to as much as 50% (31), pointing to the wide variability in maintenance of iron homeostasis through iron absorption.

Contrary to the previous studies mentioned, other single-meal studies in men and women have suggested that tannin consumption alone, particularly condensed tannins, may not contribute to reductions in iron bioavailability (**Table 5**). One study in anemic and nonanemic Indian men found that although there was a 5.2% reduction in iron absorption after consumption of a phytate- and tannin-rich sorghum meal (20 compared with 136 mg/100 g and 160 compared with 273 mg/100 g tannin and phytates in low- and high-tannin meals, respectively), there was no significant difference in iron absorption when meals were normalized for phytic acid ($n = 12$; 4.0% compared with 3.1% iron absorption in low- and high-tannin meals) (35). A comparison of red and white cowpea meals resulted in no differences in iron bioavailability with a 2-fold increase in tannin amounts in premenopausal Dutch women (66). Another study found that, despite similar tannic acid equivalents, spinach consumption resulted in a 2-fold increase in iron bioavailability compared with the consumption of black tea ($n = 9$ and 5, respectively) in 19- to 51-y-old Swedish men and women (56). Other studies have reported minimal (16, 60, 64) or no impact on iron bioavailability (65), or enhanced uptake of iron absorption (67) with tannin consumption.

Phytate content may conflate findings in these studies. Women who consumed low-polyphenol beans (29 compared with 180 mg/100 g in low- compared with high-polyphenol beans) did not significantly increase their iron absorption, whereas high-phytate beans significantly reduced iron bioavailability ($n = 20$) (68). Similarly, adding polyphenol oxidase to high tannin sorghum meals did not improve iron bioavailability in iron-replete women who consumed them, suggesting that tannins were not the cause of reduced iron bioavailability ($n = 16$ and 18, respectively) (63).

Long-term and multimeal clinical studies

To our knowledge, few multimeal antinutritional-factor iron bioavailability studies have been conducted (**Table 6**). In 19- to 32-y-old German vegetarian ($n = 6$ and 8 in black and green tea groups, respectively) and omnivorous ($n = 10$, both groups) men and women who consumed green or black tea for 4 wk, ferritin was significantly decreased in omnivorous women who consumed black tea, as well as in a subgroup analysis of anemic women who consumed black or green tea. There were no changes in ferritin in men and nonanemic vegetarian women who consumed tea, nor did total iron binding capacity, hemoglobin, serum iron, or hematocrit change in groups from baseline to end line (69). In a study that compared the iron status of Indian men and women aged 20–25 y ($n = 46$), polyphenol-rich diets that contained leafy green vegetable supplements did not significantly affect individuals' hemoglobin concentrations after 3 wk of supplementation compared with those consuming a control meal with no leafy green vegetables (70).

Table 5 Single-meal bioavailability studies showing no or minimal reductions in iron bioavailability with tannin consumption[1]

Reference	Subjects, *n*	Iron status	Population	Intervention	Tannin type	Outcome
64	14	Replete	Women	Meal with green tea, meal with rosemary extract, and control meal	Green tea or polyphenols	No significant differences in iron absorption: 12.1% vs. 8.9% (control vs. green tea, respectively) and 7.5% vs. 6.4% (control vs. rosemary oil, respectively).
65	8	Replete and depleted	Men and women	Meal with orange juice or tea vs. control (water)	Black tea	No significant differences in iron bioavailability between tea and control or ascorbic acid and control.
35	7 (D), 12 (R)	Replete and depleted	Men	Vegetable and low- or high-tannin sorghum roti	Polyphenols/ condensed tannins	Significant 5.2% reduction in absorption of iron in anemic men, normalized and nonsignificant when adjusted for phytates (0.83%). No significant difference in iron-replete men (5.05% vs. 3.81% in low- and high-tannin sorghum, respectively).
63	16 (C), 18 (I)	Replete	Women	Meal with white vs. polyphenol-rich sorghum	Condensed tannins	5.2% and 5.8% significant reduction ($P < 0.001$) in iron bioavailability from high- or medium-tannin sorghum vs. low-tannin sorghum. No differences noted with polyphenol oxidase addition to meal.
66	16	Replete	Women	Meal containing red or white cowpea	Condensed tannins	No significant differences in iron bioavailability between red and white cowpea (both groups 11%, $P = 0.69$).
67	16	Replete	Men and women	Maize meal vs. algae-containing maize meal	Polyphenols/ condensed tannins	Dose-dependent significant enhancement of iron bioavailability with algae polyphenols (6.8–17.8% more iron absorbed with algae vs. maize meal).
68	20	Replete and depleted	Women	2 × 2 factorial structure with low-phytate, low-polyphenol, high-phytate, or high-polyphenol bean meals	Polyphenols/ condensed tannins	Polyphenol-rich, low-phytate beans nonsignificantly increased iron bioavailability (6.14%; 95% CI: 2.57%, 14.65% vs. 3.99%; 95% CI: 1.83%, 8.71%) vs. low-polyphenol, low-phytate beans, respectively. High-phytate beans significantly reduced iron bioavailability (6.14%; 95% CI: 2.57%, 14.65% vs. 3.84%, 1.76%, 8.38%).

[1] C, control; D, depleted; I, intervention; R, replete.

Confounding antinutritional diet factors make intervention increases in tannin consumption alone difficult. Two studies followed 31 healthy men aged 32–56 y (40) and, later, 36 premenopausal women (71) consuming a high- or low-bioavailability diet for >12 wk. High-bioavailability diets consisted of meat and poultry, refined cereal and grain products, no coffee or tea, and foods with >75 mg ascorbic acid in each meal, whereas low-bioavailability diets consisted of whole grains, with limited meat, tea, and 60 mg ascorbic acid equivalent/d. The iron and calcium content of the diets were similar, and researchers conducted two 24-h iron absorption studies that compared iron bioavailability between the 2 groups before and after the study period was complete. Although the tannin burden of the diets was not measured, it was noted that the absorption efficiency of the low-bioavailability diets significantly increased over time, whereas the absorption efficiency of the high-bioavailability diets decreased (40, 71). This was supported by a 2015 study, where marginally iron-deficient women who consumed a high-phytate (and -tannin, although this was not measured) diet for 8 wk ($n = 16$) significantly increased iron absorption from a high-phytate test meal, whereas iron absorption in consumers of a low-phytate diet was nonsignificantly decreased. In this study, the iron status of consumers was not changed by high- or low-phytate diets (41).

Table 6 Long-term studies investigating the impact of tannin consumption on iron bioavailability[1]

Reference	Subjects, *n*	Iron status	Intervention	Tannin type	Intervention length	Outcome
69	9 (D), 25 (R)	Depleted and replete	Green or black tea supplementation in either vegetarian or omnivorous participants	Green or black tea	4 wk	Significant decrease in ferritin in anemic and omnivorous women consuming black tea without change in TIBC, Hb, or serum iron.
70	11 (C), 12 (I)	Replete	Leafy green vegetable supplementation vs. standard meal	Polyphenols/condensed tannins	3 wk	No significant inhibition of iron bioavailability after supplementation of meal with tannin vs. control; significant increase in Hb by 11% vs. baseline with leafy vegetable intake.
40	14 (C), 17 (I)	Replete	High- or low-bioavailability diet	Polyphenols/condensed tannins	12 wk	Trends toward increases in bioavailability of low-bioavailability diet over time with reduction in bioavailability of high-bioavailability diet. No significant differences in nonheme iron absorption between groups at study end.
71	9	Replete	High- or low-bioavailability diet	Polyphenols/condensed tannins	12 wk	Significant 8.8% greater iron absorption efficiency in high-bioavailability group ($P < 0.0001$) vs. low-bioavailability group.
41	16	Depleted	High- or low-phytate diet with high-phytate diet challenge at baseline and endpoint	Polyphenols/condensed tannins	8 wk	Significantly increased uptake of iron in high-phytate diet (29.3% increase) despite no changes in iron markers (ferritin, TIBC, and hepcidin) vs. low-phytate group. Decrease in absorption of iron to high phytate meal with low phytate–consuming group.

[1] C, control; D, depleted; Hb, hemoglobin; I, intervention; R, replete; TIBC, total iron binding capacity.

Discussion

The effect of tannins on iron bioavailability

The studies reviewed that noted reductions in iron bioavailability with tannin consumption commonly used hydrolyzable tannins (tannic acid) or epicatechin and catechin monomers, dimers, and oligomers found in tea. Animal or single-meal studies that resulted in significant reductions in iron bioavailability or iron status almost exclusively used tannic acid (31, 45, 44, 61, 62), a mixture of hydrolyzable gallo-tannins that are virtually absent from our diet (23), or tea (20, 22, 46, 47, 49, 56, 58, 60), which contains thearubigins and a low density of condensed tannins found in most foods (72). Of the studies reviewed, only 4 that used condensed tannins supported reductions in iron bioavailability during single meals (of 16 total). No studies reviewed that used multimeal animal or clinical models or epidemiologic analysis found reductions in iron status or bioavailability with condensed tannin consumption, which may point to a limitation of single-meal studies in assessing iron bioavailability and status for long-term outcomes. This could highlight the importance of using condensed rather than hydrolyzable tannins or tea to assess the bioavailability of iron in tannin-containing meals. It is also interesting to note that some significant findings have used polyphenol beverages, rather than food, which may increase the tannin-iron interaction in the food matrix (24). Plants such as sorghum contain proteins rich in proline, similar to salivary proteins that may protect consumers from the antinutritional properties of tannins (24). It may be that the consumption of such plants may result in an inherent mediation of tannin-nutrient binding with whole plant or food consumption, not found with tannin extracts or beverages. Phytic acid may be another factor that affects outcomes describing tannin-induced reductions in iron availability, considering the negation of antinutritional effects in the setting of normalized phytate concentrations found in 2 studies reviewed (35, 68).

It may be important to also consider outcome measures from single-meal studies. Although several single-meal studies reviewed noted reductions in iron bioavailability, these findings were often nonsignificant until data were adjusted into iron absorption ratios. Often, total iron absorption differences were

<10% between tannin consumers and nonconsumers, which may not affect iron status in the long term. This is an important normalizing factor, given the wide variability of iron absorption, but it may point to significant outcomes that make little meaningful impact on iron status when tannin-rich diets are consumed over time. It is similarly important to take into consideration population, iron status, and study design when determining whether this research will result in meaningful outcomes in the context of global nutrition. Studies that consider iron bioavailability from iron-replete and -depleted populations, in which intervention order is fully randomized, may carry more significant weight in this context.

Effect of tannins on iron status

Although tannin consumption impairs iron bioavailability, the majority of epidemiologic and long-term human studies reviewed did not support reductions in iron status with the consumption of tannin-rich diets over time. In epidemiologic studies, tannin compounds that inhibit iron bioavailability in single-meal studies were not correlated with iron status changes (55) or iron deficiency (53, 54). Furthermore, studies lasting ≥4 wk that focused on tannin-rich foods did not find alterations in iron status (69, 70). Some animal (38, 48) and human (40, 41) studies that were reviewed point instead to the idea of long-term adaptation to antinutritional factors, including tannins. It is important to note that these findings are obscured by several factors, including lack of control of concurrent antinutritional or iron-enhancing factors in diets, as well as assessment of iron deficiency, rather than adequate iron stores. More importantly, to the best of our knowledge, there are few studies that have looked into long-term antinutritional effects on either iron bioavailability or iron status, and no studies that we found isolated the effects of condensed tannin consumption over time.

Conclusions

The focus of this review was to determine the effects of tannins on iron bioavailability and status, and investigate whether possible adaptation to tannins could reduce the antinutritional effects of tannin consumption over time. Evidence from animal and single-meal studies suggests that tannic acid and tea consumption more consistently impair iron bioavailability than does the consumption of condensed tannins, although the connection between these studies' findings and individual iron status is not established. Certain tannins may inhibit iron bioavailability, but a lack of long-term studies and confounding factors in most studies reviewed that assess the effects of tannins limit generalizability. In addition, epidemiologic studies and long-term trials reviewed suggest that the iron status of individuals is often not affected by tannin consumption, although there is a dearth of this type of research conducted compared with single-meal studies. Future studies focusing on the long-term effects of condensed tannins (proanthocyanidins) on iron status are needed to determine their impact on iron bioavailability and status, and whether adaptation is the missing piece to explain the inconsistency between single-meal and longer-term studies. In addition, further studies are needed to characterize the adaptation mechanism.

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