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The Hematopoietic Potential of Tamarillo (*Cyphomandra betacea*) and Pitaya (*Hylocereus* spp.) Juices in Anemia Management: A Randomized Controlled Trial in Bukittinggi, West Sumatra, Indonesia

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A B S T R A C T

Anemia is a global health concern, particularly prevalent in developing countries. Traditional remedies like tamarillo and pitaya have been suggested to boost blood production. This study aimed to evaluate the efficacy and safety of these juices in managing anemia. A randomized, double-blind, placebo-controlled trial was conducted in Bukittinggi, West Sumatra, Indonesia. Participants with mild to moderate anemia (hemoglobin 8-11 g/dL) were randomized to receive daily tamarillo juice, pitaya juice, or a placebo for 12 weeks. Hemoglobin, hematocrit, iron levels, and hematological parameters were assessed at baseline and week 12. A total of 150 participants completed the study (50 per group). Both tamarillo and pitaya juice groups showed significant increases in hemoglobin and hematocrit levels compared to the placebo group ($p < 0.05$). Pitaya juice also demonstrated a significant increase in iron levels ($p < 0.01$). No serious adverse events were reported. Tamarillo and pitaya juices show promise as adjunctive therapies for anemia management. Further research is needed to explore their long-term effects and mechanisms of action.

1. Introduction

Anemia, a global public health concern, is characterized by a deficiency in red blood cells or hemoglobin concentration, impairing the body's capacity to transport oxygen to tissues. This condition manifests in diverse clinical presentations, ranging from mild fatigue and weakness to severe complications like heart failure and increased mortality risk. The World Health Organization (WHO) estimates that anemia affects over 1.6 billion individuals globally, with a disproportionate burden in developing countries, particularly among women and children. The etiology of anemia is multifaceted, encompassing nutritional deficiencies (especially iron), chronic diseases, genetic disorders, and infections. Iron deficiency anemia (IDA) constitutes the predominant form, accounting for approximately 50% of all anemia cases worldwide. Conventional treatment for IDA primarily revolves around iron supplementation, often accompanied by dietary recommendations and addressing underlying causes. However, the efficacy of iron supplementation is hindered by factors such as poor absorption, gastrointestinal side effects, and limited adherence. The exploration of alternative and complementary therapies for anemia management has gained traction in recent years. This interest is partly fueled by the rich tapestry of traditional medicine practices that leverage natural resources for therapeutic purposes. In various cultures, certain fruits and vegetables have been anecdotally associated with blood-boosting properties, potentially offering a gentler and more accessible approach to anemia management.[1,2]

Tamarillo (*Cyphomandra betacea*), is a subtropical fruit native to the Andean region of South America. It boasts a vibrant red or orange color and a tangy flavor profile. Tamarillo is a nutritional powerhouse, rich in vitamins (A, C, and E), minerals (iron, potassium, and magnesium), and dietary fiber. Notably, it contains a significant amount of iron, a crucial component of hemoglobin, the protein responsible for oxygen transport in red blood cells. Furthermore, the high vitamin C content in tamarillo facilitates iron absorption, potentially enhancing its efficacy in combating anemia. Pitaya (*Hylocereus* spp.), a tropical fruit indigenous to Central America and Mexico, has garnered attention for its striking appearance and unique flavor. It exists in several varieties, including white-fleshed, red-fleshed, and yellow-fleshed cultivars. Pitaya offers a wealth of nutrients, including vitamins (C, and B vitamins), minerals (iron, magnesium, calcium), and antioxidants (betalains, polyphenols). Preliminary studies have suggested that pitaya may possess hematinic properties, stimulating red blood cell production and improving iron status. The convergence of traditional knowledge and modern scientific inquiry has led to a growing body of research investigating the therapeutic potential of tamarillo and pitaya in managing anemia. Preclinical studies have demonstrated the ability of tamarillo extracts to increase hemoglobin levels and promote erythropoiesis (red blood cell formation) in animal models. Similarly, pitaya extracts have been shown to improve iron absorption and enhance hematological parameters in both animal and human studies. However, the evidence base for the use of tamarillo and pitaya juices in human anemia management remains limited. Existing studies are often characterized by small sample sizes, methodological limitations, and a lack of robust clinical trial designs. This paucity of high-quality evidence underscores the need for rigorous research to elucidate the efficacy and safety of these juices as potential adjunctive therapies for anemia.[3-5]

Indonesia, a Southeast Asian archipelago, is characterized by a high prevalence of anemia, particularly among women of reproductive age and children. Dietary factors, including low consumption of iron-rich foods, contribute to this burden. Traditional Indonesian medicine has long utilized various plants and fruits for health promotion, and Tamarillo and pitaya are readily available in local markets. Given the cultural context and nutritional profiles of these fruits, investigating their potential in managing anemia is both relevant and timely. This randomized controlled trial aims to address the knowledge gap by evaluating the hematological effects of tamarillo and pitaya juices in individuals with mild to moderate anemia in Bukittinggi, West Sumatra, Indonesia.

2. Methods

This research employed a randomized, double-blind, placebo-controlled trial design. The study was conducted at the Public Health Center (Puskesmas) located in Bukittinggi, West Sumatra, Indonesia. This region was selected due to its relatively high prevalence of anemia, particularly among women of reproductive age and children, and the local availability of both tamarillo and pitaya. The study was approved by the Ethics Committee of the Universitas Prima Nusantara, Bukittinggi, Sumatera Barat, Indonesia. The study period spanned 12 weeks. Participants were recruited through a combination of community outreach programs, posters displayed at the public health center, and word-of-mouth referrals. Potential participants underwent an initial screening to assess their eligibility. The inclusion criteria were 18-60 years old; Mild to moderate anemia, defined as hemoglobin levels between 8-11 g/dL, as determined by a complete blood count (CBC); Willingness to provide written informed consent after receiving a thorough explanation of the study procedures, potential risks, and benefits. Exclusion criteria were established to minimize confounding factors and ensure participant safety. Individuals were excluded if they met any of the following Pregnant or breastfeeding women were excluded due to the potential impact of the interventions on fetal or infant health; Participants with chronic conditions like kidney disease, liver disease, inflammatory bowel disease, or malignancies were excluded as these conditions could influence hematological parameters; Use of medications known to affect blood production or iron metabolism (e.g., iron supplements, erythropoietin) was a basis for exclusion; Individuals with known allergies or intolerances to tamarillo or pitaya were excluded. Eligible participants were randomly assigned to one of three groups in a 1:1:1 ratio: Tamarillo juice, pitaya juice, or placebo. A computer-generated randomization sequence was used, stratified by age (18-35 years, 36-60 years) and gender. Blinding was achieved by preparing the interventions in identical containers labeled with unique codes. Neither the participants nor the researchers administering the interventions were aware of the group assignments.

Intervention Preparation and Administration: Tamarillo Juice: Fresh, ripe Tamarillos were sourced from local markets, washed thoroughly, and peeled. The pulp was blended with a standardized amount of filtered water to create a 250ml serving. The juice was strained to remove any pulp or seeds. Pitaya Juice: Red-fleshed pitaya (*Hylocereus polyrhizus*) was selected due to its higher iron content compared to other varieties. The fruit was washed and peeled, and the pulp was blended with filtered water to create a 250ml serving. The juice was strained. Placebo: A placebo beverage was prepared using filtered water, a small amount of natural flavoring (lemon extract), and a non-caloric sweetener to match the taste and appearance of the fruit juices. Participants were instructed to consume their assigned beverage daily, preferably in the morning, for 12 weeks. They were asked to maintain their usual dietary habits and avoid taking any additional iron supplements during the study period.

The primary outcome measures were the changes in hemoglobin (g/dL) and hematocrit (%) levels from baseline to week 12. Secondary outcome measures included Serum iron levels (mcg/dL), Serum ferritin levels (ng/mL), and total iron binding capacity (TIBC) (mcg/dL). Blood samples for these measurements were collected at baseline and week 12. All laboratory analyses were conducted at a certified clinical laboratory using standardized protocols. Safety was monitored throughout the study. Participants were asked to report any adverse events (AEs) they experienced. The severity and potential relationship of each AE to the study intervention were assessed by a study physician. Statistical analysis was performed using SPSS version 26. Baseline characteristics were compared between groups using analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. Changes in outcome measures over time were analyzed using repeated measures ANOVA, with pairwise comparisons using Bonferroni correction. A p-value of <0.05 was considered statistically significant.

3. Results and Discussion

Table 1 provides a snapshot of the demographic and clinical characteristics of the participants at the beginning of the study (baseline), before any interventions were administered. The goal of presenting these baseline characteristics is to demonstrate the comparability of the three groups (Tamarillo juice, pitaya juice, and placebo) and to identify any potential confounding factors that might influence the study results. The average age of participants was similar across all three groups, ranging from 37.8 to 39.2 years. This suggests that age is unlikely to be a major confounding factor in the study. The distribution of females was slightly higher in the pitaya juice group (70%) compared to the other groups, but these differences were not statistically significant ($p = 0.491$). This indicates that gender is unlikely to substantially influence the outcomes. The average body mass index (BMI) was comparable across all groups, suggesting that nutritional status, as reflected by BMI, is not a significant confounding variable. Importantly, the baseline values for hemoglobin, hematocrit, iron, ferritin, and TIBC were similar across the groups ($p > 0.05$ for all comparisons). This confirms that the participants started with comparable levels of anemia and iron status, making it possible to isolate the effects of the interventions. The baseline characteristics indicate that the randomization process was successful in creating three groups that were well-balanced in terms of age, gender, BMI, and relevant hematological parameters. This strengthens the internal validity of the study and increases confidence that any observed differences in outcomes between the groups can be attributed to the interventions rather than pre-existing differences between the participants.

Table 1. Baseline characteristics of study participants.

Characteristic	Tamarillo Juice (n = 50)	Pitaya Juice (n = 50)	Placebo (n = 50)	p-value
Age (years), mean ± SD	38.5 ± 12.3	37.8 ± 11.9	39.2 ± 13.1	0.823
Gender (female), n (%)	32 (64%)	35 (70%)	30 (60%)	0.491
BMI (kg/m^2), mean ± SD	22.8 ± 3.1	23.1 ± 2.8	22.5 ± 3.4	0.567
Hemoglobin (g/dL), mean ± SD	9.5 ± 0.8	9.4 ± 0.9	9.6 ± 0.7	0.759
Hematocrit (%), mean ± SD	30.2 ± 3.5	29.8 ± 3.2	30.5 ± 3.1	0.612
Iron (mcg/dL), mean ± SD	55.3 ± 18.2	54.9 ± 17.6	56.1 ± 19.5	0.954
Ferritin (ng/mL), mean ± SD	18.6 ± 8.4	17.9 ± 7.9	18.3 ± 9.2	0.897
TIBC (mcg/dL), mean ± SD	320.5 ± 45.3	318.9 ± 42.7	322.1 ± 48.1	0.885

Table 2 reveals the key findings of the study, showcasing the impact of Tamarillo juice, pitaya juice, and the placebo on various hematological parameters over the 12-week intervention period. Both Tamarillo and pitaya juice groups demonstrated significant increases in hemoglobin levels (1.5 g/dL and 2.0 g/dL, respectively) compared to the placebo group (+0.2 g/dL). This suggests that both juices are effective in raising hemoglobin levels, a primary indicator of anemia improvement. Pitaya juice appears to have a slightly more pronounced effect. Similar to hemoglobin, both juice interventions led to significant increases in hematocrit (4.8% for Tamarillo and 5.5% for pitaya), while the placebo group saw a negligible change. This further supports the efficacy of both juices in addressing anemia. Pitaya juice was particularly effective in increasing iron levels, with a mean increase of 15.0 mcg/dL, compared to 8.2 mcg/dL for Tamarillo juice and only 1.1 mcg/dL for the placebo. This finding highlights the potential of pitaya juice as a natural source of iron for combating iron-deficiency anemia. Both juices significantly increased ferritin levels, which is a marker of iron storage in the body. The increase was more substantial for pitaya juice (+20.3 ng/mL) compared to Tamarillo juice (+12.5 ng/mL). This suggests that pitaya may be more effective in replenishing iron stores. Total iron-binding capacity (TIBC) decreased significantly in both juice groups, indicating that more iron was bound to transferrin (the protein that carries iron in the blood) and less iron-binding capacity was available. This is consistent with the observed increases in iron and ferritin levels. Table 2 provides compelling evidence for the hematological benefits of both Tamarillo and pitaya juices in individuals with mild to moderate anemia. While both juices were effective in increasing hemoglobin and hematocrit levels, pitaya juice stood out for its superior impact on iron levels and iron stores.

Table 2. Changes in hematological parameters after 12 weeks of intervention.

Parameter	Tamarillo juice	Pitaya juice	Placebo	p-value*
Hemoglobin (g/dL), mean ± SD	+1.5 ± 0.5	+2.0 ± 0.6	+0.2 ± 0.3	<0.001
Hematocrit (%), mean ± SD	+4.8 ± 1.2	+5.5 ± 1.5	+0.5 ± 0.8	<0.001
Iron (mcg/dL), mean ± SD	+8.2 ± 5.6	+15.0 ± 6.2	+1.1 ± 4.3	<0.001
Ferritin (ng/mL), mean ± SD	+12.5 ± 4.8	+20.3 ± 5.5	+2.2 ± 3.9	<0.001
TIBC (mcg/dL), mean ± SD	-15.3 ± 8.9	-18.1 ± 9.5	-2.5 ± 7.6	<0.001

*p-value for comparison between all three groups using ANOVA.

Table 3 provides a comprehensive overview of the adverse events (AEs) reported by participants during the 12-week study period. It sheds light on the safety profile of both Tamarillo and pitaya juice interventions. The majority of participants (94% in the Tamarillo group, 84% in the pitaya group, and 86% in the placebo group) did not experience any adverse events during the study. This indicates that both juices were generally well-tolerated. The most commonly reported adverse event was mild gastrointestinal discomfort, which included symptoms like nausea, bloating, and diarrhea. This was primarily observed in the pitaya group (10%), with a lower incidence in the Tamarillo (0%) and placebo (2%) groups. This suggests that pitaya juice might have a slightly higher potential to cause mild digestive issues in some individuals. A few participants reported other mild AEs, such as headache and fatigue, but these were infrequent and occurred at similar rates across all three groups. This implies that these AEs were likely not related to the interventions. Importantly, no serious adverse events requiring medical intervention or discontinuation of the study were reported in any of the groups. This reinforces the safety profile of both Tamarillo and pitaya juice as potential therapeutic options for anemia. The findings of Table 3 are reassuring from a safety perspective. The low incidence and mild nature of the reported adverse events suggest that both Tamarillo and pitaya juice can be considered safe for consumption in the context of anemia management. However, it is important to note the potential for mild gastrointestinal discomfort with pitaya juice, particularly in individuals who may be sensitive to its high fiber content.

Table 3. Reported adverse events during the 12-week intervention.

Adverse event	Tamarillo juice (n = 50)	Pitaya juice (n = 50)	Placebo (n = 50)
Mild gastrointestinal discomfort (nausea, bloating, diarrhea)	0 (0%)	5 (10%)	1 (2%)
Headache	1 (2%)	2 (4%)	2 (4%)
Fatigue	2 (4%)	1 (2%)	3 (6%)
Other (skin rash, dizziness)	0 (0%)	0 (0%)	1 (2%)
No adverse events reported	47 (94%)	42 (84%)	43 (86%)

Iron deficiency anemia (IDA) is a pervasive global health problem, affecting an estimated 2 billion people worldwide, predominantly in developing countries. It is particularly prevalent among women of reproductive age, pregnant women, and young children. The consequences of IDA extend beyond fatigue and weakness; it can impair cognitive development in children, reduce work productivity in adults, and increase susceptibility to infections. Iron is a crucial micronutrient, essential for oxygen transport, energy metabolism, and immune function. While meat and other animal products are excellent sources of heme iron, which is readily absorbed by the body, plant-based diets rely primarily on non-heme iron, which is less bioavailable. The bioavailability of non-heme iron is influenced by a variety of factors, including: Phytates: These compounds, found in grains, legumes, and nuts, bind to iron and form insoluble complexes that are not easily absorbed. Polyphenols: Certain polyphenols, such as tannins in tea and coffee, can also inhibit iron absorption. Fiber: High fiber intake can accelerate the transit of food through the gut, reducing the time available for iron absorption. Calcium: Calcium competes with iron for absorption, and high calcium intake can decrease iron uptake. Individual Factors: Factors such as iron status, gastric acidity, and the presence of other dietary components can also influence non-heme iron absorption. Due to these challenges, individuals who rely heavily on plant-based diets may be at increased risk of iron deficiency and anemia, especially if their diets are not carefully planned to maximize iron absorption.[6,7]

Both Tamarillo (*Cyphomandra betacea*) and pitaya (*Hylocereus* spp.) are noteworthy for their relatively high iron content compared to many other fruits. Tamarillo contains approximately 0.9 mg of iron per 100 grams, while pitaya contains around 1.0 mg per 100 grams. This makes them valuable additions to plant-based diets, particularly for individuals at risk of iron deficiency. The encouraging results of the present study, which showed significant increases in iron levels in participants consuming Tamarillo and pitaya juices, suggest that these fruits may possess unique properties that enhance iron absorption and utilization. Both Tamarillo and pitaya are rich sources of vitamin C (ascorbic acid). Vitamin C is a potent enhancer of non-heme iron absorption. It converts ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), which is the form more readily absorbed by the intestinal cells. Additionally, vitamin C forms soluble complexes with iron, preventing its interaction with inhibitory compounds like phytates and polyphenols. Both fruits contain organic acids, such as citric acid and malic acid. These acids can chelate iron, forming complexes that are more soluble and easily absorbed. Citric acid, in particular, has been shown to significantly enhance iron absorption from plant-based foods. The Multifaceted Facilitators: Tamarillo and pitaya are abundant in phenolic compounds, including flavonoids, anthocyanins, and betalains. These compounds have diverse biological activities, including antioxidant, anti-inflammatory, and metal-chelating properties. Some studies suggest that certain phenolic compounds may enhance iron absorption by reducing ferric iron to ferrous iron, forming soluble complexes with iron, or modulating iron transport proteins in the gut. The Gut Microbiota Modulators: Both fruits contain prebiotic fibers, such as pectin and inulin, which serve as food for beneficial gut bacteria. These bacteria play a crucial role in iron metabolism. They produce short-chain fatty acids that create an acidic environment in the gut, favoring iron absorption. Moreover, they may synthesize siderophores, molecules that bind to iron and facilitate its uptake by the intestinal cells. It is likely that the combination of vitamin C, organic acids, phenolic compounds, and prebiotic fibers in Tamarillo and pitaya juices creates a synergistic effect, optimizing iron absorption and utilization. Each component plays a distinct role, but their combined action is likely more potent than any single nutrient alone.[8-10]

Erythropoiesis, the marvel of red blood cell (RBC) production, is a finely tuned process orchestrated within the intricate microenvironment of the bone marrow. The journey begins with hematopoietic stem cells (HSCs), the master conductors of blood cell lineage. These multipotent cells possess the remarkable ability to self-renew and differentiate into various blood cell types, including erythrocytes, leukocytes, and platelets. Under the influence of a myriad of signals, HSCs embark on a path of commitment towards the erythroid lineage, giving rise to burst-forming unit-erythroid (BFU-E) and colony-forming unit-erythroid (CFU-E) cells. These progenitor cells undergo a series of well-defined morphological changes, gradually shedding their nuclei and accumulating hemoglobin, the oxygen-carrying protein that defines RBCs. The process culminates in the release of mature erythrocytes into the bloodstream, where they circulate for approximately

120 days, fulfilling their essential role in oxygen transport. The rate of erythropoiesis is exquisitely regulated to maintain a steady state of RBC mass, ensuring adequate oxygen delivery to tissues while avoiding the detrimental effects of excessive RBC production.[11,12]

At the heart of erythropoiesis regulation lies erythropoietin (EPO), a glycoprotein hormone primarily produced by the kidneys in response to hypoxia, a state of reduced oxygen availability. EPO acts as a potent mitogen and survival factor for erythroid progenitor cells, stimulating their proliferation and differentiation while preventing apoptosis. The binding of EPO to its receptor on erythroid cells triggers a cascade of intracellular signaling events, leading to the activation of transcription factors and the expression of genes essential for erythropoiesis. This includes genes involved in heme synthesis, globin chain production, iron metabolism, and anti-apoptotic pathways. The net effect is a robust increase in the number of mature erythrocytes released into circulation, thereby restoring oxygen-carrying capacity. While EPO is undoubtedly the maestro of erythropoiesis, the symphony is enriched by a diverse ensemble of cytokines and growth factors. These signaling molecules, produced by various cells within the bone marrow microenvironment, act in concert to fine-tune erythropoiesis at multiple stages. Stem Cell Factor (SCF) also known as c-kit ligand, is crucial for the survival, proliferation, and differentiation of HSCs. It acts synergistically with EPO to promote erythroid commitment and expansion. Interleukin-3 (IL-3) is a pleiotropic cytokine that supports the early stages of erythropoiesis, promoting the proliferation and differentiation of BFU-E and CFU-E cells. Granulocyte-macrophage colony-stimulating factor (GM-CSF), in addition to its role in myeloid lineage development, also contributes to erythropoiesis by enhancing the survival and proliferation of erythroid progenitor cells. Insulin-like Growth Factor-1 (IGF-1), a potent growth factor, stimulates erythroid proliferation and differentiation. It also plays a role in regulating iron uptake and utilization by erythroid cells.[13,14]

Bioactive compounds in tamarillo and pitaya potential erythropoiesis enhancers. The observed increases in hemoglobin and hematocrit levels in the intervention groups of our study suggest that Tamarillo and pitaya juices may enhance erythropoiesis. This effect could be attributed to several bioactive compounds present in these fruits. Flavonoids are a diverse group of polyphenols with potent antioxidant and anti-inflammatory properties. They have been shown to protect erythroid cells from oxidative damage, enhance EPO production, and promote erythroid differentiation. Anthocyanins are the pigments responsible for the vibrant colors of many fruits and vegetables. These flavonoids have been shown to increase EPO levels, stimulate erythroid proliferation, and protect against anemia-induced oxidative stress. Betalains are nitrogen-containing pigments found in certain plants, including Tamarillo. They exhibit antioxidant, anti-inflammatory, and anti-apoptotic activities, which could contribute to a favorable microenvironment for erythropoiesis. Ascorbic acid, or vitamin C, is a well-known enhancer of iron absorption. It reduces ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), the form that is readily absorbed in the duodenum. This could increase the availability of iron for hemoglobin synthesis and promote erythropoiesis in individuals with iron-deficiency anemia. Both Tamarillo and pitaya contain prebiotic fibers, such as inulin and oligosaccharides, which can modulate the gut microbiota. By promoting the growth of beneficial bacteria, these fibers may enhance iron absorption and contribute to a healthier gut environment for erythropoiesis.[15,16]

Anemia, while primarily characterized by a deficiency in red blood cells or hemoglobin, is not solely a consequence of inadequate iron intake or absorption. A growing body of research indicates a significant association between anemia and heightened levels of oxidative stress and inflammation. These intertwined processes create a vicious cycle that can further exacerbate anemia and hinder its effective management. Oxidative stress arises when there's an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them through antioxidants. ROS are highly reactive molecules that can damage cellular components, including lipids, proteins, and DNA. In the context of anemia, oxidative stress can wreak havoc on red blood cells, leading to their premature destruction (hemolysis) and impairing their ability to carry oxygen effectively. Iron, a crucial component of hemoglobin, is particularly susceptible to oxidation. In its oxidized state, iron can generate more ROS, further amplifying oxidative stress. This creates a self-perpetuating cycle that can worsen anemia and contribute to tissue damage.[16,17]

Inflammation is the body's natural response to injury or infection. However, chronic or excessive inflammation can have detrimental effects. In anemia, inflammation can disrupt iron metabolism. Inflammatory cytokines, such as interleukin-6 (IL-6) and hepcidin, can suppress erythropoiesis (red blood cell production) and inhibit iron absorption from the gut. This can lead to functional iron deficiency, where iron is present in the body but unavailable for hemoglobin synthesis. Moreover, inflammation can directly damage red blood cells and their precursors, further compromising their function and survival. The resulting anemia can weaken the immune system, making individuals more susceptible to infections, which in turn can trigger further inflammation. Both Tamarillo and pitaya boast an impressive array of antioxidants that can help combat oxidative stress and inflammation, thereby creating a more conducive environment for red blood cell production and iron utilization. A potent antioxidant that directly scavenges ROS and protects cells from oxidative damage. Additionally, vitamin C enhances iron absorption by reducing ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), the form more readily absorbed by the body. This dual action makes vitamin C a valuable nutrient in anemia management. These colorful pigments, such as beta-carotene and lycopene, are powerful antioxidants that neutralize ROS and protect cell membranes from lipid peroxidation. Some carotenoids can also be converted to vitamin A, which is essential for immune function and cellular differentiation. Tamarillo and pitaya contain a diverse range of phenolic compounds, including flavonoids, phenolic acids, and tannins. These compounds exhibit strong antioxidant and anti-inflammatory properties. They can scavenge ROS, inhibit pro-inflammatory enzymes, and modulate immune responses, contributing to a reduction in oxidative stress and inflammation.[15,17]

The antioxidants in Tamarillo and pitaya exert their beneficial effects through multiple mechanisms. Antioxidants neutralize ROS by donating electrons or hydrogen atoms, preventing them from damaging cellular components. This helps to maintain the integrity of red blood cells and protect them from premature destruction. Some antioxidants, like carotenoids, can activate antioxidant enzymes within the body, such as superoxide dismutase (SOD) and catalase. These enzymes further enhance the body's defense against oxidative stress. Phenolic compounds and other antioxidants can inhibit the production and activity of pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor-alpha (TNF-alpha). This helps to reduce inflammation and its negative impact on erythropoiesis and iron metabolism. Certain antioxidants, like phenolic acids, can bind to iron and form stable complexes. This can help to prevent iron from participating in oxidative reactions and generating ROS. The prebiotic fibers in these fruits can nourish beneficial gut bacteria, which in turn can produce short-chain fatty acids (SCFAs). SCFAs have been shown to have anti-inflammatory effects and may also enhance iron absorption. The antioxidant and anti-inflammatory properties of Tamarillo and pitaya juices offer a promising avenue for enhancing the effectiveness of conventional anemia treatment. By mitigating oxidative stress and inflammation, these juices can create a more favorable environment for erythropoiesis and iron utilization, leading to a faster and more sustained improvement in hematological parameters. Furthermore, the presence of vitamin C in these juices enhances iron absorption, making them a valuable addition to iron-rich diets or iron supplementation. This is particularly relevant for individuals with iron-deficiency anemia, where improving iron absorption is a key therapeutic goal.[17,18]

The human gut harbors a complex and diverse ecosystem of microorganisms, collectively known as the gut microbiota. These microbes, including bacteria, fungi, viruses, and archaea, play a pivotal role in various physiological processes, including digestion, immune function, and nutrient metabolism. Recent research has highlighted the intricate relationship between the gut microbiota and iron homeostasis, the delicate balance of iron absorption, transport, storage, and utilization in the body. Iron is an essential trace element required for oxygen transport, energy production, and various enzymatic reactions. The majority of dietary iron is absorbed in the duodenum and upper jejunum of the small intestine. However, the efficiency of iron absorption is influenced by numerous factors, including the type of iron (heme vs. non-heme), dietary composition, and the health of the intestinal epithelium. Emerging evidence suggests that the gut microbiota plays a crucial role in modulating iron absorption. Specific bacteria, such as *Lactobacillus* and *Bifidobacterium* species, have been shown to promote iron uptake by increasing the expression of iron transporters in the intestinal lining. These bacteria can also produce metabolites, like short-chain fatty acids (SCFAs), which create an acidic environment in the gut that favors iron solubility and absorption. Conversely, certain gut bacteria can hinder iron absorption. For instance, some pathogenic bacteria can compete with the host for iron or produce siderophores, iron-chelating molecules that sequester iron and make it unavailable for absorption. Therefore, the composition and diversity of the gut microbiota can significantly influence an individual's iron status.[18,19]

Dietary interventions, particularly those rich in prebiotic fibers, have emerged as a promising strategy for modulating the gut microbiota and potentially improving iron status. Prebiotics are non-digestible carbohydrates that serve as nourishment for beneficial gut bacteria, promoting their growth and activity. Tamarillo and pitaya are notable sources of prebiotic fibers, including inulin, fructooligosaccharides, and pectin. Inulin and Fructooligosaccharides (FOS), These fibers are selectively fermented by beneficial bacteria like Bifidobacterium and Lactobacillus, increasing their abundance in the gut. This, in turn, can lead to increased production of SCFAs, which enhance iron absorption and inhibit the growth of pathogenic bacteria that compete for iron. Pectin, this soluble fiber has a gel-forming property that can trap iron in the gut and slow down its transit time, allowing for more efficient absorption. Pectin also acts as a prebiotic, favoring the growth of beneficial bacteria that can further enhance iron uptake. The results of the present study, which showed significant improvements in iron parameters following consumption of Tamarillo and pitaya juices, can be partially attributed to their prebiotic content. These fruits provide a rich source of inulin, FOS, and pectin, which can selectively nourish beneficial gut bacteria and create a gut environment conducive to iron absorption. In addition to their prebiotic effects, Tamarillo and pitaya also contain other bioactive compounds that may contribute to improved iron status. These include: Vitamin C: As mentioned earlier, vitamin C enhances non-heme iron absorption by reducing ferric iron (Fe^{3+}) to the more soluble ferrous iron (Fe^{2+}) form. Polyphenols: Certain polyphenols, like flavonoids and anthocyanins, have been shown to chelate iron and protect it from oxidation, thereby increasing its bioavailability. Organic Acids: These acids can create an acidic environment in the gut, which favors iron solubility and absorption. The combined effects of these prebiotic fibers and bioactive compounds may explain the observed improvements in iron parameters in the intervention groups. While the current study provides compelling evidence for the potential of Tamarillo and pitaya juices to improve iron status, further research is needed to elucidate the precise mechanisms underlying their effects on the gut microbiota. Future studies should investigate the specific changes in microbial composition and diversity following consumption of these juices, as well as the impact of these changes on iron absorption and metabolism. Additionally, it would be valuable to explore the synergistic effects of the different prebiotic fibers and bioactive compounds present in these fruits. Understanding these interactions could lead to the development of more targeted and effective dietary interventions for improving iron status and managing anemia. The gut microbiota plays a pivotal role in iron homeostasis, and dietary interventions that modulate the microbiota hold promise for improving iron status and preventing or treating anemia. Tamarillo and pitaya, with their abundance of prebiotic fibers and bioactive compounds, represent promising natural sources for optimizing iron absorption and utilization.[19,20]

4. Conclusion

This randomized controlled trial demonstrates the significant potential of tamarillo (*Cyphomandra betacea*) and pitaya (*Hylocereus* spp.) juices as adjunctive therapies for managing mild to moderate anemia. Both juices resulted in substantial increases in hemoglobin, hematocrit, and iron parameters compared to the placebo, with pitaya juice exhibiting a particularly pronounced effect on iron levels. These findings align with and strengthen previous research on the hematinic properties of these fruits.

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