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Biotechnology Solution to Overcome Global Concern of Iron Deficiency

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ABSTRACT

Anemia remains a significant global public health issue, particularly affecting vulnerable populations such as women of childbearing age, pregnant women, and young children, with the highest prevalence reported in the African and South-East Asian regions. Deficiencies in hematopoietic nutrients, particularly iron and zinc, contribute to this widespread condition, significantly impacting childhood health and development. This study examines the potential of iron- and zinc-enriched baker's yeast, specifically Saccharomyces cerevisiae, as a novel dietary fortification strategy. By optimizing culturing conditions and employing advanced biotechnological methods such as ultrasound, we report on the successful accumulation of these essential nutrients in yeast biomass, thereby enhancing its bioavailability. Furthermore, the advantages of using iron- and zinc-enriched yeast in food fortification, especially in widely consumed products such as bread, are discussed regarding addressing nutrient deficiencies and improving overall public health outcomes. This research highlights the need for large-scale implementation and further investigation into effective and sustainable methodologies for biofortifying food sources to combat nutrient deficiencies.

What is already known:?	• Anemia affects adult women and children, in developing countries • Effective intervention strategies are required to prevent significant health problems • Fe &Zn deficiencies are identified as primary contributors to anemia • Fe- & Zn-enriched baker's yeast has potential as dietary supplementwith enhanced bioavailability.
What this article adds?:	• Fortified breads can be produced by iron and zinc- yeast. • Fortified bread provides effective means of improving nutrition and promoting public health • Potential of biofortification as an innovative approach to alleviate malnutrition and improve health among affected populations.

1. Introduction

Anemia is a global public health concern. The World Health Organization estimates that in 2019, 30% (571 million) of women aged 15–49 years, 37% (32 million) of pregnant women, and 40% (269 million) of children aged 6–59 months were affected by anemia, with the African region and the South-East Asia region being the most affected. Numerous interventions aimed at reducing the burden of anemia are being implemented in many low-, middle-, and high-income countries worldwide [1] . Recommended Dietary Allowances (RDAs) for Iron is shown in Table 1[2]and Tolerable Upper Intake Levels (ULs) for Iron Iron is shown in Table 2 [2].

Table 1. Recommended Dietary Allowances (RDAs) for Iron [2]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	0.27 mg*	0.27 mg*		
7–12 months	11 mg	11 mg		
1–3 years	7 mg	7 mg		
4–8 years	10 mg	10 mg		
9–13 years	8 mg	8 mg		
14–18 years	11 mg	15 mg	27 mg	10 mg
19–50 years	8 mg	18 mg	27 mg	9 mg
51+ years	8 mg	8 mg		

Table 2. Tolerable Upper Intake Levels (ULs) for Iron [2]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	40 mg	40 mg		
7–12 months	40 mg	40 mg		
1–3 years	40 mg	40 mg		
4–8 years	40 mg	40 mg		
9–13 years	40 mg	40 mg		
14–18 years	45 mg	45 mg	45 mg	45 mg
19+ years	45 mg	45 mg	45 mg	45 mg

Iron is one of the most abundant elements in the Earth's crust, but the very low solubility of iron (Fe^{3+}) at physiological pH significantly limits its availability to living organisms[1].Low bioavailability of iron in industrially produced foods or disorders in the regulation of iron transport, metabolism, and absorption lead to iron deficiency anemia in animals or humans [3]. 75% of iron in the body is found in hemoglobin and myoglobin, 9% exists in the form of the iron transport protein, transferrin, or combined in the structure of certain enzymes (cytochromes), and the remaining 16% is stored as ferritin and hemosiderin within the body's tissues. Therefore, iron plays an essential role in three different processes (for carrying oxygen in the body) [4].

Also, Zn^{2+} is a strong electron acceptor in biological systems without the risk of oxidative damage to cells. Zn^{2+} functions in the structure of proteins and acts as a catalytic component of more than 300 different enzymes, encompassing almost all aspects of biology, including growth, immune defense, cognitive function, and bone health [5]. Zinc has been recognized as an essential trace element for humans and animals since the 1930s. A study conducted in Iran during the 1960s identified zinc deficiency as an underlying cause of growth retardation and delayed sexual maturation in humans. More recently, moderate zinc deficiency in infants and children has been associated not only with impaired growth and development but also with immune dysfunction and increased morbidity and mortality due to infectious diseases. Zinc is required for the activity of over 300 enzymes, and its physiological role during periods of rapid growth and development highlights its critical importance during pregnancy and fetal development [6]

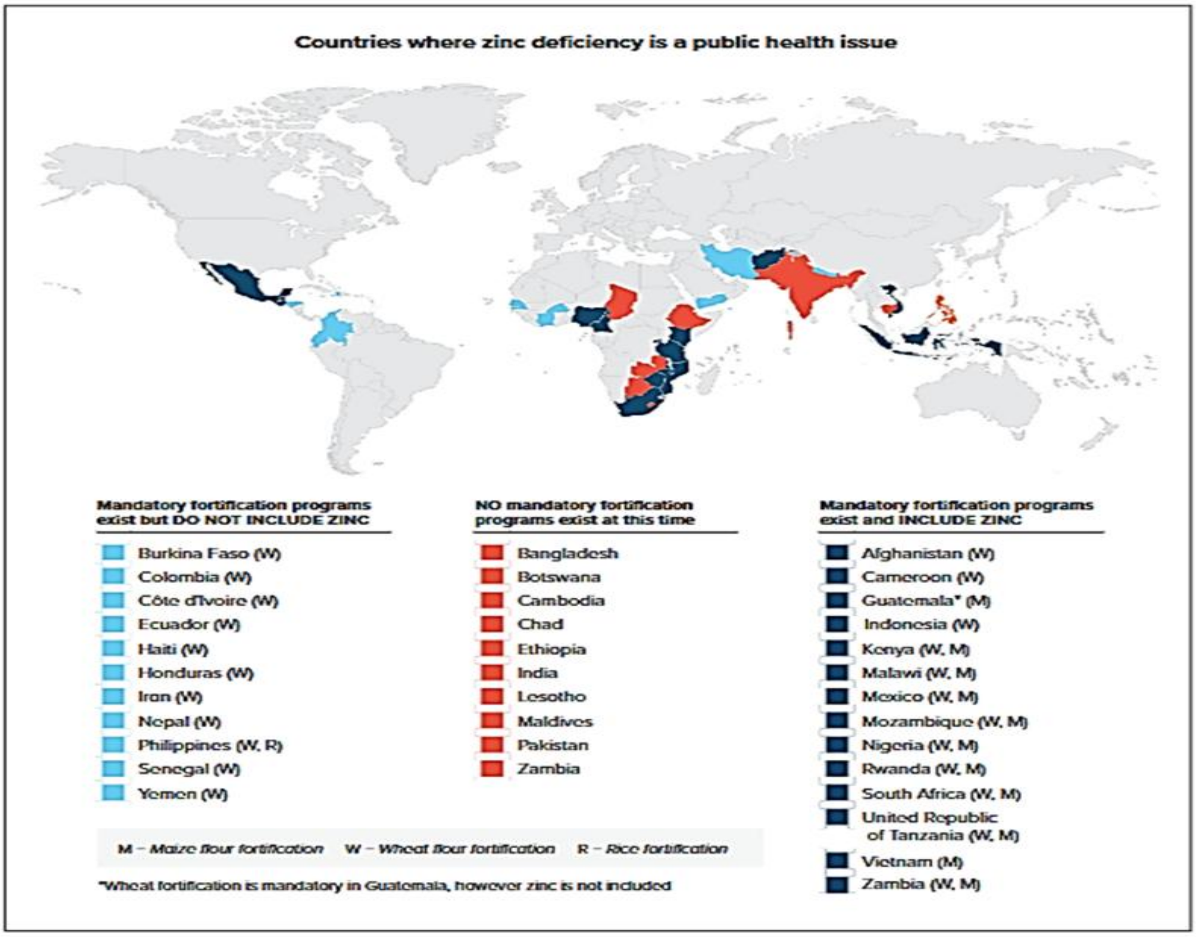

Figure 1. Bread Fortification with Various Micronutrients in Different Countries[7]

Large-scale food fortification programs have the potential to significantly increase the intake of dietary micronutrients. It is estimated that approximately 15% of the global population—equivalent to 1.13 billion people - has inadequate zinc intake. Investing in robust large-scale food fortification initiatives can have a substantial impact on improving population-level zinc status.[1].

According to nutrition science experts, one of the most effective strategies for increasing the intake of essential micronutrients with minimal side effects and broad population coverage is the fortification of food and beverages. Among the key micronutrients commonly targeted through such interventions are iron and zinc.[8] .

In general, a fortified food should have a consistent consumption pattern and pose minimal risk of excessive intake. Additionally, it should demonstrate adequate stability under storage conditions, be economically feasible, and ensure no adverse interactions occur between the fortificant and the food vehicle [9]. According to studies by the Food and Agriculture Organization (FAO), populations in the Middle East and Near East derive approximately 70% of their daily energy requirements from bread and other wheat-based products.

Iron salts, as dietary supplements, typically have low bioavailability and may cause gastrointestinal discomfort. Iron-enriched yeasts can serve as an alternative dietary source of this micronutrient, as the mineral exhibits improved bioavailability when bound to yeast cellular macromolecules [10].

Saccharomyces has played a significant role in the production of fermented foods and beverages since ancient times, due to its high nutritional value, bioavailability, safety, and non-toxic nature. Studies have shown that vacuoles and cell walls serve as the primary storage compartments for iron. Within vacuoles, iron may form complexes with polyphosphates and organic acids [11]. Iron- and zinc-enriched yeasts can serve as a valuable source of these essential nutrients in diets and nutritional programs, as they offer enhanced bioavailability compared to inorganic forms [12]. Industrial yeast production is important from two key perspectives. The first is the need to produce yeast with high fermentation capacity and extended shelf life. The second is economic feasibility, as manufacturers must aim to produce the highest quality product at the lowest possible cost. [13].

Metal uptake by Saccharomyces cerevisiae cells is a complex process. These metals are incorporated into yeast cells through various mechanisms, including the production of metal-binding proteins, mineralization, or sequestration within vacuoles.[14]

In general, the production of zinc-enriched yeast is achieved by supplementing the yeast culture medium with zinc. However, this may affect yeast growth, as zinc plays a role in structural integrity and metabolic activity. If not properly controlled, excess zinc can become toxic and inhibitory in culture environments [15].

High concentrations of zinc ions may be toxic to yeast, as zinc affects membrane permeability to potassium, leading to reduced yeast growth. Therefore, it appears that the presence of an optimal zinc concentration is crucial. However, there is limited research on the optimal zinc concentration in yeast and its impact on yeast characteristics [16] .Previous studies have shown that iron bound to organic carriers, such as proteins and enzymes within yeast cells, is more readily absorbed and its toxicity is reduced. Additionally, yeast biomass is recognized as a valuable source of protein, amino acids, and vitamins. The process of metal uptake and digestion is complex and depends on the chemistry of metal ions, the organism's surface characteristics, cell physiology, and the physical and chemical properties of the environment [17].

Yeast fortification with metals can be achieved by adding inorganic metal salts to the culture medium. Metal uptake by yeast cells is a complex process that depends on the chemistry of metal ions, the organism's specific characteristics, cell physiology, physical and chemical influences from the environment, and experimental factors such as pH, temperature, aeration, and the presence of other ions in the solution. These metals are incorporated into yeast cells through various mechanisms, including the production of metal-binding proteins, mineralization, or sequestration within vacuoles. [18].

Saccharomyces (S.) cerevisiae, due to its high nutritional value, bioavailability, safety, and non-toxicity, has played a significant role in the production of fermented foods and beverages since ancient times. Vacuoles and cell walls serve as the main compartments for iron storage. Iron may form complexes with polyphosphates and organic acids in the vacuole [11]. Iron-enriched yeast is an ideal source for dietary use, as its bioavailability is enhanced due to its binding to amino acids [12].

In recent years, there has been a significant increase in the methods for producing trace elements carriers, such as the yeast fortification method, to produce products that are non-toxic, highly bioavailable, easily digestible, and readily absorbed by the human body. These products aim to prevent deficiencies in trace elements [19].

The yeast market is continuously seeking new products and processes, which could lead to advancements in biotechnology. Iron-enriched yeast biomass, when used in baking, can offer a safer alternative for preventing anemia [18].

The most important factors and components influencing the fortification of bread yeast with iron and zinc are pH, cultivation time, and inoculation level. The greatest impact on yeast fortification with iron and zinc is attributed to cultivation time, followed by pH and inoculation level [20].

Consumption of iron- and zinc-enriched breads has demonstrated beneficial effects on human health. The presence of these trace elements in bread formulations can contribute to improved glucose metabolism and a reduced risk of chronic diseases such as cancer and type 2 diabetes. In this context, the biofortification of baker’s yeast with iron and zinc represents a novel strategy for the management and regulation of blood glucose levels [21]. Moreover, these enriched breads may help prevent diseases such as diabetes and cardiovascular disorders, while also enhancing the immune system. Additionally, fortification of baker’s yeast with iron and zinc has been shown to reduce excessive glucose absorption and postprandial triglyceride levels. This approach may also promote increased absorption of essential nutrients into tissues and the bloodstream.[22] .The results obtained from experimental studies indicate that flatbreads produced using iron-enriched yeasts exhibit high bioavailability.[23].The sensory properties of both flatbreads and leavened breads are of significant importance.In fact, the analysis and evaluation of sensory attributes in these bread types are essential for determining product quality and developing final bread products that meet consumer preferences and expectations.[24]. Bread is a widely consumed food around the world due to its affordability, availability, nutritional value, and desirable sensory and textural properties. Beyond sensory characteristics, consumers increasingly prefer functional and health-promoting bakery products. Moreover, bread serves as an important dietary source of essential nutrients.[25]

To evaluate the textural and sensory characteristics of flatbreads and leavened breads, specific analyses related to these properties are typically conducted [17].

To date, industrial-scale biofortification of Saccharomyces cerevisiae biomass with iron and zinc has not been achieved.

Although many research team has been focused on production of Selenium, Zinc and Fe enriched yeast ([26],[27],[28],[26],[11]), to the best of our knowledge, scale of production of Fe-Yeast by traditional media enrichment is impossible, because all previous reports have been carried out in laboratories scale, but industrial production has multiple stages and fermenters. Each fermenter plays the role of the mother for the next one, and regardless of the resulting efficiency which may occur due to Fe stress to yeast, the strategy is practically uneconomical. It should be noted media enrichment is amount and time consuming while a large percentage of salt is not absorbed, so the process is uneconomical for scale up production. In addition, the excess of added salts also brings huge costs and problems to production in wastewater treatment, as well as waste separation and management.

Recently, ultrasound has been utilized in various biotechnological processes such as fermentation, extraction, and the catalysis of diverse biological reactions. Concurrently, the effects of process variables and ultrasound on stimulating the biotransformation of selenium (Se) in yeast have been investigated.

To the best of our knowledge, the present study is the first report on the application of ultrasonic waves for the biotransformation of Se in Saccharomyces cerevisiae. The results demonstrated that optimization of parameters and the application of ultrasound successfully led to a 2.78-fold increase in selenium accumulation by S. cerevisiae.[26]

For the first time, the effect of ultrasound as a tool to stimulate zinc accumulation was investigated. The optimal growth conditions were reported under which the total zinc accumulation was doubled compared to similar conditions without ultrasonic stimulation[27]

Yeasts contain a high amount of protein and, in comparison to plant-based sources, are capable of incorporating selenium (Se) into proteins by substituting it for sulfur (S). Yeast can utilize soluble sugars and organic acids to produce high-protein biomass, and its production is relatively easy to manage.[29]

When grown in selenium-enriched media, yeast can accumulate significant amounts of selenium and incorporate it into organic compounds such as Se-methionine (Se-Met), primarily in the form of organic selenium. Sodium selenite (Na_2SeO_3) can be biologically transformed into organic forms and absorbed by yeast. Through this process, inorganic selenite—a toxic and poorly bioavailable compound—can be converted into safer, highly bioavailable selenium species with improved nutritional properties. Saccharomyces cerevisiae is the only yeast strain that has been used for this purpose. According to a report by Cypress Systems, Inc. (CSI), the mentioned yeast strain can be considered GRAS (Generally Recognized As Safe)[29].

Compared to plant-based sources, yeast has a relatively high protein content, which facilitates selenium uptake by the cells. By substituting sulfur in proteins, yeast serves as a reliable carrier for selenium. It can utilize soluble sugars and organic acids to produce high-protein biomass. When grown in selenium-enriched media, yeast is capable of accumulating large amounts of selenium and incorporating it into organic compounds, particularly selenomethionine (Se-Met). Sodium selenite (Na_2SeO_3) can be onverted into organic forms and absorbed by yeast.[29]

In the production of $FeSO_4$- and KH_2PO_4-enriched Saccharomyces boulardii, a positive (synergistic) interaction on biomass weight was observed: Role in Cell Growth:Considering the involvement of iron and the constituent elements of KH_2PO_4 in numerous biological processes, their combined effect may enhance cellular growth. Enhanced Iron Availability:Phosphate increases the solubility and cellular uptake of iron by indirectly lowering the medium's pH. This, in turn, ensures a greater supply of iron required for large-scale cell proliferation.[11]

After growth or post-harvest iron addition could be a startegy to avoid issues that arise during in-vitro biofortification. Maybe they encountered problems like iron toxicity affecting yeast growth or fermentation efficiency. Adding Fe post-separation could bypass these issues. But I need to think about the pros and cons of this approach. On the positive side, adding Fe after separation might prevent interference with yeast metabolism. During growth, high iron levels can stress the yeast, leading to reduced viability or altered fermentation properties. By adding Fe later, they could maintain optimal growth conditions. Also, controlling the iron dosage post-separation might be easier, allowing precise fortification without worrying about bioavailability during cultivation. However, there are a few potential drawbacks. In such cases Fe does not get into the yeast cells. Yeast cell walls are tough, so without active transport mechanisms, iron might not be absorbed effectively. They might need methods like cell permeabilization or encapsulation, which could complicate the process. Also, the form of iron used post-separation matters. If it's not in a bioavailable form, it might not be absorbed well in the human body, defeating the purpose of fortification.

Another consideration is the stability of the added iron. If Fe is simply mixed with yeast biomass, it might oxidize or interact with other components, leading to degradation or off-flavors in the final product. The user might not have thought about the need for protective measures like encapsulation or using chelating agents to enhance stability.

They might also be concerned about scalability and cost. Post-separation addition could introduce extra steps, increasing production costs. They need to evaluate whether the benefits of higher yeast viability and easier iron control outweigh the added complexity and expenses.

Alternative methods, like using non-GMO approaches or combining with prebiotics may enhance absorption. A middle ground between in-vitro biofortification and post-separation methods is also interesting, suggesting a hybrid approach where some iron is added during growth and more post-separation could be a viable solution.

Overall, the user is likely looking for a method that maintains yeast health, ensures iron bioavailability, and is cost-effective. They might not have considered all the technical challenges of post-separation iron addition, so highlighting those and offering potential solutions would be helpful.

Post-harvest fortification instead of traditional in-vivo biofortification (culturing yeast in Fe-rich media) has both potential advantages and challenges

2. Conclusion

Iron-enriched yeast is produced by biofortification, where yeast is cultivated in iron-rich media to accumulate bioavailable iron within its cells. Key strategies would be optimizing growth conditions (pH, temperature, fermentation time) and iron sources (e.g., ferrous sulfate, ferric citrate) to maximize iron uptake as well as genetic engineering(to overexpress iron transporters e.g., FET3, FTR1 or storage proteins e.g., ferritin) to enhance iron absorption and storage.

If Fe was incorporated to the media after growth key strategies would be co-supplementationby synergistic material like vitamin C or prebiotics to improve iron solubility and bioavailability. Also encapsulation would be efficient to protect Fe-yeast cells from oxidation or degradation during processing.

Anyway, the goal is to create a cost-effective, sustainable iron supplement for combating deficiencies, especially in fortified foods (e.g., bread, beverages). Unsolved problems are still bioavailability and stability. Iron in yeast may oxidize or form insoluble complexes during digestion, reducing bioavailability. Also balancing iron retention in yeast cells during food processing (e.g., baking) remains challenging. High iron levels can alter yeast metabolism, affecting fermentation efficiency (e.g., CO_2 production in bread). Also, Fe may impart metallic tastes or discolor fortified foods, reducing consumer acceptance. Of course, to overcome sensory problem, incorporation of flavorings is applicable to mask the color and taste, which certainly selection of such ingredient could be depends on the type of food. For instance, in the case of Iranian traditional bread, dried vegetables are good maskers.

Wild-type yeast has low iron storage capacity; engineered strains face regulatory and consumer skepticism (GMO concerns). Besides, scaling up genetically modified strains for industrial use is costly and technically complex. From nutrient interaction aspect, Iron in yeast may interact with other nutrients (e.g., zinc, calcium), potentially causing antagonistic effects.

There are some environmental and economic barriers, too. Iron-rich fermentation media can generate waste with heavy metal residues. High production costs compared to synthetic iron supplements (e.g., ferrous fumarate). Future Trends could be developing non-GMO yeast strains with enhanced iron uptake via adaptive evolution or CRISPR-free editing, optimize dual fortification (iron + co-nutrients like folate) to improve absorption, as well as validate efficacy in clinical trials to prove iron bioavailability and address safety concerns. Fe –yeast still requires innovations in binding/internalization methods to match the bioavailability of in-vivo biofortified yeast. It's particularly promising for non-GMO applications where genetic engineering is restricted. Prioritize techniques like chelation and cell permeabilization to maximize efficacy.

Research indicates that yeast's ability to accumulate iron depends on genetic diversity and growth conditions. Martínez-Garay et al. [30] found that iron-sensitive Saccharomyces strains accumulate iron more efficiently than resistant strains under increasing iron concentrations. Kyyaly et al. highlighted optimal baking performance (e.g., leavening ability) with yeast containing 15 mg/g iron, outperforming inorganic iron sources [17]. Similarly, Gaensly et al. [30] confirmed that iron-enriched yeast retains fermentation capacity, making it viable for iron-fortified baked goods.

The effects of process variables and ultrasound on stimulating the biotransformation of selenium in yeast have been investigated. The results demonstrated that optimization of parameters and the application of ultrasound successfully led to a 2.78-fold increase in selenium accumulation by S. cerevisiae [26]

Recently iron enrichment was reported in this research team by the production of S. boulardii, as a probiotc yeast in Fe enriched medium [11]. Nowosad & Sujka (2021) observed reduced fermentation activity in yeast overloaded with iron, particularly under pulsed electric field treatment, limiting its use to medicinal supplements rather than food application.

Industrial production of yeast is important from two aspects: a) the production with high productivity and stability, as well as the issue of economic production. However, metal absorption by S. cerevisiae cells is a complex process and involves various mechanisms, such as the production of metal-binding proteins, mineral incorporation, or compartmentalization in vacuoles within the yeast cells [14]. The yeast market is constantly seeking new products and processes, which can lead to advancements in biotechnology. Iron-enriched yeast biomass, when used in baking, can serve as a safer option for preventing anemia [18].

The industrial-scale fortification of S. cerevisiae biomass with iron has not been conducted until today, and this study represents a significant step towards the production of functional bread with enriched yeast. For the first time, this research examines the effect of different concentrations of iron on the performance of S. cerevisiae at an industrial scale. The results of this study could provide practical solutions for producing micronutrient-enriched breads with high bioavailability, thus taking a step toward improving nutritional conditions.

3. Declarations

3.1. Acknowledgments

None.

3.2. Authors' Contributions

All authors equally contributed to this study.

3.3. Declaration of Interest

The authors of this article declared no conflict of interest.

3.4. Ethical Considerations

All ethical principles were adheried in conducting and writing this article.

3.5. Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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3.7. Using Artificial Intelligent chatbots

None.

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