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PHYTOACTIVE AS CHELATORS OF IRON WITH THE POTENTIAL TO MITIGATE ITS SIDE EFFECTS AND ENHANCE IRON ABSORPTION

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ABSTRACT: Iron deficiency anaemia afflicts a large proportion of the human population, compromising productivity and quality of life. Iron supplements are widely prescribed for treating anaemia. However, poor compliance due to side effects, particularly gastrointestinal side effects, remain a hurdle in alleviating the problem, leading to unabated high prevalence. Thus, a fresh look at novel approaches to supplementation is essential. Iron toxicity is attributed to the Fenton Reaction and generation of reactive oxygen species leading to oxidative stress. Several studies suggest that the FR and ROS caused by excess iron, results in chronic inflammation, leading to metabolic syndrome, diabetes mellitus, atherosclerosis, cancer, neurodegenerative disorders. Iron chelates have been developed as treatment modalities to reduce free radical generation, reduce GI side effects, and enhance absorption. Classical Fe chelators, developed to counteract iron overload/ toxicity, cannot be used in IDA, due to severe side effects. In Ayurveda, iron formulations are prepared using phytomolecules that chelate iron and/or reduce OS. These phytomolecules are metabolized by the gut microbiota, which plays an important role in oxidative stress, release of inflammatory cytokines and GI side effects. The antioxidant, anti-inflammatory and antimicrobial actions of bio-active phytomolecules of Ayurvedic plants highlight their potential for reducing possible oxidant damage and side effects associated with iron supplementation. The present communication summarises the role of reactive oxygen species, potential of oxidant damage in causing side effects and microbial dysbiosis due to iron. Management of 'Pandu' an anaemia - like condition described in Ayurveda and use of selected medicinal phytoactives are reviewed.

INTRODUCTION:

Prevalence of IDA, Causes of Stagnation in Incidence of Anaemia: Anaemia is a highly prevalent persistent problem with potentially serious consequences **Fig. 1** [1, 2].

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The principal cause of anaemia is Iron Deficiency (ID) and some vitamins and protein most commonly. Functional and economic consequences of ID are lower work capacity and productivity, reduced immunity and increased susceptibility to infections.

In children, ID retards growth, cognitive development and endocrine maturation. These consequences impact strongly on the health and economic status of a nation [1, 3]. Globally, anaemia is prevalent in more than 20%of the population in 132 of 159 WHO-member countries [3].

ID is not restricted to middle- and low- income countries, as global statistics, indicate that anaemia prevails in industrialized and developed nations [4]. Globally, approximately 1.6 billion is anaemic and with the huge numbers of those affected, the disease puts an immense burden on global health [1, 5]. Across nations, in various sub-populations and socio-economic groups, the majority of those affected are women of reproductive age and children. Anaemia during pregnancy can lead to complications, contributing substantially to maternal and neonatal morbidity and mortality [6]. Since most cases of anaemia are due to nutritional iron (Fe) deficiency, efforts have been made to control and prevent ID using iron supplements (IS). IDA is considered as one of the most expensive diseases due to lost productivity, and the large numbers affected; [4, 7] its effect on overall health and earning potential at family level, productivity and impact on the economy at community and country level. Since the consequences of anaemia for an individual and an entire country can be devastating, prevention and control of anaemia by 2025 is one of the global targets [6, 7, 8, 9]. IDA results from not only Fe deficiency but also from haemorrhagic blood loss or diarrhoeas **Fig. 1**. Therefore, IS is needed to replenish body Fe and ensure adequate stores, whatever the cause. Towards the end of the 20th century, it was evident that Fe deficiency, with or without anaemia, needed to be addressed seriously as a major health problem. Despite constant efforts to overcome this serious but surmountable health problem, its prevalence has not reduced significantly in decades. In India, too, National anaemia prophylactic programs and Fe supplementation programs have been implemented by the Government since 1970, yet anaemia persists as a public health problem [10, 11]. According to the IVth National Family Health Survey, more than 50% of women and children and about one-fifth of men were anaemic [4].

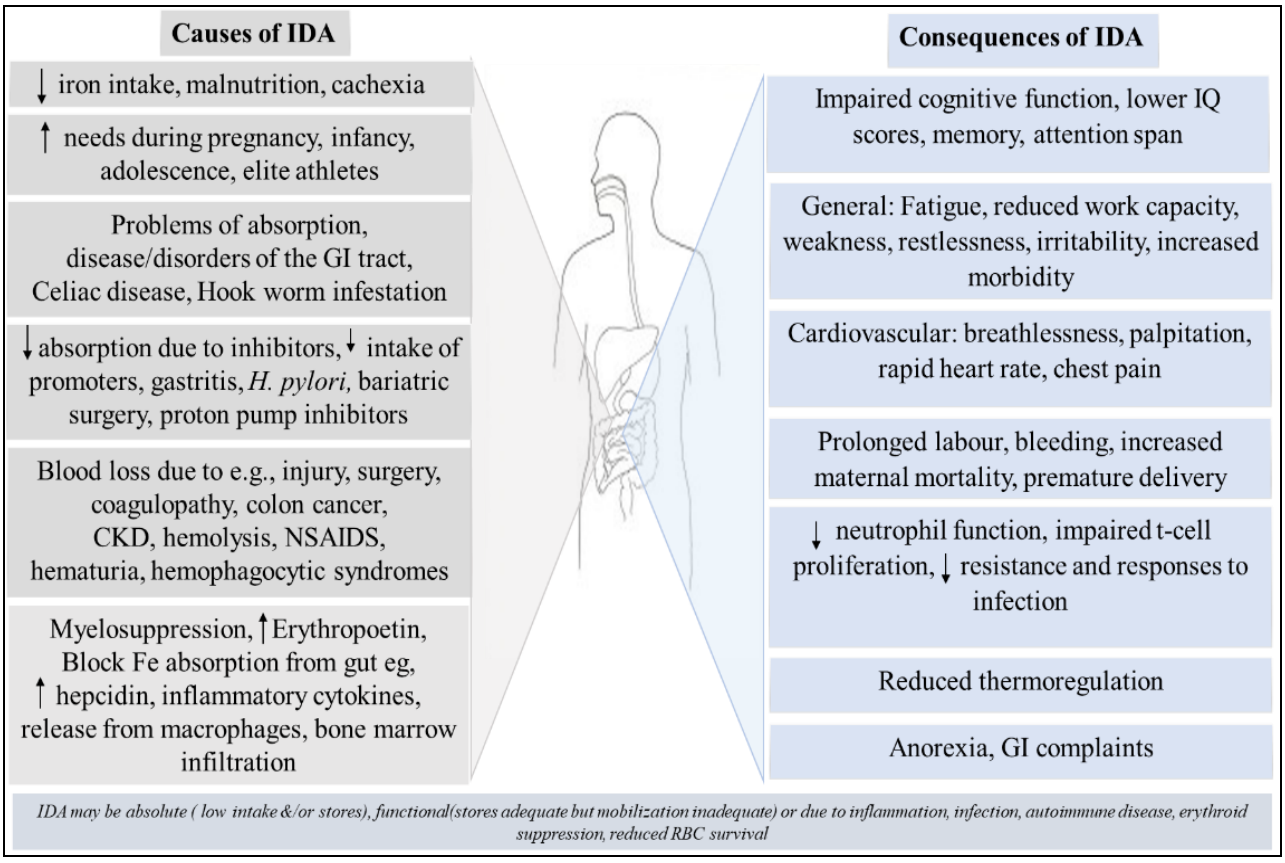

FIG. 1: CAUSES AND CONSEQUENCES OF IRON DEFICIENCY ANAEMIA

Prevalence has hardly decreased, as per the NHFS-5 report and the report of the Ministry of Health and Family Welfare (2019) [10]. The Comprehensive Nutrition Survey [11] indicated that 41% of pre-schoolers, 24% of school-age children, and 28% of adolescents were also anaemic, with a higher prevalence among female adolescents (40%) than their male counterparts (18%).

Major Reasons for Persistence of Anaemia as a Public Health Problem: The major reasons why anaemia persists as a public health problem are: a) population growth with unequal distribution of resources- poverty- Fe deficient nutrition, b) relative illiteracy in women, poor knowledge about adequate nutrition in the whole population, c) inaccessibility of health resources, d) side effects of Fe and discontinuation of IS, as continuation rates for therapy may be less than 50 % [12] and e) failure in some cases to identify metabolic defects in Fe metabolism and treatment of all cases of anaemia as 'Nutritional /IDA'.

While the first three causes are a function of policy makers and the social distribution systems, the fourth factor warrants analysis and can be remedied within the context of current scientific advances. The fifth factor is very difficult to detect on a mass scale with the current technology but may play some role in IDA management.

Side Effects of Iron of IS/Fe Therapy: First-line treatment of IDA is oral therapy with ferrous Fe salts, but a substantial proportion of patients suffers from gastro-intestinal (GI) side effects, resulting in non-adherence and treatment failure. Common side effects include constipation, dark stools, stomach pain, nausea, and vomiting, whereas diarrhoea, heartburn, urine discoloration, and teeth staining are less common [13, 14].

Side effects of oral IS, mainly related to the gastrointestinal (GI) system, are particularly troublesome during early pregnancy, which is inherently associated with nausea and vomiting. Hence, pregnant women are generally not given oral IS during the first three months unless the anaemia is severe.

The National policy prescribes routine oral IS for at least 3 months during pregnancy, given the high prevalence among pregnant women in India. However, a majority of pregnant women probably do not complete the treatment due to the side effects of IS and almost 35% of them could be noncompliant [8, 15, 16].

To overcome noncompliance, intermittent *vs.* daily Fe supplementation has been tried, and the side effects with the latter were less [17, 18]. A meta-analysis of 2133 full texts by Tolkien [19] indicated that even in women without prior GI disease, different oral Fepreparations /IS can cause side effects (constipation, nausea, and diarrhoea) in 32-47% of women.

Side effects are reported in children also [20]. In India, too, programs have not succeeded in addressing this huge problem.

Even the minor side effects of Fe interfere with the daily life of more than a third of the population treated with oral Fe. Some of these side effects can be counteracted through modifications in formulation development.

The most common approaches have been oral supplements with organic or inorganic Fe compounds to increase bioavailability and to reduce side effects. But some of these may be expensive or not very effective in reducing the side effects and have mostly not been made available in public programs.

This highlights the need to focus attention on side effects' cause (s) and investigate more acceptable alternative formulations that are also effective substitute (s) for current oral IS.

Iron, an Essential Mineral in All Body Functions: Iron is a constituent of at least 27 essential proteins and enzyme complexes in the human body that are important for cellular function **Fig. 2** [21, 22].

The plasma Fe pool of 3-4 mg is recycled manifold to meet the body's daily demand of about 20-25 mg for several functions, including erythropoiesis [23]. About 30% Fe is the storage compartment, with 20% being present in ferritin.

Fe is commonly present in the divalent ferrous (Fe^{2+}) and the trivalent ferric (Fe^{3+}) states in the body. Fe contributes to haemoglobin (Hb) and myohemoglobin (Myb) which are vital for circulatory and locomotive functions. Fe is essential for the central nervous system. Fe-containing proteins that contain about 5% of body Fe are needed for various processes **Table 1**. Besides Hb and Myb, major Fe-related protein are catalase and peroxidase participate in oxygen metabolism; cytochromes are involved in electron transport and mitochondrial respiration.

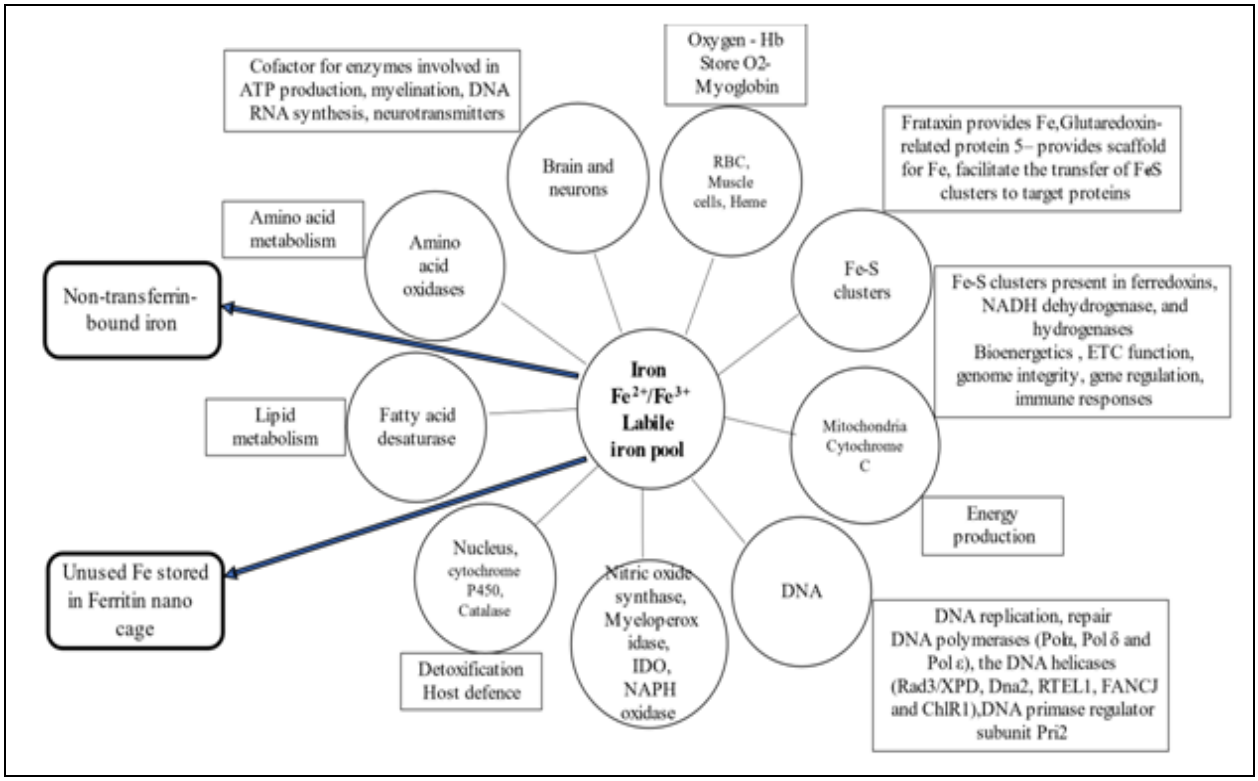

FIG. 2: ROLE OF IRON IN CELLULAR FUNCTION

Several non-heme proteins are essential for DNA synthesis, cell proliferation and differentiation, gene regulation, drug metabolism and steroid synthesis. Transferrintransports Fe for erythropoiesis, to muscle cells and T- and B-lymphocytes. Fe-sulfur clusters are non-heme essential cofactors with a role in electron transfer, substrate binding/activation, Fe/sulfur storage, regulation of gene expression, and enzyme activity [24]. Three other enzymes - hephaestin, ferroportin, and hepcidin, do not contain Fe but are involved in Fe transport, uptake or release. A metabolic defect in any of these enzymes may cause Fe insufficiency even when dietary intake is adequate. IS in these cases may correct the anaemia but may lead to undesired Fenton reaction (FR) and side effects. This has been reported for Iron Resistant IDA that is refractory to oral IS [12, 26].

TABLE 1: IRON-CONTAINING PROTEINS IN THE BODY ACCORDING TO THE LOCATION OF THE IRON-CONTAINING PROSTHETIC GROUP

Iron-containing prosthetic group	Names
Heme	Hemoglobin, myoglobin, cytochromes, cytochrome P450, Tryptophan 2,3-dioxygenase, peroxidases, catalases, cyclooxygenase (8)
Amino acids	Ribonucleotide reductase, proline hydroxylase, Phenylalanine hydroxylase,Homogentisic acid 2,3-dioxygenase, lipoxygenase, cyclooxygenase, transferrin, lactoferrin (8)
Iron-sulphide containing Fe-S complexes	Adrenodoxin, aconitase, succinate dehydrogenase, NADH dehydrogenase, xanthene oxidase, aldehyde oxidase (6)
Oxyhydroxide, Phosphate Fe	Ferritin, hemosiderin (2)

Adapted from Konteghiorghes (2020) [22]

Iron Absorption: Since, the human body lacks physiologic regulatory mechanisms for Fe excretion, maintenance of Fe homeostasis is almost entirely regulated *via* Fe absorption. Systemic Fe stores are regulated largely in the GI through Fe absorption, homeostasis at systemic and cellular levels, and storage. The daily loss of1-2 mg Fe through desquamation of intestinal cells, skin, minor blood losses is generally restored via intestinal absorption that is influenced by: (i) body Fe stores, (ii) hypoxia, and (ii) the erythropoietic rate. Dietary Fe is present as haeme and/or non-haeme Fe, with their sources and absorption mechanisms being different **Fig. 3A** and **B**.

Fe absorption from oral supplements consumed with and without food ranges from 2- 13% and 5-28%, respectively, in subjects with IDA [26] Fe absorption and its transport across the gut membrane is tightly controlled by hepcidin [Hcp] [27].

Hcp inhibits the Fe transporter/exporter protein, ferroportin (FPN1), which mediates the transport of gut Fe through enterocytes into the bloodstream. Daily administration of Fe supplements acutely increased plasma Hcp levels [28-29] and significantly reduced absorption of supplemental Fe from the intestinal lumen. In contrast, dose reduction and alternate-day dosing favoured better Fe absorption [30] **Fig. 3A** and **B**. Absorption is influenced by the body's requirements **Fig. 3B**. If a dietary Fe bolus is available and intracellular Fe levels are higher, the gut signal makes absorptive enterocytes resistant to acquiring Fe.

Thus, DMT1 expression is suppressed. Low Fe stores send a signal to stimulate and enhance absorption. Under normal conditions, once the Fe stores are replenished, the uptake returns to basal levels. Erythropoiesis modulates Fe absorption.

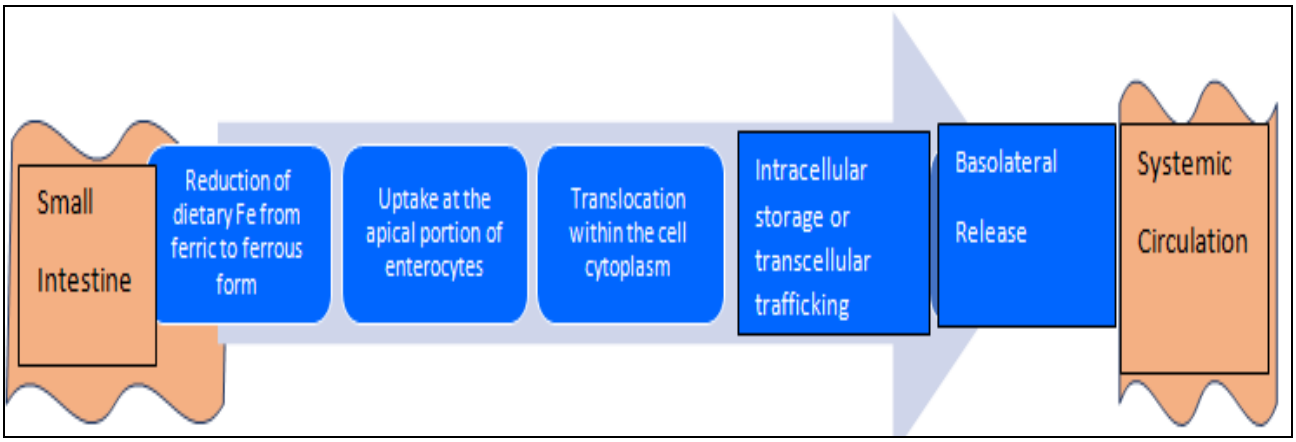

FIG. 3A: FIVE-STEP PROCESS OF IRON ABSORPTION IN INTESTINES

Storage and Recycling of Iron: Senescent/ damaged erythrocytes are phagocytosed by macrophages, and the haeme Fe is recovered byhaeme oxygenase for utilization, storage/ recycling. FPN1 has specific functions in Fe homeostasis is expressed in high amounts by enterocytes, macrophages, hepatocytes and trophoblasts. In macrophages, FPN1acts with ceruloplasmin / haepahaestin to release the ferric Fe to transferrin.

FPN1 is upregulated by haeme but down-regulated by inflammatory cytokines for sequestering Fe. Fe represses FPN1 translation.

FPN1 deletion resulted in haemolytic anaemia because of the toxic effects of Fe resulting from its oxidation in Hb, particularly because erythrocytes do not have much antioxidant capacity [31].

DMT1 is required for transport from vacuoles into the cytoplasm. In macrophages, Nramp1 plays an important role [32]. Delivery of Fe to cytosolicferritin, needs poly (RC)-binding protein 1 [32]. That can canstore up to 4500 Fe atomsin its mineral core, protecting against oxidative damage.

In the gastrointestinal tract (GIT), it can regulate Fe absorption, can convert the Fe^{3+} to the Fe^{2+} form, and prevent Fe overload.

Management of IDA: Conventional Supplements and Fortification:

Biomarkers for Assessment: Hb is generally used to diagnose anaemia, but Hb levels tend to be normal in subclinical Fe deficiency. Hb reflects IDA only in the later stages [33]. Also, it does not respond rapidly to Fe therapy/IS.

WHO [33] recommends the use of soluble transferrin receptors and serum ferritin. However, inflammation or Fe overload elevate ferritin levels because it reflects macrophage ferritin content [21, 35].

Therefore, inflammatory biomarkers need to be measured along with serum ferritin, to assess Fe status of when Fe bioavailability or toxicity are studied *in-vivo* or *in-vitro* using cell lines [36, 39].

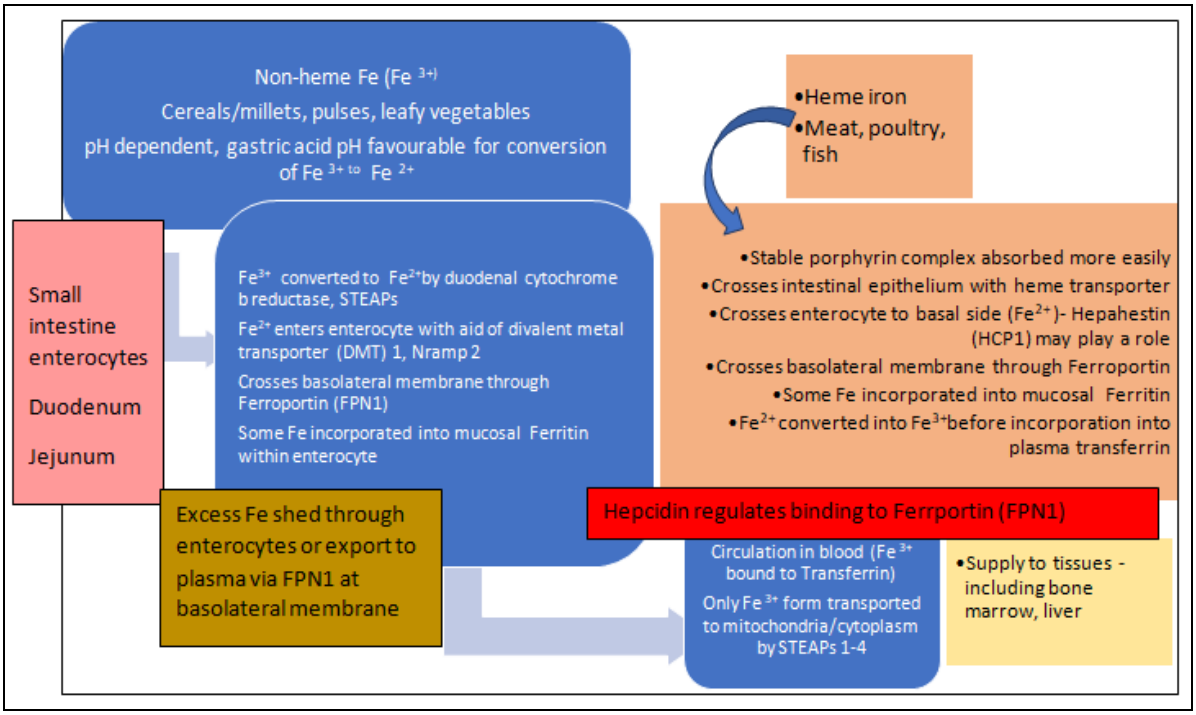

FIG. 3B: SCHEMATIC DIAGRAM OF ABSORPTION AND TRANSPORT OF IRON. Refs34-37, (STEAPs) -Six Transmembrane Epithelial Antigen of the Prostate Proteins

Iron formulations for Supplementation: Commercial Fe formulations are generally in two salt forms-ferric (Fe^{3+}) and ferrous (Fe^{2+}), or as aminoacid chelates, carbonyl Fe, polysaccharide-Fe complex, as single or combination and extended-release products **Table 2**. The objective of treating IDA is to restore Hb levels, RBCs indices and Fe stores. For effective absorption and optimum bioavailability, Fe^{3+} has to be reduced to the Fe^{2+} form that is absorbed three times more readily than Fe^{3+}. $FeSO_4$ (200mg twice daily) is the simplest and cheapest choice for initiating therapy. However, dose adjustment may be required for persons who cannot tolerate this dose. Instead of $FeSO_4$, better-tolerated salts like ferrous fumarate, ferrous gluconate, and ferrous ascorbate may be used, the latter being best tolerated [40]. Once the deficiency is corrected, oral Fe therapy should be continued to replenish Fe stores. Ascorbic acid (250-500mg) may be used to enhance Fe absorption; however, its effectiveness in improving Hb is not yet established [40-42]. Patients who are unresponsive or intolerant to oral Fe therapy can be administered parenteral formulations like Fe^{3+}carboxymaltose, Fe sucrose, Fe^{3+} hydroxide dextran either intravenously or by deep gluteal intramuscular injections. Fe sucrose is reasonably well tolerated compared to other salts when given by IV route, with a low incidence of adverse events. IV iron dextran can replenish Fe stores and increase Hb levels in one infusion, but serious adverse events, including anaphylactic reactions, may be fatal in some cases [43]. Also, this approach is not suitable for community programs as hospitalization is required. Parenteral Fe can increase oxidative stress (OS) and lead to cardiovascular complications in rare cases [44]. Oral IS results in GI side effects (*vide supra*) that include erratic Fe absorption due to the inability to localize Fe at the site of its maximum absorption. There is a need to design suitable forms of Fe or delivery system(s) that can deliver and help restore Hb with minimal side effects. Controlled release/ enteric preparations deliver Fe past the duodenum and jejunum, but they are poorly absorbed, and there is no substantial evidence that they fully alleviate side effects [45].

Fortification of Foods with Iron: Selecting a suitablefortificant and a food vehicle that will not diminish Febioavailability is important, as is minimizing undesirable organoleptic changes since some compounds tend to interact strongly with food components. Fe availability differs for different for toxicants such as those listed in **Table 2**, and others likeFe^{2+}lactate,Fe^{3+}pyrophosphate, NaFe EDTA, monosodium Fe^{3+}EDTA, Fe^{2+}bisglycinate, Fe^{2+}succinate, Fe^{3+} ortho / pyrophosphate and elemental Fe powders.

The amount used will vary with the compound. If Fe^{3+} pyrophosphate or electrolytic Fe are used, the amount needed is about twice the amount of $FeSO_4$, whereas a comparatively smaller amount of NaFe EDTA is needed, as it has higher relative bioavailability [40, 42, 45, 46, 48]. Worldwide, several foods, e.g., cereal flours, bread, pasta, salt, infant foods, milk, and yogurt, are fortified. For commercial foods, the amount of bioavailable Fe per serving generally provides 15-30% of the recommended daily allowance, or 7-8 mg Fe/day, with no risk of exceeding the Upper Limit of daily Fe intake [49]. Fe absorption from water-soluble Fe compounds and those completely soluble in gastric juice is similar to dietary Fe.

However, from the haematological perspective, universal Fe fortification of food may be problematic, notably for individuals with haemochromatosis and other Fe loading diseases. Also, its detrimental effects on gut microbiota need to be seriously considered [49, 50].

TABLE 2: COMMON FORMS OF CONVENTIONAL IRON SUPPLEMENTS, THEIR ADVANTAGES, AND DISADVANTAGES

Iron supplement	Elemental Fe (%w/w)	Dosage Forms	Advantages	Disadvantages
Carbonyl iron	100	Tablets, Chewable tablets, Suspension	Highest amount of elemental Fe Good solubility in gastric fluid, toxicity index of this form is less	Sometimes: diarrhea, constipation, nausea, vomiting, stomach pain, tooth discoloration
Fe^{3+} ammonium citrate	18	Capsules	Most commonly used Fe supplement Toxicity is low	Bioavailability is less, has to be reduced to Fe^{2+}form before absorption
Ferrous sulfate ($FeSO_4$) Is the oral soln a suspension or ??	20	Oral solution (su, tablets, Enteric-coated tablets, Film-coated tablets	Most commonly used Easily available Most economical	Tolerance is poor, Gastrointestinalside effects common
Fe^{2+}fumarate + Fe^{2+}asparto glycinate – chelated iron(2)	33	Tablets, Chewable tablets	Better palatability as it is tasteless Efficacy equivalent to $FeSO_4$, well tolerated	Sparingly soluble in water
Ferrous gluconate	12	Tablets, Intravenous	Efficacy equivalent to $FeSO_4$, Well tolerated	Causes gastrointestinal distress to some extent.
Polysaccharide -Fe complex – Fe Carbohydrate complex,Fe^{3+}Carboxymaltose, Low mol. wt Fe -dextran complex, Fe polymaltose, Sodium Fe^{3+}gluconate Fe sucrose, Fe^{3+} Carboxymaltose, Ferumoxytol polyglucose sorbitol carboxymethyl ether, Feisomaltoside Sources [44-47]	100	Capsules, Solution, Film-coated tablets, Intravenous	Ferric iron is complexed to hydrolyzed starch, making it tasteless and odorless. Bioavailability comparable to $FeSO_4$	Safety and efficacy of different Fe – carbohydrate complex administered intravenously depends on different carbohydrate coatings, and their pharmacokinetic profile (3)

Consumers' use of multiple fortified foods can theoretically result in over ingestion of Fe with possible side effects [51]. Hence, food fortification and distribution may need to be supervised.

Possible Causes of Side Effects of Iron: Oxidative Stress and Inflammation: Until recently, GI side effects were thought to be simply a unique function of a particular drug or host response. Eliminating these did not receive much attention, perhaps because they were considered unavoidable, and the benefits likely outweighed the side effects.

However, studies on diseases of Fe overload *e.g.*, hemochromatosis orhaemolyticanaemias, usually of genetic origin, have identified the specific toxicity caused by Fe. High circulating Fe levels in these diseases were associated with Fe deposition in various tissues, including the central nervous system, kidney and liver and high morbidity and mortality due to these complications. The site of Fenton reaction (FR) and Fe toxicity, resulting from the excess of free Fe, is located at the tissue level. The treatment requires parenteral administration of strong Fe chelators. However, these chelators are associated with side effects and complications; hence the treatment needs to be done in special centers under medical supervision. Also, this does not apply to IS side effects encountered in public health programs. The unabsorbed, excess free Fe in the GI tract is highly reactive and can directly mediate the formation of reactive oxygen species (ROS), generated through the Fenton and Haber–Weiss reactions [52, 53]. The FR and the resultant ROS are major sources of oxidative stress (OS). Some OS is needed for several essential biological enzymatic reactions, but a balance must be maintained because excessive free radicals can damage tissues. The FR and Fe toxicity occur at the intestinal luminal level and the tissue level, particularly in the liver, heart, pancreas, and brain, which have high levels of oxidative metabolism and are susceptible to ROS damage.

Mechanisms and Consequences of FR - Oxidative Stress and Inflammation: In 1894, HJH Fenton showed that metals like Fe and copper react with hydrogen peroxide (H_2O_2). They catalyze enzymatic reactions to produce highly reactive free radicals like superoxide(O2.-), and hydroxyl radicals (OH.), which can immediately react with other macro- and micromolecules they come in contact with, ultimately damaging cell function and structure. ROS are by-products of mitochondrial metabolism through the electron transport chain and the cytochrome P450 system **Fig. 4**. NADPH oxidases in phagocytes and endothelial cells [54] are intricately involved in the genesis of the inflammatory response [55] and are responsible for ROS generation. The major ROS include O2.-, H2O2, hydroxyl (OH-) anions, OH., peroxynitrite (ONOO-), and hypochlorous acid (HOCl). One-electron reduction of oxygen O_2, mediated by NADPH oxidase/xanthine oxidase (XO,) uncoupled endothelial nitric oxide synthase (eNOS), or mitochondrial electron transport chain (ETC); results in O2. - Formation [55-57] **Fig. 3.** The reaction starts with the donation of an electron and the conversion of the ferrous to the ferric form. The ferric salt is reconverted to the ferrous form with the Haber–Weiss reaction resulting in a chain reaction, wherein the reaction of H_2O_2 and superoxide ion (O 2 • −) catalyzed by Fe, generates hydroxyl and hydroxide ions.

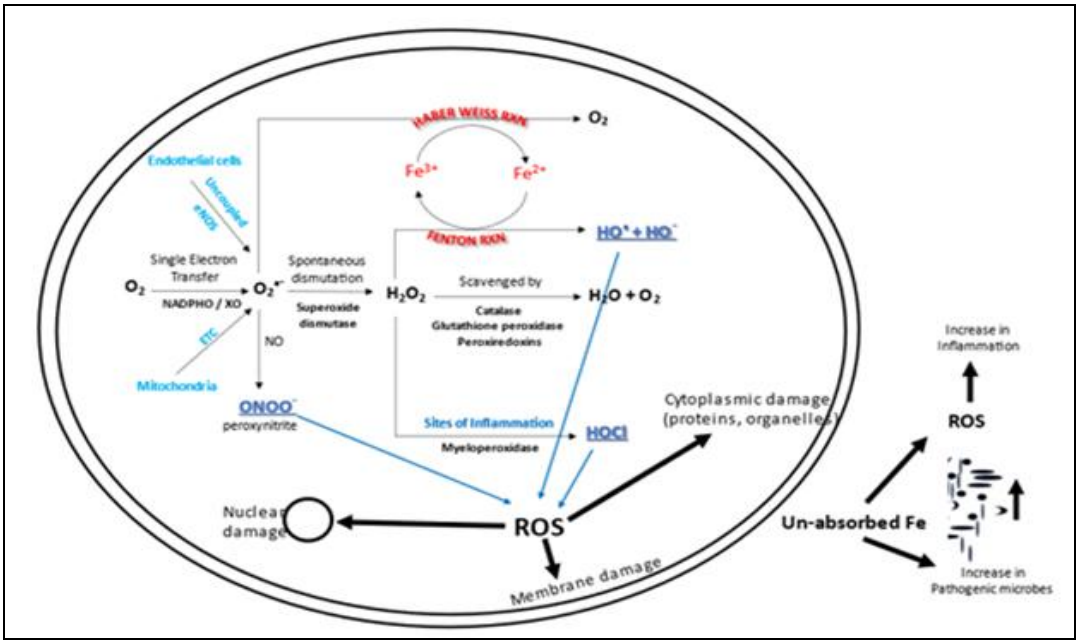

FIG. 4: MECHANISM OF FENTON REACTION, INTRACELLULAR & INTRALUMINAR ROS RELEASE IN INTESTINE

Intracellularly, ascorbate can replace $O_2^{\bullet-}$ and reduce Fe^{3+} to Fe^{2+}.Superoxide O^2.- a short-lived species can spontaneously dismutate to H_2O_2, a reaction accelerated by superoxide dismutase [55, 56]. It can also react with Fe^{3+} in the Haber-Weiss reaction to produce again Fe^{2+}, thereby affecting redox cycling. H_2O_2 is scavenged by catalase, glutathione peroxidase or peroxiredoxins and converted to H_2O and O_2.At inflammatory sites where polymorph nuclear neutrophils (PMN)are abundant, PMN-specific enzyme myeloperoxidase mediates the reaction between H_2O_2 and chloride and generates the highly reactive HOCl[58]. O_2.- rapidly reacts with nitric oxide(NO) to form the highly reactive ONOO-. This reaction itself does not cause OS toxicity, but it paves the way for the FR, where Fe^{2+} triggers the conversion of H_2O_2 to the highly reactive OH-radical and OH. Anions that are potent oxidizing species of biological membrane proteins and lipids [55, 58-60]. They interact with the surrounding biomolecules, in four ways: addition, hydrogen abstraction, electron transfer and radical interaction, consequent to which a cascade of reactions occur, with Fe-induced oxidative damage. The GIT is no exception to these effects of the unabsorbed/free Fe.

As intracellular Fe is in close proximity to DNA and other organelles, these highly reactive intermediates interact with DNA, alter its structure and function, cause polymerisation and deletions, translocations, or irreparable mutation. Modifications of various protein or sugar moieties, denaturation of proteins and proteolipid molecules, and abnormal cross-linkages, lead to cell death, apoptosis or autophagy. Proteolipid precipitation can form insoluble structures *e,g,* lipofuscin that can deposit as plaques [59-61]. Also, the intracellular events can damage microsomes, and activate Nuclear Factor Kappa-β, genes, and several other intracellular proteins with cross-linkages, oxidation, and proteolysis. Membrane damage can occur, leading to an imbalance in calcium homoeostasis, activation of Ca - dependent proteases, end nucleases, lipases, ATP depletion, NADP (H) and ultimately cell destruction [62]. Lipid peroxidation can occur, damaging the bilayer cell membrane and membrane-bound structures. The highly reactive lipid peroxidation products can cause cross-linkages and inactivate several physiological enzymes [19, 61, 62].

Further, transmembrane proteins, such as voltage-dependent anion channels (VDAC) in mitochondria, permit the transmembrane passage of the negatively charged superoxide O2.-, although it has limited permeability across membranes. H_2O_2 can cross biological membranes facilitated by aquaporin channels such as AQP3 and AQP8. Thus, superoxide and H_2O_2 can spread through cells that are in contact and the ROS-generating oxidative pathways in tissues distant from their point of origin [63-65].

Iron Supplementation and ROS: In the past, the FR was considered significant in pathological complications associated with Fe overload and Fe storage diseases like haemolytic anaemias, and liver and spleen diseases. However, subsequent reports indicated toxicity accompanying the use of therapeutic Fe load or oral IS used for treating IDA. The observations that a significant proportion of IDA patients discontinued the treatment due to GI side effects led to the suspicion and later confirmation of the possible role of Fe during Fe replacement therapy.

The excess Fe from the diet or supplements makes the GIT vulnerable to ROS that is also produced by intestinal immune cells and intestinal flora. The GIT has the highest concentration of xanthine oxidase, and numerous phagocytic cells generate considerable amounts of $O2^{\cdot-}$ [66]. Daily Fe supplementation in mildly anaemic women led to significant increase in OS [67, 68]. A 40% increase in free radicals was detected in the faeces of healthy human volunteers who consumed Fe supplements (98 mg of Fe as $FeSO_4$/day for 70 days) [64, 69]. Ethane exhalation in breath also increased, and plasma malonaldehyde levels were correlated with the increase in plasma Fe and ferritin. Even a single oral dose of 80 mg $FeSO_4$significantly increased lipid peroxidation in healthy volunteers with a high probability of oxidative damage in the small intestine [70]. In 72 healthy adults and children who exercised daily, Fe status, creatine kinase activity(CK), and redox status were assessed at baseline, before, and 72 h after exercise. The experimental group was treated with 35 mg of elemental Fe for 3 weeks before assessment. ROS increased in adults and in children, while CK activity increased only in adults. Fe concentration and transferrin saturation increased after Fe

therapy. The authors proposed that higher doses or longer duration of IS may further increase the ROS that may lead to side effects [71]

Oxidative Stress, Iron Deficiency Anemia and Chronic Diseases: The conditions that give rise to Fe deficiency also promote OS [72]. When there is infection and/or inflammation, the body tends to absorb less Fe to withhold it from the pathogens that require Fe [73]. OS occurs in many chronic diseases in which Fe deficiency occurs, wherein FPN1 is negatively regulated by hepcidin, possibly leading to Fe deficiency [74]. Additionally, the hypoxiainduced by anaemia may worsen OS, *via* pro-oxidant changes leading to increased free radical production, altered cellular metabolism, increased catecholamine metabolism, and leukocyte activation [75]. IS can help in Hb production and build up iron stores; however, it is important to manage any underlying condition that could negate the benefits of IS therapy. In this respect, antioxidant therapy can ameliorate anemia-related oxidative damage [76]. Even a small proportion of excess Fe can activate the FR and ROS-induced damage. Even if it is asymptomatic, there can be risk of chronic diseases over time, resulting from the direct toxic effect of Fe from the FR and secondly due to dysbiosis and other causes. Chronic diseases include premature aging [77], metabolic syndrome, diabetes mellitus [78] Alzheimer's disease [79], Parkinson's disease [80], inflammatory bowel disease [81] non-alcoholic fatty liver disease [82], cancer [83] cardiovascular disease [84] and arthritis [85]. Ferroptosis *i.e.* cell death and necrosis resulting from Fe toxicity has been reported [21, 22, 86, 87].

Inflammation: Enzymes with Fe complexes are vulnerable to disintegration when there is Fe - generated ROS. Disruption of the antioxidant/ oxidant balance and excess ROS lead to changes in membrane permeability, activation of NF-kB, production of many proinflammatory cytokines *e.g.*, IL-6, Tumor Necrosis Factor (TNF)-α, extracellular kinases that are mitogen activators, can activate protein kinase C, generate other stress proteins and disrupt multiple pathways. Ultimately, Fe excess can lead to cell death and inflammation. Aseptic inflammation of intestinal luminal cells occurs, resulting in the production of toxic products responsible for the side effects [86, 87].

In rodent models, Fe overload-induced ROS caused inflammation and several histopathological alterations in the duodenum and ileum, impaired cellular function, cell turnover, shortening of microvillus height, and partial to complete erosion of the duodenal microvilli. Even a single oral dose of 8 mg Fe, led to apoptosis of GI mucosal cells and necrosis of the GIT absorptive surface [88].

Fe toxicity increased infection, inflammation, and Fe deposition in the duodenal villi tips [89]. In rats, administration of ferric citrate (2.5, 5 or 10 mg/day) for 16 weeks resulted in body Fe overload, decreased jejunal villus height, the ratio of villus height to crypt depth, the number of intraepithelial lymphocytes and goblet cells [90]. Proinflammatory cytokine levels increased while anti-inflammatory cytokines and sIgA declined. Malondialdehyde, protein carbonyl, and serum lactate increased, while tight junction proteins like claudin-1, occludin, ZO-1, MUC-2, TFF3, and glutathione and antioxidant enzymes like superoxide dismutase, glutathione peroxidase decreased. These alterations reflected intestinal immune and barrier function impairment attributable to ferric citrate-caused OS [91].

However, different Fe compounds may vary in their effects. Liquid ferrous gluconate was found to be comparatively safe, whereas Fe polysaccharide was associated with diarrhea [90, 91]. In children, effects of Fe^{2+}or Fe^{3+} administration over 6 months were compared on erythrocyte malondialdehyde, urine 8-isoprostane, oxidized LDL, superoxide dismutase, catalase, and glutathione peroxidase activities. In the Fe^{3+} group, superoxide dismutase levels and oxidized LDL levels were higher at the end of the 1stand 6th months, respectively [92].

Since, dietary Fe is poorlyabsorbed–maximum of 20% among meat eaters and only 10% in vegetarians; oral Fe preparations contain more than five times the amount actually absorbed. Daily supplemental doses of up to 200 mg have been used, although the estimated average requirement for adults is only 11-32 mg. With 200 mg, side effects like abdominal cramps, diarrhoea or constipation, and an increase in C-reactive protein (CRP) were seen. Even with a lower dose of 100 mg, side effects have been reported [93], because the

unabsorbed Fe (80-90% of a single dose) is highly reactive and mediates ROS formation through the Fenton and Haber–Weiss reactions [93, 94,] causing damage and inflammation during its transit in the GIT. Also, this unabsorbed Fe promotes the growth of pathogenic intestinal microbes [95, 96], resulting in intestinal inflammation, leading to a double assault.

Inter play between Iron and the Gut Microbiome: The alteration of the intestinal microbiome by excess Fe and its effects warrant attention. The commensal organisms in the human GIT protect against opportunistic pathogens, synthesize nutrients like vitamins B12, K, metabolize undigested substances, particularly using prebiotics as substrates, and produce short-chain fatty acids (SCFA) that provide energy to the intestinal cells. Also, they contribute to the development of the intestinal structure and functioning of the immune system [97, 98].

Gut microflora plays an important role in Fe metabolism. Numerous intestinal organisms need Fe for their replication, development, and metabolism. Colonic microbiota can shift the valence state of Fe and sequester Fe through siderophore production to meet their needs [66]. The viability of gut microbiota was favored by both ferrous and ferric forms of Fe [66]. Since, only about 10-15% of dietary Fe is absorbed in the duodenum, much of the unabsorbed Fe, particularly from supplements, is available to the resident colonic microflora and can cause changes in the intestinal microenvironment. The organisms can produce harmful metabolites that may damage the lumen or be absorbed into the circulation, reach various tissues and increase the risk of chronic diseases [98, 99].

In germ-free mice, in the presence of gut microbiota, the intestinal cells acquired an ability to store Fe in ferritin, and Fe transport was favoured by increased FPN1expression [100]. Propionic acid, a SCFA produced from substrates like prebiotics in the colon has been shown to enhance luminal Fe absorption[101]. Lactic acid-producing bacteria enhance Fe absorption whereas other types of bacteria do not, suggesting that the type of organism may influence the risk of IDA. Fe can increase the replication and virulence of gut pathogens like *Salmonella*, *Shigella*, *Campylobacter*, because it is important for their gene expression [102-104]. Fe status may influence the survival of *Salmonella* in host intestinal epithelial cells[105]. A similar phenomenon has been observed in the infectivity of different organisms residing in macrophages [104, 105]. Thus, Fe can influence the infectivity of pathogens and modify the gut microbiota through metabolic changes in the colonic lumen [66, 98]. Parmanand *et al.*, [98] reported that Fe availability reduced through chelation led to significantly reduced growth of *E. coli*, *S. typhimurium*, *B. thetaiotaomicron* and *B. longum.* In contrast, a decrease in the beneficial barrier commensal gut bacteria *e.g.*, *Bifidobacteria* and *Lactobacilli* have been observed in Fe supplemental states. This is further worsened by an increase in enterobacteria, including enteropathogenic *Escherichia coli* [95, 96].

The host immune system responds to harmful pathogenic bacteria by inducing varying levels of gut inflammation. This is often manifested as diarrhoea, in many adults, but especially in vulnerable populations such as infants and children are given Fe supplements [106, 107]. Young children in the first two years are vulnerable to the adverse effects of IDA on cognitive, motor, social-emotional, and neurophysiologic development [107, 108]. IS benefits cognitive performance in school-aged children [108, 109]. WHO [110] recommends Fe supplementation as a public health preventive measure, for infants and children aged 6-59 months and for school children living in settings where anaemia is highly prevalent. However, in supplemented children, Fe supplements have been associated with hospitalization and mortality [96].

In a placebo-controlled clinical trial, African children (1-35 months old) who were at risk of complications of anaemia in addition to malaria were treated with prophylactic Fe+ folic acid supplements and followed up for hospital admissions and mortality [111]. This study was discontinued because the interim analysis showed that hospital admissions and deaths were more common in the group receiving Fe + folic acid supplements and indicated the adverse effect of Fe in promoting inflammation of the bowel and other organs. Therefore, children with IDA may benefit from IS, but those with adequate Fe intakes may be affected by Fe toxicity even in the absence of

Hemoglobinopathy or liver metabolic disorders *e.g.,* Hepatosplenomegaly- Haemochromatosis. Increased morbidity and altered gut microflora in Fe - replete infants and young children have been noted [111, 112]. A large meta-analysis found that although oral IS may contribute to general health, stamina, cognition, and brain health, it did not promote linear growth, in contrast to a positive effect seen with zinc supplements [112].

Sachdev *et al.,* [114] and Pasricha *et al.,* [115] in their systematic reviews on the effect of IS on physical growth in children, indicated that there was no significant, positive effect on anthropometric indices and physical growth, although the daily Fe supplement reduced anaemia. Children who received Fe had slightly lower length and weight gain and their risk of vomiting and fever was likely to be more [115, 116].

Such possibly differential effects of IS on Fe-replete, well-nourished children and on malnourished children warrant closer inquiry. Nchito *et al.*[116] showed that African schoolchildren givenoral Fe supplements had increased small intestinal permeability that may allow easier translocation of pathogenic bacteria across the gut wall, with severe, bloody diarrhea in some cases. In a 10-year follow up study of Chilean children who were fed Fe-fortified (12.7 mg/l) or low-Fe formula (2.3 mg/l), from 6 -12 months of age, the Fe-supplemented children were found to have lower scores for IQ, arithmetic, visual perception and motor coordination. In Cambodian primary school children, consumption of micronutrient fortified rice (including Fe) was associated with a higher risk of hookworm infection [117].

Thus, the addition of Fe to the diet or Fe supplementation in malaria-endemic areas has to be weighed against the risk of increased incidence and severity of malaria, as the parasite requires Fe for its growth [117]. Similarly, other intestinal pathogenic bacteria also show overgrowth in the presence of excess Fe, possibly leading to direct intestinal bacterial infections. Overgrowth of pathogenic bacteria can also cause OS and produce undesirable toxic products like sulphur dioxide, which can irritate the luminal cells and result in abdominal colic or diarrhoea[118, 119]. The human microbiome is altered with age, sex, diet, antibiotic treatment, hormonal dysfunction, and obesity. An altered microbiome has emerged as an important determinant of metabolic syndrome that predisposes many individuals to cardiovascular diseases [120, 121] hence, the role of Fe in dysbiosis bears scrutiny. In this context, plant components/ bioactive could be potentially useful. Those with antimicrobial properties could help in modulating the gut microbiome. Also, they could serve as anti-oxidants, chelate Fe, and help to attenuate the FR, reducing ROS. The following section discusses the role of plant/plant-based products and phytoactives.

Concepts in Traditional System of Ayurved: *'Panduroga'*has been described in ancient Ayurvedic texts (5 - 6 BC) [122]'*Pandu*' is characterized by yellowish-white skin colour of anaemic patients. Ayurvedic texts describe numerous symptoms like generalized weakness, fatigue, lethargy, loss of normal complexion, loss of appetite, giddiness, body ache, fever, breathlessness, palpitations, irritability, ringing in the ears, leg cramps *etc*., that are akin to those described for ID in modern times. '*Panduroga*' was treated with different '*bhasmas*'that are essentially metallic/mineral preparations made by special pharmaceutical processing and other measures. These formulations have been used extensively for centuries by Ayurvedic physicians and are still used presently by Vaidyas to manage *Panduroga* (IDA) [122]. Different pharmaceutical processes and medicinal plants are used for preparing different bhasmas. Various texts describe numerous formulations to be used according to the type of patient, cause of anaemia, associated conditions, and complications [123]. In case of Fe, there are more than 300 preparations, about 290 are based on iron oxide nanoparticles i.e., Lauhabhasma, approximately 80 formulations are based on iron pyrite, ferrous sulphate, and ochre [123]. Four preparations are quite commonly used: Loha/Lauha Bhasma, [124] ManduraBhasma [125] (Ferri proxy rubram), Kasis[126] (Iron sulphate), Suvarna MakshikBhasma (Iron pyrite) [124-,127]; or Ayaskruti [128].

Preparation of IS in Ayurveda: All Ayurvedic metallic drugs undergo various purification/cleansing processes, termed *'Shodhana'*for removal of external/internal impurities in the ore and to enhance the therapeutic action of the final formulation.

Shodhana consists of Samanya Shodhana'(general purification) and 'VisheshShodhana'(specific purification). 'Marana'follows'Shodhana', wherein the iron ore is ignited repeatedly in a 'Puta' (dried cow-dungfurnace) and triturated until fine powders /Bhasmasare finally obtained **Fig. 5**. *Lohabhasma* was found to exhibit irregular aggregates of various sizes and shapes with nanostructures on the surface (100 to 500 nm) [128, 129] which has been confirmed with scanning electron micrographs [130, 131].

In some studies, the *bhasmas* contained nanoparticles that may easily penetrate the human intestinal epithelium and interact at the subcellular level [131].Whether this will enhance Fe absorption and what will be their effects on ROS and inflammation needs to be studied. Many medicinal plants are used for *Shodhana* and *Marana i.e. Bhasmikaran.* **Table 3** lists the seven most commonly used plants and their properties. Many of these plant materials /phytoactive have pleiotropic action. Although numerous phytoactive have been investigated for several important pharmacological activities, e.g., anticancer, hypoglycemic, cardioprotective, wound healing, etc., these are not included. The review primarily deals with the anti-oxidant and/or anti-oxidant or anti-inflammatory activities that are likely to counter the side effects of Fe therapy.

The seven Ayurvedic plants used traditionally in the four *bhasmas* mentioned above and listed in **Table 3** have both antioxidant and anti-inflammatory effects.

FIG. 5: TYPICAL PROCESS OF BHASMA PREPARATION

These properties may reduce the side effects of Fe, and some may also increase Fe bioavailability. The use of iron oxide specially heated, powdered, and processed with medicinal plants (Lauhabhasma)

has been described, and different plants have been used for different types of anaemias [124, 125]. Most of the plants used in bhasma preparation contain bioactive constituents and are pharmacologically active. Curcumin in turmeric, ellagic acid in Amlaki / *Emblica offincinalis,* and zingiberene in ginger possess antioxidant and anti-inflammatory properties, as do all the plants listed in **Table 3**.

These phytoactives also chelate Fe1 [153, 154] and might help to reduce gut dysbiosis that can result from the unabsorbed Fe. Several clinical studies conducted on Fe preparations used in Ayurveda to treat Pandu (IDA) have shown encouraging results without exhibiting the common side effects as seen with conventional modern Fe preparations [143-148, 154-163].

Table 4 lists some plants used in other traditional systems of medicine. Most of the phytoactivesin the plants listed in Tables 3 and 4 are polyphenols that are well-known antioxidants.

TABLE 3: BENEFITS OF SELECTED AYURVEDIC MEDICINAL PLANTS USED IN SHODHANAAND MARANA OF LOHA & MANDUR ORE

Part of Plant	Botanical name	Sanskrit and Common) name	Phytoactive	Other pharmacological indications	Refs
Seeds	*Sesamum indicum*	Til (Til)	Sesamin, sesamolin, sesaminol, sesamolinol, pinoresinol, *etc*	anticancer, antihyperlipidemic, hepatoprotective,	132,133
Grains	*Oryza sativa*	Shali (Rice)	ϒ-Oryzanol, ferulic acid, β-sitosterol,* stigmasterol*, capesterol*, *etc*	antiaging, melanogenesis stimulating activity	134,135,136
Roots	*Raphanus sativus*	Mulak (Radish)	Glucoraphanin*, glucoraphanin*,	Gut stimulatory, antihypertensive, antidiabetic, antiobesity & anti tussive,	137
Grains	*Mycrotylora uniflorum / Dolichos biflorum*	Kulthha (Horsegram)	Quercetin, kaempferol, myricetin, daidzein, genistein, *etc*	Cytotoxic , analgesic, diuretic	138, 139
Fruit	*Phyllanthus emblica / Emblica officinalis*	Amalki (Amla)	Cinnamic acid, gallic acid, quercetin, β-Daucosterol*, ellagic cid, 5-hydroxymethylfurfural*,	Antimicrobial, analgesic and antipyretic, hepatoprotective, antitumor and antiulcerogenic, antidiabetic, hypolipidemic, antibacterial activities	140
Fruit	*Terminalia chebula*	Haritaki (Harda)	Gallic acid, ellagic acid, ethyl gallate, vanillic acid, terchebulin, chebulagic acid, chebulanin, *etc*	Anticarcinogenic, Antimutagenic, radioprotective and chemopreventive, Hepatoprotective, Cardioprotective, Cytoprotective, Antidiabetic and renoprotective, Antibacterial, Antifungal, Antiviral, *etc*	141,142
Fruit	*Terminalia bellerica*	Bibhitaki (Behda)	Bellericanin, ellagic acid, gallic acid, termilignan, thannilignan, ellargic acid, ethyl gallate, galloyl glucose,chebulaginic acid, phenyllemblin, α- sitosterol*	Antitussive, analgesic, hepatoprotective, antibacterial, anticancer and immune-modulatory activities	143
Rhizome	*Curcuma longa*	Nisha (Haldi)	Curcumin; demethoxycurcumin; bisdemethoxycurcumin; 1,7-bis (4-hydroxyphenyl)-1, curcumadiol 4, 6-heptatrien-3-one; α-turmerone; β-turmerone; terpinolene; α-phellandrene;	Anti-tumor, anticancer, anti-mutagenic, antifungal, antidiabetic, antifibrogenic, wound healing, immumodulatory	144

*-compounds are not polyphenols

TABLE 4: PHYTOACTIVES IN SELECTED PLANT MATERIALS WITH ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITY

S. no.	Plant source	Botanical name	Common name	Phytoactive	References
1	Leaves	Camellia sinensis	Tea	Epicatechin gallate, epigallocatechin gallate, epicatechin, epigallocatechin, carbohydrates*, caffeine, adenine, gallic acids, tannins, gallotannins, quercetin glycosides, carotenoids, tocopherols, vitamins (A, K, B, C)*, small amounts of aminophylline*	145,146
2	Leaves	Mimosa pudica	Touch-me-not	C-glycosylflavones, including 7, 8, 3',4'-tetrahydroxyl-6-C-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl flavone; 5, 7, 4'-trihydroxyl-8-C-[α-L-rhamnopyranosyl-(→2)]-β-D-glucopyranosyl flavone; and 5, 7,3',4'-tetrahydroxyl-6-C-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl flavone; 5,7,3',4'-tetrahydroxy-6-C-[β-D-apiose-(1→4)]-β-D-glucopyranosyl flavones; 5,7,4'-trihydroxyl-8-C-β-D-glu-copyranosyl flavones; 5,7,3',4'-teteahydroxy-6-C-[β-D-apiose-(1→4)]-β-D-glucopyranosyl flavones [3]; and 5,7,4'-trihydroxyl-8-C-β-D-glucopyranosyl flavones	147
3	Seed	Garcinia kola	Bitter kola	Kolaviron, garcinia hydroxybiflavanonol	148
4	Root	Scutellaria baicalensis Georgi	Chinese skull cap	Polyhydroxyflavonoids, namely baicalein, oroxylin A and wogonin	149
5	Root	Ligusticum wallichi	Szechuan lovage	Tetramethylpyrazine, (±)-3-methoxysedanenolide, sedanenolide, Z-ligustilide, Z-butylidenephthalide, methyl ferulate, trans-ferulic and trans-isoferulic acids, falcarindiol, -sitosterol, daucosterol*	150,151
6	Fruit	Vaccinium macrocarpon	Cranberry	Proanthocynadin Dimer A-type, Proanthocynadin Trimer B-type, Proanthocynadin Trimer A-type, Chlorogenic acid, Malonylcaffeoylquinic acid, Quercetin, Quercetin-3-rut, Quercetin-3-gal/glc, Quercetin-3-arab, Myricetin-3-gal/glu, Myricetin-3-ara, Syringetin-3-O-glu, Syringetin-ara, Laricitringlu, laricitrinara	152

*-compounds are not polyphenols

Iron Chelation: Chelation of transition metals can directly reduce the rate of the FR and prevent OS caused by highly reactive ·OH radicals [164, 165]. Fe chelators are chemically quite diverse they typically contain oxygen, nitrogen or sulfur (S)-donor atoms that form coordinate bonds with bound Fe. The donor atoms of the ligand affect the preference of the chelator for either the Fe (II) or Fe (III) oxidation states [165]. Chelators that prefer Fe (II) contain 'soft' donor atoms, such as nitrogen and S, and consequently retain a relatively high affinity for other biologically important divalent metals such as $Cu^{2+,}$ Zn^{2+} [166]. Fe can coordinate six ligands in an octahedral arrangement; thus, Fe chelators with the highest affinity will normally be hexadentate, binding Fe in a 1:1 ratio (chelator: iron). By contrast, bidentate (2:1 ratio) or tridentate (3:1 ratio) chelators, which bind to only two or three of the available Fe chelation sites, can potentially participate in the redox cycle and thereby promote free radical generation [167]. Kontoghiorghe, Kolnagou & Kontoghiorghes [86] pointed out that unlike drugs or chelators used to treat Fe overload, substances/compounds explored as possible candidates for treatment of IDA, "should be able to increase Fe absorption and increase Hb production to normal physiological levels". Effective Fe chelators must efficiently compete with the biological ligands that normally bind Fe; therefore, the affinity of chelators for Fe and their stoichiometry of Fe binding will greatly impact their activity as therapeutic agents [166, 169]. Several synthetic compounds like deferoxamine mesylate, desferrithiocin, deferiprone are siderophores and synthetic chelators like 8-OH hydroxyquinoline derivatives, deferasirox,

dexrazone, tachypyridine, thiosemicarbazones, pyridoxal isonicotinoyl hydrazone analogs are in focus. These compounds not only selectively chelate Fe^{3+} but also have antineoplastic activity [167]. Plants or plant products, including those consumed as food by humans, contain low molecular weight organic molecules that are candidates as Fe chelators. They could protect against the toxic effects of ROS and reactive nitrogen species by inhibiting or mitigating the effects [86]. Several compounds including polyphenols have great potential. Carboxylic acid derivatives like citrate, ascorbic acid, fulvic acid, humic acid, inositol phosphates, particularly the hexaphosphate, are also potential candidate phytomolecules [86, 87].

Antioxidant Activity of Plants / Phytochemicals: Polyphenols are among the most diverse and ubiquitous groups of plant secondary metabolites/ biomolecules. Although the anti-oxidant property of polyphenols has been known for a long time, the focus on their role as Fe chelators is recent [87, 168]. Metal chelation by polyphenols has implications for several important processes in nature and biological systems [163, 164]. They are part of the 'plant defense' against pathogens by chelating Fe and other essential minerals and thus limit the growth of invasive microorganisms by causing severe mineral depletion [169]. These compounds are heterogeneous molecules, differing in their chemical structures [169-171]. Also, they may be present as glycosides with different sugar units / acylated sugars at different positions of the polyphenol skeletons or bound to organic acids or with one another, creating additional diversity [172]. Naturally occurring phenolic compounds can be divided into three classes: i) shortly distributed, *e.g.,* simple phenols, pyrocatechol, hydroquinone, aldehydes derived from benzoic acids that are components of essential oils, e.g., vanillin, ii) widely distributed *i.e.,* flavonoids and their derivatives, coumarins and iii) phenolic acids, *e.g.*, benzoic/cinnamic acid and their derivatives) and polymers (tannins and lignins) [173].

Based on location in the plant (free in the soluble fraction of cell or bound to compounds of the cell wall), together with their chemical structures, phenolic compounds may also be: simple phenols (flavonoids and tannins of low and medium molecular weight not bound to membranes' compounds) and essentially constituted phenols (condensed tannins, phenolic acids, other phenolic compounds of low-molecular-weight bound to cell wall polysaccharides or proteins forming insoluble stable complexes). This classification is relevant in terms of the metabolic fate in the GIT, and the physiological effects of each group will depend largely on their solubility characteristics. Insoluble phenolic compounds are not digested and may be partially or fully recovered quantitatively in the faeces, while a part of the soluble ones can cross the intestinal barrier and be found in the blood, unchanged or as metabolites [174].

Several polyphenols with a 1,2-dihydroxy, a α-hydroxyketo, or β-hydroxyketo substitution efficiently chelate trace metal ions, like Al3+ and $Fe^{3+,}$ and $Cu^{+,}$ that play an important role in oxygen metabolism and free radical formation [172-174]. Polyphenols with gallol and catechol groups are the most potent antioxidants because of the large Fe-binding stability constants for these groups [171-173]. Amongst polyphenols that are free radical scavengers and metal chelators, flavonoids have been well studied for their ability to chelate metals. The Fe chelation activity of flavonoids depends on their chemical structures and the position and degree of hydroxylation appear particularly important for their biochemical and pharmacological actions [171-176]. Additionally, flavonoids have been shown to chelate Fe more efficiently when the metal ion is in bivalent form, meaning that the flavonoid needs to reduce Fe^{3+} to Fe^{2+} before association that depends upon the number of hydroxyl groups and pH of medium. The proposed binding site for trace metal ions to flavonoids is the 3′, 4′-di-OH moiety in the B ring. In addition, C-3 and C-5 OH groups and the 4-carbonyl group also contribute to metal ion chelation.

At pH 5.5, the flavones myricetin and quercetin reduced $Fe^{3+,}$ rutin, catechin, and taxifolin were moderately active but kaempherol and luteolin were poor reductants. This is because the simultaneous presence of the catechol group in the B-ring and 3-hydroxyl group in the C-ring plays a crucial role in reducing the potential of flavonoids. The presence of 2, 3-double bond in conjugation with the 4-oxo group in C ring is also important for

Fe^{3+} reducing capacity. The 2,3-double bond apparently increases the planarity of the molecule, confers higher rigidity to the ring, and holds the A and C rings in a more coplanar position, allowing the 3-hydroxyl/4-oxo groups and 5-hydroxyl/4-oxo groups to be closer. Thus, polyphenols with gallol and catechol groups are the most potent antioxidants because of the large Fe-binding stability constants for these groups [171-176]. The catechol moiety of polyphenols is not just important for metal chelation. It also confers antioxidant properties to curcumin, caffeic acid, catechin, and protocatechuic acid, gallic acid, epicatechin gallate, ellagic acid, tannins. Flavonoids like quercetin, kaempferol, myricetin, green tea catechins and black tea theaflavins, the isoflavones genistein and mangiferin all have Fe-chelating ability. Overall, all gallic acid containing compounds could be potential Fe chelators [176-178]. Another potential advantage besides binding Fe and functioning as antioxidants[86] is that compounds like flavan-3-ols and their condensation products. i.e. proanthocyanidins have anti-microbial properties [171, 176, 178].

The strong Fe binding affinities of polyphenol-rich plant materials that help to suppress Fenton chemistry [178], suggest their potential for use as Fe chelators in two new but important areas – (i) developing Fe supplements with low side effects and (ii) food supplements for diseases characterized by OS. In a way, both these ideas are not new. Ayurveda uses elemental Fe (*Lohabhasma*) for the treatment of anaemia. Many of the IS formulations contain botanicals such as *amla* (Indian gooseberry), *dadima* (pomegranate), *draksha* (raisins), and all these botanicals are rich in polyphenols. One potential reason for their inclusion in the formulations could have been to control the gut's free radical generation, but this needs to be studied.

The health benefits of dietary fruits and vegetables, especially those related to OS *e.g.,* cardiovascular disease, atherosclerosis, neurodegenerative diseases, and cancer are well recognized. These health benefits maybe partly due to the Fe chelating activity of polyphenols and flavonoids and mitigating OS through free-radical sequestration [85,169, 174-183]. While excess Fe is not regarded as the underlying cause of these diseases, it may play an important role in disease progression either through promotion of cellular growth and proliferation or through participation in redox reactions that catalyze ROS formation and increase OS.

The most well-absorbed flavonoids by humans, such as isoflavones, gallic acid, catechins, flavanones, and quercetin glucosides[176], may offer opportunities to design novel Fe-chelating food supplements and herbo-mineral Fe supplements with low side-effects. Even the non-absorbed flavonoids may play an important role in designing 'side-effect'-free IS, as that chemistry happens in the gut. The bioactivity related to Fe chelation for select foods from Ayurveda and modern diets that are polyphenol-rich are summarized herein:

Fruits: Grape seed extract (GSE) contains various polyphenols like gallic acid, catechin, epigallocatechin gallate (EGCG) and proanthocyanidins. GSE possesses antioxidant activity[183-185,] as these constituents scavenge free radicals and chelate metals such as Fe [153]. However, the effect of these compounds on uptake of dietary Fe and the uptake of Fe–polyphenol complexes needs to be assessed. Procyanidins extracted from *Vitis vinifera*, formed a complex with $Fe^{3+}$with a procyanidin–Fe ratio of 1:2. The stability constant of the procyanidin–Fe complex was comparable to another strong Fe chelating agent, nitrilotriacetate [185, 186]. The mechanism of this complex interaction between radical species requires further investigation; furthermore, *in-vivo* studies are necessary to identify the precise compounds that eventually exert biological activity.

Quercetin, a flavonol is the major phenolic compound in cranberries. It was found to bind Fe^{2+} more strongly than ferrozine-a widely used Fe^{2+} chelator [179, 184, 185]. Quercetin completely suppressed Fe-promoted Fenton chemistry at micromolar levels, even in the presence of the major cellular Fe chelators -ATP or citrate.

These data indicate that it can completely inhibit the Fenton chemistry, although it provides only partial protection against Fenton chemistry-mediated damage [179]. Flavonols, including quercetin, are rapidly absorbed and reach maximum plasma concentration within a few hours. Their elimination (*e.g.,* quercetin

metabolites) is quite slow, with reported elimination half-lives ranging from 11 to 28 h. Circulating flavonoids (and their metabolites) are further delivered into various organs, including the liver, skin, and brain. The link of Fe chelation ability of bioavailable polyphenols of Cranberry extracts to various biological activities *e.g.*, LDL oxidation [179, 183], oxidative and inflammatory damage to the vascular endothelium [187, 188], inhibition of proliferation of several human tumor cell lines [189, 190, 191] needs to be explored.

Green tea catechins & black tea theaflavins: The most abundant polyphenolic compoundsin green tea are catechins [177].

Besides their radical scavenging action, green tea catechins possess well-established metal-chelating properties. The structurally important features defining their chelating potential are the 3′,4′-dihydroxyl group in the B ring and the gallate group [192-196]. Polyphenols from green and black tea have shown promise in protective, chemotherapeutic and chemopreventive activity *in-vitro*. Dried and purified tea polyphenols from black and green teas had a profound protective effect on red blood cells challenged with exogenous oxidants via forming a redox-inactive complex with Fe [195]. Their chemotherapeutic ability has been evaluated for inducing cell death in several human cancer cells *e.g.* human breast (MCF-7), colon (HT-29), hepatoma (liver-HepG2), prostate (PC-3) and lung (HEL299) cells [197] and in rodent models of breast carcinogenesis [198-200]. The role of Fe chelation as a mechanism for these protective, chemotherapeutic and chemo preventive activities of tea polyphenols needs to be studied.

Green tea catechin polyphenols act as multimodal acting molecules that direct numerous cellular neuroprotection/ neurorescue mechanisms involving Fe chelation, scavenging oxygen and nitrogen radical species, activation of protein kinase C signaling pathway and prosurvival genes [199]. Their nontoxic, lipophilic (and thus, brain-permeable) nature is advocated for Fe removal from those brain areas where it preferentially accumulates in neurodegenerative diseases [200]. EGCG has been shown to improve age-related cognitive decline and to protect against cerebral IRIs [201, 202], brain inflammation, and neuronal damage in experimental autoimmune encephalomyelitis [202]. Long-term administration of green tea catechins or EGCG improved spatial cognition and learning ability in rats and reduced cerebral amyloidosis in Alzheimer's transgenic mice [203, 204].

Curcumin: Curcumin, the active ingredient in the traditional herbal remedy and dietary spice turmeric, is a free radical scavenger and hydrogen donor, with both pro- and anti-oxidant activity [170]. It is remarkably nontoxic and has limited bioavailability. Curcumin has great promise as a therapeutic agent and is currently in human clinical trials for varied conditions, *e.g.*, multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis, and AD. Curcumin inhibits cancer development and progression *via* its ability to target multiple steps in the pathway(s) to malignancy [206].

chelates Fe *in-vivo*, particularly in mild Fe deficiency [205, 206]. Under these conditions, dietary curcumin exerted profound effects on systemic Fe, inducing a decline in hematocrit, Hb, serum Fe, transferrin saturation, hypochromic RBC appearance, and decreases in spleen and liver Fe content, besides repressing hepcidin synthesis. Since Fe is critical to catalyzing redox cycling, Fe chelation therapy should be considered a valuable strategy for treating neurodegenerative diseases [206, 207]. Fe chelation may contribute to curcumin'santi-cancer activity [205,208,] as its chemical properties are consistent with Fe-chelator activity [209, 210].

Other neuroprotective phytoactives are apocyanin present in the rhizome of Picrorhizakurroa, a well-known herb in traditional Ayurvedic medicine [211-213]. Apocyanin exhibited potent antioxidative properties by scavenging free radicals and acted on specific signaling pathways that regulate inflammatory responses in cultured human eosinophils and neutrophils [213]. *Mucuna pruriens*, another naturally occurring antioxidant used in traditional Ayurvedic Indian medicine, has also been shown to slow the progression of PD symptoms, without having the side effects of the current pharmaceutical L-dopa. *Mucuna pruiens* inhibited the oxidation of lipids and deoxyribose sugars and exhibited divalent Fe-chelating activity [214].

As stated by Guo *et al.,* [215] phenolic compounds with an 'Fe-binding motif' are strong Fe-chelating agents that may modulate the bioactivity and bioavailability of Fe in the body and merit closer scientific scrutiny.

Future Perspectives: The recognition that a number of plant polyphenols function as Fe chelators is encouraging. The chelating activity of dietary polyphenols may partially contribute to the widely acknowledged health benefits of dietary fruits and vegetables [183, 210]. The recognition that dietary constituents are long known to have beneficial health effects contain constituents with strong binding affinities for Fe that can suppress Fenton chemistry opens the prospect of extending the use of Fechelators for designing herbo-mineral Fe supplements that have lesser side effects than current Fe salts as well as polyphenol supplements for OS-related diseases. Optimization of the use of such polyphenols will require a careful balancing of overall nutritional demands. Nevertheless, prospects for the use of Fechelators in the treatment and prevention of human disease appear greater than ever.

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