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Review

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Tackling iron deficiency: the multifunctional benefits of biopolysaccharide-iron(III) complexes from traditional Chinese medicinal plants

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Abstract: Traditional Chinese Medicinal (TCM) plants are known to contain bioactive ingredients, including beneficial biopolysaccharides that may also serve as excipients in drug formulation and delivery. Some of these biopolysaccharides also exhibit a wide range of biological activities. Biopolysaccharides have also been used in the development of biopolysaccharide-iron complexes that are characterized by high iron content, low gastrointestinal irritation and enhanced bioavailability, helping to overcome the limitations of conventional iron supplements. This review focuses on the unique properties of TCM-derived biopolysaccharides in addressing these limitations and highlights their bioavailability and therapeutic potential, including their roles in iron release and delivery, gastroprotective effects, blood sugar regulation, and antioxidant activity, as demonstrated in *in vitro* and *in vivo* experiments and clinical trials. The adverse reactions, safety profile and structure–activity relationship of biopolysaccharide-iron complexes in antioxidant activities are also thoroughly discussed. Supplementation with these next-generation iron complexes may represent a promising strategy for the treatment of iron deficiency anaemia and the promotion of overall human health and well-being.

Key words: Traditional Chinese Medicine; Polysaccharides; Iron complex; Iron deficiency anaemia; Drug delivery

1 Introduction

Iron deficiency anaemia (IDA) is a nutritional disorder primarily caused by prolonged inadequate iron intake, excessive iron loss, or impaired gastrointestinal absorption (Zhang et al., 2023). Patients affected are

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usually treated with iron supplementation. The first generation of iron supplements consists mainly of inorganic iron compounds, with ferrous sulfate ($FeSO_4$) being the most widely used choice (Jia et al., 2019). Despite their high iron content, these supplements are often associated with significant gastrointestinal irritation and other adverse effects. The second generation of iron supplements includes soluble small-molecule organic iron salts, such as ferrous lactate and ferrous gluconate (Xiu et al., 2023). However, these supplements face iron instability issues, therefore many researchers are now focusing on developing third-generation iron supplements, namely biopolysaccharide iron complexes (PICs).

Biopolysaccharides, as complex carbohydrates commonly present in nature, possess intrinsic properties and biological applications and can be isolated from plants (Guru et al., 2023), animals (Yang et al., 2024), algae (Ning et al., 2022), or microorganisms (Dedhia et al., 2022). Among these sources, plants especially TCM plants, are the most common source of biopolysaccharides. Plant-derived biopolysaccharides are photosynthetic by-products, which can be obtained from the leaves, pods, stems, fruits, grains, seeds, corms, rhizomes, roots, bark, etc. (Albuquerque et al., 2022). They are synthesized for growth and development, structural support, protection, and other vital functions. Certain biopolysaccharides help the plant cells maintain their integrity, rigidity and provide structural support.

Various types of plant biopolysaccharides can be extracted from TCM plants, including pectin (Wang and Cheong, 2023), gums (i.e., Arabic gum, guar gum, tragacanth gum, acacia gum, and xanthan gum) (Bovo et al., 2016, Madni et al., 2021), starches (i.e., rice starch, potato starch, tapioca starch, etc.), mucilage, and inulin. Biopolysaccharides are stored in various parts of plant cells. Structural polysaccharides, such as pectins and xylans stored in the cell wall, are responsible for cell wall integrity and thus influence the stability of plant tissues (Chan et al., 2023). They maintain the structural framework of the plant, supporting its growth and regulating cell hydration (Zdunek et al., 2021). Starch is the storage polysaccharide present in the amyloplasts of plants, supporting growth and development and forming the main energy storage (Bhatla and Lal, 2023). On the other hand, inulin in the plant vacuoles is the reserved carbohydrate storage that plays a similar role as starch but it is only utilized during stress conditions (Bhatla and Lal, 2023). These biopolysaccharides are included as excipients in pharmaceutical product formulations to improve their stability, bioavailability and palatability (Shan et al., 2023), while some are used to facilitate drug delivery and processability (Al-Sahlawi et al., 2024). The applications of biopolysaccharides in product formulation are listed below (Fig. 1).

Numerous studies have reported the use of biopolysaccharides as excipients in pharmaceutical product formulations. In the past decade, many researches have highlighted the benefits of PICs in the treatment of IDA. In addition to their role in iron delivery, PICs have demonstrated other therapeutic potentials that may improve the overall health of patients with IDA. Biopolysaccharides can be extracted from plant sources, and TCM plants are among the promising sources. This review critically discusses the advantages of using TCM-derived biopolysaccharides for iron delivery and highlights their potential health benefits, which include enhanced iron absorption, gastroprotective effects, blood sugar regulation, and free radical scavenging activity. The efficacy, adverse reactions and safety profile of PICs in *in vitro* and *in vivo* experiments and clinical studies are also thoroughly discussed. Furthermore, the structure–activity relationship of PICs in their antioxidant activities is evaluated.

2 Biopolysaccharides from TCM: application and therapeutic uses

TCM plants are a potential source of biopolysaccharides, which have been reported to exhibit promising pharmacological activities that can aid in the treatment of various diseases. For example, acemannan extracted from *Aloe vera* supports wound healing (Iacopetti et al., 2020); gum arabic from *Acacia senegal* demonstrates anti-microbial properties (Baien et al., 2020); inulin from Jerusalem artichoke (*Helianthus tuberosus*) has immunomodulatory effects, protects the intestinal barrier and regulates the immune system (Sheng et al., 2023); resistant starch possesses anti-inflammatory properties and promotes wound healing (de Oliveira Filho et al., 2021); and pectin has been shown to inhibit cancer metastasis by blocking galectin-3 receptors (Ganie et al., 2023).

Biopolysaccharides consist of at least 10 monosaccharides and can exist as either homopolysaccharides or heteropolysaccharides. The former are composed of repeating units of a single type of monosaccharide, while the latter are made up of two or more different types of monosaccharides (Liu et al., 2019, Xiu et al., 2023). In addition to their therapeutic potential, biopolysaccharides extracted from TCM plants are widely used as formulation excipients due to their unique properties. For instance, *Ligusticum chuanxiong* polysaccharide has been utilized as a bioadhesive agent due to its mucoadhesive properties that enhance formulation retention on mucosal surfaces (Wang et al., 2022b); *Aloe vera* biopolysaccharides are used as filler excipients in sustained-release matrix tablets and as skin permeation enhancers in transdermal drug delivery systems (Laux et al., 2019); biopolysaccharides from *Ganoderma lucidum* (Lingzhi mushroom) serve as stabilising agents in nanocomposites (Lee et al., 2020), while those from *Panax notoginseng* are employed in microneedle fabrication for rapid drug release, high solubility and permeability (Wang et al., 2021a). In addition, *Angelica sinensis* biopolysaccharides are used for active targeting drug delivery due to their high affinity for specific receptors (Wang et al., 2022a). Generally, these biopolysaccharides are safe, non-toxic and biodegradable, making them ideal for drug delivery and release systems. One notable application is in iron supplementation, where they not only aid in delivery but also offer additional health benefits, such as regulating blood circulation, controlling blood sugar and pressure, and boosting the immune system (Jia et al., 2019, Shi et al., 2023). Biopolysaccharides also exhibit various biological activities, including immunomodulation (Baien et al., 2020), anti-inflammatory (Sheng et al., 2023), anti-oxidant (de Oliveira Filho et al., 2021, Ganie et al., 2023), anti-diabetic (Ganie et al., 2023) anti-hypertensive (Ganie et al., 2023), *etc*. Table 1 summarizes the therapeutic applications of biopolysaccharides from TCM plants, along with their uses and drug delivery forms.

3 Biopolysaccharides in iron supplementation

Iron supplementation is the primary method for preventing and treating IDA. The use of oral iron supplements is the standard approach in view of their convenience, affordability and effectiveness for patients. First-generation treatment involved inorganic ferrous salts, such as ferrous sulfate ($FeSO_4$), which were subsequently improved using organic acid salts like ferrous succinate, ferrous fumarate, ferrous gluconate, ferrous citrate, and ferrous lactate. These enhanced supplements offered fewer adverse reactions compared to the previous ones. Despite being effective, inexpensive and widely accessible, ferrous salts also have notable drawbacks, as the free iron ions from these unstable salts could behave like pro-oxidants. They generate free radicals and enhance the growth of pathogenic species and alter beneficial gut microbiota composition and metabolism (Bloor et al., 2021, Yang et al., 2024). These free radicals could induce inflammation in the gut lining and lead to various gastrointestinal side effects, such as nausea, vomiting, diarrhoea and constipation. Therefore, PICs were formulated to overcome such side effects. Table 2 compares the properties, advantages and drawbacks of traditional iron supplementation (ferrous salts) with those of PICs.

Numerous animal and clinical studies have demonstrated that PICs are effective for iron supplementation. In addition to providing iron, some studies have reported that PICs can also modulate the gut microbiota, manage oxidative stress and exhibit hepatoprotective effects (Table 3). Minor adverse effects of PICs have been observed in clinical studies; however, no toxicity has been reported to date (Table 4). Overall, PICs are considered effective and safe for iron supplementation.

3.1 Gastroprotective and retentive drug-delivery

Biopolysaccharides can form complexes with iron via metal ion chelation. Wang et al. (2020b) synthesized biopolysaccharide-Fe(III) complex (AGSP) using sulfated polysaccharide. The authors reported that the high absorbance at 310 nm reflected that a high number of Fe-O bonds had been formed. This was further confirmed in the circular dichroism analysis, where a weaker negative Cotton effect in the complex also indicated the chelation of AGSP with Fe(III) *via* the Fe-O chemical bond **(**Fig. 2**).**

The chelation of iron to biopolysaccharides can provide a controlled release of iron. Supplementation with PIC ensures a continuous iron supply in the body, leading to improved iron absorption over time. Studies on AGSP-Fe(III) in simulated gastrointestinal digestion show that iron is released slowly into the gastric fluid (pH 2) over 120 minutes. In the intestinal fluid (pH 7), free iron levels decrease and stabilize after 180 minutes (Wang et al., 2020a). Besides, AGSP-Fe(III) has enhanced solubility and stability; unlike other forms, it remains soluble and stable during digestion, preventing precipitation with polyphenols. The presence of AGSP-Fe(III) helps maintain high polyphenol levels, minimizing iron-polyphenol chelation. This enables iron and polyphenols to be absorbed in their molecular forms, reducing the potential side effects.

Similar findings were observed in studies on *A. auricular* polysaccharide (AAP)-iron(III) complexes (Liu et al., 2019). AAP-iron(III) was gradually released in simulated gastric juice over 90 minutes, with 86.7% of the iron released after 120 minutes. This increased to 93.1% after 3 hours. Comparable results were reported by Lu et al. (2016), Zhang et al. (2023) and Yuan et al. (2022). Lu et al. (2016) emphasized that iron release is influenced by temperature. Zhang et al. (2023) discovered that the *Poria cocos* polysaccharide iron complex (PCP1C) released iron slowly under simulated intestinal conditions, reaching 95.3% after 5 hours. Similarly, Yuan et al. (2022) reported that the iron release from lotus root polysaccharide-iron(III) complex (LRPF) reached 85%, compared to less than 45% for $FeSO_4$ after 30 minutes. Furthermore, LRPF demonstrated better solubility and stability in *in vitro* iron release assays, maintaining 40% iron release, while $FeSO_4$ showed less than 10%. These findings suggest that PICs exhibit good water solubility in gastrointestinal environments, high bioavailability, and effective iron absorption during digestion (Jing et al., 2022; Wang et al., 2020a; Yuan et al., 2022; Zhang et al., 2023).

The effectiveness of biopolysaccharide-based iron delivery has also been demonstrated in animal models of iron deficiency anaemia (IDA). Recent studies by Yang et al. (2024) and Zhang et al. (2023) demonstrated significant therapeutic effects of iron supplementation in IDA rats. PICs were found to significantly improve the haematological indices of IDA rats, including haemoglobin levels, red blood cell count, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration, bringing them to levels comparable to healthy rats and those supplemented with iron protein succinylate and ferrous succinate (Yang et al., 2024, Zhang et al., 2023). These results suggest that PICs are effective in delivering and releasing iron, improving red blood cell indices and addressing anaemia (Fig. 3). PICs supplementation also restored the organ coefficients (heart, spleen, kidney, and testes) of IDA rats to normal levels, similar to those in the control group (Yang et al., 2024). The IDA rats exhibited significant weight gain during the PIC supplementation period, indicating recovery from iron deficiency.

3.2 Lowering of blood sugar level

Alpha-amylase catalyzes the hydrolysis of α-1,4 glycosidic bonds of polysaccharides, while α-glucosidase breaks down 1,4-α bonds to release glucose. In recent years, biopolysaccharides have been reported to inhibit the activity of both α-amylase and α-glucosidase, rather than being degraded by these enzymes. This inhibitory activity may play a critical role in regulating blood sugar levels and reducing the risk of diabetes mellitus (Wei et al., 2024).

The iron in PICs exists in its trivalent form, which has high bioavailability. Xiu et al. (2023) discovered that sugars such as mannose, glucose, fucose, galactose, and arabinose from sweet corn cob polysaccharide (SCCP) can form PICs with iron. The iron(III) binds to -OOH and -OH groups on the polysaccharides, forming a stable β-FeOOH iron core. This binding enhances the stability of the polysaccharide and increases repulsive forces between the PICs. The authors also observed that the zeta potential of polysaccharide iron complexes was higher than that of the polysaccharide alone, a finding supported by Wei et al. (2024). On the other hand, Fan et al. (2021) reported that the binding of metallic elements like iron(III) does not affect the active sites of the polysaccharides.

In addition to iron supplementation, Xiu et al. (2023) found that PICs synthesized from SCCP can lower blood sugar levels. These biopolysaccharides regulate glucose metabolism by inhibiting the activities of α-glucosidase and α-amylase. Wang et al. (2018b; 2018c) explained that the binding affinity of biopolysaccharides to α-glucosidase is likely due to the presence of carboxyl and hydroxyl groups in the polysaccharides. Strong hydrogen bonds between these groups and the amino acid residues of the enzyme inhibit its activity, helping to control blood glucose levels.

Alpha-glucosidase inhibition has also been observed in tea polysaccharides (Fan et al., 2021). Biopolysaccharides alter the conformation of α-glucosidase, partially unfolding the enzyme and increasing the exposure of its hydrophobic regions, which disrupts its function in starch hydrolysis. The inhibition of both α-glucosidase and α-amylase activities showed a concentration-dependent response, though the hypoglycaemic effect was weaker in PICs compared to biopolysaccharides alone. Wei et al. (2024) discovered that the α-glucosidase inhibition of PICs was slightly lower than that of polysaccharides alone, likely due to changes in spatial arrangement and intermolecular forces after the introduction of iron(III). Fan et al. (2021) also observed a weakened inhibitory activity due to conformational changes following metal binding. These findings explain why many studies have focused on the blood sugar-lowering effects of polysaccharides rather than PICs **(**Fig. 4).

Although certain studies have shown that PICs can lower blood glucose levels, there is evidence suggesting that iron overload may increase the risk of diabetes mellitus. For example, Petry (2022) and Li et al. (2024) both reported a positive correlation between the risk of gestational diabetes mellitus and plasma ferritin levels in healthy pregnant women, and found that excessive iron supplementation in these women is associated with insulin resistance and type 2 diabetes. However, to our knowledge, no studies have investigated the effects of PIC supplementation in pregnant women or healthy individuals regarding insulin resistance; thus, it remains unclear whether PICs could improve insulin sensitivity or contribute to insulin resistance in healthy individuals.

3.3 Anti-oxidative effects

The hydroxyl radical (•OH) is one of the most harmful free radicals due to its high reactivity: it can interact with lipids, proteins, nucleic acids, polypeptides, and other biological molecules, causing oxidative damage to cells and tissues. Anti-oxidants help protect organisms by reducing oxidative damage caused by excess free radicals. Research has increasingly identified certain natural biopolysaccharides as potential anti-oxidants, particularly those derived from TCM sources. Besides, numerous studies have shown that these biopolysaccharides retain their anti-oxidant properties even after being converted into biopolysaccharide iron complexes. For instance, biopolysaccharides from *A. auricula* (Liu et al., 2019), *Astragalus membranaceus* (Jia et al., 2019), *Rosa roxburghii* (Wang et al., 2021b), *P. cocos* (Zhang et al., 2023), sweet corn cob (Xiu et al., 2023), and mushrooms (Liu et al., 2022) exhibit anti-oxidant activity. Furthermore, some studies have reported that biopolysaccharides from TCM sources often exist as conjugates with other components, such as proteins, lipids, amino acids, neutral sugars, phenolic acids, and uronic acids (Liu et al., 2018, Mohanta et al., 2022). These conjugates, including tea polysaccharide-uronic acid, xylooligosaccharide-phenolic acid, polysaccharide-phenolic, and feruloyl oligosaccharides, have been found to exhibit strong anti-oxidant activities (Mohanta et al., 2022).

Numerous studies have consistently found that PICs possess strong anti-oxidant properties. Several parameters were investigated, including free radical scavenging, lipid peroxidation inhibition, and intracellular anti-oxidant levels, and a higher scavenging ability was indicated to yield a greater capacity to neutralize free radicals. Jia et al. (2019) reported that both *Astragalus membranaceus* polysaccharide (APS) and the APS-iron(III) complex were able to scavenge free radicals, as evaluated by the 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. A similar pattern was observed with the *Auricularia auricula* polysaccharide (AAPS)-iron complex, where anti-oxidant activity increased in a concentration-dependent manner (Liu et al., 2019). A common finding across studies on the anti-oxidant activities of biopolysaccharides and their PICs is that biopolysaccharides generally exhibit stronger anti-oxidant activities than their corresponding PICs, as seen from the 50% inhibitory concentration (IC_{50})

values. This trend has been noted by several authors in recent studies (Wang et al., 2021; Zhang et al., 2023; Xiu et al., 2023; Liu et al., 2024a).

The superoxide anion radical (O^{-}_{2}•) is the precursor of all reactive oxygen species. Through a series of reactions, it can be converted into singlet oxygen and hydroxyl radicals that trigger lipid peroxidation in the body and contribute to various diseases. Biopolysaccharides scavenge superoxide anion radicals by inhibiting their conversion into singlet oxygen, hydroxyl radicals, hydrogen peroxide, and other reactive oxygen species, thereby reducing oxidative stress. Jia et al. (2019) reported that biopolysaccharides alone exhibit better superoxide scavenging activity. This finding aligns with that of Xiu et al. (2023), who explained that the formation of a stable β-FeOOH iron core structure between biopolysaccharides and iron affects the transfer of hydrogen protons in the biopolysaccharide, resulting in reduced anti-oxidant activity in PICs. Moreover, biopolysaccharides act as hydrogen atom or electron donors through their hydroxyl and carboxyl groups while scavenging free radicals. However, the formation of an iron complex diminishes the electron-donating ability of biopolysaccharides, weakening their anti-oxidant potential (Xiu et al., 2023).

Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) are key anti-oxidative enzymes that play critical roles in protecting the body from oxidative stress by neutralizing reactive oxygen species (ROS) and preventing cellular damage. Malondialdehyde (MDA), a product of lipid peroxidation caused by ROS, is an indicator of oxidative stress, since elevated MDA levels reflect protein denaturation, genetic mutations and cellular damage. The severity of oxidative stress is often assessed by measuring MDA levels, along with the activity of SOD, CAT and GSH-Px, biomarkers of the oxidative stress response (Jia et al., 2019). The APS-iron complex has been shown to increase SOD and CAT levels while reducing MDA. Jia et al. (2019) found that rats supplemented with 75 mg/kg and 100 mg/kg of the APS-iron complex showed a return to normal levels of SOD, CAT and MDA after 15 days, indicating that the APS-iron(III) complex was more effective in boosting SOD and reducing MDA production compared to Niferex (a combination of iron polysaccharide and ascorbic acid). A similar observation was made by Yuan et al. (2022), where the LRPF also exhibited strong anti-oxidant activity. These findings suggest that PICs provide superior iron supplementation compared to conventional iron supplements for treating iron deficiencies and iron deficiency anaemia, while they also exhibit excellent anti-oxidant properties that help reduce oxidative stress.

4 Structure-activity relationship of biopolysaccharides in their biological activities

Biopolysaccharides can be classified as either homopolysaccharides or heteropolysaccharides. A large body of evidence suggests that the structural characteristics of biopolysaccharides significantly influence their biological activities and potential therapeutic efficacy. These effects are attributed to factors such as solubility, the presence of aromatic groups, molecular weight, degree of substitution, interactions with other chemical groups (*i.e.* phenolic compounds, organic acids, and protein moieties), and chemical modifications (*i.e.* sulfation, carboxymethylation, phosphorylation, acetylation).

Among the various biological activities, anti-oxidant activity is one of the most extensively studied properties in relation to the structure–activity relationship of biopolysaccharides. Research has shown that specific functional groups can enhance anti-oxidant properties, particularly through mechanisms such as free radical scavenging and metal ion chelation (Fernandes and Coimbra, 2024). Table 5 below summarizes the structure–activity relationships of some biopolysaccharides with respect to their anti-oxidant effects. A deeper understanding of these relationships can guide the structural modification of biopolysaccharides to improve their therapeutic potential.

5 Conclusions

Biopolysaccharide-iron complexes enhance the solubility and absorption of iron, leading to improved bioavailability, thus offering a high iron content that can effectively address iron deficiency anaemia. These complexes also provide controlled and gradual iron release, ensuring a consistent and prolonged supply to the body. Compared to conventional iron supplements, biopolysaccharide-iron complexes cause less gastrointestinal irritation, reducing the common side effects associated with first- and second-generation iron supplements. Moreover, they offer additional therapeutic benefits, such as regulating blood sugar, reducing oxidative stress, and supporting immune function. These combined advantages make biopolysaccharide-iron complexes a promising alternative, especially for the long-term management of iron deficiency anaemia. Variations in the formulation of polysaccharide iron complexes (PICs) can significantly affect their physicochemical properties and bioavailability. Specifically, the bioavailability of iron from PICs depends on the type of biopolysaccharide and the methods employed in the formulation process. This variability poses challenges in evaluating the clinical efficacy and safety of PICs during clinical testing, as different formulations may exhibit distinct iron dissolution profiles (Xin et al., 2025). Therefore, further studies are needed to standardize the synthesis of PICs and their iron release characteristics. Although the supplementation efficacy and adverse effects of PICs have been researched, important aspects such as their stability, long-term safety and potential long-term adverse effects remain to be thoroughly investigated (Wei et al., 2024).

Data availability statement

This study is based on previously published data, which are cited in the manuscript and available from the respective sources.

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Author contributions

Wenyang ZHAO, Chun-Wai MAI and Yik-Ling CHEW conceptualised and wrote the original manuscript. Chun-Wai MAI and Yik-Ling CHEW supervised the work. Kai Bin LIEW and Li CHEN reviewed and edited the manuscript. Siew-Keah LEE, Wei DU and Gabriel Akiyrem AKOWUAH conceptualised and edited the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Wenyang ZHAO, Chun-Wai MAI, Kai Bin Liew, Siew-Keah LEE, Li CHEN, Wei DU, Gabriel Akiyrem AKOWUAH, Yik-Ling CHEW declare that they have no conflict of interest. This review does not contain any studies with human or animal subjects performed by any of the authors.

Table 1 Therapeutic application of biopolysaccharides in drug delivery

Polysaccharide	Drug delivery system composition	Dosage Form(s)	Function(s)	Application(s)	Ref.
Seaweed polysaccharide	AMSN-Alg/FA-CMCT-Gel	Nanogels, microgels and hydrogels	Can be loaded with a variety of drugs	Anti-inflammatory and anti-cancer	Zhong et al., 2020
Angelica sinensis polysaccharide	AP-PP-DOX	Nanoparticles	Vehicle for targeted drug delivery to tumour tissue	Anti-tumour	Wang et al., 2020b
Lentinula edodes Sing polysaccharide	LES	Emulsions (Conventional)	Free radical scavenging activity	Anti-oxidant, emulsifying additives	Dai et al., 2023
Ganoderma lucidum polysaccharide	GLP	Solution (Conventional)	Inhibit overproduction of nitric oxide and pro-inflammatory cytokines	Anti-inflammatory activity, gut barrier protection	Wen et al., 2022
Jelly fig polysaccharide	JFP/pullulan	Nanofiber	Encapsulation of hydrophobic drugs	Anti-bacterial, drug delivery vehicle	Ponrasu et al., 2021
Lonicera japonica Thunb leaves polysaccharide	PHL-WPI	Nanoemulsion	Protects β-carotene from UV exposure	β-carotene stabiliser	Li et al., 2023
Glycyrrhiza polysaccharide	GP-AgNPs	Nanoparticle	Increased Ag nanoparticles stability	Anti-microbial, reducing agent, stabilising agent	Cai et al., 2019
Araucaria heterophylla L polysaccharide	AH- STMP	Nanocarrier	Biodegradable nanocarriers in drug delivery and drug release	Anti-microbial, drug loading, drug delivery	Samrot et al., 2020
Bletilla striata Polysaccharide	BSP-AgNPs	Nanoparticle	Promote wound healing	Anti-microbial	Zhang et al., 2023
Spirulina polysaccharide	PSP-NE	Nanoemulsion	Improve drug stability and slow release	Anti-tumour, anti-oxidant	Wang et al., 2018a
Poria cocos polysaccharide	FLP-MPBA-AuNRs	Nanorod	Inhibition of tumour cell growth	Anti-cancer	Zhao et al., 2024
Chestnut polysaccharide	Se-CP	Nanocopolymer	Improved anti-oxidant activity,	Anti-oxidant, hypoglycaemic	Wang et al., 2023
Chaenomeles speciosa polysaccharide	CSP-SeNP3	Nanoparticle	Inhibit cancer cell growth, induce cell apoptosis	Anti-cancer	Zhou et al., 2022
Gastrodia elata polysaccharide	PLA/PVP-CS/GEL- GEP-MT	Nanofiber	Promote absorption	Moisturising, anti-oxidant	Wang et al., 2024
Ginseng polysaccharide	GPS NPs	Nanobiomaterials	Enhancement of its oral delivery capacity	Immunomodulator	Akhter et al., 2019
Sargassum fusiforme polysaccharide	SFPS-Tw-SeNPs	Nanoparticle	Inhibit tumour metastasis	Anti-cancer	Chen et al., 2024

Ramulus mori polysaccharide	PLGA-RMP	Nanocopolymer	Reduce metabolic disorders in the colitis colon	Treatment for inflammatory bowel disease, prebiotic source	Feng et al., 2021
Dandelion polysaccharide	PD / PEO	Nanofiber	Inhibit bacterial growth	Anti-microbial food packaging	Lin et al., 2018

AMSN-Alg/FA-CMCT-Gel: amine mesoporous silica-alginate/folic acid conjugated o-carboxymethyl chitosan–gelatin; AA-PP-DOX: *Angelica sinensis*-peptide-doxorubicin; LES: *Lentinula edodes* Sing; GLP: *Ganoderma lucidum* polysaccharide; JFP/pullulan: jelly fig polysaccharide/pullulan; PHL-WPI: polysaccharides in *Honeysuckle* leaves-whey protein isolate; GP-AgNPs: *Glycyrrhiza* polysaccharide-silver nanoparticles; AH-STMP: *Araucaria heterophylla*-sodium trimetaphosphate; BSP-AgNPs: *Bletilla striata* polysaccharide-silver nanoparticles; PSP-NE: spirulina polysaccharide-nanoemulsion; FLP-MPBA-AuNRs: *Poria cocos* polysaccharides-mercaptophenylboronic acid-gold nanorods; Se-CP: selenised *chestnut* polysaccharide; CSP-SeNP3: *Chaenomeles speciosa* polysaccharide-selenium nanoparticles; PLA/PVP-CS/GEL-GEP-MT: polylactic acid/polyvinylpyrrolidone-chitosan/gelatin-*Gastrodia elata* polysaccharide-melatonin; GPS NPs: American ginseng polysaccharides nanoparticles; SFPS-Tw-SeNPs: *Sargassum fusiforme* polysaccharide-Tween-80-selenium nanoparticles; PLGA-RMP: poly(lactic-*co*-glycolicacid)-*Ramulus mori* polysaccharide; PD/PEO: dandelion polysaccharide-polyethylene oxide.

Table 2 Comparison of properties between traditional iron supplements and biopolysaccharide-iron complexes (PICs)

Parameter/metric	Traditional Iron Supplements (e.g., Ferrous sulfate)	Biopolysaccharide-iron complexes (PICs)	Ref.
Bioavailability (%)	100	101.85–116	Tang et al., 2013
Gastrointestinal side effects	Significant irritation	Moderate irritation (PIC-coated pellets and PIC powders)	Yan et al., 2025
Administration	Oral form; taken on empty stomach; advisable to take with ascorbic acid to maintain at ferrous (Fe^{2+}) form for better absorption.	Oral form; can be taken with a meal. acidic environment is not required for absorption	Ning and Zeller, 2019
Effect on gut microbiota	Not mentioned	Regulates gut microbiota dysbiosis by returning relative abundance to normal levels; able to restore gut microbiome balance; enriches beneficial gut microbiome.	Shi et al., 2023; Xie et al., 2025
Advantages	Low cost, high efficiency, wide availability	Good stability; high tolerability; high iron absorption rate; high bioavailability; able to exhibit a variety of pharmacological activities; results in fewer adverse reactions	Zhang et al., 2023; Pantopoulos, 2024
Disadvantages	Poor tolerability, poor absorption; low bioavailability; results in frequent adverse effects	High cost	Jing et al., 2022; Zhang et al., 2023; Suva and Tirgar, 2024

Table 3 Pharmacological effects and therapeutic applications of biopolysaccharide-iron complexes (PICs) in animal models

Biopolysaccharides iron complexes	Animal model	Route of administration	Major pharmacological effects	Therapeutic applications	Key findings	Ref.
APIC	IDA rats	Oral	Iron supplementation, blood-activating	IDA treatment	Increased Hb/RBC/HCT ($p<0.05$); Better iron supplementation effect than Niferex (positive control); dual efficacy	Wang et al., 2007
LRPF	IDA mice	Oral	Anti-oxidant, gut microbiota modulation	IDA treatment, Immuno-enhancement	Impacted the gut microbiome; increased anti-oxidants in vivo; regulated steroid hormones	Yuan et al., 2022
UPIC	Radiation-exposed mice	Oral	Radioprotection, anti-oxidant	Radiation damage mitigation	Iron (III) complex of low molecular-weight polysaccharides showed anti-radiation and anti-oxidative activity comparable to that of low molecular-weight polysaccharides	Shi et al., 2013
FVP1-Fe(III)	IDA rats	Oral	Hepcidin downregulation, gut microbiota modulation	IDA treatment, effects on gut microbiota	Superior to FeSO4 in efficacy; It also regulated gut microbiota dysbiosis and restored the relative abundance of gut microbiota.	Shi et al., 2023
TPIC	IDA rats	Oral	Iron absorption enhancement	IDA treatment	TPIC is a good iron supplement source for increasing uptake and bioavailability in the body	Tang et al., 2013
HPIC	IDA mice	Oral	Haematopoietic improvement, hepatoprotective effect	IDA treatment, functional iron supplement	Significantly increased RBC, MCV, MCH; alleviates liver damage	Zhang et al., 2025
RGP−Fe(III)	IDA rats	Oral	Iron supplementation, haematological improvement	IDA treatment	Promoted weight gain, improved haemoglobin, RBC count, serum iron, reduced TIBC, and showed no toxicity to liver and spleen.	Liu et al., 2024b
GP-Fe (III)	IDA mice	Oral	Iron supplementation, haematological improvement,	IDA treatment	Superior efficacy to $FeSO_4$ in improving anaemia	Qi et al., 2024
APIC	IDA rats	Oral	Iron supplementation, blood-activating	IDA treatment	Increased Hb/RBC/HCT ($p<0.05$); Better iron supplementation effect than Niferex; dual efficacy	Wang et al., 2007
LRPF	IDA mice	Oral	Anti-oxidant, gut mi-	IDA treatment, immu-	Impacted the gut microbiome; increased	Yuan et al.,

			crobiota modulation	no-enhancement	anti-oxidants in vivo; regulates steroid hormones	2022
UPIC	Radiation-exposed mice	Oral	Radioprotection, anti-oxidant	Radiation damage mitigation	Iron (III) complex of low molecular-weight polysaccharides showed anti-radiation and anti-oxidative activity comparable to that of low molecular-weight polysaccharides	Shi et al., 2013
FVP1-Fe(III)	IDA rats	Oral	Hepcidin downregulation, gut microbiota modulation	IDA treatment, effects on gut microbiota	Superior to FeSO4 in efficacy; It also regulated gut microbiota dysbiosis and restored the relative abundance of gut microbiota.	Shi et al., 2023
TPIC	IDA rats	Oral	Iron absorption enhancement	IDA treatment	TPIC is a good iron supplement source for increasing uptake and bioavailability in the body	Tang et al., 2013
HPIC	IDA mice	Oral	Haematopoietic improvement, hepatoprotective effect	IDA treatment, iron supplement	Significantly increased RBC, MCV, MCH; alleviated liver damage	Zhang et al., 2025
RGP−Fe(III)	IDA rats	Oral	Iron supplementation, haematological improvement	IDA treatment	Promoted weight gain, improved haemoglobin, RBC count, serum iron, reduced TIBC, and showed no toxicity to liver and spleen.	Liu et al., 2024b

PIC: Polysaccharide-Iron Complex; APIC: *Angelica sinensis* polysaccharide-iron complex; IDA: iron deficiency anemia; LRPF: Lotus root polysaccharide iron complex; UPIC: *Ulva pertusa* polysaccharide-iron complex; FVP1-Fe(III): *Flammulina velutipes* polysaccharide-iron complex; TPIC: Tea polysaccharides–iron complex; HPIC: Hawthorn pectin-iron(III) complex; RBC: red blood cells; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; RGP−Fe(III): *Rehmanniae radix praeparata* iron (III) complex; TIBC: total iron-binding capacity; GP-Fe (III): garlic polysaccharides iron (III) complex.

Table 4 Clinical outcomes and key findings of polysaccharide-iron complexes (PICs) in iron supplementation therapy

Study type	Population/Model (Sample size)	Intervention protocol (Dose/Duration)	Therapeutic objectives	Clinical outcomes	Adverse events	Ref.
Randomised double-blind two-period crossover study	Healthy Chinese male volunteers/ (*n*=20)	A single oral dose of 150 mg PIC capsule administered every morning	Bioequivalence evaluation	The pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$) of the test and reference formulations were similar, with no significant differences in $AUC_{0\text{-}\infty}$ or T_{max}. A significant difference was found in C_{max} ($p = 0.012$). The test formulation was found to be bioequivalent to the reference formulation.	No clinically significant adverse events reported	Zhang et al., 2009
Retrospective analysis	Pregnant women with iron-deficiency anaemia (IDA) (*n* = 1792)	Oral iron supplements, divided into six treatment groups (PIC capsules, orally administered at a dose of 150 mg, once daily)	Investigate the safety of oral iron therapy in pregnant women with IDA	The main adverse reactions were gastrointestinal, with no severe outcomes such as sequelae or death. Iron protein succinylate oral solution had a higher incidence of adverse reactions than iron polysaccharide complex capsules. The mean haemoglobin levels in all six anaemia groups increased from severe anaemia (<41.44±1.55 g/L) to the mild anaemia range (100-109 g/L).	Overall adverse reaction rate of 15.4%, with gastrointestinal issues being the most common. Specific adverse reactions by drug type ranged from 6.94% to 21.88%.	Liu et al., 2023
Double-blind, placebo-controlled, randomised clinical trial	Patients with HFrEF and iron deficiency (*n* = 98)	Oral PIC (150 mg) given twice daily for 16 weeks	To test the efficacy and safety of oral iron polysaccharide in patients with HFrEF and iron deficiency	Iron supplementation was effective in 24% of iron-deficient patients, but no significant improvements in exercise capacity, myocardial stress, and quality of life were observed.	No clinically significant adverse events reported	Ambrosy et al., 2019
Randomised controlled trial	Patients with renal anaemia (*n* = 200)	Control group: PIC experimental group: Jianpi Shengxue tablet for 8 weeks. The dose is unspecified.	Compare anaemia correction	The total effective rate for treating renal anaemia was higher in the experimental group ($p < 0.01$). The improvements in RBC, HCT, RET, and clinical symptoms in the experimental group were significantly greater than the control group.	Not reported	Yang et al., 2024
Prospective, open-label, three-phase,	Adult renal transplant recipients (*n* = 12)	Oral iron therapy coadministered with MMF on days -6–0, MMF alone on	To determine if coadministration of polysaccharide	No significant differences in dose-standardised $AUC_{0\text{–}12}$ values for MPA between the control phase and both iron	Not reported	Gelone et al., 2007

crossover, steady-state pharmacokinetic trial		days 1–8 (control phase), and iron therapy administered 2 hours after MMF on days 9–16. The dose is unspecified.	iron complex and slow-release ferrous sulfate alters the absorption of mycophenolic acid (MPA)	therapy phases. However, $AUC_{0–12}$ for MPA significantly increased when PIC was administered 2 hours after MMF (53.41 ± 11.75 mg/hr/L, $p = 0.012$). Maximum concentrations and the time to reach maximum concentrations were consistent across all phases ($p > 0.05$).		
Prospective, open-label, trial	Dialysis patients receiving epoetin alfa ($n = 38$)	All patients switched to PIC with 6-month follow-up, The dose is unspecified.	Compare the efficacy/safety of PIC vs ferrous salts	PIC is as effective as ferrous sulfate in sustaining erythropoiesis in patients receiving epoetin alfa.	PIC may produce fewer adverse effects.	Johnson et al., 1992
Retrospective analysis	Potentially toxic exposures to PIC ($n = 810$)	PIC exposure. The dose and duration are unspecified.	To evaluate the toxicity of PIC exposure	95.6% of PIC exposures resulted in no effect or minimal toxicity; no serious adverse effects or deaths	Low adverse reaction reported: vomiting (2.8%), diarrhoea (1.2%), nausea (1.4%), abdominal pain (1.2%), and lethargy/drowsiness (0.9%). No major adverse effects reported.	Klein-Schwartz, 2000
Double-blind, randomised clinical trial	Infants and children aged 9 to 48 months with nutritional iron-deficiency anaemia ($n = 80$)	3 mg/kg elemental iron daily for 12 weeks, either as ferrous sulfate or PIC	Compare efficacy of ferrous sulfate vs. iron polysaccharide complex in improving haemoglobin concentration	A greater increase in haemoglobin in the ferrous sulfate group (1.0 g/dL higher). Mean haemoglobin increased from 7.9 to 11.9 g/dL (ferrous sulfate group) vs 7.7 to 11.1 g/dL (PIC group)	Diarrhoea was reported in both the ferrous sulfate and PIC groups. The PIC group has 58% diarrhoea reported, compared to the ferrous sulfate group (35%).	Powers et al., 2017
Randomised controlled trial	Premature infants <35 weeks gestation ($n = 60$)	IPS ($n = 30$) or PIC ($n = 30$), started at 2 weeks after birth, combined with recombinant human erythropoietin. The dose	Evaluate the efficacy and safety of IPS oral solution in preventing and treating anaemia of	IPS group showed significant improvements in haemoglobin, RBC, HCT, serum iron, and ferritin compared to PIC group on day 60.	No notable adverse events were reported in either group.	Xing and Tong, 2013

is unspecified.	prematurity (AOP)

IDA: Iron deficiency anemia; IPS: Iron protein succinylate; PIC: Polysaccharide iron complex; AOP: Anemia of prematurity; HFrEF: Heart failure with reduced ejection fraction; MMF: Mycophenolate mofetil; MPA: Mycophenolic acid; AUC: Area Under the Curve; RPC: Red blood cells; HCT: Hematocrit; RET: Reticulocyte.

Table 5 Structure–activity relationships of biopolysaccharides and their anti-oxidant functions

Biopolysaccharides	Polysaccharides with attached groups	Effect of structure on anti-oxidant activities	Ref.
Chitosan	Carboxymethylated, phenolic-grafted	The presence of primary amino groups enables chitosan to scavenge free radicals and chelate metal ions like Fe^{2+} and Cu^{2+}. A lower degree of acetylation increases free–NH_2 groups, enhancing reactivity. Carboxymethylation in the C-2 amino group of chitosan switches the ionic character of the amine from positive to negative. Chitosan interacts with polyphenolic compounds via hydrophobic and hydrogen bonding and contributes to high reducing capacity, which can improve the anti-oxidant properties of these compounds. Phenolic grafting introduces hydroxyl-rich aromatic rings, further stabilizing radicals through resonance.	Rice-Evans et al., 1996; Popa et al., 2000; Kumar et al., 2004; Gassara et al., 2015; Zeb 2020
Pectic polysaccharides	Homogalacturonan, rhamnogalacturonan type I, phenolic-grafted	Uronic acid residues in homogalacturonan and rhamnogalacturonan type I offer metal chelation through –COOH groups. Lower methylesterification increases metal binding capacity. The metal chelation of xylogalacturonnans, Type I rhamnogalacturonnans and arabinan, galactan and arabinogalactan side chains of pectic polysaccharides decreases due to the lower proportion of GalA in pectin. The side chains of arabinans and galactans enhance solubility and molecular interaction with radicals. Grafted phenolic groups offer additional hydrogen donors and radical stabilization effects.	Karaki et al., 2016; Cao et al., 2020
Alginate	Sulfated, benzoylated, acetylated	Uronic acids in alginate provide chelating capability via carboxyl and hydroxyl groups. Sulfation increases electron density and anionic character, improving metal ion chelation. Benzoylation and acetylation enhance radical scavenging via the introduction of aromatic or acetyl moieties, increasing hydrophobic interactions and resonance stability.	Wang et al., 2009; Cao et al., 2020
Fucoidan	Sulfated, benzoylated, acetylated	Fucoidan contains L-fucose and sulfated groups, which are crucial for the high anti-oxidant potential. The number and position of sulfate groups significantly influence scavenging efficiency. Benzoylation adds π-electron systems that stabilize radicals, while acetylation improves hydrophobicity and may influence structure–activity flexibility.	Zhang et al., 2020;
Carrageenan	λ-carrageenan, ι-carrageenan, κ-carrageenan	Anti-oxidant strength increases with the level of sulfation ($\lambda > \iota > \kappa$). Sulfate groups provide effective radical scavenging and metal chelation. Their distribution within the polysaccharide chain affects overall molecular conformation and the accessibility of reactive sites.	Rocha de Souza et al., 2007 Campo et al., 2009)
Ulvan	Benzoylated, acetylated	Contains sulfated rhamnose and uronic acids, which components contribute both to radical quenching and metal chelation. Acetyl and benzoyl modifications provide steric accessibility and introduce redox-active sites, enhancing the scavenging of OH• radicals and superoxide anions.	Qi et al., 2006 Tzivelека et al., 2019
Mannoprotein	Carboxymethylated, phosphorylated	Anti-oxidant properties derive largely from aromatic amino acids (Tyrosine, Tryptophan) and sulfur-containing residues. Carboxymethylation enhances the water solubility and surface	Jocelyn, 1967, Harriman, 1987, Liu and

		exposure of active residues. Phosphorylation introduces negatively charged phosphate groups, boosting interaction with oxidative species and metal ions.	Huang, 2018
Galactomannan	Phosphorylated	Phosphate groups increase anionic density and metal-binding potential. Galactose side chains increase chain flexibility and solubility, allowing better dispersion and radical interaction. This branching also facilitates access to active sites for scavenging reactions.	Wang et al., 2014, Hu et al., 2016
β-Glucans	Sulfated, phosphorylated	β-(1→3)/(1→6) linkages determine backbone conformation, influencing reactivity and solubility. Chemical modifications improve flexibility and the exposure of hydroxyl and substituted groups. Sulfated and phosphorylated β-glucans exhibit stronger chelation and radical scavenging through increased polar interactions and hydrogen donation.	Machová and Bystrický, 2013; Qian et al., 2015, Tang et al., 2017
Xyloglucan	Selenious ester, sulfated	Selenylation incorporates selenium atoms into the structure, introducing redox cycling centres that enhance electron transfer. Sulfation increases negative charge and affinity for metal ions. Side chain variation supports improved solubility and molecular reactivity.	Cao and Ikeda, 2009
Starch	Phenolic-grafted	Native starch has a compact, crystalline structure that limits activity. Grafting with phenolic acids increases hydrophobicity and provides aromatic rings with delocalized electrons, improving radical stabilization and solubility in polar/non-polar solvents.	Cao and Ikeda, 2009; Wen et al., 2016

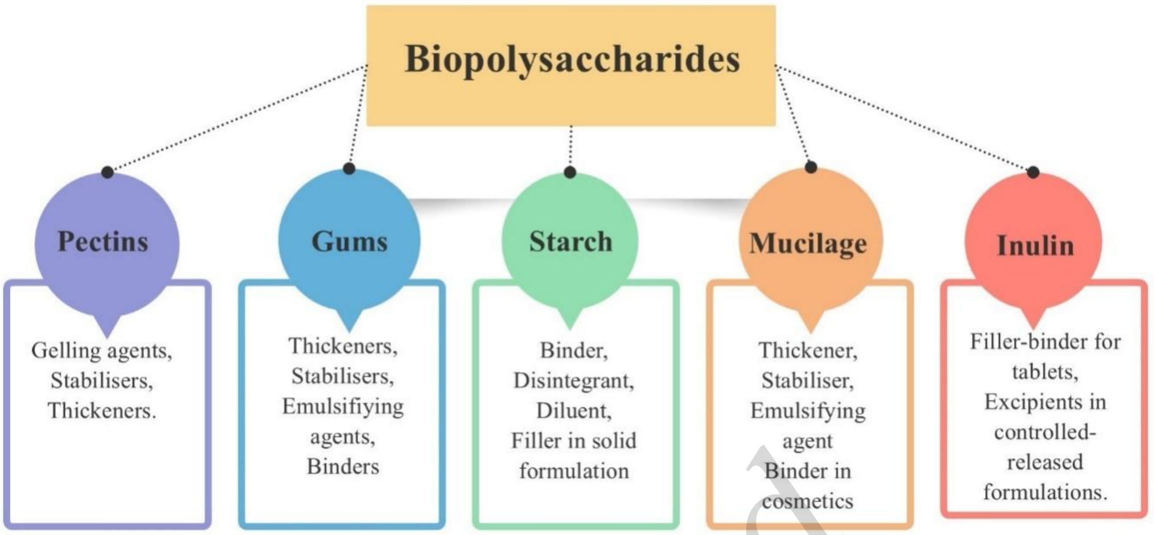


Fig. 1 Biopolysaccharides and their uses in product formulation. The figure was created in Canva.com.

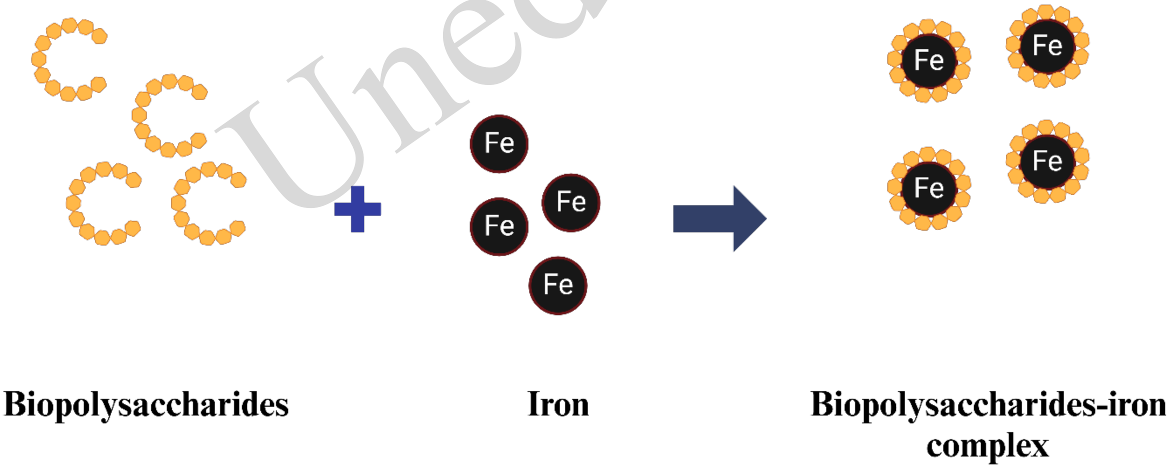
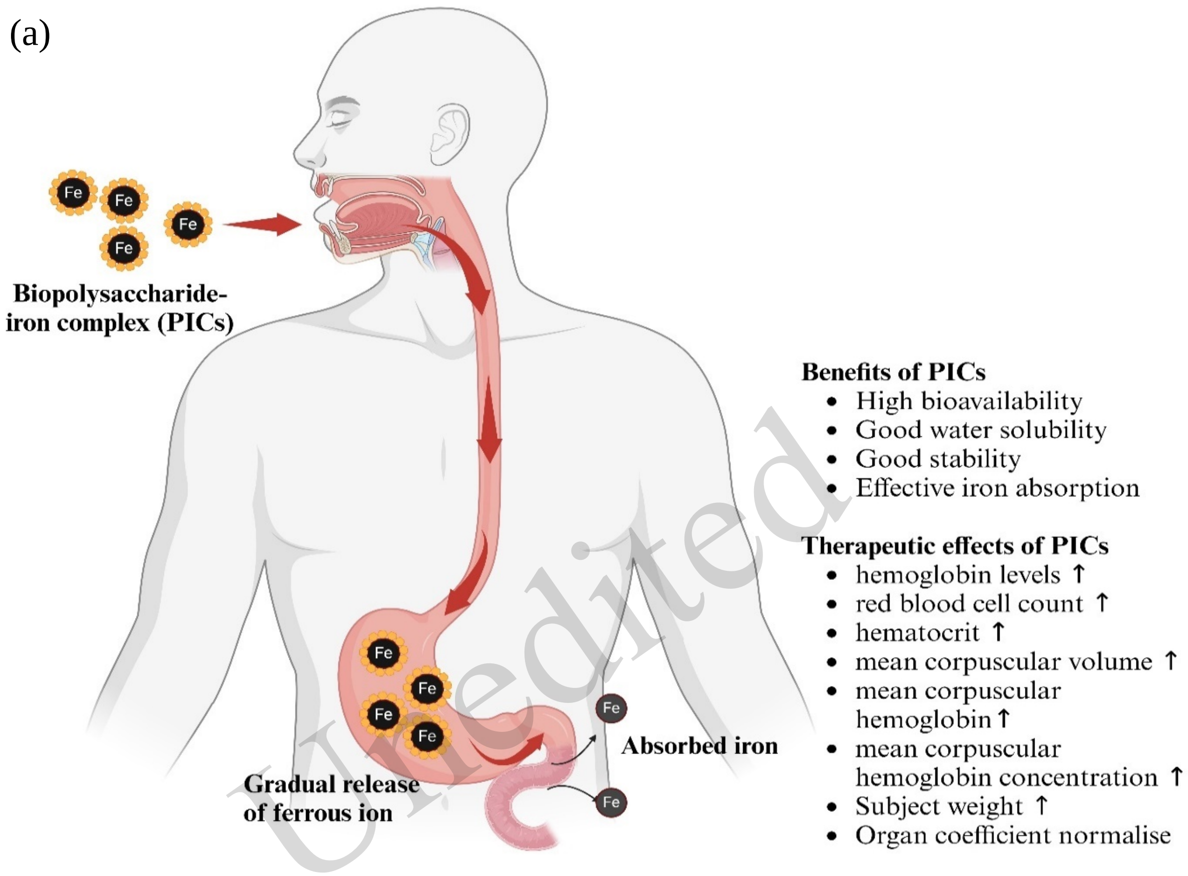


Fig. 2 Chelation of iron with biopolysaccharides. The figure was created in BioRender.c


(a)
Fe
Biopolysaccharide-iron complex (PICs)
Gradual release of ferrous ion
Absorbed iron
Benefits of PICs
High bioavailability
Good water solubility
Good stability
Effective iron absorption
Therapeutic effects of PICs
hemoglobin levels ↑
red blood cell count ↑
hematocrit ↑
mean corpuscular volume ↑
mean corpuscular hemoglobin ↑
mean corpuscular hemoglobin concentration ↑
Subject weight ↑
Organ coefficient normalise

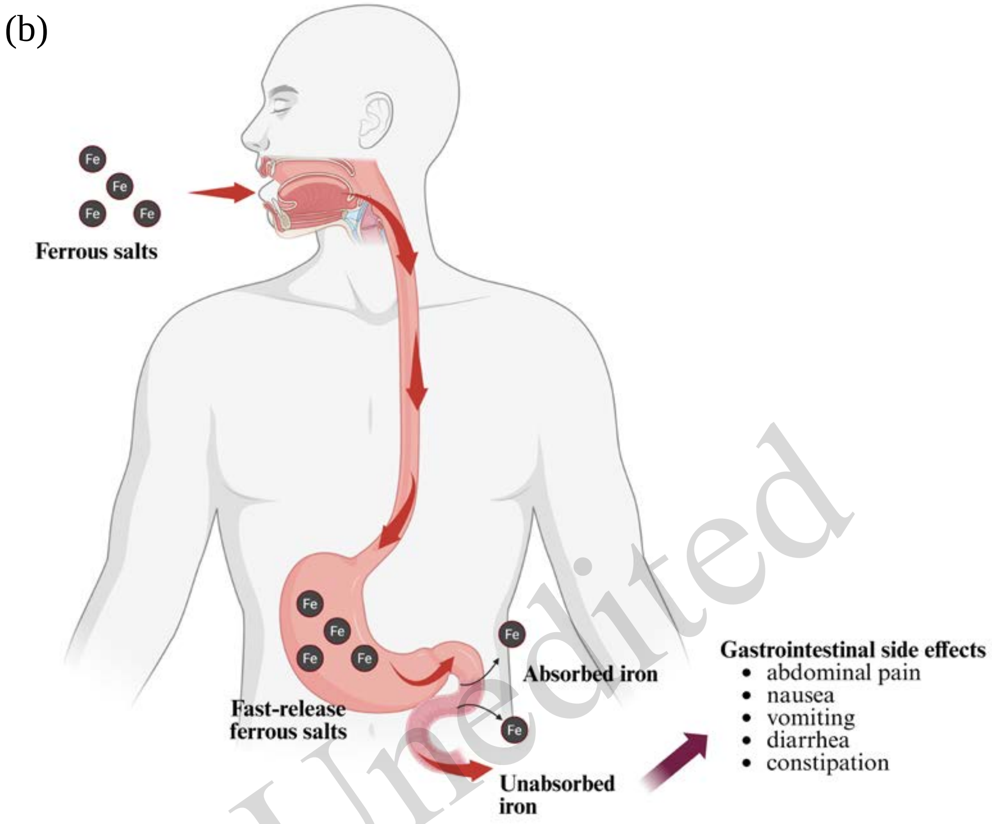
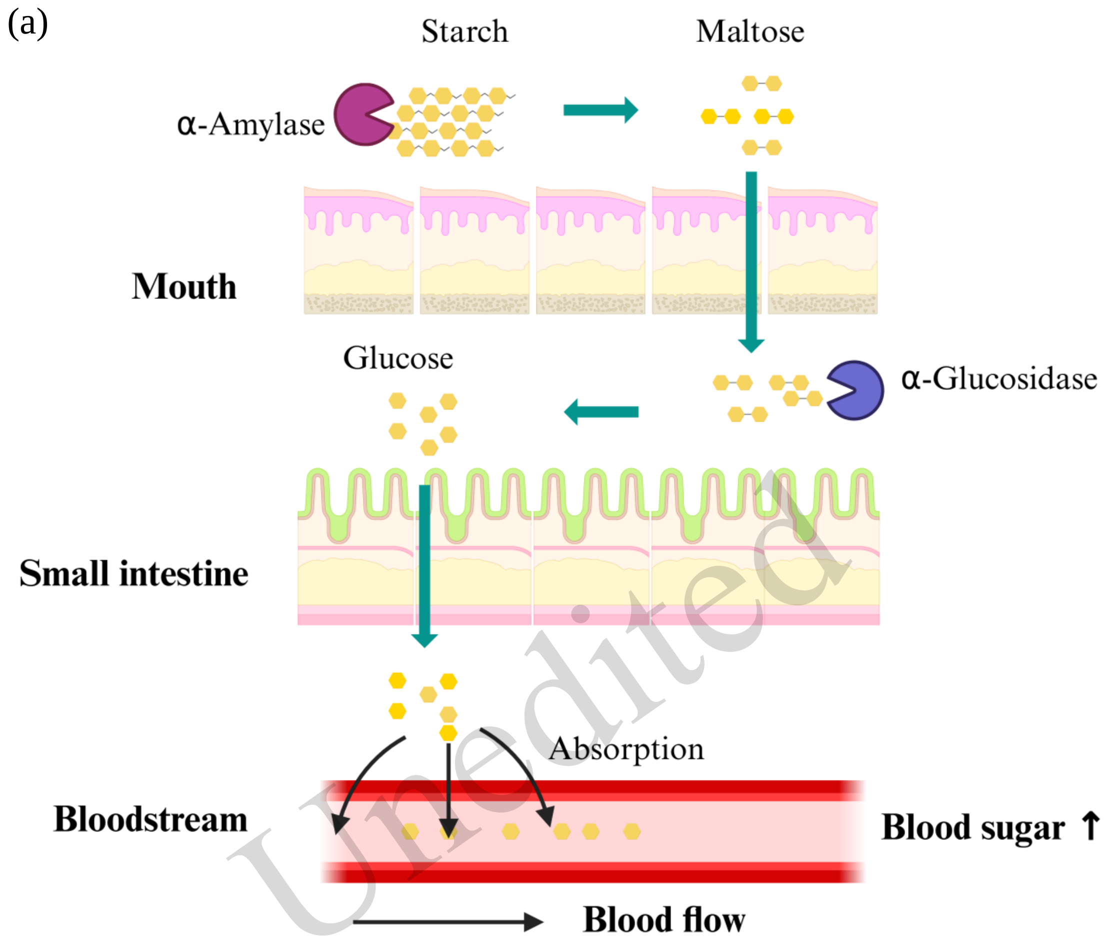


Fig. 3 Release of ferrous ion from (a) ferrous sulfate salt, (b) biopolysaccharide-iron complex (PICs) and their effects. The figure was created in BioRender.com.


(a)
Starch
Maltose
α-Amylase
Mouth
Glucose
α-Glucosidase
Small intestine
Absorption
Bloodstream
Blood sugar ↑
Blood flow

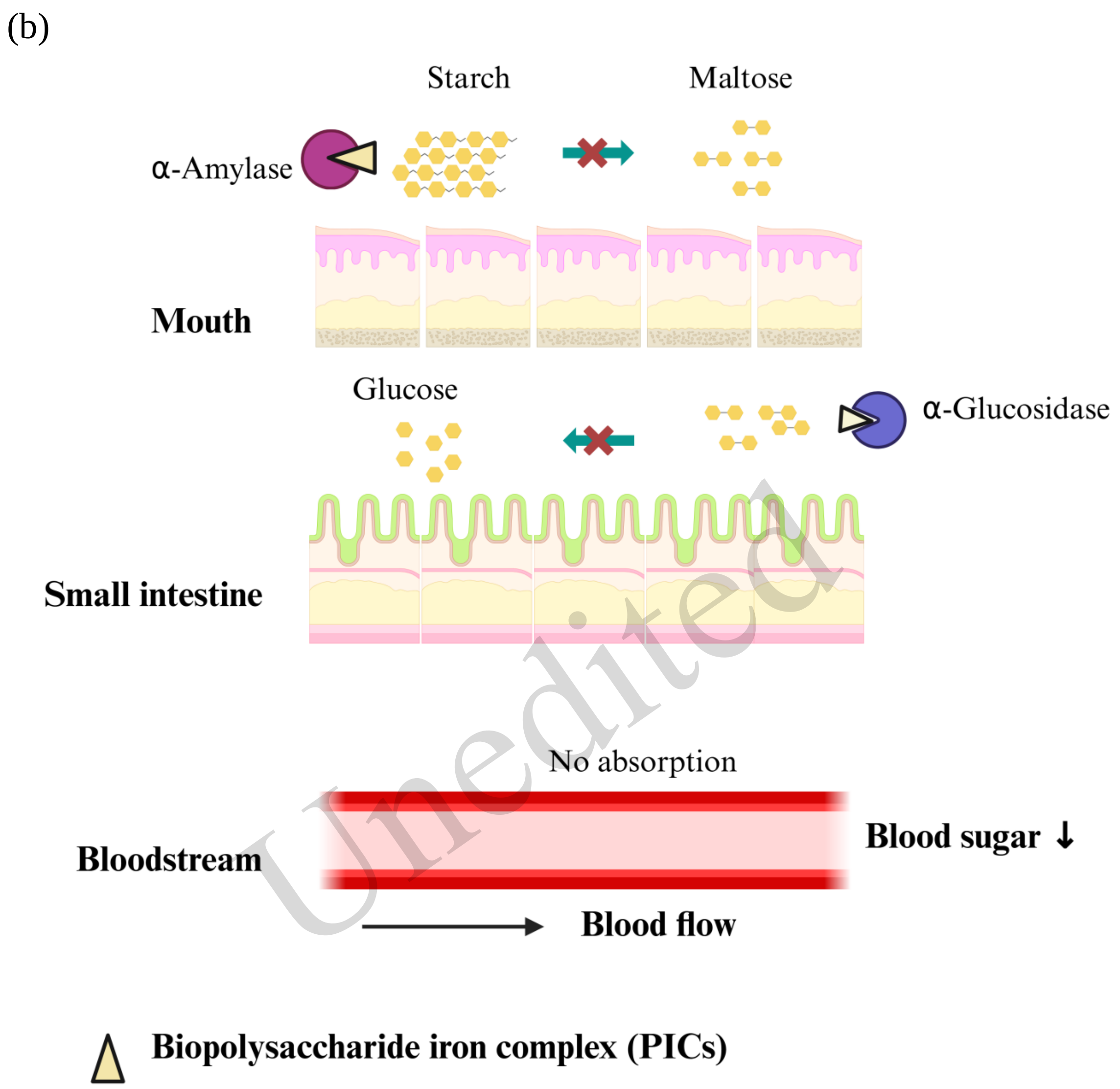


Fig. 4 Hydrolysis of carbohydrates by α-amylase and α-glucosidase (a) without biopolysaccharide iron complex and (b) with biopolysaccharide iron complex. The figure was created in BioRender.com.

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