Inulin Type Fructan: A Versatile Functional Material for Food and Healthcare

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Contents

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Abstract

Inulin type fructan (ITF), a plant derived polysaccharide, is a bio-inspired, versatile, and functional biomaterial. Chemically, ITF is glucopyranosyl-fructofuranoside polymer. ITF is very well-established prebiotics due to its ability to facilitate the growth of beneficial bacteria, i.e., bifidobacteria, lactobacilli, and bacteroides in colon. The detail study of prebiotic activity has been discussed. Furthermore, the ability of ITF as hypolipidemic agent and antioxidant with major applications in gastrointestinal disorders, especially, inflammatory bowel disease, Crohn's syndrome, and constipation, is the focus of this chapter. Additionally, hepatoprotective, anticancer, and immunomodulatory effects of ITF have made it an important functional food ingredient. Due to these diverse properties, ITF is an important and useful biomaterial for future medicine and pharmaceuticals.

1 Introduction

Biomaterials are designed to interact with living cells under physiological conditions. These materials possess inherent physical properties compatible to physiological conditions, therefore, stand as top rank choice in biomedical applications. Among different biopolymers, inulin type fructans (ITF) which are primarily linear or branched oligosaccharides or polymers containing fructose with mostly fructosyl-fructose (β-(2 $\rightarrow$ 1)) glycosidic linkages have attracted the vigil eye of researchers due to their numerous biomedical applications. Fructans can have at least one hydrolysable fructosyl-glucose glycosidic linkage at the start of the polymeric chain, which is similar to that of sucrose and gives free glucose units by enzyme sucrase secreted from epithelial villi of small intestine.

On the basis of structure, ITF can be classified into five types: (i) ITF (1-kestose), (ii) levan-type fructans (6-kestose), (iii) fructans of the inulin neoseries (neokestose), (iv) mixed-type levans (bifurcose), and (v) fructans of the levan neoseries also called mixed-type levans. ITF containing only fructose units are indigestible and are resistant to hydrolysis because of the presence of β-configuration at anomeric carbon. Actually, enzymes present in gastrointestinal tract are specific for α-glycosidic linkages [1–4].

These natural products can be obtained from cereals, fruits, and vegetables, such as wheat, leek, garlic, banana, and onion. They are stored as carbohydrates in leaves, roots, stems, or branches. As an example, inulin type fructans are extracted from fresh roots of *Cichorium intybus* (chicory), *Helianthus tuberosus*, *Polymnia sonchifolia*, and *Dahlia pinnata*. ITF possess exceptional physical and chemical properties, e.g., high molecular weight, viscosity, glass transition, melting temperatures, different glycosidic linkages, and low solubility in water. These unique characteristics make ITF a very useful material for many different applications. The ITF are very good dietary fibers, resistant to hydrolysis in small intestine and undergo fermentation in colon by microorganisms. Therefore, ITF are prebiotics that help to absorb minerals and fermentation end products. ITF improve endocrine functions by gastrointestinal peptides and protect from translocation and multiplication of pathogenic bacteria. These carbohydrates are dietary substitutes of fats and sugars with low calories. They are used as inactive pharmaceutical excipients in colon-targeted release of drugs, thus protect the stomach from adverse effects of the drugs and promote the growth of beneficial bacteria such as bifidobacteria [5–9]. Prebiotics are useful in declining the frequency of diarrhea, respiratory infections, fever, wheezing, allergy, and atopic diseases in infants. They also speed up gastrointestinal transit time, improve stool consistency, and increase stool frequency. Inulin-type prebiotics regulate the blood sugar levels and reduce the proliferation of cancerous cells in colon in model animals. They lower the triglycerides, HDL-cholesterol, and LDL-cholesterol levels in blood of individuals with hyperlipidemia and lessen the weight gain in human due to decrease in fats accumulation [10–14]. They are functional macromolecules which cause changes in the composition and activity of microflora (Bifidobacteria and Lactobacilli species) in intestine benefiting health and growth of human beings.

Keeping in view the immense importance of ITF (polysaccharides of natural origin), our aim is to review the potentials of this versatile biopolymeric material in the development of functional food and advanced drug delivery systems. To the best of our knowledge, there is no comprehensive review presenting the broad-spectrum properties such as their use in functional food and medicinal applications. Therefore, this compilation will be highly valuable for the people working in these areas. Due to broad spectrum of applications of ITF, we will focus on its general characteristics, isolation methodologies, chemical structure, and its applications in functional food, medicinal, and pharmaceutical sectors. Present review will bridge the knowledge gaps of food chemists, phytochemists, and pharmaceutical chemists. Contents of this compilation will attract and be beneficial for the audience from food and pharma industries as well as from academia. We managed the content in the way that common people may get information about beneficial health effects of ITF as a food.

2 Structure of ITF

A compound having one or more fructosyl-fructose linkages are classified as fructan [15]. Fructan is either a cyclic or a branched molecule which is also known as polyfructosyl-fructose [16]. Chemically, fructans are linear chain of β-D-glucopyranosyl-[-β-D-fructofuranosyl]$_{n\text{-}1}$-β-D-fructofuranoside (ITF) or

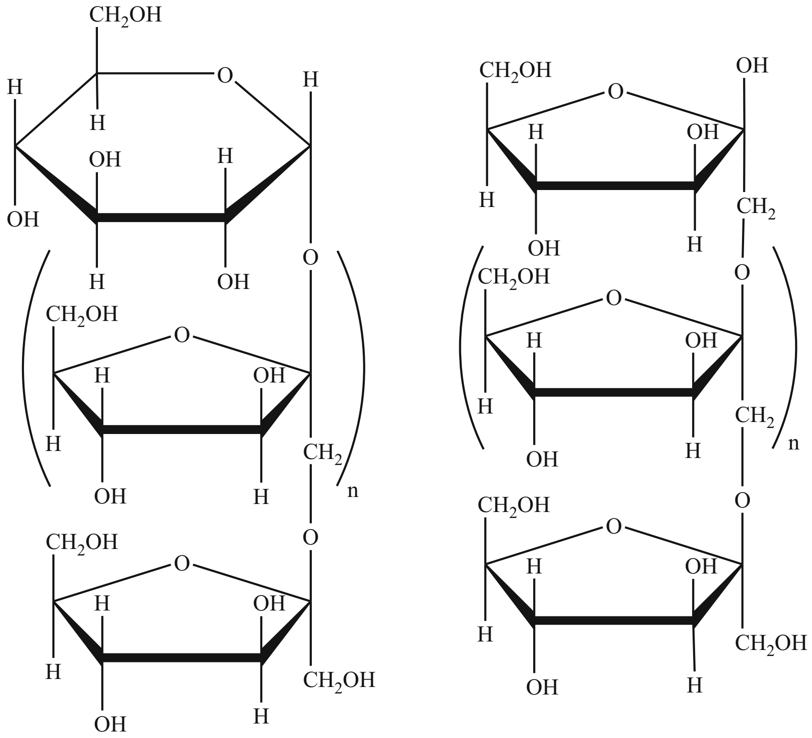

Fig. 1 Structures of fructans (ITF and inulin)

a *β*-D-fructopyranosyl-[-*β*-D-fructofuranosyl]$_{n-1}$-*β*-D-fructofuranoside (inulin) [15]. It is noted from literature that fructans isolated from all dicotyledons and some monocotyledons are ITF [17].

Moreover, it is important to mention here that other structurally related polysaccharides based on fructosyl-fructose linkages are inulin which were discovered from plant, *Inula helenium*, and may confuse the reader. A wide range of plant species (approximately 45,000, i.e., 15% of flowering plants) contain inulin as major carbohydrate storage [18]. Therefore, some basic structural information about these closely related polymers, inulin and ITF, are being reported in this chapter. Inulin has *β*-(2 → 1) fructosyl-fructose linkage (straight chain, indigestible), and if inulin contains a terminal glucose unit in the chain, then it is called ITF [15, 19–21] (Fig. 1). ITF is also straight chain fructan having indigestible fructose backbone (*β* -linked) similar to inulin but ITF has a digestible terminal glucose unit in gastrointestinal tract (GIT). Permethylation analysis of inulin revealed small degree of branching as well [22]. Cyclic forms of inulin have also been reported that contain 6, 7, or 8 fructofuranose rings [23].

3 Isolation Strategies for ITF

The ITF are normally isolated using polar solvents, e.g., water. The factors that influence the quality and yield are temperature, solvent compositions, and number of extraction cycles. As an example, ITF was isolated from the roots of *Pfaffia glomerata* Pedersen when dried roots were soaked in distilled water (1:15 w/v) for 2 h at 100 °C. The procedure was repeated thrice to ensure maximum extraction. The aqueous extract was filtered, concentrated, and precipitated using ethanol. The precipitates were separated and lyophilized to get the final product [24].

Recently, ITF was also isolated from roots of *Codonopsis pilosula*. Sample was dried at 50 °C and grind to get fine powder. After subsequent extraction employing a mixture of ethanol (96%) and distilled water (4%), the liquid extract was filtered, concentrated, and lyophilized. The optimized extraction conditions were established through response surface methodology using Box-Behnken factorial design. The optimized temperature, extraction time, and solvent to material ratio for maximum yield of ITF (20.6 ± 0.2%) are 100 °C, 2.5 h, and 40 mL/g, respectively [25].

Low (<3 kDa) and high (>3.5 kDa) molecular weight ITF were isolated from raw garlic and aged (20 months) garlic extracts. Raw garlic (100 g) was homogenized with Tris-HCl buffer (10 mM) of pH 8. The mixture was centrifuged and filtrate was lyophilized to get powdered form of fructans [26]. Aged garlic extract was collected by storing fresh garlic for a period of 20 months in 25% ethanol. Decanted solution was lyophilized to collect powder form of fructans.

Solid-liquid extraction method was also employed to isolate fructans from Agave pines using distilled water. Agave pines were homogenized with water in a blender at room temperature and pH 5.5. The extract was filtered, centrifuged, and fructans were separated by concentrating the supernatant. Different extraction conditions, i.e., water to raw material ratio, extraction time, and temperature of the solvent were optimized. The maximum fructans yield of 83.3% was achieved at 5.13 mL/g, 1.48 h, and 79 °C, respectively [27].

In a study carried out in Thailand, ITF was isolated from different varieties of plants to optimize the yield. ITF was isolated using hot water extraction method. High levels of ITF were isolated from Chinese garlic, great headed garlic, Jerusalem artichoke, and common garlic. Moreover, medium level ITF were present in red onion and shallot. Great headed garlic has the highest level (29.2 ± 5.62 g/100 g fresh weight of sample) of ITF among all varieties [28].

4 Functional Food and Medicinal Applications

ITF is an important plant derived biomaterial and widely used in many different medicinal and functional food applications. Chemically, ITF is a polysaccharide which is biocompatible and can be isolated from different parts of plants in abundant amount. It has been used as prebiotic due to its beneficial effects on microflora of gastro-intestinal tract (GIT). The ITF also exhibited hypolipidemic effect, blood sugar regulator, colon-specific drug delivery attribute, and eradication of colon specific diseases such as diarrhea, constipation, irritable bowel syndrome, and ulcerative colitis. Although ITF qualifies as potential candidate for many different applications, due to its immense use in functional food and medicine, we will restrict our discussion in these two areas.

4.1 Sugar Replacer

In food industry, low molecular weight fructans like short chain oligofructose and fructooligosaccharide are favored as sugar replacers owing to their greater solubility. Functional characteristics of such polysaccharides are similar to that of sugar or glucose syrup and they possess almost 30–50% sweetness as compared to table sugar. To balance sweetness, artificial sweeteners such as aspartame are mixed with ITF which mask the effect of sweeteners and improve the customer satisfaction [29, 30].

4.2 Prebiotics

Prebiotics is defined as “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health” [31]. Many oligosaccharides, ITF, and dietary fibers (polysaccharides) have been used for their prebiotic activities [32], though all carbohydrates are not prebiotics [33]. Scientific literature shows that only three products meet the criteria of prebiotics which include ITF, (*trans*)-galactooligosaccharides, and lactulose [33]. We also noted from the literature that inulin itself is a proved prebiotic [34–36].

In a study, prebiotic effect of fructans, i.e., inulin and oligofructose, was observed by simulating the human intestinal microbial ecosystem at a dose of 2.5 g/day and monitoring the microbial composition and fermentation activity in the colon. Inulin showed a pronounced prebiotic effect as compared to oligofructose and having positive influence on the microbial growth in different parts of colon [37]. Fermentation of ITF mainly depends on the strain of bifidobacteria rather than the species [38]. Prebiotic effects are also attributed to the production of bacterial metabolites through immune regulation which leads to increased gut microbiota, e.g., bifidobacteria, lactobacilli, and bacteroides [39, 40]. The prebiotic effect is also associated with the modulation of biomarkers and stimulation of the immune system [40]. Low dose of ITF is considered as prebiotic which reduces the symptoms of inflammatory bowel syndrome, whereas high dose has negative or neutral effect on such symptoms [39].

High protein intake may lead to the production of toxic end products in the colon as a result of bacterial proteolysis. Prebiotics have the potential to reverse the side effects of bacterial protein fermentation. After administration of ITF, an increase in bifidobacteria and decrease in the concentration of branched chain fatty acid (BCFA) and ammonia (protein fermentation metabolites) was observed. In vivo investigation in 43 volunteers was carried out to confirm the ITF benefits with high intake protein diet. Results of this study indicated that ITF supplementation has inhibitory effects on colonic bacterial proteolysis and potentially stimulate the growth of beneficial bacteria [41].

In a double-blind cross-over study, 34 persons were given low dietary fiber (LDF) and high dietary fiber (HDF) to observe the colonic microbiota response to ITF. After 3 weeks study, an increase concentration of Bifidobacterium and Faecalibacterium was observed in HDF group which indicated the greater response of gut microbiota to HDF in the presence of ITF than LDF [42].

Effect of prebiotic (ITF) on bile acid, fecal microbiota, and metabolites were studied in overweight beagle dogs. Results indicated that ITF are modulator of gut microbiota, bile acid, and metabolites [43].

A study was designed to ascertain the prophylactic effect of ITF on reoccurrence and frequency of infectious diseases in children. ITF supplement (6 g/day) was given to the children (aged from 3 to 6 year) for 24 weeks. During this period, stool consistency, stool microbiota analysis, disease symptoms, dietary habits, and kindergarten absenteeism were determined. At the end of study, the abundance of Bifidobacterium and Lactobacillus were 19.9% and 7.8% higher as compared to control. Additionally, stool sample was soft in the children taking ITF. The incidence of sinusitis and febrile episodes are also reduced from 0.06 to 0.01 and 0.9 to 0.65, respectively. Therefore, ITF supplement exerted beneficial effects on intestinal microbiota and protection against some infectious diseases [32].

4.3 Fat Replacer

Due to structural, nutritional, and physiological aspects related to ITF, their presence in daily diet is important for the growth of beneficial gut bacteria. They are not hydrolyzed by enzymes in upper GIT, but they undergo fermentation in colon and produce hydrogen gas, carbon dioxide, short-chain fatty acids, and lactate. In this way, ITF regulate the bowl, as a result fat deposition will be avoided in body. People with balance food habits such as in Europe and North America ingest 3–11 and 1–4 g ITF daily, respectively [21]. ITF are GRAS (generally recognized as safe) listed item [44] therefore, a number of food materials are supplemented with ITF to enhance fibrous content of food which are generally responsible for fat uptake [14, 36]. Trend of the use of ITF in food industry is growing day by day because they do not affect appearance, color, texture, or taste of nutritional substances. ITF with degree of polymerization greater than 10 are considered the best-known fat replacer in water-based foods without compromising the taste and texture [14]. Hydrophobic long chains of ITF reduce solubility and make smooth and creamy spreads with low fat contents [29]. Therefore, ITF supplemented food is valuable to address obesity issue.

4.4 Peptide Modulator

Diets supplemented with ITF are used to control the food intake by modulating gastrointestinal peptides such as glucagon-like peptide-I and ghrelin in Wistar rats during 3 weeks study. Fructans-based diet when fermented in caecum and proximal colon reduced the energy intake and fat mass in epididymis owing to increment in glucagon-like peptide-I and proglucagon mRNA concentrations. The diet also decreased the ghrelin concentrations in plasma of treated rats. Thus fructans fibers controlled food and energy intake by producing incretins and anorexigenic–orexigenic peptides [45].

Endothelial dysfunction is the indication of oncoming cardiovascular diseases. Microbiota present in gut played significant role in preventing endothelial dysfunction-related metabolic diseases through initiating various mechanisms. Reversal of endothelial dysfunction was observed in mesenteric and carotid arteries of mice fed with n-3 polyunsaturated fatty acid (PUFA)-depleted diet supplemented with ITF in 12 weeks study. It was due to the activation of nitric acid synthase/NO pathway, which replenished the endothelium lining by promoting growth of bacteria, *Akkermansia*, and decreasing the population of bacterial taxa in secondary bile acid synthesis. Fructans-based diet preserved the functions of endothelium by increasing concentration of glucagon-like peptide-I and causing changes in expression of gut and liver genes. Thus, diet enriched with ITF improved endothelial function by changing the gut microbiota and peptides [46].

4.5 Obesity Reducing Potential

Accumulation of fats in adipose tissues leads to obesity which may also be due to the environmental and genetic factors. ITF increase fermentation and modify gut microbiota to lessen obesity (Fig. 2). Fat-rich diet results in the production of large adipocytes which are further described by insulin sensitivity. Fat rich diet also stimulates the proliferation of peroxisome activated gamma receptors and G protein coupled receptors. Diet supplemented with ITF enhanced fermentation in the gut, which is depicted by increased weight of gut in mice. It also decreased the expression of G protein coupled receptors and peroxisome-activated receptors induced by fatty diet. Fructans-based diet also decreased the size of adipocytes [47] (Fig. 3).

4.6 Free Radical Scavenging Agent

ITF protects from oxidative stress caused by lipopolysaccharides when studied on mucosa of human colon using proteomic approach. ITF not only prevent the alteration of proteins such as myosin light chain kinase and myosin regulatory subunit but also restore their appropriate level and improve contraction of smooth muscles of intestine. This is due to free radical scavenging and bacterial growth promoting potential of ITF. They also decrease the upregulation of proteins involved

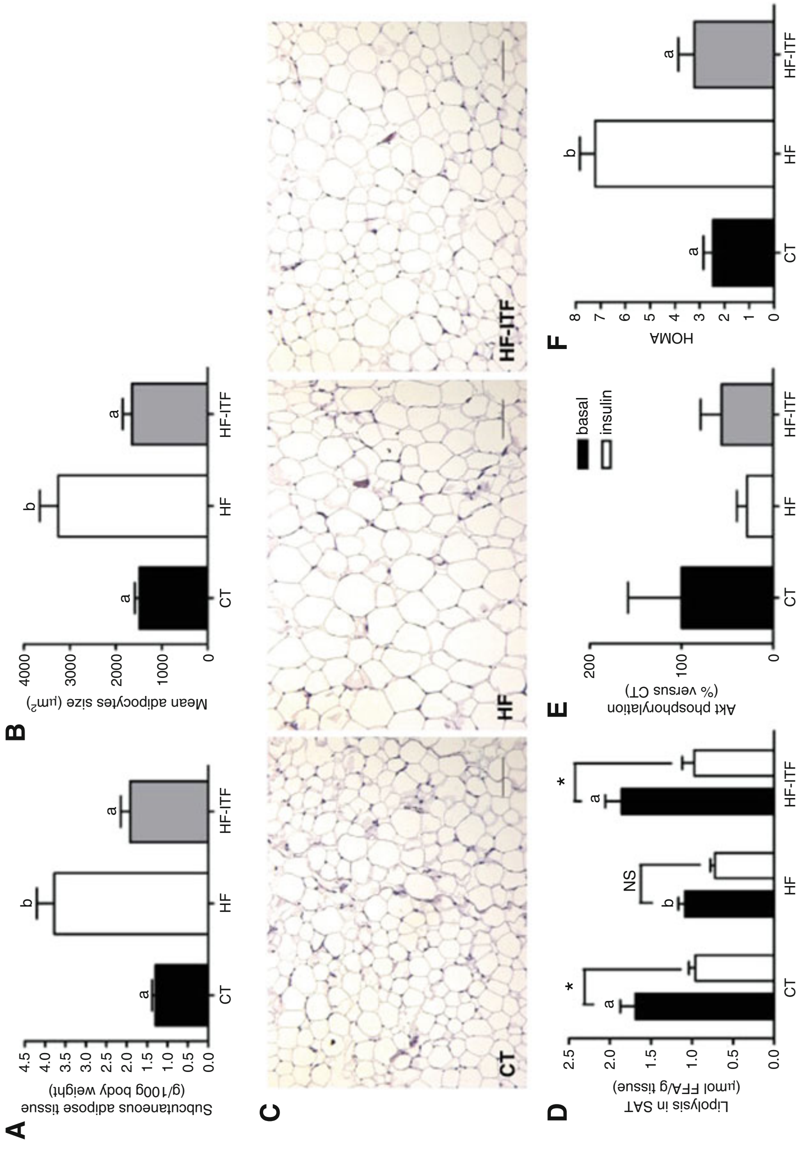

Fig. 2 Metabolic and histological analysis of subcutaneous adipose tissue in mice fed a CT diet, an HF diet or an HF-ITF diet after 4 weeks of treatment. (**A**) Subcutaneous adipose tissue mass. (**B**) Mean adipocytes size. (**C**) Histological pictures in hematoxylin and eosin stain (bar =100 µm). (**D**) Free fatty acids (FFA) released by explants of SAT after 2 h of incubation with or without insulin. (**E**) Percent of insulin-induced Akt phosphorylation reported to CT group.

in free radical oxidative stress and increase level of detoxifying enzymes such as the metallothionein-2 MT2A, the glutathione–*S*-transferase K GSTk, and two UDP glucuronosyltransferases, UGT2B4 and UGT2B17 [48].

4.7 Anticancer/Anti-Tumor Potential

ITF displayed anticancerous potential in various animal models. ITF decreased abnormal crypt foci and metastasis of tumor cells which were induced by chemicals in large intestine of mice and rats. It was noted that ITF also reduced the incidence of tumor in abovementioned animal models [11]. Fructooligosaccharide (10.0 g) was given to 74 subjects on daily basis for 3 months which was divided into three groups suffering from small colorectal adenoma, large adenoma, and without adenoma. After 3 months study, fecal pH, crypt cell proliferation, and blood parameters were not affected by fructooligosaccharide. However, fructooligosaccharide may affect the colonic environment to prevent the colorectal neoplasia [49]. Thus it can be said that ITF have potential to lessen cell proliferation at infected sites, but results in human beings are not convincing. Extensive research in human beings is still demanding to investigate the potential of ITF in preventing/curing cancer.

Another recent research work has shown the anti-tumor potential of ITF isolated from *Atractylodes chinensis* rhizome. The anti-tumor activity (in vitro) of ITF was carefully evaluated on four different cancer cell lines (human), i.e., ovarian carcinoma cell line (Skov3), liver hepatocellular carcinoma (HepG2 and 7721), and cervical cancer cell line (Hela) [50] (Fig. 4). From this study, it was inferred that ITF significantly reduced cell proliferation in all cell lines whereas 87.40% proliferation inhibition rate was noted for hepatocellular carcinoma cell lines (HepG2). However, further investigation and clinical trials are required to establish this potential.

4.8 Gastrointestinal Disorders

ITF are fibrous indigestible biomaterials, which may affect the bowel transit time, stool frequency, and consistency in various subjects. Bottle-fed 56 preterm infants of just 2 weeks received a formula augmented with inulin (oligofructose) or maltodextrin for 2 weeks. Stool frequency was increased in infants fed with oligofructose which softened the stool and altered the stool consistency [51]. Whereas, 56 healthy children with age ranging from 16 to 46 weeks were provided with fructooligosaccharide (0.74 g per day) supplemented diet for 28 days. Alongside, placebo group received normal routine diet. Stool became softened in

Fig. 2 (continued) (**F**) Homeostasis model assessment. Data are mean ± S.E.M. Data with different superscript letters are significantly different at $P < .05$, according to the post hoc ANOVA statistical analysis. The Two-way ANOVA analysis of Panel D shows a significant effect of insulin and treatment ($P < .05$); *$P < .05$ "basal lipolysis" versus "insulin-inhibited lipolysis" according to Bonferroni posttest. Reprinted from [47] with permission from Elsevier

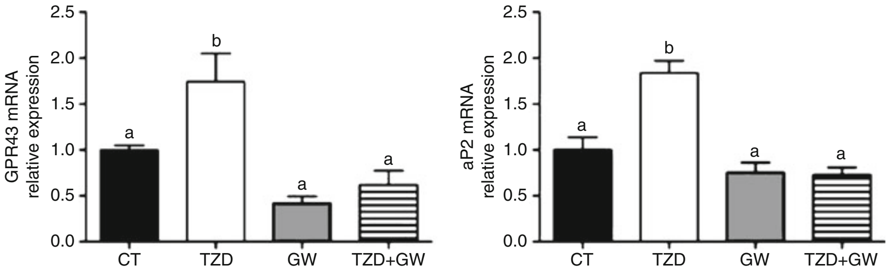

Fig. 3 Expression of GPR43 and aP2 in explants of subcutaneous adipose tissue incubated in a control medium (CT) or with different pharmacological agents: a PPARγ agonist (TZD), a PPARγ antagonist (GW9662), or a combination of both during 24 h. The CT group is set at 1 value. Data are mean ± SEM. Data with different superscript letters are significantly different at Pb.05, according to the post hoc ANOVA statistical analysis. (Reprinted from [47] with permission from Elsevier)

treated group with increase in mean number of stools per day as compared to placebo group. Infants fed with fructooligosaccharide have fewer days without stool than placebo [52]. Recently, it has also been reported that ITF profoundly modifies the composition of caecal microbiota in mice models [46].

Cow's milk with or without oligofructose fed to full term infants of 2–6 weeks age increased the frequency of stool. Oligofructose augmented diet also made the stool loose. Frequency and consistency of the stool became more significant with increase in concentration of oligofructose in milk [53]. ITF have the potential to manage gastrointestinal disorder such as acute pancreatitis by modulating gut immune and supporting fermentation. Diet supplemented with long chain ITF helps to control caerulin-induced acute pancreatitis in mice as it is evident from decreased levels of serum amylase and lipase, and activity of pancreatic myeloperoxidase. The ITF-based diet also restored the dysfunction caused by acute pancreatitis by upregulating modulatory proteins and microbicidal peptides, and downregulated the pancreatitis initiated up-regulation of IL-1 receptor-associated kinase 4 and phosphor-c-Jun *N*-terminal kinase. This diet also prevented the inflammation and damage caused to pancreas [54].

Irritable bowel syndrome (IBS) is a chronic disease having symptoms of gastroenteritis, low grade inflammation, dysbiosis, and alteration in colonic gas production. A decrease level of bifidobacteria was observed in IBS and to increase its level, prebiotic stimulated growth ingredients have shown positive effects [39]. Another study on animals showed the effectiveness of ITF in Crohn's disease and possible mechanism is through increasing the number of beneficial gut microbiota [55].

ITF changed the composition of microbiota present in rat intestine by promoting beneficial bacteria such as bifidobacteria and lactobacilli. Fructans also improved health of model animals by reducing the population of pathogenic bacteria such as *Salmonella enterica*. Fructans also modified the composition of mucosa in the colon by exciting multiplication in crypts and mucin release. Fructans-based diet also modifies the mucin components in globut cells and epithelial mucous layer [56].

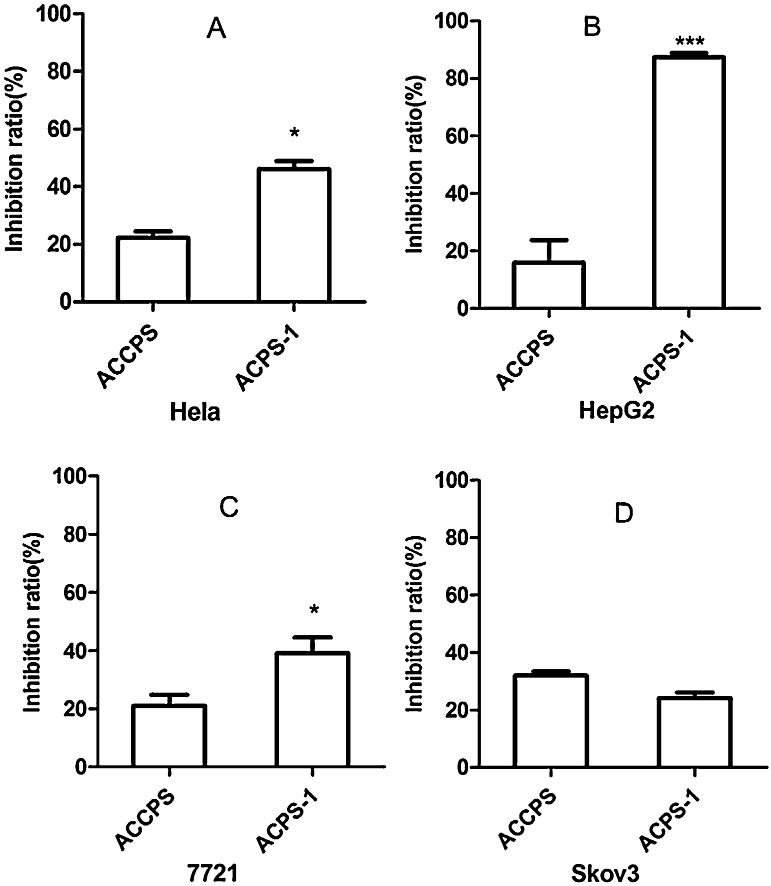

Fig. 4 Inhibitory effects on the proliferation of cancer cells. (**A**–**C**) Trypan blue exclusion assay and (**D**) MTS assay. Data are expressed as mean ± SD of triplicate analyses. Asterisks indicate significant difference versus the control group (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). (Reprinted from [50] with permission from Elsevier)

Owing to fibrous nature of ITF, they may be used to relieve constipation. ITF were ingested by 10 elderly females for 19 days to get rid of hard stool consistency. During first 8 days, dose of ITF was 20 g, which was continuously increased to 40 g from day 9 to 11. After that, dose remained 40 g till the end of study. After ITF intake, bowel consistency was increased with the softening of stool. Bowel frequency improved from 1–2 to 8–9 per week in dose independent fashion in seven female subjects. Other three female subjects showed lesser increase in stool frequency and consistency [57]. Effect of ITF fermentation on the fecal metabolites and the composition of colon bacterial ecosystem were investigated. Change in the composition of fecal metabolites, condition of stool, and occurrence of constipation were observed during the study. The decrease in Bilophila is indicated by the softness of stool. Modest effects on microbiota composition were also observed by abundance in Anaerostipes, Bilophila, and Bifidobacterium [58].

Effect of oligofructose on incidence and severity of diarrhea in 282 infants (6–12 months) were studied for 6 months. Infants received regular diet or diet mixed with oligofructose (0.55 g/15 g cereal). Incidence of diarrhea occurred after 10.3 and 9.8 days in placebo and oligofructose supplemented diets, respectively. However, prebiotic supplementation has not shown any significant effect on breast-feed infants and young children [59].

ITF enriched diet is used to relieve functional bowel disorder. Functional bowel disorder is similar in symptoms to irritable bowel syndrome and is associated with abdominal fluctuation, rumbling, abdominal pain, bloating and alternating chances of constipation and diarrhea. Fructooligosaccharide (5.0 g twice a day) decreased the symptoms of functional bowel disorder in participants as compared to placebo group which received mixture of sucrose (50%) and maltodextrins (50%). The 6 weeks study was completed by 97 participants [60].

ITF have potential to cure acute ulcerative colitis. Subjects with mild to moderate colitis randomly received high molecular weight inulin (12 g) or maltodextrin along with regular medication using mesalazine (3 g per day) for 2 weeks. Out of 15 subjects who completed trial, 14 showed reduction in disease activity. Decrease in calprotectin, protein biomarker of inflammation in intestine was observed showing that inflammation was reduced with lesser chances of colitis incidence [61]. Ethanol induced gastric ulcer was treated by ITF at two different doses (25 and 50 mg/kg body weight of mice) and results indicated that mucosa ulcer index decreased significantly as compared to control group [62]. Patients suffering from active ileocolonic or colonic Crohn's disease received inulin oligofructose (15 g) for 3 weeks. These prebiotics increased interleukin-10 positive CD11c + dendritic cells, toll-like receptor 2 (TLR2), and TLR4 expression which indicated the reduction in inflammation by commencing cytoprotective mechanisms in colonic cells [63].

4.9 Regulation of Blood Sugar

ITF do not regulate blood sugar in normoglycemic and hyperglycemic subjects as it is reported in various studies. Twelve healthy individuals divided into four groups were provided diet containing ITF for 84 days. There was investigated insignificant difference in insulin response and glucose tolerance tests [64]. Similar results were observed when 10 g high molecular weight inulin divided into two doses was provided to eight healthy subjects for 3 weeks [65]. Fructooligosaccharide (10.6 g) was used by 30 participants with mild hyperlipidemia in tea or coffee for 2 months. Placebo was provided with 15.0 g maltodextrin with aspartame. There was no statistical difference in fasting blood glucose or insulin. Postprandial plasma glucose level was also same in both groups. However, postprandial insulin was decreased in fructooligosaccharide group than placebo group [66].

Twelve individuals with type 2 diabetes were given fructooligisaccharide (20 g per day) while keeping their medical therapies as per routine. Placebo group was provided with sucrose. Blood glucose concentration was same in treated and placebo groups. Indicators of long-term sugar control such as hemoglobin A1c and fructosamine were not affected in all individuals. Insulin levels were also remained unaffected [67]. Thus it can be concluded that diet augmented with ITF cannot improve blood glucose levels in normoglycemic subjects and have no clinical advantage in improving metabolism in hyperglycemic subjects. ITF promoted modulatory T-cell response and cytokine production in colon, spleen, and pancreas. Hence, protect the body from autoimmune diabetes through modulation of gut-pancreatic immunity, microbiota homeostasis, and barrier function [68].

4.10 Immunological Properties

ITF have shown immune modulating effect in mice and human through direct and indirect mechanism [69]. In direct mechanism, ITF can be detected by gut dendritic cells through receptor ligation of pathogen recognition receptors and eventually inducing pro- and anti-inflammatory cytokines. Indirect mechanism involves the stimulation and growth of lactic acid bacteria which leads to the production of fermentation products. Being a potent immunomodulator, ITF can be used for prevention of many diseases. Numerous gut immune markers are modulated by ITF as is evident from increased fecal IgA and IL-10 levels, and IFN-γ expressed in Peyer's patches. ITF-based diet increased immune cell activity in spleen cells as well [69, 70].

4.11 Hypolipidemic Activity

Various reports involving healthy subjects showed insignificant differences in triglyceride, HDL-cholesterol and LDL-cholesterol levels among treated and placebo groups [66, 71, 72]. Studies carried out in hyperlipidemic individuals revealed the lipid lowering potential of ITF, while some studies reported insignificant hypolipidemic potential of ITF. Thirty persons were selected for the evaluation of lipid metabolism having mild hypercholesterolaemia. After stabilizing on standard diet for 1 month, subjects were given ITF (10.6 g/day) for 1 month. Fasting lipoprotein, triglyceride, and cholesterol were measured, and slight decrease in cholesterol level was observed [66].

High molecular weight inulin (10.0 g) decreased significantly plasma triglyceride levels in healthy individuals. However, diet did not affect total, HDL, and LDL cholesterol levels [66]. Twelve obese subjects with high triglyceride and cholesterol received inulin (7.0 g/day) for 4 weeks. Inulin enriched diet decreased their total cholesterol, LDL-cholesterol, VLDL-cholesterol, and triglyceride levels from 248.7 to 194.3, 36.0 to 113.0, 45.9 to 31.6, and 235.5 to 171.1 mg/dL, respectively [10]. Oligofructose-rich high molecular weight inulin caused significant reduction in body mass index of 89 adolescent subjects. Average difference in body mass index between treated and controlled groups was investigated to be 0.52 kg/m^2. Similarly, average gain in body weight (0.84 kg) due to fat accumulation was less than placebo group [73]. Various mechanisms are established to improve the lipid profile and reduce the risk of cardiovascular diseases. Such mechanisms are to increase the activity of muscle lipoprotein lipase enzyme, altering blood sugar, insulinemia, and production of polyamines, and increase in the bile salt excretion, cholesterol, and Bifidobacterium population [74].

4.12 Liver Protection

Infusion of *Artemisia vulgaris* is prepared to test its effects on liver in a recent study [75]. This *A. vulgaris* infusion (VI) of aerial parts showed hepatoprotective effects on animal model which were credited to the presence of 40% carbohydrate contents (i.e., ITF) along with antioxidant and immunomodulatory properties of VI. The mechanism of liver protection was studied and it was noted from this work that VI prevents necrosis, raises the reduced glutathione (GSH) levels, and it also reduces the levels of tumor necrosis factor alpha (TNF-α) in the liver (Fig. 5). This study unveiled the protective effect of ITF on liver.

4.13 Arthritis Preventing Effects

ITF has been rarely studied for its anti-arthritic potentials. In a recent study, ITF isolated, purified from *Artemisia japonica* showed molecular weight of 3.1 kDa. Oral administration of this water soluble ITF (200 mg/kg) significantly decreased the clinical parameters of collagen-induced arthritis (CIA) in DBA/1 mice compared with untreated mice [76] (Fig. 6). It was also noted from histopathological analysis of ITF-treated mice that there is less joint damage and inflammatory cell infiltration and reduced serum levels of the interleukins IL-17A and IL-6 which indicate that ITF is a functional food supplement with anti-arthritic properties. Further studies on cartilage repair and its clinical results will insure the said potential.

5 Pharmaceutical Applications

Being a biocompatible polysaccharide, ITF was introduced as a novel drug-delivery system for ibuprofen which belongs to nonsteroidal anti-inflammatory drugs (NSAIDs). Fructans isolated and purified from *Agave tequilana* Weber var. *azul* juice was modified to synthesize acetylated derivative for its application as excipient in sustained drug release systems. Microspheres prepared through coacervation were loaded with ibuprofen, anti-inflammatory drug, and showed sustained drug release in media containing *Bifidobacterium animalis*. With increase in degree of acetylation, solubility of fructans in water decreases. Fructans are nutrient biomaterials providing

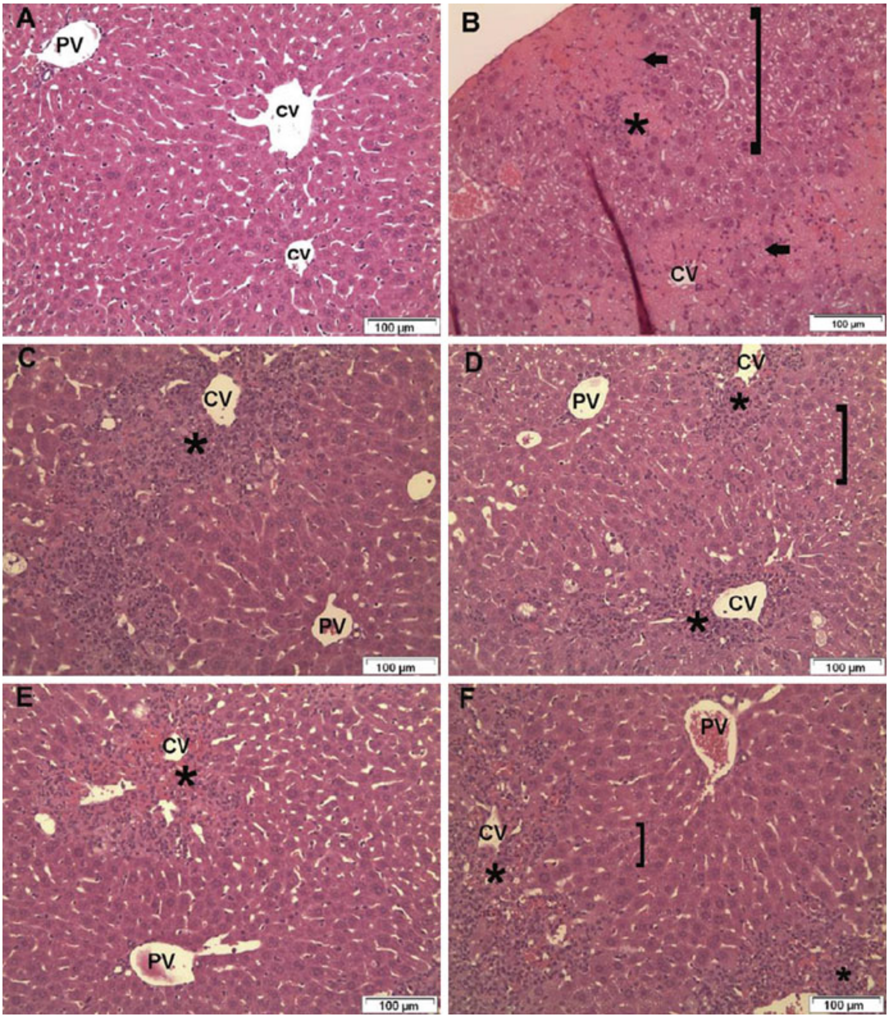

Fig. 5 Photomicrographs of liver sections stained with hematoxylin–eosin from mice representing the following groups: (**A**) control (ultrapure water + corn oil); (**B**) CCl_4 (ultrapure water + CCl_4 2%, 5 mL/kg); (**C**) VI: *A. vulgaris* infusion 4 mg/kg + CCl_4; (**D**) VPI (10 mg/kg + CCl_4); (**E**) VPI (30 mg/kg + CCl_4); (**F**) VPI (100 mg/kg + CCl_4). Symbols: black arrow: centrilobular necrosis; brackets ([]): areas with tumefaction and microvesicular steatosis; asterisks (∗): centrilobular inflammatory infiltrate (CV): centrilobular veins; (PV): portal veins. Scale bar = 100 μm. (Reprinted from [75] with permission from Elsevier)

carbon to bacteria. It delays the hydrolysis of fructans by bifidobacteria due to acetyl group and release of ibuprofen. Maximum amount of drug was released after 12 h of fermentation, which corresponds to optimum growth of bacteria. Thus, acetylated fructans is novel biomaterial, which improved bioavailability and decreased dosage frequency of the drug with lesser side effects [77]. As well as, ITF have many other

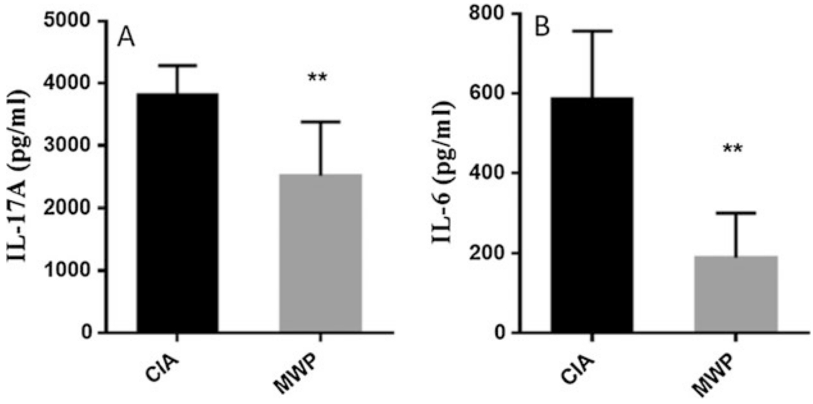

Fig. 6 Effects of MWP on the serum IL-17A and IL-6 levels in CIA mice. The serum levels of IL-17A and IL-6 were measured by ELISA. (**a**) Serum IL-17A level. (**b**) Serum IL-6 level. Data are mean ± SD, $^{**}p < 0.01$ compared with controls using Student's t-test ($n = 8$/group) and are representative of the three experiments. MWP is ITF, IL is interleukin, and CIA is collagen-induced arthritis. (Reprinted from [76] with permission from Elsevier)

biochemical and pharmaceutical technological aspects. It is considered as a renewable material for the production of fructose syrup, bioethanol, single-cell oil, single-cell protein, and many other important products [78].

6 Conclusion and Future Prospective

Inulin type fructans (ITF) appeared a highly valuable functional food supplement especially due to their prebiotic and anti-obese properties. Additionally, ITF has been potentially used in targeted delivery of ibuprofen. ITF is degraded in the colon due to the presence of inulinase; therefore, ITF-based drug delivery system may release the active ingredients in colon, hence areas are of commercial importance. Based on literature presented, it can be inferred that ITF, a polysaccharide material, could be very useful for effective delivery of nucleic acid, amino acid, and protein drugs in colon passing safely through harsh gastric pH. ITF is also used to get rid of GIT disorders and can act as a sugar replacer, antioxidant, immune modulator, and hypolipidemic agent. Moreover, acetylated derivatives of ITF through chemical modification have been used in development of novel drug delivery system. ITF is recommended functional food, pharmaceutical ingredient for various biomedical applications, and is placed in generally recognized as safe (GRAS)-listed materials.

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