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Functional Foods in Health and Disease

Plant-based polysaccharides and their health functions

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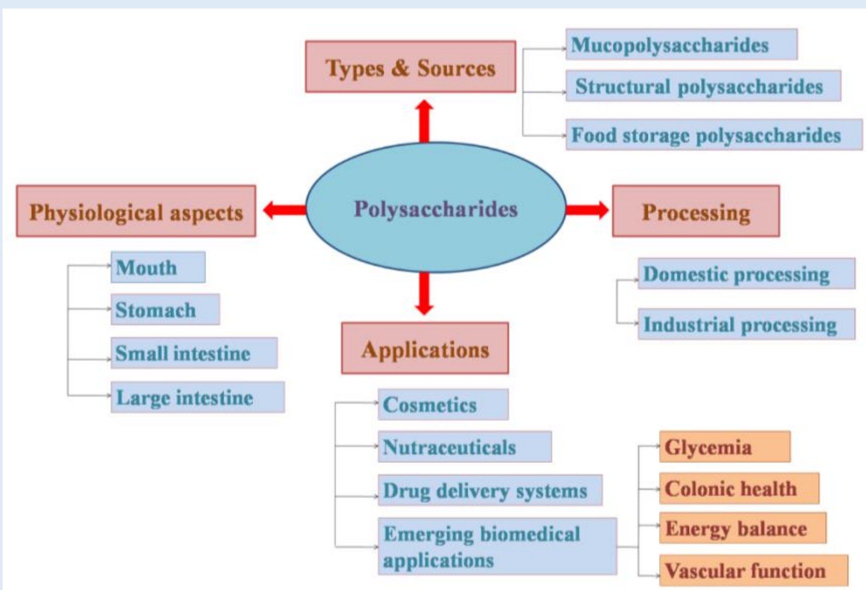
ABSTRACT

Plants, the natural polymers that are essential for life, are a valuable source of polysaccharides that make a large portion of our daily diet and provide valuable nutrition that aids the immune system, improves digestion, and assists in eliminating toxic by-products from the human body. Since Polysaccharides inhabit an indispensable role in human health, it is very important to understand the varying modifications and loss of nutritional value during the processing of plant material. Currently, plant-based polysaccharides are used for a diverse set of applications, including wound dressing, drug delivery, laxatives, cosmetics, and pharmaceutical preparations. Comprising an emerging area of plant-based medicines that reduce the side effects of synthetic sources, these polysaccharides are used to enhance the immunogenic response against a specific antigen. This review envisages some important



polysaccharides (e.g., mucilages and gums, glycosamine glycans, and chitin/chitosan) and their medical, cosmetic, and pharmaceutical applications with emphasis on the relationship between their structure and function.

Keywords: Polysaccharides; Nutrition; Health Functions; Cosmetics; Vaccine; Nutraceuticals

INTRODUCTION

Natural polysaccharides have a wide range of applications in the fields of biomedical research, pharmaceutical sciences, and the cosmetic industry. In nature, diverse polysaccharides have variable chemical structures and physical properties, constituting a foundation of biomaterial for tissue engineering, drug transporting vehicles, visco-supplementation, and controlled release of drugs in target sites, etc. [1]. Their specific properties, like biodegradability and renewability, illustrate how polysaccharides can be used in numerous technological fields.

Polysaccharides act as emulsifying, gelling, thickening, hydrating, and suspending polymers, forming a major domain of water-soluble polymers. Under well-defined thermodynamic conditions, some polysaccharides even form physical gels. Furthermore, polysaccharides often form cooperative intra-chain and inter-chain hydrogen bonds; these bonds cause insolubility or result in aggregates when solutions are prepared, as a result of the many –OH groups in the structure. The presence of –OH groups in molecules provides the property of forming a film in polysaccharides. Currently, it is known that polysaccharides possess a small hydrophobic character with –CH groups [2]. Polysaccharides can form helical conformation in solution due to stereoregularity property and provide stability because they contain units of uronic acid or ionic substituents [3]. Natural polysaccharides are a new source of natural products that show biological activities and provide numerous applications in human medical research. Plants and microbes are also used for the biosynthesis of polysaccharides such as algae and xanthan/gellan, hyaluronan (HA) respectively [3-4]. Chitosan, alginates, and hyaluronan are other polysaccharides that are considered as potential candidates in the field of biomedical research. HA and chitosan are known for their biological activities due to their proper mechanism of enzymatic degradation and act as a biodegradable source [5].

The physiological role of polysaccharides

The gastrointestinal tract is the primary site for the absorption and activity of polysaccharides. The physiological effects of dietary fibers depend on a variety of factors, such as form (partially digestible or extremely digestible), of a dosage given of ingested fiber, the structure of fiber-containing food, and the actual physiological profile of an individual taking a fiber-containing meal. Consumption of dietary fibers affects various metabolic processes by altering their physicochemical properties, including nutrient absorption, carbohydrates, fat, and sterol metabolism. It frequently induces colonic fermentation, which influences the production of stool. Since the large intestine occupies a significant region of the human immune system, dietary fibers influence the colonic structure, act as a barrier in the large intestine, and influence immune functional components. Additionally, dietary fibers differ in water solubility and can have rheological effects; well- fermented fibers frequently form viscous liquids in the gut (e.g., guar gum) such as gum arabic and inulin. Some form gels (pectins), while some (e.g., cellulose) have a high capacity to retain water (WHC). There is usually a high viscosity associated with delayed gastric emptying and decreased excretion time for the small intestines. Elevated WHC fibers (partially fermented fibers) may have a significant effect on intestinal volume and thickness. Aside from carboxymethyl cellulose (CMC), the colonic microbiota ferments almost all other fiber types. The physical properties responsible for physiological effect include its dispensability in water, colligative properties, rheology change, and ability to absorb bile acids. Although the physiological effects of the fiber depend on a multitude of causes, the plurality of these beneficial effects originates from interactions with the colonic substance from its fermentation [6-15].

Physiological aspects

Digestion of food starts from the mouth and ends at the colon after which the undigested material excretes out from the body. Different parts of the body help to digest and extract valuable nutrients from food. Here are some physiological processes that occur during the digestion of food.

Mouth: Chewing bores down the food into smaller pieces while salivary enzymes start digesting the food instantly and dissolving some components [16]. Saliva also reduces the viscosity of food for easy swallowing [17]. Oral processing has an important role in changing the physico-chemical properties of polysaccharides. Chewing reduces the particle size and increases the surface area required for easy access to enzymes. Mastication reduces the particle size depending on food type for example spaghetti is swallowed as 5-13 mm particle size. Mastication is important to get maximum nutrition, especially from plant foods. Chewing breaks the food by rupturing the cells to make their inner content available for digestion. Cell rupture or cell separation depends on the extent of mastication. Mostly, cell separation takes place when the cell walls are stronger than the adhesive force between them. On the other hand, the cell ruptures if the adhesive force is stronger than the cell wall itself. Generally, cell separation takes place if the cell wall is rich in pectin. Calcium available in the lamella gets dissolved by saliva and hence adhesive forces get weak and cell separation occurs. Cell separation allows the inner content to be intact within the cell wall. Here, if the cell wall is non-permeable which depends from food to food then minimal digestion occurs. Commonly cell wall is breached by intestinal microbiota leaving a short time for digestion. Cell rupture instantly releases the inner components to give maximum nutrition. This is the reason why doctors advise to completely chew the food before ingestion to get maximum nutrition [18].

Stomach: In the mouth, chewed food forms a bolus structure that enters the stomach. This helps salivary enzymes not to degrade in the acidic environment of the stomach. The pH of the stomach rises due to the buffering capacity of food and gradually drops (pH 2.0) after complete digestion [19]. Gastric enzymes break protein and lipids and hence soften the structure of food particles. In the upper stomach, it takes almost an hour to penetrate the gastric enzymes through the bolus. Larger particles take more time to reduce in size [20]. Hence the particle size made during chewing decides the time of complete digestion.

Small intestine: Food digested in the acidic medium of the stomach leave for the small intestine with the bicarbonate buffer. Before entering the intestine, the chyme is exposed to the bile from the gallbladder. Starch is mainly digested by α-amylase from the pancreas to yield maltose, maltotriose, isomaltose, and α-limit dextrins. This is further digested by disaccharidases specifically maltose by α-limit dextrins, and maltase-glucoamylase by maltase-glucoamylase (MGAM), sucrose, and isomaltose by sucrose-isomaltase. The resultant monosaccharides are absorbed from intestinal mucosa to the bloodstream through sodium-glucose-linked transporter (SGLT), and glucose transporter 2 (GLUT2) [21]. Starch that escapes intestinal digestion is termed resistant starch. Non-starch polysaccharides increase viscosity and hence delay the absorption of carbohydrates that results in a low concentration of blood glucose, insulin, and cholesterol. Gastric digestion dissolves the bolus structures which then re-aggregate during intestinal digestion [22].

Large intestine: Carbohydrates that are not absorbed by the small intestine enter the colon. Almost 80 to 90 percent of resistant starch ferments to small fatty acids i.e., butyrate, acetate, valerate, and isobutyrate [23]. Colonic epithelium cells use butyrate as the main energy source and repair the damaged DNA [24]. However, non-starch polysaccharides enter the colon in a major amount [25]. These polysaccharides metabolize fatty acids in the anaerobic environment of the colon by bacterial enzymes. Different foods yield a variable amount of particular fatty acid i.e., pectin yields more acetate than arabinoxylan and butyrate than propionate [26]. Non-starch polysaccharides such as fructans and lactulose impact the probiotic effect by increasing the population of bifidobacteria and lactobacilli that produce small fatty acids [27]. Cellulose is contributed in maximum to fecal material because of its slow digestion [28].

Types and Source of Polysaccharides

Presently, polysaccharides together with proteins, polynucleotides and lipids are classified as the most momentous bio-macromolecules. Hence, researchers are more passionate about the isolation and identification of bioactive compounds that naturally occur in the natural source (i.e., Plant, fruit, plant product, algae, fungus, etc) and play an afflictive role in a plethora of physiological functions [29]. Broadly, the plant polysaccharides are divided into three types as listed below:

Food storage polysaccharides: Food storage polysaccharides are hydrolyzed and placed into energy production pathways, acting as a reserve for food and used during the time of fasting. Glycogen and starch are the most common food storage polysaccharides; Starch, which is found in cereals (i.e., wheat and rice), legumes (i.e., pea and beans), potatoes, bananas, is stored in the chloroplast in the form of microscopic granules. Singly found starch are referred to as simple starch grains while starches found in groups are known as compound starch grains, consisting of two polymers, amylose, and amylopectin. Amylose is readily soluble in water while amylopectin is insoluble. Some foods contain only amylase-like pea while some contain only amylopectin like maize. Both amylose and amylopectin are formed by long chains of D-glucose. Amylose is in the form of a helical chain of D-glucose molecules while amylopectin is a straight-chain or branched glucose molecule. The straight and helical chain has 1-4 α-linkages while branching has 1-6 α-linkages. Glycogen is chemically similar to starch but is a food reserve of animals and hence called animal starch. It is mainly found in the liver in the form of complex flattened granules. Another food storage polysaccharide is inulin found in the roots and tubers of plants. It is not metabolized by the human body and filtered through the kidney in its intact form and hence is used to test kidney function [30].

***Structural polysaccharides*:** These are the polysaccharides that take part in the structural integrity of the cell wall of plants and animals. Majorly these are of two types, cellulose and chitin. Cellulose is the most abundant organic substance in plants having 50% of biosphere carbon. It has extensive ductile strength which forms the cell wall of plant cells. Cellulose has un-branched long chains of glucose molecules with the 1-4 β-linkage instead of 1-4 α-linkage in starch. It is formed by placing the alternate glucose molecules at the angle of 180 ^{0}C to each other. This geometry makes it possible to form more hydrogen bonding while placing long chains in the antiparallel fashion. The hydroxyl groups in all directions form hydrogen bonding in intramolecular chains, providing more strength [31].

***Mucopolysaccharides*:** Mucopolysaccharides are polysaccharides in the form of mucilage which are present in the plant cell wall, blue-green algae, cementing layers between cells, etc. These usually consist of galactose, sugar derivatives, and uronic acids. Some examples and their source are given in Table 1.

Table 1. Some polysaccharides and their sources.

Sr. No.	Polysaccharides		Sources
1	Monosaccharides	Glucose	Cereal grains (wheat, oats, barley, corn, rice, etc) and their products (bread, pasta, pastries, cookies, etc), potatoes, jam
		Fructose	Fruit juice (grape juice), vegetables including sugar cane, honey, sugary soft drink like coke
		Galactose	Milk, yogurt, cream, cheese, honey, celery, cherries, dried figs, plums, soy sauce, kiwi fruit, ice cream, grains, fresh meat, and eggs
2	Disaccharides	Lactose	Milk
		Sucrose	Dairy products, beverages, soda, artificially flavored juices, drinks, sweetened coffee, tea, fruits, and vegetables
		Maltose	Grains, cereals, wheat, corn, barley, and rye
3	Oligosaccharides	Raffinose	Beans, asparagus, cotton seeds, sugar beet molasses, cabbage, broccoli, Brussels sprouts, sweet potatoes, and whole grains
		Stachyose	Green beans, soybeans, and other beans
4	Polysaccharides	Starch	Potatoes, bread, cereals, rice, and grains
		Glycogen	Oatmeals, juice, whole potato, and yogurt
		Cellulose	Corn cobs or stalks, soybean hulls, sugar cane stalks, oat hulls, rice hulls, wheat straw, sugar beet pulp, bamboo, jute, flax, and ramie

Pectin is generally found in the primary layer of the cell wall and intracellular layers of fruits, e.g., peels of citrus fruits, contain around 0.5-3.5% pectin. It is used in making jelly and jams. It is a blend of galactose, galacturonic acid, arabinose, and methylated galacturonic acid. Hemicellulose which includes glucuronoxylan, xylan, mannose arabinoxylan, and galactoglucomannan is found in wheat switchgrass, straw, almond shell, sugarcane bagasse, walnut shell, leaves, and corn cob. Peptidoglycan such as murein and mucopeptides, are formed by cross-linking the chains of heteropolysaccharide with small peptides and are found in various bacterial cell walls.

Effect of processing on polysaccharides

Polysaccharides are a significant dietary source of energy for humans [32]. The content of polysaccharides should be consumed at a high level in the diet. The effect of processing on the nutritional quality of complex sugars or polysaccharides has become a major issue nowadays [33]. Starch and its derivatives constitute a major fraction of food processing. Complex sugars or polysaccharides boast sparse applications in their native form because of low thermal decomposition and shear stress resistance [34]. Processing promotes solubilization and depolymerization of insoluble components of dietary polysaccharides [35]. In processed legumes, partial solubilization of hemicellulose and pectins are increased, resulting in the formation of soluble non-starchy polysaccharides, as compared to raw [32]. Various techniques are used to process complex sugars or polysaccharides to fulfill the high need of this time. Processing is done to capitulate numerous novel derivatives of polysaccharides with improvised physio-chemical properties besides the useful structural attributes [32-35]. The digestibility of sugars is appreciably influenced by some of the known parameters such as temperature, pressure conditions, moisture, and treatment time. Processing involves gelatinization, retrogradation, resistant starch formation, and the conversion of unhurriedly digestible polysaccharides into rapidly digestible and palatable polysaccharides. Starch digestibility is enhanced with gelatinization, as it makes the starch more susceptible to hydrolyzing or digestive enzymes swiftly. High temperature and moist conditions help in the decrystallization of starch and diminution of resistant starch [33]. Polysaccharide processing is primarily carried out at the domestic and industrial levels. It would be beneficial to investigate the changes in polysaccharides in foods prepared using oriental cooking and industrial processing methods.

Domestic processing

Generally, the nutritional value of food is affected by cooking, so cooking starchy foods increases gelatinization and the proportion of amorphous starch. Many studies have suggested that different cooking methods improve the glycemic index of potatoes. When comparing the glycemic index of different potato cooking methods, it was discovered that boiled and mashed potatoes have a high glycemic index, whereas fried and baked potatoes have a low glycemic index, which is thought to be due to the gelatinization effect. Domestic heating affects the physico-chemical properties of starch in two ways: one, it induces gelatinization, which leads to the formation of resistant starch, and second, it alters the microstructure of potatoes, which alters enzyme interactions with starch [33]. Retrogradation is another effect of the processing. Low-temperature storage causes the starch to retrograde, resulting in the formation of resistant starch. Retrogradation is the process of starch chains self-associating to form aggregates that are resistant to digestion by digestive enzymes. Several studies have found that cooked food that has been stored has a higher content of resistant starch than fresh food. Cooked food that has been stored at low temperatures has had its starch degraded. Boiling potatoes can increase their resistant starch content by storing them at low temperatures. Some vegetables, such as cereals, pulses, and bakery products, are improperly processed, promoting the formation of resistant starch [36]. To improve the digestion of whole-grain starch, proper grinding and other processing methods are required. Resistant starch form or ungelatinized starch is present in raw potato, ungelatinized starch, and raw banana. Similarly, frequent heating and cooling reduce the digestibility of starch, resulting in a high percentage of resistant starch [32-35].

Industrial processing

Nowadays, food companies are concentrating their efforts on increasing the resistant starch fraction in processed foods to improve nutritional quality, as resistant starch regulates the glycemic index, fasting plasma triglyceride, cholesterol, and mineral absorption in the human body. Thermal treatments such as baking, fermentation, hydrothermal processing, steam cooking, and parboiling produce resistant starch or dietary fiber, which is a major product of different industrial processing methods. In industrial processing, gelatinization, and retrogradation have a strong relationship, just as they do in domestic processing [34]. In comparison to uncooked starchy foods, autoclaving or hydrothermal processing increases the content of resistant starch. Due to the leaching of amylose, rice pre-cooking or parboiling yields a high amount of retrograded starch. Rice's glycemic index is reduced by parboiling, resulting in a significant positive relationship between resistant starch content and amylose content [34, 37]. Fermentation lowers the amount of resistant starch while increasing starch digestibility. Baking also encourages the use of retrograded starchy foods. Low dietary fiber products, which have less insoluble fiber, supplement refinery outputs. Dietary fiber composition differs between whole grain and refined meal. Refined flour is mostly made up of glucans, whereas whole grain contains a lot of cellulose. [34].

Applications of polysaccharides

***Cosmetics*: ** Plants, animals, bacteria, fungi, and sea creatures all contain polysaccharides, which are important macromolecules for living organisms. Polysaccharides are sugar moieties that play an important role in living things and could be used as a therapeutic candidate due to their impressive pharmacological properties. Polysaccharides have recently been investigated as having potential applications in a variety of industries, including cosmetics, food, paper, medicine, and petrochemicals [29]. Marine algae are high in saccharides biomolecules, as well as proteins, peptides, lipids, amino acids, mineral salts, and polyphenols, among the various sources of polysaccharides. Antitumor, immunomodulatory, antioxidant, antiviral, and hypolipidemic properties are all present in these molecules [38-42]. Polysaccharides, such as fucoidan, alginate (Brown algae), carrageenan, agar (Red algae), mannan, porphyrin, laminarin, and ulvan (Green algae), are stabilizing biomolecules in the cosmetic industry due to their variability in structure, shape, and composition. Natural constituents or herbal products are reportedly in high demand in the market, according to consumer opinion, due to their safety, stabilizing, and eco-friendly nature. In comparison to terrestrial carbohydrate sources, algae contain a diverse range of constituents with a variety of physicochemical, biological, and interactive characteristics. [43]. Polysaccharides found in seaweeds are used to make skin moisturizers that form a thin/transparent layer on the skin that acts as a UV protectant, anti-wrinkle, and anti-aging molecule, according to the literature [44]. As a result, marine creatures are thought to be more important/useful polysaccharide sources for treating various skin diseases in humans. There are some micro and macroalgae that have a variable number of polysaccharides and have beneficial effects on skin condition such as genus *Sargassum tenerrimum, Turbinaria conoides* having fucoidan that show anti-oxidant, *Mekabu* exhibit skin anti-aging components, *Saccharina japonica*, *Laminaria cichorioides* having anti-atopic dermatitis and anti-cancer activity, *Saccharina longicruris, Ulva* having anti-aging and *Porphyra yezoensis*, *Porphyridium* exhibit anti-inflammatory and anti-melanogenesis activities respectively [45-46]. As a result, polysaccharides are an effective treatment for a variety of skin disorders, including atopic dermatitis, pigmentation, skin cancer, and skin ageing.

Anti-inflammatory, anti-diabetic, anti-cancer, anti-oxidant, and anti-bacterial properties have been discovered in pectic polysaccharides found in the cell walls of various plants. Plants such as *Ulmus pumila*, *Suaeda fruticosa*, and *Sedum dendroideum* have been reported to have anti-inflammatory properties and to reduce the release of various cytokines that are directly involved in inflammation. These polysaccharides are also known as drug carriers and a useful source in pharmacology for treating skin problems [47]. Hydrogels are a type of cosmetic formulation that is used to carry biopolymers to treat skin, hair, oral, and mucous membrane diseases. These hydrogels are applied topically to the skin and hair to improve elasticity, hydration, anti-aging, and skin health [48-49]. Because of their high retention and absorption capacity, bio-adhesive hydrogels are more advantageous than other conventional/synthetic hydrogels. Other polysaccharides found in the shells of crustaceans and insects include chitin and chitosan. Because of their superior retention and absorption capacity, bio-adhesive hydrogels are more advantageous than conventional/synthetic hydrogels. Other polysaccharides commonly found in crustacean and insect shells include chitin and chitosan [50]. Antioxidants, matrix metalloproteinase (MMPs), antiaging, and antifungal properties are among the other uses for chitin and chitosan. These polysaccharides are used in cosmetics to protect against UV rays, act as a moisturizing agent, provide protection, increase absorption, improve thermal stability, rejuvenate, reserve, and provide a deodorant and provide a defense to the skin [51-52].

Polysaccharides are indeed a core ingredient in *Gastrodia elata* Blume, a Chinese medicine that has good water absorption and retention capacity due to the presence of hydroxyl groups. *G.elata* has been used to make a variety of skin moisturizers and creams that have antioxidant, anti-aging, and anti-cancer properties [53]. Polysaccharides from *Ganoderma lucidum* are known to prevent melanogenesis by inhibiting various paracrine factors and targeting the cAMP/PKA and ROS/MAPK signal transduction cascades [54]. Fucoidan is a sulfated polysaccharide found in brown algae that has the ability to reduce wrinkles, pigment spots, and improve skin brightness, which is why it is used in cosmetics. The fucoidan inhibits the activity of MMPs, elastase, and Tyrosinaemia (TYR) [55]. Certain polysaccharides target free electrons or radicals, scavenge chelating molecules, and target electron transferability to reduce or inhibit the oxidative stress produced in skin fibroblasts [56]. In addition to marine polysaccharides, there are numerous large-sized polysaccharides found in microorganisms or fungi that are used in anti-aging skin formulations that provide moist, smooth, wrinkle-free, and even skin tone. Large-sized polysaccharides, proteins, and fatty acids are primarily used in the manufacture of skin care products such as facial cleaning products, baby care, facial care, and body care products that provide skin smoothness and suppleness [57]. As a result of the findings, polysaccharides appear to be useful therapeutics for overcoming skin-related issues such as ageing, wrinkles, and pigmentation, as well as suppressing free radical generation during UV exposure.

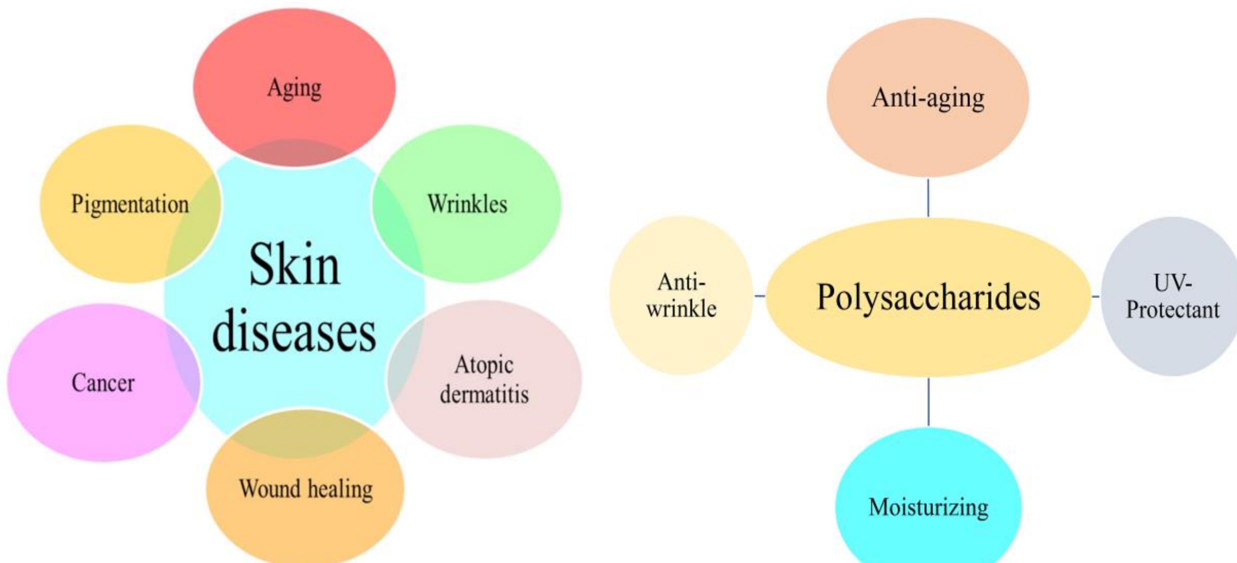


Figure 1. Different types of Skin ailments and major potent properties of Polysaccharides.

***Nutraceuticals*:** Nutraceutical is a combination of two words 'nutrition' and 'pharmaceutical'. Stephen De Felice, the president and chairman of the Foundation for Creativity in Medicine (FIM) in Cranford, New Jersey (NJ), first invented the word nutraceutical in 1989. Nutraceuticals are divided into different food categories based on new products and therapeutic areas to treat a variety of health problems[58]. Polysaccharides are now proving to be a new frontier of pharmaceutics. They are used as dietary supplements to treat various disorders. The different species of marine algae and other microorganisms which contain high polysaccharides content are used in making thickening and gelling ingredients of food in many countries. Polysaccharides of natural origin are used as medicinal and dietary supplements because of their antimutagenic, tumor suppressor, anticoagulant, and immunostimulatory properties [59].

Dietary polysaccharides are mainly extracted from natural resources such as medicinal plants, fruits, vegetables, grains, algae, fungi, and mushrooms. Literature survey revealed that the dietary polysaccharides have the potential to overcome different ailments by exhibiting anti-oxidant, anti-inflammatory, anti-diabetic, hypoglycemic and hypolipidemic activities. *In-vitro* and *in-vivo* studies revealed that the dietary polysaccharides can reduce sugar level by increasing β-cell mass, activating insulin receptors by triggering insulin signaling transduction pathways, and initiating PI3K/Akt pathway [60-61]. Dietary polysaccharides and non-starch polysaccharides have a great impact on the gut functioning of humans and live stocks. These dietary fibers maintain normal intestinal functions by increasing gastrointestinal health. Besides this, non-starch polysaccharide (NSP) improves enzyme functioning which modulates nutrient digestion and increases response to infectious disease [62-63]. Another example of NSP is plantain which reduces the invasion and adhesion of bacteria *Salmonella typhimurium* to epithelial cell line and caecal crypts. This activity is mainly due to the presence of acidic/pectic (homogalacturonan-rich) components [64]. Despite this, fucoidan (low-molecular-weight) possesses immunomodulatory activity by stimulating the innate immune system. These low molecular weight polysaccharides enhance the immunity by initiating the proliferation of splenocyte, the activity of natural killer (NK) cells, increased interleukin (IL-2 and IL-4), interferon, and phagocytic activities [65].

There are certain examples of edible mushrooms that are used as dietary supplements in various countries e.g., *Ganoderma lucidum* called “Lingzhi” in China or “Reishi” in Japan have been used to cure various disorders such as allergies, bronchitis, hepatitis, cancers, and immunological disorders. These activities are due to the presence of triterpenes and polysaccharides that are designated as markers officially in Chinese Pharmacopoeia (2015) [66]. The seaweed extracts along with polysaccharides prove a useful drug or dietary supplement to modulate or treat inflammatory bowel disease (IBD). The algal polysaccharides are not absorbed by the upper part of the gastrointestinal because of the resistance towards gastric juices and digestive enzymes. They serve as fermentation substrate for the microbial colonies present in the intestine [67]. Oxidative stress is another major cause of the generation of different disorders including neurodegenerative disorders [68]. Several polysaccharides isolated from natural resources can scavenge free radicals and reduce oxidative damage. The polysaccharides derived from *Nostoc commune* are used as food and medicine and possess the ability to scavenge superoxide as well as hydroxyl anions. Similarly, *Zizyphus jujuba* has a higher concentration of uronic acid which is responsible for their stronger radical scavenging activity than other species [69]. The antioxidant or free radical scavenging activity of polysaccharides is due to the presence of carbonyl, hydroxyl, amino, and carboxyl groups which gives hydrogen to the electron-deficient molecules and results in the formation of alkoxyl products [70]. This mechanism results in the stoppage of the further radical chain reaction. Therefore, the neuroprotective effect of polysaccharides due to radical scavenging and regulation of enzyme activity is involved in the oxidative mechanism [71].

Fucoidan is a polysaccharide isolated from *Undaria pinnatifida* possesses anti-cancer, antioxidant, and anticoagulant activities. *In-vitro* analysis revealed that fucoidan shows antiproliferative activity towards various cell lines and activates/inhibits the various signaling pathways which involve cell proliferation and metastasis. So, fucoidans play an important role in the nutrition and health of humans and are used as a functional food to cope with diseases like arthritis, malaria, influenza, etc. [72]. Similarly, glucan polysaccharide shows an immunomodulatory effect in the gastrointestinal tract, blood, and spleen. Besides, these oral polysaccharides activate or stimulate the immune system and increase the chances of survival in cancer patients [73-75].

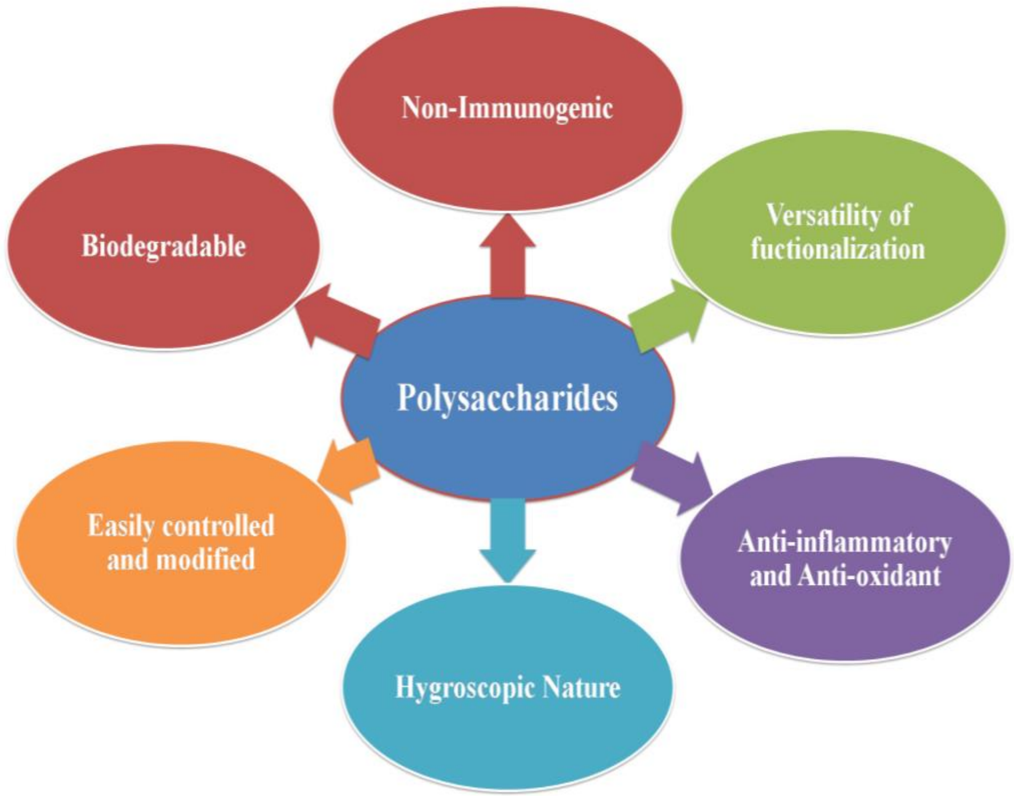


Figure 2. Schematic illustrations of physiochemical and biological properties of Polysaccharides.

The polysaccharides present in nutraceuticals have a potent role in improving the physiological functioning of many disease conditions including cancer and/or improving the health of consumers. Therefore, the above-referred suggestions, showed that the consumption of polysaccharides-rich nutraceuticals helps in minimizing the risk of several diseases.

Drug delivery systems

Polysaccharides are the polymeric carbohydrate consisting of long chains of monosaccharide units which are linked by (β 1-4) glycosidic bonds. This natural-based structural material has wide applications in the field of biomedical research. Examples of different polysaccharides cargo systems to control delivery and use of their certain bioactive agents for various applications have been given in Table 2. In a conventional drug delivery system, the major problem is the clinical efficacy of low molecular weight macromolecules like proteins and oligonucleotides. These functional biomolecules have several limitations which include loss of bioactive structure before reaching the target site, insufficient cellular uptake, poor solubility, and the short half-life of plasma due to enzymatic degradation or swift renal clearance. The over-expression of efflux transporter results in drug resistance to non-specific cytotoxic drugs with explicit side effects due to off-target effects during chemotherapy. A new form of drug delivery system is developed which is based on nanoscale called a nanoscaled drug delivery system (nano DDS). Nanoscale drug delivery systems can address the limitations of conventional systems and provide great help in the development of personalized nanomedicine for non-infectious diseases like cancer [76-77]. Polysaccharides used for the controlled drug delivery of anticancer agents have been enlisted in Table 3. Nano-vehicles are structures that are small in size having dimensions of nanoscale, and properly designed in such a way that they cross the smallest capillary walls. The nano-vehicles can evade clearance by a mononuclear phagocyte system (MPS) and remain in circulation for a longer duration because of enhanced permeability and retention effect [78-79].

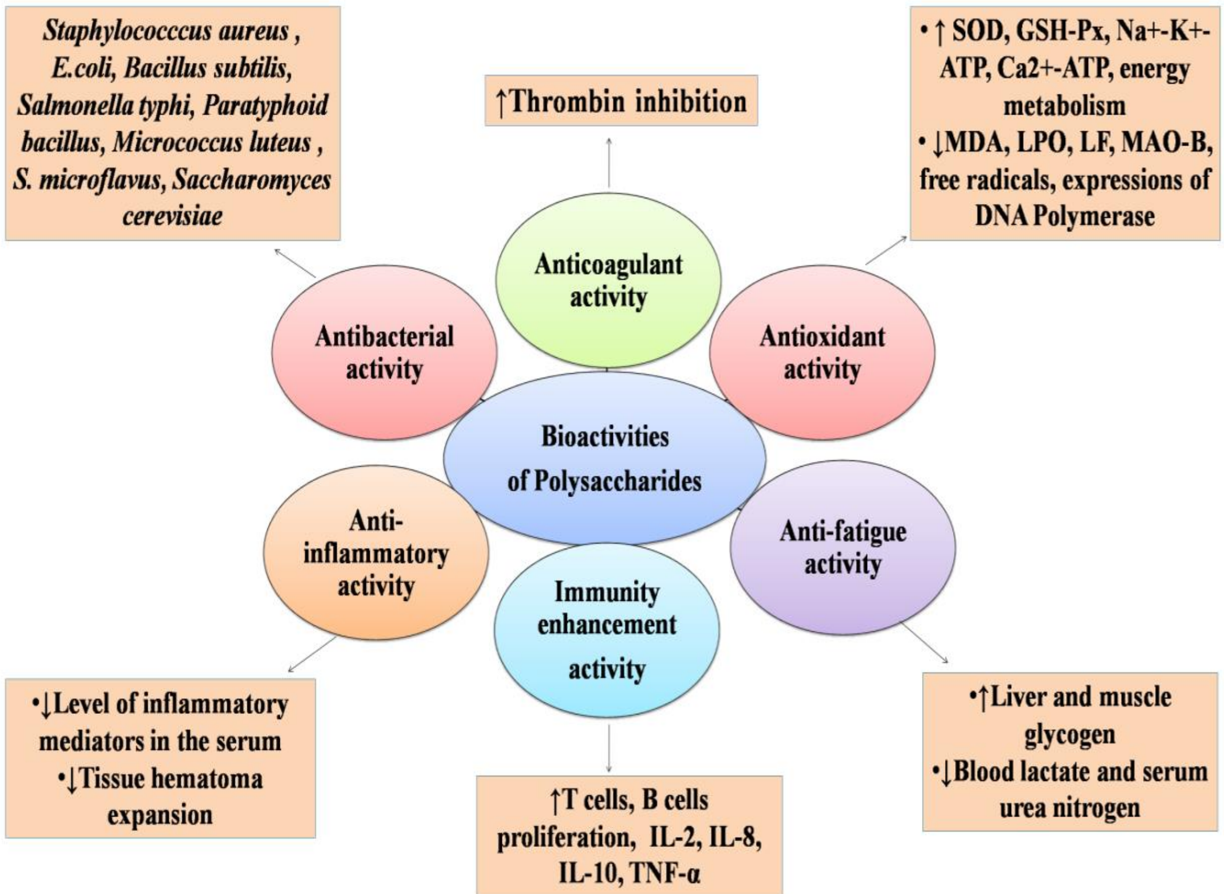


Figure 3. Bioactivities of polysaccharides and their biological actions.

In the case of tissues having tumor macromolecules for example in blood vessels, the large nano-particles enter easily and are trapped in comparison to small nano-particles and low molecular weight molecules [80]. Bioactive molecules like cytokines and growth factors have a high molecular weight due to which they show limitations like immunogenicity, shorter half-lives, and instability in delivery both *in-vitro* and *in-vivo* systems. The drawbacks of high molecular weight bioactive molecules can be overcome by the modern drug formulation technology creation of "second generation" of protein drugs. Limitations associated with molecular weight, secondary structure, and availability of surface groups are tackled by the formation of polymer protein or fusion proteins whereas protein folding can be altered through and after by modification processes [81].

Table 2. Examples of different polysaccharides cargo systems to control delivery, use of certain bioactive agents for various applications.

Polysaccharide type	Bioactive agents	Application	Role in tissue engineering	Reference
Alginate	VEGF	Osteoporosis	Promote osteogenesis differentiation of hMSCs	[82]
Alginate	Human fibroblast growth factor 1 (FGF-1)	Cartilage defects	Promote *in-vitro* development of mature adipocytes	[83]
Alginate	Human fibroblast growth factor 1 (FGF-2)	Peripheral artery disease and coronary artery disease	Promote neovascularization and restore blood flow and tissue function of the heart muscle	[84]
Alginate	FGF-1	Hypoxia	Enhancement of graft neovascularization in a retrievable rat tomentum pouch	[85]
Alginate	Transforming growth factor-beta (TGFβ)	Articular cartilage defects	Controlled delivery of TGFβ selectively to the injury site and improve the repair of articular cartilage defects in the rabbit model	[86]
Alginate	Insulin-like growth factor-1 (IGF-1)	Nervous system disorders such as stroke	Enhanced the proliferation of the encapsulated NSCs	[87]
Alginate	Amidated pectin hosting doxycycline (Antibiotics)	Wound healing	Inhibit bacterial-infection-caused necrosis in the wound healing process	[88]
Hyaluronic acid	None	Atherosclerosis	Reach the atherosclerotic lesion after systemic administration with high potential as a carrier for diagnosis and therapy of atherosclerosis	[87]
Chitosan Hyaluronic acid	VEGF	Development of vascular network during implantation	Promote angiogenesis	[89]
Alginate microspheres within hyaluronic acid hydrogels	TGFβ 3	Cartilage repair	Promote neo cartilage formation	[90]

Table 3. Examples of polysaccharide-based drug delivery systems for controlled delivery of anticancer agents.

Polysaccharide	Anticancer agent	Cancer type	Application	Reference
Chitosan	siRNA for VEGRA, VEGFR1, and VEGFR2	Breast cancer	Suppressive effect on VEGF expression and tumor volume	[91]
Alginate	Doxorubicin	Liver tumor	Tumor necrosis; heart cells and healthy liver cells surrounding the tumor were not affected	[92]
Glycyrrhetinic acid-modified alginate	Doxorubicin	Hepatoma carcinoma	Tumor inhabitation rate reach 79.3%	[93]
Hyaluronic acid	Cisplatin	Human malignant gliomas	Induce apoptosis	[94]
Chitosan	Destran–doxorubicin	Various cancer types	Induce apoptosis and reduce tumor size	[95]
N-trimethyl chitosan	Cisplatin–alginate complex	Human ovarian and lung carcinoma	Induce apoptosis	[96]
Hyaluronic acid (HA)	None	Xenograft subcutaneous dorsa of athymic nude mice	To visualize the bio-distribution of HA nano-particles accumulating into the tumor with a combination of the passable and active targeting mechanism	[97]

Due to current limitations, available drugs fail to produce desired results as more and more diseases infiltrate human life. However, drug efficiency can be improved using effective drug delivery systems. The excellent properties of polysaccharides like structural stability, flexible chemical composition, biocompatibility and biodegradability make them suitable for their use in the drug delivery system commonly called polysaccharide-based drug delivery system. To increase the functional aspects of polysaccharide polymers, various chemical modifications have been explored. Novel engineering is also applied for the development of techniques and devices for efficient drug delivery systems. By using the different fields of science like chemistry and engineering the encapsulations of different types of drug molecules (like oligonucleotides, proteins and small molecules) with controlled drug release profiles to target tissue and improved pharmacokinetic/pharmacodynamic properties (PK/PD) are made possible. Polysaccharide-based drug delivery systems show the potential to enhance the therapeutic efficacy of biopharmaceutics supported by preclinical and clinical studies. There is a lower conversion rate of polysaccharide-based drug delivery systems into clinical studies, due to the limited knowledge of properties like targeting and therapeutic efficacy, drug-releasing properties, etc. We need to acquire more knowledge and understanding of material and tissue interaction to develop more efficient drug delivery systems. There is a need for compilations of characterization in both *in-vitro* and *in-vivo* models, utilization of different aspects of sciences like engineering modeling and monitoring, chemical engineering, etc., to predict the results for clinical applications. The de-novo fabrication techniques will produce stable, evenly distributed polysaccharide-based drug carriers that can be used to modify the disease targeting models. In the future, the use of polysaccharides-based drug delivery systems and their clinical studies are expected to get popularized.

Emerging biomedical applications

Polysaccharides derived from plant sources, especially medicinal plants, have great acceptance. Examples of different medicinal plants having bioactive polysaccharides include *Acacia tortilis, Mactra veneriformis, Saccharina japonica, Dendrobium* plants*, Acanthopanax senticosus, Aloe barbadensis*, *Prunus persica, etc.* [98-99]. Many polysaccharides have a versatile range of biocompatible, physiochemical, and biodegradable properties, making them suitable and attractive candidates for biomedicine in recent decades [100]. It is evident that compared to synthetic polymers, plant-origin polysaccharides are readily recognized by the body as they mimic components found in biological extracellular matrices and have numerous potent bioactivities, including antioxidants, anticoagulants, antidiabetics, anti-osteoporosis, anti-tussive, anti-fatigue, and immunomodulatory functions [101-102].

Such pharmacological and bioactive applications are linked to their structural variability and flexibility to undergo a range of chemical modifications, thus altering the characteristics of polysaccharides for different purposes [103]. Moreover, the non-toxic nature without side effects of plant polysaccharides contributes to the production of polysaccharides-based biomaterials for various applications in regenerative medicines such as tissue engineering scaffolds, vaccine adjuvants, wound management products, drug carriers, medical fibers, and bio textiles [104]. Owing to these properties, the most commonly used polysaccharides in the biomedical field are alginate, fucoidan, chitosan, carrageenan, chondroitin sulfate, cellulose, hyaluronic acid, starch, and their derivatives [105].

The alginate-algal polysaccharide is a frequently used biomaterial as a hydrogel for wound healing, cartilage repair and tissue regeneration. Alginate crosslinked chitosan mixed membranes are useful for disposable wound dressings. Similarly, the essential oils encapsulated with sodium alginate matrices such as lavender, cinnamon, eucalyptus, tea tree, peppermint, lemongrass, and lemon oils are also significant because of their antimicrobial and antifungal efficacy [106]. Moreover, bilayer hydrocolloid films made up of alginate are suitable for the treatment of low suppurating wounds [107]. As a bioadhesive, carrageenan in the poloxamer gels enabled the ease of delivering drugs to the mucosal system. Chitosan is useful for creating self-expanding stents [105]. In bone tissue engineering, alginate, chitosan, dextran, and hyaluronic acid are key candidates for the creation of tissue scaffolds as they form loose viscoelastic gel through non-covalent interactions in aqueous vehicles [108]. The cationic polysaccharide chitosan made up of N-acetylglucosamine is known for improving bone formation as well as wound healing, thus function as an efficient scaffolding material for *in-vitro* tissue-engineered bone formation and osteoblast transplantation for *in-vivo* bone regeneration [109]. Dendritic cell (DC) vaccines are a promising, modern, and evolving form of immune treatment for cancer. It is found that the DC-based cancer vaccine can result from the bioactivity of glucans extracted from the *Astragalus membranaceus* and *Codonopsis pilosulae* plants [110]. Chitosan-crosslinked surgical sutures with genipine and hyaluronic acid are used as meso threads for suturing postoperative wounds and also in plastic surgery [111]. A xylan derivative, pentosane polysulfate, derived from beechwood is another medical agent that is used for the treatment of interstitial cystitis, a bladder pain condition. For the manufacturing of long-term drug-release systems, nano fibrillated cellulose-based films are used in the pharmaceutical industry [29]. For applicability as drug excipients, the high mucilaginous content of psyllium seeds and husk is an important feature. Various maca polysaccharide health products from the plant *Lepidium meyenii* (Walp.) (Maca) are available in the market, for example, MACA capsules to enhance sexual function; MACA COMPLEX to improve body function; MEN'S Maca Man to enhance blood flow [112].

The multiple bioactivities of different polysaccharides have been exploited for their clinical applications so far. Because of the ongoing efforts to optimize the capacity of polysaccharides as therapeutics and raw materials for use in the biomedical engineering and pharmaceutical industries, the range of applications of polysaccharides will be extended to include novel advantages not achieved with existing polymers.

In health

***Energy balance/satiety*:** WHO recommends taking a 55% portion of energy from a carbohydrate source. But due to differences in site, rate, the extent of digestion, and yield of metabolic energy, care has to be taken for taking polysaccharides. As the fully fermented resistant starch yields only 8.8 kJ/g while glucose yields 17 kJ/g. The physiological impact of polysaccharides is controversial due to the difference in the metabolism of different types of polysaccharides. For example, sugar-sweetened foods are known to cause obesity while satiety-promoting more complex polysaccharides are used to help the weight loss [113]. Out of several, three mechanisms are explained: (1) effect of hormones i.e., insulin and gastrointestinal hormones, (2) physical properties of polysaccharides, and (3) fermentation of resistant starch to short-chain fatty acids by colonic microflora. However, foods with low sugar content and high resistant starch are correlated to aid weight loss [113].

Glycemia: Digestion of polysaccharides regulates the levels of glucose and insulin in the blood [114]. The glycemic index usually refers to the glycemic response of available carbohydrates from food relative to the equal amount of actual carbohydrates [115]. Examples of food having a high glycemic index include potato, white bread, and low glycemic index (GI) include legumes, fruits. The speed and amount of starch digested in the lumen of the intestine play an important role in the regulation of glucose and insulin homeostasis [114]. Hence the glycemic index of any food plays an important role for people with abnormalities specifically diabetes. Foods with a low glycemic index digest slowly and do not give a sharp rise in glucose levels and hence can be helpful for the management of diabetes and, obesity [116].

***Colonic health*:** The degree of breakdown of food after swallowing in the upper gastrointestinal tract is important as it decides the extent of fermentation to take place in the colon for complete digestion [117]. This also determines the appetite through a colonic feedback mechanism. The digestion of food in the colon influences the whole body through regulation of the immune system, neuronal system and hormonal feedback to the upstream gastrointestinal tract [118]. The colonic health impacts energy metabolism through hormonal feedback from the pancreas and adipose tissue [119]. Furthermore, it is estimated that obesity is directly linked with the efficient fermentation of undigested food by colonic microbiota [120].

***Vascular function*:** Polysaccharides specifically non-starch suspend the absorption of bile acids resulting in the formation of new bile acids from cholesterol [121-122]. Hence the NSPs help to reduce the fasting cholesterol levels and ultimately reduce the risk of cardiac arrest [123].

CONCLUSION

Presently, more and more complicating diseases are making their way in human life, and the available synthetic drugs in the market fail to produce desired results due to many limitations. Plant-based polysaccharides are emerging natural candidates for their vital role in health, diet, and food processing. With more advancement in the biomedical field, the research on plant polysaccharides is gaining more comprehensive attention and their wide therapeutic applications make them a significant guide for the production of new drugs. Researchers are using their characteristic feature of invoking the immune system for vaccination and drug delivery applications. Moreover, the excellent properties of polysaccharides like structural stability, flexible chemical composition, biocompatibility, and biodegradability make them suitable for their utility in several other industries such as cosmetic and nutraceutical. Soon, exploitation of unexplored properties of known polysaccharides, as well as the discovery of new ones, will be beneficial for the well-being of society.

Abbreviations: HA: Hyaluronan, CMC: Carboxymethyl cellulose, MGAM: Maltase-glucoamylase, MMP:Matrix metalloproteinase, FIM:Foundation for Innovation in Medicine, IBD: Inflammatory bowel disease, MPS: Mononuclear phagocyte system, Nano-DDS: Nanoscaled drug delivery system, PK/PD: Pharmacokinetic/pharmacodynamic properties

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