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Review Article

Pharmaceutical analysis for Novel drug formulation

Immunomodulatory Activity of Natural Polysaccharides in Combating Covid -19, Cancer, Inflammatory Disorders: A Review

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Abstract : Natural polysaccharides are a source of carbohydrates with potent biological functions that can be explored for increasing its utilization in the field of food and medicine. If characterized, studied and explored, they would have a vital contribution in the health care policy of the world, and more particularly in numerous developing countries in the next decades. There are thousands of polysaccharides isolated from various natural sources which can affect the immune system by stimulating the immune response or by influencing the formation of antibodies. They consist of various monomer units such as β-glucan, mannan, arabinose, galacturonic acid, fucoidan, laminarin, carrageenan etc. These polysaccharides follow different mechanisms to show the desired biological activity. This review presents a detailed account of the immunomodulatory properties of polysaccharides isolated from microorganisms, plants and marine sources. The outbreak of the novel coronavirus disease COVID-19 which is caused by the SARS-COV-2provide full description of SARS-COV-2 virus has been a serious threat to public health as there are no clinically significant vaccines yet produced for its prevention. Polysaccharide with good immunomodulator and antivirus activity have potent anti-coronavirus applications. This study focuses on the advancements in the inhibition of SARS-COV-2 virus responsible for COVID-19. It also gives a detailed account of the anti-cancer activity of various natural polysaccharides and anti-inflammatory effects. The established therapy strategy for the treatment of cancer and inflammatory disorders involves the use of various chemotherapeutic agents and non-steroidal anti-inflammatory drugs respectively, which have prominent side effects. Polysaccharides obtained from natural sources have gained attention owing to their safety and less side effects. The mechanism of action of the polysaccharides showing immunomodulatory activity owing to treatment of COVID-19, cancer and inflammatory disorders has been discussed in the review. Most polysaccharides are tested using preclinical animal models or by clinical trials. This review will provide guidelines for the development of new formulations for utilising the various biological activity of the natural polysaccharides.

Keywords : Immunomodulator, Plant Polysaccharides, Marine polysaccharides, SARS COV 2, COVID -19, Anticancer, Anti-inflammatory.

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1. INTRODUCTION

Polysaccharides belong to the category of biomacromolecules and are found in various traditional herbs, marine organisms or microorganisms. They exhibited a variety of biological activities such as immunomodulatory, antioxidant, antiaging, antitumor and anti-inflammatory activities [1,2]. Many studies have been carried out to study the bioactivity of these plant polysaccharides. These polysaccharides have shown broad-spectrum antiviral properties which contribute to its efficacy in treatment of COVID 19. The polysaccharides are believed to be a T-cell independent antigen and they usually do not show any cell-mediated immune responses. This shows the induction of IgM and IgG antibodies [4]. The T-cells does not take part in the development of immunologic memory due to which the response is not long-lasting [5]. The antigen-presenting cell (APC) does not process the polysaccharide antigens. This is why T cell doesn't contributes and this results in exhibiting the stimulation of long-lived cell-mediated and humoral responses. The APCs are internalizing the different proteins antigens, carry out their degradation to peptide units. Thereafter present these subunits and the major histocompatibility complex (MHC)-II molecules on the surface of the cells. The T cells are capable of recognizing these antigens and they are activated further to perform the various effector functions: which provides the T cell help for producing specific IgG antibodies by the different B cells. It can also act as the cytotoxic cells in causing lysis of the various infected host cells. The investigation on the different polysaccharides obtained from microbial sources proved to possess potent immunomodulator property particularly activities of T cells and APC cells like the monocytes and macrophages [6]. This review aims to explore the established immunomodulatory function of polysaccharides from different sources such as microbial, plant and marine. The plants such as Artemisia species, Astragalus species, Glycyrrhiza, potato pectin etc [7]. contain these polysaccharides. The various microbial sources consisting of various types of mushrooms and marine sources consisting of carrageenans and laminarin [8,9]

1.1 ETIOLOGY OF IMMUNOMODULATION

Immunomodulators are defined as the different biological or synthetic substances capable of inducing, suppressing, or modulating the adaptive and innate immune system. The cells of the immune system can recognize the non-self-antigens and their products and the compounds present in the dietary substances and environment. Pattern recognition receptors (PPRs) are involved in mediating the interaction of host cells and the environment. One of the common examples of PPRs is toll-like receptors (TLRs) [10,11]and are found in innate immune response cells. They function in recognizing the expression of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These receptors stimulate the secretion of cytokines, microbial molecules and inducing adaptive immunity [12-14]. Regulatory T cells regulate the immune response by inhibiting the activity of Th1, Th2, and Th17 cells, mainly by the secretion of transforming growth factor-β(TGF-β) or IL-10. T-helper cells are essential for the activation of naive CD8+ T cells [15], B lymphocytes, and phagocytes. The gut-associated lymphoid tissue (GALT) is the largest immune compartment in the body and consists of both organized lymphoid tissues, such as mesenteric lymph node and Peyer's patches, and diffuse scattered lymphocytes in the intestinal lamina propria and epithelium. The immune system is regulated not only by its symbiotic relationship with microbiota, but is very sensitive to diet. The mechanism of immunomodulation has been shown in Fig.1.

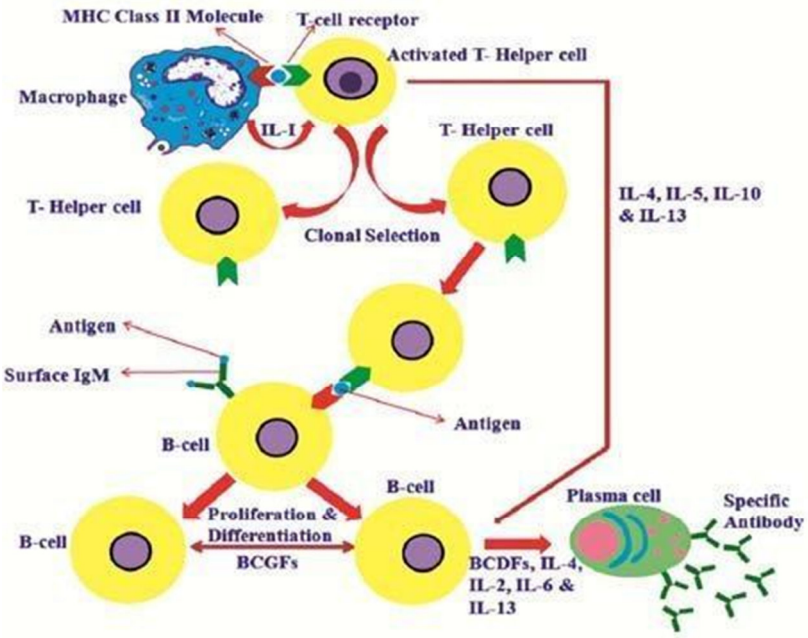

Fig1. Mechanism of immunomodulation [16]

1.2 STRUCTURAL CHARACTERISTICS OF THE POLYSACCHARIDES

1.2.1 *Structural features of biologically active polysaccharides from Microbial sources.*

The therapeutic activity of the polysaccharides largely depends upon the structure, conformation, their composition and molecular weight. Amongst them β-glucans is a polysaccharide which yields higher biological activity [17] . They are the homopolymers of D-glucose are the most abundant carbohydrates in the cellular walls of several microorganisms, such as mushrooms, yeast, algae, bacteria, lichens, and plants, and exhibit immunomodulatory, antitumor, and anti-inflammatory activities[8] . The other components are Mannan-oligosaccharides which contains polymers of mannose that are obtained from yeast cell walls, and are located on the outer surface of yeast cell walls attached to β-glucans of the inner matrix via β-(1,6) and β-(1,3) glycosidic linkages. The structures are given in Fig.2.

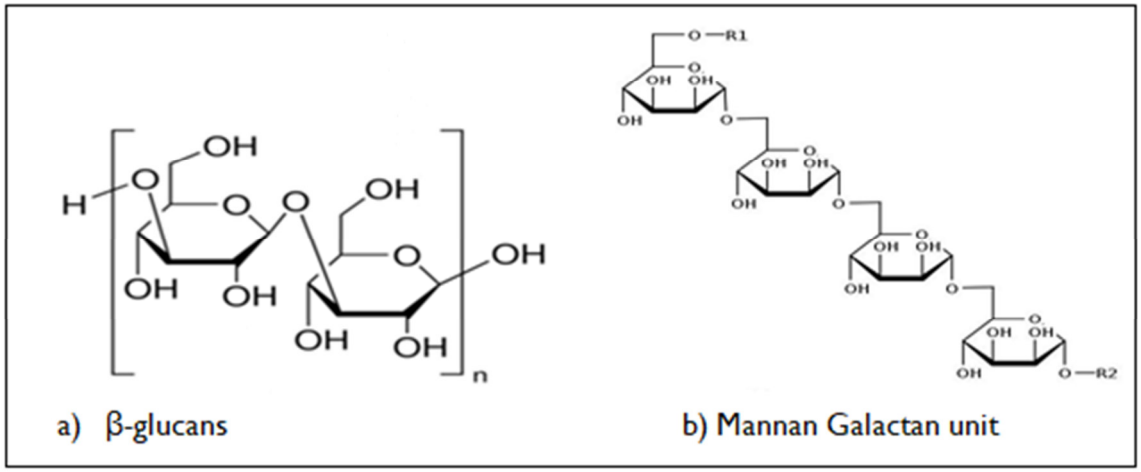

Fig2. Biologically important chemical moieties present in microbial polysaccharides [18]

1.2.2 *Structural features of biologically active polysaccharides from Plant sources.*

The several plant derived polysaccharides contain monosaccharide units of arabinose, rhamnose, galacturonic acid, galactose, xylose, glucose, and mannose [19] . The structures are shown in Fig 3.

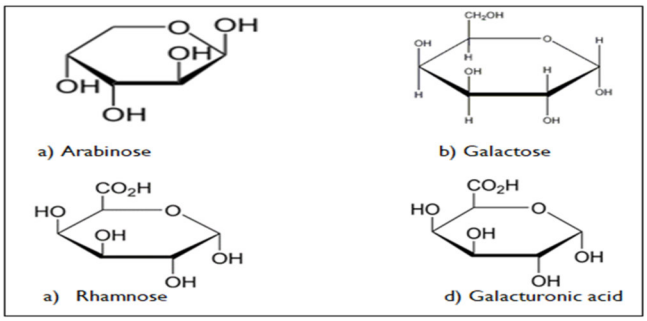

Fig3. Biologically important chemical moieties present in plant polysaccharides[20]

1.2.3 *Structural features of biologically active polysaccharides from Marine sources.*

The marine sources of polysaccharides chiefly consist of Laminarin, Fucoidan and Carrageenan derived from the seaweeds and brown algae. Structurally, laminarin is composed of β-(1,3)-linked glucose containing large amounts of sugars and a low fraction of. Uronic acids [21]. Two types of polymeric chains are present in laminarin, G-chains with glucose at the end and M-chains with mannitol as the terminal reducing end [22]. The structure of fucoidan consists mainly of α(1,3)-linked L-fucopyranose residues with sulphates at the C-2 position [23].Carrageenan is a polysaccharide obtained from Red algae and the biological activity is shown mainly due to the sulphate ester residue of the structure [24]. The structure of the chief components of these polysaccharides with biological activity is represented in Fig 4.

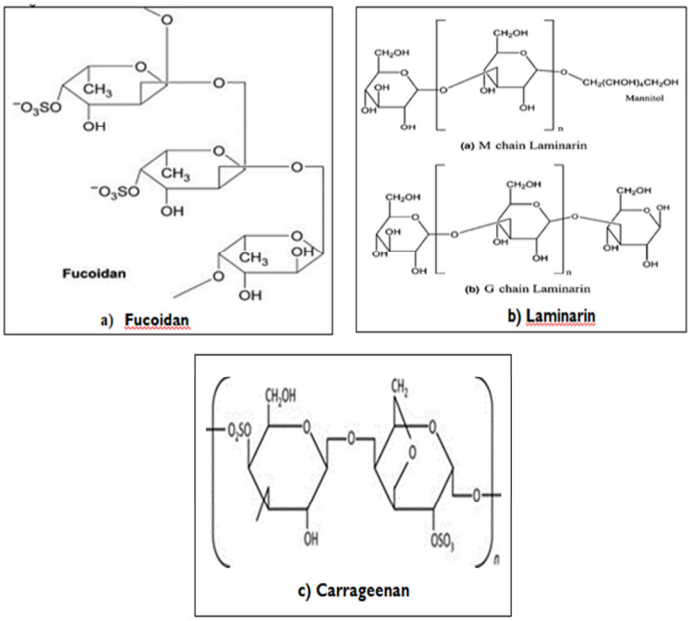

Fig4. Biologically important chemical moieties present in marine polysaccharides[60]

2. IMMUNOMODULATORY ACTION OF POLYSACCHARIDES

Polysaccharides from various sources such as microorganism, plants, marine sources have potential and has increased the economic and clinical interest in them. They have exhibited clinical interest in them by demonstrating nutraceutical and chemo preventive activities and are relatively nontoxic. Their activity greatly depends on the active chemical constituent present, structural conformation and molecular size [26].

Various polysaccharides can be obtained from different microbial sources specially from the fungus. Amongst them the most commonly available are β-glucans, non-starchy carbohydrates, Glycan, mannan obtained from different microbial sources such as fungus bacteria, etc. They vary in conformational complexity, molecular weight, and number of branches [27] Table I represents the different polysaccharides from the microbial sources showing immunomodulatory action.

Table 1. Immunomodulator Activity of polysaccharides from microorganisms.

S.No	Name of the Plant source	Active chemical composition	Mechanism of Immunomodulation	Reference
1.	Agaricus blazei Agaricaceae	β-Glucan	-Stimulates the different immune cells such as NK cells, dendritic cells, macrophages and granulocytes (polymorphonuclear leukocytes)	28-30
2.	*Pleurotus ostreatus* Pleurotaceae	Dietary fibres, β-glucans, non-starchy carbohydrates	-Shows potent immunostimulant activity by improving CD4+/CD8+ ratio	31-32
3.	*Lentinula edodes* Omphalotaceae	β-Glucan	-Improves cellular immunity, humoral immunity and innate immunity.	33-34
4.	*Grifola frondosa* Meripilaceae	β-Glucan	-Induces cytokine production in macrophages through the Dectin-1/Syk/NF-B signalling pathway resulting in immunomodulatory and antitumor activities	35-36
5.	*Coriolus versicolor* Polyporaceae	β-Glucan	-Induces pro-inflammatory cytokines -Shows effect on tumour necrosis factor (TNF)-α -Induces apoptosis	37-38
6.	*Trametes versicolor* Polyporaceae	Polysaccharopeptides	-Enhances mitogenic activity -Induces cytokines (interleukin (IL)-1β and IL-6) production in stimulated macrophages; -Increases the proliferation of cell	39
7.	*Bacillus Calmette-Guerin (Natural BRM)*	Live mycobacteria	-Induces granulomatous reaction at the site of administration	40
8.	*Candida albicans* Saccharomycetaceae	Glycan, Mannan	-Enhances the suppression of the various antibody responses when administered with type III pneumococcal polysaccharide (SSS-III) and with sheep erythrocytes (SRBC) in mice.	41
9.	*Aspergillus fumigatus* Trichocomaceae	Galactosaminogalactan	-Inhibits the T-helper 1 and 17 G cytokine production in human PBMCs by inducing Interleukin-1 receptor antagonist * *It is a potent anti-inflammatory cytokine IL-1 signalling	42
10.	*Cryptococcus neoformans* Tremellaceae	β-Glucan	-Role of 'protective' Th1 (tumour necrosis factor-α, interferon (IFN)-γ, interleukin (IL)-12, and IL-18) and Th17 (IL-23 and IL-17) and 'non-protective' Th2 (IL-4, IL-10, and IL-13) cytokines has been extensively studied *in vitro* and in animal models of cryptococcal infection.	43
11.	*Laminaria digitata* Laminariaceae	β-Glucan	-Dose-dependent induction of cell death -Increase in the percentage of cells in the sub-G1 and G2-M phases -Inhibits heregulin-stimulated phosphorylation of ErbB2 -Decreases in proliferation of cell	27
12.	*Caulerpa lentillifera*	β-Glucan	-Stimulates the NO production by murine macrophage RAW 264.7 cells, activates both NF-κB and p38 mitogen-activated protein kinase (MAPK) signalling pathways, increased the phagocytosis of latex beads -Induces the expression of proinflammatory cytokines IL-1β, TNF-α, and IL-6	44

Several polysaccharides have been derived from the plant source which can act on the immune system[39]. Many plant-based polysaccharides are pectic which are enriched in arabinan, galactan, arabinogalactan side chains. Apart from pectic polysaccharides there are different plant polysaccharides which composed of monomers units of arabinose, rhamnose, galacturonic acid, xylose, glucose, mannose, Rhamnogalacturonan type I and II etc.[40] They exhibit very potent immunomodulatory activity. An account of the several plant sources of polysaccharides, chemical composition, method of extraction, mechanism of action and therapeutic activity is given in Table 2.

Table 2. Immunomodulatory Activity of Plant cell polysaccharides

S.no	Name of the plant source	Active chemical composition	Method of extraction	Mechanism of Immunomodulation	Therapeutic uses	Ref
1.	*Sambuci flos*, Family – Adoxaceae Plant part-Aerial parts	Rahmnose, Arabinose, galacturonic acid, Galactose, Xylose Mannose	It is extracted from 50% ethanol at 50 ^{0}C. and from water at 100^{0}C	-Suppress of macrophages activity - Inhibits the delayed-type hypersensitivity reaction. -stimulation of phagocytosis -Increases production of antibodies	Used for instance chill, influenza, or pyrexia.	47-49
2.	*Artemisia afra* Family– Asteraceae Plant part-Leaves	Galactose, Arabinose Galactose, Xylose, Arabinogalactans	The leaves were taken and extracted with organic solvents in order to remove the lipophilic substances -the ppt obtained was then extracted with 50% ethanol in water and then extracted at 100 ^{0}C with water.	-Shows significant effect in vitro when tested in complement assay for the immunomodulating properties.	Used for cough and cold, fever, loss of appetite, treatment of malaria.	50
3.	*Terminalia macroptera* GuillFamily-Combretaceae Plant part-Stem bark, Root bark, leaves	Rhamnogalacturonan type I Arabinogalactan type II	The extraction is carried out by using 96% ethanol which is followed by extraction with hydroalcoholic solvent of water and ethanol.	-Mediates the stimulation of antibodies production	Used for cough and sores, *H.pylori* infection ,arthritis hepatitis and tuberculosis	51
4.	*Lycium ruthenicum* Murr Family-Solanaceae Plant part -Fruit	Galacturonic acid, Xylose, Rhamnose, Arabinose,Galactose	Isolated by water extraction from the fruits of *L. ruthenicum*	-Inhibits NO production and mRNA expression of inducible nitric oxide synthase -Suppresses proinflammatory cytokines in lipopolysaccharides stimulated macrophages -Inhibits HT -29 cell proliferation	Used in hypertension, heart disease, antioxidation, anti fatigue, and hypoglycaemic activity	2,52
5.	Potato pectin *Solanum tuberosum* Family-Solanaceae Plant part-Tubers	Pectin	Galacturonic acid and rhamnose	-Inhibits HT 29 proliferation -Induces cell cycle arrest of G2/M colon cancer cells.	-effective in inflammatory and allergic responses	49
6.	*Ziziphus jujuba Family-Rhamnaceae* Plant Part-Fruits	Arabinose and Galactose	Isolated as a purified water-soluble polysaccharide	-Elevates activity of glutathione peroxidase and superoxide dismutase -Induced T lymphocyte proliferation	Chronic Fatigue Syndrome	53
7.	*Artocarpus*	D-Galactose and D-	Isolated as a purified water-soluble	-Increased	Effective in colon cancer	54

	heterophyllus Family-Moraceae Plant part-Fruits	Galacturonic acid, D-Xylose and D-Glucose.	polysaccharide (WSP)	IL 6 level -Stimulates IL-1β production by tumour cell		
8.	*Aloe vera* Family-Liliaceae Plant plant-Gel from the leaves	Acamannan	The gel obtained was washed with normal water and rinsed with distilled water. It was kept in distilled water at 4^0C to get rid of yellow exudation. The clear gel is then homogenized followed by centrifugation.	-Induces haematopoiesis -Shows upregulation of cytokines such as TNF α and IL 1.	-Anti allergic -protects against radiation hazard -Anticancer	39.55 .56
9.	Echinacea purpurea Family- Asteraceae Plant part-Aerial parts	Arabinogalactan	-aqueous extract of the aerial parts yield polysaccharides	Increases activation of macrophages. -Increases the IL-1, TNF α and IFN β	Used for treatment of wounds, burns, measles and mumps	57.58
10.	Glycyrrhiza glabra Family-Fabaceae Plant part-Root and stolons	β-1,3-linked d-galactose residues; α-1,4-linked d-glucose	-aqueous extract of roots yield polysaccharides	-Activates the RE system -Reproduces immune cells such as lymphocytes and macrophages -Promotes the maturation of immune cells	-Expectorant -Lung detoxifying agent -Stomach ulcer	59.60
11.	Plantago asiatica Family-Plantaginaceae Plant part-Seeds	Glucurono-arabinoxylane	Aqueous extract of the seeds yields the polysaccharide	-Induces the maturation of murine DCs.	Stimulate maturation transformation of bone marrow	61
12.	Trigonella foenum-graecum L Family-Fabaceae Plant part -Seeds	Galactomannan	Seeds are crushed and then aqueous extract is made. The polysaccharide is precipitated from the slurry by alcohol.	-Immunostimulatory activity	-Used in stomach ulcer -Cough suppressant	62
13.	*Dendrobium officinale* Family-Orchidaceae Plant part- Stem	Arabinose, Rhamnose, Galactose, Mannose, Xylose	Subjected to aqueous extraction followed by ethanol precipitation	-Promotes proliferation of splenocyte -Enhances natural killer cell-mediated cytotoxicity -Increases the phagocytosis and nitric oxide production of macrophages.	promote the production of body fluids, benefit the stomach, moisten the lungs, and relieve cough	63
14.	*Chlorophytum borivilianum* Family -Liliaceae Plant part-Roots	Fructans, Acetylated Mannans	Hot water extraction	-Improves NK cell response -Increases phagocytosis	-hypolipidemic -prevents testicular damage	64

Many marine organisms are excellent sources of polysaccharides. Although some similarities may be found between the polysaccharides from each group of organisms, they can be heterogeneous and structurally different [65]. The renewable source and biodegradable nature of these polysaccharides makes them promising compounds for the application in pharmaceuticals, therapeutics, and regenerative medicine. The immunomodulatory action of these polysaccharides has been listed in Table 3.

Table 3. Immunomodulator Activity of Marine polysaccharides

S.N0	Name of the Marine organism	Active chemical composition	Mechanism of Immunomodulation	Ref
1.	*Laminaria digitata* Laminariaceae	β-1,3 Glucan oligomer (from Laminarin)	-Stimulates TNF α production in human monocytes	65
2.	*L. hyperborean* *L. digitata* Laminariaceae	Laminarin, Fucoidan	-Extracts from both sources increases IL-8 expression when studied on pigs	66
3.	*Fucus Evanescens* Fucaceae	Sulphated polysaccharides	-Activates the NF -JB in HEK 293 eukaryotic cells	67
4.	*F. vesiculosis* Fucaceae	Fucoidan	-Enhances dendritic cells (C) maturation in human monocytes -Up regulation of TNF-a induced secretion of matrix metalloproteinase-9 (MMP-9) (an enzyme necessary for migration of immune cells) in monocytic cell line U937 -Increases phagocytosis, lysozyme activity and production of nitric oxide (NO), hydrogen peroxide, TNF-a, and IL-6 in ssplenic lymphocytes of BALB/c mice	68-70
5.	*Undaria Pinnatifida* Alariaceae	Fucoidan	-Suppresses anti-inflammatory cytokines— IL-4, IL-5, IL-13 in male BALB/c mice	71
6.	*Fucus vesiculosus* Fucaceae	Fucoidan	-Increases production of TNF-a, IL 12, and maturation of dendritic cells via NF-kB signalling pathway in C57BL/6 mice	72
7.	*L. japonica* Caprifoliaceae	β-D-Mannuronate residue of Alginate	-Stimulates immunological activity of intestinal cells through the Peyer's patch cells of C3H/HeJ mice	73
8.	*Chlorella stigmatophora* Syngnathidae	Carrageenan	-Shows immunosuppressant effects	74
9.	*Phaeodactylum tricornutum,* Phaeodactylaceae	Sulphated α-mannan	-Shows immunostimulatory effects	75
10.	*Chlorella pyrenoidosa,* Mytilidae	Xylose, Arabinose, Rhamnose	-Enhances phagocytic rate and phagocytic index	11
11.	*Spirulina fusiformis, Oscillatoriaceae*	Fucoidan	-Shows immunosuppressive effect	75
12.	*Crenomytilus grayanus,* Mytilidae	Bioglycan (Mytilan)	-Shows immunomodulating activity	76
13.	*Chlorella stigmatophora Syngnathidae*	Carrageenan	-Shows immunosuppressant effects by proliferation of NK cells	74
14.	*Phaeodactylum tricornutum,* Phaeodactylaceae	Sulphated α-mannan	-Shows immunostimulatory effects	74
15.	*Litopenaeus vannamei,* Penaeoidea	Fucoidan, Glycoprotein	-Shows immunomodulatory action of superoxide dismutase (SOD)	77
16.	*Endarachne binghamiae,* Phaeophyceae	Sodium Alginate, Alginic Acid, Glycoprotein	-Sodium alginate and alginic acid exhibits stimulation activity for macrophage and T cell proliferation -Induces the production of TNF-α and nitric oxide by macrophages and IFN-γ by T cells in a concentration-dependent manner	78

17.	*Phoma herbarum* Pleosporaceae	Alginic acid,Fucoidan	Activates and proliferates T cell, -Promotes IL-12 secretion and expression of markers (CD80, CD86, and MHC II) *via* TLR-4 on DCs.	79
18.	*Laminaria japonica*, Laminariaceae	Laminarin oligosaccharides	-Induces immune response proteins were induced and apoptotic cell death proteins were reduced significantly by LO (Laminarin oligosaccharides)	80
19.	*Litopenaeus vannamei*, Penaeoidea	Fucoidan	-Shows immunomodulatory action of superoxide dismutase (SOD) and its possible use as an indicator of immune responses	77
20.	*Chondrus ocellatus*, Gigartinaceae	Carrageenan	-λ-carrageenan samples of polysaccharides antitumor and immunomodulation activities	81

3. THERAPEUTIC ROLE OF POLYSACCHARIDES

3.1 COVID -19

In the present situation when the world is going through a pandemic situation due to the spread of SARs COV 2 virus. There are a total 49,207,942 cases of coronavirus recorded till date causing 12,42,308 deaths. Therefore, it is creating a need for effective inhibitors to the virus. The antiviral properties of polysaccharides are functions of their vast structural characteristics, chain length etc [82]. The carbohydrate binding agents present in the natural polysaccharides helps to inhibit the coronaviruses along with infectious bronchitis (IBV), mouse hepatitis virus (MHV) and feline coronaviruses serotypes I and II [78,79].

3.1.1 Immunomodulators from marine sources

Polysaccharides obtained from marine sources are chitosan, carrageenan, chitosan and their derivatives, have shown the antiviral activities. This provides the basis for studying their activity against SARS COV -2. Chitosan's cationic modified form named as N-(2- hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC), shows significant inhibition against the human coronavirus HCoV- 229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, and the hydrophobic derivative (HM-HTCC) has shown inhibitory property against coronaviruses. This signifies that the polymers which are based on chitosan is showing inhibitory action on the low pathogenic human coronaviruses [85] .Antiviral activity of the polysaccharides from Red algae *Gelidium robustum* has been established. It protects the embryonic egg against influenza B or mumps virus [86] .

3.1.2 Immunomodulators from plant sources

Hedysarum multijugum can be used to treat viral infections. The Avian coronavirus is capable of causing infectious bronchitis (IB). The polysaccharides from Astragalus species are capable of reducing the infectious bronchitis virus by inhibiting its replication in the chicken embryo kidney cells. The Astragalus polysaccharides (APS) treatment has increased the lymphocyte proliferation, levels of expression for interleukin (IL)-1β, IL-2, IL-8, and TNF-α. These findings show that APS can enhance immunity. During the outbreak of SARS coronaviruses in China, RI, as a Chinese medicinal herb, was prepared as an antiviral drug [87] .The polysaccharide from another herb named *Radix isatidis* stimulates the expression of cytokines like IL 2 and interferon. This helps to regulate and increase the nonspecific immunological function, humoral and cellular immunity when tested in mice. This is the mechanism of antiviral effects of *Radix isatidis* [88] . The polysaccharides from Ginkgo biloba has been studied and analysed against Porcine epidemic diarrhoea virus (PEDV) infection showed potent inhibitory activity. It is particularly inhibited on viral attachment entry steps of PEDV life cycle. The α-glucan-based polysaccharide of *Lentinula edodes* mycelia has been studied against influenza virus, herpes virus ,avian influenza virus ,HPV .It shows the immunostimulant action of inducing protective immune response[89] .

3.2 *ANTICANCER*

3.2.1 Immunomodulators from plant sources

Many plant polysaccharides have shown potent anticancer activity. Potato pectin which is Rhamnogalacturonan-1(RG-1) acts on HT-29 cells and inhibits its proliferation. It also induces arrest of the G2/M phase of the cell cycle and shows activity against colon cell cancer [90] . *Lonicera japonica* flower with active composition of RG-I along with rhamnose, galactose and arabinose inhibits the pancreatic cell cancer [91] . Persimmon leaves composed of RG I and RG II have developed NK cell-mediated cytotoxicity for the lymphoma tumour cells. It has also inhibited the lung metastasis and lymphoma tumour cells. *Astraeus hygrometricus* was studied on the Daltons lymphoma-bearing mice and showed inhibition of tumour growth, induction of process of cell apoptosis and activation of immune system [92] .Inhibition of tumour growth and induction of cell apoptosis was shown by the polysaccharides from *Auricularia auricula-judae* when investigated on S180-bearing mice [93] .Buckwheat was studies on THP-1 cells and it increased the cell proliferation and maturity [94] .*Curcuma kwangsiensis* investigated on CNE-2 cells inhibited cell proliferation and also induced the cell apoptosis process [95] . *Ginkgo biloba* polysaccharide was studied on U937 cells and resulted in the inhibition of cell proliferation [96] . *Melia toosendan Sieb* also inhibited cell proliferation when studied on Et Zucc BGC-823 cells [97] *Passiflora edulis* inhibited the growth of tumour when tested on S180-bearing mice .*Prunella vulgaris* L showed inhibition of tumour growth when investigated on lung carcinoma mice model and also improved the immune function [98] . Inhibition of cell proliferation was shown by the polysaccharides of *Punica granatum* when studied on MCF-7 and K562 cells. The pectin from sweet Potato inhibited tumour cells [99] . *Ziziphus jujuba* investigated on melanoma cells shows inhibition ofcell proliferation, induced cell apoptosis [100] .

3.2.2 Immunomodulators from microorganisms

A mushroom named *Agaricus subrufescens* was studied on Walker-256 (W256) tumour-bearing rats for its antitumor activity and it showed beneficial effects on tumour treatment [101] . The cell wall of *L.edodes* contains Lentinan which showed better antitumor effects than other mushroom polysaccharides [102] . *Cordyceps gunnii* analysed on K562 cells results in inhibition of cell growth [103] . *Flammulina velutipes* polysaccharides was tested on both BGC-823 cells, A549 cells and it inhibited cell growth [104] . Another polysaccharides obtained from *Phellinus ribis* inhibited cell growth and also caused blockage of new angiogenic vessel formation when studied on Zebrafish model [105].

3.2.3 Immunomodulators from marine sources

Several polysaccharides from marine sources have been studied and shown to find potent anticancer properties. Polysaccharide obtained from *Ascophyllum nodosum* were tested on U937 cells .It has shown potent inhibitory action on cell proliferation ,induced DNA-fragmentation and apoptosis [106] . *Cladosiphon okamuranus* Tokida showed inhibition of growth of tumour and stimulation of macrophages when investigated on S180 bearing mice[107] . *Fucus evanescens* has been investigated MT-4 cells which enhanced etoposide induced cell death [108] . *Fucus vesiculosus* investigated on AGS cells ,inhibited cell growth, induced apoptotic and autophagic cell death [109] .*Saccharina japonica*, Undaria pinnatifida T-47D and SK-MEL-28 cells Inhibited cell proliferation and colony formation [110] . *Undaria pinnatifida*

studied on A549 cells Inhibited cell proliferation, induced apoptosis [111].

3.3 ANTI-INFLAMMATORY

3.3.1 Immunomodulators from microorganisms.

Antrodia cinnamomea polysaccharides were studied using LPS-induced RAW264.7 model and it caused inhibition of TNF-a and IL-6 release [112]. *Pleurotus* eryngii causes a decrease of the ratios of pro or anti-inflammatory cytokines secretion [113]. *Ganoderma lucidum* yielding β-1,3 or 1,6-glucan was obtained from high-cholesterol diet-induced inflammation in male C57BL/6 mice and it caused the induction of the serum IgA and IgG production [114]. Polysaccharide-extracts of the fruits of the plant *Polyporus dermoporus* contain β-Glucose as the active chemical constituents. It was investigated on the models of oil-induced ear edema in male BALBc mice and Carrageenan-induced pleurisy in male Wistar rats shown decrease of the nitrate/nitrite ratio and also inhibited diapedesis [115]. *Echinodontium tinctorium* containing the monosaccharides glycan, galacturonic acid, mannose, fucoidan was tested on LPS-induced RAW264.7 macrophages and histamine-induced inflammatory event in mouse gluteus maximus muscle and it has inhibited the TNF-α and production of NO [116]. *Hericium erinaceus* studied on model of ethanol-induced gastric mucosal lesion and pylorus ligation-induced gastric ulcer in Sprague-Dawley rats decreased the expression of TNF-α, IL-1β and inhibit the MPO activity [117].

3.3.2 Immunomodulators from Plant sources

The polysaccharide isolated from Seabuckthorn berry was studied on the carbon tetrachloride (CCl4)-induced hepatotoxicity in male C57BL/6 mice and it causes inhibition of the TLR4-MAPK-NF-κB signalling pathway [113]. Inhibition of NO, IL-6, IL-1β and TNF-α along with the increased level of production of IL-10 was caused by the pectin obtained from purple sweet potato when studied on the model of LPS-treated RAW 264.7 macrophage cells[114]. Another study analyses the effect of sulphated polysaccharides, fucans, from *Lophophora variegata* showed reduction of oedema and serum on zymosan-induced arthritis in rats.

3.3.3 Immunomodulators from marine sources

Inhibition of MAPK and NF -kB signalling pathway was shown by brown alga *Sargassum cristaefolium* when its polysaccharide was investigated on LPS-stimulated RAW264.7 [120].

4. CONCLUSION

Immunomodulators can act through various mechanisms on innate immunity or adaptive immunity systems. Polysaccharides obtained from microbial sources have shown potential immunomodulatory activity in pre-clinical models. The plant derived polysaccharides can be a potential therapeutic strategy to treat COVID 19 due to their immunomodulatory properties along with anticancer and anti-inflammatory activities. The marine polysaccharides possess immunomodulatory activity which is mainly due to the presence of sulphate residue in their chemical structures and Chitosan has shown potent activity against SARS COV-2 virus. The natural polysaccharides from different sources are a promising subject for further research in the field of pharmaceutical and nutraceutical formulation development. Their considerable availability from renewable sources and the non-toxic effect can be an additional benefit. Therefore, the current review can provide a roadmap to the development of new formulations for utilising the versatile therapeutic activity of the natural polysaccharides.

5. AUTHOR'S CONTRIBUTION STATEMENT

Ms. Priyanka Ray collected the data from the available literature on Pubmed, Research Gate, Mendeley, ScienceDirect etc. under the able guidance of Dr. Sumana Chatterjee and Dr. Prerona Saha. The data was then compiled to draft the manuscript. Dr. Sumana Chatterjee and Dr. Prerona Saha made critical revisions and approved the final version of the manuscript. All authors reviewed and approved the final manuscript.

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8. CONFLICT OF INTEREST

Conflict of interest declared none.

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