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

Priyanka Ray, Sumana Chatterjee*, Prerona Saha

Guru Nanak Institute of Pharmaceutical Science & Technology
157/F Nilgunj Road, Sodepur, Panihati, Kolkata -700114, West Bengal, India

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-2 provide 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 antiviral 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.

*Corresponding Author

Sumana Chatterjee, Guru Nanak Institute of Pharmaceutical Science & Technology
157/F Nilgunj Road, Sodepur, Panihati, Kolkata -700114, West Bengal, India

Received On 13 November 2020
Revised On 15 December 2020
Accepted On 17 December 2020
Published On 19 December 2020

Funding We acknowledge the resources and support for the study provided by Guru Nanak Institute of Pharmaceutical Science & Technology.


http://dx.doi.org/10.22376/ijpbs/lpr.2020.10.5.P191-206

This article is under the CC BY-NC-ND Licence (https://creativecommons.org/licenses/by-nc-nd/4.0)

Copyright @ International Journal of Life Science and Pharma Research, available at www.ijlpr.com

I. 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. 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 \(^8,9\).

I.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](image-url)
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. 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. 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](image)

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. The structures are shown in Fig 3.

![Fig3. Biologically important chemical moieties present in plant polysaccharides](image)

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. 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. The structure of fucoidan consists mainly of α(1,3)-linked L-fucopyranose residues with sulphates at the C-2 position. Carrageenan is a polysaccharide obtained from Red algae and the biological activity is shown mainly due to the sulphate ester residue of the structure. The structure of the chief components of these polysaccharides with biological activity is represented in Fig 4.
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.

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.

Table I represents the different polysaccharides from the microbial sources showing immunomodulatory action.
Table 1. Immunomodulator Activity of polysaccharides from microorganisms.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of the Plant source</th>
<th>Active chemical composition</th>
<th>Mechanism of Immunomodulation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Agaricus blazei</em></td>
<td>β-Glucan</td>
<td>-Stimulates the different immune cells such as NK cells, dendritic cells, macrophages and granulocytes (polymorphonuclear leukocytes)</td>
<td>28-30</td>
</tr>
<tr>
<td>2.</td>
<td><em>Pleurotus ostreatus</em></td>
<td>Dietary fibres, β-glucans, non-starchy carbohydrates</td>
<td>-Shows potent immunostimulant activity by improving CD4+/CD8+ ratio</td>
<td>31-32</td>
</tr>
<tr>
<td>3.</td>
<td><em>Lentinula edodes</em></td>
<td>β-Glucan</td>
<td>-Improves cellular immunity, humoral immunity and innate immunity.</td>
<td>33-34</td>
</tr>
<tr>
<td>4.</td>
<td><em>Grifola frondosa</em></td>
<td>β-Glucan</td>
<td>-Induces cytokine production in macrophages through the Dectin-1/Syk/NF-κB signalling pathway resulting in immunomodulatory and antitumor activities</td>
<td>35-36</td>
</tr>
<tr>
<td>5.</td>
<td><em>Coriolus versicolor</em></td>
<td>β-Glucan</td>
<td>-Induces pro-inflammatory cytokines -Shows effect on tumour necrosis factor (TNF)-α -Induces apoptosis</td>
<td>37-38</td>
</tr>
<tr>
<td>6.</td>
<td><em>Trametes versicolor</em></td>
<td>Polysaccharopeptides</td>
<td>-Enhances mitogenic activity -Induces cytokines (interleukin (IL)-1β and IL-6) production in stimulated macrophages; -Increases the proliferation of cell</td>
<td>39</td>
</tr>
<tr>
<td>7.</td>
<td><em>Bacillus Calmette-Guerin (Natural BRM)</em></td>
<td>Live mycobacteria</td>
<td>-Induces granulomatous reaction at the site of administration</td>
<td>40</td>
</tr>
<tr>
<td>8.</td>
<td><em>Candida albicans</em></td>
<td>Glycan, Mannan</td>
<td>-Enhances the suppression of the various antibody responses when administered with type III pneumococcal polysaccharide (SSS-III) and with sheep erythrocytes (SRBC) in mice.</td>
<td>41</td>
</tr>
<tr>
<td>9.</td>
<td><em>Aspergillus fumigatus</em></td>
<td>Galactosaminogalactan</td>
<td>-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</td>
<td>42</td>
</tr>
<tr>
<td>10.</td>
<td><em>Cryptococcus neoformans</em></td>
<td>β-Glucan</td>
<td>-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.</td>
<td>43</td>
</tr>
<tr>
<td>11.</td>
<td><em>Laminaria digitata</em></td>
<td>β-Glucan</td>
<td>-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</td>
<td>27</td>
</tr>
<tr>
<td>12.</td>
<td><em>Caulerpa lentillifera</em></td>
<td>β-Glucan</td>
<td>-Stimulates the NO production by murine macrophage RAW 264.7 cells, activates both NF-kB 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</td>
<td>44</td>
</tr>
</tbody>
</table>
Several polysaccharides have been derived from the plant source which can act on the immune system. 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. 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>
<thead>
<tr>
<th>S.no</th>
<th>Name of the plant source</th>
<th>Active chemical composition</th>
<th>Method of extraction</th>
<th>Mechanism of Immunomodulation</th>
<th>Therapeutic uses</th>
<th>Ref</th>
</tr>
</thead>
</table>
| 1.   | Sambuci flos, Family – Adoxaceae Plant part-Aerial parts | Rahmnose, Arabinose, galacturonic acid, Galactose, Xylose, Mannose | It is extracted from 50% ethanol at 50 °C and from water at 100°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, Arabinogalactan | 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 °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 |
-Induced T lymphocyte proliferation | Chronic Fatigue Syndrome | 53 |
<p>| 7.   | Artocarpus | D-Galactose and D- | Isolated as a purified water-soluble polysaccharide | -Increased | Effective in colon cancer | 54 |</p>
<table>
<thead>
<tr>
<th>Plant</th>
<th>Family</th>
<th>Plant part</th>
<th>Polysaccharide</th>
<th>Biological activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heterophyllus</strong>&lt;br&gt;Family: Moraceae&lt;br&gt;Plant part: Fruits</td>
<td>Galacturonic acid, D-Xylose and D-Glucose</td>
<td>Polysaccharide (WSP)</td>
<td>Stimulates IL-1β production by tumour cell</td>
<td>39.55 39.56</td>
<td></td>
</tr>
<tr>
<td><strong>Aloe vera</strong>&lt;br&gt;Family: Liliaceae&lt;br&gt;Plant part: Gel from the leaves</td>
<td>Acamannan</td>
<td>-aqueous extract of the gel</td>
<td>Increases activation of macrophages&lt;br&gt;-Increases the IL-1, TNF α and IFN β</td>
<td>57.58</td>
<td></td>
</tr>
<tr>
<td><strong>Echinacea purpurea</strong>&lt;br&gt;Family: Asteraceae&lt;br&gt;Plant part: Aerial parts</td>
<td>Arabinogalactan</td>
<td>Aqueous extract of the aerial parts</td>
<td>Increases the IL-1, TNF α and IFN β&lt;br&gt;-Enhances natural killer cell-mediated cytotoxicity&lt;br&gt;-Increases the phagocytosis and nitric oxide production of macrophages</td>
<td>59.60</td>
<td></td>
</tr>
<tr>
<td><strong>Glycyrrhiza glabra</strong>&lt;br&gt;Family: Fabaceae&lt;br&gt;Plant part: Root and stolons</td>
<td>β-1,3-linked d-galactose residues; α-1,4-linked d-glucose</td>
<td>Aqueous extract of roots</td>
<td>Promotes the maturation of immune cells&lt;br&gt;-Activates the RE system&lt;br&gt;-Reproduces immune cells such as lymphocytes and macrophages</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td><strong>Plantago asiatica</strong>&lt;br&gt;Family: Plantaginaceae&lt;br&gt;Plant part: Seeds</td>
<td>Glucurono-arabinoxylane</td>
<td>Aqueous extract of the seeds</td>
<td>Induces the maturation of murine DCs.&lt;br&gt;-Induces the maturation of murine DCs.</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td><strong>Trigonella foenum-graecum L</strong>&lt;br&gt;Family: Fabaceae&lt;br&gt;Plant part: Seeds</td>
<td>Galactomannan</td>
<td>Seeds are crushed and then aqueous extract is made.&lt;br&gt;The polysaccharide is precipitated from the slurry by alcohol.</td>
<td>Immunostimulatory activity&lt;br&gt;-Improves NK cell response&lt;br&gt;-Increases phagocytosis</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td><strong>Dendrobium officinale</strong>&lt;br&gt;Family: Orchidaceae&lt;br&gt;Plant part: Stem</td>
<td>Arabinose, Rhamnose, Galactose, Mannose, Xylose</td>
<td>Subjected to aqueous extraction followed by ethanol precipitation</td>
<td>Enhances natural killer cell-mediated cytotoxicity&lt;br&gt;-Increases the phagocytosis and nitric oxide production of macrophages.</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td><strong>Chlorophytum borivilianum</strong>&lt;br&gt;Family: Liliaceae&lt;br&gt;Plant part: Roots</td>
<td>Fructans, Acetylated Mannans</td>
<td>Hot water extraction</td>
<td>Improves NK cell response&lt;br&gt;-Prevents testicular damage</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

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. 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>
<thead>
<tr>
<th>S.N0</th>
<th>Name of the Marine organism</th>
<th>Active chemical composition</th>
<th>Mechanism of Immunomodulation</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Laminaria digitata Laminariaceae</td>
<td>β-1,3 Glucan oligomer (from Laminarin)</td>
<td>Stimulates TNF α production in human monocytes</td>
<td>65</td>
</tr>
<tr>
<td>2.</td>
<td>L. hyperborean L. digitata Laminariaceae</td>
<td>Laminarin, Fucoidan</td>
<td>Extracts from both sources increases IL-8 expression when studied on pigs</td>
<td>66</td>
</tr>
<tr>
<td>3.</td>
<td>Fucus Evanescens Fucaceae</td>
<td>Sulphated polysaccharides</td>
<td>Activates the NF -JB in HEK 293 eukaryotic cells</td>
<td>67</td>
</tr>
<tr>
<td>4.</td>
<td>F. vesiculosis Fucaceae</td>
<td>Fucoidan</td>
<td>Enhances dendritic (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 monocyctic cell line U937 -Increases phagocytosis, lysozyme activity and production of nitric oxide (NO), hydrogen peroxide, TNF-a, and IL-6 in splenic lymphocytes of BALB/c mice</td>
<td>68-70</td>
</tr>
<tr>
<td>5.</td>
<td>Undaria Pinnatifida Alariaceae</td>
<td>Fucoidan</td>
<td>Suppresses anti-inflammatory cytokines—IL-4, IL-5, IL-13 in male BALB/c mice</td>
<td>71</td>
</tr>
<tr>
<td>6.</td>
<td>Fucus vesiculosus Fucaceae</td>
<td>Fucoidan</td>
<td>Increases production of TNF-a, IL 12, and maturation of dendritic cells via NF-kB signalling pathway in C57BL/6 mice</td>
<td>72</td>
</tr>
<tr>
<td>7.</td>
<td>L. japonica Caprifoliaceae</td>
<td>β-D-Mannuronate residue of Alginate</td>
<td>Stimulates immunological activity of intestinal cells through the Peyrer's patch cells of C3H/HeJ mice</td>
<td>73</td>
</tr>
<tr>
<td>8.</td>
<td>Chlorella stigmatophora Syngnathidae</td>
<td>Carrageenan</td>
<td>Shows immunosuppressant effects</td>
<td>74</td>
</tr>
<tr>
<td>9.</td>
<td>Phaeodactylum tricornutum, Phaeodactylaceae</td>
<td>Sulphated α-mannan</td>
<td>Shows immunostimulatory effects</td>
<td>75</td>
</tr>
<tr>
<td>10.</td>
<td>Chlorella pyrenoidosa, Mytilidae</td>
<td>Xylose, Arabinose, Rhamnose</td>
<td>Enhances phagocytic rate and phagocytic index</td>
<td>76</td>
</tr>
<tr>
<td>11.</td>
<td>Spirulina fusiformis, Oscillatoriaceae</td>
<td>Fucoidan</td>
<td>Shows immunosuppressive effect</td>
<td>77</td>
</tr>
<tr>
<td>12.</td>
<td>Gromenmytilus grayanus, Mytilidae</td>
<td>Bioglycan (Mytilan)</td>
<td>Shows immunomodulating activity</td>
<td>78</td>
</tr>
<tr>
<td>13.</td>
<td>Chlorella stigmatophora Syngnathidae</td>
<td>Carrageenan</td>
<td>Shows immunosuppressant effects by proliferation of NK cells</td>
<td>79</td>
</tr>
<tr>
<td>14.</td>
<td>Phaeodactylum tricornutum, Phaeodactylaceae</td>
<td>Sulphated α-mannan</td>
<td>Shows immunostimulatory effects</td>
<td>80</td>
</tr>
<tr>
<td>15.</td>
<td>Litopenaeus vannamei, Penaeoidea</td>
<td>Fucoidan, Glycoprotein</td>
<td>Shows immunomodulatory action of superoxide dismutase (SOD)</td>
<td>81</td>
</tr>
<tr>
<td>16.</td>
<td>Endarachne binghamiae, Phaeophyceae</td>
<td>Sodium Alginate, Alginic Acid, Glycoprotein</td>
<td>Sodium alginates and algic 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</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Species</td>
<td>Genus/Morphotype</td>
<td>Component/Action</td>
<td>Reference</td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------</td>
<td>----------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>17.</td>
<td><em>Phoma herbarum</em></td>
<td>Pleosporaceae</td>
<td>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.</td>
<td>79</td>
</tr>
<tr>
<td>18.</td>
<td><em>Laminaria japonica</em></td>
<td>Laminariaceae</td>
<td>Laminarin oligosaccharides: Induces immune response proteins were induced and apoptotic cell death proteins were reduced significantly by LO (Laminarin oligosaccharides)</td>
<td>80</td>
</tr>
<tr>
<td>19.</td>
<td><em>Litopenaeus vannamei</em></td>
<td>Penaeoidea</td>
<td>Fucoidan: Shows immunomodulatory action of superoxide dismutase (SOD) and its possible use as an indicator of immune responses</td>
<td>77</td>
</tr>
<tr>
<td>20.</td>
<td><em>Chondrus ocellatus</em></td>
<td>Gigartinaceae</td>
<td>Carrageenan: λ-carrageenan samples of polysaccharides antitumor and immunomodulation activities</td>
<td>81</td>
</tr>
</tbody>
</table>
Many plant polysaccharides have shown potent anticancer activity. Potato pectin which is Rhamnogalacturonan-I (RG-I) 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 cancer cell 91. Persimmon leaves composed of RG I and RG II have developed NK cell-mediated cytoxicity 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 studied 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 of cell proliferation, induced cell apoptosis 100.

### 3.3 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.

### 3.4 Immunomodulators from marine sources

Several polysaccharides from marine sources have been studied and shown to find potent anticancer properties. Polysaccharide obtained from *Ascosiphum 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 evanesens* has been investigated MT-4 cells which enhanced etoposide induced cell death 108. *Fucus vesiculosus* investigated on AGS cells, induced 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*
Antrodia cinnamomea polysaccharides were studied using LPS-induced RAW264.7 model and it caused inhibition of TNF-α 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 dermatopus 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 induced 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 118. 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 cells119. Another study analyses the effect of sulphated polysaccharides, fucans, from Lophophora variagata showed reduction of oedema and serum on zymosan-induced arthritis in rats.

3.3.3 Immunomodulators from marine sources

Inhibition of MAPK and NFκB signalling pathway was shown by brown alga Sargassum cristaeolifolium 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.

6. ACKNOWLEDGEMENT

The authors are grateful to Guru Nanak Institute of Pharmaceutical Science and Technology for providing provisions and facilities to complete the research work.

7. FUNDING ACKNOWLEDGEMENT

We acknowledge the resources and support for the study provided by Guru Nanak Institute of Pharmaceutical Science & Technology.

8. CONFLICT OF INTEREST

Conflict of interest declared none.


114. Li S, Shah NP. Anti-inflammatory and anti-proliferative


