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THE CLINICAL OVERVIEW ON NATURAL IMMUNOPOLYSACCHARIDES AS AN ADJUVANT THERAPY OF CANCER

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ABSTRACT: Considering the increasing trend of the cancer rate of numerous organs, efficient treatments are highly required to restrain human melanomas. Cancer is among the most prevalent illnesses ascertained in developed countries, estimating more than 1.50 million fresh instances in the US alone in 2017. Though, approximately most of the chemotherapeutic drugs presently on the market cause major adverse effects like immunodeficiency, fatigue, alopecia, anaemia, peripheral neuropathy, neurological problems, and fertility issues, to name a few of them. Polysaccharides have developed as potential chemical entities revealing effective immunomodulatory activity within a variety of cell lines and can be developed as alternatives to existing cancer chemotherapeutic agents, possessing minimal toxic side-effects. Polysaccharides isolated from plants, microorganisms, fungi, and marine sources have been reported. They function via TLR modulation, activation and maturation of Dendritic cells, Cytokines signalling pathway, macrophage activation, and miscellaneous pathways like PI3K, MAPK activation, the complement supplement system. This review concentrates on the polysaccharides explored over the past five to seven years as an adjuvant therapeutic agent, their suggested mechanism of action for immunomodulation.

INTRODUCTION: Cancer is surveyed to be upheld to cardiovascular diseases in 2019, interpreted from universal cancer load and is one of the primary causes of death worldwide. According to the statistics specified by the National Institute of Health, 60,9640 cancer-associated deaths were reported and 17,35,350 new cancer cases occurred in 2018 in the US [1]. Scientists have engrossed in improved approaches to control and treat cancer because of the load triggered by cancer and its side effects related to target therapies.

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Recently, cancer immunotherapy is the main focused area by researchers. It proposes moderate and controllable effects than side effects correlated with therapies [2, 3]. Though, there are some restrictions of medicinal drugs in clinical sites like inadequate efficacy, drug resistance, adverse effects, hemopoietic suppression, immuno-toxicity [2, 4]. Thus, researchers are trying to implement novel strategies [5, 6].

The National Institute of Health estimates 1735350 new cases and 609640 cancer-related deaths in 2018 in the US [1].

Therapeutic plants contain several polysaccharides having antitumor, immunoenhancing and anti-oxidant properties, both *in-vitro* and *in-vivo*. Meanwhile, conventional cancer treatments every so often have much side effects, 'Polysaccharides'

can be a strong weapon from remedial plants which provide additional efficient cancer treatment. Polysaccharides majorly obtained from micro-organisms, plants, and animals are sources for food and therapeutic relevance [8]. Polysaccharides are a structurally distinct class of biomacromolecules that aremade up of polymers of monosaccharides deposits are connected to each other by glycosidic bonds [9].

According to the scientific community, poly-saccharides have been underappreciated correlated with nucleic acid and proteins. Many more investigators fail to solve the mystery of poly-saccharides in a wide range of biological activities, for example, cell-cell recognition, inflammation, fertilization, metastasis, and immune responses [10]. Polysaccharides are most frequently treated in combination with radiotherapy/chemotherapy for several types of cancers [11-13]. In fact, when it was found that certain polysaccharides could induce complete remission in patients with cancer, Nauts *et al*., in 1946 first recognized the anti-cancer efficacy of polysaccharides.

Consequently, polysaccharides known to be novel and developed therapeutics, also the next frontline in the pharmaceutical investigation was anticipated beyond ten years ago [14, 15]. Immunoenhancing polysaccharides are efficient of interrelating with the immune function and improve specialized mechanisms of the host reaction. There are various types of polysaccharides stated with immuno-modulatory effect such as pectic polysaccharides, glucans, arabinogalactans, mannans, fucoidans, fructans, galactans, hyaluronans and xylans [16]. Many reports have indicated that polysaccharides can stimulate immune activities by means of subsequent mechanisms: (a) Reaction of poly-saccharide with Toll-like receptors (TLR) such as Schisandra, Ascophyllum, and *Ganoderma atrum* (b) Maturation of dendritic cells (DCs) like Ginseng, *Portulaca oleracea* L, *etc*. (c) Reaction with cytokines like Interleukins (IL) and tumor necrosis factor-α (TNF-α) and (d) Complement system. Some additional polysaccharides are able to function as immunomodulators, which not only enhance the body's defence against cancer cells, but if used in conjunction with conventional chemotherapeutic agents, can also help to combat the immunosuppression that they cause. This article aims to unify the current literature and categorize these polysaccharides into mechanistic classes and provide leads for the development of novel anticancer agents based on isolated polysaccharides or their functionalized analogues.

Pharmacological Activity of Immuno-polysaccharides:

TLR Modulation: TLRs are highly conserved pattern recognition receptors, activating the immune system and play a crucial role in initiation of inflammatory response [17]. Dysregulation of TLR activity leads to the augmented risk of chronic inflammatory and diverse autoimmune disease development, aging, immunosenescence diabetes, hepatitis, inflammatory bowel disease, systemic lupus erythematosus, and rheumatoid arthritis [18].

A total of 13 members have been identified in TLR family of mammals. TLRs are classified into sub-families based on ligand type recognized by them. For example, TLRs 1, 2 and 6 are recognized by glycolipids and lipopeptides, TLR4 is recognized by fibronectin, Heat-shock protein and lipopoly-saccharides [17]. TLR activation leads to increased levels of NF-κb transcription factor-mediated through Myeloid Differentiation primary response gene 88/IL receptor-associated kinase (MyD88/IRAK). This eventually leads to increased expression of genes encoding cytokines like interleukin 12, resulting in enhanced immunity. TLR 2 is a major target for immunotherapy in malignant diseases through upregulation of immune response [19, 20].

A large number of *in-vitro* and *in-vivo* studies has proven the immunomodulatory property of poly-saccharide from fruits of *Schisandra chinensis* (SCP). SCPP11 is one of the SCP with the backbone made up of 1, 4 disubstituted β Galactose, α Galactose, 1, 6 disubstituted β mannose and 1, 4, 6, trisubstituted α- Galactose.

SCPP11 was found to upregulate secretion of markers including interleukin-1β, TNFα, mRNA, and iNOS protein in RAW2647 macrophage cells. This effect was mediated through the TLR-4 pathway, resulting in activation of macrophages and upregulation of inducible nitric oxide synthase (iNOS) expression. SCPP11 pre-treated RAW26.7 cells caused significant inhibition of HepG-2 cell proliferation [21, 22]. In cyclophosphamide-induced

immunocompromised mice, SCPP11 elevated the thymus and spleen indices, IgA, interleukin 2, TNF-α serum levels, haemolyse in formation, and pinocytic activity of peritoneal macrophages. This results in augmentation of immune function mediated through TLR4 facilitated stimulation of NO and TNFα [23].

In addition, SCP was found to enhance the phagocytic rate of macrophages for *Escherichia coli* [24]. On administration to mice exposed to damaging radiation, SCP stimulated both the arms of the immune system, humoral immunity, and cellular immunity. Effect of SCP on cellular immunity involved improving cyclophosphamide-induced inhibition of $CD4^+$ and $CD8^+$ T cells in the blood and thymus of mice after radiation injury. SCP also induced lymphocyte apoptosis exhibited through stimulation of B cell lymphoma-2 (Bcl-2) expression and suppression of Bcl-2 associated X protein (Bax) and Fas cell surface death receptor (Fas). SCP restored immune function by stimulating complement C3 and immunoglobulin G (IgG). Post radiotherapy administration of SCP was found to augment the number of lymphocyte and white blood cells in the peripheral blood with negligible side effects. Thus SCP could be of potential use as an adjuvant treatment for radiotherapy [25].

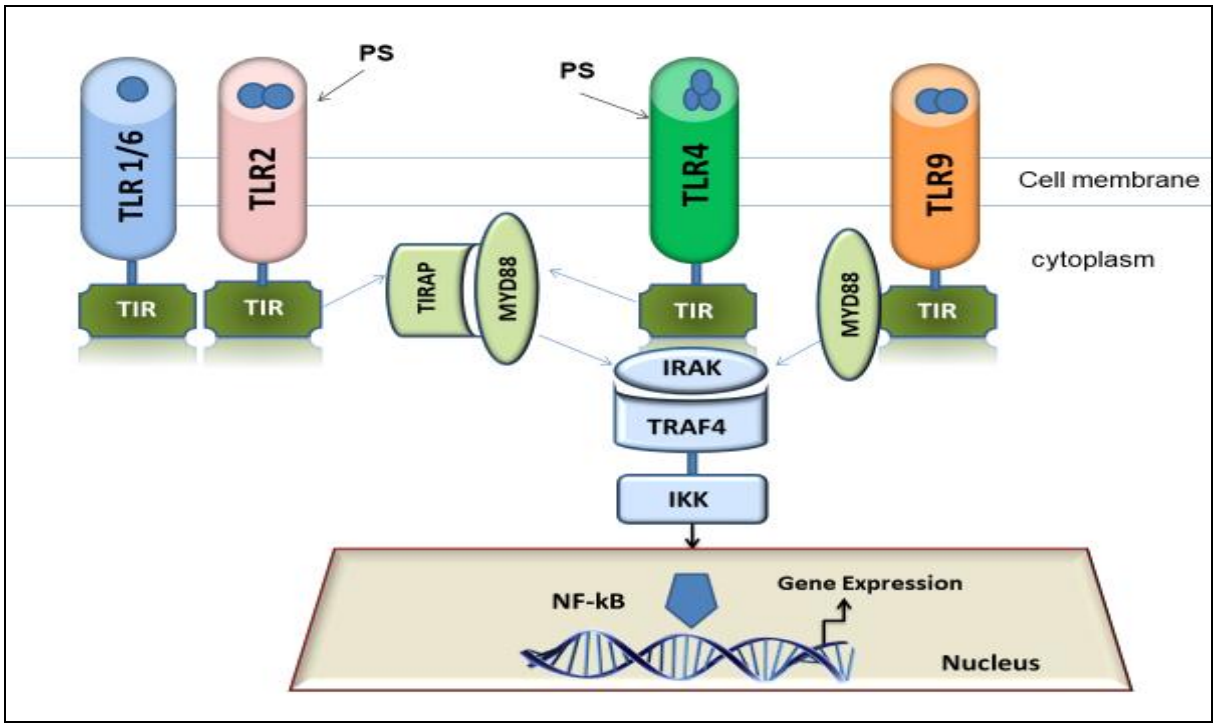

FIG. 1: MEDIATION OF POLYSACCHARIDES IN TLR ACTIVATION INCLUDING DOWNSTREAM MOLECULES MYD88 AND IKK INHIBITOR OF NUCLEAR FACTOR κB KINASE COMPLEX. TLR; TIR, Toll/IL-1R; TIRAP, MyD88; Toll-Interleukin 1 Receptor domain-containing Adaptor Protein; IRAK; TRAF, Tumor Necrosis Factor Receptor Associated Factors; IKK, Inhibitor of nuclear factor κB Kinase complex; TNF Receptor Associated Factors; NF-κB.

A water-soluble polysaccharide (WSPS) obtained from *Schisandra chinensis* leaves, comprised of Mannose, Glucose, and Glucuronic acid in the molar ratio of 5.6:3.3:1. WSPS significantly improved secretion of TNF-α and nitric oxide, resulting in potentiation of phagocytic activity of macrophages. The enhancement in immune response exhibited by WSPS was proposed to be associated with its anti-lymphoma activity [26]. A Water-soluble polysaccharide named SCPIIA, isolated from fruits of *Schisandra chinensis*, on evaluation in an immunocompromised mice model, was found to exhibit significant immune-stimulation through activation of peritoneal macrophages and enhancement of the thymus and spleen indices. Moreover, SCPIIA in combination with concanavaline A (ConA) or lipopolysaccharide caused stimulation of spleenocyte proliferation. SCPIIA was also found to potentiate humoral immunity in the cyclophosphamide-induced immuno-suppression model via enhancement of the serum haemolysin formation [24].

Polysaccharides obtained from *Astragalus membranaceus* have been widely employed to improve immune function in the treatment of various diseases. Antitumor activity of Astragalus polysaccharide (AP) was attributed to immuno-modulation activity like enhancement of IL-1, IL-2, IL-6, and TNFα and reduction in expression of IL-10 [27]. These polysaccharides were shown to exhibit potential immunomodulation in TLR4 signalling pathways, -lymphocytes, DCs, and macrophages [28, 29].

A water-soluble polysaccharide, called *Radix astragali* polysaccharide (RAP) with an average molecular weight 1334 kDahave backbone made up of α1,4 linked GalAp6Me, α-1,4 linked GlcP, 1,2,4 linked Rhap, β-1,3,6 linked Galp, with branched at oxygen atom 3 or oxygen atom 4 of β-1,3,4 linked Galp and oxygen atom 4 of the 1,2,4 linked Rhap [30]. Testing of RAP and supernatant of RAW264.7 cells in mouse mammary carcinoma 4T1 cells revealed significant synergism in terms of enhancement in the cytotoxic effect of RAW264.7 cells supernatant. Moreover, RAP was also found to stimulate the production of cytokines and NO in RAW264.7 cells and significantly upregulate expressions of genes coding for iNOS, TNFα, IL-6. In molecular investigations, blockade of RAP activity by TLR4 inhibitors proved TLR as a key receptor involving immunomodulation caused by RAP. RAP was also found to rapidly activate mitogen-activated protein kinases (MAPKs) related to TLR-4, which include phosphorylated extra-cellular signal-regulated kinase (ERK), protein kinase 38 (p38) and c-Jun N-terminal kinase (JNK), and induceNF-κB and Iκβ-α degradation [31].

The immunomodulatory effect of Astragalus membranous water extract was explored to be mediated through significant downregulation of the expression of mRNA of TLR4, NF-κb/p65, IRAK-1 associated with TLR4 signalling pathways [32].

Astragalus mongolicus on an investigation in mouse DCs actuated by IL-4, Granulocyte-macrophage colony-stimulating factor (GM-GSF) indicated that its treatment caused stimulation of DCs maturation through upregulation of TLR4 in SYBR-Green I (SG) and suppression of IκB-α. Also, AM treatment induced apoptosis in synergism to T cells and DCs [32].

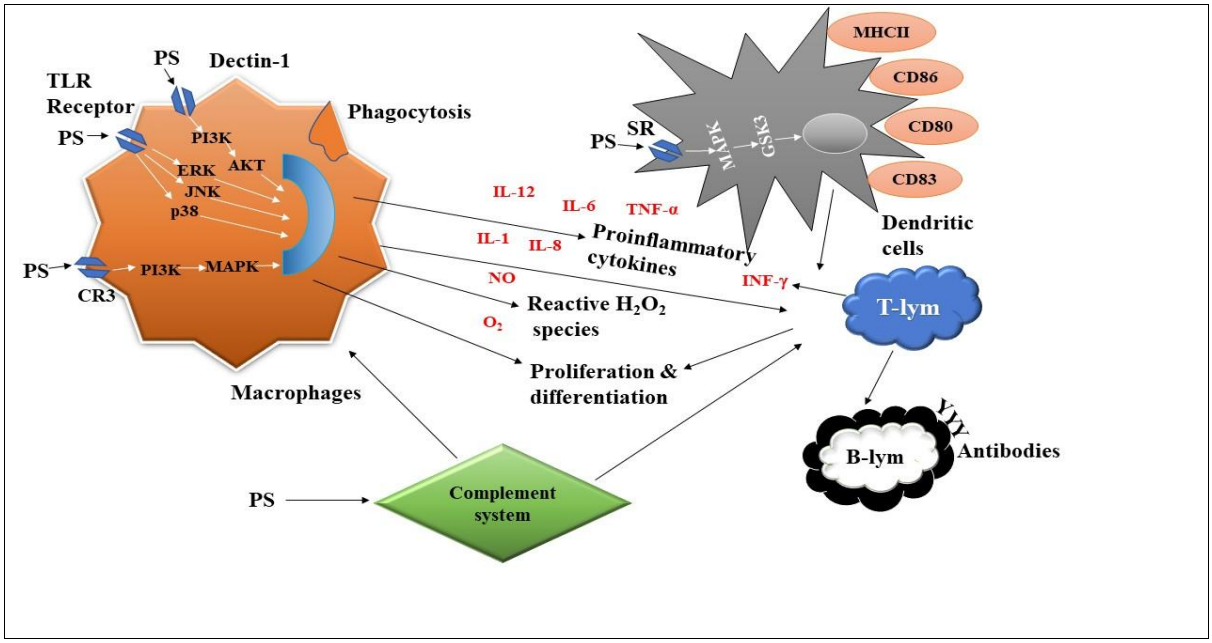

FIG. 2: ACTIVATION OF IMMUNE SYSTEM BY IMMUNOPOLYSACCHARIDES AFTER INTERACTION AND STIMULATION OF SEVERAL MOLECULAR/CELLULAR MECHANISMS. Akt, protein kinase B; CD, cluster of differentiation; CR3, complement receptor 3; ERK, extracellular signal-regulated kinase; GSK3, glycogen synthase kinase 3-; H_2O_2, hydrogen peroxide; IFN;JNK; IL; MAPK, p38; MHCII; NO; O_2, superoxide anion; TLR; PAK, p21-activated kinase; PI3K; SR, scavenger receptor; and TNF-α.

Several *in-vivo and in-vitro* studies have proven the immunomodulatory property of *Ganoderma atrum* (GA) polysaccharide [33]. Qiangyu *et al*., studied a Ganoderma polysaccharide termed PSG-1 obtained from *Ganoderma atrum*. During macrophage activation, PSG-1 interacted with TLR-4 receptor,

associated with stimulation of TNFα production. PSG-1 induced TNF-α secretion involved MAPKs/ phosphotidyl inositol triphosphate (Pi3K)/AKT/ NF-Kb signalling pathways playing vital role in immunomodulation [34]. Zhang *et al.*, established that interaction of PSG-1 with TLR-4 receptor is responsible for upregulation of TNFα and trigger of NF-κB and impediment of CT26 cells multiplication occurred through stimulation of peritoneal macrophages. The phagocytosis of macrophages and substantial rise in immune organ index were triggered by the PSG-1 administration. PSG-1 suppressed tumour progression in CT26 tumor bearing mice with boost in the action of NF-κB and TLR-4 and p38 MAPK phosphorylation in addition to deprivation of IKBα. This could be the classical example of build-up immunization followed by inhibition of tumor growth [35]. PSG-1 inhibited the growth of relocatable sarcoma S180 bearing mice. Mechanistic findings were significant increase in the level of cytokines and nitric oxide, macrophages mediated phagocytosis and transportation of p65 subunit of NF-κB from cytosol to nucleus with enhanced degradation of IKBα. PSG-1 enhanced the phosphorylation of extracellular signal kinases 1/2, p38 MAPK and JNK in macrophages in dose-dependent way. PSG-1 conclusively showed its antitumor activity by stimulating immune function through MAPK and TLR4 mediated NF-κBsignaling pathway [33].

The fungus *Agaricus blazei* Murill (ABM) is particularly rich in polysaccharides. The extract promoted the levels of IL-6 and IFN-ϒ but reduced the levels of IL-4, and the percentage of macrophages with phagocytosis after ABM extract treatment increased, and these immunomodulatory effects are of dose-dependent manners, both *in-vitro* and *in-vivo* [36]. In addition, a polysaccharide obtained from *Agaricus blazei* Murill was found to be a specific TLR2 agonist and had potent anti-tumour effects through the opposite of the suppressive function of Gr-1(+) CD11b(+) MDSCs, which also results in modification in immune system [37].

Dendritic Cells Activation and Maturation: Numerous treatments of cancer are available, but only some of them have attained clinical efficiency, and this accredited to the proficiency of cancer to evade immunity of host by renovating antigen-presenting cell *i.e.,* dendritic cells from intense triggers or stimulators to negative modulators immunity. To solve this difficulty, dendritic cell-based immunotherapy challenges can be used by changing the efficient characteristics of DCs. The maturation of DC can be stimulated by plant-derived polysaccharides (PdPs). They can abolish tumors when promoting T cells and *naïve T cells* adopt antigens that are tumorogenic. Various PdPs shows exceptional immunomodulating effects, and it can be used as stimulators for maturation of DCs by which they successfully trigger the antigen-specific immunity.

Even though FDA has been approved DCs as cellular bio-drugs in cancer immunotherapy. Some contests have restricted their achievement, which involves their weakened condition of maturation at the tumor microenvironment. *In-vitro* produced DCs are not similar to those *in-vivo* DCs because *in-vitro* DCs are present at a steady state and are compromised in their movement to lymph junction or nodes [39]. The maturity stage of dendritic cells can be determined by cell morphology and generation of particular cytokines and countenance of costimulatory molecules and Major Histo-compatibility Complex (MHC). In this way, immunostimulation or inactivity can be defined [40]. Consequently, maturation is a complicated process and tightly organized, which is necessary for the relocation of DCs into effector T cells which are present in lymphoid tissue. T-cells in lymphoid tissue dendritic cells provide a signal which is antigenic, intermediated by a co-stimulatory molecule, and signal MHC-peptide complex. Here, for extension and stimulation of specific cytotoxic CD8+ T cells, a co-stimulatory signal like IL-12 is required, which stimulates immune actions regarding T helper cells and their various types [41].

Immunostimulant polysaccharide moiety of *Panax ginseng* extract is termed Ginsan, which is composed of fructofuranoside and glucopyranoside [42]. Ginseng extract may serve as an innovative therapeutic vaccine adjuvant for tumors mediated through the promotion of DC and T cell activation. *In-vivo* administration of the extract from ginseng berries to tumor-bearing C57BL/6 mice caused stimulation of co-stimulatory molecules like IL-12, IL-6, and MHC class I and MHC class II, TNF-α in spleen DCs, CD86 up-regulation eventually leading

to DC activation. MHC class II and CD86 are the DC maturation markers. The polysaccharide stimulating the expression of these markers can be claimed as DC maturation inducer. TLR4 and MyD88 signalling pathways are crucial for DC activation caused by the extract. *In-vitro* treatment of the extracted bone marrow-derived DCs also induced upregulation of co-stimulatory molecules supporting *in-vivo* findings. Co-administration of Ovalbumin with the extract resulted in the inhibition of growth of B16-OVA tumor cell in the mice model. The synergistic effect of the extract could be attributed to its ability to cause increased proliferation of ovalbumin (OVA)-specific CD4 and CD8 T cells [43]. Ginsan, when tested in isolated form, showed significant stimulation of TNF-α, IL-12, IL-4, INF-α secretion by the DC in addition to elevated expression of MHC class II and CD86 DC surface markers. This proved DC maturation-inducing activity of Ginsan. Ginsan treatment also induced allogeneic CD4(+) T-lymphocyte production by DCs. Fractionation of crude American Ginseng polysaccharide extract revealed SPS-3 fraction to possess potent immunostimulation activity [44].

In the case of POL-P3b, a water-soluble polysaccharide isolated from *Portulaca oleracea* maturation of murine bone marrow-derived DCs was driven by TLR 4. Effect of POL-P3b was associated with induction of TNF-α, IL-12, and stimulation of surface maturation markers like MHC class II, CD80, CD83, and CD86. Thus POL-P3b was proclaimed to find its use as an add-on supplement for DC-based vaccines [45]. Ethyl acetate extract of *Portulaca oleracea* leaves was observed to ameliorate the immunosuppressive activity of cyclophosphamide in mice mediated through a significant rise in phagocytosis and proliferation of splenic lymphocytes.

Soluble β-glucan maitake D-fraction extracts obtained from the maitake mushroom *Grifola frondosa*, functions as a potent immunopotentiating agent, provoking innate and adaptive immune responses, thereby contributing to its antitumor activity *via* maturation of dendritic cells into more-immunostimulatory dendritic cells by stimulation [46]. Oral administration of a polysaccharide extract from Maitake mushroom is associated with both immunologically stimulatory and inhibitory measurable effects in peripheral blood [47].

Ascophyllan, a sulphated polysaccharide extracted from brown algae *Ascophyllum nodosum* exhibits a crucial role as therapeutic and preventive vaccine adjuvant in tumor treatment. It stimulates the splenic natural killer cells activation, macrophages, and spleen dendritic cells [48, 49]. *In-vivo* administration of ascophyllan to B16 tumor-bearing mice exhibited anti-tumor effect as a result of an increase in the number of DCs, induction of spleen DCs activation, and the subsequent activation and proliferation of antigen-specific T cells. In the mouse melanoma model ascophyllan stimulated DCs migration to lymph nodes draining tumor and spleen. In addition, ascophyllan induced DCs activation and secretion of IFN-γ, IL-6, IL-12, and TNF-α by DCs, resulting in Th1 immune response in a tumor mouse model. C-C chemokine receptor 7 (CCR7) is the marker for DCs migration, C-C motif ligand 19 (CCL19) and CCL21 are ligands for CCR7. Ascophyllan augmented secretion of MHC class I and II, CCR7, CCL19, and CCL21 molecules. Ascophyllan showcased synergism with ovalbumin exactly similar to ginseng extract wherein enhanced OVA-specific CD4 and CD8 T cell proliferation followed by their migration into the tumor cells results in tumor growth inhibition. Therefore in comparison to immunization with OVA alone combination of OVA with ascophyllan offers almost complete prevention of tumor growth on successive tumor induction challenge [50]. Zhang *et al*., substantiated, ascophyllan causes a significant rise in the formation of CD4 and CD8 T cells by the spleen and tumor-draining lymph nodes stimulating Th1 and Tc1 immune responses, Ag-specific T-cell immune responses. Consequently, it investigated whether ascophyllan in tumor-bearing mice can facilitate the production of pro-inflammatory cytokines through DCs. Treatment of ascophyllan has resulted in significant increases in the proportions of CD4 and CD8 T cells producing in the tumor and spleen drLN, whereas ascophyllan therapy has not increased the proportions of IL-4 or IL-17 producing CD4 and CD8 T cells. Thus, these findings show that in tumor-bearing mice, ascophyllan therapy stimulates Th1 and Tc1 responses, Ag-specific T-cell responses, and functions as an immunoenhancing adjuvant through DCs [52].

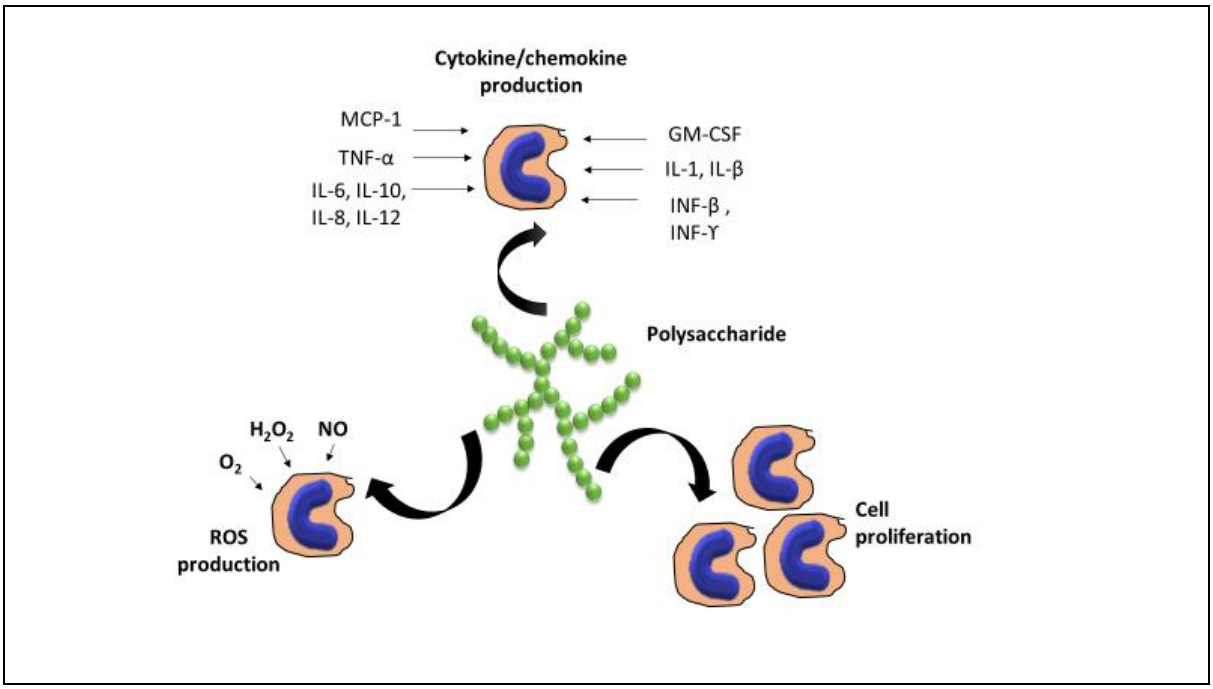

FIG. 3: INTERVENTION OF POLYSACCHARIDES IN MACROPHAGE RESPONSES. MACROPHAGES CAN FUNCTION AS ANTIGEN-PRESENTING CELLS AND INTERACT WITH T LYMPHOCYTES TO MODULATE THE ADAPTIVE IMMUNE RESPONSE IL; IFN; TNF-A; GM-CSF; MCP-1, MONOCYTE CHEMO ATTRACTANT PROTEIN-1; NO.

When mice were treated with the combination of ascophyllan and OVA, it was noted that the combined effect of ascophyllan and OVA triggered the formation of long-term memory immune function against OVA Ag and helped to protect against B16-OVA melanoma cells from liver invasion and metastasization. Such results indicate that ascophyllan may be a therapeutic adjuvant to the vaccine [53].

Rehmannia glutinosa belongs to the family of Scrophulariaceae. Its steamed roots have been used as traditional Chinese medicine (TCM) for thousands of years for various medical purposes. It is being used in formulas as a predominant herb to treat cancer. They are generally made up of 10:1:1:10(rehmannan SA) and 14:3:8:7(rehmannan SB) l-arabinose: d-galacturonic acid: d-rhamnose.[54] Analysis showed that RGP completely induced bone marrow-derived dendritic cell (BMDC) maturation by stimulating phenotype and function with the following fact:(1) BMDC morphology had more protrusions, rougher surface with induced expression of MHC II, CD80, CD40, CD86, and CD83. (2) RGP induced the functional maturation of BMDCs characterized by reducing the potential of phagocytosis and ACP activity, typically indicating the degree of BMDCs maturation. As they matured, RGP also increased the production of IL-12 and TNF- α of BMDCs, resulting in the activation of T cell reaction which leads to potentiation in the immunity [55].

At the very same time, Yee Huang investigated the immunological adjuvant effect of *Rehmannia glutinosa* polysaccharide liposome (RGPL) triggering protective and long-lasting immunity. As a marker of DC maturation, the upregulation of surface molecules such as MHC II, CD80 and CD86 could be considered. In lymph nodes, RGPL could provide optimal antigen exposure. They were not only able to stimulate DC maturation, but also to promote mature DC function *in-vitro*. Ultimately, the results have shown that RGPL can act as an effective controlled release vaccine adjuvant [56].

Cordycep smilitaris is one of the conventional herbal ingredients which contain a number of anticancer components of such as Cordlan. It includes arabinogalactan-type immunostimulants polysaccharide. It comprised of neutral sugars including L-arabinose, D-galactose, D-xylose, and L-rhamnose, and uronic acid as a D-galacturonic acid. A research reported that the heightened expressions of CD80, CD40, CD86, MHC-I and MHC-II molecules, IL-12, IL-1β, TNF-α and IFN-αβ increased z-allogenic T cell stimulation and reduced endocytosis indicated phenotypic maturation

of DCs by curdlan (polysaccharide). These findings suggest that cordlan uses TLR4 signaling pathways to induce DC maturation [57].

Cordyceps militaris water extract (WE) formed morphologically mature DCs and clusters and also triggered primarily functional maturation. It significantly increased the expression of CD54, CD40, CD86, CD80, and MHC class II in myeloid DC derived from murine bone marrow (BM). In addition, it is demonstrated that WE promote the cytotoxicity of DC-induced specific-cytotoxic T lymphocyte (CTL) that was pulsed with P815 tumor-lysate during the antigen presentation phase [58].

A novel polysaccharide extracted from *Cordyceps militaris* fruit bodies named as 'CP2-S' consisting mainly of glucose. CP2-S may induce the production of nitric oxide, interleukin-2 secretion, and macrophage interleukin-1β, and phagocytosis, *in-vitro*. Outcomes revealing that this water-soluble polysaccharide from the *Cordyceps militaris* fruit body has immunopotentiation activity [59].

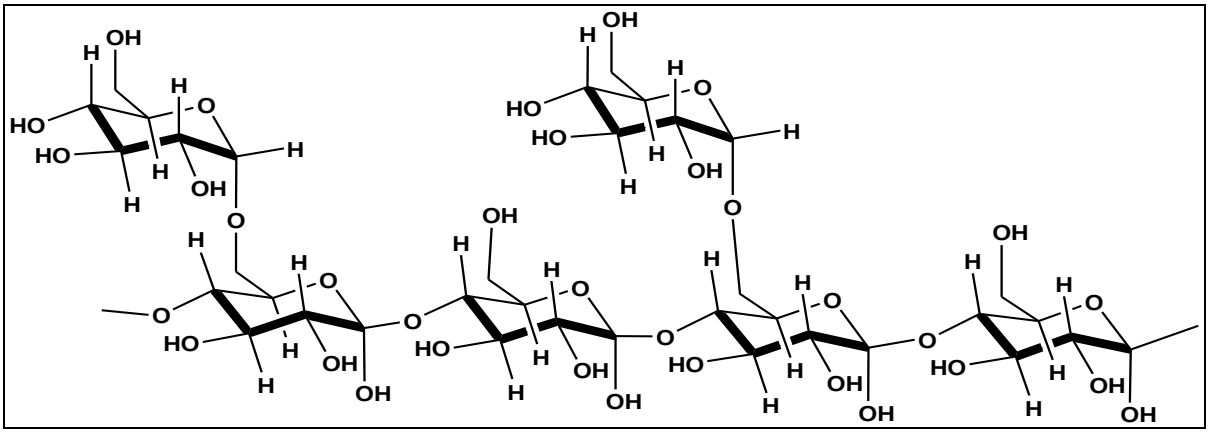

FIG. 4: REPEATING STRUCTURE OF *ASTRAGALUS* POLYSACCHARIDES

Protein-bound polysaccharide K (PSK) obtained from *Coriolus versicolor* (Fr.) Quél's cultured mycelium is used for colorectal cancer, gastric cancers, and small cell lung cancer as an anti-cancer agent, In Japan [60]. PSK also has been disclosed to overcome a cancer-bearing host's immunosuppressive condition and may be directly associated with DC maturation. Akamatsu *et al*., looked at the impact of PSK generated by IL-4 and GM-CSF on DCs from the bone marrow of SCID mice or BALB / c mice, *in-vitro*. Enhanced expression of antigen MHC class II, CD40, and CD80 molecules, improved production of IL-12 (p70), and declining the level of FITC-dextran uptake was found. The researchers noted that DCs maturation was stimulated by PSK [61]. Okuzawa *et al*., explored the interaction between PSK and supernatant of tumor culture (TSN) on DCs from peripheral blood mononuclear cells (PBMC) of healthy individuals exacerbated by IL-4 and GM-CSF [13]. The addition of PSK, however, diminished the inhibition of DC maturation induced by TSN. Tsujitani *et al*., investigated the connection between prognosis and DC infiltration in cancer sites in patients with stage III gastric cancer [62].

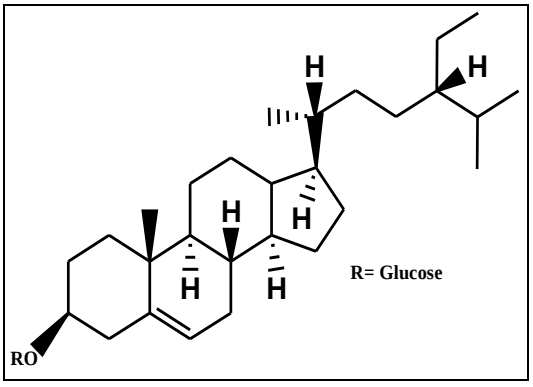

FIG. 5: *PORTULACA OLERACEA*

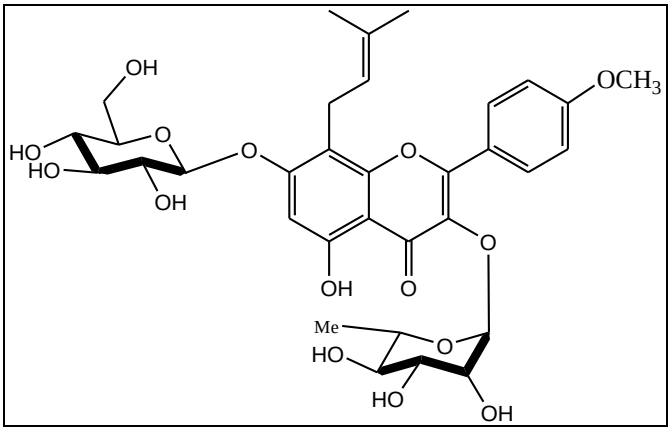

FIG. 6: *EPIMEDIUM KOREANUMNAKAI* POLYSACC-HARIDE

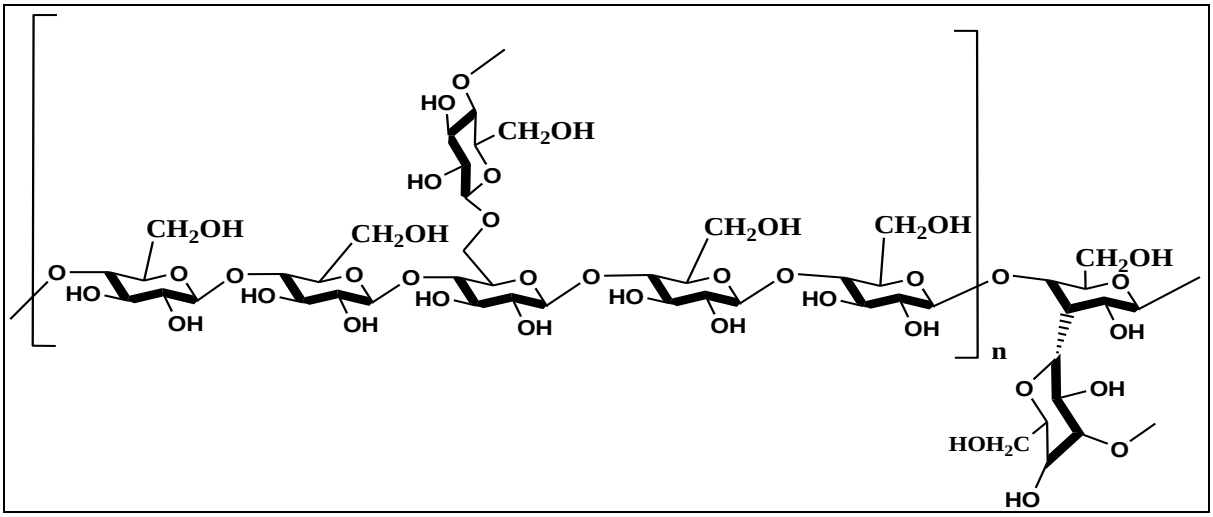

FIG. 7: β-GLUCAN PORTION OF POLYSACCHARIDE-K

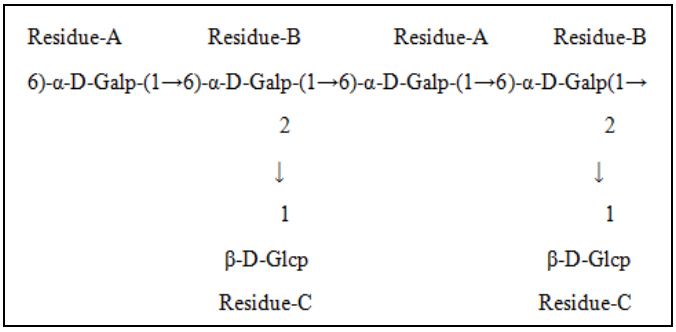

FIG. 8: STRUCTURE OF POP ISOLATED FROM THE FRUITING BODY OF *P. ASTREATUS*

Patients with 20 or less infiltrated DCs were reported to have a significantly better immunotherapy outcome with PSK. Masashi Kanazawa *et al*., investigated the influence of PSK on the DC maturation derived from CD14-positive cells derived from peripheral monocytes of human blood. It markedly increased the expression and amount of CD86-, CD80- and CD83-positive cells; reduced fluorescein isothiocyanate (FITC)–dextran intake; increased production of IL-12; improved allogeneic mixed lymphocyte reaction; induced antigen-specific cytotoxicity and lymphocyte reaction. Such data show that PSK facilitates the functional and phenotypic maturation of DC derived from mononuclear human CD14-positive cells [62]. There remains for study the clinical significance of combined use of PSK in DC vaccine therapy. An extract with hot water from *Trametes versicolor* mushroom contains Protein-bound Polysaccharide-K (PSK). Traditionally, it has been used for its anti-cancer and immuno-potentiating effects in Asian countries. Engel *et al*., discovered that it possible to activate TLR2 using BMDC through the treatment of PSK, *in-vitro*. TLR2 is strongly reflected on dendritic cells (DC), and so that the present research has been conducted to assess the activity of PSK on DC activation and the potential of using PSK as an adjuvant vaccine. It has been shown that PSK stimulates DC maturation according to a dose-dependent rise in expression of CD86, CD80, CD40, and MHCII. The production of multiple DC inflammatory cytokines, including IL-12, IL-6, and TNF-α on both mRNA and protein levels, is stimulated by PSK. *In-vivo* experimentation using PSK to the OVAp323-339 vaccine reveals that PSK as an adjuvant result in increased exhausting lymph nodes with a larger number of activated DC and induces the proliferation of OVA-specific T cells and multispecific T cells that produce multiple cytokines like TNF-α, IL-2, and IFN-α [63].

Epimedium koreanum Nakai has been reported for over a thousand years as a tonic herbal in China and has the ability to potentiate the immune system of the body as per the traditional Chinese medicine principle. The experimental findings of Cheng-cheng Wang *et al*., proposed that *Epimedium koreanum* Nakai polysaccharides (EPS) was made up of mannose (Man), galactose (Gal), rhamnose (Rha), galactosamine (GalN), glucuronic acid (GlcUA), glucose (Glc), fructose (Fuc) and arabinose (Ara). It significantly reduces the number of immunomodulatory cytokines and trigger CD4 T-cell differentiation could promote maturation and Ag presentation function of DCs. It may also prevent the growth of tumors in LLC-bearing mice by monitoring the function of the host immune function [64].

Cytokines Signalling Pathway: Cytokines are key signalling inflammation molecules and the immune function. In reaction to a modified homeostatic environment, cytokines are produced and participate in various cellular processes. They are typically categorized into two classes: (1) pro-inflammatory cytokines including IL-1β, IL-15, IL-6, IL-23, IL-17, and TNF-αand anti-inflammatory cytokines such as IL-10, IL-4, IL-13, tumor growth factor-β (TGF), and IFN-α. [65] TNF-α is regarded as a high concentration anti-tumorigenic factor; even so, at moderate levels, TNF-α may induce metastasis, angiogenesis, and lead to DNA damage which is shown in animal models [66]. TNF-α is often produced in small quantities by cancerous cells and macrophages [67]. Alarming cytokines secreted by different immune cells are IL-1 and TNF-α.

A water-soluble polysaccharide, *Boletus edulis* polysaccharide (BEP) isolated by Dong Wang *et al*., from the fruiting bodies of *Boletus edulis* Bull which is one of China's most famous delightful mushrooms, consisted of 1.6:2.9:3.2:1.3 molar ratios of Arabinose, Glucose, Galactose and Rhamnose [68].

A backbone composed of (1→2,6)-linked — d-galactopyranosyl, (1→6)- linked- d- galactopyranosyl, (1→6)- linked - d-glucopyranosyl, (1→3)-linked-d-rhamnopyranosyl residues that ended with a single terminal (1→)-linked-l-arabinofuranosyl residue at the O-2 position of (1→2,6)-linked-d-galactopyranosyl residue al-linked to O-2 position. In addition, BEP may exponentially induce splenocyte proliferation, increase NK cell and CTL spleen activity, enhance spleen and thymus indices and facilitate cytokine IL-2 and TNF- α secretion in Rencatumor-bearing mice [68].

Jingyue Yang *et al*., evaluated the various activities like antitumor and immunoregulatory activity of corn silk polysaccharides (CSP) obtained from *Zea mays* L. in a model of H22 tumor-bearing mice. Results also indicated an improvement in thymus index, peripheral WBC count and H22 tumor-bearing spleen index. Additionally, administration of CSP in mice bearing H22 tumor could substantially increase serum production of IL-6, IL-2 and TNF-α. In brief, the whole investigational study noted that CSP could increase immunity in H22 tumor-bearing mice to strengthen antitumor activity, and CSP appears to be an effective and safe agent for hepatocellular carcinoma treatment [69].

Licorice polysaccharides exhibited immuno-modulatory activities and significantly suppressed tumor growth by affecting the production of various cytokines by increasing IL 2, IL 6, IL 7 levels and decreasing TNFα levels. Chinese licorice, (*Glycyrrhiza uralensis* Fisch.) is one of the commonly prescribed herbs in Traditional Chinese Medicine (TCM). Gancao, as commonly known in China, is associated with immune-modulating and anti-tumor potential by increasing the expression of IL-7 [7].

Chaenomeles speciosa (Sweet) belongs to the family Nakai (Rosaceae) is a very well-known Chinese food and is widely used in traditional Chinese medicine as a dried fruit [94]. In antioxidant and anti-inflammatory activities, polysaccharides from *C. speciosa* were observed to be involved [70-71].

Polysaccharides from *Chaenomeles speciosa* dried fruits comprised of galactose (Gal), glucose (Glc), arabinose (Ara) and rhamnose (Rha) polysaccharide with a relative molar ratio of 1.3:4.6:0.5:0.8. Splenocyte proliferation induced by concanavalin Aand lipopolysaccharide (LPS) and peritoneal macrophage phagocytosis were enhanced by administration of CSP. In addition, treatment of CSP enhanced delayed-type hypersensitivity (DTH) and serum IL-2, TNF- α and IFN-α secretion. The overall results suggested the strong connection of potent immunostimulatory activity of CSP to its antitumor effect [72].

Another reported study found that the polysaccharide obtained from *Solanum nigrum* Linn. had significant anti-tumor activity by boosting the T-lymphocyte subgroup ratio of CD4+/CD8+ [73]. A fraction of semi-purified polysaccharide from *S. nigrum* L., SN-ppF3 has shown in recent *in-vitro* finding its ability to activate RAW 264.7 macrophage cell line. The triggered macrophage produced cytokines and NO and had an increased phagocytic activity [74]. These characteristics showed the potential of the cells to defeat diseases and to induce other immune reactions. Increased infiltration of NK cells, T cells, and macrophages was found in the treated mice's

tumor tissues, which partly explained the higher apoptosis tumor cells detected in the treated mice. In addition, IL-4, TNF-α, and IFN-α levels were increased, whereas IL-6 levels were substantially reduced in the treated mice serum. These outcomes proposed that the mechanisms of tumor suppression recorded in mice treated with SN-ppF3 were much more likely due to improving the immune system of the host [75]. *In-vitro* and *in-vivo* the effects of crude polysaccharides separated from *Solanum nigrum* Linn. (SNL-P) on cervical cancer in U14 investigated by Jian Li *et al*., led to a significant increase in IFN-g and a noteworthy reduction in IL-4, these data indicate that SNL-P had effective antitumor activity and that SNL-P could show antitumor activity by activating various immune responses in the host rather than directly targeting cancer cells on U14 cervical cancer mice. Thus, as an immuno-modulator and an anticancer agent, SNL-P could be used. Hai Chen and Xiaodong Qi investigated the effect of *Solanum nigrum* Linne polysaccharides and their association with the immune function of tumor-bearing organisms. Varying doses of *Solanum nigrum* polysaccharides Linne significantly negatively affected the growth of H22 solid tumors in the mouse, improved tumor-bearing mice's survival time, improved lymphocyte proliferation, increased IL-2 levels and enhanced lymphocyte-related calcium ion concentration associated with the body's cellular immune function [76]. F. Razali *et al*., analysed modulating effects of polysaccharide from *S. nigrum* on RAW 264.7 murine macrophage cells as macrophages play a crucial role in stimulating both innate and adaptive immune reactions. It triggered macrophage, TNF-α and IFN-C activate the macrophage, which further begins to produce pro-inflammatory cytokines such as IL-6, IL-1 and IL-23 [76]. One of the fractions *i.e.* α8 SN-ppF3, substantially driven phagocytosis activity and induced TNF-α and IL-6 production. This study concluded that macrophages could be activated classically by fraction SN-ppF3. The manner in which polysaccharides from *S. nigrum* is maybe induction of macrophage can prevent the growth of tumor [77].

Macrophage Activation: Macrophages are phylogenetically preserved cells and, together with neutrophils, represent the first line of host defense after the epithelial barrier. Moreover, macrophages can act as antigen-presenting cells and interact to modulate the adaptive immune reaction with T lymphocytes [78]. However, it is believed that the basic mechanism of the immunoenhancing, bacteri-cidal, anti-tumor and other therapeutic effects of botanical polysaccharides occurs via macrophage stimulation and complement system modulation [79]. particularly, Polysaccharides are said to increase cytotoxic activity of macrophage against tumor cells and microorganisms, enable phagocytic activity, increase production of reactive oxygen species (ROS) and nitric oxide (NO), and increase chemokine and cytokine secretion including TNF-a, IL-1h, IL-8, IL-6, IL-12, IFN-h2, and IFN-g. Activation of macrophage through polysaccharides is assumed to be facilitated mainly by the recognition by particular receptors of polysaccharide polymers. Such receptors are recognized as molecules for pattern recognition and can recognize foreign ligands during the initial immune response phases [80]. In particular, macrophages could bind plant polysaccharides and/or glycoproteins through TLR4, CD14, complement receptor 3 (CR3; Mac-1 or integrin Mh2, also known as CD11b / CD18), dectin-1, scavenger receptor and mannose receptor [81]. These receptor activation leads to intracellular signaling cascades, leading to transcriptional activation and pro-inflammatory cytokine production [82].

Haibin Tong illustrated the effects of poly-saccharides from the roots of *Sanguisorba officinalis* Linne (SOPs) on macrophage activation and induced molecular mechanism. SOPs increased macrophage phagocytosis to aseptic neutral red solution and accelerated secretion of TNF-α and NO. When macrophages were exposed to SOPs, the amounts of TNF-α and iNOS transcript increased massively at the mRNA level. In the meantime, macrophage stimulation by SOPs mediated p65 phosphorylation at serine 536 and a marked decline in IkB expression. This study showed that SOPs demonstrated major properties of macrophage activation *via* the NF-kB signaling pathway, suggesting that SOPs could be considered a novel immune enhancer for activating the immune responses [83, 84].

The macrophage activation and anti-tumor mechanism of alkali-extracted water-soluble polysaccharide isolated from the *Pleurotus ostreatus* fruiting bodies was illustrated by

FanliKong et al. WPOP-N1 was found to improve the phagocytic capacity of *in-vitro* peritoneal macrophages. In addition, when the peritoneal macrophages were exposed to WPOP-N1, the secretion of TNF-α and NO and the amount of TNF-α and iNOS transcript significantly increased. These results showed that WPOP-N1 may activate macrophages via the NF-B signaling pathway, and its immunostimulating property can achieve by the anti-tumor activity of WPOP-N1 [85-87].

The major polysaccharide fraction PS-F2 from *Ganoderma fungusis* made up of D-galactose, D-mannose, and D-glucose could stimulate macrophage activation and safeguard the mice against Listeria monocytogenes infection [88]. An extracellular heteropolysaccharide fraction *i.e.* PS-F2, from the submerged mycelia culture of D-galactose, D-mannose, and D-glucoseformosanum induces macrophages through the involvement of multiple pattern-recognition receptors such as CR3, Dectin-1 and TLR4, leading to an increase in the activation of JNK, Syk, p38, ERK, and NK-α but also TNF-α production [89].

Many researchers demonstrated two opposing views on *Acanthopanax* senticosus's immunomodulatory effect that is stimulation [90] and suppression of immune responses. It inhibits both prophylactic and therapeutic tumor metastasis, and its antitumor effect is correlated with macrophage and NK cell activation [91]. EN-3, the crude polysaccharide fraction of ES, has been shown to have activities that could improve humoral and cellular immune function to bovine serum albumin or ovalbumin [92]. ES has long been recommended as an adaptive for the use of complex treatment of cardiovascular and nervous disease and as a general restorative and tonic agent due to immune-suppressive or-stimulating functions rather than immune-suppressive response [93].

Macrophage cells activated by crude Modified Aloe Polysaccharide (MAP) and triggered fibroblast growth [94]. Acemannan is a combination of polymer chains of β-(1, 4)-linked acetylated galactomannan with various lengths. It is the most characterized immunomodulatory polysaccharide in Processed Aloe Gel (PAG) [95]. It has been shown that acemannan has antiviral and antitumor activity [96]. Aloe gels comprise of polysaccharides that are immunomodulatory. Some specially prepared extracts of *A. vera* have numerous biological functions such as anti-cancer, anti-inflammation, antioxidant, anti-diabetes, and activation of macrophage [97]. Acemannan has immunomodulatory activities are mainly facilitated by activation of specialist presenting antigen (APC) cells like macrophages and dendritic cells. Acemannan activated macrophages and upregulated their candidicidal activity to produce inflammatory cytokines such as IL-6. Zhan Hai Yu investigated the effects of polysaccharides from *A. vera* on various *in-vivo* variables of the activity of innate immunity and antioxidant enzymes in oral ulcer animals and suppressed oxidative injury in oral ulcer animals [98]. Moreover, acemannan induced immature dendritic cells to mature phenotypically and functionally and also activated IL-1, TNF-α, and NO [96].

Effects of higher plant polysaccharides like *Anadenanthera colubrina* (Fabaceae), *Angelica gigas* Nakai (Apiaceae), *Arnica montana* (Asteraceae), *Astragalus membranaceus* (Fabaceae), *Bupleurum falcatum* L. (Apiaceae), *Carthamus tinctorius* (Asteraceae), *Celosia argentea* (Amaranthaceae), *Curcuma zedoaria* (Zingiberaceae), *Dioscorea batatas* (Dioscoreaceae), *Dipsacus asperoides* (Dipsacaceae), *Echinacea purpurea* (Asteraceae), *Glycine max* (Fabaceae), *Panax quinquefolius* (Araliaceae), *Perilla frutescens* var. crispa (Lamiaceae), *Pinus parviflora* (Pinaceae), *Plantago ovata* (Plantaginaceae), *Silene vulgaris* (Caryophyllaceae) and *Tripterygium wilfordii* (Celastraceae) shows increase in phagocytosis. Additionally, it activates iNOS, NO, ROS, IL-1, IL-6, IL-12, TNF-a, and IL-10 on murine peritoneal macrophages [82].

Miscellaneous Pathways: Phosphoinositide-3-kinase (pi3k) receives upstream signals from G-protein-coupled receptors (GPCR) and tyrosine kinases receptors [99]. The immune recognition of tumor cells was reported to involve the PI3K / Akt pathway. For example, In NK cells, after interaction between NKG2D and activating ligands, the NKG2D-associated adapter protein DAP10 undergoes Tyr phosphorylation in its cytoplasmic tail. This allows DAP10 to anchor either the p85 subunit of PI3K or the Grb2 adapter, leading respectively to activation of PKB/AKT or MAP

kinase signals. These signaling cascades allow NK cells to produce cytolytic activity and chemokine [100]. In GM-CSF-induced differentiation of monocyte DCs, the PI3K/Akt-dependent mTOR pathway is reported to be crucial [101]. On the other hand, as the PI3K signaling pathway is crucial for antitumor immunity, it could be dangerous also. Therefore, therapeutic inhibition of PI3Ks should be as selective as possible for targeting cancer cells without having an inhibitory effect on the immune system to minimize deleterious effects [102].

Activation of MAPK involves cell growth, differentiation, survival, and reactions to immune and stress [103]. For example, the conclusions assisted in clarifying the *Russula griseo carnosa's* PRG1-1 polysaccharide has the ability to activate macrophages through the NF-kB MAPK pathway, leading to R polysaccharide's immune-modulatory properties [104].

The complement system a crucial factor in host defense against infection and plays important elements in many other biological systems. It includes complex immune handling and immune response generation [105]. For example, RR1, a *Tinospora cordifolia* polysaccharide, has triggered the alternative pathway (C3a) of complement activation, and there's been very little effect on the classical pathway (C4a). This observation is similar to many documents of other polysaccharides activating complements. C3a and C4a are bioactive cleavage products produced from plasma subsystems C3 and C4 during the activation cascade in alternative and classical pathways that are rapidly converted into less active forms of C3a des Arg and C4a des Arg and are involved in cellular immune response mediation [105].

CONCLUSION: Since cancer is a multi-factorial disease with very complicated growth and genesis connected with evolving multidrug resistance, extensive study has resulted in the growth of new cancer agents that could possibly operate on different cancer signaling pathways. A number of chemopreventive cancer agents are being tested in clinical trials. However, most of these interesting medicines are highly poisonous or not suitable for continuous administration. Natural product therapy is a fast-growing field from which polysaccharides can provide a unique source for chemopreventive or therapeutic agents due to its prospective safety profiles. Numerous entities have earlier identified anticancer and immune therapies for natural products.

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