The Journal of Phytopharmacology 2015; 4(6): 307-310
Online at: www.phytopharmajournal.com

Review Article

ISSN 2230-480X
JPHYTO 2015; 4(6): 307-310
November- December

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Pharmacological potential of naturally occurring non-starch polysaccharides (NSP)

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ABSTRACT

Since ancient times, plants have been serving as a promising source of medicines and in recent times, extensive research has been made to isolate, characterize and screen a number of phytoconstituents/secondary plant metabolites for their pharmacological activities and safety in various disease models – both *in vitro* and *in vivo*. One such category of phytoconstituents is "polysaccharides". These are found in different parts of the plant such as roots, leaves, stem and leaves and are extracted maximally in polar solvent – for eg. water extract of the afore mentioned plant parts contain the crude polysaccharide fraction. These are non-starch type in nature and can be a mixture of more than one type of polysaccharide too. In this review, an attempt has been made to discuss such therapeutically active plant polysaccharides in terms of their wide pharmacologically active profile along with methods to isolate and characterize them in brief.

Keywords: Biological Response Modifiers (BRMs), Pattern Recognition Receptors (PRRs), Immunomodulatory polysaccharides, Toll-like receptors (TLRs).

INTRODUCTION

Polysaccharides are chemically carbohydrates comprising of monosaccharide units. Well known polysaccharides include starch, glycogen, cellulose, pectin and chitin; however, apart from these, there are number of non-starch, heteropolysaccharides that occur in nature viz. bacteria, fungi, algae and photosynthetic plants – either in the cytoplasm or cell wall at cellular level, possessing significant pharmacological activities. These heteropolysaccharides consist of two or more different monosaccharide units linked to each other in a definite pattern – either in linear or branched fashion. Plant polysaccharides are however rich in uronic acid content. Since these macromolecules are polydisperse in nature, they can be characterized by their average molecular weight (in Daltons or Kilo Daltons), number of monosaccharide units (degree of polymerization) and types of monosaccharides present – all of which have an effect on their pharmacological properties; for eg. Larger polysaccharides are known to have better pharmacological activity since they collide better with the target receptors/proteins to elicit a cellular response [1]. Since the current available treatment for certain diseases is associated with drawbacks such as high cost, multiple dose regimen, undesired side effects and resistance at times; researchers are inspired to develop biodegradable, cheap, patient compatible and devoid of any side effects plant derived molecules/products and plant polysaccharides are one of them.

General procedure for isolation of NSP [2]

A generalized method of isolation and purification of plant polysaccharides reported by many is as follows:

Step1 – Raw materials are shadow dried and powdered.

Step2 – Powdered material is extracted in hot water (prior methanol treatment can be made to remove pigments, tannins and reducing sugars if required).

Step3 – The water extract filtered and concentrated under vacuum.

Step4 – This concentrated extract precipitated with 70-80% methanol to obtain crude polysaccharides.

Step5 – Further, for isolating individual fractions, the crude mixture can be subjected to gel permeation or affinity chromatography along with appropriate standards for molecular weight determination.

Methods to determine purity of NSP [2]

Crude polysaccharides are probable to contain other substances such as proteins (quantified by Lowry method), uronic acid (quantified by Carbazole method), hexosamine (quantified by Morgan-Elson assay) and sialic acid (quantified by Warren assay). Total carbohydrate content can be determined using Phenol Sulphuric Acid Assay method.

Characterization of NSP

Various analytical methods to determine structure and monosaccharide units in a polysaccharide reported earlier include, methylation analysis, β-elimination, partial acid hydrolysis, paper chromatography, gas liquid chromatography, mass spectrometry, polarimetry, circular dichroism adsorption, ^{1}H NMR, ^{13}C NMR, affinity chromatography and antigen-antibody complex formation [2]. However, apart from these, IR spectroscopy, HPLC coupled with UV or fluorescence or ELSD detector and HPTLC have also been used to characterize various pharmacologically active natural polysaccharides [3-5].

Pharmacological activities of NSP

As immunomodulators

Naturally occurring polysaccharides are also referred to as “biological response modifiers” (BRMs). These are substances which are recognised as non-self molecules, via targets of Pattern Recognition Receptors (PRRs) superfamily of receptors, thereby triggering an immune response as well as various pharmacological actions such as anti-tumour,anti-microbial, anti-viral and anti-parasitic to name a few [1]. Mechanism through which they act as BRMs is represented in Fig. 1. Polysaccharides such as glucans, pectins, heteroglycans, glucomannans, fucoidans, galactomannans, arabinogalactans and mixed types have been reported for their immunomodulatory potential in rodents when given orally; however, via this route they are highly affected by gut microbiota in terms of their hydrolysis, metabolism and hence pharmacological activities locally and/or systemically. Additionally, studies indicate that such polysaccharides are well tolerated and found to be safe in both animals and humans. A detailed review carried out by Ramberg *et al*., describes such dietary immunomodulatory polysaccharides along with their source, effective dose, mechanism of actions and clinical data [6]. Moreover, β-glucans from fungi have also been reported for their immunomodulatory potential. They activate both innate and adaptive immunity; mechanism is described in Fig. 2. Possible mechanisms through which they and probably other types of polysaccharides act (via types of PRRs) is described in Table 1. Moreover, medicinal importance of these glucans have also been reported in treatment of cancer, infectious diseases, diabetes, hypercholesterolemia, blood pressure and wound healing; therapeutic activity depending again on their molecular weight, solubility, branching and route of administration [7]. Additionally, several other reports on immunomodulatory potential of plant polysaccharides in various *in vitro* and *in vivo* models are found in the literature (References not quoted).

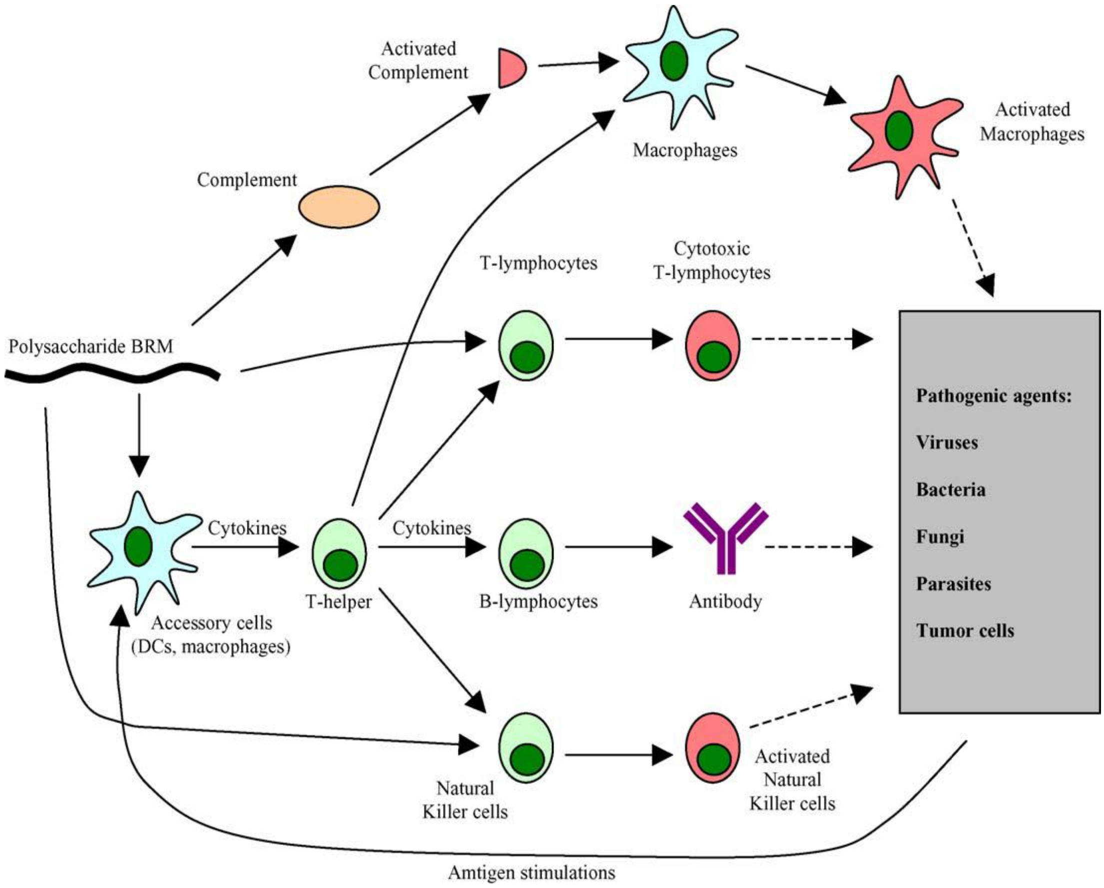

Figure 1: Activation of immune cells by polysaccharides [1]

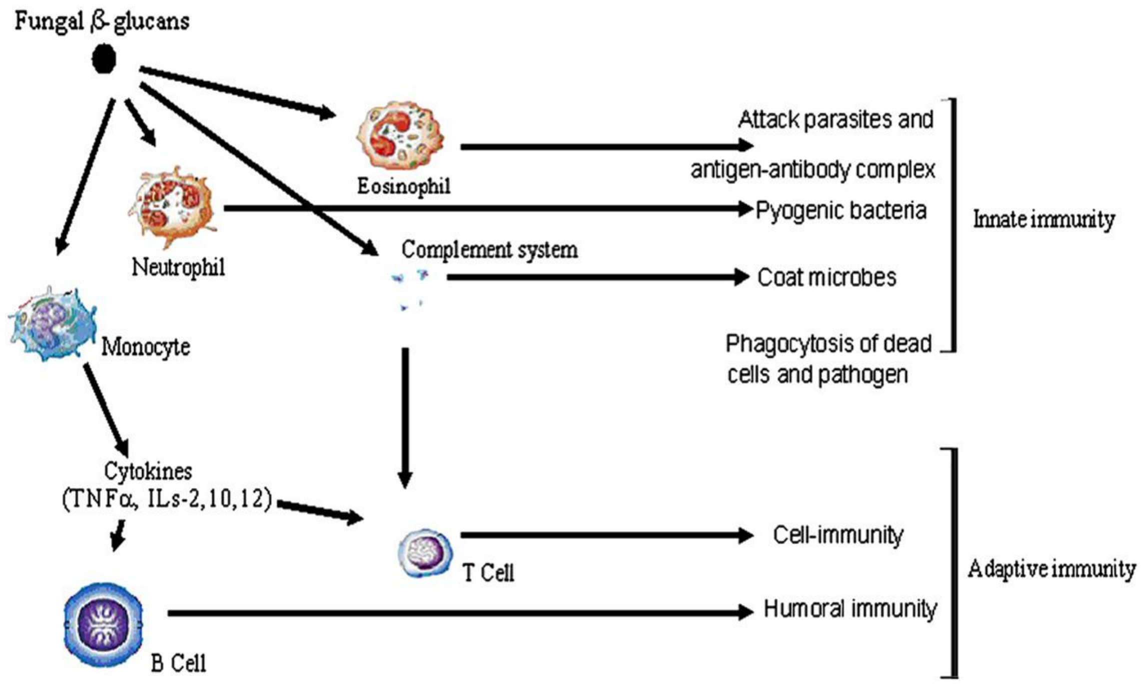

Figure 2: Immunostimulation by fungal β-glucans [7]

As antitumor agents

A detailed review by Kwong *et al* describes many traditional chinese plant polysachharides for their immunomodulatory potential via the same target cells as described in Table 1. In addition to this property, they are also reported to stimulate production of antitumor cytokines such as interferon-γ, TNF-α and colony stimulating factors. They also possess anti-complementary and tumoricidal properties. Hence, devoid of any side effects and being promising immunostimulatory molecules, these can be very well used in patients suffering from HIV or cancer when given either alone or in combination with currently available treatment options [2]. To quote a few, other such traditional plant polysaccharides having anticancer properties are also reported [5,8].

As anti-diabetic agents

Numerous plant polysaccharides have been reported so far for their anti-diabetic potential in various animal models of diabetes mellitus via oral and systemic route. Few such anti-diabetic polysaccharides are: Crude polysaccharides and water extract from the tuberous root of *Liriope spicata* (Thund.) var. prolifera. demonstrated a significant anti-hyperglycemic and antihypercholesterolemic activities in streptozotocin induced diabetic mice by improving glucose tolerance and insulin resistance, decreasing fasting blood glucose, total cholesterol and triglycerides [9]; Low molecular weight galactomannan from fenugreek (*Trigonella foenum-graecum* L.) seeds showed hypoglycemic activity in alloxan induced diabetic mice (acute and sub-acute studies were performed). The probable mechanism of action reported for such effect are increased glucose uptake in hepatocytes and adipocytes via GLUT4 and/or by inhibition of pro-inflammatory cytokines [10]; A sulphated polysaccharide "fucoidan" isolated from a brown seaweed *Saccharina japonica* significantly improved glucose tolerance, insulin resistance and lipid profile in alloxan induced diabetic rats – the probable mechanisms conferred were increased insulin secretion and thereby improved insulin sensitivity since insulin levels elevated significantly post the polysaccharide treatment against the disease control [11]; Two polysaccharides isolated from the roots of *Psacaliumdecompositum* exhibited a significant hypoglycemic activity in normal mice in an acute study [12]; Polysaccharides isolated from Lotus plumule demonstrated hypoglycemic and hypolipidemic activities in non-obese female mice which may be attributed to an increased islet cell mass and thereby increased insulin levels post polysaccharide treatment observed in the study. Additionally, polysaccharides F1 and F2 isolated from the lotus plumulehave been reported to reduce release of pro-inflammatory cytokine significantly from mouse splenocytes and m-RNA expression of TLR-2 and TLR-4 in LPS stimulated splenocytes – suggesting their strong protective role against pancreatic injury mediated complications seen in type 1 diabetes [13] and crude polysaccharides isolated from the endodermis of *Citrus maxima* significantly inhibited α-glucosidase and α-amylase enzymes – suggesting possible potential of plant polysaccharides in diabetes via oral route [14]. Certain water soluble non-starch polysaccharides such as oats, glucans and guar gum, because of their ability to increase viscosity in the GIT, have been reported to decrease glucose absorption, gastric emptying rate and thereby reducing post-prandial rise in blood sugar as well as insulin levels in both healthy and diabetic subjects. Hence, by modulating GI function and reducing stimulation of entero-insular axis to a greater level they tend to alter lipid and carbohydrate metabolism [15]. However, concentration, molecular weight, degree of hydration and physical form are key factors in determining this effect [16].

In Rasayana therapy [17]

In Ayurveda, "Rasayana" means – path of elixir: *Ras* meaning elixir and *ayana* meaning path or home. Herbs of rasayana category act via modulating neuro-endocrino-immunological system to render physiological homeostasis to the body against various stresses. Polysaccharides of such rasayana herbs have been reported for their immunomodulatory, anti-inflammatory, complement activation, antithrombotic, anti-diabetic, anti-infective, antitumor, anti-oxidant and wound healing properties. Types of polysaccharides having such activities are usually mannans, pectins, arabinogalactans, fructans and xylans. Moreover, reports on role of mannan, glucan and fructan rich rasayana herbs in improving reproductive functionality have also been found.

Challenges associated with NSP therapy [1, 7]

Inspite of their wide pharmacological utility, biodegradable nature and no major side effect profile, following aspects related to polysaccharide therapy are to be explored yet:

(a) Detailed mechanism of action/s via receptor type/s involved.

(b) Defined structure-activity relationship (SAR) and receptor binding information for different types of pharmacologically active polysaccharides reported so far.

Translating pre-clinical findings to clinical stage to make better and cost-effective treatment options available.

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HOW TO CITE THIS ARTICLE
Dave DT, Shah GB. Pharmacological potential of naturally occurring non-starch polysaccharides (NSP). The Journal of Phytopharmacology 2015;4(6):307-310.