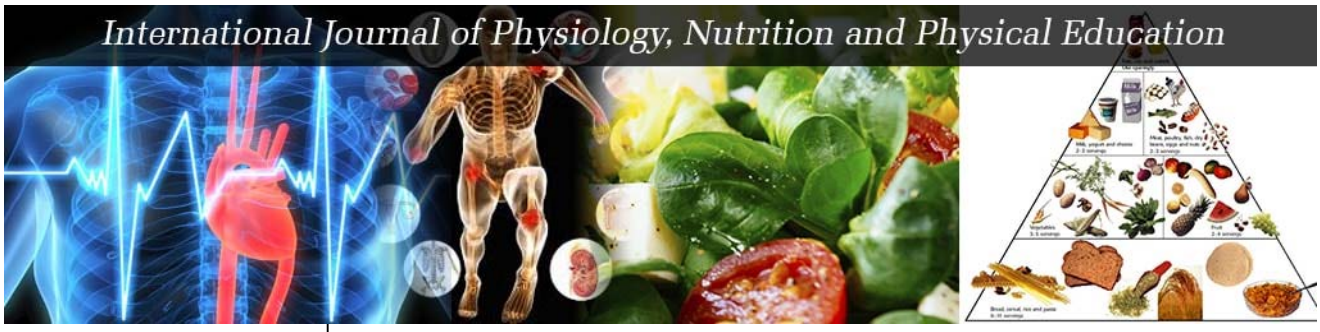

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Dr. ArnabKanti Ojha
Department of Chemistry
Mahishadal Girls' College, West Bengal, India.

Correspondence
Dr. ArnabKanti Ojha
Department of Chemistry
Mahishadal Girls' College, West Bengal, India.

Mushroom polysaccharide: A review on structural and immunological study

Dr. ArnabKanti Ojha

Abstract
The number of mushrooms on earth is estimated at 140,000, yet maybe only 10% (approximately 14,000 named species) are known. Mushrooms comprise a vast and yet largely untapped source of powerful new pharmaceutical products. In particular, and most importantly for modern medicine, they represent an unlimited source of polysaccharides with antitumor and immunostimulating properties. Many, Basidiomycetes mushrooms (if not all) contain biologically active polysaccharides in fruit bodies, cultured mycelium, culture broth. Data on mushroom polysaccharides have been collected from 651 species and 7 infra specific texa from 182 genera of higher Hetero-and Homo Basidiomycetes. These polysaccharides are of different chemical composition, with most belonging to the group of β-glucans; these have β-(1,3) linkages in the main chain of the glucan and additional β-(1,6) branch points that are needed for their antitumor action. High molecular weight glucans appear to be more effective than those of low molecular weight. Chemical modification is often carried out to improve the antitumor activity of polysaccharides and their clinical qualities (mostly water solubility). Most of the clinical evidence for antitumor activity comes from the commercial polysaccharides lentinan, PSK (krestin), and Schizophyllan, but polysaccharides of some other promising medicinal mushrooms species also show good results. Polysaccharides from mushrooms do not attack cancer cells directly, but produce their antitumor effects by activating different immune responses in the host. The information presented in this review is helpful in exploring and understanding the different mushroom polysaccharides and their biological activities.

Keywords: Medicinal mushrooms, mushroom polysaccharides, higher Basidiomycetes, immune modulating effect, immunopotentiators, antitumor substances

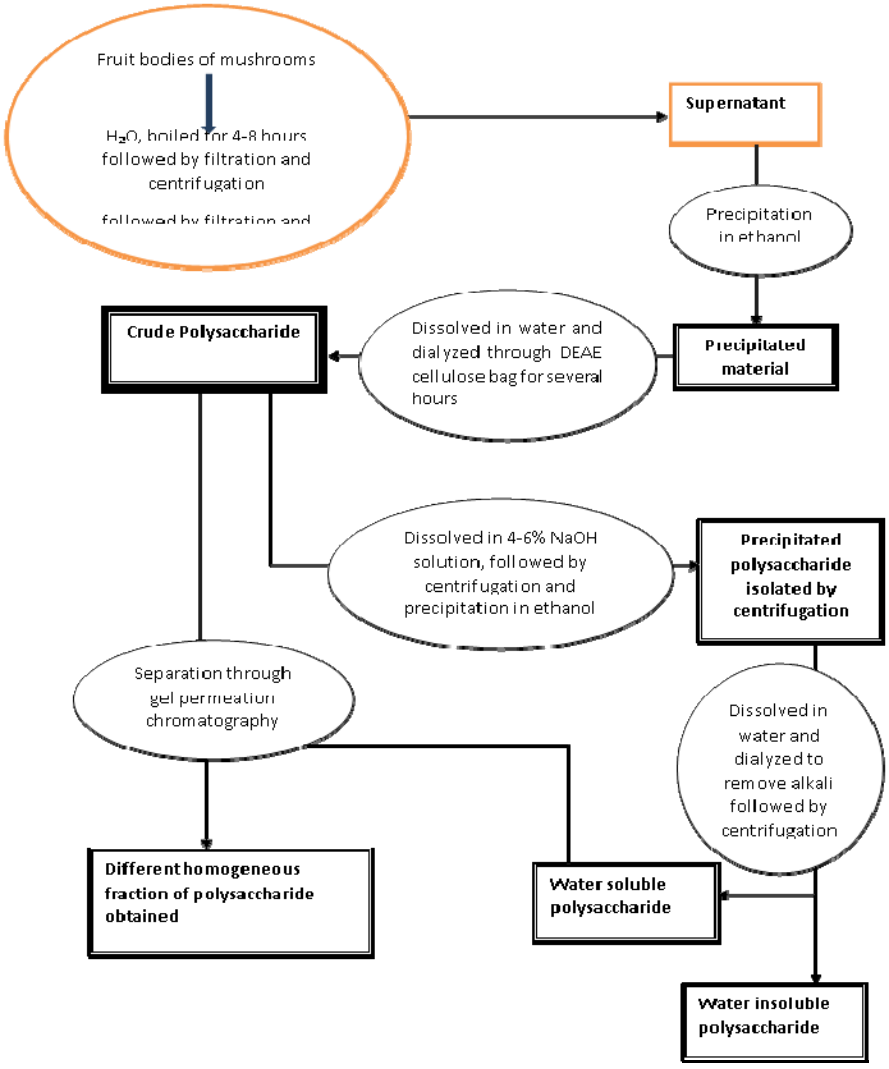
Introduction
For millennia, mushrooms have been valued by human kinds an edible and medicinal resource. A large number of mushroom derived compounds, both cellular components and secondary metabolites, have been shown to affect the immune system and could be used to treat a variety of disease status (e.g.' Chihara, Maeda, and Hamuro)[1]. Historically, hot-water–soluble fractions from medicinal mushrooms, i.e., mostly polysaccharides were used as medicine in the Far East, where knowledge and practice of mushroom use primarily originated [2]. Mushrooms such as *Ganoderma Lucidum* Reishi), *Lentinus edodes* (Shiitake), *Inonotus obliquus* (Chaga) and many others have been collected and used for hundreds of years in Korea, China, Japan and eastern Russia. It is notable and remarkable how reliable the facts collected by traditional eastern medicine are in study of medicinal mushrooms [3-5]. Ikekawa *et al*. (1969) published one of the first scientific reports on antitumor activities of essences obtained from Aphyllophoromycetideae and a few other families, manifested as host-mediated activity against grafted cancer- such as Sarcoma 180 – in animals. In Russian medicine, an extract from Chaga (Inonotus obliquus) is used as an antitumor medicine and diuretic. Soon thereafter the first three major drugs were developed from medicinal mushrooms. All three were polysaccharides, specifically are glucans; krestin from cultured mycelia biomass of *Trametes versicolor*, lentinan from fruiting bodies of *L. edodes,* and schizophyllan from the liquid cultured broth product of *Schizophyllum commune.* Some species of edible higher Basidiomycetes have been found to markedly inhibit the growth of different kinds of tumors. There are approximately 200 species of higher Basidiomycetes the have been found possess this activity [6-11].

The search for new antitumor and other medicinal substances from higher Basidiomycetes and the study of the medicinal value of these edible mushrooms have become matters of great interest. Thus, some authors have combined the use of mushrooms both for nutritional (food) and medicinal purposes [12-15]. Those which appear to enhance or potentiate host resistance are sought for the treatment of cancer, immunodeficiency diseases (including AIDS), or generalized immunosuppression after drug treatment. Edible higher Basidiomycetes are being evaluated for their nutritional value and acceptability, as well as their pharmacological properties. Mushrooms are a nutritionally functional food and a source of physiologically beneficial and no invective medicines. It was recorded that mushrooms have significant pharmacological effects or physiological properties, such as bio regulation (immunological enhancement), maintenance of homeostasis, regulation of biorhythm, cure of various diseases and prevention and improvement of life threatening diseases such as cancer, cerebral stroke, and heart diseases. This review highlights some of the most recently isolated and identified polysaccharides of mushroom origin which are promising immunomodulators and have demonstrated significant antitumor, antiviral, antibacterial, and antidiabetic activities.

Structural composition of antitumor polysaccharides in mushrooms:

Polysaccharides belong to a structurally diverse class of Macromolecules, polymers of monosaccharide the greatest potential for structural variability. The nucleotides in nucleic acids and the amino acids in proteins can interconnect in only way whereas the monosaccharide units in polysaccharides can interconnected at several points to form a wide variety of branched or linear structures [16]. 262 mushroom polysaccharides are present as glucans with different types of glycosidic linkages, such as (1,3/1,6) β-Glucans and only (1,3)-β-Glucans, but some are true heteroglycans. The others mostly bind to protein residues as PSP complexes [17]. The main source of antitumor as for structure of schizophyllan tertiary conformation, active β-Glucan has a triple-strand right-winding structure [18]. Acidic glucuronoxylomannan isolated from the fruit body of *Tremella fuciformis* was also demonstrated as having a left-handed, threefold helical backbone conformation [19]. Besides the well-known antitumor (1,3)-β-Glucans, a wide range of biologically active glucans with other structures have been described. These polysaccharides have linear or branched molecules ina backbone composed of α or β –linked glucose units, and they contain side chains that are attached in different ways. Heteroglycans side chains contain glucuronic acid, xylose, galactose, mannose, arabinose, or ribose as a main component or in different combinations.

Isolation & Purification of polysaccharides



Review of earlier works Mushroom Polysaccharides

Mushroom, the popularity called miracle food is one the important nutritional supplements to overcome protein energy malnutrition. Mushroom basically a fungus belongs to class Basidiomycetes. As far as mycological point of view, the edible part of the fungus is mainly the fruit body called basidiocarp, which is the outcome of the modification of secondary and territory mycelium. The secondary dichotic followed by diploid structure called basidia that refuge basidiospore.

The basidiocarp basically comprises of the four parts- sillr, pileus, stipe, and volva. The fruit body comprises of different stsrile and fartile layers along with basidia. The entire part of the body is basically consumed as food for the preparation palatable dishes. Attention has been paid to scientific cultivation of mushroom since the 17th century, and it is reported that mushroom are being used extensively in many countries for food and fodder [20-23]. Mushrooms have good flavor and taste, and the same nutritive value, as do Torula species. They possesses extensive enzyme complexes which enable them to flourish successfully on a wide variety of inexpensive substrates, such as lignin, cellulose, hemicelluloses, pectin, and other industrial wastes which are not suitable even for animal feed. Studies on the nutritive value and composition of a few species of mushrooms and recent investigations have shown that in addition to the flavorings properties. The proteins of some mushrooms are equal muscle protein in nutritive value. Mushrooms are excellent source of vitamins, minerals and fibers. Since they contain low fat, low calories with low sodium to potassium ratio, they are useful to people suffering with hypertension, diabetes and also pregnant and lactating mothers. Varieties of mushrooms are used in food industry, such as the fruiting bodies of *Lentinus edodes* (shiitake), *Agaricus bisporus, Pleurotus ostreatus, Pleurotus florida, Pleurotus-sajor-caju*(oyster mushroom). Oyester mushrooms now rank second among the important cultivated mushrooms in the world. One of the species of the genus Pleurotus is *Pleurotus florida.* P. florida is cultivated on a commercial scale in many parts of the world, including India. This is a delicious edible mushroom. It is a nutritionally functionally food with valuable therapeutic use. According to Robinson and Davidson [24], the efficiency of protein production from a given quantity of carbohydrates in mushrooms and other higher fungi is about 65% compared with about 20% for pork, 15% for milk, 5% for poultry, and 4% for beef. Nutritive values [25] of the fruit bodies of *P. florida* have been determined as 37.19% protein, 3.72% fat and 10.98% ash on a dry weight basis.

Approximate composition [26] of the fresh mushroom (*Pleurotus* sp.) has also been reported as following:

Constituent	Percent
Moisture	90.95
Ash	0.974
Protein	2.78
Non protein nitrogen	0.14
Fat (ether extract)	0.165
Crude fibre	1.08

Higher basidiomycetes mushrooms are nutritionally functional food and a source of physiologically beneficial and nontoxic medicines [27]. They have been used in folk medicine throughout the world since ancient times [28]. The most significant medicinal effect of mushrooms and their metabolites has attracted the attention of the chemists and biologists for their antitumor properties. There are approximately two hundred species of higher basidiomycetes that have been found to possess this activity [29]. Mushroom metabolites are usually used as adaptogens and immunostimulants and they are now considered to be one of the most useful antitumor agents for clinical uses [30]. Chihara and coworkers [31, 32] isolated a water insoluble polysaccharide from the fruiting bodies of *Lentinus edodes*. This polysaccharide is known as "*Lentinan*". It has antitumor activity much stronger than that of polysaccharides obtained from many other fungi or from higher plants. The principal component of such kind water insoluble polysaccharides is (1→3,1→6)-β-D-glucan. Several antitumor polysaccharides, such as (1→3)-β-glucans, hetero-β-glucans (xyloglucans), and their protein complexes (α-mannan peptide) as well as dietary fibers, lectins, and terpenoids have been isolated from medicinal mushrooms [27]. The available evidence indicated that the anti-carcinogenic properties of these polysaccharides were attributable to enhancement of the numbers or functions of macrophages, NK cells, and subsets of T cells, that is, to the modulation of both innate and adaptive immunity. β-Glucans can stimulate macrophages [33], neutrophils [34], and NK cells [35] to kill sensitive tumor cells. Some data also suggest that β-glucans can promote T cell-specific responses [36] through triggering the secretion of IFN-g, IL-6, IL-8, and IL-12 from macrophages, neutrophils, and NK cells [37]. Thus these immunological activities play a governing role in host recognition, targeting and destroying unwanted tumour-potentiating viruses and abnormal cancerous cells. For example, the key immune mechanisms that are involved in Lentinan mediated destruction of cancer cells are illustrated in Figure 1 [38].

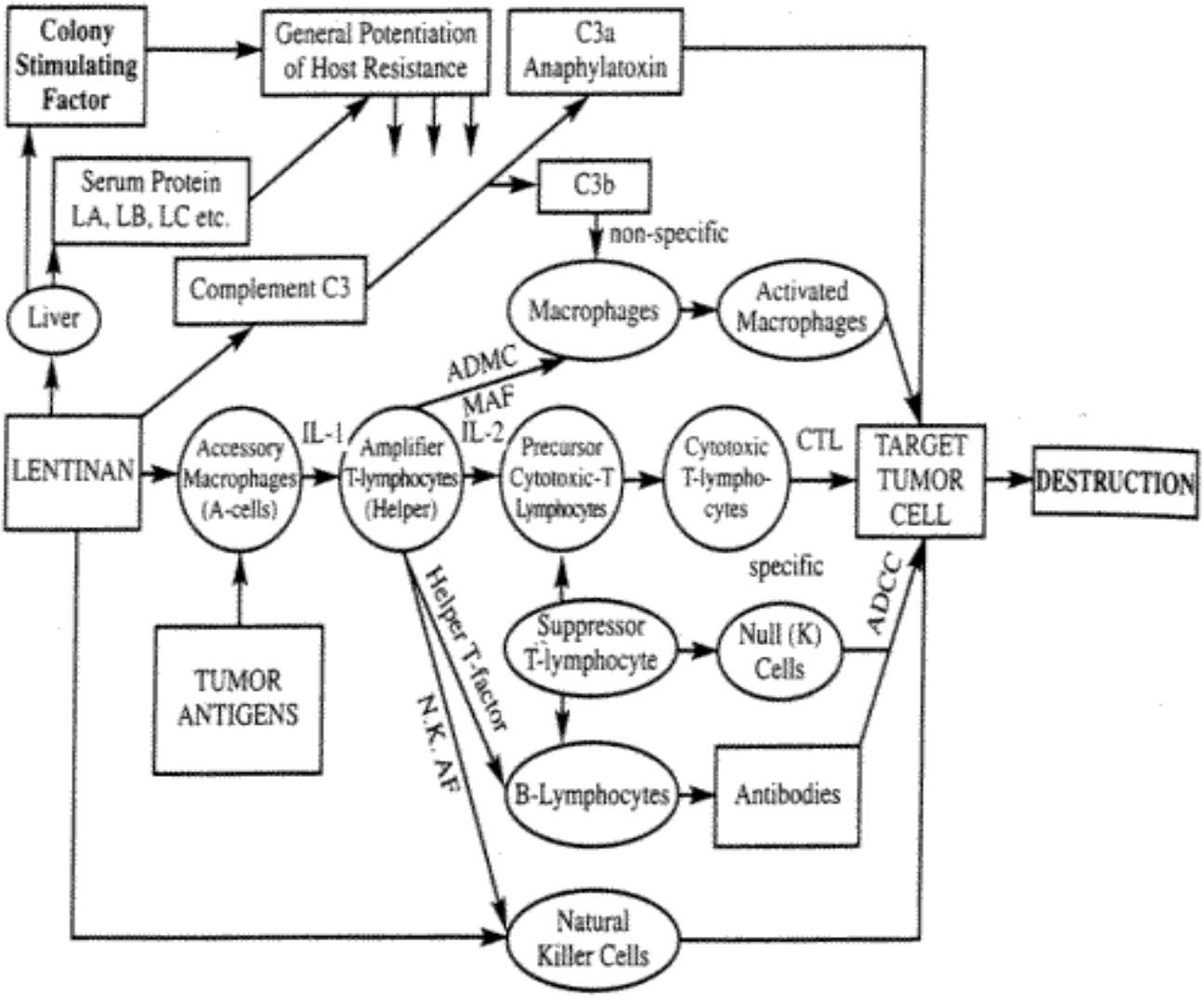
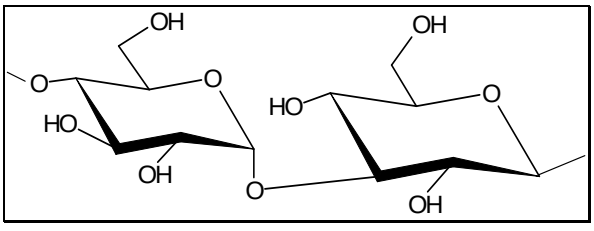


Fig 1: Host immune responses involved in Lentinan-mediated destruction of cancer cells (Chihara *et al*., 1992) [38] NK: Natural Killer cell; AF: Antibody Formation; LPS: Liver Protein Serum; ADCC: Antibody Dependent Cell mediated Cytotoxicity; CTL: Cytotoxic T-Lymphocyte; MAF: Macrophage Activating Factor; IL-1: Interlukine 1; IL-2: Interlukine 2.

Different mushrooms extract and their structure of polysaccharides

Termitomyces Microcarpus mushrooms water extract contain two fractions. The one of the fraction consist→ 4)-α-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→ this type of polysaccharide [39]. The Structure of this polysaccharide as -



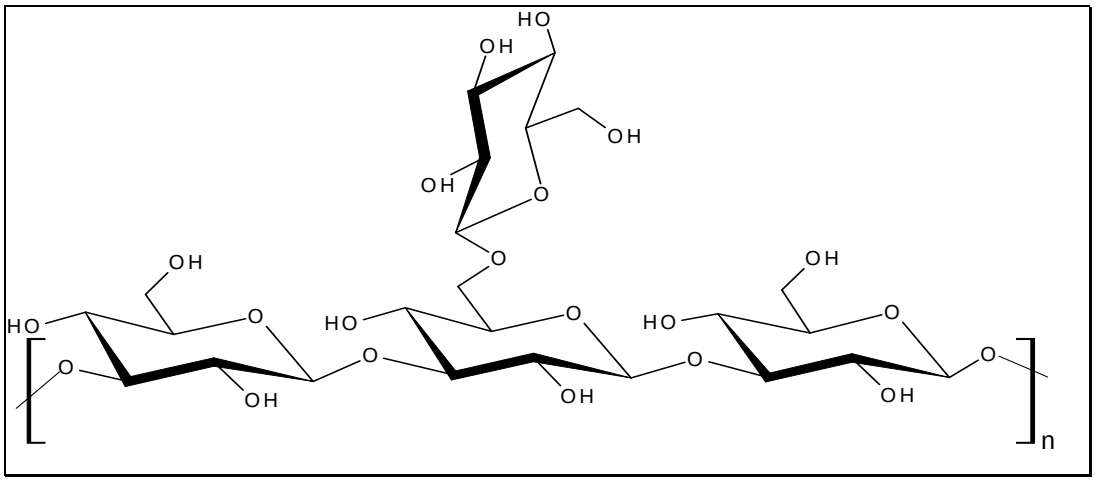
A new (1→3)-, (1→6)-branched water-soluble glucan (Fraction I) from an edible mushroom, *Pleurotus florida* [40]. The structure of this polysaccharide as

→3)-α-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→3)-α-D-Glc*p*-(1→
6
↑
1
α-D-Glc*p*

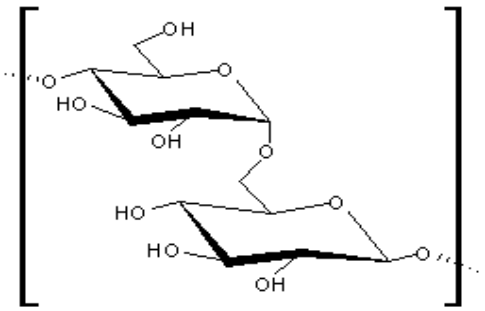
Another a water soluble glycan (Fraction II) isolated from an edible mushroom, *Pleurotus florida* [41]. The structure of this polysaccharide as

α-D-Glc*p*
1
↓
4
→6)-α-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→
2
↑
1
β-D-Man*p*

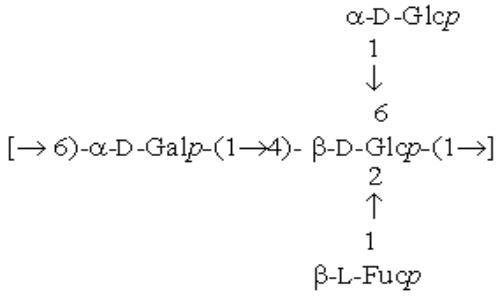
A water-insoluble branched (1→3, 1→6)-β-D-glucanisolated from the fruiting bodies of *Pleurotus florida* [42]. The structure of the repeating unit of this polysaccharide as



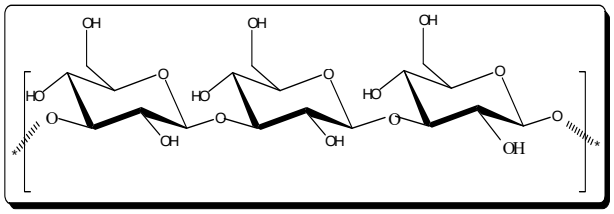
A water-soluble glucan isolated from an edible mushroom, *Astraeus hygrometricus* [43]. The structure of the repeating unit of this polysaccharide as



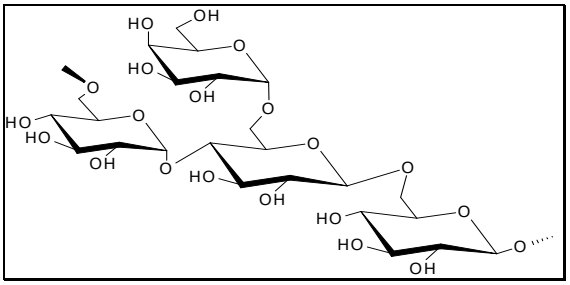
A heteroglycan isolated from the fruit bodies of an ectomycorrhizal fungus, *Astraeus hygrometricus* [44]. The structure of the repeating unit of this polysaccharide as



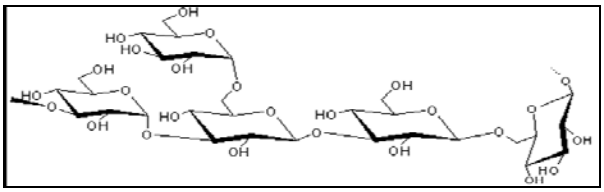
A water-insoluble (1-3)-β-D-glucan isolated from the alkaline extract of an edible mushroom, *Termitomyces eurhizus* [45]. The structure of the repeating unit of this polysaccharide as



A polysaccharide isolated from the aqueous extract of an edible mushroom, *Pleurotus sajor-caju*, cultivar Black Japan [46]. The structure of the repeating unit of this polysaccharide as

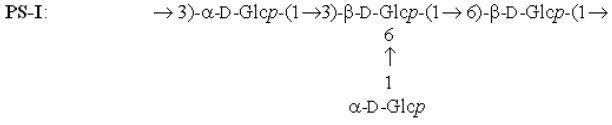


An immunoenhancing water soluble glucan isolated from hot water extract of an edible mushroom, *Pleurotus florida*, cultivar Assam Florida [47]. The structure of the repeating unit of this polysaccharide as



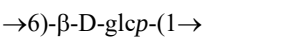
This polysaccharide has shown macrophage activity as well as splenocyte and thymocytes active.

Glucans from alkaline extract of an edible mushroom, *Pleurotus florida*, cv Assam Florida [48]. The structure of the repeating unit of these polysaccharides as



The polysaccharide (PS-I) has shown macrophage activity as well as splenocytes and thymocytes active.

The polysaccharide isolated from the aqueous extract of the fruit bodies of somatic hybrid raised through intergeneric protoplast fusion between edible mushroom strains of *Pleurotus florida* and *Volvariella volvacea* [49]. The structure of the repeating unit of this polysaccharide as



This polysaccharide has shown macrophage activity as well as splenocytes and thymocytes active.

Structural analysis of the polysaccharides

The biological activities of polysaccharides depend on the size of molecule, branching rate and form. So, it is very important to determine the exact structure of the polysaccharides, isolated either from medicinal plant or from mushroom.

For the analysis of the exact structure of the polysaccharide it is the prime job to purify the polysaccharide as much as possible. Different techniques like chromatography, ultra centrifugation, dialysis, precipitation and re-precipitation are adapted for this purpose. After the purification of this polysaccharide, several chemical reactions are carried out with this polysaccharide including total acid hydrolysis, methylation study, per-iodate oxidation, Smith degradation studies, partial hydrolysis etc. These chemical reactions provided the primary idea of the polysaccharide. But, the exact structure of the polysaccharide is determined on the basis of different 1 D (^{1}H, ^{13}C) and 2D (DQF-COSY, TOCSY, NOESY, HSQC, HMQC, HMBC etc) NMR and Maldi Mass spectroscopic analyses.

A schematic presentation of isolation, purification and structure determination of a polysaccharide by chemical and NMR spectroscopic methods has been given in Figure 2 and Figure 3.

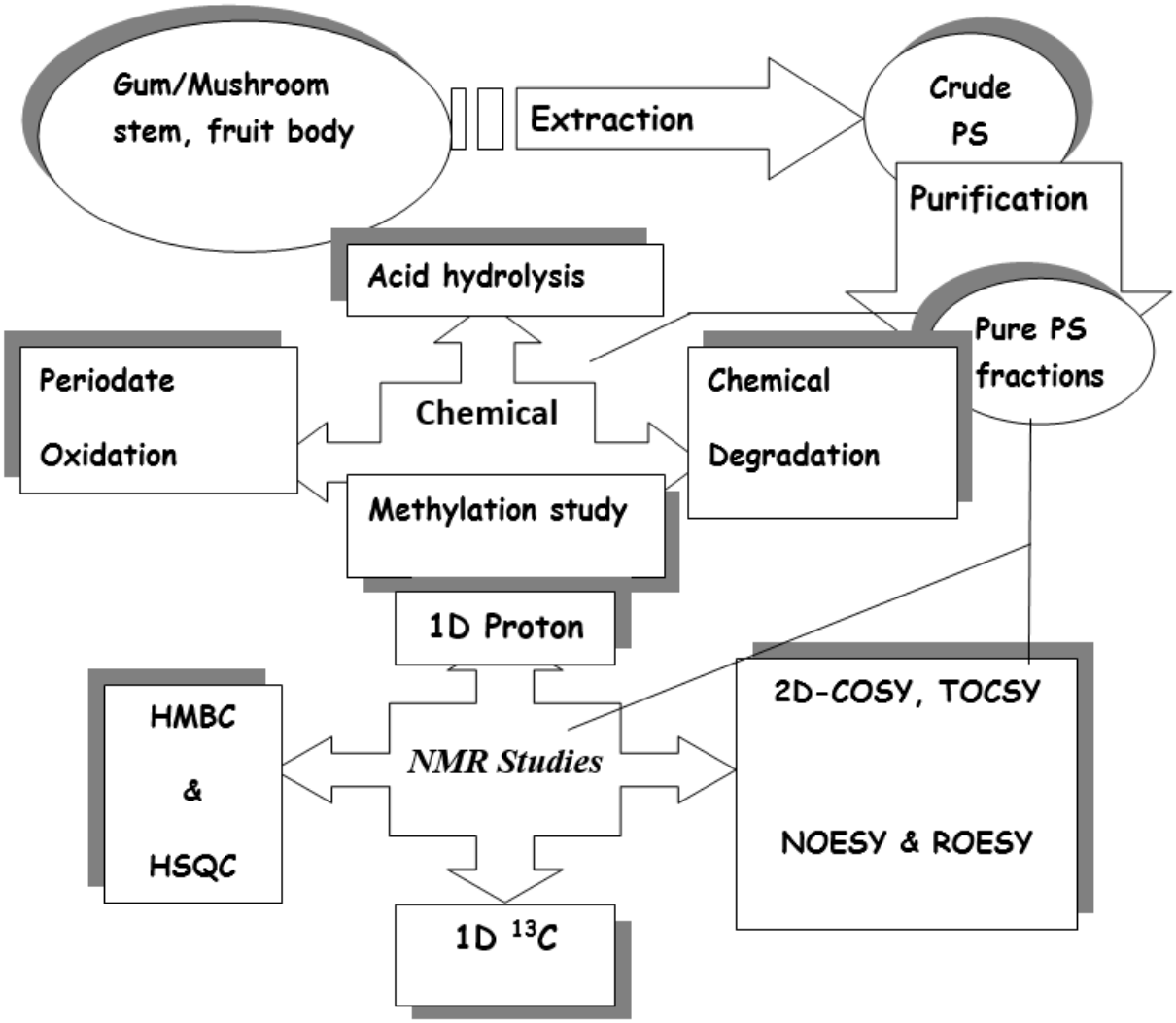


Fig 2: Schematic diagram of structural analysis of polysaccharid

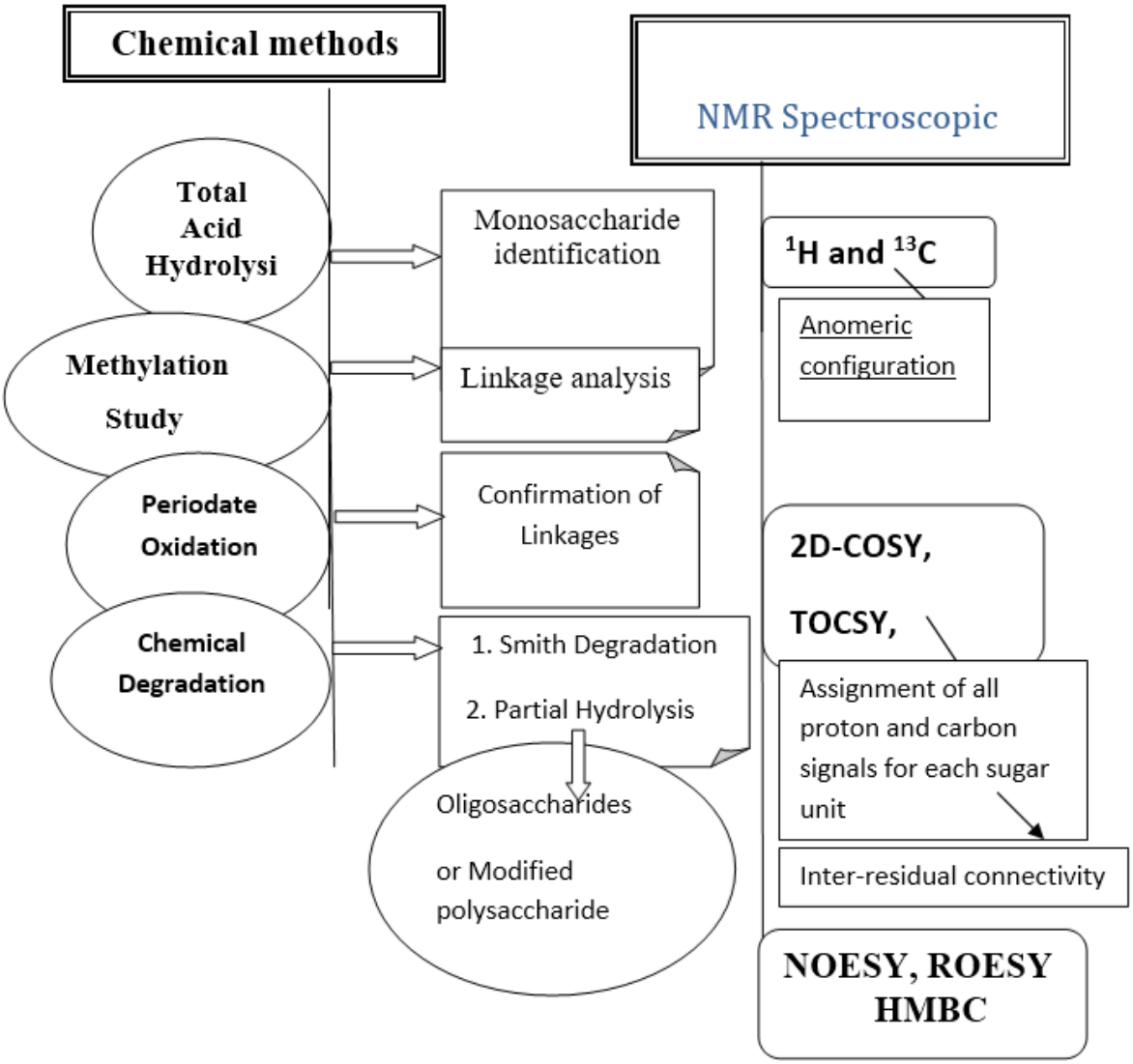


Fig 3: Schematic diagram of determination of structure of a polysaccharide bychemical and NMR spectroscopic methods.

Conclusions

Higher Basidiomycetes mushrooms are still far from being thoroughly studied; even the inventory of known species is incomplete, comprising maybe only 10% of the true number of species existing [50]. The number of mushrooms with known pharmacological qualities is much lower still. Neverthless, the species studied so far represent a vast source of anticancer and immunostimulating polysaccharides.

The following purposes: (1) Prevention of oncogenes is by oral consumption of mushrooms or their preparations; (2) direct antitumor activity against various allogeneic and syngeneic tumors; (3) immunopotentiation activity against tumor in conjunction with chemotherapy; (4) preventive effects on tumor metastasis. Most of the clinical evidence comes from the commercial polysaccharides lentinan, PSK (krestin), and schizophyllan, but there are also impressive new data for polysaccharides from *phellinus linteus*, *Flammulina velutipes*, *Hypsizygus marmoreus*, *Agaricus blazei* and others. The biochemical mechanisms that mediate the biological acivity of polysaccharides are still not clearly understood. Polysaccharides from mushrooms do not attack cancer cells directly, but produce their antitumor effects by actvating different immune responses in the host. The antitumor action of polysaccharides requires an intact T-cell component; their activity is mediated through a thymus- dependent immune mechanism [51]. Mushroom polysaccharides are known to stimulate natural killer cells, T-cells, B-cells, and macrophage dependent immune system responses. The immunomodulating action of mushroom polysaccharides is especially valuable as a means of metastatic tumors, and as a co-treatment with chemotherapy.

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