Chapter 12

# Bioactive Polysaccharides from TCM Herbs as Anti-Cancer Adjuvants

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**Abstract**

*Purpose*: To review the nature, extent, bioactivities and clinical application of bioactive polysaccharides in Traditional Chinese Medicine (TCM), especially as adjuvants in cancer treatment.

*Methodology*: Literature Review.

*Findings*: Many fungal and plant derived bioactive polysaccharides with a broad range of immunomodulatory activities are found in TCM. Some such polysaccharides have been developed into drugs and showed clinical efficacy in controlled trials while the majority of such compounds remain as nutraceuticals with only preliminary research. Such polysaccharides are generally non-toxic and also possess other bioactivities such as inducing differentiation, stimulating hematopoiesis, anti-metastasis, and anti-angiogenesis, which make them ideal adjuvants in modern cancer therapy.

*Conclusion*: Bioactive polysaccharides occur extensively in TCM herbs and is the basis of potential useful application of TCM as adjuvant in cancer therapies.

*Keywords*: Polysaccharides; Medicinal Plants; Traditional Chinese Medicine; Cancer.

## 12.1 Introduction

As a major class of biomolecules, carbohydrates are the most complex and least appreciated for their bioactivity (Stryer, 1995). In the past three decades, an increasing number of reports describing the isolation and bioactivity of polysaccharide glucans and proteoglucans from plant and other sources highlight the potential role of this class of molecules in cancer therapy as a result of its immunostimulatory properties (Wong *et al.*, 1994). More recently, other biological mechanisms such as apoptotic and anti-angiogenic effects including its effects on the c-Myc, c-Fos, and vascular endothelial growth factor (VEGF) expression (Yang, 2005) highlight the potential broad spectrum bioactivity of this class of compounds as anti-cancer adjuvants.

## 12.2 Bioactive Polysaccharides in Chinese Herbs

Known bioactive polysaccharides are found in fungi, lichens, higher plants, marine as well as animal sources throughout the world, but some of the most well characterized and clinically relevant polysaccharides are found in Traditional Chinese Medicine (TCM) (Ooi and Liu, 2000), especially those herbs from the TCM materia medica classically characterized as tonic in nature or having 'Fu-Zhen' (Sun *et al.*, 1981) properties. Many such tonic Chinese herbs have been found to possess immunomodulatory and other anti-tumor bioactivities and are potentially useful in cancer therapy (Sun, 1986). As such, the search and characterization of novel, safe and effective natural compounds from Chinese herbs is a significant goal for anti-cancer research.

## 12.3 Immunomodulatory Property of Polysaccharides and the β-Glucan Receptor

Naturally derived polysaccharides including heteroglycans and proteoglycans of certain molecular weight and structure have specific broad-ranged immunomodulatory properties which have been recognized for several decades. Such immunomodulating activity includes activation of macrophages (Adachi *et al.*, 1990), monocytes (Czop and Austen, 1985a), natural killer cells (Peter *et al.*, 1988), lymphocyte activated killer cells (Yamasaki *et al.*, 1989), dendritic cells (Kim, 2007), tumor-infiltrating lymphocytes (Kariya *et al.*, 1991) and other lymphocytes (Kumazawa *et al.*, 1985). The stimulated release of various cytokines including interferons (Kandefer-Szerszen and Kawecki, 1973), interleukins (Sakagami *et al.*, 1988), tumor necrosis factor (Abel and Czop, 1992) and colony stimulating factors (Hashimoto *et al.*, 1990) have also been well documented. Such polysaccharides are thus considered multi-cytokine inducers and this is probably due to induction of gene expression of various immunomodulatory cytokines and cytokine receptors (Liu *et al.*, 1999).

An important feature of the bioactivity of immunomodulatory polysaccharides is the importance of its structure-function relationship. Differences in molecular weight, tertiary structure or conformation, and composition all affect polysaccharide bioactivity. In general, polysaccharides in a configuration with β1–3, 1–4, or 1–6 branch chains are necessary for activity and complex branch-chained polysaccharides with anionic structures and higher molecular weights have greater immunostimulating activities (Cleary *et al.*, 1999). Differences in bioactivity may be due to differences in receptor affinity or receptor-ligand interaction on the cell surface (Mueller *et al.*, 2000).

The description of a beta-glucan receptor on monocytes by Czop & Austen (1985b) served as a basis to understand the immunopotentiating bioactivity of polysaccharides and explained why herbs and materials from different sources with similarly structured polysaccharide content share similar immunomodulatory activity.

## 12.4 Immunomodulatory Property of Polysaccharides and the Toll-Like Receptor (TLR) System

The toll-like receptor (TLR) system constitutes a pylogenetically ancient, evolutionary conserved, archetypal pattern recognition system, which is the basis of antigen recognition by and activation of the immune system. Toll-like receptor agonists have long been used as immunoadjuvants in anti-cancer immunotherapy and increasing evidence suggests that cancer may progress via subversion of the TLR signalling pathways (Killeen *et al.*, 2006). Natural as well as synthetic ligands of TLR receptors such as lipid A analogs, poly(I:C), loxoribine, oligodeoxynucleotides have all been shown to be effective in regulating immune response (Fasciano and Li, 2006). The TLRs are expressed on macrophages and dendritic cells which are key in newly developed immunotherapeutic protocols against cancer (Buchsel and Demeyer, 2006). Immunomodulatory polysaccharides from single TCM herbs (Lin *et al.*, 2005) as well as TCM/Kampo herbal formulae (Chino *et al.*, 2005) have recently been found to modulate TLR receptors thus opening a new avenue to understand the biological basis of potential usefulness of polysaccharides from TCM in cancer therapies.

## 12.5 Polysaccharides as Anti-Tumor Adjuvants

The usefulness of bioactive polysaccharides found in TCM with a beta-1,3 1,4 or 1,6 in enhancing the immune system and therefore indirectly reducing tumorigenesis as well as tumor growth has been extensively demonstrated in animals while prolonged survival as a result of treatment with polysaccharide derived nutraceuticals and drugs have been noted in a number of controlled clinical trials carried out in Japan and China.

## 12.6 Immunomodulatory and Anti-Tumor Polysaccharides in TCM

Immunopotentiating traditional Chinese herbs with proven anti-tumor activity may be broadly considered as fungals or botanicals. Almost 200 species of such fungi have demonstrable anti-tumor activity, although not all such fungi are in the TCM pharmacopeia (Borchers *et al.*, 1999). Fungals especially from the Basidiomycetes family have been found to possess bioactive polysaccharides (Wasser and Weis, 1999). According to a survey by Jong and Donovick (1989), 109 anti-tumor subsances from fungi were from Basidiomycetes, and 51 of these were glucans or polysaccharide compounds from no less than 26 different species. Some of these fungal polysaccharides have been systematically studied as well as developed into nutraceuticals [e.g., *Agaricus blazei* (Itoh *et al.*, 1994), *Cordyceps sinensis* (Kuo *et al.*, 1996), *Ganoderma sp.* (Chang, 1996), *Grifola frondosa* (Hishida *et al.*, 1988)] or drugs [e.g., Krestin from *Coriolus versicolor* (Kondo and Torisu, 1985), Lentinan from *Lentinus edodes* (Chihara *et al.*, 1987), Schizophyllan from *schizophyllum communes* (Komatsu *et al.*, 1963)], but others have also been preliminarily studied (see Table 12.1).

As a representative agent, Lentinan from Lentinus edodes was identified in the late 1960s by Chihara *et al.* (1970). It is a branched chain molecule with a backbone of 1,3 β-D-glucan and side chains

**Table 12.1.** Select medicinal fungi reported to contain bioactive polysaccharides.

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| *Agaricus blazei* (Ohno *et al.*, 2001) |
| *Auricularia auricula* (Misaki, 1981) |
| *Flammulina velutipes* (Leung *et al.*, 1997) |
| *Hericium erinaceum* (Mizuno *et al.*, 1992) |
| *Inonotus sp.* (Ohtsuka *et al.*, 1977) |
| *Phellinus sp.* (Han *et al.*, 1999) |
| *Pleurotus sp.* (Chenghua *et al.*, 2000) |
| *Polyporus sp.* (Zhang *et al.*, 1991) |
| *Poria sp.* (Kanayama *et al.*, 1986) |
| *Tricholoma aggregatum* (Komatsu *et al.*, 1973) |
| *Tremella sp.* (Xia and Lin, 1989) |

of β1,3 and β1,6 D-glucose residues. It has been demonstrated to elicit anti-tumor activity by the stimulation of host-mediated immune responses and thus inhibit the growth of implanted tumors in laboratory animals (Chihara, 1983). Lentinan has also been demonstrated to be active as a parenteral agent in prolonging survival in recurrent and metastatic gastric and colorectal cancer when given in combination with chemotherapy in controlled clinical trial (Nimura *et al.*, 2006; Wakui *et al.*, 1986). Recent advances in the biological understanding of polysaccharide function identifies the effect of Lentinan on dendritic cells to perhaps be a key factor for its anti-tumor effect in chemoimmunotherapy (Mushiake *et al.*, 2005).

Another representative agent is Krestin [PSK], which is a protein-bound polysaccharide extracted from the CM-101 strain of Coriolus versicolor (Kondo and Torisu, 1985). Unlike Lentinan, PSK is a β1,4 glucan containing 10% protein and is active orally. PSK has also been statistically demonstrated to prolong survival in clinical trials involving gastric (Nakazato *et al.*, 1994), colorectal (Mitomi *et al.*, 1992) esophageal (Ogoshi *et al.*, 1995), nasopharyneal (Go and Chung, 1989), non-small cell lung (Hayakawa *et al.*, 1993), and breast cancer (Toi *et al.*, 1992). The polysaccharide peptide (PSP) isolated from the COV-1 strain mycelia of *Coriolus versicolor* has proven benefits in clinical trials in China for esoplageal, gastric and lung cancers (Ng, 1998).

**Table 12.2.** Representative Traditional Chinese/Kampo Herbs reported to contain bioactive polysaccharides.

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| *Acanthopanax Giraldii Harms* (Wang *et al.*, 1992) |
| *Achyranthes bidentata* (Li and Li, 1997) |
| *Aloe sp.* (Zhang and Tizard, 1996) |
| *Atractylodes* (Inagaki *et al.*, 2001) |
| *Beniscasa cerifera* (Kumazawa *et al.*, 1985) |
| *Cinnamomum cortex* (Haranaka *et al.*, 1995) |
| *Curcuma zedoaria* (Kim *et al.*, 2000) |
| *Codonopsis pilosula* (Wang *et al.*, 1996) |
| *Dipsacus asperoides* (Zhang *et al.*, 1997) |
| *Epimedium sagittatum* (Liu *et al.*, 1991) |
| *Imperata cylindrica* (Pinilla and Luu, 1999) |
| *Isatis indigotica* (Xu and Lu, 1991) |
| *Malva verticillata* (Gonda *et al.*, 1990) |
| *Panax notoginseng* (Gao *et al.*, 1996) |
| *Pseudostellaria heterophylla* (Wong *et al.*, 1992) |
| *Radix bupleuri* (Geng and Chen, 1989) |
| *Radix glycyrrhizia* (Nose *et al.*, 1998) |
| *Radix hadysari* (Lan *et al.*, 1987) |
| *Radix pseuoginseng* (Lin, 1988) |
| *Radix Rehmannia* (Xu, 1992) |
| *Salvia miltiorrhiza* (Hromakova *et al.*, 1999) |
| *Zizyphi fructus* (Yamaoka *et al.*, 1996) |

Besides fungals, many so called '*Fu-Zhen*' (tonifying) traditional Chinese herbs contain bioactive polysaccharides and have been studied for their immunomodulatory and anti-tumor activity. All of these are catalogued in a comprehensive online database on anti-cancer Asian herbal material (www.asiancancerherb.info). These botanicals include common herbs such as Actinidia chinensis (Zhang and Lin, 1986), *Angelica sinensis* (Choy *et al.*, 1994), *Astralgalus membranaceus* (Huang *et al.*, 1982), *Ligustrum lucidum* (Lau *et al.*, 1994), *Panax ginseng* (Lee *et al.*, 1997) as well as others (see Table 12.2).

TCM usually employs herbal formulae and most useful TCM formulae for cancer patients contain herbs with immunopotentiating activity from its polysaccharide content (Ito and Shimura, 1985a; 1985b). Examples of standard TCM (and Kampo) formulae with published experimental results demonstrating such immunostimulatory properties include *Xiao-Chai-Hu-Tang* [*Sho-saiko-to*] (Nagatsu *et al.*, 1989), *Shi-quan-da-bu-tang* [*Juzen-taiho-to*] (Zee-Cheng, 1992) and *Bu-zhong-yi-qi-tang* [*Hochu-ekki-to*] (Li *et al.*, 1999).

## 12.7 Clinical Observations on Polysaccharides as Anti-Cancer Adjuvants

It is important to realize that although TCM herbs that contain bioactive polysaccharides may derive some of their anti-cancer efficacy via immunopotentiation, many such herbs contain other complementary anti-neoplastic substances.

Conversely, such bioactive polysaccharides may have other anti-tumor actions beyond immunopotentiation. Such anti-tumor mechanisms include induction of cellular differentiation (Chen *et al.*, 1997), anti-angiogenesis (Kanoh *et al.*, 1994), and anti-metastasis (Kobayashi *et al.*, 1995). Furthermore, the polysaccharides have other applications beyond anti-tumor in cancer patients. Such agents may also be useful in enhancing hematopoiesis (Liu *et al.*, 1991), ameliorating side-effects of chemotherapy and radiation as well as generally improving the well-being of the cancer patient.

Most clinical trials of bioactive polysaccharides in cancer have used the agents with conventional treatments such as chemotherapy and radiation. It is important to note that such polysaccharides have been found to be clinically useful across a spectrum of solid-tumors, including colorectal, gastric, lung, and breast cancers, with the overall result of enhancing survival.

Regarding the issues of side-effects, besides the report of a low incidence of allergic reactions to individual herbs or polysaccharide drugs, major complications and/or organ toxicity has not so far been reported with this family of agents.

As there is always a concern of potential adverse interaction with conventional therapy with herbal or nutraceutical products, it is important to note that there have been no studies to suggest negative interactions with polysaccharide derived agents and chemotherapy or radiation.

Not all polysaccharides are comparable and it is not prudent to entirely rely on *in vitro* data on one aspect of a polysaccharide's effectiveness (e.g., NK cell stimulation) as a basis of comparing various different polysaccharide derived agents. While clinical trial data may not be available for many such agents, clinical decision should be guided trial data if available, or by the extent and quality of available medical literature on each agent. Furthermore, it is important to carefully consider the choice of polysaccharide agent as there can be significant differences in bioactivity secondary to differences in species, cultivation, method of extraction, formulation, as well as route and amount of dosage. Practically, availability of agent, cost, and potential efficacy are the main clinical considerations when choosing a suitable polysaccharide to prescribe to a patient.

## 12.8 Future Directions in the Development of Polysaccharides as Cancer Adjuvants

From existing laboratory and clinical evidence, it is certain that bioactive polysaccharides in TCM herbs are multifaceted and useful adjuncts in cancer care. However, lack of standardization and pharmacokinetic data among a spectrum of popular polysaccharide based nutraceuticals, limited controlled trial data in the West on such agents, and relative lack of knowledge about these herbal agents among conventional cancer care professionals hamper the wide application of this unique class of agents. It is hoped that standardization as well as further clinical studies will be a basis for advancement in our knowledge and use of such agents.

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