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ORIGINAL RESEARCH PAPERS

Bioactive Polysaccharides from Traditional Chinese Medicine Herbs as Anticancer Adjuvants

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ABSTRACT

Purpose of study: To review the nature, extent, bioactivities, and clinical application of 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 show clinical efficacy in controlled trials while the majority of such compounds remain as nutraceuticals with only preliminary research. Such polysaccharides are generally nontoxic and possess other bioactivities such as inducing differentiation, stimulating hematopoiesis, antimetastasis, and antiangiogenesis, which make them ideal adjuvants in modern cancer therapy.

Conclusion: Bioactive polysaccharides occur extensively in TCM herbs and are the basis of potentially useful application of TCM as an adjuvant in cancer therapies.

BIOACTIVITY OF POLYSACCHARIDES

As a major class of biomolecules, carbohydrates are the most complex and least appreciated for their bioactivity (Stryer, 1995). Recently, 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 as well as other anticancer properties (Wong et al., 1994).

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

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have been found to possess immunomodulatory bioactivity 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 anticancer research.

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 that have been recognized for several decades. Such immunomodulating activity includes activation of macrophages (Adachi et al., 1990), monocytes (Czop and Austen, 1985a), natural killer (NK) cells (Peter et al., 1988), lymphocyte-activated killer cells (Yamasaki et al., 1989), dendritic cells (Tsujitani et al., 1992), 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 documented. Such polysaccharides are thus considered multicytokine inducers and this is probably because of 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 relation. 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 caused by differences in receptor affinity or receptor-ligand interaction on the cell surface (Mueller et al., 2000).

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

POLYSACCHARIDES AS ANTITUMOR ADJUVANTS

The usefulness of bioactive polysaccharides found in TCM with a β1,3 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.

IMMUNOMODULATORY AND ANTITUMOR POLYSACCHARIDES IN TCM

Immunopotentiating traditional Chinese herbs with proven antitumor activity may be broadly considered as fungals or botanicals. Almost 200 species of such fungi have demonstrable antitumor activity although not all such fungi are in the TCM pharmacopeia (Borchers et al., 1999). Fungals, especially those 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 antitumor 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* spp. [Chang, 1996], *Grifola frondos*a [Hishida et al., 1988]) or drugs Krestin™ (Kureha Chemicals Industry Corp., Tokyo, Japan) from *Coriolus versicolor* (Kondo and Torisu, 1985), Lenti-

Table 1. Medicinal Fungi Reported to Contain Bioactive Polysaccharide

Agaricus blazei (Ohno et al., 2001)
Auricularia auricula (Misaki, 1981)
Flammulina velutipes (Leung et al., 1997)
Hericium erinaceum (Mizuno et al., 1992)
Inonotus spp. (Wasser and Weis, 1999)
Phellinus spp. (Han et al., 1999)
Pleurotus spp. (Chenghua et al., 2000)
Polyporus spp. (Zhang, et al., 1991)
Poria spp. (Kanayama et al., 1986)
Tricholoma spp. (Liu et al., 1996)[a]
Tremella spp. (Xia and Lin, 1989)

[a]Liu F, Ooi VE, Liu WK, Chang ST. Immunomodulation and antitumor activity of polysaccharide–protein complex from the culture filtrates of a local edible mushroom, *Tricholoma lobayense*. Gen Pharmacol 1996;27:621–624.

nan from *Lentinus edodes* (Chihara et al., 1987), Schizophyllan from *Schizophyllum communes* (Komatsu et al., 1962), but others have been only studied preliminarily (See Table 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 of β1,3 and β1,6-D-glucose residues. It has been demonstrated to elicit antitumor 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 (Wakui et al., 1986).

Another representative agent is Krestin [PSK] (Kureha Chemicals Industry Corp.), which is a protein-bound polysaccharide extracted from *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.

In addition to fungals, many so-called *Fu-Zhen* (tonifying) traditional Chinese herbs contain bioactive polysaccharides and have been studied for their immunomodulatory and antitumor activity. These botanicals include common herbs such as *Actinidia chinensis* (Zhang and Lin, 1988), *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 (Table 2).

TCM usually uses herbal formulae and most useful TCM formulas for patients with cancer contain herbs with immunopotentiating activity from its polysaccharide content (Ito andShimura, 1985a, 1985b). Examples of standard TCM (and Kampo) formulas 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).

Table 2. Representative Traditional Chinese/Kampo Herbs Reported to Contain Bioactive Polysaccharides

Acanthopanax Giraldii Harms (Wang et al., 1992)
Achyranthes bidentata (Li and Li, 1997)
Aloe spp. (Zhang and Tizard, 1996)
Atractylodes (Inagaki et al., 2001)
Beniscasa cerifera (Kumazawa et al., 1985)
Cinnamomum cortex (Haranaka et al., 1985)[a]
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)[b]
Pseudostellaria heterophylla (Wong et al., 1992)
Radix bupleuri (Geng and Chen, 1989)
Radix glycyrrhizia (Nose et al., 1998)
Radix hadysari (Lan et al., 1987)[c]
Radix pseuoginseng (Lin, 1988)
Radix Rehmannia (Xu, 1992)
Salvia miltiorrhiza (Hromakova et al., 1999)
Zizyphi fructus (Yamaoka et al., 1996)

[a]Haranaka K, Satomi N, Sakurai A, Haranka R, Okada N, Kobayashi M. Antitumor activities and tumor necrosis factor producibility of traditional Chinese medicines and crude drugs. Cancer Immol Immunother 1985;20 (1):1–5.

[b]Gao H, Wang F, Lien EJ, Trousdale MD. Immunostimulating polysaccharides from *Panax notoginseng*. Pharm Res 1996;13(8):1196–1200.

[c]Lan ZF, Zhang ZL, Cheng GQ, Wang FL, Xi SF. Effects of radix hadysari polysaccharide on immunlogical function and transplanted tumors in mice [in Chinese]. Zhongguo Yao Li Xue Bao 1987;8(3):275–277.

CLINICAL OBSERVATIONS ON POLYSACCHARIDES AS ANTICANCER ADJUVANTS

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

Conversely, such bioactive polysaccharides may have other antitumor actions beyond immunopotentiation. Such antitumor mechanisms include induction of cellular differentiation (Chen et al, 1997), antiangiogenesis (Kanoh, 1994), antimetastasis (Kobayashi et al., 1995). Furthermore, the polysaccharides have other applications beyond antitumor in patients with cancer. 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 patients with cancer.

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 issue of side-effects, in addition to the report of a low incidence of allergic reactions to individual herbs or polysaccharide drugs, major complications and/or organ toxicity has not yet been reported with this family of agents.

Because there is always concern regarding potential adverse interaction with conventional therapy with herbal or nutraceutical products, it is important to note that there have not been studies to suggest negative interactions with polysaccharide-derived agents and chemotherapy or radiation.

Not all polysaccharides are comparable and it is not prudent to rely entirely 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 making should be guided by trial data, if available, or by the extent and quality of available medical literature on each agent. Furthermore, it is important to consider the choice of polysaccharide agent carefully because 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. Practicality, availability of agent, cost, and potential efficacy are the main clinical considerations when choosing a suitable polysaccharide to apply in a patient.

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 the basis for advancement in our knowledge and use of such agents.

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