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The physicochemical properties of a new class of anticancer fungal polysaccharides: A comparative study

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ABSTRACT

The structural and physicochemical properties of polysaccharides isolated from fungi with anticancer properties were investigated. The majority of the polysaccharides considered, have the β-D-Glc*p* component mostly connected by 1→3 and 1→6 linkages in the backbones and the short branches, respectively. The established parameters of *lead-like*, *drug-like* and of known dug space (KDS) were used and the repeating units of the polysaccharides exhibit some overlap with these. It was found that a unique region of chemical space is occupied by the polysaccharides, with MW: 1.0×10^5 to 2.5×10^5 g mol^{-1}; Log *P*: -3.0×10^3 to -1.0×10^3; HD: 1.0×10^3 to 5.0×10^3; HA: 5.0×10^3 to 1.0×10^4; PSA: 5.0×10^4 to 1.0×10^5 and RB: 5.0×10^3 to 1.0×10^4. These findings can be exploited in antitumor drug discovery projects.

1. Introduction

The extracts from medicinal mushrooms are used as prophylactics and for treating diseases (Israilides & Philippoussis, 2003). The therapeutic effects of mushrooms extracts are found for various indications, such as anticancer, antibacterial, antiviral, and antifunal (Ooi & Liu, 1999). One of the potent mushroom-derived bioactive macromolecules are polysaccharides, in particular β-glucan which has anticancer effect by stimulating natural killer cell, T-cells, B-cells, and macrophage-dependent immune system responses through distinct receptors, such as dectin-1, the toll-like receptor-2, scavenger receptors and lactosylceramide (Brown & Gordon, 2005; Dalmo & Bogwald, 2008). For the innate and adaptive immune responses, activated macrophages are responsible for the production of cytokines, interleukin-1 beta (IL-1β), tumour necrosis factor-alpha (TNF-α), nitric oxide (NO), and other inflammatory mediatiors (Porcheray et al., 2005). Compared with many antitumor drugs, the polysaccharides derived from mushrooms are nontoxic and have been consumed since antiquity (Lull, Wichers, & Savelkoul, 2005). Hence, mushroom extracts can be considered as an excellent source for drug candidates. Some fungal polysaccharides are marketed as anticancer pharmaceutical agents in Japan, such as lentinan from *Lentinus edodes*, schizophyllan from *Schizophyllum commune* and krestin from *Coriolus versicolor* (Mizuno, Saito, Nishitoba, & Kawagishi, 1995; Zhang, Cui, Chueng, & Wang, 2007). These polysaccharides and their derivatives have been proved useful against various cancers, especially in the stomach, prostate and lungs (Wasser, 2002).

Definitions of chemical space based on physicochemical parameters are widely used in drug discovery programmes (Hann, 2011; Muchmore, Edmunds, Stewart, & Hajduk, 2010; Reymond, Deursen, Blum, & Ruddigkeit, 2010; Zuegg & Cooper, 2012). There are currently three useful definitions of chemical spaces, i.e., *lead-like*, *drug-like* and *known drug space* (KDS) and the parameters are given in Table 1. The Lipinski's rule of five is the most widely used to define *drug-like* chemical space, which indicates oral absorption of the complying compounds (Lipinski, 1997, 2004). Also the concepts of lead-like chemical space and KDS are used to define useful regions of chemical space. Leads are less complex and have lower molecular weights and lipophilicity (Log *P*) (Oprea, Davis, Teague, & Leeson, 2001). KDS includes all small organic compounds that are in medical use (Bade, Chan, & Reynisson, 2010; Mirza, Desai, & Reynisson, 2009). The idea therefore emerged whether sugar based drugs have a unique region in chemical space, which would enable drug developers to focus their efforts. The aim of this work is to investigate sugar based drugs in clinical use as well as polysaccharides with antitumor properties to establish their region in chemical space, based on main stream molecular descriptors.

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Table 1
Criteria of lead-like, drug-like and known drug space (KDS) in terms of molecular descriptors.

	Lead-like space	Drug-like space	Known drug space
Molecular weight ($g\,mol^{-1}$)	300	500	800
Lipophilicity (Log *P*)	3	5	6.5
Hydrogen bond donors (HD)	3	5	7
Hydrogen bond acceptors (HA)	3	10	15
Polar surface area ($Å^2$) (PSA)	60	140	180
Rotatable bonds (RB)	3	10	17

2. Methodology

The drugs and drug candidates were collected from DrugBank (Knox et al., 2011; Wishart et al., 2008, 2006). To find drugs with sugar moieties, substructure search was conducted using pentose and hexose molecular scaffolds. Three categories, namely pure sugar, modified sugar, and sugar moieties, were used. Six molecular descriptors: molecular weight (MW), Log *P*, hydrogen bond donors (HD), hydrogen bond acceptors (HA), polar surface area (PSA), and rotatable bonds (RB) were utilised and were collected from DrugBank. This information is given in the supplementary information (Table 1).

Mushroom polysaccharides with antitumor properties were found in the literature. Web of Knowledge, ScienceDirect, Scopus and Google Scholar databases were used. The structures of the polysaccharides were drawn in 2D ChemBioDraw Ultra 12.0 (CambridgeSoft, 1986–2009). These structures were converted into 3D objects using the default conversion procedure implemented in the CS ChemBio3D Ultra 12.0 (CambridgeSoft, 1986–2009). The generated structures were optimised using the MM2 (Allinger, 1977) force field with Scigress (Project Leader, Scigress Explorer Ultra, 2000–2007). The QikProp 3.2 (2009) software package was used to calculate the molecular descriptors based on whole molecular predictions. The reliability of QikProp is established for the molecular descriptors used (Ioakimidis, Thoukydidis, Naeem, Mirza, & Reynisson, 2008). A total of 58 polysaccharides exhibiting antitumor ability were gathered from the literature, including 40 polysaccharides from mushrooms and 18 from other natural sources. All the data are given in Table 2.

3. Results and discussion

3.1. Drugs and drug candidates

Overall, 769 drugs and drug candidates were found containing sugar moieties. They comprised of 88 approved and 681 experimental drugs. This is consistent with the study of Bade et al. (2010) who reported that sugar based drugs are relatively uncommon. The categories used were pure sugars, modified sugars, and drugs with sugar moieties. Only 4% (33) are pure sugar and 16% (121) as modified saccharides. Of the drugs found, just over half (52.4%) consist of pentose derivatives, while 5.6% contain both pentose and hexose moieties and the rest (42.0%) has the hexose scaffold. Fig. 1 shows examples of the three categories used.

3.2. The structure of the fungal polysaccharides

The structural attributes of the mushroom antitumor polysaccharides were investigated and the results are shown in Table 3. In general, seven monosaccharide residues including α-D-Glc*p*, β-D-Glc*p*, α-D-Gal*p*, β-D-Gal*p*, α-Man*p*, β-Man*p* and α-L-Fuc*p* are found as the building blocks for the backbone of the polysaccharides. β-D-Glc*p* is the major component which presents the greatest abundance (59%) in the backbone chain. β-D-Gal*p* and α-L-Fuc*p* show the lowest occurrence at just 1%. Those components are connected by four types of linkages, namely 1→2, 1→3, 1→4, and 1→6. The most common linkage is 1→3 at 44%. The monosaccharide units that constitute the branches of the polysaccharides demonstrate a greater diversity as two more monosaccharides are present (α-L-Ara*f*, and β-L-Rha). Similarly, β-D-Glc*p* has the largest percentage in branches at 46%. Besides the four types of linkages found in the backbone, the monosaccharide units also link together through 2→3 substitution (1.8%). The 1→6 linkage is most common in the branches at 54.4%.

The number of branches is apparently one of the important characteristics which significantly affect the antitumor ability (Chihara, Hamuro, Maeda, Arai, & Fukuoka, 1970). When comparing the repeating units of the polysaccharides, different numbers of branches are found to be attached to the backbone of the units. As shown in Table 3, 12.5% of the repeating units do not contain any branches. For the repeating units possessing branches, the numbers of branches are found as only 1, 2, and 4. There is a trend that as the increase in branching, the percentages of their corresponding repeating units decrease. Most repeating units (55.0%) possess only one branch. The rest of the repeating structures hold either 2 or 4 branches. 78% of the repeating units show the branching frequencies from 0.1 (1 in 10 backbone residues) to 0.5 (1 in 2 backbone residues). This range is broader than reported by Miyazaki et al. (1979) who suggested that the optimal branching frequency was from 0.2 to 0.33. Moreover, the polysaccharides exhibiting anticancer activity contain only short branch chains. Taking into account the number of monosaccharide residue, the branches have four types of chains that contain 1, 2, and 3 monosaccharides blocks, respectively. Especially, 86% of them have only one monosaccharide residue to form the branches. Others with short chains of 2 and 3 residues present low percentages.

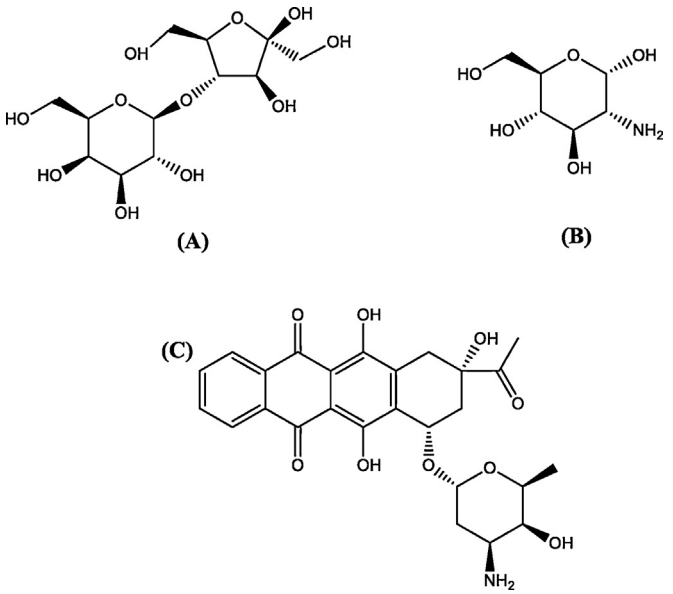

Fig. 1. Structures of lactulose as a pure sugar (A), glucosamine as a modified sugar (B) and doxorubicin as a compound containing a sugar moiety (C).