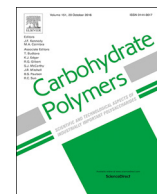




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# The important role of polysaccharides from a traditional Chinese medicine- Lung Cleansing and Detoxifying Decoction against the COVID-19 pandemic

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## ABSTRACT

The new coronavirus pneumonia, named COVID-19 by the World Health Organization, has become a pandemic. It is highly pathogenic and reproduces quickly. There are currently no specific drugs to prevent the reproduction and spread of COVID-19. Some traditional Chinese medicines, especially the Lung Cleansing and Detoxifying Decoction (Qing Fei Pai Du Tang), have shown therapeutic effects on mild and ordinary COVID-19 patients. Polysaccharides are important ingredients in this decoction. This review summarizes the potential pharmacological activities of polysaccharides isolated by hot water extraction from Lung Cleansing and Detoxifying Decoction, which is consistent with its production method, to provide the theoretical basis for ongoing research on its application.

## 1. Introduction

Since the outbreak of a large number of a new coronavirus infection in Wuhan, China in December 2019, the WHO has pronounced this novel coronavirus pneumonia epidemic to be a Public Health Emergency of International Concern (PHEIC), and named this infectious disease as “COVID-19” (Wu, Zhao et al., 2020). By mid-March 2020, more than 80,000 patients had been diagnosed with the disease in China, with 3000 deaths. The Chinese government has initiated a joint prevention and control initiative to prevent the spread of this COVID-19 epidemic. This coronavirus has spread to 44 countries on all continents except Antarctica, and transmission of COVID-19 in Italy, Iran and the Republic of Korea has brought the total number of infected cases in these three countries to nearly 35,000 as of March 14, 2020, from less than two percent that number just three weeks before. The situation is becoming worse daily, although in mid-March 2020, the number of new cases in China dropped noticeably.

Despite world-wide intense scientific effort, there is as yet no drug showing significant clinical effects on COVID-19 (Cao et al., 2020). However, traditional Chinese medicine has been playing a critical role in the prevention, treatment and rehabilitation of the COVID-19 (Ren, Zhang, & Wang, 2020). According to recent data collected by the

National Administration of Traditional Chinese Medicine, a Traditional Chinese Medicine (TCM) named “Lung Cleansing and Detoxifying Decoction (Qing Fei Pai Du Tang)”, of which the main components are carbohydrate polymers, has shown notable therapeutic effects on COVID-19 (Liu et al., 2020). Specifically, 214 confirmed cases in four provinces were administered with this drug for three treatment courses between January 27 and February 5, 2020, with more than 60 % of patients showing obvious improvement in symptoms and computed tomography (CT) manifestation and the remaining 30 % being stable without deterioration (Ren et al., 2020). As a result, the Lung Cleansing and Detoxifying Decoction was deployed in four mobile “Fangcang” hospitals in the epicenter city, Wuhan, which were temporary hospitals to quarantine mild cases. This decoction showed satisfactory efficacy, with nearly all the patients recovering from the symptoms of fever, fatigue and cough, according to the data collected in 66 designated medical institutions in 10 provinces (Stated by National Administration of Traditional Chinese Medicine, <http://www.satcm.gov.cn>).

As a result, the latest version of “Diagnosis and treatment of novel coronavirus pneumonia” (新型冠状病毒肺炎诊疗方案) statement issued by the National Health Commission of the People’s Republic of China (<http://www.nhc.gov.cn>, the sixth and seventh editions accessed 2020-02-19 and 2020-03-04, respectively), the Lung Cleansing and

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Detoxifying Decoction is recommended for all COVID-19 patients, especially in combination with western medical treatment. Even though this TCM has been used clinically for a long time in improving symptoms of fever, cough and fatigue as well as lung condition, and recently manifested definite therapeutic effect on COVID-19 patients (Ren et al., 2020; K. Zhang, 2020), its active ingredients remain unknown. This is probably because this TCM decoction has 21 herbal components which is derived from several classic recipes in a traditional Chinese medicine work. The complex constituents of Lung Cleansing and Detoxifying Decoction makes it a hard work to deeply explore its active ingredient in a short time.

It is generally acknowledged that polysaccharides are the main active ingredients of TCM decoction (Cao et al., 2018; Yu, Shen, Song, & Xie, 2018). Polysaccharides generally have a rather low toxicity, and contain hundreds or even thousands of monosaccharide units (Delattre, Fenoradosa, & Michaud, 2011). These polar macromolecular compounds are usually readily soluble in water. By employing the principle of "similar miscibility", polar macromolecular polysaccharides are extracted in boiled water. The present review summarizes the polysaccharides isolated by hot water extraction, which is consistent with the preparation method of Lung Cleansing and Detoxifying Decoction. So, we suppose that the polysaccharides are important activate ingredients in Lung Cleansing and Detoxifying Decoction and polysaccharides may play a vital role in treating COVID-19 patients.

## 2. The bioactive polysaccharides in Lung Cleansing and Detoxifying Decoction

Among the raw materials of Lung Cleansing and Detoxifying Decoction, the majority of their polysaccharide components have been elucidated. The structures of the following polysaccharides were well established (Fig. 1): *Bupleurum* polysaccharide (Zhao, Li, Yue, Zhang, & Dou, 2012), *Glycyrrhiza glabra* polysaccharide (Mutailifu et al., 2020), *Scutellaria baicalensis* polysaccharide (Cui et al., 2019a), *Poria cocos* polysaccharide (Lu, Cheng, Lin, & Chang, 2010), almond polysaccharide (Bouaziz, Koubaa, Ellouz Ghorbel, & Ellouz Chaabouni, 2017), *Pinelliae Rhizoma* polysaccharide (Hu et al., 2019), Chinese yam polysaccharide (Zhao, Kan, Li, & Chen, 2005), ginger polysaccharide (Chen, Chen, Wang, & Kan, 2020), *Rhizoma alismatis* polysaccharide (Zhao, Zhang, Li, Dong, & Liu, 2015), *Polyporus umbellatus* polysaccharide (He, Zhang, Zhang, Linhardt, & Sun, 2016), *Aster tataricus* polysaccharide (Zhang et al., 2012), *Ephedra* polysaccharide (Kuang, Xia, Liang et al., 2011), *Rhizoma Atractylodis* polysaccharide (Liang, Zhu, & Bai, 2011), *Fructus aurantii* polysaccharide (Shu et al., 2020), tangerine peel polysaccharide (Chen et al., 2016). However, there is no report relating to the identification of polysaccharides extracted from *Asarum*, *Cassia Twig*, *Flos Farfarae*, *Belamcanda chinensis* or *Agastache rugosa* (Table 1).

Based on the raw TCM materials and clinical evidence of Lung Cleansing and Detoxifying Decoction, we give an overview of its potential bioactive polysaccharides in treating COVID-19, the biological benefits of which appear to involve immunomodulatory activity, anti-inflammatory activity, anti-oxidative activity and regulation of gut microbiota balance.

### 2.1. Immunomodulatory activity

Since the outbreak of COVID-19, it has been realized that an effective body immune response plays an important role in the elimination of the virus and the prognosis of the disease (Chen, Zhou et al., 2020). Viruses are intracellular parasitic non-cellular microorganisms, and cellular immunity plays a leading role in eliminating viral infections (Li et al., 2020). From the perspective of general viral infections and individual immune responses, Immunomodulatory drugs have thus attracted attention because artificial passive immunity induced by administering immunomodulatory drugs can rapidly enhance cellular

immunity and may help fight viral infection. For example, clinical studies have found that the immunomodulatory thymosin drugs can increase the therapeutic effect of viral infections including hepatitis C virus (HCV) and rotavirus (Ciancio et al., 2012). The immunomodulatory effects of macrolides are also beneficial in pneumonia or chronic pulmonary inflammatory syndromes, decreasing disease severity and mortality (Kovaleva et al., 2012). Immune cells such as macrophages, neutrophils, monocytes, lymphocytes and NK cells are the main targets of coupling between immunostimulatory polysaccharides and specific proteins (Altan-Bonnet & Mukherjee, 2019). Polysaccharides with immunostimulatory activity can directly or indirectly interact with the host immune system, initiating a series of molecular interactions, leading to the activation of the immune system (Xie, Hao et al., 2016).

An immunomodulatory activity is one of the most significant properties of polysaccharides (Wang et al., 2020; Wu, Feng et al., 2020). In the Lung Cleansing and Detoxifying Decoction, there are a number of immunomodulatory polysaccharides, as follows. *Glycyrrhiza* polysaccharide could activate the immune system by promoting the maturation, differentiation and reproduction of immune cells such as lymphocytes and macrophages, as well as activating the reticuloendothelial system (Ayeka, Bian, Githaiga, & Zhao, 2017; Cheng, Wan, Wang, Jin, & Xu, 2008; He et al., 2011; Hong, Wu, Ma, Liu, & He, 2009; Yang & Yu, 1990). The immunomodulatory effects of *Bupleurum* polysaccharides had been demonstrated by enhancing phagocytic functions of murine peritoneal macrophages including phagocytosis of apoptotic thymocytes, chicken red blood cells, and IgG-opsonized sheep red blood cells (Cheng et al., 2010; Jiang et al., 2012; Matsumoto, Guo, Ikejima, & Yamada, 2003). Of note, polysaccharides in water extract of *Bupleurum* manifested anti-complementary activity, whereas the ethanol extract of that didn't show any activity (Xie et al., 2012). *Ephedra* polysaccharides isolated by hot water extraction contained four homogeneous fractions, of which ESP-B4 exhibited the highest bioactivity, which might be ascribed to its higher content of GalA and branches (Kuang, Xia, Yang, Wang, & Wang, 2011). *Poria cocos* polysaccharide, an oral drug approved by the Chinese Food and Drug Administration (CFDA) for treating hepatitis, cancers and other diseases (Li, Ma, & Zhang, 2019), was able to enhance both cellular and humoral immunity in mice (Lee et al., 2004; Ma, Chang, Chang, & Wu, 2010; Tian, Liu, Pu, & Bao, 2019), and thus showed potential as an adjuvant in vaccination (Zhang, Cheng et al., 2019). Chinese yam polysaccharides could be efficacious for immunomodulatory functions and immune enhancement, and also acted as adjuvants in developing vaccines (Luo et al., 2017, 2016). *Polyporus umbellatus* polysaccharide was a potent activator of B cells, macrophages and dendritic cells, manifesting significant ability to enhance innate immune function (Dai et al., 2012; Huang, Li, Chen, Liu, & Wang, 2019), probably via the activation of the TLR-4 signaling pathway (Li & Xu, 2011; Li, Xu, & Chen, 2010). *Rhizoma Atractylodis* polysaccharide promoted productions of NO, ROS and cytokines, enhancing immune response and immune function via a pivotal interaction network including NF- $\kappa$ B and JAK-STAT signaling pathways (Xu, Fang, Wang, Zhang, & Hu, 2020). In general, the relation between immunomodulatory activity of polysaccharides and their structures remains obscure. Some studies speculated that the complete structure, high molecular weight and basic structure-oligosaccharide unit were highly desired for the immunomodulatory action polysaccharides (Yan et al., 2003). Based on the sugar composition analysis, some investigations suggested that polysaccharides composed of glucan were known to stimulate the immune system (Kuang, Xia, Yang et al., 2011).

### 2.2. Anti-inflammatory activity

According to a recent paper in *Lancet*, the levels of inflammatory factors in the plasma of critical patients, such as IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1A and TNF- $\alpha$ , are all higher than those without



Fig. 1. The processed raw materials of “Lung Cleansing and Detoxifying Decoction” in treating COVID-19. (The images are collected from Internet, with no conflict of interest).

intensive care, suggesting that the occurrence of this “cytokine storm” is closely related to the severity of COVID-19 patients (Huang et al., 2020). A cytokine storm, a term initially proposed in 1993 (Ferrara, 1993), is considered to be an important signal for the transformation from ordinary patients to progress to severe and critically ill, and it is also the main cause of acute respiratory distress syndrome (ARDS) and sepsis, which are the leading causes of COVID-19 death (W. Zhang, 2020). A direct suppression on the lung inflammatory response seems warranted as the cytokine storm may be relieved after inflammatory therapy. Previous studies had demonstrated the benefits of anti-inflammatory agents in lung diseases. Drugs that target inflammation have been shown to slow the decline in lung function and improve survival (Konstan et al., 2011; VanDevanter et al., 2012). Ibuprofen, a commonly used anti-inflammatory drug, is recommended for the long-term treatment of airway inflammation in cystic fibrosis lung disease (Flume et al., 2007).

An anti-inflammatory activity is very common in various sources of polysaccharides (Bezerra et al., 2018; Gao et al., 2019; Kang et al.,

2011). It was reported that polysaccharides consisting of Gal, Glc, GalA and Rha revealed potent anti-inflammatory activity (Capek et al., 1988). The anti-inflammatory polysaccharides in the Lung Cleansing and Detoxifying Decoction may play crucial roles in suppressing the cytokine storm, thus effectively treating mild COVID-19 patients and blocking the conversion from mild cases to severe stage. As an example, an acid component of *Ephedra* polysaccharide, ESP-B4, possessed obvious protective effects on pulmonary inflammation and rheumatoid arthritis by reducing the production of TNF- $\alpha$ , IL-6, IL-8 and MMP-9 (Liang et al., 2018) and inhibiting the TLR4 signaling pathway (Wang et al., 2016), respectively. A polysaccharide from *Scutellaria baicalensis* might be a drug candidate in treating colitis via suppressing NF- $\kappa$ B signaling and NLRP3 inflammasome activation (Cui et al., 2019b). *Bupleurum* polysaccharide could significantly relieve lung injury in an acute pneumonia model by inhibiting P-selectin-mediated recruitment of neutrophils rolling along the CHO-P cells (Sun et al., 2010; Tong et al., 2014, 2018). A *Poria cocos* polysaccharide could suppress the production of IP-10, the marker of interferon (IFN)-c-induced

**Table 1**  
Bioactive polysaccharides in “Lung Cleansing and Detoxifying Decoction”.

Bioactivities	Polysaccharides	Proposed structure	Composition	Molecular Weight	Mechanisms	References
Immunomodulatory activity	<i>Glycyrrhiza</i> polysaccharide	$\beta$ -1,3-linked D-galactose residues; $\alpha$ -1,4-linked D-glucose	Not determined	10kD	Promoting the maturation, differentiation and reproduction of immune cells such as lymphocytes and macrophages, as well as activating the reticuloendothelial system	Cheng et al. (2008)
	<i>Bupleurum</i> polysaccharide	Not determined	Ara: Gal: Glc: Rha = 6.35: 3.15: 1.47: 1	2000kD	Enhance phagocytic functions of murine peritoneal macrophages	Cheng et al. (2010)
	<i>Ephedra</i> polysaccharides	Not determined	ESP-B4: Xyl (1.5 %), Ara (6.8 %), Glc (1.5 %), Rha (3.0 %), Man (1.5 %), Gal (8.3 %), GlcUA (2.3 %) and GalUA (75.2 %)	> 2000 × 10 <sup>6</sup> Da for ESP-B4	Inhibition on splenocyte proliferation	Kuang, Xia, Yang et al. (2011)
	<i>Portia cocos</i> polysaccharide	(1→3)- $\beta$ -D-glucan possessing 9–10 branches of (1→6) linked $\beta$ -D-glucopyranosyl groups and internal (1→6)- $\beta$ -D-linkages	Man (92 %), Gal (6.2 %), and Ara (1.3 %)	8kD	Enhance both cellular and humoral immunity in mice; Activate T cells; Activate NF- $\kappa$ B/Rel and iNOS expression by upregulating p38 kinase in murine macrophages	Lee et al. (2004), Ma et al. (2010), Tian et al. (2019)
Anti-inflammatory activity	Chinese yam polysaccharide	1, 3-linked-glc, 1-linked-gal and 1, 6-linked-gal glycosidic bonds	Glu: Gal = 1.52:1	16619Da	Chinese yam polysaccharide nanoparticles: Promote lymphocyte proliferation and trigger the transformation of T lymphocytes into Th cells	Luo et al. (2017, 2016)
	<i>Polyporus umbellatus</i> polysaccharide	(1→6, 1→4)-linked $\beta$ -D-glucopyranosyl backbone, substituted at O-3 position of (1→6)-linked $\beta$ -D-glucopyranosyl by (1→3)-linked $\beta$ -D-glucopyranosyl branches	$\beta$ -Glucans (> 90 % D-glucose)	2.27kD	Activator of B cells, macrophages and dendritic cells; Promote the activation and maturation of murine bone-derived dendritic cells via TLR4	Dai et al. (2012), Huang et al. (2019), Li et al. (2010)
	<i>Rhizoma Atractylodis</i> polysaccharide	1, 3-linked-D Galp and 1, 6-linked-D Galp residues	Glu (60.67 %), Man (14.99 %), Rha (10.61 %), Ara (8.83 %) and Gal (4.90 %)	1.87kD	Promotes productions of NO, ROS and cytokines via an interaction network including NF- $\kappa$ B and JAK-STAT signaling pathways	Xu et al. (2020)
	<i>Ephedra</i> polysaccharide	Not determined	ESP-B4: Xyl (1.5 %), Ara (6.8 %), Glc (1.5 %), Rha (3.0 %), Man (1.5 %), Gal (8.3 %), GlcUA (2.3 %) and GalUA (75.2 %)	> 2000 × 10 <sup>6</sup> Da for ESP-B4	Regulate Factor-1/Smad2 signaling pathway; Inhibit the TLR4 signaling pathway	Liang et al. (2018), Wang et al. (2016)
Anti-inflammatory activity	<i>Scutellaria baicalensis</i> polysaccharide	Not determined	Man: Rib: GlcUA: Glu: Xyl: Ara = 2.14:3.61:1.2:86:5.98:36.39	456kD	Suppress NF- $\kappa$ B signaling and NLRP3 inflammasome activation	Cui et al. (2019b)
	<i>Bupleurum</i> polysaccharide	(1→5)-linked Ara, (1→4)-linked Gal and (1→3)-linked Gal residues with occasionally branches at O-6	Ara: Gal: Glc = 2.1:2:5:1	29kDa	Inhibit P-selectin-mediated recruitment of neutrophils rolling along the CHO-P cells	Sun et al. (2010), Tong et al. (2014, 2018)
	<i>Portia cocos</i> polysaccharide	neutral 1,6-branched 1,3- $\alpha$ -D-galactan	myo-inositol, sorbitol, fucose, galactosamine, glucosamine, galactose, glucose and mannose	610.7, 40.7, 7.9, 1.6, and 0.3 kDa	Suppress IP-10	Lu et al. (2010)
						(continued on next page)

Table 1 (continued)

Bioactivities	Polysaccharides	Proposed structure	Composition	Molecular Weight	Mechanisms	References
Anti-oxidative activity	<i>Bupleurum</i> polysaccharide	Not determined	51.20 % total carbohydrate and 48.47 % uronic acid; Gal: Ara: Glc: Rha: Man = 13.43: 11.57: 4.02: 1.02: 1.0	Not determined	Reduce the content of MDA in serum and bronchoalveolar lavage fluid (BALF) and enhancing the SOD, in acute lung injury model	Xie et al. (2012)
	<i>Ephedra</i> polysaccharide	Not determined	Not determined	Not determined	Increase the SOD activity and reduce the production of MDA	Fan et al. (2015)
	<i>Glycyrrhiza</i> polysaccharide	Not determined	Glu: Gal: Ara = 23.4: 25.18: 8.32(GUPs-1), 14: 25.67: 17.54(GUPs-2), 1.13: 22.04: 31.44(GUPs-3)	10160(GUPs-1), 11680(GUPs-2) and 13360(GUPs-3) Da	Fe <sup>2+</sup> -chelating activity; scavenge hydroxyl radicals, superoxide radical and DPPH radical	Zhang et al. (2015b)
	<i>Polyporus umbellatus</i> polysaccharide	Backbone: 1→6, 1→3-linked; side chains: →6)-β-D-Glcp-(1→, →3)-β-D-Glcp-(1→, →4)-β-D-Glcp-(1→, β-D-Glcp-(1→, →4)-β-D-GlcpA-(1→ and →3,6)-β-D-Glcp-(1→	glucose and 8.5 % uronic acid	PUP80S1: 8.8kDa	Absorb oxygen radical and scavenge 2,2-diphenyl-1-picrylhydrazyl radical	He, Zhang, Zhang et al. (2016)
	<i>Portia cocos</i> polysaccharide	Backbone: (1→6)-β-D-glucopyranosyl; side chains: β-D-Glcp, (1→3)-β-D-Glcp, (1→3)-β-D-GlcpA, (1→4)-β-D-Glcp and (1→4)-β-D-GlcpA	glucose and 22.3 % glucuronic acid	PUP60S2: 14.4 kD		He, Zhang, Wang et al. (2016)
	<i>Portia cocos</i> polysaccharide	Not determined	Man: Glu: Gal: Ara = 0.92: 86.88: 0.18: 12.01	21.5kDa	Relieve ox-LDL-induced oxidative stress via the ERK/Nrf2/HO-1 signaling pathway; Reduce DPPH radical and hydroxyl radical	Wang et al. (2016), Zhao et al. (2020)
	<i>Rhizoma Atractylodis</i> polysaccharide	Not determined	Rha: Xyl: Ara: Glu: Man: Gal = 1: 1.3: 1.5: 1.8: 2.1: 3.2	19.6kD	Reduce NOS, NO and MDA activity or contents, increase SOD and GSH-Px activities	Han et al. (2016)
	Ginger polysaccharide	Sugar residues: →1,4)-α-D-Glcp-(1→; →2,3,4)-α-D-Manp-(1→; →1,4,6)-α-D-Galp-(1→	Man: Glu: Gal = 4.96: 92.24: 2.80	GP1: 6128Da	Eliminate DPPH free radical	Wang, Wei et al. (2018)
	Chinese yam polysaccharide	Sugar residues: →1,4)-α-D-Glcp-(1→; →2,3,4)-α-D-Manp-(1→; →1,4,6)-α-D-Galp-(1→; →3)-β-D-Arap-(1→	Ara: Man: Glu: Gal = 4.78: 16.70: 61.77: 16.75	GP2: 12619Da		
	Chinese yam polysaccharide	1,3-linked-glc, 1-linked-gal and 1,6-linked-gal glycosidic bonds	Glu: Gal = 1.52: 1	16619Da	Remove superoxide anion	Yang et al. (2015)
Maintain intestinal homeostasis	<i>Bupleurum</i> polysaccharide	Not determined	Man: Rha: GlcA: GalA: Glc: Gal: Xyl: Ara = 2.93: 2.62: 1.00: 4.57: 15.11: 23.28: 1.46: 25.34	2.917731, 281670 and 2707 Da	<i>Firmicutes/Bacteroidetes</i> ↓ <i>Rikenellaceae</i> ↑ <i>Ruminococcus</i> ↓ <i>Oscillospira</i> ↑ <i>Roseburia</i> ↑ <i>Bifidobacteria</i> ↑ <i>Lactobacilli</i> ↑	Feng et al. (2019)
	Chinese yam polysaccharide	Not determined	Not determined	Not determined	<i>Enterococcus</i> ↓ <i>Clostridium perfringens</i> ↓ <i>Lachnospiraceae</i> ↑ <i>Alloprevotella</i> ↑ <i>Parabacteroides</i> ↑ <i>Clostridium IV</i> ↑ <i>Ruminococcus</i> ↑ <i>Bacteroides</i> ↓ <i>Megamonas</i> ↓ <i>Proteus</i> ↓	Zhang, Liang et al. (2019)
	<i>Portia cocos</i> polysaccharide	Not determined	Not determined	4486kDa, 403kDa	<i>Alkermansia muciniphila</i> ↑ <i>Alisipipes massiliensis</i> ↓ <i>Robinsoniella peoriensis</i> ↓ <i>Helicobacter hepaticus</i> ↓ <i>Lactococcus</i> ↑ <i>Lactobacillus</i> ↑ <i>Faecalibacterium</i> spp. ↑ <i>Bacteroides</i> spp. ↑	Khan et al. (2018)
Antibacterial activity	Chinese yam polysaccharide	1,3-linked-glc, 1-linked-gal and 1,6-linked-gal glycosidic bonds	Glu: Gal = 1.52: 1	16619Da	Inhibit <i>E. coli</i> (MIC 2.5 mg/mL)	Yang et al. (2015)
	<i>Portia cocos</i> polysaccharide	Not determined	Glu: Gal = 40.9: 1	20.5kDa	Inhibit <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> growth	Li et al. (2018), Wang, Zhang et al. (2018)
Antitussive activity	<i>Asarum</i> polysaccharides	Not determined	Not determined	Not determined	Decrease cough sensitivity and suppress airway inflammation	US20160339054A1 US20180271896A1

inflammation, in a dose-dependent manner, suggesting its anti-inflammatory potential (Lu et al., 2010). Pachyman, a kind of *Poria cocos* polysaccharide, showed antinephritic effect in rats with nephritis, probably via the inhibition of inflammation caused by C3 deposition in the glomeruli (Chihara, Hamuro, Maeda, Arai, & Fukuoka, 1970; Hattori et al., 1992).

### 2.3. Anti-oxidative activity

An anti-oxidative activity is an important pharmacological action in polysaccharides (Li et al., 2018; Mzoughi et al., 2018; Raguraman et al., 2019). Oxidative stress and inflammation can act together to form a positive feedback cycle (Mittal, Siddiqui, Tran, Reddy, & Malik, 2014). Under normal circumstances, the production and elimination of reactive oxygen species (ROS) in the body maintains an oxidation-anti-oxidation balance, which plays an important role in regulating signal pathway transduction and cell proliferation (Cao et al., 2019; Forrester, Kikuchi, Hernandez, Xu, & Griendling, 2018). When the balance is broken by inflammatory factors, the body will produce an oxidative stress response, leading to cell oxidative damage and development of multi-system diseases (Kruk, Aboul-Enein, Kladna, & Bowser, 2019; Sies, 2015). Oxidative stress in turn activates multiple signaling pathways to induce inflammation, such as activation of NF- $\kappa$ B and NOD-like receptor protein 3 (NLRP3), further promoting the maturation of pro-inflammatory factors (Ahmad & Ahsan, 2020). Vitamin C, a powerful antioxidant, has been demonstrated to play a role in lowering the incidence of pneumonia in several controlled trial with human subjects (Hemila, 2017).

A large body of researches have suggested that many polysaccharides possess anti-oxidative properties (Yu et al., 2018), which may be critical to their multiple pharmacological activities. *Bupleurum* polysaccharides had been demonstrated to exert definite protective effects in murine lung-injury models (Cheng et al., 2012; Xie et al., 2012). Specifically, this kind of polysaccharide could alleviate the degree of acute lung injury by reducing the amount of malondialdehyde (MDA) in serum and bronchoalveolar lavage fluid and enhancing superoxide dismutase (SOD) activity (Xie et al., 2012). *Ephedra* polysaccharide could significantly increase the activity of SOD and reduce the production of MDA, thereby protecting the liver from free radical and lipid peroxidation damage on hyperlipidemic mice (Fan et al., 2015). *Glycyrrhiza* polysaccharide had significant ability to scavenge hydroxyl, superoxide radical and DPPH radicals in vitro, and also enhanced the SOD, CAT, GSH-Px and TAOC activities in vivo (Hong et al., 2009; Zhang, Yu, Liang, & Chen, 2015). It was shown that *glycyrrhiza* polysaccharide with lower molecular weight and higher ratio of glucose exhibited more effective antioxidant activities at the same concentration (Zhang, Yu, Liang, & Chen, 2015). This phenomenon might be explained as a high molecular weight polysaccharide possesses a high viscosity, which may have great influence on its bioactivities (Chen, Lu, Cheng, & Wang, 2005). Two kinds of antioxidative polysaccharides, named PUP60S2 and PUP80S1, were isolated from *Polyporus umbellatus*, among which PUP60S2 showed higher antioxidative activity (He, Zhang, Zhang et al., 2016; He, Zhang, Wang et al., 2016). This might be ascribed to more uronic acid residues and a higher level of branching of PUP60S2 when they have similar structures, as demonstrated that higher degree of polysaccharide branching is beneficial for exerting antioxidant activity (Zhao et al., 2014). *Poria cocos* polysaccharide could significantly relieve ox-LDL-induced oxidative stress via the ERK/Nrf2/HO-1 signaling pathway in vascular smooth muscle cells (Tang et al., 2014; Zhao et al., 2020). It was demonstrated that *Poria cocos* polysaccharides extracted by different methods manifested different antioxidative properties, with microwave-assisted extraction possessing best antioxidant activity (Wang et al., 2016). *Rhizoma Atractylodis* polysaccharide acted as a potent antioxidant by reducing NOS activity, increasing SOD and GSH-Px activities, and decreasing NO and MDA contents in mice (Han et al., 2016; Liang et al., 2011). Ginger

polysaccharides also showed high oxidation resistance in several studies (Chen, Yuan, Wang, Qi, & Cheng, 2019; Wang, Wei et al., 2018).

### 2.4. Regulation of population balance of gut microbiota

The composition of intestinal microbiota is closely related to human health and plays a vital role in maintaining physiological balance. Intestinal microbiota acts as a protective mediator during pneumococcal pneumonia by enhancing primary alveolar macrophage function (Schuijt et al., 2016). It has also been demonstrated that modulating gut microbiota can reduce ventilator-associated pneumonia and enteritis (Bradley et al., 2019). Probiotic bacteria such as *Bifidobacterium* and *Lactobacillus* can stimulate the immune system and reduce serum lipids, while increased amounts of pathogens like *Enterococcus* and *Clostridium perfringens* may cause diseases (Buffie & Pamer, 2013; Gerritsen, Smidt, Rijkers, & de Vos, 2011). The risk of heterotopic intestinal flora is increased if the intestinal mucosal immune barrier is in a vulnerable state, when microbiota dysbiosis makes patients prone towards secondary bacterial infections (Gao, Chen, & Fang, 2020). COVID-19 patients show intestinal microbial dysbiosis with decreased levels of certain probiotic microbiota, including *Lactobacillus* and *Bifidobacterium*. Even though there is currently no direct clinical evidence proving that modulation of gut microbiota has a therapeutic role in treating COVID-19, we suggest that modulating gut microbiota might be a new therapeutic strategy or at least an adjuvant therapeutic choice (Konig & Brummer, 2020). The latest version of "Diagnosis and treatment of novel coronavirus pneumonia", published by National Health Commission of the People's Republic of China, suggests using intestinal microbiological regulators to maintain the intestinal microecological balance in severe and critical cases.

Regulating gut microbiota is a major focus of current polysaccharide research. In a study on the effect of *Bupleurum* polysaccharide on diabetic nephropathy in mice, the ratio of phyla *Firmicutes/Bacteroidetes*, which has been widely regarded as the marker of gut microbiota homeostasis, was elevated in diabetic mice but could be reversed by a supplementation of *Bupleurum* polysaccharide (Feng et al., 2019). In addition, the abundances of *Rikenellaceae*, *Ruminococcus* and *Oscillospira* were also increased after polysaccharide treatment, among which *Ruminococcus* is a probiotic that is found dominantly in healthy gut (Ma et al., 2018), and *Oscillospira* may relieve inflammation by utilizing host glycans as growth substrates (Konikoff & Gophna, 2016). Butyrate is an essential energy source that can influence microbial environment and protect the host against the pathogenic bacteria (Cani, 2018). It is noteworthy that *Roseburia*, a bacterium producing butyrate (Delzenne, Cani, Everard, Neyrinck, & Bindels, 2015), was also elevated after polysaccharide intervention. These results suggest that *Bupleurum* polysaccharide may alleviate gut microbiota dysbiosis by increasing the relative abundance of beneficial bacteria, including proliferating butyrate-producing ones.

It has been found that polysaccharides from Chinese yam enriched beneficial intestinal bacteria and inhibited the growth of bacterial pathogens in the cecum of SD rats (Kong et al., 2009). The effect of Chinese yam polysaccharides on intestinal microbiota was also evaluated in a model of antibiotic-associated diarrhea (Zhang, Liang et al., 2019). In this experiment, the effect of yam polysaccharides on fecal microbiota was assessed by the colony-count technique, and the results suggested that these polysaccharides elevated the richness and diversity of bacterial communities. In addition, administrating yam polysaccharides increased probiotic *Bifidobacteria* and *Lactobacilli* by 47 % and 21 %, and decreased pathogen *Enterococcus* and *Clostridium perfringens* by 8 % and 27 %, respectively, compared with a model group (Turroni et al., 2014; Wagley et al., 2019).

*Poria cocos* polysaccharide is also a prebiotic in *ob/ob* mice, significantly reducing glucose- and lipid-metabolism disorders and reducing inflammation through modulating the gut microbiota (Sun, Wang, Ma, Bao, & Liu, 2019). It altered the bacterial contents of 20 genera,

with six elevated SCFAs-production bacteria (*Lachnospiracea*, *Alloprevotella*, *Parabacteroides*, *Clostridium IV*, *Ruminococcus* and *Bacteroides*) reaching significant statistical differences. Further, *Poria cocos* polysaccharide significantly reduced the abundance of the pro-inflammatory bacteria *Megamonas* and *Proteus*, by 120- and 101-fold, respectively (Byndloss et al., 2017). These results demonstrate that the beneficial effects of *Poria cocos* polysaccharide is dependent on modulating gut microbiota composition, which is shown to be causative by a fecal transplantation test (Sun et al., 2019).

In another study, normal C57BL/6 mice were intragastrically administered with *Poria cocos* polysaccharide for 15 consecutive days, followed by 16S rRNA gene sequencing of their feces (Khan et al., 2018). *Poria cocos* polysaccharide significantly promoted the growth of *Akkermansia muciniphila*, a beneficial bacterium that enhances host immunity (de Vos, 2017), whereas the abundances of pro-inflammatory bacteria, including *Alistipes massiliensis*, *Robinsoniella peoriensis* and *Helicobacter hepaticus*, were reduced after polysaccharide gavage (Halfvarson et al., 2017). In addition, *Poria cocos* polysaccharide enriched lactic acid-producing (LAP) genera, namely *Lactococcus* and *Lactobacillus*, both of which have been shown to possess anti-inflammatory and immunoenhancement properties (Castillo, de Moreno de LeBlanc, Galdeano, & Perdigon, 2013; Luerce et al., 2014). Moreover, *Faecalibacterium* spp. and *Bacteroides* spp., the SCFA producing bacteria, were particularly promoted with polysaccharide treatment (Chang et al., 2015; Rios-Covian et al., 2016).

### 2.5. Other effects

Anti-virus and anti-bacterial activities are also important properties of polysaccharides. Considering that there is no evidence demonstrating anti-viral activity of these polysaccharides helps to eliminate coronavirus, and no antiviral drug has been demonstrated to cure COVID-19 till now. Thus, it is reasonable to suppose that the antiviral activity of polysaccharides in the Lung Cleansing and Detoxifying Decoction does not play a significant role in its therapeutic action.

Secondary bacterial co-infection is common in COVID-19 infected patients, which may lead to serious outcomes (MacIntyre et al., 2018). Antibiotic treatment is therefore necessary in a portion of patients infected by the bacteria. Apart from the predominant bioactivities mentioned above, some polysaccharides also display antibacterial activity (He, Yang, Yang, & Yu, 2010), which might be helpful to some extent in treating the COVID-19 pandemic. *Glycyrrhiza* polysaccharide displayed antimicrobial activity, inhibiting the growth of *B. cereus*, *S. aureus*, *E. Aerogens* and *E. coli* (Harish & Jyoti, 2019). The purified Chinese yam polysaccharide showed an inhibitory activity against *Escherichia coli*, with a minimum inhibitory concentration (MIC) of 2.5 mg/mL (Yang, Wang, Li, & Yu, 2015). A recent study found that *Poria cocos* polysaccharide could inhibit the growth of *Staphylococcus aureus* and *Escherichia coli* (Wang, Zhang et al., 2018).

There is a lack of studies on the structure and activity of *Asarum* polysaccharide, but it has been reported in two patents (US20160339054A1 and US20180271896A1) that the total polysaccharides extract from *Asarum* exerted excellent antitussive activity. This suggests that *Asarum* polysaccharides can decrease cough sensitivity and suppress airway inflammation. It is reasonable to suppose that the *Asarum* polysaccharides in the Lung Cleansing and Detoxifying Decoction play an important role in relieving cough symptoms, which are prevalent in COVID-19 patients.

### 3. Summary and future prospects

Most COVID-19 infected individuals are diagnosed as in the mild or ordinary stages. There is not at present any conventional drug that can cure this disease. However, according to the data collected by National Health Commission of the People's Republic of China, clinical practice in Chinese hospitals has reported that TCMs have definite therapeutic

actions at the early stage of disease (Liu et al., 2020), while common antiviral drugs such as oseltamivir, Arbidol and Lopinavir/Ritonavir failed to cure these patients (Cao et al., 2020). As the main component of the medical practice, TCM has been used for more than 5000 years in China in treating human diseases (Li & Kan, 2017). It is a natural chemical library which leads to synergistic actions through multiple mechanisms. Modern medical research has demonstrated that polysaccharides are one of the main active ingredients of TCM (Liu, Sun, Liu, & Yu, 2012; Zheng et al., 2019). In recent decades, polysaccharides extracted from medicinal plants are attracting increasing attention due to their significant bioactivities, such as antioxidant activity, anti-viral activity and immunomodulatory activities (Xie, Jin et al., 2016). In addition, they are non-toxic and rarely show side effects, making them suitable as medicinal candidates. This review summarizes the underlying actions of TCM in view of polysaccharides. It would appear that the immunomodulatory, anti-inflammatory, anti-oxidative and regulating gut balance activities of these polysaccharides play the most important roles in the treatment of COVID-19 infected patients.

In addition to drug therapy, effort is now going toward developing novel vaccines to slow the COVID-19 pandemic. In the development of a novel vaccine, adjuvants are a vital component because they boost and accelerate the innate immune response (Xia et al., 2018). Producing vaccines with polysaccharides as the adjuvants is an innovative strategy. In recent years, the pharmaceutical industry has made an effort to discover active ingredients from natural products for clinical use, due to their low toxicity. Polysaccharide-based vaccines have the potential to be adjuvants. For instance, *Pinus massoniana* pollen polysaccharide improved the effects of various vaccines, by acting as an immune adjuvant (Guo et al., 2014). Bacterial capsular polysaccharides vaccines had shown significant effects in the prevention of pneumonia and epidemic meningitis (Yu et al., 2018). *Streptococcus pneumoniae* polysaccharide vaccine and *Haemophilus influenzae* Hib polysaccharide vaccine have been successfully applied to prevent encephalitis. From a clinical view, TCM polysaccharides are very promising to act as new adjuvants in the formulations of vaccines, due to their universal immunomodulation and promotion effects, safety and biocompatibility. These data have proven the adjuvant benefits of the active polysaccharides from TCM, which may represent an attractive source of the vaccine development against COVID-19.

There is no doubt that the bioactive TCM polysaccharides are going to take important place in the fight against COVID-19 world-wide. However, each TCM prescription is a complex system and has multiple targets and links in curing disease, but that also makes it difficult to illustrate its function mechanism clearly and completely in a short time. More research on TCM polysaccharides should be undertaken to clarify the regulatory mechanisms, assess the possible side effects and conduct standard clinical trials. The insights provided in this review may help mitigate the COVID-19 pandemic.

### CRediT authorship contribution statement

**Peng Cao:** Writing - original draft, Conceptualization. **Sanlan Wu:** Writing - review & editing. **Tingting Wu:** Visualization, Investigation. **Yahui Deng:** Investigation. **Qilin Zhang:** Investigation. **Kaiping Wang:** Validation. **Yu Zhang:** Supervision.

### Declaration of Competing Interest

The authors declare no conflicts of interest.

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