


## REVIEW

# Molecular basis for *Poria cocos* mushroom polysaccharide used as an antitumour drug in China

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## Abstract

*Poria cocos* is an edible medicinal fungus known as “Fuling” in Chinese and has been used as a Chinese traditional medicine for more than two thousand years. Pharmacological studies reveal that polysaccharide is the most abundant substance in *Poria cocos* and has a wide range of biological activities including antitumour, immunomodulation, anti-inflammation, antioxidation, anti-ageing, antihepatitis, antidiabetics and anti-haemorrhagic fever effects. As a result, “*Poria cocos* polysaccharide oral solution” was developed and sold as an over-the-counter health supplement since 1970s. In 2015, “Polysaccharidum of *Poria cocos* oral solution” was approved as a drug by Chinese Food and Drug Administration for treating multiple types of cancers, hepatitis and other diseases alone or during chemo- or radiation therapy for patients with cancer. In this article, biochemical, preclinical and clinical studies of *Poria cocos* polysaccharide from 72 independent studies during the past 46 years (1970–2016) based on PubMed, VIP (Chongqing VIP Chinese Scientific Journals Database), CNKI (China National Knowledge Infrastructure) and Wanfang database searches are summarized. The structure, pharmacological effects, clinical efficacy, immunobalancing molecular mechanism and toxicity of *Poria cocos* polysaccharide are deliberated to provide a general picture of *Poria cocos* polysaccharide as a clinically used antitumour drug.

## KEYWORDS

antitumour, clinical application, pharmacological activities, polysaccharides, *Poria cocos*

## 1 | INTRODUCTION

*Poria cocos* (Figure 1), known as “Fuling” in Chinese, is an edible medicinal mushroom belonging to dry sclerotium of polyporaceae fungi. It has more than 2000 years of medical application history for its remarkable pharmaceutical effect.<sup>1</sup> The bioactive components in *Poria cocos* include polysaccharides, triterpenoids, fatty acids, sterols and enzymes. *Poria cocos* polysaccharide (PCP) accounts for 84% by weight among all constituents in the dried sclerotium.<sup>2</sup> PCP is also the main bioactive component in *Poria cocos*.

### 1.1 | The structural composition and properties of PCP

PCP is extracted from the sclerotium of *Poria cocos*. Different solvent extraction methods can obtain different polysaccharide fractions, such as WPS (NaOH-HAc), PAP (1 mol/L NaOH), PCP2 (hot water), PCP1 (0.9% NaCl), PCP3-I and PCP3-II (0.5 mol/L NaOH), PCP4-I and PCP4-II (88% formic acid).<sup>3,4</sup> Thus, PCP is a mixture of different types of polysaccharides with the molecular weight ranged from  $4.1 \times 10^4$  to  $5 \times 10^6$  Da.<sup>5</sup> Glucose, fucose, arabinose, xylose,

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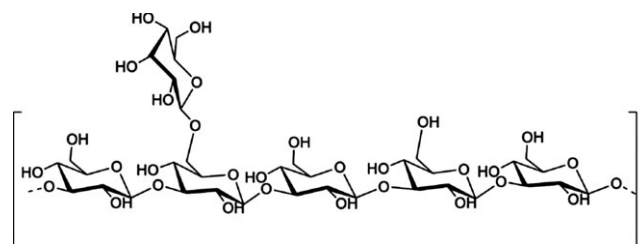
mannose and galactose are detected in PCP.  $\beta$ -Glucan is the major PCP with  $\beta$ -(1 $\rightarrow$ 3)-linked glucose backbone and  $\beta$ -(1 $\rightarrow$ 6)-linked glucose side chains as shown in Figure 2.<sup>3,6</sup> The  $\beta$ -glucan from *Poria cocos* has poor water solubility but decent anticancer activity.<sup>7</sup> Chihara et al removed the  $\beta$ -(1 $\rightarrow$ 6) glucose in the  $\beta$ -glucan of PCP by periodate oxidation and Smith degradation. The derivative is named "pachymaran," which exhibits better anti-S-180 tumour activities.<sup>8</sup> Hamuro et al further improved the water solubility issue of pachymaran by chemical carboxymethylation. The carboxymethylated pachymaran (CMP) has enhanced antitumour activity compared to that of pachymaran.<sup>9</sup> Subsequently, different chemical modifications, such as sulfation,<sup>10</sup> carboxymethylation plus sulfation,<sup>11</sup> methylation, hydroxyethylation and hydroxypropylation, have been conducted and different types of modified pachymarans are reported.<sup>12</sup> In general, these chemical modified pachymaran derivatives are water-soluble and show improved bioactivities.

## 1.2 | PCP-based drug in China

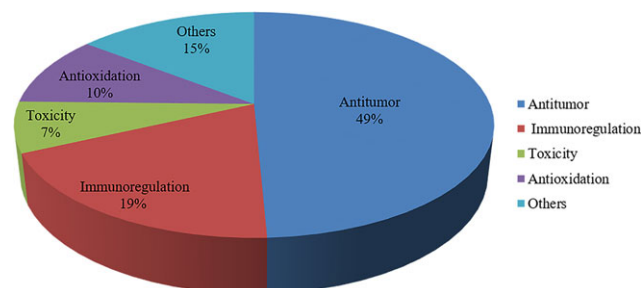
PCP-based product named "compound polysaccharide oral solution" was developed in the 1970s and was very popular with consumers as health supplement products. In 2006, "Polysaccharidum of *Poria cocos* oral solution" was developed by Hunan Butian pharmaceutical company of China and was granted a Chinese patent (20061 0163425-X). The major component (95%) in the patented product is CMP. The water solubility of CMP allows 98% of the components to be absorbed through the human digestive track. In 2015, "Polysaccharidum of *Poria cocos* oral solution" was approved by Chinese Food and Drug Administration with a certified drug number B20050015 for treating multiple types of cancers, hepatitis and other diseases alone or during chemo- or radiation therapy for patients with cancer.



**FIGURE 1** The fruiting body of Mushroom *Poria cocos*. *Poria cocos* is an edible medicinal fungus known as "Fuling" in Chinese and has been used as a Chinese traditional medicine for more than two thousand years



**FIGURE 2** A schematic diagram of  $\beta$ -glucan structure in *Poria cocos*.  $\beta$ -Glucan is the major *Poria cocos* polysaccharide with  $\beta$ -(1 $\rightarrow$ 3)-linked glucose backbone and  $\beta$ -(1 $\rightarrow$ 6)-linked glucose side chains. The  $\beta$ -glucan from *Poria cocos* has poor water solubility but decent anticancer activity



**FIGURE 3** Pharmacological activities of *Poria cocos* polysaccharides (PCPs). Sixty-six articles related to pharmacological activities of PCPs are summarized. Thirty-eight per cent of studies are about antitumour activities of PCPs. Twelve per cent of studies are about antitumour mechanisms. Studies on immunoregulation, antioxidant and toxicity account for 19%, 10% and 7%, respectively. Fourteen per cent of pharmacological activity studies of PCPs are defined as "others" that are further explained in Figure 4

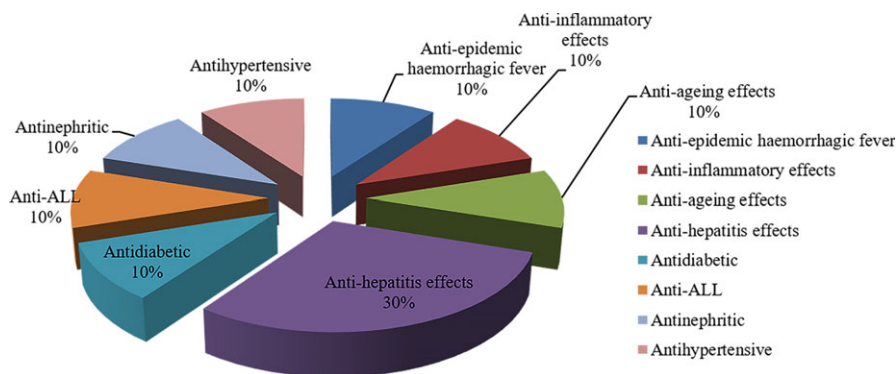
## 1.3 | The approach for the literature searching

In this article, a total of 72 publications related to different kinds of *Poria cocos* polysaccharides (PCPs), pachymaran, the derivatives and the biochemical/preclinical/clinical studies up to date were identified through searching PubMed, VIP (Chongqing VIP Chinese Scientific Journals Database), CNKI (China National Knowledge Infrastructure) and Wanfang database. The reported biological and pharmacological activities of PCP are classified based on these publications and shown in Figures 3 and 4. The pharmacological and other biological functions and possible molecular mechanisms shown in Figures 3 and 4 will be the major topics discussed in this article. Moreover, the data that show PCPs can overcome immunosuppression and adverse reactions associated with radiation therapy and chemotherapy<sup>13</sup> will also be presented and discussed.

## 2 | PHARMACOLOGICAL ACTIVITIES OF PCP

### 2.1 | Antitumour

Parallel to other reported polysaccharides from fungi,<sup>14–16</sup> PCP and its derivatives have more impressive anticancer cell proliferation activities



**FIGURE 4** Other pharmacological activities of PCPs. Antihepatitis effects: 30%; antidiabetic effects: 10%; anti-epidemic haemorrhagic fever: 10%; anti-ageing effects: 10%; anti-inflammatory effects: 10%; and anti-acute lymphoblastic leukaemia (ALL): 10%

**TABLE 1** Abbreviation list

Abbreviation	Full name	Abbreviation	Full name
ALL	Acute lymphoblastic leukaemia	LCT	Lymphocytes transformation
ACV	Acyclovir	LLC	Lewis lung carcinoma
Bcl-2	B-cell lymphoma-2	-L	Low dosage
Bcap-37	Breast carcinoma cells	-M	Medium dosage
Bax	Bcl-2 Associated X protein	MPCP	Methylated <i>poria cocos</i> polysaccharide
BHT	Butylated hydroxytoluene	MAO	Monoamine oxidase
CMP	Carboxymethylated pachymaran	MDA	Malondialdehyde
CTX	Cyclophosphamide	NS	Normal saline
CA	Cortisone acetate	NK	Natural killer cell
CP	Hericium erinaceus polysaccharide+Lentinan+Pachymaran	OH	Hydroxyl free radical
CPABM	Agaricus blazei murill polysaccharide+Lentinan+CMP	PCP	<i>Poria cocos</i> polysaccharide
DAG	Dianhydrogalactitol	PCP1	Polysaccharide extracted using 0.9% NaCl
DXM	Dexamethasone	PCP2	Polysaccharide extracted using hot water
DPPH	1,1-Diphenyl-2-picrylhydrazyl radical 2,2-Diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl	PCP3	Polysaccharide extracted using 0.5 mol/L NaOH
EC50	50% effective concentration	PCP4	Polysaccharide extracted using 88% formic acid
Ea	Active erythrocyte rosettle test	PTPP	Phosphorylation of protein tyrosine phosphatase
Et	Total erythrocyte rosettle test	PT	Pachymaran and triterpens
EAC	Ehrlich ascites carcinoma cells	PS	Pachymaran (Sulphated)
FP	Ferulic acid pachymaran	Pt	Cisplatin
HBsAg	Hepatitis B surface antigen	PAP	Acidic pachymaran
HBeAg	Hepatitis Be Antigen	SGC-7901	Gastric carcinoma cells
HE-PCP	Hydroxyethylated <i>poria cocos</i> polysaccharide	SOD	Superoxide dismutase
HP-PCP	Hydroxypropylated <i>poria cocos</i> polysaccharide	SGPT	Serum glutamic pyruvic transaminase
H <sub>22</sub>	H <sub>22</sub> hepatoma	TNF	Tumour necrosis factor
HPBL	Human peripheral blood lymphocyte	TPK	Tyrosine protein kinase
-H	High dosage	U <sub>-14</sub>	U-14 ascitic fluid tumour cells
IC50	Half maximal inhibitory concentration	Vc	Vitamin C
IFN- $\gamma$	Interferon- $\gamma$	WPS	Polysaccharide extracted using NaOH-HAc
KSC	Kappa-selenocarrageenan	5-Fu	5-fluoro-2,4(1H,3H) pyrimidinedione
LH	Levamisole hydrochloride		
Lewis	Lung carcinoma cell		

**TABLE 2** Inhibition rates of PCPs on different cancer cells

Cell types	Groups	Cancer inhibition rates (%)	P-value	References
SGC-7901 (human)	Distilled water	0		17
	5-Fu-L	34.98		
	5-Fu-M	69.92		
	5-Fu-H	85.05		
	PCP2-L	60.09		
	PCP2-M	90.04		
	PCP2-H	96.10		
Bcap-37 (human)	5-Fu-L	35.41		
	5-Fu-M	61.04		
	5-Fu-L	88.72		
	PCP2-L	42.48		
	PCP2-M	85.09		
	PCP2-H	88.54		
HepG2 (human)	PAP1	14.22 ± 1.06		4
	PAP2	16.65 ± 3.01		
	PAP3	6.94 ± 2.08		
	PAP4	15.98 ± 4.16		
	PAP5	16.71 ± 1.72		
	PAP6	16.02 ± 2.65		
	PAP7	59.76 ± 5.47	P < .05	
	PAP8	23.45 ± 1.31	P < .05	
	PAP9	78.67 ± 1.68	P < .01	
	PAP10	82.92 ± 2.8	P < .01	
K562 (human)	NS	0		30
	PS-L	16.95 ± 5.16		
	PS-M	27.80 ± 3.57		
	PS-H	52.95 ± 1.2		

in vivo than in vitro when the same PCP samples are tested both in cancer cell lines and in cancer cell-injected animal models. The in vitro anticancer cell proliferation effects of PCPs are summarized in Table 1, whereas the in vivo antitumour growth effects of PCPs are summarized in Table 2 from 15 independent studies.<sup>17–30</sup>

PCPs possess decent anticancer cell proliferation effect in vitro, which is measured in cell cultures where different tumour cell lines derived from human or mouse tumours have been tested, such as SGC-7901 (human), Bcap-37 (human), HepG2 (human) and K562 (human) cells (Table 2). For example, the inhibition rate for SGC-7901 cells is 96% compared to that of 88% for Bcap-37 cells.<sup>17</sup> As shown in Table 2, the inhibition rates of PCP or its derivatives on the proliferation of cancer cells are largely concentration-dependent, which resembles the control drug 5-fluoro-2,4(1H,3H) pyrimidine-dione or 5-Fu.

In contrast, in cancer cell-injected animal models (Table 3), the inhibition rates of PCP or its derivatives on tumour growth are only partially concentration-dependent in that within a certain range, the higher the concentrations, the higher the inhibition rates are. But

beyond the range, the inhibition rates will drop. For example, the experiment conducted by Cheng et al<sup>18</sup> showed that the inhibition rates of cancer cell growth are 0, 69%, 87%, 92% and 89%, respectively, with increasing CMP concentrations.

The inhibition of tumour growth in vivo is measured either by the reduced tumour weight or by ultrasound compared to controls in different animal models and presented as tumour inhibition rates (%). The controls include blank and positive controls where the chemotherapeutic drug, such as 5-fluoro-2, 4 (1H, 3H) pyrimidine-dione (5-Fu), is used. PCPs have potent antitumour activities in different animal tumour models when compared to blank or 5-Fu controls (Table 3). When PCP is modified with different chemical groups, such as carboxymethyl, sulphate, methyl, hydroxypropyl and hydroxyethyl, the derivatives exhibit better inhibition rates. For example, Wang et al extracted six polysaccharides from the fresh sclerotium of *Poria cocos* using different solvents sequentially, including PCP1 (0.9% NaCl), PCP2 (hot water), PCP3-I and PCP3-II (0.5 mol/L NaOH), PCP4-I and PCP4-II (88% formic acid). They then modified PCP3-II chemically and obtained five different PCP3-II derivatives.<sup>3</sup> They showed<sup>19</sup> that all the derivatives inhibit tumour growth better than PCP3-II with the inhibiting rates increased by 36% and 35% for sulphated and carboxymethylated derivatives, respectively, and by 24%, 15% and 20% for methylated, hydroxypropylated and hydroxyethylated derivatives, respectively. They further demonstrated that the increased degree of chemical modifications and the increased molecular weight in the derivatives correlate with better inhibiting rates in vivo.

Furthermore, the curing effects can be further enhanced when PCPs are combined with chemotherapeutic drugs in different animal models. In addition, the combined therapy also reduces the adverse effects associated with chemotherapeutic drugs (Table 4). For example, Liu et al<sup>31</sup> Tang et al<sup>32</sup> and Chen et al<sup>29</sup> reported that PCPs exhibit better tumour inhibition rates when it is used with other chemotherapeutic drugs. For instance, inhibition rates were 46% when PCP is used with 5-Fu compared with the inhibition rates of 41% when 5-Fu is used alone.<sup>29</sup>

## 2.2 | Antitumour mechanisms

PCPs exert their antitumour activity via assisting the host to overcome adverse biological stresses, to increase immunity against the tumours and to promote the apoptosis of tumour cells directly. The possible mechanisms reported so far are summarized in Table 5A-D and Figure 5<sup>33–38</sup> and discussed below.

### 2.2.1 | Enhancing the innate immunity through activating the immune cells

Polysaccharides could activate effector immune cells, such as macrophages, lymphocytes and natural killer (NK) cells to activate the innate immune system to exert antitumour activity by accelerating the host's defence mechanisms.<sup>33</sup> It is reported that the ratio of lymphocytes could increase to 62% in the treatment group compared

**TABLE 3** Tumour inhibition rates of PCPs in animal models

Models	Administration route	Cell types	Groups	Tumour weight (g)	P-value	Tumour inhibition rates (%)	P-value	References
ICR mice	Intragastric administration	S <sub>-180</sub> (mouse)	Distilled water	2.742 ± 0.378		0		20
			5-Fu	1.341 ± 0.135	<i>P</i> < .001	45.73		
			CMP-L	1.972 ± 0.399	<i>P</i> < .05	2.23		
			CMP-H	1.675 ± 0.412	<i>P</i> < .01	32.22		
			5-Fu+CMP-L	1.413 ± 0.394	<i>P</i> < .001	42.83		
			5-Fu+CMP-H	1.283 ± 0.483	<i>P</i> < .001	48.11		
ICR/JCL mice	Intraperitoneal injection	U <sub>-14</sub> (mouse)	NS	1.385 ± 0.101		0		18
			CMP (30 mg/kg)	0.433 ± 0.105	<i>P</i> < .01	68.7		
			CMP (120 mg/kg)	0.182 ± 0.121	<i>P</i> < .01	86.9		
			CMP (180 mg/kg)	0.108 ± 0.053	<i>P</i> < .01	92.2		
			CMP (360 mg/kg)	0.151 ± 0.113	<i>P</i> < .01	89.1		
Kunming mice	Intraperitoneal injection	S <sub>-180</sub> (mouse)	NS	1.23 ± 0.11		0		21
			CTX	0.49 ± 0.07	<i>P</i> < .01	60.21		
			WPS-L	0.99 ± 0.10		19.53		
			WPS-M	0.89 ± 0.12	<i>P</i> < .01	28.01		
			WPS-H	0.72 ± 0.08	<i>P</i> < .01	43.94		
			WPS1-L	0.98 ± 0.13		2.32		
			WPS1-M	0.96 ± 0.06	<i>P</i> < .1	22.45		
			WPS1-H	0.70 ± 0.07	<i>P</i> < .01	41.57		
			WPS2-L	1.09 ± 0.08		11.45		
			WPS2-M	0.98 ± 0.10	<i>P</i> < .1	2.32		
			WPS2-H	0.74 ± 0.04	<i>P</i> < .01	39.81		
Kunming mice	Intragastric administration	S <sub>-180</sub> (mouse)	NS	0.753 ± 0.191		0		22
			CTX	0.155 ± 0.091	<i>P</i> < .05	79		
			PCP-L	0.437 ± 0.117	<i>P</i> < .05	42		
			PCP-M	0.482 ± 0.105	<i>P</i> < .05	36		
			PCP-H	0.527 ± 0.152	<i>P</i> < .05	30		
BALB/c mice	Intraperitoneal injection	S <sub>-180</sub> (mouse)	PBS	1.61 ± 0.32		0		19
			5-Fu	0.76 ± 0.16		52.76	<i>P</i> < .01	
			PCP3-II-L	1.56 ± 0.42		2.46		
			PCP3-II-H	1.57 ± 0.66		3.02		
			PS-L	1.39 ± 0.27		13.88		
			PS-H	1.21 ± 0.41		34.63	<i>P</i> < .05	
			CMP-L	1.23 ± 0.48		23.45	<i>P</i> < .05	
			CMP-H	1.04 ± 0.20		35.27	<i>P</i> < .01	
			MPCP3-II-L	1.34 ± 0.46		16.65		
			MPCP3-II-H	1.22 ± 0.38		24.48	<i>P</i> < .05	
			HE-PCP3-II-L	1.63 ± 0.36				
			HE-PCP3-II-H	1.29 ± 0.29		20.20		
			HP-PCP3-II-L	1.45 ± 0.27		10.00		
			HP-PCP3-II-H	1.37 ± 0.48		14.88		
			PBS	1.40 ± 0.32		0		
			5-Fu	0.76 ± 0.27		46.0	<i>P</i> < .01	

(Continues)

**TABLE 3** (Continued)

Models	Administration route	Cell types	Groups	Tumour weight (g)	P-value	Tumour inhibition rates (%)	P-value	References
			PS-2-L	1.09 ± 0.26		22.32		
			PS-2-H	0.90 ± 0.36		35.71	<i>P</i> < .05	
			PS-4-L	0.89 ± 0.18		36.51	<i>P</i> < .05	
			PS-4-H	0.97 ± 0.36		30.95		
			PS-5-L	0.91 ± 0.34		34.92	<i>P</i> < .05	
			PS-5-H	0.86 ± 0.26		38.39	<i>P</i> < .05	
			PS-6-L	1.14 ± 0.12		18.25		
			PS-6-H	1.16 ± 0.39		17.35		
			PS-9-L	0.92 ± 0.29		33.93	<i>P</i> < .05	
			PS-9-H	0.93 ± 0.38		33.33	<i>P</i> < .05	
Balb/c mice	Intraperitoneal injection	S <sub>-180</sub> (mouse)	PBS	1.407 ± 0.32		0		23
			5-Fu	0.867 ± 0.26		46	<i>P</i> < .01	
			PS	0.767 ± 0.27		38.39	<i>P</i> < .05	
ICR/JCL mice	Intragastric administration	S <sub>-180</sub> (mouse)	NS	1.989 ± 0.594		0		24
			5-Fu	0.363 ± 0.286	<i>P</i> < .01	81.7		
			CMP-L	1.282 ± 0.166	<i>P</i> < .05	35.5		
			CMP-M	1.159 ± 0.126	<i>P</i> < .05	41.6		
			CMP-H	0.963 ± 0.364	<i>P</i> < .05	51.6		
	Intravenous injection	S <sub>-180</sub> (mouse)	NS	3.425 ± 0.958		0		
			5-Fu	0.323 ± 0.261	<i>P</i> < .01	90.6		
			CMP-L	2.106 ± 1.037	<i>P</i> < .05	38.5		
			CMP-M	2.294 ± 1.037	<i>P</i> < .05	32		
			CMP-H	2.049 ± 0.752	<i>P</i> < .05	40.2		
	Intragastric administration	H <sub>22</sub> (mouse)	NS	1.721 ± 0.571		0		
			5-Fu	0.269 ± 0.230	<i>P</i> < .01	84.65		
			CMP-L	0.760 ± 0.470	<i>P</i> < .05	55.58		
			CMP-M	1.044 ± 0.438	<i>P</i> < .05	39.03		
			CMP-H	0.644 ± 0.438	<i>P</i> < .01	62.24		
ICR/JCL mice	Intraperitoneal injection	U <sub>-14</sub> (mouse)	NS	1.225 ± 0.122		0		25
			CMP (25 mg/kg)	0.253 ± 0.11	<i>P</i> < .01	79.4		
			CMP (50 mg/kg)	0.26 ± 0.137	<i>P</i> < .01	78.8		
			CMP (100 mg/kg)	0.089 ± 0.003	<i>P</i> < .01	92.7		
			CMP (500 mg/kg)	0.30 ± 0.095	<i>P</i> < .01	75.5		
	Intravenous injection	S <sub>-180</sub> (mouse)	NS	3.431 ± 1.136		0		
			CMP-L	2.237 ± 0.977	<i>P</i> < .05	34.8		
			CMP-M	2.141 ± 0.969	<i>P</i> < .05	37.6		
			CMP-H	1.339 ± 0.683	<i>P</i> < .01	61		
	Intravenous injection	H <sub>22</sub> (mouse)	NS	2.167 ± 0.812		0		
			CMP-L	1.732 ± 0.988		20.1		
			CMP-M	1.372 ± 0.673	<i>P</i> < .05	36.7		
			CMP-H	1.485 ± 0.931	<i>P</i> < .05	31.5		

(Continues)

TABLE 3 (Continued)

Models	Administration route	Cell types	Groups	Tumour weight (g)	P-value	Tumour inhibition rates (%)	P-value	References
NIH mice	Intragastric administration	S <sub>-180</sub> (mouse)	NS	1.34 ± 0.32		0		26
			5-Fu	0.54 ± 0.43	<i>P</i> < .001	59.7	<i>P</i> < .01	
			CMP-L	0.48 ± 0.34	<i>P</i> < .001	64.18	<i>P</i> < .01	
			CMP-M	0.70 ± 0.36	<i>P</i> < .001	47.76	<i>P</i> < .05	
		S <sub>-180</sub> (mouse)	CMP-H	0.51 ± 0.53	<i>P</i> < .001	61.94	<i>P</i> < .01	
			NS	1.30 ± 0.22		0		
			5-Fu	0.67 ± 0.14	<i>P</i> < .001	48.46	<i>P</i> < .05	
			CMP-L	0.54 ± 0.12	<i>P</i> < .001	58.46	<i>P</i> < .01	
		EAC(mouse)	CMP-M	0.78 ± 0.14	<i>P</i> < .001	40.00	<i>P</i> < .05	
			CMP-H	0.74 ± 0.16	<i>P</i> < .001	43.08	<i>P</i> < .05	
			NS	1.06 ± 0.16		0		
			5-Fu	0.45 ± 0.16	<i>P</i> < .001	57.55	<i>P</i> < .01	
		EAC(mouse)	CMP-L	0.43 ± 0.18	<i>P</i> < .001	59.43	<i>P</i> < .001	
			CMP-H	0.54 ± 0.21	<i>P</i> < .001	49.06	<i>P</i> < .05	
			NS	1.02 ± 0.15		0		
			5-Fu	0.41 ± 0.19	<i>P</i> < .001	59.80	<i>P</i> < .01	
ICR/ICJ mice	Intragastric administration	S <sub>-180</sub> (mouse)	NS	2.49 ± 0.42		0		28
			PCP-L	1.29 ± 0.28	<i>P</i> < .01	48.1		
			PCP-M	1.46 ± 0.46	<i>P</i> < .01	41.37		
			PCP-H	2.25 ± 0.67		.96		
CFW mice	Intraperitoneal injection	S <sub>-180</sub> (mouse)	NS	5.1 ± 0.9		0		29
			PCP-H	2.9 ± 1.0		43.1	<i>P</i> < .01	
			PCP-M	3.1 ± 1.1		39.2	<i>P</i> < .01	
			PCP-L	3.2 ± 1.7		37.3	<i>P</i> < .01	
Rats	Intraperitoneal injection	S <sub>-180</sub> (mouse)	NS	10.2 ± 2.6		0		27
			PCP	5.77 ± 2.7		39.9	<i>P</i> < .01	
			PS	6.10 ± 3.0		43.2	<i>P</i> < .01	

with control group (47%)<sup>34</sup> and phagocytic ability of macrophages could reach 59% compared with control group of 27%.<sup>36</sup>

## 2.2.2 | Increasing cytokine levels

TNF (tumour necrosis factor) secreted by macrophages and lymphocytes is used as a drug for tumour biotherapy. IL-6 (interleukin-6) secreted by T lymphocytes and fibroblasts improves the killing ability of NK cells. Miu et al and Chen et al found that carboxymethyl pachymaran could improve the levels of IFN- $\gamma$ , IL-2, TNF and IL-6.<sup>35,38</sup>

## 2.2.3 | Stimulating the expression of apoptosis-related genes

Bcl-2 and Bax are members of the Bcl-2 family, which are important for the regulation of apoptosis. The Bax/Bcl-2 ratio

determines the survival of cells. Meng reported that sulphated pachymaran could enhance the expression of apoptosis-related genes Fas and Bax and reduce the expression of Bcl-2 gene. The increased Bax/Bcl-2 ratio is responsible for the apoptosis of S180 tumour cells in the mouse model.<sup>33</sup> Zhang et al showed that WPS could inhibit the growth of human breast carcinoma MCF-7 cells by inducing G1 arrest of the cell cycle and by elevating the Bax/Bcl-2 ratio.<sup>39</sup>

## 2.2.4 | Regulating the activities of TPK and PTPP in cancer cells

TPK (tyrosine protein kinase) and PTPP (phosphotyrosine protein phosphatase) are two important enzymes controlling the growth, proliferation and differentiation of cells. Several studies reported that the activities of TPK and PTPP have changed significantly when the

**TABLE 4** Tumour inhibition rates of PCPs ± chemotherapy on mice

Models	Administration routs	Cell types	Groups	Tumour weight(g)	P-value	Tumour inhibition rates (%)	P-value	References
Kunming mice	Intragastric administration	S <sub>180</sub> (mouse)	NS	3.01 ± 0.38		0		31
			CTX	0.84 ± 0.21	<i>P</i> < .01	72.1		
			CPABM-L	2.10 ± 0.28	<i>P</i> < .01	30.2		
			CPABM-M	1.43 ± 0.24	<i>P</i> < .01	52.5		
			CPABM-H	2.69 ± 0.32		10.6		
			CPABM+CTX-L	0.52 ± 0.16	<i>P</i> < .01	82.7		
			CPABM+CTX-M	0.50 ± 0.19	<i>P</i> < .01	83.4		
			CPABM+CTX-H	1.03 ± 0.31	<i>P</i> < .01	65.8		
Kunming and NIH mice	Intragastric administration	S <sub>180</sub> (mouse)	NS	1.89 ± 0.24		0		32
			CP-L	1.18 ± 0.29	<i>P</i> < .05	37.73 ± 13.11		
			CP-M	1.03 ± 0.36	<i>P</i> < .05	44.74 ± 19.33		
			CP-H	0.98 ± 0.26	<i>P</i> < .05	48.34 ± 13.08		
CFW mice	Intraperitoneal injection	S <sub>180</sub> (mouse)	NS	1.4 ± 0.6		0		29
			5-Fu	0.7 ± 0.2		50	<i>P</i> < .05	
			CTX	1.1 ± 0.4		21.4		
			DAG	0.9 ± 0.4		35.7	<i>P</i> < .05	
			PCP	1.0 ± 0.4		28.6		
			PCP+5-Fu	0.9 ± 0.3		35.7	<i>P</i> < .05	
			PCP+CTX	0.8 ± 0.3		42.9	<i>P</i> < .05	
			PCP+DAG	0.8 ± 0.3		42.9	<i>P</i> < .05	

cells become cancerous, but PCP normalizes the activities of TPK and PTPP in cancer cells and slowdowns cancer cell growth.<sup>37</sup>

### 2.3 | Immunomodulation

Studies showed that PCP could enhance host immune function and activate the immune response.<sup>26,36,40–47</sup> It is reported that PCPs could modulate their specific immune response via the activation of T cells.<sup>40</sup> Pachymaran strongly enhances the generation of alloreactive cytotoxic T lymphocytes *in vivo*.<sup>41</sup> Generally speaking, the strength of the immune function can be judged through three aspects: the capability of macrophage's phagocytosis, the cellular immune function by detecting the index of immune organs<sup>42,43</sup> and the humoral immunity function by measuring the production of antibodies and serum haemolysins. As shown in Table 5C,D, Zhang et al and Xu et al found that the capability of macrophage's phagocytosis, thymus index and spleen index have significantly improved by PCP.<sup>26,42</sup> Zhang et al and Peng et al reported that the levels of IgA, IgG and IgM in serum are increased and the levels of IFN- $\gamma$  and IL-4 are also enhanced by PCPs.<sup>46–48</sup>

### 2.4 | Antioxidation

Free radicals refer to the dissociative molecules, atoms or ions with unpaired electron that reacting rapidly with other substances. Under certain range, free radicals can help to eliminate microorganisms intruding into body or abnormal cells. However, if free radicals are

excessively produced, they would attack the normal cells and tissues. Therefore, human body constantly produces and removes free radicals to maintain a dynamic balance. Studies showed that PCP has antioxidant activity by scavenging free radicals. As shown in Table 6,<sup>49–53</sup> Li et al and Zhang et al found that PCP2 and FP could clear free radicals (O<sub>2</sub><sup>-</sup>, ·OH and DPPH·) and the clearance rate of DPPH· could reach 93%.<sup>51,52</sup> Wang et al also found that carboxymethylated PCP has DPPH·, O<sub>2</sub><sup>-</sup> and ·OH radical-scavenging activity *in vitro*.<sup>54,55</sup> Superoxide dismutase (SOD) is an important antioxidant enzyme in organisms and Chen et al showed that CMP could increase the expression of SOD and reduce the amount of MAD (malondialdehyde).<sup>53</sup>

### 2.5 | Other pharmacological activities

PCPs have other biological effects, such as anti-inflammatory,<sup>56</sup> anti-ageing,<sup>57</sup> antihepatitis,<sup>58,59</sup> antidiabetic,<sup>60</sup> anti-ALL (acute lymphoblastic leukaemia),<sup>61</sup> anti-nephritic<sup>62</sup> and antihypertensive effects.<sup>63</sup> These pharmacological activities are summarized in Table 7A,B. Hou et al observed that PCP reduces the size of granuloma.<sup>56</sup> As an anti-ageing reagent, PCPs enhance the activities of both T-SOD and Cu-SOD and reduce MAD and MAO (monoamine oxidase) activities.<sup>57</sup> To understand the antihepatitis effects of CMP, it is found that CMP reduces the expression of HBsAg and HBeAg in a concentration-dependent manner.<sup>58</sup> Zheng et al reported that PCP could reduce blood glucose level and increase the weight of mice in a diabetic mouse model.<sup>60</sup>





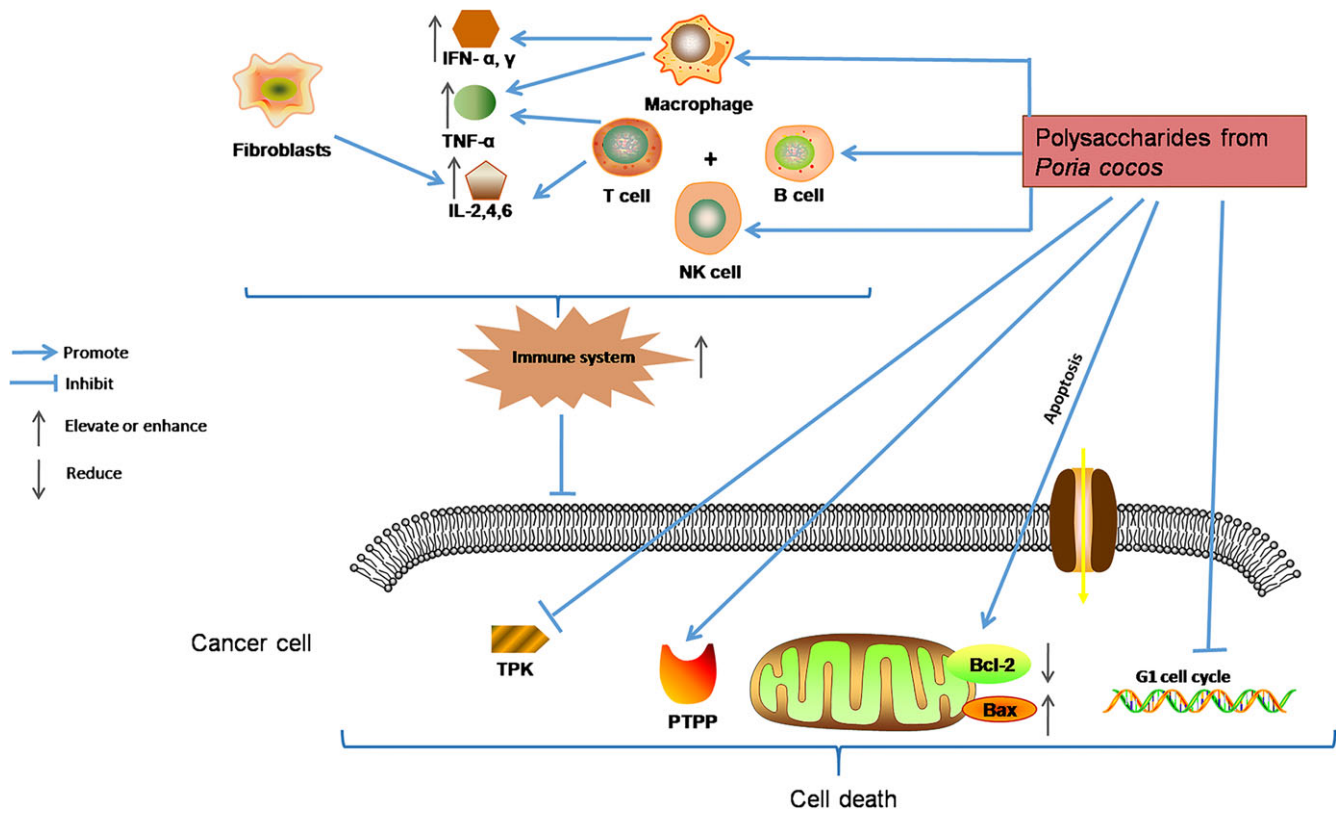
TABLE 5 (Continued)

Models	Administration routs	Cell types	Groups	IFN- $\gamma$ (IU/mL)	TNF (ug/mL)	Phagocytic ability (%)	IL-6 (IU)	TPK in cytoplasm (min <sup>-1</sup> × $\mu$ m <sup>-1</sup> )	TPK in cytomembrane (min <sup>-1</sup> × $\mu$ g <sup>-1</sup> )	PTPP in cytoplasm (min <sup>-1</sup> × $\mu$ g <sup>-1</sup> )	PTPP in cytomembrane (min <sup>-1</sup> × $\mu$ g <sup>-1</sup> )	References
Cancer cells	HL-60		Control					105.1	197.8	1.93	0.97	37
			PCP					62.5	158.1	6.08	3.14	38
Cancer cells	HPBL		Control	3400	315 (U/mL)		4232					
			CMP	6216	450 (U/mL)	6478						
Models	Administration routs		Groups	Phagocytic ability (%)	Thymus index	Spleen index	IFN- $\gamma$ (pg/mL)	References				
(C)												
Kunming mice	Intragastric administration		NS	45.5	2.19	2.10		42				
			LH	67.83	2.73	2.92						
			PT-L	58.83	2.72	2.85						
			PT-M	70.17	2.74	2.93						
			PT-H	69.67	2.73	2.91						
C57BL/6 mice	Intravenous injection		NS			1.15	44					
			Pt			0.42						
			PCP-L			1.1						
			PCP-H			1.41						
Kunming mice	Intraperitoneal injection		NS		3.09		45					
			DXM		1.11							
			PS+DXM		1.89							
			PS		2.84							
BALB/c mice	Intraperitoneal injection		NS			77.00	43					
			CMP			248.33						
NIH mice	Intragastric administration		NS	58.36	47.14	73.00	26					
			CTX	37.64	23.17	42.34						
			CMP-L	48.36	27.91	43.55						
			CMP-M	51.09	30.28	54.88						
			CMP-H	55.18	36.73	58.69						

(Continues)

TABLE 5 (Continued)

Models	Administration routs	Groups	Phagocytic ability (%)	Thymus index	Spleen index	IFN- $\gamma$ (pg/mL)	References
ICR/ICJ mice	Subcutaneous injection	NS	39.65				36
		CMP	59.26				
		NS	30.39				
		CA	18.86				
		CA+CMP	34.81				
		CMP	50.48				
		NS		24.75	56.84		
		CTX		22.25	45.7		
		CTX+CMP		19.08	45.57		
		CMP		33.82	69.87		
<b>(D)</b>							
Kunming mice	Intragastric administration	NS		61.45	286.64	2.23	46
		LH		97.32	378.46	2.81	
		PCP (60%-L)		103.67	376.19	2.78	
		PCP (60%-M)		122.38	570.30	3.53	
		PCP (60%-H)		139.65	706.79	4.58	
		NS	0.4081	67.8	852.1	655.4	
Kunming mice	Intragastric administration	CTX	0.1891	43.8	585.5	302.4	47
		CTX+PCP-L	0.2630	56.6	773.3	465.2	
		CTX+PCP-H	0.2949	64.1	822.5	504.1	
		PCP	0.4967	84.1	1071.2	655.4	



**FIGURE 5** Possible antitumour mechanisms of PCPs. PCPs exert their antitumour activity via assisting the host to overcome adverse biological stresses, to assist the host to enhance the lethality of macrophages, T cells, B cells and NK cells by releasing cytokines to increase immunity, and to promote the apoptosis of tumour cells directly by up-regulating the expression of apoptosis-related genes

**TABLE 6** Antioxidant effects of PCPs

Groups	Deoxidization (abs)	Antioxidation (abs)	Clearance rate (%)	EC50 (g/L)	MDA in serum (nmol/mL)	MDA in hepar (nmol/mg.pro)	SOD activity in serum (U/mL)	SOD activity in hepar (U/mg.pro)	IC50 (mg/mL)	References
BHT	0.912	0.406								49
PCP	0.490	0.546								
CMP				2.5 (OH)						50
Vc				0.2 (-OH)						
CMP				>1.5 (O <sub>2</sub> <sup>-</sup> )						
Vc				1.5 (O <sub>2</sub> <sup>-</sup> )						
PCP (8 mg/mL)			76.7 (-OH)							51
PCP (10 mg/mL)			59.3 (O <sub>2</sub> <sup>-</sup> )							
PCP (5 mg/mL)			93.4 (DPPH)							
FP (4 mg/mL)			58.72 (-OH)	2.5 (-OH)						52
FP (4 mg/mL)			39.7 (DPPH)							
CMP								2.57 (O <sub>2</sub> <sup>-</sup> )		53
								7.66 (-OH)		
								4.56 (H <sub>2</sub> O <sub>2</sub> )		
NS					12.38	40.54	9.12	187.56		
CMP-L					12.05	31.75	9.87	190.52		
CMP-M					11.52	28.53	10.25	204.78		
CMP-H					8.74	24.62	12.67	224.63		

**TABLE 7** (A) Other pharmacological effects of PCPs: anti-inflammatory, anti-ageing and antihepatitis effects (B) Other pharmacological effects of PCPs: antidiabetic and anti-acute lymphoblastic leukaemia effects

Other effects	Groups	Swelling degree (mg)	Granuloma (mg/10 g)	T-SOD	Cu-SOD	MDA	MAO	Death time of swimming (min)	Inhibition of HBsAg (%)	Inhibition of HBeAg (%)	Inhibition of Anti-HBc	Inhibition of SGPT	References	
(A) Anti-inflammatory effects	NS	6.2	47										56	
	DXM	3.2	13											
	PCP-L	3.6	36											
	PCP-M	7.4	40											
	PCP-H	8.5	38											
Anti-ageing effects	Double distilled water			108	46	7.1	16	2.48					57	
	PCP-L			114	54	6.7	19	3.68						
	PCP-M			125	60	6.5	16	4.93						
	PCP-H			127	62	6.3	13	6.15						
(A) Antihepatitis effects	ACV-L								23.5	18.7			58	
	ACV-M								50.7	30.5				
	ACV-H								61.4	51.1				
	CMP (1.5 g/L)								37.4	30.4				
	CMP (3.0 g/L)								46.3	47.0				
	CMP (6.0 g/L)								56.2	58.5				
	CMP (12.0 g/L)								71.8	65.3				
	Traditional Chinese medicine								22.3	36.3	28.5	32.3		59
	CMP-induced IFN- $\alpha$ + Traditional Chinese medicine								52.1	95.4	75	80		
(B) Antidiabetic effects	Distilled water	163.8											60	
	Melbina	168.64												
	PCP-L	201.32												
	PCP-H	213.58												
	NS													
Effects on ALL mice	CTX											18.4	61	
	KSC											40.5		
	CMP											68.9		
	KSC+CMP											36.3		
	KSC+CMP+CTX											40.1		
									0			26.7		
									58.84			40.5		
									25.83			68.9		
									35.88			36.3		
									43.97			40.1		
									79.68			26.7		

IFN- $\alpha$  was obtained from human peripheral blood lymphocytes treated with CMP.

**TABLE 8** PCP-related clinical studies

Diseases types	Cases	Groups	Total effective rate (%)	NK cell activity (%)	Cure rate (%)	Et (%)	LCT (%)	Ea (%)	References
Antitumour effects	71	Mitomycin/cis-platinum/pharmorubicin/5-Fu	25.9						<sup>63</sup>
		Mitomycin/cis-platinum/pharmorubicin/5-Fu + CMP-induced IL-2	86.7						
	44	Mitomycin/cis-platinum/doxorubicin/5-Fu + CMP-induced IL-2	86.4						<sup>65</sup>
	37	<sup>60</sup> Co radiotherapy + CMP-induced IL-2	97.3						
	77	<sup>60</sup> Co radiotherapy + CMP-induced IFN- $\alpha$	97.4						<sup>59</sup>
	25	Mitomycin/cis-platinum/pharmorubicin/5-Fu+ CMP-induced IFN- $\alpha$	92						
Effects on epidemic haemorrhagic fever	128	Balanced salt solution	60		68.7				<sup>64</sup>
		Balanced salt solution+ IFN- $\alpha$	63		100				
Antihepatitis effects	35	CMP	88.57		54.28				<sup>66</sup>
	30	CMP	90		36.67				
	30	CMP	90		30				
	60	Mitomycin/cis-platinum/pharmorubicin/5-Fu				30.7	38.7	20.5	<sup>67</sup>
		Mitomycin/cis-platinum/pharmorubicin/5-Fu+ PCP				38.5	50.4	27.5	
Control	50	Control				47.4	46.2	23.3	<sup>68</sup>
		PCP				49.2	55.4	33.3	

IL-2 and IFN- $\alpha$  were obtained from human peripheral blood lymphocytes treated with CMP.

Meanwhile, CMP significantly improves the survival rates of mice suffering acute lymphoblastic leukaemia or ALL.<sup>61</sup>

### 3 | CLINICAL EFFICACY OF PCP

Seven clinical studies on PCPs were found through literature search.<sup>59,64–68</sup> The clinical data are summarized in Table 8. Most of studies are related to the antitumour effects of CMP where these studies use IL-2 or IFN- $\alpha$  obtained from human peripheral blood lymphocytes induced by CMP in combination with chemotherapy or radiotherapy. Sheng et al reported that the total effective rate could reach 97% when CMP-induced IL-2 is combined with chemotherapy during cancer treatment compared to that of 27% by chemotherapy alone.<sup>65</sup> The effectiveness is defined as improving the symptoms of the disease by increasing appetite, elevating the levels of cAMP in blood circulation, regulating the ratio of cAMP/cGMP, protecting and restoring damaged liver and reducing the side effects of chemotherapy.<sup>66</sup> In treating epidemic haemorrhagic fever, cure rate could reach 100% when CMP-induced IFN- $\alpha$  is combined with normal therapy compared to that of 63% with normal therapy alone.<sup>64</sup> Chen et al also found that the total effective rate could reach 90% during hepatitis treatment.<sup>66</sup> The changes of immune functions are measured with Et (total erythrocyte rosettle test), Ea (active erythrocyte rosettle test) and LCT (lymphocytes transformation) during PCP treatment. These values are significantly increased compared to the control groups when PCP is combined with chemotherapy<sup>67</sup> (Table 8).

### 4 | TOXICITY

CMP has very low toxicity. It is reported by Chen et al<sup>69</sup> that the mice moves freely, no abnormal reaction is observed when CMP is used during standard acute toxicity test. No teratogenic effects are detected on rats when CMP is used in the teratogenic tests. No toxic reaction is witnessed when the dogs are continuously injected by intravenous injection reported by Ye et al<sup>70</sup> They further demonstrated that blood pressure, heart rate, electrocardiogram and breathy of dogs are not affected after intravenously injecting either 400 mg/kg or 800 mg/kg CMP. In consistent, Chai et al<sup>71</sup> reported that CMP has no adverse effects on mice as well. Wang et al showed that CMP could enhance the tumour inhibition rate of 5-FU and decrease the liver injuries simultaneously caused by 5-FU in CT26 tumour-bearing mice.<sup>72</sup>

### 5 | FUTURE PERSPECTIVES

In this article, the structure, pharmacological effects, clinical efficacy, immunobalancing molecular mechanism and toxicity of PCPs are summarized in Figures 1-5 and Tables 1-8. The broad spectrum of therapeutic properties, relatively low toxicity and low costs make

PCPs attractive immune therapeutics for treating not only different types of cancers but also hepatitis B and other diseases.

Both advantages and disadvantages of PCPs as drugs rely on their complicated polysaccharide structure-dependent immune regulatory functions. Thus, there is a great need for clarifying the active ingredients in PCPs besides  $\beta$ -glucan/pachyman and their molecular targets responsible for their drug effects. In addition, how to standardize the quality of PCPs, especially the degree of chemical modifications of pachyman derivatives and how to perform reliable pharmacokinetic studies of PCPs are some of important issues to be solved in near future to make use of PCPs for treating patients with cancer worldwide.

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### CONFLICT OF INTEREST

The authors declare no conflict of interests. All grants and funding agencies play no role in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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### REFERENCES

1. Wang YZ, Zhang J, Zhao YL, et al. Mycology, cultivation, traditional uses, phytochemistry and pharmacology of *Wolfiporia cocos* (Schwein.) Ryvarden et Gilb.: a review. *J Ethnopharmacol*. 2013;147:265-276.
2. Wen YQ, Jia B, Peng T. Studied on pharmacology of *Poria cocos* polysaccharides and their modifications. *Lishizhen Med Mater Med Res*. 2014;25:432-434.
3. Wang YF, Zhang M, Ruan D, et al. Chemical components and molecular mass of six polysaccharides isolated from the sclerotium of *Poria cocos*. *Carbohydr Res*. 2004;339:327-334.
4. Lu HJ, Lu Y, Liu YW. Studies on the fractionation, structure analysis and bioactivities of *Poria cocos* acidic polysaccharides. Hubei: Hubei University of Chinese Medicine; 2014.
5. Jiao QC, Wang AY. Sulfation of pachyman with chlorosulfonic acid using the improved Wolfrom method. *Chinese J Polym Sci*. 2006;24:637-646.
6. Jin Y, Zhang LN, Chen L, et al. Effect of culture media on the chemical and physical characteristics of polysaccharides isolated from *Poria cocos* mycelia. *Carbohydr Res*. 2003;338:1507-1515.
7. Jia XJ, Ma LS, Li P, et al. Prospects of *Poria cocos* polysaccharides: isolation process, structural features and bioactivities. *Trend Food Sci Tech*. 2016;54:52-62.
8. Chihara G, Hamuro J, Maeda Y, et al. Antitumour polysaccharide derived chemically from natural glucan (pachyman). *Nature*. 1970;225:943-944.

9. Hamuro J, Yamashita Y, Ohsaka Y, et al. Carboxymethylpachymaran, a new water soluble polysaccharide with marked antitumor activity. *Nature*. 1971;233:486-488.
10. Huang QL, Zhang LN. Solution properties of (1→3)- $\alpha$ -D-glucan and its sulfated derivative from *Poria cocos* mycelia via fermentation tank. *Biopolymers*. 2005;79:28-38.
11. Chen X, Zhang L, Cheung PCK. Immunopotential and anti-tumor activity of carboxymethylated-sulfated  $\beta$ -(1→3)-D-glucan from *Poria cocos*. *Int Immunopharmacol*. 2010;10:398-405.
12. Wang YF, Zhang LN, Li YQ, et al. Correlation of structure to antitumor activities of five derivatives of a  $\beta$ -glucan from *Poria cocos* sclerotium. *Carbohydr Res*. 2004;339:2567-2574.
13. Gao XJ, Sun YR, Li YB. Antitumor effects and pharmacological research of pachymaran. *Acta Chin Med Pharm*. 1996;1:45.
14. Zhou ZJ, Han ZR, Zeng YY, et al. Chinese FDA approved fungal glycan-based drugs: an overview of structures, mechanisms and clinical related studies. *Transl Med*. 2014;4:141.
15. Chang YJ, Zhang M, Liu Y, et al. Preclinical and clinical studies of *Coriolus Versicolor* polysaccharopeptide as an immunotherapeutic in China. *Discov Med*. 2017;23:207-219.
16. Jiang YF, Chang YJ, Liu Y, et al. Overview of *Ganoderma Sinense* polysaccharide—an adjunctive drug used during concurrent chemo/radiation therapy for cancer treatment in China. *Biomed Pharmacother*. 2017;96:865-870.
17. Wang XF, Liu CY, Dou DQ. Studies on the effective components of *Poria cocos* in antitumor activity. *Liaoning J Tradit Chin Med*. 2014;41:1240-1243.
18. Chen JS, Zhao J, Huang H. The preparation and study on pharmacodynamics of antitumor of carboxymethyl pachymaran. *Youjiang Med J*. 2008;36:386-388.
19. Wang YF. The structure and biological activity of *Poria cocos* sclerotium polysaccharide and its derivatives. Wuhan: Wuhan University; 2004.
20. Wang AY, Chen Q, Li CF, et al. Antitumor function and mechanism study of modified pachymaran. *Chin Herbal Med*. 2009;40:268-271.
21. Bian C. The preparation of water-soluble pachymaran and the study of its antitumor activities. *Huazhong Agricultural University*. 2006: 65.
22. Luo LQ. Studies on antitumor effects and mechanisms of Chinese medicine polysaccharide in signal transduction pathway. Hubei: Hubei University of Chinese Medicine; 2005.
23. Tan XT, Wang YF, Zhang LN, et al. Histological observation on antitumor effect of *Poria cocos* polysaccharide modified by chemical technology. *J Wuhan Univ*. 2004;25:652-654.
24. Chen CX, Zhao DM, Zhang XJ, et al. Antitumor experiments of carboxymethyl pachymaran. *Fujian J Tradit Chin Med*. 2002;33:38-40.
25. Chen CX. The antitumor activities and immune effects of carboxymethyl pachymaran. *Acta Edulis Fungi*. 2001;8:39-44.
26. Xu LB, Xiao MY, Fan XH. Studies on immune function and antitumor effect of carboxymethyl pachymaran oral liquid. *Chin Tradit Pat Med*. 2000;22:44-46.
27. Zhao JF, Me YJ, Chen YJ, et al. The preparation and anti-tumor effect of sulfonyl pachymaran. *J Shenyang Pharm Univ*. 1996;13:125-128.
28. Lv SC, Cao QL, Zhang L, et al. The effects of pachymaran on immune function in normal and tumor-burdened mice. *J First Military Med Univ*. 1990;10:267-268.
29. Chen DN, Fan YJ, Zhou J, et al. The antitumor and related pharmacological effects of pachymaran. *Chin J Chin Mater Med*. 1987;12:43-45.
30. Tong L, Huang TY, Li JL, et al. The effects of botanical polysaccharides on the proliferation of S180 and K562 cells and the levels of sialic acid, phospholipid and cholesterol. *Chin J Integr Med*. 1994;14: 482-484.
31. Liu JC, Su FQ, Zhao XM. The antitumor effects of pachymaran after chemotherapy. *Pharmacol Clin Chin Mater Med*. 2006;22:73-76.
32. Tang SS, Zhu XQ. The antitumor and immune effects of compound fungal polysaccharides. *Basic Clin Med*. 2004;24:599-600.
33. Meng YL, Cai LH, Wu HF, et al. Histological observation on antitumor effect of *Poria cocos* polysaccharide modified by chemical technology. *J Wuhan Univ*. 2007;28:67-69.
34. Ji F, Li PF, Xu SY, et al. The preparation and antitumor effect of carboxymethyl pachymaran in vivo. *Chin J Microecol*. 2003;15:22-23.
35. Miu JC, Yang JC, Sheng WH. The effects of carboxymethyl pachymaran on increasing lymphocyte induce cytokines. *Chin Tradit Pat Med*. 1999;21:25-27.
36. Chai BL, Lin ZB, Cao SL. The effects of carboxymethyl pachymaran on phagocytizing function of macrophages. *Beijing Med J*. 1983;15:9-11.
37. Yang JS, Qin XP, Zhang N, et al. Effects of two fungal polysaccharides on protein tyrosine phosphorylation of HL-60 cells. *Chin J Pharm*. 2000;35:17-19.
38. Chen CX. The application of carboxymethylpachymaran-inducers. *Acta Edulis Fungi*. 1998;3:41-42.
39. Zhang M, Chiu LCM, Cheung PCK, et al. Growth-inhibitory effects of a  $\beta$ -glucan from the mycelium of *Poria cocos* on human breast carcinoma MCF-7 cells: cell-cycle arrest and apoptosis induction. *Oncol Rep*. 2006;15:637-643.
40. Ma CY, Chang WC, Chang HM, et al. Immunomodulatory effect of the polysaccharide-rich fraction from sclerotium of medicinal mushroom *Poria cocos* F.A. Wolf (Aphylophoromycetidae) on Balb/c Mice. *Int J Med Mushrooms*. 2010;12:111-121.
41. Hamuro J.  $\beta$  (1→3) Glucan-mediated augmentation of alloreactive murine cytotoxic T-lymphocytes in vivo. *Cancer Res*. 1978;38:3060-3065.
42. Zhang WY, Yang Y, Chen CL, et al. The effects of *Poria cocos* on immune function of immune deficit mice. *Chin J Vet Sci*. 2014;34:283-287.
43. Liu YY, Chen YX, Hou AJ. The effects of carboxymethyl pachymaran on lymphocyte secreting cytokines in mice. *Pharmacol Clin Chin Mater Med*. 2006;22:71-73.
44. Zhang MX, Li YW, Zhang DS, et al. Inhibition of spontaneous lung metastasis of pachymaran on Lewis lung cancer in mice and its mechanism. *Drug Clinic*. 2013;28:842-846.
45. Wei XJ, Hu TJ, Gao JF, et al. The preliminary research on the pharmacological effects of sulfation pachymaran. *Vet Pharm Feed Additives*. 2009;14:1-2.
46. Zhang ZJ, Feng X, Jiang J, et al. The effects of pachymaran on the biosynthesis of IgA, IgG and IgM in serum in mice. *Chin J Immunol*. 2013;29:1213-1215.
47. Peng XB, Qiu XH, Yu CL, et al. The effects of pachymaran on humoral immunity function in immunosuppressive mice caused of cyclophosphamide. *Pharmacol Clin Chin Mater Med*. 2013;29:69-72.
48. Chu M, Wang D, Zhang Y, et al. Pachyman treatment improves CD4 + CD25 + Treg counts and serum interleukin 4 and interferon  $\gamma$  levels in a mouse model of Kawasaki disease. *Mol Med Rep*. 2012;12:1237.
49. Zheng LL, Jiang JP, Xu HS, et al. The response surface method to optimize pachymaran extraction technology and research on its antioxidant activity. *Chin J Tradit Chin Med Pharm*. 2014;29:918-922.
50. Cao Y, Gao WY, Zhang LM, et al. Studies on the antioxidative activities of pachymaran. *Food R&D*. 2009;30:148-151.
51. Li YL, Zhang ZX, Hu L. Studies on the antioxidative activities of pachymaran. *Nat Prod Res Develop*. 2012;24:1126-1128.
52. Zhang Q, Zhang LM. Studies on the antioxidative activities of ferulic acid pachymaran. *Mod Food Sci Tech*. 2011;27:1077-1080.
53. Cheng SM, Liu Y, Mei GM, et al. Studies on the antioxidative activities of carboxymethyl pachymaran. *Food R&D*. 2013;34:1-5.
54. Wang Y, Yu Y, Mao J. Carboxymethylated  $\beta$ -Glucan derived from *Poria cocos* with biological activities. *J Agr Food Chem*. 2009;57: 10913-10915.
55. Wang Y, Liu S, Yang Z, et al. Oxidation of  $\beta$ -glucan extracted from *Poria Cocos* and its physiological activities. *Carbohydr Polym*. 2011;85: 798-802.



56. Hou AJ, Peng SP, Xiang R. Studies on the anti-inflammatory effects of pachymaran. *Pharmacol Clin Chin Mater Med.* 2003;19:15-16.
57. Hou AJ, Chen TY, Peng SP, et al. Studies on the anti-aging effects of pachymaran. *Pharmacol Clin Chin Mater Med.* 2004;20:10-11.
58. Duan HP, Hou AJ, Lu FE, et al. Studies on carboxymethyl pachymaran on the impact of HBV transfection cells expressing function. *Chin J Exp Clin Virol.* 2005;19:290-292.
59. Yang JC, Liu JS, Sheng WH, et al. The application of Chinese medicine effective component in interferon biotechnology experiment and clinical research. *Prog Biotechnol.* 1993;3:30-34.
60. Zheng CY. Studies on the anti-diabetic effects of pachymaran. *Chin Healthc Innov.* 2010;5:12-13.
61. Yang HX, Bo XZ, Yang Y, et al. Studies on the anti-leukemia effects of pachymaran combined with selenium in mice. *J Leukemia.* 2006;15:94-95.
62. Hattori T, Hayashi K, Nagao T, et al. Studies on antinephritic effects of plant components (3): effect of pachyman, a main component of *Poria Cocos Wolf* on original-type anti-GBM nephritis in rats and its mechanisms. *Jpn J Pharmacol.* 1992;59:89-96.
63. Wang CY, Chen Q, Shen B, et al. Synthesis and antihypertensive activity of pachyman sulfate. *Curr Top Nutraceut Res.* 2016;14:215-218.
64. Chen CX. The clinical trials of carboxymethyl pachymaran inducers. *J Fujian Univ Tradit Chin Med.* 2003;13:20-22.
65. Sheng WH, Yang JC, Gao YM, et al. Experimental and clinical studies on carboxymethyl pachymaran on promoting the induction of IL-2. *Chin J Cancer Biother.* 1996;3:51-54.
66. Chen CX. The medical function of carboxymethyl pachymaran. *Acta Edulis Fungi.* 1994;3:38.
67. Lv SC, Cao QL. The observations of pachymaran on the cell immune function of patients with lung cancer and clinical curative effects. *Shanghai J Immunol.* 1994;14:109.
68. Lv SC, Kong W, Cao QL, et al. The effects of pachymaran on immune function of tumor-burdened mice, the elderly and patients with tumor. *J Curr Phys.* 1996;1:5-7.
69. Chen C, Ye J, Lin J. Carboxymethyl tuckahoe polysaccharide the safety of the experiment. *Fujian J Tradit Chin Med.* 2003;34:27-30.
70. Ye JR, Lin JF, Lin DJ, et al. Toxicity studies on sodium carboxymethyl pachymaran. *Fujian Med J.* 1988;10:29-32.
71. Chai BL, Lin ZB, Cao SL, et al. Pharmacological effects and toxicity about carboxymethyl pachymaran. *Beijing Med J.* 1984;16:47-48.
72. Wang C, Huo X, Gao L, et al. Hepatoprotective effect of carboxymethyl pachyman in fluorouracil-treated CT26-bearing mice. *Molecules.* 2017;22:756.

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