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Review

Dose matters: Direct killing or immunoregulatory effects of natural polysaccharides in cancer treatment

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ABSTRACT

Polysaccharides from natural resources possess anti-tumor activities for decades, but the efficacy of polysaccharides as the adjuvant drugs for cancer treatment at prescribed doses remains open for debate. In this review, molecular mechanisms involved in direct killing effects of polysaccharides, including apoptosis, cell cycle arrest and mitochondria/DNA damage were described. However, the concentrations/doses used to reach the direct killing effects are too high to be applicable. Polysaccharides can also exert anti-tumor effects through immunoregulation at lower doses, and the effects of polysaccharides on natural killer cells, dendritic cells and other lymphocytes for tumor destruction, along with the receptor recognition and downstream signaling pathways, were delineated. Unfortunately, the prescribed doses of polysaccharides are too low to stimulate immunoresponse, resulting in the failure of some clinical trials. Therefore, understanding the sophisticated mechanisms of the immunoregulatory function of natural polysaccharides with refined doses for clinical use will help the standardization of traditional medicine.

1. Introduction

Cancer is one of the major threats to human health worldwide with millions of new cases each year, among which the lung cancer, breast cancer, colorectal cancer, prostate cancer, liver and stomach cancer are the most common types with highest rates of death (Siegel, Miller, & Jemal, 2018). Many factors including inheritance, obesity, infection, tobacco abuse, repetitive inflammations and even negative emotions, are all triggers for cancer development (Torre et al., 2015). Chemotherapy and radiotherapy are very common for tumor therapy, both of which exert their functions through direct killing on tumor cells but also on adjacent healthy cells. Other than injury of healthy tissues, traditional therapeutic strategies lead to systemic disorders such as nausea, vomiting, fatigue, anemia, anorexia and other adverse effects. As the result, the quality of patient's life is extremely low (Metri, Bhargav, Chowdhury, & Koka, 2013). To alleviate these adverse effects and reduce drug resistance, the concepts of targeted, complementary and combined therapy are widely accepted clinically. Due to the increased number of antibody based drugs, targeted therapy has been applied clinically and chemo-immunotherapy has attracted public attention (Xiang, Sharma, Freter, & Yan, 2012). Natural compounds with prominent bioactivities and minimal toxicity exhibit a synergistic effect when combined with chemotherapeutic drugs for cancer treatment (Uzoigwe & Sauter, 2012). Different from the latest approved recombinant antibodies, polysaccharides extracted from natural resources have demonstrated outstanding anti-tumor efficacy for a long period of time. *Lentinan* polysaccharide and polysaccharide-protein complex extracted from *coriolus versicolor* (polysaccharide-kureha, PSK) have been recognized as an adjuvant for treatment of malignant tumor in China or Japan for many years(Ren, Perera, & Hemar, 2012). Although very few natural polysaccharides have been approved to be adjuvant drugs for cancer therapy, a large amount of polysaccharides from more than four hundred herbs are being extracted and studied by researchers. These natural polysaccharides are currently available in health-food market, while their actual efficacy, doses and associated mode of action on tumor therapy remain to be explored.

Polysaccharides are the major bioactive ingredient extracted from natural resources including bacteria, higher plants, animals and algae. Polysaccharide is a type of long polymer, which consist of monosaccharides covalently connected via glycosidic bond. For a certain

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Table 1
Direct effects of natural polysaccharides on tumor cells.

Classification	Sources	Concentration Range/Cell line/LC_{30} (μg/ml)	% Apoptotic Cells (Concentration)	Mechanisms for Direct Cytotoxicity	Ref.
Higher plant (rootstock)	*Stachys floridana Schuttl. Ex Benth*	0-2000/HepG2 > 2000, PC–3 > 2000, HT-29 ~500	10% (125 μg/ml, HT-29)	Apoptosis***; Cell cycle arrest*	Ma et al. (2013)
	Panax ginseng	0-800/K562 > 800	23% (400 μg/ml)	Apoptosis*; Cell cycle arrest*	Xiong et al. (2017)
	Panax ginseng C.A. Meyer	0-5000/HT–29 > 600	N/A	Apoptosis*	Cheng et al. (2011)
	Radix hedysari	0-400/BGC823 > 400	N/A	Cell cycle arrest*	Wei et al. (2012)
	Menispermum dauricum	0-400/SKOV-3 ~200	50% (200 μg/ml)	Apoptosis*	Lin et al. (2013)
Higher plant (except for rootstock)	*Litchi* pulp	0-750/HepG2 ~450, Hela ~550, A549 > 750	N/A	N/A	Huang et al. (2014)
	Polygala tenuifolia	0-1600/OVCAR-3 ~500	23.5% (400 μg/ml), 51.2% (800 μg/ml)	Apoptosis***; Mitochondria damage*	Zhang, Song et al., (2015), Zhang, Qiang et al. (2015)
	Peony seed dreg	0-500/HEK293 > 500, Pc-3 ~400, HCT116 ~350, MCF-7 ~170, Hela ~180	20.22% (200 μg/ml, PC-3), 17.87% (200 μg/ml, HCT116), 30.94% (200 μg/ml, Hela), 38.73% (200 μg/ml, MCF-7)	Apoptosis***; Cell cycle arrest*; Mitochondria damage*	Zhang et al. (2017)
	Coix lachryma-jobi	0-300/A549 > 300	17% (300 μg/ml)	Apoptosis*; Mitochondria damage*; DNA damage	Lu et al. (2013)
	Boschniakia rossica	0-400/HepG2 ~270	43.86% (200 μg/ml), 53.67% (400 μg/ml)	Apoptosis**	Wang et al. (2014)
	Glycyrrhiza inflata	0-200/SCC25 ~50	41.4% (100 μg/ml), 52% (200 μg/ml)	Apoptosis**; Mitochondria damage*	Shen et al. (2015)
Fungus (Ganoderma)	*Ganoderma lucidum*	0-10000/HCT116 > 2500	9.84% (2500 μg/ml)	Apoptosis**; Cell cycle arrest*; Mitochondria damage*; DNA damage	Liang et al. (2015)
	Ganoderma tsugae	0-3000/Colo205 > 300	N/A	Cell cycle arrest*	Hsu et al. (2008)
	Ganoderma atrum	0-320/CT–26 > 320	N/A	Apoptosis***; Mitochondria damage**	Zhang et al. (2014)
Fungus (except for Ganoderma)	*Pleurotus linteus*	0-1000/HepG2 ~750	no change	Apoptosis***; Cell cycle arrest*; Mitochondria damage*	OuYang et al. (2013)
	Grifola frondosa	0-1000/SMMC-7721 ~500,HepG2 ~400	9% (200 μg/ml, SMMC-7721), 8.65% (200 μg/ml, HepG2)	Apoptosis**	Zhao et al. (2017)
	Agaricus blazei	0-400/HOS > 400	57% (100 μg/ml), 63% (200 μg/ml), 69% (400 μg/ml)	prevent DNA synthesis	Wu et al. (2012)
	Cordyceps gunnii	0-800/S180 ~400	N/A	N/A	Zhu, Dong et al. (2016), Zhu, Lv et al. (2016)
	Cordyceps sinensis	0-300/S180 > 300	25.4% (300 μg/ml)	Apoptosis*	Mei et al. (2014)
	Hirsutella sinensis	0-500/H1299 ~150	65% (400 μg/ml)	Apoptosis**; Mitochondria damage**	Liu, Tian et al. (2017), Liu, Xie et al. (2017)
Algae (Sulfated)	*Saccharina cichorioides*	0-800/HCT116 > 800	no change	no change	Vishchuk et al. (2013)
	Capsosiphon fulvescens	0-2500/AGS ~750	N/A	Apoptosis***	Kwon and Nam (2007)
	Sargassum henslowianum C. Agardh	0-1000/B16 ~350	41% (200 μg/ml)	Apoptosis*	Ale, Maruyama, Tamauchi, Mikkelsen, and Meyer (2011)
	Fucus vesiculosus	0-1000/B16 ~300	30% (200 μg/ml)	Apoptosis*	Ale et al. (2011)
	sigma	0-200/4T1 ~200	22.8% (50 μg/ml), 43.2% (100 μg/ml), 63.5% (200 μg/ml)	Apoptosis*; Cell cycle arrest*	Xue et al. (2013)
	Gracilariopsis lemaneiformis	0-100/A549 ~60, MKN28 ~100, B16 ~60	6.2% (60 μg/ml, A549), 7% (60 μg/ml, MKN28), 6.5% (60 μg/ml, B16)	Apoptosis*	Kang et al. (2017)
	Fucus vesiculosus	0-100/U937 ~20	18.86% (20 μg/ml), 45.71% (40 μg/ml)	Apoptosis***; Mitochondria damage**	Park et al. (2013)

Notes: The number of "*" represents the number of altered parameters. For example, “Apoptosis***" represents the changes of three apoptotic indicators. Four apoptotic indicators are usually available in the literatures: (1) Bax or Bak-1↑, Bcl-2↓; (2) caspase-3/8/9 or PARP↑; (3) MAPK or Akt signaling blackage; (4) p53↑. Mitochondria damages include two indicators: (1) Mitochondria Membrane Potential (MMP)↓; (2) Cytochrome C↑. Cell cycle arrest has one parameter: cyclinD/E or CDK-2/4/6↓.