Pharmacological Effects and Related Mechanisms of Ganoderma Lucidum Polysaccharides at the Cellular Level

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Abstract. Ganoderma lucidum polysaccharides are the primary active constituents of Ganoderma lucidum. Existing researches indicate that they possess multiple pharmacological effects and benefits, including anti-tumor, antioxidant, anti-aging, hypoglycemic, and immune-modulating properties. Studies on the cellular impact of Ganoderma polysaccharides have predominantly focused on various cell types, including malignant tumor cells, immune cells, cardiac myocytes, neurons, hepatocytes, and fibroblasts. In this paper, we review and summarize recent literature primarily related to these pharmacological effects at the cellular level and their underlying mechanisms. Our aim is to provide insights and references for the deep clinical development and utilization of Ganoderma lucidum polysaccharides.

Keywords: Ganoderma lucida; Ganoderma lucidum polysaccharide; Pharmacological effect; Anti-tumor; anti-oxidation; anti-aging; hypoglycemic; immune regulation.

1. Introduction

Ganoderma lucidum, as a traditional Chinese herbal medicine, has the functions of tonifying, invigorating qi, strengthening heart, protecting liver, etc.and it is widely used in disease treatment.According to research reports,Ganoderma lucidum polysaccharides (GLP) is one of the main components of polysaccharides in Ganoderma lucidum. It has many pharmacological functions such as anti-tumor, anti-oxidation, anti-aging, hypoglycemic and immunological regulation. Ganoderma lucidum as a treasure in Chinese medicine, GLP plays an important role in the treatment of diseases, so it has been widely valued.The cell is the basic unit of the structure and function of the organism. Through its unique biochemical process, the cell completes the transformation and communication of signals inside and outside the cell, thus having the ultimate influence on the drug therapy and biological process of disease.Studies have found that GLP plays a pharmacological role in malignant tumor cells, immune cells, cardiomyocytes, neurons, hepatocytes, fibroblasts and other cells.

Therefore, this review reviews the pharmacological effects and mechanisms of GLP on the above cells, in order to explore the potential medical value of GLP to humans from the "root", and provide theoretical support for the clinical application of GLP.

2. Basic pharmacological effects of Ganoderma lucidum polysaccharide in various cells

Ganoderma lucidum polysaccharide is one of the main active ingredients in Ganoderma lucidum. Due to its relatively simple extraction method and ideal development and application prospect, more and more researchers pay attention to it.Literature has shown that GLP exerts multiple pharmacological effects and effects in malignant tumor cells, immune cells, cardiomyocytes, neurons, hepatocytes, fibroblasts and other cells, such as anti-tumor, anti-oxidation, anti-aging, hypoglycemic, and immune regulation, respectively.

2.1. Malignant tumor cell

Malignant tumor can damage the function of human organs, cause cachexia, and lead to the decline of immunity, which seriously affects human life and health. At present, studies have shown that GLP has a good anti-tumor effect. For example, GLP and its enzymatic hydrolysates can inhibit the accumulation of autophagosomes by activating MAPK/ERK signaling pathway[1] and regulate the expression of p-Akt1/P-ERK and Bax/Bcl-2 proteins by activating Akt/ERK signaling pathway[2] to induce apoptosis of colorectal cancer cells. GLP activates MAPK-P38 and MAPK-JNK pathways and regulates its downstream genes and proteins (p53, c-myc, c-fos, c-jun, Bcl-2, Bax, caspase3 and cyclin D1) to induce apoptosis and cycle arrest of HL-60 acute leukemia cells and exert anti-tumor effect by blocking MAPK/ERK signaling pathways.GLP and ganoderma lucidum spore polysaccharide inhibit the growth of liver cancer cells and promote the apoptosis of liver cancer cells by activating PI3K/AKT signaling pathway[4, 5]. GLP regulates the expression of apoptosis-related proteins Bcl-2, PI3K and Akt, inducing apoptosis of lung cancer A549 cells and inhibiting proliferation of lung cancer A549 cells[6]. In addition, GLP is closely related to the epithelial-stromal pathway when it exerts anti-tumor activity. For example, GLP reduces the expression of E-cadherin and increases the expression of N-cadherin, Vimentin and Slug in cervical cancer cells by inhibiting the epithelial-stromal pathway. It can also change the morphology and particle size of tongue squamous cell cells, thereby reducing the aggressiveness and migration ability of cancer cells[7, 8]. GLP can also promote the expression of Bax, caspase3 and caspase9 apoptotic proteins by inhibiting JAK/STAT5 pathway, thus inducing the apoptosis of cervical cancer cells.

The above results showed that GLP exerts anti-tumor effects by regulating tumor cell autophagy, promoting tumor cell apoptosis, inhibiting tumor cell proliferation, migration and invasion, and affecting tumor cell cycle. The possible mechanism is closely related to MAPK, Akt/ERK, PI3K/Akt, JAK/STAT5 and epithelial-mesenchymal signaling pathways. Therefore, GLP is expected to be developed as a specific targeted signaling pathway inhibitor to exert anti-tumor effects.

2.2. Immune cell

Immune cells are the cells involved in or related to immune response, such as macrophages, T cells, B cells, dendritic cells, NK cells and other immune cells play an important role in immune surveillance, immune defense and immune self-stabilization in the body. Studies have reported that GLP regulates the immune response and plays an anti-tumor role. For example, ganoderma lucidum spore polysaccharide can promote the transformation of primary macrophages into M1 type, and promote the secretion of cytokines (TNF-α, IL-1β, IL-6 and TGF-β1) to reshape the tumor immune microenvironment[5]. GLP promotes the transformation of macrophages into M2 by regulating MAPK and NF-κB signaling pathway, and exerts anti-hepatocellular carcinoma effect[9]. GLP stimulates macrophages to produce NO in a dose-dependent manner, promotes phagocytosis of macrophages, activates T cells, and enhances cytotoxicity and tumor invasion[10]. Ganoderma lucidum spore crude polysaccharide up-regulates the expression of costimulatory factor CD28 to promote T cell activation[11]. In mice immunized with enterovirus 71 (EV-A71), it was found that the combination of EV-A71 and GLP induced cellular immunity, activated T cells, and increased the production of IFN-γ and IL-17. In terms of enhancing T cell toxicity, GLP can enhance the cytotoxicity of T cells by increasing the expression of IL-2, TNF-α and IFN-γ in serum[12]. GLP can induce the phosphorylation and protein degradation of IKB-α through the NF-κB pathway, enhance the expression and transcriptional activation of NF-κB, and thus promote the expression of intercellular adhesion molecule-1 (ICAM-1) in endothelial cells, and enhance the tumor invasion of T lymphocytes [13]. In addition, a number of studies have shown that GLP can act on other immune cells and participate in the regulation of immune response. For example, GLP can activate B cells and promote their proliferation[14, 15], and regulate the secretion of cytokines by B cells[16]. Regulating NF-κB and MAPK pathways induces dendritic cell maturation and activation[17-19], and promotes cytokine production[20]. It can also enhance the killing ability of NK cells[21] and increase the number of NK cells[22] and neutrophils[23].

The above results showed that GLP participated in the immune response by activating immune cells, promoting the proliferation of immune cells, and regulating the cytokine secretion level of immune cells. In conclusion, GLP can be used as a good immunomodulator to play anti-inflammatory and anti-tumor roles.

2.3. Myocardial cell

In recent years, the study of GLP on cardiomyocytes has gradually attracted attention. It has been reported that GLP inhibits CUL3-mediated K48-associated Nrf2 polyubiquitination by inhibiting the expression of Cul3, and maintains the expression of Nrf2 and HO-1 in H9C2 cardiomyocytes with anthracyclines and Doxorubicin (DOX), thereby alleviating the apoptosis, oxidative stress and inflammation of H9C2 cardiomyocytes induced by doxorubicin[24]. In the rat H9C2 cardiomyocyte injury induced by anthracycline anticancer drug doxorubicin, GLP inhibited the production of inflammatory factors such as TNF-α and IL-6, increased the production of anti-inflammatory factors, and increased the activities of superoxide dismutase, glutathione, and catalase, thereby reducing the H9C2 cardiomyocyte injury induced by doxorubicin[25]. In addition, GLP reduces the expression of activated PARP by regulating Bcl-2 family proteins, thereby inhibiting cardiomyocyte apoptosis induced by DOX and playing a role in protecting cardiomyocytes[26]. In conclusion, the protective effects of GLP on cardiomyocyte damage induced by DOX are mainly reflected in antioxidant, anti-inflammatory and anti-apoptotic aspects, thereby reducing the risk of cardiomyopathy in cancer patients. PPARγ can ameliorate myocardial cell damage caused by ischemia/reperfusion, reduce myocardial fibrosis and myocardial cell apoptosis, and inhibit cardiac hypertrophy. Studies have reported that GLP can inhibit cardiac hypertrophy by down-regulating key genes involved in hypertrophy and fibrosis, and reduce stress overload-induced pathological cardiac hypertrophy by activating PPARγ[27, 28]. Therefore, GLP has great potential in the treatment of pathologic heart hypertrophy and heart failure. In addition, GLP can increase the expression of SIRT1 in mouse heart tissue, decrease the levels of serum inflammatory factors TNF-α, IL-1α, IL-6 and inflammatory cells, inhibit the apoptosis of cardiomyocytes, and promote the proliferation of cardiomyocytes in hypersepsis model mice[29]. In conclusion, GLP may regulate inflammatory response, apoptosis and proliferation by activating SIRT1, and play a protective role in cardiac dysfunction caused by sepsis. Therefore, GLP is expected to be a new drug for the treatment of sepsis.

The above research results indicate that GLP can play a role in protecting myocardium by antagonizing the negative effects of DOX on cells, alleviating cardiac damage caused by DOX, regulating related genes to inhibit cardiac hypertrophy and fibrosis, and activating related proteins to regulate inflammatory response and improve cardiac dysfunction caused by sepsis.

2.4. Nerve cell

Neuronal cells are permanent cells that have no regenerative function and are therefore essential for the protection of neurons. Recent studies have found that GLP has a protective effect on neurons. On the one hand, GLP can inhibit the accumulation of calcium in hippocampal neurons and play an anti-epileptic role. On the other hand, GLP can promote the expression of Camkiα, bind to Ca^{2+} to form Ca^{2+}/CaM complex, reduce the concentration of Ca^{2+} in neurons, and thus play a protective role in neurons and anti-epileptic effects[30]. In the apoptosis model of rat cerebellar granulosa cells induced by H_2O_2, GLP inhibited the activation of caspase-3, the increase of Bax and Bim levels and the decrease of Bcl-2 levels in a time-dependent manner[31]. In conclusion, GLP can protect neurons by regulating the expression of apoptosis-related proteins. In a spinal cord trauma model, GLP exerts neuroprotective effects by reversing the activities of caspase-3 and myeloperoxidase, as well as the elevated levels of TNF-α, malondialdehyde and NO after traumatic spinal cord injury[32]. GLP not only has a protective effect on nerve cells, but also can reduce microglia-mediated neuroinflammation and promote neurogenesis. For example, GLP can inhibit the expression of LPS or β-amyloid-induced pro-inflammatory cytokines IL-1β, IL-6 and iNOS, and increase the expression of anti-inflammatory cytokine TGF-β to weaken the LPS or Aβ-induced inflammatory response in microglia. GLP can

inhibit the increase in the number of microglia and the enhancement of phagocytosis induced by LPS and Aβ activation to achieve the effect of inhibiting their phagocytosis[33]. In conclusion, GLP can reduce microglia-mediated neuroinflammation and regulate microglial phagocytosis and behavioral response. It has also been suggested that GLP can promote neurogenesis and reduce cognitive deficits in Alzheimer's mice. For example, by activating FGFR signaling pathway, GLP leads to reduced Aβ deposition and enhanced neurogenesis in Alzheimer's mice, thereby alleviating cognitive deficits in AD mice[34].

In conclusion, Ganoderma lucidum polysaccharide can protect neurons, reduce neuroinflammation and promote neurogenesis, so GLP is expected to be developed and used as a drug to protect the nervous system.

2.5. Hepatocyte

The liver has many functions such as metabolism, synthesis, detoxification and bile secretion, which is of great significance to human health. Studies have reported that GLP has a good role in protecting the liver from damage and inflammation. For example, in the carp hepatocyte injury model induced by carbon tetrachloride (CCl_4), GLP increased hepatocyte viability, inhibited CCL_4-induced marker enzymes glutamic oxalacetic transaminase, alanine aminotransferase, lactate dehydrogenase and oxidative damage index MDA, increased SOD level, and down-regulated CYP1A and CYP3A genes related to toxic metabolites of CCl_4. It can reduce the damage of CCl_4 to hepatocytes. The activation of caspase-3 and caspase-8 induced by exogenous inducer CCl_4 can also be inhibited to inhibit exogenous induced apoptosis[35]. The study was conducted in carp, and further research is needed to determine the efficacy and safety of GLP in treating liver damage and inflammation in humans. In addition, GLP exerts an anti-fibrotic effect by regulating TGF-β/Smad signaling pathway, inhibiting the decreased expression of type I collagen and a-SMA, and reducing the activation of liver stastrocytes induced by TGF-β1[36].

Therefore, GLP can not only improve the viability of hepatocytes, protect hepatocytes from damage and inhibit exogenous induced apoptosis of hepatocytes, but also play an anti-fibrosis role through related signaling pathways. It can be seen that GLP has potential development in liver protection.

2.6. Mechanocyte

Numerous studies have shown that GLP has the functions of anti-oxidation, anti-photoaging and promoting skin healing. For example, GLP can enhance the activity of antioxidant enzymes and activate the Keap1-Nrf2/ARE signaling pathway, which has a protective effect on oxidative damage of human skin fibroblasts caused by hydrogen peroxide, suggesting that GLP can be used as a natural antioxidant to protect skin from oxidative stress[37]. GLP can protect fibroblasts from ultraviolet light (UVB) -induced photoaging, which may be mediated by reducing UVB induced reactive oxygen species (ROS) levels and inhibiting MAPK signaling pathway, thereby inhibiting MMP-1 expression and promoting type I collagen expression, suggesting that GLP may have clinical therapeutic potential in photoaging[38]. Fibroblasts can form fibers and secretory matrix, have strong regenerative ability, and play a very important role in the repair of different degrees of cell degeneration, necrosis and tissue defect. Research reports. GLP can enhance the vitality, migration ability and collagen synthesis ability of fibroblasts, and shorten the skin wound healing time of mouse models, which may be caused by up-regulating TGF-β1 expression or activating Wnt/ß-catenin signaling pathway to promote wound healing[39]. It can be seen that GLP can be used as a drug to promote skin wound healing in the future.

2.7. Other cells

Studies on GLP are not limited to the above cells, but also involve pancreatic beta cells, human aortic smooth muscle cells, melanocytes, adipocytes, human tissue stem cells/progenitor cells, etc. It has been reported that GLP has a hypoglycemic effect on streptozotocin induced diabetic rats by

inhibiting pancreatic β cell apoptosis and enhancing β cell regeneration, suggesting that GLP may be a potential drug for hypoglycemic treatment[40]. Other researchers have found that GLP also inhibits the expression of IL-1β by preventing LPS-induced phosphorylation of ERK1/2 and phosphorylation and transplacement of NF-κBp65, thereby reducing the level of IL-1β in human aortic smooth muscle cells and playing the anti-inflammatory role of GLP, which is helpful in preventing vascular and inflammatory diseases[41]. Similarly, studies on the vascular protection of GLP have reported that GLP can interfere with stress-activated protein kinase, prevent human aortic smooth muscle cells from entering the cell cycle in vitro, reduce cell proliferation in the neovascularization and reduce the neovascularization area in vivo, suggesting that GLP may become a safe and effective new drug for the prevention and treatment of angioproliferative diseases[42]. GLP can inhibit parasecretory action of keratinocytes and fibroblasts through IL-6/STAT3/FGF2 pathway to reduce melanin production in melanocytes, which is extremely important for people to maintain beautiful skin and reduce melanoma[43]. By stimulating AMPK phosphorylation, GLP promotes the phosphorylation of its downstream target ACC1, down-regulates adipocyte differentiation transcription factors PPARγ, C/EBP-α, SREBPlc, some adipocyte genes ACC1, PLIN1, FASN and activated lipolysis gene HSL to inhibit fat formation and enhance lipolysis in adipocytes. This suggests that GLP has a good anti-fat effect and has the potential to be developed into anti-obesity products[44]. GLP activates cytokine-like and chemokine-like functions of human tissue stem cells/progenitors by regulating CAM expression and biological activity. At the same time, GLP has anti-angiogenesis and immunomodulatory functions, and promotes homing of hematopoietic stem cells/progenitor cells, so as to better protect human tissues, block disease progression and promote human health[45]. It can be seen that GLP has important significance in regenerative medicine, aging and cancer treatment.

3. Conclusion and prospect

GLP is the main active component of Ganoderma lucidum, which has many pharmacological activities and potential clinical value. GLP can promote apoptosis, regulate autophagy, inhibit proliferation and migration, and regulate cycle of tumor cells by regulating signaling pathways such as MAPK, and may become a potential target drug for the treatment of malignant tumors. GLP can also regulate a variety of immune cells, enhance the body's immunity, improve the body's resistance to disease, and has a significant contribution in anti-inflammatory and anti-tumor aspects, and is expected to be developed as an immunomodulator to assist the treatment of immune deficiency diseases, autoimmune diseases, and malignant tumors in the future. In addition, GLP has shown potential pharmacological effects in protecting the heart, liver, nerve, blood vessels and other important organs and tissue structures, which is extremely beneficial to human health. However, whether GLP can also play a strong protective role on important organs such as kidney, lung, spleen and tissue structures such as muscle and bone needs to be further explored, which will help expand the pharmacological effects of GLP and explore the potential medical value of GLP. Finally, GLP has great development value in lowering blood sugar, anti-oxidation, anti-obesity, anti-aging, anti-photoaging, repairing damaged or necrotic tissues, and promoting skin wound healing, which may be the focus of future research.

4. Summary

By reviewing relevant literature in recent years, we found that the pharmacological action and mechanism of GLP involve many fields, including oncology, immunology, biochemistry, pharmacology, etc. Its pharmacological action mainly includes anti-tumor, anti-oxidation, anti-aging, hypoglycemic, immune regulation and so on. By exploring the pharmacological effects of GLP at the cellular level, we find that GLP is expected to be developed as specific targeted signaling pathway inhibitors, immunomodulators, protective drugs for the heart, liver and other important organs of the body and the nervous system, so as to bring more new breakthroughs and development for human

health. In addition, we also find that there is a lack of research on GLP in other organs, such as kidney, spleen, pancreas, etc. and there is also a lack of research on protecting blood vessels, anti-aging, anti-obesity, anti-photoaging, repairing damaged or necrotic tissues and promoting tissue regeneration. Therefore, we hope that researchers will conduct more in-depth and extensive research in these aspects in the future to explore the potential application value of Ganoderma lucidum polysaccharide.

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