

Research progress in cancer treatment based on TLR4 related genes

Hua Li^{1,a}, Jiehong Wang^{2,b,*}

¹Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China

²Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712000, China

^a845157420@qq.com, ^bwangjiejie68@163.com

*Corresponding author

Abstract: Gastric cancer is a common malignant tumor of digestive tract tumors. TLR4 is a natural immune cell regulator. In recent years, the molecular mechanism and prevention and treatment of TLR4-related pathways affecting the progression of gastric cancer have become a hot topic. This paper reviews TLR4 and its related signaling pathways, the correlation between TLR4-related pathways and gastric cancer, and the regulation of TLR4-related signaling pathways in the treatment of gastric cancer, in order to provide more evidence for new approaches to treat gastric cancer in the future.

Keywords: Gastric cancer; TLR4. Signal pathway; The research progress

1. Introduction

Gastric cancer is the fifth most common malignant tumor and the third largest cause of tumor-related death in the world [1]. As a high incidence area of gastric malignant tumor in the world, the incidence rate in China accounts for 44.1% of the global total [2], nearly 50% of the global total [3,4]. At present, the proliferation, invasion and metastasis of gastric cancer are closely related to human immune function. (toll like receptor, TLR) plays an important role in the occurrence of gastric cancer, and TLR recognition plays a crucial role in resisting infection and immune system regulation. Its polymorphism may lead to the imbalance of proinflammatory and anti-inflammatory cytokine responses and regulate immune pathogenesis and cancer [5]. The polymorphism of toll like receptor 4 (TLR4) is related to the modified immune response of gastric mucosa, and can significantly promote the occurrence and development of gastric cancer [5]. At present, surgical resection is still the first choice for the treatment of gastric cancer, and chemotherapy is the most important way for middle and advanced gastric cancer [6]. Recently, tumor immunotherapy has been regarded as a new treatment method after traditional therapy [7]. Its molecular targeted therapy is the core of precision tumor therapy, and has gradually become a research hotspot in the field of tumor therapy [8,9]. Therefore, this paper reviews the treatment of gastric cancer based on TLR4 related pathways.

2. Signal path related to TLR4

TLR4 is subdivided into three parts: the extracapsular region, transmembrane region and cytoplasmic region. The extracapsular region is composed of leucine rearrangement, which is mainly responsible for recognizing and binding with other auxiliary receptors to form receptor complexes. The cytoplasmic region is the Toll/IL1R homology domain (TIR domain), which mainly transmits signals downstream and is the core component. The transmembrane region is dominated by cysteine [10]. TLR4 is the only receptor mediated by two pathways in TLR. The activated signaling pathways are the myeloid differentiation factor 88 (MyD88) dependent pathway and the non-MyD88-dependent pathway. The Myeloid differentiation protein2 (MD2) and cluster of differentiation 14 (CD14) are two important co-receptors in the activation of TLR4 signaling pathway.

The MyD88-dependent pathway is that TLR4 forms TLR4\MD2 complex with the assistance of CD14 and MD2 auxiliary receptors and dimerization occurs, which binds to the TIR domain of MyD88 and activates MyD88 to form TLR4/MyD88 active complex. The MyD88-dependent pathway is that TLR4 forms TLR4\MD2 complex with the assistance of CD14 and MD2 auxiliary receptors and dimerization occurs, which binds to the TIR domain of MyD88 and activates MyD88 to form TLR4/MyD88 active complex. Further activation of interleukin-1 receptor associated kinase 4 (IRAK-4)

results in phosphorylation of interleukin-1 receptor associated kinase 1 (IRAK-1) and interleukin-1 receptor associated kinase 2 (IRAK-2) to form the IRAK1/2 complex. Then activate tumor necrosis factor receptor associated factor 6 (TRAF6), which in turn activates inhibitor of kappaB kinase (IKK), which acts on nuclear factor kappa-B (NF- κ B) Union I κ B B complex, resulting in I κ B subunit regulates serine phosphorylation at sites.

The I κ B subunit is modified with ubiquitination, and the dimer of NF- κ B is released by protease degradation. NF- κ B enters the nucleus, binds to the genes at the binding site, and promotes the expression and activation of various inflammatory cytokines through the initiation of signal transduction in the nucleus. MyD88 independent pathway refers to activation of TIR-domain containing adapter-inducing interferon- β TRIF and tumor necrosis factor receptor-associated molecule 3 receptor-associated factor 3 (TRAF3), interferon regulatory factor 3 (IRF-3) and further activation of downstream signals, IRF-3 enters the cell and acts on NF- κ B, inducing interferon production and promoting various inflammatory responses. After recognizing or binding to pathogen-related molecular patterns, TLR4 must activate the above two pathways to initiate downstream signals, and then release cytokines and chemokines to cause inflammatory response, or promote the maturation of antigen-presenting cells, induce immune response, and ultimately lead to the generation and development of diseases. The MyD88 dependent pathway mainly promotes the expression of inflammatory cytokines, and the MyD88 independent pathway mainly induces the production of type I interferon [11]. The two pathways exert different functions and affect the course of disease.

3. Correlation between gastric cancer and TLR4-related signaling pathways

TLR4 can regulate the activation of signaling pathway by up-regulating or inhibiting its own expression, causing or inhibiting the inflammatory and immune responses of the body, thus affecting the occurrence and development direction of gastric cancer. Zou Xinmei et al. [12] have shown that the positive rate of TLR2/4 in the gastric cancer group is significantly higher than that in the paracancer group and the hyperplasia group, and the overexpression of TLR2/4 leads to inflammatory response and promotes the occurrence and development of gastric cancer. Li et al. [13] found the correlation between TLR genetic polymorphism and genetic susceptibility to gastric cancer in case-control studies, indicated that TLR4 is highly expressed in gastric cancer and affects the inflammatory and immune response of the body, and genetic variation of TLR4 can reduce the susceptibility to gastric cancer. TLR4 can affect the progression of gastric cancer by regulating related signaling pathways. Because multiple cytokines in its related pathways participate in the whole process of inflammatory response and immune response, different inhibition of pathways may lead to different directions of disease development. Zhang Yameng et al. [14] have been confirmed that *Helicobacter pylori* infection promotes chronic atrophic gastritis and intestinal metaplasia by regulating the expression of TLR4 and NF- κ B signaling pathway related molecules, thus gradually leading to gastric cancer in animal experiments. TLR4 can also directly participate in the proliferation of gastric tumor cells, thus promoting the progression of gastric cancer. Hu Chenghao et al. [15] have confirmed that TLR4 may be involved in the occurrence and development of gastric malignant tumor cells by affecting the growth of tumor microvessels and increasing the density of microvessels. In clinic, TLR4 and its related pathways can also predict the occurrence and development of gastric cancer, Zou Xinmei et al. [12] suggests that TLR2/4 can be used as a serum marker to evaluate the disease status and predict the prognosis of gastric cancer. Wang Yang et al. [16] showed that the expression levels of TLR4, MyD88 and NF- κ B in peripheral blood mononuclear cells of patients with gastric cancer were significantly increased, which further suggested that the expression levels of TLR4-related signaling pathway could objectively reflect *Helicobacter pylori* infection in patients with gastric cancer, and could be used to evaluate the severity of gastric cancer.

4. Research progress of regulating TLR4-related pathways in the treatment of gastric cancer

4.1. Inhibition of TLR4 expression

TLR4 is a type I pattern recognition receptor, widely distributed on a variety of cell surfaces, and its ligands are mainly of two types, endogenous damage associated molecular pattern (DAMP) and exogenous pathogen associated molecular pattern (pathogen-associated molecular pattern, PAMP) [17]. The first step in the occurrence and development of gastric cancer is that the extracapsular region of TLR4 first plays the biological function of recognizing ligands. The TIR domain of the cytoplasmic

region of TLR4 can combine with downstream TIR signaling molecules, and then activate two signaling pathways to cause inflammatory response and immune response, thus leading to the generation and development of gastric cancer. Current studies have shown that TLR4, due to its own polymorphism, as a result, the transcriptional signals and encoded proteins are different from the normal ones, which leads to the susceptibility of certain people to gastric cancer [18,19]. Therefore, inhibition of TLR4 expression can reduce the recognition of pathogene-related molecular patterns and activation of downstream signaling pathways, regulate the inflammatory response and immune response of the body, and play a role in protecting gastric mucosa and preventing the occurrence of gastric cancer.

In recent years, TLR4 expression has been regulated in different ways in order to treat gastric cancer. Among them, traditional Chinese medicine has achieved good clinical efficacy and can also prevent the occurrence of gastric cancer by multi-link, multi-target and comprehensive targeting of TLR4 in patients with gastric cancer. Kang Zhenchao et al. [20] up-regulated the expression of microRNA-448 (miRNA-448) in gastric cancer cells through ophiopogonin D, the main active monomer component of *Radix ophiopogonis*, and TLR4, as the target gene of miRNA-448, indirectly inhibited the expression of target gene TLR4. Furthermore, lipopolysaccharide-induced gastric cancer cells secreted interleukin-6, tumor necrosis factor- β , vascular endothelial growth factor and other immune cytokines, and blocked the immune escape of gastric cancer cells. This study also demonstrated that overexpression of miRNA-448 or knockout of TLR4 inhibited the secretion of interleukin-6, tumor necrosis factor- β , and vascular endothelial growth factor in lipopolysaccharide-induced human undifferentiated gastric cancer cells. Kang Zhenjo et al. [20] have confirmed that the effect of TCM components on gastric cancer cytokines plays a role through indirect regulation of TLR4, but more studies have proved that TCM or other methods directly regulate TLR4 expression. Geng Jing et al. [21] have confirmed that tripterygium lactone alcohol, the main active ingredient of *Tripterygium wilfordii*, can directly inhibit the expression of TLR4 to enhance the sensitivity of gastric cancer to therapeutic drugs and play an anti-gastric cancer role. The mechanism of action is that triptolide alcohol can enhance the sensitivity of gastric cancer cells to 5-fluorouracil by inhibiting the expression of TLR4 on gastric cancer cells, blocking the phosphatidylinositol 3 kinase/protein kinase B signal transduction pathway, down-regulating Survivin and promoting the activation of Caspase-3. The reduction of drug resistance eventually reached the 5-fluorouracil effect in the treatment of gastric cancer. And Zhong Chan et al. [22] found that Qingrehuasu prescriptions could down-regulate the mRNA expression of interleukin 8, tumor necrosis factor- α and TLR4 in gastric mucosa to achieve the effect of treating gastric cancer through the intervention of Qingrehuasu prescription on mice after gavage of Methylnitrosourea (MNU) combined with *Helicobacter pylori*. Yi Qingting et al. [23] demonstrated that polyene phosphatidylcholine combined with oxaliplatin can down-regulate the mRNA and protein expressions of TLR4, ABCF2 and Nanog through experiments in nude mice, thus playing a role in inhibiting the development of human gastric cancer.

4.2. Block the MyD88 dependent pathway

The MyD88-dependent pathway is a classical signaling pathway of TLR4 involved in inflammatory response and innate immunity. After the TLR4 extracellular region recognizes the ligand, the cytoplasmic region binds to the joint molecule and activates the downstream signaling molecules of the MyD88-dependent pathway to play a role. Current studies have shown that through the characteristics of the multi-direction of drug effect and wide range of intervention of traditional Chinese medicine, molecules in the MyD88-dependent pathway play a regulatory and inhibitory role. Wang Xue et al. [24] The results showed that the total flavonoids of *Hydroglossum japonicum* extract can reduce the serum tumor markers of MFC tumor bearing mice, regulate immune cytokines, maintain the balance of helper T cell 1/ helper T cell 2, inhibit the activation of TLR4/MyD88/NF- κ B signaling pathway, and show anti-tumor activity, improve immune function and anti-tumor purpose. Lv Pintian and Duan Xinbo [25] showed that the expression of TLR4, MyD88, NF- κ B and mRNA in spleen of mice in high-dose and low-dose groups were significantly decreased by the treatment of polygonum polysaccharide, which indicated that polygonum polysaccharide could inhibit the activation of TLR4/MyD88/NF- κ B signaling pathway. And play the effect of inhibiting tumor and regulating immune prescription. Lei Shengping et al. [26] also had similar results. Wang Juanyi et al. [27] showed that the protein expressions of TLR4, MyD88 and NF- κ B65 phosphorylated sites in gastric mucosa of rats in the model group were significantly higher than those in the conventional feeding blank group after *n*-methyl-*N*'-nitroso-*n*-nitroso guanidine compound modeling. The expression of TLR4, MyD88 and NF- κ B65 phosphorylated proteins in gastric mucosa of rats was significantly down-regulated after different doses of matrine, which indicated that matrine could protect gastric

mucosa and prevent the development of tumor by inhibiting the activation of the signaling pathway of TLR4/MyD88/NF- κ B phosphorylated sites. Zhang Manling ^[28] have confirmed that Jianpi Huoxue formula has a significant therapeutic effect on chronic atrophic gastritis accompanied by precancerous lesion through traditional Chinese medicine data mining, clinical studies and in vitro experiments. The results of in vitro studies show that administering Jianpi Huoxue medicated serum to rats stimulated by 1-methyl-3-nitro-1-nitroso guanidine is better than adding folic acid tablets medicated serum. By regulating TLR4/MyD88/NF- κ B signaling pathway, the drug-containing serum of Jianpi Huoxue formula can inhibit the malignant characteristics of malignant transformation of gastric epithelial cells. High mobility group protein B1, as a protein in the high mobility group box superfamily, has a wide range of expression. The main biological characteristics of malignant progression of gastric cancer are invasion and migration, and high mobility group protein B1 plays an important role in the migration of inflammatory and tumor cells. Therefore, the relationship between high mobility group protein B1 and gastric cancer is currently studied. Wu Qi et al. ^[29] further confirmed that high mobility group protein B1 can promote the invasion and metastasis of gastric cancer cells by activating TLR4/MyD88/NF- κ B signaling pathway through cell experiments, and inhibit the expression of high mobility group protein B1 in gastric cancer cells. The expression of TLR4/MyD88/NF- κ B signaling pathway was also inhibited, and the invasion and metastasis ability of corresponding tumor cells were also inhibited.

4.3. Down-regulated TLR4/NF- κ B

NF- κ B, as a homologous or heterodimer protein composed of NF- κ B/Rel family proteins, contains two subunits, P65 and P50, and its main role is to induce transcription of related genes. TLR4 expression in gastric cancer plays the role of information transcription through NF- κ B entering the intracellular binding site gene, so as to promote the release of inflammatory factors and chemokines. Therefore, NF- κ B plays a key role in the regulation of gastric cancer progression through TLR4 signaling pathway. As the active component of Codonopsis Codonopsis, Codonopsis polysaccharide has great potential in the targeted treatment of tumors. However, there are few studies on the therapeutic mechanism in gastric cancer, which needs further exploration. Yang Zihao and Zhou Henglu et al. ^[30] investigated that the molecular mechanism of Codonopsis polysaccharide regulating proliferation, apoptosis and inflammatory factor expression of gastric cancer cells through cell proliferation and flow cytometry. The results showed that the expression of TLR4, p65 and p-I κ B- α protein decreased after Codonopsis polysaccharide treatment, which confirmed that Codonopsis polysaccharide could inhibit the expression of TLR4/NF- κ B signaling pathway. Thus, it can play an anti-gastric cancer role and provide more possibilities for TCM prevention and treatment of gastric cancer.

As nanoscale vesicles secreted by tumor cells, tumor exosomes also play a role in regulating tumor proliferation, metastasis and immune escape, and its genetic material, long-chain RNA CASC11, can regulate the development of gastric cancer. Zhou Anfu et al. ^[31] have shown that both gastric cancer exosomes and long-chain RNA CASC11 containing genetic material can promote the M2 polarization of macrophages by inhibiting the expression of TLR4 and phosphorylation of NF- κ B, and inhibit the activation of TLR4/NF- κ B signaling pathway, thus affecting the development of gastric cancer. Existing studies suggest that *Lactobacillus casei* can enhance immunity and inhibit cancer ^[32]. A controlled experiment was set up to further observe the effect of *Lactobacillus casei* on the occurrence and development of gastric cancer rats. The results showed that the expression of TLR4 and NF- κ B65 phosphorylated protein decreased significantly in gastric cancer rats after the administration of *Lactobacillus casei*. It is concluded that *Lactobacillus casei* can down-regulate the expression of TLR4 and NF- κ B65 phosphorylated protein. Inhibition of TLR4/NF- κ B signaling pathway can inhibit the growth and development of gastric cancer cells, and the experimental effect is best when the level of *Lactobacillus casei* is adjusted to 8ml/kg.

5. Summary

As the primary barrier against infectious diseases, the activation or inhibition of TLR4 is closely related to immune diseases and inflammatory responses. Every factor and cell in the TLR4 signaling pathway has a significant impact on the course of diseases. Therefore, in-depth research on the molecular mechanism of TLR4 signaling pathway is of great importance for disease treatment. TCM has the advantages of small adverse reactions, high safety factor, good therapeutic effect, holistic syndrome differentiation and multi-target and comprehensive action. Therefore, under the guidance of immunological theory, the targeted treatment of TLR4 signaling pathway by traditional Chinese

medicine on its molecular mechanism is discussed, in order to play a great potential in the treatment of gastric cancer in the future. TLR4 is closely related to the occurrence and development of gastric cancer. Inhibition of TLR4 or TLR4/MyD88/NF- κ B or TLR4/NF- κ B can inhibit the progression of gastric cancer to varying degrees, and activation of these signaling pathways can accelerate the progression of gastric cancer. Based on the existing research results, it is also possible to search for treatment of gastric cancer by inhibiting TLR4 or TLR4/MyD88/NF- κ B or TLR4/NF- κ B.

However, the current research still has the following deficiencies: (1) The specific mechanism of TLR4 signaling pathway and related signal transduction factors has not been fully clarified, which lacks guidance for accurate use of drug targets for treatment. (2) TLR4 signaling pathway involves a large number of cells and factors and requires a large amount of research data and in-depth analysis of results, which leads to limited research results on the correlation between TLR4 and gastric cancer. Therefore, the correlation between TLR4 and gastric cancer cannot be fully clarified at first. (3) Traditional Chinese medicine has the characteristics of multiple components and multiple parts, which makes it more difficult to study the specific mechanism of traditional Chinese medicine. In this regard, relevant studies will be further carried out in the hope of providing more possibilities for targeted treatment of gastric cancer through traditional Chinese medicine, Chinese herbal compound and other methods.

Acknowledgement

Fund: (1) Key Laboratory of Traditional Chinese Medicine Prevention and Treatment of Gastrointestinal Precancerous Lesions, Shaanxi Provincial Administration of Traditional Chinese Medicine (Shaanxi Traditional Chinese Medicine [2019] No. 9).

(2) Research Project of Shaanxi University of Traditional Chinese Medicine Affiliated Hospital (2020XZ001)

References

- [1] Smyth EC, Nilsson M, Grabsch HI, et al. Gastric cancer[J]. *Lancet*, 2020, 396(10251): 635-648.
- [2] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. *CA Cancer J Clin*, 2018, 68(6): 394-424.
- [3] Sano T. Gastric cancer: Asia and the world[J]. *Gastric Cancer*, 2017, 20(Suppl 1): 1-2.
- [4] Chen WQ, Li H, Sun KX, et al. Report of Cancer Incidence and Mortality in China, 2014[J]. *Zhonghua Zhong Liu Za Zhi*, 2018, 40(1): 5-13.
- [5] Tongtawee T, Simawaranon T, Wattanawongdon W, et al. Toll-like receptor 2 and 4 polymorphisms associated with *Helicobacter pylori* susceptibility and gastric cancer[J]. *Turk J Gastroenterol*, 2019, 30(1): 15-20.
- [6] Karimi P, Islami F, Anandasabapathy S, et al. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention [J]. *Cancer Epidemiol Biomarkers Prev*, 2014, 23(5): 700-713.
- [7] Yang Ying, Hou Tingting, Wang Wei, Chen Yanjun, Liu Dong. Research progress on pharmacological effects of polysaccharides from *Polygonati Rhizoma* [J]. *Drugs & Clinic*, 2022, 37(3): 659-665.
- [8] Lazăr DC, Tăban S, Cornianu M, et al. New advances in targeted gastric cancer treatment[J]. *World J Gastroenterol*, 2016, 22(30): 6776-6799.
- [9] Zeng D, Li M, Zhou R, et al. Tumor microenvironment characterization in gastric cancer identifies prognostic and immunotherapeutically relevant gene signatures[J]. *Cancer Immunol Res*, 2019, 7(5): 737-750.
- [10] Chen Junli, Pei Ming, Zhou Haokun, et al. Research progress of Toll-like receptor 4 signaling pathway in fibrosis[J]. *Hebei Medical Journal*, 2022, 44(13): 2044-2048.
- [11] Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway[J]. *Cytokine*, 2008, 42(2): 145-151.
- [12] Zou Xinmei, Wang Yang, Zhong Liping. Clinical significance of TLR2 and TLR4 expression in *Helicobacter pylori* infection-related gastric cancer tissues[J]. *Zhejiang Journal of Integrated Traditional Chinese and Western Medicine*, 2022, 32(2): 136-139.
- [13] Li Z, Gao H, Liu Y, et al. Genetic variants in the regulation region of TLR4 reduce the gastric cancer susceptibility [J]. *Gene*, 2021, 767: 145181.
- [14] Zhang Yameng, Zhang Yueying, Xiang Hongjie. The Role of TLR4/NF- κ B Pathway in Hp Induced

Gastric Cancer[J].*World Journal of Integrated Traditional and Western Medicine*, 2019, 14(12): 1691-1694.

[15] Hu Chenghao, Luo Qingqin, Zhang Danfeng, et al. Expression of Toll-like receptor 4 in gastric cancer and its clinical significance[J]. *Chinese Journal of Clinical Research*, 2018, 31(4): 459-462.

[16] Wang Yang, Zou Xinmei, Pan Qinmei, et al. Clinical significance of changes of TLR4/ MyD88/ NF- κ B signaling pathway in peripheral blood mononuclear cells of gastric cancer patients with *Helicobacter pylori* infection[J]. *World Chinese Journal of Digestology*, 2021, 29(6): 319-324.

[17] Newton K, Dixit VM. Signaling in innate immunity and inflammation[J]. *Cold Spring Harb Perspect Biol*, 2012, 4(3): a006049.

[18] Hishida A, Matsuo K, Goto Y, et al. Toll-like receptor 4 +3725 G/C polymorphism, *Helicobacter pylori* seropositivity, and the risk of gastric atrophy and gastric cancer in Japanese[J]. *Helicobacter*, 2009, 14(1): 47-53.

[19] Santini D, Angeletti S, Ruzzo A, et al. Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms in gastric cancer of intestinal and diffuse histotypes[J]. *Clin Exp Immunol*, 2008, 154(3): 360-364.

[20] Kang Zhenchao, Li Xiao, Zhu Xiaomei, et al. Ophiopogonin D inhibits the secretion of cytokines from LPS-induced gastric cancer cell line HGC-27 by regulating miR-448/TLR4 axis[J]. *Chinese Journal of Immunology*, 2022, 38(5): 416-423.

[21] Geng Jing, Zhang Shuxian, Sun Yunliang. Triptolide enhances the sensitivity of gastric cancer BGC823 cells to 5-FU by suppressing TLR4 expression [J]. *Chinese Journal of Integrated Traditional and Western Medicine on Digestion*, 2022, 30(4): 263-267.

[22] Zhong Chan, Zhang Tao, Huang LiBingbing, et al. Effects of Qingrehuashifang on levels of TNF- α , IL-8 and TLR-4 in gastric tissue of mice infected with MNU and *Helicobacter pylori*[J]. *Chinese Traditional Patent Medicine*, 2020, 42(5): 1339-1343.

[23] Yi Qingting, Zhang Hongjun, Jiang Tao, et al. Reversal effect and mechanism of polyene phosphatidylcholine on oxaliplatin resistance of gastric cancer cells in a nude mouse model[J]. *Practical Oncology Journal*, 2018, 32(5): 385-390.

[24] Wang Xue, Ling Jiayin, Zhai Yongcong, et al. Effects of total Flavonoids of *Hedyotis diffusa* on serum tumor markers and immune function of MFC gastric cancer bearing mice[J]. *The Chinese Journal of Clinical Pharmacology*, 2021, 37(19): 2627-2630.

[25] Lv Pintian, Duan Xinbo. Antitumor and immunomodulatory effects of *Polygonatum polygonatum* polysaccharide on MFC gastric cancer mice[J]. *Chinese Traditional Patent Medicine*, 2020, 42(8): 2169-2172.

[26] Lei Shengping, Wang Liang, Long Zijiang, et al. Inhibitory effect of *Polygonatum sibiricum* polysaccharides on release of inflammatory cytokines of anoxia/reoxygenation H9c2 myocardial cells through TLR4-MyD88-NF- κ B signaling pathway[J]. *Chinese Pharmacological Bulletin*, 2017, 33(2): 255-259, 260.

[27] Wang Juanyi, Liu Zhongqiu, Li Wei, et al. Matrine alleviates N-methyl-N'-nitro-n-nitrosoguanidine (MNNG) -induced gastric mucosal injury in rats and its mechanism[J]. *Chinese Journal of Cellular and Molecular Immunology*, 2020, 36(2): 157-163.

[28] Zhang M L. Study on the therapeutic effect and mechanism of Jianpi Huoxue Formula in the treatment of atrophic gastritis accompanied by precancerous lesions based on TLR4 pathway [D]. Wuhan: Hubei University of Traditional Chinese Medicine, 2021.

[29] Wu Qi, Wang Hongwei, Zheng Huizhe, et al. Effect of HMGB1 expression on invasion and migration of gastric cancer cells and TLR4/MyD88/NF- κ B signaling pathway[J]. *Journal of Guizhou Medical University*, 2021, 46(9): 1047-1053.

[30] Yang Zihao, Zhou Henglu. Effects of *Codonopsis pilosum* polysaccharide on the proliferation, apoptosis and expression of inflammatory factors in gastric cancer cells AGS by regulating miR-361-5p/TLR4/NF- κ B pathway [J]. *Chinese Journal of Immunology*, 2022, 38(4): 347-353.

[31] Zhou Anfu, Tan Yan, Zhang Huijing. Gastric cancer exosome lncRNA CASC11 regulates TLR4/ NF- κ B pathway to induce polarization of M2-type macrophages[J].*Hebei Medicine*, 2021, 27(12): 1948-1957.

[32] Zhang Dan, Wang Yunye. Anti-tumor effect and immunological mechanism of *Lactobacillus casei* in a rat model of gastric cancer[J]. *Chinese Journal of Comparative Medicine*, 2018, 28(12): 48-54.