1 Kaempferol Compound effect:Reduced mortality in mice,To improve the pathological changes of lung tissue.Reduce the number of inflammatory cells such as macrophages, lymphocytes and neutrophils.Reduce the content of TNF-, IL-6, IL-1 and MDA,Inhibit the activity of MPO and increase the activity of SOD.

2 Morin Compound effect:Reduce inflammatory cell infiltration in lung tissue, reduce pulmonary edema. Reduce the expression of TNF- and IL-1, inhibit the phosphorylation of NF- κB and IKK, and inhibit the up regulation of TLR4 protein expression.

3 Quercetin Compound effect:Reducing the content of MDA in plasma and BALF.Elevated GSH-Px and SOD activity.It relieves congestion, thickening of the alveolar wall .Decreased the expression of NF- κB p65 and W/D in lung tissue.

4 Breviscapine Compound effect:Significantly reduce the degree of lung injury.To relieve congestion, hemorrhage, edema, neutrophil infiltration in alveolar space and vascular wall.To decrease the levels of W/D, MPO and MDA in acute lung injury of rats, and increase the activity of SOD, which was dose dependent.

## APPLICATION OF HYALURONIC ACID IN TARGETING TUMOR

**Hong-FangWang1, Xue-YingYan***

School of Pharmacy,HeiLongJiang University of Chinese Medicine,P.R.China * Corresponding authors Xue-YingYan Address:Heping Road 24,Harbin 150040,School of Pharmacy,HeiLongJiang University of Chinese Medicine,Harbin,P.R.ChinaE-mail addresses: 15159267@qq.com.

Abstract Tumors have become important killers of human health, especially malignancies. Currently, chemotherapy is the most important means of treatment of cancer, but chemotherapy drugs can not be targeted enrichment in the tumor area, and its toxicity is often not selective. Hyaluronan(or named Hyaluronic acid, HA) with simple chemical structure and complex physicochemical properties is an acidic mucopolysaccharide and an important member of glycoaminoglycan family. Because the hyaluronic acid receptor CD44 is specifically overexpressed in a variety of tumor cells, the natural ligand of hyaluronic acid has become a hot research topic, and on this basis, many hyaluronic acid-CD44 As the core of the tumor for the active range of nano drug delivery system research. This review focuses on the application of hyaluronic acid in tumor targeting.

Key words: Hyaluronic acid, Tumor targeting

Hyaluronic acid (HA) is composed of N-acetylglucosamine and D-glucaldehyde Acid monosaccharides consist of a repeating linear molecule, which is Meyer and Palmer Isolated from the bovine vitreous body separation in 1934 for the first time. HA surface contains a large number of negatively charged carboxyl, so can reduce the macrophage phagocytic system uptake thus hyaluronic acid drug delivery system can effectively extend the drug blood circulation time. Additionally, HA has attracted great attention as a targeted ligand, since manykinds of cancer cells overexpress HA receptor like CD44 [1]. As reported , HA modified nanocarriers could enter into the cells quickly via CD44-medicated endocytosis pathway to increasethe drug accumulation specifically in cancer cells over-expressing CD44, thus improve the anti-tumor efficacy of chemotherapeu-tic drugs.

The HA-drug conjugate is a prodrug prepared by covalently bonding between the small molecule antineoplastic agents and HA. These covalent bonds are not easily cleaved in the blood, but after reaching the target, they are cleaved by hydrolysis or enzymolysis to release the drug. Xin Wei et al. [2] synthesis of nanogel–drug conjugates based on membranotropic cholesteryl-HA (CHA) for efficient targeting and suppression of drug-resistant tumors. Importantly, CHA–drug nanogels demonstrated 2–7 times higher cytotoxicity in CD44-expressing drug-resistant human breast and pancreatic adenocarcinoma cells compared to that of free drugs and nonmodified HA–drug conjugates. Anchoring by cholesterol moieties in the cellular membrane after nanogel unfolding evidently caused more efficient drug accumulation in cancer cells compared to that in nonmodified HA–drug conjugates. CHA–drug nanogels were able to penetrate multicellular cancer spheroids and displayed a higher cytotoxic effect in the system modeling tumor environment than both free drugs and HA–drug conjugates.

Amphoteric HA derivatives can be self-assembled in aqueous solution core - shell - structured nanoparticles .Self-assembled nanoparticles have been regarded asan advanced system for hydrophobic drugs or nucleic acids delivery [3]. After self-assembly, the hydrophilic segments serve as protective shell to avoid being removed by the reticuloendothelial system (RES). .Linet al[4] were prepared the pH-sensitive and targeted nanoparticles LHRH-HA-cys-ADOX and HA-cys-ADOX by the self-assembly of HA. The uptake of LHRH-HA-cys-ADOX was higher than free drugs and HA- Cys-ADOX. Detection of cytotoxicity using 3T3 cell lines The above two nanoparticles reduced the toxicity of doxorubicin .

HA surface modification nano-drug delivery system, not only can improve the targeting of nano-formulations, but also to extend the body cycle time.Rivkind et al.[5] first PTX paclitaxel and lipid blending to form nanoclusters, and then with EDAC activated hyaluronic acid added to the drug suspension, the preparation of hyaluronic acid-coated nano-drug-containing system. The results of this experiment show that the HA-coated carrier has significant tumor enrichment and antitumor activity compared with the drug carrier without HA.

Discussion HA has the advantages of good biocompatibility, diversity of chemical modification and targeting of tumor cells. It has attracted much attention in the anti-tumor drug delivery system and has a good carrier platform for the delivery of tumor therapeutic drugs. The development potential and unique advantages. HA as anti-tumor drug carrier research has

made great progress, but some problems still need further study,as an anti-tumor drug delivery vector, HA has targeting tumor cells, the role of the site is mainly CD44 receptor, and CD44 receptors may exist a wide range of expression, the variation itself reduces the selectivity of the target, short update cycle and easy saturation disadvantages. Therefore, to overcome these shortcomings of CD44 receptors, to improve the active targeting of tumors is the future direction of research.

References:

1.Yu M, Jambhrunkar S, Thorn P, et al. Hyaluronic acid modified mesoporous silica nanoparticles for targeted drug delivery to CD44-overexpressing cancer cells. //Nanoscale, – 2012.– 5(1) .– C.178.

2. Wei X, Senanayake T H, Warren G, et al. Hyaluronic acid-based nanogel-drug conjugates with enhanced anticancer activity designed for the targeting of CD44-positive and drug-resistant tumors // Bioconjugate Chemistry, – 2013. – 24(4) .– C.658.

3. Liu Y, Sun J, Zhang P, et al. Amphiphilic polysaccharide-hydrophobicized graft polymeric micelles for drug delivery nanosystems. // Current Medicinal Chemistry, – 2011. – 18(17):2638-2648.

4.Lin C J, Kuan C H, Wang L W, et al. Integrated self-assembling drug delivery system possessing dual responsive and active targeting for orthotopic ovarian cancer theranostics. // Biomaterials, – 2016. – 90.– C.19-20.

5. Rivkin I, Cohen K, Koffler J, et al. Paclitaxel-clusters coated with hyaluronan as selective tumor-targeted nanovectors .//Biomaterials, – 2010. – 31(27) .– C.7106.

## INDUCING CALLUS OF GENTIANA MANSHURICA KITAG.

**HongKun LI, YuPeng CHENG*.**

（Hei LongJiang University of Chinese Medicine, Harbin, HeiLongJiang, China. 150040)Hong-kun Li: Tel: 15645013602; E-mail address: 404540551@qq.com

Abstract The time of surface sterilization by 10% NaClO for sprouting seeds of Gentiana manshurica Kitag. was evaluated. The conditions of callus inducing from the explants of hypocotyls were examined. The results indicated that the optimal time for seeds surface sterilization by NaClO is 8 min, the proportion of different concentration of hormones have the same effects on inducement of callus, and 1/2 MS medium containing 6-BA 0.5mg/L and 2,4-D 2mg/L is the optimal condition for the growth of callus of G. manshurica Kitag.

Keyword Gentiana manshurica Kitag . ; Seeds sprouting; Callus

Objection and Meanings Recently, overexploitation of wild plants has resulted in extensive cropping. The term "callus" originates from the Latin word callum, which refers to the massive growth of cells and cell masses[5]. Callus could converted into suspension cells which are used to ferment bioactive compounds. This study can lay the foundation for establishing the asexual reproduction system and producing the bioactive secondary metabolites by large scale fermentation of suspension cells.

Materials and methods Seeds of G. manshurica Kitag. are kindly offered by professor Chen Wang of Harbin Normal University. Seeds of Gentiana manshurica Kitag. were soaked in distilled water for 48 hours and sterilized with 75% ethanol for 40s. Then the seeds were washed with sterile distilled water repeatedly . The treated seeds were surface sterilized by using10% of NaClO for 6min, 8min and10min, respectively. One drop of Tween-80 was also added as surfactant. After 6, 8, 10 minutes the seeds were washed 4-5 times with sterile distilled water to remove the traces of bleach with gentle shaking under sterile conditions[1]. The seeds were incubated on MS solid medium containing no hormones at 25 ℃ for 16 hours with light conditions[2]. Hypocotyls were cut from aseptically germinated seedlings. Each kind of explants was cut into small segments and incubated on 1/2 MS solid medium containing different concentration hormones at 25 ℃ with 16 hours with light. The growth status of each group was compared. Callus in good growth status was picked, cut off the browning part and cut into 1cm segments[3,4]. The segments were incubated on MS medium contain different concentration of hormones. The growth status were compared among the groups.

Results and discussion Germination rate of the seeds with different surface sterilized time was compared (Table1) (Figure 1). The results showed that 8 min is the best timing for seeds surface sterilizing of Gentiana manshurica Kitag. for sprouting. When the length of sterilization time is shorter than 8 min, there are more survival microorganisms of surface, and can result in more contaminated opportunities in later tissue culture. On the other hand, the length of sterilization time is longer than 8 min, the seeds would be damaged, and the rate of germination would decrease. Callus induced on mediums containing different concentration of hormone was compared (Figure 2). The results showed that the effect of different concentrations of hormones on callus of Gentiana manshurica Kitag. inducement is basically the same. The growth of subculture callus is affected by the variation of concentration of 6-BA combined with 2,4-D. When the concentration of 6-BA in medium is high the callus become partly browning, and different concentration of 6-BA with 2,4-D is important to callus growth.

Table 1 The germination rate of Gentiana manshurica Kitag. seeds with different sterilize time

| surface sterilize time | 6min | 8min | 10min |
|---|---|---|---|
| Germination rate | 50% | 87.2% | 71.8% |