

# Current Situation of Medicine used for Infectious Disease in China

中国抗感染病药物现状

**Wang Jun Zhi (王军志)**

**National Institute for Control of Pharmaceutical & Biological  
Products , NICPBP**

(中国药品生物制品检定所)



## Outline

- Development of Biological Products in China  
中国生物制品的发展历史简介
- Present Situation of Biologics for Prophylaxis  
(vaccine)预防用生物制品
- Present Situation of Biologics for Therapeutic  
use 治疗用生物制品
- Chemical Drugs of anti-infectious diseases  
抗感染化学药
- Chinese Traditinal MedicineCTM  
抗感染中药



# Development of Biological Products in China

The research, production, and application of biological products in China started since 1919. Biological products developed slowly and in small scale, only several species before 1949.

At present time, China could produce over 200 kinds of biological products(Vaccines, Antitoxins/Antisera, Blood products,Cytokines , and also developed many new prophylaxis and therapeutic biological products continuously.

我国从1919年开始研究、生产和使用生物制品。在1949年以前的30年中，生物制品发展缓慢，规模很小，只有几十个品种。目前生产使用了细菌类、病毒类、毒素、抗毒素、抗血清、血液制品、细胞因子、微生态制剂、重组药物、体内及体外诊断试剂等各类生物制品200多个品种，并且还在不断地研制和生产出防治疾病所需要的各种新生物制品。



Before 1980's almost biological products had been produced by 6 national institutes of biological products in Beijing, Shanghai, Changchun, Lanzhou, Wuhan, Kungming. These national institutes could produce the several vaccines up to 1 billion doses a year, which could meet the demand of vaccinating the whole nation.

在生物制品制造业方面，1980年代以前主要由北京、长春、成都、兰州、上海、武汉、昆明6大卫生部生物制品研究所承担。其中疫苗每年生产近10亿人份，满足了我国防疫预防接种的数量要求。

In the 1980's, biological products industry was booming in China, there are more than 200 enterprises engaged in this field. Varieties and number of biological products increased significantly.

• 20世纪80年代后，我国生物制品事业跨入了高速发展的新时期，生物制品企业超过了200多家。生产的种类、型别、剂型也大幅度增加。预防用生物制品60多个，治疗用生物制品40多个，诊断用生物制品200多个。

The output and wide application of biological products in China are unique in the world . Biological products play an very important role in diseases prevention, diagnosis and treatments.

All of enterprises achieved GMP requirements in order to keep quality of biological products consistent with international level.

我国目前每年生产供应各种疫苗、类毒素、抗毒素、抗血清等生物制品规模之大、使用面之广是全世界绝无仅有的。生物制品在疾病的预防、诊断和治疗中发挥着极其重要的作用。

目前所有生产企业已完成GMP认证，从而保证了生物制品产品的质量与国际水平一致。



- **Prophylaxis** is playing most important role in Chinese strategy of public health . Vaccination was put in practice throughout the whole country since People's Republic of China was founded in 1949. Incidence of a infectious disease and death rate decreased significantly.
- Smallpox has been extinguished ;
- Poliomyelitis case infected by wild strain has not been found since 1995;
- In the area of using hepatitis B vaccine the carriers decreased from 16% to 1% of the population vaccinated .

1949年建国以来，我国在“预防为主”方针的指导下，普遍实行预防接种，使相关传染病的发病率和死亡率数十倍下降，天花 (Smallpox) 已被彻底消灭，脊髓灰质炎自1995年以来未发现国内野毒株感染，使彻底消灭小儿麻痹成为可能。在乙肝疫苗普种地区，乙肝带毒率由16%下降到1%。

# Vaccines in market



- **Bacterial vaccines(细菌性疫苗):**
- Typhoid(伤寒),
- Typhoid and paratyphoid A & B combined vaccine(伤寒和副伤寒结合疫苗),
- Vi Polysaccharide typhoid(伤寒Vi多糖疫苗),
- Diphtheria, Tetanus and Pertussis, DTP(白百破联合疫苗),
- A Meningococcal Polysaccharide(脑膜炎球菌多糖疫苗),
- BCG(卡介苗),
- Plague(鼠疫),
- Anthrax(炭疽),
- Brucellosis(布氏),
- Leptospira Vaccine(钩端螺旋体疫苗).



- **Viral Vaccines**病毒性疫苗:
- Japanese Encephalitis (inactivated and live)(乙型脑炎灭活（减毒）疫苗)
- Tick- borne Encephalitis(森林脑炎灭活疫苗)
- Measles(麻疹疫苗),
- Rubella(风疹疫苗),
- Mumps(腮腺炎疫苗),
- Yellow fever(黄热病疫苗),
- Haemorrhagic fever(出血热疫苗),
- HBV(乙肝),
- HAV(甲肝),
- OPV (脊髓灰质炎),
- Rota (轮状病毒疫苗),
- Rabies Vaccines(狂犬病疫苗).



# Japanese Encephalitis live Vaccine 乙型脑炎活疫苗

Japanese Encephalitis live Vaccine is the only one having Chinese patent produced in China .

The wild JE virus, SA14 isolated from a pool of *Culex pipiens* larvae from Xian, China in 1953. Researchers of NICPBP obtained the wild-type parental virus SA 14 by 11 passages in mouse brain in 1960, started the research for neuroattenuation.

乙型脑炎活疫苗拥有中国的自主知识产权。

野生型JE病毒株是1953从库蚊中分离得到的。1960年中检所通过兔脑传代（11代）进行神经毒力减毒，获得减毒株。



# Japanese Encephalitis live Vaccine

## 乙型脑炎活疫苗

- This strain was demonstrated having a fine balance between safety and immunogenicity, with sufficient viral replication to stimulate immunity.
- Clinical trial Phase I, II, III and IV was completed in 1980-1996 respectively. The vaccine was demonstrated having good safety and potency.
- long term study 11 years' (1989-1999) for safety and effectiveness of live JE vaccine was carried out. Only few showed mild or middle fever, slight local reaction. No severe adverse reactions were observed.

该株具有很好的安全性和免疫原性，能在机体复制刺激免疫产生分别于 1980-1996进行了疫苗的I、II、III和IV期临床研究，证明该疫苗具有和好的安全性和效果。

对乙型脑炎活疫苗进行长达11年的安全性和有效性研究，没有发现严重的副反应，只观察到轻度、中度发热和轻微局部反应。



# Japanese Encephalitis live Vaccine

## 乙型脑炎活疫苗

11 years before the immunization (1978-1988), there were 769 cases of JE found in Yongfeng area. The 11 years during immunization, there were 138 cases of JE. The average incidence rate decreased 84.51% compared with 11 years before immunization. The total incident rate decreased from 21.89/100,000 to 2/100,000. The protection rate reached 98.99%.

江西永丰县免疫前11年与后11年比较，发病人数从769人降到138人，平均发病率降低了84.51%。总发病率从21.89/100,000 降到2/100,000，保护率为98.99%。



## New Vaccines under development or clinical trial

- HIV, Phase II
- SARS, Phase II
- Bird Flu Phase I
- Malaria vaccines Phase III
- HEV (戊肝) Phase II
- Helicobacter pylori HP Phase III



# Biologicals for therapeutical use

## 治疗用生物制品

1. Human immunoglobulins, including specific immunoglobulin (人免疫球蛋白, 特免球蛋白)
2. Antiserum biologicals (抗血清)
3. Recombinant DNA products (基因重组产品)
4. Bacterial vaccines for therapeutical use (治疗用菌苗类产品)



# Human immunoglobulins

## 人免疫球蛋白

- **Human Hepatitis B immunoglobulin**  
人乙型肝炎免疫球蛋白
- **Human rabies immunoglobulin**  
人狂犬病免疫球蛋白
- **Human tetanus immunoglobulin**  
人破伤风免疫球蛋白



# Antiserum Biologicals in market

## 抗血清类生物制品

- Tetanus toxin antiserum (抗破伤风)
- Rabies virus antiserum (抗狂犬)
- Anthrax antiserum (抗炭疽)
- Anti-botulinum serum (抗肉毒)

These kinds of anti-serum have been used for the treatment of corresponding diseases.

# Bacterial vaccines for therapeutical use

## 治疗用菌苗类产品

### 1. Tuberculosis Therapeutic Use 用于结核病治疗用生物制剂

Freeze-dried M.vaccine 冻干治疗用母牛分枝杆菌菌苗  
(商品名: 微卡)

Mycobacterium Phlei F.U.36 Injection 草分枝杆菌  
F. U. 36注射液 (商品名: 乌体林斯)

### 2. Brucella Vaccine for Therapeutic Use

(治疗用布氏杆菌制剂)



# rDNA Protein products 基因重组蛋白产品

**IFN**  $\alpha$  1b、IFN  $\alpha$  2a、IFN  $\alpha$  2b、IFN  $\omega$



## IFN- $\alpha$ (干扰素- $\alpha$ )

- IFN- $\alpha$  can be wide used in curing chronic active hepatitis B and acute and chronic hepatitis C in China. the efficient rate is : 30%~40% for HBV and 50%~70% for HCV. The efficient rate of HBV is lower than that reported because the types of HBV of infected Chinese mostly are gene type B and C of HBV, which are more difficult to be cured than gene type A infected occidental.
- IFN- $\alpha$  可以用于治疗慢性活动性乙型肝炎和急慢性丙型肝炎, 对丙型肝炎一般有效率在50%~70%左右。乙型肝炎用IFN- $\alpha$  治疗效果较差, 有效率在30%~40%左右, 可能是由于我国感染的乙肝病毒基因型以B、C型为主, 较西方人感染的A基因型难治。



## IFN- $\alpha$ -1b(干扰素- $\alpha$ -1b)

- Recombined IFN  $\alpha$ -1b is a gene engineering product cloned and expressed basing on Leukocyte of Chinese , So IFN  $\alpha$ -1b is more equal to Chinese natural condition theoretically. It was proved that IFN  $\alpha$ -1b is comparable with IFN  $\alpha$ -2 in activity and curative effect in equal mass . So It can bring fewer side effects and less neutralization antibody.
- 中国人的白细胞经病毒刺激后诱生的干扰素中最主要亚型是  $\alpha$ -1b，其次是  $\alpha$ -2，因此从理论上讲，干扰素  $\alpha$ -1b 更接近中国人的自然状况。相同重量的  $\alpha$ -1b 与  $\alpha$ -2 的疗效相当，但发热等不良反应较少，且产生中和抗体的几率也更小。



## Biologicals for therapeutical use are under development or clinical trial.

- Human Immunoglobulin for Treatment of SARS  
人(SARS 特异性免疫球蛋白 )

Anti-SARS immunoglobulin is a novel drug of anti-SARS by means of neutralizing SARS virus. It is prepared from pooled plasma of SARS convalescent by cold ethanol fractionation and viral inactivation process.

- approved by SFDA as Anti-SARS immunoglobulin for emergence use in 2004
- 该药物是我国自主研发的治疗SARS的药物。系SARS康复患者血浆提取的免疫球蛋白的浓缩物，采用现行低温乙醇工艺结合病毒灭活工艺制备。2004年SFDA正式批准该药物用于SARS的应急治疗。



## Viral macrophage Inflammatory Protein-II

### 病毒巨噬细胞炎性蛋白-II

- Indication of R&D: a broad-spectrum anti-HIV agent. derived from K4 gene of human herpes virus-8.  
来源于人疱疹病毒8 K4基因的基因工程产品。
- vMIP-II binds broadly to chemokine receptors such as CCR5 and CXCR4, and can inhibit entry of multiple HIV-1 strains.  
vMIP-II可广谱结合CCR5、CXCR4等受体，阻断多种HIV病毒株感染靶细胞。
- Approval of clinical trial by SFDA.  
目前处于临床研究的阶段。



# Recombinant Mannose Binding Lectin(MBL)

Indication : preventing agent of HIV for external use

- Recognize carbohydrate such as N-acetyl glucose in mannose and pathogen  
Combine pathogen(HIV) or infected cells。

Exert effects through following pathways: Mechanical blocking; Complement activation; Opsonization/Phagocytosis

识别如甘露糖和病原体上的N-乙酰葡萄糖等碳水化合物 结合病原体（HIV）或已感染细胞 通过机械阻断，激活补体和调理途径发挥效用：

- Value of MBL for HIV-1 is more than 1030.93
- MBL can inhibit the fusion of the HIV-1-chronic-infected cells and normal cells. 能够阻断HIV-1慢性感染细胞与正常细胞融合的作用
- Research of Dosage Form 剂型研究
  - To alter dosage form 改变剂型
  - To alter the way of administration (For external use) 改变给药途径：

Endovaginal 阴道内；

Condom 避孕套



# Recombinant Human Lysozyme

## (重组人溶菌酶喷雾剂)

Indication : Upper respiratory tract infection

1,4-  $\beta$  -N-Lysozyme: Good therapeutic action by spray in mice with laryngeal infection on Staphylococcus aureus; ED50 is 0.51mg/ml/time

Inhibit the release of inflammatory medium, protect normal tissue in the inflammatory location, inhibit virus replication

➤ Approval of Phase II by SFDA

溶菌酶是一种有效的抗菌剂, 喷雾给药对金葡菌致小鼠咽喉部细菌感染具有较好的治疗作用, 其ED<sub>50</sub>为0.51mg/ml/次。抑制炎性介质的释放, 保护炎症部位的正常组织, 抑制病毒复制。 临床II期。

# The Diagnostic Products For Infectious Disease

The diagnostic products were widely used for clinical test and blood screening. It is important for early diagnosis and preventing infectious disease transmission. Such as HAV, HBV, HCV, HEV, HIV, Tuberculosis, Treponema Pallidum (Syphilis), Japanese Encephalitis Virus, Rotavirus, etc.

ELISA and PCR technique are most popular to be used in the diagnostic products. With the development of science and technique , more and more a new diagnostic products will be developed . Certainly, all of these diagnostic products must be licensed by SFDA.



# 我国批准注册的医用生物芯片产品

## Biochips related to infectious disease Approved in China

- 丙型肝炎病毒抗体片段检测试剂盒  
Antibody Fragments of HCV virus Diagnosis Chip
- 幽门螺旋杆菌抗体蛋白芯片检测系统  
Helicobacter pylori antibody Diagnosis Chip
- 人HPV，沙眼衣原体抗体检测系统  
Human HPV, Diagnosis Chip



# 申请临床研究的生物生物芯片

## Biochips related to infectious disease Applied for IND

- 丙型肝炎病毒多抗体蛋白芯片检测试剂盒  
HCV multi clone antibody diagnosis Chip
- 乙型肝炎病毒基因多态性检测芯片  
HBV gene polymorphsim diagnosis Chip
- 乙型肝炎病毒DNA及拉米夫定耐药基因芯片检测试剂盒  
HBV multi drug resistant gene diagnosis Chip
- 乙、丙型肝炎双检基因(诊断)芯片  
HBV, HCV diagnosis Chip
- 结核多种抗原IgG抗体蛋白芯片检测系  
Tuberculosis antigen IgG antibody diagnosis Chip
- SARS冠状病毒基因芯片检测试剂盒  
SARS coronal virus gene diagnosis Chip



# Chemical Drugs of anti-infectious diseases (抗感染病化学药物)

1. Antibiotics for treatment of bacterial infectious diseases such as penicillin, streptomycin, erythrocin, cephalosporin, Gatifloxacin, Antofloxacin Hydrochloride, Caderofloxacin Lactate;

抗生素类药物（如：青霉素、链霉素、红霉素、先锋霉素、加替沙星、盐酸安妥沙星、乳酸卡德沙星）



2. Ribonucleotide medicine for treatment of viral infectious diseases such as zidovudine, Lamivudine, strvudine didanosine, nevirapine;

核苷酸类药物如：齐多夫定、拉米夫定、司坦夫定、去羟肌苷（抗病毒类药物）、奈韦拉平（抗病毒类药物），主要用于病毒性传染病的治疗；

3. Proteinase inhibitors for treatment of AIDS such as Indinavir, Saquinavir, Ritonavir, Nelfinavir, Amprenavir.

用于AIDS治疗的蛋白酶抑制剂类药物如：茚地那韦（抗病毒类药物）、沙奎那韦（抗病毒类药物）、利托那韦（抗病毒类药物）、奈非那韦（抗病毒类药物）、安普那韦（抗病毒类药物）等。

4. Anti- tuberculosis drugs 抗结核病药: Rifampicin利福平, Isoniazid异烟肼, Pyrazinamide吡嗪酰胺 etc.



# The Chinese traditional medicine anti-infectious diseases 抗感染中草药

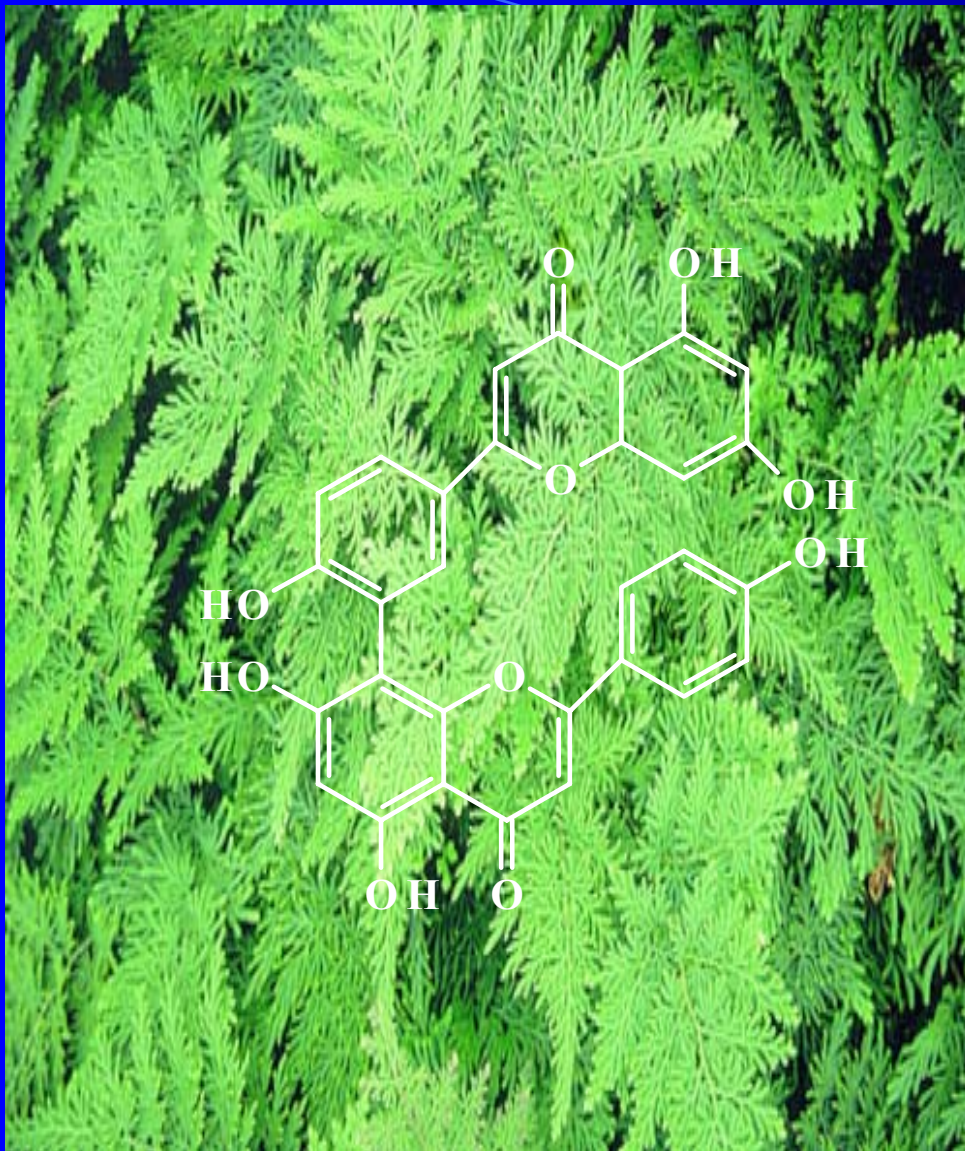
Chinese traditional medicine, such as folium isatidis, rhizoma coptidis, Flos lonicerae, have been proven to have anti-bacterial and viral roles.

中医和中草药是我国的传统医药，其抗病毒和抗细菌的作用已得到了肯定，如：大青叶、黄连、金银花等。



# Antiviral TCM Complex (抗病毒中药复方)

1. Ganmao Kangning Keli (感冒康宁颗粒): Anti-Flu, RSV
2. Jiawei Shengmai San (加味生脉散) :Anti-Coxsackie virus B
3. SARS TCM Complex (防治SARS中药复方)
  - SARS No.1 Complex
  - SARS No.2 Complex
  - SARS No.3 Complex
  - SARS No.4 Complex
4. Kangbingdu Koufuye (抗病毒口服液) :Anti-RSV, Flu



*Selaginella sinensis*

(卷柏)

**Flavonoid: Amentoflavone**

**Anti-RSV : IC<sub>50</sub>: 5.0 μg/ml**

*In vitro*



***Lonicera japonica* 金银花**

**Anti-respiratory syncytial virus, RSV  
(抗呼吸道合胞体病毒)**

*Lonicera japonica*

金银花

Anti-RSV *in vitro*:

(1) 3,4-di-O-caffeoylquinic acid

$IC_{50} = 2.5 \mu\text{g/ml}$

SI = 240

(2) 3,5-di-O-caffeoyl quinic acid

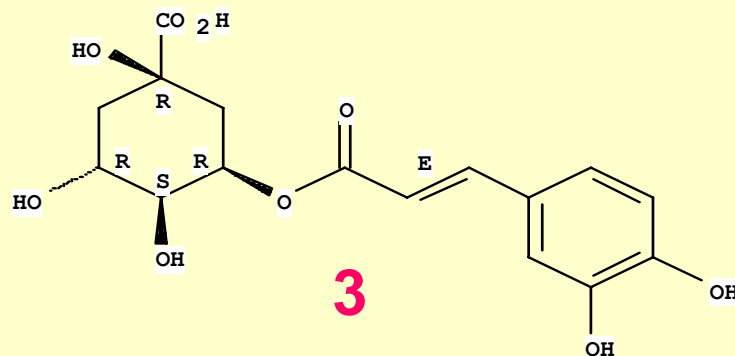
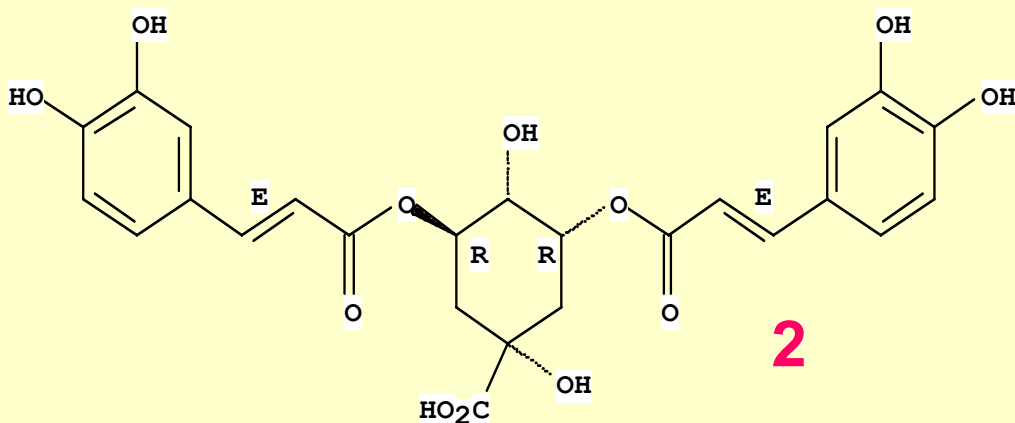
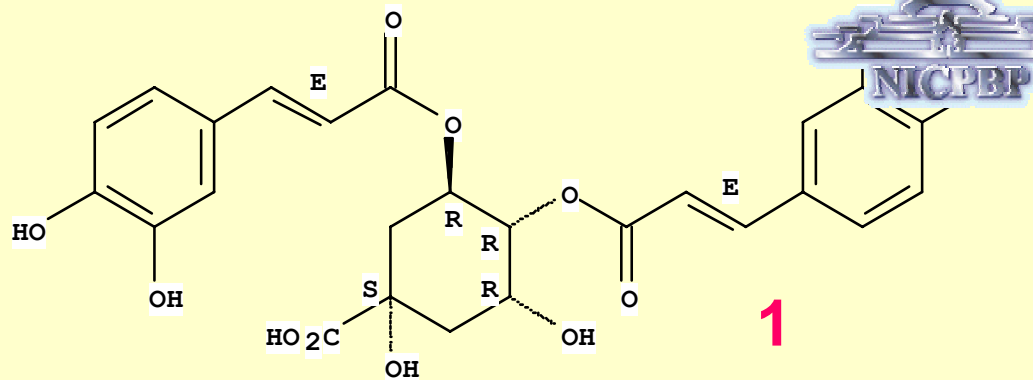
$IC_{50} = 1.2 \mu\text{g/ml}$

SI = 588

(3) 5-O-caffeoylquinic acid

$IC_{50} = 25 \mu\text{g/ml}$

SI = 8.8



# *Isatis indigotica*

(板蓝根)



(1) Amino acid (氨基酸)

(2) alkaloid:  
epigoitrin(表告依春)

**Anti-Flu** (抗流感病毒)  
*in vitro*

# Da-Huang

## (大黄)

(1) 掌叶大黄

*Rheum palmatum*  
L.

(2) 唐古特大黄

*Rheum tanguticum*  
Maxim. Ex Balf.

(3) 药用大黄

*Rheum officinale*  
Baill.

**Effective  
components:**  
anthraquinone





# Da-Huang(大 黄)

1. Anti-Coxsackie virus B type 3 (抗柯萨奇病毒)
2. Anti-epidemic hemorrhagic fever virus, EHF) (流行性出血热病毒)
3. Anti-Rubella virus (风疹病毒)
4. Anti-HSV (单纯疱疹病毒)
5. Anti-Varicella-zoster virus (水痘-带状疱疹病毒)
6. Anti-Human immuno-deficiency virus, HIV) (人体免疫缺陷病毒)
7. Anti-HBV (肝炎病毒)
8. Anti-Influenza virus (流感病毒)





## Anti-HSV-1(抗单纯疱疹病毒-1)

Names of samples	Anti-HSV-1 activity (IC <sub>50</sub> ) (μg/ml)		
	Standard strain	ACV-resistant strain	Clinical strain
<i>Agrimonia pilosa</i> 仙鹤草	125	100	125
<i>Pithecellobium clypearia</i> 猴耳环	62.5	125	100
<i>Punica granatum</i> 石榴皮	83.3	62.5	50



# Conclusion

In treatment and prevention of several infectious diseases, China has different kinds of medicines for viral and bacterial infectious diseases, being the same as other advanced countries. These medicines include chemical drugs, biologicals for prophylaxis and therapeutical use and the Chinese traditional medicine. All these medicines have played an important role on treatment of infectious diseases and preventing its spread. New products also are under development as science and technology development.

**Welcome to China**

*Thank you!*

