

Review article

Prevention and treatment of viral respiratory infections by traditional Chinese herbs

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Keywords: Chinese herbs; respiratory tract; infectious disease; virus

Objective This review focuses on current knowledge of traditional Chinese herbs on prevention and treatment of viral respiratory infections, especially caused by Severe Acute Respiratory Syndromes (SARS) virus, respiratory syncytial virus (RSV) and influenza viruses.

Data sources The data used in this review were obtained from PubMed and CNKI up to May 2013. Terms of Chinese herbs and infections of respiratory tract were used in the search.

Study selection Articles related that Chinese herbs preventing and treating infections in respiratory tract were retrieved and reviewed. The risk of bias of included studies was assessed by the method in the "Cochrane Handbook of Systematic Reviews of Interventions and studies" with high risk of bias were excluded. Four criteria for selections were set as following: randomized controlled trial, particular effective compound or derivative, reproducible result and animal test.

Results Infectious respiratory tract diseases cause most mortality among infectious illnesses around the world. As traditional medicines, Chinese herbs have been widely used to deal with diseases for centuries and have been proved effective in practice. The administration of some Chinese herbs stimulates, suppresses or regulates the activity of immune system, thus protecting the respiratory tract or relieving infections of pathogens. Many herbs have remarkable antiviral effects, therefore they are used as substitutes of antimicrobial drugs. Based on the theory of traditional Chinese medicine, mix-using herbs provide a synergistic benefit on preventing and healing respiratory tract infections. Many commercial herbal medicines containing one or more compounds have been successfully applied to prevent and treat viral infections of respiratory tract clinically.

Conclusions Traditional Chinese herbs could directly inhibit pathogens infecting respiratory tract, or coordinate the activity of immune system to avoid or relieve infections. With the emergence of antidrug pathogens or new variants, Chinese herbs give strong evidence to protect human health.

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The human history is accompanied with combats against infectious diseases caused by pathogens including virus, bacteria and fungus. Since last century the interval between outbreaks of pandemic infectious diseases has been dramatically shortened, especially for respiratory illnesses.¹ This could be attributed to the following reasons. First, the rise of populated cities with the proliferation of large-scale animal farms contributes to the persistence of pathogens. The shrinkage of wildlife habitats forces the emergence of new pathogens from wild animals with dense populations.¹ Second, the mass population movements also leads to transmission and hybridization of pathogens, thus emerging new variants.² The absence of effective immunity to new pathogens causes enormous lethality. Compared with traditional therapy, modern medical technology has largely reduced the number of mortality, panic and fear caused by infectious disease brings huge economic loss and severe social problems.³⁻⁵

As the passage of breath, the human respiratory tract is easily infected by contaminated aerosol particles containing pathogens. According to the report from WHO, respiratory tract infection is the leading cause of death among all infectious diseases.⁶ Prior to the upper respiratory tract where most respiratory tract infections appear, lower

respiratory infections, however are more serious.⁶ Various symptoms caused by respiratory tract infections could be observed clinically, including runny nose, coughing, fever, inflammation, shortness of breath and fatigue.

Vaccination is an effective way to prevent infectious diseases, however, it is not sufficient for outbreaks of pandemic diseases. Traditionally, it takes several months or even years to develop an effective vaccine against a new infectious disease will after the outbreak of certain pandemic disease.⁷ The high frequency of genetic exchange among different strains or subtypes and high rates of nucleotide substitution increase the difficulty for the persistent efficiency of vaccines. To some specific groups of patients, vaccines may be less efficient or have strong adverse effects.^{8,9} Antibiotic treatments are the primary

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ways to deal with infectious diseases, nevertheless, they are not available in viral infections.¹⁰ Long-term application and misuse of antibiotics to treat infectious diseases has unfortunately cause the emergence of resistant pathogens, which has been one of the pre-eminent public health concerns now.¹¹ Antiviral medicines also have some side effects and limitations to be applied to relative diseases.^{12,13}

Chinese herbs have been recorded to cure infectious diseases for almost 2 000 years.¹⁴ Over 10 000 herbal medicines and 100 000 recipes have been documented in ancient literatures,¹⁵ which gives us a rich sources to screen effective medicines. Comparing to other anti-infection drugs, Chinese herbs show less side effect and mild cured process against infections. Since many antibiotics are very effective for bacterial infections and the roles of Chinese medicine or herbs in bacterial respiratory infections are debatable, this review will focus on the importance of Chinese herbs in preventing and treating viral respiratory infections.

Alterations of immune systems

Chinese medical theories refer to the origins and transmissions of infectious diseases, and the role of the immune system to deal with pathogens. Many herbs are able to improve human immune system against infectious diseases. Accordingly the distribution and expression of cytokines and their receptors are regulated by multiple immune related cells under the stimuli of herbs.¹⁶

Herbal adjuvants for anti-infections

Some herbs have been used as adjuvants for medicinal enhancement. The extract from the root of *Polygala tenuifolia* was reported to contain potent mucosal adjuvant activity.¹⁷ The active adjuvant substances were purified by hydroxyapatite and Phenyl column HPLC, and identified to be onjisaponins A, E, F and G. Co-immunized with vaccines for influenza virus, onjisaponins enhanced the levels of serum antibody and nasal anti-influenza virus IgA and IgG in comparison to inoculation of vaccines alone. Furthermore intranasal vaccination with onjisaponin F reduced the activity of mouse adapted influenza virus A/PR/8/34 (H1N1) in bronchoalveolar lavages of mice.¹⁷ Subsequently the same research group found another adjuvant, 9S, 12S, 13S-trihydroxy-10E-octadecenoic acid (pinellic acid) isolated from the tuber of *Pinellia ternate* Breitenbach, was an effective oral adjuvant for the nasal influenza vaccine.¹⁸ As a traditional herb against influenza, the compounds of *Astragalus membranaceus* were well researched. The saponins extracted from *Astragalus membranaceus* significantly enhanced the proliferation of ovalbumin induced splenocyte and antibody titers of ovalbumin specific IgG, IgG1 and IgG2b in serum, indicating the effective adjuvant function of saponins.¹⁹ The Chinese medicine mao-bushi-saishin-to (MBST), which is a mixture of extracts from three medicinal herbs, *Ephedra sinica* Stapf, *Aconitum carmichaeli* Debx. and *Asarum heterotropoides* Fr. Schmidt var. *mandshuricum*

(Maxim.) Kitag., significantly increased the anti-*Mycobacterium avium* complex therapeutic activity of benzoxazinorifamycin.²⁰ Co-treated with antibiotics, MBST caused a marked decrease on the mRNA levels of cytokines, especially IL-10 and IFN- γ . However, administration of MBST alone had no effect on the immune system.

Influence on immune systems by single herbs

As a traditional herb against pneumonia, *Houttuynia cordata* Thunb. could significantly stimulate the proliferation of mouse splenic lymphocytes and enhance the proportion of CD4+ and CD8+ T cells.²¹ Accordingly the secretion of IL-2 and IL-10 was also induced by the increased mouse splenic lymphocytes. Moreover the extract of *Houttuynia cordata* Thunb. effectively inhibited the activities of 3C-like protease (3CL^{pro}) and RNA-dependent RNA polymerase (RdRp) of the coronavirus causing severe acute respiratory syndrome (SARS).²¹ Extracts of *Forsythia suspense* Vahl, *Lonicera japonica* Thunb., *Isatis indigotica* Fort., *Astragalus membranaceus* (Fisch.) Bge., *Strobilanthes cusia* (Ness.) O. Kuntze, *Hedysarum polybotrys* Hand.-Mazz., *Andrographis paniculata* (Burm. f.) Ness., *Glycyrrhiza uralensis* Fischer. and *Ligusticum wallichii* Franch. exhibited a consistent inhibitory effect on the secretion of influenza A/PR/8/34 (H1N1) virus-stimulated RANTES (regulated on activation, normal T cell expressed and secreted).^{22,23} Furthermore the application of *Pueraria lobata* (Willd.) Ohwi (pueraria) inhibited the yield of IL-1 α , presenting abundantly at the primary period of influenza virus infection, via stimulating the activity of interferon, thus relieving the infection of virus.¹³ The glycyrrhizin extracted from *Glycyrrhiza uralensis* Fisch. fully protected mice exposed to a lethal dose of influenza virus A2 (H2N2) through the stimulation of IFN- γ production by T cells.²⁴ Interestingly transformation of splenic T cells from glycyrrhizin-treated mice to mice exposed to influenza virus, 100% of the recipients survived under the lethal dose of the virus. TSL-1, extracted from the tender leaf of *Toona sinensis* Roem, inhibited viral attachment and yields of influenza A (H1N1) virus in cell culture with high selectivity index.²⁵ Further evidence showed adhesion molecules and chemokines (VCAM-1, ICAM-1, E-selectin, IL-8, and fractalkine) of cells were significantly downregulated in comparable of Amantadine treatment.

Influence on immune systems by complex herbs

On basis of the synergistic theory in traditional Chinese medicine, mixed herbs are used to prevent or treat infection diseases. One traditional Chinese medicine, Ma xing shi gan tang, mainly consisting of extracts from *Ephedra sinica* Stapf, *Prunus armeniaca* and *Glycyrrhiza uralensis* Fisch., increased the expression of IL-2 and IL-4, induced the secretion of IFN- γ and adjusted the ratio of subsets of T cells in influenza virus A infected mice.^{26,27} It suggested this formula was potential to prevent influenza by the stimulation of immunity system. A commercial Chinese medicine, Yi qi qing wen jie du he ji, containing extracts

of *Astragalus membranaceus* (Fisch.) Bge, *Ephedra sinica* Stapf., *Perilla frutescens* and *Scutellaria baicalensis* Georgi, was proved to reduce the level of pro-inflammatory cytokines TNF- α , IL-6 and IFN- γ and increase the expression of IL-10. All the reaction of immunity system treated by this medicine was against the infection process of influenza FM1.²⁸ Yu ping feng consisting of extracts from *Astragalus membranaceus* (Fisch.) Bge., *Ledebouriella seseloides* Wolff and *Atractylodes macrocephala* Koidz has been used to prevent and cure infectious upper respiratory diseases for hundreds of years. The administration of this formula enhanced the percentage of CD4+ and CD8+ T cells, stabilization of IgG and IgM, increased the level of IgA and boosted phagocytic functions of macrophages in mouse model.²⁹ One clinical research clearly showed administration of Qing fei Decoction, mainly consisting of extracts from *Ephedra sinica* Stapf, *Glycyrrhiza uralensis* Fisch. and *Pueraria lobata* (Willd.) Ohwi, increased the activity of serum natural killers and the levels of IFN- γ and IL-2. The application of this medicine improved the symptoms of infectious respiratory tract diseases.³⁰ The treatment of Keishi-ni-eppi-ichi-to, containing compounds from *Cinnamomum cassia* Presl, *Ephedra sinica* Stapf and *Glycyrrhiza uralensis* Fisch., significantly increased the survival time, reduced virus titers and the mortality rate, lowered down the pulmonary consolidations and enhanced the expression of IFN- γ in the influenza virus A2 infected mice.³¹ Since viricidal and viristatic activities of the agent against influenza virus were not demonstrated, the antiviral effects of this medicine may be expressed through the host's antiviral functions including interferon production. One more complicated herbal medicine, Lian hua qing wen, mainly consisting of extracts from *Forsythia suspensa* (Thunb.) Vahl, *Houttuynia cordata* Thunb., *Lonicera japonica* Thunb., *Isatis indigotica* Fort., *Ephedra sinica* Stapf and *Glycyrrhiza uralensis* Fisch., significantly reduced the mortality rate, increased the survival time and attenuated the symptoms of influenza virus FM1 infected mice.³² Moreover the expressions of IFN- α , IL-1 β and IL-6 were down-regulated with the administration of this medicine. The appearance of heat shock proteins (HSPs) is accompanied with invasions of pathogens in animals.³³ Composing of extracts from *Stemona sessilifolia* (Miq.) Miq., *Aster tataricus* L. f., *Scutellaria baicalensis* Georgi and *Houttuynia cordata* Thunb., Ke ning fang Decoction significantly induced the synthesis of HSP70 and attenuated histological impairments of lungs in influenza virus pneumonia mice.³⁴

Herbal inhibitions on pathogens

Many Chinese medicinal herbs have remarkable wide spectrum of antimicrobial effect on various pathogens. In recent decades, much more attentions are received on herbal treatments of respiratory tract infections caused by SARS virus, respiratory syncytial virus (RSV) and influenza viruses. The SARS virus in the global 2002/2003 SARS pandemic is a new emerging coronavirus with zoonotic origin, which is highly infectious and causes high

mortality. So far there is no cure or protective vaccine available for SARS in humans.³⁵ RSV is a major cause of lower respiratory tract infections during infancy and childhood. No vaccine has been developed against RSV and present medicines have limits to control infections of RSV.³⁶ Influenza is the most common respiratory tract infection in human. Although effective vaccines have been developed against influenza virus, new emerging variants cause periodical pandemics around the world.

Anti SARS virus

During the outbreak of SARS in China, extracts from *Isatis indigotica* Fort. were used for prevention of virus infection. Subsequent study supported that the extract of *Isatis indigotica* Fort. directly inhibit the enzyme activity of 3CL^{pro} of SARS virus.³⁷ Three components of *Isatis indigotica*, sinigrin, beta-sitosterol and indigo, dose-dependently inhibited cleavage activities of the 3CL^{pro} in cell-free and cell-based assays. In the same research, two phenolic herbal derived compounds, aloemodin and hesperetin, also inhibited the cleavage activity of the 3CL^{pro} *in vitro*. Two small molecules isolated from Chinese herbs, tetra-*O*-galloyl- β -D-glucose (TGG) and luteolin, were identified to exhibit prominent anti-SARS virus activity.³⁸ These natural molecules bound avidly with the surface spike protein of SARS virus and thus interfered with the entry of the virus to its host cells. TGG is a component from *Galla chinensis* and luteolin has been identified in extracts of many Chinese herbs such as *Veronica lina riifolia* Pall. As mentioned above, TSL-1 extracted from tender leaf of *Toona sinensis* Roem was found to have an evident effect against SARS-CoV with selectivity index 12–17.³⁹ Another component from *Toona sinensis* Roem, quercetin which is structurally related to luteolin, showed also inhibitory activity on the cellular entry of SARS-CoV.³⁹ Baicalin derived from *Scutellaria baicalensis* inhibited the replication of SARS-CoV in Vero and FRhK-4 cells at concentrations which may be achievable *in vivo* after intravenous administration.⁴⁰ A large compound screening test showed ginsenoside-Rb1 extracted from *Panax ginseng*, aescin isolated from the horse chestnut tree, reserpine containing in the genus *Rauwolfia* and extracts of eucalyptus and *Lonicera japonica* inhibited SARS-CoV replication at non-toxic concentrations.⁴¹ Glycyrrhizin isolated from the root of *Glycyrrhiza glabra* was active in inhibiting replication of the SARS-associated virus (FFM-1 and FFM-2).⁴² Comparing to other commercial drugs, glycyrrhizin was the most effective drug against SARS virus and had the lowest toxic effect to human. Two systematic reviews and meta-analysis were employed on Chinese herbal medicines for SARS on basis of randomized controlled trials (RCTs).⁴³

Anti RSV

An anti-RSV screening test with 21 herbs was employed, and extracts from 14 herbs showed moderate to strong anti-RSV activity.⁴⁴ Among the effective herbs, six herbs exhibited anti-RSV activity with 50% inhibitory concentration values lower than 50 μ g/ml and selective

index values higher than 10, including *Blumea laciniata*, *Elephantopus scaber*, *Laggera pterodonta*, *Mussaenda pubescens*, *Schefflera octophylla* and *Scutellaria indica*. Subsequent findings indicated the polyphenolic compounds took part into the antiviral function of these herbs. Aqueous extracts from 41 traditional Chinese herbs were tested to possess antiviral activity against RSV.⁴⁵ Among them, compounds in *Sophora flavescens* and *Scutellaria baicalensis* were analyzed, and anagryne, oxymatrine, sophoranol, wogonin and oroxylin A were identified as the potent anti-RSV components. *Glycyrrhiza uralensis* was another herbal candidate for cure of RSV infection.^{46,47} The compound GD4 isolated from root of *Glycyrrhiza uralensis* fisch was effective to inhibit the number of RSV *in vitro*. Rengyonic acid, 2-(1,4-dihydroxy cyclohexanyl)-acetic acid isolated from the seeds of *Forsythia suspensa* (Thunb.) Vahl, has been proved to have potent antiviral effect on RSV *in vitro*.⁴⁸ As an over 40-year clinical medicine, *Shuang huan lian* consisting of extracts from three Chinese herbs shuanghua (*Lonicera japonica* Thunb.), huangqin (*Scutellaria baicalensis* Georgi) and lianqiao (*Forsythia suspensa* (Thunb.) Vahl) was effective to cure acute bronchiolitis caused by RSV.⁴⁹ The application of these mixed herbs clearly reduced the duration of symptoms in a randomized single blind trial.

Anti influenza virus

As a corynanthe-type monoterpenoid indole alkaloid, hirsutine isolated from *Uncaria rhynchophylla* MIQ. inhibited the replication of influenza virus A (H3N2) *in vitro*.⁵⁰ Furthermore the 50% effective concentration of hirsutine was 11- to 20-fold lower than the clinically used ribavirin. The extract from Chinese quince (*Cydonia oblonga* Mill.) was identified to inhibit the activity of influenza virus *in vitro*.⁵¹ It suggested that high concentration of phenolics mainly consisting of high polymeric procyanidins might play the antiviral function of Chinese quince via preventing adherence of hemagglutinins. Hypericin isolated from *Hypericum perforatum* L. could directly kill high infectious avian influenza viruses, H5N1 and H9N2.⁵² Within 30 minutes, influenza viruses were completely eliminated with hypericin of 3.72 mg/ml. *Andrographis paniculata* was proved to be effective to prevent and treat acute respiratory tract infections, especially influenza.⁵³ A systematic review of Chuanhuning isolated from *Andrographis paniculata* for acute respiratory tract infections illustrated that Chuanhuning had a broad range of anti-virus on basis of RCTs.⁵⁴ A large scale screening for effective Chinese herbs against influenza virus A/PR/8/34 (H1N1) showed extracts from *Toddalia asiatica* possessed potent antiviral activities against influenza virus, with 50% effective concentration value of 4.7 mg/L in MTS assay and 0.9 mg/L in quantitative PCR assay respectively.⁵⁵ As a popular Chinese herb against flu, crude extracts from the root of *Isatis indigotica* Fort. were effective against the infection of influenza virus A.^{56,57} Crude fruit extracts of wild *Ribes nigrum* L. (Kurokarin extract) inhibited the plaque formation of influenza virus A and B. Further analysis of virus titers in the culture fluid

indicated that the extract inhibited the virus release from the infected cells.⁵⁸ The extract from Catechu (*Acacia catechu*) could dramatically prevent influenza virus A infecting cells and inhibit the proliferation of virus in chick embryo.⁵⁹ Furthermore the extract from Catechu significantly lowered down hemagglutination titer by inhibitory on influenza virus A directly. Two traditional herbs, *Notopterygium incisum* and *Ganoderma applanatum*, showed significant protective effects on mice infected by influenza virus FM1.^{60,61} The extract from *Notopterygium incisum* significantly increased the survival time, decreased the number of virus, reduced the titer of hemagglutination in influenza virus FM1 infected mice. *Ganoderma applanatum* was identified to be effective against influenza virus FM1 from a screening of 34 traditional herbs. An aerosol containing extract from *Lonicera japonica* Thunb. has been developed to suppress the proliferation of influenza virus in rat lungs and cured the upper respiratory tract infection.⁶² The activity of influenza virus B was reported to be inhibited by *Bupleurum chinense* DC. in infected mice model.⁶³ The analysis of histopathology showed the lung was protected and the symptom was reduced during the infection of influenza virus B in the herbal treated group.

Xiao chai hu tang consisting of extracts from *Bupleurum chinense*, *Scutellaria baicalensis* Georgi, *Glycyrrhiza uralensis* Fisch. and *Isatis tinctoria* L. effectively inhibited the proliferation of influenza virus in chick embryo.⁶⁴ A *vivo* test showed aqueous extracts of Bupleuri and Ramuli Cinnamomi containing *Bupleurum chinense*, *Glycyrrhiza uralensis* Fisch., *Scutellaria baicalensis* Georgi and *Panax ginseng* C. A. Mey. reduced the index of lung damage and increased the survival rate of influenza virus FM1 infected mice.⁶⁵ The previous referred Ma xing shi gan tang exhibited an inhibitory activity against different strains of human influenza A viruses, including influenza virus A/WSN/33 (H1N1) and clinical oseltamivir-resistant isolates.⁶⁶ The treatment of Ma xing shi gan tang profoundly inhibited the synthesis of both viral RNA and blocked the virus entry phase. High-resolution images and quantitative measurements made with atomic force microscopy confirmed that the viral surface structure was disrupted by this medicine. Furthermore the viral entry, regulated by the PI3K/AKT signaling pathway, was abolished by this herbal medicine. Yin qiao san, consisting of extracts mainly from *Lonicera japonica* Thunb., *Forsythia suspensa* (Thunb.) Vahl and *Glycyrrhiza glabra*, effectively inhibited the proliferation of influenza virus FM1 and relived the clinic symptoms.⁶⁷ The herbal formula Ma xing shi gan-Yin qiao san was an alternative of oseltamivir on the treatment of influenza virus A H1N1 infection in a RCT.⁶⁸ The Shi-cha capsule, composing of *Boeninghausenia sessilicarpa*, *Elsholtzia bodinieri* Van, *Astragalus membranaceus*, *Houttuynia cordata* Thunb, *Climbing groundsel* Herb and *Forbes Notopterygium*, was efficacious and safe for the treatment of patients with wind-cold type common cold.⁶⁹ In a randomized, double-blind, placebo-controlled trial, Antiwei capsule consisting of extracts from *Herba Ephedra*, *Rhizoma Imperatae*, *Radix*

puerariae, *Ramulus Cinnamoumum*, *Semen Armeniacae* Amarum., *Rhizoma Zingiberis* and *Radix Glycyrrhizae* was effective and well tolerated in treatment of natural influenza infection in adults.⁷⁰ Two components contained in Gingyo-San, extracts from *Glycyrrhizae* radix and *Arctii fructus*, expressed antiviral activities in mice infected with influenza virus A2.⁷¹ The application of Gingyo-San completely inhibited the mortality and decreased the consolidation scores in treated mice with lethal dose virus. According to the practical call from WHO for traditional Chinese medicines, RCTs are required as clinical research evidence for Chinese medicinal applications. As the gold standard for a clinic trial, RCTs are applied for the treatment of influenza. Systematic reviews of RCTs focusing on Chinese herbal medicines for the treatment of influenza have been well summarized.⁷²⁻⁷⁶ Many Chinese herbal medicines are identified to alleviate the symptoms of influenza, however more high-standard RCTs are required in the future study.

Conclusions

To prevent and treat infections of respiratory tract, traditional Chinese herbs may effectively improve the immune system as immunomodulators. Besides, pathogens would be directly inhibited by the antiviral or antibacterial functions of herbs. With the emergence of fast mutations and drug resistance of pathogens, traditional herbs give us another route to fight with respiratory tract infections. Chinese herbs usually have a wide spectrum of antimicrobial effect and effective cure various infections. Since a group of antimicrobial compounds are acting together, the opportunity of drug resistance in microorganisms is reduced during the treatment of traditional herbs.¹⁶ Furthermore most traditional herbs are safer and have lower side effects comparing to other anti-infection drugs. For some new emerging pathogens, Chinese herbs can still effectively avoid infections as therapeutic medicines. It suggests that Chinese herbs may be used as an alternative treatment and prophylaxis against viral infections. Therefore, attentions should be drawn to discover new drugs from traditional Chinese herbs.

However, the evaluation of traditional Chinese herbs by the conventional Western medicine model was found to be impractical and inappropriate.⁷⁷ The prescription of Chinese herbs is mainly based on the symptoms of patients and empirical experience without knowing the causative agents.¹³ Additionally the Chinese medicinal theory indicates the whole herb or complex herbs are effective to cure infections, referring to synergistic functions of different constituents. Therefore, it is difficult to identify a compound which is specific to a particular infectious disease. Furthermore some active compounds are extremely hard to be isolated and extracted from Chinese herbs.⁷⁸ Although some progresses have been achieved on prevention and treatment of respiratory tract infections by traditional Chinese herbs, much more efforts on basis of traditional knowledge and modern technologies should be employed for the herbal therapy.

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