Journal of Traditional and Complementary Medicine Vo1. 4, No. 2, pp. 93-98

Journal of Traditional and Complementary Medicine
Journal homepage http://www.jtcm.org

Anti-inflammatory and Antimicrobial Effects of Heat-clearing Chinese Herbs: A Current Review

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ABSTRACT

Inflammation is a normal immune response; but if the body's regulation of inflammation is dysfunctional, then it will have an adverse effect on the body. Although use of modern drugs for inflammation has a relieving effect, it is still unsatisfactory. Moreover, the emergence of drug-resistant strains and even new kinds of microorganisms is causing significant morbidity and mortality. Recently, more attention has been focused on herbal medicine to treat various diseases because of the ability of the herbs to affect multiple target signaling pathways and their multiple mechanisms of action. Thus, a large number of studies have reported on the anti-inflammatory and antimicrobial effects of the traditional Chinese herbs. Literature survey was performed by conducting systematic electronic search in PubMed, Science Direct, Google Scholar, and in books. This review has listed 11 heat-clearing Chinese herbs (HCCHs) including *Scutellaria baicalensis* (黃芩 Huáng Qín), *Coptis chinensis* (黃連 Huáng Lián), *Flos Lonicerae* (金銀花 Jīn Yín Hūa), *Forsythia suspensa* (連翹 Lián Qiào), *Isatidis Folium* (大青葉 Dà Qīn Yè), *Radix Isatidis* (板藍根 Bǎn Lán Gēn), *Viola yedoensis* (紫花地丁 Zǐ Huā Dì Dīn), *Pulsatilla Radix* (白頭翁 Bái Tóu Wēn), *Andrographis paniculata* (穿心蓮 Chuān Xīn Lián), *Houttuynia cordata* (魚腥草 Yú Xīng Cǎo), and *Patrinia Herba* (敗醬草 Bài Jiàn Cǎo), which have anti-inflammatory and antimicrobial effects, and has described their effects through different mechanisms of action and multiple targets. Their ability to affect multiple target signaling pathways and their potential mechanisms of action contributing to their anti-inflammatory and antimicrobial activity may be related to their action of removing heat and counteracting toxicity. Further studies are needed on the collection of HCCHs to know the detailed mechanism of action of herbs in this group for the assessment of effective drug.

Key words: Anti-inflammatory activity, Antimicrobial activity, Heat-clearing Chinese herbs, Traditional Chinese Medicine

INTRODUCTION

Inflammation is a part of the immune response that can prevent infection through production of pro-inflammatory cytokines and generation of inflammatory mediators in response to microbial products.[1] Although inflammation is crucial to maintaining the health and integrity of an organism, when the inflammatory process is poorly controlled, it can cause massive tissue destruction and a series of chain reactions.[2-4] The current treatment of inflammatory disorders involves extensive use of nonsteroidal anti-inflammatory drugs and corticosteroids. Although use of modern drugs for inflammation has a relieving effect, it is still unsatisfactory.[5] Moreover, bacterial resistance to antibiotics and the emergence of new kinds of microorganisms are becoming an increasing problem all over the world, causing significant morbidity and mortality.[6,7] In order to combat this problem, novel

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DOI: 10.4103/2225-4110.126635

antibiotic and anti-inflammatory compounds need to be found which are both effective and safe.

Traditional Chinese Medicine (TCM) has been used in China over thousands of years for the prevention and treatment of various diseases.[6,8,9] TCM uses yin–yang theory to explain the organizational structure, physiological functions, and pathological changes in the human body and to guide diagnosis and treatment of disease.[5,10] Although yin and yang are contradictory in nature, they depend on each other for existence. Keeping balance between yin and yang is very important to maintain the healthy state of human body. TCM theory states that the occurrence of the disease depends on the interaction between zheng qi (nonpathogenic qi) and xie qi (pathogenic qi). The idea of disease is the struggle between pathogenic qi and nonpathogenic qi; in this struggle process, there will be changes between yin and yang. TCM holds that variation between the evil aspect and healthy trend determines the occurrence of disease. Therefore, in TCM, inflammatory and antimicrobial therapy lies in strengthening the healthy trend and dispelling the evil aspect in order to keep a balanced state between yin and yang.[5,11]

Herbal medicine is one of the main components of TCM which has long been used for its multiple types of disease treatment. In recent times, it is making a rapid progress in scientific investigation and attracting great attention due to the good therapeutic effects and minimal side effects of the herbs.[6,8,12] Chinese herbs used in the treatment of diseases are grouped into many categories. One of these is heat-clearing Chinese herbs (HCCHs). Herbs in this group are mostly cold in nature and can clear away heat, purge fire, dry dampness, cool blood, and relieve toxic material. Their main action is clearing away interior heat, and thus they are considered to be antipyretic.[11,13] Because of all these properties, HCCHs may be effective in the treatment of inflammatory disease and microbial infection. This review tries to summarize the effect of HCCHs which have shown anti-inflammatory and antimicrobial activities and their mechanisms of action.

Scutellaria baicalensis (黄芩 Huáng Qín)

Scutellaria baicalensis is a species of flowering plant belonging to Lamiaceae family It is a heat-clearing, phlegm-removing herb, traditionally used to cool heat, drain fire, clear damp-heat, stop bleeding, calm the fetus, and descend yang.[11,13,14] The dry root part of *Sc. baicalensis* has many pharmacological effects including antipyretic, hepatoprotective, antihypertensive, diuretic, and antibiotic activities. It is mildly sedating and also used to treat dysentery and chronic hepatitis.[6,7,14,15] *Sc. baicalensis* has distinct effects in the treatment of inflammatory diseases; it alleviates inflammation by decreasing the expression of interleukin (IL)-1b, IL-6, and IL-12, and the production of tumor necrosis factor (TNF)-α and soluble intercellular adhesion molecule-1 (ICAM-1).[5,16] In Xie xin herbal decoction, huang qin, in combination with huang lian, inhibits nitric oxide (NO) production *in vitro* and *in vivo* in lipopolysaccharide (LPS)-stimulated RAW264.7 cells. Oroxylin A, which is a flavonoid found in dried root of *Sc. baicalensis,* has also shown good anti-inflammatory effect.[17,18] Moreover, *Sc. baicalensis* has antibacterial effect against *Helicobacter pylori* as well as inhibits the growth of *Escherichia coli* B, coagulase-negative staphylococci, and *Saccharomyces cerevisiae*.[7,15]

Coptis chinensis (黃連 Huáng Lián)

Coptis chinensis belongs to Ranunculaceae family. Traditionally, it has been used to drain fire, detoxify and disinfect, stop bleeding, cure eczema, burns, and ulcer, and to descend yang.[7,11,13,14,19] The main pharmacodynamic properties have long been recognized in the treatment of intestinal infections including acute gastroenteritis, cholera, and bacillary dysentery. It also used for treating various diseases including skin diseases, conjunctivitis, otitis, and hypertension.[14,19,20] *C. chinensis* has been demonstrated to have anti-inflammatory effects through different mechanisms. It inhibits TNF-induced Nuclear factor-kappaB(NF-kB) signaling in human keratinocytes by blocking the NF-kB–dependent pathway. It also decreases Th17 cytokine secretion and differentiation by activation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) and down-regulation of phosphorylated signal transducer and activator of transcription 3 (p-STAT3) and retinoic acid–related orphan receptor ϒt (RORγt) expression. It also reduces Th1 cytokine secretion and differentiation by inhibition of protein 38 (p38) mitogen activated protein kinase (MAPK) and Jun N-terminal kinase (JNK) activation along with down-regulation of STAT1 and STAT4 activities.[21,22] In combination with other herbs, *C. chinensis* exhibited a good anti-inflammatory effect; the ethanol extract from Zuojin Pill inhibited inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), IL-6, IL-1β, and TNF-α expression by preventing the nuclear translocation of the NF-κB p50 and p65 subunits in RAW 264.7 cells.[23] Another Chinese medicinal formula, IBS-20, containing *C. chinensis* decreased LPS-stimulated pro-inflammatory cytokine secretion from JAWS II dendritic cells and also blocked the interferon gamma (IFNγ)-induced drop in transepithelial electric resistance which is an index of permeability, in fully differentiated Caco-2 monolayer.[24] *C. chinensis* has also significant antimicrobial activity against a variety of microorganisms including bacteria, viruses, fungi, protozoans, helminths, and *Chlamydia*, including *Staphylococcus aureus, Pseudomonas aeruginosa, E. coli, Propionibacterium acnes, Streptococcus pneumoniae, Vibrio cholerae, Bacillus anthracis*, *Bacillus dysenteriae*, and *Sa. cerevisiae*.[7,21,25] Berberine, the major active component of *C. chinensis*, was found to be bactericidal on *V. cholera* and capable of inhibiting bacterial adherence to mucosal or epithelial surfaces.[26]

Flos Lonicerae (金銀花 Jīn Yín Hūa)

Flos lonicerae is a honeysuckle flower belonging to Caprifoliaceae family. It is a widely used herb in China for the treatment of infection by exopathogenic wind-heat or epidemic febrile diseases.[11,14,27,28] The dried flower and buds of *Flos Lonicerae* have shown various pharmacological effects including anti-nociceptive, anti-diabetic, anti-tumor, antioxidant, anti-angiogenic, antipyretic, antiviral, and hepatoprotective activities.[6,29-31] *Flos Lonicerae* demonstrated anti-inflammatory properties through suppression of mediator release from the mast cells activated by secretagogues.[32] In addition, the *n*-butanol fraction containing *Flos Lonicerae* can alleviate inflammation better than celecoxib

in carrageen- and croton oil-induced paw edema and ear edema.[29] *Flos Lonicerae* contains various active compounds that have marked anti-inflammatory effect, including luteolin (suppresses inflammatory mediator release by blocking NF-kB and MAPKs pathway activation in HMC-11 cells), chlorogenic acid (inhibits rat reflux esophagitis induced by pylorus and forestomach ligation), and loncerin (reduces edema by suppressing T cell proliferation, NO production from the macrophages, and shifting cellular immunity from Th1- toward Th2-type responses).[33-35] *Flos Lonicerae* has significant antimicrobial activity against diverse species of bacteria and fungi. It has inhibitory effect against *H. pylori* and *Porphyromonas gingivalis*,[15] and it treats candidal septic arthritis.[35] It also has antimicrobial effect against oral pathogens including *Streptococcus mutans, Actinomyces viscosus*, and *Bacteroides melaninogenicus*.[6]

Forsythia suspensa **(**連翹 **Lián Qiào)**

Forsythia suspensa is a flowering plant belonging to the family Oleaceae. Traditionally, it used to treat carbuncle, disperse lumps, and stagnation, and to expel wind and heat.[11,13,14] The fruit of *F. suspensa* has potent pharmacological actions such as antiviral, choleretic, antipyretic, hepatoprotective, antiemetic, and diuretic effects.[14,27] *F. suspensa* alleviates inflammation by reducing the anaphylactic antibodies, mast cell degranulation, and histamine release. It also significantly suppresses β-conglycinin–induced T lymphocyte proliferation and IL-4 synthesis.[36,37] *F. suspensa* fruit inhibits NO production and iNOS gene expression by its active components rengyolone, dibenzylbutyrolactone lignans, as well as its butanol fraction of the aqueous extract. It also inhibits TNF-α and COX-2 production.[38-40] Another bioactive agent, arctigenin, inhibits increase in capillary permeability and leukocyte recruitment into inflamed tissues, by reduction of the vascular leakage and cellular events through inhibition of production of inflammatory mediators such as NO and pro-inflammatory cytokines such as IL-1b, IL-6, TNF-α, and prostaglandin E2 (PGE2).[38,39,41] Moreover, *F. suspensa* inhibits NF-kB nucleus translocation through reduction in I-kappa-B (IkB) phosphorylation and suppression of NF-kB–regulated proteins, and also reduces the activation of MAPKs.[39-41] Various studies have reported the antimicrobial effect of *F. suspensa*. It has potent antibacterial activity against *E. coli, Sta. aureus*, *Bacillus subtilis*, *Str. mutans*, and *Po. gingivalis* and antifungal activity against *Aspergillus flavus, Rhizopus stolonifer, Penicillium citrinum, Aspergillus niger,* and *Saccharomyces carlsbergensis*.[6,42] *F. suspensa* suppresses influenza A virus–induced RANTES secretion by human bronchial epithelial cells to stop accumulation of inflammatory cells in the infective sites, which has been reported to play a crucial role in the progression of chronic inflammation and multiple sclerosis after viral infection.[27]

Isatidis folium **(**大青葉 **Dà Qīng Yè)**

Isatidis folium is a flowering plant belonging to the family Brassicaceae. The leaves of *Isatidis Folium* are traditionally used for the treatment of sore throat, redness of skin, and as an antipyretic.[13,14,27,43,44] *Isatidis Folium* has also been used to treat encephalitis, acute dysentery, hepatitis, measles, pneumonia, influenza, epidemic cerebrospinal meningitis, encephalitis B, viral pneumonia, mumps, and diabetics.[27,45,46] Tryptanthrin, an alkaloid isolated from Isatidis leaves, has shown anti-inflammatory effect due to its strong inhibitory effect on the COX-2 enzyme.[47] Several derivatives of hydroxycinnamic acid, including ferulic acid and sinapic acid, are also thought to be important to inhibit inflammation.[25] *Isatidis Folium* possesses valuable viricidal effect in the control of pseudorabies infection in swine.[48,49]

Radix Isatidis **(**板藍根 **Bǎn Lán Gēn)**

Isatidis radix belongs to the family Brassicaceae. Traditionally, it used to cool blood.[13,14,19] The dry root of *Isatidis Radix* has many pharmacological activities such as antibiotic, anti-diabetic, and immune-stimulating effects and is used to treat encephalitis B and viral infections.[48,50] Methanolic extracts of *Isatidis Radix* can significantly inhibit the release of inflammatory mediators from the macrophages, such as NO, PGE2, and pro-inflammatory cytokines.[51] *Isatidis Radix* has also been demonstrated to suppress the growth of *E. coli* and *H. pylori* and increases blood neutrophil phagocytosis of ^{32}P-labeled *Sta. aureus*.[15,52,53] Syringic acid isolated from *Isatidis Radix* inhibited LPS-induced endotoxin shock.[51] Besides, *Isatidis Radix* is found to be clinically effective against the infections caused by various subtypes and strains of influenza viruses including Severe Acute Respiratory Syndrome (SARS).[44,50]

Viola yedoensis **(**紫花地丁 **Zǐ Huā Dì Dīng)**

Viola yedoensis is a flowering plant belonging to the violet family of Violaceae. Traditionally, it used to cool heat, and disinfect and detoxify.[11,13,14] *V. yedoensis* has several pharmacological effects including antibiotic, anti-inflammatory, and antipyretic activities. It can also be used for the treatment of skin diseases, i.e. eczema, impetigo, acne, pruritus, and cradle cap, and for upper respiratory tract infections with fever.[12,14] It has been reported to have antimicrobial activity against *B. subtilis*, *Str. mutans*, and *Po. gingivalis*.[54] It inhibits the replication of herpes simplex virus-1 and enterovirus 71 in the human neuroblastoma SK-N-SH cell line. Cyclotides from *Viola* are shown to be effective in inhibiting human immunodeficiency virus (HIV) replication.[50,55]

Pulsatilla radix **(**白頭翁 **Bái Tóu Wēng)**

Pulsatilla radix is a medicinal root plant of the Ranunculaceae. It used to cool heat, disinfect and detoxify, and clear damp-heat in TCM.[13,14] The root of *Pulsatilla Radix* has anti-inflammatory, antiparasitic, and antimicrobial action. It can treat dyspepsia, premenstrual tension, and psychosomatic disturbances.[14] A quinine-type compound, pulsaquinone, isolated from the aqueous ethanol extract of the roots of *Pulsatilla Radix* exhibited antimicrobial activities against an anaerobic non–spore-forming gram-positive bacillus, *Pr. acnes*, which is related to the pathogenesis of the inflamed lesions in a common skin disease, acne vulgaris.[56] Moreover, 4-hydroxy-3-methoxycinnamic acid of *Pulsatilla Radix* is found to have a selective growth inhibitor of the human intestinal bacteria, *Clostridium perfringens* and *E. coli*.[57]

Andrographis paniculata **(**穿心蓮 **Chuān Xīn Lián)**

Andrographis paniculata is also known as *nemone chinensi* and belongs to Acanthaceae family.[11] The active compounds isolated from *An. paniculata*, including diterpene, lactone, and

andrographolide, have shown anti-inflammatory, anti-allergic, immune-stimulatory, and antiviral activities.[58,59] *An. paniculata* alleviates inflammation by inhibiting iNOS, TNF-α, IL-1b, IL-6, and IL-12 expression and NO production by down-regulation of p38MAPKs signaling pathways.[5,60] It also suppresses influenza A virus–induced RANTES secretion by human bronchial epithelial cells.[27]

***Houttuynia cordata* (魚腥草 Yú Xīng Cǎo)**

Houttuynia cordata is one of the two species in the genus *Houttuynia* and belongs to the family Saururaceae.[14] It has many pharmacological effects including immune-stimulating, anti-inflammatory, antibiotic, antiviral, diuretic, analgesic, and hemostatic effects. It also used to treat pneumonia, bronchitis, colitis, urogenital tract infections, and chronic obstructive respiratory diseases, and topically to treat herpes simplex.[61]

***Patrinia Herba* (敗醬草 Bài Jiàn Cǎo)**

Patrinia herba is a medicinal herb belongs to family of Valerianaceae.[12,14] It has antibiotic, hepatoprotective, sedating, and hypnotic effects, and it can be used to treat mumps.[14] *Patrinia Herba* can inhibit adjuvant-induced inflammation and hyperalgesia. In rats, it attenuates Freund's adjuvant (CFA)–induced hyperalgesia and facilitates the recovery from hyperalgesia, and also reduces edema.[62]

CONCLUSION

Investigation of the functions of different Chinese herbs by modern research has allowed us to determine the importance of using Chinese herbs for treatment of many diseases. Various studies have revealed that HCCHs are used for treating inflammatory and microbial diseases due to their multiple active ingredients. Since inflammation is the result of interaction of various inflammatory mediators, HCCHs can exert anti-inflammatory effect through different mechanisms of action including inhibition of inflammatory cytokines and mediators, blocking of inflammatory signaling, and interfering with chemokines [Table 1]. Moreover, HCCHs have also shown antimicrobial effect through inhibition of microbial adherence to mucosal or epithelial surfaces, inhibition of endotoxin shock, and selective inhibition of microbial growth [Table 2]. Collectively, all the above mechanisms are likely to be important for the anti-inflammatory and antimicrobial activity of HCCHs. This review reveals the anti-inflammatory and antimicrobial effects of HCCHs, in general, from different aspects and through different mechanisms. This may be linked to their action of removing heat and fire and counteracting toxicity. Therefore, further studies are needed on the collection of HCCHs to find the detailed mechanism of action of herbs in this group and to determine whether their nature of clearing away heat is related to their anti-inflammatory and antimicrobial effects according to Chinese medical theory, rather than focusing on simple gradient or single herbs for the assessment of effective therapeutic drugs from HCCHs.

ACKNOWLEDGMENT

This study was supported by Tianjin University of Traditional Chinese Medicine (TUTCM).

Table 1. Anti-inflammatory effects of HCCHs

Plant name	Pin yin	Experimental model/dose	Disease	Mechanism of action	References
Andrographis paniculata	穿心蓮 Chuān Xīn Lián	Murine macrophage cells (1.5-90 μM) H1N1-infected human bronchial epithelial cells (200 μg/ml)	Inflammation RANTES secretion	↓iNOS, NO↓TNF↓IL-1B, IL-6, IL-12↓MAPKs	[5,27,58,60]
Coptis chinensis	黃連 Huáng Lián	RAW 264.7 cells (1, 10, 100 g/ml) JASW-II cells (0.1 mg/ml) Type 1 diabetic NOD mice (200 mg/kg) Human keratinocytes (200 μl/ml)	Gastritis, gastric ulcer Inflammatory bowel disease Type 1 diabetes Dermatological disorders	↓iNOS, NO↓TNFα ↓IL-1B, IL-6↓COX-2↓NF-kB, p38MAPK, and JNK↓Th17 and Th1	[9,21-24,50]
Forsythia suspensa	連翹 Lián Qiào	BALB/c mice (1-2 mg/dose/time) LPS-stimulated RAW 264.7 cells (10-160 μM) RAW264.7 cells (100 μg/ml) Rat peritoneal mast cells (RPMC) (100 μg/ml) Weaned piglets	Arthritis Inflammatory diseases Inflammation Allergic inflammatory reactions Food allergies	↓iNOS, NO↓TNFα ↓IL-1B, IL-4, IL-6↓COX-2↓T-lymphocyte↓PGE2↓NF-kB, p38MAPK↓Anaphylactic antibodies, histamine release	[35-40]
Radix Isatidis	板藍根 Bǎn Lán Gēn	RAW 264.7 macrophages (0-5 mg/ml)	Inflammatory diseases	↓PGE2↓NO	[51]
Flos Lonicerae	金銀花 Jīn Yín Huā	BALB/c mice (1 and 2 mg) HMC-11 cells (10 and 50 μM)	Fungal arthritis Mast cell–mediated inflammation	↓T cell↓iNOS, NO↓NF-kB, p38MAPK Shift Th1 to Th2	[29,31,34,35]
Scutellaria baicalensis	黃岑 Huáng Qín	*Pneumocystis carinii* infected rats (100-400 mg/kg/day)	Lung tissue inflammation	↓NO↓TNFα ↓IL-1B, IL-6, and IL-12↓ICAM-1	[5,16,17]

HMC: Human mast cell; RANTES: Regulated on activation, normal T cell expressed and secreted; RAW: Mouse leukaemic monocyte macrophage cell line; JASW-II: Murine dendritic cell line; HINI: Influenza A virus subtype H1N1; BALB: An albino mice; LPS: Lipo polysaccharide; RPMC: Rat peritoneal mast cells; NOS: Inducible Nitric oxide synthase; ICAM: Inter cellular adhesion molecule; JASW: Murine dendritic cell line; NOD: Non-obese diabetic; p38MARK: Protein38 mitogen-activated protein kinases; HCCHs: Heat clearing Chinese herbs

Table 2. Antimicrobial effects of HCCHs

Plant name	Pin yin	Experimental model/dose	Activity against	References
Coptis chinensis	黃連 Huáng Lián	Brain heart infusion broth (200 μg)	*E. coli*	[21,26]
Forsythia suspensa	連翹 Lián Qiào	Nutrient agar or potato dextrose agar (1.66–100 μl/ml)	*E. coli, Sta. aureus, B. subtilis, Str. mutans As. flavus, R. stolonifer, Pe. citrinum, As. niger, and Sac. carlsbergensis*	[6,27,42]
		Horse blood agar (2.5 g/ml)	Po. gingivalis	
		H1N1-infected bronchial epithelial cells (200 μg/ml)	Influenza A	
Isatidis Radix	板藍根 Bǎn Lán Gēn	Blood neutrophil phagocytosis (100, 10, and 1% v/v)	*Sta. aureus*	[15,38,48, 50]
		Tomato juice culture medium	*H. pylori*	
		Lactose broth (LB) culture medium	*E. coli*	
		MDCK cells (12.6 mg/ml)	Influenza	
Flos Lonicerae	金銀花 Jīn Yín Huā	Tomato juice culture medium	*H. pylori*	[6,15]
		Horse blood agar (0.1563, 0.0781, and 0.0003 g/ml)	*Po. gingivalis, Str. mutants, Streptococcus sanguis*	
Pulsatilla Radix	白頭翁 Bái Tóu Wēn	Broth medium (2.0, 4.0 μg/ml)	Pr. acnes	[56,57]
		Impregnated paper disk method	*C. perfringens, E. coli*	
Scutellaria baicalensis	黃岑 Huáng Qín	Tomato juice culture medium	H. pylori	[7,15]
		Disk diffusion method (0.15 ml)	*E. coli* B, coagulase-negative staphylococci, and *Saccharomyces*	
Viola yedoensis	紫花地丁 Zǐ Huā Dì Dīn	Bioautographic assay (6.25 μg/ml)	B. subtilis, Pseudomonas syringae	[50,54,55]
		Neuroblastoma SK-N-SH cell line	Herpes simplex virus-1, entero virus 71	
		HIV-infected cell cultures	HIV	

HINI: Influenza A virus subtype H1N1; HCCHs: Heat clearing Chinese herbs; MDCK: MDCK: Madin Darby canine kidney; SK-N-SH: Human neuroblastoma cell line; HIV: Human immune virus

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