

A Renal-Protective and Vision-Improved Traditional Chinese Medicine - *Cordyceps cicadae*

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CLASSIFICATION OF *C. CICADA*

Cordyceps cicadae (*C. cicadae*), also known as cicadae flower, Chanhua and Sandwhe, belongs to the family *Clavicipitaceae* and the genus *Cordyceps* (Table 1), which strictly parasitize on cicada nymph or larva of *Cicada flammata*, *Platypleura kaempferi*, *Cryptotympana pustulata* and *Patylomia pili*. The host larva were consumed as nutrition and became a tightly packed mass of mycelium, then formed flower bud-shaped stroma from mouth, head or bottom of cicada larva. It is a wonderful biological complex of fungus and larva.

C. cicadae can be roughly divided into *Cordyceps cicadae* Shing (*C. cicadae* Shing) and *Cordyceps sobolifera* (*C. sobolifera*) based on their morphology (Figure 1) [1]. The parasitic nymphs of *C. cicadae* Shing are relatively large with pale or pale yellow bodies of about 3 cm long and 1-1.5 cm wide. Heads of the nymphs are clavate, displaying white at the front. Dried nymphs of *C.*

cicadae Shing are chocolate-brown, pervaded by grey-white mycelia. Fine mycelia or fruiting body growing within nymph body are referred to as coremium. Stroma will develop on coremium and extruded from soil. Stroma usually has 3-4 branches in rod-like shape, with length of 4-10 cm, which form flower bud-shaped stroma. The anamorph of *C. cicadae* Shing is called as *Isaria cicadae* that was originally described by Miquel in 1838, after which many scientific names such as *Isaria basili*, *Sphaeria sinclairi* and *Paecilomyces cicadae* were developed [2].



Figure 1: Cicada nymph infected with *C. cicadae* or *C. sobolifera*.

(a) Cicadae nymph infected with *C. cicadae*. (b) Cicadae nymph infected with *C. sobolifera*. (c) The stroma of *C. cicadae* extruded from the soil. (d) The stroma of *C. sobolifera* extruded from the soil. (e) The coremium of *C. sobolifera*. (f) Different lengths of stroma of *C. sobolifera*.

As compared with *C. cicadae* Shing, *C. sobolifera* has smaller parasitic nymphs, and the front of fruiting bodies are not in flower-bud appearance but normally clavate shape. The stipes are cinnamon with thickness of 1.5-4 mm. The nymph bodies are clean and intact, without pervading of hairy mycelium. Appearance of *C. sobolifera* is more attractive than that of *C. cicadae* Shing. The anamorph of *C. sobolifera* is referred to as *Beauveria sobolifera* (Table 1).

Table 1: Classification of *C. cicadae*.

Scientific classification	
Kingdom	Fungi
Subkingdom	Dikarya
Phylum	Ascomycota
Subphylum	Pezizomycotina
Class	Sordariomycetes
Order	Hypocreales
Family	Clavicipitaceae
Genus	<i>Cordyceps</i>
Species	<i>C. cicadae</i> and <i>C. sobolifera</i>

DISTRIBUTION OF *C. CICADAE*

C. cicadae is usually distributed in tropical and subtropical region with temperature ranging from 18-24°C and relative humidity of > 80%. *C. cicadae* is usually grow vertically on sunny slopes at an altitude of 700-950 m. In China, *C. cicadae* is most frequently seen in Fujian, Zhejiang, Yunnan, Sichuan and Jiangsu province or river valley of the Yunnan-Tibet Plateau [3-5]. In Japan, *C. cicadae* is mainly distributed in mountain and forest region at low altitude, south of Fukushima. In South Korea, *C. cicadae* is found on Jeju Island. In Taiwan, *C. cicadae* Shing is present in bamboo forest of northern Taiwan mountain and *C. sobolifera* occurs in pomelo orchard in Ruisui Township, Guangfu Township and Yuli Township in Hualien County. Furthermore, they are also seen in Thailand, Southeast Asia, North America and Europe [6].

RECORD OF *C. CICADAE* IN ANCIENT TRADITIONAL CHINESE MEDICINES (TCM) WORKS

C. cicadae is one of the most valued traditional Chinese medicines (TCM) and have been used for about 1,600 years in China, which was 800 years longer than *Cordyceps sinensis* (Table 2). It was first mentioned in *Lei's Treatise on Preparing Drugs* (*Lei Gong Pao Zhi Lun*) written by Xiao Lei in the Liu Song Period of Northern and Southern Dynasties [7]. Its morphology was first described in *Tu-Ching Pents'ao* compiled by Song Su in the Song Dynasty, that horn-like protuberances occurred on heads of Cicada in mountain. Shi-Zhen Li in the Ming Dynasty clarified in *Compendium of Materia Medica* that *C. cicadae* exhibits activities of dispelling wind and heat, relieving convulsion, improving eyesight, removing cloudiness of eyes, and promoting eruption. Shi-Zhen Li also mentioned that *C. cicadae* which has the same efficacy as *Periostracum cicada* was primarily used in treatment of infantile convulsions and morbid night crying of babies, palpitation and malaria.

Table 2: Record of *C. cicadae* in Famous TCM works.

Author	Title	Description
Northern and Southern Dynasties		
Xiao Li	<i>Li's Treatise on Preparing Drugs (Li Qiang Jie Zhi Lun)</i>	Choose <i>C. cicadae</i> with white flower. Coating mud of <i>C. cicadae</i> should be removed before boiling overnight. The next day, it is dried and grinded into powder.
Tang Dynasty		
Si-Miao Sun	<i>Xin Nai Jing</i> (Xin) volume one	<i>C. cicadae</i> Powder is composed of <i>Pericentracum cicadae</i> , <i>dryantherum</i> , thistle, frodoia viticola, cassia obtusa filia, semen plantaginis, windproof radix astellariae and liquorice, which should be simmered before taking.
Si-Miao Sun	<i>Xin Nai Jing</i> (Xin) volume two	<i>C. cicadae</i> Powder treats inflammatory blepharodema.
Song Dynasty		
Song Su	<i>Tu-Ching Pen-tiao</i>	In mountain, horn-like protuberance occurred on the head of Cicada, which is called <i>C. cicadae</i> . The worm is used to pay tribute to capital of Song Dynasty. The medical professionals all appreciated its wonderful medicinal effect.
Kuan Yao	<i>Xiao Song Jiu</i> volume 2	There is a kind of herb in Chengdu known as <i>C. cicadae</i> . Flower bud-shaped stroma formed from the head of cicada larva, which is an effective treatment for eye diseases.
Shen-Wu Tang	<i>Ching Shih Ching Lai Pei Chi Pen-tiao</i>	<i>C. cicadae</i> is sweet in flavor, cold in nature and nontoxic, which can disperse wind and heat from the body, relieve convulsion and spasm. It is intended for morbid night crying of babies and palpitation. <i>C. cicadae</i> is widely distributed. It is harvested in July and those grown in <i>gleboulus amarus</i> forest have the best quality, with flower occurred above the ground.
Yi Qian	<i>Key to Therapeutics of Children's Diseases (Xiao Er Zheng Zhi Jie)</i>	<i>C. cicadae</i> Powder is composed of <i>Descurainia bursaria</i> , liquorice, <i>Rhizoma scydalis</i> , which is mainly used in treatment of infantile convulsions and morbid night crying of babies, teeth grinding, cough and sore throat.
Cheng Chen	<i>Prescriptions of the Bureau of Taijing People's Welfare Pharmacy (Taijing Huimin Heji Ju Fang)</i>	Suppose <i>C. cicadae</i> Powder is used locally for treatment of acute conjunctivitis, chronic blepharitis, chronic dacryocystitis and pterygium.

Author	Title	Description
Cheng Chen	<i>Prescriptions of the Bureau of Taijing People's Welfare Pharmacy (Taijing Huimin Heji Ju Fang)</i> volume 7	<i>C. cicadae</i> Powder is used for treatment of heat accumulated in liver meridian and wind-heat, swollen and pain of eyes, blurred vision, lacrimation and inner and outer border of eyes.
Tan Yang	<i>Yang Shi Jia Cang Fang</i> volume 11	<i>C. cicadae</i> Powder is used for treatment of heat accumulated in liver meridian and wind-heat, a source toxin, swollen and pain of eyes, formation of pterygium, and blurred vision.
Yuan Dynasty		
Hao-Gu Wang	<i>Ben Cao Pin Hai Jing Yao</i>	<i>C. cicadae</i> growth usually occurs in May and is collected in July.
Hao-Gu Wang	<i>Herbs for Making Formulas (Zang Ye Ben Cao)</i> volume 6	<i>C. cicadae</i> has the same pharmacological efficacy as snake slough. It can treat infantile hyperpyretic convulsion, and it can also quench thirst. There is a flower-like horn on the head of larva, that is why it is called Cicadae flower. <i>C. cicadae</i> is sweet in flavor, cold in nature and nontoxic, which is used for therapy of morbid night crying of babies and palpitation.
Anonymous	<i>Zang Guang He Ji Ju Fang Yao Ming</i> Zang Lun	<i>C. cicadae</i> is sweet in flavor, cold in nature and nontoxic, which is mainly used in treatment of infantile convulsions and morbid night crying of babies, palpitation, breast milk absence of puerpera as well as placenta retention. It is also recorded that <i>C. cicadae</i> is sour in flavor, which is primarily used in treatment of morbid night crying of babies. It has insecticidal activities and can remove vigorous heat and botborygmus. It is also termed as <i>Pericentracum cicadae</i> , which is mainly used in treating vigorous heat of whole body in children and infantile convulsions, and it also quenches thirst. It is found in Kingdom of Shu (Sichuan province).
Turning of Yuan and Ming Dynasty		
Wei-De Ni	<i>Revealing the Mystery of Medical Origin (Xian Ji Qi Wu)</i> volume two	Multi-purpose <i>C. cicadae</i> Powder is composed of <i>Pericentracum cicadae</i> , <i>Notopterygium incisum</i> , <i>Radix saposhnikowiae</i> , <i>Angelica sinensis</i> , <i>Ligusticum wallishii</i> and <i>Radix paeoniae rubra</i> . The powder can be in oral and external use. It is intended for treatment of eye diseases, dry mouth and coated tongue.

Author	Title	Description
Wei-De Ni	<i>Revealing the Mystery of Medicinal Origin (Xian Ji Qi Wei)</i> -volume two	Vision-improving prescription of <i>C. cicadae</i> is mainly used in treating eye disorders such as swelling eyes, photophobia and flares.
Wei-De Ni	<i>Revealing the Mystery of Medicinal Origin (Xian Ji Qi Wei)</i> -volume two	"Heat-clearing prescription of <i>C. cicadae</i> ", "Cortex/lysis radical prescription of <i>C. cicadae</i> " and "Trauma-management prescription of <i>C. cicadae</i> "
Ming Dynasty		
Shi-Zhen Li	<i>Compendium of Materia Medica</i>	<i>C. cicadae</i> is sweet in flavor, cold in nature and nontoxic, which can be used as a medicine after drying. It exhibits activities of dispelling wind and heat, relieving convulsion, improving eyesight, removing cloudiness of eyes, and promoting eruption. It is primarily used in treatment of infantile convulsions and morbid night crying of babies, palpitation and malaria, which has the same efficacy as <i>Periostema cicadae</i> .
Shi-Zhen Li	<i>Compendium of Materia Medica</i> - volume 41	<i>C. cicadae</i> Powder is mainly used in treatment of morbid night crying of babies.
Jie-Bin Zhang	<i>Jingui Quan Shu</i>	<i>C. cicadae</i> is mainly used in treatment of heat accumulated in liver meridian and wind-heat scurge toxin, reddish and pain of eyes, and inner and outer barrier of eyes.
Jie-Bin Zhang	<i>Jingui Quan Shu</i> -volume 27	<i>C. cicadae</i> Powder is mainly used in treatment of heat accumulation.
Shi-Cai Li	<i>Lei Gong Pao Zhi Yao Xing Ji</i> -volume 6	<i>C. cicadae</i> is sweet and salty in flavor, cold in nature and nontoxic, which can be used in expediting child delivery, laxative, expelling heat and treatment of morbid night crying of babies. It has insecticidal and throat-quenching activity. There are 3 kinds of cicadas, and those has big shape and louder and uninterrupted sound is the best for medication. There is a <i>C. cicadae</i> distributed in Sichuan province, the cicada doesn't come out from the shell, instead of flower-like horns occurring on the head of the larva.

Author	Title	Description
Su Dong	<i>Qi Xiao Liang Fang</i> -volume 64	<i>C. cicadae</i> can be used in treatment of infantile convulsion and teeth-grinding. Equal portion of <i>C. cicadae</i> (with the shell), muscardine caterpillar, licorice and <i>Orthocentrus corydalis</i> is grinded into 3.125 g (1 Qian of Chinese ancient measure unit) powder, which is taken with <i>Periostema cicadae</i> soup preparation.
Su Dong	<i>Qi Xiao Liang Fang</i> -volume 65	Pruritus with blurred vision is a good indication for <i>C. cicadae</i> Powder.
Jia-Mo Chen	<i>Ben Cao Meng Quan</i> -volume 11	<i>C. cicadae</i> has flower-like horns on the head, which can be used in treatment of palpitation.
Qing Dynasty		
Xing-Yan Sun	<i>Shennong Ben Cao Jing</i>	<i>C. cicadae</i> is proved to prolong life expectancy.
Chang-Xi Tao	<i>Hui Zhi Tang Jing Ji n Fang</i> -volume 2	<i>C. cicadae</i> can be used both in adults and children, for treatment of eye disorders, intermittent headache and convulsion. It is applicable in treatment of reddish ulcer of eyes, dark spots in the whites of eyes or white spots in the pupil, reddish circle between black and white eyeball, blurred vision, or dry mouth and bitter taste, lacrimation and pediatric exanthema varicellous and eye disease.
Guo-Peng Chang	<i>Enlightenment in Medicine (Yao Xue Xin Wu)</i> -volume 4	Superb <i>C. cicadae</i> Powder has favorable therapeutic effect in treatment of eye disorders, reddish, swollen and pain of eyes, catarrh or orbital emulsion, pterygium, outstanding pupil, trichiasis and pediatric exanthema varicellous.
Chen-Zhan Feng	<i>Feng Shi Jin Nang Mi Lu</i> -volume 3	Grind 7 <i>Periostema cicadae</i> into powder and added it into mint soup containing small amount of alcohol. <i>C. cicadae</i> Powder is primarily used in treatment of infantile morbid night crying.
Chen-Zhan Feng	<i>Feng Shi Jin Nang Mi Lu</i> -volume 47	There is the flower-bud-shaped stroma formed from head of the <i>C. cicadae</i> , that's why it is also called Cicadae flower. <i>C. cicadae</i> can be used in the treatment of palpitation.

Author	Title	Description
Qian Wu	<i>Golden Mirror of the Medical Tradition</i> (<i>Xi Zong Jin Jian</i>)- Wai Ke Juan Xia	For those smelly, rotten and gobby sores that occur in summer, the treatment is an urgent <i>C. cicadae</i> Powder can cure it.
Qian Wu	<i>Golden Mirror of the Medical Tradition</i> (<i>Xi Zong Jin Jian</i>)-volume 5	<i>C. cicadae</i> Powder can be used in treatment of infantile morbid night crying.
Shi-Cheng Gu	<i>Yang Xi Du Quan</i> -volume 9	The <i>C. cicadae</i> powder is effective in treating those smelly, rotten and gobby sores that occur in summer. The snake slough (50 g, burn into ashes), <i>Periostracum cicadae</i> (18 g) and indigo naturalis (18g), as arum (8.5g) is ground into powder. The powder is taken twice daily. Each time, 10.5 g of the powder is diluted in alcohol before medication.
Ji Pan	<i>Xi Dong Xu Yan</i> -volume 16	Restless and sleepless of babies with morbid night crying and dysphoria is usually due to heat of the internal organs. If the babies are crying at the whole night, it is due to cold of the internal organs. If the babies are crying and suffering from vigorous abdominal pain, opening mouth breathing and frowning, the reasons might be dyspepsia or food retention.
Yuan Deng	<i>Xi Cao Jing Mu Xi Quan Shi</i>	<i>C. cicadae</i> Powder is mainly used in treatment of heat accumulated in liver meridian and wind-heat's orange toxin, reddish and pain of eyes, lacrimation, as well as various of cloudiness of eyes caused by wind-heat toxins.
Modern age		
Zong-Xiang Zhang	<i>Ben Cao Jian Yao Fang</i> -volume 7	<i>C. cicadae</i> Powder is mainly applied in treatment of wind-heat accumulated in upper warmer, headache and dizziness, blurring vision with nebula, sore-throat and pharyngitis, diptheria, pediatric convulsion and vigorous heat, tetanus, furuncle, aphonia in adult, dysocia. <i>C. cicadae</i> has the same efficacy as <i>Periostracum cicadae</i> in terms of treating infantile convulsions, morbid night crying of babies and palpitation.
Others		
	<i>You Xi Xin Fa Yao Ju</i> -volume 2	<i>C. cicadae</i> powder can be applied in treatment of infantile morbid night crying.
	<i>Bao Hu Xin Shu</i>	<i>C. cicadae</i> powder can be applied in treatment of infantile morbid night crying.

Ancient TCM works emphasized the therapeutic effect of *C. cicadae* for various eye diseases. For example, *Prescriptions of the Bureau of Taiping People's Welfare Pharmacy* (*Taiping Huimin Heji Ju Fang*) written by Cheng Chen during the Song Dynasty stated that Superb *C. cicadae* Powder is specifically for treatment of acute conjunctivitis, chronic blepharitis, chronic dacryocystitis and pterygium.

BIOACTIVITY OF *C. CICADAE*

Modern pharmacological studies have indicated that *C. cicadae* exhibits a variety of biological functions (Tables 3,4,5). *C. cicadae* has been used to recede nephelium of eyeball and improving vision for a long time. The ideal efficacy of *C. cicadae* in eye treatments may be attributed to produced antibiotics or specific active constituents. It is of great significance to explore bioactive components targeting vision improvement and its underlying mechanisms. There are two patent pending on "Preparation and application of active ingredients and its drug combinations of *C. cicadae*" in Taiwan (pending number 104112814) and China (pending number 201510303766.1).

Table 3: Physiological Activity of *C. cicadae*.

Year/Author	Test Article	Bioactivity
Immunomodulation		
Activate Macrophages:		
2001 Li-Qin Jin	<i>Panilomyces cicadae</i> mycelium	Rat were intravenously injected with <i>Panilomyces cicadae</i> (500 mg/kg) resulted in increased LDH and ACP activity of rat pulmonary macrophages and enhanced phagocytic capacity for neutral red of rat alveolar macrophages. It could boost immune function without affecting the membrane permeability or destroying the cell membrane structure [11].
2008 Li-Qin Jin	Polysaccharides of <i>Panilomyces cicadae</i> mycelium	<i>Panilomyces cicadae</i> polysaccharides alleviated decline in the number of leukocytes induced by environmental ammonium sulfate in tumor-burdened mice, thus increasing numbers of leukocytes and elevating spleen index [12].
Promote the Phagocytosis of Macrophage		
1996 Qiu-Yang Chi	Artificially cultivated <i>C. cicadae</i> mycelia	Lymphatic transformation experiment, the erythrocyte rosette test and EA rosette test, immunospecific rosette forming cell test (R-F-C), assay for phagocytosis of macrophage antibody titer in response to challenge by sheep red blood cells (SRBC) were conducted and results showed that <i>C. cicadae</i> could obviously boost immune system [13].
2002 Shi-Cheng Wang	<i>C. cicadae</i> extracted with the same proportion of water and methanol	<i>C. cicadae</i> promoted monocyte proliferation and human body's immunological response, which might be attributed to the cytokines such as IL-12 and IFN- γ contained in <i>C. cicadae</i> [14].
2007 He-Min Song	Wild <i>C. cicadae</i>	It improved the humoral immune response and enhanced the phagocytosis of macrophage in mice [15].
2008 He-Zan Yang	<i>Panilomyces cicadae</i> polysaccharides	It enhanced the phagocytosis of macrophage, spleen lymphocyte proliferation response as well as the ACP, LDH, and ARG activity in spleen [16].
Improve immune response in the liver, kidney, spleen and thymus:		
2003 Li-Qin Jin	Polysaccharides of <i>Panilomyces cicadae</i> mycelium	It could improve ACP, LDH, and Arg activities in liver, kidney, spleen and thymus, suggesting the macrophage origin of the ACP, LDH, and Arg in those Organs. Thus, it conferred immune regulatory function the liver, kidney, spleen and thymus [17].
Anti-aging Properties		
2001 Li-Qin Jin	<i>Panilomyces cicadae</i> polysaccharides	It increased the GSH levels and decreased the LPO contents in the liver and kidney tissue significantly in the aged rats. Results suggested that <i>panilomyces</i> could inhibit the lipid peroxidation of cell membrane, which might serve as an ideal free radical scavenger or free radicals' reaction inhibitors [18].
2004 He-Zan Yang	Polysaccharides of <i>Panilomyces cicadae</i> mycelium	Aged Rat were subcutaneously injected for 3 weeks resulted in significantly increase in the wet weight of spleen and spleen-to-body-weight ratio. Elevated peripheral white blood cells (WBC) were also observed in aging rats [19].
Protection of Renal Function		
2004 Yang Min	<i>Panilomyces cicadae</i> mycelium	It significantly inhibited progression of chronic renal failure in rats, delivering therapeutic effect on chronic renal failure [20].
2006 Zhou-Hai Jin	<i>Cordyceps cicadae</i> Sheng Tang	It effectively increased the clearance rates of blood and urine Creatinine, improved serum protein contents and lessened protein discharge in urine. <i>C. cicadae</i> improved renal tubulointerstitial lesions and protected the renal tubular function. It also regulated renal hemodynamics and triglyceride levels, reducing the serum cholesterol level [21].
2006 Lin Wang	Artificially cultivated <i>C. cicadae</i> mycelia	It inhibited the progression of glomerulosclerosis and proliferation of mesangial cells. It could block the main source of the ECM by inhibiting MSC proliferation, thus suppressing the cellular proliferation and spread of inflammation. The down-regulation effect on FN is similar to that of western medicine losartan [22].
2011 Rong Zhu	Artificially cultivated <i>C. cicadae</i> fruiting bodies	It could effectively down-regulate the expression of type IV collagen and fibronectin (FN) and decreased production of TGF- β 1 and CTGF, which thereby reduced the risk of renal fibrosis progression to kidney failure [23].
Lower Blood Glucose Levels		
2007 He-Min Song	Wild <i>C. cicadae</i>	Water extract of wild <i>C. cicadae</i> significantly reduced blood glucose levels in mice with diabetes induced by alloxan in a dose-dependent manner. It should be noted that <i>C. cicadae</i> also lowered the blood glucose levels in normal mice [24].

Year/Author	Test Article	Bioactivity
Anti-tumor Properties		
Mouse Sarcoma Cell Line (S180)		
1990 Kibo	<i>C. cicadas</i> polysaccharides	Mice were orally administered with <i>C. cicadas</i> (20 mg/kg) resulted in 47% inhibition against S180 mouse sarcoma [25].
Leukemia Cell Line (U937 and K562)		
2006 Bi-Kun Chen	<i>Paniclemyces cicadas</i> polysaccharides	<i>Paniclemyces cicadas</i> polysaccharide elevated proliferation of human peripheral blood monocytes and directly retarded the progression of leukemia by increased secretion of hTNF- α and hINF- γ in tumor tissues after 44 hours of treatment [26].
Lung Cancer Cell Line (PAA-1)		
2006 Bo-Zhen Lu	<i>C. cicadas</i>	Crude extract of <i>C. cicadas</i> selectively killed PAA cells in C2-M phase and significantly inhibited growth of PAA cells [27].
2010 Ju-Yen Cai	<i>Paniclemyces cicadas</i> polysaccharides	The IC ₅₀ of <i>Paniclemyces cicadas</i> polysaccharides for PAA cells were 10.86 mg/ml. Adenosine in combination with ADM could boost its anti-tumor capacity and reduce the colonies formation of pulmonary adenoma <i>in vivo</i> [28].
Liver Cancer Cell Line (MHCC97H)		
2014 Hui-Wang	<i>C. cicadas</i>	Water extract of <i>C. cicadas</i> inhibited liver cancer MHCC97H cells via interfering the cellular cycle [29].
Chinese Hamster Ovary Cell (CHO)		
2015 An-Hui Chen	Solid-state fermentation of <i>C. cicadas</i> and wild <i>C. cicadas</i>	Both of them demonstrated inhibitory effect on CHO cells proliferation. The active component was moderately polar compounds including cordycepin [30].
Lower Blood Lipids		
2001 Li-Qin Jin	<i>Paniclemyces cicadas</i> mycelium	It decreased blood cholesterol and triglyceride in rats. It can be an ideal healthcare product for cardiovascular disease [11].
Year/Author	Test Article	Bioactivity
Analgesic, Sedation and Antipyretic Effect		
1991 Guang-Yu Liu	Wild or artificially cultivated <i>C. cicadas</i>	Both of them significantly prolonged sleep time, shortened loss of righting reflex induced by pentobarbital, and enhanced rate of re-onset sleep in mice. Inhibitory effect on chemical and thermal stimulation was confirmed by body-writhing test and hot plate test. Inhibitory rate of 1.5 g/kg <i>C. cicadas</i> on chemical stimulation of acetic acid was 97.3%, similar to that of morphine [31].
Anti-fatigue Effect		
2001 Yan Wang	Fruiting body of <i>C. cicadas</i>	Fruiting body of <i>C. cicadas</i> could significantly prolong mice's swimming time, increase survival period of mice under the conditions of high-pressure, anoxia or high temperature [32].
Anti-oxidant and Antibacterial Effect		
2008 An-Hui Chen	Fermentation broth and mycelia of liquid fermentation of <i>Paniclemyces cicadas</i>	The clearance rate of DPPH free radicals was 55.52% and 74.56% in concentrations of 5.0 mg/ml and 0.4 mg/ml, respectively. The diameter of inhibition zone was 11.23 and 21.42 mm [33].
2013 Yan-Po Chen	Liquid fermentation of <i>C. cicadas</i> mycelium	<i>C. cicadas</i> protected Neuro2a cell line from Tunicamycin-induced endoplasmic reticulum stress-mediated apoptosis, and against 1-methyl-4-phenylpyridinium (MPP ⁺)-induced neurotoxicity in NG108-15 cell line. <i>C. cicadas</i> slightly increased neurite outgrowth of PC12 cells, and neurite branch number. <i>C. cicadas</i> reduce oxidative stress and MPP ⁺ neurotoxicity, implying the protective potential in neurodegenerative diseases [34].
Year/Author	Test Article	Bioactivity
Improving Vision		
2009 Dong-Qing Cheng	Liquid fermentation of <i>Paniclemyces cicadas</i> mycelia	<i>Paniclemyces cicadas</i> inhibited the cytostatic effect in Vero cells by HSV-1 at concentrations ranging from 1.6-6.2 μ g/ml, and the highest inhibition (152.2%) was obtained at a concentration of 6.2 μ g/ml, and was still 78.7% at 0.8 μ g/ml [35]. The efficacy in improving vision and cataract removal of cicadas flower is very likely related to the antiviral effect of its parasitic fungus <i>Paniclemyces cicadas</i> .
Anti-radiation Effect		
1991 Zhu-An Chen	<i>Paniclemyces cicadas</i>	It could protect against ultraviolet (UV) radiation [36].
Promote Bone Health		
2014 Yu-Qin Wang	Wild and artificial lyophilized <i>C. cicadas</i> mycelia	It promoted proliferation of human osteoblast, which can be used in treatment of osteoporosis [37].
Anti-inflammation		
2012 Meng-Ying Lu	Solid-state fermentation of <i>C. cicadas</i> fruiting body	HEA suppressed the lipopolysaccharide (LPS)-stimulated release of pro-inflammatory cytokines by RAW264.7 macrophages by suppressing the toll-like receptor (TLR)4-mediated nuclear factor- κ B (NF- κ B) signaling pathway [38].

Table 4: Physiological Activity of *C. sobolifera*.

Year/Author	Test Article	Bioactivity
Promotion of Renal Function		
2005 Rong Zhu	Solid cultured mycelium of <i>C. cicadae</i>	It inhibited the progression of glomerulosclerosis and chronic renal failure in rats [39].
2005 Zhou-Hui Jin	Mycelium of <i>C. cicadae</i>	It mitigated glomerular injury and improved renal function as well as the complications of renal failure such as anemia and malnutrition in mice [40].
2011 Ming-Feng Wu	Liquid fermentation of <i>C. sobolifera</i> mycelium	It mitigated LPS-induced renal tubular injury in rats [41].
2011 Chi-Hung Cheng	<i>C. sobolifera</i> mycelium	It alleviated Cyclosporine-induced kidney damage in rats [42].
2011 Chao-Hung Chiu	Liquid fermentation of <i>C. sobolifera</i>	It ameliorated Streptozotocin-induced diabetic kidney damage caused by diabetes in rats [43].
2014 Chao-Hung Chiu	Extract of polysaccharides	It mitigated kidney damage resulting from LPS-induced endotoxin sepsis in rats [44].
2014 Chany-Chang Chyau	Mycelium glycoprotein	It alleviated Cyclosporine-induced renal tubular injury in rats [45].

Table 5: Physiological Activity and Clinical Application of *C. cicadae* powder.

Year/Author	Test Article	Bioactivity
Improving Vision		
Revealing the Mystery of Medical Origin [Multi-purpose <i>C. cicadae</i> powder]		
2010 Da-Mei Huo	Cicada slough	The clinical trials conducted in 100 patients diagnosed with vernal conjunctivitis revealed that Cicada slough could alleviate conjunctival congestion, reduce the incidence of relapse. The response rates was 78% in the treatment group, whereas, only 26% in the control group (n=50). The 1-year recurrence rate was 2.2% and 55%, respectively [46].
Combined use of arbutin and Superb <i>C. cicadae</i> Powder		
2010 Qing-Hui Kong	Cicada slough	Based on the routine application of insulin in treatment of diabetes, combined medication of arbutin and TCM superb <i>C. cicadae</i> powder could improve the retinal blood supply and function of photoreceptor cells. It could also reduce embolism, bleeding, edema, prevent proliferation in non-proliferative DR [47].
Individualized <i>C. cicadae</i> Soup Preparation		
2001 Hong-Qian Wang	<i>Pericardium cicadae</i>	Since November 1996 to December 1999, good curative efficacy of <i>C. cicadae</i> Soup Preparation has been found in 50 patients with herpes simplex keratitis [48].
Shengye powder and 5-drugs powder containing <i>C. cicadae</i>		
1994 Guang-Hua Peng		Among the patients subjected to therapy project of combining TCM and western medicine, 14 subjects of which achieved a normal intraocular pressure (>1.33kPa), with a response rate of 46.67%. However, among 30 patients underwent western medicine treatment group, 8 patients achieved a normal intraocular pressure, with an average intraocular pressure of 0.41 kPa and a response rate of 26.67% [49].

Year/Author	Test Article	Bioactivity
Prescription of the Taiping Huimin Bureau [Superb <i>C. cicadae</i> Powder]		
1986 Kai-Wai Tian	Cicada slough	Four kinds of outer barrier eye disease including acute conjunctivitis, chronic blepharitis, chronic dacryocystitis and pterygium were all cured [50].
Promotion of Renal Function		
Combined use of <i>C. cicadae</i>, Codonopsis pilosula and Astragalus		
2000 Hai-Ying Wang	<i>C. cicadae</i> or cicada slough	Combined application of <i>C. cicadae</i> , Codonopsis and Codonopsis in treating renal disease [8].
Promotion of Lung		
[<i>C. cicadae</i> Long-Zi Soup Preparation]		
2010 Yong-Xing Mao	Cicada slough	It was intended for treatment of cough caused by pneumonia [51].
[<i>C. cicadae</i> Erchen Soup Preparation]		
2007 Ying Ye	Supplemented <i>C. cicadae</i> or cicada slough	It was used in the treatment of pneumonia in children [52].

Table 6: Products of *C. cicadae*.

Product Name	Manufacturer	Product Image
Cicadaf Herbal Rejuvenating Face Mask	Isogreen Biotechnology Inc.	
<i>Cordyceps cicadae</i> (decoction pieces)	Chengdu Bioactive Pharmaceutical Co., Ltd.	
Vegetable cicadae powder of synnemata	BioAsia Pharmaceutical Co., Ltd.	
Chun Xiang Xu (edible fungus compounds)	Beijing Ding Fu Lai Trading Co., Ltd.	
<i>Cordyceps cicadae</i>	Wan Rui Tang (China)	
Wild <i>Cordyceps cicadae</i>	Autumn Cicada Summer Flowers Yang Sheng Tang (China)	

Another great commercial potential of *C. cicadae* application lies in prevention of chronic renal failure. Wang et al. [8] showed that *C. cicadae* obviously improved renal tubular function in chronic renal failure patients with renal tubular dysfunction. Studies have also found that active ingredients from *C. cicadae* exhibit renal protection. For example, Zhu et al. [9] reported that 12.5 µg/ml ergosterol peroxides from *C. cicadae* could ameliorate TGF-β1-induced renal fibroblast proliferation and fibronectin expression, thus combating progression of renal fibrosis. Another example is that Peng et al. [10] demonstrated the protective effect of HEA on renal

ischemia-reperfusion injury in mice [10]. There are many mushrooms possessing functions of lowering blood glucose levels and immunomodulation, but protection capacity on kidney of those mushrooms are rarely reported. In Taiwan, numbers of patients undergoing hemodialysis have leaped to the first place worldwide. *C. cicadae* that had the equivalent pharmacological effect with *C. sinensis* might act as a better alternative, offering potential kidney-specific nutritional and health benefits.

POTENTIALLY BIOACTIVE CONSTITUENTS OF *C. CICADAЕ*

Myriocin (ISP-1)

Fujita et al. [53] isolated and identified myriocin from fermented liquid of *C. cicadae*. It is a potent immunosuppressor used in organ transplantation and autoimmune diseases, with less adverse effect on kidney. Its derivate FTY720 was developed in Japan and transferred to Novartis (Basel, Switzerland) for approval as a treatment for multiple sclerosis in USA and Europe, and obtained approval in USA in 2010 [54]. Pharmacological activities of FTY720 include immune adjustment [55], atherosclerosis alleviation [56], and anti-fungus [57].

Nucleosides (Adenosine, cordycepin, HEA)

Adenosine

Adenosine is a metabolite of adenine nucleotides. It's an FDA approved drug in the USA and widely used for arrhythmia management [58]. Adenosine is an indicator for quality evaluation of *C. sinensis*. The content of adenosine in *C. cicadae* mycelium and *C. cicadae* fruiting body is 1.90 mg/g and 3.437 mg/g, which is higher than that in *C. sinensis* (0.48 mg/g) [38,59]. Pharmacological studies showed that adenosine has beneficial effects on central nervous system [60], cardiovascular disorders [61], anti-platelet aggregation, radiation resistance and anti-tumor effect [62].

Cordycepin

Cordycepin is the first active ingredient of nucleosides isolated from fungi, displaying notable cytotoxicity. Li et al. [63] found that cordycepin concentration in *C. cicadae* mycelia was 2.77 mg/g, substantially higher than that in *C. sinensis* and equivalent to those in *Cordyceps militaris* (*C. militaris*). Cordycepin concentration in *C. cicadae* fruiting body is 0.736 mg/g [38]. Cordycepin exhibits biological activities such as anti-tumor [64], anti-microbial [65], anti-HIV effects [66], immunomodulation and endocrine modulation [67] as well as lowered serum cholesterol and lipoprotein levels. At present, cordycepin has been manufactured into drugs mainly intended for leukemia treatment, which have been under clinical trials.

N6-(2-hydroxyethyl) adenosine (HEA)

Endogenous nucleosides and their analogues may participate in pain modulation [68,69]. The level of HEA in *C. cicadae* fruiting body was 7.025 mg/g [38]. HEA is the pivotal quality

indicator for *C. cicadae*. HEA can bind to α -receptors, thus exerting analgesic effect by curbing neurotransmitter release. Mechanism underlying pain regulation of HEA is different from that of opioid analgesics, so there is no dependence following treatment of HEA and is safer for clinical application. The great commercial potential in cancer treatment is worthy expecting [70]. Other researches revealed that HEA might be involved in calcium ion and myocardial contraction, which was beneficial to cardiovascular disorders [71]. In addition, its protective effect on renal ischemia-reperfusion injury in mice was proved [10].

Ergosterol and its Peroxides

Ergosterol and its peroxides are isolated from *C. cicadae* mycelium. Ergosterol possesses anti-oxidative capacity and is a precursor of vitamin D2 [72]. Ergosterol peroxides have many bioactivities such as anti-tumor, anti-inflammatory, anti-viral and anti-atherosclerosis activities. It also inhibited T cell activation and proliferation induced by PHA activation and works as an immunosuppressor [73]. Zhu et al. [9] reported that ergosterol peroxides (12.5 $\mu\text{g/ml}$) from *C. cicadae* ameliorated TGF- β 1-induced renal fibroblast proliferation and fibronectin expression, thus combating progression of renal fibrosis.

Cyclic Heptapeptide

Duarte et al. [74] obtained 5 cyclic heptapeptides from *C. cicadae*, including bassintin, bassintin A, beauvericin, beauvericin A and beauvericin B. Bassintin and bassintin A exhibit significant inhibitory effect on platelet aggregation induced by adenosine diphosphate (ADP) in rabbit ($\text{IC}_{50}=1.4\times 10^{-4}$ mol/l) [75]. Pharmacological studies showed that beauvericins could against convulsion and tumor and had effect on arrhythmia and sedation [76]. Wang et al. [77] revealed that beauvericin J, beauvericin and beauvericin A from *C. cicadae* suppressed multiple drug-resistance hepatocellular carcinoma Hep G2/ADM cells, with a IC_{50} of 2.40-2.93 μM that far lower than 71.8 μM for doxorubicin.

Polysaccharide

Polysaccharide has distinct bioactivities sharing with other TCM, such as anti-tumor, anti-bacteria, anti-virus, anti-radiation and anti-aging. Polysaccharides are also used for beautifying and moisture-holding of skin [78] and lowered blood glucose levels [79]. Recently, its immunomodulatory effect becomes the hotspot. *C. cicadae* polysaccharides significantly enhanced host's immunity by enhancing phagocytic activity of reticuloendothelial cells in mice [13]. Takano et al. [2] also found that *C. cicadae* polysaccharide promoted Th1 immune response and up-regulated IL-2 and IFN- γ expression in Pyle collection of lymph nodes in rats [2]. No toxicity resulting from polysaccharide was found in animal toxicity test. Kim et al. [80] showed that polysaccharides derived from *C. cicadae* mycelium promoted maturity of dendritic cells, thus inducing anti-tumor immune responses.

ARTIFICIAL CULTIVATION OF *C. CICADAE*

Because of long-term excessive collection of wild *C. cicadae*, supply of wild *C. cicadae* fails to meet the market demands. Artificially cultivated *C. cicadae* is an ideal substitute in developing healthcare products, by which time cost and bacterial contamination rates can be reduced and bioactive components can be manipulated. Different cultivation techniques offer markedly different bioactive metabolites. Therefore, distinct bioactive constituents can be obtained by different cultivation methods to meet different aspects of healthcare demands.

Fruiting Body Production Based on Wild Culture Matrix

Chai et al. [81] established a novel solid-state fermentation method, by which fruit body with yellow pointed end could occur within 30 days. The Lab of Bioengineering Center of Grape King Bio Ltd also successfully cultivated fruiting body of *C. cicadae* from brown rice-based culture matrix in 2011 (Figure 2a) [7]. It took only one month to harvest fruiting bodies [7]. In 2014, professor Jian-Yi Wu of Dayeh University also reported the cultivation method for substantial fruiting body by grains-based culture matrix [82].

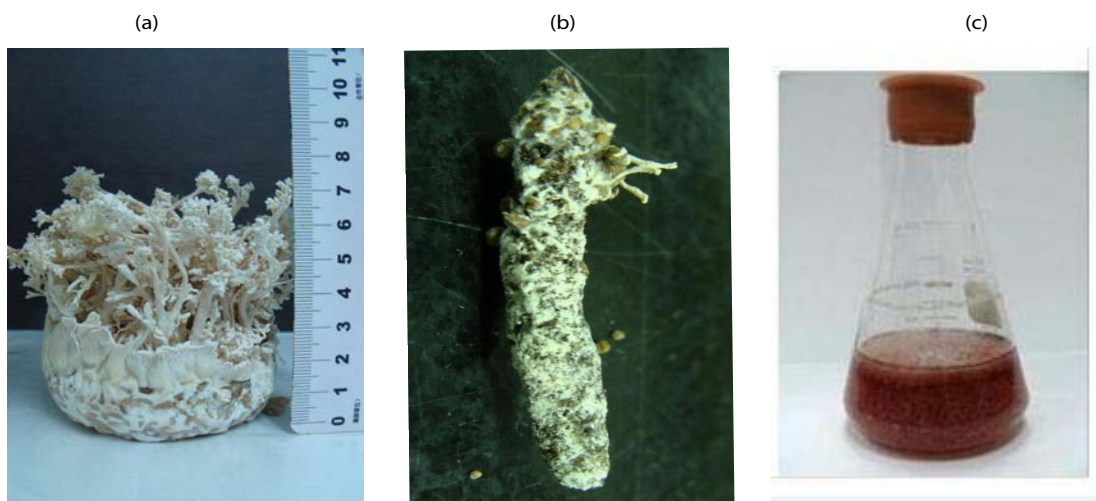


Figure 2: Artificial Cultivation of *C. cicadae*. (a) Fruiting body production based on wild culture matrix. (b) Cultivation based on infected nymphs. (c) Liquid fermentation of mycelium.

Cultivation based on Infected Nymphs

Hu et al. [83] made silkworm larva and silkworm chrysalis infected with *Paecilomyces cicadae*, and infection rates of two hosts were higher than 70%. South Korean scholar Jeong also successfully inoculated *C. cicadae* mycelia onto silkworm and developed fruiting bodies in 2009. In 2013, the Lab of Bioengineering Center of Grape King Bio Ltd cultivated 3 branches of fruiting bodies of *C. cicadae* Shing on edible mealworms (**Figure 2b**). Hosts of *C. cicadae* are not as specific as that of *C. sinensis*, indicating more feasible in terms of mass cultivation and development.

Liquid Fermentation of Mycelium

Solid-stage cultivation ties up a great deal of manpower, and the remaining matrix may affect quality of produced *C. cicadae*. Therefore, many institutions are flocking to liquid fermentation of *C. cicadae* mycelium (**Figure 2c**). Hsu et al. [84] yielded mass production of *C. cicadae* mycelium using a variety of carbon source, nitrogen source and inorganic salts combined with liquid fermentation technique in a 50-ton fermenter, offering obvious advantages of less pollution and short production cycle. Furthermore, functional component contents and physiological activity of produced *C. cicadae* mycelium was not inferior to that of wild *C. cicadae* mycelium.

SAFETY OF *C. CICADAЕ*

Reports on Mistaken Ingestion of Wild *C. cicadae*

There are many reports on mistaken ingestion of *C. cicadae* in China. People are likely to mistakenly eat *C. cicadae* and be poisoned [85]. Harvested wild *C. cicadae* are mud-covered and can easily turn mouldy if not being fully cleaned. The reason of poisoning might be attributed to molds growth under the humid storage conditions.

Food Safety Evaluation Tests

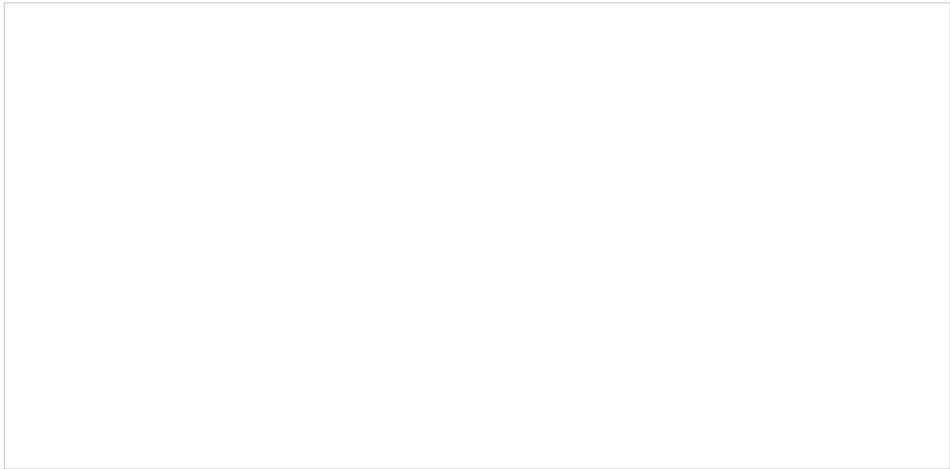
Safety evaluation of artificially cultivated *C. cicadae* is an imperative process in development of *C. cicadae*-related products. Jeong et al. [86] showed that rats were orally administered with 5% fruiting bodies of *Paecilomyces sinclairii* for 13 weeks had no significant effect on serum levels of BUN and creatinine [86]. In acute toxicity test, Chen et al. [87] demonstrated that mice were orally administrated with extracts of *C. cicadae* or *Paecilomyces cicadae* (60 g/kg) had no significant effect on mortality 72 h following treatment. Song et al. [88] found that the maximum tolerable dose of *C. cicadae* was 80 g/kg in acute toxicity test, which was 444 times higher than clinically recommended dose [88]. In the subacute toxicity test, Kwack et al. [89] revealed that mice were orally administered with extracts of *C. cicadae* or *Paecilomyces cicadae* for 14 days had no significant effect on mortality, with a LD₅₀ higher than 5 g/kg. There were no abnormalities except for decreased thymus weight in male mice [89]. Other research further confirmed that a 28-day consecutive oral administration of extracts of *Paecilomyces cicadae* at dose of 9 g/kg caused no toxicity-related lesions in rats. No toxic effect was observed in acute toxicity test (piglet) [90], 3 different test systems of genotoxicity test [84], 90-day oral toxicity test (rats) [91], as well as teratogenicity test (data unpublished) of artificially cultivated *C. cicadae* mycelium.

CONCLUSIONS

C. cicadae possesses multiple pharmacological activities that offers several featured advantages such as low toxicity, low price and easy availability of raw materials from artificial cultivation. Gene mutation rate of *C. cicadae* is only 1%, which is greatly lower than 10% seen in *C. sinensis*, indicating that *C. cicadae* has relatively stable genetic structures and expected to be easily cultivated [92]. Because of convenient cultivation technique for *C. cicadae*, a broad line of functional products and

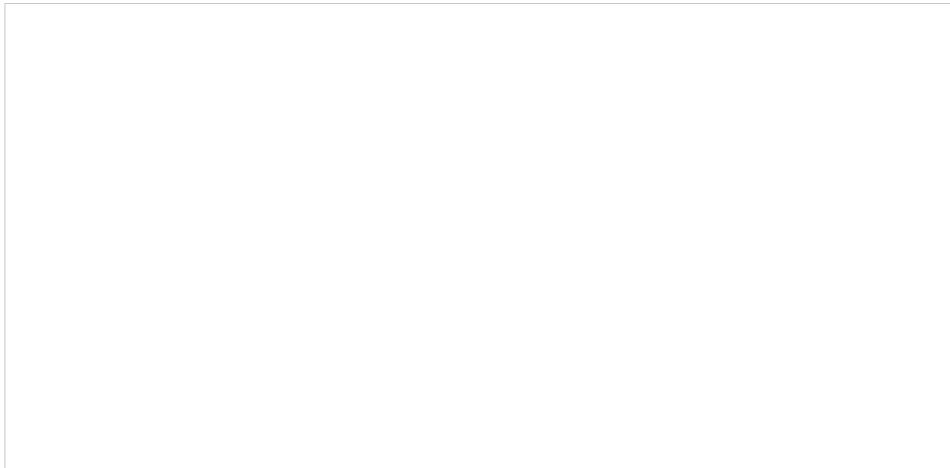
supplements can be manufactured based on fermented mycelia, incorporating healthcare foods, cosmetics, biological agriculture [93], and pharmaceuticals. At present, researches on *C. cicadae* are limited to preliminary medicinal chemistry and pharmacology studies. Further exploration on bioactive metabolites of *C. cicadae* is expected to expand its application scope and better exert its healthcare efficacy. Through advanced extraction and purification technique, bioactive components of *C. cicadae* can be used to develop botanical new drug. Development of *C. cicadae* on vision and kidney healthcare is worthy of expectation.

Video 1:



Video 1:

Video 2:



Video 1:

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