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Healthcare Functions of *Cordyceps cicadae*

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Abstract

Cordyceps cicadae (*C. cicadae*) is one of the most valued traditional Chinese medicines (TCM) and have been used for about 1,600 years in China. Both TCM works and modern pharmacological studies indicate that *C. cicadae* exhibits a variety of biological functions, including vision improvement and protection of renal function. There are at least five active ingredients in *C. cicadae*, suggesting that further exploration on bioactive metabolites of *C. cicadae* is expected to expand for its application scope and better exert its healthcare efficacy. Because of the shortage of wild *C. cicadae*, artificially cultivated is an ideal substitute. The methods we developed include fruiting body production based on wild culture matrix, cultivation based on infected nymphs, liquid fermentation of mycelium. Safety evaluation of the artificially cultivated *C. cicadae* is important in development of *C. cicadae*-related product. No toxic effect was observed in the acute toxicity test (piglet), 3 different test systems of genotoxicity test, a 90-day oral toxicity test (rats), as well as teratogenicity test of *C. cicadae* mycelium. *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, paving a broad way for functional products and supplements incorporating healthcare foods, cosmetics, biological agriculture, and pharmaceuticals.

Keyword: *Cordyceps cicadae*; *Paecilomyces cicadae*; *Isaria cicadae*; Cicadae flower; Healthcare functions; Traditional chinese medicines (TCM)

Introduction

Cordyceps. cicadae (*C. cicadae*) also known as cicadae flower, Chanhua or Sandwhe, belongs to the family *Clavicipitaceae* and the genus *Cordyceps*, which strictly parasitize on the cicada nymph or the larva of *Cicada flammate*, *Platypleura kaempferi*, *Cryptotympana pustulata* and *Patylomia pieli*. The host larva were consumed as nutrition and became a tightly packed mass of mycelium, then formed the flower bud-shaped stroma from the mouth, head or bottom of the cicada larva. It is a kind of wonderful biological complex of fungus and larva. The anamorph of *C. cicadae* is called as *Isaria cidadae* that was originally described by Miquel in 1838, after which many scientific names such as *Isaria basili*, *Sphaeria sinclairi* and *Paecilomyces cicadae* were developed [1].

Distribution of *C. cicadae*

C. cicadae is usually distributed in the tropical and subtropical region with temperature ranging from 18-24℃ and relative humidity of >80%. *C. cicadae* is usually grow vertically on sunny slopes at an altitude of 700-950 m. In China, they are most frequently seen in Fujian, Zhejiang, Yunnan, Sichuan and Jiangsu province or river valley of the Yunnan-Tibet Plateau [2-4]. In Japan, *C. cicadae* are mainly distributed in mountain and forest region at low altitude, south of Fukushima. In South Korea, *C. cicadae* are found on Jeju Island. In Taiwan, the fruiting body of *C. cicadae* is present in bamboo forest of northern Taiwan Mountain. Furthermore, they are also seen in Thailand, Southeast Asia, North America and Europe [5].

Record of *C. cicadae* in ancient traditional chinese medicines works

C. cicadae are one of the most valued traditional Chinese medicines (TCM) and have been used for about 1,600 years in China. 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 [6]. Its morphology was first described in *Tu-Ching Pents'ao* compiled by Song Su in the Song Dynasty that horn-like protuberances occurred on the 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* were primarily used in treatment of infantile convulsions and morbid night crying of babies, palpitation and malaria. 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

Modern pharmacological studies have indicated that *C. cicadae* exhibit a variety of biological functions (Table 1). Shi-Zhen Li claimed in *Compendium of Materia Medica* that *C. cicadae* have equivalent effect as cicada slough, so we also listed cicada slough in clinical application of *C. cicadae* (Tables 2 and 3). *C. cicadae* have 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

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Year/Author	Test Article	Bioactivity
Immunomodulation		
Activate Macrophages		
2001 Li-Qin Jin	*Paecilomyces cicadae* mycelium	Rat were intravenously injected with *Paecilomyces cicadae* (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 [10].
2008 Li-Qin Jin	Polysaccharides of Paecilomyces cicadae mycelium	*Paecilomyces cicadae* 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 [11].
Promote the Phagocytosis of Macrophage		
1996 Qiu-Yang Chi	Artificially cultivated *C. cicadae* mycelia	Lymphatic transformation experiment, the erythrocyte rosette test and EA rosette test, immunospecific rosette forming cell test (IR-FC), assay for phagocytosis of macrophages antibody titers in response to challenge by sheep red blood cells (SRBC) were conducted and results showed that *C. cicadae* could obviously boost immune system [12].
2002 Shu-Cheng Weng	*C. cicadae* extracted with the same proportion of water and methanol	*C. cicadae* promoted monocyte proliferation and human body's immunological responses, which might be attributed to the cytokines such as IL-12 and IFN-γ contained in *C. cicadae* [13].
2007 Jie-Min Song	Wild *C. cicadae*	It improved the humoral immune response and enhanced the phagocytosis of macrophage in mice [14].
2008 Jie-Zan Yang	*Paecilomyces cicadae* polysaccharides	It enhanced the phagocytosis of macrophage, spleen lymphocyte proliferation response as well as the ACP, LDH, and ARG activity in spleen [15].
Improve immune responses in the liver, kidney, spleen and thymus		
2005 Li-Qin Jin	Polysaccharides of *Paecilomyces cicadae* 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 [16].
Anti-aging Properties		
2001 Li-Qin Jin	*Paecilomyces cicadae* 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 paecilomyces could inhibit the lipid peroxidation of cell membrane, which might serve as an ideal free radical scavenger or free radicals reaction inhibitors [17].
2004 Jie-Zuan Yang	Polysaccharides of *Paecilomyces cicadae* mycelium	Aged Rats 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 [18].
Protection of Renal Function		
Alleviate Glomerulosclerosis and Improve the Chronic Renal Failure		
2011 Rong Zhu	Artificially cultivated *C. cicadae* fruiting bodies	It could effectively down-regulate the expression of type IV collagen and fibronectin (FN) and decreased production of TGF-ß1 and CTGF, which thereby reduced the risk of renal fibrosis progression to kidney failure [19].
2004 Yang Min	*Paecilomyces cicadae* mycelium	It significantly inhibited progression of chronic renal failure in rats, delivering therapeutic effect on chronic renal failure [20].
2006 Zhou-Hui Jin	*Cordyceps cicadae Shing Tang*	It effectively increased the clearance rates of blood and urine Creatinine, improved serum protein contents and lessened protein discharge in urine. *C. cicadae* improved renal tubulointerstitial lesions and protected the renal tubular function. It also regulated renal hemodynamics and triglyceride levels, reducing the serum cholesterol level [23].
2006 Lin Wang	Artificially cultivated *C. cicadae* 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 lotensin [24].
Alleviate Renal Anemia		
2007 Jie-Min Song	Mycelia of *C. cicadae*	The efficacy of *C. cicadae* on improving renal anemia was superior to that of the mycelia of *C. sinensis*. *C. cicadae* significantly increased hemoglobin content, numbers of erythrocyte and hematocrit in rats [25].
Lower Blood Glucose Levels		
2007 Jie-Min Song	Wild *C. cicadae*	Water extract of wild *C. cicadae* significantly reduced blood glucose levels in mice with diabetes induced by alloxan in a dose-dependent manner. It should be noted that *C. cicadae* also lowered the blood glucose levels in normal mice [26].
Anti-tumor Properties		
Mouse Sarcoma Cell Line (S180)		
1990 Kiho	*C. cicadae* polysaccharides	Mice were orally administrated with *C. cicadae* (20 mg/kg) resulted in 47% inhibition against S180 mouse sarcoma [27].
Leukemia Cell Line (U973 and K562)		
2006 Bai-Kun Chen	*Paecilomyces cicadae* polysaccharides	*Paecilomyces cicadae* polysaccharide elevated proliferation of human peripheral blood monocyts and directly retarded the progression of leukemia by increased secretion of hTNF-α and hINF-γ in tumor tissues after 44 hours of s treatment [28].
Lung Cancer Cell Line (PAA-1)		
2006 Bo-Zhen Lu	*C. cicadae*	Crude extract of *C. cicadae* selectively killed PAA cells in C2/M phage and significantly inhibited growth of PAA cells [29].
2010 Ju-Fen Cai	*Paecilomyces cicadae* polysaccharides	The IC_{50} of *paecilomyces cicadae* 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 *in vitro* [30].
Liver Cancer Cell Line (MHCC97H)		
2014 Hualin Wang	*C. cicadae*	Water extract of *C. cicadae* inhibited liver cancer MHCC97H cells via interfering the cellular cycle [31].
Chinese Hamster Ovary Cell (CHO)		
2014 An-Hui Chen	Solid-state fermentation of *C. cicadae* and wild *C. cicadae*	Both of them demonstrated inhibitory effect on CHO cells proliferation. The active component was moderately polar compounds including cordycepin [32].
Lower Blood Lipids		
2001 Li-Qin Jin	*Paecilomyces cicadae* mycelium	It decrease blood cholesterol and triglyceride in rats, suggesting it can be used as an ideal healthcare product for treating cardiovascular disease [10].
Analgesic, Sedation and Antipyretic Effect		

1991 Guang-Yu Liu	Wild or rtificially cultivated *C. cicadae*	Both of them significantly prolonged sleep time, shortened loss of righting reflex induced by pentobarbital, and enhanced the rate of re-onset sleep in mice. Inhibitory effect on chemical and thermal stimulation was confirmed by body writhing test and hot plate test. The inhibitory rate of 1.5 g/kg C. cicadae on chemical stimulation of acetic acid was 97.3%, similar to that of morphine [33].
Anti-fatigue Effect		
2001 Yan Wang	Fruiting body of *C. cicadae*	Fruiting body of C. cicadae could significantly prolong mice's swimming time, increase survival period of mice under the conditions of high pressure, anoxia or high temperature [34].
Anti-oxidant and Antibacterial Effect		
2008 An-Hui Chen	Fermentation broth and mycelia of liquid fermentation of *Paecilomyces cicadae*	The clearance rate of DPPH free radicals was 55.52% and 74.86% in concentrations of 5.0 mg/ml and 0.4mg/ml, respectively. The diameter of inhibition zone was 11.23 and 21.42 mm [35].
2013 Yen-Po Chen	Liquid fermentation of *C. cicadae* mycelium	*C. cicadae* protected Neuro2a cell line from Tunicamycin-induced endoplasmic reticulum stress-mediated apoptosis, and against 1-methyl-4-phenylpyridinium (MPP^+)-induced neurotoxicity in the NG108-15 cell line. Furthermore, *C. cicadae* slightly increased neurite outgrowth of PC12 cells, and neurite branch number. *C. cicadae* reduce oxidative stress and MPP^+ neurotoxicity, implying the protective potential in neurodegenerative diseases [36].
Improving Vision		
2009 Dong-Qing Cheng	Liquid fermentation of *Paecilomyces cicadae* mycelia	*Paecilomyces cicadae* inhibited the cytopathogenic effect in Vero cells by HSV-1 at concentrations ranging from 1.6-6.2 μg/ml, and the highest inhibition (152.2 %) was obtained at a concentration of 6.2 μg/ml, and was still 78.7 % at 0.8 μg/ml [37]. The efficacy in improving vision and nebula removal of cicadae flower is very likely related to the antiviral effect of its parasitic fungus *Paecilomyces cicadae*.
Anti-radiation Effect		
1991 Zhu-An Chen	*Paecilomyces cicadae*	It could protect against ultraviolet (UV) radiation [38].
Promote Bone Health		
2014 Yu-Qin Wang	Wild and artificially cultivated *C. cicadae* mycelia	It promoted proliferation of human osteoblast, which can be used in treatment of osteoporosis [39].
Anti-inflammation		
2015 Meng-Ying Lu	Solid-state fermentation of *C. cicadae* fruiting body	HEA suppressed the lipopolysaccharide (LPS)-stimulated release of pro-inflammatory cytokines by RAW 264.7 macrophages by suppressing the toll-like receptor (TLR)4-mediated nuclear factor-κB (NF-κB) signaling pathway [40].

Table 1: Physiological Activity of *C. cicadae*.

attributed to the antibiotics produced to fight fungal and bacterial infection, 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). Another great commercial potential of *C. cicadae* application lies in prevention of chronic renal failure. Wang et al. [7] showed that *C. cicadae* obviously improved renal tubular function in chronic renal failure patients with the renal tubular dysfunction [7]. Studies have also found that active ingredients from *C. cicadae* exhibit renal protection. For example, Zhu et al. [8] reported that 12.5 μg/ml ergosterol peroxides from *C. cicadae* could ameliorate TGF-β1-induced renal fibroblast proliferation and fibrtonectin expression, thus combating progression of renal fibrosis [8]. Another example is that Peng et al. [9] demonstrated the protective effect of HEA on renal ischemia-reperfusion injury in mice [9]. 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, the 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.

Year/Author	Test Article	Bioactivity
Improving Vision		
Revealing the Mystery of Medical Origin [Multi-purpose *C. cicadae* powder]		
2010 Da-Mei Hsu	Cicada slough	The clinical trials conducted in 100 patients diagnosed with vernal conjunctivitis revealed that Cicada slough could alleviate onjunctival 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 22% and 88%, respectively [41].
Combined use of urokinase and Superb *C. cicadae* Powder		
2010 Qing-Hui Kong	Cicada slough	Based on the routine application of insulin in treatment of diabetes, combined medication of urokinase and TCM superb *C. cicadae* 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 [42].
Individualized *C. cicadae* Soup Preparation		
2001 Hong-Quan Wang	*Periostracum cicadae*	Since November 1996 to December 1999, good curative efficacy of *C. cicadae* Soup Preparation has been found in 50 patients with herpes simplex keratitis [43].
Shengye powder and 5-durgs powder containing *C. cicadae*		
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% [44].
Prescriptions of the Taiping Huimin Bureau [Superb *C. cicadae* Powder]		
1986 Kai-Wei Tian	Cicada slough	Four kinds of outer barrier eye disease including acute conjunctivitis, chronic blepharitis, chronic dacryocystitis and pterygium were all cured [45].
Protection of Renal Function		
Combined use of *C. cicadae*, *Codonopsis pilosula* and Astragalus		
2000 Hai-Ying Wang	*C. cicadae* or cicada slough	Combined application of *C. cicadae*, Codonopsis and Codonopsis in treating renal disease [46].
Protection of Lung		
[*C. cicadae* Long-Zi Soup Preparation]		
2010 Yong-Xing Mao	Cicada slough	It was intended for treatment of cough caused by pneumonia [47].
[*C. cicadae* Erchen Soup Preparation]		
2007 Ying Ye	Supplemented *C. cicadae* or cicada slough	It was used in the treatment of pneumonia in children [48].

Table 2: Physiological Activity and Clinical Application of *C. cicadae* Powder.

Year/Author	Test Article	Results
2012 Mihye Jeong	Oral administration with 5% *Paecilomyces sinclairii* for 13 weeks in rats	It had no significant effect on serum levels of BUN and creatinine.
1993 Zhu-An Chen	Oral administration with extracts of *C. cicadae* or *Paecilomyces cicadae* (60 g/kg) in mice	It had no significant effect on mortality 72 h following treatment, with a LD_{50} of 14.2 ± 2.1 g/kg and 12.5 ± 2.1 g/kg.
2004 Jie-Min Song	Oral administration with *C. cicadae* for 7 days in mice	The maximum tolerable dose of *C. cicadae* was 80 g/kg, which was 444 times higher than that the clinically recommended dose.
2009 Seung Jun Kwack	Oral administration with extracts of *C. cicadae* or *Paecilomyces cicadae* for 14 days in mice	It had no significant effect on mortality, with a LD_{50} of 5 g/kg. There were no other abnormalities except for decreased thymus weight presented in male mice.
2013 Shu-Hsing Yeh	Feed adding 5% *C. cicadae* mycelium produced using artificial fermentation method	No toxic effect was observed after 28 days of feeding experiment in pig.
2015 Jui-Hsia Hsu	*C. cicadae* mycelium	No cytotoxic or mutagenic potential in the Ames test at levels of up to 5 mg/plate. In the chromosomal aberration test, *C. cicadae* mycelium also showed no genetic toxicology when exposed to the CHO-K1 cells in the presence and absence of a metabolic activation system derived from rat liver S9 mix at levels of up to 5 mg/ml. Moreover, no *C. cicadae* mycelium-related increase was observed in the bone marrow cell micronucleus test at levels of up to 5,000 mg/kg BW. Additionally, *C. cicadae* mycelium did not interfere with mouse bone marrow hematopoiesis in the proportion of polychromatic erythrocytes in the peripheral blood.
2015 Yen-Lien Chen	Oral administration with *C. cicadae* for 90 days in rats	No toxic effect was observed and the no-observed-adverse-effect-level (NOAEL) of *C. cicadae* whole broth is greater than 2000 mg/kg (as 114.3 times of recommended daily dosage for human) for rats.

Table 3: Food Safety Evaluation Tests of *C. cicadae*.

Potentially bioactive constituents of *C. cicadae*

Myriocin (ISP-1): Fujita et al [48] isolated and identified myriocin from fermented liquid of *C. cicadae* [48]. Its derivate FTY720 was developed 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 [49]. Pharmacological activities of FTY720 include immune adjustment [50], atherosclerosis alleviation [51] and anti-fungus [52].

Nucleosides: Adenosine: Adenosine is a metabolite of adenine nucleotides, which is an FDA approved drug in the USA and widely used for arrhythmia management [53]. The highest content of adenosine (1.90 mg/g) is seen in *C. cicadae* mycelium, which is 4 times higher (0.48 mg/g) than that in *C. sinensis* [54]. The content of adenosine in *C. cicadae* fruiting body is 3.437 mg/g [39]. Pharmacological studies showed that adenosine has beneficial effects on central nervous system [55], cardiovascular disorders [56], anti-platelet aggregation, radiation resistance and anti-tumor effect [57].

Cordycepin: Cordycepin is the first active ingredient of nucleosides isolated from fungi, displaying notable cytotoxicity. Li et al. [58] 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*) [58]. Cordycepin concentration in *C. cicadae* fruiting body is 0.736 mg/g [39]. Cordycepin exhibits biological activities such as anti-tumor [59], anti-microbial [60], anti-HIV effects [61], immunomodulation and endocrine modulation [62] 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 [63,64]. The level of HEA in *C. cicadae* fruiting body was 7.025 mg/g [39]. HEA is the pivotal quality indicator for *C. cicadae*. HEA can bind to α-receptors, thus exerting analgesic effect by curbing neurotransmitter release. The 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 [65]. Other researches revealed that HEA might be involved in calcium ion and myocardial contraction, which was beneficial to cardiovascular disorders [66]. In addition, its protective effect on renal ischemia- reperfusion injury in mice was proved [67].

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 [68]. Ergosterol peroxides have many bioactivities such as anti-tumor, anti-inflammatory, anti-viral and anti-atherosclerosis activities. It can also inhibit T cell activation and proliferation induced by PHA activation and works as an immunosuppressor [69]. Zhu et al. [8] reported that ergosterol peroxides (12.5 μg/ml) from *C. cicadae* ameliorated TGF-ß1-induced renal fibroblast proliferation and fibrtonectin expression, thus combating progression of renal fibrosis [8].

Cyclic Heptapeptide: Duarte et al. [70] obtained 5 cyclic heptapeptides from *C. cicadae*, including bassintin, bassintin A, beauvericin, beauvericin A and beauvericin B [70]. Bassintin and bassintin A exhibit significant inhibitory effect on platelet aggregation induced by adenosine diphosphate (ADP) in rabbit (IC_{50}=1.4 × 10-4 mol/l) [71]. Pharmacological studies showed that beauvericins could against convulsion and tumor and had effect on arrhythmia and sedation [72]. Wang et al. [73] revealed that beauvericin J, beauvericin and beauvericin A from *C. cicadae* suppressed multiple drug-resistance hepatocellular carcinomas Hep G2/ADM cells, with an IC_{50} of 2.40-2.93 μM that far lower than 71.8 μM for doxorubicin [73].

Polysaccharide: Polysaccharide has distinct bio-activities 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 [74] and lowered blood glucose levels [25]. Recently, its immune-modulatory effect becomes the hotspot. *C. cicadae* polysaccharides significantly enhanced host's immunity by enhancing phagocytic activity of reticuloendothelial cells in mice [75]. Takano et al. [1] 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 [1]. No toxicity resulting from polysaccharide was found in animal toxicity test. Kim et al.

[76] showed that polysaccharides derived from *C. cicadae* mycelium promoted maturity of dendritic cells, thus inducing anti-tumor immune responses [76].

Artificial cultivation of *C. cicadae*

Because of long-term excessive collection of wild *C. cicadae*, the 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 the time cost and bacterial contamination rates can be reduced and bioactive components can be manipulated (Figure 1). Different cultivation techniques offer markedly different production of 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. [77] established a novel solid-state fermentation method, by which fruit body with yellow pointed end could occur within 30 days [77]. 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, from cultivation to harvesting fruiting bodies within about one month period [6]. In 2014, professor Jian-Yi Wu of Dayeh University also reported the cultivation method for substantial fruiting body by grains-based culture matrix [78].

Cultivation based on infected nymphs

Hu et al. [79] made the silkworm larva and silkworm chrysalis infected with *Paecilomyces cicadae*, and found that the infection rates of the two hosts were higher than 70%, with higher infection rate (90%-100%) seen in the silkworm chrysalis [79]. In 2009, South Korean scholar Jeong successfully inoculated *C. cicadae* mycelia onto the silkworm and developed fruiting bodies, on which high-dose oral toxicity test was carried out afterwards. The hosts of *C. cicadae* are not as specific as that of *C. sinensis*, indicating more easy availability 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 the quality of produced *C. cicadae*. Therefore, many institutions are flocking to liquid-state fermentation of *C. cicadae* mycelium. Hsu et al. [80] yielded mass production of *C. cicadae* mycelium using a variety of carbon source, nitrogen source and inorganic salts combined with liquid fermentation technique, offering obvious advantages of less pollution and short production cycle [80]. Furthermore, the functional component contents and physiological activity of produced *C. cicadae* mycelium was not inferior to that of wild *C. cicadae* mycelium.

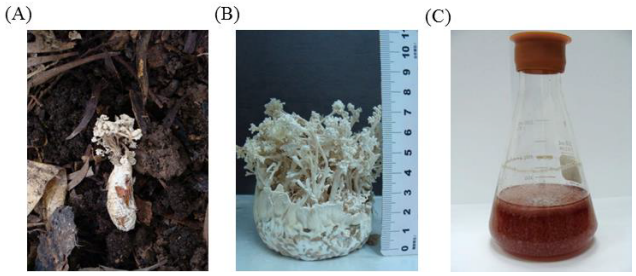

Figure 1: Wild and artificially cultivated *C. cicadae*. (A) Wild *C. cicadae*. The parasitic nymphs of C. cicadae are with pale or pale yellow bodies of about 3 cm long and 1-1.5 cm wide. The head of the nymphs were clavate and roughened, displaying white at the front. The fine mycelia or fruiting body growing within the nymph body are referred to as coremium, presenting oval shape. The stroma will develop on the nymph body and extruded from the soil. The stroma usually has 3-4 branches in antler-like, cylindrical or rod-like shape, which form flower bud-shaped stroma. (B) Solid-state fermentation of *C. cicadae*. (C) Liquid fermentation of *C. cicadae*. After several days of inoculation, the color of the fermented fluid was turned purple.

Safety of *C. cicadae*

Safety evaluation of the artificially cultivated *C. cicadae* is an imperative process in development of *C. cicadae*-related products due to variance in bioactive components resulting from diverse cultivation procedures.

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 [81]. 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

Jeong et al. [82] showed that rats were orally administered with fruiting bodies powder of the *Paecilomyces sinclairii* in concentration of 5% for 13 weeks had no significant effect on serum levels of BUN and creatinine [82]. In the acute toxicity test, Chen et al. [83] 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, with a LD_{50} of 14.2 ± 2.1 g/kg and 12.5 ± 2.1 g/kg, respectively [83]. Song et al. [84] found that the maximum tolerable dose of *C. cicadae* was 80 g/kg in acute toxicity test, which was 444 times higher than that the clinically recommended dose [84]. In the subacute toxicity test, Kwack et al. [85] 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 LD_{50} of 5 g/kg [85]. There were no other abnormalities except for decreased thymus weight presented in male mice. 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 the acute toxicity test (piglet) [86], 3 different test systems of genotoxicity test [80], a 90-day oral toxicity test (rats) [87], as well as teratogenicity test (data unpublished) of *C. cicadae* mycelium produced using artificial fermentation method.

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. The gene mutation rate of *C. cicadae* is only 1%, which is greatly lower than 10% seen in the *C. sinensis*, indicating that *C. cicadae* has relatively stable genetic structures and expected to be easily cultivated [88]. Because of the 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, 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, the bioactive components of the *C. cicadae* can be used to

develop botanical new drug. Development of *C. cicadae* on vision and kidney healthcare is a worth expecting project.

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