Review Paper

Cordiceps sinensis: The Chinese Rasayan- Current Research Scenario

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ABSTRACT

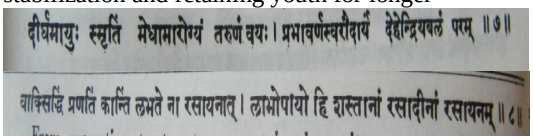
Cordiceps sinensis is age old herb in traditional Chinese herbology. It has been widely researched. It is true Rasayan (Rejuvenator / Antiaging) herb as it is immunomodulator, adaptogen, antioxidant, anti-cancer, neuroprotective, nootropic, aphrodisiac and hepatoprotective. Additionally it protects kidney, GIT , provides stamina and relieves fatigue. This review is an abridged version as the volume of research is really too much to be contained in small article. But this article does provide the panoramic view of the work undertaken.

Key words

Cordiceps sinensis, Rasayan, Anti aging, Anti oxidant, Immunomodulator, adaptogen

INTRODUCTION

The Rasayan branch of Ayurveda deals specifically with and Rasayan herbs and formulations that bestows upon the user, the longevity with age stabilization and retaining youth for longer[1]



दीर्घमायुः स्मृतिं मेधामारोग्यं तरुणं वयः। प्रभावर्णस्वरौदार्यं देहेन्द्रियबलं परम् ॥७॥

वाक्सिद्धिं प्रणतिं कान्तिं लभते नरः रसायनात्। लाभोपायो हि शस्तानां रसादीनां रसायनम् ॥८॥

From the rasayan treatment, one attains longevity, memory, intelligence, freedom from disorders, youthful age, excellence of luster, complexion and voice, oratory, optimum strength of physique and sense organs, respectability and brilliance. It means the attaining the excellent Rasa etc.

These antiaging attributes will also incorporate being Adaptogen, Antioxidant Immunomodulator**,** Aphrodisiac, Anticancer, Neuroprotective, Nootropic and Hepatoprotective.

1.2 Scientific classification

Kingdom: Fungi
Subkingdom: Dikarya
Phylum: Ascomycota
Subphylum: Pezizomycotina
Class: Sordariomycetes
Subclass: Hypocreomycetidae
Order: Hypocreales
Family: Clavicipitaceae
Genus: Cordyceps Species
Spp. about 400 described species
C. bassiana (Bals.-Criv.)
C. gunnii
C. militaris
C. ophioglossoides
C. sinensis
C. subsessilis (Petch)
C. unilateralis

Random amplified polymorphic DNA (RAPD) markers are used to investigate genetic variation and evolutionary relationships of 29 samples of Cordyceps sinensis from different geographical populations on the Qinghai-Tibet plateau. Out of 137 RAPD bands scored, 100 are polymorphic. A correlation is revealed between geographical distance and genetic distance. The molecular phylogenetic tree suggests that the 29 samples are divided into three notable clusters, corresponding to the geographical populations, i.e., the north population (NP), middle population (MP), and south population (SP). The NP consists of 7 northern samples from Menyuan, Maqu, and Luqu, the MP consists of 8 samples from Yushu and Chengduo, and the SP consists of 14 samples from Byma Snow Mountain, Renzhi Snow Mountain, Chongcaoxiwa, and Dacaodi. It is demonstrated that extensive genetic diversity is found among different geographical populations of C. sinensis. The genetic diversity pattern of C. sinensis may be caused by the founder effects. The taxonomic status of NP, MP, and SP populations should be that they are different subspecies rather than different species.[2]

1.3 Names in other languages:

English: Cordyceps mushroom, caterpillar fungus
Japanese: Totsu kasu, tochukasu
Chinese: Hia tsao tong tchong, dongchongxiacao [chongcao]*
Nepali: Yarsagumba, Jeebanbuti, Sanjivani, Kiraghans
Tibetian: Yarchakunbu, dbyar rtswa dgun 'bu**

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Chinese: Dong chong xia cao
Japanese: Tochukaso
* The translation in English- Summer-grass winter-worm
**In Tibetan, it is called Yarchakunbu, which literally means 'Yar' for rain; 'Cha' for plant; 'Kun' for winter; and 'Bu' for insect. So, the literal meaning of Yarchakunbu becomes summer plant winter insect.

Tibetan people consider it as a 'Bu', which means living insect. In Buddhism, the collection of 'Bu' is considered as a sin act, which may be the reason of Yarsagumba being protected in the Himalayas for thousands of years.

The botanical name of Yarsagumba comes from a latin word 'Cord'and 'Ceps' which mean club and head respectively. So, the meaning derived from its Latin name is an insect with its head in a horse's tail like body.[3]

1.4Morphology:
It is 5-15 cm long and 0.14 to 0.4 cm thick and resembles a caterpillar in shape and colour. It has a black or brown stem about 2-5cm long. Based on colour, it has 2 types. The whitish yellow is larger and good in quality. The other type is of copper colour and is smaller as well as qualitatively compromised.

There are 310 types of fungus of this genus but three of them are found to have medicinal value. Among these three, the Cordyceps sinensis is found to have the best quality. Two other species of Cordyceps that are used as medicines are Cordyceps millitaris and Cordyceps barnesii, found in Korea.

1.5 Cultivation of Cordyceps sinensis:
Since native Cordyceps (wild Cordyceps sinensis) is rare and very expensive, countries like China and Korea have been investing a great effort in research for cultivation of this fungus. However, the exact method of cultivation of this fungus has not still known in Nepal. Some individuals and business organization are working on in this aspect. In 1982, Institute of Materia Medica, Chinese Academy of Medical Sciences isolated the commercial strains of Cordyceps for the first time. This strain named CS-4 was fermented in aseptic environment to develop a mycelium, which underwent extensive human testing, and clinical trials during the 1980's. In this way, commercial production of Yarsagumba begun from China in the name of JinShuiBao capsules. A wide range of population was encouraged to use it as a clinical trial in order to establish its chemical composition, therapeutic activity, toxicity and many other facts.[4]

1.6 Cordiceps history:

The fungus cordyceps (Cordyceps sinensis, Ophiocordycipitaceae) has been known as an effective tonic and aphrodisiac in Traditional Chinese Medicine (TCM) and is increasingly used in China as a popular dietary supplement and/or medicine. Owing to the upsurge in consumer demand for this ingredient in the past few decades, Tibetan peoples have been gathering increased amounts of cordyceps over the high-altitude expanses of Tibetan regions, and this activity has become one of their most important sources of income in certain parts of the country. Prices rose significantly from the early 1980s until 2008,at which point they dropped due to the global economic crisis.[5, 6, 7]

Cordyceps is also renowned within other international markets, and it is available in several countries around the world, where it is sold in different forms. Although not as highly prized in the Tibetan traditional system of medicine as in Chinese medicine, the fungal ingredient is included in the materia medica of Tibetan medicine. Its first citation in Tibetan medical treatises actually pre-dates its reference in Chinese texts by a few centuries.

This article analyzes the use of cordyceps among Tibetans with particular reference to its classification and therapeutic properties, gathering and processing, combination with other medicinal substances in Tibetan medicine, as well as its use on the popular level.

Data in this article were obtained during several field-research trips conducted by the authors in different Tibetan cultural regions: Lithang and Dardo/Kangding Counties (Ganzi/Kandze Tibetan Autonomous Prefecture, Sichuan Province, China), where the authors spent 9 months during 2 consecutive vegetative seasons in 1999 and 2000; the region of Baragaon located in Mustang District, central Nepal (2001); and Repkong/Tongren County (Huangnan Tibetan Autonomous Prefecture) and Rushar, Huangzhong County (Xining Prefecture-level city) in Qinghai Province, China (2007).

Excerpts from Tibetan medical treatises have been thoroughly examined, particularly the Mennag chewa rinsel (Ten Millions of Instructions: a Relic), written by the famous Tibetan doctor Zurkhar Namnyi Dorje in the 15th century[8], the Tibetan materia medica that the Mongol Jampal Dorje compiled in the 19th century,[9] and a few modern treatises devoted to Tibetan pharmacopeias and medical preparations [10, 11, 12]

1.7 Economic value and the soaring prices of Cordiceps:

Following economic liberalization in the early 1980s, cordyceps prices increased dramatically from Chinese yuan (CNY) 1,800 (8 CNY = $1 USD in 2005) per kg in the Tibetan capital Lhasa, to CNY 8,400 in 1997 (an increase of 366%), then to CNY 36,000 in 2004 (a further increase of 1,900%). In June 2005, prices in Tibet ranged from CNY 10,000–60,000 (USD 1,250–7,500) per kg. Yet in late 2008, due to the global crisis, prices went down significantly. [13, 14]

2. MODERN METHOD OF CULTURING MODIFIED CORDICEPS

The mushroom species Cordyceps sinensis has long been used in folk medicine throughout the Orient. It has only been in the last few years however that Science has had the ability to thoroughly analyze this mushroom, and identify the bioactive compounds present. In the course of our research with cultivated Cordyceps strains over the last five years, we have noted that there is perhaps a greater biodiversity of compounds within different strains of this single species, than in almost any other organism we have analyzed. Due to the great difference in the concentration of native compounds, a wide range of quality is found in Cordyceps cultivated from different strains and utilizing different culture methodology. This article looks at the techniques and methods we have used in the development of hybridized strains of Cordyceps sinensis, and the modifications of their culture parameters such as light, oxygen concentration, temperature, substrate and mineral composition, with the goal of producing artificially cultivated Cordyceps for the health supplement trade, which contains the maximum content of scientifically recognized bioactive compounds. The techniques and methods detailed in this article offer great promise in allowing cultivators of Cordyceps sinensis and other Cordyceps species to take their artificially cultivated products to a higher and more consistent level of quality**.** [15]

3. CHEMISTRY:

3.1 Chemical constituents-

Important components of Cordyceps sinensis

Sn	Component	Unit	Value
1	D-mannitol	mg/g	76.81
2	Polysaccharide	%	11.2
3	Protein	%	25.44
4	Viatamin A	mg/g	0.315
5	Viatamin B12	mg/g	0.02
6	Zinc	Ppm/g	13.9
7	Copper	Ppm/g	2.8

Source: China Science Institute Shimyang Edible Center

3.2 Chemical composition of Cordyceps sinensis

S.N.	Component	Unit
1.	Water	10.84%
2.	Fat	8.4%
3.	Coarse protein	25.32%
4.	Coarse fiber	18.53%
5.	Carbohydrate	28.9%

There are a number of components like deoxy-nucleosides produced by Cordyceps sinensis, such as the compounds 2', 3' deoxyadenosine which is marketed in the United States as a drug for the treatment of AIDS under the trade name "Didanosine" (Holliday et al.). Similarly Quinic acid derived from Cordycepin (3' deoxyadenosine) present in Cordyceps is found to have anti viral and antibacterial property. [3]

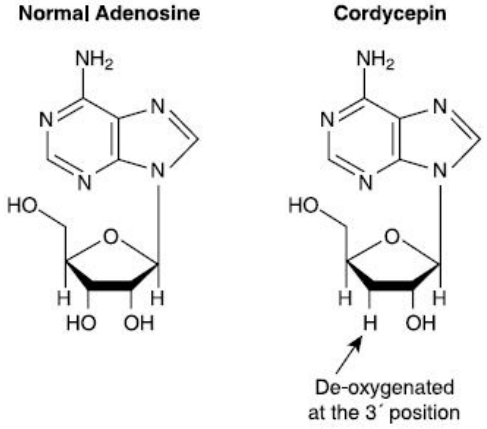
3.3 Nutritional Constituents

Cordyceps contains a broad range of compounds, which are considered nutritional.[23,24] It contains all of the essential amino acids, vitamins E and K, and the water-soluble vitamins B1, B2, and B12. In addition, it contains many sugars, including mono-, di-, and oligiosaccharides, and many complex polysaccharides, proteins, sterols, nucleosides,and trace elements (K, Na, Ca, Mg, Fe, Cu, Mn, Zn, Pi, Se, Al, Si, Ni, Sr, Ti, Cr, Ga, V, and Zr).

3.4 Potentially bioactive constituents

Cordycepin [30-deoxyadenosine] and cordycepic acid [D-mannitol] were the initial bioactive compounds first isolated from C. militaris. Chen and Chu[16] announced the characterization of cordycepin and 20-deoxyadenosine, using nuclear magnetic resonance (NMR) and infrared spectroscopy (IR) in an extract of C. sinensis. Other components found included various saccharides and polysaccharides, including cyclofurans, which are cyclic rings of five-carbon sugars, whose function is yet unknown, beta-glucans, beta-mannans, crosslinked beta-mannan polymers, and complex polysaccharides consisting of both five- and six-carbon sugars joined together in branching chains, employing both alphaand beta-bonds. Many other nucleosides have been found in Cordyceps, including uridine, several distinct structures of deoxyuridines, adenosine, 2030-dideoxyadenosine, hydroxyethyladenosine, cordycepin [30-deoxyadenosine], cordycepin triphosphate, guanidine, deoxyguanidine, and altered and deoxygenated nucleosides, which were not found anywhere else in nature (structure given below). Of particular note are various immunosuppressive compounds found in Cordyceps, including

cyclosporin, a constituent of the species C. subsessilis [anamorph: Tolypocladium infalatum]. Other immunosuppressant compounds have also been found in Isaria sinclairii, a species closely related to Cordyceps.[17]



Some of the unique nucleosides found in Cordyceps.

3.5 Polysaccharides

In the fungal kingdom, and particularly in Cordyceps, polysaccharides are perhaps the best known and understood of the medicinally active compounds.[18,19] A number of polysaccharides and other sugar derivatives, such as cordycepic acid [D-mannitol], have been identified. Research has shown that these polysaccharides are effective in regulating blood sugar,[20] and have antimetastatic and antitumor effects.[21] Proteins and nitrogenous compounds Cordyceps contains proteins, peptides, polyamines, and all essential amino acids. In addition, Cordyceps contains some uncommon cyclic dipeptides, including cyclo-[Gly-Pro], cyclo-[Leu-Pro], cyclo-[Val-Pro],cyclo-[Ala-Leu], cyclo-[Ala-Val], and cyclo-[Thr-Leu].Small amounts of polyamines, such as 1,3-diamino propane, cadaverine, spermidine, spermine, and putrescine, have also been identified. Sterols A number of sterol type compounds have been found in Cordyceps: ergosterol, Delta-3 ergosterol, ergosterol peroxide, 3-sitosterol, daucosterol, and campeasterol, to name a few.[22]

3.6 Other constituents

Twenty-eight saturated and unsaturated fatty acids and their derivatives have been isolated from C. sinensis. Polar compounds of Cordyceps extracts include many compounds of alcohols and aldehydes.[22] Particularly interesting are the range of polycyclic aromatic
hydrocarbons produced by C. sinensis as secondary metabolites. These PAH compounds react with the polypropylene used in common mushroom culture bags, resulting in the production of byproducts toxic to Cordyceps that stunt its growth as time progresses.
Eventually, these polypropylene=PAH byproducts will kill the organism.
C. sinensis must be grown in glass or metal containers.[23] The PAH compounds are present in the living culture,but are volatile compounds and are lost upon drying.

4.DOSAGE

In general, clinical trials have been conducted using 3–4.5 g of C. sinensis per day, except in cases of severe liver disease, where the dosage has usually been higher, in the range of 6–9 g=day. [17,24]

5 PHARMACOLOGICAL AND CLINICAL PROPERTIES

5.1 IMMUNOMODULATION:

5.1.1 Chinese tonifying herbs such as herba cistanche, ganoderma and cordyceps, which possess antioxidant and/or immunomodulatory activities, can be useful in the prevention and treatment of age-related diseases. Pharmacological studies on Yang and Yin tonifying herbs suggest that Yang tonifying herbs stimulate mitochondrial adenosine triphosphate (ATP) generation, presumably through the intermediacy of reactive oxidant species, leading to the enhancement of cellular/mitochondrial antioxidant status. Yin tonifying herbs, however, apart from possessing antioxidant properties, exert mainly immunomodulatory functions that may boost a weak immune system and may also suppress overreactive immune responses. The abilities of Yang and Yin Chinese tonifying herbs to enhance ATP generation and to exhibit antioxidant and/or immunomodulatory actions are the pharmacological basis for their beneficial effects on the retardation of aging. [25]

5.1.2 Animal model of chronic renal failure (CRF) was induced in wistar rats by 5/6 nephrectomy. Half of the rats were treated with Cordyceps sinensis (CS) in form of decoction. It was found that CS has mitogenic effect on spleen lymphocytes, and is capable of increasing the production of IL-2 from splenocytes of the CRF rats. IL-2 absorbency of the splenocytes was promoted by CS. CS also exhibited such therapeutic effects on CRF animal as to decrease the level of BUN and serum creatinine and to increase the level of hemoglobin. These results indicate that CS has a regulative effect on cellular immunity in CRF rats.[26]

5.1.3 While the drug cyclosporin has allowed some advances in medicine, facilitating the transplant of

organs, there has been a drawback to its use. The high toxicity of cyclosporin has caused many patients suffer from serious kidney damage, related to the use of the drug. In 1995, a study was undertaken in China in which 69 kidney-transplant patients were given either cyclosporin alone or in conjunction with C. sinensis, at 3g=day. After 15 days it was clearly evident that the group receiving C. sinensis in addition to cyclosporin had a much lower incidence of kidney damage than the group receiving only cyclosporin, as
measured by the levels of urinary NAG, serum creatinine, and blood urea nitrate.[27]

5.1.4 It is also used in the treatment of immune disorders and as an adjunct to modern cancer therapies (chemotherapy,radiation treatment, etc.).[22]

5.1.5 Cordyceps sinensis is a fungus that has been used for over 2,000 years in China as a treatment for a variety of conditions including infectious diseases. The available evidence suggests a hypothesis that any efficacy of C. sinensis as an anti-infective therapeutic would be related to a role as an activator of innate immune responses. The objectives of this study were first to investigate the ability of C. sinensis to activate pro-inflammatory responses in macrophages in vitro and induce protective responses against intracellular pathogens in vivo, and second to characterize a method of action. We found that C. sinensis activates murine macrophages to produce a variety of pro-inflammatory cytokines. IFN-γ synergizes with C. sinensis to amplify this response. Bacterial endotoxin contamination was ruled out as a potential artefact. The evidence presented in this study supports a hypothesis that C. sinensis activates macrophages by engaging Toll-like receptors and inducing mitogen-activated protein kinase (MAPK) pathways characteristic of inflammatory stimuli.[28]

5.1.6 It was shown by flow cytometry analysis that crystalized preparation of Cordyceps sinensis (Cs-Cr) caused significant elevation of the number of T helper cells and Lyt-1/Lyt-2 (T helper to T suppressor cell) ratio both in peripheral blood and the treated mice spleen. The spleen weight, phagocyte counts and phagocytic activity were also elevated in the treated group. In addition, Cs-Cr could protect T helper cells from the immunosuppressive effects of prednisolone acetate and cyclophosphamide. These results further substantiate the fact that Cs-Cr is an immunoregulator/biological response modifier of cellular immunity and may be potentially useful in handling immunodeficient or immunosuppressed patients.[29]

5.1. 7 Cordyceps sinensis (CS) is a traditional Chinese medicine with immunomodulatory effect and is effective in improving the survival of lupus mice. In the present study we isolated a pure compound (H1-A) from CS and investigated its effect on inhibiting autoimmune disease progression in MRL lpr/lpr mice. Our results demonstrated that MRL lpr/lpr mice treated daily with H1-A (40 μg/kg/d orally) for 8 weeks had a progressive reduction in anti-ds-DNA production (optical density value decreased from 0.172 ± 0.009 to 0.112 ± 0.015) when compared with the control group (optical density value increased from 0.141 ± 0.036 to 0.198 ± 0.047). In clinical presentation, the treated group had a reduction in lymphadenopathy, a delayed progression of proteinuria, and an improvement in kidney function. Histologic analysis of kidney tissue indicated that H1-A could inhibit the mesangial proliferation that was evident in lupus nephritis. However, there was no significant change in immune complex deposition. The studies reveal that the pure compound (H1-A) may be potentially useful for treating systemic lupus erythematosus in human patients, and they provide some questions for further investigation of the pathogenesis of systemic lupus erythematosus and lupus nephritis.[30]

5.1.8 Previous studies suggest that down-regulation of the major histocompatibility complex (MHC) antigens on the cell surface of certain tumors results in an escape of immune surveillance. Cordyceps sinensis is well known for its modulatory effect on host immune system. To investigate the modulatory effect of Cordyceps sinensis on MHC class II antigen expression on hepatoma cells, immunostaining with monoclonal antibody (MAb) L243, against the HLA DR region of MHC class II antigens on human hepatoma cell line HA22T/VGH was analyzed by using flow cytofluorimetry. The study concludes that VGH-CS-ME-82, either alone or with IFN-gamma induction, increases the MHC class II antigen expression on hepatoma cell line HA22T/VGH, which will shed light into the present immunotherapy, and make the host immune surveillance more effective against tumor cells with down-regulated MHC class II antigen expression.[31]

5.1.9 The effects of early application of cordyceps sinensis alcohol extractive (CSAE) on myocardial injury, level of serum IFN-gamma and splenic T lymphocyte subset in murine viral myocarditis (VMC) was studied.
100 male BALB/c mice were divided randomly into control group (CG), infectious group (IG) and CSAE therapy group (CTG). Mice in IG and CTG were infected with Coxsackie virus B3 (CVB3). The 14-day survival rates and myocardial histopathology were observed. Serum IFN-gamma

level was detected by ELISA and splenic CD3+, CD4+, CD8+ T lymphocytes were detected by flow cytometry.
Serum IFN-gamma level and the percentage of splenic T lymphocyte subset in IG were decreased significantly, and CD4+/CD8+ T cell ratio increased significantly as compared with those of CG. Myocardial lesions in CIG were attenuated, while the 14-day survival of mice 85% (vs IG 55%, P<0.05), serum IFN-gamma and the percentage of splenic CD3+, CD8+ T lymphocytes in CTG were significantly higher than those in IG. There were no significant differences of the percentage of T lymphocyte subset and CD4+/CD8+ T cell ratio between CTG and CG.
CSAE plays an important protective role against viral-induced murine myocarditis by inducing IFN-gamma and regulating T lymphocyte.[32]

5.1.10 The effect of Cordyceps sinensis (CS) on peripheral NK cells from healthy persons and leukemia patients were studied. The results showed that CS could argument the NK cell activity, meanwhile, the dose-dependent effect was found within the range of dosage adopted (r = 0.984, P less than 0.01; r = 0.988, P less than 0.01). Furthermore, CS could also improve the CD16 marker expression on lymphocytes and the binding capacity to K562 cells. Cytotoxicity could not present when the PBNCs were co-incubated with CS. These results suggested that CS could be exploited and utilized as an approach of biological responsive modifier therapy (BRMT) in the treatment of leukemia.[33]

5.1.11 The immunosuppressive effect of cultured Cordyceps sinensis (Bei Lin Capsule) was studied in vitro and in vivo. When the drug was added from 0.6 mg/ml to 5 mg/ml a significant dose-dependent inhibition effect was shown in the following immune reactions of mice (P less than 0.05-0.01): phagocytic function of peripheral blood leucocytes assayed by chemiluminescence; mitogenic response of spleen lymphocytes to Con A; mixed lymphocyte culture and LPS induced interleukin-1 release of macrophages. The survival rate of mice spleen lymphocytes cultured with Cordyceps sinensis 5 mg/ml in 37 degrees C 5% CO2 for 5 days was more than 80%. Cordyceps sinensis 4 g/kg daily significantly prolonged the mice skin allograft survival time (12.7 +/- 2.2 days v.s. 8.3 +/- 0.7 days in the control, P less than 0.01) and its immunosuppressive effect was close to that of Cyclosporin A 5 mg/kg daily on skin allograft.[34]

5.1.12 Broiler chicks were orally dosed with a hot-water extract of mycelia from Cordyceps sinensis (CS-HW) to assess possible substitution of Avilamycin as an antibiotic growth promoter (AGP). The growth performance (body weight gain and survivability) and the health index (the microflora in the small intestines and the antibody titer to Newcastle disease virus) of chicks were significantly improved in the CS-HW (600 mg/kg diet) and the Avilamycin (20 mg/kg diet) fed group in comparison with the control group ($p < 0.05$). The Avilamycin-fed group and the CS-HW-fed group had similar growth performances but the latter gave a better microbial flora in the small intestines. These results indicate that CS-HW enhances the physiological activity in chicks and can be used as a substitute for AGPs.[35]

5.2 ADAPTOGENIC ACTIVITY:

5.2.1 This study was conducted to investigate the chemical component of the hot water (HW) fraction of mycelia of Cordyceps sinensis and its antifatigue and antistress effect against a stimulus in vivo using rats and mice. The growth of mycelia reached a maximum level of 31.6 g/l after 120 h of incubation. The main chemical composition of the HW fraction of mycelia of C. sinensis was found to be carbohydrate (78.9%) with 5% moisture. The swimming endurance capacity of mice orally administered with the HW fraction (150 and 300 mg/kg/d, respectively) was significantly prolonged from 75 to 90 min with a lessening of fatigue. When the HW fraction (150 mg/kg/d) was given to rats for 8 d including a 48 h stress period, the weight changes of the adrenal gland, spleen, thymus, and thyroid, which is an index of stress, were suppressed. The HW fraction also significantly inhibited the increase in total cholesterol and the decrease in alkaline phosphatase levels as biochemical parameters of immobilization stress in rats.[36]

5.3 ANTIOXIDANT ACTIVITY:

5.3.1 Chinese tonifying herbs such as Herba Cistanche, Ganoderma and Cordyceps, which possess antioxidant and/or immunomodulatory activities, can be useful in the prevention and treatment of age-related diseases. Pharmacological studies on Yang and Yin tonifying herbs suggest that Yang tonifying herbs stimulate mitochondrial adenosine triphosphate (ATP) generation, presumably through the intermediacy of reactive oxidant species, leading to the enhancement of cellular/mitochondrial antioxidant status. Yin tonifying herbs, however, apart from possessing antioxidant properties, exert mainly immunomodulatory functions that may boost a weak immune system and may also suppress overreactive immune responses. The abilities of Yang and Yin Chinese tonifying herbs to enhance ATP generation and to exhibit antioxidant and/or immunomodulatory actions are the pharmacological basis for their beneficial effects on the retardation of aging.[37]

5.3.2 Cordyceps, one of the well-known traditional Chinese medicines, consists of the dried fungus Cordyceps sinensis growing on the larva of the caterpillar. It is commonly used for the replenishment of body health. One of the known pharmacological effects is its anti-oxidation activity. However, there is a great variation of the quality in different sources of Cordyceps. Here, the water extracts of various sources of natural C. sinensis and cultured Cordyceps mycelia were analyzed for their anti-oxidation activity by using three different assay methods such as the xanthine oxidase assay, the induction of hemolysis assay and the lipid peroxidation assay. The results showed that Cordyceps, in general, possesses a strong anti-oxidation activity in all assays tested. However, both natural and cultured Cordyceps showed the lowest inhibition in the lipid peroxidation when compared with the other two assay methods. The cultured Cordyceps mycelia had equally strong anti-oxidation activity as compared to the natural Cordyceps. Besides, the anti-oxidation activities were increased to 10–30 folds in the partially purified polysaccharide fractions from the cultured Cordyceps mycelia, which suggested that the activity could be derived partly from Cordyceps polysaccharides.[38]

5.3.3 A water-soluble polysaccharide named CPS1 had been isolated from C. sinensis mycelium by hot water extraction, ethanol precipitation, anion-exchange, and gel-permeation chromatography. UV spectra, FTIR spectra, partial acid hydrolysis, PMP precolumn derivation, periodate oxidation and Smith degradation studies were conducted to elucidate its structure. The results indicated that CPS1 was a glucomannogalactan with the monosaccharide composition of glucose: mannose: galactose = 2.8: 2.9: 1. The total carbohydrate content of CPS1 was 99.0%. The weight-average molecular weight was 8.1 x 10(3) Da. The results predicted (1-->2) and (1-->4)-linkage of mannose, (1-->3)-linkage of galactose, (1-->) and (1-->3, 6)-linkage of glucose composed the backbone of CPS1. CPS1 was also evaluated for its antioxidant activity in vitro, including scavenging effects on the hydroxyl radicals, the reducing power, Fe(2+)-chelating activity, scavenging effect on superoxide radicals, as well as the inhibition of hydrogen peroxide induced haemolysis. CPS1 showed a high antioxidant effect, especially scavenging effect of hydroxyl radicals, the reducing power and Fe(2+)-chelating activity. The results provide scientific support for the antioxidant activity and indicated a connection between antioxidant activity and reparation of renal failure.[39]

5.3.4 The effects of purple sweet potato anthocyanin (SPA) and Cordyceps mushroom extract (CME) on lipid peroxidation, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and cognitive deficits were examined. Both SPA and CME exhibited DPPH radical scavenging activities with similar potency. In contrast, only SPA was shown to effectively inhibit lipid peroxidation initiated by Fe2+ and ascorbic acid in rat brain homogenates. Furthermore, SPA markedly enhanced cognitive performance, assessed by passive avoidance test in ethanol-treated mice. Combined treatments with SPA and CME did not significantly influence the effects of SPA alone. These results demonstrate that anthocyanin prepared from purple sweet potato exhibits memory enhancing effects, which may be associated with its antioxidant properties. [40]

5.4 Anti-Cancer

5.4.1 We investigated the effect of the water extract of Cordyceps sinensis(WECS) on liver metastasis of Lewis lung carcinoma(LLC) and B16 melanoma(B16) cells in mice. C57BL/6 mice were given a s.c. injection of LLC and B16 cells and sacrificed 20 and 26 days after tumor inoculation, respectively. WECS was daily administered p.o. to the mice in a dose of 100mg/kg body weight(wt.) in the experiment of LLC and in a dose of 100 or 200mg/kg body wt. in the experiment of B16 from one week before tumor inoculation to one day before the date of sacrifice. The tumor cells increased in the thigh in LLC-inoculated mice and in the footpad in B16-inoculated mice. The relative liver wt. of the tumor-inoculated mice significantly increased as compared to that of the normal mice due to the tumor metastasis, as verified by the hematoxylin-eosin staining pathological study in the LLC experiment. The relative liver wt. of the WECS-administered mice significantly decreased relative to that of the control mice in both the LLC and B16 experiments. WECS showed a strong cytotoxicity against LLC and B16 cells, while cordycepin(3'-deoxy-adenosine), an active component of WECS, was not cytotoxic against these cells. These findings suggest that WECS has an anti-metastatic activity that is probably due to components other than cordycepin.[41]

5.4.2 The survival time of mice inoculated with murine B16 melanoma cells and treated with a combination of water extracts from C. sinensis and the conventional agent, methotrexate, has been shown to be significantly longer than that of either the untreated control group or those treated with methotrexate alone, indicating that some water extracts of C. sinensis may be beneficial in the prevention of tumor metastasis.[42]

5.4.3 Antitumor and immuno-stimulating activities were observed in the treatment of mice inoculated with Sarcoma 180 tumor cells, when treated with an ethanol extract of C. sinensis [43](the reference

refers to Paecilomyces japonica, which is believed to be an anamorph of C. sinensis),

5.4.4 A study using murine models verified that oral administration of a hot water extract of C. sinensis consequently resulted in the activation of macrophages, thereby increasing the production of GM-CSF and IL-6, which act on the systemic immune system.[44]

5.4.5 In a study of mice subcutaneously implanted with lymphoma cells, oral administration of an extract of C. sinensis led to a decrease in tumor size and a prolonged survival time.[45] Furthermore, mice treated with cyclophosphamide, which suppresses immune function, also treated with the same hot water extract saw their immune function return to normal, as measured by the IgM and IgG response and macrophage activity.[45]

5.4.6 Further evidence of the immunoenhancing action of C. sinensis was provided by another study treating mice inoculated with Erhlich ascites carcinoma (EAC) cells with a warm water extract of Cordyceps. The median survival time of the treated mice compared to untreated controls was over 300%, and the lack of activity of the extract against EAC cells grown in vitro indicated that the antitumor effect in the mice may be mediated through immunoenhancing activity, rather than directly.[46]

5.4.7 In a related study, B-(1-3)-D-glucan, fraction CO-1 and the galactosaminoglycan fraction CO-N, derived from C. ophioglossoides, inhibited the growth of ascitic Sarcoma 180. Increased immune function was noted as well, quantified by an increase in carbon clearance activity.[47,48]

5.4.8 Oral administration of polysaccharide fractions CI-P and CI-A, derived from C. sinensis, in doses of 1–10 mg=kg=day, demonstrated antitumor activities in mice inoculated with Sarcoma 180. Similar results were observed with an alkali soluble polysaccharide (CI-6P), derived from the species C. sobolifera, when administered in doses of 10 mg=kg=day.[17]

5.4.9 It is well established that numerous fungal derived simple- and protein-bound polysaccharides exert a significant potentiation of immune function.[19] This is thought to be one of the major mechanisms of antitumor activity in Cordyceps.

5.4.10 Among the multiple polysaccharides produced by C. sinensis, beta-d-glucans are one class of polymers that have been shown to increase both innate and cell-mediated immune response. These polysaccharides increase the production of such cytokines as TNF-a, interleukins, interferons, NO, and antibodies by the activated immune cells. This activation of immune response may be triggered by polysaccharide binding to specific receptors on the surface of the immune systems cells, called the CR3 receptor.[49]

5.4.11 The extracts of chloroform (1) and methanol (2) from Antrodia camphorata (AC), and chloroform (3) and n-butanol (4) fractions of methanol extract from Cordyceps sinensis (CS), and hexane (5), ethyl acetate (6), and methanol (7) from Cinnamomum osmophloeum bark (CO) were evaluated for their anti-inflammatory as well as tumor-cell growth inhibitory activities in vitro. All the tested extracts dose dependently inhibited the enhanced production of inflammatory mediators such as nitric oxide (NO) through reducing inducible NO synthase expression, and cytokines (tumor necrosis factor (TNF)-alpha and interleukin (IL)-12 in LPS/IFN-gamma activated murine peritoneal macrophages. Taken together, these data suggest that the anti-inflammatory and anti-cancer properties of AC, CS, and CO might result from the growth inhibition of NO, TNF-alpha and IL-12, and tumor cells proliferation, respectively.[50]

5.4.12 While there are a wide range of reported uses of Cordyceps sinensis in the literature, the reports that extracts of this fungus may alter apoptotic homeostasis are most intriguing. However, there are significant challenges regarding research surrounding Cordyceps sinensis, such as the difficulty identifying the various species of Cordyceps and the many conflicting reports of pharmacological function in the literature. In this review we outline what is known about the ability of Cordyceps sinensis to alter apoptotic homeostasis, attempt to reconcile the differences in reported function, identify the challenges surrounding future Cordyceps sinensis research, and delineate options for overcoming these critical hurdles.[51]

5.5 NEUROPROTECTIVE AND NOOTROPIC ACTIVITIES:

5.5.1 The effects of purple sweet potato anthocyanin (SPA) and Cordyceps mushroom extract (CME) on lipid peroxidation, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and cognitive deficits were examined. Both SPA and CME exhibited DPPH radical scavenging activities with similar potency. In contrast, only SPA was shown to effectively inhibit lipid peroxidation initiated by Fe2+ and ascorbic acid in rat brain homogenates. Furthermore, SPA markedly enhanced cognitive performance, assessed by passive avoidance test in ethanol-treated mice. Combined treatments with SPA and CME did not significantly influence the effects of SPA alone. These results demonstrate that anthocyanin prepared from purple sweet potato

exhibits memory enhancing effects, which may be associated with its antioxidant properties.[52]

5.6 Anti depressant activity:

5.6.1 Cordyceps sinensis (CS) has been known as a component of traditional medicines that elicit various biological effects such as anti-fatigue, immunomodulatory, and hypoglycemic actions. Since it has been well-established that fatigue is closely related to depression, this study used the tail suspension test (TST) in mice to examine the antidepressant-like effects of hot water extract (HWCS) and supercritical fluid extract (SCCS) of CS. Immobility time in the TST was reduced by administration of SCCS (2.5-10 ml/kg, p.o.) dose-dependently though it was not reduced by treatment with HWCS (500-2000 mg/kg, p.o.). Neither HWCS nor SCCS altered locomotor activity in the open field test, excluding the possibility that the effect of SCCS is due to activation of locomotion. Pretreatment with prazosin (an adrenoreceptor antagonist) or sulpiride (a dopamine D2 receptor antagonist) reduced the effect of SCCS on the immobility time. In contrast, pretreatment with p-chlorophenylalanine (p-CPA, a serotonin synthesis inhibitor) did not alter the anti-immobility effect of SCCS. The last finding is consistent with an additional observation that SCCS had no effect on head twitch response induced by 5-hydroxy-L-tryptophan in mice. Taken altogether, these results suggest that SCCS may elicit an antidepressant-like effect by affecting the adrenergic and dopaminergic systems, but not by affecting the serotonergic system.[53]

5.7 APHRODISIAC ACTIVITY

5.7.1 Erectile dysfunction is one of the important health problems affecting man and his partner. Recently, many treatments have evolved for the treatment of erectile dysfunction or sexual health. Of the available treatments several are pharmacologically proven and tested medications. However, in Asia, there are significant users of unproven medications for sexual health. These medications are traditionally used by the folklore living in the countryside. These untested medications may have a profound effect on the body system and their interactions with other medications may be harmful. However, comprehensive accounts of such medications are unavailable. This paper descriptively highlights the common medications used for sexual health in Asia.[54]

5.7.2 Preclinical data on the effects of C. sinensis on mice showed sex-steroid-like effects.[17, 24]

5.7.3 Human clinical trials have demonstrated similarly the effectiveness of Cordyceps in combating decreased sex-drive and virility.[14,44]

5.7.4 Human clinical trials have demonstrated similarly the effectiveness of Cordyceps in combating decreased sex-drive and virility.[55,56]

5.8 CARDIO- AND CEREBROVASCULAR ACTIVITY

5.8.1 In studies of patients suffering from chronic heart failure, the long-term administration of Cordyceps, in conjunction with conventional treatments—digoxin, hydrochlorothiaside, dopamine, and dobutamine—promoted an increase in the overall quality of life. Thisincluded general physical condition, mental health, sexual drive, and cardiac function, compared to the control group.[57]

5.8.2 The administration of 65% alcohol extracts of Cordyceps sinensis can counteract the arrhythmias induced by aconitine or BaCl2 in rats, and increase the tolerant dose of ouabain to produce the arrhythmias in guinea pigs. The drug can reduce the heart rate of anesthetic rats, decreasing the contractility of isolated papillary muscle or atria in guinea pigs, but showing no effect on the automatic rhythmicity and the functional refractory period of the atria.[58]

5.9 STAMINA AND ATHLETIC PERFORMANCE IMPROVEMENT

5.9.1 Cordyceps sinensis contains a factor that stimulates corticosteroid production in the animal model. However, it is not known whether this drug acts directly on the adrenal glands or indirectly via the hypothalamus-pituitary axis. In the present study, we used primary rat adrenal cell cultures to investigate the pharmacological function of a water-soluble extract of Cordyceps sinensis (CS) and the signaling pathway involved. Radioimmunoassay of corticosterone indicated that the amount of corticosterone produced by adrenal cells is increased in a positively dose-dependent manner by CS, reaching a maximum at 25 microg/ml. This stimulating effect was seen 1 h after CS treatment and was maintained for up to 24 h. Concomitantly, the lipid droplets in these cells became small and fewer in number. Immunostaining with a monoclonal antibody, A2, a specific marker for the lipid droplet capsule, demonstrated that detachment of the capsule from the lipid droplet occurs in response to CS application and that the period required for decapsulation is inversely related to the concentration of CS applied. The mechanism of CS-induced steroidogenesis is apparently different from that for ACTH, since intracellular cAMP levels were not increased in CS-treated cells. However, combined application with calphostin C, a PKC inhibitor, completely blocked the effect of CS on steroidogenesis, suggesting that activation of

PKC may be responsible for the CS-induced steroidogenesis.[59]

5.9.2 Cordyceps Reduces Fatigue

Several studies with animals have demonstrated that Cordyceps sinensis increases the cellular energy production and oxygen supply. A double blind, placebo controlled investigation showed a marked reduction in fatigue in elderly patients when they were given three grams of Cordyceps daily. In another study, Cordyceps sinensis improved shortness of breath and reduced fatigue in patients suffering from chronic heart failure [60]

5.9.3 Cordyceps Helps Discomforts from Tired Legs

Several studies have shown that Cordyceps sinensis improves the flow of blood in the body by relaxing the smooth muscles of the blood vessels allowing them to expand. Cordyceps also improves the functioning of the heart and lungs. Cordyceps therefore prevents or reduces the contraction of blood vessels which interferes with the flow of blood vessels in the legs, the main cause of tired legs.[61]

5.9.4 Cordyceps Improves Stamina and Athletic Performance

Several studies with animals have shown that Cordyceps sinensis increases the cellular energy production and oxygen uptake.[60]
A study with mice demonstrated their improve swimming capabilities after six weeks of Cordyceps supplementation compared with a control group.[62]

5.9.5 Cordyceps Improves the Respiratory Function

Several scientific studies have demonstrated the benefits of Cordyceps sinensis in alleviating the symptoms of several respiratory illnesses including chronic bronchitis and asthma.[61]

5.9.6 In a double blind, placebo controlled study with 30 elderly volunteers Cordyceps significantly improved the maximum amount of oxygen these people were able to assimilate.[63]

5.9.7 An increase in cellular ATP [64,65] results in an increase in useful energy, in contrast to the perceived increase in energy, which occurs from the use of CNS stimulants, such as caffeine, ephedrine, and amphetamines, ultimately resulting in an energy deficiency.

5.9.8 It should be noted that in a recent study with highly trained professional athletes, C. sinensis was shown to have no appreciable effect in enhancing the performance in this group of people.[66]

5.9.9 In a placebo-controlled clinical study of elderly patients with chronic fatigue, results indicated that most of the subjects treated with C. sinensis reported a significant clinical improvement in the areas of fatigue, cold intolerance, dizziness, frequent nocturia, tinnitus, hypo sexuality, and amnesia, while no improvement was reported in the placebo group.[17,67,68]

5.9.10 Another study involving healthy elderly volunteers, with an average age of 65, tested the output performance and oxygen capacity of subjects while exercising on stationary bicycles. A portion of the volunteers consumed C. sinensis for six weeks, while others consumed a placebo. The results demonstrated that the group that consumed Cordyceps had a significant increase in energy output and oxygen capacity over the other group after six weeks.[69]

5.9.11 The time-to-exhaustion is measured for each group, which was compared and contrasted with that of the other. If the group receiving the test compound swims longer than the group on the standard diet without the test compound, then it has been determined that they had increased energy output=decreased fatigue when compared with the control group. Trials of this nature have been conducted using Cordyceps as the test compound and have invariably shown that the use of Cordyceps significantly increasesthe time-to-exhaustion in laboratory animals when compared with the control groups.[17]

5.9.12 Therapeutic applications of Cordyceps and its extracts are hypothesized to be centered primarily on the key effects of increased oxygen utilization, increased ATP production, and the stabilization of blood sugar metabolism.[22]

5.10 Cholesterol lowering activity (Anti-Hyperlipidemic):

5.10.1 In both human and animal studies, administration of Cordyceps has been associated with cholesterol and triglyceride reduction and an increase in the ratio of HDL to LDL cholesterol.[22,24,64]

5.11 Anti-Diabetes activity:

5.11.1 In one randomized trial, 95% of patients treated with 3 g=day of C. sinensis saw improvement in their blood sugar profiles, while the control group showed only 54% improving with treatment by other methods.[70]

5.11.2 In animal studies, isolated polysaccharides have been shown to improve blood glucose

metabolism and increase insulin sensitivity in normal animals.[71]

5.11.3 CS lowers blood sugar levels in genetically diabetic animals,[72]

5.11.4 Cordyceps sinensis, a well-known traditional Chinese medicine, possesses anti-tumor, immunostimulant and antioxidant activities; however, the identities of active components have not been determined. In our previous study using antioxidant activity-guided fractionation [Li et al., 2003. A polysaccharide isolated from Cordyceps sinensis, a traditional Chinese medicine, protects PC12 cells against hydrogen peroxide-induced injury. Life Sci. 73, 2503-2513], a polysaccharide of molecular weight approximately 210kDa was isolated from cultured Cordyceps mycelia by ion-exchange and sizing chromatography. The isolated polysaccharide, named CSP-1, which has strong anti-oxidation activity, contains glucose, mannose and galactose in the ratio of 1:0.6:0.75. In the present study, we demonstrated the hypoglycemic effect of CSP-1 on normal and alloxan-diabetic mice and streptozotocin (STZ)-diabetic rats. The basal glucose level did not differ significantly among the normal mice. CSP-1 (at 200 and 400mg/kg body wt./day for 7 days, p.o.), however, significantly reduced the blood glucose level by 12.0+/-3.2% and 22.5+/-4.7% in normal mice, respectively ($p<0.05$). When administered at a dose of higher than 200mg/kg body wt. daily for 7 days, CSP-1 produced a significant drop in blood glucose level in both STZ-induced diabetic rats and alloxan-induced diabetic mice. The serum insulin levels in diabetic animals were also increased by administration of CSP-1 ($p<0.05$). CSP-1 with hypoglycemic properties increased circulating insulin level in diabetic animals, which suggests that CSP-1 may stimulate pancreatic release of insulin and/or reduce insulin metabolism.[73]

5.12 GIT AND KIDNEY PROTECTION

5.12.1 Traditional views of the Cordyceps mushroom held that its consumption strengthened the kidneys. Studies have shown that much of Cordyceps' kidneyenhancing potential stems from its ability to increase 17-hydroxy-corticosteroid and 17-ketosteroid levels in the body.[22]

5.12.2 In another human clinical study, 57 patients with gentamicin-induced kidney damage were either treated with 4.5 g of Cordyceps per day or by other, more conventional methods. After six days, the group that received Cordyceps had recovered 89% of their normal kidney function, while the control group had recovered only 45% of normal kidney function. The time-torecovery was also significantly shorter in the Cordyceps group when compared with that of the control group.[22]

5.12.3 Chronic renal failure is a serious disease, one often affecting the elderly. In a study among 51 patients suffering from chronic renal failure, it was found that the administration of 3–5 g=day of C. sinensis significantly improved both the kidney function and overall immune function of treated patients, compared to the untreated control group.[74]

5.12.4 Nephrotoxic ARF model of rat was induced by IP injection of either Gentamycin or Kanamycin and treated with CS. The results of study showed that the simultaneous administration of CS with Gentamycin could protect the proximal tubular cells from Gentamycin toxicity and the use of CS after the establishment of Kanamycin nephrotoxic ARF could prompt an earlier recovery from ARF as compared with the control group. The possible mechanisms of CS on ARF include: (1) protecting tubular cell sodium pump activity; (2) attenuating tubular cell lysosome overfunction stimulated by phagocytosis of aminoglycoside; (3) decreasing tubular cell lipoperoxidation in response to toxic injury.[75]

5.12.5 The protective effect on aminoglycoside nephrotoxicity by Cordyceps sinensis in the old patient was observed. 21 old patients were randomly divided into two groups. Each group received amikacin sulfate for 6 days. In addition, group A was administered Cordyceps sinensis for 7 days and group B was given placebo. The results revealed that group A developed less prominent nephrotoxicity compared with group B as evidenced by less urinary nephro-aminoglycosidase (NAGase) and beta-microglobulin in group A than those in Group B. These results suggested that Cordyceps sinensis exerted a protective effect on aminoglycoside nephrotoxicity in the old patients.[76]

5.12.6 In order to evaluate the effect of Cordyceps sinensis (CS) on aminoglycoside (AG) induced nephrotoxicity, gentamycin was imposed on the young and old rats with CS administration. The renal tubular injury was ameliorated as evidenced by less prominent increment of BUN, SCr, sodium excretion, urinary NAGase and less severity of histopathological changes as compared with control. In addition, the use of CS could promote an earlier recovery of renal oxygen consumption insulin clearance, and sodium absorption in isolated perfused kidney from CS treated intoxicated rat than that from control. Possible mechanisms of CS on drug-induced nephrotoxicity include: (1) Accelerating the regeneration of tubular cells; (2) Protecting the sodium pump activity of tubular cells; (3) Attenuating the tubular cell lysosome hyperfunction stimulated by phagocytosis of AG as well as decreasing the tubular cell lipoperoxidation in response to toxic injury; (4) Reducing the tissue Ca++ content.[77]

5.12.7 Cordyceps sinensis (CS) is a parasitic fungus that has been used as a Chinese medicine for a long time in the treatment of nephritis. Today, the hypothesis about the pathogenesis of immunoglobulin A nephropathy (IgAN) is that nephritogenic IgA immune complexes (IgAIC) go to the kidney to stimulate resting mesangial cells to release cytokines and growth factors. These cytokines and growth factors cause mesangial cell proliferation and release matrix, chemical mediators that lead to the glomerular injury. However, nephritogenic IgAIC in humans is still unknown. To solve this problem previously, we established an in vitro model that showed that cultured human mesangial cells (HMC) stimulated with interleukin-1 (IL-1) plus IL-6 can cause mesangial cell proliferation, increasing production of chemical mediators and superoxide anion. An in vivo model also proved that this culture medium may lead to renal injury with hematuria and proteinuria. Therefore, to fractionate the crude components that can be used in the treatment of patients with IgAN, we cultured HMC, and then an HMC activating model with HMC incubated with IL-1 and IL-6 was established. We fractionated the crude methanolic extracts from fruiting bodies of CS with the use of this in vitro inhibition of HMC activation model as our assay method. In brief, the fruiting bodies were extracted by silica gel column chromatography. One out of 6 column fractions, F-2, significantly inhibited the HMC activation by IL-1 plus IL-6. The acute toxicity test with male Institute of Cancer Research mice showed no liver toxicity or mutagenicity. Then we established an IgAN animal model with R36A (Pneumococcal C-polysaccharide purified from Streptococcus pneumoniae) as antigen and anti-R36A IgA monoclonal antibody to form nephritogenic IgA-IC, which can induce hematuria and proteinuria in mice with IgA deposition in the mesangial area. The mice in the IgAN model fed with 1% F-2 in diet had significant reduction of hematuria and proteinuria together with histopathologic improvement. Therefore this fraction was then purified by silica gel column chromatography and high-performance liquid chromatography, which got a purified compound H1-A, which can suppress the activated HMC and alleviate IgAN (Berger's disease) with clinical and histologic improvement. These results give us a new regimen for the treatment of patients with IgAN in the future.[78]

5.12.8 High doses of cyclosporin A (CsA) can not be used in the long term treatment of kidney allograft recipients primarily due to severe side effects. In the present study, we investigated the potential application of Cordyceps sinensis (CS) in the long term treatment of renal transplant patients. The renal function and survival rates of grafts and patients did not show significantly different between the control group and the treatment group. However, the incidences of complications were significantly lower in the treatment group compared with that in control group with the exception of those showing acute rejection. Furthermore, the dosage and the whole blood trough concentrations of CsA were significantly lower than control group. However, there was no significant difference in the serum level of IL-2 in the two groups. Interestingly, the serum level of IL-10 in the treatment group was significantly higher than that in control group. These data demonstrat that CS may be used in combination with a low dose of CsA in the long term treatment of kideny transplant patients.[79]

5.12.9 Patients (n = 202) were divided randomly by lottery into a treatment (n = 93) and a control group (n = 109). Patients in the treatment group were treated with CS 1.0 g 3 times a day in addition to the immunosuppressive regimen given to the control group. We compared patient and graft survivals, incidence, time and severity of acute rejection episodes, chronic allograft nephropathy (CAN), hepatotoxicity and nephrotoxicity, biochemistry parameters including indicators of liver and kidney functions, fats, proteinuria, dosages, and whole blood concentrations of cyclosporine (CsA). Patient and graft survival rates, serum creatinine (SCr), and blood urea nitrogen (BUN) were not significantly different between the 2 groups ($P > .05$). Serum uric acid (UA) and 24-hour urinary total protein (24-hour UTP) were significantly lower in the treatment group than in the control group ($P < .05$). The incidences (11.83% vs 15.60%) and times to acute renal allograft rejection (23.48 +/- 7.22 vs 22.27 +/- 8.03 days posttransplantation) were not significantly different between the treated and control groups ($P > .05$). Patients receiving thymoglobulin antirejection therapy (3 cases) were fewer in the heated versus control group (13 cases; $P = .014$). The incidences of hepatotoxicity and nephrotoxicity in the treated group were 12.90% and 19.35%, significantly lower than 24.77% and 33.94% in the control group, respectively ($P < .05$). At 2 to 6 months posttransplantation, the CsA dosages in the treated group were significantly lower than those in the control group ($P < .05$). The whole blood trough CsA concentrations in the treated group were significantly lower than those in the control group at 3 to 6 months posttransplantation ($P < .05$). The decreasing trends of the 2 aforementioned parameters in the treatment group were approximately linear among treated subjects compared with approximately quadratic in the control group ($P < .05$). The incidence of CAN in the treated group was 7.53%, which was significantly lower than 18.35% in the control

group (P = .024). The 24-hour UTP level in CAN patients within the treated group was significantly lower than the control group after transplantation (P = .045). The differences in total bilirubin, SCr, serum UA, and total cholesterol levels among otherwise normal patients in the treated group were significantly lower than those among the control group (P < .05).
The use of CS may allow decreased dosages and concentrations of CsA causing fewer side effects without an increased risk of acute rejection. In addition, CS with reduced dose CsA may decrease proteinuria and retard CAN progression.[80]

5.13 HEPATOPROTECTIVE ACTIVITY:

5.13.1 In one study, Cordyceps extract was used in combination with several other medicinal mushroom extracts as an adjunct to lamivudine for the treatment of hepatitis B. Lamivudine is a common antiviral drug used in the treatment of hepatitis. In this study, the group receiving Cordyceps along with other medicinal mushroom extracts had much better results in a shorter period of time than the control group who received only lamivudine.[81]

5.13.2 In another study using 22 patients who were diagnosed with posthepatic cirrhosis,[82] after three months of consuming 6–9 g of Cordyceps per day, each patient showed improvement in liver function tests.

5.13.3 SD rats were divided into normal control group, untreated group and Cordyceps sinensis-treated group. The rats in each group were fed with corresponding drug for 4 weeks. The rat's liver collagen deposition was observed with collagen staining. Hydroxyproline (Hyp) contents in liver tissue of the rats in 3 groups were determined with HCl hydrolysis. The tissue inhibitor of metalloproteinase-2 (TIMP-2) and type IV collagen contents were observed by Envision, and matrix metalloproteinases-2 (MMP-2) activity was detected by the method of enzyme-picture. Type I collagen was detected by Western blotting. The contents of Hyp, TIMP-2, type IV collagen, and the expression of type I collagen in untreated group were significantly higher than those in the normal control group, while those in Cordyceps sinensis-treated group were significantly lower than those in the untreated group. The content of MMP-2 in untreated group was significantly lower than that in the normal control group, while that in Cordyceps sinensis-treated group was significantly higher than that in the untreated group.Cordyceps sinensis can considerably relieve the liver fibrosis, and the mechanism may be related to promoting the degradation of the collagens.[83]

5.13.4 Rats were randomly allocated into a normal control group, a model control group and a CS group. The latter two groups were administered with CCl(4) and ethanol solution at the beginning of the experiment to induce hepatic fibrosis. The CS group was also treated with CS 10 days after the beginning of CCl(4) and ethanol administration. All control groups were given corresponding placebo at the same time. At the end of the 9th week, rats in each group were humanely sacrificed. Blood and tissue specimens were taken. Biochemical, radioimmunological, immunohistochemical and molecular biological examinations were used to determine the level change of ALT, AST, HA, LN content in serum and TGFbeta(1), PDGF, collagen I and III expression in tissue at either protein or mRNA level or both of them. Cordyceps sinensis could inhibit hepatic fibrogenesis derived from chronic liver injury, retard the development of cirrhosis, and notably ameliorate the liver function. Its possible mechanism involves inhibiting TGFbeta(1) expression, and thereby, down regulating PDGF expression, preventing HSC activation and deposition of procollagen I and III.[84]

5.14 LUNGS PROTECTIVE ACTIVITY:

5.14.1 There have been trials on humans, using Cordyceps to treat many respiratory illnesses, including asthma, COPD, and bronchitis, either alone or as an adjunct to standard antibiotic therapy, and in many studies that have been conducted, it appears to be useful for all of these conditions.[85,86,87,88,89]

5.14.2 Much of its reputation for protecting the lungs, again, is believed to stem from its ability to promote enhanced oxygen utilization efficacy. In environments lacking sufficient oxygen, mice treated with Cordyceps were able to survive up to three times longer than those left untreated, demonstrating a more efficient utilization of the available oxygen. This provides support for Cordyceps' long history of use in preventing and treating altitude sickness.[85]

5.15 ANTI-INFLAMMATORY ACTIVITY

5.15.1 Its anti-inflammatory properties may prove to bring further relief to asthma patients, whose airways become obstructed, because of an allergic reaction resulting in the swelling of the bronchial pathways.[22,24]

6 Adverse effects:

6.1 This medicine may cause the following reactions to the user allergic to it Breathing problems or tightness chest; chest pain, skin rashes, itchy or swollen skin.

Studies have shown following two major side effects in some cases: Low blood sugar (hypoglycemia) and upset stomach and dry mouth.[88]

7 Conclusion : This herb is one of the thoroughly researched rasayan, rejuvenator or antiaging drug. The one field that needs the attention is the standardization, formulation of appropriate dosage forms and conducting accelerated stability studies of the same.

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