International Journal of Pharmacognosy and Life Science

E-ISSN: 2707-2835
P-ISSN: 2707-2827
www.pharmacognosyjournal.com
IJPLS 2023; 4(1): 116-120
Received: 25-01-2023
Accepted: 09-03-2023

Darpan Thapa
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, India

Akshita Giri
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, Sikkim, India

Abhijit Kundu
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, Sikkim, India

Pallab Ghosh
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, Sikkim, India

JP Mohanty
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, Sikkim, India

Corresponding Author:
Darpan Thapa
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, Sikkim, India

Cordyceps sinensis: The Shangri-La to Life

Darpan Thapa, Akshita Giri, Abhijit Kundu, Pallab Ghosh and JP Mohanty

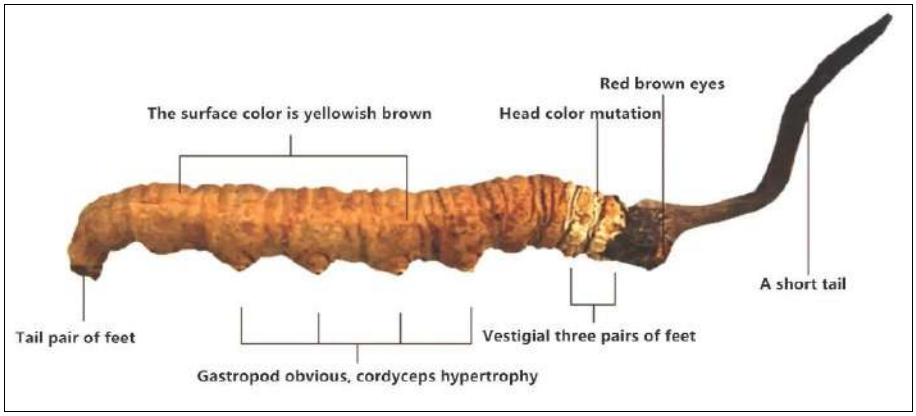
DOI: https://doi.org/10.33545/27072827.2023.v4.i1b.82

Abstract
A therapeutic fungus used in Traditional Chinese Medicine is called *Cordyceps sinensis*. Despite the wide variety of claimed applications for *Cordyceps sinensis*, the claims that its extracts may change apoptotic homeostasis are the most fascinating. However, there are several obstacles to overcome while doing *Cordyceps sinensis* research, such as the challenge of distinguishing amongst the numerous Cordyceps species and many conflicting pharmacological actions reported in the review. This review will discuss how *Cordyceps sinensis* can change apoptotic homeostasis, Identify the difficulties facing the future while balancing the variances in function and investigate the benefits of *Cordyceps sinensis* and outline potential solutions to its serious challenges.

Keywords: *Cordyceps sinesis*, apoptotic homeostasis, potential, challenges

1. Introduction
Cordyceps is an interesting genus for its characteristic parasitic habit on
Hea Tsao, Taong Chung Taog Chung, subalpine pastureland of Nepal including Jumla and Dolpa region which belongs to Karnali zone. The Yarsa Gunba; several names meaning worm in winter and grass in summer.
Cordyceps sinensis known as caterpillar fungus or Yarsagumpa, is an entomopathogenic (a fungus that grows on insects). They may be discovered in the meadows that are higher above 3,500 meters (11,500 feet) on the Tibetan Plateau in Tibet as well as in the Himalayan areas of Bhutan and Nepal. It parasitizes larvae of a Ghost moth i.e., Lepidoptera that produces a fruiting body which used to be used as an herbal treatment in traditional Chinese medicine history. Caterpillar fungus contains the compound cordycepin, and adenosine derivative.

1.2 Growth Pattern
It grows from dead caterpillars that are filled with mycelia and has a fruiting body like a plant. Firstly, the parasite Ophio *Cordyceps sinensis* feeds on moth (Lepidoptera) larvae that live underground. Second, the fungus infects the insect host's body, forming mycelium, which is then transformed into a sclerotium, without affecting the exoskeleton in any way. After the stroma of the fungus grows from the sclerotium and emerges from the ground, it is collected with the sclerotium as a whole for medicine.
After becoming afflicted by the fungus, they often pass away in the winter. In early April to late May, the fungus stroma emerges.
Caterpillar fungus is a slow-growing fungus that needs to be cultured at a relatively low temperature.



Condyceps sinensis (Berk.) Sacc. 1878

1.3 *Cordyceps sinensis* background and uses

The fungus emerges out as a parasite from the anterior part of the caterpillar of a Lepidoptera Moth, it was not possible to determine exactly to which species the host belonged, as most of its characteristics of diagnosis were found either greatly disrupted or lost. The lower caterpillar portion, in the dry state is dark brown in colour outside.

The Yarsa-Gunpa is mostly used for boosting the immune system in traditional Nepali medication. Modern pharmacological studies have proved its therapeutic effects over a varid range of diseases and conditions, such as respiratory, nervous system, renal failure, liver sclerosis, and cardiovascular diseases, anti-tumour, anti-viral, anti-cancer activity, immuno-modulating, and anti-oxidant effects, and has potential to increase the human stamina.

1.4 Anti-oxidant property

Only two studies have looked at the effects of combining Rhodiola and Cordyceps on athletes' muscle oxygen saturation and exercise performance. In a prior study, the team found that using *Rhodiola crenulata* and *Cordyceps sinensis* supplements for two weeks (2000 mg/day) helped to reduce the physiological stress caused by high-altitude exercise while also enhancing aerobic oxidation. Researchers looked examined the short-term effects of *Rhodiola rosea* and *Cordyceps sinensis* supplements (2000 mg/day) on the oxygen saturation of muscular tissue in male cyclists performing their hardest. They asserted that this supplement did not increase the muscles' oxygen saturation level. It is currently unknown, nevertheless, if chronic administration of a *Rhodiola crenulata* and *Cordyceps sinensis* combination is able to enhance health-related factors in young people.

1.5 Anticancer activity of cordycepin in mice

Using C57BL/6Cr mice, injected with B16- BL6 cells, *in vivo* tests on cordycepin were conducted to see whether it had an anticancer impact. Subcutaneous inoculation of B16-BL6 (1 106) cells was performed on mice's right paw. Two weeks after injecting the cell, the initial tumour mass was expanded and measured. Two weeks following the date of the tumour injection, the mice were given cordycepin (15 mg/kg daily) orally. This medication had no impact on the animals' body weight or systemic toxicity, but reduced the primary tumour's wet weight by 36% when compared to the untreated control mice. The findings demonstrated that cordycepin, when given orally to mice, reduces the proliferation of melanoma cells with little to no negative effects.

1.6 Isolation of polysaccharides

Wanfong Pharmaceutical Factory cultivated mycelia of Cordyceps which were employed for the polysaccharide extraction. They spent two hours being cooked in water. After centrifuging, the concentrated supernatant was treated with four volumes of ethanol till precipitation. The crude polysaccharide fraction is created by lyophilization. To get rid of any insoluble material, 500 mg of a crude polysaccharide sample were centrifuged after being suspended in water. The sample was put to a DEAE-cellulose DE52-filled column (3.5 30 cm). A buffer of 10 mM Tris-HCl pH 7.4 was used to combine the sample with 0 to 0.5 M NaCl. The sample's flow rate was discovered to be 30 ml/h. The sulfuric acid-phenol detection technique was used to track the polysaccharide profile. A 60 mg sample of a partially pure polysaccharide was obtained. Anthrone test and Assay of Bio-Rad protein were used to assess the polysaccharide and protein content of various polysaccharides.

1.7 *Cordyceps sinensis* inhibits apoptosis

Clinical trial findings indicate that this caterpillar fungus could include substances that prevent apoptosis (Zhu *et al.*, 1998) [10]. In order to evaluate *Cordyceps sinensis* capacity to prevent apoptosis *in vitro*, these clinical outcomes have produced mixed results. By preventing the peroxynitrite generator SIN-1 from generating malondialdehyde, Reactive oxygen species are purported to be scavenged by *Cordyceps sinensis*. (Zhang *et al.*, 1995). The outcomes of, hemolysis, and lipid peroxidation experiments were performed *in vitro* (Li *et al.*, 2001) [5]. Dimethyl sulfoxide DMSO, which promotes apoptosis by permeabilizing the cell membrane and up regulating nitric oxide synthase (Trubiani *et al.*, 2003), was demonstrated to be inhibited by an isolated extract of *Cordyceps sinensis* H1-A. In a rat kidney ischemia reperfusion model, Further research on *Cordyceps sinensis*' ability to regulate apoptosis revealed a significant decrease in the expression of Fas ligand, and tumour necrosis factor (TNF), and inhibits caspase-3 activity. The same is true with *Cordyceps sinensis*, which has been shown to reduce TNF expression (Kuo, *et al.*, 1996). Alcohol extracts of *Cordyceps sinensis*, however, were unable to prevent apoptosis when it was triggered by the Fas agonist antibody CH-11.

1.8 The challenge of identifying *Cordyceps sinensis*

Due to lack of a clear technique to identify its authenticity is the biggest difficulty while dealing with Caterpillar fungus. Despite the fact many recent molecular phylogenetic

investigations of the Cordyceps species have shown. (Artjariyasripong *et al.*, 2001; In the majority of these studies, *Cordyceps sinensis* has either been left out or has been included with insufficient additional taxa to allow for phylogenetic resolution between *Cordyceps sinensis* and other closely related Cordyceps species. The majority of DNA-based investigations involving Caterpillar fungus have focused on population-level rat studies of genetic differentiation.

These facts, as well as the positioning of a Hirsutella within a wider evolutionary group that also contains Cordyceps ophioglossoides, an anamorph (though with low bootstrap support) suggest that Caterpillar fungus may belong to a basal Clavicipitaceae clade that contains both entomopathogenic and fungicolous fungi. However, there is presently no direct molecular evidence indicating where *Cordyceps sinensis* belongs in a polyphyletic Cordyceps' phylogeny., and A thorough reassessment of Clavicipitaceae and Cordyceps is urgently needed.

2. Materials and Methods

2.1 Plant materials and sample preparation

We bought dried, natural *C. sines* from the sub alpine pastureland of Nepal including Jumla and Dolpa regions provided cultured Cordyceps mycelia. The department of Biology at the Hong Kong University of Science and Technology in, China, received the voucher specimen of Cordyceps. Dried samples were grind into powder. In general, cordyceps were boiled in water for medications. As a result, Cordyceps was extracted during a 12-hour period using saline phosphate buffer (PBS, pH 7.4) at 37 degrees Celsius. The supernatant was collected and lyophilized following a 10-minute centrifuged at 3,000 rpm. The sample weight was calculated based on the raw material's original weight.

2.2 Nucleosides-authentication of Cordyceps

The sample weight was calculated using the starting weight of the raw ingredients. In 1964, a similar species of Cordyceps that is frequently used as a replacement, *Cordyceps militaris*, was grown and 3-deoxyadenosine, cordycepin was isolated. Nucleosides in Cordyceps have received interest when cordycepin was demonstrated to have an anti-tumor effect. It has been discovered that Cordyceps contains more than 10 nucleosides and similar chemicals. Including adenine, adenosine, uracil, uridine, guanidine, guanosine, hypoxanthine, inosine, thymine, thymidine, deoxy uridine. However, in recent years, there has been debate regarding whether cordycepin exists in naturally occurring *C. sinensis*. A low amount of cordycepin has recently been found in natural *C. sinensis* according to several publications additionally, it was discovered that the Cordyceps mycelia in culture contain N6-(2-hydroxyethyl)-adenosine, which functions as a Ca2+ antagonist and an ion tropic agent. Adenosine has been employed as a quality control indicator for *C. sinensis*. Currently, it is believed that the active components in cordyceps are nucleosides. nucleotides play a very vital role in the central nervous system's (CNS) control and modulation of a various physiological processes. It is well known that adenosine lowers the excitability of CNS neurons and inhibits the pre-synaptic release of numerous neurotransmitters. Adenosine has anticonvulsant efficacy, which is supported by expanding pharmacological data from numerous animal seizure model disease. However, compared to dried and processed *C. sinensis*, fresh natural *C. sinensis* has a relatively little number of nucleosides, and more intriguingly, cultured Cordyceps mycelium includes a significant level of nucleosides.

2.3 Gas chromatography (GC)

By using GC-MS, the chemical make-up of Cordyceps essential oil was examined. The results showed that 72 peaks were separated of which 41 were recognised. Finding vorticial was a fascinating discovery and certain antilogs in *C. sinensis*. The former was a chemical which has a lot of structural similarities with verticine, a drug used to treat respiratory conditions. Further research is required, however it's possible that verticiol and its analogues have a role in the expectorant and anti-tussive properties of *C. sinensis*. Six hydroxyl groups make up the carbohydrate mannitol, which doesn't possess any volatile properties. A derivatizing process is necessary for mannitol analysis by GC. In order to quantify the amount of mannitol in *C. militaris*, Wang *et al.* developed a GC method. After adding 2.5 mL pyridine and 5.0 mL acetic anhydride, sample powder (75 mg) was derivatized. The reaction was allowed to run for 1 h at 90 °C.

2.4 Through activating the adenosine A3 receptor, cordycepin has anticancer properties followed by glycogen synth. Kinase -3b (GSK-3b) activation and cyclin D1 suppression

Using specific adenosine A3 receptors antagonists, in their *in vitro* studies, Yoshikawa *et al.* confirmed that adenosine A3 receptors Cordycepin works via activating receptors. These findings demonstrated that adenosine A3 receptors are expressed by B16-BL6 cells and that cordycepin binds to these receptors. The growth inhibition of B16-BL6 cells brought on by cordycepin was then countered by the GSK-3b inhibitor indirubin. Furthermore, Cordycepin reduced the quantity of cyclin D1 protein in B16-BL6 cells, according to Western blot examination. By activating adenosine A3 receptors, then the Wnt signalling pathway, which includes GSK-3b activation and cyclin D1 inhibition, cordycepin prevents the growth of melanoma cells in mouse overall. According to research done by Ko, *et al.*) cordycepin increased proteasome-dependent degradation and blocked b-catenin's nuclear translocation. Furthermore, cordycepin-reduced b-catenin. The inclusion of a GSK-3b inhibitor (SB216763) improved stability, showing that the activation of GSK-3b is the mechanism by which this stability is mediated. Their findings are a solid confirmation of ours.

3. Discussion

Invasion of the insect host by the caterpillar fungus, which uses it as a substrate to produce the mycelium, is the most crucial stage of the complete development cycle of the fungus, which is converted to sclerotium. Intentionally introducing the fungus into the insect host as a substrate to create the mycelium is too challenging since we currently have very little understanding about this process, which is the primary reason that laboratory attempts to cultivate caterpillar fungus constantly fail. (Paterson, 2008; Zhong *et al.*, 2009; Lo *et al.*, 2012; Yan *et al.*, 2014). Therefore, the majority of caterpillar fungus grows spontaneously and is harvested by locals from untamed fields. We only covered the distribution of Ophio *Cordyceps sinensis* in China's

prospective and suitable habitats in this article using MaxEnt modelling. The sole sources for the samples are our field research and literature reviews on caterpillar fungus. MaxEnt excels in modelling plants and fungi, hence validations of distribution modelling of animals and moths are quite few. Additionally, our study on moths (Lepidoptera), particularly species of Thitarodes, is quite poor. (Paterson, 2008; Zhong *et al.*, 2009; Au *et al.*, 2012). It is challenging to calculate the Thitarodes larvae distribution and investigate its susceptibility to climatic change and impact on caterpillar fungus.

3.1 Anthropogenic influence and trading

Although climate is a major factor in influencing the dispersal of species, Journal Pre-proof in recent years, anthropogenic activities have become increasingly important in the deterioration of the Caterpillar fungus. Due to its great nutritional and therapeutic value, overharvesting, commercial trade, and even illegal smuggling have become quite profitable. An analysis revealed that collecting caterpillar fungus has developed into a significant method of generating income for mountain tribes in Nepal. The income, which contributed 21.1% of the total household income and 53.3% of the total cash income, was the second-largest contributor to the household income after agricultural revenue. Caterpillar fungus sales brought in 60–78% of collectors yearly family income, with no collectors making 15-55% less than collectors. (Laha *et al.*, 2018). In rural Tibet, the gathering of caterpillar fungus provided an average of 40% of the country's financial revenue (Winkler, 2008, 2010) [18]. The price has increased in line with rising market demand, with a 35% rise in the amount given to pickers between 1997 and 2004. (Winkler, 2008) [18]. Shrestha and Bawa (2013) revealed that between 2001 and 2011, the cost of caterpillar fungus in Nepal's local markets increased by much to 2300%. Numerous studies document a sharp decline in caterpillar fungus as a result of widespread overexploitation employing a method based on numerous pieces of information that takes using the synergies between ecological models and local knowledge. The output of caterpillar fungi has reduced as a result of habitat loss, change in climatic condition and particularly overexploitation. Another study found that the Himalayan region's caterpillar fungus population was declining, between 2006 and 2010, the average harvest per collector decreased by around 50%. (Shrestha, 2012) Following the legalisation of trade in Nepal in 2001, trade volume steadily grew, and 95.1% of harvesters thought that the caterpillar fungus's abundance in the pastures was reducing and 67% considered current harvesting practices to be unsustainable (Shrestha and Bawa, 2013). Be that individual harvests have been seen to drop as the number of harvesters has increased. (Laha *et al.*, 2018).

3.2 Climate changes

The PCA results discovered that five of top ten important environmental factors were connected to the climate, including precipitation during the warmer quarter (Bio18; 16.6% of variation), mean temperature during the coldest quarter (Bio11, 3.9% of variation), annual rainfall (Bio12, 3.4% of variation), minimum temperature during the coldest month (Bio6, 2.3% of variation), and precipitation during the driest month (Bio14, 0.8% of variation).The collective role of them were 37%. Therefore, climate change should be considered as a primary and critical factor that effects the distribution of caterpillar fungus in future. The model's findings showed that Ophio *Cordyceps sinensis* thrived best at moderate elevations, with a mean elevation of 3865 m), high humidity, and low temperatures (the coldest quarter's mean temperature ranged from -22.8 °C to 8.6º, with a mean of -7.1 °C). Caterpillar fungus can only be found in the Himalayas and Tibet at high elevations due to these climate factors. Locations with the most risk and impact from global warming. In the Himalaya and parts of extreme Asia, especially at the "third pole," due to their extreme vulnerability to change of climate. The rate of global warming is currently accelerating, and continued temperature rise is predicted.

4. Conclusion

Due to its excellent nutritional and medicinal qualities, caterpillar fungus is in high demand. The main cause why caterpillar fungus has been steadily declining in the past decade has been either local output or export to other countries. Furthermore, there are no comprehensive strategy for protection and control of the collectors. Despite the influence of climate change, overharvest and intensively exploitation are regarded as the main reasons for caterpillar fungus shrinkage. Comparatively to climate change, human impact has grown in importance. The habit and long-term survival of Cordyceps face significant dangers from human activity and climate change in the years to come.

Furthermore, no molecular study has been done on *Cordyceps sinensis*. Instead, several papers describe treatment of model systems with *Cordyceps sinensis* and tracking the results. However, the foundation for identifying molecular pathways must be laid by developing a consensus strain. Currently, species may be identified phenotypically and biochemically through the use of marker chemicals and voucher specimens.

The quality control method is necessary to ensure the authenticity and excellence of cordyceps and its products. The reasonable indicators that are connected to the security and effectiveness of cordyceps are crucial. Currently, several markers are employed to check the quality of cordyceps and its derivatives, including nucleosides, ergosterol, mannitol, and polysaccharides. Unfortunately, these indicators are not fully optimised, and a lot of work still has to be done to determine exactly how these substances affect Cordyceps pharmacological effectiveness.

5. Reference

1. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, *et al.* Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Annals of internal medicine. 2015 Jan 20;162(2):123-32.
2. Nakamura K, Shinozuka K, Yoshikawa N. Anticancer and antimetastatic effects of cordycepin, an active component of *Cordyceps sinensis*. Journal of pharmacological sciences. 2015 Jan 1;127(1):53-6.
3. Buenz EJ, Bauer BA, Osmundson TW, Motley TJ. The traditional Chinese medicine *Cordyceps sinensis* and its effects on apoptotic homeostasis. Journal of ethnopharmacology. 2005 Jan 4;96(1-2):19-29.
4. Liao YH, Chao YC, Sim BY, Lin HM, Chen MT, Chen CY. Rhodiola/Cordyceps-based herbal supplement

promotes endurance training-improved body composition but not oxidative stress and metabolic biomarkers: A preliminary randomized controlled study. Nutrients. 2019 Oct 3;11(10):2357.
5. Li SP, Li P, Dong TT, Tsim KW. Anti-oxidation activity of different types of natural *Cordyceps sinensis* and cultured Cordyceps mycelia. Phytomedicine. 2001 Jan 1;8(3):207-12.
6. Li SP, Yang FQ, Tsim KW. Quality control of *Cordyceps sinensis*, a valued traditional Chinese medicine. Journal of pharmaceutical and biomedical analysis. 2006 Aug 28;41(5):1571-84.
7. Qi W, Zhou X, Wang J, Zhang K, Zhou Y, Chen S, *et al*. *Cordyceps sinensis* polysaccharide inhibits colon cancer cells growth by inducing apoptosis and autophagy flux blockage via mTOR signaling. Carbohydrate polymers. 2020 Jun 1;237:116113.
8. Chen YJ, Shiao MS, Lee SS, Wang SY. Effect of *Cordyceps sinensis* on the proliferation and differentiation of human leukemic U937 cells. Life Sciences. 1997 May 16;60(25):2349-59.
9. Li SP, Li P, Dong TT, Tsim KW. Determination of nucleosides in natural *Cordyceps sinensis* and cultured Cordyceps mycelia by capillary electrophoresis. Electrophoresis. 2001 Jan;22(1):144-50.
10. Zhu JS, Halpern GM, Jones K. The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis* Part I. The Journal of alternative and complementary medicine. 1998 Oct;4(3):289-303.
11. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: A systematic review and meta-analysis. Annals of internal medicine. 2015 Jan 20;162(2):123-32.
12. Chen YJ, Shiao MS, Lee SS, Wang SY. Effect of *Cordyceps sinensis* on the proliferation and differentiation of human leukemic U937 cells. Life Sciences. 1997 May 16;60(25):2349-59.
13. Chen YJ, Shiao MS, Lee SS, Wang SY. Effect of *Cordyceps sinensis* on the proliferation and differentiation of human leukemic U937 cells. Life Sciences. 1997 May 16;60(25):2349-59.
14. Chen S, Li Z, Krochmal R, Abrazado M, Kim W, Cooper CB. Effect of Cs-4® (*Cordyceps sinensis*) on exercise performance in healthy older subjects: A double-blind, placebo-controlled trial. The Journal of alternative and complementary medicine. 2010 May 1;16(5):585-90.
15. Ji DB, Ye J, Li CL, Wang YH, Zhao J, Cai SQ. Antiaging effect of *Cordyceps sinensis* extract. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2009 Jan;23(1):116-22.
16. Zuo-Yi LI, Yi-Jian YA, Liang ZQ, Ai-Ying LI, Pegler DN, Chase MW. Molecular evidence for the anamorph–teleomorph connection in *Cordyceps sinensis*. Mycological Research. 2001 Jul;105(7):827-32.
17. Buenz EJ, Bauer BA, Osmundson TW, Motley TJ. The traditional Chinese medicine *Cordyceps sinensis* and its effects on apoptotic homeostasis. Journal of ethnopharmacology. 2005 Jan 4;96(1-2):19-29.
18. Winkler D. Yartsa Gunbu (*Cordyceps sinensis*) and the fungal commodification of Tibet's rural economy. Economic botany. 2008 Nov;62(3):291-305.
19. Bok JW, Lermer L, Chilton J, Klingeman HG, Towers GN. Antitumor sterols from the mycelia of *Cordyceps sinensis*. Phytochemistry. 1999 Aug 1;51(7):891-8.
20. Wang Y, Yin H, Lv X, Wang Y, Gao H, Wang M. Protection of chronic renal failure by a polysaccharide from *Cordyceps sinensis*. Fitoterapia. 2010 Jul 1;81(5):397-402.
21. Nakamura K, Shinozuka K, Yoshikawa N. Anticancer and antimetastatic effects of cordycepin, an active component of *Cordyceps sinensis*. Journal of pharmacological sciences. 2015 Jan 1;127(1):53-6.