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# Biological Activity and Chemical Characterization of Different Extracts Compounds in Different *Cordyceps* Species

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**ABSTRACT**

*Natural products and resources are getting the attention of the scientific society and public communities due to their interesting and beneficial biological activities. Cordyceps are being used in traditional Chinese medication. Cordyceps distribution is diverse, including all terrestrial areas excluding Antarctica. Many extractions methods are being used for the extraction of Cordyceps and various bioactive components such as nucleosides & nucleotides, carbohydrates, ergosterols, polysaccharides, sterols, and fatty acids have been extracted. This review focuses on the Cordyceps principle extracts their vast range of pharmacological activities such as antitumor, anti-inflammatory, antioxidants, and anti-aging.*

**Keywords:** *Cordyceps,* antitumor, anti-inflammatory, antioxidants, and anti-aging activities.

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## INTRODUCTION

*Cordyceps* are group of fungi on the insects and was discoveredby Wang Ang inBen-Cao-Bei-Yao. It has been used for the purpose of medication in China for over three hundred years. 'Dong Chong Xia Cao' is the common name of this fungus which describes that it is the winter worm and summer grass and is usually referred to *Cordyceps sinensis* (Berk.) Sacc. The parasitic fungus insect lives on the larva head of a specific specie of moth (Lepidoptera) but it also grows on the other species of moth. In the 17th century, It was discovered in the West. The name *Cordyceps* was given by the Saccardo which was derived from its endorsed Chinese name *Cordyceps sinensis* (Berk.) Sacc. This nomenclature is being used for the *Cordyceps*up to the present-day. *Cordyceps*are being used as a beneficial natural product due rich abundant resources and numerous biological activities to treat various diseases. *Cordyceps* as a medicine has been used in the past especially in China and other regions of Asia. Recently, it gets more attention and importance in scientific societies and the public [1-3].

Cordycepin, polysaccharides, aminophenol, mannitol, nucleosides, sterols, and fatty acids have been reported as bioactive constituents of *Cordyceps.* Various chemical elements are extracted from the *Cordyceps*which have useful pharmacological activities.Artificial and immature cultivations generate fears in the minds and hinder it to meet at international medical standards. With the increasing attention in *Cordyceps* both for mycology and medication, further research is important to get an impression about the capability of these mushrooms. Hence, this paper has surveyed the most recent advances in the extraction techniques and their improvements for extractions of different *Cordyceps* compounds and their biological activities to cure several types of diseases, natural action and science of the class *Cordyceps* for its better use in the improvement of new medications and therapeutics for different illnesses in the future.

## BIOLOGY AND DISTRIBUTION

*Cordyceps,* including over 400 species, were verifiably ordered in the Clavicipitaceae family, depending on round and hollow asci, filiform ascospores and thickened ascus apices which frequently disarticulate into

part-spores. The *Cordyceps* are portrayed also, recognized from different genera of the family by its creation of shallow to drenched perithecia on stipitate and regularly clavate to capitate stromata, what's more, its biology as a microorganism of arthropods and the contagious genus *Elaphomyces* [4]. However, the scientific classification of the class *Cordyceps* is dubious. To refine the characterization of *Cordyceps* and Clavicipitaceae, Sung et al.assessed the phylogenetic relationship of 162 taxa dependent on investigation comprising of five to seven loci [5]. The outcomes firmly uphold the presence of three clavicipitaceous clades and reject the monophyly of both *Cordyceps* and Clavicipitaceae. The scientific classification of *Cordyceps* and Clavicipitaceae was updated to be steady with the multi-quality phylogeny. The family Cordycipitaceae is approved dependent on the kind of *Cordyceps*, C. militaris, and incorporates most *Cordyceps* species that have brilliantly shaded, beefy stromata. The new family Ophiocordycipitaceae is proposed dependent on Ophio*Cordyceps* Petch, which was upgraded. Most of the species in this family produce obscurely pigmented, extreme to flexible stromata that frequently have perithecial apices. The new variety Elapho *Cordyceps* is proposed for a subclade of the Ophiocordycipitaceae, which incorporates all types of *Cordyceps*that parasitize the contagious sort Elaphomyces and a few firmly related that parasitize arthropods. Two new species have been depicted, and arrangements of acknowledged names for species in *Cordyceps* are Elapho *Cordyceps*, Meta *Cordyceps* and Ophio*Cordyceps* [6-7,1].

*Cordyceps* distribution is diverse, including all terrestrial areas excluding Antarctica, with the stature of known species variety happening in tropical and subtropical areas, particularly east and south-east Asia. *C. sinensis* breeds in an exceptionally limited habitat and is typically found in the soil of grassland at a height from 3500 to 5000 m, primarily in regions like Sichuan, Yunnan, Gansu, Qinghai, and Tibet. *C. sinensis* was recorded in India, Nepal, and Bhutan as well. In China, more than 60 species have been found, among which *C. sinensis* and *C. militaris* are the most esteemed species flowed in the crude drug markets for use in customary Chinese medication [8-9,1].

**Chemical Characterization**

The greater pharmacological and biological effects of the *Cordyceps* species are attributed to the chemical components extracted from different species. This has led to increased research entrust in the chemical characterization of these compounds [11,12]. Greater advances have been made in the chemical analysis of *Cordyceps* species within past few years. Several analytical methods such as HPLC, Liquid chromatography, capillary electrophoresis, LC-MS, etc. have been used for the separation of different chemical constituents [13]. Modern extraction techniques based on imprinted sites such as molecularly imprinted polymers (MIPs) molecular orbital frameworks (MOFs) and covalent orbital frameworks (COFs) have led to highly selective extraction of different chemical components [14,15]. Among several biologically active compounds nucleobases nucleosides & nucleotides, carbohydrates, ergosterol, polysaccharides, sterols and fatty acids are of great importance [16]. Here we will discuss most recent advancements in the chemical extraction of these compounds.

**Nucleosides**

Nucleosides are among the major components to be found in the *Cordyceps* and more than 20 nucleosides and their analogs have been originated from natural or cultural Cordysep species. They have great biological importance as they can be used for inhibition of urinary tract infections, to promote blood circulation, and increase immune response. Moreover, the adenosine receptors have been used as therapeutic drug targets. They are also found to be the important mediators of cellular signaling that play a keen role in the protection of tissues and organs from damage [17,18].

Traditional methods such as organic solvent extraction, ambient temperature water extraction, high pressure liquid extraction and boiling water extraction have been used in the past for the extraction of active compounds from the natural or cultured*Cordyceps* species [19,20]. But recent advancement has optimized the extraction process because of their higher selectivity. High performance liquid chromatography (HPLC) based methods have got an increased entrust in nucleoside extraction due to availability of several extraction methods and high selectivity [21]. Li *et al.* used 10% methanol aqueous solution for the extraction of nucleosides from *Cordyceps* s. The flow rate was kept 1.0 mL/min for better separation and the wavelength was 260nm while 10 microliters of the solution was injected. Different extraction solvents and conditions were applied for accurate quantification and determination of guanosine, thymidine, inosine, cordycepin, adenine, and 2-deoxyadenosine components present in the solution. The ultrasonic method was used for extraction that showed excellent extraction ability but the time of extraction was90 minutes [22]. Adenosine was determined by Qian et al using online extraction pressurized HPLC method for the determination of adenosine in *Cordyceps.* Pore shell column 120 SB-Aq having 4.6 × 50 mm length and a width of 2.7μm was used for rapid detection of analyte. The powder containing *Cordyceps* sample was filled in a guard column and extraction was performed with thermal and pressurized water at 75℃ and pressured was kept at 150bar. The detection method was less than 6

minutes very low as compared to other techniques. A standard equilibrium curve was obtained within a testing range of 4.3-80.5 µg/ml. The recorded inter and intra-day precision of adenosine was (0.94% and 0.24%) respectively with a sample recovery rate of 96.1%. The authentication method was also successfully used to determine adenosine in six other *Cordyceps* species within a concentration range of 0.28 to 0.48 mg/g [23].

Solis phase extraction (SPE) is the most developed and commonly practicing nucleoside extraction technique because of its short extraction time, higher sensitivity, lessintake of organic solvents [24]. Among various available adsorbents, molecularly imprinted polymers (MIPs) have been proved more effective sorbents due to their higher selectivity, regenerate-ability, and robustness. Also, the bulk and surface imprinting techniques have made them more suitable for macromolecules like nucleoside extraction [25].Hollow molecularly imprinted polymers (h-MIPs) with boronate-affinitywere fabricated by Hu *et al.* for selective extraction of four nucleosides in injections of traditional Chinese medicines. The h-MIP surface was enriched by introduction of boronic acids groups on outer polymer shells of MIP through 3-aminophenylboronic acid. The hollow structure of h-MIPS enhanced the extraction process due to easy template removal and, accessibility to the active sites available on inner and outer surface of h-MIP. The prepared h-MIP was able to detect four types of nucleosides within the range of 0.012–0.033 µg $mL^{-1}$ with a template recovery of 63.8 to 108.9% under optimal conditions [26].Magnetic MIPs have an advantage of complete template removal and rapid extraction of the analyte on entrusting. Zhou et al prepared ferroferric oxide ($Fe_3O_4$@PDA@$Ti^{4+}$) core-shell magnetic MIPs that were functionalized with titanium ion ($Ti^{4+}$) polydopamine to selectively extract *Cordyceps* and Lentinus Edodes nucleosides. Different metals ($Ti^{4+}$ , $Al^{3+}$, $Zn^{2+}$, $Fe^{3+}$ , $Zr^{4+}$and $Mg^{2+}$ were attachedto the surface of $Fe_3O_4$@PDA particles and the extraction proficiency for four different types of nucleosides were tested and compared. The results showed that $Fe_3O_4$@PDA@$Ti^{4+}$ had the highest competencefor nucleoside extraction and was further characterized with FTIR spectroscopy, SE, TE microscopy, and by using X-ray spectroscopy. The prepared magnetic particles successfully extracted adenosine monophosphate, guanidine monophosphate, thiamine monophosphate and uracil monophosphate with in a range of 0.063 to 19.000 µg/mL with a R constant value of $R^2 > 0.999$. The sensor exhibited a very low detection limit of 0.0047 and 0.0141 µg/mL for *Cordyceps* and Lentinus edodes respectively [27].

**Polysaccharides**

Polysaccharides are among the most abundant and important components of biologically active compounds present in *Cordyceps*. They can be extracted from the fruiting bodies, fermentation broth, and mycelium of the fungi each having different physicochemical properties. Additionally, they have been also used for the quality control of *C. militarus* in different food products (28,29). Several extraction techniques by using pure water, heating buffer, and water/alkaline solutions have been used but they have several disadvantages such as low yield, high temperature, and long extraction time. Scientists have developed some novel methods such as ultra-high pressure extraction, ultrasonic-mediated extraction, microwave extraction, and subcritical water extraction. Amongst these techniques, ultrasonic-mediated extraction has gained more entrust in the extraction of polysaccharides due to high yield of extracted product [30, 31]. Luo *et al.* applied subcritical water extraction method to extract and isolate water-soluble polysaccharides obtained from *Cordyceps militarus*. Column chromatography (DAEA-52 and Sephadex G-150) was used for the separation of two polysaccharide types(CMP-$W_1$ and CMP-$S_1$)and their structural characteristics were examined. Results revealed that both of these polysaccharides had heterogeneous composition that consisted of D-mannose &glucose, and D-lactose having a molarity ratio of 2.84:1:1.29 and 2.05:1:1.09. Thefourier transform infrared(FT-IR) spectrum analysis was also performed which proposed that CMP-$W_1$ and CMP-$S_1$ relates to the pyranose type of polysaccharides [32]. Zhang *et al*. isolated an water-soluble neural polysaccharide (SDQCP-$_1$) from the fruiting body of *Cordycepsmilitarus* that was cultivated on a hull-less barley plant. Structural investigation showed that it has a composition ofmannose, glucose and galactose sugarswith a molar ratio of 13.3:1.0:9.7 and, the average molecular was 19.3 kDa. Methylation analysis, NMR, SDQCP-$_1$, and GC-MS were used for structure elucidation that revealed that it is a glucoglactomanan molecule and has a mainstay composition of (1→2)-***α***-D-Man***p*** (48.4 %) and (1 → 4)-***β***-D-Glc***p*** (1.2 %) molecules [33].Recently an enzyme-based extraction process was used by Yang et al. for the extraction of polysaccharides from *Cordyceps militarus* mycelia. Kinetic analysis was performed and optimal conditions as (cellulose concentration 2.0%, temperature 40 °C, soled-solvent ratio 1:20, and extraction PH of 4.0) yielded polysaccharide concentration of 5.99%. This extracted polysaccharide was further used for the biosorption of $Pb^{2+}$ from the aqueous solution and FT-Ir analysis was performed that showed that the adsorption of $Pb^{2+}$ was mainly due to the involvement of carbonyl, hydroxyl, and carboxylic functional groups attached to the polysaccharide core structure [34].

**Sterols and Fatty acids**

Sterols and fatty acids are also important biofunctional compounds of *Cordyceps* species. Several types of sterols and fatty acids have been isolated from the *Cordyceps* and have been found very important due to their pharmacological and biological properties. For example,ergosterol is a predominant sterol found in *Cordyceps* that can be converted into vitamin $D_2$ by using ultraviolet radiation which is useful for proper bone development and growth in humans [34, 35]. Ergosterol peroxide is another very important sterol type that has antioxidant, anticoagulant, procoagulant, and anti-tumorproperties. Zhang et al used silica gelcolumn chromatography (Sephadex LH-$_{20}$) for the separation of six compounds ergosterol, ergosterol peroxide, adenosine, and cordycepin from *Cordyceps*. The structures of these isolated compounds were determined by using spectral techniques and their physiochemical properties were determined [36]. Wang et al used repeated column chromatography using pure silica gel (Sephadex LH-$_{20}$) beforereverse phase HPLC for separation and purified isolation of 12 compounds from *Cordyceps* including ergosterol and ergosterol peroxide and their antitumor properties were determined [37].

Fatty acids can be divided into saturated and unsaturated fatty acids. Saturated fatty acids are more abundant at 57.84% while unsaturated fatty acids content was found to be 42.16%. Unsaturated fatty acids are found effective against cardiovascular diseases and a unique function of decreasing blood pressure [38]. Zhang *et al*. used simultaneous distillation extraction (SDE) and GC-MS for the separation of several volatile compounds present in *Cordycepsmilitarus*. Five fermentation products were tested and several compounds were isolated and their structure was determined. Statistical analysis suggested that fatty acids including linoleic acid and palmitic acid were found to be the major component among other constituents [39].

**Other related compounds**

Many other biologically active compounds such as metal elements, volatile compounds, amino acids, and crude proteins have been extracted that have exhibited a variety of pharmacological properties [40].

## BIOLOGICAL ACTIVITIES OF *CORDYCEPS* COMPOUNDS

Development of different cultural techniques and several extraction processes has led to great entrust in the determination of biological activities and pharmacological properties of different compounds present in *Cordyceps*. Several efforts have been made by previous researchers that reviewed biological activities and pharmacological properties of different *Cordyceps* compounds such as Zhang et al previously reviewed the biological activities of only polysaccharides in *Cordyceps*but no recent effort has been made to comprehensively describe different biological activities [41,42,43, 44]. Here we describe recent advancements made in the determination of the biological activity of different compounds present in *Cordyceps*.

**Antitumor activity**

A great variety of isolated compounds from *Cordyceps* have been found useful in antitumor activity. Cordicipine extracted from the fruiting bodies and stem of the fungi are found very effective in the regulation and enhancement of antitumor activity. It stimulates adenosine A [3] receptors and glycogen synthase kinase-3ß that hinders the development of B16 melanoma cells [45,46]. The p38MAPKs play a vital part in the instruction of maintaining equilibrium between cell death and survival when various types of cancers get developed within the body. Huang et al. studied the effect of cordycepin and it demonstrated that *Cordycepin* (3′-deoxyadenosine) specifically initiated apoptosis process within Leydig tumor cells in MA-10 mouse by managing the p38 MAPK and PI3K/AKT flagging pathways. Cordycepin diminished practicality in MA-10 and TM4 cells but was'nta reason to the death of leydig cells on modest fixation. Cordycepin expanded receptive oxygen species (ROS) levels, which is related to the initiation of apoptosis. Hindrance of p38 MAPKs movement by SB203580 essentially inhibited cordycepin-initiated apoptosis in MA-10 cells. Co-treatment with the autophagy inhibitor 3-methyladenine (3-MA) raised degrees of apoptosis in cordycepin-treated MA-10 cells. These outcomes recommended that cordycepin has been an exceptionally particular treatment to incite cell apoptosis through p38 MAPKs flagging [47]. Production of cordycepin in large quantity is difficult that makes its availability limited. Li et al. described that the availability of liver extracts enhances the production of cordycepin and also the availability of fresh air (2h/day) increases the cordycepin level in liquid-cultures of *Cordyceps militaris* after two weeks. They used the mycelia for extraction of cordycepin from *C. mililitaris* and checked their *in vivo* and *in vitro* activities against oral cancer. Obtained results demonstrated that the extract significantly inhibited the activity of SCC-$_4$ oral tumor cells, stopped the cell sequence in the $G_2$/M phase. Mitochondrial splitting and oxidative pressure were observed in the SCC-4 cells that were mixed with water extracts of *Cordyceps militarus* for 12 hours. Also the water extracts of *Cordyceps militarus* disrupted tumor arrangement of 7,12-dimethylbenzanthracene-prompted hamster buccal pocket carcinogenesis by the regulation of multiplying cell vascular endothelial development factor. The outcomes duggests that porcine liver

distillates illuminated with blue light-emanating diode and availability of fresh air can be utilized as an appropriate mechanism for the production of cordycepin, which can be utilized for therapy of oral disease [48].Yang *et al* studied the actions and molecular mechanism of cordycepine in the renal cell carcinoma Caki-1 cell line. The outcomes suggested that cordycepin was able to induce apoptotic cell death and also restricted cell migration in Caki-1 cells. Quantitative analysis were also performed by real-time PCR, western bolt analysis designated that cordycepin defined dose-dependently reduced microRNA expression and phosphorylation levels in Caki-1 cells but at the same time it caused an increase in PTEN phosphate levels. The mechanism suggested was that blocks of cordycepin regulated decrease in microRNA- 21 or an increase in PTEN concentration that resulted in reduced apoptotic cell death in renal canal cells [49].Fong *et al* investigated the inhibition effect of cordycepin derivatives on the growth of endometrial cancer cell. Cytotoxicity measures, clonogenic tests, stream cytometry were utilized to notice the impacts on apoptosis and guideline of the cell pattern of Ishikawa cells by making different groups of cordycepin, cisplatin, also the blends of these two. Cordycepin showed a critical portion subordinate inhibitory impact on cell enlargement and they also delivered more prominent hindrance impacts as compared to cordycepin only. Apoptosis examinations affirmed the capacity of cordycepin to initiate the apoptosis process in the Ishikawa cells. *In silico* outcomes showed that the MRS5698 compound is minimally exploited by ADA that have satisfactory medication resemblance and wellbeing profiles [50. Lin et al synthesized a new compound named 5'-furanoyl ester-3'-deoxyadenosine (compound B) by using cordycepin (compound A) as raw material and, then modified the synthesized compound B with the gold nanoparticles that formed a complex named (compound C). The structural morphology of compound B was investigated by using MS, $^{13}C$ NMR and $^{1}H$ NMR, while characterization of complex C was performed by using a transmission electron microscope XRD, IR and, ultraviolet-visible spectrophotometer. MTT tests demonstrated that compound A, compound B, and complex C had great inhibitory consequences for the expansion of HepG2 cells. The consequences of bacteriostatic examination demonstrated that every one of them had critical bacteriostatic impacts on *E. coli, Bacillus subtilis* and, *Staphylococcus aureus*. The antibacterial properties of complex C were researched. The outcomes indicated that the base inhibitory groupings of *E. coli, B. subtilis*, and *S.aureus* were 30,7.5, and 30µg/mL respectively [51]. Zheng *et al.* designed a study to study the inhibitory effect of *Cordycepine* on tongue tumor cells and to discover the mechanism behind the effect. He treated the CAL-27 human tongue cells with the purified cordycepin before the examination with CCK-8 assays to measure their proliferation. He also measured the progress in the cell cycle and apoptotic death by using flow cytometry. Expression of apoptosis-associated genes and proteins was determined with Real-time PCR. The intracellular assembly of reactive oxygen species was also measured by with xenograft model for determination anti-tumor activity of *Cordyceps* ***I****n vivo* **.** The outcomes suggested that cordycepin decreased the expansion of CAL-27 cells depending upon the quantity of the defined-dose (IC50 = 40 µg/mL for 24 hours). The tumor cells treated utilizing cordycepin likewise displayed raised degrees of reactive oxygen species within the cell. Also, the Cordycepin was found to be effective against development of tumor in tongue cells when tested in a murine xenograft model framework and comparable messenger RNA and protein levels *in vivo* [52].

In recent years polysaccharides have been extensively used as antitumor compounds. Zheng et al. reviewed the biologically activities of *Cordyceps* polysaccharides [53]. But recent work hasn't been described. The antitumor activity of numerous modified polysaccharide compounds has got a great entrust in recent years and has been extensively used to cure different types of human cancers. Chemical modifications considerably increase the antitumor activity of polysaccharides [54]. Shi et al reported two water-soluble polysaccharide portions named as SCP II-1 and SCP II-2 acquired from silkworm *Cordyceps* using DEAE by using segments chromatography. The portrayal of essential design was concentrated by using infrared spectroscopy elite fluid chromatography, superior particle chromatography, and nuclear power magnifying instrument (AFM). The outcomes demonstrated that the atomic mass of SCP II-1 was 35.2 kDa and 23.4 kDa of SCP II-2 respectively The atomic force microscopy AFM geography affirmed exceptionally fanned chain adaptation of SCP II-1 and SCP II-2 . Both of these parts had amazing cancer prevention agents and antitumor exercises, particularly SCP II-1 indicated preferable restraint over SCP II-2.The information proposed that these polysaccharides from silkworm *Cordyceps* are useful in food and drug industry [55]. Docetaxel-stacked acidic modified *C.* sinensis polysaccharide nanoparticles were set up by dialysis and zeta potentials, delivery rates, in vitro analysis, drug stacking limits, molecule sizes and, embodiment competences were tested *Cordyceps* sinensis (Berk)Sac. At that point, the AA-altered CSPs were examined by 1H-NMR and fourier transform-IR.. The nanoparticles were circular with a normal size of 98.91±0.29 nm and zeta potential inside the −19.75±1.13 mV. The nanoparticles had indicated great biocompatibility against tumor cells [56].Wu et al separated two polysaccharides from *Cordyceps militarus* species and checked their antitumor activity. The compound construction and

inhibitory action of polysaccharides from cordyceps on α-glucosidase was investigated. Outcomes demonstrated that construction and inhibitory movement on α-glucosidase with various formative phases had critical contrasts. The polysaccharides that were obtained from fruiting bodies would have increased inhibitory action on α-glucosidase [57]. Xu *et al*. studied and compared the polysaccharide extracts from artificially cultured and naturally occurring wild type of *Cordyceps cicadae.* Ultrasonic water process was used for extraction and purification of polysaccharides. The impacts of various polysaccharide concentrations against cytotoxicity and multiplication of Hela cells were identified by MTT and lactate dehydrogenase techniques. Results indicated that polysaccharides treatment at the concentration (25 μg/mL-1600 μg/mL) hinders the multiplication of hela cells. The consequences of stream cytometry affirmed that polysaccharides impeded the cell cycle in the S stage and enhanced apoptosis. The outcomes demonstrated that polysaccharides action repressed declaration of Cyclin E, Cyclin An, CDK2 and up managed outflow of P53 [58].These studies show that *Cordyceps* compounds have great potential for the preparation of anticancer natural drugs that will provide a great breakthrough towards non-invasive and safe medications to cure different types of cancers in humans and other animals.

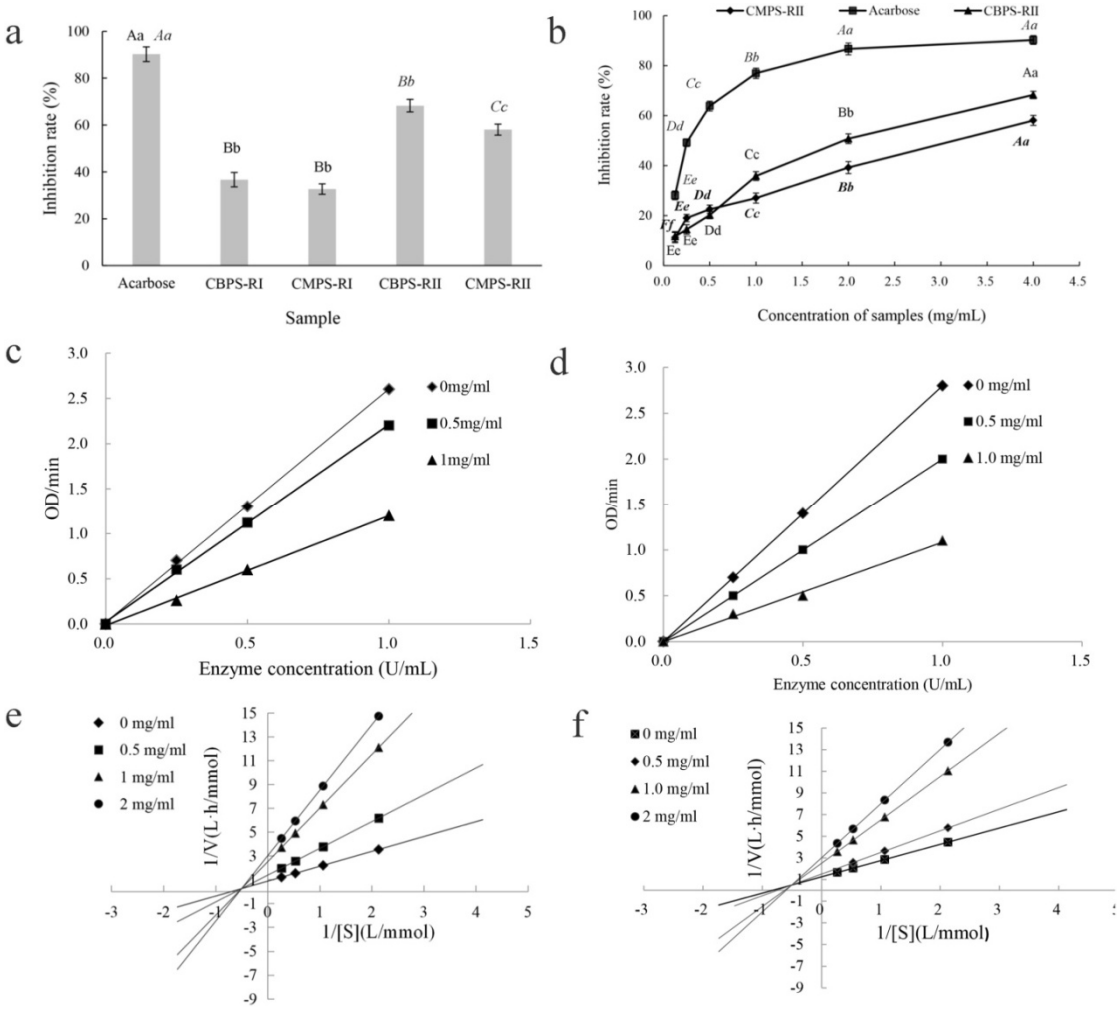


Figure1: Rates of inhibition for CMPS-RII and CBPS-RII with various purities on α-glucosidase action. (b) Inhibition rates of CMPS-RII and CBPS-RII with various concentrations on α-glucosidase movement. (c) and CMPS-RII (d); Lineweaver-Burk plots indicating hindrance energy of α-glucosidase by CBPS-RII (e) and CMPS-RII (f) [58].

**Anti-Inflammatory**

Inflammation is a protective innate response of the body to cope up with any harmful substance that enters the body and is regulated and controlled by the inflammatory response system in the body. But sometimes the response is irregular or out of control that leads to chronic inflammatory disorders like inflammatory bowel disease, arthritis, and chronic hepatitis [59, 60]. Li *et al* studied anti-inflammatory response by exopolysaccharide that was generated by a Cordyceps *sinesis* (Cs-$HK_1$) that is used as medicinal fungus. The exo-polysaccharide was purified from Cs-HK1 mycelial fermentation stock using ethanol precipitation, then dialysis and was used for further purification. The exopolysaccharide

consisted of complete sugar substance of 74.8% and a greatest normal atomic weight of more than 107 Dalton, with the major composition of glucose, mannose, and a modest quantity ribose. Within THP-1 and RAW264.7 cell societies, exopolysaccharide essentially restrained lipopolysaccharide prompted provocative reactions of cells including arrival of NF-κB.. The outcomes recommend that Cs-HK1 EPS have shown eminent anti-inflammation activity and can be possible contender for additional improvement of anti-cancer therapeutics [61]. Rupa *et al* prepared nanoemulsions of *Cordyceps* extracts and checked their anti-inflammatory, anti-oxidant and anti-microbial response. The Cordyceps nanoemulsion was characterized by utilizing field-outflow transmission electron magnifying lens, Fourier-transform infrared spectroscopy, and dynamic light dispersing .Dynamic light dispersing examinations showed that emulsions were 87.0 ± 2.1 nm wide, and zeta capability as −26.20 ± 2. The stability of nanoemulsions was checked at a various temperature in the range of (4 °C to 60 °C), while the storage capacity was checked at 4 °C. At last, in vitro anti-inflammatory activity and cytotoxicity were evaluated. The outcomes recommended that NE is not harmful to RAW 264.7 or HaCaT (human keratinocyte) cell lines up to a concentration of 100μL/mL. Further the liposaccharides - prompted RAW 264.7 cells exhibited maximum anti-inflammatory activity at 50 μg/mL and demonstrated hindrance towards NO creation. It also down regulated the anti-inflammatory gene reaction. Also, the NE displayed considerable anti-cancer activity at the concentration of (2.96 ± 0.10 mg/mL) that restrained the bacterial growth [62]. Lipids have been also found effective agents against the anti-inflammatory response of the cells. Nallathamby *et al.* described that the lipids present in ethyl acetate extracts obtained from *Codycepsmilitaris* can be useful to reduce the production of nitric oxide during the inflammatory response. The fractions of CE2 from ethyl acetic acid derivation remove didn't apply any cytotoxic impacts toward the BV2 cells at a concentration from 0.1 to 100μg/mL. The CE2 part additionally indicated a critical ($p < 0.05$) decrease in nitric oxide creation at 1-100μg/mL. At 10μg/mL, the CE2 portion weakened 85% of the NO creation in BV2 cells. Further the CE2 portion (10μg/mL) down-regulated incendiary qualities, iNOS and COX-2, and up-regulated mitigating qualities, HO-1 and NQO-1. The CE2 division diminished NO creation through the initiation of NRF2 and NF-κB records. The compound constituents of the bioactive CE2 portion were distinguished through GCMS. Eleven lipid parts were recognized including unsaturated fats, unsaturated fat esters, and sterols (63). Allergic rhinitis and asthma are normal chronic allergic illnesses that mostly effect the respiratory tract, joined by immunoglobulin E (IgE)- mediated inflammation and inclusion of eosinophils.Sacc is known as contagious parasite on the hatchling of Lepidoptera. It has been viewed as healthy food and, likewise, much more useful as compared to other known natural solutions for the treatment of asthma. Chen et al studied the antiallergic rhinitis impact of a compound named as Cs-4,that is water extract of Cordyceps *sinensis* (Berk). Treatment with Cs-4 smothered the nasal manifestations incited in OVA-sharpened and tested mice. Cs-4 treatment likewise diminished aviation route receptiveness and improved the scratching conduct within capsaicin-tested rodents. Cs-4 treatment stifled the expansions in IL-4, IL-5, and IL-13 levels in rodent lung tissue. The outcomes suggested that that Cs-4 can be a potential agent to cure the inflammatory disorders and hypersensitivity of the cells towards allergic rhinitis and asthma [64].

**Antioxidant and activity**

Cordyceps compounds have been found effective in the enhancement of antioxidant activities. They have gained a great entrust and are being enormously used as a natural ant oxidative agent. Among other *Cordyceps* compounds, polysaccharides have been used to a greater extent than the others. Chen et al. studied the antioxidant activity of polysaccharides obtained from naturally occuring *Cordyceps sinensis* (CSP) in cyclophosphamide (Cy)-induced intestinal immunosuppressed mice that had Cy-prompted intestinal injury. Enhancement of CSP concentration from25 to 50 and 100 mg/kg·bw fundamentally expanded degrees of flagon cells and bodily fluid in the digestive system with subordinate way. The arrangement of immunoglobulin A emitting cells and the secretory immunoglobulin A substance was advanced clearly in CSP gatherings. Besides, CSP essentially advanced the discharge of messenger-RNA articulations. The outcomes showed that CSP adequately promoted intestinal mucosal resistance that directed polarization of Th1/Th2 cells. [65]. Liu et al used the ***β***-glucan content for testing the antioxidant capacity of *Cordyceps* polysaccharides at different PH. RNA sequencing was used for testing the mechanism of ***β***-glucan growth. The results suggested that *Cordyceps*. *militaris* growing in the pHrange 5–7 (CMsA) was recognized due to considerable difference from the others gwowing in the pH range of 8–9 (CMsB) and their uni-genes indicated the remarkable gene expression. The average of β-glucan substance obtained fromCMsB bunch was 32.7% (w/w), 10% higher than that obtained fromCMsA. After-effects of RNA-seq indicated 1088 differentially communicated qualities among two different groups. Besides, oxidative phosphorylation-related Gene philosophy conditions were controlled in CMsB groups. Moreover, consequences of monosaccharide structure assessments, periodate oxidation and biological activity assessment estimated that *C. militaris* polysaccharides in CMsA group had higher glucan content

and higher antioxidant activities as related to other compounds in the CMsB group [66]. Hung et al. tested and described the mycelial biomass, antioxidant activity of extra-and intra-cell polysaccharides creation [EPS, IPS] of *Cordyceps militaris* strains. AG-1, PSJ-1 were assessed under various lowered fluid culture (SLC) conditions. At 24 0C mycelial biomass and polysaccharide creation of AG-1, PSJ-1 was ideal utilizing PVC media and static culture conditions. Most extreme biomass, EPS and IPS creation were seen when the underlying pH was 6.7: AG-1: 12.92 ± 0.33, 209.70 ± 1.56, 32.62 ± 0.87; PSJ-1: 9.03 ± 0.24 g l-1 , 198.16 ± 0.85 mg g-1, 30.63 ± 1.96 mg g-1, individually. The utilization 3.5 % coconut oil improved biomass, EPS, IPS creation, which were 8.27 ± 0.09, 8.01 ± 0.01 g l-1 ; 1208.00 ± 8.60, 1110.40 ± 7.20 mg g-1; 32.43 ± 0.49, 29.74 ± 0.44, for AG-1 and PSJ-1, separately. Both culture condition and stove drying techniques effectively affected H2O2. ABTS.+ revolutionary action, lipid peroxidation, had impacts on all-out flavonoid and phenolic substance. The utilization of unrefined lowered fluid culture and broiler drying on strains AG-1, PSJ-1 prompted removes with strong cell reinforcement movement, proposing the restorative utilization of polysaccharides from strains AG-1, PSJ-1 [67].

**Anti-Aging Activity**

Aging is a cycle where tissues and their related organs start to enter in the phase of deteriorating changes after the development and growth of body, joined by the slow decrease of physiological elements of the body. Recent studies have revealed an excessive concentration of reactive oxygen species (ROS) within body may cause lipid peroxidation, produce lipid peroxidation items, damage biofilms from polyunsaturated unsaturated fats, DNA, proteins and compounds, and the oxidative harm brought about by ROS was the fundamental factor prompting the maturing of the body [68]. Some of the biologically active *Cordyceps* compounds have been found very effective with their anti-aging properties. Different reviews have briefly discussed the role of different *Cordyceps* compounds as anti-agent agents [69,70]. Here a brief discussion about recent progress in the evaluation of anti-aging properties of different Cordyceps compounds.

Zhu et al extracted different types of polysaccharides from *Cordyceps cicadae* (CP) and checked their anti-aging properties. Several types of polysaccharide fraction (CP30-CP80) were extracted, isolated and their antioxidant activity was checked by in vitro methods, while in vivo analysis was performed to perfomanti-aging activities and a detailed comparison was made. The in vitro cell reinforcement action results uncovered that all the parts CP30–CP80 were powerful but the CP70 was the most strong. Quite, CP70 hindered the life anticipation of Drosophila, expanded the activity of catalase and glutathione peroxidase that restrained the arrangement of malondialdehyde. Furthermore, CP70 upregulated articulation level of cell reinforcement linked qualities. These outcomes demonstrated that CP70 may drag out life expectancy of Drosophila through the up-guideline of the articulation level of cell reinforcement related qualities in Drosophila [71]. Xerostomia also known as dry mouth is an condition mostly found in aged humans. Cordycepin is found effective against anti-aging effects. An in vitro model that comprised of hydrogen peroxide initiated salivary hypofunction was used to study anti-aging properties of cordeycepine. Human submandibular organ (HSG) cells were exposed to hydrogen peroxideand then were treated with different concentrations of cordycepin in the range of 6.25-50 μM for one day, two days and three days. To assess cell expansion and receptive oxygen species age informtion, diacetate tests were accomplished. Amylase action was actively estimated by 2-chloro-p-nitrophenol connected with maltotrioside. The amylase activity of the anti-cancer agents by apoptotic markers at messenger RNA and different protein levels were performed by switch transcriptase-polymerase chain response and immune-fluorescence examination, separately. The outcomes showed that under oxidative pressure, HSG cells demonstrated extraordinary dysfunction. Moreover, *Cordycepin* saved the protective effects mostly through reducing ROS age and reestablishing the declaration of salivary proteins. Additionally, the measure of amylase that was discharged from HSG cells cultivated within *Cordycepin*e increased to a greater extent [72]. These studies suggest that Cordyceps compound can be benefitial against aging effects and can be commercially available natural medicine to cure the aging effects and diseases.

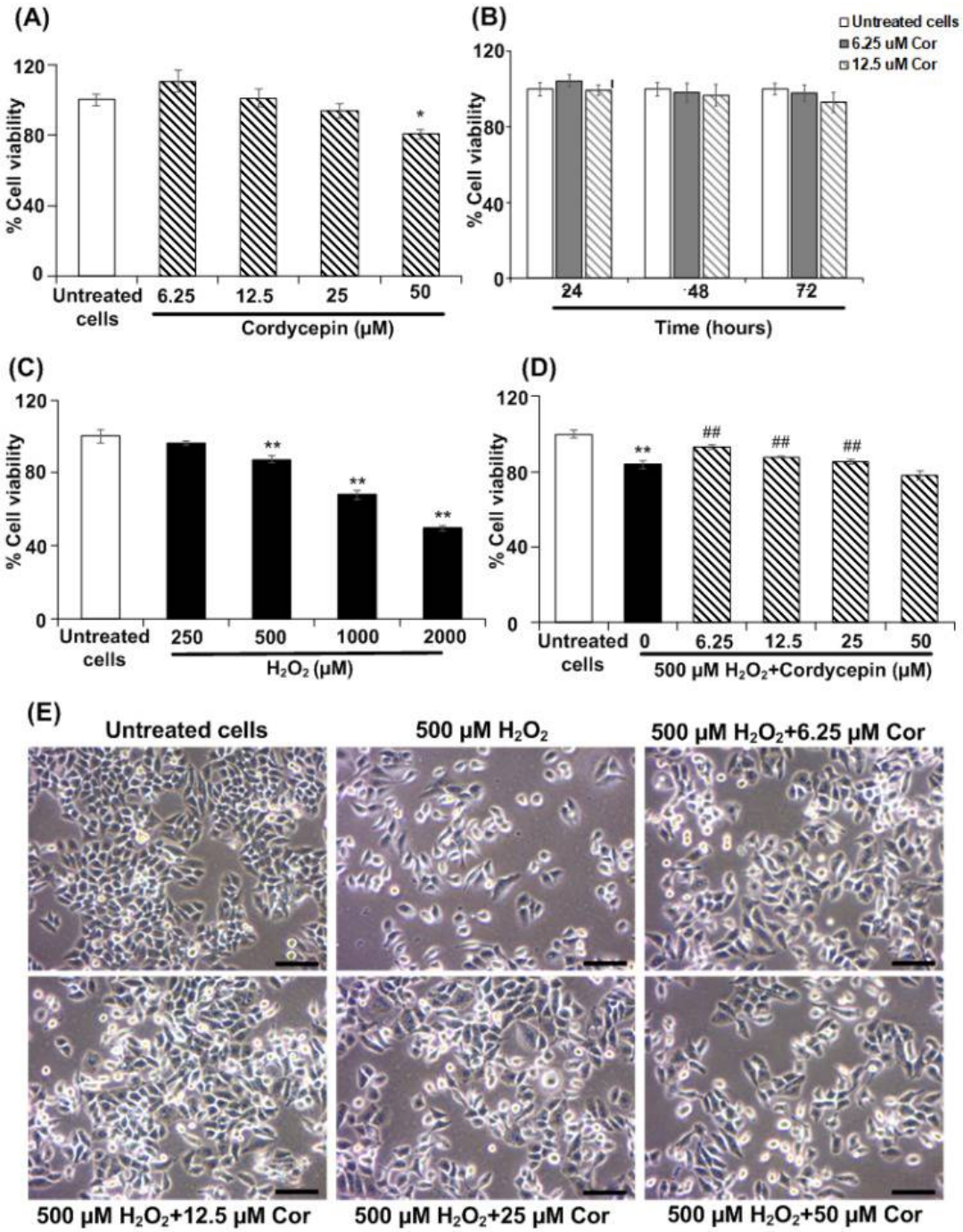


Figure 2:The figure illustrates the effects of Cordycepin in preventing HSG cells from hydrogen peroxide induced cell toxicity. Cells were treated with different convergences of cordycepin at concentration of 6.25-50 μM for 1,2 and 3 days (71).

## CONCLUSION

*Cordyceps* species are traditional Chinese medicines that have been used to cure many types of infections and internal injuries by ancient Chinese people from prehistoric days. But restricted growth and increasing commercial demand have made it costly. Therefore, it has gained great entrusts of the scientific community in the last two decades. Scientists have discovered several methods to culture and artificially grow different *Cordycpes* species but still unable to fulfill the demands. Chemical extractions of different biologically active compounds and their synthesis is an alternative way to determine the medicinal use of these compounds more precisely. Recent advancements and progress in several types of extraction techniques and their usage in the extraction of different types of biologically active compounds such as nucleosides, polysaccharides, sterols, and fatty acids have been reviewed in the content. Further, the most valuable biological activities performed recently by using these *Cordyceps* compounds have been

discussed. Available anti-tumor drugs have several side effects as they damage normal and healthy cells. The antitumor effect of the *Cordyceps* compounds has progressed to a great extent in recent years and there is a great hope to develop natural medicines that will be much safer with very minute side effects. Moreover, the recent advancement in improving anti-oxidative and anti-aging properties has also been reviewed and the most recent work has been described from the literature. Given all these findings, we hope that very soon the availability of natural and highly effective medicines will be possible that will reduce many side effects of traditional medicines especially the threat of drug resistance.

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