Chapter

Broad Efficacy of Scavenging Free Radicals: *Cordyceps* sp.

Loknath Deshmukh, Rajendra Singh and Sardul Singh Sandhu

Abstract

Scavenging free radical potency of cordycepin is the major bioactive segment extricated from *Cordyceps* species. In some new years, *Cordyceps* has gotten growing thought inferable from its distinctive restorative/pharmacological tests. This assessment reviews continuous explores on the counter oxidant impacts and the associated analyses of *Cordyceps* species. The results from our review show that *Cordyceps* of the cordycepin applies protective effects against hostile to oxidant injury for certain, afflictions including constant obstructive pneumonic infection (COPD), hepatitis, asthma, cerebral paralysis, Parkinson's illness (PD), coronary course sickness (CAD), Alzheimer illness, respiratory failure, malignancy infection, maturing, waterfalls, and mind brokenness. *Cordyceps* coordinates the NF-κB, RIP2/Caspase-1, Akt/GSK-3β/p70S6K, TGF-β/Smads, and Nrf2/HO-1 hailing pathways among others of cordycepin. A couple of assessments focusing in on *Cordyceps* auxiliaries were surveyed and found to down metabolic speed of *Cordyceps* and augmentation its bioavailability. In addition, cordycepin further developed opposition, prevented the duplication of viral RNA, and covered cytokine storms, therefore proposing its capacity to treat COVID-19 and other viral defilements. From the accumulated and assessed information, this article gives the speculative reason to the clinical usages of cordycepin and inspects the way for future assessments focusing in on expanding the restorative use of *Cordyceps* species. Cordycepin and its analogs show unfathomable potential as the accompanying new class of against oxidant specialists.

Keywords: *Cordyceps* species, anti-oxidant, cordycepin, oxidant diseases, fruiting body and secondary metabolite, pharmacodynamics

1. Introduction

Cordyceps species (Ascomycetes *genus*) is a bug parasitizing development; they are thusly entomopathogenic life forms. The name *Cordyceps* begins from the Latin words line and ceps, meaning 'club' and 'head', independently. From a genuine perspective "summer grass, winter worm", Chinese caterpillar development, is the Chinese name given to the complex of hatchlings and parasites [1–3] which this helpful mushroom has been found ordinarily at high heights of around 14,000 ft. in the Himalayan territories including Nepal, China, Bhutan, Thailand, Tibet, and India [4]. The *Cordyceps* as*genus*ment consolidates more than 400 species, among which *Cordyceps* species have been used generally for millennia in China as a food, tonic, and natural drug for various prosperity related issues, for instance, kidney and lung brokenness, weakness, and exhaustion [5, 6]. This development lives in

a general sense on the highest point of the hatchling of one explicit *genus* of moth, Hepialus armoricanus, and yet is unexpectedly found creating on other moth species [7]. It is generally called 'Dong Chong Xia Cao' in Chinese and 'Tockukaso' in Japanese, implying 'winter-frightening little animal and summer-plant' because of the creating cycle: the development at first parasitizes the hatchling of specific species Hepiaidae, outlining a parasitic complex that includes the leftover pieces of the caterpillar and the stroma of the creature [8]. *Cordyceps* are a stunning cordycepin wellspring of bioactive metabolites that show various clinically asserted advantages for human prosperity. Since people have an inclination towards trademark/home grown medicines, the usage of *Cordyceps* as a trademark remedial mushroom is unpreventable [9]. The bio metabolite cordycepin was first isolates from the matured supply of the therapeutic mushroom *Cordyceps* militaris [10]. Which is an entomopathogen creature that grows parasitically on lepidopteron hatchlings and bug pupae. The family *Cordyceps* is prominent in standard Chinese medicine and shows a variety of clinical prosperity impacts including hostile to diabetic, immunomodulatory, against oxidant, against oxidant, anticancer, cardiovascular effects, against fibrotic, and against microbial exercises [11–13]. *Cordyceps* sp. has been represented to have a various extent of pharmacological effects of which, its antitumor, against angiogenic, and antagonistic to oxidative properties are for the most part examined [14, 15]. Growing considers showing that it applies solid malignant growth counteraction specialist exercises in different cell types including macrophages, chondrocytes, glial, and lung epithelial cells [16]. Then, at that point, against oxidant impacts are furthermore found in liver, and LPS-impelled exceptional lung injury, alcohol started Hyperlipidemia, ominously vulnerable asthma, doxorubicin-instigated, cardiotoxicity, irritation actuated osteoporosis, and cerebral ischemia–reperfusion injury when various animal mice models are used [17–19]. With a rising income in cordycepin, the usage of assistant changes to block the metabolic speed and augmentation efficiency has been explored [20]. There are as of now a gigantic number of studies zeroing in on its enemy of oxidant impacts; regardless, an aggregate and productive overview of composing is inadequate. In this review, we surveyed the late enemy of oxidant focuses on cordycepin to choose its future perspective as an enemy of oxidant drug and to clarify its critical enemy of oxidant systems of activity.

2. Oxidative stress and damage to nucleic acid, protein and lipids

Oxidative mischief to nucleic acid (DNA), proteins, and various macromolecules gathers with age and has been conjectured to be a major, yet by all record not the sole, sort of endogenous damage inciting developing [6, 21, 22]. Superoxide (0_2), hydrogen peroxide (H_20_2), and hydroxyl progressive (– OH), which are mutagens conveyed by radiation, are also results of normal processing [12, 23]. Endogenous oxidants similarly hurt proteins and lipids [24] have demonstrated that the activity of proteolytic mixtures that hydrolyze oxidized proteins isn't fit thwart an age-related augmentation of oxidized proteins. In two human diseases related with inauspicious developing, Werner issue, and progeria, oxidized proteins increase at tons higher rate than is common [25]. Lipid peroxidation offers to rise to mutagenic lipid epoxides, lipid hydro-peroxides, lipid alkoxyl and peroxyl fanatics, and enals (a,4-unsaturated aldehydes) [26]. Singlet oxygen, a high-energy and mutagenic sort of oxygen, are frequently conveyed by the move of energy from light, the respiratory burst from neutrophils, or lipid peroxidation [27]. Animals have different malignancy avoidance specialist securities, yet since these watchmen aren't incredible, some DNA is oxidized. Oxidatively hurt DNA is fixed

by intensifies that remove the wounds, which are then released inside the pee. Strategies are made to take a gander several of those separated hurt bases inside the pee of model rodents and others [28], basically all of which show up on the grounds that the free base from a fix by glycosylases. We check that the quantity of oxidative hits to DNA per cell daily is around 100,000 inside the model rodents and around 10,000 inside the human. DNA-fix synthetics capably dispense with most, yet not all, of the wounds outlined [6, 29–31] for instance, the significant change repeat in human lymphocytes, of which the responsibility of oxidative DNA bruises is dark, is around numerous occasions more vital in elderly people than in youths [32]. Mitochondrial DNA (mtDNA) from rat liver has in more than numerous occasions the level of oxidative DNA hurt than does nuclear DNA from an indistinguishable tissue [16, 33]. This extension could be because of a shortfall of mtDNA fix proteins, a shortfall of histones getting mtDNA, and subsequently the closeness of mtDNA to oxidants delivered during natural cycle. The cell shields itself against this high speed of mischief by a uniform turnover of mitochondria, thusly presumably killing those hurt mitochondria that produce extended oxidants. Notwithstanding this turnover, oxidative wounds appear to gather with age in mtDNA at a preferable rate over in nuclear DNA [34, 35]. Fluorescent tones, which are accepted to be relied upon somewhat to crosslinks among protein and lipid peroxidation things, moreover increase with age [36]. The significance of oxidative DNA wounds in illness and developing is highlighted by the presence of express fix glycosylases that separate these injuries from DNA. Because of 8-oxo-2′- deoxy-guanosine, a physical issue molded from oxidative mischief to guanine stores in DNA, loss of a particular glycosylase development prompts a reasonable extension inside the unconstrained change rate [12, 20, 37, 38], exhibiting the trademark mutagenic ability of this DNA sore. Various other oxidative DNA injuries are probably going to be huge too [39].

3. Sources and effects of cordycepin

Cordyceps sp. cordycepin (3′-deoxyadenosine) prominent as purine or pyrimidine nucleobase adenosine, cytidine, and guanosine straightforward that have particular sort of bioactivities [40]. The cordycepin will be changed over into 5′-mono, di, and triphosphates and thusly obstruct the advancement of ribose-phosphate pyrophospho kinase and 5-phosphoribosyl-1-pyrophosphate amido-transferase in the again purines biosynthesis, just as the nucleic acids, mix causing the counter metastatic, antitumor and antimicrobial results [12, 41, 42]. Similarly, cordycepin with its enemy of leukemic limit normally get along with adenosine deaminase inhibitor and this will cause the inhibitory effect on happen which serves to analogs of 2′, 5′-oligoadenylate towards the human immunodeficiency contamination illness [43]. Immense degree refined of mycelial through designed can be used as another wellspring of cordycepin on account of its limited total in a typical source. Tow stage control of deteriorated oxygen or development of NH4+ to the brought down medium can help with working on the formation of cordycepin [44]. Despite creation using development advancement, cordycepin could be in like manner conveyed misleadingly. In any case, the manufactured blend has some hindrance, for instance, the trouble of the cycle and the utilization of gigantic volume of normal solvents which decrease the allure of this cycle [18, 45]. Exploration that the lifestyle created on xylose showed high creation yield of cordycepin on dry biomass. Standing out xylose from other carbon sources, a lot of essentially up-coordinated characteristics in xylose were progressed in pentose and glucoronate interconversion, and cordycepin biosynthesis [46]. The place of the current examination was to choose if cordycepin controls duplication, development, and angiogenesis in a

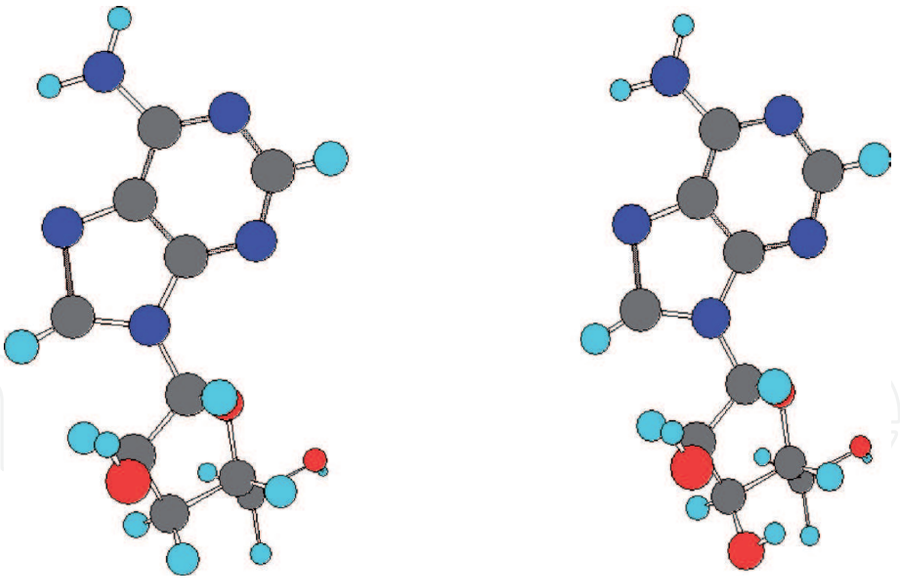

Figure 1.
Chemical structure of Cordycepin and Adenosine [40].

human umbilical vein endothelial (huve) cell line and in a hepatocellular carcinoma (hcc) cell line [47–49]. MTT was used to study cell development. Apoptosis was poor somewhere near stream cytometry (propidium iodide recoloring). Transwell and wound repairing measures were used to research the movement and interruption of hcc cell line and huve cells. Angiogenesis in huve cells was studied using a chamber advancement test. Cordycepin immovably smothered hcc cell line and huve cell increase in a dose- and time-dependent way. Cordycepin activated huve cell apoptosis in a dose-dependent way (2,000 μg/ml, 50.20 ± 1.55% versus 0 μg/ml, 2.62 ± 0.19%, $P < 0.01$) [50–53]. The genome-wide transcriptome assessment showed 8747 imparted characteristics in the glucose and sucrose social orders created under light-programming and faint conditions. Cordycepin curbed cell improvement and set off apoptosis in U87MG cells with wild-type p53, yet not in T98G cells with freak type p53 [54, 55] (**Figure 1**).

4. Fruiting body and secondary metabolites action

The entomopathogenic development *Cordyceps* species is a consumable mushroom with numerous drug/therapeutic properties. Numerous past research analyzed the cell reinforcement exercises that of the refined where refined fruiting collection of *Cordyceps sinensis* and *Cordyceps militaries* class [56, 57]. Methanolic concentrate of *Cordyceps* sp. was tasted when exercises for its antibacterial, cancer prevention agent, antifungal, and antiproliferative properties in different human cell lines. The methanolic concentrate of *Cordyceps* showed to thwart lipid peroxidation, have reducing force and search free radicals [58]. The assessment was coordinated under research facilities produce *Cordyceps* sp. improvement, with five Selenium (Se) different centers (μg g^{-1}) and three sorts of Selenium components like selenate. *Cordyceps* can hold inorganic component from the compound and overhaul it to normal Selenium blends in fruiting bodies [59–62]. As per Yamaguchi and partners the concentrates investigated, the high temperature water discrete (70°C for 5 min) demonstrated the best without oxygen extremist searching activity. Moreover, when low-thickness lipoprotein (LTL) was incubated with macrophages inside seeing copper dichloride (1 mM), the high temperature water eliminate demonstrated a strong inhibitory effect against lipid peroxidation in

medium and resulting assortment of cholesteryl ester in macrophages [63–66]. As per the as of late examinations, the fruiting body tests were set up in four particular model plans, which were flawless fruiting bodies, cut fruiting bodies, dried powder, and dried unpleasant concentrate [67, 68]. The real proportion of the adenosine and cordycepin obsessions in fresh fruiting bodies was inspected by world class liquid chromatography [69]. These optimal models gave a coefficient of confirmation of assumption, standard botch of figure, inclination, and waiting farsighted deviation, which were independently 0.95, 16.60 mg kg^{-1}, −8.57 mg kg^{-1}, and 5.04 for adenosine conjecture, and 0.98, 181.56 mg kg^{-1}, −1.05 mg kg^{-1}, and 8.9 for cordycepin gauge by Singpoonga and partners [70].

There is uncommon potential for the creation of metabolites from *Cordyceps* species, this is one phase towards finding and depicting with the bounty of nuclear essential assortment in this genera. Presented here is the essential chromosome level social affair of a genome from the *Cordyceps* genera. This get-together and assessment has revealed that *Cordyceps* militaris has seven chromosomes containing a wealth of value bunches for optional metabolite creation that entomopathogenic sort. With this genome, further assessment and depiction of the discretionary metabolites conveyed by *Cordyceps* militaris might benefit from outside input through genome based procedures including heterologous explanation of value gatherings. Of the 36 quality gatherings recognized using the antiSMASH and SMURF computations, three gatherings are found to have a genuine degree of equivalence with bunches from various life frames that produce a known molecule [58, 62, 71, 72].

5. Anti-oxidant potency

5.1 Antioxidants secure against disease

Different affirmation parts inside the living being have advanced to restrict the degrees of open oxidants and the underhandedness they cause to the human body [73]. Among the protections are compounds, for example, glutathione peroxidase, catalase, and superoxide dismutase. The glutathione S-transferases inactivate responsive electrophilic mutagens, including the aldehyde delayed consequences of lipid peroxidation. There are also different partner guards, for example, sequestration of H202-production engineered substances in peroxisomes and chelation of any free iron or copper salts in transferrin and ferritin or ceruloplasmin to keep away from Fenton science. O_2, in any case, can pass on iron from ferritin [65, 74]. Oxidized DNA is fixed by a development of glycosylases that are unequivocal for express oxidized bases and perhaps by questionable extraction fix compounds. Without cell division, these oxidative wounds are discarded from DNA sensibly and the change rate is kept to a base [20, 75]. Oxidized proteins are destroyed by proteases. Lipid hydroperoxides are crushed by glutathione peroxidase. Basically these safeguards show up, clearly, to be inducible, as are most different sorts of watchmen i.e., the sums increment because of hurt. There is enormous making exhibiting that cells react to low degrees of radiation, and oxidative mutagen, by beginning infection aversion expert shields that help to promise them against change by gigantic levels of radiation [44, 68, 71]. In spite of the defensive impacts of endogenous enzymatic harm evasion expert safeguards, utilization of dietary cell fortresses shows up, evidently, to be fundamental. Food sources created all along, fundamental wellspring of cell fortresses in the eating schedule, are associated with a cut down hazard of degenerative issues [76]. Square and her associates have really inspected various numbers amasses in the epidemiological forming that relate, with

unimaginable consistency, the deficit of good use of verdant food assortments to destructive advancement rate. The quarter of everybody with low dietary affirmation of food assortments created beginning from the soonest stage twofold the infection rate for most kinds of hurtful turn of events (lung, larynx, oral melancholy, throat, stomach, colon and rectum, bladder, pancreas, cervix, and ovary) when stuck out and the quarter from high attestation [14, 40, 77]. Information on the genus of perilous improvement known to be associated with compound levels are not as reliable and show less affirmation by food sources created beginning from the most punctual stage: chest disease the defensive impact was about 30% [78]. The expense of after effects of the soil is an immense factor in agitating use. Less fortunate individuals spend a more raised level of their remuneration on food, eat less consequences of the soil, and have more confined future than all the more wealthy individuals [79]. A basic partner of thriving in this century was made pesticides, which very diminished the expense of food creation and guaranteed that by a wide margin the vast majority of the harvests planted would be eaten by people as opposed to bugs [80]. Planned pesticide stores don't show up in everybody to be a huge defense compromising turn of events.

5.2 Birth defects, childhood tumour and oxidation

Oxidative stresses in sperm DNA are extended products number when levels of dietary ascorbate are insufficient to keep unique fluid ascorbate at an adequate level [81]. A sizable level of the few country people ingests lacking levels of dietary ascorbate, particularly single folks, destitute individuals, and smokers [82]. The oxidants in tobacco smoke channel the cell fortifications in plasma. Smokers should eat 2–3 times more ascorbate than non-smokers to achieve a comparable level of ascorbate in the blood [83], nonetheless, they only sometimes do. In assessments of sperm from smokers and non-smokers [84] the amount of sperm and the degree of motile sperm decay basically in smokers, and this reducing was dependent upon the part and term of smoking. Paternal smoking, explicitly, appears to in-wrinkle the peril of birth distortions and youth threatening development in successors [85, 86]. One expects, and discovers, much greater obligation to the germ-line change rate from the father than from the mother, with the age of the father being a huge peril factor [87, 88]. As such, inadequate eating regimens (and smoking) of fathers appear to achieve hurt not only to their own DNA yet moreover to the DNA of their sperm, an effect that may resonate down individuals later on and new age [81, 89, 90].

5.3 Cardiovascular system diseases

Coronary vein illness (CAD) is a condition reliant upon various factors or causes diligent vascular provocative bruises that lead to the start of cardiovascular framework infections [91]. Atherosclerotic coronary illness related irritation is mediated by great for combustible cytokines, provocative hailing pathways, bioactive lipids, and bond particles [92]. Extended extension and development of cardio vascular smooth muscle cells also intercede in the beginning and development of CAD [93]. *Cordyceps* controls the duplication of aortic smooth muscle cells (RatAOSMCs) in the carotid stock course of inflatable hurt Sprague–Dawley rodent model. In addition, in collagen type I-incited RatAOSMCs, Cordycepin (3′- deoxyadenosine) famously controls the inception of MMP-2 and - 9 and the surge of particles [94]. Myocardial ischemia–reperfusion (I/R) injury is a cardiovascular sickness caused in view of an outrageous prevention in coronary blood adaptability. It can provoke tissue hypoxia, cell decay, organ brokenness, and even apoptosis in outrageous conditions [95]. 3′- deoxyadenosine applies cardio-defensive effects against I/R-started

rat heart injury; its arrangement of action can be credited to the obstacle of Bax, isolated caspase-3 enunciation, the ascent of Bcl-2 verbalization, and activation of the Akt/GSK-3β/p70S6K hailing pathways. Plus, *Cordyceps* sp. in like manner grows the affirmation of the disease anticipation specialist protein HO-1 [93, 96]. In a mouse cardiovascular exchange model, *Cordyceps* 3′- deoxyadenosine got together with ECDI-SPs has an immense effect in lessening the production of good for combustible cytokines including IL-1β, IL-6, IL-17, and TNF-α, growing the release of quieting cytokines IL-10 and TGF-β, and upsetting Th17 and progressing Tregs, then, at that point ECDI-SPs monotherapy alone [92]. All things considered, *Cordyceps* could ease up disturbance activated by CAD through impeding the extension and development of smooth muscle cells similarly as tweaking diverse related cytokines and chemokines and the assertion of record factors. Additionally, *Cordyceps* applies therapeutic ramifications for myocardial ischemia–reperfusion (I/R) injury by obstructing cell apoptosis, lessening the making of positive for red hot cytokines, and overseeing safe cell limits [97].

5.4 Central nervous system diseases

Parkinson's affliction is a neurodegenerative disease that shows as an improvement issue, in which degeneration and loss of dopaminergic neurons of the substantia nigra are the brand name features. Oxidative pressing factor and neuro-aggravation accept critical parts in the pathogenic frameworks of Parkinson's disorder [98–100]. In a continuous report, cordycepin is found to direct the motor issues in MPTP-treated Parkinsonism rodents and seemed to apply neuroprotective effects through easing up bothering and oxidative pressing factor response. Likewise, such neuroprotective effects may be connected with the limitation of the TLR/NF-κB hailing pathway in MPTP-started Parkinson's disorder rodents and LPS-incited BV2 cells [101]. Stroke is perhaps the most notable ailments in cerebrovascular affliction and can be clinically isolated into two genuss: ischemic and hemorrhagic. Extreme ischemic stroke is responsible for 80%, in light of everything, and the fundamental wellspring of failure and end from one side of the planet to the other. Recovery of circulation system (reperfusion) and contravention of cell injury (neuroprotection) are two potential treatment frameworks got in the organization of strokes [102, 103]. Extending evidence suggests that a blazing response is related with stroke and contributes by and large to mind injury [104]. In a MCAO-started preliminary frontal cortex injury model with pathogenesis taking after that of human ischemic stroke, cordycepin applies neuroprotective effects by preventing the outpouring of MMP-3, lessening glutamate and aspartate levels, working on the development of SOD, and reducing MDA levels [105]. The standardized *Cordyceps* in improved concentrate of *C. militaris*, which contains 8.2% (w/w) cordycepin, on a very basic level reduces the attack of ED-1-and MPO-positive searing cells into ischemic wounds, diminishes infarct volume, and debilitates cerebral edema and blood–mind limit hurts in MCAO rodents [102, 105, 106]. Likewise, cordycepin quite eases up frontal cortex edema, neurological lacks, and perihematomal tissue hurt after ICH, joined by an immense decline in the statement of HMGB1. Foolishly, cordycepin applies a neuroprotective effect in ICH models possibly through the prevention of NLRP3 inflammasome commencement [107]. Another assessment shows that cordycepin can enough get BBB genuineness by recovery of tight crossing point proteins, relief of close by exacerbation, and restriction of NOX activity [108].

Different sclerosis is a provocative demyelinating disease of the central tangible framework depicted by motor brokenness, neuro-aggravation, glial-cell institution, loss of foster oligodendrocytes, and axonal injury [109]. The CPZ-prompted demyelination model has been by and large used to assessment MS, especially in

investigating de-and re-myelination in the corpus callosum. Cordycepin mitigates CPZ-prompted incidental effects in mice by protecting motor brokenness, propelling re-myelination, stifling glial-cell incitation, lessening the outpouring of the steady of combustible cytokines, IL-1β and IL-6, and growing the levels of the quieting cytokine IL-4 [101, 106, 110]. All around, cordycepin is useful in Parkinson's infection and applies its possessions generally by reducing oxidative pressing factor and against oxidant bothering through the TLR/NF-κB hailing pathway. Besides, cordycepin could further develop stroke by diminishing the infarct volume, reducing cerebral edema, controlling the levels of the connected cytokines, and obstructing the commencement of the NLRP3 inflammasome. Additionally, cordycepin applies impacts on MS through protecting motor brokenness, propelling re-myelination, stifling glial-cell incitation, and dealing with the steady of and against oxidant cytokines [111].

5.5 Dietary antioxidants

The effect of dietary affirmation of the malignant growth anticipation specialist's ascorbate, tocopherol, and carotenoids is difficult to disentangle by epidemiological assessments from other critical supplements and trimmings in verdant food sources [112, 113]. Taking everything into account, a couple of conflicts suggest that the disease avoidance specialist content of results of the dirt is a critical ally of their protective effect. Biochemical data, discussed above, show that oxidative damage is gigantic and is likely going to be the major endogenous mischief to DNA, proteins, and lipids [114]. Oxidative damage to sperm DNA is extended when dietary ascorbate is inadequate. Epidemiological assessments and intervention fundamentals on neutralization of harmful development and cardiovascular disease in people taking malignancy counteraction specialist supplements are interesting, notwithstanding, greater examinations ought to be done [115]. Clinical starters using disease anticipation specialists will be the essential test for an enormous number of considerations inspected here [116]. Studies on oxidative instruments and the investigation of infection transmission on malignant growth anticipation specialist protection for individual degenerative ailments are discussed underneath. Little particle dietary disease counteraction specialists [112, 117], for instance, supplement C (ascorbate), supplement E (tocopherol), and carotenoids have made explicit interest as adversaries of malignancy causing specialists and as shields against degenerative sicknesses [118]. Most carotenoids have cell support development, particularly against singlet oxygen, and many, including/- carotene, can be utilized to supplement A (retinal) [119]. Earlier papers have called attention to different as of late dismissed physiological cell fortifications, including urate, bilirubin, carnosine, and ubiquinol [120]. Ubiquinone (CoQ1o), for example, is the fundamental little molecule for delivery electrons in mitochondria for the period of energy [121]. Its reduced construction, ubiquinol, is an amazing disease counteraction specialist in films [122]. Optimal levels of dietary ubiquinone/ubiquinol could be of importance in an enormous number of degenerative contaminations.

5.6 Respiratory system diseases

Cordyceps has been seemed to apply against oxidant impacts in exploratory models of avionics course provocative contaminations including extremely touchy asthma and intense lung injury [123]. Ominously vulnerable asthma is a continuous provocative sickness of the flight course divider that is depicted by means of aeronautics course aggravation, flying course divider overhauling, organic liquid hypersecretion, and avionics course hyper-responsiveness [12, 124]. It is credited to the infiltration of leukocytes including lymphocytes, eosinophils and neutrophils into the lungs. Also, the tallness of Th2 cytokines, for instance, IL-4, IL-5, and

IL-13, and extended levels of IgE are watched [38, 123, 125]. T accomplice type 2 (Th2) cells and the cytokines conveyed by them are clinically associated with the presentation of a wide range of asthma and are the fundamental drivers of extremely touchy asthma. The Th2 cytokine pathway is one of the rule centers in developing new prescriptions for asthma [126]. *Cordyceps* sp. has been all around archived by different assessment social affairs and is known to have expected therapeutic properties for the treatment of ominously defenseless asthma [127].

Cordycepin concedes the release of allergen-unequivocal IgE, eotaxin, and ICAM-1, decreases the BAL fluid Th2 cytokines IL-4, IL-5, and IL-13 levels, and tightens ovalbumin-driven cup cell hyperplasia, organic liquid hypersecretion, and AHR in a bit subordinate way in the ovalbumin-incited mouse exploratory easily affected asthma model [128]. Carelessly, cordycepin has against asthmatic properties including the deterrent of Th2-type responses, no doubt through interfering with the MAPKs and NF-κB hailing course pathways. In another assessment, cordycepin is appeared to basically subdue an ovalbumin-affected augmentation in eosinophil check; it smothers IL-17A and fabricates IL-10 cytokine levels in the BALF, and supports [129]. Treg responses and covers Th17 responses in ovalbumin-honed mice [130]. In an ovalbumin-started rat model of steady asthma, cordycepin tightens immunoglobulin IgE, eases up the avionics course divider thickness, and reduces eosinophils and neutrophils in the BALF. Noticeably, cordycepin decreases the upregulation of IL-5, IL-13, and TNF-α in the BALF, and controls the development of A2AAR mRNA and the decay of TGF-β1 explanation. Besides, *Cordyceps* when co-controlled with glucocorticoids shows synergistically huge feasibility in quelling avionics course remodeling [123, 131]. From these results it might be derived that cordycepin applies medicinal effects in negatively powerless asthma by upsetting eotaxin verbalization, conveying cytokines, and dealing with the Th1/Th2 balance. The ideal for combustible cytokines TNF-α, IL–1β, IL-6, IL-8, and IL-18 are among the most reassuring biomarkers for predicting bleakness and mortality [132]. LPS-impelled ALI models resemble certain features of human ALI; *Cordyceps* is found to exceptionally decrease neutrophil gathering and MPO activity in lung tissues, decay the production of provocative cytokines including TNF-α, IL-6, and IL-1β, and debilitate lung disturbance in this model apparently by the sanctioning of Nrf2 and upregulation of HO-1 verbalization [133]. The inhibitory effect of cordycepin on TNF-α and IL-6 emanation is debilitated by before association of SnPP, an amazing HO-1 inhibitor, including that cordycepin gives protection against ALI through inception of HO-1. Extraordinarily, cordycepin treatment constructs the combination of IL-10, which insistently oversees disturbance [126, 130, 132]. These examinations suggest that cordycepin can ease up ALI by lessening the social affair of neutrophils and the production of strong of red hot cytokines. SARS-CoV-2, the causative microorganism of Coronavirus Disease 2019 (COVID-19), has caused a pandemic of respiratory infirmity all throughout the planet. The quick famous replication is fundamentally associated with gigantic provocative cell entrance and raised strong of combustible cytokine/chemokine responses. Raised levels of the cytokines GCSF, IP10, MCP1, MIP1A, and TNF-α, are perceived in the plasma of patients who test positive for COVID-19, showing the cytokine storm that is connected with contamination earnestness [134]. Adenosine is an amazing regulator of disturbance, which intervenes its effects on cells by interfacing with four particular receptor subtypes, explicitly, A1, A2A, A2B, and A3 [135]. In particular, the impelling of adenosine receptors A2A and A3 could cause quieting impacts, which are intervened by the covering of steady of combustible cytokines [136]. These revelations showed the capacity of cordycepin in the treatment of COVID-19, hence, it was invaluable to moreover research its enemy of oxidant component activity.

5.7 Cataracts and antioxidants

Cararacts departure is the most generally perceived action in the overall around (65.5 million consistently) with expenses of more than 98.45 billion dollars [137, 138], has actually investigated the imperative confirmation that Cataract have an oxidative etiology and that dietary cell fortifications can prevent their game plan in individuals [139]. Five epidemiological examinations that have investigated the effect of dietary cell fortifications on Cataract show strong insurance effects of ascorbate, tocopherol, and carotenoids [140, 141]. Those individuals taking regular upgrades of ascorbate or tocopherol had around 33% the risk of making Cataract. Smoking, a genuine oxidative pressing factor, is a huge peril factor for Cataract, and radiation, an oxidative mutagen, is striking to cause Cataract [142]. Eye proteins show an extended level of methionine sulfoxide with age, and proteins in human Cataract have >60% of their methionine stores oxidized [143]. Pregnant mice depleted of glutathione, the essential sulfhydryl disease avoidance specialist in cells, produce any kind of future family with Cataract [144]. The most reassuring hindrance framework against Cataract radiates an impression of being to extend dietary malignancy anticipation specialists (cell reinforcement specialists) and to lessen smoking [145].

5.8 Brain dysfunction and antioxidants

Biochemical assessments recommend that oxidation may be huge in different brain pathologies [146]. A few epidemiological assessments are dependable with a guarded effect of verdant food varieties or cell fortifications [147] in different neurological pathologies, including mind ischemia, Parkinson disease, and familial amyotrophic level sclerosis (Lou Gehrig's disorder), a degenerative issue of motor neurons [148, 149]. Ischemic scenes free iron, a critical stimulus in reactions forming oxygen progressives; iron chelators diminish neuron incident after this injury [150]. In individuals encountering Parkinson's ailment, oxidative DNA hurt is raised inside mind districts rich in dopaminergic neurons (E. Overvik, J. Sanchez-Ramos, and B.N.A., unpublished work) [151]. The most convincing confirmation so far for an association between neurological issues and oxygen progressive improvement is the strong alliance found between familial amyotrophic sidelong sclerosis and changes in the Cu/Zn superoxide dismutase quality, suggesting that oxygen progressives might be obligated for the specific degeneration of motor neurons occurring in this deadly sickness [152–155]. The cautious piece of superoxide dismutase against frontal cortex injury due to ischemia is maintained by the finding that its overproduction is guarded in a transgenic mouse model [156]. Considering the similar cautious effects against ischemia-activated brain injury by limitation of NO turn of events, and the continuous evidence involving these two radical species in cytotoxicity of neuronal cells [157, 158], without a doubt peroxynitrite, a historic oxidant molded from the mix of Oj and NO (1%), expects a huge capacity in neuronal injury following ischemia and reperfusion [159].

6. Lack of side effects

Cordyceps containing bioactive compounds with lower health risk. A month after oral association of *Cordyceps* (5 mg/kg), the hematology, blood science, and hypochondriac changes of the rodents show no basic changes are comparable to those of the conventional rodents. Furthermore, the Ames test exhibits that *Cordyceps* is a non-mutagenic compound [160, 161]. Another report in mice shows that *Cordyceps* shows slight destructiveness when controlled at oral doses of 20 mg/kg for 21 days

[162]. *Cordyceps* is found to apply unsafe effects when controlled at a part of 8 mg/kg for 3 days. Signs of toxicity, for instance, wasting and detachment of the guts are not seen when *Cordyceps* is overseen at a bit of 2 mg/kg or lower [163]. What's more, following 3 days of intravenous imbuements association of *Cordyceps* (20 mg/kg) in beagle canines, *Cordyceps* shows no prescription related toxic substance levels, displaying the security profile of *Cordyceps* [164]. *Cordyceps* is noxious just to hurtful threat cells and doesn't show cytotoxicity toward strong cells, subsequently showing it's anything but a foe of infection expert [165, 166]. In any case, a previous report communicates that *Cordyceps* shows toxicity toward sound erythrocytes and maybe starts feebleness in patients with harm when used in chemotherapy [167]. Despite these promising prosperity profiles, comprehensive preclinical toxicological assessments on *Cordyceps* ought to be coordinated and further checked for their effects.

7. Pharmacodynamics

Being a *Cordyceps* species simple, physiologic and biochemical impacts of medications (specifically, drug tranquilizes), the metabolic and pharmacodynamics profiles of *Cordyceps* cordycepin resemble those of adenosine. In vivo breaks down recommend that *Cordyceps* can be utilized to 30-deoxyinosine coming about in light of the fast deamination by Adenosine deaminase, or may go through phosphorylation by adenosine kinase to be changed over into 30-deoxyadenosine mono-, di-, and triphosphate [168]. It has been suggested ahead of time that 30-deoxyinosine is an inactive metabolite, while 30-deoxyadenosine triphosphate is the powerful moiety at risk for the accommodating effects of *Cordyceps* [169]. A continuous report shows that 30-deoxyinosine can be changed over to the unique moiety, 30-deoxyadenosine triphosphate, in mammalian cells [170]. In addition, the pharmacokinetics and bioavailability examinations of *Cordyceps* show that it is held and released rapidly in rodents. *Cordyceps* has a short removal half-life (t1/2) of 1.6 min at a bit of 10 mg/kg when overseen intravenously. In the meantime, the region under the curve, most noteworthy obsession, and the opportunity of *Cordyceps* have been made plans to be 38.5 ± 10.3 min μg/ml, 3.1 ± 0.9 μg/l and 2.1 ± 1.2 L/min/kg, independently [171]. In a biopharmaceutical assessment study, *Cordyceps* is seemed to have low protein official, high plasma breathing space, low vulnerability, and high hepatic first-pass sway in vitro, which can explain the shortfall of its oral bioavailability [172].

8. Conclusion and future perspectives

As a working fragment of customary Chinese drug, *Cordyceps* species has been seen to have expansive enemy of oxidant and safe managerial effects of cordycepin. The sensitive rule of provocative safe response is another course for the improvement of imaginative meds for the treatment of resistant framework ailments. *Cordyceps* species has shown its probable accommodating motivating force in various red hot contamination models, for instance, asthma, Parkinson's, rheumatoid joint torment, atherosclerosis, pneumonia, hepatitis, and atopic dermatitis. Many hailing pathways including MAPKs, TGF-β/Smads, and NF-κB, Nrf2/HO-1, and Akt/GSK-3β/p70S6K check out the disturbance cycle in various afflictions/infections [173]. As of late investigations, RNA-seq demonstrated 1088 differentially imparted characteristics among CMsA and CMsB social events. Furthermore, oxidative phosphorylation-related Gene reasoning terms were up-overseen in CMsB social affairs. Additionally, the eventual outcomes of fundamental examination (FTIR range, monosaccharide sythesis, periodate oxidation) and bioactivity

appraisal guessed that *C. militaris* polysaccharides had higher β-(1 → 6)- glucan substance and malignancy counteraction specialist practices in CMsB social occasions [174]. Similarly, the water remove (CW) contained the on a very basic level most significant substance of cordycepin, phenolics, and flavonoids, which were at risk for cell support activity. CW was the most grounded disease avoidance specialist. CW had for all intents and purposes indistinguishable 2,2′-diphenyl-1-picryl-hydrazyl progressive looking through activity and lipid peroxidation restriction to l-ascorbic corrosive (96.9 ± 3.1%) and alpha-tocopherol (87.2 ± 1.0%). worked on the adequacy of CW, had no cytotoxicity sway and no skin irritation, conveyed the most CW (0.9 ± 0.0% w/w after 24 h), and passed on the most raised CW into the skin layer (33.5 ± 0.7% w/w) by Marsup and colleagus [175].

As indicated by zhu and associates examined the cell support activity related with the polysaccharides from *Cordyceps* cicadae (CP). To moreover research which of the division of CP had the best strength, in here, the in vitro cell support and in vivo against developing activities of the parts CP30–CP80 of CP were evaluated. The in vitro malignancy avoidance specialist development results revealed that every one of the divisions (for instance CP30–CP80) were incredible with CP70 as the most grounded. Conspicuously, CP70 postponed the future of Drosophila ($P < 0.05$), extended the activities of catalase (CAT) and glutathione peroxidase (GSH-Px) ($P < 0.01$), and subdued the plan of malondialdehyde (MDA) ($P < 0.01$). Also, CP70 upregulated the enunciation level of cell support related characteristics CAT, SOD1 and MTH in Drosophila ($P < 0.05$). These results showed that CP70 may draw out the future of Drosophila through the up-rule of the verbalization level of cell support related characteristics CAT, SOD1 and MTH in Drosophila. Thusly, polysaccharides from *Cordyceps* cicadae have gigantic malignant growth anticipation specialist and threatening to developing activities, and could be examined as another dietary upgrade to ruin the developing cycle [176].

In this assessment, the NBW-liquid maturing system was first settled to evaluate the effects of NBW on mycelia of *Cordyceps* militaris. The most raised mycelium center (3.90 mg/mL) and crude polysaccharides extraction yield (12.76%) were obtained in 25%-NBW (v/v) gathering. The malignancy counteraction specialist activities of mycelia were on a very basic level progressed after supplementation with NBW. The polysaccharides from 25%-NBW, 75%-NBW, and half NBW bundles showed the most grounded DPPH progressive, ABTS radical scrounging works out, and diminishing power, independently, achieving the most raised progressive looking through rate (practically 100% at 1.2 mg/mL), the least IC50 regard (1.09 mg/mL) and the most raised OD regard (2.13 at 2.0 mg/mL) [177].

In any case, there are still some data openings and limitations in energy research. First thing, most assessments revolve around the cell level; accordingly, more in vivo assessments in various animal models that appear as though human fanatical conditions and clinical applications are expected to support the sufficiency of *Cordyceps* in treating diverse blazing diseases and clarifying its nuclear parts. Second, a couple of examinations show that *Cordyceps* has staggering enemy of oxidant and safe authoritative contacts with less outcomes. Regardless, broad preclinical toxicological screens and clinical security research on *Cordyceps* are at this point inadequate. Accordingly, construct more productive assessments to survey the effects of its estimations on pharmacological activity and choose destructiveness so it will in general be used safely. Likewise, pharmacodynamics and active analyzes show that *Cordyceps* has a short half-life and vulnerable oral bioavailability generally in view of the quick deamination by adenosine deaminase (ADA), which confines its applications in affliction countering and treatment. Along these lines, the impediment of cordycepin to ADA addresses a basic issue which ought to be tended to in future assessment. Lately, this issue has been tended to through the mix of cordycepin and

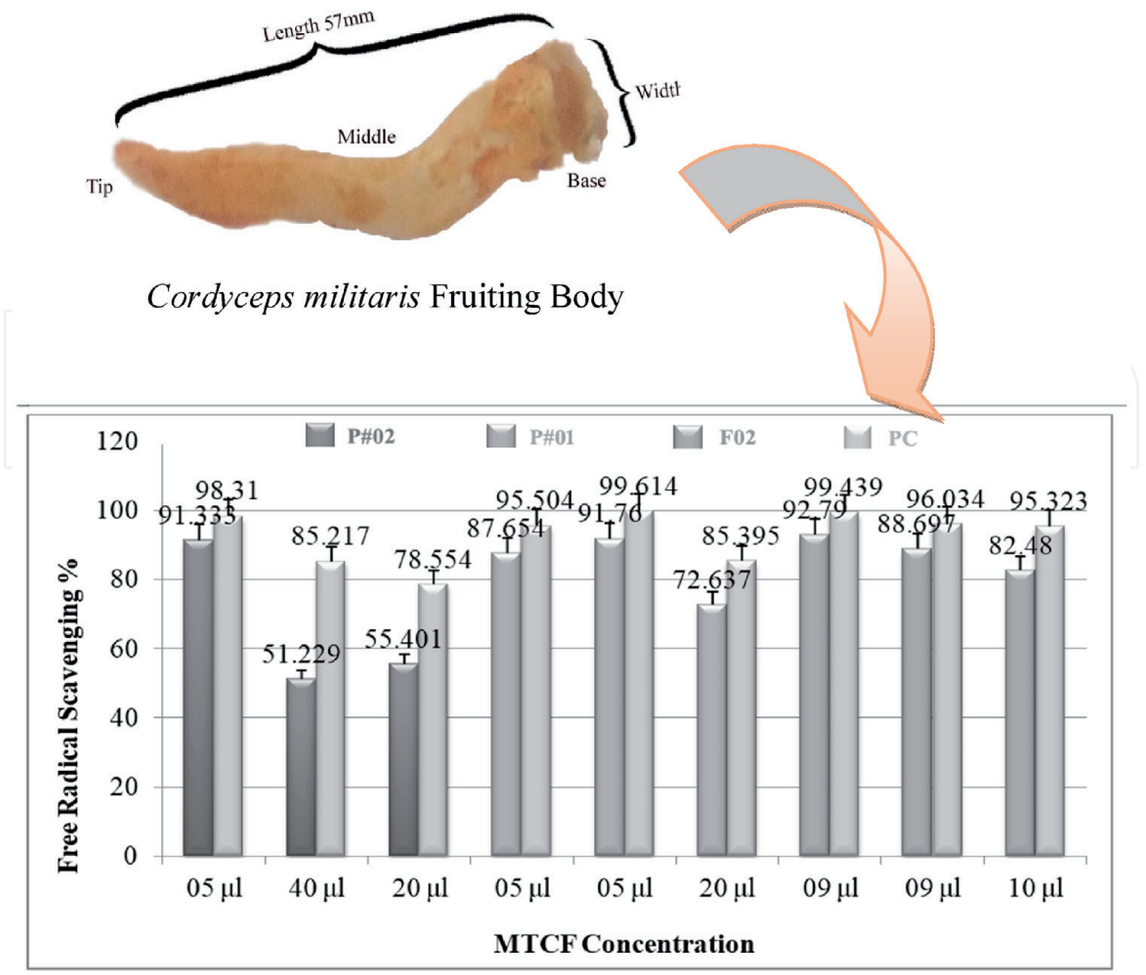

Figure 2.
Showing research output: Cordyceps militaris have broad spectrum free radical scavenging activity with their improved strains (P#01, P#02, F02).

ADA inhibitors to design ADA-safe cordycepin subordinates using nanotechnology or scaled down atom movement systems to fight ADA-resistance. These systems may be important for growing the oral bioavailability of cordycepin. Essential change is a promising system for procuring cordycepin auxiliaries with a respectable accommodating effect and high bioavailability. Appropriately, the insightful arrangement of new *Cordyceps* auxiliaries is of unfathomable vitality for the headway of new meds later on. With everything taken into account, more assessments are relied upon to progress cordycepin bioavailability and accomplish an amicability between its toxicological security and remedial practicality. This review intends to plot the medicinal potential and possible frameworks of *Cordyceps* in various provocative ailments and to give the reason to its use in the incredible treatment of searing issues (**Figure 2**).

Acknowledgements

The authors are obliged to Vice Chancellor, R.D. University, Jabalpur and interminable thankfulness to Director, Bio-Design Innovation Centre, R.D. University, Jabalpur (M.P.), for finishing this review & to avail in words for publication.

Conflict of interest

The authors declare no conflict of interest.

Author details

Loknath Deshmukh[1*], Rajendra Singh[2] and Sardul Singh Sandhu[1]

1 Department of Biological Science, Bio-Design Innovation Centre, R.D. University, Jabalpur, M.P., India

2 Department of Biological Science, Fungal Biotechnology and Invertebrate Pathology Laboratory, R.D. University, Jabalpur, M.P., India

*Address all correspondence to: loknath.deshmukh3108@gmail.com

References

[1] Zhu JS et al. The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis*: part I. J Altern Complement Med. 1998; 4: 289-303.

[2] Meena H, Mohsin M, Pandey HK, Negi PS, Ahmed Z. Estimation of cordycepin by improved HPLC method in the natural and cultured mycelia of high medicinal value Himalayan entomogenous fungus *Cordyceps sinensis*. EJEAF Che. 2010;9: 1598-603.

[3] Deshmukh, L., Agrawal, D., Sandhu, S.S., 2019. Development of Marker in the Soft Gold Mushroom *Cordyceps* spp. for Strain Improvement. In: Kundu R, Narila R. Advance in plant & microbial biotechnology. Springer Nature, Singapore; 2019.p.33-39.

[4] Pegler DN. The Chinese 'caterpillar fungus'. Mycologist. 1994; 8: 3-5.

[5] Mizuno T. Medicinal effects and utilization of *Cordyceps* (Fr.) Link (Ascomycetes) and Isaria Fr. (Mitosporic Fungi) Chinese caterpillar fungi, 'Tochukaso' (review). Int J Med Mushrooms. 1999; 1: 251-261.

[6] Hardeep S. Tuli, Anil K. Sharma, Sardul S. Sandhu, and Dharambir Kashyap. Cordycepin: A bioactive metabolite with therapeutic potential Life Sciences. 2013; 93:863-869.

[7] Sung GH, Hywel-Jones NL, Sung JM, Luangsa-ard JJ, Shrestha B, Spatafora JW. Phylogenetic classification of *Cordyceps* and the clavicipitaceous fungi. Stud Mycol. 2007; 57:5-59.

[8] Cunningham KG, Manson W, Spring FS, Hutchinson SA. Cordycepin, a metabolic product isolated from cultures of *Cordyceps militaris* (Linn.) link. Nature. 1950; 166:949-54.

[9] Li, N., Song, J.G., Liu, J.Y. and Zhang, H. Compared chemical composition between *Cordyceps militaris* and *Cordycpes sinensis*. Journal of Jilin Agriculture University. 1995; 17: 80-83. (in Chinese).

[10] Hur H. Chemical ingredients of *Cordyceps militaris*. Mycobiology. 2008; 36:233-5.

[11] Liu Y, Wang J, Wang W, Zhang H, Zhang X, Han C. The chemical constituents and pharmacological actions of *Cordyceps sinensis*. Evid Based Complement Alternat Med 2015;2015: 575063.

[12] Tuli HS, Sandhu SS, Sharma AK. Pharmacological and therapeutic potential of *Cordyceps* with special reference to cordycepin. Biotechnology. 2013;3. http://dx.doi.org/10.1007/s13205-013-0121-9.

[13] Lu H, Li X, Zhang J, Shi H, Zhu X, He X. Effects of cordycepin on HepG2 and EA. hy926 cells: potential antiproliferative, antimetastatic and anti-angiogenic effects on hepatocellular carcinoma. Oncol Lett. 2014; 7: 1556-1562.

[14] Kodama EN, McCaffrey RP, Yusa K and Mitsuya H: Antileukemic activity and mechanism of action of cordycepin against terminal deoxynucleotidyl transferasepositive (TdT+) leukemic cells. Biochem Pharmacol. 2000; 59:273-281.

[15] Rong Wu, Jian-Ping Gao, Hui-Lin Wang, Yan Gao, Qian Wu, Xiao-Hua Cui. Effects of fermented *Cordyceps sinensis* on oxidative stress in doxorubicin treated rats. 2015; 11, 44: 724-731.

[16] Shengli Yanga, Xi Yanga and Hui Zhangb. Extracellular polysaccharide biosynthesis in *Cordyceps*. 2020. https://doi.org/10.1080/1040841X.2020.1794788.

[17] Jian-Hui Xiao, Dai-Min Xiao, Dai-Xiong Chen, Yu Xiao, Zong-Qi Liang, and Jian-Jiang Zhong. Polysaccharides from the Medicinal Mushroom *Cordyceps* taii Show Antioxidant and Immunoenhancing Activities in aD-Galactose-Induced Aging Mouse Model. Evidence-Based Complementary and Alternative Medicine. 2012, Article ID 273435, 15 pages doi:10.1155/2012/273435.

[18] Park, E. S., Kang, D. H., Yang, M. K., Kang, J. C., Jang, Y. C., Park, J. S., Shin, H. S. Cordycepin, 30-deoxyadenosine, prevents rat hearts from ischemia/reperfusion injury via activation of Akt/GSK- 3β/p70S6K signaling pathway and HO-1 expression. Cardiovascular Toxicology. 2014; 14(1), 1-9. https://doi.org/10.1007/s12012-013-9232-0.

[19] Lei, J., Wei, Y., Song, P., Li, Y., Zhang, T., Feng, Q., & Xu, G. Cordycepin inhibits LPS-induced acute lung injury by inhibiting inflammation and oxidative stress. European Journal of Pharmacology. 2018; 818:110-114. https://doi.org/10.1016/j.ejphar.2017.10.029.

[20] Deshmukh, L., Singh, R., Sandhu, S.S. Far ranging antimicrobial and free radical scavenging activity of Himalayan soft gold mushroom; *Cordyceps sp*. Biotechnology and Biological Sciences. 2019; pp. 297-302. DOI: 10.1201/9781003001614-50.

[21] Hui Mei Yu, Bor-Sen Wang, Shiow Chyn Huang, and Pin-Der Duh. Comparison of Protective Effects between Cultured *Cordyceps* militaris and Natural *Cordyceps sinensis* against Oxidative Damage. J. Agric. Food Chem. 2006; 54:8,3132-3138 https://doi.org/10.1021/jf053111w.

[22] Deng-Bo Ji, Jia Ye, Chang-Ling Li, Yu-Hua Wang, Jiong Zhao and Shao-Qing Cai. Antiaging effect of *Cordyceps sinensis* extract. 2008. https://doi.org/10.1002/ptr.2576.

[23] Opeyemi J. Olatunji, Yan Fenga, Oyenike O. Olatunji, Jian Tanga, Yuan Wei a, Zhen Ouyanga, and Zhaoliang Suc. Polysaccharides purified from *Cordyceps cicadae* protects PC12 cells against glutamate-induced oxidative damage. Carbohydrate Polymers, 2016; 153, 187-195. doi:10.1016/j.carbpol.2016.06.108.

[24] Shen, W., Song, D., Wu, J., & Zhang, W. Protective effect of a polysaccharide isolated from a cultivated *Cordyceps* mycelia on hydrogen peroxide-induced oxidative damage in PC12 cells. Phytother. Res. 2010;25: 675-680. DOI: 10.1002/ptr.3320.

[25] Mei Tong He, Ah Young Lee, Chan Hum Park, and Eun Ju Cho. Protective effect of *Cordyceps militaris* against hydrogen peroxide-induced oxidative stress *in vitro*. Nutr Res Pract. 2019; 13(4): 279-285. doi: 10.4162/nrp.2019.13.4.279.

[26] Singh, M., Tulsawani, R., Koganti, P., Chauhan, A., Manickam, M., & Misra, K. *Cordyceps sinensis* Increases Hypoxia Tolerance by Inducing Heme Oxygenase-1 and Metallothione in via Nrf2 Activation in Human Lung Epithelial Cells. BioMed Research International. 2013; 1-13. doi:10.1155/2013/569206.

[27] Li, S. P., Zhao, K. J., Ji, Z. N., Song, Z. H., Dong, T. T.., Lo, C. K., Tsim, K. W. A polysaccharide isolated from *Cordyceps sinensis*, a traditional Chinese medicine, protects PC12 cells against hydrogen peroxide-induced injury. Life Sciences. 2003; 73(19), 2503-2513. doi:10.1016/s0024-3205(03)00652-0.

[28] Zhang, L., Wu, T., Olatunji, O. J., Tang, J., Wei, Y., & Ouyang, Z. N6-(2-hydroxyethyl)-adenosine from *Cordyceps cicadae* attenuates hydrogen peroxide induced oxidative toxicity in PC12 cells. Metabolic Brain Disease. 2019. doi:10.1007/s11011-019-00440-1.

[29] Liu, H., Cao, D., Liu, H., Liu, X., Mai, W., Lan, H., ... Zheng, Q. The Herbal Medicine *Cordyceps sinensis* Protects Pancreatic Beta Cells from Streptozotocin-Induced Endoplasmic Reticulum Stress. Canadian Journal of Diabetes. 2016; 40(4), 329-335. Doi:10.1016/j.jcjd.2016.02.001.

[30] Xiao, Y., Zhang, Q., Miao, J., Rui, X., Li, T., & Dong, M. (2015). Antioxidant activity and DNA damage protection of mung beans processed by solid state fermentation with *Cordyceps militaris* SN-18. Innovative Food Science & Emerging Technologies, 31, 216-225. doi:10.1016/j.ifset.2015.06.006.

[31] Li, Z., Zhang, Z., Zhang, J., Jia, J., Ding, J., Luo, R., & Liu, Z. *Cordyceps militaris* Extract Attenuates D-Galactose-Induced Memory Impairment in Mice. Journal of Medicinal Food. 2012; 15(12), 1057-1063. doi:10.1089/jmf.2011.2105.

[32] Wang, J., Chen, C., Jiang, Z., Wang, M., Jiang, H., & Zhang, X. Protective effect of *Cordyceps militaris* extract against bisphenol A induced reproductive damage. Systems Biology in Reproductive Medicine. 2016; 62(4),249-257. doi:10.1080/19396368.2016.1182234.

[33] Karbownik M and Reiter RJ. Antioxidative effects of melatonin in protection against cellular damage caused by ionizing radiation. Proc Soc Exp Biol Med. 2000; 225:9-22.

[34] Chen C, Luo SS, Li Y, Sun YJ and Zhang CK: Study on antioxidant activity of three *Cordyceps sp*. by chemiluminescence Shanghai. J Trad Chinese Med. 2004; 38:53-55.

[35] Yu HM, Wang BS, Huang SC and Duh PD. Comparison of protective effects between cultured *Cordyceps militaris* and natural *Cordyceps sinesis* against oxidative damage. J Agric Food Chem. 2006; 54:3132-3138.

[36] Ogawa Y, Kobayashi T, Nishioka A, et al. Radiation-induced reactive oxygen species (ROS) formation prior to oxidative DNA damage in human peripheral T cells. Int J Mol Med. 2003; 11:149-152.

[37] Chu HL, Chien JC and Duh PD. Protective effect of *Cordyceps militaris* against high glucose-induced oxidative stress in human umbilical vein endothelial cells. Food Chem. 2011; 129:871-876.

[38] Li SP, Zhang GH, Zeng Q, et al. Hypoglycemic activity of polysaccharide, with antioxidation, isolated from cultured *Cordyceps* mycelia. Phytomedicine. 2006; 13:428-33.

[39] Yan, F., Wang, B., & Zhang, Y. Polysaccharides from *Cordyceps sinensis* mycelium ameliorate exhaustive swimming exercise-induced oxidative stress. Pharmaceutical Biology. 2013; 52(2), 157-161. doi:10.3109/13880209.2013.820197.

[40] Overgaard-Hansen, K. The inhibition of 5-phosphoribosyl-1-pyrophosphate formation by cordycepin triphosphate in extracts of Ehrlich ascites tumor cells. Biochimica et Biophysica Acta (BBA) - Specialized Section on Nucleic Acids and Related Subjects. 1964; 80(3), 504-507. doi:10.1016/0926-6550(64)90154-9.

[41] Deshmukh, L., Sharma, A. K., & Sandhu, S. S. Contrive Himalayan Soft Gold *Cordyceps Species*: a Lineage of Eumycota Bestowing Tremendous Pharmacological and Therapeutic Potential. Current Pharmacology Reports. 2020. doi:10.1007/s40495-020-00223-8.

[42] Robins, M. J., & Robins, R. K. The Synthesis of 2′,3′-Dideoxyadenosine from 2′-Deoxyadenosine. Journal of the American Chemical Society. 1964; 86(17), 3585-3586. doi:10.1021/ja01071a055.

[43] Ota, T., Suzuki, Y., Nishikawa, T., Otsuki, T., Sugiyama, T., Irie, R., Nagai, K. Complete sequencing and characterization of 21,243 full-length human cDNAs. Nature Genetics. 2003; 36(1), 40-45. doi:10.1038/ng1285.

[44] Rottman, F., & Guarino, A. J. The inhibition of purine biosynthesis De novo in *Bacillus subtilis* by cordycepin. Biochimica et Biophysica Acta (BBA) - Specialized Section on Nucleic Acids and Related Subjects. 1964; 80(4), 640-647. doi:10.1016/0926 -6550(64)90308-1.

[45] S. Katayama et al. Antisense Transcription in the Mammalian Transcriptome. Science, (2005). 309(5740), 1564-1566. doi:10.1126/ science.1112009.

[46] Yi Liu, Jihui Wang, Wei Wang, Hanyue Zhang, Xuelan Zhang, and Chunchao Han. The Chemical Constituents and Pharmacological Actions of *Cordyceps sinensis.* Evidence-Based Complementary and Alternative Medicine. 2015; Article ID 575063, 12 pages http://dx.doi. org/10.1155/2015/575063.

[47] Liyang Yang, Guilan Li, Zhi Chai, Qiang Gong, Jianquan Guo. Synthesis of cordycepin: current scenario and future perspectives. Fungal Genetics and Biology. 2020; S1087-1845(20)30122-5. DOI: https://doi.org/10.1016/j. fgb.2020.103431.

[48] Ahn Y. J, Park S. J, Lee S. G, Shin S. C, Choi D. H. Cordycepin: Selective growth inhibitor derived from liquidculture of *Cordyceps militaris* against *Clostridium spp.* J Agric Food Chem. 2000;48:2744-8.

[49] Balon T. W, Jasman A. P, Zhu J. S. A fermentation product of *Cordyceps sinensis* increases whole-body insulinsensitivity in rats. J Altern Complement Med. 2002; 8:315-23.

[50] Xian-Bing Mao, Jian-Jiang Zhong. Significant effect of NH4+ on cordycepin production by submerged cultivation of medicinal mushroom *Cordyceps militaris.* Enzyme and Microbial Technology. 2006; 38:343-350. doi:10.1016/j. enzmictec.2004.10.010.

[51] M. Soltani, R. A. Malek, N. A. Elmarzugi, M. F. Mahomoodally, D. Uy, O. M. Leng, and H. A. El-Enshasy. Cordycepin: A Biotherapeutic Molecule from Medicinal Mushroom. Biology of Macrofungi, Fungal Biology, 2018; 319-349. https://doi. org/10.1007/978-3-030-02622-6_16.

[52] Ji-Sue Baik, Seo-Won Mun, Kyoung-Sook Kim, Shin-Ji Park, Hyun-Kyoung Yoon, Dong-Hyun Kim, Min-Kyu Park, Cheorl-Ho Kim, and Young-Choon Lee. Apoptotic Effects of Cordycepin Through the Extrinsic Pathway and p38 MAPK Activation in Human Glioblastoma U87MG Cells. J. Microbiol. Biotechnol. 2016; 26(2), 309-314. http:// dx.doi.org/10.4014/jmb.1507.07090.

[53] Boontariga Wongsaa, Nachon Raethongb, Pramote Chumnanpuena,c, Jirasak Wong-ekkabutc,d, Kobkul Laotenge, Wanwipa Vongsangnak. Alternative metabolic routes in channeling xylose to cordycepin production of *Cordyceps militaris* identified by comparative transcriptome analysis. Genomics. 2019. https://doi. org/10.1016/j.ygeno.2019.04.015.

[54] Roypim Thananusak, Kobkul Laoteng, Nachon Raethong, Yu Zhang and Wanwipa Vongsangnak. Metabolic Responses of Carotenoid and Cordycepin Biosynthetic Pathways in *Cordyceps militaris* under Light-Programming Exposure through Genome-Wide Transcriptional Analysis. Biology 2020, 9, 242. doi:10.3390/ biology9090242.

[55] Haisheng lu, Xiting li, Jianying zhang, Hui shi, Xiaofeng zhu and

Xiaoshun he. Effects of cordycepin on HepG2 and EA.hy926 cells: Potential antiproliferative, antimetastatic and anti-angiogenic effects on hepatocellular carcinoma, oncology letters. 2014; 7: 1556-1562. DOI: 10.3892/ol.2014.1965.

[56] Dong, J. Z., Ding, J., Yu, P. Z., Lei, C., Zheng, X. J., & Wang, Y. Composition and distribution of the main active components in selenium-enriched fruit bodies of *Cordyceps militaris* link. Food Chemistry. 2013; 137(1-4), 164-167. doi:10.1016/j.foodchem.2012.10.021.

[57] Hu, T., Liang, Y., Zhao, G. *et al.* Selenium Biofortification and Antioxidant Activity in *Cordyceps militaris* Supplied with Selenate, Selenite, or Selenomethionine. Biol Trace Elem Res. 2019; 187, 553-561. https://doi.org/10.1007/s12011-018-1386-y.

[58] Song, J., Wang, Y., Teng, M., Cai, G., Xu, H., Guo, H., Teng, L. Studies on the Antifatigue Activities of *Cordyceps militaris* Fruit Body Extract in Mouse Model. Evidence-Based Complementary and Alternative Medicine. 2015; 1-15. doi:10.1155/2015/174616.

[59] Shin, K. H., Lim, S. S., Lee, S. H., Lee, Y. S., & Cho, S. Y. Antioxidant and Immunostimulating Activities of the Fruiting Bodies of Paecilomyces japonica, a New Type of *Cordyceps sp.* Annals of the New York Academy of Sciences. 2006; 928(1), 261-273. doi:10.1111/j.1749-6632.2001.tb05655.x.

[60] Yamaguchi, Y., Kagota, S., Nakamura, K., Shinozuka, K., & Kunitomo, M. Inhibitory effects of water extracts from fruiting bodies of cultured *Cordyceps sinensis* on raised serum lipid peroxide levels and aortic cholesterol deposition in atherosclerotic mice. Phytotherapy Research. 2000; 14(8), 650-652. doi:10.1002/1099-1573(200012)14:8<650::aid-ptr675>3.0.co;2-0.

[61] N. Singpoonga, R. Rittiron, B. Seang-on, and P. Chaiprasart, Determination of Adenosine and Cordycepin Concentrations in *Cordyceps militaris* Fruiting Bodies Using Near-Infrared spectroscopy. ACS Omega. 2020; 5, 27235−27244. https://dx.doi.org/10.1021/acsomega.0c03403.

[62] Lin, R., Liu, H., Wu, S., Pang, L., Jia, M., Fan, K., ... Jia, L. Production and in vitro antioxidant activity of exopolysaccharide by a mutant, *Cordyceps militaris* SU5-08. International Journal of Biological Macromolecules. 2012; 51(1-2), 153-157. doi:10.1016/j.ijbiomac.2012.04.011.

[63] Li, Y., Yang, H., Yang, H. *et al.* Assessment of drying methods on the physiochemical property and antioxidant activity of *Cordyceps militaris*. Food Measure. 2019; 13, 513-520. https://doi.org/10.1007/s11694-018-9965-3.

[64] Leung, P. H., Zhao, S., Ho, K. P., & Wu, J. Y. Chemical properties and antioxidant activity of exopolysaccharides from mycelial culture of *Cordyceps sinensis* fungus Cs-HK1. Food Chemistry. 2009; 114(4), 1251-1256. doi:10.1016/j.foodchem.2008.10.081.

[65] Won, S.-Y., & Park, E.-H. Anti-inflammatory and related pharmacological activities of cultured mycelia and fruiting bodies of *Cordyceps militaris*. Journal of Ethnopharmacology. 2005; 96(3), 555-561. doi:10.1016/j.jep.2004.10.009.

[66] Yang, T., Guo, M., Yang, H. et al. The blue-light receptor CmWC-1 mediates fruit body development and secondary metabolism in *Cordyceps militaris*. Appl Microbiol Biotechnol. 2016; 100, 743-755 (2016). https://doi.org/10.1007/s00253-015-7047-6.

[67] Kramer, G.J., Nodwell, J.R. Chromosome level assembly and

secondary metabolite potential of the parasitic fungus *Cordyceps militaris*. BMC Genomics 2017; 18, 912. https://doi.org/10.1186/s12864-017-4307-0.

[68] Woolley, V. C., Teakle, G. R., Prince, G., de Moor, C. H., & Chandler, D. Cordycepin, a metabolite of *Cordyceps militaris*, reduces immune-related gene expression in insects. Journal of Invertebrate Pathology. 2020; 107480. doi:10.1016/j.jip.2020.107480.

[69] Lu, Y., Luo, F., Cen, K., Xiao, G., Yin, Y., Li, C., Wang, C. Omics data reveal the unusual asexual-fruiting nature and secondary metabolic potentials of the medicinal fungus *Cordyceps cicadae*. BMC Genomics. 2017; 18(1). doi:10.1186/s12864-017-4060-4.

[70] Yang, T., Guo, M., Yang, H., Guo, S., & Dong, C. The blue-light receptor CmWC-1 mediates fruit body development and secondary metabolism in *Cordyceps* militaris. Applied Microbiology and Biotechnology. 2015; 100(2), 743-755. doi:10.1007/s00253-015-7047-6.

[71] Kramer, G. J., & Nodwell, J. R. Chromosome level assembly and secondary metabolite potential of the parasitic fungus *Cordyceps* militaris. BMC Genomics. 2017; 18(1). doi:10.1186/s12864-017-4307-0.

[72] Jiaojiao, Z., Fen, W., Kuanbo, L. *et al.* Heat and light stresses affect metabolite production in the fruit body of the medicinal mushroom *Cordyceps militaris*. Appl Microbiol Biotechnol. 2018; 102, 4523-4533. https://doi.org/10.1007/s00253-018-8899-3.

[73] Yu, H. M., Wang, B.-S., Huang, S. C., & Duh, P.-D. Comparison of Protective Effects between Cultured *Cordyceps militaris* and Natural *Cordyceps sinensis* against Oxidative Damage. Journal of Agricultural and Food Chemistry. 2006; 54(8), 3132-3138. doi:10.1021/jf053111w.

[74] Ashraf, S. A., Elkhalifa, A. E. O., Siddiqui, A. J., Patel, M., Awadelkareem, A. M., Snoussi, M., ... Hadi, S. Cordycepin for Health and Wellbeing: A Potent Bioactive Metabolite of an Entomopathogenic Medicinal Fungus *Cordyceps* with Its Nutraceutical and Therapeutic Potential. Molecules. 2020; 25(12), 2735. doi:10.3390/molecules25122735.

[75] Buenz, E. J., Weaver, J. G., Bauer, B. A., Chalpin, S. D., & Badley, A. D. *Cordyceps sinensis* extracts do not prevent Fas-receptor and hydrogen peroxide-induced T-cell apoptosis. Journal of Ethnopharmacology. 2004; 90(1), 57-62. doi:10.1016/j.jep.2003.09.025.

[76] Dong, C.-H., & Yao, Y.-J. In vitro evaluation of antioxidant activities of aqueous extracts from natural and cultured mycelia of *Cordyceps sinensis*. LWT - Food Science and Technology. 2008; 41(4), 669-677. doi:10.1016/j.lwt.2007.05.002.

[77] Yan, J.-K., Wang, W.-Q., & Wu, J.-Y. Recent advances in *Cordyceps sinensis* polysaccharides: Mycelial fermentation, isolation, structure, and bioactivities: A review. Journal of Functional Foods. 2014; 6, 33-47. doi:10.1016/j.jff.2013.11.024.

[78] Jin, LQ., Xu, ZW., Zhang, B. *et al.* Genome sequencing and analysis of fungus Hirsutella *sinensis* isolated from *OphioCordyceps sinensis*. AMB Expr. 2020;10, 105. https://doi.org/10.1186/s13568-020-01039-x.

[79] Buranrat B, Sangdee K, Thammawat S, Sangdee A. Mechanisms of crude protein from medicinal mushroom *Ophiocordyceps sobolifera* against human breast MCF-7 cancer cells. Biologia. 2020. https://doi.org/10.2478/s11756-020-00482-2.

[80] Zhang, Z., Lv, G., Pan, H., Fan, L., Soccol, C. R., & Pandey, A. Production

of powerful antioxidant supplements via solid-state fermentation of wheat (*Triticum aestivum* Linn.) by *Cordyceps militaris*. Food Technology and Biotechnology. 2012; 50(1), 32-39.

[81] Kang, H. J., Baik, H. W., Kim, S. J., Lee, S. G., Ahn, H. Y., Park, J. S., ... Lee, S. M. *Cordyceps militaris* Enhances Cell-Mediated Immunity in Healthy Korean Men. Journal of Medicinal Food. 2015; 18(10), 1164-1172. doi:10.1089/jmf.2014.3350.

[82] Jin, J., Kang, W., Zhong, C., Qin, Y., Zhou, R., Liu, H., ... Zhang, S. (2018). The pharmacological properties of *OphioCordyceps xuefengensis* revealed by transcriptome analysis. Journal of Ethnopharmacology. 2018; 219, 195-201. doi:10.1016/j.jep.2018.02.007.

[83] Qin, Y., Zhou, R., Jin, J., Xie, J., Liu, H., Cai, P., ... Zhang, S. UPLC-ESI-Q-TOF-MS/MS analysis of anticancer fractions from *OphioCordyceps xuefengensis* and *OphioCordyceps sinensis*. Biomedical Chromatography. 2020; e4841. doi:10.1002/bmc.4841.

[84] Ng, T. B., & Wang, H. X. Pharmacological actions of *Cordyceps*, a prized folk medicine. Journal of Pharmacy and Pharmacology. 2005; 57(12), 1509-1519. doi:10.1211/jpp.57.12.0001.

[85] Quan, X., Kwak, B. S., Lee, J.-Y., Park, J. H., Lee, A., Kim, T. H., & Park, S. *Cordyceps militaris* Induces Immunogenic Cell Death and Enhances Antitumor Immunogenic Response in Breast Cancer. Evidence-Based Complementary and Alternative Medicine, 2020, 1-11. doi:10.1155/2020/9053274.

[86] Das, S. K., Masuda, M., Sakurai, A., & Sakakibara, M. Medicinal uses of the mushroom *Cordyceps militaris*: Current state and prospects. Fitoterapia. 2010; 81(8), 961-968. doi:10.1016/j.fitote.2010.07.010.

[87] Kuo, H.-C., Su, Y.-L., Yang, H.-L., & Chen, T.-Y. Identification of Chinese Medicinal Fungus *Cordyceps sinensis* by PCR-Single-Stranded Conformation Polymorphism and Phylogenetic Relationship. Journal of Agricultural and Food Chemistry. 2005; 53(10), 3963-3968. doi:10.1021/jf0482562.

[88] Jo, E., Jang, H.-J., Shen, L., Yang, K. E., Jang, M. S., Huh, Y. H., ... Park, S. J. *Cordyceps militaris* Exerts Anticancer Effect on Non–Small Cell Lung Cancer by Inhibiting Hedgehog Signaling via Suppression of TCTN3. Integrative Cancer Therapies. 2020; 19, 153473542092375. doi:10.1177/1534735420923756.

[89] Yue, K., Ye, M., Zhou, Z., Sun, W., & Lin, X. The genus *Cordyceps*: a chemical and pharmacological review. Journal of Pharmacy and Pharmacology. 2012; 65(4), 474-493. doi:10.1111/j.2042-7158.2012.01601.x .

[90] Xu, G., Yuan, G., Lu, X., An, L., Sheng, Y., & Du, P. Study on the effect of regulation of *Cordyceps* militaris polypeptide on the immune function of mice based on a transcription factor regulatory network. Food & Function. 2020. doi:10.1039/d0fo01043j.

[91] Won, S.-Y., & Park, E.-H. Anti-inflammatory and related pharmacological activities of cultured mycelia and fruiting bodies of *Cordyceps militaris*. Journal of Ethnopharmacology. 2005; 96(3), 555-561. doi:10.1016/j.jep.2004.10.009.

[92] Marchbank, T., Ojobo, E., Playford, C. J., & Playford, R. J. Reparative properties of the traditional Chinese medicine *Cordyceps sinensis* (Chinese caterpillar mushroom) using HT29 cell culture and rat gastric damage models of injury. British Journal of Nutrition. 2011; 105(09), 1303-1310. doi:10.1017/s0007114510005118.

[93] Pirinccioglu AG, Gökalp D, Pirinccioglu M, Kizil G, Kizil M.

Malondialdehyde (MDA) and protein carbonyl (PCO) levels as biomarkers of oxidative stress in subjects with familial hypercholesterolemia. Clin Biochem. 2010; 43:1220-4.

[94] Zhang J, Yu Y, Zhang Z, Ding Y, Dai X, Li Y. Effect of polysaccharide from cultured *Cordyceps sinensis* on immune function and anti-oxidation activity of mice exposed to 60Co. Int Immunopharmacol. 2011; 11:2251-7.

[95] Takemura G, Fujiwara H. Doxorubicin-induced cardiomyopathy from the cardiotoxic mechanisms to management. Prog Cardiovasc Dis. 2007; 49:330-52.

[96] Rong Wu, Jian-Ping Gao, Hui-Lin Wang, Yan Gao, Qian Wu, and Xiao-Hua Cui. Effects of fermented *Cordyceps sinensis* on oxidative stress in doxorubicin treated rats. Pharmacogn Mag. 2015, 11(44): 724-731.doi: 10.4103/0973-1296.165562.

[97] Eunhyun Choi, Junsang Oh & Gi-Ho Sung. Antithrombotic and Antiplatelet Effects of *Cordyceps militaris*. Mycobiology. 2020; 48:3, 228-232, DOI:10.1080/12298093.2020.1763115.

[98] Buenz, E. J., Bauer, B. A., Osmundson, T. W., & Motley, T. J. The traditional Chinese medicine *Cordyceps sinensis* and its effects on apoptotic homeostasis. Journal of Ethnopharmacology. 2005; 96(1-2), 19-29. doi:10.1016/j.jep.2004.09.029.

[99] Wang, J., Liu, Y.-M., Cao, W., Yao, K.-W., Liu, Z.-Q., & Guo, J.-Y. Anti-inflammation and antioxidant effect of Cordymin, a peptide purified from the medicinal mushroom *Cordyceps sinensis*, in middle cerebral artery occlusion-induced focal cerebral ischemia in rats. Metabolic Brain Disease. 2012; 27(2), 159-165. doi:10.1007/s11011-012-9282-1.

[100] Onasanwo, S. A., Oyagbemi, A. A., & Saba, A. B. Anti-inflammatory and analgesic properties of the ethanolic extract of *Cnidoscolus aconitifolius* in rats and mice. Journal of Basic and Clinical Physiology and Pharmacology. 2011; 22(1-2). doi:10.1515/jbcpp.2011.010.

[101] Min Yin, Na Li, Emmanuel Ayobami Makinde, Opeyemi Joshua Olatunji & Ziyuan Ni. N6 -2-hydroxyethyl-adenosine ameliorate cisplatin induced acute kidney injury in mice, All Life. 2020; 13:1, 244-251, DOI: 10.1080/26895293.2020.1760149.

[102] Yang, N.-N., Jiang, N., Ma, Q.-Y., Kong, F.-D., Xie, Q.-Y., Zhou, L.-M., ... Zhao, Y.-X. Chemical study of the strain *Cordyceps spp.* from cell fusion between *Cordyceps militaris* and *Cordyceps cicadae*. Journal of Asian Natural Products Research. 2018; 1-7. doi:10.1080/10286020.2018.1451518.

[103] Thongchai, S., Sangdee, K. & Sangdee, A. Antibacterial activity of crude protein and development of species-specific molecular marker for fungus *OphioCordyceps sobolifera*. Biologia. 2020. https://doi.org/10.2478/s11756-020-00589-6.

[104] Xiao, Y., Zhang, Q., Miao, J., Rui, X., Li, T., & Dong, M. Antioxidant activity and DNA damage protection of mung beans processed by solid state fermentation with *Cordyceps militaris* SN-18. Innovative Food Science & Emerging Technologies. 2015; 31, 216-225. doi:10.1016/j.ifset.2015.06.006.

[105] Yadav, R. Entomopathogenic Mushroom (*Cordyceps sp.*) as Immunity Booster. Biotica Research Today. 2020; 2, 7 (Jul. 2020), 690-692.

[106] Yao, L.-H., Li, C.-H., Yan, W.-W., Huang, J.-N., Liu, W.-X., & Xiao, P. Cordycepin decreases activity of hippocampal CA1 pyramidal neuron through membrane hyperpolarization. Neuroscience Letters. 2011; 503(3), 256-260. doi:10.1016/j.neulet.2011.08.048.

[107] Cheng, C., & Zhu, X. Cordycepin mitigates MPTP-induced Parkinson's disease through inhibiting TLR/NF-κB signaling pathway. Life Sciences. 2019. doi:10.1016/j.lfs.2019.02.037.

[108] Ying Sun, Wen-min Huang, Pei-chen Tang, Xin Zhang, Xiao-yan Zhang, Bo cheng Yu, Yi-Yun Fan, Xiao-qun Ge, Xiao-Ling Zhang. Neuroprotective effects of natural cordycepin on LPS-induced Parkinson's disease through suppressing TLR4/NF-κB/NLRP3-mediated pyroptosis. Journal of Functional Foods. 2020; 104274 https://doi.org/10.1016/j.jff.2020.104274.

[109] Olatunji, O. J., Feng, Y., Olatunji, O. O., Tang, J., Ouyang, Z., & Su, Z. Cordycepin protects PC12 cells against 6-hydroxydopamine induced neurotoxicity via its antioxidant properties. Biomedicine & Pharmacotherapy. 2016; 81, 7-14. doi:10.1016/j.biopha.2016.03.009.

[110] He, M.T., Lee, A.Y., Kim, J.H. et al. Protective role of *Cordyceps militaris* in $A\beta_{1-42}$-induced Alzheimer's disease in vivo. Food Sci Biotechnol. 2019; 28, 865-872. https://doi.org/10.1007/s10068-018-0521-z.

[111] He, M. T., Lee, A. Y., Kim, J. H., Park, C. H., Shin, Y. S., & Cho, E. J. Protective role of *Cordyceps militaris* in Aβ1-42-induced Alzheimer's disease in vivo. Food Science and Biotechnology. 2018. doi:10.1007/s10068-018-0521-z.

[112] Yang, H.-Y., Leu, S.-F., Wang, Y.-K., Wu, C.-S., & Huang, B.-M. *Cordyceps sinensis* mycelium induces MA-10 mouse leydig tumor cell apoptosis by activating the caspase-8 pathway and suppressing the NF-κB pathway. Archives of Andrology. 2006; 52(2), 103-110. doi:10.1080/01485010500315818.

[113] Qian, G., Pan, G.-F., & Guo, J.-Y. Anti-inflammatory and antinociceptive effects of cordymin, a peptide purified from the medicinal mushroom *Cordyceps sinensis*. Natural Product Research. 2012; 26(24), 2358-2362. doi:10.1080/14786419.2012.658800.

[114] Au, D., Wang, L., Yang, D., Mok, D. K. W., Chan, A. S. C., & Xu, H. Application of microscopy in authentication of valuable Chinese medicine i-*Cordyceps sinensis*, its counterfeits, and related products. Microscopy Research and Technique. 2012; 75(1), 54-64. doi:10.1002/jemt.21024.

[115] Long, H., Qiu, X., Cao, L., Liu, G., Rao, Z., Han, R., Toxicological safety evaluation of the cultivated Chinese *Cordyceps*, Journal of Ethnopharmacology. 2020. https://doi.org/10.1016/ j.jep.2020.113600.

[116] Neeranjini Nallathamby, Sri Nurestri Abd Malek, Sharmili Vidyadaran, Chia-Wei Phan, Vikineswary Sabaratnam. Lipids in an Ethyl Acetate Fraction of Caterpillar Medicinal Mushroom, *Cordyceps militaris* (Ascomycetes), Reduce Nitric Oxide Production in BV2 Cells via Nrf2 and NF-? B Pathways. DOI: 10.1615/IntJMedMushrooms.2020037001.

[117] Wang, L., He, Y., Li, Y., Pei, C., Olatunji, O. J., Tang, J., ... Yan, B. Protective effects of nucleosides-rich extract from *Cordyceps cicadae* against cisplatin induced testicular damage. Chemistry & Biodiversity. 2020. doi:10.1002/cbdv.202000671.

[118] Eunhyun Choi, Junsang Oh & Gi-Ho Sung. Beneficial Effect of *Cordyceps militaris* on Exercise Performance via Promoting Cellular Energy Production, Mycobiology. 2020; 48:6, 512-517, DOI: 10.1080/12298093.2020.1831135.

[119] Xiong C, Xia Y, Zheng P et al. Increasing oxidative stress tolerance and subculturing stability of *Cordyceps militaris* by overexpression of a

glutathione peroxidase gene. Appl Microbiol Biotechnol. 2013; 97(5):2009-2015.

[120] Rintu Das, Silpak Biswas and Ena Ray Banerjee. Nutraceutical-prophylactic and Therapeutic Role of Functional Food in Health. J Nutr Food Sci. 2016; 6:4. http://dx.doi.org/10.4172/2155-9600.1000527.

[121] Zhang Y, Xu L, Zhang S, et al. Genetic diversity of *OphioCordyceps sinensis*, a medicinal fungus endemic to the Tibetan Plateau: implications for its evolution and conservation. BMC Evol Biol. 2009; 9(1):290.

[122] Qin, P.; Wang, Z.; Lu, D.; Kang, H.; Li, G.; Guo, R.; Zhao, Y.; Han, R.; Ji, B.; Zeng, Y. Neutral Lipid Content in Lipid Droplets: Potential Biomarker of Cordycepin Accumulation in Cordycepin-Producing Fungi. *Molecules.* 2019; *24*, 3363.

[123] Wang, Ningqun; Li, Jie; Huang, Xiaobo; Chen, Wenqiang; Chen, Yujing. Herbal Medicine (*Cordyceps sinensis*) Improves Health-Related Quality of Life in Moderate-to-Severe Asthma. Evidence-Based Complementary and Alternative Medicine. 2016; 1-8. doi:10.1155/2016/6134593.

[124] Patel, V. J., Biswas Roy, S., Mehta, H. J., Joo, M., & Sadikot, R. T. (2018). Alternative and Natural Therapies for Acute Lung Injury and Acute Respiratory Distress Syndrome. BioMed Research International. 2018; 1-9. doi:10.1155/2018/2476824.

[125] X. Yang, Y. Li, Y. He et al., Cordycepin alleviates airway hyperreactivity in a murine model of asthma by attenuating the inflammatory process. International Immunopharmacology. 2015; 26: 2, 401-408.

[126] J. C. Heo, S. H. Nam, D. Y. Nam, J. G. Kim, K. G. Lee, and J. H. Yeo. Anti-asthmatic activities in mycelial extract and culture filtrate of *Cordyceps* sphecocephala J201. International Journal of Molecular Medicine. 2010; 26:3, 351-356.

[127] K. Samitas, V. Delimpoura, E. Zervas, and M. Gaga. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. European Respiratory Review. 2015; 24:138, 594-601.

[128] Yue-Qin, C., Ning, W., Hui, Z., & Liang-Hu, Q. Differentiation of Medicinal *Cordyceps species* by rDNA ITS Sequence Analysis. Planta Medica. 2002; 68(7), *635-639*. doi:10.1055/s-2002-32892.

[129] Liu, Y.-N., Liu, B.-Y., Ma, Y.-C., Yang, H.-L., & Liu, G.-Q. (2020). Analysis of reference genes stability and histidine kinase expression under cold stress in *Cordyceps militaris.* Plos one. 2020; 15(8) e0236898. doi:10.1371/journal.pone.0236898.

[130] Shrestha B, Zhang W, Zhang Y, Liu X. What is the Chinese caterpillar fungus *OphioCordyceps sinensis* (Ophiocordycipitaceae)? Mycol. Int J Fungal Biol. 2010; 1:228-236. https://doi.org/10.1080/21501203.2010.536791.

[131] Sangdee A, Sangdee K. Isolation, identification, culture and production of adenosine and cordycepin from cicada larva infected with entomopathogenic fungi in Thailand. Afr J Microbiol Res. 2013; 7(2):137-146. https://doi.org/10.5897/AJMR12.1038.

[132] Y.-C. Kuo, W.-J. Tsai, J.-Y. Wang, S.-C. Chang, C.-Y. Lin, and M.-S. Shiao. Regulation of Broncho alveolar lavage fluids cell function by the immunomodulatory agents from *Cordyceps sinensis*. Life Sciences. 2001; 68:9, 1067-1082.

[133] Peng XX, Chai YQ, Zhu BC, Jin YW, Li XL, Yu LS. The protective

effects of N6-(2-hydroxyethyl)-adenosine extracted from *OphioCordyceps sobolifera* on renal ischemia reperfusion injury (IRI) in mice. Mycosystema. 2015; 34:311-320. http://jtp.cnki.net/bilingual/detail/html/JWXT201502016.

[134] Chen, G.-S., Huang, K.-F., Huang, C.-C., & Wang, J.-Y. Thaliporphine Derivative Improves Acute Lung Injury after Traumatic Brain Injury. BioMed Research International. 2015; 1-10. doi:10.1155/2015/729831.

[135] Chyau CC, Chen CC, Chen JC, Yang TC, Shu KH, Cheng CH. Mycelia glycoproteins from *Cordyceps sobolifera* ameliorate cyclosporine-induced renal tubule dysfunction in rats. J Ethnopharmacol. 2014; 153:650-658. https://doi.org/10.1016/j.jep.2014.03.020.

[136] Huo, M., Cui, X., Xue, J., Chi, G., Gao, R., Deng, X., ... Wang, D. Anti-inflammatory effects of linalool in RAW 264.7 macrophages and lipopolysaccharide-induced lung injury model. Journal of Surgical Research. 2013; 180(1), e47–e54. doi: 10.1016/j.jss.2012.10.050.

[137] Sperduto, R. D. The Linxian Cataract Studies. Archives of Ophthalmology. 1993; 111(9), 1246. doi:10.1001/archopht.1993.01090090098027.

[138] Flaxman SR, Bourne RR, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, Das A, Jonas JB, Keeffe J, Kempen JH, Leasher J, Limburg H, Naidoo K, et al. Vision Loss Expert Group of the Global Burden of Disease Study. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. 2017; 5:e1221-34. https://doi.org/10.1016/S2214-109X(17)30393-5.

[139] Shuqi Liang, Shengqian Dou, Wenfeng Li, and Yusen Huang. Profiling of circular RNAs in age-related cataract reveals circ ZNF292 as an antioxidant by sponging miR-23b-3p. Aging. 2020; 12:17:17271-17287.

[140] Li, L., Li, S., Wang, S., Xing, X., Zhang, Y., Su, L., ... Gong, X. Antioxidant and anti-glycated TAT-modified platinum nanoclusters as eye drops for non-invasive and painless relief of diabetic cataract in rats. Chemical Engineering Journal. 2020; 398, 125436. doi:10.1016/j.cej.2020.125436.

[141] Heidari, N., Jabbari, M., Babashahi, M., Nabie, R., Asghari Jafarabadi, M. and Arefhosseini, S.R. The association between healthy eating index and serum antioxidant indices in patients with different degrees of cataract compared to healthy subjects: a case-control study. Nutrition & Food Science. 2020. https://doi.org/10.1108/NFS-04-2020-0153.

[142] Shuqi Liang, Shengqian Dou, Wenfeng Li,Yusen Huang. Profiling of circular RNAs in age-related cataract reveals circZNF292 as an antioxidant by sponging miR-23b-3p. Aging. 2020; 12:17. doi: 10.18632/aging.103683.

[143] Ling, X., Jarubula, R. Synthesis of Negatively Charged CeO_2 NPs and in Vitro Cytotoxicity Human Lens Epithelial (HLE) Cell Lines—Investigation for New Therapy for Cataract Treatment. J Inorg Organomet Polym. 2020. https://doi.org/10.1007/s10904-020-01793-2.

[144] Roupas, Peter; Keogh, Jennifer; Noakes, Manny; Margetts, Christine; Taylor, Pennie. The role of edible mushrooms in health: Evaluation of the evidence. Journal of Functional Foods. 2012; 4(4), 687-709. doi:10.1016/j.jff.2012.05.003.

[145] Spector A. Oxidative stress-induced cataract: mechanism of action. FASEB J. 1995; 9:1173-82. https://doi.org/10.1096/fasebj.9.12.7672510.

[146] Ravindran Kalathil Veena, Eluvathingal Joy Carme, Haridas Ramya, Thekkuttuparambil Ananthanarayanan Ajith, Solomon P Wasser, Kainoor K Janardhanan. Caterpillar Medicinal Mushroom, *Cordyceps militaris* (Ascomycetes) Mycelia Attenuates Doxorubicin-Induced Oxidative Stress and up Regulates Krebs Cycle Dehydrogenases Activity and ATP Level in Rat Brain. Janardhanan. 2020. DOI:10.1615/IntJMedMushrooms.2020035093.

[147] W. A. Elkhateeb and G. M. Daba. The endless nutritional and pharmaceutical benefits of the Himalayan gold, *Cordyceps*; Current knowledge and prospective potentials. Biofarmasi J nat prod biochem. 2020; 18,70-77. DOI: 10.13057/biofar/f180204.

[148] Hong T, Cui LK, Wen J et al. *Cordycepin* protects podocytes from injury mediated by complements complex C5b-9. Sichuan Da Xue Xue Bao Yi Xue Ban. 2015; 46(2):173-178. 227.

[149] Cheng, Y., Wei, Y., Yang, W. *et al.* Cordycepin confers neuroprotection in mice models of intracerebral hemorrhage via suppressing NLRP3 inflammasome activation. Metab Brain Dis. 2017; 32, 1133-1145. https://doi.org/10.1007/s11011-017-0003-7.

[150] Hwang, S., Cho, G.-S., Ryu, S., Kim, H. J., Song, H. Y., Yune, T. Y., ... Kim, W.-K. Post-ischemic treatment of WIB801C, standardized *Cordyceps* extract, reduces cerebral ischemic injury via inhibition of inflammatory cell migration. Journal of Ethnopharmacology. 2016; 186, 169-180. doi:10.1016/j.jep.2016.03.052.

[151] Jin, M. L., Park, S. Y., Kim, Y. H., Oh, J.-I., Lee, S. J., & Park, G. The neuroprotective effects of cordycepin inhibit glutamate-induced oxidative and ER stress-associated apoptosis in hippocampal HT22 cells. Neuro Toxicology. 2014; 41, 102-111. doi:10.1016/j.neuro.2014.01.005.

[152] Liu, Z., Li, P., Zhao, D. *et al.* Protective effect of extract of *Cordyceps sinensis* in middle cerebral artery occlusion-induced focal cerebral ischemia in rats. Behav Brain Funct. 2010; 6, 61. https://doi.org/10.1186/1744-9081-6-61..

[153] Chaicharoenaudomrung, N., Jaroonwitchawan, T., & Noisa, P. Cordycepin induces apoptotic cell death of human brain cancer through the modulation of autophagy. Toxicology in Vitro. 2018; 46, 113-121. doi:10.1016/j.tiv.2017.10.002.

[154] Yuan, J., Wang, A., He, Y., Si, Z., Xu, S., Zhang, S., ... Liu, Y. (2016). Cordycepin attenuates traumatic brain injury-induced impairments of blood-brain barrier integrity in rats. Brain Research Bulletin, 127, 171-176. doi:10.1016/j.brainresbull.2016.09.010.

[155] Jeong, J.-W., Jin, C.-Y., Kim, G.-Y., Lee, J.-D., Park, C., Kim, G.-D., ... Choi, Y. H. Anti-inflammatory effects of cordycepin via suppression of inflammatory mediators in BV2 microglial cells. International Immunopharmacology. 2010; 10(12), 1580-1586. doi:10.1016/j.intimp.2010.09.011.

[156] Sang-Hak Lee, Il-Gyu Ko, Sung-Eun Kim, Lakkyong Hwang, Jun-Jang Jin, Hyun-Hee Choi, Chang-Ju Kim. Aqueous extract of *Cordyceps* alleviates cerebral ischemia-induced short-term memory impairment in gerbils. Journal of Exercise Rehabilitation. 2016; 12(2): 69-78. DOI: https://doi.org/10.12965/jer.1632586.293

[157] He, X., Tian, Y., Lei, L., Zhi, Q., Zhao, J., & Ming, J. Protective effects of *Coreopsis tinctoria* buds extract against cognitive impairment and brain aging induced by d-galactose. Journal of Functional Foods. 2020; 73, 104089. doi:10.1016/j.jff.2020.104089.

[158] W. Li, P. Li, Q. Hua, J. Hou, J. Wang, H. Du, H. Tang, Y. Xu. The

impact of paracrine signaling in brain microvascular endothelial cells on the survival of neurons, Brain Res. 2009; 1287 (10): 28-38, https://doi.org/1.1016/j.brainres.2009.06.057.

[159] Bai, X., Tan, T.-Y., Li, Y.-X., Li, Y., Chen, Y.-F., Ma, R., ... Liu, Z.-Q. The protective effect of *Cordyceps sinensis* extract on cerebral ischemic injury via modulating the mitochondrial respiratory chain and inhibiting the mitochondrial apoptotic pathway. Biomedicine & Pharmacotherapy. 2020; 124, 109834. doi:10.1016/j.biopha.2020.109834.

[160] Hayden, M., West, A. & Ghosh, S. NF-*κ*B and the immune response. Oncogene. 2006; 25, 6758-6780. https://doi.org/10.1038/sj.onc.1209943.

[161] Qin, P.; Li, X.; Yang, H.; Wang, Z.-Y.; Lu, D. Therapeutic Potential and Biological Applications of Cordycepin and Metabolic Mechanisms in Cordycepin-Producing Fungi. *Molecules*. 2019; *24*, 2231.

[162] Chen, B., Sun, Y., Luo, F., & Wang, C. Bioactive Metabolites and Potential Mycotoxins Produced by *Cordyceps* Fungi: A Review of Safety. Toxins. 2020; 12(6), 410. doi:10.3390/toxins12060410.

[163] Cai, Z. L., Wang, C. Y., Jiang, Z. J., Li, H. H., Liu, W. X., Gong, L. W., Li, C. H. Effects of cordycepin on Y-maze learning task in mice. European Journal of Pharmacology. 2013; 714(1-3), 249-253. https://doi.org/10.1016/j.ejphar.2013.05.049.

[164] Ren, Y., Sun, P., Li, H., & Zhu, Z. Effects of Na2SeO3 on growth, metabolism, antioxidase and enzymes involved in polysaccharide synthesis of *Cordyceps militaris*. Process Biochemistry. 2020. doi:10.1016/j.procbio.2020.06.018.

[165] Durán-Aranguren, D., Chiriví-Salomón, J. S., Anaya, L., Durán-Sequeda, D., Cruz, L. J., Serrano, J. D., Sierra, R. Effect of bioactive compounds extracted from *Cordyceps nidus* ANDES-F1080 on laccase activity of Pleurotus ostreatus ANDES-F515. Biotechnology Reports. 2020; 26, e00466. doi:10.1016/j.btre.2020.e00466.

[166] Rottenberg, M. E., Masocha, W., Ferella, M., Petitto-Assis, F., Goto, H., Kristensson, K., ... Wigzell, H. Treatment of African trypanosomiasis with cordycepin and adenosine deaminase inhibitors in a mouse model. Journal of Infectious Diseases. 2005; 192(9), 1658-1665.

[167] Lui, J.C.K., Wong, J.W.Y., Suen, Y.K. *et al.* Cordycepin induced eryptosis in mouse erythrocytes through a Ca^{2+}-dependent pathway without caspase-3 activation. Arch Toxicol. 2007; 81, 859-865. https://doi.org/10.1007/s00204-007-0214-5.

[168] Sornchaithawatwong, C., Kunthakudee, N., Sunsandee, N., & Ramakul, P. Selective extraction of cordycepin from *Cordyceps militaris* – optimisation, kinetics and equilibrium studies. Indian Chemical Engineer. 2020; 1-13. doi:10.1080/00194506.2020.1776163.

[169] Tsai, Y.-S., Hsu, J.-H., Lin, D. P.-C., Chang, H.-H., Chang, W.-J., Chen, Y.-L., & Chen, C.-C. Safety Assessment of HEA-Enriched *Cordyceps cicadae* Mycelium: A Randomized Clinical Trial. Journal of the American College of Nutrition. 2020; 1-6. doi:10.1080/07315724.2020.1743211.

[170] Chen, B.; Sun, Y.; Luo, F.; Wang, C. Bioactive Metabolites and Potential Mycotoxins Produced by *Cordyceps* Fungi: A Review of Safety. *Toxins* 2020; *12*:410.

[171] Zheng, P., Xia, Y., Zhang, S. *et al.* Genetics of *Cordyceps* and related fungi. Appl Microbiol Biotechnol. 2013; 97, 2797-2804. https://doi.org/10.1007/s00253-013-4771-7.

[172] Li, B., Hou, Y., Zhu, M., Bao, H., Nie, J., Zhang, G. Y., ... Du, J. 3'-Deoxyadenosine (Cordycepin) Produces a Rapid and Robust Antidepressant Effect via Enhancing Prefrontal AMPA Receptor Signaling Pathway. International Journal of Neuropsycho pharmacology. 2015; 19(4), pyv112. doi:10.1093/ijnp/pyv112.

[173] Tan, L., Song, X., Ren, Y., Wang, M., Guo, C., Guo, D., Deng, Y. Anti-inflammatory effects of cordycepin: A review. Phytotherapy Research. 2020. doi:10.1002/ptr.6890.

[174] Liu, Y., Li, Y., Zhang, H., Li, C., Zhang, Z., Liu, A., ... Wu, W. Polysaccharides from *Cordyceps miltaris* cultured at different pH: Sugar composition and antioxidant activity. International Journal of Biological Macromolecules. 2020. doi:10.1016/j.ijbiomac.2020.06.182.

[175] Marsup, P. Yeerong, K. Neimkhum, W. Sirithunyalug, J. Anuchapreeda, S. To-anun, C. Chaiyana, W. Enhancement of Chemical Stability and Dermal Delivery of *Cordyceps militaris* Extracts by Nanoemulsion. N*anomaterials.* 2020; *10*:1565.

[176] Zhu, Y., Yu, X., Ge, Q., Li, J., Wang, D., Wei, Y., & Ouyang, Z. Antioxidant and anti-aging activities of polysaccharides from *Cordyceps cicadae*. International Journal of Biological Macromolecules. 2020. doi:10.1016/j.ijbiomac.2020.04.163.

[177] Xiao, L., Sun, S., Li, K., Lei, Z., Shimizu, K., Zhang, Z., & Adachi, Y. Effects of nanobubble water supplementation on biomass accumulation during mycelium cultivation of *Cordyceps militaris* and the antioxidant activities of extracted polysaccharides. Bioresource Technology Reports. 2020; 12, 100600. doi:10.1016/j.biteb.2020.100600.