Cordyceps spp.: A Review on Its Immune-Stimulatory and Other Biological Potentials

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In recent decades, interest in the Cordyceps genus has amplified due to its immunostimulatory potential. Cordyceps species, its extracts, and bioactive constituents have been related with cytokine production such as interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor (TNF)-α, phagocytosis stimulation of immune cells, nitric oxide production by increasing inducible nitric oxide synthase activity, and stimulation of inflammatory response via mitogen-activated protein kinase pathway. Other pharmacological activities like antioxidant, anti-cancer, antihyperlipidemic, anti-diabetic, anti-fatigue, anti-aging, hypocholesterolemic, hypotensive, vasorelaxation, anti-depressant, aphrodisiac, and kidney protection, has been reported in pre-clinical studies. These biological activities are correlated with the bioactive compounds present in Cordyceps including nucleosides, sterols, flavonoids, cyclic peptides, phenolic, bioxanthracenes, polyketides, and alkaloids, being the cyclic peptides compounds the most studied. An organized review of the existing literature was executed by surveying several databanks like PubMed, Scopus, etc. using keywords like Cordyceps, cordycepin, immune system, immunostimulation, immunomodulatory, pharmacology, anti-cancer, anti-viral, clinical trials, ethnomedicine, pharmacology, phytochemical analysis, and different species names. This review collects and analyzes state-of-the-art about the properties of Cordyceps species along with ethnomedical properties, application in food, chemical compounds, extraction of bioactive compounds, and various pharmacological properties with a special focus on the stimulatory properties of immunity.
INTRODUCTION

The fungus Cordyceps spp. belongs to Tibetan medicine and consumers describe it as an important source of energy. Cordyceps spp. belongs to Ascomycota, Pyrenomycetes, Hypocreales, and Clavicipitaceae, and at least 700 species are known. The word Cordyceps originates from the Greek term "kordyle", which means "club", and the Latin etymon "ceps", which means "head" (Olatunji et al., 2018). Cordyceps species invade insects, arthropods, other fungi, and evades the host immune system by harmonizing the life cycle of its host with the intention of survival and multiplication. Their interaction with the host will produce different secondary metabolites such as cordycepin, adenosine, γ-guanosine, cordymin, kordyle, which means head (Olatunji et al., 2018).

The different species of Cordyceps have beneficial properties such as anti-cancer, anti-proliferative, anti-angiogenic, anti-metastasis, apoptosis induction, anti-inflammatory, antioxidant, anti-fibrotic, anti-arteriosclerosis, anti-hypertensive, anti-thrombotic, anti-inflammatory, anti-fungal, hypolipidemic, anti-diabetic, hypoglycemic, anti-asthmatic, steroidogenesis, spermatogenic, anti-metastasis, apoptosis induction, anti-inflammatory, antioxidant, and immunomodulatory effects (Liu Y et al., 2015). These properties are concentration-dependent, and in most cases, no adverse effects were reported, although the evaluation of isolated compounds such as cordycepin is preferred.

Interestingly, Cordyceps spp. contains different compounds with the ability to strengthen the response of the immune system and also to control its exacerbated response. Most of the information on the effect of Cordyceps on the immune system derives from studies in cancer. In particular, Cordyceps spp. increases the production of interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor (TNF)-α, induces phagocytosis of macrophages, mononuclear cells, nitric oxide (NO) release, and stimulates the inflammatory response via the mitogen-activated protein kinase (MAPK) route (Lee et al., 2006; Wang M et al., 2012). Furthermore, it presents synergism with interferon (INF)-γ in the production of cytokines. These properties are attractive in the search for new applications where the stimulation in the immune system response is wanted. Therefore, this review collects and analyzes the state-of-the-art about properties of Cordyceps spp. focused on the stimulatory properties of immunity.

METHODOLOGY

An organized review of the existing literature was executed by surveying pertinent peer-reviewed research articles, review articles, etc. from several available bibliographic databanks such as PubMed, SpringerLink, Elsevier journal, Science Direct, Scopus databases, Google search, etc., using keywords and its combination like Cordyceps, cordycepin, natural medicine, immune system, immunostimulation, immunomodulatory, clinical studies.
high altitudes (low temperature, lack of oxygen, and exposure to UV radiation).

On the other hand, the dispersion of this rare and interesting medicinal mushroom is carried out through air, rain, and insects; in its whole life cycle in three phases namely infection, parasitism, and saprophytism (Pal and Misra, 2018). In the first phase, *Cordyceps* spp. infects the host in the larval stage through ascospores, (released in the air from mature fruiting bodies during summer and early autumn), and germinate. In some cases, the infection is produced by the ingestion of food contaminated by *Cordyceps* spp. mycelia. The parasitic stage occurs after the infection, and during this phase, the *Cordyceps* spp. nurtures from the bowel of the host. The fungal cells spread throughout the body and proliferate rapidly during the winter, consuming all internal organs of the larva, leaving intact the exoskeleton. After that, the fungal cell transform into a white mass inside the larva's body (endosclerotium) (Tuli et al., 2013a; Baral et al., 2015). During this process, the environmental conditions are inclement, and the mushroom has to resist the snow and cold conditions. When the spring begins, and the outside temperature increases, the endosclerotium germinates and extrudes through the oral cavity of the host, maturing in summer, forming the fruiting body, and beginning to release ascospores (saprophytic stage). In this season, the fungus collection is carried out.

Traditionally, the primary collectors of these plants are the villagers, who collected it during the time of grazing practice (Baral et al., 2015). During months, the primary gatherers stay in the alpine regions to care for their pet animals (Yak) and collect the fungus and other medicinal plants (Panda, 2010). Local medicine men, who also visit the areas to collect the mushrooms, store the dried material to use it in the future. Due to the medicinal importance of *Cordyceps* spp., its popularity has increased besides the over-harvesting, triggering the scarcity of wild species. For this reason, since the 70s, many scientists have been searching for options to achieve the fermentation and cultivation of fungi isolated. *Cordyceps* spp. have been related to therapeutic properties and healing activities for several years; thus, they have been employed as treatment of different diseases in folk medicine.

**ETHNOPHARMACY AND TRADITIONAL USES OF CORDYCEPS SPP.**

For hundreds of years, *Cordyceps* has been utilized in traditional Chinese medicine (TCM) as a tonic to treat several conditions such as respiratory diseases, liver or renal problems, hyperglycemia, and cancer or tumor disorders. Similarly, *Cordyceps* spp. has been applied as an energy level and endurance enhancer, to improve aerobic capacity, and to boost cellular immunity. It was officially classified as a drug in 1964 in Chinese Pharmacopoeia (Shashidhar et al., 2013), being *C. sinensis* and *C. militaris* (L.) Fr. the most frequent species employed.

In some regions such as China, Tibetan plateau, Bhutan, Nepal, and India, the dosage and the administration of *C. sinensis* are dependent on the knowledge and skills of local folk practitioners based on the use of a trial-and-error method (Maity, 2013). For example, some community dissolves the fungus in milk, and alcohol or hot water, to drink it as an enhancer of the desire and sexual potency and as a tonic for the mornings, respectively (Panda and Swain, 2011). The action of the mushroom merged with other bioactive molecules has been reported too. For instance, some folk healers prescribe the use of the *Cordyceps* spp. mixed with taxus leaf and root of ginseng as a cancer treatment.

Furthermore, *C. sinensis* has been described as nutritious food by the Chinese population, probably due to their composition presents nutritional components such as essential amino acids, vitamins (B1, B2, B12, and K), and carbohydrates, among others. Remarkably, this fungus species is a dietary complement that complies with the U.S. Food and Drug Administration (FDA) considerations, which render the cordyceps a demand product in many countries (Wu et al., 2015).

On the other hand, *Cordyceps* spp. has been applied as a remedy for fatigue and weakness, slowing down the symptoms of altitude sickness and giving the patient a boost of energy. At advanced ages, people decrease aches and pains. Similarly, TCM specialists recommend the regular intake of *C. sinensis* to avoid infections, colds, and flues, due to its ability to decrease cough and phlegm, asthma as well as bronchial diseases (Lo et al., 2013). For these reasons, the *Cordyceps* spp. have been applied as a treatment for lung fibrosis, particularly in patients suffering from severe acute respiratory syndrome (SARS). Following the TCM beliefs, all these properties are related to the *C. sinensis* ability to enrich the lung yin and yang (Chiu et al., 2016a). The benefits of *Cordyceps* spp. have also been observed in athletes due to energy improvement derived from the increment of the cellular ATP level, which releases energy in muscle cells.

Similar to *C. sinensis*, the applications of *C. militaris* (L.) Fr. (found in China, Japan, Korea, and East Asia), are related to its properties as an energy enhancer, aphrodisiac source, and respiratory conditions treatment. Besides, hypoglycemic, anti-inflammatory, antitumor, antibacterial, antifungal, antioxidant, and immuno-protective properties have been attributed to this species. Thus, it ranks second in the most commercialized species in China, Japan, and Korea, being considered a suitable cheaper substitute for *C. sinensis* (Chou et al., 2014).

Other species that have been utilized by the folk healers are *C. pruinosa* Petch, *C. baissiana*, *C. cicadae* S.Z. Shing, *C. gunnii* (Berk.) Berk., *C. guangdongensis* T.H. Li, Q.Y. Lin and B. Song, and *C. ophioglossoides* (*T. ophioglossoides*). The main applications of *C. pruinosa* Petch are in stomach diseases are inflammatory disorders. *C. baissiana* Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan, has been used for skin conditions such as dermatitis and eczema. It also is applied as a biological insecticide for pest control (Wu et al., 2015; Olutunji et al., 2018). In TCM, *C. cicadae* S.Z. Shing has been used to treat infantile convulsions, elevation of temperature, and tremors. Moreover, therapeutic activities such as antitumor, immunoregulatory, and renoprotective have been attributed to this species (Olutunji et al., 2018). Similarly, *C. gunnii* (Berk.) Berk. exhibits immunomodulatory activity, an enhancer effect on the memory, and delay of
### TABLE 1

Chemical compounds of *Cordyceps* spp. (mentioned here only those compounds which were tested in a laboratory) adapted from Olatunji et al. with permission (Originally some portion of Table 3) (Olatunji et al., 2018).

| Compounds                        | Species                        | Mode of action                                                                 | References                        |
|----------------------------------|--------------------------------|--------------------------------------------------------------------------------|-----------------------------------|
| Palmitic acid                    | *C. militaris* (L.) Fr.        | Inactive                                                                       | Yoon et al. (2015)                |
| Linoleic acid                    | *C. militaris* (L.) Fr.        |                                                                                 |                                   |
| Linoleic acid methyl ester       | *C. militaris* (L.) Fr.        |                                                                                 |                                   |
| Cordytopoline                    | Cordyceps spp. BCC 1681        | Antimalarial, cytotoxicity against KB, BC-1, and Vero lines                     | Seephonkai et al. (2001)          |
| Helvolic acid                    | C. tai Z.Q. Liang and A.Y. Liu | Cytotoxicity against HeLa, HepG2, 95-D and SW1990 cell lines                   | Dou et al. (2013)                 |
| Cordycepiamide A                 | C. ninchiikspora (C.H. Su and H.H. Wang) G.H. Sung, J.M. Sung, Hywel-Jones and Spatafora | Anti-inflammatory                  | Reis et al. (2013)                |
| Cordycepiamide B                 |                                |                                                                                 |                                   |
| Cordycepiamide C                 |                                |                                                                                 |                                   |
| Cordycepiamide D                 |                                |                                                                                 |                                   |
| N-(2-hydroxybenzyl)acetamide     |                                |                                                                                 |                                   |
| (-)-Syngarasinol                |                                |                                                                                 |                                   |
| Cordycebrinose A                 | *C. militaris* (L.) Fr.        | Anti-inflammatory                                                               | Chiu et al. (2016b)               |
| Soyacebrinose I                  |                                |                                                                                 |                                   |
| Glucoebrinose                    |                                |                                                                                 |                                   |
| Ergosterol peroxide              | *C. cicadæ S.Z. Shing*         | Anti-inflammatory, renoprotective                                               | Kuo et al. (2003)                 |
| Jiangxienone                     | C. sinenisis (Berk.) Sacc.     | Anti-tumor                                                                      | Bok et al. (1999)                 |
| H-1-A                            | C. sinenisis (Berk.) Sacc.     | Cytotoxicity against SGC-7901 and A549 cell lines                             | Zhan et al. (2005)                |
| Cordyheptapeptide A              | Cordyceps spp. BCC 16173      | Renoprotective                                                                  | Yang et al. (2003)                |
| Cordyheptapeptide B              | Cordyceps spp. BCC 16176      | Cytotoxicity against KB, BC, NCI-H187, and Vero cells lines                     | Isaka et al. (2007)               |
| Cordycommunin                    | Ophiocordyceps Communis Hywel-Jones and Samson | Anti-mycobacterial                                                             | Hartakun et al. (2010)            |
| Beauvericin J                    | *C. cicadæ S.Z. Shing*         | Cytotoxicity against HepG2 and HepG2/ADM cell lines                            | Wang et al. (2004)                |
| Beauvericin                      |                                |                                                                                 |                                   |
| Beauvericin A                    |                                |                                                                                 |                                   |
| Beauvericin B                    |                                |                                                                                 |                                   |
| Beauvericin E                    |                                |                                                                                 |                                   |
| Cordyceamide A                   | *C. sinenisis* (Berk.) Sacc.   | Cytotoxicity against L929, A375, and HeLa cell lines                           | Jia et al. (2009)                 |
| Cordyceamide B                   |                                | Cytotoxicity against HeLa and MCF-7 cell lines                                | Zhang et al. (2009)               |
| Cycloaspeptide A                 |                                |                                                                                 |                                   |
| Cycloaspeptide B                 |                                |                                                                                 |                                   |
| Cycloaspeptide C                 |                                |                                                                                 |                                   |
| Cycloaspeptide F                 |                                |                                                                                 |                                   |
| Cycloaspeptide G                 |                                |                                                                                 |                                   |
| Cordycepin                       |                                |                                                                                 |                                   |
| N²-hydroxyethyl-adenosine        | *C. pruinosa* Petch            | Neuroprotection, anti-metastatic, anti-platelet aggregation, anti-inflammatory activity, anti-cancer | Yu H M et al. (2006)              |
| Guanosine                        | *C. sinenisis* (Berk.) Sacc.   | Anti-inflammatory, Ca²⁺ antagonistic                                           | Meng et al. (2015)                |
| CordysinnB                       |                                | Immunomodulatory                                                               | Yu L. et al. (2006)               |
| Dimethylguanosine                |                                | Antioxidant and HIV-1 protease                                                | Yang et al. (2011)                |
| Ergosterol                       |                                | Anti-inflammatory, anti-fibrotic                                               | Jang et al. (2011)                |
| Ergosteryl-3-O-β-hydroxy-22E-ergosta-6,9-(11)-22-trien-3β-ol |                                | Anti-inflammatory, antioxidant, Cytotoxic against HL-60 cell line             | Nalalthamby et al. (2015)         |
| Ergosteryl-3-O-β-hydroxy-7,22-dien-3β-ol |                                |                                                                                 |                                   |
| Ergosteryl-3-O-β-hydroxy-24(R)-methylcholesta-6,22-dien-3β-D-glucopyranoside |                                |                                                                                 |                                   |
| Cardinalisamid A                 | *C. cardinis* G.H. Sung & Spatafora | Antitryptosanomal                                                             | Umezaya et al. (2014)             |
| Cardinalisamide B                |                                |                                                                                 |                                   |
| Cardinalisamide C                |                                |                                                                                 |                                   |
| Cicadapeptin I                   | *C. heteropoda* Kobayasi       | Antibacterial and antifungal                                                    | Krasnoff et al. (2005)            |
| Cicadapeptin II                  |                                |                                                                                 |                                   |
| Cordycepsidone A                 | *C. dipterigena* Berk. and Broome | Antifungal                                                                    | Varughese et al. (2012)           |
| Cordycepsidone B                 |                                |                                                                                 |                                   |
| Cyclo (L-Pro-L-Val)              | *C. sinenisis* (Berk.) Sacc.   | Antioxidant, anti-inflammatory, anti-inflammatory                              | Yang et al. (2011)                |
| Cyclo (L-Phe-L-Pro)              |                                |                                                                                 |                                   |
| Cyclo (L-Pro-L-Tyr)              |                                |                                                                                 |                                   |
| Cordycepid A                     | *C. bifusispora* O.E. Erkess.  | Inactive                                                                       | Lu et al. (2013)                  |

(Continued on following page)
TABLE 1 (Continued) Chemical compounds of Cordyceps spp. (mentioned here only those compounds which were tested in a laboratory) adapted from Olatunji et al. with permission (Originally some portion of Table 3) (Olatunji et al., 2018).

| Compounds                  | Species                              | Mode of action                                      | References                |
|----------------------------|--------------------------------------|-----------------------------------------------------|---------------------------|
| Cordysinin A               | C. sinensis (Berk.) Sacc.            | Anti-inflammatory, antioxidant                       | Yang et al. (2011)        |
| Fazlin                     |                                      |                                                     |                           |
| Pefolyrine                 |                                      |                                                     |                           |
| Cordyformamide             | C. brunnearubra BCC 1396             | Antimalarial                                         | Isaka et al. (2007a)      |
| Deacetylcytochalasin C     | C. tai Z.Q. Liang and A.Y. Liu       | Cytotoxicity against 95-D, A-549, and HL-7702 cell lines | Li et al. (2015)          |
| Zygosporin D               |                                      | Cytotoxicity against 95-D, A-549, and HL-7702 cell lines |                           |
| Cordypadronone A           | C. nipponica Kobayasi                | Antimalarial                                         | Isaka et al. (2001)       |
| Cordypadronone B           |                                      |                                                     |                           |
| Cordypadronone C           |                                      |                                                     |                           |
| Cordypadronone D           |                                      |                                                     |                           |
| 1-Dehydroxycordypadronone A| C. sinensis (Berk.) Sacc.            | Antioxidant                                          | Yang et al. (2011)        |
| 3',4',7-Trihydroxyflavone  |                                      |                                                     |                           |
| Dicadzine                  |                                      |                                                     |                           |
| Rugulosin                  | C. formosana Kobayasi & Shimizu      | Cytotoxicity against CHO cell line                   | Lu et al. (2014)          |
| Skyrin                     | Cordycep spp. BCC 16173              | Antimalarial                                         | Isaka et al. (2007b)      |
| Annulatin A                | C. annulata Kobayasi & Shimizu       | Cannabinoid receptors agonist                        | Asai et al. (2012)        |
| Annulatin B                |                                      |                                                     |                           |
| Annulatin C                |                                      |                                                     |                           |
| Annulatin D                |                                      |                                                     |                           |
| Annulatin E                |                                      |                                                     |                           |
| Erythrostoninone Deoxyerythrostominone | 4-O-methyl-erythrostoninone | Cytotoxicity against BC, KB, and Vero cell lines | Kittakoop et al. (1999)  |
| Epierythrostominol         | Deoxyerythrostominol                 | Antimalarial                                         |                           |
| Cordycepol                 | C. ophioglossoides (T. ophioglossoides) (Ehrh.) | Cytotoxicity against HeLa and HepG2 cell lines | Sun et al. (2013)         |
| Cordycepol B               |                                      | Cytotoxicity against HeLa and HepG2 cell lines      |                           |
| Cordycepol C               |                                      | Inactive                                            |                           |
| Cordycol                   | Ophicordin                           | Anti-inflamatory                                     |                           |
| Terreusinone A             |                                      | Protein tyrosine phosphatases inhibitor              |                           |
| Pinophilin C               | CryptosporioptideA                   | Anti-inflamatory, antioxidant                        | Yang et al. (2011)        |
| Furanocarboxylicacid      |                                      |                                                     |                           |
| Hydroxy-2-methyl-4-pyrene  | Bassiamide A (KTH-7-1)               | Anti-inflamatory                                     |                            |
| Bassiamate (KTH-7-2)       | IPCC-PEPPhenol (KTH-19)              | Anti-inflamatory, antioxidant                        |                            |
| KTH-15–2                   |                                      |                                                     |                            |
| KTH-17                     | 4-Quinolinol                        | Anti-inflamatory                                     |                            |
| 1-Naphthol                 |                                      |                                                     |                            |

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senescence (Zhu et al., 2012b; Zhu Z-Y et al., 2014). C. guangdongensis is employed against fatigue, avian influenza, inflammation, renal failure, and oxidation (Yan et al., 2013). On the other hand, C. ophioglossoides (T. ophioglossoides) has been used as food, presenting antitumor, estrogenic, and anti-aging products, besides its application in births to avoid excessive bleeding in women (Kawagishi et al., 2004; Olatunji et al., 2018).

The traditional consumption of Cordyceps spp. has been through an herbal product, and its massive marketing dates back to the beginning of the year 2000. In several countries, it is consumed as a food supplement due to its different health attributes. To date, it is a highly sought-after product since its fame increased accompanied by scientific evidence. Prices range up to $20,000 per kilogram for wild C. sinensis, making it the most expensive mushroom in the world.

CHEMICAL COMPOUNDS OF CORDYCEPS SPP.

The genus Cordyceps spp. contains a large number of chemical compounds and their derivatives in the form of secondary
metabolites. The presence of such diverse chemical compounds makes them quite intriguing in analyzing therapeutic effects and pharmacological studies. Major chemical compounds such as nucleosides, sterols, flavonoids, cyclic peptides, phenolics, binoxanthrecenes, polyketides, and alkaloids are found in Cordyceps species (Table 1, Figure 1). While in most of the Cordyceps species, cyclic peptides are present in large quantity as compared to other molecules. Besides that, cordycepin and cordycepic acid (CA) are also prominently present in some species of Cordyceps spp. such as C. militaris (L.) Fr. The presence of cordycepin (3′-deoxyadenosine) and 2′-deoxyadenosine in C. sinensis was characterized by using atomic attractive reverberation (NMR) and infrared spectroscopy (IR) (Shunzhi and Jingzhi, 1996). In addition to this, a class of saccharides and polysaccharides such as cyclofurans, a cyclic ring of five-carbon sugars, heteropolysaccharides beta-glucans, beta-mannans cross-connected beta-mannan polymers, and complex polysaccharides comprising of both five and six carbon sugars were also discovered from Cordyceps spp. Even though, Cordyceps spp. contains a lot of bioactive molecules, it also has immunosuppressive compounds, cyclosporine usually found in Cordyceps subsessilis Petch (Segelken, 1996). Besides this, some immunosuppressant compounds were also isolated from the closely related Cordyceps species Isaria sinclairii (Berk.) Lloyd (Mizuno, 1999).

**Cordycepin and Cordycepic Acid**

Cordycepin and CA are prominently found in C. militaris (L.) Fr. They are important bioactive molecules having potential therapeutic applications (Huang et al., 2003). Structurally, cordycepin is 3′-deoxyadenosine and CA is D-mannitol. Cordycepin is an analog of adenosine derivatives which themselves differentiated from adenosine nucleoside by the absence of one oxygen molecule at third position carbon of ribose sugar. Different types of extraction methods of this compound can be followed, however, one of the most frequently used methods in which acetonitrile and water mixed in the ratio of 5:95 v/v at a flow rate of 1.0 ml/min can be adapted (Ikeda et al., 2008). Cordycepin has been associated with various therapeutic ailments including intracellular targets, nucleic acid, apoptosis, and cell cycle. This diverse role of cordycepins in cellular molecular activities is due to its resemblance to adenosine (Tuli et al., 2013b). On the other hand, CA is structurally an isomer of quinic acid possessing various potential medicinal applications. Previously, CA structure was concluded as 1,3,4,5-tetrahydroxycyclohexane-1-carboxylic acid (Chatterjee et al., 1957) later, it was found to be crystalline substance of D-mannitol (Sprecher and Sprinson, 1963). It differs mainly from quinic acid as it forms dextrorotatory instead of forming lactone (Chatterjee et al., 1957). There is a great variation of CA content in the Cordyceps spp. However, in C. sinensis, it is usually 7–29% with differing in growing stages of the Cordyceps spp. (Jiang, 1987). CA plays a great influence in treating liver fibrosis (Guo and Friedman, 2007), diuretic, plasma osmotic pressure, and anti-free radical properties (Nomani et al., 2014).

**Polysaccharides**

Cordyceps spp. contains different types of polysaccharide components. The fruiting bodies of Cordyceps spp. consist of 3–8% polysaccharides (Li et al., 2001a). It was known that the
polysaccharides obtained from *Cordyceps* species are medicinally important and can play as one of the main constituents in drug formulation (Ukai et al., 1983; Wasser, 2002). These polysaccharides can effectively control the blood sugar level in the body (Kihno et al., 1993), show antitumor and antimicrobial effects (Nakamura et al., 1999), and also have anti-influenza, immunoprotective, and antioxidant effects. *Cordyceps* spp. polysaccharides represent structurally diverse biologically active macromolecules of wide physicochemical properties. These polysaccharides are either intracellular or extracellular. Molecular weight greater than 16,000 is shown to have effective antitumor properties (Zhou et al., 2009). The polysaccharides derived from edible, medicinal mushrooms were successfully shown to exhibit antitumor and immunomodulating properties which were firstly reported from the fruit body of *Lentinus edodes* in 1969 (Chihara et al., 1969). Therefore, a large number of edible and medicinal polysaccharides including *Cordyceps* spp. have been rigorously investigated over the past 30 years. Apart from this, many novel antitumor and immunomodulatory polysaccharides have been developed and commercialized (Wasser, 2002; Xiao et al., 2002; Xiao et al., 2003).

The important species of *Cordyceps* spp. from which polysaccharides have been isolated and developed which possess antitumor activities includes *C. sinensis*, *C. cicadae* S.Z. Shing, *C. ophioglossioides* (Tolypocladium ophioglossoides (Ehrh.) Quandt, Kepler & Spatafora), *C. militaris* (L.) Fr. and *C. kyushuensis* A. Kawam. As per the study, the polysaccharides combined with other chemotherapeutic drugs showed synergism and increased body-resistance (Xiao et al., 2002; Yang et al., 2005; Zhang W et al., 2005; Chen et al., 2006). Polysaccharides derived from *Cordyceps* spp. primarily include glucan, mannan, heteroglycan, and glycoprotein but only β-(1→3) glucan, galactosaminoglycan, and proteopolysaccharide from *C. cicadae* S.Z. Shing, *C. ophioglossioides* and *Cordyceps* spp. showed antitumor activity (Xiao et al., 2002; Xiao et al., 2003).

**Proteins and Nitrogenous Compounds**

*Cordyceps* spp. contains all essential amino acids, proteins, peptides, and polyamines. Additionally, the *Cordyceps* spp. contains several rare cyclic dipeptides, including cyclo-[Gly-Pro], cyclo-[Leu-Pro], cyclo-[Val-Pro], cyclo-[Ala-Leu], and cyclo-[Thr-Leu]. Significant quantities of polyamines were also detected, such as 1,3-diamino propane, cadaverine, spermidine, spermine, and putrescine (Mizuno, 1999; Mishra and Upadhyay, 2011). Other nitrogenous compound like putrescine and putrescine, were also identified (Mizuno, 1999).

**Nucleotides/Nucleotide Derivatives**

Besides the other components, *Cordyceps* spp. is rich in nucleotide and its derivatives. In *C. sinensis*, nucleosides are the main component contributing to therapeutic applications (Li et al., 2001b). Nucleosides such as adenine, adenosine, inosine, cytidine, cytosine, guanine, uridine, thymidine, uracil, hypoxanthine, and guanosine have been isolated from *C. sinensis*. Among the nucleotide components, guanosine has the highest content ratio than other components (Shaoqing et al., 2001). There is a usual difference between the nature of nucleosides from that of normal and cultured *C. sinensis* (Li et al., 2001c). Many specific nucleosides that are not found elsewhere in nature can be found in the *Cordyceps* spp. which includes several distinct deoxyuridin structures, adenosine, 2′-3′-dideoxyadenosine, hydroxyethyladenosine, cordycepin triphosphate, guanidine, and deoxyguanidine. Adenosine and cordycepin (3′-dideoxyadenosine) possess multiple functions such as immunomodulatory, antioxidant, etc., Chen and Chu (Chen and Chu, 1996), identified cordycepin by using magnetic resonance (NMR) and infrared spectroscopy (IR) in a *C. sinensis* sample. In identification of cordycepin, several analytical methods and techniques including RP-HPLC (Shaio et al., 1994; Yu H M et al., 2006; Yu L et al., 2006), HPLC–ESI-MS (Huang L F et al., 2004), and HPLC-DAD (jiang et al., 2008) were adopted.

**Sterols and Fatty Acid**

Fungi contain sterols in the form of ergosterol an essential part of the great therapeutic important part of vitamin D2. *Cordyceps* spp. has identified a host of several sterol-type compounds and a few of these names: ergosterol, ergosterol-3, ergosterol peroxide, 3-sitosterol, daucosterol, and campester (Zhou et al., 2009). In *Cordyceps* spp., the existence of ergosterol varies depending on their growth stage, i.e., ergosterol was 1.44 mg/g in *Cordyceps* spp. mycelium, while 10.68 mg/g in fruit bodies (Li et al., 2011). Some derivatives of *Cordyceps* spp. are found in D-3-ergosterol, 3-sitosterol, daucosterol, and campester, and so on. It is important to mention that HPLC in *C. sinensis* detects ergosterol (Li and Li, 1991; Li et al., 2004).

The fatty acids found in *Cordyceps* spp. can be classified loosely into two kinds of fatty acids, saturated and unsaturated. *Cordyceps* spp. are more common and can compensate for up to 57.84% of unsaturated fatty acids (Zhou et al., 2009). Fatty acid such as lauric acid, myric acid, pentadecanolic acid, palmitic acid, linoleic acid, oleic acid, stearic acid, and docosanolic acid, are reported in *Cordyceps* spp. (Mishra and Upadhyay, 2011). Zhu et al. (1998), reported that 28 saturated and unsaturated fatty acids and their derivatives were isolated from *C. sinensis* along with polar compounds include several alcohols and aldehydes. The unsaturated fatty acids have various physiological activities, including decreased lipid blood and cardiovascular disease. Two methanol isolated sterols displayed antitumor sequence, and were detected by 1D and 2D NMR spectroscopy in their structure (Bok et al., 1999). Usage of pressurized fluid extraction (PLE), derivation of trimethyl silyl (TMS), GC-MS, cholesterol, campesterol, and β-sitosterol, like ergosterol from natural (wild) *C. sinensis* were described (Yang et al., 2009).

**Other Constituents**

In addition to the core ingredients, *C. sinensis* is made mostly from proteins, peptides, polyamine, both important amino acids, and other unusual cyclic dipeptides such as cyclo-[Gly-Pro-], cyclo-[Leu-Pro-], cyclo-[Val-Pro] and cyclo-[Thr-Leu]. Cyclic dipeptides including cyclo-[Leu-Pro] and cyclo-[Phe-Pro] were seen to have antimicrobial activity and anti-mutagenic properties in the battle against the production of vancomycin-resistant
Enterococcus (VRE) and pathogenic yeasts (Rhee, 2004). As per the study, cyclic (bacterial) dipeptides inhibit the development of aflatoxin (Yan et al., 2004) and protein rates differ greatly in the sum of dead larvae (29.1%), fruit body (30.4%), and mycelial fermentation (14.8%). The major amino acids are present in the larvae such as glutamic acid, aspartic acid, and amino acid (Hsu et al., 2002). The anti-inflammatory and anti-nociceptive properties of cordymine, a peptide isolated from C. sinensis medicinal mushrooms, have been reported (Qian et al., 2012).

The exopolysaccharide fraction (EPSF), is derived from the harvested C. sinensis supernatant. The cultured supernatant has been collected and then processed with the three times in volume of 95% ethanol for precipitation. As a consequence, a large amount of EPSFs was found on the soil (Zhang et al., 2012). EPSF has a wide spectrum of pharmacologic effects, with immunomodulatory and antitumor effects are most important (Sheng et al., 2011). EPSF has already shown that it can scavenge free radicals, promote the differentiation of cell cancer, and improve the ability of antitumor activity by triggering many immune responses (Sheng et al., 2011). Ion-exchanging and size chromatography is used to isolate polysaccharide (PS) from cultivated C. sinensis mycelia. Polysaccharide fraction (PSF) has been extracted from C. sinensis fungus has a relaxing effect on macrophage (Chen W et al., 2010). PSF has been shown to transform M2 macrophages to M1 phenotypes by activating the nuclear factor kappa-B (NF-κB) pathway. PSF also has immunomodulatory impacts, including many other polysaccharides (Chen et al., 2012). In a study to document the effect of C. sinensis on T-lymphocyte subsets of chronic renal failure patients, it was reported that different components of Cordyceps spp. polysaccharides enhanced the cellular immune function, phagocytic function of monocyte-macrophage, improved renal functions, spleen, and thymus index (Guan et al., 1992).

EXTRACTION AND ISOLATION OF MAJOR COMPOUNDS FROM CORDYCEPS SPP.

Extraction
A few extraction strategies have been used for solvents extraction utilized for the confinement of particular bio-dynamic mixes (Chen P X et al., 2013). Different extracts exhibit significant biological activities.

Aqueous Extraction
In aqueous extraction, water is used as an extraction medium due to the polar nature of the molecule and extracts polar compounds like-nucleosides and polysaccharides. Sun et al. (2003) standardized the suitable conditions for aqueous extraction as water: plant powder ratio (2.5:1), pH-7.5-8.0, and 24 h extraction time (Sun et al., 2003). Moreover, in hot water extraction, the yield varies between 25-30% with potential health benefits like antioxidant activities (Yamaguchi et al., 2000a; Gu et al., 2003).

Alcoholic Extraction
An alcoholic extraction method mainly methanol, ethanol, aqueous methanol, and aqueous ethanol are used for extraction as per bioactive principles. Yamaguchi et al. studied the alcoholic extraction because it allows a higher extraction of bioactive molecules, such as nucleosides, polysaccharides, proteins, as a result, exhibits strong antioxidant activity and preserves B-cell function and provides protection (Yamaguchi et al., 2000a; Kan et al., 2012). Another study revealed that methanol extract obtained from C. sinensis was found to have cytotoxicity impact on cancer cell lines (Jia et al., 2009).

Ethyl Acetate Extraction
Ethyl acetic acid derivation concentrate C. sinensis includes an intensification range not as similar to water and alcohol. Although the yield in this technique is small, the technique includes sugar, adenosine, ergosterol, and cordycepin, which are differentiated by ergosterol and similar mixes as a significant class of dynamic portion. The cause of apoptosis in human pre-myelocytic leukemia HL60 is due to 2 days of treatment in ED 50 ± 25 µg/ml, as a result, restrains the proliferation of malignancy growth of the cell lines (Zhang et al., 2004; Wu et al., 2007). Further research is utilized to comprehend basic highlights and adequacy of dynamic mixes in ethyl acetic acid derivation extractive. Ethyl acetate extract of C. sinensis showed antioxidant and immunomodulatory potential (Wu et al., 2006; Wu et al., 2007).

Supercritical Carbon Dioxide (CO2) Extraction
The extraction of supercritical CO2 has been an emerging technique in the chemical and food sectors in recent years. It is the best method carried out under moderate conditions and its purest form to extract bioactive compounds (especially non-polar compounds), without toxic organic solvents for extraction. Many literatures on simple and supercritical methods for the extraction of fluids in different fields are available (Pereira and Meireles, 2010). Ethanolic C. sinensis extract was fractionated with supercritical CO2 as an elution solvent, demonstrating its strong scavenging potential and inhibiting colorectal and hepatocellular cell development via the apoptosis cycle (Wang et al., 2005).

PHARMACOLOGICAL POTENTIAL OF CORDYCEPS SPP.

Plethora of naturally occurring chemical entities attributes to the broad and remarkable pharmacological activities of Cordyceps spp. (Zhu et al., 1998; Tuli et al., 2013a). Out of the diverse variety of species, C. sinensis is the most investigated one, as far as research and the inspection of its pharmacological potential is concerned (Paterson, 2008; Olatunji et al., 2018). Besides, other species includes C. militaris (L.) Fr.; C. pruinosa Petch; C. ophioglossoides (T. ophioglossoides); C. bassiana Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan; C. guangdongensis T.H. Li, Q.Y. Lin and B. Song; C. gunnii (Berk.) Berk.; C. jiangxiensis Z.Q. Liang, A.Y. Liu & Yong C. Jiang; C. kyushuensis A. Kawam.; C.
pseudomilitaris Hywel-Jones and Sivichai; *C. sphacocephala* (Berk.) Sacc; *C. sobifera* (Hill ex Watson) and *C. taii* Z.Q. Liang and A.Y. Liu.

The proposed applications of *Cordyceps* spp. in medicine include as immune-stimulatory, immunomodulatory, anti-inflammatory, antioxidant, antitumor, antemetastatic, antibacterial, antifungal, antimalarial, HIV-1 protease inhibitor, antihyperlipidemic, anti-obesity, anti-diabetic, anti-arteriosclerosis, anti-thrombotic, anticoagulant, and anti-fatigue (Qian et al., 2012; Liu Y et al., 2015). Details of the *Cordyceps* spp. induced pharmacological actions have been described as below.

**Immuno-Modulatory Action of *Cordyceps* spp.**

The immunomodulators are the substances or compounds that help to control the immune system of the body. There are a number of compounds present in the *Cordyceps* spp. that possesses the immunomodulatory activity. Some of these are discussed below. Active constituents of *Cordyceps* spp. are spotted by Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) during initiation of immunomodulation and hyporesponsiveness in antigen-presenting cells (APCs). These active constituents not only alter the TLRs and CLRs expression in APCs but also masterfully manipulate their intracellular signaling. TLRs use the Toll/IL-1 receptor (TIR)-domain covering adapter proteins such as MyD88 and TRIF (TIR domain-containing adapter inducing IFN-β). Active bio-constituents of *Cordyceps* spp. (C. *cicadae* S.Z. Shing, *C. militaris* (L.) Fr., *C. sinensis*, *C. sobifera* (Hill ex Watson)) transmit TLR4 signaling to MAPK pathway and extracellular signal-related kinase one and 2 (ERK1/2) activation backing Treg/Th2 induction. Furthermore, coherence of DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) along with TLR4 enables active constituents of *Cordyceps* spp. to trigger unknown intracellular pathways that cross-inhibit MyD88 and NF-κB activation. These constituents are further restrained NF-κB activity via the upregulation of negative regulators of TLRs signaling like a suppressor of cytokine signaling (SOCS) and phosphatidylinositol-3-kinase (PI3K) along with DC-SIGN-mediated rapidly accelerated fibrosarcoma (RAF) signaling.

In the prevention of priming Th1 cells, the role of NF-κB is a core factor due to its support's inflammation by inhibition. The multiplicity of signaling pathways is improved by co-receptors' involvement of CLRs (DC-SIGN). Activated mannose receptor (MR) and macrophage galactose-type C-type lectin (MGL) helps for the differentiation of Treg/Th2. Degrading host key intracellular molecules is another strategy that *Cordyceps* spp. exploit to reprogram host immunity. Polysaccharide constituents of *Cordyceps* spp. degrades endosomal TLR2, TLR3, TLR4, TLR6, and host mRNA which provides Treg/Th2 responses support. The active bio-constituents stimulate Treg/Th2 cell priming which have been stated by CLRs involvements. NLRP3 inflammasome (NLRP3 and caspase-1) modulate inflammatory processes via secretion of IL-1β and Th1 intensification (Figure 2).

Xu et al. (1992) delineated the effects of the *C. sinensis* (ethanolic extract) on murine and human natural killer (NK) activity and on colony formation of B16 melanoma in mouse lungs, where they reported the augmentation of the in vivo and in vitro NK activities of the mouse. Moreover, the pre-incubation of peripheral blood mononuclear cells (PBMCs) with *C. sinensis* elevated *in vitro* NK activity of human PBMCs, whereas the colony formation of B16 melanoma in mouse lungs was reduced drastically. This report hinted at the *C. sinensis*
| Activity              | Species                        | Extract/Compound                  | In vitro/in vivo                          | Results                                                                                                                                                                                                 | References |
|-----------------------|--------------------------------|-----------------------------------|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Immunostimulant       | C. militaris (L.) Fr.          | Polysaccharides                   | RAW264.7 macrophages                      | ↓NO, ROS, TNF-α production, NF-κB activation and MAPKs pathways, melanoma growth ↓NO, TNF-α and IL-1β production ↓NO, TNF-α and activates macrophages through the MAPKs and NF-κB signaling pathways | Lee and Hong (2011) |
|                       |                                |                                   |                                            |                                                                                                                                                                                                        | Lee et al. (2010) |
|                       |                                |                                   |                                            |                                                                                                                                                                                                        | Lee et al. (2015) |
|                       | C. japonica Lloyd              | Aqueous and methanol              | Forced swimming performances, immobilizing stress | ↑Liver enzyme activities, ↓lipid peroxidation                                                                                     | Shin et al. (2001) |
| Immunomodulatory      | C. bassiana Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan | Ethanol                           | LPS-activated macrophages                 | ↓Expression of IL-12, IFN-γ                                                                                                         | Byeon et al. (2011a) |
|                       |                                | Butanol fraction                  | Molecular basis of inhibition of cytokine expression | ↓JIL-12 and TNF-α expression, Syk, JAK-2, and ERK ↓JIL-12 and TNF-α expression, Syk, JAK-2, and ERK ↓JIL-12 and TNF-α expression, Syk, JAK-2, and ERK | Byeon et al. (2011b) |
|                       |                                | Methanol                          | HMNC proliferation                        | ↓HMNC proliferation, EC50 = 32.5 ± 5.2 μg/ml, ↑IL-2 and IFN-γ                                                                 | Weng et al. (2002) |
|                       | C. gunnii (Berk.) Berk.        | Polysaccharide                    | Macrophage phagocytosis along with humoral and cellular immunity | ↑Thymus and spleen indexes, macrophage phagocytosis, the proliferation of splenic cells, level of IFN-γ and TNF-α, ↓IL-4 | Zhu et al. (2012b) |
|                       |                                |                                   | Spleen lymphocytes proliferation, peritoneal macrophage (PMph) phagocytosis, and CTL | ↑Spleen lymphocytes proliferation, PMph phagocytosis of neutral red and CTL ↓Spleen lymphocytes proliferation, PMph phagocytosis of neutral red and CTL | Xiao et al. (2004b) |
|                       | C. pruinosa Petch              | Polysaccharide                    | Splenic T cell and Mphi phagocytosis      | ↑Proliferation of activated splenic T cell and cellular immune functions | Liu and Fei (2001) |
|                       |                                |                                   | Renal injury in endotoxemic rats          | ↑Oxidative stress and inflammatory cytokines, NF-κB activation, ↓body’s cellular antioxidant defense system. | (Chiu et al., 2014) |
|                       | C. taii Z.Q. Liang and A.Y. Liu | Polysaccharides                   | Splenic T cell and Mphi phagocytosis      | ↑Proliferation of activated splenic T cell and cellular immune functions | (Liu and Fei, 2001) |
|                       | C. sinensis (Berk.) Sacc.      | Adenosine and guanosine Polysaccharide | RAW264.7 cells                           | ↓NO, ↓IL-1β, ↓TNF-α Activation of the MAPK and NF-κB signaling pathways ↓Neutral red uptake capacity, spleen lymphocyte proliferation, levels of Bcl-2 | (Yu et al., 2007) |
|                       |                                | Polysaccharide                    | Macrophages proliferation, phagocytosis   | ↑Survival, CD8+ T cells%, ↓proteinuria, titers of anti-double-stranded DNA antibody CD4+ T cells% | (Cheong et al., 2016) |
|                       |                                | Exopolysaccharide                 | B16 melanoma-bearing mice                 | ↑Phagocytosis                                                                                                                                                                                    | (Zhang Q et al., 2005) |
|                       |                                |                                   | Lupus-prone (NZB/NZW) F1 hybrids          |                                                                                                                                                                                                 | (Chen et al., 2009) |
|                       |                                | Exopolysaccharide                 | Macrophage J774 cell                      | Stimulate the release of cytokines                                                                                                       | (Jia and Lau, 1997) |
|                       |                                |                                   | Raw264.7 macrophage cell                  | Activation of BM-DCs in a TLR7-dependent manner                                                                                          | (Wang et al., 2011) |
|                       |                                |                                   | Chloroquine and baflomycin A Methanol     | Inhibited blastogenesis response, NK cell activity, IL-2, and TNF-α production                                                        | (Kuo et al., 2013) |
TABLE 2 | (Continued) Immunostimulatory and related bioactivities of Cordyceps spp.: in vitro and in vivo.

| Activity                          | Species                  | Extract/Compound                        | In vitro/in vivo     | Results                                                                 | References |
|-----------------------------------|--------------------------|-----------------------------------------|----------------------|-------------------------------------------------------------------------|------------|
| Immunomodulatory and antioxidant  | C. militaris (L.) Fr.    | Polysaccharides                         | Cyclophosphamide-induced immunosuppression | ↑Spleen lymphocyte activity, macrophage function, SOD, catalase, GPx, and TAOC level, and the spleen and thymus indices, ↓MDA level | Wang M et al. (2012) |
|                                   |                          | Polysaccharides                         | Viscera index, leukocyte count, differential leukocyte count, IgG levels | Upregulated the expression of TNF-α, IFN-γ, and IL-1β mRNA, ↑spleen and thymus indices, the spleen lymphocyte activity, the total quantity of white blood cells, and IgG function, ↓MDA inhibiting cellular immunologic and humoral immunologic function | [Lu et al., 2016](#) |
| Immunosuppressive                 | C. gunnii (Berk.) Berk.  | Polysaccharide                          | Cytotoxic T lymphocytes | Blockade of luciferase activity caused by NF-κB and AP-1, suppress the mRNA levels of COX-2 and TNF-α | [Kim T W et al., 2014](#) |
| Anti-inflammatory                 | C. bassiana Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan | 1,9-Dimethylguanine | Reporter gene assay and mRNA analysis | NO and ROS production, mRNA expression, NF-κB activation | [Yang et al., 2015b](#) |
|                                  |                          | Butanol fraction                        | LPS-induced inflammation in RAW 264.7 cells | ↓NO, iNOS, COX-2, MAPKs activation, JNK, and p38 phosphorylation | [Yoon et al., 2017](#) |
|                                  |                          | 4-Isopropyl-2,6-bis{1-phenylethyl} phenol | LPS and sodium nitroprusside treated RAW264.7 cells | ↓NO and ROS production, mRNA expression, NF-κB activation | [Yang et al., 2015b](#) |
|                                  |                          | Aqueous                                 | LPS-treated RAW264.7 cells | ↓COX-2, IL-12, and iNOS, Syk kinase activity | [Yang et al., 2017](#) |
|                                  | C. cicadae S.Z. Shing    | Ergosterol peroxide                     | Human T cells | ↓T-cell proliferation, IL-2, IL-4, IL-10, and IFN-γ, AP-1 proteins expression | [Kuo et al., 2003](#) |
|                                  |                          | N6-(2-Hydroxyethyl) adenosine           | LPS-induced pro-inflammatory signaling pathway | ↓TLR4-mediated NF-κB signaling pathway | [Lu et al., 2015](#) |
|                                  |                          | CCl4-induced liver fibrosis            | ↓BUN and SCR levels, IL-12 and TNF-α expression, TGF-β1/CTGF | | [Kim et al., 2018](#) |
|                                  | C. guangdongensis T.H. Li, Q.Y. Lin and B. Song | Aqueous                                 | Chronic bronchitis caused by tobacco smoking | ↓Bronchial lesions and inflammatory cell infiltration, Attenuated body weight loss, diarrhea, gross bleeding, epithelial damage, loss of goblet cell, loss of crypts infiltration of inflammatory cells | [Yang et al., 2014](#) |
|                                  | C. militaris (L.) Fr.    | Aqueous                                 | Dextran sodium-sulfate-induced acute colitis | | [Han et al., 2011](#) |
| Anti-inflammatory and anti-cancer | C. prunosa Petch        | Cordycebroside A, soyacerebroside I and glucocerebroside | RAW264.7 macrophages | ↓Accumulation of pro-inflammatory iNOS and COX-2 protein expression | (Continued on following page) |
|                                  |                          | C. prunosa Petch | RAW264.7 macrophages | | |
|                                  |                          | Methanol                                | RAW264.7 macrophages | ↓NO production, TNF-α, ROS, IL-6, iNOS, phosphorylation of p65/p50 | Kim H G et al. (2014) |
|                                  |                          | Methanol                                | RAW264.7 macrophages | ↓NO production, TNF-α, ROS, IL-6, iNOS, phosphorylation of p65/p50 | Kim H G et al. (2014) |
|                                  | C. militaris (L.) Fr.    | Cordycepin                              | RAW264.7 macrophages and colon 205, PC-3, and HepG2 cells | | Kim H G et al. (2014) |
|                                  |                          | Cordycepin                              | RAW264.7 macrophages and colon 205, PC-3, and HepG2 cells | | [Kim et al., 2003](#) |
|                                  |                          | Cordycepin                              | RAW264.7 macrophages and colon 205, PC-3, and HepG2 cells | | [Feng et al., 2010](#) |

(Continued on following page)
| Activity | Species | Extract/Compound | In vitro/in vivo | Results | References |
|----------|---------|------------------|-----------------|---------|------------|
| Antioxidant | C. cicadae S.Z. Shing | Water-soluble polysaccharides | Total reducing power and scavenging activities | IC<sub>50</sub> = 28.99 μg/ml (DPPH scavenging), 0.19 and 0.30 mg/ml L mg/ml (hydroxyl and superoxide anion radicals) | (Song et al., 2018) |
| | C. formosana Kobayasi & Shimizu | Aqueous | DPPH and ROS scavenging | Strong antioxidant capability | Wang Y W et al. (2015) |
| | C. gunnii (Berk.) Berk. | Polysaccharide | D-galactose-induced | ↓ LPO, GPx, ↑ SOD, catalase (Zhu et al., 2009) | |
| | | | | ↓ MDA, GPx, ↑ SOD (Zhu et al., 2011) | |
| | C. japonica Lloyd | Aqueous and methanol | TBA reagent assay | ↑ Cytosolic SOD, catalase, and GSH-px, ↓ MDA (Shin et al., 2001) | |
| | | Ethanol | DPPH | IC<sub>50</sub> = 163 μg/ml, ↑ SOD, catalase (Jung et al., 2009) | |
| | C. jiangxiensis Z.Q. Liang, A.Y. Liu & Yong C. Jiang | Polysaccharide | DPPH EC<sub>50</sub> = 18.06 mg/ml (Xiao et al., 2011) | | |
| | C. kyushuensis A. Kawam. | Methanol | DPPH, hydroxyl and superoxide radical | Strong antioxidant capability (Reis et al., 2013) | |
| | C. militaris (L.) Fr. | Polysaccharides | DPPH, hydroxyl and superoxide radical | | |
| | | Methanol | | | (Lu et al., 2016) |
| | C. pruinosa Petch | Polysaccharide | DPPH, hydroxyl and superoxide radical | | |
| | | | | | (Chen et al., 1997) |
| | C. sinensis (Berk.) Sacc. | Polysaccharide | PC12 cells against hydrogen peroxide-induced injury | ↓ LPO, scavenging reducing power and free radicals (Yamaguchi et al., 2000a) | |
| | | Aqueous and ethanol | DPPH, hydroxyl, and superoxide radical | | |
| | | Exopolysaccharide | Trolox equivalent antioxidant | | |
| | C. taii Z.Q. Liang and A.Y. Liu | Polysaccharides | D-galactose-induced aging | | |
| | | Methanol | | | (Kuo et al., 2015) |
| | C. bassiana Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan | Methanol | DPPH radical inhibition | 47.7% scavenging activity of stage 3 | (Hyun et al., 2013) |
| | C. sinensis (Berk.) Sacc. | Methanol | K562, Jurkat, WM-1341, HL-60, and RPMI-8226 cells | 10–40% at 10 μg/ml inhibitor to the proliferation | (Bok et al., 1999) |
| | | Polysaccharide | U937 cells | 78–83% growth inhibition rate, ↑ IFN-γ, and TNF-α | (Kuo et al., 1994) |
| | Cordycepin | | | Significantly inhibited | |
| | C. japonica Lloyd | Ethanol | Sarcoma-180 tumor cells | Phagocytosis and acid phosphatase activity | (Shin et al., 2003) |
| | C. gunnii (Berk.) Berk. | Polysaccharide | S180 cells | Stronger inhibition at 800 μg/ml | (Zhu et al., 2013) |
| | | | | 56.65% tumor inhibition ratio | (Zhu et al., 2016a) |
| | | | | 45.3% tumor inhibition ratio | (Zhu et al., 2012a) |
| | | | | 69.92% tumor inhibition ratio | (Zhu et al., 2014) |
| | | | | 85% tumor inhibition ratio | (Zhu et al., 2013) |
| | | | | Stimulate apoptosis through p53-Bax-caspase pathway | (Sun et al., 2018) |
| | | | | 85% tumor inhibition ratio | (Xie et al., 2019) |
| | C. cicadae S.Z. Shing | Ethanol | SGC-7901 cells | Prohibition of SGC-7901 cells, ↓ calpain-1, caspase-12, and caspase-9 expression | (Liu R M et al., 2015) |
| | | | | | (Continued on following page)
TABLE 2 | (Continued) Immunostimulatory and related bioactivities of Cordyceps spp.: in vitro and in vivo.

| Activity   | Species            | Extract/Compound                  | In vitro/in vivo | Results                                                                 | References               |
|------------|--------------------|-----------------------------------|------------------|-------------------------------------------------------------------------|--------------------------|
| Anti-cancer| C. cicaeae S.Z. Shing | Aqueous                           | MHCO97H         | [MHCO97H cells growth via G2/M cell cycle arrest, IC50 = 1.0 mg/ml (A549 cells), IC90 = 0.53 mg/ml (A549 cells), IC50 = 0.44 mg/ml (Huh7 cells), IC90 = 0.19 mg/ml (Huh7 cells)] | Wang H et al. (2014)     |
|            | C. formosana        | Aqueous                           | A549             | [A549 lung cancer, MDA-mb-231 breast cancer, Huh7 liver cancer, and HL-60 leukemia cells activity up to 3 h] | Wang J et al. (2014)     |
|            | K. Kobayasi &       |                                   |                  | [K. Kobayasi & M.A. Curtis activity up to 3 h]                         |                         |
|            | A. Kawam.           |                                   |                  | [A. Kawam. U937 and K562 cells]                                         |                         |
|            | C. japonica         | Methanol                           | CHO cells        | Cell death ratio (4.14 ± 0.25) at 4,000 μg/ml concentration, LD50 > 8.0 g/kg | (Li et al., 2015)        |
|            | L. Lloyd            | Methanol                           | CHO cells        | Cell death ratio (4.14 ± 0.25) at 4,000 μg/ml concentration, LD50 > 8.0 g/kg | (Li et al., 2013)        |
|            | A.Y. Liu & Yong C. Jiang |                    |                  | [Activation of caspase-3, and modulation of Bcl-2 and Bax]               |                         |
|            | C. militaris (L.) Fr. | Curdian                           |                  |                                                                 |                         |
| C. tai    | Z.Q. Liang & A.Y. Liu | Methanol                           | CHO cells        | Cell death ratio (4.14 ± 0.25) at 4,000 μg/ml concentration, LD50 > 8.0 g/kg | (Li et al., 2014)        |
|           | A. Curtis           | Methanol                           |                  | [Cell death ratio (4.14 ± 0.25) at 4,000 μg/ml concentration, LD50 > 8.0 g/kg] | (Li et al., 2013)        |
| Cytotoxicity| C. bicusiispora    | Polysaccharides                    |                  | [Activation of caspase-3, and modulation of Bcl-2 and Bax]               |                         |
|            | O.E. Erikss.       |                                    |                  | [Activation of caspase-3, and modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Activation of caspase-3, and modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Activation of caspase-3, and modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Activation of caspase-3, and modulation of Bcl-2 and Bax]               |                         |
| Antidiabetic| C. cicaeae S.Z. Shing | Aqueous                           |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            | C. japonica        | Methanol                           |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            | L. Lloyd           | Methanol                           |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            | C. militaris (L.) Fr. | Cordycepin                        |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
| Antimicrobial| C. cicaeae S.Z. Shing | Hydroalcoholic                      |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
| Antibacterial| C. heteropoda      | Agar diffusion method              |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
| Antifungal  | C. dipterigena     | Potato dextrose agar plates        |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            | Berk. and Broome   | Cordycepsidone A                   |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
|            |                    |                                    |                  | [Detection of IRF-3 pathway, modulation of Bcl-2 and Bax]               |                         |
### TABLE 2 | Immunostimulatory and related bioactivities of Cordyceps spp.: in vitro and in vivo.

| Activity              | Species                  | Extract/Compound                  | In vitro/in vivo | Results                                                                 | References |
|-----------------------|--------------------------|-----------------------------------|------------------|--------------------------------------------------------------------------|------------|
|                       |                          |                                   |                  |                                                                          |            |
| Neuroprotective        | C. cicadae S.Z. Shing    | Polysaccharides, adenosine        | Glutamate-induced PC12 cells | ↑Cell survival rate, GPx, SOD, Bcl-2/Bax ratio, ↓ROS and Ca<sup>2+</sup>, ERK, p38, and JNK expression | (Olatunji et al., 2016) |
|                       |                          | Butanol fraction                  | Glutamate-induced PC12 cells | ↓ROS accumulation, GSH-Px, and SOD levels                                | (Wang et al., 2018) |
| Antiviral              | C. guangdongensis T.H. Li, G.Y. Lin and B. Song | Aqueous                           | Influenza virus H9N2 | ↓Pulmonary index by 22.1%                                                | (Yan et al., 2010) |
| Antimalarial           | C. brunneaurubra BCC 1395 | Ethyl acetate                     | Malarial parasite plasmodium falciparum K1 | IC<sub>50</sub> = 18 μM                                                  | (Isaka et al., 2007a) |
| Cannabinoid receptors  | C. annulata Kobayasi & Shimizu | Ethyl acetate                     | HEK293 cells      | 15.5–75.5% inhibition                                                    | (Asai et al., 2012) |
| CB1 and CB2 (agonistic) |                          |                                   |                  |                                                                          |            |
| Anti-proliferative     | C. bassiana Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan | Ethanol                           | VSMC and carotid artery of balloon-injured rats | ↓VSMC proliferation and ↑ERK<sub>1/2</sub> phosphorylation              | (Jin et al., 2016) |
| Anti-trypanosomal      | C. cardinalis G.H. Sung & Spatafora | Methanol                          | Against trypanosoma brucei | IC<sub>50</sub> = 8.63 μg/ml                                            | (Umeyama et al., 2014) |
| Anti-fibrotic          | C. cicadae S.Z. Shing    | Ergosterol peroxide               | NRK-49 F cell line | Blockage of TGF-β<sub>1</sub>-stimulated phosphorylation of ERK1/2, p38 and JNK pathway, ↓ TGFB-1-induced fibroblasts | (Zhu R et al., 2014) |
| Anti-atopic dermatitis | C. bassiana Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan | Butanol fraction                  | Topical use of DNFB in NC/Nga mice | Blockade of histamine release, IgE production, IL-4, and IFN-γ           | (Wu G et al., 2011) |
| Pro-apoptotic          |                          | 4-Isopropyl-2-(1-phenyl-ethyl) aniline | MDA-MB-231, HeLa, and C6 glioma cells | ↓Proliferation of MDA-mb-231, HeLa, and C6 glioma cells, reduced the phosphorylation of STAT3, Src, and PI3K/p85 | (Kim M S et al., 2015) |
| Antitubercular         | Ophiocordyceps Communis Hywel-Jones and Samson | Cordycommunin                     | Mycobacterium tuberculosis H37Ra | MIC = 15μM, weak cytotoxicity to KB cells                               | (Haritakun et al., 2010) |
| Anti-fatigue           | C. guangdongensis T.H. Li, G.Y. Lin and B. Song | Ethanol                           | Forced swimming   | ↓Blood lactate acid levels                                               | (Yan et al., 2013) |
| Protein tyrosine phosphatase inhibitor | C. graciloiodes Kobayasi | Terreusinone A, pinophi-lin C and cryptosporiop-tide A | PTP1B, SHP2, CDC25B, LAR and SHP1 enzyme | IC<sub>50</sub> = 3.4–50 μg/ml                                           | (Wei et al., 2015) |
| Antihyperlipidemic     | C. militaris (L.) Fr.    | Polysaccharides                   | HFD-induced       | ↓Blood and liver lipid, ↑SGPT, and antioxidant activity                | (Chen et al., 1997) |
| Renoprotective         | C. pruinosa Petch        | Whole broth                       | LPS-induced renal cell injury | ↓Blood leukocyte counts, plasma blood urea nitrogen and creatinine level | (Das et al., 2012) |
| Anti-HIV-1             | Cordysobin               |                                   | HIV-1 reverse transcriptase | IC<sub>50</sub> = 8.2 × 10<sup>-7</sup> μM                              | (Das et al., 2012) |
| Renoprotective         | Cyclosporine A           |                                   | Cyclosporine-induced renal tubule dysfunction | ↓Apoptosis, caspase-3 activation, ↑magnesium reabsorption channels TRMP6 and TRMP7, ↓IL-4, IL-13, and IL-25 expression and undesirable immune responses | (Das et al., 2012) |
| Anti-asthmatic         | C. sphecocephala (Klotzsch ex Berk.) Berk. and M.A. Curtis | Culture filtrate                  | Ovalbumin-induced asthmatic mice | ↓SOD, catalase, GSH, ↓MDA, monoamine oxidase                             | (Das et al., 2012) |
| Antaging               | C. sinensis (Berk.) Sacc. | Aqueous                           | D-galactose-induced aging | ↓SOD, catalase, GSH, ↓MDA, monoamine oxidase                             | (Das et al., 2012) |
immunopotentiation in immunodeficient patients (Xu et al., 1992). Interestingly, the induction of macrophages and the intestinal immune system in mice by oral administration of hot water decoction from cultured mycelia of *C. sinensis* has also been reported (Koh et al., 2002). They inferred modulatory IL-6 production by activating macrophages and enhance secretion of hematopoietic growth factors like granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 from Peyer’s patch cells (mainly composed of T and B cells) (Koh et al., 2002). *Cordyceps* spp. induced modulation of cytokines has been reported by others as well (Yu et al., 2004). *C. sinensis* play an immunomodulatory role in the pathogenesis of GAS (Group A Streptococcus) infection in U937 cells by inducing the expression of cytokines like IFN-γ, IL-12, and TNF-α, that eventually augmented the phagocytosis (Kuo et al., 2007). *C. militaris* (L.) Fr. polysaccharides (CMP) induced immune activation were studied in cyclophosphamide-induced immunosuppressed mice by assessing the lymphocyte proliferation, phagocytic index, and other biochemical parameters (Wang M et al., 2012), thus hinting its use as a future immunomodulatory agent.

The immuno-stimulatory action of a compound is explicated by its competence to trigger the immune system of the living organism through inducing or activating its components. Numerous species of *Cordyceps* spp. exhibits immuno-stimulatory activities in distinct parts of the body (Table 2). The use of *C. sinensis* has been documented in the medication of respiratory infections by activating the immune response via innate immunity promotion (Lin and Li, 2011). *Cordyceps* spp. also promotes the adaptive immune system, comprising the cellular and humoral immunity (Lin and Li, 2011). Zhu et al. (2012b) investigated the role of *C. gunnii* (Berk.) Berk.-derived polysaccharides for immunostimulatory and antitumor purposes, and cytokines expression in normal, immuno-compromized, and H22-bearing mice. They inferred that the polysaccharides from the *C. gunnii* (Berk.) Berk. probably boost the non-specific immunity, humoral and cellular immunity, and restrain the tumor growth. CP2-S, (a novel polysaccharide) purified from *C. militaris* (L.) Fr. exhibits immunostimulatory activity by inducing phagocytosis, NO production, respiratory burst, and secretion of IL-1β and IL-2 (from macrophages). Bi et al. (2018) reported the immunostimulatory action of the novel polysaccharide (low-molecular-weight) obtained from the fruiting bodies (cultured) of *C. militaris* (L.) Fr. in splenic lymphocytes and natural killer cells through induction of MAPK, NF-κB, and Toll-like receptor (TLR) two pathways. Ethanol extracts of *C. sinensis* enhance phagocytosis activity as evidenced by carbon clearance in tumor-bearing mice. It also caused a remarkable increment in an acid phosphatase activity and lysosomal enzymes in macrophages suggesting its antitumor action via the immuno-stimulating function (Shin et al., 2001; Shin et al., 2003).

**Anti-inflammatory Potential of Cordyceps spp.**

The extract (ethanolic) of cultured mycelia of *C. militaris* (L.) Fr. possess potent anti-inflammatory activity in the carrageenin-triggered edema and decrement in inducible nitric oxide synthase (iNOS) expression in macrophages. Since the synthesis of NO by iNOS is elevated in inflammatory ailments and leads to cellular injury, this activity confirms its anti-inflammatory action (Won and Park, 2005). In lipopolysaccharide (LPS)-induced macrophage, NO production was restrained by butanolic fraction of *C. militaris* (L.) Fr. and the chief component was cordycepin. It was inferred that cordycepin inhibited the phosphorylation of protein kinase B (Akt), IkBa, and p38. It also suppressed TNF-α, cyclooxygenase-2 (COX-2), iNOS, and NF-κB translocation in these macrophages. Thus, hinted at the use of cordycepin for inflammation-linked disorders (Kim et al., 2006). *C. sinensis* has been reported to strengthen the cell-mediated immunity as well (Liu et al., 2007).

Interestingly, others have reported the application of *C. sinensis* as a cost-effective immunosuppressive agent after renal transplantation without obvious adverse effects (Li et al., 2009). Moreover, cordycepin and *C. sinensis* regulates the functions of human immune cells in vitro by promoting the expression of IL-1β, -6, -8, -10 and TNF-α of resting cells, and inhibited the phytohemagglutinin-induced expression of IL-2, -4, -5, -12 and IFN-γ and TNF-α. Furthermore, the cordycepin and *C. sinensis* treated human monocytic cell line (THP-1) exhibited a higher affinity for the transcription factors that are important in the gene regulation of various cytokines. Thus, cordycepin and *C. sinensis* regulates the immune cells via its immunoregulatory activity (Zhou et al., 2008). A heteropolysaccharide from cultured *C. sinensis* was reported to enhance the immunity in mice exposed to ionizing radiation by reducing oxidative injury and modulating the secretion of cytokines (IL-4, -5 and -17) (Zhang et al., 2011). It has been reported that methanolic fractions of *C. sinensis* contain ingredients having an immunosuppressive effect that inhibits blastogenesis, the activity of NK cell, and phytohemagglutinin induced IL-2 and TNF-α production by human mononuclear cells (Kuo et al., 1996). The crude extract and partially purified fractions of *C. sinensis* inhibit the generation of superoxide anion and release of elastase. Further, it was revealed that five constituents, cordysinins A-E accounted for these actions (Yang et al., 2011). The treatment of macrophages with diverse concentrations of *C. militaris* (L.) Fr. fruiting bodies (hot water extract) has potent suppressive effects on the production of these inflammatory mediators as evident by LPS-induced NO production, TNF-α, and IL-6 secretion (Jo et al., 2010).

Similar results were also reported in another study where the immune activation by CMP was improved. Moreover, CMP increased the thymus and spleen indices, the spleen lymphocyte activity, immunoglobulin G (IgG) function, and the total quantity of white blood cells in mice serum. CMP also enhanced the expression of IFN-γ, TNF-α, and IL-1β mRNA (Liu et al., 2016). Anti-inflammatory effects of another species of *Cordyceps* spp. i.e. *C. bassiana* Z.Z. Li, C.R. Li, B. Huang and M.Z. Fan was investigated (Kim T W et al., 2014). Its butanolic fraction showed the most effective anti-inflammatory response against LPS-activated RAW 264.7 macrophages by inhibiting IkB/NF-κB pathway and suppressing p38 and c-Jun.
### TABLE 3 | Mechanism of action of the Cordyceps spp.-induced pharmacological activities.

| Pharmacological activity               | Mechanism of action                                                                                     | References                                                                                     |
|----------------------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Immunomodulatory and anti-inflammatory activities | • Augmented the in vivo and in vitro NK activities phagocyte reactions via the activation of macrophages  
• Modulation of IL-6 production activated macrophages and enhance secretion of hematopoietic growth factors such as GM-CSF  
• Modulation of cytokines  
• Increase in an acid phosphatase activity, representing lysosomal enzymes, in macrophages  
• Inducing the expression of cytokines like IFN-γ, IL-12, and TNF-α  
• Increased TNF-α and IFN-γ, enhanced NO production, and induced INOS mRNA and protein expressions in macrophage. Induction of mRNA expression of IL-1β, IL-6, IL-10, and TNF-α  
• Modulation of transcription factors involved in the gene regulation of various cytokines.  
• Upregulated the expression of TNF-α, IFN-γ, IL-6, and IL-1β  
• Stimulate NO production, phagocytosis, respiratory burst activity, secretion of IL-1β and IL-2 of macrophages  
• The decrement in INOS expression in macrophages  
• Inhibited the phosphorylation of Akt, IκBα, and p38. Suppressed TNF-α, COX-2, INOS, and translocation of NF-κB in macrophages  
• Inhibitory effects on the production of inflammatory mediators  
• Inhibition of IκB/IFN-κB pathway and suppression of JNK and p38 activation  
• Suppresses the production NO, iNOS, and pro-inflammatory cytokines in macrophages via inhibition of NF-κB and AP-1  | (Kiho et al., 1996; Kiho et al., 1999; Balon et al., 2002; Shin et al., 2003; Yu et al., 2004; Won and Park, 2005; Chen et al., 2008; Kim et al., 2008; Kuo et al., 2007; Ohta et al., 2007; Zhou et al., 2008; Zhu L et al. (2014); Kim T W et al. (2014); Park et al., 2014; Yang et al., 2015a; Chiu et al., 2016b; Liu et al., 2016; Jung et al., 2019) |
| Antioxidant and antiaging activity     | • Inhibited MDA formation, anti-lipid peroxidation action and inhibited the accumulation of cholesterol ester in macrophages  
• Attenuating the changes of GPx and SOD activities, inhibited MDA formation  
• Modulating antioxidation activity via significantly enhancing SOD activity of liver, brain, and serum as well as GPx activity of liver and brain in tumor-bearing mice  
• Improve the activity of SOD of RBCs, brain and liver, the activity of Na⁺-K⁺-ATPase of the brain, the activity of catalase and GPx of blood, decrease the activity of monoamine oxidase of the brain and the contents of MDA of brain and liver in aged mice.  
• Improved the activity of SOD, glutathione peroxidase and catalase and lowered the level of lipid peroxidation and monoamine oxidase activity  | (Yamaguchi et al., 2000a; Gu et al., 2003; Wang et al., 2004; Chen et al., 2006; Ji et al., 2009; Wang M et al. (2012)) |
| Antitumor effects                     | • Via immunomodulation  
• Stimulating adenosine A3 receptors, Wnt signaling pathway, GSK3β activation cyclin D1 inhibition  
• Caspase activation and mitochondrial dysfunction  
• Via mTOR and AMPK signaling  
• Enhancing JNK and p38 kinase activity and activity of Bcl-2 pro-apoptotic molecules  
• Downregulating MDR/HER-1a via AMPK/mTORC1 signaling  
• Antiangiogenic via inhibiting tube formation in endothelial cells and MMP reduction  
• Regulating Bcl-2 family and caspase activity and inhibition of COX-2 and prostaglandin E2 accumulation  
• Regulation of p85/Akt-dependent or GSK3β-related caspase-3-dependent apoptosis  
• Involvement of hedgehog, apoptosis, p53, and estrogen signaling  | (Yoshida et al., 1989; Yoo et al., 2004; Park et al., 2005; Yoshikawa et al., 2007; Jin et al., 2008; Yoshikawa et al., 2008; He et al., 2010; Wong et al., 2010; Jen et al., 2011; Wu et al., 2014; Park et al., 2017; Lee et al., 2019) |
| Hypoglycemic activity                 | • Potentiated the activities of glucokinase, hexokinase and glucose-6-phosphate dehydrogenase  
• Increased the activity of hepatic glucokinase, the decline in the protein content of facilitative GLUT2  
• By enhancing insulin sensitivity and improving oral glucose tolerance  
• Stimulates the expression of HNF-1α to activate GLUT2 for glucose uptake, induced AMPK phosphorylation, and glucoconogenesis inhibition  
• anti-PTP1B activity  | (Kho et al., 1998; Kho et al., 1999; Baton et al., 2002; Zhao et al., 2002; Kim et al., 2017; Sun et al., 2019) |

(Continued on following page)
### Table 3 (Continued) Mechanism of action of the Cordyceps spp.-induced pharmacological activities.

| Pharmacological activity | Mechanism of action | References |
|--------------------------|---------------------|------------|
| **Hypocholesteremic, hypotensive and vasorelaxation activities** | • The endothelium-dependent vasorelaxant effect through stimulating the production of nitric oxide and endothelium-derived hyperpolarizing factor | Yamaguchi et al., 2000a; Yamaguchi et al., 2000b; Chiu et al., 2000; Koh et al., 2003; Won et al., 2009b; Gao et al., 2011; Guo et al., 2011; Wang L et al. (2015) |
|  | • anti-oxidation activities and inhibit the accumulation of cholesteryl ester in macrophages via suppression of LDL oxidation | | |
|  | • Inhibiting LDL oxidation through scavenging free radicals | | |
|  | • Increased the HDL cholesterol level, but decreased VLDL LDL cholesterol level | | |
|  | • Inhibited PDGF-BB-induced RASMCs migration and proliferation via interfering with adenosine receptor-mediated NOS pathways | | |
|  | • Reduced serum total cholesterol, triglyceride, LDL-C, VLDL-C as well as LDL-C/HDL-C and TC/HDL-C ratios. Increase in lipoprotein lipase (LPL) and hepatic lipase (HL) activity | | |
|  | • Increase in levels of serum insulin | | |
|  | • Reduction in the levels of blood and liver lipid, and improvement of the glutamate pyruvate transaminase and antioxidant activity | | |
| **Anti-fatigue and antidepressant activity** | • Facilitating efficient oxygen utilization, enhance energy metabolism in the mitochondria | Zhang et al., 1995; Xiao et al., 1999; Dai et al., 2001; Li and Li, 2009; Chen S et al. (2010); Kumar et al., 2011; Yan et al., 2012; Yan et al., 2013; Song et al., 2015; Geng et al., 2017 |
|  | • The increasing level of β-ATP | | |
|  | • Increased the metabolic threshold and the ventilatory threshold of the subjects | | |
|  | • Extended the exhaustive swimming time of mice, hepatic and muscle glycogen levels, and decrease the blood lactic acid and blood urea nitrogen (BUN) levels | | |
|  | • Upregulation of skeletal muscle metabolic regulators AMPK, PGC-1 and PPAR-α as well as activation of NRF-2-ARE pathway | | |
|  | • Reducing the accumulation of blood lactic acid level. | | |
|  | • Via decreasing MDA and 8-OHdG levels and increasing antioxidant enzymes activities (SOD, catalase and GPx) in the serum, liver and muscle of mice | | |
|  | • Activating AMPK and protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathways and regulating serum hormone level | | |
| **Aphrodisiac potential** | • PKC, cAMP-protein kinase A signal pathway | Wang et al. (1998), Huang et al. (2000), Hsu et al. (2003a), Hsu et al. (2003b), Huang B M et al. (2004), Chen et al. (2009), Leu et al. (2005), Chen S et al. (2010), Leu et al. (2011), Pao et al. (2012), Wang et al. (2016) |
|  | • Induce the expression of steroidogenic acute regulatory (StAR) protein | | |
|  | • Induce in vivo plasma corticosterone level | | |
|  | • Adenosine receptors activated cAMP-PKA-StAR pathway | | |
|  | • PLC/PKC and MAPK signal transduction pathways | | |
|  | • Stimulating CYP11A1, 3β-HSD, and CYP17A1 expressions | | |

Footnote: DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; ERK, 1/2 extracellular signal-related kinases one and two; IL, interleukin; JNK, c-jun N-terminal kinase (JNK) activation. Moreover, 4-quinolinol and 1-naphthol were found from *C. bassiana* as an anti-inflammatory compound.

*Paecilomyces hepiali* Q.T. Chen and R.Q. Dai, CBG-CS-2 strain, isolated from *Cordyceps* spp. was investigated for the anti-inflammatory effects (Park et al., 2014). It was documented that CBG-CS-2 downregulates the NO production, iNOS, and pro-inflammatory cytokines in LPS-stimulated macrophages by inhibition of NF-κB and activating protein (AP)-1, which are important in inflammation. Thus, the modulatory activity of CBG-CS-2 on the inflammatory response in macrophages, makes it useful as an anti-inflammatory drug or supplement. They further extended their study to confirm the immunoregulatory efficacy and safety of CBG-CS-2 separated and cultivated from *P. hepiali* from *C. sinensis* in healthy Korean adults (Jung et al., 2019). The major components reported i.e. CBG-CS-2, cordycepin, Polysaccharides, and adenosine induce immunomodulation by enhancing both the NK-cell activity and phagocyte reactions via macrophages activation. Moreover, cerebrosides have been reported to account for the anti-inflammatory activity of *C. militaris* (L.) Fr. namely cordycebroside A, soyacerebroside I, and glucocerebroside (Chiu et al., 2016b). Summary of the factors involved in cordyceps-induced immunomodulatory and anti-inflammatory activity is depicted in Table 3. *C. sinensis* partially protected animal models of bacterial growth by activating macrophages. It can also induce the expression of IL-1β, IL-10, TNF-α, serum immunoglobulin IgG1, and IgG2b, as well as stimulates Th1 immune response using IFN-γ and IL-12 (Kuo et al., 2001; Lee et al., 2006). Concerning anti-inflammatory effects, cordymin, a purified compound from *C. sinensis* exhibited a decline in IL-1β, TNF-α, and pro-inflammatory markers in a carrageenan-induced inflammation model. Complementarily, the extracted compounds cordymin-1, cordymin-2, and cordymin-4...
presented an antinociceptive effect in acetic acid-induced abdominal constrictions model (Qian et al., 2012). Similarly, the anti-inflammatory activity of *C. sinensis* extracts on the human neutrophils’ response was verified by inhibiting superoxide anion and elastase release. Most of the compounds produced an anti-inflammatory response superior to the indomethacin control, reaching a concentration necessary for 50% inhibition of 0.45 μg/ml for superoxide anion generation, and 1.68 μg/ml for elastase release. While for indomethacin, 38.32, and 31.98 μg/ml, respectively, were required (Yang et al., 2011). In another more detailed report, Cordycepin inhibited the overproduction of NO, prostaglandin E2, and pro-inflammatory cytokines in a dose-dependent manner on the production of inflammatory mediators in LPS-stimulated murine BV2 microglia. Those outcomes inferred that cordycepin has a high potential in restraining inflammatory mediators in neurodegenerative diseases (Jeong et al., 2010).

**Antiviral effects of Cordyceps spp.**

Intranasal administration of an acidic polysaccharide (APS), obtained from the extract of *C. militaris* (L.) Fr. cultivated on germinated soybeans, decreased the virus titers in the bronchoalveolar lavage fluid and the lung of mice infected with influenza A virus with increased survival rate. Furthermore, APS also increased TNF-α and IFN-γ levels. It enhanced NO production and induced iNOS mRNA and protein expressions in RAW 264.7 murine macrophage cells. The induction of mRNA expression of cytokines including IL-1β, IL-6, IL-10, and TNF-α demonstrated its beneficial therapeutic effects on influenza A virus infection by modulating immune function of macrophages (Ohta et al., 2007).

**Antioxidant and Antiaging Activity**

The antioxidative profile of ethanol and water extract of *C. sinensis* (cultured) was assessed and initiated to be minimal on superoxide but it moderately inhibited MDA (malondialdehyde) formation (Yamaguchi et al., 2000a). *C. sinensis* has anti-lipid peroxidation potential and inhibits cholesteryl ester accumulation in macrophages thru LDL oxidation destruction. Li et al. (2001b) described that the adenosine content in Cordyceps spp. has no apparent relationship with anti-oxidation potential but later they confirmed that polysaccharides have the antioxidation profile.

Further, they extended their studies (Gu et al., 2003) and isolated a polysaccharide (210 kDa) from cultivated Cordyceps spp. mycelia having strong anti-oxidative activity. Thus, they concluded that Cordyceps spp. protects against neuronal cell toxicity. Chen et al. (Chen et al., 2006) informed that polysaccharide from *C. sinensis* probably inhibits tumor evolution mainly by modifying hosts’ antioxidative action thru significantly enhancing SOD activity of brain, liver, and serum as well as GPx activity of liver and brain in tumor-bearing mice whereas, it remarkably reduces the MDA level in liver and brain (Chen et al., 2006).

Wu et al. performed an in vitro antioxidant activity of CM-hsCPS2 (a polysaccharide) which was isolated from fruiting bodies of *C. militaris* (L.) Fr. grownup on solid rice medium. (Wu F Y et al., 2011). Similarly, CBP-1 a novel polysaccharide was isolated from cultured *C. militaris* (L.) Fr. was testified to have the hydroxyl radical-scavenging power. Since these radicals are associated with the pathogenesis of several ailments, the study implicit for latent clinical applications of *C. militaris* (L.) Fr. as a substitute for *C. sinensis* in TCM (Yu et al., 2009).

Aging has been reported to involve oxidative stress by many researchers (Romano et al., 2010). A study by Wang et al., 2004 confirmed, that *C. sinensis* increases the capability of learning and memory, improve the action of SOD of RBC’s, mind and liver, the action of Na’-K’-ATPase of the brain, the potential of catalase and GPx of blood, and remarkably decline the activity of monoamine oxidase of the brain and the contents of MDA of brain and liver in aged mice by improving the antioxidative profile and eradicating free radicals (Wang et al., 2004). Ji et al. treated (Ji et al., 2009) D-galactose-induced senescence mice with *C. sinensis* extract. The results documented that *C. sinensis* extract can ameliorate the brain function and possess antioxidant activity by improving the activity of SOD, GPx, and catalase as well as lower the level of lipid peroxidation and monoamine oxidase. Another species i.e. *C. guangdongensis* has already been stated to have noteworthy antioxidative stress properties (Zeng et al., 2009). Another study with *C. guangdongensis* showed that it prolongs the mean lifespan and the half-death time of fruit flies in lifespan tests (Yan et al., 2011).

Structural and antioxidant analysis of W-CBP50, W-CBP50 I, and W-CBP50 II polysaccharides (from cultured *C. militaris* (L.) Fr.) was performed and all of them exhibited significant antioxidative strength (Chen X et al., 2013). Four polysaccharide fractions (CMP-1, CMP-2, CMP-3, and CMP-4) were extracted from cultured *C. militaris* (L.) Fr. depicted noticeable concentration-dependent antioxidant activities (Chen and Huang, 2014). Similarly, a novel low-molecular-weight polysaccharide (CMP-1) was isolated by Jing et al. (Jing et al., 2014) from the cultured *C. militaris* (L.) Fr. showed free-radical-scavenging effects. The same group further isolated a novel polysaccharide (CMPA90–1; compound 1) from the cultured fruiting bodies of *C. milhitaris* (L.) Fr. that exhibited free-radical-scavenging effects (Jing et al., 2015). Summary of the factors involved in cordyceps-induced antioxidant and antiaging activity is depicted in Table 3.

**Antitumor Effects**

Many genera of Cordyceps spp. (natural or cultured) has been documented to display the capability to restrain the growth of tumors due to various bioactive compounds present for e.g. polysaccharides, sterols, and adenosine (Yoshida et al., 1989; Bok et al., 1999; Li and Wang, 2008; Zhou et al., 2009). The glycosylated Ergosterol from the methanolic extract of *C. sinensis* was reported as a remarkable antiproliferative compound against various tumor cell lines (Bok et al., 1999). Moreover, the water extract of *C. sinensis* also accelerates the Kupffer cells mediated phagocytosis to prevent metastasis (Nakamura et al., 1999). Since Cordyceps spp. can be cultivated artificially, it was documented in a comparative study that as compare to natural Cordyceps spp., the cultivated fungus has stronger antitumor activity against MCF-7, B16, HL-60, and HepG2 cancer cell lines (Zhang Q et al., 2005).
Cordycepin restrains the proliferation of cancer cells by triggering adenosine A3 receptors followed by the Wnt signaling pathway, including glycogen synthase kinase three beta (GSK3β) activation and cyclin D1 inhibition (Yoshikawa et al., 2004, 2007; Yoshikawa et al., 2008). In another study on MA-10 mouse Leydig tumor cell, cordycepin induced apoptosis was reported to involve caspase -9, -3, and -7 dependent pathway (Jin et al., 2011). Moreover, the antiproliferative response of cordycepin is documented to be mediated via the mammalian target of rapamycin (mTOR) and 5′/AMP-activated protein kinase (AMPK) signaling (Wong et al., 2010). In human colorectal cancer cells, cordycepin triggers apoptosis via increasing B-cell lymphoma 2 (Bcl-2, proapoptotic molecules), JNK, and p38 kinase activity (He et al., 2010). As an adjuvant, a low concentration of cordycepin enhances the chemosensitivity of gall bladder cancer cells for gemcitabine and 5-fluorouracil, possibly via downregulating multiple drug-resistant/hypoxia-inducible factor 1 (MDR/HIF-1α) through regulating AMPK/mTORC1 signaling (Wu et al., 2014). Thus, it can be inferred that cordycepin induced antitumor profile involves plethora of pathways depending upon the cell type. Ji et al. reported the co-effect of fermented C. sinensis and selenium on uterine cervix cancer, where they reported that this combination attenuates the oxidative stress and refine the immune function as compared to their effect (Ji et al., 2014).

Aqueous extract from another species, C. militaris (L.) Fr. showed cytotoxic profile against stomach adenocarcinoma (SNU-1); colorectal adenocarcinoma (SUN-C4); and hepatocellular carcinoma (SNH-354), where cordycepin was reported as an active component (Lim et al., 2004). Extract of C. militaris (L.) Fr. possesses antiangiogenic properties as evident via inhibition of tube formation in endothelial cells and matrix metalloproteinase (MMP) reduction, a factor related to metastasis and invasion (Yoo et al., 2004). Similarly, C. militaris (L.) Fr. induces apoptosis via mitochondrial dysfunction and caspase activation in human breast cancer cells as well (Jin et al., 2008). Furthermore, pure compounds isolated from the extracts of C. militaris (L.) Fr. have been reported to be antiproliferative against PC-3, colon 205, and HepG2 cells (Rao et al., 2010). Furthermore, it was reported that C. militaris (L.) Fr. inhibit cancer growth through regulation of p85/Akt-dependent or GSK3β-related caspase-3-dependent apoptosis on a xenograft mouse model bearing murine T cell lymphoma (RMA) cell-derived cancers (Park et al., 2017).

It has also been documented that C. sinensis inhibits tumor-cell proliferation activities in different types of cancer cell lines, such as Jurkat, HepG2, PC 3, Colon 205, and MCF-7 (Rao et al., 2007). C. militaris (L.) Fr. concentrate and cordycepin elicit apoptosis via caspase-7, -8, and -9 involving the increase of Bel-2-associated x protein (Bax)/Bel-2 protein expression ratio and decreasing X-linked inhibitor of apoptosis protein (XIAP) thus confirming its anti-cancer property (Lee et al., 2019). Cordycepin exhibited an anti-cancer effect against B16 mouse melanoma by inducing the adenosine A3 receptor, and eventual activation of glycogen synthase kinase-3β, and the suppression of cyclin D1. Furthermore, cordycepin exerts a coadjuvant effect with other drugs, as demonstrated when combined with 2′-deoxycoformycin increased three hundred-fold the anti-cancer effect in B16 cells (Nakamura et al., 2015). Other mechanisms that describe the anti-cancer activity of Cordyceps spp. involve apoptosis and autophagy, as depicted in LNCaP (human prostate carcinoma) cells. Furthermore, the autophagy mechanism was evident by the increase and accumulation of microtubule-associated protein light chain-3 (LC3) (Lee et al., 2014). A summary of the factor involved in cordyceps-induced antitumor activity is depicted in Table 3.

### Hypoglycemic Activity

Kiho et al. (1993) displayed that polysaccharides obtained from the cultivated mycelium of C. sinensis (CS-F30) lower the plasma glucose level in normal and streptozotocin (STZ) induced diabetic mice by intraperitoneal administration in comparison to slight lowering through oral administration. Additionally, they also verified that CS-F30 potentiate the activities of glucokinase, hexokinase, and glucose-6-phosphate dehydrogenase thus accelerating the glucose metabolism, which in turn was responsible for its antidiabetic activity (Kiho et al., 1996). Kiho et al. (1993) also presented the intraperitoneal administration of CS-F10, a polysaccharide purified from hot water extract of cultured mycelium of C. sinensis, on normal, STZ-induced diabetic and epinephrine-induced hyperglycemic mice lowered the plasma glucose level and increased the activity of hepatic glucokinase. An industrial fermentation product i.e. CordyMax™ Cs-4 gained by a proprietary mycelial strain from natural C. sinensis, is described to be effective in lowering basal blood glucose and plasma insulin. Additionally, it improves the metabolism of glucose by increasing insulin sensitivity and improving oral glucose tolerance (Balon et al., 2002; Zhao et al., 2002). A study confirmed that the Cordyceps spp. has a hypoglycemic activity in nicotinamide (NA) and STZ-induced diabetic rats as evident by attenuation of the polydipsia, hyperglycemia, and weight loss (Lo et al., 2004). The extract from C. sinensis has been documented to promote β-cell survival in the diabetes mellitus-II mouse model. (Kan et al., 2012).

C. sinensis has already been stated to give a shielding effect on podocytes in rats with diabetic nephropathy (Hao et al., 2014). In the same way, CmNo1, a novel combination of the fruiting body and C. militaris (L.) Fr. mycelia, has also been testified to deliver renoprotection in high-fat diet and STZ-NA-induced diabetic (type 2) mice (Yu et al., 2016). Kim et al. in a study concluded that C. militaris (L.) Fr. water extract (CMW) stimulates the expression of hepatocyte nuclear factor (HNF)-1α to activate GLUT2 for glucose uptake in liver cells. Recently a study to isolate and characterize cerebrosides with anti-PTP1B activity from C. militaris (L.) Fr. was performed. The results documented that all four cerebrosides obtained from C. militaris (L.) Fr. exhibited inhibitory activity against PTP1B (Sun et al., 2019). A summary of the factors involved in cordyceps-induced hypoglycemic activity is depicted in Table 3.

### Hypcholesterolemic, Hypotensive and Vasorelaxation Activities

In previous studies, the existence of a protein component in C. sinensis is reported to diminish the mean arterial pressure of rats...
and induce a direct endothelium-dependent vasorelaxant effect through stimulating the production of NO and endothelium-derived hyperpolarizing factor. They reported the effect to be triggered by a single active constituent or by the combined action of many agents found in the extract that contributes to hypotensive and vasorelaxation activities (Chiou et al., 2000). Besides antioxidant profile, *C. sinensis* possess potent anti-lipid peroxidation activities and prevent the accumulation of cholesteryl ester in macrophages via suppression of LDL oxidation (Yamaguchi et al., 2000a).

Yamaguchi et al. (Yamaguchi et al., 2000b) performed the effect of the water extract from cultured CMW on serum lipid and lipid peroxide levels and aortic cholesterol accumulation using an atherosclerosis mouse model and concluded that CMW prevents cholesterol deposition in the aorta by impeding LDL oxidation via scavenging free radicals. Remarkably, a study was completed (Won et al., 2009) to determine the effect of cordycepin obtained by *C. militaris* (L.) Fr., on responses of rat aortic smooth muscle cells (RASMCs) and vascular disorders, especially neointimal formation. It was documented that cordycepin inhibited platelet-derived growth factor-BB (PDGF-BB)-induced RASMCs migration and proliferation via interfering with adenosine receptor-mediated NOS pathways, thus resulting in the attenuation of neointima formation and thus could act as atherosclerosis agent. Furthermore, an increase in lipoprotein lipase (LPL) and hepatic lipase (HL) activity by cordycepin hint its contribution to lipid profiles regulation with no toxicity (Gao et al., 2011).

In a contemporary treatment approach toward both diabetes and depression management by vanadium-enriched *C. sinensis* (VECS). It was reported that in STZ-induced hyperglycemic rats administration of VECS, significantly reduces the blood glucose levels with the increase in levels of serum insulin (Guo et al., 2011). The study also revealed a remarkable decrease in immobility with a corresponding increase in the swimming and climbing behavior in hyperglycemic rats following VECS treatment thus concluding a contemporary treatment approach that advocates an aggressive stance toward both diabetes and depression management (Guo et al., 2011). Wang L et al. (2015) reported that the residual polysaccharide from *C. militaris* (L.) Fr. exhibited potential antihyperlipidemic, hepatoprotective, and antioxidant properties as depicted by the reduction in the levels of blood and liver lipid, and improvement of the glutamate pyruvate transaminase and antioxidant activity. Summary of the factors involved in Cordyceps-induced hypcholesterolemic, hypotensive and vasorelaxation activities is depicted in Table 3.

**Larvicidal Activity**

Due to its eco-friendly nature and less or no side effects of microbial metabolites as an insecticide, they are of great use (Berdy, 1989). Kim et al. (2002) reported that *C. militaris* (L.) Fr. fruiting body-derived cordycepin acts as a naturally occurring insecticide against *Plutella xylostella* L. larvae via direct effect rather than an inhibitory action of chitin synthesis and that this compound has stomach action.

### Anti-fatigue and Antidepressant Activity

*Cordyceps* spp. has been used for ages as a medicine for increasing physical stamina to deal with weakness and fatigue by people of high altitude. *Cordyceps* spp. mushroom began to be in the spotlight in 1993, when some world athletics champions revealed part of their strategy for success, including a diet based on *Cordyceps* spp. ingredients (Kashyap et al., 2016). It works by an increase in cellular ATP increasing bioenergy and thus facilitating efficient oxygen utilization (Geng et al., 2017). Interestingly, athletes also use *Cordyceps* spp. to deal with fatigue and weakness thus increasing energy levels and extra endurance (Zhu et al., 1998). Dai et al. (2001) performed a study to evaluate the effects of CordyMax™ Cs-4, a mycelial fermentation product of *C. sinensis*, on energy metabolism. They documented that CordyMax remarkably improved the bioenergy status in the murine liver by increasing the level of β-ATP (adenosine triphosphate). Thus, the study supported the energy-promoting properties of CordyMax. As discussed above, the antioxidant properties of *Cordyceps* spp. enhance energy metabolism in the mitochondria and facilitate the efficient utilization of limited oxygen supply, thus increasing the anaerobic threshold (Zhang et al., 1995; Xiao et al., 1999). Since it has been well-established that fatigue is closely related to depression, a study was performed using the tail suspension test in mice to examine the antidepressant effects of supercritical fluid extract (SCCS) of *C. sinensis*. Results suggest that SCCS may elicit an antidepressant-like effect by affecting the adrenergic and dopaminergic systems, but not by affecting the serotonergic system (Nishizawa et al., 2007). To examine the effect of Cs-4 on erobic capacity in healthy elderly volunteers a double-blind, placebo-controlled trial was performed (Chen S et al., 2010). It was documented that administration of Cs-4 for 12 weeks, increased the metabolic threshold and the ventilatory threshold of the subjects. Such higher thresholds indicate better aerobic performance without fatigue in older human subjects.

The effects of polysaccharides from *C. sinensis* mycelium on physical fatigue in mice documented that *C. sinensis* polysaccharides extended the exhaustive swimming time of mice, hepatic and muscle glycogen levels, and decrease the blood lactic acid and blood urea nitrogen (BUN) levels. Such observations confirmed the anti-fatigue effects of *C. sinensis* polysaccharides (Li and Li, 2009; Yan et al., 2012). To explore the underlying mechanisms behind the exercise endurance promoting activities of *C. sinensis*, Kumar et al. (2011) reported that such beneficial effects are mediated by upregulation of skeletal metabolic regulators AMPK, peroxisome proliferator-activated receptor gamma (PGC)-1 and peroxisome proliferator-activated receptors (PPAR)- as well as activation of NF-E2-related factor 2 (NRF-2)-antioxidant responsive element (ARE) pathway that reduces exercise-induced oxidative stress and inflammation. To other species, i.e. *C. guangdongensis* has also been reported that it exhibits anti-fatigue effect as evident by the longest swimming time in mice (Yan et al., 2011). Moreover, the active constituent accounting for *C. guangdongensis* induced anti-fatigue effect was
reported to be a polysaccharide that alleviates fatigue by reducing the accumulation of blood lactic acid level (Yan et al., 2013).

Interestingly, it was reported that natural as well as laboratory cultured mycelia of \textit{C. sinensis} can increase the motor coordination with improved metabolic and ventilatory that results in increased muscle endurance or anti-fatigue activity and mood elevator or antidepressant-like activity as a result of decreased endogenous depression (Singh et al., 2014). The antioxidative property of \textit{C. sinensis} might be the reason for the increased skeletal muscle activity. Furthermore, \textit{C. militaris} (L.) Fr. induces fatigue recovery is mainly through activating AMPK and AKT/mTOR pathways and regulating serum hormone level (Song et al., 2015). Summary of the factors involved in \textit{Cordyceps}-induced anti-fatigue and antidepressant activity is depicted in Table 3.

\section*{Aphrodisiac Potential}
Because \textit{Cordyceps} spp. is a benchmark for a highly energetic source, its applications as a sexual stimulant and in sexual dysfunction are attractive (Zhu et al., 1998; Tuli et al., 2013a; Chen et al., 2017), even popularly known as the Himalayan Viagra (Kashyap et al., 2016). \textit{Cordyceps} spp. modulates the release of sexual hormones such as testosterone, estrogen, and progesterone, controlling reproductive activity, and restoring the impaired functions (Sohn et al., 2012). Mechanistically \textit{Cordyceps} spp. stimulates steroidogenesis through PKA and PKC signal transduction pathways, testosterone production, and plasma testosterone levels, even in sexually inactive murine models (Huang et al., 2001; Chen et al., 2005). One study described that \textit{C. sinensis} promoted prostate cancer cells grown in mice by enhancing testosterone production and androgen receptor expression (Ma et al., 2018). Hsu et al. (2003a) explored the effect of \textit{C. sinensis} and its extracted fractions on testosterone secretion in mice using \textit{in vivo} and \textit{in vitro} approaches. Another research by Huang Y L et al. (2004) documented the effects of \textit{C. sinensis} and its fractions on steroidogenesis in mice, where they inferred the remarkable stimulation of testosterone production.

In particular, the administration of cordycepin can increase the weight of the epididymis, sperm motility, and movement, and the number of mature sperm (Kashyap et al., 2016), namely, the quality and quantity of the sperm. Wang et al. (1998) demonstrate that PKC may be responsible for the \textit{C. sinensis}-induced steroidogenesis in primary rat adrenal cell cultures. \textit{C. sinensis} also triggers the steroidogenesis process in primary mouse Leydig cell and induces dose-dependent apoptosis in MA-10 mouse Leydig tumor cells (Leu et al., 2011; Pan et al., 2011). Moreover, \textit{C. sinensis} has been reported by Huang et al. (2000) to induce the expression of steroidogenic acute regulatory (STAR) protein, a critical protein for steroidogenesis, in MA-10 mouse Leydig tumor cells. The same group further extended their studies (Huang et al., 2001) for \textit{C. sinensis}-induced steroidogenesis in normal Leydig cells and reported that it had different effects on hCG-stimulated steroidogenesis between normal vs. tumor cells. They documented that \textit{C. sinensis} significantly stimulated testosterone production and new protein synthesis was required for steroidogenesis (Huang et al., 2001). These results were also supported by others (Hsu et al., 2003a; Huang Y L et al., 2004) who documented that \textit{C. sinensis} and its extracted fractions could stimulate testosterone production \textit{in vitro} and \textit{in vivo}. Hsu et al. (2003b) further explored the regulatory mechanism of action of \textit{C. sinensis}-induced steroidogenesis using inhibitors of PKA or PKC pathways in normal mouse Leydig cells. Results documented that \textit{C. sinensis} activated the cAMP-protein kinase A signal pathway, but not protein kinase C, and attenuated P450 side-chain cleavage enzyme (P450scC) activity to reduce human chorionic gonadotropin-stimulated steroidogenesis in purified mouse Leydig cells (Hsu et al., 2003b). However, Chen et al. (2005) reported that the mechanisms underlying \textit{C. sinensis}-stimulated steroidogenesis in MA-10 mouse Leydig tumor cells possibly go through the PKA and PKC pathways simultaneously. They further explored the mechanisms of \textit{C. sinensis}-stimulated steroidogenesis and found that \textit{de novo} protein synthesis, increased steroidogenic acute regulatory protein mRNA expression, a calcium signal, and a mitochondria electrochemical gradient were required for \textit{C. sinensis}-stimulated steroidogenesis (Chen et al., 2010). Similarly, the effect of \textit{C. sinensis} on the female reproductive system was also explored. It was showed that \textit{C. sinensis} stimulates E2 production in human granulosa-lutein cells (GLCs) by upregulating the expression of several key enzymes, especially StAR and aromatase, making it a brilliant candidate for increasing the fecundity of women (Huang B M et al., 2004). Moreover, \textit{C. sinensis} and its fractions have been reported to induce \textit{in vivo} plasma corticosterone levels in immature and mature mice (Leu et al., 2005). Besides, \textit{C. sinensis} could improve the function of reproduction and testis morphology in mice (Jin and Guo, 2006).

The \textit{in vitro} effect of extracted fractions of \textit{C. sinensis} mycelium on hCG-treated testosterone production from purified normal mouse Leydig cells was examined (Wong et al., 2007). It was reported that in normal mouse Leydig cells, all fractions of \textit{C. sinensis} decreased hCG-stimulated testosterone production, which was opposite to the stimulatory effects of \textit{C. sinensis} and fractions in tumor cells with hCG treatment. Different receptor subtypes between normal and tumor cells to activate different cellular functions are responsible for the difference (Huang et al., 1995; Huang et al., 1997). Administration of \textit{C. militaris} (L.) Fr. mycelium improves sperm quality and quantity as evidenced by the improvement in the percentages of motile sperm cells and sperm morphology (Lin et al., 2007; Chang et al., 2008). Moreover, \textit{in vivo} and \textit{in vitro} effects of Cordycepin, were studied on primary mouse Leydig cell steroidogenesis. Cordycepin increased the plasma testosterone concentration as well as stimulated \textit{in vitro} mouse Leydig cell testosterone production. It was reported that cordycepin associates with adenosine receptors to activate the cAMP-PKA-STAR pathway and steroidogenesis in the mouse Leydig cells (Leu et al., 2011).

Besides, others reported that cordycepin can stimulate progesterone production but also activate AR thus simultaneously induce steroidogenesis and apoptosis in MA-10 mouse Leydig tumor cells (Pan et al., 2011). Later intracellular
phospholipase C/protein kinase C (PLC/PKC) and MAPK signal transduction pathways were reported to be responsible cordycepin induced steroidogenesis and cell death in MA-10 mouse Leydig tumor cells (Pao et al., 2012). However, long-term administration of cordycepin can counteract the decline of testicular function in middle-aged rats (Sohn et al., 2012). C. militaris (L.) Fr. remarkably protect testicles against oxidative damage caused by bisphenol A, a commonly used plasticizer, and relieved degeneration of serum T and LH concentration caused by it, via stimulating Star, CYP11A1, 3β-HSD, and CYP17A1 expressions (Wang et al., 2016). Summary of the factors involved in cordycepin-induced aphrodisiac potential is depicted in Table 3.

Kidney Protection

The kidney is the main organ responsible for filtering and eliminating waste through the production of urine. Among the various applications of the components of C. sinensis, one can also find its valuable use to regulate some imbalances of the kidney, for example for the reduction of hematuria and proteinuria with an evident restoration of the tissue evidenced by histological analysis (Ding et al., 2011). In addition to supporting kidney transplantation in combination with drugs such as cyclosporin A. That combination is beneficial because high doses of cyclosporin A can induce kidney damage (Ding et al., 2009). Likewise, C. sinensis exhibits nephroprotection properties to mitigate damage from aminoglycosides, broad-spectrum antibiotics (Bao et al., 1994; Heggers et al., 1996). These properties are associated with an increase of 17-hydroxy-corticosteroid, 17-ketosteroid, SOD enzymes, and free radical scavenging.

TOXIC EFFECTS OF CORDYCEPS SPP.

The array of secondary metabolites of polycyclic aromatic hydrocarbons (PAH) primarily developed from C. sinensis react with the polypropylene in popular bags, resulting in by-products toxic to C. sinensis and spectacular progress over time. These polypropylene/PAH by-products inevitably damage the organism. To extend the growth period of the organism, C. sinensis must be cultured in glass or metal vessels (Holliday et al., 2004). The PAH compounds are present in the living culture, but they are volatile compounds and lost after drying. While Cordyceps spp. cannot usually be grown in polypropylene bags, new strains that produce considerably less PAH are designed to allow them to grow in plastic bags.

CONCLUSIONS AND PROSPECTS

Natural products are increasing the trust of people for the treatment and management of several chronic diseases. For hundreds of years, Cordyceps spp. have been used in Tibetan medicine and TCM, and in the last decades, the consumption of its fruiting bodies or related products as supplements has become popular. The most consumed and studied are C. sinensis and C. militaris (L.) Fr. Cordyceps spp. genus compromises a plethora of compounds and some of them showed therapeutic and pharmacological activities in pre-clinical studies, in vitro, and in vivo. Cordycepin and CA are important Cordyceps spp. bioactive constituents with important therapeutic applications associated with other compounds such as nucleotides, polysaccharides, cyclic peptides, sterols, and fatty acids are present in this genus and have shown a wide range of biological activities. The reservoir of Cordyceps spp. bioactive components show their therapeutic activities by modulating several cell signaling pathways due to the modulation of inflammation and oxidative/nitrosative stress processes. Cytokines releases, NO production via iNOS stimulation, and MAPK pathway are some of the cell signaling pathways modulated by Cordyceps spp. bioactive components. In the future, new chemical studies are needed to elucidate the unknown molecules present in Cordyceps spp., and new preclinical studies are needed to understand which compounds have the most interesting biological activities and the existing synergies between Cordyceps spp. components. Likewise, new drug formulations as nano drugs with cordycepin and other Cordyceps spp. biological compounds need to be developed and studied. However, new toxicological studies are needed to ensure their safety and promote its clinical studies. Clinical pilot studies with a few numbers of participants are needed as the first step to elucidate the potential of Cordyceps spp. as hypoglycaemic, hypcholesterolemic, and hypotensive agents. Other potential therapeutic effects such as anticancer may be more difficult to be elucidated in clinical studies and more pre-clinical studies are needed to a better understanding of the mechanisms involved. In conclusion, new future efforts are needed to elucidate the bioactive compounds present in Cordyceps genus and its therapeutic potential.

AUTHOR CONTRIBUTIONS

GD: Conceptualization, Methodology, Data curation, Writing-Original draft preparation. H-SS: Methodology, Writing-Reviewing and Editing. GL-G: Data curation, Writing-Original draft preparation, Writing- Reviewing and Editing. MP-A: Data curation, Writing- Original draft preparation. HC: Data curation, Writing- Original draft preparation. YS: Data curation, Writing- Original draft preparation, Writing- Reviewing and Editing. MP: Data curation, Writing- Original draft preparation. AM: Data curation, Writing- Original draft preparation, Writing- Reviewing and Editing. MN: Methodology, Data curation, Methodology, Data curation, Writing- Original draft preparation. SS: Data curation, Writing- Original draft preparation PC: Data curation, Writing- Original draft preparation. MM: Writing-Original draft preparation, Writing- Reviewing and Editing. NM: Methodology, Data curation, Methodology, Data curation, Writing- Original draft preparation. VS: Writing-
Original draft preparation. NG: Writing- Original draft preparation. RS: Writing- Original draft preparation. JKP: Visualization, Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Software, Writing-Reviewing and Editing, Funding.

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