Cordyceps sinensis: A Comprehensive Meta-Analysis of its Potential Health Benefits

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Abstract:- *Cordyceps sinensis,* a revered traditional Chinese medicine, has garnered significant attention for its diverse pharmacological properties. This comprehensive review delves into its potential health benefits, focusing on its bioactive compounds, clinical efficacy, and underlying mechanisms of action. Key findings reveal its anti-cancer properties, including anti-proliferative, anti-metastatic, and immune-boosting effects against various cancer cell lines. Additionally, its anti-inflammatory properties are evident in its ability to suppress inflammation by regulating key signaling pathways and reducing oxidative stress. Furthermore, *Cordyceps sinensis* exhibits anti-tumor activity, particularly through compounds like cordycepin, which induce apoptosis and cell cycle arrest in cancer cells. The anti-fibrotic potential is highlighted by its capacity to mitigate inflammation, reduce fibrosis, and regulate key proteins involved in tissue repair. Cellular protection against oxidative damage is attributed to the antioxidant properties of its polysaccharides and other bioactive compounds. Additionally, its anti-proliferative effects are reflected in the inhibition of cell growth and proliferation. While these findings are promising and encouraging, more extensive clinical research is required to completely clarify its effectiveness and safety in human populations. However, *Cordyceps sinensis* offers a promising supplemental or alternative medicine and a natural approach to a number of medical disorders.

Keywords:- *Medicinal Mushroom, Natural Remedy, Bioactive Compounds, Pharmacological Properties, Traditional Chinese Medicine.*

I. INTRODUCTION

Cordyceps Sinensis, a traditional Chinese medicine, has recently attracted much attention due to its various pharmacological actions. In recent years, *Cordyceps sinensis* has been widely accepted for various diseases such as pulmonary hypertension, cancer, and neuropsychiatric disorders. This bioactive fungus comprises cordycepin and polysaccharides that have has promising pharmacological effects. With the further study of its effects, the natural adaptogen, *Cordyceps sinensis* is establishing itself as a potential candidate for a modern pharmacological supplement. One of the most popular topics to explore has been the efficacy of *Cordyceps Sinensis* in the treatment of primary pulmonary hypertension. *Cordyceps sinensis*, particularly Yarsagumba, is found to contain potent anti-proliferative and vasorelaxant activities. These effects are significant because pulmonary hypertension is defined by narrowing of the small blood vessels and sclerosis leading to excessive cell growth within the vessels. Several studies have shown that Yarsagumba could prevent these pathophysiological processes, meaning that it could be used to treat pulmonary hypertension [10]. At the end, the use of *Cordyceps sinensis* is suggested to be a natural source of therapy that can be used as an alternative to the conventional therapies for the patients seeking for an alternative therapy to use together with the conventional ones. In cancer treatment, *Cordyceps sinensis* has received much interest because of its bioactive constituent named cordycepin. Aside from its immunomodulatory properties, cordycepin has been credited with anticancer and antimetastatic properties capable of restraining the growth and metastasis of many forms of cancers. Cordycepin significantly inhibits the metastasis of breast cancer cells with low density lipoprotein receptor-related protein [1]. From the viewpoint of the molecular mechanisms of cancer cell migration and invasion that have been modulated by cordycepin, there is a clear indication that cordycepin could be very meaningful in how cancer is handled, especially in the prevention of cancer metastasis. Such anticancer properties make it essential to incorporate *Cordyceps Sinensis* into other traditional therapeutic plans for cancer patients. *Cordyceps sinensis* has other benefits, not restricted in its usage to pulmonary and oncological health, it also offers benefits in mental health. Different previous investigations have shown that polysaccharides derived from *Cordyceps sinensis* possess some features of antidepressant activity. From these observations, these studies propose that *Cordyceps sinensis* polysaccharides can alter neurochemical dopamine dynamics related to mood disorders such as depression and anxiety [21]. This points to potential as *Cordyceps sinensis* on physical and mental health thus, offering to be an all-embracing therapeutic entity. The existing research on *Cordyceps sinensis* has led to many studies exploring the universality of its health benefits, including the immune system regulation and anti-inflammatory effects in different diseases and tumor growth inhibition [23]. Studies point to its potential antifibrotic bioactivity, suggesting a role in mitigating tissue damage [18].

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Nonetheless, there are divergent views regarding the effectiveness and safety of *Cordyceps sinensis*. These different approaches indicate that a comprehensive meta-analysis needs to be conducted with a view of compiling present information to present clearer outcomes. This systematic review aims to comprehensively summarize the current understanding of *Cordyceps sinensis'* effects on human health, encompassing its pharmacological properties, clinical efficacy, and the quality of supporting research. By synthesizing and critically analyzing information from numerous studies, this meta-analysis seeks to bridge the gap between traditional folk use and modern scientific evidence, thereby illuminating the true potential and limitations of this revered natural remedy.

II. METHODOLOGY

A systematic review design was used in this study. Publications discussing the possible health benefits of *Cordyceps sinensis* were chosen using the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA System) as a guideline.

A. Data sources

All of the published and scientific papers pertaining to the aforementioned studies were methodically chosen and examined from three widely used search databases—Google Scholar, ScienceDirect/Elsevier, and the National Center for Biotechnology Information—using the PRISMA guidelines for conducting this study.

B. Literature Search

The aforementioned databases' search engines employed phrases and words to help choose a suitable and successful search approach. To find relevant references, a variety of keyword sets were employed and searched in online databases. *Cordyceps sinensis*-related terms including "*Hirsutella sinensis*," "*Ophiocordyceps sinensis*", "Yarsagumba", "Caterpillar fungus," and "Cordyceps" were included in the first batch of keywords. Terms pertaining to health benefits, such as "health benefits" and "body effects," were utilized in the second group of keywords.

C. Inclusion and Exclusion Criteria

The following criteria were used to categorize all relevant articles included in this review: (1) studies that mention the target organ, cells, and tissues; (2) studies that mention the type of illness; (3) studies that mention the effect or effects on the body; (4) studies that mention the bioactive compound present in *Cordyceps sinensis*; (5) studies that mention the dosage of *Cordyceps sinensis* being used in the experiment; (6) the study must be a quantitative scientific paper; (7) original studies published as research articles or review articles; (7) original studies published in English or with an English translation; and (9) the study papers can come from multiple countries.

Exclusion criteria for studies include if they are (1) case series, case reports, systematic reviews, or narrative reviews; (2) lack of related research data or outcome factors; (3) lack of complete text available; or (4) lack of English translation.

D. Search Results

Using combinations of search phrases from the three research directories (13 from Elsevier, 14 from Google Scholar, and 8 from NCBI), 35 studies pertaining to the previously described study were first found. 18 studies were removed from the initial findings of these web directories because they only included review and research articles written in English and had to be published between 2009 and 2024. After three duplicate studies were eliminated, 10 review and research articles were left, and they underwent a final screening process in accordance with the inclusion criteria. After additional screening and evaluation of the research and review papers' eligibility based on the titles, abstracts, and availability of research data, ten in all were eventually included in the quantitative analysis. The PRISMA flow diagram (see Fig. 1) displays the selection and outcome stages.

E. Data Extraction

A thorough summary of the health advantages of *Cordyceps sinensis* and its bioactive component is included in this article. The collected literature was evaluated, and pertinent information relevant to the review objectives was entered into Google Sheets. The following information is collected from each article for the quantitative analysis: author and year of publication, target organ, tissue, or cell, target disease, effect or effects on the body, bioactive substance, and dosage.

F. Data Analysis

The selected literature is assessed for eligibility for quantitative analysis based on its qualitative features. To measure the health advantages of *Cordyceps sinensis*, various relevant literature and publications that show the effects on the body were included.

III. RESULTS AND DISCUSSION

A. Scientifific Studies and Authoritative Records on the Health Benefits of Cordyceps

The collection of scientific articles and reviews on the health benefits of Cordyceps indicates that research has focused on its various therapeutic properties yet remains limited in scope due to constraints in large-scale clinical trials and long-term studies. The studies analyzed and reviewed by the researchers, largely sourced through databases like Google Scholar and Elsevier. These studies have highlighted Cordyceps' bioactive components, such as cordycepin, which have shown promising effects in animal models and in vitro experiments but require more evidence for widespread clinical application. A systematic review was conducted on available research published between 2009 and 2024, encompassing 10 studies to assess specific health effects, such as anti-inflammatory, antioxidant, immunomodulatory, anti-cancer, anti-tumor, and anti-fibrotic activity. Most of these studies involved laboratory and animal testing, with limited human clinical trials. The collected findings were organized and tabulated to evaluate the overall efficacy and understand their significance to the review study. Table 1. summarizes the pharmacological and therapeutic potential of Cordyceps species, a medicinal fungus known for a wide range of health benefits. Cordyceps demonstrates promising effects in treating various diseases, particularly cancers, inflammatory conditions, and cardiovascular issues. It has anti-cancer properties, including anti-proliferative, anti-metastatic, and immune-boosting effects, making it effective against multiple cancer cell lines such as breast, colon, and melanoma. In addition, Cordyceps shows anti-inflammatory properties, aiding in conditions like inflammation and tissue recovery, as well as cardiovascular benefits by reducing platelet aggregation, which helps prevent clot formation. These therapeutic effects are attributed to bioactive compounds in Cordyceps, including polysaccharides, cordycepin, nucleosides, and ergosterol, which work at the cellular level to produce beneficial outcomes. The table also highlights that different dosages of Cordyceps are used depending on the desired effect, indicating its versatility and potential for tailored treatments. Overall, Cordyceps offers a promising natural approach to managing a wide range of diseases, particularly cancer, inflammation, and cardiovascular health, suggesting its value in both complementary and alternative medicine.

B. Therapeutic potential of Cordyceps in human Health

Previous studies on Cordyceps have shown its potential for various health benefits, including anti-Inflammatory, antioxidant, anti-cancer, anti-tumor, anti-fibrotic activity, and anti-proliferation.

➢ *Anti-Cancer*

There are several excellent works about the anticancer effect of Cordyceps militaris polysaccharide (CMPs). The in vitro anticancer activity of the polysaccharide was further investigated through cell morphology studies and live/dead cell imaging experiments. As a result, the polysaccharide effectively induced cancer cell death. Additionally, a cell apoptosis study revealed that the polysaccharide suppressed cell proliferation by triggering apoptosis (Li et al.). Cordycepin reduced hematogenic metastasis of cancer cells by inhibiting ADP-induced platelet aggregation without affecting the interaction between cancer cells and platelets. This paper demonstrated that ADP, a platelet aggregation inducer, accelerated hematogenic metastasis of B16-F1 cells in mice, while cordycepin reduced the number of metastatic lung nodules, potentially through the inhibition of ADP-induced platelet aggregation. This study indicated that cordycepin exerted an anticancer effect by stimulating adenosine A3 receptor on cancer cells [20].

➢ *Anti-Inflammatory*

The study revealed that EPS-LM, an exopolysaccharide derived from Cordyceps sinensis, significantly inhibits the TLR4/MyD88/NF-κB signaling pathway, a crucial pathway involved in inflammatory responses triggered by LPS in macrophage cells. Additionally, EPS-LM effectively suppressed LPS-induced ROS production in these cells. These findings collectively demonstrate the multifaceted anti-inflammatory properties of EPS-LM, making it a promising candidate for further research and development as a potential therapeutic agent for various inflammatory and oxidative stress-related conditions. However, further in vivo and clinical studies are essential to fully establish its efficacy and safety in humans [23].

➢ *Anti-Tumor Activity*

Cordyceps sinensis (natural or cultured) has been documented to display the capability to restrain the growth of tumors due to various bioactive compounds present. Few studies demonstrated that cordyceps have an anti-tumor effect. Cordycepin combined with ADAi or developing stable cordycepin derivative compound is therefore a potential adjuvant used for leukemia therapy [6].

➢ *Anti-Fibrotic Activity*

Reference [22] provided some findings of insight into the preventive and therapeutic potentials of Cordyceps for treating lung fibrosis. Cordyceps has shown potential in reducing inflammation and fibrosis by mitigating the infiltration of inflammatory cells, decreasing fibroblast and collagen deposition, reducing reactive oxygen species production, and regulating cytokines. Treatment with Cordyceps also helped restore the balance of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) in fibrotic rat models, with both preventive (initiated from the day of BLM administration) and therapeutic (starting 14 days post-BLM) approaches. In fibrotic human lung epithelial A549 cell models, induced by transforming growth factor-beta 1 (TGF-β1), Cordycepin, a primary component of Cordyceps, was able to partially reverse epithelial–mesenchymal transition (EMT). This was evidenced by reduced vimentin expression and increased E-cadherin levels, highlighting Cordyceps' potential therapeutic value in lung fibrosis treatment [22].

➢ *Antioxidant*

A study investigates the potential bioactivities of a specific strain of *Cordyceps sinensis*, named *Ophiocordyceps sinensis* OS8. The research focuses on the antioxidant, anticancer, and immunomodulatory properties of cultured mycelial enriched β-D-glucan polysaccharides extracted from this strain. IT also mentions that polysaccharides derived from *Cordyceps sinensis* have demonstrated significant antioxidant properties. However, the main finding of the study is that the β-D-glucan polysaccharides extracted from *Ophiocordyceps sinensis* OS8 possess strong antioxidant properties. These polysaccharides were able to scavenge free radicals and inhibit DPPH radical activity. Overall, the study suggests that *Ophiocordyceps sinensis* OS8 is a potential source of natural antioxidants due to the presence of β-D-glucan polysaccharides with strong free radical scavenging activity [2].

➢ *Anti-Proliferation*

A study found that Cordyceps sinensis has anti-proliferative effects on aortic smooth muscle cells and pulmonary artery smooth muscle cells. This effect is thought to be due to the decreased expression of cyclins and cyclin-dependent kinase (CDK), induction of G1-phase cell-cycle arrest and upregulation of CDK inhibitor p27kip1. Additionally, Cordyceps sinensis has been shown to reduce the proliferation of pulmonary artery smooth muscle cells in the context of hypoxia-induced proliferation [10].

C. The Primary Bioactive Compounds Responsible for the Therapeutic Effects of Cordyceps

The genus Cordyceps, particularly its extracts, is a rich source of various bioactive compounds with potential therapeutic benefits. Major compounds include cordycepin, adenosine, polysaccharides (EPSF and APS), and amino acids like cordymin and tryptophan. These compounds contribute to various health effects: cordycepin is noted for its immunomodulatory and antitumor activities, adenosine for anti-inflammatory and analgesic effects, and polysaccharides for antioxidant benefits. [10]

- *Polysaccharides*

The polysaccharide CPS1, isolated from cultured Cordyceps sinensis, is a complex molecule with a backbone primarily composed of glucose and mannose linked by (1→2) and (1→4) glycosidic bonds. Additionally, galactose residues are present and likely contribute to branching in the structure. The precise arrangement of these sugars and the nature of the branching patterns remain to be fully elucidated. This polysaccharide has been shown to possess significant antioxidant properties, including scavenging hydroxyl radicals, reducing power, and chelating ferrous ions. These activities suggest its potential role in mitigating oxidative stress and its potential therapeutic applications. However, further research is necessary to fully understand the structure-activity relationship and the exact mechanisms underlying its antioxidant effects [16]

- *Nucleosides*

Cordyceps sinensis has a variety of nucleosides, including adenosine, uridine, and guanosine. Adenosine, a fundamental building block for RNA, is crucial for energy transfer within cells and might contribute to Cordyceps' potential benefits like improved blood flow and reduced inflammation. Uridine, another vital RNA component, plays a role in brain function and cognitive health. Guanosine is commonly found in Cordyceps sinensis and is essential for cell signaling and protein synthesis, potentially bolstering the fungus's overall health benefits [8].

- *Cordycepin*

A study shows evidence for the anti-proliferative effects of cordycepin, a bioactive compound derived from *Cordyceps sinensis*. Specifically, the study demonstrates that cordycepin induces apoptosis and G2/M phase cell cycle arrest in esophageal cancer cells through the activation of the ERK signaling pathway. Cordycepin's mechanism of action involves the inhibition of RNA polymerase II, leading to the premature termination of RNA transcription. This disruption in RNA synthesis results in cell cycle arrest and apoptosis. Additionally, cordycepin has been shown to upregulate pro-apoptotic proteins and downregulate anti-apoptotic proteins, further promoting cell death. The study's findings suggest that cordycepin may have potential as a novel therapeutic agent for the treatment of esophageal cancer. However, further research is necessary to elucidate the precise molecular mechanisms underlying these effects and to evaluate its efficacy and safety in clinical settings. Exploring the potential synergistic effects of cordycepin with other bioactive compounds in *Cordyceps sinensis* could also enhance its therapeutic potential [17].

- *CPS-2*

CPS-2, a *Cordyceps sinensis* polysaccharide, was found to be mostly of α-(1 → 4)-D-glucose and α-(1 → 3)-D-mannose, branched with α-(1 → 4,6)-D-glucose every twelve residues on average. A monosaccharide analysis conducted by the PMP precolumn derivation method showed that CPS-2 was composed of mannose, glucose, and galactose with the ratio of 4 : 11 : 1. CPS-2, which appeared as white powder, has been demonstrated to have significant therapeutic activity against chronic renal failure. Recently, the underlying molecular mechanism has been explored by scientists. Wang et al. found that CPS-2 could reduce PDGF-BB-induced cell proliferation through the PDGF/ERK and TGF-b1/Smad pathways. As a result, CPS-2 inhibits PDGF-BB-induced human mesangial cells (HMCs) proliferation in a dose-dependent manner. [15]

- *Ergosterol*

Ergosterol, a precursor to vitamin D2, plays a crucial role in maintaining fungal cell membrane integrity. Upon exposure to UV-B radiation, ergosterol converts to vitamin D2, which is essential for calcium and phosphorus absorption, bone health, and immune function. Additionally, ergosterol possesses antioxidant properties, helping to neutralize harmful free radicals and protect cells from oxidative stress. While the specific anti-proliferative effects of ergosterol in Cordyceps sinensis may require further investigation, its potential role in maintaining cellular health and immune function suggests that it contributes to the overall health benefits associated with this medicinal mushroom [12].

IV. CONCLUSION

In conclusion, this review shows *Cordyceps sinensis*' great pharmacological promise in treating a variety of disorders, including primary pulmonary hypertension and cancer. According to the literature, *Cordyceps sinensis* and its bioactive components, particularly cordycepin and polysaccharides, have significant therapeutic benefits, including anti-proliferative, vasorelaxant, immunomodulatory, anticancer, and antimetastatic properties. These findings highlight its dual role as a promising natural adaptogen and a potential supplement to conventional treatment. For primary pulmonary hypertension, the vasorelaxant and anti-proliferative properties of *Cordyceps sinensis* components may provide an innovative approach to preventing or mitigating pathophysiological processes that cause excessive cell proliferation in blood vessels, which is characteristic of the disease. This shows that *Cordyceps sinensis* may be a potential natural therapy for individuals with pulmonary hypertension, either as an alternative or in addition to current medications. The available data clearly supports *Cordyceps sinensis* as a promising natural medicinal agent with numerous uses. Its incorporation into current pharmacology may result in significant advancements in the treatment of pulmonary hypertension, cancer, and maybe other disorders. More controlled clinical trials are encouraged to confirm its effectiveness and improve its medicinal uses.

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REFERENCES

[1]. Cai, H., Li, J., Gu, B., Xiao, Y., Chen, R., Liu, X., Xie, X., & Cao, L. (2017). Extracts of Cordyceps sinensis inhibit breast cancer cell metastasis via down-regulation of metastasis-related cytokines expression. *Journal of Ethnopharmacology*, *214*, 106–112. https://doi.org/10.1016/j.jep.2017.12.012

[2]. Chatnarin, S., & Thirabunyanon, M. (2023). Potential bioactivities via anticancer, antioxidant, and immunomodulatory properties of cultured mycelial enriched β-D-glucan polysaccharides from a novel fungus Ophiocordyceps sinensis OS8. *Frontiers in Immunology*, *14*. https://doi.org/10.3389/fimmu.2023.1150287

[3]. Chen, M., Cheung, F. W., Chan, M. H., Hui, P. K., Ip, S., Ling, Y. H., Che, C., & Liu, W. K. (2012). Protective roles of Cordyceps on lung fibrosis in cellular and rat models. *Journal of Ethnopharmacology*, 143(2), 448–454. https://doi.org/10.1016/j.jep.2012.06.033

[4]. Li, J., Cai, H., Sun, H., Qu, J., Zhao, B., Hu, X., Li, W., Qian, Z., Yu, X., Kang, F., Wang, W., Zou, Z., Gu, B., & Xu, K. (2020). Extracts of Cordyceps sinensis inhibit breast cancer growth through promoting M1 macrophage polarization via NF-κB pathway activation. *Journal of Ethnopharmacology*, *260*, 112969. https://doi.org/10.1016/j.jep.2020.112969

[5]. Li, L., Song, A., Yin, J., Siu, K., Wong, W., & Wu, J. (2020). Anti-inflammation activity of exopolysaccharides produced by a medicinal fungus Cordyceps sinensis Cs-HK1 in cell and animal models. *International Journal of Biological Macromolecules*, *149*, 1042–1050. https://doi.org/10.1016/j.ijbiomac.2020.02.022

[6]. Liang, S., Lu, Y., Ko, B., Jan, Y., Shyue, S., Yet, S., & Liou, J. (2017). Cordycepin disrupts leukemia association with mesenchymal stromal cells and eliminates leukemia stem cell activity. *Scientific Reports*, 7(1). https://doi.org/10.1038/srep43930

[7]. Liang, S., Lu, Y., Ko, B., Jan, Y., Shyue, S., Yet, S., & Liou, J. (2017b). Cordycepin disrupts leukemia association with mesenchymal stromal cells and eliminates leukemia stem cell activity. *Scientific Reports*, 7(1). https://doi.org/10.1038/srep43930

[8]. Liu, Y., Wang, J., Wang, W., Zhang, H., Zhang, X., & Han, C. (2015). The Chemical Constituents and Pharmacological Actions of Cordyceps sinensis. *Evidence-based Complementary and Alternative Medicine*, *2015*, 1–12. https://doi.org/10.1155/2015/575063

[9]. Lu, W., Chang, N., Jayakumar, T., Liao, J., Lin, M., Wang, S., Chou, D., Thomas, P. A., & Sheu, J. (2014). Ex vivo and in vivo studies of CME-1, a novel polysaccharide purified from the mycelia of Cordyceps sinensis that inhibits human platelet activation by activating adenylate cyclase/cyclic AMP. *Thrombosis Research*, *134*(6), 1301–1310. https://doi.org/10.1016/j.thromres.2014.09.023

[10]. Luitel, H., Novoyatleva, T., Sydykov, A., Petrovic, A., Mamazhakypov, A., Devkota, B., Wygrecka, M., Ghofrani, H. A., Avdeev, S., Schermuly, R. T., & Kosanovic, D. (2020). Yarsagumba is a Promising Therapeutic Option for Treatment of Pulmonary Hypertension due to the Potent Anti-Proliferative and Vasorelaxant Properties. *Medicina*, *56*(3), 131. https://doi.org/10.3390/medicina56030131

[11]. Park, S., Jung, S., Ha, K., Sin, H., Jang, S., Chae, H., & Chae, S. (2014). Anti-inflammatory effects of Cordyceps mycelium (Paecilomyces hepiali, CBG-CS-2) in Raw264.7 murine macrophages. *Oriental Pharmacy and Experimental Medicine*, 15(1), 7–12. https://doi.org/10.1007/s13596-014-0173-3

[12]. Peng, Y., Tao, Y., Wang, Q., Shen, L., Yang, T., Liu, Z., & Liu, C. (2014). Ergosterol Is the Active Compound of Cultured MyceliumCordyceps sinensison Antiliver Fibrosis. *Evidence-based Complementary and Alternative Medicine*, *2014*(1). https://doi.org/10.1155/2014/537234

[13]. Qi, W., Zhou, X., Wang, J., Zhang, K., Zhou, Y., Chen, S., Nie, S., & Xie, M. (2020). Cordyceps sinensis polysaccharide inhibits colon cancer cells growth by inducing apoptosis and autophagy flux blockage via mTOR signaling. *Carbohydrate Polymers*, *237*, 116113. https://doi.org/10.1016/j.carbpol.2020.116113

[14]. Shin, Seulmee & Lee, Sungwon & Kwon, Jeonghak & Moon, Sunhee & Lee, Seungjeong & Lee, Chong-Kil & Cho, Kyunghae & Ha, Nam-Joo & Kim, Kyung. (2009). Cordycepin Suppresses Expression of Diabetes Regulating Genes by Inhibition of Lipopolysaccharide-induced Inflammation in Macrophages. *Immune network*. 9. 98-105. 10.4110/in.2009.9.3.98.

[15]. Wang, Y., Liu, D., Zhao, H., Jiang, H., Luo, C., Wang, M., & Yin, H. (2013). Cordyceps sinensis polysaccharide CPS-2 protects human mesangial cells from PDGF-BB-induced proliferation through the PDGF/ERK and TGF-β1/Smad pathways. *Molecular and Cellular Endocrinology*, *382*(2), 979–988. https://doi.org/10.1016/j.mce.2013.11.018

[16]. Wang, Y., Wang, M., Ling, Y., Fan, W., Wang, Y., & Yin, H. (2009). Structural Determination and Antioxidant Activity of a Polysaccharide from the Fruiting Bodies of Cultured Cordyceps sinensis. *The American Journal of Chinese Medicine*, *37*(05), 977–989. https://doi.org/10.1142/s0192415x09007387

[17]. Xu, J., Zhou, X., Wang, X., Xu, M., Chen, T., Chen, T., Zhou, P., & Zhang, Y. (2019). Cordycepin Induces Apoptosis and G2/M Phase Arrest through the ERK Pathways in Esophageal Cancer Cells. *Journal of Cancer*, *10*(11), 2415–2424. https://doi.org/10.7150/jca.32071

[18]. Yao, X., Meran, S., Fang, Y., Martin, J., Midgley, A., Pan, M., Liu, B., Cui, S. W., Phillips, G. O., & Phillips, A. O. (2013). Cordyceps sinensis: In vitro anti-fibrotic bioactivity of natural and cultured preparations. *Food Hydrocolloids*, *35*, 444–452. https://doi.org/10.1016/j.foodhyd.2013.06.023

[19]. Ying, M., Yu, Q., Zheng, B., Wang, H., Wang, J., Chen, S., Gu, Y., Nie, S., & Xie, M. (2019). Cultured Cordyceps sinensis polysaccharides attenuate cyclophosphamide-induced intestinal barrier injury in mice. *Journal of Functional Foods*, *62*, 103523. https://doi.org/10.1016/j.jff.2019.103523

[20]. Yoshikawa, N., Kunitomo, M., Kagota, S., Shinozuka, K., & Nakamura, K. (2009). Inhibitory Effect of Cordycepin on Hematogenic Metastasis of B16-F1 Mouse Melanoma Cells Accelerated by Adenosine-5′-diphosphate. *Anticancer Research*. https://ar.iiarjournals.org/content/29/10/3857.long

[21]. Zhang, X., Qiao, Y., Li, G., Rong, L., Liang, X., Wang, Q., Liu, Y., Pi, L., Wei, L., & Bi, H. (2024). Exploratory studies of the antidepressant effect of Cordyceps sinensis polysaccharide and its potential mechanism. *International Journal of Biological Macromolecules*, *277*, 134281. https://doi.org/10.1016/j.ijbiomac.2024.134281

[22]. Zhou, X., Gong, Z., Su, Y., Lin, Z., & Song, W. (2020). Effects of Cordyceps on lung fibrosis: Reduction of inflammatory cell infiltration, fibroblast and collagen deposition, and oxidative stress. *Journal of Ethnopharmacology*, 249, 112358. https://doi.org/10.1016/j.jep.2019.112358

[23]. Zhu, Y., Dong, Y., Gu, F., Zhao, Z., Huang, L., Cheng, W., & Wu, J. (2024). Anti-Inflammatory effects of cordyceps CS-HK1 fungus exopolysaccharide on Lipopolysaccharide-Stimulated macrophages via the TLR4/MYD88/NF-KB pathway. *MDPI*. https://doi.org/10.3390/nu16223885

[24]. Zhu, Z., Liu, X., Fang, X., Sun, H., Yang, X., & Zhang, Y. (2015). Structural characterization and anti-tumor activity of polysaccharide produced by Hirsutella sinensis. *International Journal of Biological Macromolecules*, *82*, 959–966. https://doi.org/10.1016/j.ijbiomac.2015.10.075

APPENDICES

Table 1: This Table Shows the Summary of Various Pharmacological and Therapeutic Effects of Cordyceps Sinensis.

Article No.	Target Organ / Issue / Cell	Illness treated	Effect(s) on the body	Bioactive compound	Dosage	Reference
1	Human pulmonary artery smooth muscle cells (hPASMCs), Blood vessels	PASMCs proliferation, Idiopathic Pulmonary Arterial Hypertension (IPAH)	Anti-proliferation	Cordycepin	0.05 - 2 mM	Luitel et al. (2020)
2	Breast cancer cells	Breast cancer metastasis	anti-metastatic	polysaccharide, nucleosides	50 mg/kg	Cai et al. (2017)
3	Human platelets	Platelet aggregation	antiplatelet	CME-1 polysaccharide (mannose and galactose)	50 to 100 mg/kg	Lu et al. (2014)
4	Human colon cancer cell line HCT116	colon cancer	anti-proliferation, anti-autophagy, anti-apoptosis, anti-cancer	galactose (36.40%), glucose (28.99%), mannose (24.81%), galacturonic acid (7.55%0, arabinose (3.34%)	0 - 800 0 µg/mL	Qi et al. (2020)
5	Murine peritoneal macrophage cells	breast cancer	anti-proliferation, anti-tumor, anti-cancer, promote macrophage polarization	nucleosides, polysaccharide	100 mg/kg to 200 mg/kg	Li et al. (2020)
6	THP-1-Dual cell line	inflammation	anti-inflammatory	extracellular polysaccharide, glucose, mannose, galactose	Low dose of 150 mg/kg, high dose of 300 mg/kg	Li et al. (2020)
7	Jejunum tissues	intestinal damage	promotes intestine tissue recovery	polysaccharide	25, 40, 50, 200 mg/kg	Ying et al. (2019)
8	Human mesangial cells	proliferation	inhibitory activity against PDGF-BB-in-277 duced HMC proliferation	CPS-2	12.5, 25, 50 µg/mL	Wang et al. (2013)
9	H22 Cells	tumor	anti-tumor	polysaccharide (d-Glucose, d-galactose, l-rhamnose, d-xylose, d-mannose, and d-arabinose)	25, 50, 100, 200 400 µg/mL	Zhu et al. (2015)
10	Mouse melanoma cell	metastatis of cancer cells	antimetastatic effect, immunoactive action, antioxidant activity, antiatherosclerotic property	nucleosides, cordycepin, polysacchariddes, ergosterol,	5, 25 mg/kg	Yoshikawa et al. (2009)

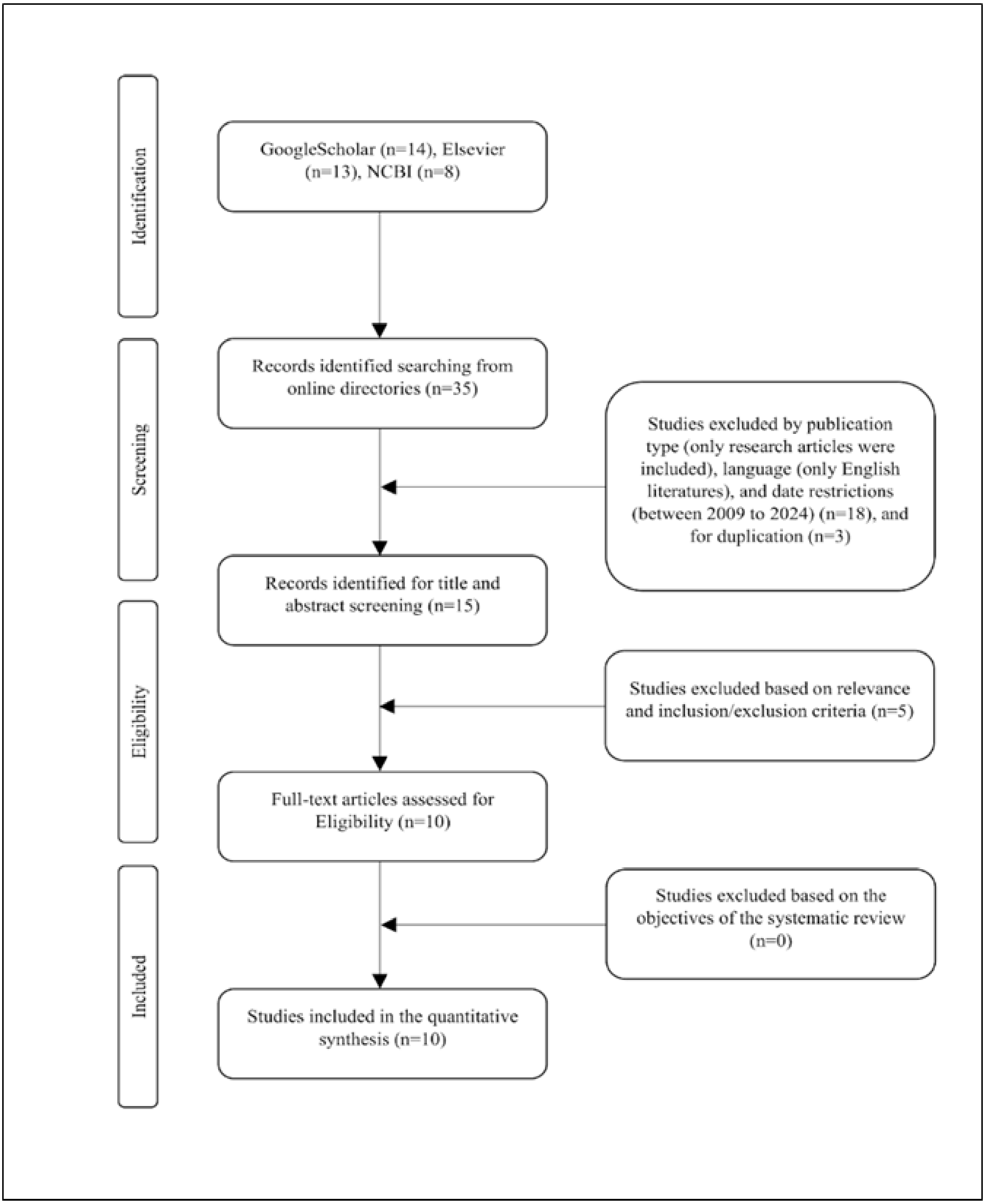

Fig 1: PRISMA Study Selection Stages Flow Diagram for Related Studies